Bicyclo[m.n.k]alkane Building Blocks as Promising Benzene and Cycloalkane Isosteres: Multigram Synthesis, Physicochemical and Structural Characterization

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Dedicated to the people of Ukraine

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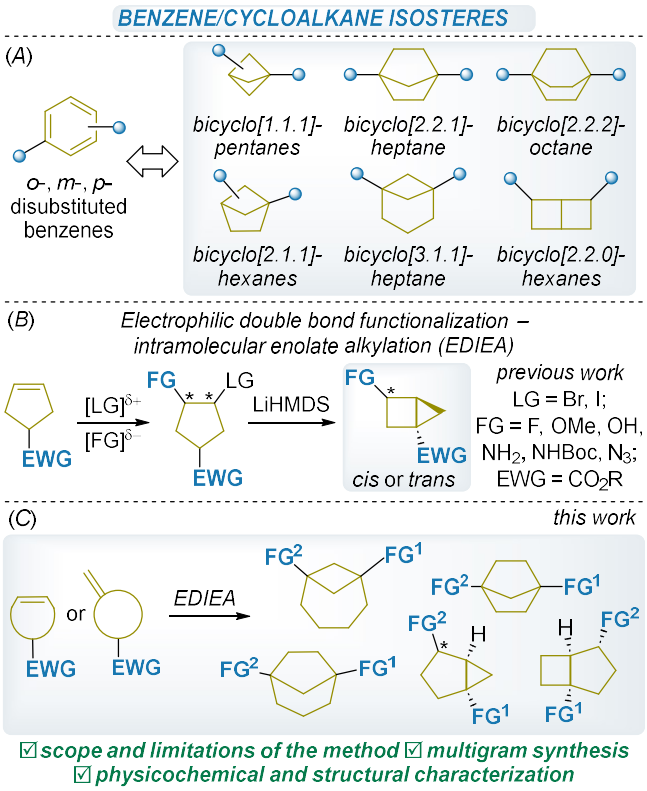
Abstract: Electrophilic double bond functionalization – intramolecular enolate alkylation sequence was used to obtain a series of bridged and fused bicyclo[m.n.k]alkane derivatives (i.e., bicyclo[4.1.1]octanes, bicyclo[2.2.1]heptanes, bicyclo[3.2.1]octanes, bicyclo[3.1.0]hexanes, and bicyclo[4.2.0]heptanes). The scope and limitations of the method were established, and applicability to the multigram synthesis of target bicyclic compounds was illustrated. Using the developed protocols, over 50 mono- and bifunctional building blocks relevant to medicinal chemistry were prepared. The synthesized compounds are promising isosteres of benzene and cycloalkane rings, which is confirmed by their physicochemical and structural characterization (pK_a, Log*P*, and exit vector parameters (EVP)). “Rules of thumb” for the upcoming isosteric replacement studies were proposed.

Introduction

Bicyclic saturated compounds have reached leading positions in the modern design of organic molecules. This phenomenon could be addressed to the molecular rigidity and the distinct spatial arrangement of substituents connected to the sp^3-enriched non-planar bicycling scaffolds.[1–4] Nature itself widely utilizes carbocyclic molecules with mono- and bicyclic framework that have a wide range of biological activities.[5–11] The rigidity of bicyclic scaffolds has noticeable features in drug discovery since it may decrease the enthalpic penalty of the protein-ligand binding and improve overall physicochemical properties of the molecule.[5–7,12–14] In the last few years, bicyclo[m.n.k]alkanes have attracted much attention in medicinal chemistry as non-classical isosteres of benzene and cycloalkanes that allow improve pharmacokinetic parameters of the compound and fine-tune its affinity to the biological target.[15–21] In this view, bicyclo[1.1.1]pentanes (BCPs),[22,23] -[2.1.1]hexanes,[24] -[2.2.1]-heptanes (norbornanes), -[3.1.1]heptanes,[25] -[2.2.2]octanes,[26] or -[2.2.0]hexanes ([2]-ladderanes)[27] can be particularly outlined (Scheme 1, *A*).



Scheme 1. (*A*) Some remarkable examples of the known bicyclic benzene/cycloalkane isosteres. (*B*) Electrophilic double bond desymmetrization – intramolecular enolate alkylation sequence for the synthesis of 1,3-disubstituted bicyclo[2.1.0]pentanes (housanes). (*C*) The main targets of this work.

