THESIS ON NATURAL AND EXACT SCIENCES B162

Synthesis of Heterobicyclo[3.2.0]heptane Derivatives *via* Multicomponent Cascade Reaction

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Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any academic degree.

/Kerti Ausmees/

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Heterobitsüklo[3.2.0]heptaanide süntees multikomponentse kaskaadreaktsiooniga

KERTI AUSMEES

TTÜ KIRJASTUS

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List of Publications

I Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. A Novel Diastereoselective Multicomponent Cascade Reaction. *Organic Letters* **2010**, *12*, 2230-2233.

II Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T. Chemoenzymatic synthesis and evaluation of 3-azabicyclo[3.2.0]heptane derivatives as dopaminergic ligands. *European Journal of Medicinal Chemistry* **2012**, *55*, 255-261.

III Ausmees, K.; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M.; Kanger, T. Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds. *Journal of Organic Chemistry* **2012**, *77*, 10680-10687.

Author's Contribution

The contribution by the author to the papers included in the thesis are as follows:

I Participated in the planning of experiments, carried out the experiments, analysis of the final compounds.

II Participated in the planning of experiments and carried out the experiments, analysis of the final compounds and participated in the final manuscript preparation.

III Participated in the planning of experiments, carried out the experiments, wrote the manuscript draft and participated in the final manuscript preparation.

Abbreviations

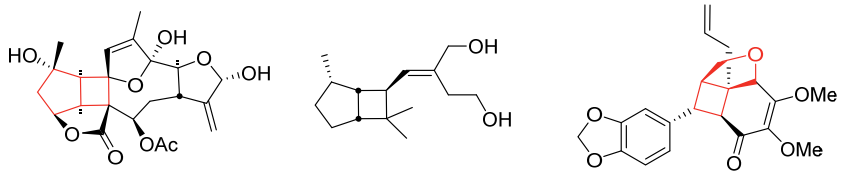
Ac	acetyl
Boc	*tert*-butyloxycarbonyl
CBD	conditions-based divergence
Cbz	carboxybenzyl
cod	1,5-cyclooctadiene
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
DKR	dynamic kinetic resolution
dr	diastereomeric ratio
ee	enantiomeric excess
EWG	electron withdrawing group
GABA	γ-aminobutyric acid
HIV	human immunodeficiency virus
LAH	lithium aluminium hydride
LG	leaving group
LUMO	lowest unoccupied molecular orbital
MC	multicomponent
MCR	multicomponent reaction
MRS	modular reaction sequence
MS	molecular sieves
MW	molecular weight
MWr	microwave reactor
ND	not determined
NHC	*N*-heterocyclic carbene
NOE	nuclear Overhouser effect
Nu	nucleophile
OTf	trifluoromethanesulfonate
PG	protective group
PMP	*p*-methoxyphenyl
rt	room temperature
sat.	saturated
SOMO	singly occupied molecular orbital
SRR	single reactant replacement
TBAF	tetra-*N*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

Introduction

The importance of small organic molecules in everyday life is undisputed; they provide us with an almost infinite collection of properties with applications ranging from supramolecular chemistry and material science to biology and medicine. Synthetic organic chemistry provides us access to this diverse set of compounds (chemical space). The total number of possible small organic molecules (MW < 500) has been estimated to exceed 10^{60}.[1] Thus, it is not surprising that through exploration by linear multistep synthesis we have discovered only a fraction of these compounds. Multicomponent and domino reactions are known concepts in organic synthesis and provide the higher efficacy needed, but their application has been challenging. Therefore, the invention of new reactions, reaction sequences, reagents or strategies that allow for this increase in efficacy in a one-pot reaction are critical to the realization of step-economical syntheses to achieve high complexity.

1. Literature Overview

Bicyclo[3.2.0]heptane derivatives are an interesting group of compounds with several applications. They can be used as starting material for the construction of more complex molecules as there are several ways to open, expand or contract the small cyclobutane rings.[2] Bicyclo[3.2.0]heptane cores themselves are found in many natural products[3,4,5] (Scheme 1) and several therapeutic applications are in development containing the core (Scheme 2).[6]



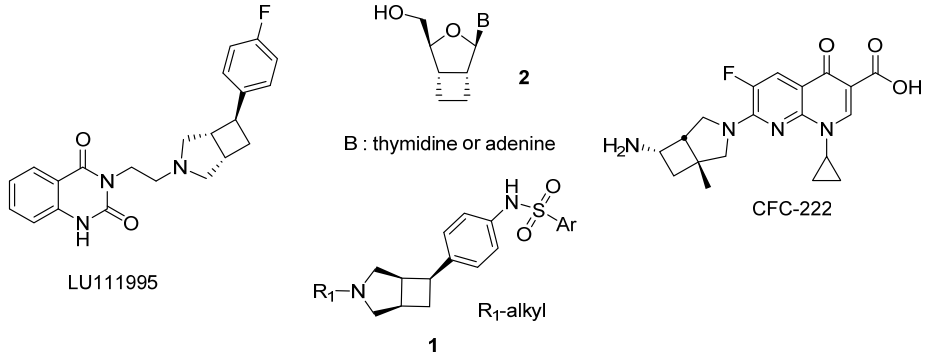
Bielschowskysin Raikovenal (+)-Kunstlerone

Scheme 1. Some examples of natural products with bicyclo[3.2.0]heptane ring systems.

LU111995 and its analogues are antipsychotic agents known to have dopamine D_4 receptor affinity and dopamine D_4 versus D_2 receptor selectivity.[7,8,9,10] Azabicyclo[3.2.0]heptane skeletons **1** on their own are also known to have biological activity, but as dopamine D_3 receptor modulators.[11]

Alibes *et al*[12,13] synthesized 3-oxabicyclo[3.2.0]heptane for the substitution of the sugar part of the nucleoside **2**. The authors hoped to make more efficient antivirals, especially as anti-HIV agents.

Kim *et al*[14] attached azabicyclo[3.2.0]heptane skeletons to known antibacterial agents: fluoroquinolones. They showed that the novel compound CFC-222 was more active on gram positive bacteria (*ig Streptococcus pneumonia* and *Staphylococcus aureus*) than other fluoroquinolones.

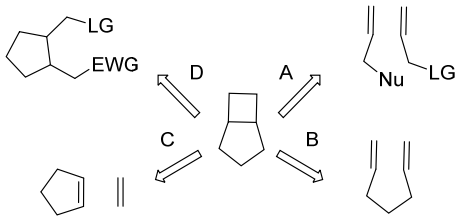


Scheme 2. Some examples of the bicyclo[3.2.0]heptane ring system in drug development.

1.1. Synthesis of bicyclo[3.2.0]heptanes

Bicyclo[3.2.0]heptane skeleton synthesis in most cases involves methods which are used for the synthesis of cyclobutane rings[2] (Scheme 3).

- Intermolecular [2+2]-cycloaddition (route A, C)
- Intramolecular [2+2]-cycloaddition (route B)
- 1,4-cyclization of acyclic substrates (route D)



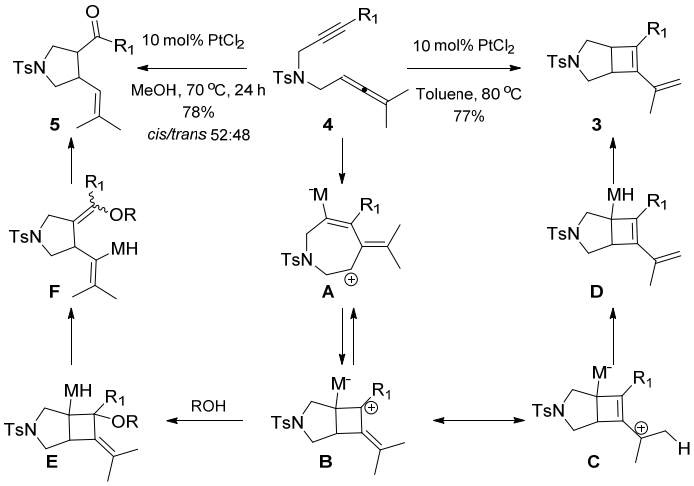
Scheme 3. Strategies for the synthesis of bicyclo[3.2.0]heptane skeletons.

The five-membered ring of the target molecule is formed either in the course of cyclization (routes A and B), or it may already exist in the cyclic starting material (route C or D). Route B is the most often used synthetic strategy for the synthesis of a bicyclo[3.2.0]heptane skeleton. In the heterobicyclic compounds, various heteroatoms (N, O and S) are present in the desired location in the starting material(s). [2+2]-cycloadditions can be photochemical, thermal or metal- catalyzed.

In the following, the author has selected and covered the most interesting/general examples from the literature.

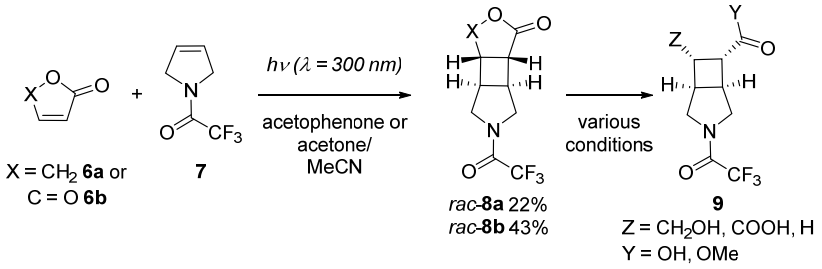
1.1.1. 3-azabicyclo[3.2.0]heptanes

Nitrogen-containing bicyclic cyclobutenes[15,16] **3** with aliphatic R-substituents were synthesized from allenynes **4** in toluene with a catalytic amount of $PtCl_2$. When methanol was used as a reaction medium, monocyclic product **5** was formed (Scheme 4). The authors propose that the Pt metal coordinates to the triple bond in allenyne **4**, forming a complex, which then undergoes *endo*-cyclization with an allenic carbon-carbon double bond to form a seven-membered ring **A**. The carbocation **A** is in equilibrium with its bicyclic resonance forms **B** and **C**, the latter being in dominance. Pt abstracts the proton from the methyl group in intermediate **D** and then undergoes a reductive elimination to furnish **3**.



Scheme 4. Pt-catalyzed cycloisomerization of allenyne to 3-azabicyclo[3.2.0]heptane (M = $PtCl_2$).

On the other hand, when methanol was used as a reaction medium, carbocation **B** was captured by the nucleophilic solvent, forming an intermediate **E**. The four-membered ring of **E** was opened through β-carbon elimination to afford the (alkenyl)platinum(II) species **F**. After reductive elimination of Pt and hydrolysis of the enol in **F** by water, the monocyclic product **5** was obtained.

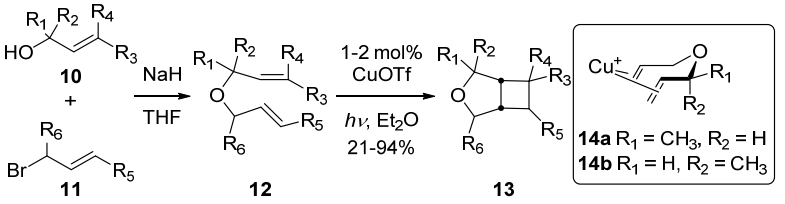


Scheme 5. Synthesis of potential GABA-uptake inhibitors.

Recently, Wanner *et al*[17] published a route for the synthesis of potential GABA-uptake inhibitors **9** (Scheme 5). The intermolecular [2+2]-photocycloaddition of maleic anhydride **6b** or furan-2(5*H*)-one **6a** with *N*-protected 3-pyrroline **7** was used for the formation of the 3-azabicyclo[3.2.0]heptane skeleton **8**; only *exo* diastereomer was isolated in up to 43% yield.

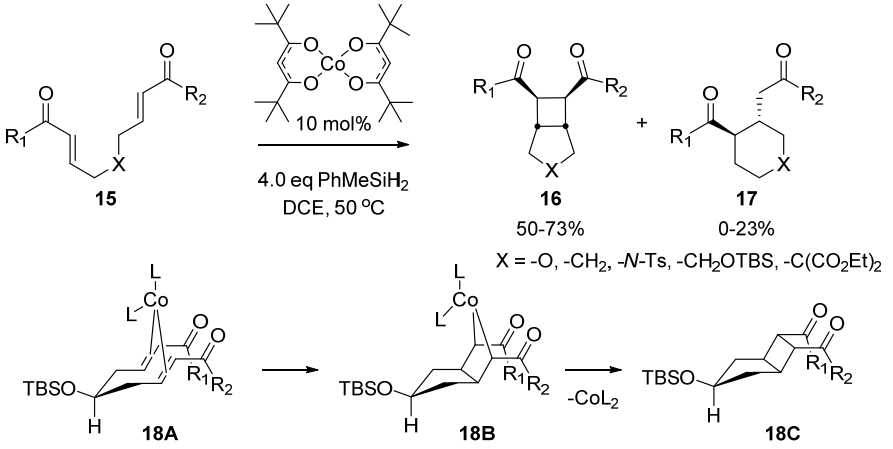
1.1.2. 3-oxabicyclo[3.2.0]heptanes

Salomon *et al*[18] used copper(I) catalysis for the synthesis of multicyclic tetrahydrofurans **13** *via* photocycloaddition of homoallyl vinyl or diallyl ethers **12** (Scheme 6). Several different substituents, including hydroxy, acetoxy, allyl and vinyl, were tolerated; however, the yields of the cycloaddition were highly dependent on the starting material giving low to high yields of 21-94%. In copper catalyzed [2+2]-photocycloaddition both reacting C=C bonds must be coordinated to the Cu^{I} atom, so the diastereoselectivity must have arisen from the formation of the less sterically hindered copper-diene complex (**14a** was preferred over **14b**). In all cases, only a single diastereomer was isolated and observed in ^{1}H NMR.



Scheme 6. Cu(I)-catalyzed synthesis of 3-oxabicyclo[3.2.0]heptanes **13**.

In 2010[19] and 2012[20] Yoon *et al* utilized a Ru- and Ir-catalyzed oxidative visible light [2+2]-cycloaddition of bis(alkenes) (wide library of analogues of **12**) for the synthesis of 3-oxabicyclo[3.2.0]heptanes.

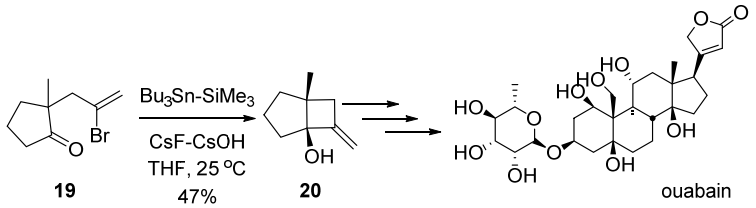


Scheme 7. Cobalt-catalyzed synthesis of bicyclo[3.2.0] ring systems.

A carbonyl functional group containing bicycle [3.2.0] ring systems were synthesized by Krische *et al*[21] from bis-enones **15**. Depending on the type and amount of silane used, bicyclo[3.2.0]heptane **16** ([2+2]-cycloaddition) or substituted cyclohexane **17** (Michael cycloreduction occurred when $PhSiH_3$ was used, 73% yield for **17**) was obtained as the major product. When $PhMeSiH_2$ was used the yields for bicyclic product **16** ranged from 50-73%, and a *cis* isomer of the product was isolated as a single diastereomer. The intermediates **18A** and **18B** in Scheme 7 were proposed by the authors as a general model for the observed diastereoselectivity.

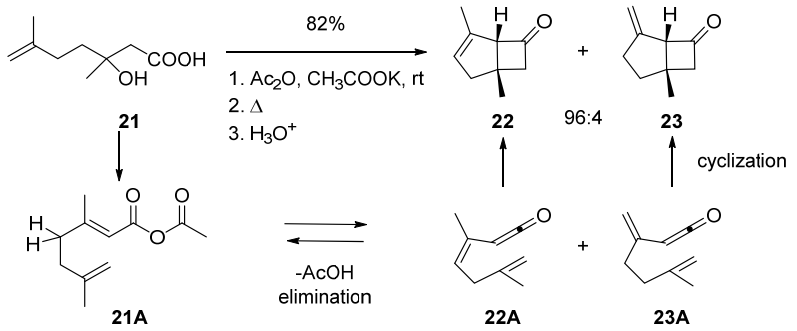
1.1.3. Bicyclo[3.2.0]heptanes

Jung *et al*[22] synthesized bicyclo[3.2.0]heptanol **20** with the aim of using it as the starting material in their synthesis of cardioactive steroid ouabain (Scheme 8). Bromovinyl ketone **19** as their starting material proved to be surprisingly nonreactive towards metal insertion reactions. A successful metal-halogen exchange and subsequent cyclization was achieved by a Bu_3Sn-$SiMe_3$ complex, in combination with CsF-CsOH-fused salt.



Scheme 8. Synthesis of bicyclo[3.2.0]heptanol **20** from bromovinyl ketone **19**, as an intermediate in the total synthesis of natural product ouabain.

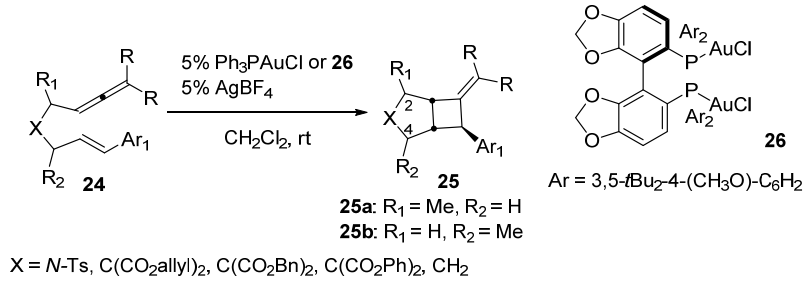
Rosini *et al*[23,24] reported the synthesis of bicyclo[3.2.0]hept-3-en-6-ones **22** from 3-hydroxy-6-heptenoic acid **21** (Scheme 9). *α,β*-unsaturated ketene **22A**, formed by acetate elimination from compound **21A**, underwent an intramolecular [2+2]-cyclization to give the thermodynamically more stable final product in 82% yield and 96:4 selectivity. Three analogues of bicyclo[3.2.0]hept-3-en-6-one **22** were synthesized in 48-82% yield. Bicyclo[3.2.0]hept-3-en-6-ones **22** are important intermediates in the synthesis of several pheromones (grandisol, lineatin and filifolone) and sesquiterpenes.



Scheme 9. Synthesis of bicyclo[3.2.0]hept-3-en-6-ones **22**.

1.1.4. Asymmetric synthesis of bicyclo[3.2.0]heptanes

In 2007 Toste *et al*[25] reported the first transitional metal- (gold-) catalyzed [2+2]-cyclization of various allenenes **24** in high yields, 57-92%. Methyl substituent in the second (-R_1) or fourth (-R_2) position gave rise to diastereomers of **25**, with good and excellent selectivity of > 95:5 (**25a**) and 6:1 (**25b**), respectively. In some examples, it was demonstrated that, when chiral catalyst **26** was used, high enantioselectivities could also be achieved: 92-97% *ee* for X = C(CO_2Me) containing substrates. With X = *N*-Ts, the lower 54% *ee* was obtained.

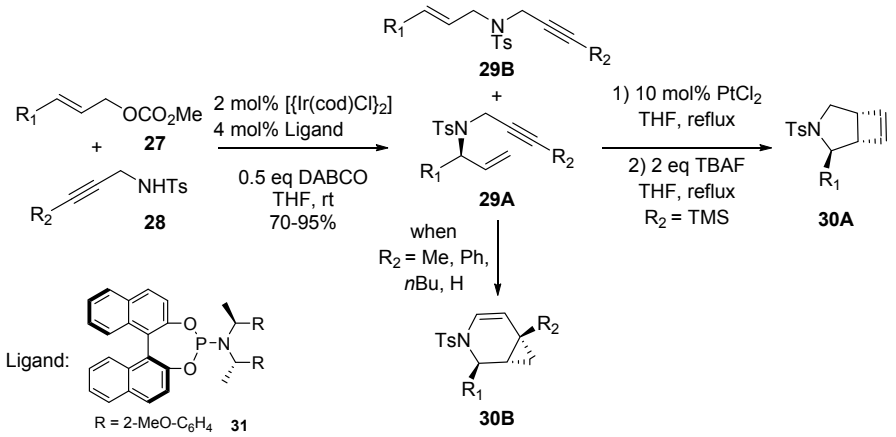


Scheme 10. Gold-catalyzed enantioselective [2+2]-cyclization of allenenes **24**.

In 2011[26] it was shown that a ruthenium catalysis ($RuH_2Cl_2(PiPr_3)_2$) can also be used for [2+2]-cyclization of very similar allenenes **24** in 45-86% yield and with full diastereoselectivity.

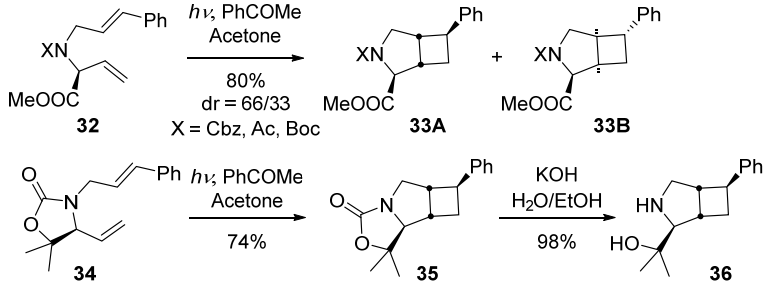
As described above, the general strategy for the synthesis of bicyclo[3.2.0]heptanes is the cycloisomerization of polyenes or enynes, either synthesized separately or *in situ*. You *et al*[27] proposed to insert the chirality in the crucial intermediate **29A** stage by using an iridium-catalyzed asymmetric allylic amination reaction; excellent enantioselectivity (92-99% *ee*) and chemoselectivity (**29A**/**29B** ratio from 88:12 to 99:1) were achieved with phosphoramidate ligand **31** (Scheme 11). A $PtCl_2$ catalyst was used for the cyclization of the enynes **29A** to corresponding azabicyclo[3.2.0]heptanes **30A**

in moderate yields of 21-60%, but only when R_2 = TMS; no change in enantiopurity was observed. When the R_2 substituent was Me, Ph, *n*Bu or H, cyclopropane containing bicyclic product **30B** was obtained.



Scheme 11. Azabicyclo[3.2.0]heptanes **30A** *via* $PtCl_2$ catalyzed cyclization of enantiopure enynes **29**.

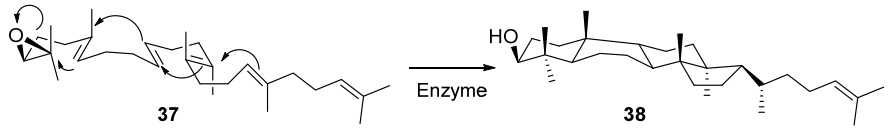
Bach *et al*[28,10] have reported the synthesis of enantiomerically pure azabicyclo[3.2.0]heptanes from optically active starting material *via* [2+2]-photocyclization (Scheme 12). Vinylglycine derivative **32** failed to give high diastereoselectivity; in order to improve diastereoselectivity, they opted to fix the conformational freedom of **32**. 3-Cinnamyl-4-vinyloxazolidinone **34** was synthesized and cyclized with very high diastereoselectivity, and the enantiomerically pure azabicyclo[3.2.0]heptane **35** was obtained. In order to broaden the scope of substrates, they demonstrated that Cu^I catalysis could also be used for the [2+2]-cyclization.



Scheme 12. Synthesis of azabicyclo[3.2.0]heptane **35** *via* [2+2]-photocyclization.

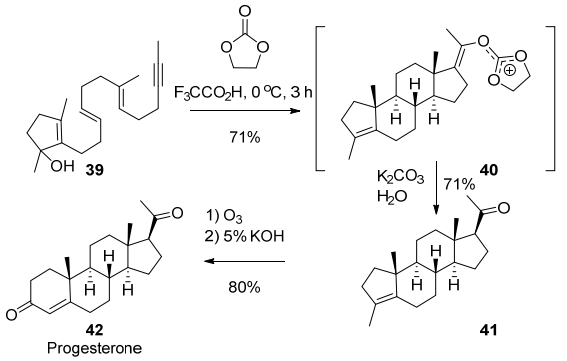
1.2. Cascade and Multicomponent Reactions: Introduction and background

Domino or cascade reactions are an interesting class of reactions prevalent in biosynthesis and mimicked by synthetic chemists. Professor L. Tietze has defined a cascade reaction as follows: *"a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step."*[29]



Scheme 13. Biosynthesis of steroids from squalene epoxide.

In the 1960s Corey *et al*[30] published a beautiful example of a cascade reaction in Nature magazine. They found evidence that steroids were biosynthesized from squalene epoxide **37** by enzyme initiation (Scheme 13). Corey's work inspired Johnson[31] to use acid catalysis to efficiently synthesize progesterone *via* polycyclization of **39** (Scheme 14). Since then, the use of cascade reactions has increased steadily.

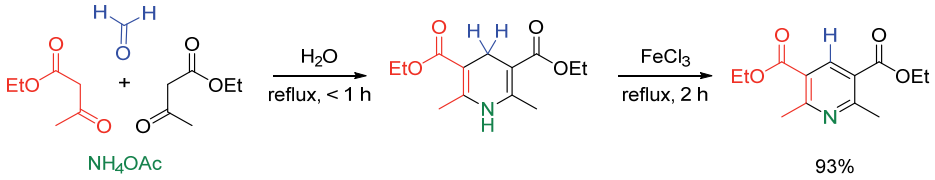


Scheme 14. Synthesis of progestrone.

Currently there is a debate over the classification methods for cascade reactions; several possibilities have been proposed by Tieze *et al*,[32] Jorgensen *et al*[33] and Orru *et al*,[34] to name a few (Prof. Orru's proposal is depicted in Scheme 17). The usefulness of a cascade reaction can be judged by its bond-forming efficiency, i.e. the number of bonds formed, the obtained structural complexity, i.e. the number of stereocenters formed, and the suitability for general applications.

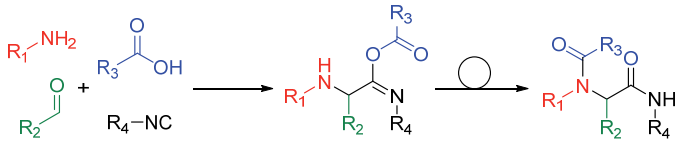
A multicomponent reaction (MCR) is considered to be a subclass of cascade reactions and can be defined as a reaction in which three or more compounds react in a single operation to form a single product that contains essentially all of the atoms of the starting materials. MCRs typically involve a number of subreactions, ideally all in equilibrium, and the last, product-forming reaction step is irreversible, thus providing the driving force to shift all intermediates and starting materials towards a single final product.[35]

The history of MCRs dates back to the second half of the 19th century with Strecker amino acid,[36] Hantzsch pyridine[37] (Scheme 15) and Biginelli dihydropyrimidone[38] synthesis, to name a few. Most of these reactions were found by early organic chemists *via* trial and error.



Scheme 15. Hantzsch pyridine synthesis.

Multicomponent reactions were rediscovered with the work of Ivar Ugi[39] and his co-workers in 1960; the four-component reaction ended up being the most well-known and widely used and modified MCR in organic synthesis.

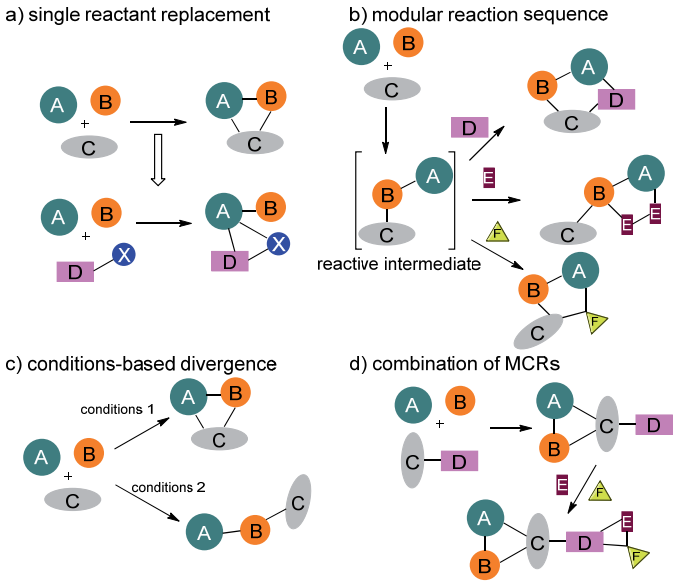


Scheme 16. Ugi four-component synthesis of bis-amides.

Many MCRs and cascade reactions have been described over the years and have even found their way into industrial applications (Crixivan® and Adalat®). However, the discovery of novel reactions is mainly the product of the past decade, reflected in the steady growth in the number of publications. The rational design of MCRs and cascade reactions is still difficult and requires a deep knowledge of known reactions; serendipity still plays a large role.

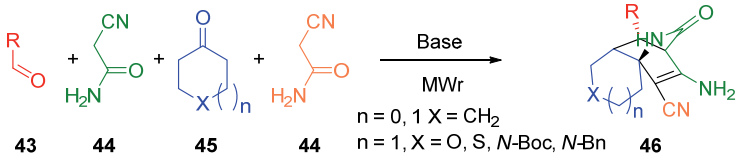
For the conscious design of novel multicomponent reactions, the following strategy has been proposed (Scheme 17):[34]

(a) single reactant replacement (SRR)
(b) using modular reaction sequences (MRSs)
(c) conditions-based divergence (CBD)
(d) using a combination of MCRs (MCR2)



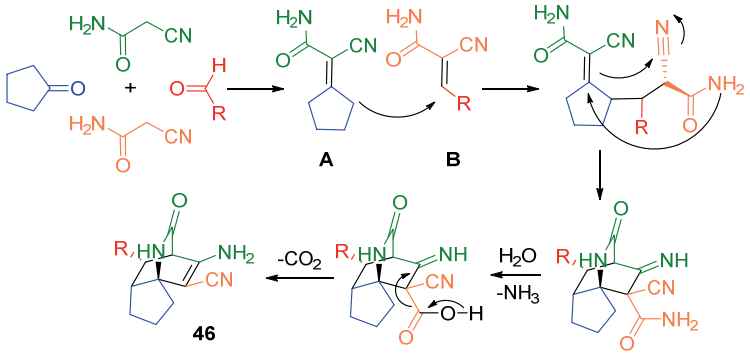
Scheme 17. Development of novel multicomponent reactions.

To the best of our knowledge, prior to our work, there are no examples of the multicomponent synthesis of bicyclo[3.2.0]heptanes described in the literature. The following example of the four-component synthesis of tricyclo[6.2.2.$0^{1,6}$]dodecane derivatives **46** is described below (Scheme 18), as an example of how highly diastereoselective multicomponent reactions. Highly polycyclic products can be obtained.



Scheme 18. Four-component domino reaction.

The microwave assisted diastereoselective four-component synthesis of multifunctionalized quinazoline derivatives **46** has been described.[40] The authors proposed the formation of two different Knoevenagel intermediates (Scheme 19, **A** and **B**), followed by C=C bond rearrangement, the addition of intermediate **A** to **B** and an intramolecular Michael addition and carbonyl addition to form the tricyclic skeleton. Successive amide hydrolysis and decarboxylation results in the final product. A wide range of commercially available substrates were used and the tricyclic lactams **46** were synthesized in complete stereo- and regioselectivity, with good yields (49-74%).



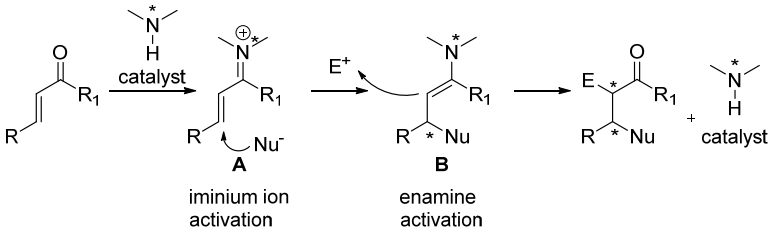
Scheme 19. Proposed mechanism of the formation of tricyclo[5.2.2.0^{1,5}]undecanes.

1.2.1. Catalytic methods for asymmetric cascade reactions and MCRs

Organometallic, enzymatic and organocatalytic are the three known major catalytic methods for stereocontrol in organic reactions. Organocatalysis – catalysis by small organic molecules – is the newest and least developed of the three.[41,42,43,44] The field has been intensely investigated over the past 10 years.

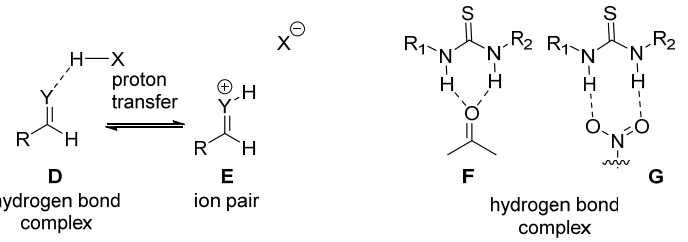
Several activation modes have been identified:

- Iminium activation of α,β-unsaturated aldehydes (Scheme 20 **A**)
- Enamine activation of aldehydes and ketones (Scheme 20 **B**)
- Hydrogen bonding catalysis (Scheme 21 **D**, **F**, **G**)
- Counter ion catalysis[45] (Scheme 21 **E**)
- Umpolung, NHC-catalysis
- SOMO catalysis



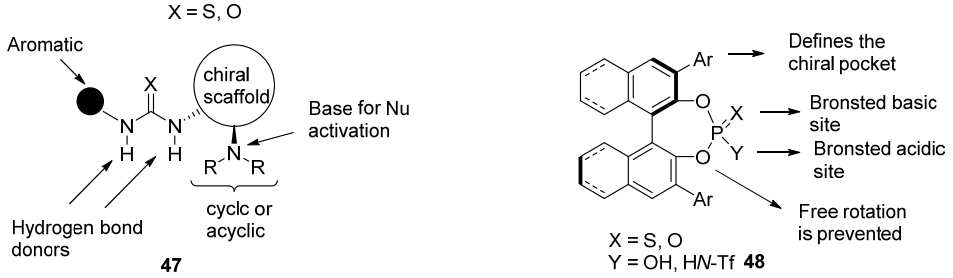
Scheme 20. Activation of carbonyl compounds by chiral amines.

