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Synthesis of azabicyclo[n.1.0]alkane-derived bifunctional building blocks *via* the Corey–Chaykovsky cyclopropanation

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ABSTRACT

An efficient approach towards the synthesis of monoprotected azabicyclo[5.1.0]octane-derived conformationally restricted γ-amino acids and diamines is reported. Optimization of the conditions for the key Corey–Chaykovsky reaction allowed the construction of two isomeric methanoazepane frameworks on a multigram scale in 55–65% yield. Additionally, the developed approach was used in the three-step synthesis of 3,4-methano-β-proline and its diamine derivatives.

Extension of the natural amino acid repertoire by newly designed synthetic analogues has made a significant contribution to both small molecule drugs and peptide therapeutics development.[1–7] The success of tailor-made unnatural amino acids in medicinal chemistry can be partially attributed to their ability to modulate physical parameters, improve stability and provide structural pre-organization of the designed ligands.[8,9] This is often addressed by the introduction of conformational restriction to the substrate backbone, thus enhancing its binding affinity to the target biomolecule.[10] This effect can be achieved by the cyclization of initially linear fragments, construction of bridged, spirocyclic or fused bi- and polycyclic frameworks, and increasing the substituent steric bulk.

Proline is the most conformationally restricted among the 20 standard proteinogenic amino acids. Along with its closest homologue, pipecolic acid, and their structural isomers bearing the endocyclic amine functionality in the β- and γ-positions to the carboxylic group, proline has attracted the attention of organic chemists as the starting template for further structural modifications. One of the most advantageous and atom-economic tactics for such optimization is introduction of a methylene unit as a part of a fused cyclopropane ring.[11] This approach was crucial to achieve improved *in vivo* stability of the anti-diabetic drug Saxagliptin,[12,13] as well as to enhance binding of the pharmacophoric groups in the case of the triple reuptake inhibitor GSK1360707F.[14]

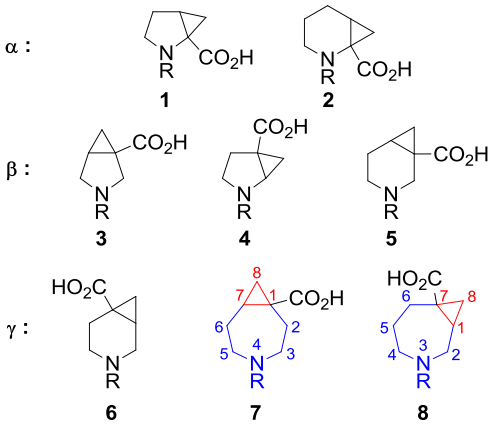

Figure 1. Amino acids bearing azabicyclo[n.1.0]alkane moieties and their derivatives known in the literature (only the parent structures are shown)

Synthetic approaches towards tailor-made conformationally rigid amino acids have been comprehensively surveyed in several reviews.[15–19] In particular, a number of amino acids or their derivatives bearing fused cyclopropane moieties (compounds **1**–**6**) were reported in the literature (Fig. 1).

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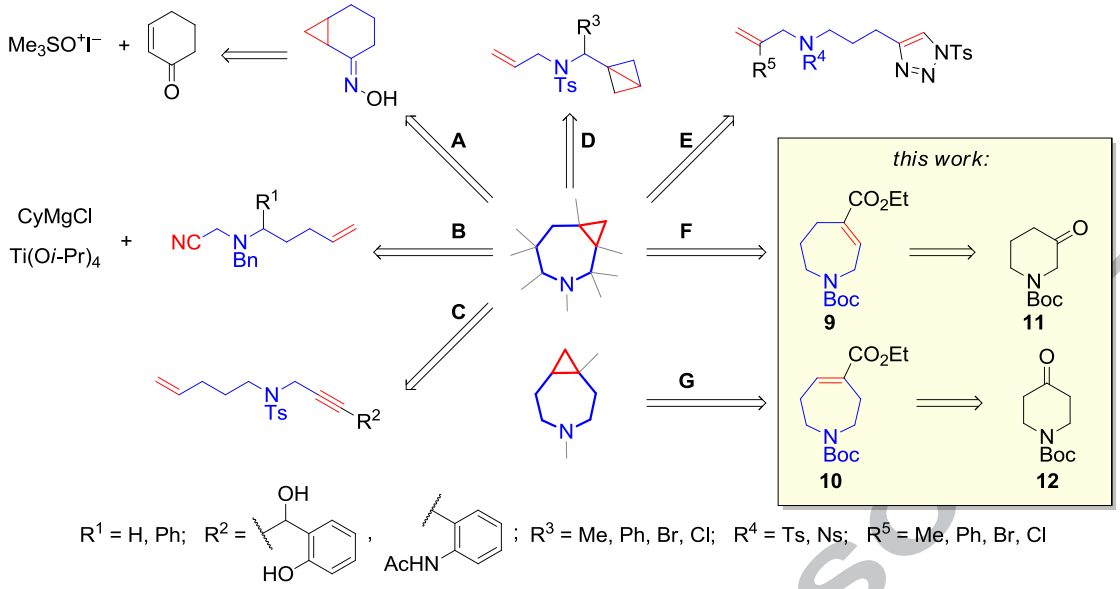