To date, synthetic approaches to bicyclic saturated ring systems were typically unique for each bicyclo[m.n.k]alkane, especially if a required substitution of the parent scaffold is taken into account. General strategies allowing for the construction of various properly functionalized saturated bicyclic systems using the same

synthetic approach are very rare but highly desirable. In our previous work, we have shown that electrophilic double bond desymmetrization (functionalization) – intramolecular enolate alkylation (*EDIEA*) is a very efficient method for the preparation of 1,3-disubstitued bicyclo[2.1.0]pentanes (housanes) from properly functionalized cyclopentanes (Scheme 1, *B*).[28] The synthetic sequence allowed for the preparation of both *cis*- and *trans*-1,3-disubstituted housane-1-carboxylic acids in a diastereoselective manner on up to 80 g scale.

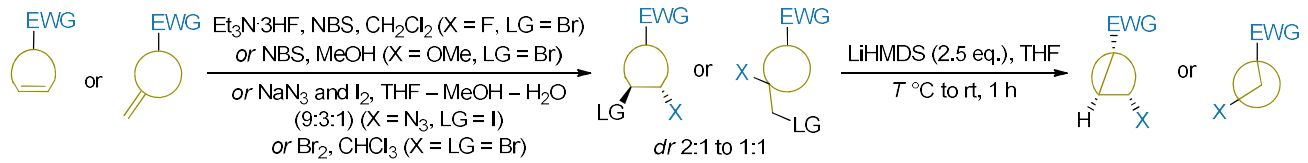
Herein, we demonstrate the utility of the *EDIEA* sequence for the preparation of various fused and bridged saturated bicyclic ring systems starting from the corresponding cyclic esters bearing an endo- or exocyclic double bond (Scheme 1, *C*). We show the scope and limitations of the method, as well as its applicability for the multigram synthesis. Furthermore, we illustrate the potential of the synthesized mono- and bifunctional building blocks as benzene/cycloalkane isosteres by characterization of their physicochemical (pK_a, Log*P*[29]) and structural (exit vector parameters, EVP[20,30]) properties.

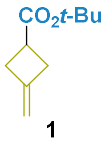
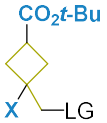
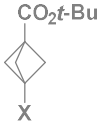
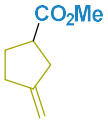
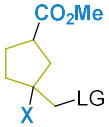
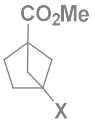
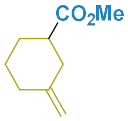
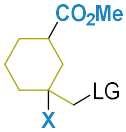
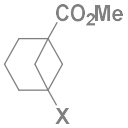
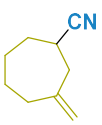
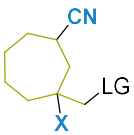
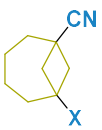
Results and Discussion

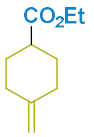
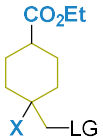
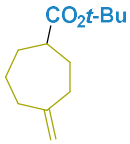
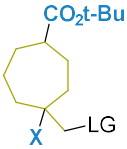
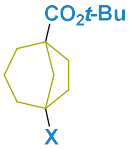
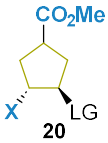
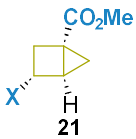
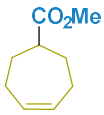
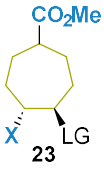
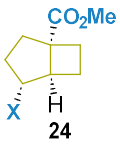
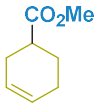
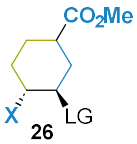
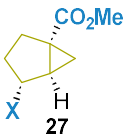
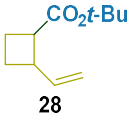
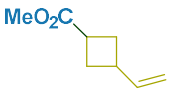
Preliminary synthetic experiments: scope and limitations

We started our study with application of the *EDIEA* reaction sequence to 11 model cycloalka(e)ne carboxylic acid derivatives bearing an exo- or endocyclic double bond (Table 1). All preliminary experiments were performed at 10 mmol scale. Three model electrophilic functionalization reactions were used at the first step: fluorobromination, methoxybromination, and iodoazidation. In particular, fluorobromination was performed by action of $Et_3N{\cdot}3HF$ and NBS in CH_2Cl_2. The method worked well with all cyclic esters with exocyclic double bond except cyclobutane derivative **1**, as well as symmetric cycloalkene derivatives **19** (previous work[28]) and **26** (Table 1, Entries 2–8). In the case of ester **1**, considerable formation of elimination by-product was observed (Entry 1). Methoxybromination was performed with NBS in MeOH and worked well with all the substrates mentioned above (Table 1, Entries 1–8). Finally, iodoazidation was carried out upon action of NaN_3 and I_2 in THF – MeOH – H_2O (9:3:1, v/v/v), and the method was efficient with all substrates discussed (Table 1, Entries 1–8).