The most widely used is the first, enamine catalysis, but for the purpose of this thesis the literature review will cover reactions which use hydrogen-bonding (**F**, **G**) and counter-ion (**E**) catalysis (Scheme 21).



Scheme 21. Activation of carbonyl compounds by Brønsted-acid and hydrogen-bonding catalysts.

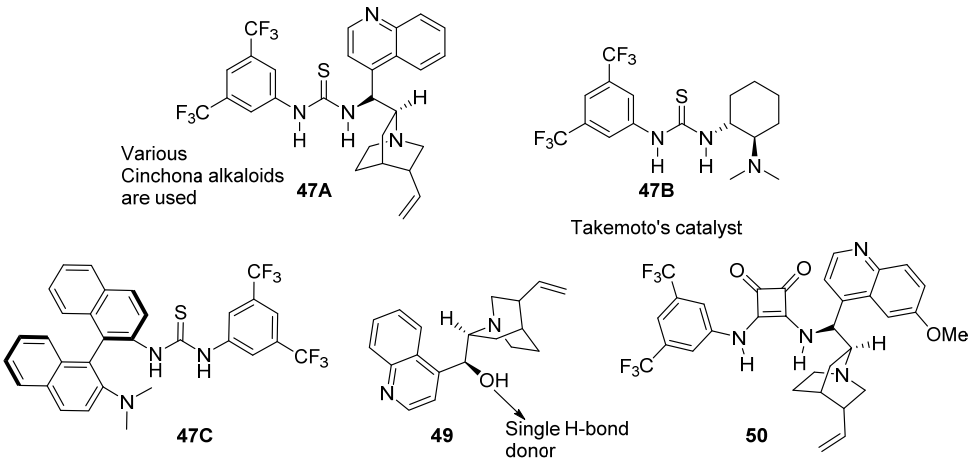
Hydrogen-bonding and Brønsted-acid (counter-ion) catalysts activate substrates by lowering the LUMO energy *via* hydrogen bonding or by the protonation (Scheme 21) of the C=Y bond (Y = *O*, *N*-R, *C*-R_2), thus forming a hydrogen-bond complex **D** or **F** or a chiral counter-ion **E**.[46,47] Several C-C and C-heteroatom bond-forming reactions are known to be promoted *via* this kind of catalysis. Prominent classes of known catalysts in this area are cinchona alkaloids **49**, bifunctional ureas/thioureas **47A-C**, squaramides **50** and phosphoric acids **48** (Scheme 22 for general catalyst structure and Scheme 23 for examples of specific catalysts).



Scheme 22. Widely used hydrogen-bonding and counter-ion catalysts.

BINOL-derived chiral phosphoric acids **48** were first used independently by the Akiyama[48] and Tereda[49] groups in Mannich reactions. Since then, many groups have expanded the scope and application of these catalysts.

It is assumed that phosphoric acids are unique in the sense that, in addition to strong Brønsted acidic sites they have adjacent Brønsted basic sites, thus allowing for simultaneous activation or orientation of nucleophile and electrophile *via* hydrogen bonding.



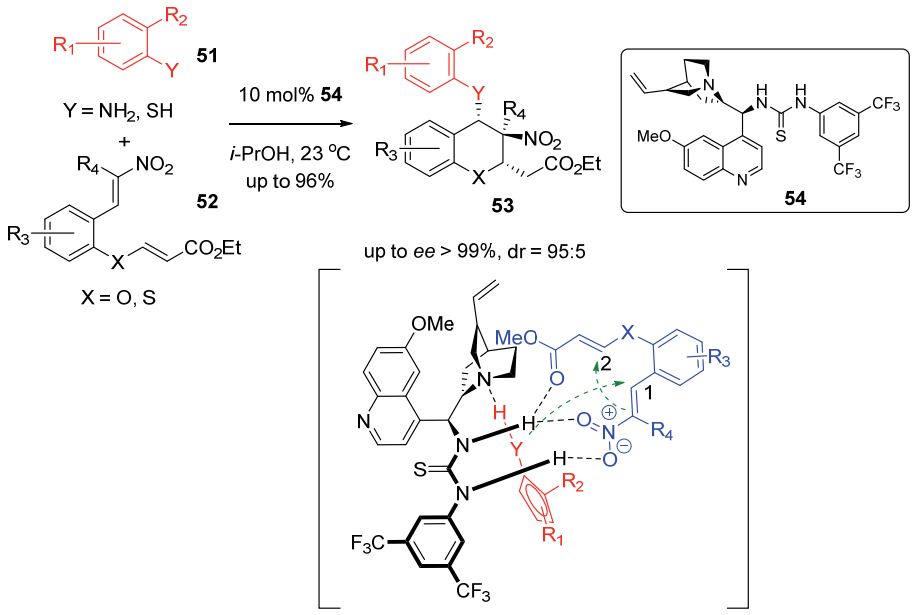
Scheme 23. Various hydrogen-bond donor catalysts currently used for catalysis.

1.2.2. Asymmetric cascade reactions initiated by Michael addition

An asymmetric Michael addition is often used as a first step in various cascade reactions. Recently Xiao *et al*[50,51] published a hetero-Michael-Michael cascade for the synthesis of a chiral chromane skeleton **53** (Scheme 24), which forms the core of various natural products displaying a broad range of biological activities.[52]

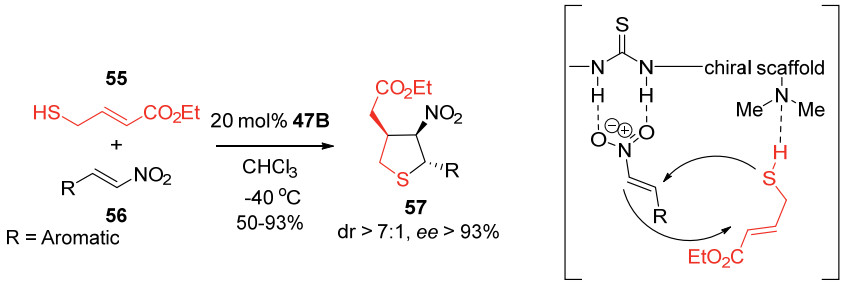
The described cascade reaction, catalyzed by bifunctional chiral thiourea **54**, generates three stereocenters, including one quaternary, with enantioselectivities up to 99% *ee* and excellent diastereoselectivities of > 95:5 dr. Nitroolefin-enoates **52** were prepared over three steps and used in the cascade reaction initiated by various aromatic thiols and anilines **51**. Reversibility of the reaction was not observed, which is a phenomenon often observed with heteroatom nucleophiles.[53]

The authors propose that the catalyst activates nitroolefin-enoates **52** *via* hydrogen-bonding, and the basic tertiary amino moiety on the catalyst activates the nucleophile. The formed complex undergoes an intermolecular hetero-Michael addition, which leads to an intra-molecular Michael addition, forming the desired chromane **53**.



Scheme 24. Hetero-Michael-Michael cascade reaction of nitroolefin-enoates with various aromatic thiols and anilines.

In 2011 Wang *et al*[54] described the synthesis of tetrahydrothiophenes *via* an asymmetric domino thia-Michael-Michael reaction catalyzed by chiral bifunctional thiourea **47B**, initiated by sulfur nucleophile **55** (Scheme 25). *trans*-ethyl-4-mercapto-2-butenoate **55** reacted with (*E*)-*β*-nitrostyrenes **56**, forming biologically significant trisubstituted tetrahydrothiophenes **57**, bearing three stereocenters with high enantio- and diastereoselectivities of up to 97% *ee* and > 7:1 dr, respectively. Substituents in the aromatic ring of (*E*)-*β*-nitrostyrene did not influence the yield nor the stereocontrol of the reaction.

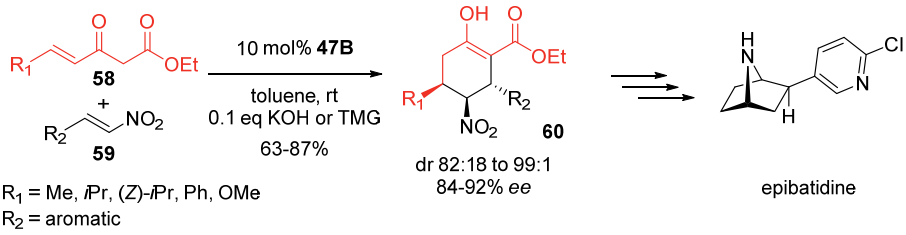


Scheme 25. Synthesis of tetrahydrothiophenes *via* thia-Michael-Michael cascade reaction.

Relying on their earlier work,[55] they demonstrated that, in addition to the direct stereocontrol of the substrates by the bifunctional catalyst through hydrogen

bonds, dynamic kinetic resolution (DKR) also occurred *via* basic tertiary amino moiety, cooperatively giving rise to the observed high enantioselectivity.

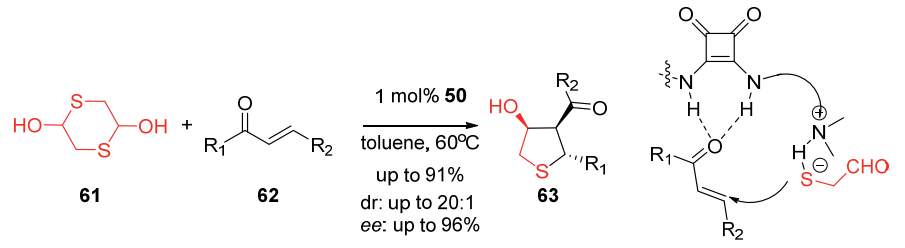
Takemoto *et al*[56,57] reported total synthesis of biologically active frog alkaloid (-)-epibatidine (Scheme 26). A thiourea-catalyzed Michael-Michael domino process gave them the crucial intermediate **60** in high enantioselectivity, which enabled them to complete the total synthesis in seven steps, with 30% overall yield. Three stereocenters of 4-nitrocyclohexenones were synthesized *via* a cascade reaction initiated by the addition of unsaturated *β*-ketoesters **58** to nitrostyrenes **59** in high yields (63-87%). By employing bifunctional thiourea as a catalyst they obtained high enantio- and diastereoselectivities (84–92% *ee*, dr = 82:18 to > 99:1). To complete the second Michael addition, it was necessary to use a strong base, such as KOH or 1,1,3,3-tetramethylguanidine (TMG), in a catalytic amount.



Scheme 26. Thiourea-catalyzed asymmetric tandem Michael-Michael reaction.

Squaramides are an interesting class of catalysts, giving enantioselectivity in cases where thiourea catalysts fail. The authors[58] described the use of the bifunctional squaramide catalyst **50** in a sulfa-Michael-aldol cascade. Trisubstituted tetrahydrothiophenes **63** were synthesized from 1,4-dithiane-2,5-diol **61** and chalcones **62**, with high yields (71-91%). The effects of various bifunctional H-bond donor catalysts were investigated and it was found that squaramides performed better than thiourea catalysts, giving high diastereo- and enantioselectivities (dr = 9:1 to > 20:1, *ee* 84-96%).

The authors propose that the catalyst activates the chalcone *via* hydrogen-bonding, and the basic tertiary amino moiety on the catalyst activates the nucleophilic dithiane.

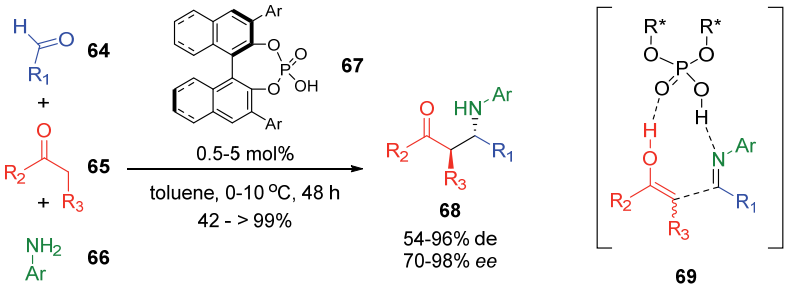


Scheme 27. Synthesis of trisubstituted tetrahydrothiophenes **63**.

1.2.3. Enantioselective MCR using noncovalent catalysis

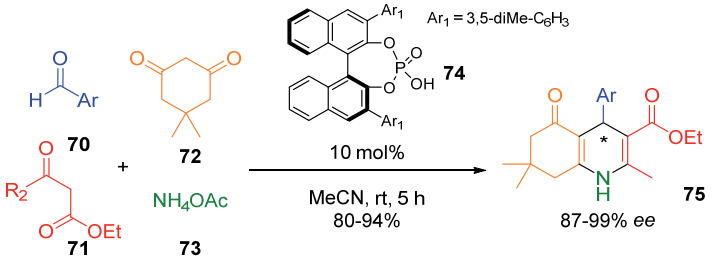
The literature review in this section covers reactions catalyzed by catalysts that form ion pairs (phosphoric acids and cinchona alkaloids) and thioureas. Enamine catalysis (covalent catalysis), often used in enantioselective MCR-s, is not covered. Phosphoric acids as catalysts are known but not limited to reactions where the electrophilic activation of imines is needed: Diels-Alder, Mannich and Friedel-Crafts reactions, to name a few.

An elegant example of an enantioselective catalytic three-component Mannich reaction was published by Gong and co-workers.[59] H_8-BINOL- or BINOL-based phosphoric acids (**67**, 0.5–5 mol%) were used to catalyze a reaction between aldehydes **64**, aliphatic ketones **65** and aromatic amines **66**. Anti-*β*-amino carbonyl compounds **68** were obtained in moderate to excellent yields (42-99%), and high diastereo- and enantioselectivities (up to 98/2, 70-98% *ee*). They proposed that the chiral phosphoric acid is able to co-ordinate the *in situ* formed imine and enolized ketone **69**, as shown in Scheme 28, promoting the reaction and giving rise to the observed high enantioselectivity.



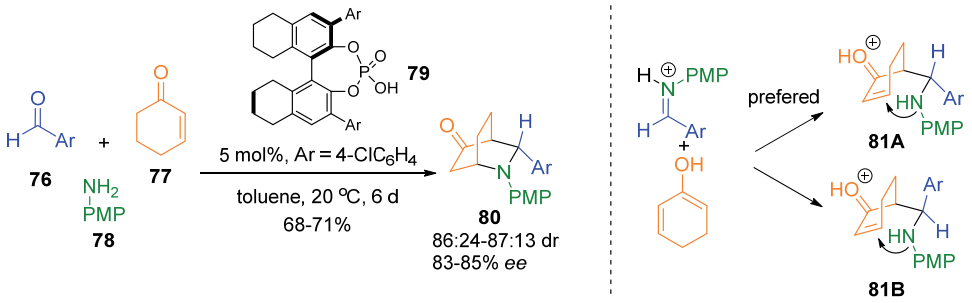
Scheme 28. Chiral Brønsted acid-catalyzed asymmetric Mannich MCR.

An enantioselective Hantzsch four-component reaction was reported by Evans and Gestwicki[60] in 2009. BINOL-phosphoric acids **74** were used as catalysts and dihydropyridines **75** were obtained in good yields (80-94%) and high to excellent enantioselectivities (87-99%) when aromatic aldehydes **70** were used; alkyl aldehydes gave good yields (66-94%) but no enantio-enrichment.



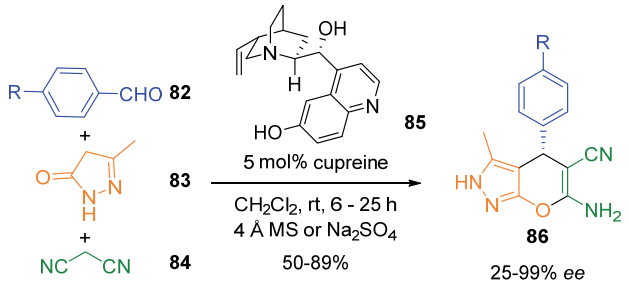
Scheme 29. BINOL-phosphoric acid-catalyzed synthesis of dihydropyridines **75**.

The first Brønsted acid-catalyzed aza-hetero Diels-Alder reaction was reported by Gong and co-workers.[61] H_8-BINOL-phosphoric acid catalyzed MCR between various aldehydes **76** in combination with *p*-anisidine **78** and 2-cyclohexenone **77**, resulting in substituted bicyclic piperidines **80**, which can be converted into various chiral building blocks (Scheme 30). Products were obtained in moderate to good yields (68–71%) and enantioselectivities (83–85% *ee*); intermediate **81A** was preferred for the formation of *endo*-diastereomer (76:24–87:13 dr). When imine from aldehyde **76** and amine **78** was premade the reaction yields (70-82%) and diastereoselectivities (80:20–84:16 dr) were a little bit better, enantioselectivities, however were the same (76-87% *ee*).



Scheme 30. H8-BINOL-phosphoric acid-catalyzed MCR aza-hetero Diels-Alder reaction.

In their publication Gogoi and Zhao[62] used another popular bifunctional catalyst, cinchona alkaloid **85**, which acts as a chiral base and has functional groups which form hydrogen bonds for additional co-ordination. Cupreine **85** catalyzed a three-component Michael/Thorpe-Ziegler cascade to give dihydropyrano[2,3*c*]pyrazole derivatives **86**, which are known to have a wide range of biological activities. Several cinchona alkaloid derivatives and urea catalysts were screened, and the



Scheme 31. Enantioselective organocatalytic Michael/Thorpe–Ziegler MCR sequence.

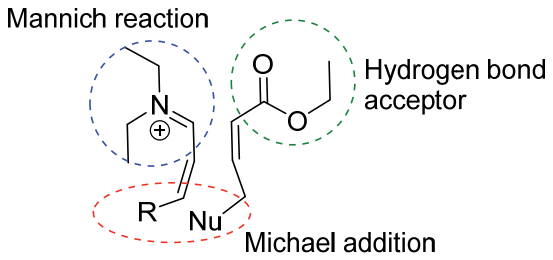
results showed that cupreine **85** gave the best enantioselectivity, 96% *ee*, while the alkaloid in combination with thiourea gave only 10-14% *ee*. Under optimized conditions, the reaction between heterocycle **83**, aromatic aldehydes **82** and malononitrile **84** furnished pyranopyrazoles **86** in 50-89% yields and 25-99% *ee*. The authors were able to extend the methodology, by making the reaction four-component *via* forming the heterocycle **83** *in situ* from hydrazine and β-ketoester. The best enantioselectivity and yield combination was obtained in CH_2Cl_2 at 0 ^oC (99% *ee* and 43% yield). Yields and enantioselectivities were highly dependent on the drying agent used (sodium sulfate, 4 Å MS, no drying agent).

1.3. Summary of Literature Overview

Based on the literature cited above, the "go to" method for the synthesis of bicyclo[3.2.0]heptanes is the intramolecular or intermolecular [2+2]-cycloaddition (photochemical, thermal or metal-catalyzed) of polyenes or enynes (Chapter 1.1, Scheme 3). To get highly functionalized bicyclo[3.2.0]heptane derivatives, complicated starting material synthesis might be needed. It is evident from the limited number of synthetic strategies that variability in methods is needed for the synthesis of bicyclo[3.2.0]heptane skeletons.

In recent years, a lot of attention has been paid to the efficiency and step economy of organic synthesis. One of the proposed tools for this involves one-pot cascade and multicomponent reactions; ideally, these reactions should generate highly complex molecules in a very stereocontrolled manner. The discovery and use of these reactions have increased steadily in recent years, although the rational design of MCRs and cascade reactions is still difficult and requires a deep knowledge of known reactions; serendipity still plays a large role.

To the best of our knowledge, prior to our work, there are no multicomponent or cascade reactions available for the organocatalytic stereochemically controlled synthesis of bicyclo[3.2.0]heptane derivatives. Thus, the literature review in this part was divided into two different strategies. The first part covered hydrogen-bonding catalysts used for the Michael reaction, including ways of introducing chirality in the first Michael addition step. The second part looked at the available activation modes for the introduction of chirality in MCR that have imines as part of their system (Scheme 32).



Scheme 32. Possible sites for the introduction of stereochemical control.

1.4. Aims of the present work

The current study directs its efforts toward widening synthetic strategies for the synthesis of bicyclo[3.2.0]heptane skeletons, from simple readily available starting materials, in a step economical-fashion.

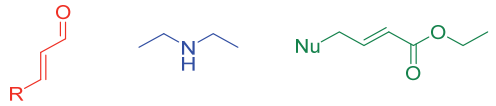
Bicyclo[3.2.0]heptanes are an interesting class of compounds with a wide range of applications. It has been shown that few strategies for the synthesis of bicyclo[3.2.0]heptanes exist and new additions are needed. Based on this, the main aims of the thesis are:

- To provide a simple step-economical synthetic approach for the synthesis of functionalized bicyclo[3.2.0]heptanes from readily available starting materials
- To investigate the structural features that influence the yield, chemo- and diastereoselectivity of bicyclo[3.2.0]heptanes
- To compare the reactivity and selectivity of hetero and carbon nucleophiles in a three-component cascade reaction initiated by a Michael reaction
- To devise a method to obtain enantiomerically pure bicyclo[3.2.0]heptanes
- To determine the relative and absolute stereochemistry of bicyclo[3.2.0]heptanes by available analytical methods
- To provide a series of bicyclo[3.2.0]heptane derivatives (including heterocyclic) for the screening of their biological properties.

2. Results and discussion

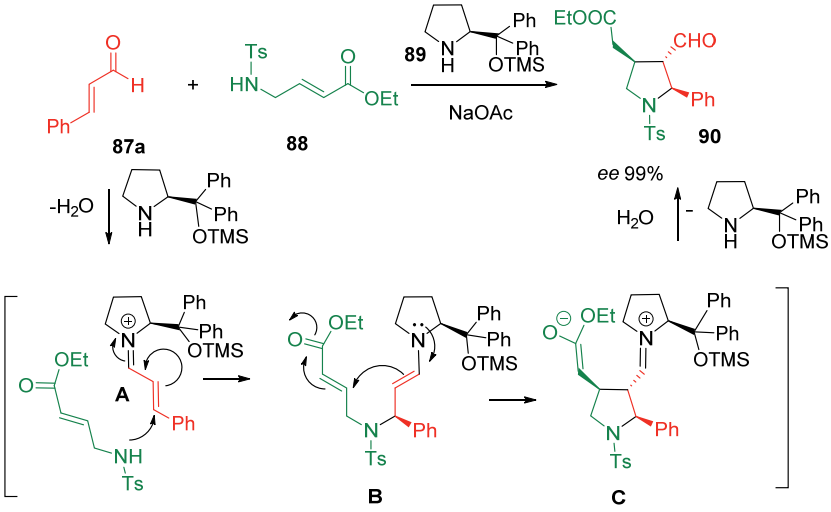
Ongoing investigations in our group and in the field of organocatalysis have steadily pushed the research into an area of efficiency and step economy. One way to achieve this and get closer to an "ideal synthesis" is through multicomponent reactions.

Our strategy for the synthesis of bicyclo[3.2.0]heptanes is based on conditions-based divergence (see Chapter 1.2). By tweaking the reaction conditions between secondary amine, α,β-unsaturated aldehyde and α,β-unsaturated ester with a tethered nucleophile (Scheme 33), the outcome of a reaction can be influenced.



Scheme 33. Starting materials of the three-component cascade reaction.

In multicomponent and cascade reactions reactive intermediates are formed *in situ*. A combination of iminium and enamine activation sequence (see chapter 1.2.1, Scheme 20) provides an ideal pathway for the cascade reaction. This strategy was used by Wang *et al* (Scheme 34).[63] Chiral secondary amine **89** activated
α,β-unsaturated aldehyde **87a** *via* the formation of an iminium ion **A** which is susceptible to a Michael addition by the ethyl (*E*)-4-*N*-Ts-but-2-enoate **88**. The formation of an enamine intermediate **B** permits the next step of the cascade, affording a five-membered ring **C**. After hydrolysis, the catalyst is released and the next catalytic cycle takes place. The organocatalytic reaction afforded, in the presence of trimethylsilyl prolinol derivative **89**, only one diastereoisomer of **90** in very high enantiomeric purity and yield. The formation of bicyclic product under these conditions was not detected.



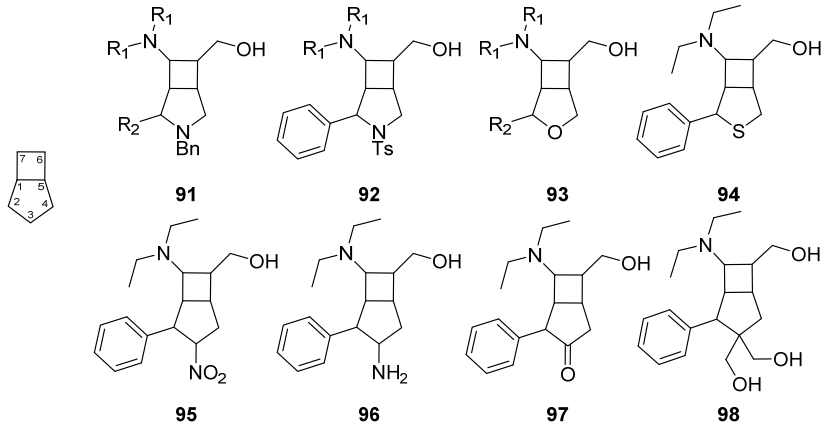
Scheme 34. Synthesis of pyrrolidines *via* iminium-enamine activation cascade.

By using the above-mentioned dually active (containing a good nucleophile and an electrophile) reagent **88** and its analogues, in combination with a sterically

less demanding amine, we were able to continue the cascade, which resulted in a compound with a bicyclo[3.2.0]heptane skeleton, where secondary amine (*i.e.* a catalyst for the first Michael addition) was also incorporated into the target, turning a cascade into MCR. To carry out the full cascade, the following problems had to be solved:

- the chemoselectivity of the cascade (formation of monocyclic versus bicyclic product)
- diastereoselectivity (there are up to five stereocentres in the target, giving rise to eight possible diastereomers)
- enantioselectivity (use of the above mentioned chiral amine **89**, as the source of enantioselectivity in the cascade was not possible, as the secondary amine becomes a part of the target and the catalytic cycle is not possible)

Under optimized reaction conditions, we were able to obtain bicyclo[3.2.0]heptanes instead of a five-membered ring. By varying the secondary amine, the substituent in unsaturated aldehyde and the dually active reagent, we synthesized a library of new compounds (**91**-**98**), with promising biological properties.



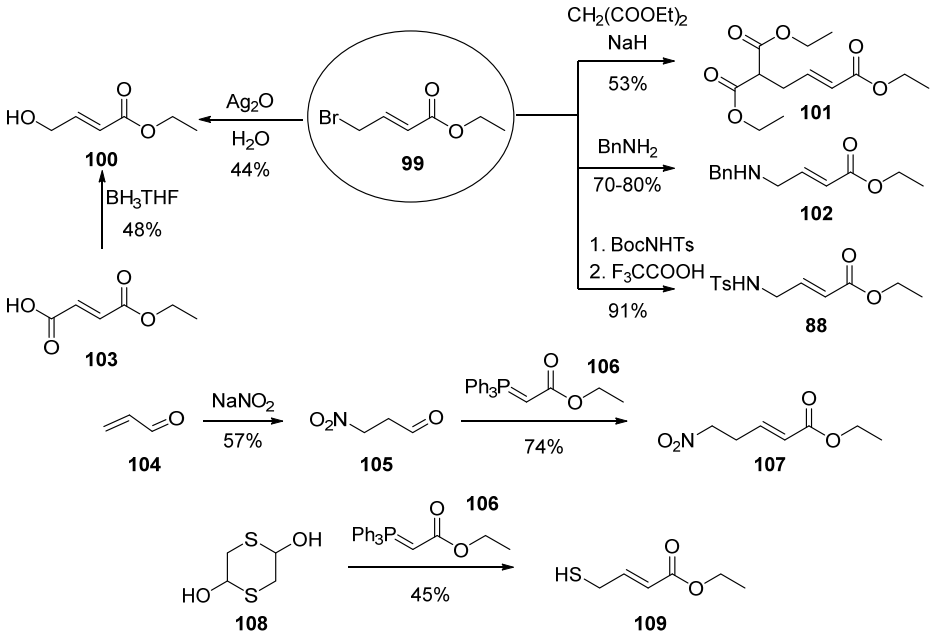
Scheme 35. Library of synthesized bicyclo[3.2.0]heptanes.

2.1. Synthesis of α,β-unsaturated esters

Four different α,β-unsaturated esters with a tethered nucleophile **100**-**102** and **88** (including C-, O-, and N-nucleophiles), were synthesized according to literature procedures from commercially available ethyl-(*E*)-4-bromobut-2-enoate **99** (Scheme 36). An amino and carbon nucleophile containing α,β-unsaturated esters were obtained *via* simple alkylation of ethyl-(*E*)-4-bromobut-2-enoate **99** with benzylamine,[64] diethyl malonate or Boc-protected tosylamide (followed by deprotection),[65] in 70-80%, 53% and 91% yields, respectively.

Ethyl-(*E*)-5-nitropent-2-enoate[66] **107** was prepared by adding sodium nitrite to acrylaldehyde **104** (57%), followed by a Wittig reaction (74%). 1,4-Dithiane-2,5-diol **108** was a very convenient substrate for the synthesis of ethyl-(*E*)-4-mercaptobut-2-enoate[67] **109** in one step *via* a Wittig reaction in 45% yield.

Two alternative methods were used for the synthesis of ethyl-(*E*)-4-hydroxybut-2-enoate **100**. The substitution reaction mediated by silver(I)oxide[68] was an easy and very reliable synthetic route for ethyl-(*E*)-4-hydroxybut-2-enoate **100**, but with expensive starting material and reagent. The selective reduction[69] of acid-functional group in monoethyl fumarate **103** was the more attractive method because of the lower cost of thestarting material and reagent, although the reaction was not very reliable and was dependent on the freshness of the BH_3•THF complex.



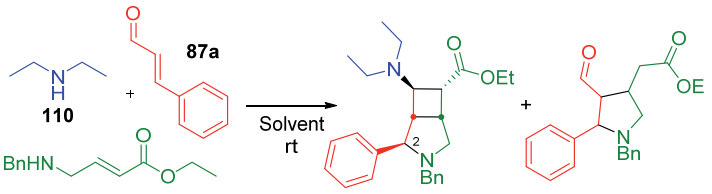
Scheme 36. Synthesis of α,β-unsaturated esters with tethered nucleophiles.

2.2. Synthesis of 3-azabicyclo[3.2.0]heptanes (Publication I and II)

For the synthesis of azabicyclo[3.2.0]heptanes **91** cinnamaldehyde **87a**, diethyl amine **110** and ethyl (*E*)-4-(benzylamino)but-2-enoate **102** was chosen as the model reaction. Various solvents and reaction conditions were screened to suppress the monocycle **112** formation (finally < 5%). MCR chemoselectivity was highly dependent on the solvent used, with CH_2Cl_2 giving the best results (Table 1, entries 1-3). Anhydrous conditions (oven dried MS and dry CH_2Cl_2), an excess of Et_2NH **110** and cinnamaldehyde **87a** favored the multicomponent reaction (Table 1, entry 3).

^{1}H NMR analysis of the crude mixture showed the formation of a 2-*endo*:2-*exo* diastereomer of the azabicyclo[3.2.0]heptane-6-carboxylate **111a** in a 25:1 ratio (for numbering see Scheme 35 and Chapter 2.4 for the assignment of the relative configuration). An analysis of the purified ester showed a degradation of diastereo- and chemoselecitvity. The reversibility of the cascade reaction proved to be the main culprit. Esters were stable enough to be isolated and analyzed, but decomposed upon storage. When the ester functionality was reduced by LAH, the azabicyclo[3.2.0]heptanes **91** were very stable. LAH reduction of the ester after the completion of MCR improved the isolation yield and diastereo- and chemoselecitivity of azabicyclo[3.2.0]heptanes **91**.

Table 1. Optimization of the three component reaction conditions.[a]



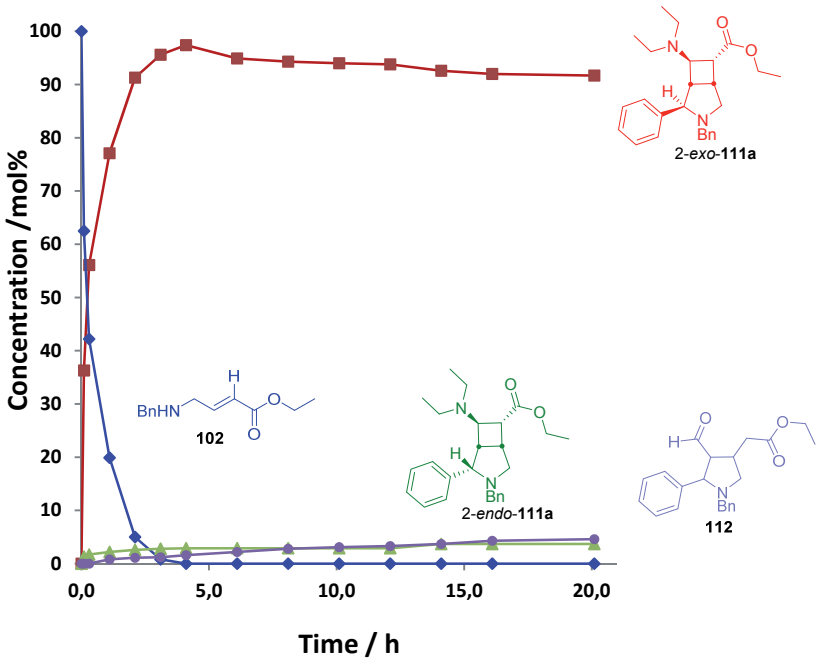
Entry	Solvent	Ratio of **111a**:**112**	Yield of **111a** (%)	Yield of **112** (%)
1	CH_2Cl_2	3:1	60	19
2[b]	CH_2Cl_2	3.8:1	53	14
3[c]	CH_2Cl_2	6.3:1	70	11
4	Toluene	1:2	22	40
5	CH_3CN	1:1.4	27	38
6	CCl_4	1:1.6	30	48
7[d]	$CHCl_3$	2:1	59	30

[a]Cinnamaldehyde **87a** (1 eq), Et_2NH (1.1 eq), and (*E*)-4-*N*-Bn-but-2-enoate (1 eq) were stirred in an appropriate solvent at rt for 24 h, and only the major diastereomer was isolated. [b]MS (4 Å) were added. [c]Cinnamaldehyde **87a** (2 eq), Et_2NH (2 eq), and (*E*)-4-*N*-Bn-but-2-enoate (1 eq) were stirred in the presence of MS. [d]MW irradiation: 10 W, 30 min 50 °C (internal cooling).