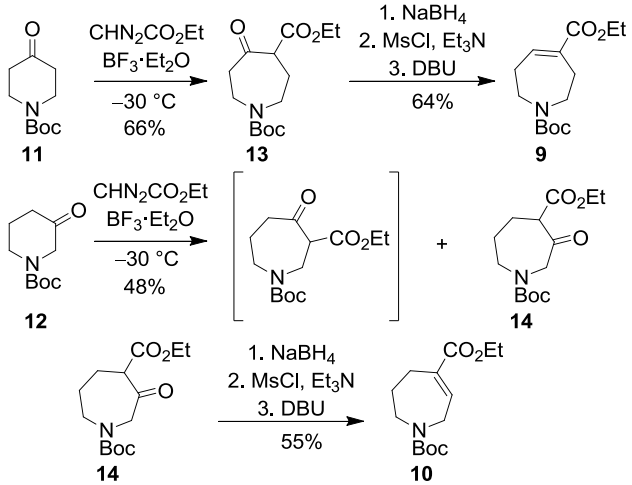
Scheme 1. Known approaches towards azabicyclo[5.1.0]octane core synthesis

Most efforts have been put into the synthesis of α- and β-amino acids of this type;[20–29] preparation of their γ counterparts is studied to a lesser extent.[30–32] Meanwhile, the synthetic analogues of γ-aminobutyric acid (GABA), an important neurotransmitter in the mammalian central nervous system, remains of great interest for the treatment of neurological disorders.[33,34] Being inspired by previous successful syntheses of the amino acids shown in Figure 1, we aimed to develop an approach towards novel γ-amino acids based on a homologous methanoazepane ring system. Specifically, *N*-protected 4-azabicyclo[5.1.0]octane-1-carboxylic (**7**) and 3-azabicyclo[5.1.0]octane-7-carboxylic (**8**) acids derived from the 3-azabicyclo[5.1.0]octane scaffold were chosen as the synthetic targets.

Several approaches to the synthesis of 3-azabicyclo[5.1.0]-octanes with the free C-8 position are described in the literature. Apart from the Beckmann rearrangement of bicyclo[4.1.0]heptan-2-one derived oxime[35] (Scheme 1, **A**), most of these methods are based on intramolecular transition metal-catalyzed cyclizations, including the Kulinkovich–Szymoniak reaction (**B**),[36] Pd- and Rh-catalyzed 5-*exo*-*trig* cyclopropanation of 1,8-enynes (**C**),[37,38] and Rh-catalyzed recyclization of *N*-allylated bicyclo[1.1.0]butylalkylamine (**D**)[39] or (triazolylalkyl)amine (**E**)[40] derivatives. Whereas the aforementioned methods showed good performance for 3-azabicyclo[3.1.0]hexane and 3-azabicyclo[4.1.0]heptane derivatives, they were less effective for the construction of the azabicyclo[5.1.0]octane core. To the best of our knowledge, synthesis of the isomeric 4-azabicyclo[5.1.0]octanes has not been reported to date.