Table 1. Preliminary synthetic experiments on the *EDIEA* reaction sequence



Entry	Substrate	Intermediate[a]	Product[a]	Yield, % (over two steps)		
				X = F, LG = Br	X = OMe, LG = Br	X = N_3, LG = I
1	 **1**	 **2**	 **3**	*complex mixture* (*T* = –70 °C)	*complex mixture* (*T* = –70 °C)	–
2	 **4**	 **5**	 **6**	*no reaction* (*T* = –70 °C or –40 °C) *complex mixture*[c]	*complex mixture*[d]	–
3	 **7**	 **8**	 **9**	*complex mixture* (*T* = –50 °C)	*complex mixture* (*T* = –20 °C)	–
4	 **10**	 **11**	 **12**	55 (*T* = –10 °C)	51 (*T* = –10 °C)	68 (*T* = –10 °C)

Entry	Substrate	Intermediate[a]	Product[a]	Yield, % (over two steps)		
				X = F, LG = Br	X = OMe, LG = Br	X = N_3, LG = I
5	 **13**	 **14**	 **15**	23 (*T* = –10 °C)	29 (*T* = –10 °C)	21 (*T* = –10 °C)
6	 **16**	 **17**	 **18**	37 (*T* = –10 °C)	57 (*T* = –10 °C)	69 (*T* = –10 °C)
7[b]	 **19**	 **20**	 **21**	44 (*T* = –70 °C)	54 (*T* = –70 °C)	24 (*T* = –70 °C)
8	 **22**	 **23**	 **24**	70 (*T* = –10 °C)	71 (*T* = –10 °C)	61 (*T* = –10 °C)
9	 **25**	 **26**	 **27**	69 (*T* = –70 °C; X = LG = Br)[e]	41 (*T* = –70 °C)[f]	37 (*T* = –70 °C)[f]
10	 **28**	*complex mixture*	–		–	
11	 **29**	*complex mixture*	–		–	

[a] Relative configurations are shown.

[b] Results of the previous work.[28]

[c] Conditions for the second step: LiHMDS (1.4 eq.), –10 °C, 1 h, reverse addition; *or* LDA (1.2 eq.), –78 °C to rt, 2 h; *or* LDA (1.5 eq.), HMPTA (4 eq.), –78 °C to rt, 2 h.

[d] Conditions for the second step: LDA (1.5 eq.), HMPTA (7 eq.), –78 °C to rt, 2 h.

[e] The corresponding products **26a** and **27a** (X = LG = Br) were obtained with bromine in $CHCl_3$ as the electrophile at the first step.

[f] Methoxybromination and azidoiodination gave mixtures of regioisomers **26b,c** and **28b,c** (ca. 1:1 ratio) according to LC-MS and ^{1}H NMR spectra. Only compounds **26b** and **26c** underwent cyclization at the second step.

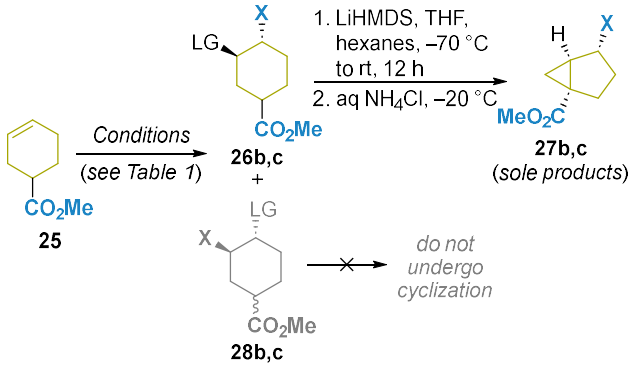
In all the above cases, the reactions proceeded regioselectively (where appropriate), while the diastereoselectivity relatively to the configuration at the carboxylate (nitrile) moiety was modest (*dr* 2:1 to 1:1; note *anti* addition for the endocyclic double bonds in **19** and **22**). Nevertheless, the observed diastereomeric ratio had no impact at the further step, i.e., intramolecular enolate alkylation, since the stereogenic center near the EWG group disappeared upon the deprotonation with a base.