In order to gain additional insight into the reaction, it was continuously monitored by ^{1}H NMR. Cinnamaldehyde **87a** (2 eq), diethyl amine **110** (2 eq) and ethyl-(*E*)-4-(benzylamino)but-2-enoate **102** (1 eq) were mixed together in the NMR tube, $CDCl_3$ was used as reaction medium and no MS were added.

All the reaction products and starting materials showed distinct chemical shifts which did not overlap in one-dimensional ^{1}H NMR (Scheme 37). Only the starting materials **102**, **110** and **87** and the final products 2-*exo*-**111a**, 2-*endo*-**111a** and **112** were visible in the ^{1}H NMR; none of the intermediates formed in

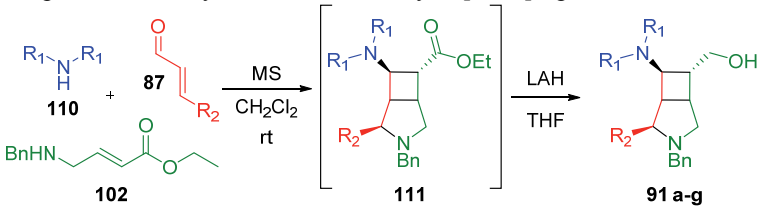
detectable amounts. From the study, it was evident that the MCR diastereomeric ratio between 2-*exo* and 2-*endo* diastereomers (**111a**) changed over time (best ratios were determined after 4 h: 2-*exo*-**111a** 97.4 mol%, 2-*endo*-**111a** 1.6 mol%, **112** 2.9 mol%), forming more 2-*endo* diastereomer (4.6% after 20 h). The five-membered monocycle **112** was also present from the start and concentration increase slowly during the experiment (3.7% after 20 h).



Scheme 37. Reaction progress profile for the MCR between cinnamaldehyde **87a**, diethyl amine **110**, and ethyl (*E*)-4-(benzylamino)but-2-enoate **102**, obtained using ^{1}H NMR spectroscopy. $CDCl_3$ was used as a reaction medium.

Table 2 shows the scope of the MCR with *N*-benzyl aminocrotonate **102** as a nucleophile. The acyclic amines gave better yields (64-73%), compared to the cyclic secondary amines pyrrolidine and piperidine (entries 5, 9 and 11). The aliphatic α,β-unsaturated aldehydes had lower diastereoselectivity but good conversion to 3-azabicyclo[3.2.0]heptanes **91c**, **91b** and **91f** (entries 2, 3 and 6). The aromatic substituents in the α,β-unsaturated aldehydes had little influence on the diastereoselectivity and yield (entry 1 vs entries 4 and 8). When 3-(pyridin-2-yl)acrylaldehyde **87j** was used, monocyclic product was not detected, but almost 40% of *N*,*N*-diethylindolizin-3-amine **S91j** (see experimental section) was isolated as a condensation product between the aldehyde **87j** and Et_2NH.

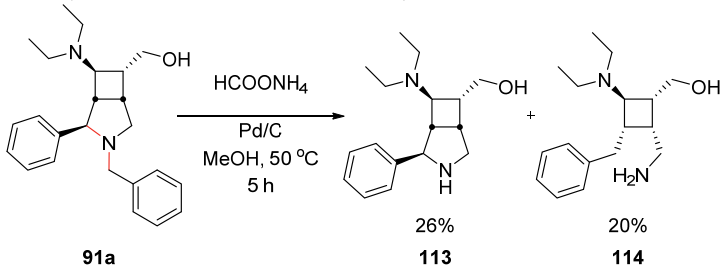
Table 2. Scope of the MC synthesis of 3-azabicyclo[3.2.0]heptanes.



Entry	R_2	Amine **110**	Product	Time (h)	Yield (%)[a]	dr[b]
1	Ph	Et_2NH	**91a**	17	68	45:1
2	Me	Et_2NH	**91b**	24	64	8:1
3	Et	Et_2NH	**91c**	24	65	8:1
4	*p*-MeOPh	Et_2NH	**91d**	42	66	24:1
5	Ph	pyrrolidine	**91e**	24	52	7:1
6	Me	Me_2NH[f]	**91f**	24	73	6.5:1[c,d]
7	Ph	Me_2NH[f]	**91g**	24	69	5:1[c,d]
8	*p*-BrPh	Et_2NH	**91h**	20	68	40:1
9	Ph	piperidine	**91i**	27	30 (32[h])	ND
10[g]	2-pyridyl	Et_2NH	**91j**	24	53	ND
11	Me	pyrrolidine	**91k**	24	51	ND
12	*o*-NO_2Ph	Et_2NH	**111h**	29	ND	65:1[e]

[a]Isolated yield of the major diastereomer. [b]Ratio of 2-*exo*:2-*endo* determined from ^{1}H NMR of the crude mixture. [c]2-*exo*-6-*exo*-7-*exo* as the major diastereomer [d]Ratio of 6-*exo*:6-*endo*. [e]Determined from the ^{1}H NMR of the crude ester. [f]2 M in THF. [g]A major side product was *N*,*N*-diethylindolizin-3-amine **S91j**, isolated yield 40%. [h]Yield for the 2-*exo*-6-*exo*-7-*endo* diastereomer.

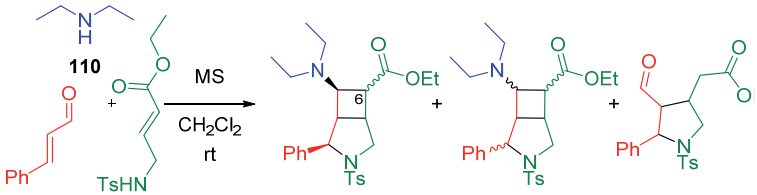
As potential pharmacophores (See publication II) *N*-Ts-azabicyclo [3.2.0]heptanes **92** were of great interest to us. The attempt to remove the *N*-benzyl protective group from *N*-Bn-3-azabicyclo[3.2.0]heptane **91a** gave a poor yield of **113** and as a major side product cyclobutane **114** was isolated. The formation of the cyclobutane **114** can be explained by the two competing N-C-Ph bonds (marked in red in Scheme 38).



Scheme 38. Attempted removal of benzyl protective group from **91a**.

We decided that it might be possible to use ethyl-(*E*)-4-*N*-Ts-but-2-enoate **88** as a starting material directly in the MCR. It reacted the fastest of all the *α,β*-unsaturated esters used, but gave the worst chemoselectivity under the best conditions, giving an approximate 1:1 mixture of monocycle **90** and *N*-Ts-azabicyclo[3.2.0]heptane esters **115** (Table 3). An ^{1}H NMR study showed that shorter reaction times (2-5 h at rt, Table 3, entries 1-3) or low reaction temperature (Table 2, entries 5, 6) indicated a preference for the 6-*exo* diastereomer of **115**. A long reaction time (16 h) at rt gave almost an equal amount of all detected diastereomers of **115** (Table 3, entry 4).

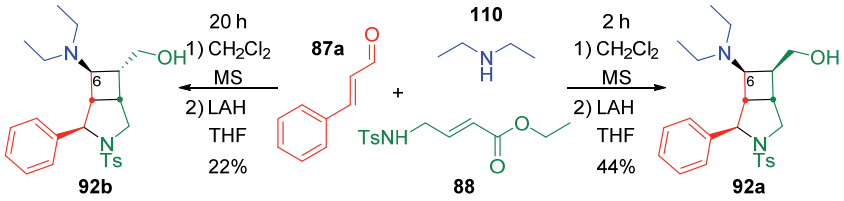
Table 3. Optimization of MCR with ethyl (*E*)-4-((4-methylphenyl)sulfonamido) but-2-enoate **88**.[a]



Entry	t (°C)	Time (h)	Ratio of			(Σ**115**):**90**
			6-*exo*-**115**	6-*endo*-**115**	**115a**[c]	
1	20	2	0.74	0.16	0.10	1:0.6
2[b]	20	2.5	0.75	0.15	0.10	1:1.4
3	20	5	0.61	0.17	0.22	1:1.4
4	20	16	0.39	0.28	0.33	1:2.8
5	0	20	0.68	0.30	0.3	1:0.8
6	0	48	0.67	0.33	-	1:0.6

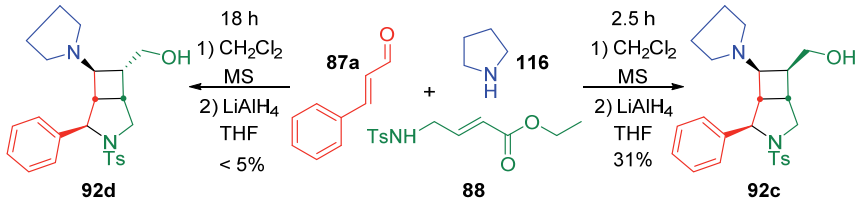
[a]Diastereomers and monocycle detected in the ^{1}H NMR of crude reaction mixture. [b]5 eq of Et_2NH. [c]Diastereomer seen in ^{1}H NMR of crude reaction mixture, but not isolated.

^{1}H NMR study showed that the diastereoselectivity of the reaction was dependent on time and temperature. In order to isolate *N*-Ts-3-azabicyclo[3.2.0]heptanes **92**, two reactions were conducted (Scheme 39). Kinetic product **92a** (6-*exo*) was obtained in 2 h, with 42% isolated yield. Thermodynamic bicyclic product **92b** (6-*endo*) formed during a prolonged reaction time, reaching a 1:1 equilibrium with **92a** in 20 h. The absolute configuration of the product **92b** was determined by using X-ray diffraction (see Publication II).



Scheme 39. Synthesis of *N*-Ts-3-azabicyclo[3.2.0]heptanes **92**.

After working out the optimal reaction conditions on *N*-Et$_2$-*N*-Ts-bicyclo[3.2.0]heptane **92a** and **92b**, pyrrolidine **116** containing a *N*-Ts-azabicyclo[3.2.0]heptane **92c** and **92d** synthesis was attempted as it was of great interest as a potential dopamine receptor ligand (see Publication II). Kinetic diastereomer **92c** was successfully obtained after 2.5 h of reaction time in 31% yield (Scheme 40). Several attempts to synthesize a 2-*exo*-6-*endo*-7-*exo* diastereomer of pyrrolidine containing *N*-Ts-azabicyclo[3.2.0]heptane **92d** failed and less than 5% of the desired compound was obtained after 18 h (also isolated were 32% diastereomer **92c** and 57% monocycle **90**).



Scheme 40. Synthesis of pyrrolidine-*N*-Ts-bicyclo[3.2.0]heptane **92c** and **92d**.

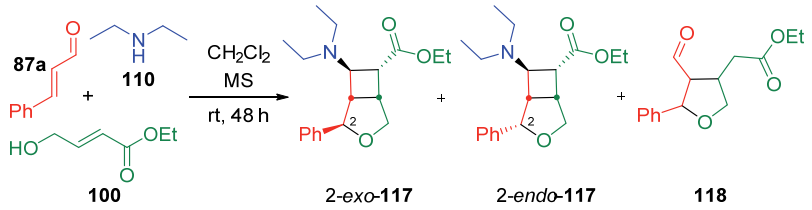
In conclusion, a new three-component cascade reaction leading to 3-azabicyclo[3.2.0]heptane derivatives **91** and **92** was developed. In this reaction sequence four new chemical bonds and five new stereocenters were formed simultaneously. Next, we broadened the scope of the reaction with other nucleophiles based on α,β-unsaturated esters.

2.3. Synthesis of 3-oxabicyclo[3.2.0]heptanes (Publication III)

Cascade reactions involving initiation by an oxa-Michael addition of phenols[70,71,72,73] to α,β-unsaturated aldehydes are relatively well documented, but few examples are available for the addition of aliphatic alcohols.[74,75] This is probably due to the low nucleophilicity of alcohols, the reversibility of the reaction and the competing acetal formation, making the oxa-Michael reaction, especially intermolecular, challenging.[76,77] At the same time, 3-oxabicyclo[3.2.0]heptane **93** derivatives are valuable synthetic intermediates.

When (*E*)-4-(benzylamino)but-2-enoate **102** was replaced with ethyl-(*E*)-4-hydroxybut-2-enoate **100** in the optimized MCR with Et$_2$NH **110** and cinnamaldehyde **87a** 3-oxabicyclo[3.2.0]heptane ester **117** was obtained in a

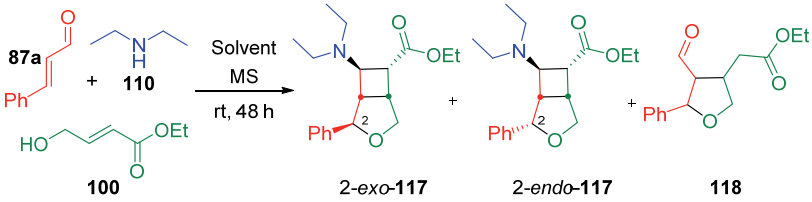
96:4 ratio to monocycle **118** in 48 h (Scheme 41). The reaction was moderately diastereoselective as, 2-*exo* **117** and 2-*endo* **117** diastereomers were obtained in a 5:1 ratio.



Scheme 41. MCR between ethyl-(*E*)-4-hydroxybut-2-enoate **100**, Et_2NH **110** and cinnamaldehyde **87a**.

Several solvents were tested to increase the reaction rate, chemo- and diastereoselectivity (Table 4). Of the chlorinated solvents $CHCl_3$ and CH_2Cl_2 were the only solvents where the reaction went to completion (entries 4 and 5).

Table 4. Solvent screening to improve diastereoselectivity.[a]



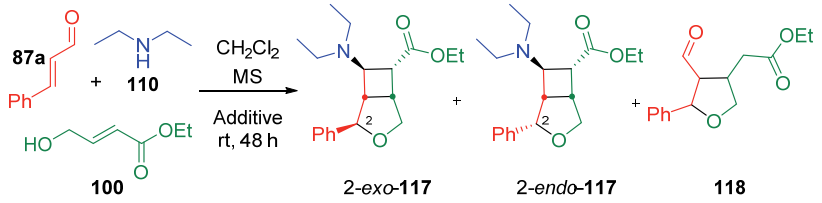
Entry	Solvent	Ratio of **100**:2-*exo*-**117**:**118**[b]	Ratio of 2-*exo*-**117**:2-*endo*-**117**[c]
1	CH_3CN	49:46:5	3:1
2	Toluene	22:58:20	1.8:1
3	THF	42:47:11	3.5:1
4	CH_2Cl_2	0:96:4	5:1
5[d]	$CHCl_3$	0:85:15	3.5:1
6	CCl_4	40:40:20	1.6:1
7	DCE	19:75:6	4:1
8	Dioxane	45:35:20	2.3:1
9	*t*-AmylOH	57:32:11	2.1:1

[a]Cinnamaldehyde (2 eq), Et_2NH (2 eq), and (*E*)-4-hydroxybut-2-enoate (1 eq) were stirred in an appropriate solvent at rt for 48 h with MS. [b]Ratios were determined by ^1H NMR in relation to the major diastereomer. [c]Ratio of 2-*exo*:2-*endo* diastereomers determined by ^1H NMR. [d]Reaction time 24 h.

The reaction in $CHCl_3$ was the fastest (24 h) but with poor chemo- and diastereoselectivity. DCE was the only other reaction medium where the chemo- and diastereoselectivity were comparable to CH_2Cl_2 (entry 4 vs entry 7). All other aprotic solvents (entries 1-3 and 8) hindered the reaction rate and gave poorer chemo- and diastereoselectivity. There was no evident correlation between solvent polarity and reaction rate, and chemo- and diastereoselectivity.

Next, different base and acid additives were tested (Table 5). The reasoning behind the acid additives was that they are known to increase the rate of iminium ion formation, and thus might increase our reaction rate as well. Acids with different pK_a values were tested. *p*-NO_2-benzoic acid and TFA both hindered the bicycle **117** formation and monocycle **118** was detected as the major product (Table 5, entries 4 and 5). When the weaker benzoic acid was used, the formation of bicycle **117** was again favored (entries 3 and 6). An acid additive was not suitable for our MCR; it did not improve the rate, chemo- or diastereoselectivity of the reaction.

Table 5. Screening of additives to improve diastereoselectivity.[a]

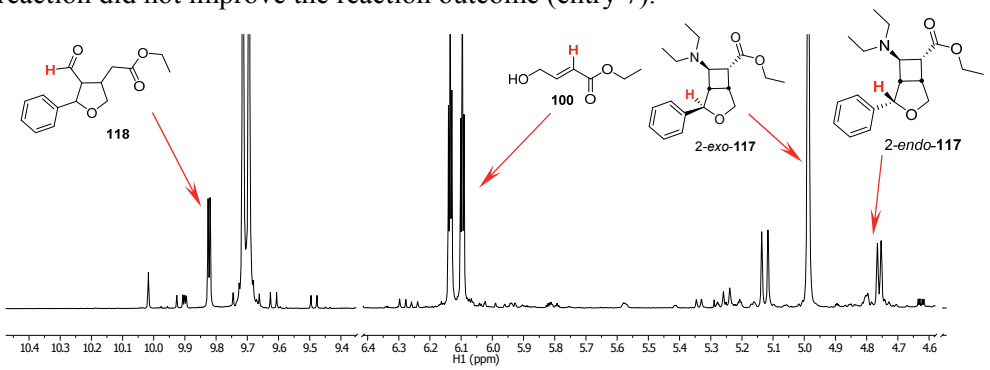


Entry	Additive	Ratio of **100**:2-*exo*-**117**:**118**[b]	Ratio of 2-*exo*-**117**:2-*endo*-**117**[c]
1	-	0:96:4	5:1
2	NaOAc	15:79:6	5:1
3	Benzoic acid	25:47:28	3:1
4	*p*-NO_2-benzoic acid	44:13:43	ND
5	TFA	47:13:40	1.6:1
6[d]	Benzoic acid	17:64:19	3.5:1
7[e]	Et_2NH	20:73:7	3.6:1

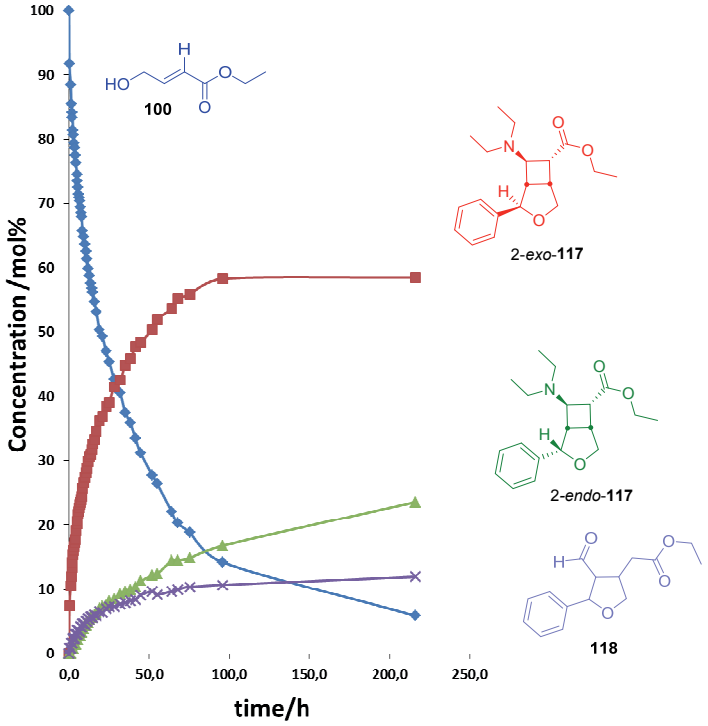
[a]Cinnamaldehyde (2 eq), Et_2NH (2 eq), additive (1 eq) and hydroxycrotonate (1 eq) were stirred in an appropriate solvent at rt for 48 h, with MS. [b]Ratios were determined by ^1H NMR in relation to the major diastereomer. [c]The ratio was determined by ^1H NMR of the crude reaction mixture. [d]20 mol% of the additive. [e]3 eq of Et_2NH was used.

A base additive was added in the hopes that it would help to shift the balance of the deprotonation of the -OH proton of the ethyl-(*E*)-4-hydroxybut-2-enoate **100** and thus improve the reaction. The addition of 1 eq NaOAc kept the reaction chemo- and diastereoselectivity the same, but decreased the reaction rate

(entry 2 vs entry 1). Also, the addition of an extra equivalent of Et_2NH **110** to the reaction did not improve the reaction outcome (entry 7).



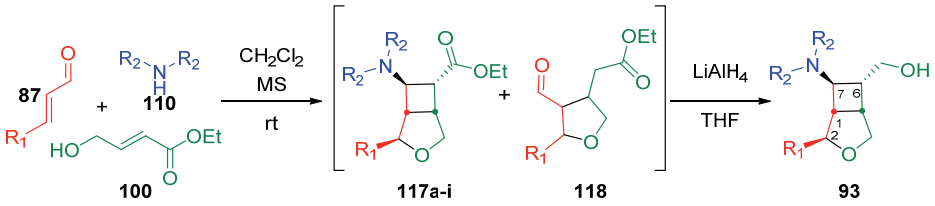
Scheme 42. ^{1}H NMR spectrum of the reaction mixture after 25 h.



Scheme 43. Reaction progress profile for the reaction in Scheme 40, obtained using ^{1}H NMR spectroscopy. Molecular sieves were added and $CDCl_3$ was used as a reaction medium.

In order to gain mechanistic insight, a ^{1}H NMR study of the reaction mixture was conducted to monitor the reaction kinetics. The reaction components depicted in Scheme 41 were combined in an NMR tube in optimal ratios, $CDCl_3$ was used as the reaction medium and MS were added. All the reaction products and starting materials showed distinct chemical shifts which did not overlap in one-dimensional ^{1}H NMR (Scheme 42). Only the starting materials **100**, **110** and **87** and the final products 2-*exo*-**117**, 2-*endo*-**117** and **118** were visible in the ^{1}H NMR, none of the intermediates formed in detectable amounts. From the study it was evident that the MCR was indeed reversible, as the diastereomeric ratio of 2-*exo* and 2-*endo* diastereomers (**117**) changed over time (from 5:1 at 48 h to 2.5:1 at 215 h to 1.3:1 in 22 days). However, it was not clear if the monocyclic structure was in equilibrium with the bicyclic product or if it was a competing reaction (Scheme 43).

Table 6. Scope of the MCR with ethyl-(*E*)-4-hydroxybut-2-enoate **100**.[a]



Entry	Pro-duct	R_1	Amine **110**	Time (h)	Ratio of **100:117:118**[b]	dr[c]	Isolated yield **93**[d]
1	**93a**	Ph	Et_2NH	48	0:96:4	5:1	76
2	**93b**	Ph	Pyrrolidine	72	0:64:36	4:1	43
3	**93c**	Ph	Piperidine	48	8:44:48	1:1:4[e]	20 (43)[f]
4	**93d**	Ph	Me_2NH	72	21:79:0	6:1[g]	51
5	**93e**	*p*-MeO-Ph	Et_2NH	48	16:74:10	5:1	37
6	**93f**	*p*-Br-Ph	Et_2NH	48	8:84:8	5:1	55
7	**93g**	*p*-NO_2-Ph	Et_2NH	48	12:82:6	8:1	ND
8	**93h**	Me	Et_2NH	96	ND[h]	-[i]	51
9	**93i**	diMe	Et_2NH	96	ND[h]	-[i]	52

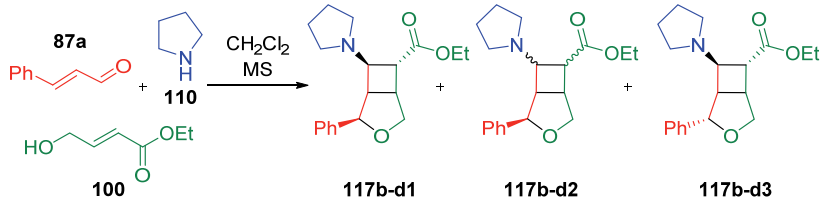
[a]*α,β*-unsaturated aldehyde (2 eq), amine (2 eq), and hydroxycrotonate (1 eq) were stirred in CH_2Cl_2 at rt for the appropriate time in the presence of MS. [b]Ratios were determined by ^{1}H NMR from the crude reaction mixture before reduction with LAH in ratio to major diastereomer. [c]Ratio of (2-*exo*:2-*endo*) diastereoisomers was determined by ^{1}H NMR. [d]Isolated yield of the major diastereoisomer. [e]Ratio of 2-*exo*-6-*endo*-7-*exo*:2-*endo*-6-*endo*-7-*exo*:2-*exo*-6-*exo*-7-*endo* diastereoisomers. [f]Yield stated respectively for 2-*exo*-6-*endo*-7-*exo* and 2-*exo*-6-*exo*-7-*endo* diastereoisomers. [g]Major diastereoisomer in 2-*exo*-6-*exo*-7-*exo*-configuration. 1 M Me_2NH in THF was used for the reaction. [h]Ratio was not determined due to overlapping of signals ^{1}H NMR. [i]Only one diastereoisomer was detected.

After exhaustive optimization of the reaction conditions, the scope of the reaction was investigated, and this is shown in Table 6. Various secondary

amines **110** can be used, although acyclic amines (entries 1, 4) gave better diastereo- and chemoselectivity over cyclic amines (entries 2 and 3). Various substituents at the aromatic ring of cinnamaldehyde **87a** had little influence on the diastereoselectivity of the reaction, but did influence the reaction time (entries 5, 6 and 7). The reactions with aliphatic aldehydes **87h** and **87i** did not proceed to completion, giving quite a lot of monocyclic product **118**. Only one diastereomer of bicyclic products **93h** and **93i** was detected and isolated (entries 8 and 9).

Similar to *N*-Ts-azabicyclo[3.2.0]heptane **92** (see Table 3), the diastereoselectivity of 3-oxabicyclo[3.2.0]heptane ester **117** formation was also dependent on time. Table 7 shows that temperature had a great influence on the diastereo-preference of the reaction. Reactions run at 5 ºC and -20 ºC showed a preference for the kinetic diastereomer **117b-d2** over the thermodynamic **117b-d1**, which was the major product if run at rt.

Table 7. Influence of reaction temperature on reaction rate and diastereoselectivity.[a]



Entry	Time (h)	Temp (ºC)	Ratio of			
			100	**117b-d1**	**117b-d2**	**117b-d3**
1	16	5	42	10	39	9
2	40	5	22	25	36	17
3	120	-20	29	4.5	55	11.5
4	40	rt	22	52	9	17

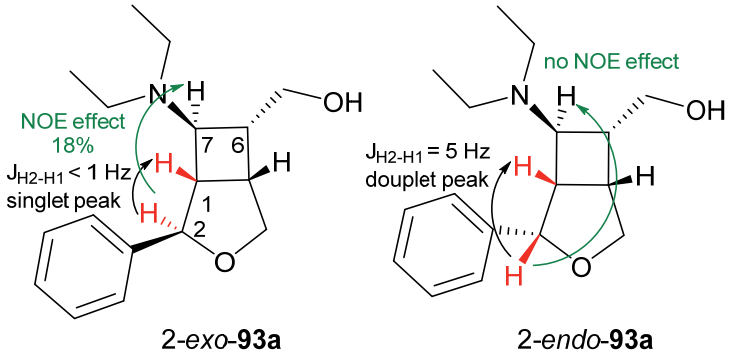
[a]All ratios were determined by ^{1}H NMR from the crude reaction mixture.

2.4. Determination of relative and absolute configuration of 3-aza- and 3-oxabicyclo[3.2.0]heptanes

The structures and relative configurations of 2,3,6,7-tetrasubstituted-***N***-Bn-3-azabicyclo[3.2.0]heptane and 2,6,7-trisubstituted-3-oxabicyclo[3.2.0]heptane derivatives were determined by a detailed ^{1}H-^{13}C NMR analysis, using the 2D FT COSY, HSQC, and HMBC methods, including chemical shift and coupling constant analysis (discussed in more detail in Publication I).

The configuration of substituents on 3-aza- and 3-oxabicyclo[3.2.0]heptane skeleton, can be determined by ^{1}H-^{1}H spin-spin coupling constants from a four-

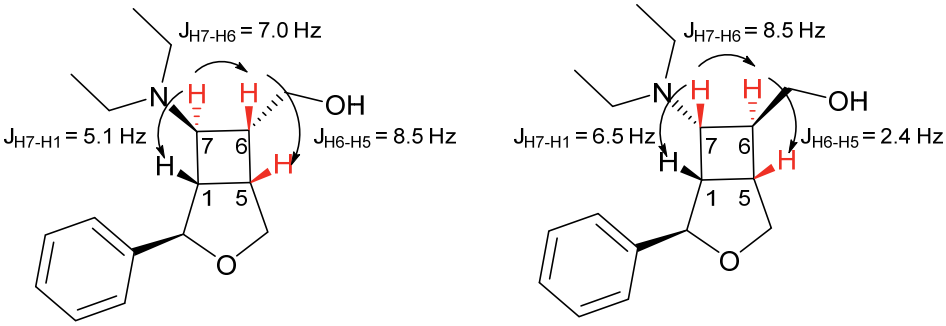
membered ring (see the Experimental part for additional information Table 14 and 15).



Scheme 44. Determination of the relative configuration at C2.

The determination of the relative configuration at the C2 position was the easiest (Scheme 44). In compound **93a**, when the H-1 and H-2 were in *trans* configuration the ^{1}H-^{1}H spin-spin coupling between the protons was < 1 Hz, visible as a singlet in the ^{1}H NMR spectrum, corresponding to the *exo* configuration of the phenyl substituent at C2. The *cis* configuration between H-1 and H-2 gave rise to J_{H2-H1} = 5 Hz, visible as a doublet, corresponding to the *endo* configuration of the phenyl substituent at C2.

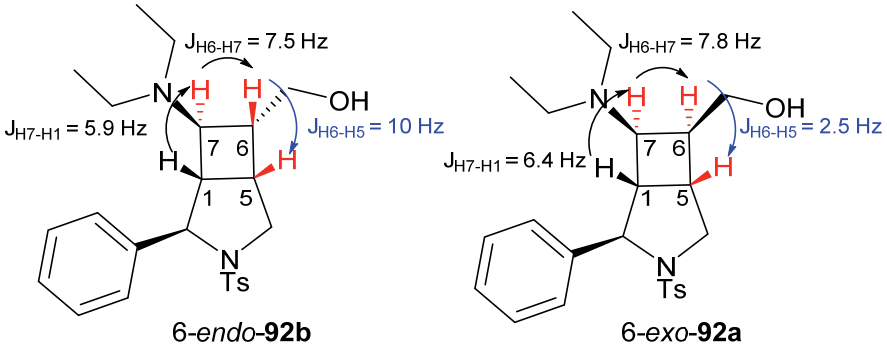
Additional information about the three-dimensional structure of the molecule was obtained from the NOE experiment (Scheme 44). It showed that in diastereomer 2-*exo*-**93a** the protons H-1 and H-7 were spatially in close proximity *i.e.* on the same side of the molecule. In a 2-*endo* diastereomer, this effect was not present, showing that the H-7 was on the same side of the molecule as the phenyl substituent.



Scheme 45. Determination of relative configuration at C7 and C6.

The *trans* relative configuration of the substituents at C7 and C6 was determined from the ^{1}H-^{1}H spin-spin coupling between H-5, H-6, H-7 and H-1 (Scheme 45). When the ^{1}H-^{1}H spin-spin coupling between H-6 and H-5 was large

(J_{H6-H5} = 8.5 Hz) the protons were in *cis* configuration; when they were in *trans*, the coupling constant was considerably smaller: J_{H6-H5} = 2.4 Hz. The difference in *cis-trans* ^{1}H-^{1}H spin-spin coupling constants between H-7 and H-1 was not as notable (*cis* J_{H7-H1} = 6.5 Hz, *trans* J_{H7-H1} = 5.1 Hz).



6-*endo*-**92b** 6-*exo*-**92a**

Scheme 46. Determination of relative configuration at C6.

The *cis* relative configuration of the substituents at C7 and C6 can be explained based on *N*-Ts-3-azabicyclo[3.2.0]heptane **92**, and can also be deduced from the ^{1}H-^{1}H spin-spin coupling between H-5, H-6, H-7 and H-1 (Scheme 46). It is interesting to note that there was no big difference in *cis-trans* configuration ^{1}H-^{1}H spin-spin coupling between H-6 and H-7 (J_{cis} = 7.8 Hz and J_{trans} = 7.5 Hz). The difference in configuration at C6 became evident again from the ^{1}H-^{1}H spin-spin coupling constants between H-6 and H-5 (J_{cis} = 10 Hz and J_{trans} = 2.5 Hz).