In this work, we envisaged the Corey-Chaykovsky cyclopropanation of tetrahydro-1*H*-azepines **9** and **10** as the key step for the formation of azabicyclo[5.1.0]octane bicyclic frameworks (Scheme 1, **F** and **G**). In contrast to methods **B**–**E**, this approach does not include intramolecular cyclization of linear substrates, which is usually less favorable for larger than six-membered rings. Instead, construction of the seven-membered ring is achieved *via* the known reaction of commercially available *N*-Boc protected piperidinones **11** and **12** with ethyl diazoacetate (Scheme 2).[41,42] This method allowed for the preparation of β-ketoester **13** as a single product in 68% yield, while **14** was obtained in 48% yield after chromatographic separation of the regioisomeric mixture. The key α,β–unsaturated esters **9** and **10** were obtained *via* a three-step reaction sequence including reduction of ketones **13** and **14** with $NaBH_4$, alcohol mesylation, and elimination (64% and 55% yield, respectively).[43]

Although the Corey–Chaykovsky cyclopropanation is used extensively in organic synthesis, this step required tedious optimization of the reaction conditions when applied to tetrahydro-1*H*-azepines **9** and **10**. Synthesis of the bicyclic compound **15** was carried out with an excess of the ylide generated by deprotonation of trimethylsulfoxonium iodide. Optimization of the cyclopropanation step included variation of the base and the solvent, as well as reaction temperature and time (Table 1). As a result, a procedure applying moderate heating (50 °C) of the substrate with the trimethylsulfoxonium ylide generated from $Me_3SO^+I^-$ using NaH in DMSO for 18 h provided the highest yield (55%).[43] When the reaction was performed at increased temperature (70 °C), the crude product contained neither the target compound **15** nor the starting material **9** according to ^1H NMR, indicating their instability at elevated temperatures. In the case of the *t*-BuOK – DMSO system, formation of product **15** was also observed, but its yield was unsatisfactory. Finally, replacing DMSO as the solvent with DMF was not effective.

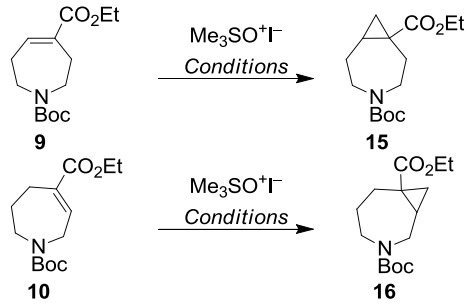


Scheme 2. Synthesis of tetrahydro-1*H*-azepines **9** and **10**.

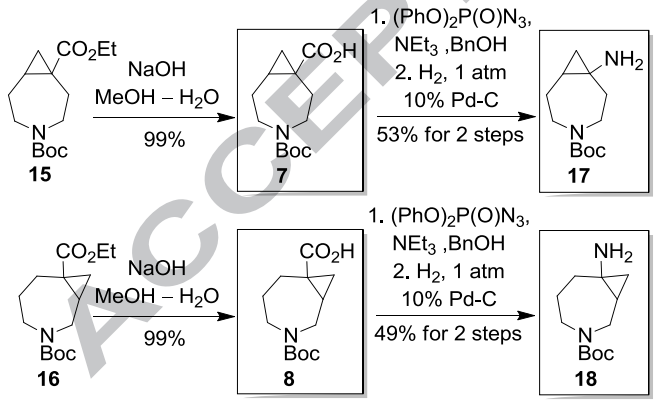
In the case of substrate **16**, variation of the reaction conditions followed similar trends (although alkene **10** was somewhat more stable compared to **9** at elevated temperatures); again, the highest yield of the product (65%) was obtained using NaH in DMSO at 50 °C for 18 h. In addition, the utility of the trimethylsulfonium iodide – NaH system as a source of the ylide was studied; this modification of the reagent was not fruitful.

Alkaline hydrolysis of bicyclic esters **15** and **16** led to the target amino acids **7** and **8** in 99% yield (Scheme 3). Subsequent Curtius rearrangement of **7** and **8** using benzyl alcohol as the isocyanate trapping reagent, followed by hydrogenolysis, resulted in the formation of monoprotected diamines **17** and **18**, respectively (53% and 49% yield for two steps, respectively). It should be noted that the synthesis of building blocks **7**, **8**, **17** and **18** was performed on a multigram scale (8–31 g).

Table 1. Corey – Chaykovsky cyclopropanation of **15** and **16**.