Initially, the optimized conditions from the previous work were implemented for the cyclization step (2.5-fold excess of LiHMDS, THF, –70 °C to rt, 1 h).[28] As was found, the construction of the methylene bridge could be achieved for the relatively large ring systems, i.e., bicyclo[4.1.1]-, -[2.2.1]-, and -[3.2.1]alkanes (albeit the reaction was performed at higher temperature, i.e., –10 °C to rt) (Table 1, Entries 4–6). Notably, norbornane (bicyclo[2.2.1]-alkane) derivatives were obtained in modest yield (21–29%),

which might be related to unfavorable geometry of the transition state for the cyclization. Furthermore, all attempts to obtain even more strained bicyclo[1.1.1]pentane, -[2.1.1]hexane, and -[3.1.1]-heptane derivatives were unfruitful (Entries 1–3). Meanwhile, the method worked well for intermediates **20** (previous work[28]) and **23** derived from substrates with endocyclic double bond (Entries 7 and 8).

As might be expected, cyclohexene derivative **25** reacted non-regioselectively at the electrophilic functionalization conditions mentioned above. Nevertheless, an elegant solution for this problem was envisaged and implemented successfully. Thus, compound **25** was involved into the simple bromination reaction to give dibromide **26a**. In principle, intramolecular enolate alkylation could provide two possible products depending on the bromine atom involved into the reaction, i.e., bicyclo[3.1.0]-hexane or bicyclo[2.2.0]hexane derivative. Luckily for us, only bicyclo[3.1.0]hexane **27a** was formed in 69% yield upon reaction of compound **26a** with 2.5-fold excess of LiHMDS in THF at –70 °C to rt.

Being inspired by excellent cyclization regioselectivity observed in the case of dibromide **26a**, we put a closer look on the products of non-symmetric electrophilic functionalization of unsaturated ester **25**. Thus, regioisomeric mixtures of methoxybromination (**26b** and **28b**) and iodoazidation (**26c** and **28c**) products were introduced into the intramolecular enolate alkylation step under the conditions described above for the compound **26a** (Scheme 2). It was found that only isomers **26b** and **26c** underwent the cyclization providing bicyclo[3.1.0]hexane derivatives **27b** and **27c** in 41% and 37% yield, respectively.

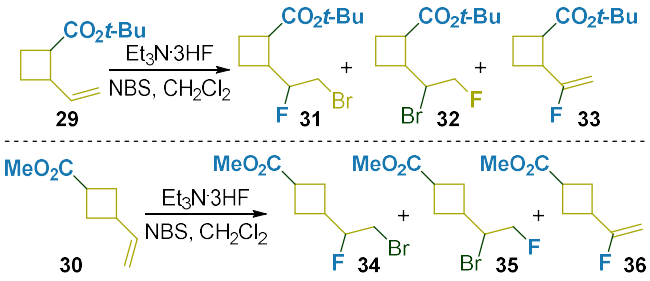


Scheme 2. Chemoselective formation of bicyclo[3.1.0]hexane derivatives **27** starting from unsaturated ester **25**

Unfortunately, vinyl-substituted cyclobutanes **29** and **30** were not suitable for the *EDIEA* reaction sequence since at the first step (electrophilic functionalization), complex mixtures were obtained (Table 1, Entries 10 and 11). According to LC-MS and ^{1}H NMR spectra of these mixtures, they presumably contained target regioisomers **31**/**32** or **34**/**35** (as mixtures of diastereomers), elimination products **33** or **36**, and other unidentified by-products (Scheme 3). The reaction was not fruitful even when bromine was used as the electrophile.

Multigram synthesis of target building blocks

With the optimized protocols, as well as scope and limitation of the method in hands, we have performed multigram synthesis of building blocks derived from bicyclic scaffolds that were successfully prepared in the preliminary experiments.

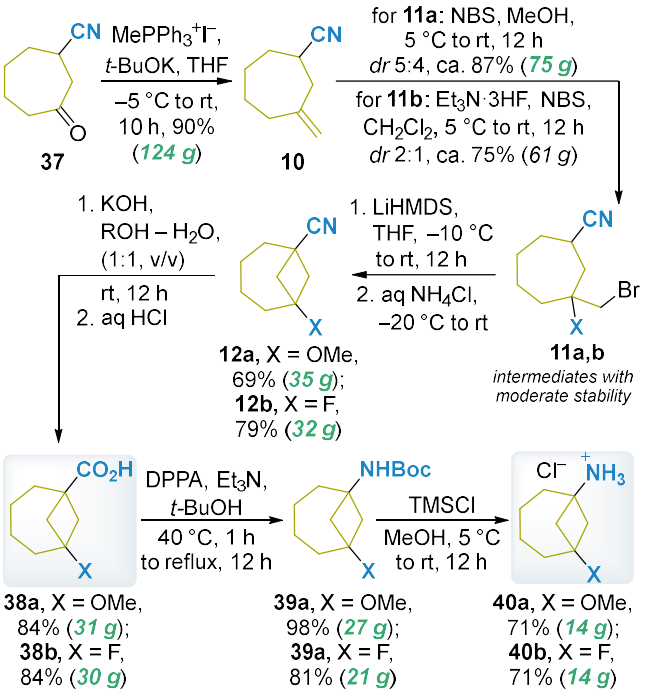


Scheme 3. Unsuccessful attempts on the fluorobromination of unsaturated esters **29** and **30** (the structures of the plausible products are proposed according to LC-MS and ^{1}H NMR spectra).