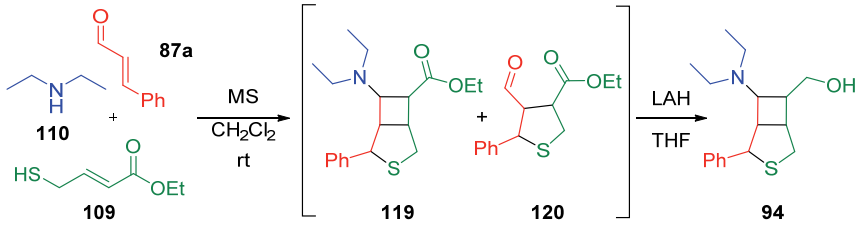
Additional conformation by single-crystal X-ray diffraction was later obtained to support the assignment of relative configuration by ^{1}H NMR. The absolute configuration of the 2-*exo*-6-*endo*-7-*exo* diastereomers of 3-oxabicyclo[3.2.0]heptane **93a** and *N*-Ts-3-azabicyclo[3.2.0]heptane **92a** were determined by single-crystal X-ray diffraction after separation of the enantiomers by enzymatic kinetic resolution (see Chapter 2.9). The crystal structures were published in Publications II and III.

2.5. Synthesis of 3-thiabicyclo[3.2.0]heptane

Wang *et al* used ethyl-(*E*)-4-mercaptobut-2-enoate **109** in combination with cinnamaldehyde[78] **87a** and nitrostyrene[54] (Scheme 25, Chapter 1.2.2) with success, forming five-membered rings **120** and **57** catalyzed by enamine catalysis (TMS prolinol catalyst **89**) or bifunctional thiourea **47B**, respectively. Based on this, we decided to continue the cascade reaction to obtain our bicyclo[3.2.0]heptane core structure.

When ethyl-(*E*)-4-mercaptobut-2-enoate **109** was used in our MCR, at least five different diastereomers of **119** were detected by ^{1}H NMR after 24 h, with average chemoselectivity (**119**:**120** 7:1). The isolated yield of one

3-thiabicyclo[3.2.0]heptane diastereomer **94** was <10%. In addition, when the reaction was monitored in ^{1}H NMR it became evident that ethyl-(*E*)-4-mercaptobut-2-enoate **109** was not stable under the reaction conditions (Scheme 47).



Scheme 47. MCR with ethyl-(*E*)-4-mercaptobut-2-enoate **109**.

In summary, we can say that our new three-component cascade was general and four different unsaturated esters with tethered hetero-nucleophiles (**102**, **88**, **100**, **109**) all proceeded to form the hetero-bicyclo[3.2.0]heptane skeleton (**91-93**, **94**) with the corresponding heteroatom at third position. A comparison of N-, O- and S- nucleophiles showed that nitrogen gave the best diastereoselectivity, but chemoselectivity was dependent on the protective group on the nitrogen (*N*-Bn vs *N*-Ts) and was the most reactive of the three.

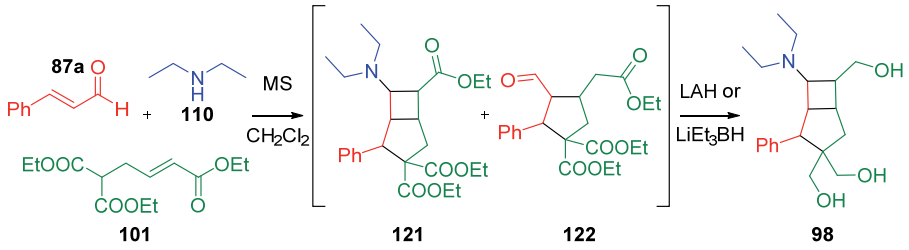
2.6. Synthesis of bicyclo[3.2.0]heptanes

Widely used carbon nucleophiles in organocatalysis are carbon atoms in malonate analogues or are next to nitro functional group. When triethyl-(*E*)-but-3-ene-1,1,4-tricarboxylate **101** and ethyl-(*E*)-5-nitropent-2-enoate **107** were chosen as α,β-unsaturated esters in the MCR, analogues of bicyclo[3.2.0]heptane with fully carbon skeletons were obtained.

In the case of triethyl-(*E*)-but-3-ene-1,1,4-tricarboxylate **101**, the MCR was highly sensitive to moisture, resulting in low chemoselectivity (Table 8, entries 1 and 2). When care was taken to keep the reaction dry, the ratio of bicyclo[3.2.0]heptane **121** to monocycle **122** on average was 16:1 (entries 3-5). Two diastereomers **121a** and **121b** were detected in an approximate 1:1 ratio; however, only one diastereomer was isolated after reduction of the ester functionalities.

Full conversion of triethyl-(*E*)-but-3-ene-1,1,4-tricarboxylate **101** to the products was observed in the crude reaction mixture, although the isolated yields were very poor, <26%. It was assumed that the main problem was the high hydrophilicity of the final triole **98**. Several attempts (an addition of Grignard reagent to the ester functionality, esterification and acetalization of the hydroxyl group) to reduce the hydrophilicity of the final product in the crude mixture failed. These are depicted in Scheme 48.

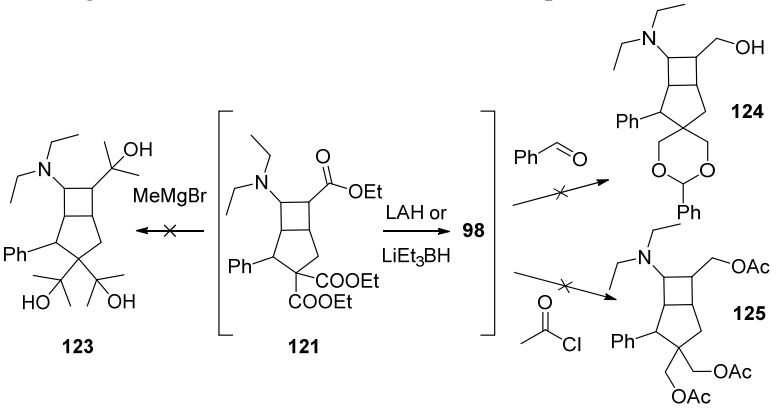
Table 8. MCR with α,β-unsaturated ester with tethered malonate.[a]



Entry	Reducing agent	Ratio of **121**:**122**[b]	Isolated yield **98**
1	$LiAlH_4$	1.5:1	5.5
2[d]	$LiAlH_4$	2.5:1	13.5
3	$LiAlH_4$	18:1	6
4	$LiEt_3BH$	13:1	26
5[c]	$LiEt_3BH$	15.5:1	14.5

[a]Cinnamaldehyde (2 eq), Et_2NH (2 eq) and malonate **101** (1 eq) were stirred in CH_2Cl_2 at rt for 24 h, with MS. [b]Ratios were determined by the ^1H NMR of the crude ester reaction mixture. [d]Reaction time 5 h; a different diastereomer was isolated. [a]Cinnamaldehyde (2 eq), Et_2NH (4 eq) and malonate **101** (1 eq) were stirred in CH_2Cl_2 at rt for 24 h, with MS.

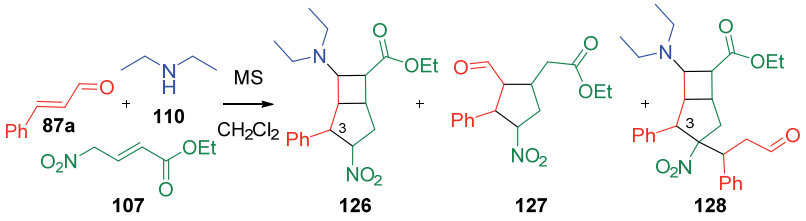
On the other hand, MCR with ethyl-(*E*)-5-nitropent-2-enoate **107** under previously optimized conditions also resulted in a full conversion of the limiting starting material to 3-nitro-bicyclo[3.2.0]heptane ester **126**, monocycle **127** and byproduct **128** in a 50:1:25 ratio (Table 9, entry 1). A by-product **128** structure was proposed based on ^1H NMR, COSY and HPLC-HRMS, but the compound was never isolated. The formation of compound **128** could be rationalized with a carbon nucleophile C3 in the final 3-nitro-bicyclo[3.2.0]heptane ester **126**, which gave another Michael addition in the presence of excess amine**110** and



Scheme 48. *In situ* derivatization of bicyclo[3.2.0]heptane **98** and **121**.

cinnamaldehyde **87**. In order to suppress the byproduct (**128**), the reaction was conducted at a higher temperature (entry 2), but unfortunately with poor results. Much better chemoselectivity was achieved when a small excess of cinnamaldehyde **87a** and Et_2NH was used (Table 9, entries 3 and 4).

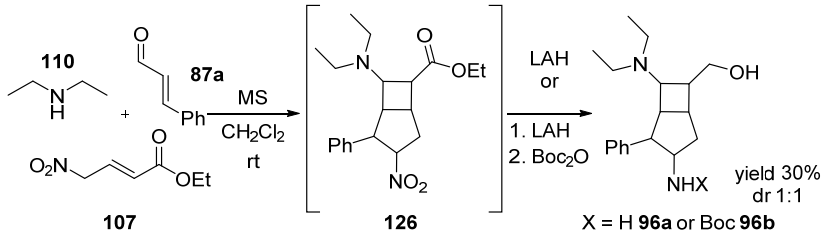
Table 9. MCR utilizing *α,β*-unsaturated ester **107**.[a]



Entry	Ratio of **87a**:**110**:**107**	Ratio of **126:127:128**[b]
1	2:2:1	50:1:25
2[c]	2:2:1	5.5:0:1
3	1.2:1.2:1	100:1:0.6
4	1.5:1.5:1	100:1:3

[a]Appropriate rati of *α,β*-unsaturated ester **107**, Et_2NH **110**, cinnamaldehyde **87a** were stirred in CH_2Cl_2 for 45 h. [b]Ratio determined by ^1H NMR of the crude reaction mixture [c]Reaction in DCE at 50 °C for 6 h.

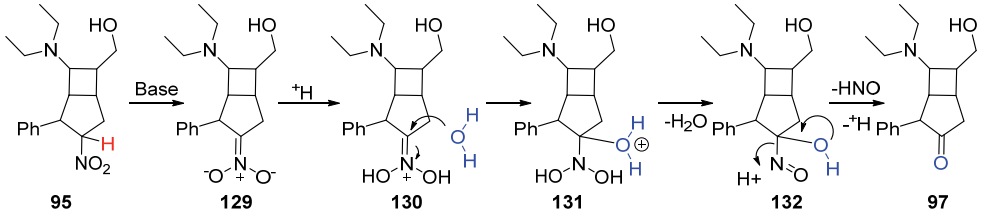
An analysis of the crude reaction mixtures in Table 9 by ^1H NMR showed the presence of two diastereomers of the C3 carbon atom in a 1:1 ratio. This can be explained by the basic reaction medium and the acidity of the proton next to the nitro functional group.



Scheme 49. Reduction of 3-nitro-bicyclo[3.2.0]heptane-carboxylate.

A $LiAlH_4$ reduction of the crude MCR mixture resulted in the formation of very hydrophilic aminoalcohol **96a** in 30% isolated yield, as a mixture of inseparable diastereomers. *In situ* Boc_2O protection of the amino functionality (**96b**) did not improve the yield, but the diastereomers were separable by column chromatography.

$LiEt_3BH$ was able to selectively reduce the ester functionality over $-NO_2$, but after basic/acidic workup, a mixture of three different products (**95**, **97** and **133**) was observed in the crude ^1H NMR spectrum of the reaction mixture (Table 10). After isolation and identification of product **97** (entry 1), it was evident that an acid- catalyzed hydrolysis of $–NO_2$ had occurred *via* an intermediate nitronate **129** (Scheme 50). This kind of reaction – a Nef reaction – is frequently observed in organic synthesis and widely used for the synthesis of carbonyl compounds from nitroalkanes.[79]

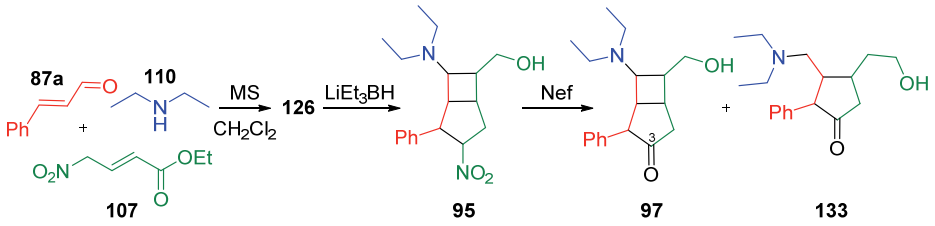


Scheme 50. The Nef reaction – acid-catalyzed hydrolysis of $-NO_2$.

An analysis of the ^1H NMR spectra of the crude three-component reaction showed full conversion of the starting materials to product **126** with a 1:1 mixture of C3 diastereomers. In the course of the reduction of the ester **126**, cleavage of the cyclobutane ring occurred and product **133** was isolated. The amount of the cyclopentanone **133** depended on the ratio of cinnamaldehyde **87a** and diethyl amine (Table 10, entry 1 vs entry 2).

Full conversion of 3-nitro-bicyclo[3.2.0]heptane **95** to the corresponding carbonyl compound was difficult (Table 10, entries 1 and 2). The use of additional base after the $LiEt_3BH$ reduction considerably improved the ratio of **95** to **97**, but the isolated yield of **97** was still low (Table 10, entry 3). Only one diastereomer of **97** was isolated, because of the disappearance of the stereocenter from position C3. The overall isolated yield of bicyclo[3.2.0]heptane alcohols **95** and **97** was around 50% over three steps. Additional optimization of the Nef reaction conditions was still needed to improve the isolated yield.

Table 10. Optimization of Nef reaction conditions after reduction of ester functionality with $LiEt_3BH$.[a]



Entry	Ratio of **87a**:**110**:**107**	Nef conditions	Isolated yield (%)		
			95	**97**	**133**
1	2:2:1	3 M HCl, 24 h, rt	21	25	8
2	1.2:1.2:1	3 M HCl, 60 °C, 3 h	14	30	16
3	1.5:1.5:1	NaOH, 24 h RT, HCl 24 h, rt	7	25	14
4	1.2:1.5:1	Only H_2O work up	24	-	nd

[a]10 eq 1 M $LiEt_3BH$ in THF added at 0 °C-rt.

In conclusion, we can say that MCR with carbon nucleophile containing unsaturated ester **107** and **101** resulted in full conversion of the starting materials to bicyclo[3.2.0]heptane esters **126** and **121**. High diastereoselectivity was observed with ethyl-(*E*)-5-nitropent-2-enoate **107** after hydrolysis of the $–NO_2$ functional group**,** while triethyl-(*E*)-but-3-ene-1,1,4-tricarboxylate **101** resulted in a 1:1 mixture of diastereomers. Isolation of the corresponding alcohols was difficult and additional work is needed.

2.7. Summary of the synthesis of racemic bicyclo[3.2.0]heptanes

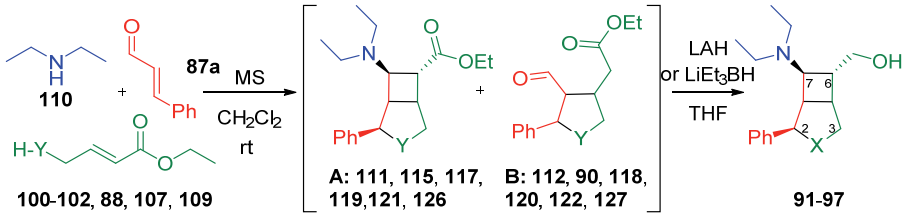
Table 11 summarizes the synthesized bicyclo[3.2.0]heptanes. *N*-Bn-3-azabicyclo[3.2.0]heptane **91a** was obtained in 68% isolated yield with very high chemo- and diastereoselectivity (entry 1). The preferred diastereomer was in 2-*exo*-6-*endo*-7-*exo* configuration (as show in the scheme of Table 11). When the *N*-Bn protective group was changed to *N*-Ts, the reaction time went up but chemoselectivity went down and another diastereomer 2-*exo*-6-*exo*-7-*exo* is preferred (entry 3). Only 22% yield was obtained for the 2-*exo*-6-*endo*-7-*exo* *N*-Ts-3-azabicyclo[3.2.0]heptane **92b** (entry 2) after a prolonged reaction time.

3-oxabicyclo[3.2.0]heptane **93a** was also obtained in high chemoselectivity, although the diastereoselectivity of 5:1 was considerably lower than the 45:1 for *N*-Bn-3-azabicyclo[3.2.0]heptane **91a** (entry 4 vs entry 1). The same 2-*exo*-6-*endo*-7-*exo* diastereomer was preferred. The reaction was slower: 48 h for **93a** versus 17 h for **91a**.

Regrettably, ethyl-(*E*)-4-mercaptobut-2-enoate **109** gave poor chemo- and diastereoselectivity. Five different diastereomers of 3-thiabicyclo[3.2.0]heptane **94** were detected and only one diastereomer with very poor yield was isolated (entry 5).

A fully carbon skeleton containing bicyclo[3.2.0]heptanes gave relatively good chemoselectivities, but poor diastereoselectivities 1:1 (entries 6 and 7). However, replacing a stereocenter at the α-position to the nitro group in 3-nitro-bicyclo[3.2.0]heptane **95** with carbonyl carbon *via* hydrolysis, merged the two diastereomers into a single diastereomer (entry 8). Malonate containing unsaturated ester **101** gave a faster reaction than nitro containing **107**, 24 h vs 45 h. However, isolation was the main problem with a full carbon skeleton containing bicyclo[3.2.0]heptanes, where a lot of optimization was still needed (entries 6-8).

Table 11. Comparison of MCR with different unsaturated esters.

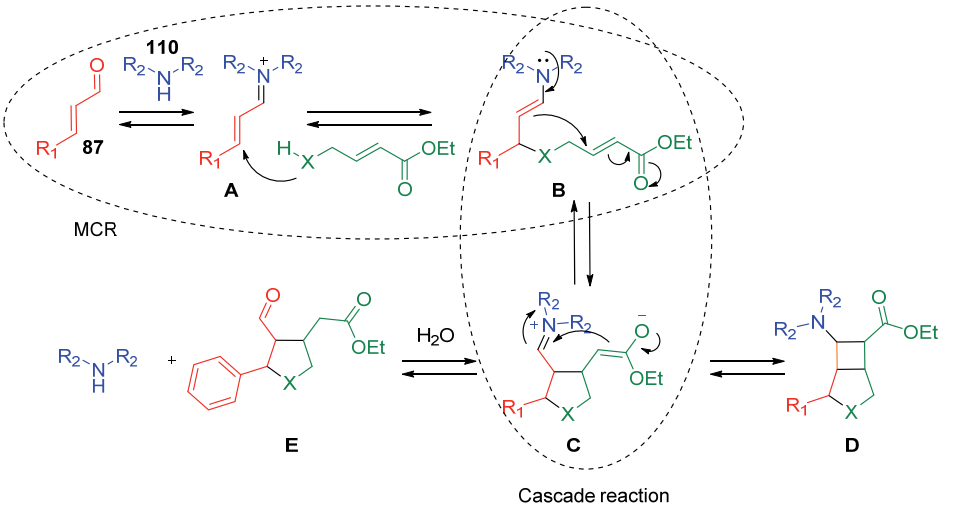


Entry	X	Product	Time (h)	dr[a]	A:B[b]	Isolated yield
1	-*N*-Bn	**91a**	17	45:1	95:5	68
2	-*N*-Ts	**92b**	20	1.4:1	30:73	22
3[d]	-*N*-Ts	**92a**	2	5:1	62:38	44
4	-O-	**93a**	48	5:1	96:4	76
5[c]	-S-	**94**	24	5 diast.	7:1	<10
6[c]	$C(CH_2OH)_2$	**98**	24	1:1	16:1	<26
7[c,e]	$-CH-NO_2$	**95**	45	1:1	97:3	24
8[c]	C=O	**97**	45	1 diast.	97:3	30

[a]Ratio of diastereomers in ^{1}H NMR of the crude reaction mixture. [b]Ratio of bicyclo product to its corresponding five membered monocycle. [c]The relative configuration of diastereomer was not determined. [d]Major diastereomer in all *exo* configuration. [e]diastereomeric ratio from position C3.

Based on all the previous experimental results, we propose the following reaction mechanism, illustrated in Scheme 51. The reaction proceeds *via* a multicomponent cascade that consists of a Michael addition to an iminium ion **A** derived from α,β-unsaturated aldehyde **87** and secondary amine **110**, followed by a second, intramolecular Michael addition (intermediate **B**). The last step of the cascade is the formation of a four-membered ring *via* an ester enolate attack

on the newly formed iminium ion **C**, giving rise to the bicyclo[3.2.0]heptane product **D**. If there is any additional water in the reaction medium, the iminium ion **C** is hydrolyzed and monocycle **E** is formed.



Scheme 51. Proposed reaction mechanism.

2.8. Enantioselective MCR

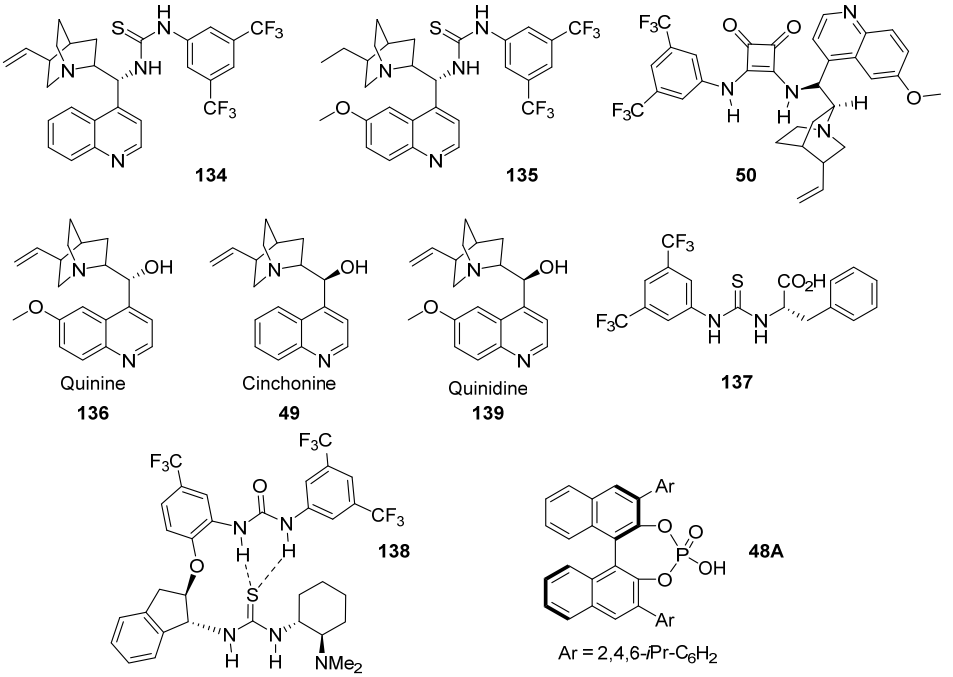
Based on literature examples (see Chapter 1.2.1), widely used groups of organocatalysts were chosen as chiral catalysts in the MCR (Scheme 52):

- Hydrogen bonding catalysts **134**, **135**, **137**, **138** and **50**
- Counter ion catalysts **48A**, **136**, **139** and **49**
- Single H-bond donors catalysts **136**, **139** and **49**

It is known from the literature that activation of α,β-unsaturated aldehydes *via* iminium ion formation with TMS-prolinol **89** affords monocyclic product.[63] Therefore, we concentrated our attention on hydrogen bonding and counter ion catalysts. The stereoselectivity of MCR is determined by the formation of the first stereocenter in the first Michael addition. Almost all of the used hydrogen bonding catalysts are bifunctional. In addition to their hydrogen-bonding donor properties they possess a tertiary amino group which is capable of enhancing the nucleophilicity of the α,β-unsaturated ester derivative. The formation of a hydrogen-bonded catalyst-nucleophile complex and thus a stereoselective MCR was expected. Alternatively, a chiral ion pair from an iminium ion and a counter ion catalyst was able to efficiently block one face of the iminium ion, affording a stereoselective first Michael addition. Both of these approaches also influenced the diastereoselectivity and kinetics of the reaction.

The various catalysts depicted in Scheme 52 were added to our MCR in combination with three α,β-unsaturated ester derivatives. The results are summarized in Table 12.

In the case of 3-oxabicyclo[3.2.0]heptane **93a**, the Cinchona alkaloid and thiourea catalysts all caused degradation of chemo- and diastereoselectivity (entries 1-8), having an effect similar to the acidic and basic additives in Table 5 (Chapter 2.3). The only exception was chiral phosphoric acid **48A**, which sped up the reaction and improved diastereoselectivity (entry 8 vs entries 1 and 2).

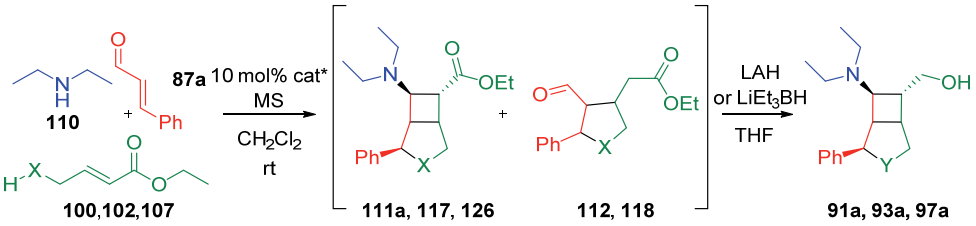


Scheme 52. Catalyst screened in the MCR.

In the case of bicyclo[3.2.0]heptane-3-one **97**, no catalyst influence was observed (Table 12, entries 9-12), full conversion of the limiting starting material occurred and only one diastereomer was seen in ^{1}H NMR after hydrolysis of the nitro group.

In the case of *N*-Bn-azabicyclo[3.2.0]heptane **91a**, only a small degradation of diastereoselectivity was observed (entries 13-17). The cinchona alkaloid **49** used in the reaction only retarded the reaction and it was not completed in 17 h. As in the case of 3-oxabicyclo[3.2.0]heptane **93a**, chiral phosphoric acid **48A** improved the reaction diastereoselectivity (entry 13 vs entry 14).

Table 12. Influence of chiral catalysts on the multicomponent reaction.[a]



Entry	Y	Cat	Time	Ratio of[b]	*ee* of[c]	dr[d]
				100:**117**:**118**	**93a**	
1	O	-	24 h	16:79:5	-	5:1
2	O	-	48 h	0:94:6	-	5:1
3	O	**137**	48 h	24:61:15	rac	3.6:1
4	O	**134**	48 h	36:43:21	rac	2.9:1
5	O	**135**	48 h	31:32:37	rac	2.6:1
6	O	**136**	48 h	34:41:25	rac	3.5:1
7	O	**49**	48 h	16:70:14	rac	3.8:1
8	O	**48A**	24 h	8:81:11	rac	15:1
					97	
9	-C=O	**138**	72 h	ND	rac	1 diast.
10	-C=O	**134**	72 h	ND	rac	1 diast.
11	-C=O	**50**	72 h	ND	rac	1 diast.
12	-C=O	**49**	72 h	ND	rac	1 diast.
				102:**111**:**112**	**91a**	
13	-NBn	**-**	17 h	0:95:5	-	45:1
14	-NBn	**48A**	17 h	0:95:5	rac	100:1
15	-NBn	**134**	17 h	0:91:9	rac	32:1
16	-NBn	**49**	17 h	13:85:2	rac	37:1
17	-NBn	**139**	17 h	ND	rac	33:1

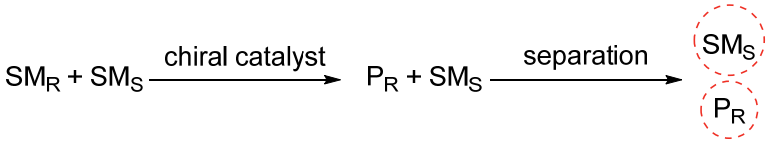
[a]Cinnamaldehyde **87a** (2 eq) and Et_2NH (2 eq) were combined and 10 mol% of catalyst was added. Appropriate α,β-unsaturated ester was added (1 eq). [b]Determined by ^1H NMR from the crude ester reaction mixture. [c]Determined from alcohol by chiral HPLC (see Publications II and III). [d]Determined by ^1H NMR from the crude ester or alcohol reaction mixture.

To conclude, the chiral compounds in Scheme 52 had no influence on the enantioselectivity of the MCR and only racemic products were obtained.

2.9. Kinetic resolution of the heterobicyclic compounds (Publications II and III)

As our several attempts to use asymmetric organocatalysis for the introduction of enantioselectivity into the MCR failed, we turned to kinetic resolution.

Kinetic resolution is a widely used technique in separating racemic mixtures into enantiomers. Kinetic resolution essentially means that enantiomers have different reaction rates when reacting with a reagent, mediated by a chiral catalyst. In the case of enzymes, one of the enantiomers fits better into the active site of the enzyme and will react a lot faster.



Scheme 53. Kinetic resolution of a racemic mixture with a chiral catalyst.

Most important in kinetic resolution is the catalyst selectivity S (or *E* in the case of enzymes), which is calculated according to the formula in Scheme 54.[80] Application of the equation is straightforward, provided that reaction conversion c and enantiomeric excess *ee* are known. Web based applications are available for easy calculation.[81]

$$S = \frac{\ln\left[(1-c)\,(1-ee)\right]}{\ln\left[(1-c)(1+ee)\right]}$$

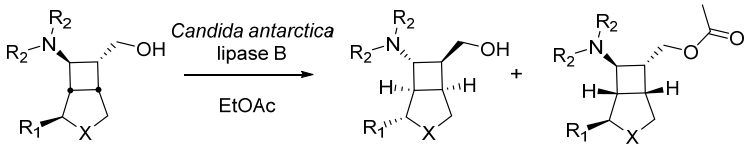
Scheme 54. Formula for calculating catalyst selectivity in kinetic resolution.

The most common catalysts for kinetic resolution are enzymes,[82] but recently purely synthetic catalysts have also been developed.[83]

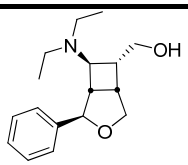
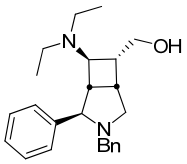
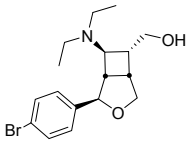
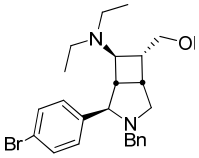
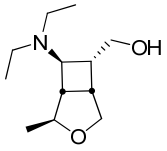
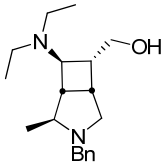
Several different immobilized enzymes[84] are available for the kinetic resolution of alcohols, which also tolerate organic solvents very well.

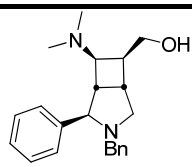
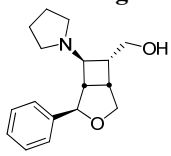
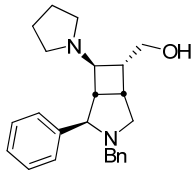
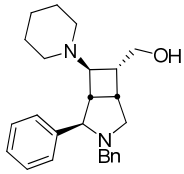
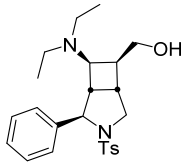
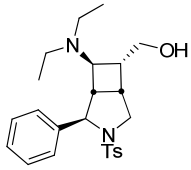
The reaction conditions for the kinetic resolution (Table 13 scheme) were chosen based on literature and previous experience. Ethyl acetate was chosen as the reaction medium, which was also an acyl donor in combination with Lipase B of *Candida antarctica*. The reaction was monitored by TLC and ^{1}H NMR and stopped when approximately 50% of the conversion was observed. The acylated ester **142** and unreacted alcohol **91-93** were separated by column chromatography. The *ee* of the unreacted alcohol was determined by chiral HPLC. The acylated ester was hydrolyzed with NaOH and then analyzed.

Table 13. Kinetic resolution of 3-aza- and 3-oxabicyclo[3.2.0]heptanes



rac-**91-93** (-)-**91-93** (+)-**142**

Entry	Compound	time (h)	Alcohol *ee* (%)	Hydrolyzed ester *ee* (%)	Conversion (%)	*E*
1	 rac-**93a**	2.5	86.4	89.8	49.0	52.7
2	 rac-**91a**	5	99.0	90.8	52.2	106
3	 rac-**93f**	2.5	89.7	90.6	49.8	60.5
4	 rac-**91h**	5	95.5	92.5	50.8	97.9
5	 rac-**93h**	2.5	81.6	94.7	46.3	92.1
6	 rac-**91b**	5	83.6	93.8	47.1	83.7

Entry	Compound	time (h)	Alcohol *ee* (%)	Hydrolyzed ester *ee* (%)	Conversion (%)	*E*
7	 rac-**91g**	23	68.9	66.8	50.8	10.1
8	 rac-**93b**	2.5	95.3	80.4	54.2	34.4
9	 rac-**91e**	5	92.2	85.6	51.9	41.8
10	 rac-**91i**	5	95.4	85.6	52.7	48.5
11[a]	 rac-**92a**	72	43.5	62.6	41.0	6.6
12[a]	 rac-**92b**	72	68.5	97.5	41.3	153

[a] K_2CO_3 was used as an additive to remove acid from the reaction medium.

The enzyme enantioselectivity *E* value greatly depended on the structure of the diastereoisomer of the bicyclic substrate (Table 13). *Candida antarctica* lipase B formed the best fit with 3-azabicyclo[3.2.0]heptanes **91** giving selectivity in the range *E* 41-106 in most cases (entries 2, 4, 9 and 10), with the exception of compound **91g**, which gave *E* 10.1. 3-oxabicyclo[3.2.0]heptanes (entries 1, 3 and 8) gave similar results, although with slightly lower selectivity, *E* 34-92.