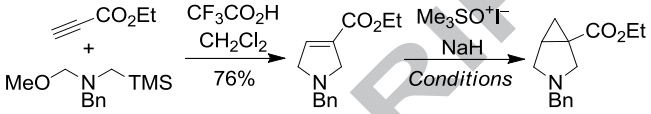
Entry	Base	Solvent	Temp.	Time (h)	Yield **15** (%)	Yield **16** (%)
1	NaH	DMSO	rt	3	15	0
2	NaH	DMSO	70 °C	3	0	15
3	NaH	DMSO	50 °C	3	40	40
4	NaH	DMSO	rt	18	15	0
5	NaH	DMSO	70 °C	18	0	50
6	NaH	DMSO	50 °C	18	55	65
7	NaH	DMF	rt	3	0	0
8	NaH	DMF	rt	18	0	0
9	*t*-BuOK	DMSO	rt	3	20	15
10	*t*-BuOK	DMSO	rt	48	30	25



Scheme 3. Synthesis of amino acids **7** and **8** and diamines **17** and **18**.

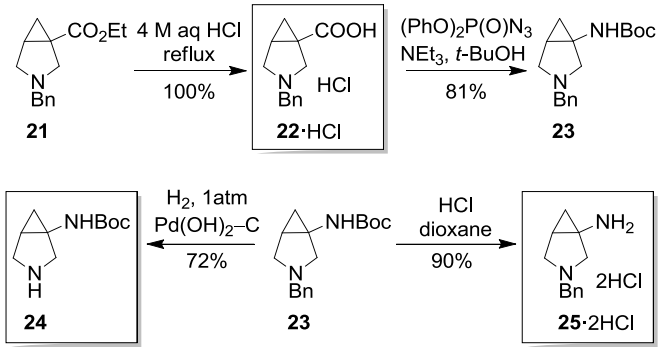
Being inspired by successful application of the Corey–Chaykovsky cyclopropanation for the synthesis of azabicyclo[5.1.0]octane derivatives, we anticipated its potential utility for the preparation of other homologous bicyclic systems. In particular, we have implemented this method for construction of the 3-azabicyclo[3.1.0]hexane system in two steps starting from readily available *N*-(methoxymethyl)-*N*-(trimethylsilyl)-benzylamine (**19**) and ethyl prop-2-ynoate. The synthetic scheme commenced with the known [3+2] cycloaddition reaction of these starting materials, followed by the Corey–Chaykovsky cyclopropanation. In this case, additional optimization of the latter step was required since the conditions described above for **15** and **16** did not led to the target product **21** (Table 2). It was found that increasing the reaction temperature or time, as well as variation of the solvent were not efficient. In this case, the reagent ratio appeared to be critical: upon decreasing the amount of NaH and $Me_3SO^+I^-$ to 1.1 and 1.0 equivalents, respectively, and the reaction time to 1 h, the target product **21** could be obtained in 29% yield. We believe that these results can be explained by decomposition of the starting material **20** and the product **21** under the basic reaction conditions.

Table 2. Corey – Chaykovsky cyclopropanation of **20**.



Entry	NaH (eq)	$Me_3SO^+I^-$ (eq)	Solvent	Temp. (°C)	Time (h)	Yield **21** (%)
1	2.2	1.1	DMSO	80	3	0
2	2.2	1.1	DMSO	25	14	0
3	2.2	1.1	THF	25	14	0
4	1.1	1.0	DMSO	25	3	10
5	1.1	1.0	DMSO	25	1	29

The acidic hydrolysis of **21** quantitatively provided the monoprotected amino acid **22** as the hydrochloride salt (Scheme 4). Subsequent modified Curtius rearrangement of **22** involving the use of *t*-BuOH to trap the intermediate isocyanate gave orthogonally protected diamine derivative **23** (81% yield). The intermediate **23** was transformed into the corresponding monoprotected diamine derivatives **24** and **25** by hydrogenolysis (72% yield) or removal of the Boc protective group under acidic conditions (90% yield, obtained as the dihydrochloride salt), respectively.



Scheme 4. Synthesis of amino acid **22**, monoprotected diamines **24** and **25**.