Synthesis of 1,6-disubstituted bicyclo[4.1.1]octanes. The proposed reaction sequence commenced from commercially available 3-oxocycloheptane-1-carbonitrile (**37**) that was involved into the Wittig reaction with $MePPh_3^+I^-$ in the presence of *t*-BuOK to give methylenecycloheptane **10** in 90% yield on up to 124 g scale in a single run (Scheme 4). The subsequent methoxy- and fluorobromination of **10** proceeded smoothly with good yields of the target bromomethyl-substituted intermediates **11a** and **11b** that had moderate stability towards attempted purification and storage. Therefore, it was advantageous to perform the subsequent cyclization immediately with halogenides **11** (and the following related homologs and isomers) isolated with over 90% purity. Notably, the formation of bicyclo[4.1.1]octane system proceeded in good yields (69% for **12a**, 79% for **12b**) on up to 35 g scale. The mild alkaline hydrolysis of nitrile group of **12** followed by the treatment with aq HCl was successfully performed to obtain two carboxylic acids **38a** and **38b**, both in 84% yield.

The modified DPPA-mediated Curtius rearrangement in the presence of *t*-BuOH was suitable to obtain *N*-Boc protected amines **39a** and **39b** in good to excellent yields. The subsequent carbamate group cleavage was performed with *in-situ* generated HCl (TMSCl – MeOH), and amines **40a** and **40b** were obtained as hydrochlorides both in 71% yield on up to 14 g scale.

Iodoazidation of methylenecycloheptane **10** was performed on up to 300 g scale; no diastereoselectivity was observed (Scheme 5). Iodomethyl derivative **11c** was immediately involved in the LiHMDS-mediated cyclization without additional purification, and the target bifunctional azido nitrile **12c** was obtained in 77% yield on 129 g scale in a single run. The subsequent alkaline hydrolysis provided azido carboxylic acid **38c** (57% yield, 140 g scale), which was transformed into ester **41** using CDI – MeOH (97% yield). Azide reduction was performed via the mild catalytic hydrogenation in the presence of Boc_2O, which gave *N*-Boc-protected amino ester **42** in 79% yield. Compound **42** served as a precursor for the preparation of amino ester **43** (via acidic carbamate cleavage), and *N*-Boc-protected amino acid **44** via reflux in the presence of $LiOH·H_2O$ in MeOH – H_2O (2:1, v/v) in good yields. Finally, free amino acid **45** was synthesized from compound **44** in 91% yield on up to 24 g scale as hydrochloride.

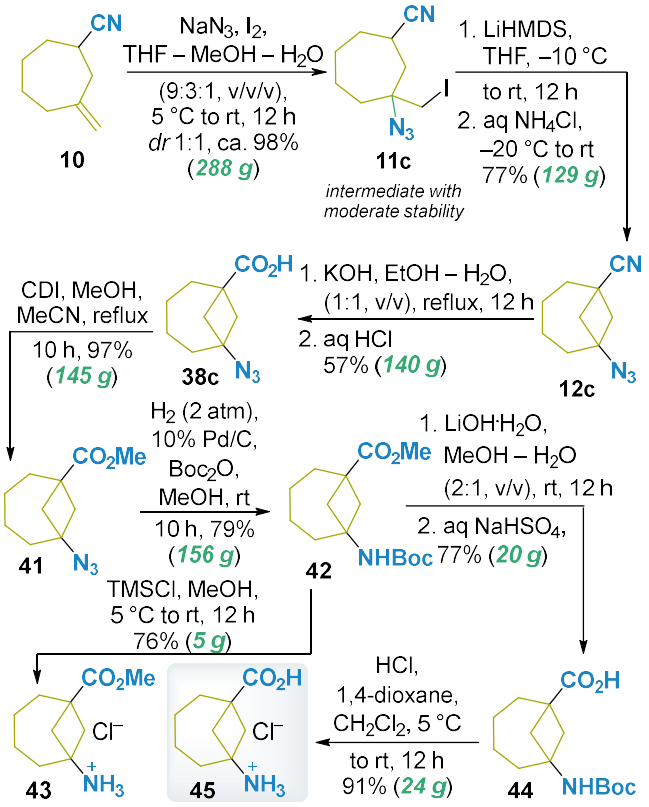


Scheme 4. Synthesis of bicyclo[4.1.1]octane-derived building blocks **38a**, **38b**, **40a**·HCl, and **40b**·HCl.