N-Ts-azabicyclo[3.2.0]heptanes **92a** and **92b** did not provide a good fit with the enzyme and the resolution slowed down drastically from 5 h to 3 days (entries 11 and 12). However, compound **92b** gave the highest selectivity (E = 153) of all the bicyclo[3.2.0]heptanes tested.

The spatial arrangement around the chiral center C6, adjacent to the hydroxy group, was the most important factor influencing enzyme selectivity. The kinetic resolutions of compounds in 6-*exo* configuration were slower and gave noticeably poorer selectivities (entries 7 and 11).

In conclusion, enzymatic kinetic resolution proved to be a good method for the separation of bicyclo[3.2.0]heptane enantiomers. Both enantiomers were obtained and their selectivities towards dopamine receptors were tested (see Publication III).

Conclusions

- In the present study simple step economical synthetic approach was devised for the diastereoselective synthesis of heteroatom (N, O, S) containing and fully carbon bicyclo[3.2.0]heptane skeleton. In this reaction four new C-C or C-heteroatom bonds and five new stereogenic centers are formed in one step.
- Chemoselectivity between formation of bicyclo[3.2.0]heptanes via MCR over organocatalyzed five-membered ring was highly dependent on the water content in the reaction medium. Under optimized conditions MRC is predominant reaction enabling chemoselective synthesis of bicyclic targets.
- Chemoselectivity was also dependent on the structure of the secondary amine. When cyclic amines were used lower chemo- and diastereoselectivity was observed, compared to acyclic amines.
- Chemo- and diastereoselectivity of the synthesis of 3-azabicyclo[3.2.0]heptanes was greatly dependent on the protective group on the ethyl-(*E*)-4-*N*-PG-but-2-enoate. Reaction with *N*-Bn derivative was more chemo- and diastereoselective but slower than with *N*-Ts protective group.
- Synthesis of 3-oxabicyclo[3.2.0]heptane derivatives was less diastereoselective and slower than formation of corresponding 3-azabicyclo[3.2.0]heptane derivatives.
- Substituents in the aromatic ring of cinnamaldehyde had little influence over the MC synthesis of 3-oxa- and 3-azabicyclo[3.2.0]heptanes. Aliphatic aldehydes could also be used with good conversion, however lower diastereoselectivity was obtained in case of 3-azabicyclo[3.2.0]heptanes.
- Thiols could also be exploited in MCR but they gave rise to nonselective and low-yielded reaction. 3-mercaptobicyclo[3.2.0]heptane was isolated as a mixture of at least five different diastereomers, with the isolated yield of less than 10%.
- Carbon nucleophiles could be used for the synthesis of fully carbon skeleton containing bicyclo[3.2.0]heptane derivatives. High chemoselectivity was obtained but diastereoselectivity was very low. Except for bicyclo[3.2.0]heptane-3-one were only single diastereomer was isolated, although in low yield.
- Relative and absolute configurations of the isolated diastereomers were determined by NMR and single-crystal X-ray diffraction analysis, respectively. The major diastereomer in most cases was in 2-*exo*-6-*endo*-7-*exo* configuration and isolated minor diastereomer was in 2-*endo*-6-*endo*-7-*exo* configuration.
- Hydrogen bonding and counterion catalysts were inefficient in asymmetric synthesis of bicyclo[3.2.0]heptanes. However, it was shown that enantiomers of 3-aza- and 3-oxa-bicyclo[3.2.0]heptanes were separable by

enzymatic kinetic resolution by immobilized lipase B of *Candida antarctica* with high selectivity.

- ❖ Library of enantiomerically pure derivatives of 3-azabicyclo[3.2.0]heptanes were tested as dopamineric ligands.

3. Experimental

General

Full assignment of ^{1}H and ^{13}C chemical shifts was based on the 1D and 2D FT NMR spectra 400 MHz instrument. Chemical shifts are reported in ppm with internal reference to tetramethylsilane, and *J* values are given in Hertz. Mass spectra were obtained in GC−MS mode (EI, 70 eV). High resolution mass spectra were recorded on an Accurate-Mass Q-TOF LC−MS spectrometer recorded by using AJ-ESI ionization. All HPLC analysis were done using Chiralcel AS-H or Lux Amylose-2 columns. Precoated silica gel 60 F254 plates were used for TLC. Reactions sensitive to oxygen or moisture were conducted under an Ar atmosphere in flame-dried glassware. Dichloromethane was freshly distilled from P_2O_5 and stored on K_2CO_3 and anhydrous tetrahydrofuran from $LiAlH_4$. Commercial reagents were used as received. The petroleum ether used had bp 40−60 °C.

General procedure for the synthesis of racemic compounds 91-94. To a solution of the corresponding aldehyde **87** (3.0 mmol) in anhydrous CH_2Cl_2 (10 mL) in the presence of molecular sieves (4 Å) secondary amine **110** (3.0 mmol) and α,β-unsaturated ester **88**, **100**, **102** or **109** (1.5 mmol) were added. The mixture was stirred at room temperature for 17 - 96 h. The mixture was concentrated under reduced pressure and the crude bicyclic ester **111**, **115**, **117** or **119** was reduced with LAH (10.8 mmol) in anhydrous THF (20 mL). After 3-16 h, the reaction mixture was cooled to 0 °C and the reaction was quenched by the addition of water and an aqueous solution of 4 M NaOH. The mixture was dried over K_2CO_3. The crude product was purified by column chromatography on silica gel (a CH_2Cl_2:MeOH/NH_3 eluent system), affording bicyclic alcohols **91-94**.

General procedure for the synthesis of racemic compounds 95-98. To a solution of the corresponding aldehyde **87** in anhydrous CH_2Cl_2 in the presence of molecular sieves (4Å), secondary amine **110** and α,β-unsaturated ester **101** or **107** were added. The mixture was stirred at room temperature for 5 - 45 h. The mixture was concentrated in vacuum and the crude bicyclic ester **121** or **126** was reduced under appropriate conditions.

A) Crude bicyclic ester **121** or **126** was dissolved in anhydrous THF and cooled to 0 °C. LAH was added in patches and allowed to warm to rt. After 3-16 h, the reaction mixture was cooled to 0 °C and the reaction was quenched by the addition of water and an aqueous solution of 4 M NaOH. The mixture was dried over K_2CO_3. The crude product was purified by column chromatography on silica gel (a CH_2Cl_2:MeOH/NH_3 eluent system), affording bicyclic alcohols **98** or **96**.

B) Crude bicyclic ester **121** or **126** was dissolved in anhydrous THF and cooled to 0 °C. $LiEt_3BH$ was added drop wise and allowed to warm to rt. After 3-16 h the reaction mixture was cooled to 0 °C and the reaction was quenched by the addition of water (to obtain compound **96**) or 3 M or 6 M HCl solution and allowed to stir overnight. THF was removed and the acidic water was extracted 2x with Et_2O. The water phase was cooled to 0 °C and basified with sat. Na_2CO_2 or sat. $NaHCO_2$. After stirring for 1-3 h, the water phase was extracted several times with CH_2Cl_2. The mixture was dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel (a CH_2Cl_2:MeOH/NH_3 eluent system) affording bicyclic alcohols **97** or **98**.

General procedure for enzymatic kinetic resolution of 91, 92 and 93. Lipase B of *Candida antarctica* (Novozym 435) (50 mg) was added to a solution of the racemic compound **91**, **92** or **93** (50 mg) in EtOAc (1.0 mL). The resulting mixture was stirred occasionally at room temperature and monitored by TLC and ^{1}H NMR. The reaction was stopped when about 50% conversion was achieved, typically after 2.5 to 5 h. Immobilized lipase was filtered off and the filtrate was concentrated under reduced pressure. This mixture was purified by column chromatography on silica gel, affording alcohol **91**, **92** or **93** (A-enantiomer) and ester **142**. As the enantiomeric excess of ester **142** could not be determined by chiral HPLC, it was hydrolyzed to **91**, **92** or **93** (B-enantiomer), with 4 M NaOH in MeOH by stirring for 3 h at room temperature.

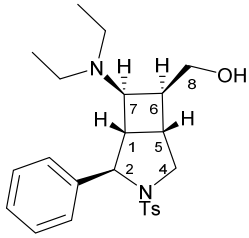
Table 14. Supporting information pertaining to compounds discussed in the thesis.

Entry	Compound number in thesis	Compound number in			Thesis
		Publication I	Publication II	Publication III	
1	**111a**				✓
2	**112**	**5a**			
3	**91a**	**6a**	**9a**		
4	**91b**	**6b**	**9c**		
5	**91c**	**6c**			
6	**91d**	**6d**			
7	**91e**	**6e**	**9b**		
8	**91f**	**6f**			
9	**91g**	**6g**			
10	**91h**		**9e**		

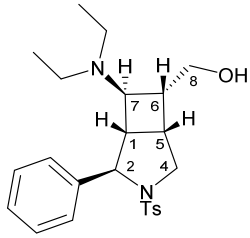
Entry	Compound number in thesis	Compound number in			Thesis
		Publication I	Publication II	Publication III	
11	**91i**		**9g**		
12	7-*endo*-**91i**				✓
13	**91j**		**9f**		
14	**91k**		**9d**		
15	**111h**	**4h**			
16	**113**				✓
17	**114**				✓
18	**S91j**				✓
19	6-*endo*-**115**				✓
20	6-*exo*-**115**				✓
21	**92b**		**11**	**10b**	
22	**92a**			**10a**	
23	**92c**				✓
24	**92d**				✓
25	2-*exo*-**117**			**7**	
26	**93a**			**9a**	
27	**93b**			**9b**	
28	**93c**			**9c**	
29	**93d**			**9d**	
30	**93e**			**9e**	
31	**93f**			**9f**	
32	**93g**			**9g**	
33	**93h**			**9h**	
34	**93i**			**9i**	
35	**94**				✓
36	**121**				✓

Entry	Compound number in thesis	Compound number in			
		Publication I	Publication II	Publication III	Thesis
37	**98**				✓
38	**96b**				✓
39	**95**				✓
40	**97**				✓
41	**133**				✓

Table 15. ^{1}H-^{1}H spin-spin coupling constants (Hz) in 6-*exo*- and 6-*endo*-**92b**



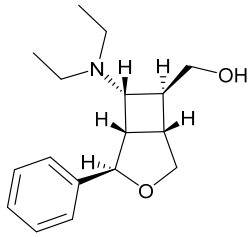
6-*exo*-**92b**



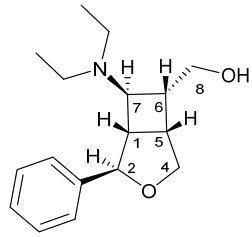
6-*endo*-**92b**

	1-2	4A-5	4B-5	1-5	5-6	6-7	1-7	6-8A	6-8B	4-4	8-8
6-*exo*-**92b**	<1	3.5	7.3	8.2	2.5	7.8	6.4	3.1	2.0	11.0	12.0
6-*endo*-**92b**	<1	2.0	8.4	8.0	10.0	7.5	5.9	5.6	9.8	11.3	10.8

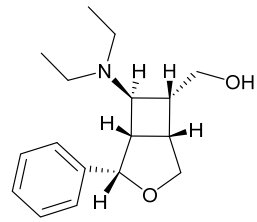
Table 16. ^{1}H-^{1}H spin-spin coupling constants (Hz) in **93a**



2-*exo*-7-*endo*-6-*exo*-**93a**



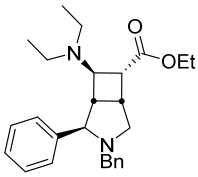
2-*exo*-7-*exo*-6-*endo*-**93a**



2-*endo*-7-*exo*-6-*endo*-**93a**

	1-2	4A-5	4B-5	1-5	5-6	6-7	1-7	6-8A	6-8B	4-4	8-8
2-*exo*-6-*exo*-7-*endo*-**93a**	<1	7.2	2.4	8.3	2.4	8.5	6.5	3.0	1.8	9.4	11.9
2-*exo*-6-*endo*-7-*exo*-**93a**	<1	1.4	6.6	8.1	8.5	7	5.1	5.6	8.9	10.3	10.9
2-*endo*-6-*endo*-7-*exo*-**93a**	5	<1	6.4	8.7	8.9	5.9	4.7	5.3	9.2	10.2	10.2

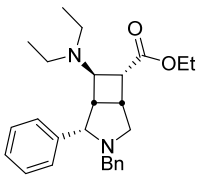
Ethyl-3-benzyl-7-*exo*-(diethylamino)-2-*exo*-phenyl-3-azabicyclo[3.2.0]heptane-6-*endo*-carboxylate 111



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.1 Hz, 6H), 1.22 – 1.16 (m, 3H), 2.56 – 2.48 (m, 5H), 2.58 (ddd, *J* = 8.2, 5.6, 2.4 Hz, 1H), 2.89 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.07 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.16 (tt, *J* = 11.2, 4.4 Hz, 1H), 3.50 – 3.32 (m, 2H), 3.61 (dd, *J* = 7.4, 5.8 Hz, 1H), 3.64 (t, *J* = 2.4 Hz, 1H), 4.15 – 4.05 (m, 2H), 7.25 – 7.16 (m, 3H), 7.29 – 7.25 (m, 5H), 7.36 – 7.29 (m, 2H).

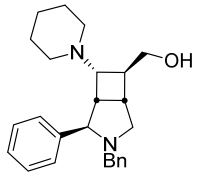
^{13}C NMR (101 MHz, $CDCl_3$) δ 10.26 (2C), 14.26, 35.13, 41.43, 43.15, 48.65, 53.27, 55.75, 60.30 (2C), 63.68, 73.42, 126.66, 127.18, 127.90 (2C), 128.09 (2C), 128.27 (2C), 128.36 (2C), 139.74, 141.45, 172.93.

Ethyl-3-benzyl-7-*exo*-(diethylamino)-2-*endo*-phenyl-3-azabicyclo[3.2.0]heptane-6-*endo*-carboxylate 111



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (t, *J* = 7.1 Hz, 6H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.93 (dq, *J* = 13.8, 7.0 Hz, 2H), 2.21 – 2.03 (m, 3H), 2.76 – 2.67 (m, 1H), 2.89 (d, *J* = 13.7 Hz, 1H), 3.00 (dd, *J* = 10.5, 6.3 Hz, 1H), 3.14 – 3.03 (m, 2H), 3.60 – 3.53 (m, 2H), 4.12 – 4.00 (m, 3H), 7.23 (ddd, *J* = 12.7, 6.8, 4.7 Hz, 2H), 7.39 – 7.27 (m, 6H), 7.49 (t, *J* = 8.7 Hz, 2H).

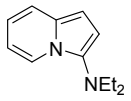
3-benzyl-2-*exo*-phenyl-7-*endo*-(piperidin-1-yl)-3-azabicyclo[3.2.0]heptan-6-*exo*-yl)methanol 91i



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 – 1.33 (m, 6H), 2.52-1.93 (m, 4H, very broad), 2.20 (d, *J* = 6.4 Hz, 1H), 2.57 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.92 – 2.84 (m, 1H), 3.11 – 3.01 (m, 2H), 3.40 (d, *J* = 13.6 Hz, 1H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.59 (d, *J* = 1.9 Hz, 1H), 3.67 (dd, *J* = 11.8, 1.4 Hz, 1H), 4.13 (dd, *J* = 11.8, 3.0 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.27 – 7.19 (m, 3H), 7.34 – 7.28 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 24.39, 25.75 (2C), 37.07, 41.17, 50.40, 52.24 (2C, bs) 55.73, 57.55, 64.54, 67.60, 73.73, 76.71, 77.03, 77.35, 126.62, 127.05, 127.93 (2C), 128.11 (2C), 128.17 (2C), 128.39 (2C), 139.88, 141.49.

***N*,*N*-diethylindolizin-3-amine S91j**



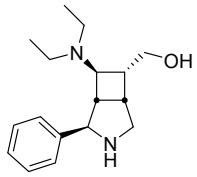
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.1 Hz, 6H), 3.01 (q, *J* = 7.1 Hz, 4H), 6.36 (d, *J* = 3.9 Hz, 1H), 6.42 (ddd, *J* = 7.5, 6.3, 1.3 Hz, 1H), 6.46 (d, *J* = 3.9 Hz, 1H), 6.55 (ddd, *J* = 9.0, 6.4, 1.1 Hz, 1H), 7.27 (dt, *J* = 8.9, 1.0 Hz, 1H), 8.01 (dd, *J* = 7.2, 0.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 12.79 (2C), 49.05 (2C), 96.72, 104.93, 109.22, 115.44, 118.97, 121.42, 128.58, 132.13.

m/z (EI^+) 188 (M^+, 55 %), 159 (83), 131 (100), 78 (25)

IR (KBr), υ (cm^{-1}) 3101, 2970, 1503, 1355, 1071, 752, 420.

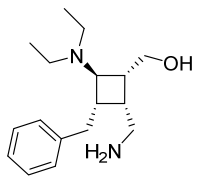
7-*exo*-(diethylamino)-2-*exo*-phenyl-3-azabicyclo[3.2.0]heptan-6-*endo*-yl)methanol 113



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 6H), 2.60 – 2.50 (m, 2H), 2.64 (q, *J* = 7.2 Hz, 4H), 2.88 – 2.84 (m, 1H), 2.91 (dd, *J* = 10.5, 6.3 Hz, 1H), 3.12 – 3.06 (m, 1H), 3.15 (d, *J* = 10.7 Hz, 1H), 3.29 – 3.25 (m, 1H), 3.66 (dd, *J* = 11.8, 5.1 Hz, 1H), 3.85 (dd, *J* = 11.7, 1.6 Hz, 1H), 4.25 (s, 1H), 7.12 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.47 (2C), 35.39, 39.77, 41.82 (2C), 43.99, 45.37, 60.63, 61.97, 66.86, 126.33 (2C), 127.18, 128.64 (2C), 143.45.

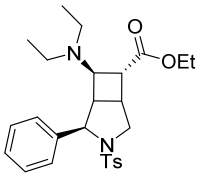
(2-(aminomethyl)-3-benzyl-4 -(diethylamino)cyclobutyl)methanol 114



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.1 Hz, 6H), 1.27 (bs, 1H), 2.46 (dd, *J* = 17.0, 8.5 Hz, 1H), 2.58 – 2.49 (m, 4H), 2.79 – 2.60 (m, 4H), 2.87 (dd, *J* = 14.4, 3.8 Hz, 1H), 2.97 – 2.92 (m, 2H), 3.68 (dd, *J* = 11.8, 4.6 Hz, 1H), 3.81 – 3.74 (m, 1H), 7.18 (t, *J* = 6.8 Hz, 3H), 7.35 – 7.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.89 (2C), 34.77, 36.11, 38.29, 39.20, 42.19, 42.73 (2C), 62.48, 62.74, 125.92, 128.09 (2C), 128.45 (2C), 140.76.

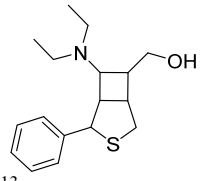
Ethyl-7-*exo*-(diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptane-6-*endo*-carboxylate 115



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.1 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.37 (s, 3H), 2.52 – 2.40 (m, 4H), 2.66 – 2.60 (m, 1H), 3.07 – 2.96 (m, 2H), 3.22 (ddd, *J* = 16.5, 8.4, 3.5 Hz, 1H), 3.63 (dd, *J* = 11.5, 8.6 Hz, 1H), 3.77 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.23 – 4.08 (m, 3H), 4.75 (s, 1H), 7.12 – 7.07 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.54 – 7.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.32 (2C), 14.26, 21.45, 35.40, 41.43 (2C), 43.45, 49.37, 50.32, 60.73, 60.82, 68.25, 126.26 (2C), 127.32 (2C), 127.47, 128.56 (2C), 129.32 (2C), 135.94, 141.04, 143.00, 171.60.

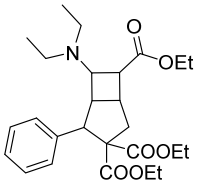
(7-(diethylamino)-2-phenyl-3-thiabicyclo[3.2.0]heptan-6-yl)methanol 94



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.2 Hz, 6H), 2.10 (d, *J* = 6.5 Hz, 1H), 2.58 (ddt, *J* = 20.5, 13.6, 6.7 Hz, 4H), 2.71 (d, *J* = 12.0 Hz, 1H), 3.15 (dd, *J* = 12.1, 7.1 Hz, 1H), 3.42 – 3.23 (m, 3H), 3.69 (t, *J* = 17.2 Hz, 1H), 4.17 – 4.08 (m, 2H), 7.25 – 7.12 (m, 3H), 7.29 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 11.17 (2C), 37.45, 42.07, 42.72, 43.45 (2C, br), 53.19, 58.45, 61.96, 64.14, 126.36 (2C), 126.82, 128.60 (2C), 143.94.

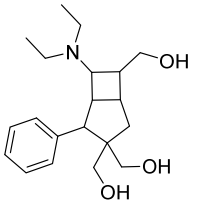
Triethyl-7-(diethylamino)-2-phenylbicyclo[3.2.0]heptane-3,3,6-tricarboxylate 121



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 6H), 1.25 (dt, *J* = 19.2, 7.1 Hz, 6H), 2.16 (dd, *J* = 14.5, 7.5 Hz, 1H), 2,46 – 2,4 (q, 4H), 2.81 – 2.73 (m, 2H), 3.02 – 2.94 (t, 1H), 3.46 (m, 3H), 3.78 (m, 1H), 4.31 – 4.08 (m, 5H),7.25 – 7.15 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.10 (2C), 13.40 (3C), 13.97, 14.36, 36.95, 37.07, 41.38 (2C), 42.41, 49.70, 57.20, 60.35 (3C), 60.99, 61.45, 64.49, 126.80, 128.00 (2C), 128.43 (2C), 140.77, 170.27, 171.33, 173.19.

(7-(diethylamino)-2-phenylbicyclo[3.2.0]heptane-3,3,6-triyl)trimethanol 98



^{1}H NMR (400 MHz, MeOD) δ 0.90 (t, *J* = 7.2 Hz, 6H), 2.11 – 1.93 (m, 2H), 2.54 – 2.45 (m, 1H), 2.59 (qd, *J* = 6.8, 3.5 Hz, 4H), 2.74 (d, *J* = 11.1 Hz, 2H), 2.91 (m, 2H), 2.98 (t, *J* = 6.6 Hz, 1H), 3.22 (d, *J* = 6.1 Hz, 1H), 3.65 (d, *J* = 11.2 Hz, 2H), 3.82 – 3.69 (m, 2H), 4.88 (s, 3H), 7.31 – 7.17 (m, 5H),.

^{13}C NMR (101 MHz, MeOD) δ 9.05 (2C), 30.61, 33.63,

40.71, 43.08 (2C), 47.88, 56.73, 57.93, 63.00 (3C), 64.19, 64.59, 70.05, 127.63, 129.30 (2C), 129.94 (2C), 140.37.

IR (KBr), υ (cm^{-1}) 3348, 2940, 2876, 2068, 1600, 1495, 1453, 1379, 1198, 1120, 1031, 979, 781, 738, 706.

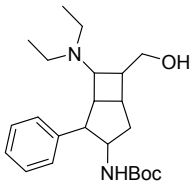
HRMS (ESI^+) calculated $(C_{20}H_{31}NO_3)^+$ 334.2377 [M + H^+], found 334.2370

Other isolated diastereomer of 98 (Table 8, entry 2)

^{1}H NMR (400 MHz, MeOD) δ 1.34 – 1.26 (m, 6H), 2.11 – 1.95 (m, 2H), 2.84 – 2.79 (m, 3H), 3.12 – 2.94 (m, 5H), 3.28 - 3.24 (m, 1H), 3.37 - 3.32 (m, 1H), 3.64 – 3.58 (m, 3H), 3.87- 3.74 (m, 2H), 4.88 (s, 3H), 7.50 – 7.06 (m, 5H),

^{13}C NMR (101 MHz, MeOD) δ 8.30 (2C), 30.52, 33.68, 40.09, 44.55 (2C), 47.22, 56.11, 58.26, 62.18 (3C), 63.85, 64.20, 69.96, 128.04, 129.55 (2C), 129.95 (2C), 139.30.

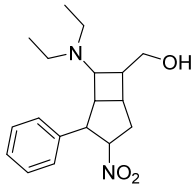
***tert*-butyl-(7-(diethylamino)-6-(hydroxymethyl)-2-phenylbicyclo[3.2.0]heptan-3-yl)carbamate 96b**



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.1 Hz, 6H), 1.27 (d, *J* = 13.7 Hz, 1H), 1.42 (s, 8H), 1.59 – 1.46 (m, 1H), 2.05 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.57 (q, *J* = 7.2 Hz, 4H), 2.69 – 2.60 (m, 2H), 2.83 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.01 (q, *J* = 8.7 Hz, 1H), 3.16 (d, *J* = 6.8 Hz, 1H), 3.76 (d, *J* = 7.0 Hz, 2H), 3.95 (d, *J* = 8.9 Hz, 1H), 4.44 (ddd, *J* = 15.9, 13.1, 7.2 Hz, 1H), 7.03 – 6.96 (m, 2H), 7.26 – 7.19 (m, 1H), 7.36 – 7.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.01 (2C), 28.39 (3C), 29.73, 31.77, 40.75, 41.48 (2C), 46.44, 51.21, 55.73, 61.97, 62.33, 76.70, 77.02, 77.22, 77.34, 79.26, 126.65, 128.35 (4C), 140.55, 155.53.

(7-(diethylamino)-3-nitro-2-phenylbicyclo[3.2.0]heptan-6-yl)methanol 95 1:1 mixture of diastereomers (d1:d2)



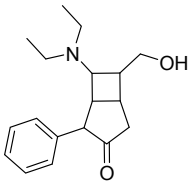
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.1 Hz, 6H, d2), 0.97 (t, J=7.1 Hz, 6H, d1), 2.81 – 2.25 (m, 16H, d1+d2), 3.18 – 2.87 (m, 4H, d1+d2), 3.97 – 3.50 (m, 6H, d1+d2), 4.85 (ddd, *J* = 10.2, 8.6, 7.0 Hz, 1H, d2), 5.43 (dt, *J* = 10.8, 7.0 Hz, 1H, d1), 7.46 – 7.08 (m, 10H, d1+d2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.11 (2C, d1), 10.19 (2C, d2), 27.44 (d2), 33.06 (d1), 33.34 (d2), 33.45 (d1), 40.05 (d2), 40.28 (d1), 41.73 (2C, d2), 42.07 (2C, d1), 46.63 (d2), 48.43 (d1), 54.40 (d2), 57.54 (d1), 62.01 (d2), 62.82 (d2), 63.04 (d1), 67.63 (d1), 90.36 (d2), 95.53 (d1), 129.03 - 127.01 (d1+d2).

IR (KBr), υ (cm^{-1}) 3339, 2971, 1647, 1600, 1547, 1453, 1375, 1077, 911, 701, 646.

HRMS (ESI^+) calculated $(C_{18}H_{26}NO_3)^+$ 319.2016 [M + H^+], found 319.2022

7-(diethylamino)-6-(hydroxymethyl)-2-phenylbicyclo[3.2.0]heptan-3-one 97



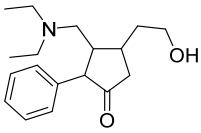
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.1 Hz, 6H), 2.60 – 2.52 (m, 6H), 2.78 – 2.69 (m, 2H), 3.04 – 2.98 (m, 1H), 3.22 – 3.14 (m, 1H), 3.32 (s, 1H), 3.67– 3.62 (m, 1H), 3.8 – 3.77 (m, 1H), 7.35 – 7.14 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.33, 29.57, 36.51, 41.63, 41.92 (2C), 44.27, 60.15, 61.98, 63.51, 126.84, 128.96 (2C), 135.57 (2C), 138.52, 219.00.

IR (KBr), υ (cm^{-1}) 3369, 2971, 1737, 1600, 1495, 1452, 1377, 1125, 1078, 911, 700, 646.

HRMS (ESI^+) calculated $(C_{18}H_{25}NO_2)^+$ 288.1958 [M + H^+], found 288.1956

3-((diethylamino)methyl)-4-(2-hydroxyethyl)-2-phenylcyclopentan-1-one 133



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.2 Hz, 6H), 1.54 – 1.51 (m, 1H), 1.94 (m, 1H), 2.79 – 2.30 (m, 10H), 3.11 (d, *J* = 10.0 Hz, 1H), 3.66 – 3.60 (m, 1H), 3.84 – 3.75 (m, 1H), 7.42 – 7.13 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 10.14 (2C), 32.22, 32.37, 44.85, 45.72 (2C), 46.91, 52.48, 58.14, 61.42, 127.16, 128.21, 128.81, 137.84, 217.00.

IR (KBr), υ (cm^{-1}) 3339, 3029, 2969, 1739, 1601, 1496, 1453, 1377, 1061, 701, 646.

HRMS (ESI^+) calculated $(C_{18}H_{27}NO_2)^+$ 290.2115 [M + H^+], found 290.2113

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Publication I

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A Novel Diastereoselective Multicomponent Cascade Reaction

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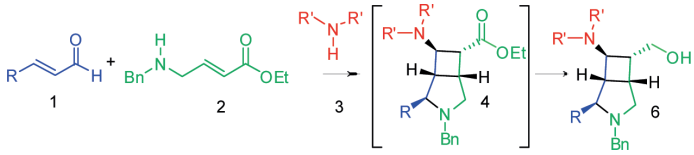
ABSTRACT

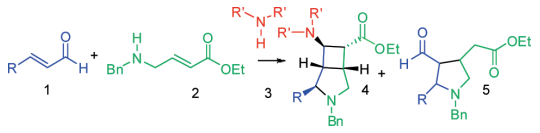


A novel multicomponent cascade reaction led to the formation of a strained 3-azabicyclo[3.2.0]heptane derivative 4. The unstable ester 4 was reduced in a one-pot procedure to a stable alcohol 6. The formation of the bicyclic product is highly diastereoselective, predominantly affording one diastereoisomer. The obtained azabicycloheptanes are important pharmacophores.

Synthetic organic chemistry has reached a turning point in which a new paradigm is needed.[1] A traditional single-step procedure affording only one (or two) new chemical bond(s) will be replaced by more efficient multicomponent cascade or domino reactions. The number of protective groups decreases and atom-efficiency and step-efficiency increase by using these approaches. The chemistry of multicomponent and domino reactions which started with the pioneering work of Ivar Ugi[2] is now developing quickly and well-documented in the literature.[3,4]

In the course of our ongoing investigations in the field of aminocatalysis,[5] we discovered a new and unexpected multicomponent cascade reaction (Scheme 1). The reaction of α,β-unsaturated aldehyde **1**, *N*-benzylaminocrotonate **2**, and secondary amine **3** afforded the expected pyrrolidine derivative with general formula **5** as well as the bicyclic product with general formula **4**. The formation of the monocyclic product can be rationalized by the organocatalytic domino aza-Michael reaction via iminium−enamine

Scheme 1. Reaction between α,β-Unsaturated Aldehyde **1**, *N*-Benzylaminocrotonate **2**, and Secondary Amine **3**



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activation as described recently by Wang et al.[6] However, we found that if we use two secondary amines (instead of sulfonamide and amine like Wang), the sterically less demanding amine **3** can be incorporated into the target through 3,4-*cis* substitution of the pyrrolidine intermediate, leading to the formation of the highly strained tetrasubstituted 3-azabicyclo[3.2.0]heptane derivative **4**.

This new chemical reaction leads to structures which are known to act as pharmacophores in modulating the dopamine D_3 receptor[7] (treatment of schizophrenia, depression, and Parkinson's disease (belaperidone),[8] in antibacterial agents (ecenofloxacin),[9] and in antitumor drugs (mitindomide).[10] The strained azabicyclo[3.2.0]heptane skeleton is an interesting tool for synthetic chemists engaged in the synthesis of natural products.[11]

However, in our first experiments, we achieved low selectivity between the formation of bicycle **4** and pyrrolidine derivative **5**. Therefore, we further investigated the reaction in more detail in order to get azabicyclo[3.2.0]heptane skeleton more selectively.

The reaction of cinnamaldehyde (**1**: R = Ph), *N*-benzylaminocrotonate **2**, and diethyl amine (**3**: R′ = Et) was selected as a model reaction, and various solvents were screened under different reaction conditions (Table 1).

Table 1. Reaction of Cinnamaldehyde (**1**: R = Ph), *N*-Benzylaminocrotonate **2**, and Diethylamine (**3**: R′ = Et)[a]

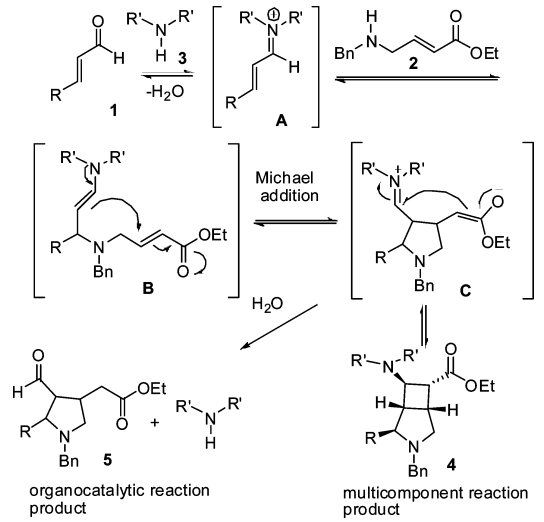
entry	solvent	ratio of **4**:**5**	yield of **4** (%)	yield of **5** (%)
1	CH_2Cl_2	3:1	60	19
2[b]	CH_2Cl_2	3.8:1	53	14
3[c]	CH_2Cl_2	6.3:1	70	11
4	toluene	1:2	22	40
5	CH_3CN	1:1.4	27	38
6	CCl_4	1:1.6	30	48
7[d]	$CHCl_3$	2:1	59	30

[a] Cinnamaldehyde (1 equiv), Et_2NH (1.1 equiv), and *N*-benzylaminocrotonate (1 equiv) were stirred in an appropriate solvent at rt for 24 h. [b] Molecular sieves (4 Å) were added. [c] Cinnamaldehyde (2 equiv), Et_2NH (2 equiv), and *N*-benzylaminocrotonate (1 equiv) were stirred in the presence of molecular sieves. [d] MW irradiation: 10 W, 30 min, 50 °C (internal cooling).