In conclusion, the Corey–Chaykovsky reaction of tetrahydro-1*H*-azepines containing an α,β-unsaturated ester moiety with the trimethylsulfoxonium ylide is an efficient method for construction of the azabicyclo[5.1.0]octane ring system. With optimized reaction conditions for this step, the corresponding *N*-protected bicyclic amino esters were obtained in 55–65% yield on up to 25 g scale. As a result, two novel bicyclic amino acids **7** and **8** were obtained in 23% and 17% yield over 6 steps, respectively. Moreover, conformationally restricted diamine derivatives **17** and **18** were also prepared in 12% and 8% overall yield over 8 steps. In addition, the developed method can also be applied for the synthesis of lower homologous

azabicyclo[n.1.0]alkanes, in particular, 3-azabicyclo[3.1.0]-hexanes, which was demonstrated by the preparation of the 3,4-methano-β-proline derivative. It should be noted that this synthetic sequence included only 3 steps; moreover, it commenced from readily available starting compounds. Therefore, it might be preferable over the existing multistep approaches to the derivatives of amino acid **22** despite the moderate yield of the key step – the Corey–Chaykovsky cyclopropanation (29%).

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Supplementary data

Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectrum of products can be found, in the online version, at http://dx.doi.org/

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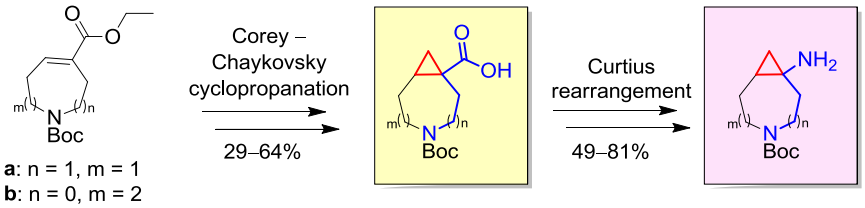
44. **4-*tert*-Butyl 1-ethyl 4-azabicyclo[5.1.0]octane-1,4-dicarboxylate (15).** To a suspension of NaH (21.2 g, 0.318 mol, 60 % dispersion in mineral oil) in DMSO (650 mL), *S*,*S*,*S*-trimethylsulfoxonium iodide (72.9 g, 0.331 mol) was added in small portions and stirred at rt for 1 h until gas evolution ceased. A solution of 1-*tert*-butyl 4-ethyl 2,3,6,7-tetrahydro-1*H*-azepine-1,4-dicarboxylate (**9**) (34.3 g, 0.127 mol) in DMSO (150 mL) was added dropwise and the reaction mixture was stirred at 50 °C overnight. The resulting solution was cooled to rt, poured into ice-cold H_2O (1 L) and extracted with *t*-BuOMe (3×700 mL). The combined organic extracts were washed with brine (3×500 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was purified by column chromatography (gradient hexane to hexane – *t*-BuOMe (7:3) as eluent). Yield: 19.8 g (55 %); colourless oil. ^{1}H NMR(500 MHz, $CDCl_3$): δ 4.14 – 4.06 (m, 2H), 3.98 – 3.78 (m, 2H), 3.10 (s, 1H), 2.96 (s, 1H), 2.77 (dd, *J*=15.3, 6.4 Hz, 1H), 2.36 (dt, *J*=14.1, 6.5 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.49 (dd, *J*=9.2, 4.3 Hz, 1H), 1.43 (s, 9H), 1.37 – 1.26 (m, 2H), 1.23 (t, *J*=7.1 Hz, 3H), 0.77 (t, *J*=6.6, 4.3 Hz, 1H). ^{13}C NMR(126 MHz, $CDCl_3$): δ 175.4, 155.1, 79.3, 60.6, 47.6, 47.2, 32.7, 32.4, 28.4, 27.7, 26.9, 24.7, 14.2. MS (APCI): *m/z* = 284 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{25}NO_4$: C 63.58; H 8.89; N 4.94. Found: C 63.86; H 8.58; N 5.13.

Graphical Abstract.



a: n = 1, m = 1
b: n = 0, m = 2
c: n = 0, m = 0

Highlights

- Synthesis of azabicyclo[5.1.0]octane(methanoazepane)-derived amino acids and diamines is reported.
- The Corey–Chaikovsky cyclopropanation is a key step of the synthetic strategy used.
- Utility of the method is demonstrated by preparation of 3,4-methano-β-proline and its diamine derivatives.
- The target building blocks can be obtained at multigram scale.