Synthesis of 1,4-disubstituted bicyclo[2.2.1]heptanes. Notably, synthesis of 1,4-disubstituted bicyclo[2.2.1]heptanes by intramolecular enolate alkylation was documented in the literature, albeit different retrosynthetic disconnections were used.[31–36] Our approach commenced with a known preparation of 4-methylenecyclohexane carboxylate **13** based on the use of $MePPh_3^+Br^-$ and *n*-BuLi in the reaction with **46** (Scheme 6).[37] In our hands, better results for the scaled-up synthesis of **13** were obtained with *t*-BuOK as a base for this step. Alkoxybromination was performed with MeOH or EtOH as the alcohol component, providing derivatives **14a** and **14d** both in ca. 90% yield on up to 465 g scale. The fluorobromination also proceeded with good efficiency to give fluorinated intermediate **14b**. The subsequent LiHMDS-mediated cyclization of bromoalkyl carboxylates **14a**, **14b**, and **14d** provided target norbornane carboxylates **15a**, **15b**, and **15d** in relatively low yields (31–36%). Nevertheless, the proposed method was suitable for the scaled-up synthesis of bicyclic carboxylate intermediates for a series of further functional group transformations on up to 68 g scale in a single run.

KOH-mediated hydrolysis of carboxylates **15a, 15b**, and **15d** proceeded smoothly and gave the corresponding carboxylic acids **47a** (90% yield), **47b** (86% yield), and **47d** (77% yield). The Curtius rearrangement of derivatives **47a–d** was performed by the action of DPPA and *t*-BuOH in the presence of Et_3N (80–88% yield of *N*-Boc-protected derivatives **48a–d**), while the carbamate group cleavage with *in situ* generated HCl allowed for the preparation of norbornane amines **49a**, **49b**, and **49d** in good yields (71–75%).

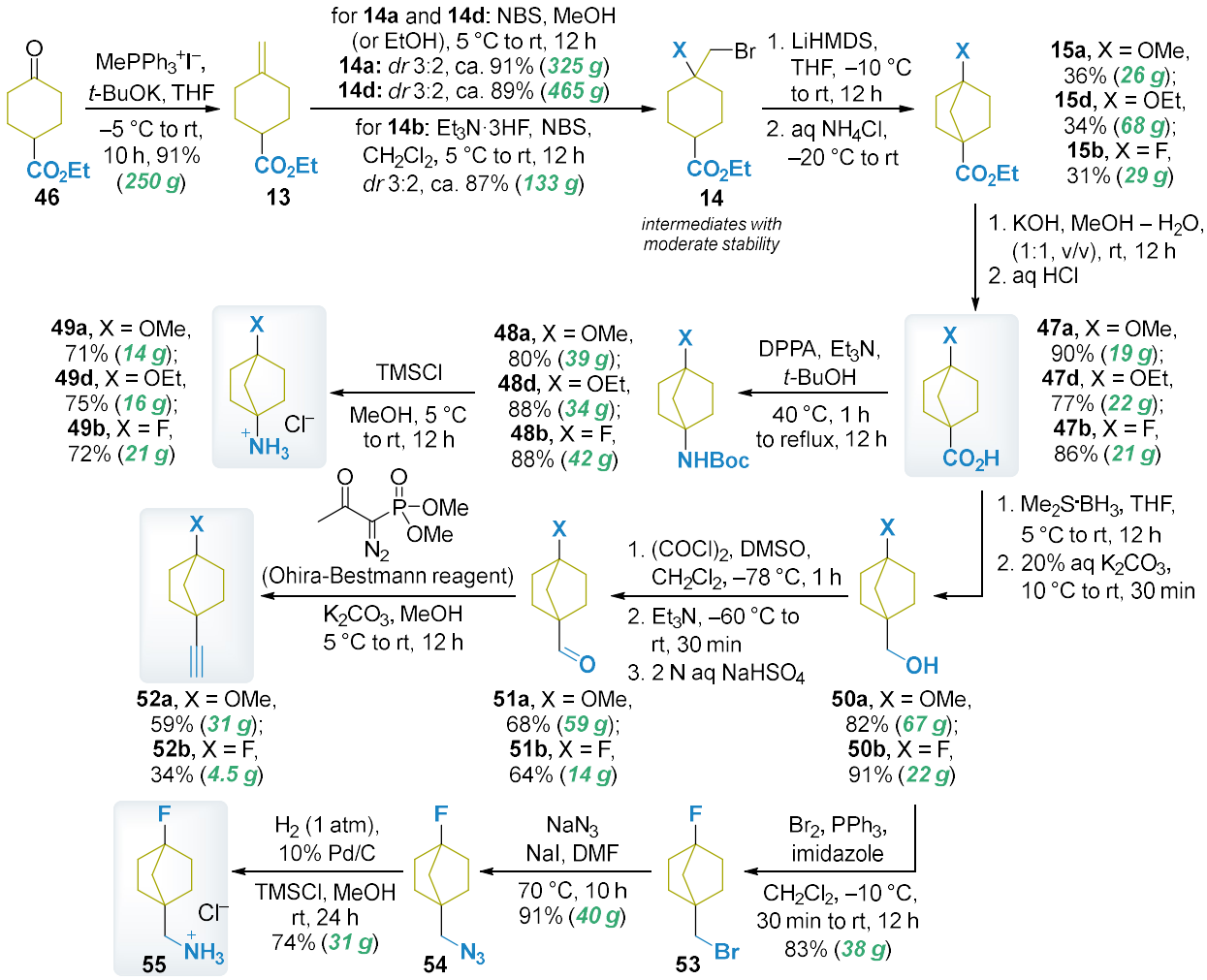
Reduction of the carboxylic group in compounds **47a** and **47b** was easily achieved with borane – dimethylsulfide complex and gave primary alcohols **50a** and **50b**. Further Swern oxidation of these products provided aldehydes **51a** and **52b**, that were transformed into acetylenes **52a** and **52b** using Ochira-Bestmann reagent. Also, alcohol **50b** was subjected to Appel bromination providing intermediate **53** that was introduced into reaction with NaN_3 (giving azide **54**) and then – catalytic hydrogenation giving amine **55** as hydrochloride.