When the reaction was carried using approximately equimolar amounts of reagents in CH_2Cl_2, the ratio of obtained products was 3:1 (Table 1, entry 1). Elimination of water from the reaction media using molecular sieves favored the formation of the bicyclic compound **4** (Table 1, entry 2). Increasing concentration of the cinnamaldehyde and the secondary amine 2× to force the formation of the iminium intermediate led to substantial improvement in the selectivity, and bicyclic compound **4** was obtained in 70% of the isolated yield (Table 1, entry 3). Toluene, acetonitrile, $CHCl_3$, and CCl_4 considerably increased the amount of the pyrrolidine derivative **5** (Table 1, entries 4−7).

Formation of the bicyclic compound **4** is highly diastereoselective. In the best case, the diastereoisomeric ratio of main 2-*exo*-Ph isomer of compound **4** (as depicted in Scheme 1), and its minor 2-*endo*-Ph isomer was 25:1 (determined from the crude product by ^{1}H NMR). To our surprise, the diasteromeric ratio of the isolated products (17:1) and the ratio of isolated compounds **4** and **5** were much smaller than in the crude mixture. This data revealed that two competitive and reversible reactions take place simultaneously: the organocatalytic reaction affording pyrrolidine product and the multicomponent reaction leading to the bicyclic product. The proposed pathways of the competing reactions are outlined in Scheme 2. The presented mechanism can be

Scheme 2. Proposed Pathway of the Reaction



rationalized as follows: formation of iminium ion **A** activates unsaturated aldehyde **1**, and that leads to aza-Michael addition of amine **2** to **A**, affording intermediate **B**.[12] As in every iminium-activated aza-Michael reaction, discrimination between two secondary amines takes place.[13] Alkyl amine **3** participates in the formation the iminium ion, whereas amino crotonate **2** acts as a nucleophile. Intermediate **B** undergoes a second, intramolecular Michael reaction where enamine acts as a nucleophile and the crotonate subunit as an electrophile, leading to the intermediate **C**. This is a crucial intermediate of the transformation: it may hydrolyze

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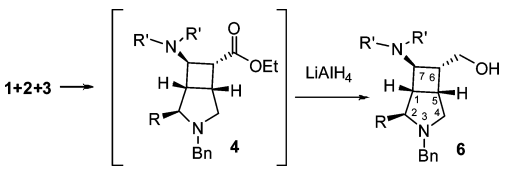
to a pyrrolidine derivative **5** or undergo an intramolecular Mannich-type ester enolate attack to iminium ion, affording a highly strained tetrasubstituted bicyclic compound **4**.[14] Reversibility of the reactions causes decrease in the ratio of compounds **4** and **5** (apparent as a change in the product ratio) during workup and purification.

Reduction of the ester group excludes the possibility of the retro-reactions. When we reduced the unstable esters **4** in one-pot procedure to the corresponding alcohols **6** with $LiAlH_4$, no later isomerization was detected during workup and other manipulations (Scheme 3).[15]

Scheme 3. Synthesis of Alcohols **6** via a One-Pot Procedure



Anhydrous conditions (molecular sieves and anhydrous CH_2Cl_2) favor the multicomponent reaction, and the competing formation of the pyrrolidine derivative **5** is suppressed. Indeed, when the reaction was run under strictly anhydrous conditions, the pyrrolidine derivative **5** was formed only as a minor byproduct (<5%) and because of that it was not further isolated in the following experiments (see the Supporting Information for the experimental details).

Having improved the reaction conditions to achieve practically useful levels, the scope of the reaction was investigated. As presented in Table 2, various α,β-unsaturated aldehydes **1** and secondary amines **3** react with *N*-benzylaminocrotonate **2** to afford after reduction substituted bicyclic compound **6**.

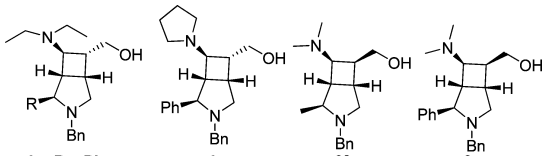
The reaction was run in CH_2Cl_2 at room temperature using a 2-fold excess of aldehyde **1** and amine **3,** followed by a change of the solvent and reduction with $LiAlH_4$. The isolated yield of the single diastereoisomer of bicyclic compound **6** was generally high. The highest yield was obtained with dimethylamine and crotonaldehyde (entry 6). The cyclic secondary amine (pyrrolidine) reacted with lower yield (52%, entry 6) than acyclic amines.

The discovered multicomponent reaction is highly diastereoselective, affording predominantly one diastereoisomer **6** in a 2-*exo*,6-*endo*,7-*exo* configuration. The main factor that governs the stereodifferentiation is a steric hindrance of the substituent in α,β-unsaturated aldehyde **1**. Sterically more demanding derivatives of cinnamaldehyde gave the most diastereoselective reactions (the ratio of 2-*exo* and 2-*endo* isomers up to 45:1, entry 1). Diastereoselectivity was even higher in the case of *o*-nitrocinnamaldehyde. Because of the intolerance of the nitro group to the reduction with $LiAlH_4$ the diastereomeric ratio in that case was determined in the crude product of ester **4h** (entry 8). The only exceptions from the described general tendency are compounds **6f** and **6g**, whose main diastereoisomers have an *all-cis* configuration (entries 6 and 7).

We also investigated the possibilities of the asymmetric version of the discovered multicomponent reaction. We assumed that the absolute stereochemistry of the product is determined by aza-Michael addition. Therefore, first we tried the auxiliary-based methods in which the multicomponent reaction was performed with enantiomerically pure aminocrotonate derivatives derived from (*S*)-α-methylbenzylamine or (*S*)-phenylalanine methyl ester and 4-bromocrotonate. However, in that case, a racemic product was obtained. Next, several organocatalysts (quinidine, cinchonine, (*R*)-TRIP) were used in different experiments under typical conditions.[16] Unfortunately, none of the catalysts showed any stereochemical induction.

The structures and relative configurations of 2,3,6,7-tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives were determined by a detailed $^1H-^{13}C$ NMR analysis, using 2D FT COSY, HSQC, and HMBC methods, including chemical shift and coupling constant analysis. The useful benchmark compounds for the chemical shift analysis are the unsubstituted bicyclo[3.2.0]heptane and *N*-3-benzyl-3-azabicyclo-

Table 2. Synthesis of Azabicycles **6a**−**h**



6a: R = Ph **6e** **6f** **6g**
b: R = Me
c: R = Et
d: R = p-MeO-Ph

entry	compound 1, R	amine 3	time (h)	product	yield[a] (%)	dr[b]
1	Ph	Et_2NH	17	**6a**	68	45:1
2	Me	Et_2NH	24	**6b**	64	8:1
3	Et	Et_2NH	24	**6c**	65	8:1
4	*p*-MeOPh	Et_2NH	42	**6d**	66	24:1
5	Ph	pyrrolidine	24	**6e**	52	7:1
6	Me	Me_2NH (2 M in THF)	24	**6f**	73	6.5:1[c]
7	Ph	Me_2NH (2 M in THF)	24	**6g**	69	5:1[c]
8	*o*-NO_2Ph	Et_2NH	29	**4h**	ND	65:1[d]

[a] Isolated yield of the major diastereoisomer. [b] Diasteromeric ratio determined from the crude mixture by NMR. [c] Ratio of 6-*exo*/6-*endo* diastereoisomers. [d] Determined in the crude product of ester.

(14) Photochemical cycloaddition leading to disubstituted 3-azabicyclo[3.2.0]-heptane: (a) Bach, T.; Krüger, C.; Harms, K. *Synthesis* **2000**, 305–320. (b) Bach, T.; Pelkmann, C.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 2103–2104.

(15) General method for the multicomponent synthesis of substituted 3-azabicyclo[3.2.0]heptanes: To a solution of the corresponding aldehyde **1** (0.4 mmol) in CH_2Cl_2 (1.0 mL) were added dialkylamine **3** (0.4 mmol), *N*-benzylaminocrotonate **2** (0.2 mmol), and 4A molecular sieves. The mixture was stirred at room temperature for 24 h. Molecular sieves were filtered, and solvent was evaporated under reduced pressure. The crude bicyclic ester was dissolved in THF and reduced with $LiAlH_4$.

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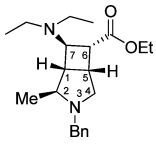
[3.2.0]heptane (although, only partially assigned).[17] These data show that the introduction of the benzyl-substituted nitrogen has a very small NMR effect on the four-membered ring. ^{13}C chemical shifts and $^{1}H-^{1}H$ spin−spin coupling constants from a four-membered ring determine the configuration of substituents on 3-azabicyclo[3.2.0]heptane skeleton. The representative data for 2-*exo* and 2-*endo* isomers of **4b** (the substitution pattern is the same as in compound **6b**) are given in Table 3. Relative configuration at C-2 is determined by three-bond coupling constants between the H-1 and H-2: for the 2-*endo* proton this coupling is 1.2 Hz (generally in present samples from 0 to 1.9 Hz) and for the 2-*exo* proton 5.4 Hz (in the **6a** *endo*-Ph isomer it is 6.7 Hz). The chemical shifts of C-6 and H-6 show that the configuration at this position of two isomers of **4b** is unchanged. The chemical shifts of the two isomers at C-4 have a 3.7 ppm difference, but in comparison with the unsubstituted *N*-3-benzyl-3-azabicyclo[3.2.0]heptane C-2 and C-4 (61.0) they are strongly shifted to a higher field, pointing to the presence of an *endo*-substituent at C-6. The influence of a C-2 substituent in the five-membered ring to C-4 shielding is of minor importance. $^{1}H-^{1}H$ spin−spin coupling between H-6 and H-5 (10−11 Hz) and between H-1 and H-7 (about 5 Hz) supports the assignment of *cis* orientation of H-5 and H-6 and *trans* orientation of H-1 and H-7, which corresponds to *exo* orientation of the C-7 substituent. In a recent review on the NMR spectroscopy of cyclobutanes,[18] limited outdated data on the coupling constants within a four-membered ring show that *cis* vicinal coupling constants are about 9 Hz, but *trans* coupling constants may be as low as 4.5 Hz and reach in some cases 10 Hz. This is understandable on the basis of the Karplus equation. The different *exo-endo* orientation in the two isomers of **4b** is also reflected on the C-7 ^{13}C chemical shifts; a high-field shift is caused by the 2-*endo* substituent, as usually observed in bicyclic systems.[19]

Table 3. NMR Data for 2-*Exo* and 2-*Endo* Isomers of **4b** (2-Methyl-3-benzyl-6-*endo*-carbethoxy-7-*exo*-diethylamino-3-azabicyclo-[3,2.1]heptane, $CDCl_3$, 800 MHz)



	2-*exo*-methyl derivative		2-*endo*-methyl derivative	
atom	^{1}H,mult, (*J*, Hz)	^{13}C	^{1}H,mult, (*J*, Hz)	^{13}C
1	2.28 (8.0, 5.0, 1.2)	47.7	2.51 (8.0, 5.4, 4.6)	45.1
2	2.91 (6.3q, 1.2)	62.5	2.33 (6.3q, 5.4)	61.7
4	2.57 (10.4, 6.9)	51.6	2.84 (10.7)	55.3
4	2.56 (10.4, 3.0)		1.90 (10.7, 6.8)	
5	2.99 m	34.1	2.87 m	32.8
6	3.02 (10, 7)	42.9	3.04 (11, 6.5)	43.3
7	3.50 (7, 5)	61.9	3.64 (11.2, 6.5, 4.6)	55.9
Me	0.93 (6.3)	13.2	1.18 (6.3)	11.2
Bn	3.68 (13.5)	55.0	4.08 (13.3)	56.8
Bn	3.67 (13.5)		2.92 (13.3)	
CO		172.8		172.7
OEt	4.06 (7.2)	60.1	4.06 (7.2)	60.0
OEt	1.15 (7.2)	14.2	1.05 (7.2)	14.1
NEt	2.57 (7.2)	41.7	2.57 (7.2)	41.5
NEt	1.02 (7.2)	10.5	1.05 (7.2)	10.9

In conclusion, we have found an efficient, one-step multicomponent reaction to yield the tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives. The obtained compounds are important pharmacophores or could be used as the starting material for the other N-containing heterocycles via ring fission. The investigation continues toward the asymmetric version of multicomponent coupling.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Publication II

Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T.

Chemoenzymatic synthesis and evaluation of 3-azabicyclo[3.2.0]heptane derivatives as dopaminergic ligands.

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Original article

Chemoenzymatic synthesis and evaluation of 3-azabicyclo[3.2.0]heptane derivatives as dopaminergic ligands

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ABSTRACT

New 3-azabicyclo[3.2.0]heptane derivatives were synthesized using a multicomponent reaction. Racemic compounds were efficiently resolved by kinetic resolution with immobilized lipase B of *Candida antarctica* (Novozym 435). The obtained compounds demonstrated greater binding affinity at D_{2L} and D_3 dopamine receptors compared to D_1 binding sites, and individual enantiomers of the same compound possessed distinct affinities.

1. Introduction

Dopamine is a monoamine neurotransmitter and its receptors are distributed throughout the body, both in CNS and in the periphery. According to their structural differences and signaling properties, dopamine receptors are divided roughly into D_1-like and D_2-like receptors, of which D_1-like receptors are comprised of D_1 and D_5 subtypes and D_2-like receptors include D_2, D_3 and D_4 subtypes. Disturbances in brain dopamine receptor signaling lead to such medical conditions as Parkinson's disease, schizophrenia and many other diseases resulting from genetic or environmental factors [1].

The structure–activity relationship of efficient dopamine receptor modulators indicates that a wide variety of structural units may be needed for the activity. However, a rigid heteroatom containing a bicyclic scaffold is often present in compounds with a therapeutic potential (Fig. 1) [2].

Substituents at the azabicyclo template are usually different and unique for every ring system. The ring size of the bicyclic heterocycle is a crucial feature. 3-Azabicyclo[3.1.0]hexane **1** derivatives with sulfonamide [3] or triazol [4] are selective dopamine D_3 antagonists. 3-Azabicyclo[3.2.1]octane **2** benzamide derivative SSR181507 [5] and indolyl-substituted bicyclic compounds [6] are D_2 antagonists. Benzamides of 3-azabicyclo[3.3.1]nonane **3** were found to be non-selective and showed nearly identical binding to dopamine D_2 and D_3 receptors [7]. Compounds with a 3-azabicyclo[3.2.0]heptane structure **4** have been shown to bind dopamine D_2-like receptors [8]. Our recent paper describes the synthesis of tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives **9** (Scheme 1) [9]. The method is characterized by a high diastereoselectivity, simplicity and a wide substrate scope. The starting unsaturated aldehyde **5** can be either aromatic, heteroaromatic or aliphatic, and secondary amine **7** can be either acyclic or cyclic. In addition, the primary hydroxyl group is a possible site for the further derivatization of the compound. This multicomponent cascade reaction is highly diastereoselective. The cascade involved an aza-Michael addition of benzyl aminocrotonate **6** to an iminium-activated α,β-unsaturated aldehyde, followed by the intramolecular Michael addition and an intramolecular Mannich-type ester enolate attack to iminium ion. The initially formed bicyclic ester **8** was unstable under reaction conditions and it was reduced in a one-pot procedure with $LiAlH_4$ to form the target **9**.

From the synthetic aspect, the access to 3-azabicyclo[3.2.0]heptanes is limited mainly to [2 + 2] photocycloaddition methods

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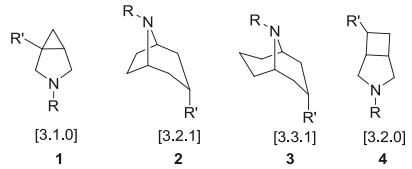


Fig. 1. Azabicyclo scaffolds found among dopamine receptor modulators.

[10,11] or Au- [12,13] or Pt-mediated [14] cycloisomerization. Their asymmetric synthesis has been even less explored. To the best of our knowledge, crystallization via ditoluyl tartaric acid salt [15] and Ir-catalyzed asymmetric allylic amination followed by Pt-catalyzed cyclization [16] are the only examples described in the literature so far.

Herein, we report the synthesis of various new derivatives of 3-azabicyclo[3.2.0]heptanes, a general method for the kinetic resolution of the obtained racemic products by lipase-catalyzed reaction, and assess the binding of obtained individual enantiomers at their potential biological target, dopamine receptors. 3-azabicyclo[3.2.0]heptanes are more likely to block D_2-like receptors [8], which is beneficial for antipsychotic drugs used i.e. for treating schizophrenia or related disorders [1]. Therefore the aim of the study was to determine selectivity profile of the synthesized 3-azabicyclo[3.2.0]heptane derivatives and find moieties that would substantially affect ligand binding to three dopamine receptor subtypes, D_1, D_{2L} and D_3.

2. Results and discussion

2.1. Lipase-catalyzed kinetic resolution of 3-azabicyclo[3.2.0] heptane derivatives

The stereodetermining step of the cascade in the synthesis of heterocycle **9** is the first aza-Michael addition. Our several attempts to use asymmetric organocatalytic approaches, such as iminium catalysis with chiral secondary amines (such as diaryl prolinol derivatives) or hydrogen bonding catalysts (quinidine, cinchonine, (*R*)-TRIP and chiral thiourea derivatives) afforded a racemic product. The same result was obtained with the auxiliary-based methods, where enantiomerically pure aminocrotonate derivatives were used in the multicomponent reaction.

As chemical methods of the enantioselective synthesis failed, we addressed this problem in the enzymatic reactions. It is well known that lipases are efficient enzymes for the acylation of alcohols [17]. The lipase-catalyzed kinetic resolution of the racemic secondary or even primary alcohols [18] is a widely used method for the synthesis of enantiomeric alcohols. We used immobilized lipase B of *Candida antarctica* (Novozym 435) as an acylating agent for the kinetic resolution of enantiomers of 3-azabicyclo[3.2.0] heptane **9** derivatives in EtOAc at room temperature (Scheme 2 and Table 1).

In addition to the previously known racemic compounds **9a**–**c** [9], the new derivatives **9d**, **9e**, **9f** and **9g** were synthesized and resolved enzymatically (the structures are depicted in Table 2). The method allowed us to obtain both enantiomers needed for the following pharmacological studies. In most cases, the enantioselectivity of the resolution was not high enough and a repeated resolution strategy was used. It afforded both enantiomers with sufficient enantiomeric excess. An acylated (B)-enantiomer (typically (−)-enantiomer) and nonacylated (A)-enantiomer (typically (+)-enantiomer) were separated by column chromatography and acylated (B)-isomer was hydrolyzed under alkaline conditions. Exceptions were the compounds **9e** and **9f**, with *p*-bromophenyl and pyridyl substituents, respectively. They behaved to the contrary, affording an (−)-enantiomer as nonacylated and (+)-enatiomer as acylated compounds.

For the determination of the absolute configuration the *N*-tosyl derivative **11** of 3-azabicyclo[3.2.0]heptane was synthesized and resolved (Scheme 3).

Kinetic resolution and hydrolysis of the obtained acylated B-enantiomer afforded a highly crystalline compound. Its absolute configuration was determined by using X-ray diffraction as (1*S*, 2*R*, 5*R*, 6*R*, 7*R*)-configuration (Fig. 2). It is assumed that all B-enantiomers of azabicycles that have been acylated by Novozym 435 possess the same configuration as shown.

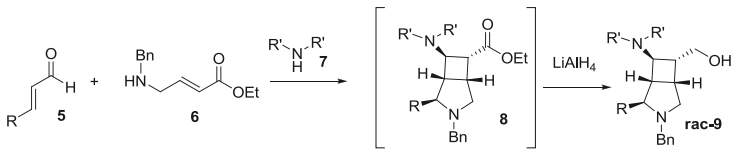
2.2. Ligand binding to dopamine receptors

Some azabicycloheptyl compounds, similar to the title compounds, have been shown to bind to D_2 and D_3 subtypes of dopamine receptors with a slight preference for the D_3 subtype [8]. Therefore, we saw dopamine receptors as a potential target for the present 3-azabicyclo[3.2.0]heptane derivatives and decided to test the compounds binding affinities for three different dopamine receptor subtypes, namely D_1, D_{2L} and D_3 receptors. In our earlier studies with dopaminergic compounds various host cell lines for different receptor subtypes, both human and rat, had been used, mainly for what was available [19,20]. However, the membrane environment [21,22] as well as the origin of the receptor gene [23] might have a substantial impact on ligand binding and signal transduction properties, so we created a single host (HEK293) based cell lines stably expressing individual subtypes of human dopamine receptors (D_1, D_{2L} and D_3), which is described in detail in the Experimental Section (Sections 4.3 and 4.4).

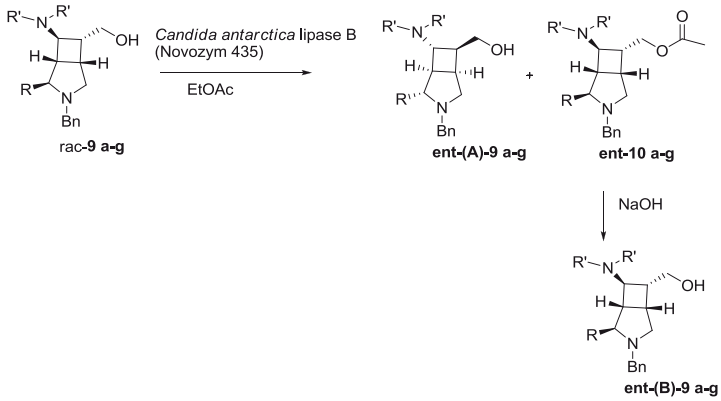
All tested 3-azabicyclo[3.2.0]heptane derivatives showed a preference for D_2-like receptors (see Table 2 for results and for the structures of tested compounds). None of them reached the affinity of apomorphine, but were comparable with dopamine. On the other hand, several B-enantiomers had better D_{2L} over D_1 selectivity compared to the reference compounds, but none achieved the level of D_3/D_{2L} selectivity of dopamine.

(B)-Enantiomers had substantially higher affinities (4- to 40-fold) toward D_2-like receptors compared to (A)-enantiomers, while the influence of the compounds absolute configuration on the affinities for the D_1 receptor was much less pronounced.

The addition of bromine to the phenyl moiety at position 2 of the core structure slightly improved the affinity for D_1 receptors (compare the compounds **9e** and **9a**). The highest affinity



Scheme 1. A multicomponent synthesis of racemic tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives.



Scheme 2. Kinetic resolution of 3-azabicyclo[3.2.0]heptane **9** derivatives.

compound of the current study was compound (B)-**9b**,which contained a pyrrolidinyl moiety at position 7 and a phenyl substituent at position 2, of which the pyrrolidinyl group seemed to improve the binding to D_{2L}/D_3 receptors, while the binding to D_1 receptors remains the same (compare (B)-**9b** and (B)-**9a**). The substitution of the pyrrolidine ring by a piperidine decreased both the affinity and selectivity (compounds (B)-**9b** and (B)-**9g**).

Comparing methyl and phenyl groups, the latter improved the affinity both for D_1 and D_{2L}/D_3 receptors, 10- and 50-fold, respectively (compare the compounds (B)-**9d** and (B)-**9b**). Generally, phenyl at position 2 increased the affinity for D_1 receptors irrespective of the substituents at position 7 (see compounds **9a**, **9b**, **9e** and **9f**). Significant selectivity was detected for only one compound, (B)-**9b**, having 80- to 90-fold higher affinity for D_2-like receptors compared to the D_1 receptor subtype.

For all the other higher affinity enantiomers, the preference for D_{2L} and D_3 receptors (between 10- and 30-fold) compared to D_1 was low. The exception was compound (B)-**9c** with a methyl at position 2 which bound very weakly to D_1 receptors while maintaining a considerable affinity for D_{2L} and D_3 receptors, increasing thereby the selectivity for D_2-like receptors to more than 40. The lack of selectivity between D_2 and D_3 receptor subtypes, as we encountered here, is a common feature for dopaminergic compounds and finding ligands that are specific for the D_3 rather than the D_2 receptor is one of the major challenges in dopaminergic receptor pharmacology [24]. In the current study however the goal was to identify the compounds preference for selected dopamine receptor subtypes. The binding studies confirmed our hypothesis that the newly synthesized 3-azabicyclo [3.2.0]heptane derivatives preferentially bind to D_2-like dopamine receptors.

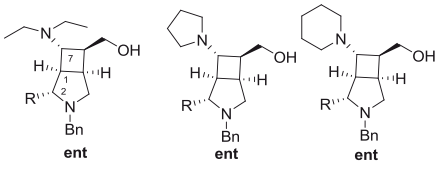
Table 1
Kinetic resolution of 3-azabicyclo[3.2.0]heptane **9** derivatives.

Entry	Compound	R	NR_2'	ee of (A)-enantiomer	ee of (B)-enantiomer
1	**9a**	Ph	NEt_2	99	97
2	**9b**	Ph	Pyrrolidinyl	96	99
3	**9c**	Me	NEt_2	98	94
4	**9d**	Me	Pyrrolidinyl	99	99
5	**9e**	*p*-BrPh	NEt_2	97	96
6	**9f**	2-pyridyl	NEt_2	97	99
7	**9g**	Ph	Piperidinyl	95	99

3. Conclusions

Enantiomers of 3-azabicyclo[3.2.0]heptane **9** derivatives were efficiently resolved by kinetic enzymatic resolution with immobilized lipase B of *Candida antarctica* (Novozym 435). The pharmacological evaluation of the obtained compounds revealed that all

Table 2
Binding affinities and binding selectivity of 3-azabicyclo[3.2.0]heptane derivatives **9a**–**g** ((A)- and (B)-enantiomers) to selected subtypes of the human dopamine receptors stably expressed in human embryonic kidney (HEK293) cells.

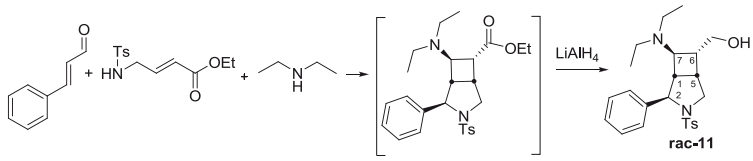


(A)-9a: R = Ph **(A)-9 b: R = Ph** **(A)-9 g: R = Ph**
c: R = Me **d: R = Me**
e: R = p-BrPh
f: R = 2-pyridyl
(B)-9 a-g are enantiomers of corresponding (A)-**9** compounds

Compounds	K_i [a] (μM)			Selectivity[b]		
	D_1	D_{2L}	D_3	D_{2L}/D_1	D_3/D_1	D_3/D_{2L}
(A)-**9a**	42 ± 7	12 ± 2	13.2 ± 0.4	3.4	3.2	0.9
(B)-**9a**	22 ± 8	1.7 ± 0.3	1.3 ± 0.2	13	17	1.3
(A)-**9b**	40.8 ± 0.7	7.4 ± 0.3	11 ± 2	5.5	3.6	0.6
(B)-**9b**	22 ± 3	0.25 ± 0.02	0.28 ± 0.04	90	80	0.9
(A)-**9c**	>100	38 ± 2	21 ± 9	>7	>10	1.8
(B)-**9c**	>100	3.9 ± 0.4	1.77 ± 0.01	>40	>85	2.2
(A)-**9d**	>100	66 ± 7	36 ± 8	>2	>4	1.8
(B)-**9d**	>100	16 ± 3	11 ± 1	>10	>15	1.5
(A)-**9e**	7 ± 1	5 ± 1	7.93 ± 0.02	1.4	0.9	0.7
(B)-**9e**	8 ± 1	2.0 ± 0.1	2.14 ± 0.01	3.9	3.6	0.9
(A)-**9f**	>100	42 ± 7	36 ± 10	>3	>3	1.2
(B)-**9f**	>100	12 ± 1	8.8 ± 0.3	>10	>15	1.4
(A)-**9g**	44 ± 2	7 ± 1	5.3 ± 0.3	6.4	8.3	1.3
(B)-**9g**	49 ± 0.1	2.0 ± 0.3	1.5 ± 0.1	25	34	1.4
Dopamine	12 ± 3	2.1 ± 0.2	0.015 ± 0.004	5.7	800	140
Apomorphine	0.66 ± 0.02	0.05 ± 0.01	0.010 ± 0.004	13	65	4.8

[a] K_i value in μM represents mean ± SEM from at least two independent experiments carried out in duplicates.

[b] Selectivities for D_{2L} over D_1 (D_{2L}/D_1), for D_3 over D_1 (D_3/D_1) and for D_3 over D_{2L} (D_3/D_{2L}) receptors are calculated as a ratio of $K_i(D_1)/K_i(D_{2L})$, $K_i(D_1)/K_i(D_3)$ and $K_i(D_{2L})/K_i(D_3)$, respectively. Selectivities marked as >are rough estimations due to very low affinity for the particular subtype.



Scheme 3. Synthesis of N-tosyl-3-azabicyclo[3.2.0]heptane derivative **11.**

compounds studied showed a moderate preference for D_2-like receptors and, not surprisingly, the binding affinity depended on the enantiomeric form of the tested 3-azabicyclo[3.2.0]heptane derivative.

4. Experimental section

Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker Avance^{III} 400 instruments. Deuterosolvent peaks (C**H**Cl_3 $\delta = 7.27$, **C**DCl_3 $\delta = 77.00$) or TMS peak was used as chemical shift references. Mass spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer in GC/MS mode (EI, 70 eV). High resolution mass spectra were recorded on LTQ Orbitrap (Thermo Electron). IR spectra were recorded on Perkin–Elmer Spectrum BX FTIR spectrometer. X-ray diffraction data was collected on a Bruker SMART X2S at 200 K.

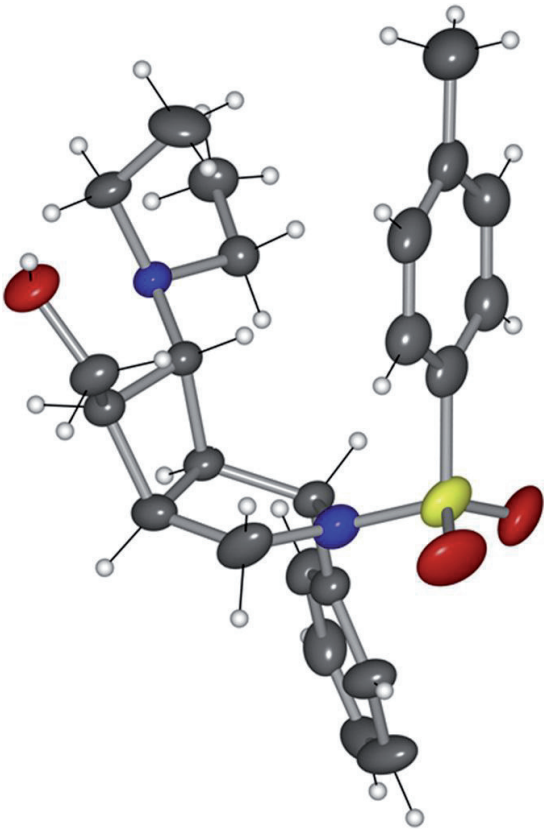


Fig. 2. Molecular moiety in the crystal structure of N-tosyl-3-azabicyclo[3.2.0]heptane derivative **11**. For clarity one formula unit is shown ($Z' = 2$). Displacement ellipsoids are drawn at the 50% probability level.

Reactions sensitive to oxygen or moisture were conducted under argon atmosphere in flame-dried glassware. Anhydrous dichloromethane was freshly distilled with CaH_2 and anhydrous tetrahydrofuran with $LiAlH_4$. Commercial reagents were generally used as received. Petroleum ether used had bp 40–60 °C.

4.1. General procedure for the synthesis of racemic *9*

To a solution of the corresponding aldehyde **5** (0.4 mmol) in anhydrous CH_2Cl_2 (1.0 mL) with molecular sieves (4Å) dialkyl amine **7** (0.4 mmol) and *N*-benzylaminocrotonate **6** (0.2 mmol) were added. The mixture was stirred at room temperature for 17–42 h. The mixture was concentrated in vacuum and the crude bicyclic ester **8** was reduced with $LiAlH_4$ (0.8 mmol) in anhydrous THF (1.0 mL). After 3 h the reaction mixture was cooled to 0 °C and the reaction was quenched by the addition of water and an aqueous solution of 4 M aq NaOH. The mixture was dried over K_2CO_3. The crude product was purified by chromatography on silica gel affording bicyclic alcohol **9**.

4.1.1. (3-Benzyl-2-exo-methyl-7-exo-pyrrolidin-1-yl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol ***9d***

Yield: 51%, off-white solid mp 102–104 °C. IR (KBr): 3191, 3062, 3028, 2958, 2909, 2800, 1748, 1632, 1494, 1454, 1331, 1240, 1174, 1152, 1128, 1075, 1029, 899, 786, 752, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4H), 7.30–7.24 (m, 1H), 3.85 (d, $J = 13.1$ Hz, 1H), 3.78 (dd, $J = 11.6$, 2.0 Hz, 1H), 3.63 (d, $J = 13.1$ Hz, 1H), 3.62 (dd, $J = 11.5$, 5.1 Hz, 1H), 3.07 (q, $J = 6.6$ Hz, 1H), 3.00 (dd, $J = 10.6$ Hz, 1H), 2.97 (ddd, $J = 9.8$, 7.9, 6.2 Hz, 1H), 2.87 (dd, $J = 5.7$, 3.9 Hz, 1H), 2.63 (dd, $J = 10.5$, 6.2 Hz, 1H), 2.45 (m, 5H), 2.31 (dd, $J = 8.1$, 3.7 Hz, 1H), 1.83–1.73 (m, 4H), 0.84 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.23, 128.78, 128.48, 127.19, 63.77, 61.85, 60.12, 53.77, 51.20, 50.50, 47.57, 40.50, 34.31, 23.32, 11.70. HRMS (*m*/*z*): $[M + H^+]$ calcd for $(C_{19}H_{29}N_2O)^+$, 301.22744; found, 301.22748.

4.1.2. (3-Benzyl-7-exo-diethylamino-2-exo-p-bromophenyl-3-azabicyclo[3.2.0]hept-6-endo-yl) methanol ***9e***

Yield: 67%, pale yellow solid mp 43–45 °C. IR (KBr): 3131, 2969, 2906, 2859, 2801, 1945, 1905, 1809, 1639, 1586, 1487, 1468, 1450, 1368, 1343, 1325, 1294, 1195, 1130, 1010, 981, 814, 735, 701, 523 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.25–7.20 (m, 2H), 6.81 (m, 2H), 3.87 (s, 1H), 3.81 (dd, $J = 11.4$, 2.9 Hz, 1H), 3.70 (dd, $J = 11.4$, 6.1 Hz, 1H), 3.46 (d, $J = 13.4$ Hz, 1H), 3.28 (d, $J = 13.5$ Hz, 1H), 3.25 (dd, $J = 6.3$, 4.8 Hz, 1H), 3.08 (dd, $J = 16.3$, 8.3 Hz, 1H), 2.97 (dd, $J = 10.8$, 1.4 Hz, 1H), 2.74 (dd, $J = 10.9$, 6.8 Hz, 1H), 2.70 (dd, $J = 8.4$, 4.7 Hz, 1H), 2.55 (q, $J = 7.2$ Hz, 5H), 0.98 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.34, 131.19, 130.26, 128.59, 128.43, 127.16, 121.39, 70.04, 62.43, 61.79, 54.74, 51.17, 47.63, 41.95, 40.09, 34.36, 10.59. HRMS (*m*/*z*): $[M + H^+]$ calcd for $(C_{24}H_{31}BrN_2O)^+$, 443.16925; found, 443.16862.

4.1.3. (3-Benzyl-7-exo-diethylamino-2-exo-pyridyl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol ***9f***

Yield: 53%, off-white solid mp 92–93 °C. IR (KBr): 3136, 2974, 2939, 2913, 2829, 1589, 1568, 1490, 1474, 1448, 1432, 1368, 1338,

1288, 1233, 1190, 1174, 1151, 1127, 1079, 1019, 992, 852, 779, 764, 747, 707, 650, 604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, J = 0.7, 1.7, 4.8, 1H), 7.59 (td, J = 1.8, 7.7, 1H), 7.34–7.14 (m, 6H), 6.90 (d, J = 7.8, 1H), 4.01 (s, 1H), 3.80 (dd, J = 3.0, 11.4, 1H), 3.66 (dd, J = 6.0, 11.5, 1H), 3.51 (d, J = 13.2, 1H), 3.41 (d, J = 13.2, 1H), 3.29 (dd, J = 4.7, 6.2, 1H), 3.14 (m, 1H), 3.13 (d, J = 8.6, 1H), 2.99 (d, J = 8.5, 1H), 2.76 (dd, J = 4.6, 7.7, 1H), 2.57 (q, J = 7.2, 4H), 2.53–2.49 (m, 1H), 0.99 (t, J = 7.2, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.57, 149.16, 138.63, 135.97, 128.78, 128.30, 127.11, 122.87, 122.11, 72.44, 62.45, 61.91, 55.10, 52.03, 47.04, 42.00, 39.88, 34.78, 10.55. HRMS (m/z): [M + H^+] calcd for $(C_{23}H_{31}N_3O)^+$, 366.25399; found, 366.25322.

4.1.4. (3-Benzyl-2-exo-phenyl-7-exo-piperidin-1-yl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol **9g**

Yield: 30%, off-white solid mp 148–151 °C. IR (KBr): 3183, 3065, 3029, 2924, 2782, 1601, 1490, 1452, 1368, 1339, 1261, 1236, 1122, 1027, 861, 777, 750, 711, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 6H), 7.23 (m, 2H), 6.92 (m, 2H), 3.91 (s, 1H), 3.83 (dd, J = 11.4, 2.6 Hz, 1H), 3.69 (dd, J = 11.4, 5.9 Hz, 1H), 3.42 (d, J = 13.6 Hz, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.14 (m, 1H), 3.00 (dd, J = 10.7, 1.1 Hz, 1H), 2.82–2.75 (m, 3H), 2.56 (m, 1H), 2.41–2.20 (m, 4H), 1.61–1.50 (m, 4H), 1.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.07, 138.61, 128.71, 128.65, 128.35, 128.03, 127.44, 127.03, 70.50, 66.11, 62.64, 54.60, 51.17, 51.09, 46.91, 39.83, 34.74, 25.46, 24.39. HRMS (m/z): [M + H^+] calcd for $(C_{25}H_{33}N_2O)^+$, 377.25874; found, 377.25854.

4.2. General procedure of enzymatic kinetic resolution of **9**

Lipase B of *C. antarctica* (Novozym 435) (50 mg) was added to a solution of the racemic compound **9** (50 mg) in EtOAc (1.0 mL). The resulting mixture was stirred occasionally at room temperature and the reaction was monitored by TLC (about a conversion 50%). The typical time of the reaction varied from 4.5 to 7 h, then the lipase was filtered off and the filtrate concentrated under reduced pressure. This mixture was purified by chromatography on silica gel affording alcohol (A)-**9** and ester **12**. As the enantiomeric excess of ester **12** could not be determined by chiral HPLC, it was hydrolyzed to (B)-**9**, with 4 M NaOH in MeOH by stirring 3 h at room temperature. The enantiomeric excess of (A)-**9** and (B)-**9** was determined by HPLC (Chiralcel AS or Lux Amylose-2).

4.2.1. (3-Benzyl-7-exo-diethylamino-2-exo-phenyl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol **9a**

The enantiomeric excess was determined by HPLC, Chiralcel AS, Hex:iPrOH 98:2 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 11.6, *ee* 99%, [α] = +10 (c 0.82, CH_2Cl_2) and acylated (B)-enantiomer t_R = 16.3, *ee* 95%, [α] = −10 (c 0.47, CH_2Cl_2).

4.2.2. (3-Benzyl-2-exo-phenyl-7-exo-pyrrolidin-1-yl-3-azabicyclo [3.2.0]hept-6-endo-yl) methanol **9b**

The enantiomeric excess was determined by HPLC, Chiralcel AS, Hex:iPrOH 97:3 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 11.5, *ee* 96%, [α] = +10 (c 1.22, CH_2Cl_2) and acylated (B)-enantiomer t_R = 15.5, *ee* 99%, [α] = −11 (c 1.46, CH_2Cl_2).

4.2.3. (3-Benzyl-7-exo-diethylamino-2-exo-methyl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol **9c**

The enantiomeric excess was determined by HPLC, Lux Amylose-2, Hex:iPrOH 98:2 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 22.6, *ee* 99%, [α] = +31 (c 0.16, CH_2Cl_2) and acylated (B)-enantiomer t_R = 18.2, *ee* 94%, [α] = −28 (c 0.61, CH_2Cl_2).

4.2.4. (3-Benzyl-2-exo-methyl-7-exo-pyrrolidin-1-yl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol **9d**

The enantiomeric excess was determined by HPLC, Lux Amylose-2, Hex:iPrOH 97:3 with 0.1% Et_2NH, 1.5 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 16.6, *ee* 99%, [α] = +30 (c 0.31, CH_2Cl_2) and acylated (B)-enantiomer t_R = 13.9, *ee* 99%, [α] = −29 (c 0.48, CH_2Cl_2).

4.2.5. (3-Benzyl-7-exo-diethylamino-2-exo-p-bromophenyl-3-azabicyclo[3.2.0]hept-6-endo-yl)methanol **9e**

The enantiomeric excess was determined by HPLC, Chiralcel AS, Hex:iPrOH 98:2 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 12.2, *ee* 96% and acylated (B)-enantiomer t_R = 17.4, *ee* 99%, [α] = +4.9 (c 2.93, CH_2Cl_2).

4.2.6. (3-Benzyl-7-exo-diethylamino-2-exo-pyridyl-3-azabicyclo [3.2.0]hept-6-endo-yl)methanol **9f**

The enantiomeric excess was determined by HPLC, Chiralcel AS, Hex:iPrOH 98:2 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 23.1, *ee* 97%, [α] = −30 (c 1.97, CH_2Cl_2) and acylated (B)-enantiomer t_R = 29.4, *ee* 99%, [α] = +29.5 (c 1.53, CH_2Cl_2).

4.2.7. (3-Benzyl-2-exo-phenyl-7-exo-piperidin-1-yl-3-azabicyclo [3.2.0]hept-6-endo-yl) methanol **9g**

The enantiomeric excess was determined by HPLC, Chiralcel AS, Hex:iPrOH 97:3 with 0.1% Et_2NH, 1.0 mL/min, UV 254 nm, nonacylated (A)-enantiomer t_R = 10.2, *ee* 95%, [α] = +19 (c 0.37, CH_2Cl_2) and acylated (B)-enantiomer t_R = 14.5, *ee* 99%, [α] = −20 (c 0.37, CH_2Cl_2).

4.2.8. 7-(Exo-(diethylamino)-2-exo-phenyl-3-tosyl-3-azabicyclo [3.2.0]heptan-6-endo-yl)methanol **11**

To a solution of *trans*-cinnamaldehyde (0.4 mmol) in anhydrous CH_2Cl_2 (1.0 mL) diethyl amine (1.0 mmol) and *N*-tosylaminocrotonate (0.2 mmol) were added in the presence of molecular sieves (4Å). The mixture was stirred at room temperature for 20 h. The mixture was concentrated in vacuum and the crude bicyclic ester was reduced with $LiAlH_4$ (0.8 mmol) in anhydrous THF (1.0 mL). After 3 h the reaction mixture was cooled to 0 °C and was quenched by the addition of water and an aqueous solution of 4 M aq NaOH. The mixture was dried over K_2CO_3. The crude product was purified by chromatography on silica gel affording bicyclic alcohol **11** (smp 115–121 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 6H), 2.32 (s, 4H), 2.58–2.48 (m, 5H), 2.68–2.63 (m, 1H), 2.73–2.68 (m, 1H), 3.16–3.06 (m, 1H), 3.36 (dd, J = 11.3, 8.3 Hz, 1H), 3.75–3.62 (m, 2H), 3.87 (dd, J = 11.3, 1.9 Hz, 1H), 4.83 (s, 1H), 7.08–6.98 (m, 4H), 7.23–7.14 (m, 3H), 7.36–7.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.24, 21.41, 34.53, 40.03, 41.71, 47.17, 49.27, 61.58, 62.54, 68.97, 126.70, 127.02, 127.53, 128.50, 129.11, 136.13, 140.43, 142.77. HRMS (ESI^+): calculated for $(C_{24}H_{32}N_2O_3S)^+$ 248.2134 [M^+], found 248.2134.

4.3. Production of cell lines expressing human D_1, D_{2L} and D_3 dopamine receptors

We created a human embryonic kidney cells (HEK293) based stable lines expressing individual subtypes of human dopamine receptors (D_1, D_{2L} and D_3). Shortly, HEK293 cells (American Type Culture Collection, Rockville, MD) were maintained in Dulbecco's Modified Eagle's Medium (DMEM) (PAA Laboratories) supplemented with 10% fetal bovine serum (Gibco®), 100 U/mL penicillin and 100 μg/mL streptomycin (PAA Laboratories). Cells were grown at 37 °C in a humidified incubator with 5% CO_2. The pcDNA3.1+ expression vectors (Invitrogen) containing the desired gene of

human wild type dopamine receptor (*DRD1*, *DRD2L* and *DRD3*) were purchased from the Missouri S&T cDNA Resource Center. For transfection, cells were seeded on 6-well plates, cultured 24 h to reach ~90% confluence and transfected with 4 μg of DNA per well using Lipofectamine™ 2000 (Invitrogen) according to manufacturer's instructions. To obtain stable lines cells were maintained and passed for 2 weeks in the presence of 800 μg/mL geneticin (G418). Four to six G418 resistant colonies per each receptor subtype were selected and after five further passages the clonal cultures were tested for receptor expression by radioligand binding. Henceforth the cells were maintained in the presence of 400 μg/mL of G418. The clonal cell lines with similar receptor densities were further tested for their binding of known dopaminergic ligands and then used in experiments with the test compounds.

4.4. Radioligand binding and competition binding of 3-azabicyclo [3.2.0]heptane derivatives

The binding characteristics of the new cell lines were assessed by radioligand binding and competition binding of known dopaminergic ligands (dopamine and apomorphine). The radioligands [^{3}H]SCH23390 and [^{3}H]raclopride have high affinity for D_1-like and D_2-like dopamine receptors, respectively, which was also evident from our saturation binding experiments (data shown below). All ligand binding experiments were done on membrane suspensions, prepared as follows. The cells were centrifuged at 800 × *g* at room temperature and the pellet stored at −80 °C. The frozen pellets were melted on ice and washed by homogenization with a tissue homogenizer (Coleparmer Labgen 125) for 30 s in ice-cold PBS and centrifugation at 800 × *g* for 5 min at 4 °C. The pellet was re-homogenized in 50 mM Tris–HCl buffer, (pH = 7.4) and centrifuged at 30,000 × *g* for 20 min followed by a second resuspension and homogenization step. The latter homogenization and centrifugation steps were repeated once and the final pellet was homogenized in incubation buffer (IB: 50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.4) typically at a concentration of 1×10^7 cells/mL (corresponding to ~0.5 mg protein/mL quantified using Bio-Rad protein assay Kit (Bio-Rad Laboratories) with BSA as a standard). The membrane preparations were stored at −80 °C until further testing.

Receptor expression and affinity of radioligands was determined as described earlier [25,26] with some modifications. Reactions were carried out in U-bottom 96-well plates in a final volume of 250 μL in IB and incubated at 25 °C for 60–90 min. In all assays 150 μL of membrane suspension was added to wells containing 50 μL of radioligand and 50 μL of competing unlabeled ligand (or buffer) at their five times final concentration. Receptor-positive clones were identified by one-point assay at a saturating concentration of [^{3}H]SCH23390 or [^{3}H]raclopride (Perkin Elmer) with or without an unlabeled dopaminergic antagonist, 1 μM (+)-butaclamol (Sigma–Aldrich). Receptor bound radioactivity ("specific binding") was calculated as a difference between radioactivity bound in the absence ("total binding") and in the presence ("non-specific binding") of an unlabeled antagonist. In saturation binding experiments the concentration of radioligand was varied from 0.2 to 10 nM and "non-specific binding" was determined in the presence of 1 μM (+)-butaclamol. Dissociation constants obtained, 0.5 nM for [^{3}H]SCH23390 binding to D_1 receptor and 0.7 nM for [^{3}H] raclopride binding to both D_{2L} and D_3 receptors, were in good agreement with the data reported earlier for these radioligands and receptors [27,28]. For 8-point competition assay the concentration of radioligand was fixed to near K_d value (~1 nM) and concentration of the test compounds was varied from 0.3 mM to 0.1 nM, the incubation buffer was supplemented with 1 mM DTT. Reactions were initiated by addition of membrane suspension (5×10^4 to 5×10^5 cells/assay for different receptor subtypes).

All the reactions were stopped by filtration through thick GF/B glass fiber filter mats (Whatham) using a FilterMate Harvester (Model D961962, Perkin Elmer). After five washes with ice-cold phosphate buffer (20 mM K-phosphate, 100 mM NaCl, pH 7.4), filter mats were dried in a microwave oven and impregnated with a MeltiLex™ B/HS scintillant (Wallac) using a MeltiLex® Heatsealer (Wallac). Filter-bound radioactivity was counted using a Wallac MicroBeta TriLux 1450 LSC Luminescence Counter (Perkin Elmer).

All pharmacological data were analyzed by means of non-linear least squares regression analysis using the commercial program GRAPHPAD PRISM™ 4.03 (GraphPad Software Inc.). Data were fit to one-site binding curve and inhibition constant values (K_i) calculated according to Cheng–Prusoff equation [29] (in Table 2 represented as means ± SEM from at least two independent experiments carried out in duplicates).

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejmech.2012.07.025.

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Publication III

Ausmees, K.; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M.; Kanger, T.

Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds.

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Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds

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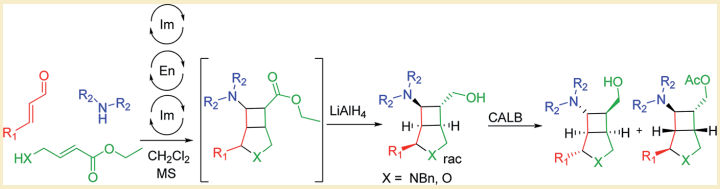
Supporting Information



ABSTRACT: A general three-component triple cascade reaction through an iminium−enamine−iminium sequential activation initiated by a hetero-Michael addition to α,β-unsaturated aldehydes affords [3.2.0]heterobicycles in high diastereoselectivity. The rate and diastereoselectivity of the reaction depended on the (*E*)-4-heterocrotonate and size of the secondary amine. The enantiomers of the major diastereoisomer of oxa- and azabicyclo[3.2.0]heptane derivatives were separated by enzymatic kinetic resolution with immobilized *Candida antarctica* Lipase B (CALB), with *E* values up to 153. The absolute configuration of the nonacylated enantiomer of oxabicyclo[3.2.0]heptane was determined by single crystal X-ray analysis.

INTRODUCTION

Synthetic organic chemistry has reached a crucial point in which a new paradigm has been generated.[1] An increasing interest in multicomponent or cascade reactions reflects that tendency, making these reactions superior over a traditional single-step procedure, where only one or two new chemical bonds are formed.[2−12] In multicomponent cascade or domino reactions, three or more reagents in multiple transformations lead to the formation of complex structures with several new C−C or C−heteroatom bonds in a single operation. This new strategy has several advantages over the classical approach, such as lower cost, decreased time and energy consumption, therefore being environmentally benign.

In the course of our ongoing investigations in the field of aminocatalysis,[13−16] we recently discovered a new multicomponent cascade reaction (Scheme 1).[17] The reaction of α,β-unsaturated aldehyde **1**, *N*-benzyl-(*E*)-4-aminocrotonate **2**, and secondary amine **3** afforded the racemic bicyclic ester with general formula **4**, together with a certain amount of the byproduct, which contains a pyrrolidine ring. The formation of the byproduct was suppressed by using a 2-fold excess of the α,β-unsaturated aldehyde and secondary amine in respect to aminocrotonate in methylene chloride, in the presence of molecular sieves. The obtained ester **4** was reduced in situ, because of its instability, into the corresponding alcohol **5**. The reaction was highly diastereoselective, affording mainly one diastereoisomer of **4** (dr up to 65:1; isolated and characterized by a wide substrate scope as alcohol **5**). Both aromatic and aliphatic unsaturated aldehydes **1** can be used as Michael acceptors, and various cyclic or acyclic secondary amines **3** are tolerated.

The mechanism of the reaction can be rationalized by assuming that the reaction proceeds via a cascade that consists of an aza-Michael addition to an iminium ion derived from α,β-unsaturated aldehyde **1** and secondary amine **3**, followed by a second, intramolecular Michael addition. The last step of the cascade is the formation of a four-membered ring via an ester enolate attack on the newly formed iminium ion. (Scheme 1)[17]

The obtained bicyclic scaffold can be found in several pharmacophores with different biological activities. For example, the similar structures are known to be present in the modulating agents of the dopamine D_3 receptor[18,19] (the treatment of schizophrenia, depression, and Parkinson's disease (belaperidone),[20] in antibacterial agents (ecenofloxacin),[21] and in antitumor drugs (mitindomide)).[22] The strained bicyclo[3.2.0]heptane skeleton is an interesting object for further modifications for synthetic chemists engaged in the synthesis of natural products.[23] Therefore, the scope of the reaction needs to be broadened with other heteroatom substituted crotonates.

Domino reactions involving initiation by a hetero-Michael addition of amines,[24] thiols[25−27] and phenols[28−31] to α,β-unsaturated aldehydes are relatively well documented, but few

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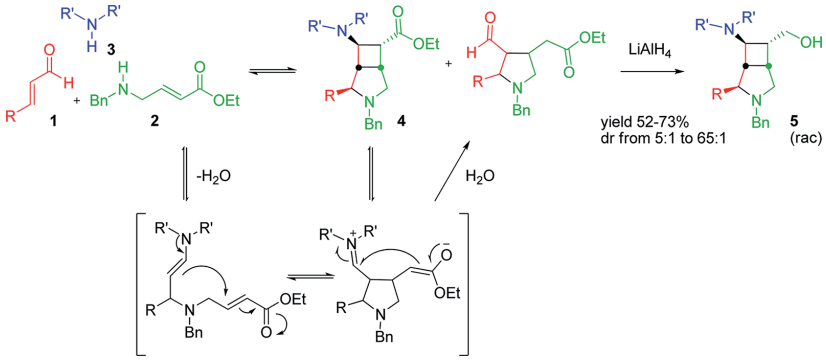
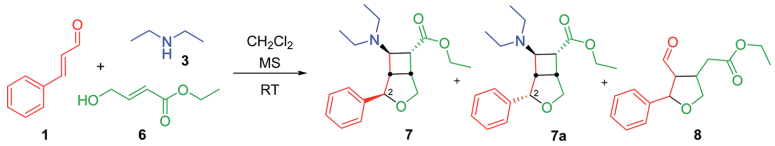
Scheme 1. Reaction between α,β-Unsaturated Aldehyde 1, *N*-Benzyl-(*E*)-4-aminocrotonate 2, and Secondary Amine 3



Scheme 2. Reaction Between α,β-Unsaturated Aldehyde 1, (*E*)-4-Hydroxycrotonate 6, and Secondary Amine 3



examples are available for the application of aliphatic alcohols in oxa-Michael reactions.[32,33] This is probably due to the low nucleophilicity of alcohols, the reversibility of the reaction and the competing acetal formation, making the oxa-Michael reaction, especially intermolecular, challenging.[34,35] At the same time 3-oxabicyclo[3.2.0]heptane derivatives are valuable synthetic intermediates, and they have been used in the synthesis of cyclobutane-fused nucleoside analogues.[36,37] This heterobicyclic skeleton has previously been synthesized via metal-catalyzed [2 + 2] cycloaddition.[38,39]

RESULTS AND DISCUSSION

We envisioned that by using hydroxycrotonate instead of aminocrotonate it might also be possible to synthesize a 3-oxabicyclo[3.2.0]heptane skeleton via the multicomponent cascade reaction. When the reaction between cinnamic aldehyde **1a** (2 equiv), ethyl (*E*)-4-hydroxycrotonate **6** (1 equiv) and diethyl amine (2 equiv) was run under the same optimum conditions as in our previous work (CH_2Cl_2, rt, presence of molecular sieves), an oxabicyclic compound **7** and a tetrahydrofurane derivative **8** were obtained in a 96:4 ratio (Scheme 2, Figure 1). The reaction was moderately diastereoselective, affording only [3.2.0]-oxabicyclo heptane 2-*exo* and 2-*endo* diastereoisomers **7** and **7a** in a 5:1 ratio, respectively. The relative configuration of the product was determined by NMR.[17] The diastereoselectivity and the rate of the reaction could not be increased by changing the solvent or adding basic or acidic additives (see the Supporting Information).

To obtain a mechanistic insight, a ^{1}H NMR study of the multicomponent reaction was conducted and the kinetics of the process was monitored. The determination of the reaction products and limiting starting material (ethyl (*E*)-4-hydroxycrotonate **6**) was straightforward on the basis of their characteristic resonances in one-dimensional ^{1}H spectrum (Figure 2). Neither of the crucial intermediates, an iminium

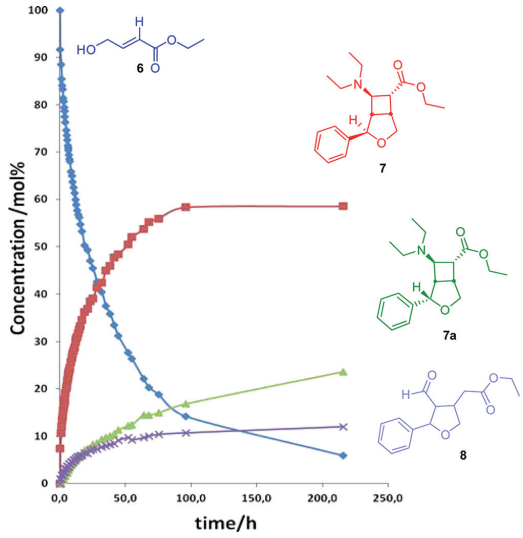


Figure 1. Reaction progress profile for the reaction in Scheme 2, obtained using ^{1}H NMR spectroscopy. Molecular sieves were added, and $CDCl_3$ was used as a reaction medium.

ion or oxa-Michael addition product, were observed. The conversion pathway of the starting material **6** and the formation of 2-*exo*-[3.2.0]oxabicyclo heptane ester **7**, its diastereoisomer **7a**, and aldehyde **8** in the reaction is presented in Figure 1. The formation of a monocycle and bicycle are competing reactions. It was assumed that the reaction would follow a similar pathway as with an aza-nucleophile (Scheme 1). However, it was not clear if the monocyclic structure was in equilibrium with the bicyclic product **7**. Since the diastereoisomeric ratio of 2-*exo*

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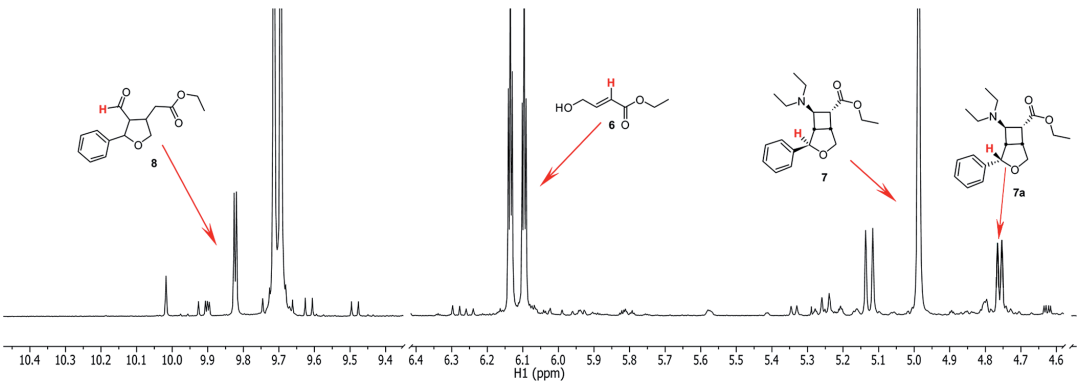
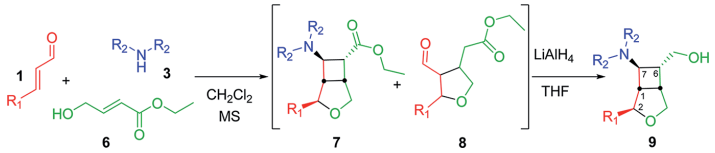


Figure 2. ^{1}H NMR spectrum of the reaction mixture after 25 h.

Table 1. Scope of the Multicomponent Reaction[a]



entry	compound	R_1	amine **3**	time (h)	ratio of **6**/**7**/**8**[b]	dr[c]	isolated yield **9**[d]
1	**9a**	Ph	Et_2NH	48	0/96/4	5:1	76
2	**9b**	Ph	pyrrolidine	72	0/64/36	4:1	43
3	**9c**	Ph	piperidine	48	8/44/48	1:1:4[e]	20 (43)[f]
4	**9d**	Ph	Me_2NH	72	21/79/0	6:1[g]	51
5	**9e**	*p*-MeO-Ph	Et_2NH	48	16/74/10	5:1	37
6	**9f**	*p*-Br-Ph	Et_2NH	48	8/84/8	5:1	55
7	**9g**	*p*-NO_2-Ph	Et_2NH	48	12/82/6	8:1	n.d.
8	**9h**	Me	Et_2NH	96	n.d.[h]	–[i]	51
9	**9i**	diMe	Et_2NH	96	n.d.[h]	–[i]	52

[a] α,β-Unsaturated aldehyde (2 equiv), amine (2 equiv), and hydroxycrotonate (1 equiv) were stirred in CH_2Cl_2 at rt for the appropriate time in the presence of MS. [b] Ratios were determined by ^{1}H NMR from the crude reaction mixture before reduction with $LiAlH_4$. [c] Ratio of (2-*exo*:2-*endo*) diastereoisomers was determined by ^{1}H NMR. [d] Isolated yield of the major diastereoisomer. [e] Ratio of 2-*exo*-6-*endo*-7-*exo*:2-*endo*-6-*endo*-7-*exo*:2-*exo*-6-*exo*-7-*endo* diastereoisomers. [f] Yield stated accordingly for 2-*exo*-6-*endo*-7-*exo* and 2-*exo*-6-*exo*-7-*endo* diastereoisomers. [g] Major diastereoisomer in 2-*exo*-6-*exo*-7-*exo*-configuration. 1 M Me_2NH in THF was used for the reaction. [h] Ratio was not determined because of overlapping of signals in ^{1}H NMR. [i] Only one diastereoisomer was detected.

and 2-*endo* isomers changed over time (from 5:1 at 48 h to 2.5:1 at 215 h to 1.3:1 in 22 days), the cascade was reversible. The reduction of the ester group excluded that equilibrium, so in the following reactions a one-pot procedure was employed.

Next, the scope of the multicomponent reaction was assessed under standard conditions. The summarized results in Table 1 show that the reaction has broad applicability, as various secondary amines **3** and α,β-unsaturated aldehydes **1** can be used. The diastereoisomeric ratio of the obtained bicycles was generally high, and it was determined from the crude mixture before the reduction of the ester by ^{1}H NMR. The predominant diastereoisomer of compound **7** was formed in a 2-*exo*-6-*endo*-7-*exo* configuration as depicted in the heading of Table 1. Exceptions to this general tendency were the compounds **9c** in 2-*exo*-6-*exo*-7-*endo* and **9d** in 2-*exo*-6-*exo*-7-*exo* configuration (Table 1, entries 3 and 4). The sterical hindrance of the secondary amine **3** had a strong influence on the chemoselectivity of the reaction, as pyrrolidine and piperidine (entries 2 and 3) gave a close to 1:1 mixture of the bicyclic product **7** and the tetrahydrofurane derivative **8**. On the other hand, sterically less demanding dimethyl amine gave no monocyclic product and resulted in the formation of a different diastereoisomer of bicycle **7** (entry 4). The reaction proceeded efficiently with different α,β-unsaturated aldehydes, not only with electron-rich aromatic substituents such as *p*-methoxyphenyl, but also with those that are electron-deficient, such as *p*-bromophenyl and *p*-nitrophenyl (entries 5–7). The reactions with aliphatic aldehydes did not proceed to completion, giving quite a lot of monocyclic product, and only one diastereomer of bicyclic product **7** was detected and isolated (entries 8, 9).

In general, the multicomponent cascade reaction of aromatic unsaturated aldehydes with (*E*)-4-hydroxycrotonate was less diastereo- and chemoselective than the corresponding reaction with *N*-benzyl-(*E*)-4-aminocrotonate.[17]

Our attempts to apply asymmetric organocatalytic approaches, such as iminium catalysis with chiral secondary amines (such as diaryl prolinol derivatives) or hydrogen

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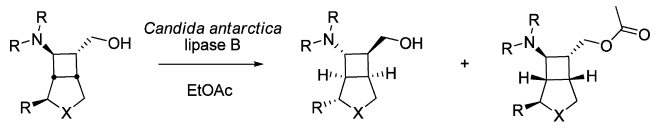
Table 2. Enzymatic Kinetic Resolution of Aza- and Oxa[3.2.0]bicyclic Compounds[a]



rac-9 (X = O, NBn)
rac-10b (X = NTs)

9A
(-)-10b

11
(+)-10b

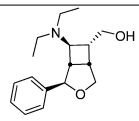
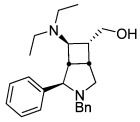
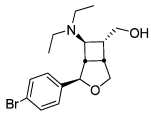
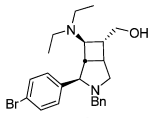
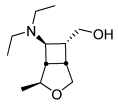
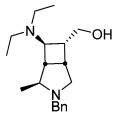
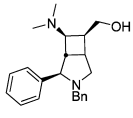
Entry	Compound	time (h)	Alcohol *ee* %	Hydrolyzed ester *ee* %	Conversion %	*E*
1	 rac-**9a**	2.5	86.4	89.8	49.0	52.7
2	 rac-**9j**	5	99.0	90.8	52.2	106
3	 rac-**9f**	2.5	89.7	90.6	49.8	60.5
4	 rac-**9o**	5	95.5	92.5	50.8	97.9
5	 rac-**9h**	2.5	81.6	94.7	46.3	92.1
6	 rac-**9r**	5	83.6	93.8	47.1	83.7
7	 rac-**9m**	23	68.9	66.8	50.8	10.1

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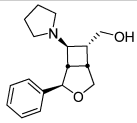
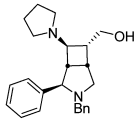
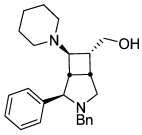
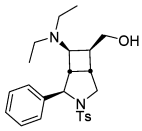
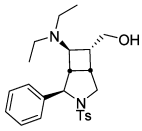
Table 2. continued

Entry	Compound	time (h)	Alcohol *ee* %	Hydrolyzed ester *ee* %	Conversion %	*E*
8	 rac-**9b**	2.5	95.3	80.4	54.2	34.4
9	 rac-**9k**	5	92.2	85.6	51.9	41.8
10	 rac-**9l**	5	95.4	85.6	52.7	48.5
11[b]	 rac-**10a**	72	43.5	62.6	41.0	6.6
12[b]	 rac-**10b**	72	68.5	97.5	41.3	153

[a]For the synthesis of *N*-benzyl azabicyclo[3.2.0]heptane derivatives, see ref 17. [b]K_2CO_3 was used as an additive to remove acid from the reaction media

bonding catalysts (quinidine, cinchonine, (*R*)-TRIP and chiral thiourea derivatives) to the oxa- or aza-Michael cascade reaction in order to generate enantiomeric aza- or oxabicyclo[3.2.0]heptane derivatives were unsuccessful, and racemic compounds were always obtained. As catalytic chemical methods failed to yield enantiopure bicyclic products, we looked into enzymatic kinetic resolution options. Lipases are widely used for the acylation of secondary and primary alcohols.[40,41] We chose immobilized lipase B of *Candida antarctica* (Novozym 435) as the catalyst and ethyl acetate as an acyl donor and reaction medium. A kinetic resolution of enantiomers of certain [3.2.0]heterobicycles **9** and **10** derivatives was run at room temperature (Table 2). The process was monitored by Chiral HPLC, which allows for the direct determination of the enzyme enantioselectivity *E*. The acylated enantiomer **11** and nonacylated enantiomer of **9** were separated by column chromatography, affording both enantiomers needed for biological assays. The enantiomeric purity of the acylated enantiomer was determined after hydrolysis of the ester.