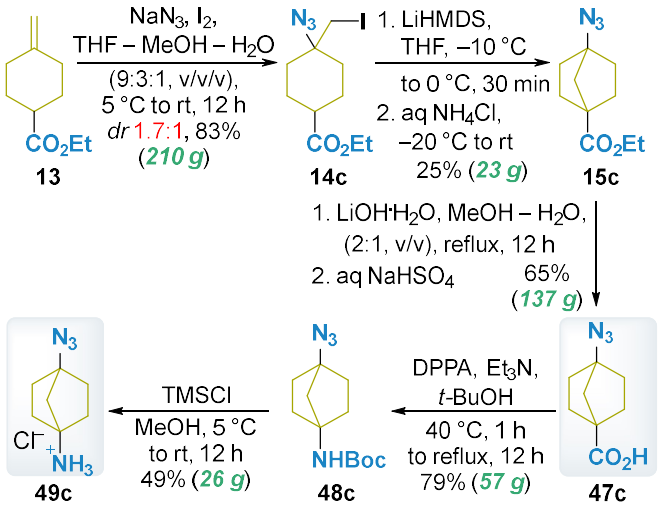
Scheme 5. Synthesis of bicyclo[4.1.1]octane-derived amino acid **45** and its derivatives.

The iodoazidation of intermediate **13** proceeded smoothly to give iodide **14c** in 83% yield on up to 210 g scale in a single run (Scheme 7). The cyclization of carbanion formed from **14c** proceeded with comparable efficiency to that of **14a**, **14b**, and **14d** and provided norbornane derivative **15c** in 25% yield. Mild alkaline hydrolysis and the subsequent Curtius reaction of carboxylic acid **47c** thus obtained provided amino azide **49c** (26 g scale in a single run) after *N*-Boc deprotection.

In order to further expand the present scope of known 1,4-difunctionalized norbornanes, we have also prepared 4-hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (**47e**) and the corresponding amino alcohol **49e** (Scheme 8). The synthesis started with hydroxybromination of alkene **13** giving bromohydrin **14e** that required an additional *O*-protection step prior to the cyclization. The corresponding *O*-TBDMS-protected derivative **14f** was easily obtained on up to 81 g scale and then subjected to carbanion-mediated cyclization. Notably, the reaction proceeded much higher efficiently as compared to analogs **14a–d** – norbornane **15f** was obtained in 68% yield. This result might be addressed to the bulkiness of the OTBDMS substituent favoring axial disposition of the CH_2Br moiety necessary for the cyclization step. After alkaline hydrolysis of compound **15f**, compound **56** transformed into carboxylic acid **47e** and amino alcohol **49e** (in three steps via **48f** and **57**) using the standard functional group transformations.