The enzyme enantioselectivity *E* value greatly depended on the structure of the diastereoisomer of the bicyclic substrate (Table 2). It was found that the selectivity was slightly higher for *N*-benzyl bicycles (entries 2, 4, 9) than oxa-bicyclic compounds (entries 1, 3, 8). For the major diastereoisomer of *N*-benzylazabicyclo[3.2.0]heptanes, the kinetic resolution resulted in 90% *ee* for both enantiomers after the first resolution (entries 2, 4). To obtain substrates in high *ee* for biological activity testing, repeated resolutions were needed. The spatial arrangement around the chiral centers adjacent to the hydroxy

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group is the most important factor in stereoselectivity. The kinetic resolution of compounds in 6-*exo* configuration was slower and gave poorer selectivities (entries 7, 11). *N*-Tosylazabicyclo[3.2.0]heptanes **10**[42] did not provide a good fit with the enzyme, and the resolution slowed down drastically from 5 h to 3 days (entries 11, 12).

The absolute configuration of nonacylated enantiomer of **9f** was determined to be in (1*R*,2*S*,5*R*,6*S*,7*R*)-configuration by single crystal X-ray diffraction (see the Supporting Information). It is assumed that all 2-*exo*-6-*endo*-7-*exo* configuration enantiomers of oxabicyclo[3.2.0]heptane derivatives that have been acylated by Novozym 435 possess the same configuration as shown in the heading of Table 2. The absolute configuration of the azabicyclo[3.2.0]heptane derivatives was determined by us previously,[42] and enantiopreference of the enzyme was the same.

■ CONCLUSIONS

In summary, we have shown that a one-step multicomponent hetero-Michael/Michael/Mannich-type reaction is a general reaction that can be used for the synthesis of tetrasubstituted 3-oxabicyclo[3.2.0]heptane derivatives as well as 3-azabicyclo[3.2.0]heptane derivatives. This chemistry provides quick access to important pharmacophores, and could be used for the synthesis of starting materials for other heterocycles with more complicated structures. A method to obtain both enantiomers of the major diastereomer via enzymatic kinetic resolution immobilized lipase B of *Candida antarctica* (Novozym 435) was developed. The absolute configuration of resolved bicyclic compounds was unambiguously assigned by single crystal X-ray diffraction.

■ EXPERIMENTAL SECTION

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra 400 MHz instrument. Chemical shifts are reported in ppm with internal reference to TMS, and *J* values are given in Hertz. Mass spectra were obtained in GC−MS mode (EI, 70 eV). High resolution mass spectra were recorded on Accurate-Mass Q-TOF LC−MS spectrometer recorded by using AJ-ESI ionization. All HPLC analysis were done using Chiralcel AS-H or Lux Amylose-2 columns. Precoated silica gel 60 F_{254} plates were used for TLC.

Reactions sensitive to oxygen or moisture were conducted under Ar atmosphere in flame-dried glassware. Dichloromethane was freshly distilled from P_2O_5 and stored on K_2CO_3 and anhydrous tetrahydrofuran from $LiAlH_4$. Commercial reagents were used as received. Petroleum ether used had bp 40−60 °C.

General Procedure for the Synthesis of Racemic Compound 9. To a solution of the corresponding aldehyde **1** (3.0 mmol) in anhydrous CH_2Cl_2 (10 mL) in the presence of molecular sieves (4 Å), secondary amine **3** (3.0 mmol) and (*E*)-4-hydroxycrotonate **6** (1.5 mmol) were added. The mixture was stirred at room temperature for 20−96 h. The mixture was concentrated in a vacuum, and the crude bicyclic ester **7** was reduced with $LiAlH_4$ (10.8 mmol) in anhydrous THF (20 mL). After 16 h, the reaction mixture was cooled to 0 °C, and the reaction was quenched by the addition of water and an aqueous solution of 4 M aq NaOH. The mixture was dried over K_2CO_3. The crude product was purified by chromatography on silica gel (CH_2Cl_2:MeOH/NH_3 eluent system) affording bicyclic alcohol **9**.

General Procedure for Enzymatic Kinetic Resolution of 9 and 10. Immobilized lipase B of *Candida antarctica* (Novozym 435) (50 mg) was added to a solution of the racemic compound **9** or **10** (50 mg) in EtOAc (1.0 mL). The resulting mixture was stirred occasionally at room temperature and monitored by TLC. Reaction was stopped when about 50% conversion was achieved, typically after 2.5−5 h. Immobilized lipase was filtered off, and the filtrate was concentrated under reduced pressure. This mixture was purified by chromatography on silica gel affording alcohol **9** (A-enantiomer) and ester **11**. As the enantiomeric excess of ester **11** could not be determined by chiral HPLC, it was hydrolyzed to **9** (B-enantiomer), with 4 M NaOH in MeOH by stirring 3 h at room temperature.

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9a. 40.4 mg, yield 76%. Light yellow oil: dr (2-*exo*:2-*endo*) 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 6H), 2.14 (s, 1H), 2.44−2.55 (m, 1H), 2.57−2.69 (m, 4H), 2.78−2.84 (m, 1H), 2.97−3.06 (m, 1H), 3.09 (dd, J = 8.1, 5.0 Hz, 1H), 3.67−3.83 (m, 3H), 4.09 (dd, J = 10.2, 1.4 Hz, 1H), 4.94 (s, 1H), 7.23−7.30 (m, 3H), 7.30−7.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5 (2C), 35.3, 39.6, 41.8 (2C), 47.2, 61.9, 62.4, 66.2, 84.3, 125.9 (2C), 127.4, 128.5 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3085, 2960, 1454, 1062, 765; m/z (EI$^+$) 275 (M$^+$, 0.62%), 188 (43), 129 (100), 98 (47); HRMS (ESI$^+$) calculated for $(C_{17}H_{26}NO_2)^+$ 276.1958 [M + H$^+$], found 276.1960.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 96/4, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 8.6 min, $t_{(-)\text{-B}}$ = 13.1 min. $[\alpha]^{25}_D$ +57.6 (*c* 0.82 in $CHCl_3$, *ee* = 96%), $[\alpha]^{25}_D$ −63.6 (*c* 0.86 in $CHCl_3$, *ee* > 99%).

(7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9a-2-*endo* diastereoisomer. 9.7 mg, yield 18%. Light yellow transparent oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (t, J = 7.1 Hz, 6H), 1.97−2.09 (m, 2H), 2.12−2.28 (m, 2H), 2.44 (tt, J = 9.2, 6.0 Hz, 1H), 2.58 (t, J = 5.5 Hz, 1H), 2.88−2.98 (m, 1H), 3.06−313 (m, 1H), 3.66−3.83 (m, 3H), 4.29 (d, J = 10.2 Hz, 1H), 4.77 (d, J = 5.0 Hz, 1H), 7.17−7.27 (m, 1H), 7.28−7.42 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.9, 35.7, 39.8, 41.0, 45.76, 55.5, 61.5, 68.2, 82.5, 126.3, 127.2, 128.0, 137.8; HRMS (ESI$^+$) calculated for $(C_{17}H_{26}NO_2)^+$ 276.1958 [M + H$^+$], found 276.1954.

7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]-heptane-6-*endo*-carboxylate 7 (9a-2-*exo* diethyl ester). 25 mg, yield 41%. Yellow oil: Column chromatography petroleum ether:EtOAc 10−50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 6H), 1.21 (t, J = 7.1 Hz, 3H), 2.60 (q, J = 7.2 Hz, 4H), 3.02−3.19 (m, 3H), 3.46 (dd, J = 7.0, 5.7 Hz, 1H), 3.74 (dd, J = 10.3, 6.4 Hz, 1H), 3.84 (dd, J = 10.2, 2.0 Hz, 1H), 4.04−4.19 (m, 2H), 4.92 (s, 1H), 7.16−7.22 (m, 4H), 7.22−7.34 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2, 14.4, 36.6, 41.5, 42.6, 47.4, 60.6, 60.9, 67.8, 84.3, 125.8, 127.5, 128.5, 140.6, 172.1; HRMS (ESI$^+$) calculated for $(C_{19}H_{28}NO_3)^+$ 318.2064 [M + H$^+$], found 318.2062.

(2-*exo*-Phenyl-7-*exo*-(pyrrolidin-1-yl)-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9b. 182.7 mg, yield 43%. Yellow oil, dr (2-*exo*:2-*endo*) 4:1. After 24 and 48 h, additional 3 equiv of cinnamaldehyde and pyrrolidine were added: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78−1.86 (m, 4H), 2.42−2.63 (m, 7H), 2.99−3.15 (m, 2H), 3.64−3.78 (m, 3H), 4.09 (d, J = 10.2 Hz, 1H), 4.94 (s, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.29−7.38 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.3 (2C), 36.0, 39.9, 47.1, 51.3 (2C), 61.4, 65.8, 66.3, 84.1, 125.8 (2C), 127.3, 128.5 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3385, 2957, 1012, 729; m/z (EI$^+$) 273 (M$^+$, 0.40%), 186 (35), 127 (100), 96 (36); HRMS (ESI$^+$) calculated for $(C_{17}H_{24}NO_2)^+$ 274.1802 [M + H$^+$], found 274.1802.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 80/20, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 6.8 min, $t_{(-)\text{-B}}$ = 10.8 min. $[\alpha]^{25}_D$ +60° (*c* 0.74 in $CHCl_3$, *ee* = 95.3%), $[\alpha]^{25}_D$ −55° (*c* 0.72 in $CHCl_3$, *ee* = 80.4%).

(2-*exo*-Phenyl-7-*endo*-(piperidin-1-yl)-3-oxabicyclo[3.2.0]-heptan-6-*exo*-yl)methanol 9c 2-*exo*-7-*endo*-6-*exo* diastereomer (major). 190 mg, yield 43%. Yellow amorphous solid, mp 52−58 °C. After 24 h, additional 3 equiv of cinnamaldehyde and pyrrolidine were added: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.52 (m, 2H), 1.55−1.66 (m, 4H), 2.19 (d, J = 7.6 Hz, 1H), 2.23−2.68 (m, 4H), 2.86−2.94 (m, 1H), 2.98 (t, J = 7.0 Hz, 1H), 3.15−3.28 (m, 1H), 3.69 (dd, J = 11.9, 1.5 Hz, 1H), 3.91 (dd, J = 9.5, 2.4 Hz, 1H), 4.00 (dd, J = 9.4, 7.3 Hz, 1H), 4.15 (dd, J = 11.9, 3.0 Hz, 1H), 4.88 (s, 1H), 5.29 (s, 1H), 7.22−7.28 (m, 3H), 7.29−7.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.7, 25.1 (2C)37.8, 40.7, 48.7, 51.6 ((2C, bs), 63.6, 64.4, 71.8, 84.6, 125.3 (2C), 126.7, 127.8 (2C), 140.3; IR (KBr, neat), ν (cm^{-1}) 3373, 2935, 1452, 1036, 732; m/z (EI$^+$) 287 (M$^+$, 0.48%),

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200 (37), 141 (100), 110 (53); HRMS (ESI$^+$) calculated for $(C_{18}H_{26}NO_2)^+$ 288.1958 [M + H$^+$], found 288.1862.

(2-*exo*-Phenyl-7-*exo*-(piperidin-1-yl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol 9c 2-*exo*-7-*exo*-6-*endo* diastreoisomer. 89 mg, yield 20%. Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.53 (m, 2H), 1.57−1.66 (m, 4H), 2.26−2.31 (m, 1H), 2.32−2.41 (m, 4H), 2.46−2.55 (m, 2H), 3.00−3.07 (m, 1H), 3.10 (dd, J = 7.9, 4.9 Hz, 1H), 3.66−3.71 (m, 1H), 3.71−3.75 (m, 2H), 4.09 (dd, J = 10.2, 0.9 Hz, 1H) 4.90 (s, 1H), 7.23−7.26 (m, 2H), 7.30−7.36 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.3, 25.5 (2C), 35.4, 39.0, 46.6, 51.3 (2C), 61.8, 66.2, 67.0, 84.4. 125.9 (2C), 127.3, 128.5 (2C), 140.8; HRMS (ESI$^+$) calculated for $(C_{18}H_{26}NO_2)^+$ 288.1958 [M + H$^+$], found 288.1857.

(7-*exo*-(Dimethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]heptan-6-*exo*-yl)methanol 9d. 96.5 mg, yield 51%. Light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15−2.20 (m, 1H), 2.24 (s, 6H), 2.85−2.94 (m, 2H), 3.12−3.23 (m, 1H), 3.70 (dd, J = 11.9, 1.8 Hz, 1H), 3.91 (dd, J = 9.5, 2.4 Hz, 1H), 3.99 (dd, J = 9.4, 7.2 Hz, 1H), 4.17 (dd, J = 11.9, 3.1 Hz, 1H), 4.91 (s, 1H), 5.14 (s, 1H), 7.22−7.26 (m, 1H), 7.26−7.29 (m, 2H), 7.29−7.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.9, 41.5, 43.2 (2C), 49.9, 64.1, 66.7, 72.4, 85.2, 125.9 (2C), 127.4, 128.4 (2C), 140.9; IR (KBr, neat), ν (cm^{-1}) 3181, 2905, 1497, 1057, 729; m/z (EI$^+$) 273 (M$^+$+H, 0.11%), 160 (57), 101 (100); HRMS (ESI$^+$) calculated for $(C_{15}H_{22}NO_2)^+$ 248.1645 [M$^+$], found 248.1646.

(7-*exo*-(Diethylamino)-2-*exo*-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol 9e. 174 mg, yield 37%. Light yellow solid: mp 62−65 °C; dr (2-*exo*:2-*endo*) 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 6H), 2.04 (s, 1H), 2.44−2.55 (m, 1H), 2.56−2.68 (m, 4H), 2.79 (dd, J = 6.8, 4.5 Hz, 1H), 2.97−3.10 (m, 2H), 3.66 (dd, J = 10.2, 6.1 Hz, 1H), 3.80 (s, 3H) 3.71−3.79 (m, 2H), 4.05 (d, J = 10.0 Hz, 1H), 4.89 (s, 1H), 6.83−6.91 (m, 2H), 7.14−7.23 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.4 (2C), 35.3, 39.6, 41.8 (2C), 46.8, 55.3, 61.9, 62.3, 65.8, 83.9, 113.8 (2C), 127.4, 132.9 (2C), 158.9; IR (KBr, neat), ν (cm^{-1}) 2975, 2859, 1611, 1513, 1251, 1184, 1031, 825; m/z (EI$^+$) 273 (M$^+$+H, 1%), 218 (52), 129 (100), 98 (39); HRMS (ESI$^+$) calculated for $(C_{18}H_{28}NO_3)^+$ 306. 2064 [M + H$^+$], found 306.2066.

(2-*exo*-(4-Bromophenyl)-7-*exo*-(diethylamino)-3-oxabicyclo-[3.2.0]heptan-6-*endo*-yl)methanol 9f. 117.3 mg, yield 55%. Colorless sticky oil (rac). (+)-A-enantiomer was crystallized from EtOAc, resulting in white crystals: mp 94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 6H), 2.02 (bs, 1H), 2.44−2.54 (m, 1H), 2.55−2.69 (m, 4H), 2.80 (dd, J = 6.9, 4.5 Hz, 1H), 2.94−3.06 (m, 2H), 3.67 (dd, J = 10.2, 6.2 Hz, 1H), 3.70−3.82 (m, 2H), 4.05−4.12 (m, 1H), 4.88 (s, 1H), 7.12−7.17 (m, 2H), 7.40−7.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.5 (2C), 35.2, 39.4, 41.9 (2C), 47.2, 61.9, 62.3, 66.4, 83.6, 121.2, 127.6 (2C), 131.6 (2C), 139.9; IR (KBr, neat), ν (cm^{-1}) 3145, 2975, 1458, 1062, 1010; m/z (EI$^+$) 355 (M$^+$, 0.05%), 268 (19), 266 (19), 129 (100), 98 (53); HRMS (ESI$^+$) calculated for $(C_{17}H_{25}BrNO_2)^+$ 354.1063 [M + H$^+$], found 354.1062.

HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 90/10, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 9.4 min, $t_{(-)\text{-B}}$ = 13.9 min. $[\alpha]^{25}_D$ +66° (c 0.57 in $CHCl_3$, ee = 89.7%), $[\alpha]^{25}_D$ −59° (c 0.84 in $CHCl_3$, ee = 90.6%).

(7-*exo*-(Diethylamino)-2-*exo*-methyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9h. 166 mg, yield 51%. Light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 6H), 1.05 (d, J = 6.6 Hz, 3H), 2.31 (bs, 1H) 2.41 (ddd, J = 12.4, 7.9, 5.1 Hz, 1H), 2.47 (dd, J = 8.0, 5.1 Hz, 1H), 2.50−2.58 (m, 4H), 2.58−2.65 (m, 1H), 2.92−3.03 (m, 1H), 3.61−3.76 (m, 3H), 4.00 (dd, J = 10.2, 1.0 Hz, 1H), 4.02−4.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.4 (2C), 18.6, 34.4, 39.1, 41.8 (2C), 47.7, 61.8, 62.0, 65.1, 79.4; m/z (EI$^+$) 213 (M$^+$, 0.72%), 129 (100), 112 (55), 98 (59); IR (KBr, neat), ν (cm^{-1}) 3143, 2967, 1454, 1112, 1051; HRMS (ESI$^+$) calculated for $(C_{12}H_{24}NO_2)^+$ 214.1802 [M + H$^+$], found 214.1801.

HPLC: (Chiracel Lux Amylose-2 column, hexanes/2-propanol/ethanol = 94/5/1, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 230 nm) $t_{(+)\text{-A}}$ = 10.5 min, $t_{(-)\text{-B}}$ = 11.6 min. $[\alpha]^{25}_D$ +19° (c 0.71 in $CHCl_3$, ee = 81.6%), $[\alpha]^{25}_D$ −19° (c 0.19 in $CHCl_3$, ee = 94.7%).

(7-*exo*-(Diethylamino)-2,2-dimethyl-3-oxabicyclo[3.2.0]-heptan-6-*endo*-yl)methanol 9i. 181 mg, yield 52%. Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 6H), 1.09 (s, 3H), 1.30 (s, 3H), 2.34−2.45 (m, 2H), 2.47−2.62 (m, 5H), 2.78 (t, J = 5.9 Hz, 1H), 2.94−3.05 (m, 1H), 3.60−3.78 (m, 3H), 3.97 (d, J = 10.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.6 (2C), 22.2, 24.8, 35.4, 38.7, 41.6 (2C), 50.0, 57.6, 61.8, 64.8, 81.0; m/z (EI$^+$) 227 (M$^+$, 0.31%) 140 (67), 129 (100), 112 (24), 98 (54); IR (KBr, neat), ν (cm^{-1}) 3245, 2969, 1378, 1183, 1014; HRMS (ESI$^+$) calculated for $(C_{13}H_{26}NO_2)^+$ 228.1958 [M + H$^+$], found 228.1959.

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-phenyl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl)methanol 9j. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.05% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 11.3 min, $t_{(-)\text{-B}}$ = 16.6 min. $[\alpha]^{25}_D$ +10 (c 0.82 in CH_2Cl_2, ee = 99%), $[\alpha]^{25}_D$ −10 (c 0.47 in CH_2Cl_2, ee = 95%).

(3-Benzyl-2-*exo*-phenyl-7-*exo*-pyrrolidin-1-yl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl) methanol 9k. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 18.3 min, $t_{(-)\text{-B}}$ = 24.8 min. $[\alpha]^{25}_D$ +10 (c 1.22 in CH_2Cl_2, ee = 96%), $[\alpha]^{25}_D$ −11 (c 1.46 in CH_2Cl_2, ee = 99%).

(3-Benzyl-2-*exo*-phenyl-7-*exo*-piperidin-1-yl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl) methanol 9l. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 97/3, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 10.2 min, $t_{(-)\text{-B}}$ = 14.8 min. $[\alpha]^{25}_D$ +19 (c 0.37 in CH_2Cl_2, ee = 95%), $[\alpha]^{25}_D$ −20 (c 0.37 in CH_2Cl_2, ee = 99%).

(3-Benzyl-7-*exo*-dimethylamino-2-*exo*-phenyl-3-azabicyclo-[3.2.0]hept-6-*exo*-yl)methanol 9m. HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 98/2, 0.05% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(A)}$ = 17.8 min, $t_{(B)}$ = 13.5 min.

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-*p*-bromophenyl-3-azabicyclo[3.2.0]hept-6-*endo*-yl) methanol 9o. HPLC: (Chiralcel AS-H column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 14.5 min, $t_{(+)\text{-B}}$ = 18.9 min. $[\alpha]^{25}_D$ −2.4 (c 0.90 in CH_2Cl_2, ee = 96%), $[\alpha]^{25}_D$ +4.8 (c 2.94 in CH_2Cl_2, ee = 99%).

(3-Benzyl-7-*exo*-diethylamino-2-*exo*-methyl-3-azabicyclo-[3.2.0]hept-6-*endo*-yl)methanol 9r. HPLC: (Chiralcel Lux Amylose-2 column, hexanes/2-propanol = 98/2, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(+)\text{-A}}$ = 22.2 min, $t_{(-)\text{-B}}$ = 20.9 min. $[\alpha]^{25}_D$ +31 (c 0.16 in CH_2Cl_2, ee = 99%), $[\alpha]^{25}_D$ −28 (c 0.61 in CH_2Cl_2, ee = 94%).

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo-[3.2.0]heptan-6-*exo*-yl)methanol 10a.[42] 34 mg, yield 20.5%. Light yellow sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 6H), 2.12 (d, J = 6.1 Hz, 1H), 2.34 (s, 3H), 2.40−2.59 (m, 4H), 2.87−2.95 (m, 1H), 2.96−3.03 (m, 1H), 3.08 (t, J = 7.0 Hz, 1H), 3.61−3.72 (m, 3H), 4.03 (dd, J = 12.0, 3.1 Hz, 1H), 4.85 (s, 1H), 6.99−7.06 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.16−7.22 (m, 3H), 7.38−7.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.0, 21.4, 37.2, 42.5, 43.0, 51.4, 53.7, 61.3, 64.0, 69.6, 126.4 (2C), 127.0 (2C), 127.5, 128.5 (2C), 129.2 (2C), 136.4, 140.6, 142.9; HRMS (ESI$^+$) calculated for $(C_{24}H_{33}N_2O_3S)^+$ 249.2206 [M + H$^+$], found 249.2203.

HPLC: (Chiralcel AS-H column, hexanes/ethanol = 92/8, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 20.6 min, $t_{(+)\text{-B}}$ = 14.4 min. $[\alpha]^{25}_D$ −52 (c 0.66 in CH_2Cl_2, ee = 88%), $[\alpha]^{25}_D$ +59 (c 0.51 in CH_2Cl_2, ee = 93%).

(7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo-[3.2.0]heptan-6-*endo*-yl)methanol 10b. 37 mg, yield 22%. White solid: mp 115−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 6H), 2.32 (s, 3H), 2.48−2.58 (m, 5H), 2.63−2.68 (m, 1H), 2.68−2.73 (m, 1H), 3.06−3.16 (m, 1H), 3.36 (dd, J = 11.3, 8.3 Hz, 1H), 3.62−3.75 (m, 2H), 3.87 (dd, J = 11.3, 1.9 Hz, 1H), 4.83 (s, 1H), 6.98−7.08 (m, 4H), 7.14−7.23 (m, 3H), 7.32−7.36 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.2 (2C), 21.4, 34.5, 40.0, 41.7 (2C), 47.2, 49.3, 61.6, 62.5, 69.0, 126.7 (2C), 127.0 (2C), 127.5, 128.5 (2C), 129.1 (2C), 136.1, 140.4, 142.8; IR (KBr, neat), ν (cm^{-1}) 2968, 2972, 1550, 1346, 1161; HRMS (ESI$^+$) calculated for $(C_{24}H_{33}N_2O_3S)^+$ 249.2206 [M + H$^+$], found 249.2206.

HPLC: (Chiralcel AS-H column, hexanes/ethanol = 92/8, 0.1% Et_2NH in hexane, flow rate = 1.0 mL/min, λ = 254 nm) $t_{(-)\text{-A}}$ = 19.5 min, $t_{(+)\text{-B}}$ = 10.5 min. $[\alpha]^{25}_{D}$ −27 (*c* 0.29 in CH_2Cl_2, *ee* = 96%), $[\alpha]^{25}_{D}$ +26 (*c* 0.24 in CH_2Cl_2, *ee* = 98%).

■ ASSOCIATED CONTENT

Supporting Information

Chiral-phase HPLC chromatograms and crystallographic data (CIF files), NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Abstract

Bicyclo[3.2.0]heptane derivatives are an interesting group of compounds with various applications. Their skeletons occur in many natural products, which for example act as pheromones or antioxidants in plants. Several therapeutics, containing the bicyclo[3.2.0]heptane core, are also in development as antibacterials and antivirals. Azabicyclo[3.2.0]heptanes on their own are known to have dopamine receptor affinity and are developed as new antipsychotic agents.

Currently, the functionalized bicyclo[3.2.0]heptane skeleton construction requires several steps and lengthy synthesis. In recent years, a lot of attention has been paid to the efficiency and step economy of organic synthesis. One of the proposed tools for improvement involves one-pot cascade and multicomponent reactions; the rational design of MCRs and cascade reactions is still difficult and requires a deep knowledge of known reactions.

Our group has discovered a new MCR for the synthesis of heteroatom (N, O, S) containing or fully carbon skeleton bicyclo[3.2.0]heptanes. Optimization of the MCR conditions resulted in chemoselective synthesis of bicyclo[3.2.0]heptanes **91-98** over the organocatalyzed five-membered rings. The MCR tolerated various secondary amines and substituted α,β-unsaturated aldehydes. Which abled us to synthesize a library of 3-aza- (**91a-k**, yield 30-73%) and 3-oxabicyclo[3.2.0]heptanes (**93a-i**, yield 20-76%). It was also shown that the construction of 3-thia- and carbabicyclo[3.2.0]heptanes was possible, although, optimization of reaction conditions is still necessary, due to low isolated yield (up to 30%).

The MCR was highly diastereoselective and in most cases only two diastereomers of the possible eight realized (dr for 3-aza- and 3-oxabicyclo[3.2.0]heptanes were 5:1-65:1 and 4:1-8:1, respectively). In case of bicyclo[3.2.0]heptane-3-one **97** only single diastereomer was detected and isolated.

Relative configuration of 3-aza- and 3-oxabicyclo[3.2.0]heptane was determined by the analysis of ^{1}H-^{1}H coupling constants in ^{1}H NMR. The major diastereomer in most cases was in 2-*exo*-6-*endo*-7-*exo* configuration and the minor diastereomer in 2-*endo*-6-*endo*-7-*exo* configuration. Absolute configuration was assigned by single-crystal X-ray diffraction analysis.

Catalytic enantioselective synthesis of bicyclo[3.2.0]heptanes was unsuccessful, however enantiomerically pure products were obtained *via* enzymatic kinetic resolution by lipase B of *Candida antarctica*. Selectivities (*E*) ranged from 41-106 for 3-azabicyclo[3.2.0]heptanes and 34-92 for 3-oxabicyclo[3.2.0]heptanes. The enzyme preferred the 3-aza- and 3-oxabicyclo[3.2.0]heptanes with 6-*endo* configuration

The enantiomerically pure 3-azabicyclo[3.2.0]heptane derivatives were successfully tested as dopaminergic ligands.

Kokkuvõte

Bitsüklo[3.2.0]heptaani derivaadid on huvitav ja laialdast rakendust leidnud ühendite grupp. Taolist bitsüklilist skeletti esineb mitmetes looduslikes ühendites (näiteks feromoonid ja antioksüdandid) ning arenduses olevate ravimikandidaatide struktuurides (antibakteriaalsed ja antiviraalsed). On teada, et lämmastikku sisaldavad bitsüklo[3.2.0]heptaani derivaadid omavad afiinsust dopamiini retseptori suhtes ning nendest loodetakse arendada uusi antipsühhootilisi ravimeid.

Bitsüklo[3.2.0]heptaanide süntees on teadlastele huvi pakkunud pikema aja vältel, kuid väljatöötatud sünteesiteed on siiani mitmeetapilised. Viimasel kümnendil on toimunud orgaanilises sünteesis mõtteviisi muutus ning üha olulisem on protsesside efektiivsus ja aatomefektiivsus eesmärgiga säästa raha, aega ja loodust. Üheks protsesside efektiivsuse tõstmise võimaluseks on multikomponentsete kaskaadreaktsioonide kasutamine, milles kolm või enam lähteainet reageerivad üksteise järel ning saadakse üks produkt. Taoliste reaktsioonide disain on endiselt väga keeruline ning vajab põhjalikku reaktsioonimehhanismide tundmist.

Käesolevas töös on välja töötatud uus multikomponentne kaskaadreaktsioon bitsüklo[3.2.0]heptaanide, mis sisaldavad heteroaatomit (N, O, S) või omavad täielikult süsinikskeletti, sünteesiks. Kolmekomponentses reaktsioonis reageerivad omavahel sekundaarne amiin **110**, α,β-küllastumata aldehüüd **87** ning erineva nukleofiilse funktsionaalse rühmaga asendatud α,β-küllastumata ester (**88**, **100**-**102**, **107**, **109**). Peale reaktsioonitingimuste põhjalikku optimeerimist õnnestus kemoselektiivselt sünteesida bitsüklo[3.2.0]heptaanid **91**-**98** ning vältida organokatalüütilise reaktsiooni tulemusena tekkivat monotsüklilist produkti. Näidati, et multikomponentne kaskaadreaktsioon on üldine, lähteaineteks sobisid mitmed sekundaarsed amiinid ja asendatud α,β-küllastumata aldehüüdid. Antud töös sünteesiti mitmed erinevad 3-asa- ja 3-oksabitsüklo[3.2.0]heptaanid (vastavalt **91a-k**, saagisega kuni 73% ja **93a-i**, saagisega kuni 76%). Lisaks näidati, et on võimalik sünteesida ka väävliaatomit sisaldavat ja ainult süsinikskeletiga bitsüklo[3.2.0]heptaane (saagisega kuni 30%).

Bitsüklo[3.2.0]heptaanide sünteesiks kasutatud kolmekomponente kaskaadreaktsioon oli enamasti kõrge diastereoselektiivsusega, tekkis ainult kaks diastereomeeri kaheksast võimalikust. 3-asa- ja 3-oksabitsüklo[3.2.0]heptaanide diastereomeerne suhe oli vastavalt kuni 65:1 ja kuni 8:1. Väävliaatomit sisaldavate bitsükloheptaanide moodustumisel diastereoselektiivsus puudus. Täielikult süsinikskeletiga bitsüklo[3.2.0]heptaan-3-ooni **97** sünteesis detekteeriti aga ainult üks diastereomeer.

3-asa- ja 3-oksabitsüklo[3.2.0]heptaanide suhteline konfiguratsioon määrati ^{1}H-^{1}H sidestuskonstantide kaudu, analüüsides ^{1}H NMR spektreid. Leiti, et eraldatud põhidiastereomeer oli 2-*exo*-6-*endo*-7-*exo* konfiguratsioonis ning teine

minoorne diastereomeer 2-*endo*-6-*endo*-7-*exo* konfiguratsioonis. Ühendite **92a** ja **93a** absoluutne konfiguratsioon määrati, kasutades monokristall-röntgendifraktsiooni meetodit.

Bitsüklo[3.2.0]heptaanide enantioselektiivne süntees kiraalsete katalüsaatorite mõjul ebaõnnestus, kuid enantiomeerselt puhtad ühendid saadi, kasutades ensümaatilist kineetilist lahutamist *Candida antarctica* lipaas B-ga. Ensüümi selektiivsus (*E*) oli 41-106 3-asabitsüklo[3.2.0]heptaanide ja 34-92 3-oksabitsüklo[3.2.0]heptaanide korral. 3-asa- ja 3-oksabitsüklo-[3.2.0]heptaanide puhul eelistas ensüüm 6-*endo* konfiguratsioonis diastereomeeri.

Lisaks uuriti enantiomeerselt puhaste 3-asabitsüklo[3.2.0]heptaanide afiinsust dopamiini retseptorite suhtes.

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"*You must unlearn, what you have learned.*" - Yoda

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8. Original publications

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