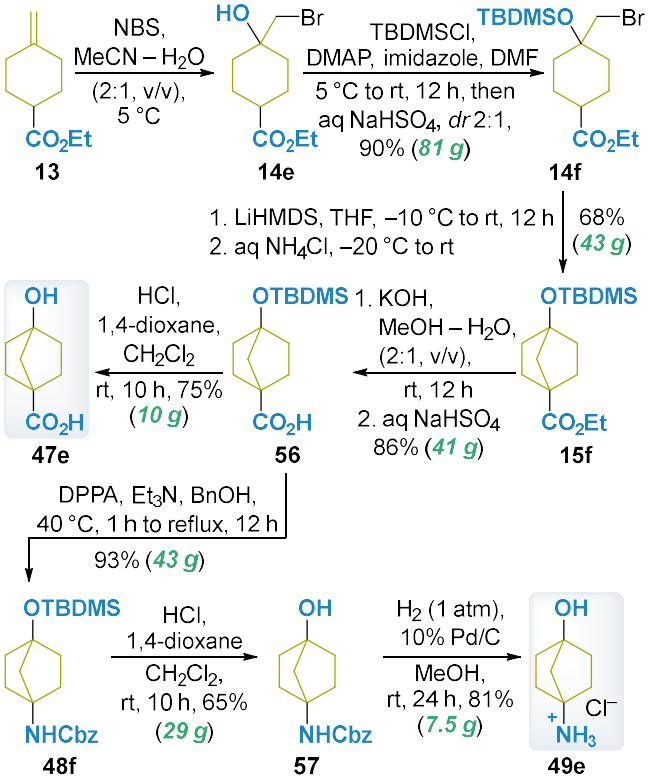


Scheme 6. Synthesis of bicyclo[2.2.1]octane-derived building blocks.**47a**–**55**.

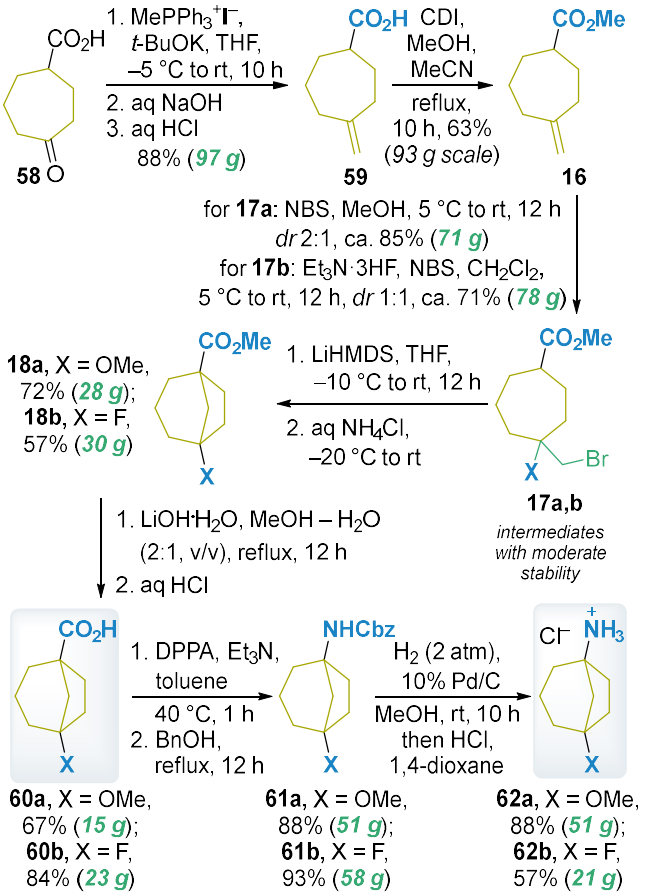


Scheme 7. Synthesis of building blocks **47c** and **49c**.

Synthesis of 1,5-disubstituted bicyclo[3.2.1]octanes. A series of bicyclo[3.2.1]octane-derived building blocks were obtained from 4-oxocycloheptane-1-carboxylic acid (**58**), which was introduced into the Wittig reaction (88% yield of **59**, 97 g scale) and then – esterification (63% yield of **16**, 93 g scale) (Scheme 9). Next, methoxy- and fluorobromination of unsaturated ester **16** were performed to obtain bromides **17a** and **17b** that were successfully involved into the cyclization reaction upon the common conditions to give bicyclo[3.2.1]octanes **18a** and **18b** in 72% and 57% yield, respectively, on up to 30 g scale. The target building blocks were obtained by the treatment of esters **18a** and **18b** with $LiOH·H_2O$ in $MeOH – H_2O$. The corresponding carboxylic acids **60a** and **60b** thus formed were introduced into the Curtius rearrangement in the presence of BnOH, which gave *N*-Cbz-amines **61a** and **61b** for the further catalytic deprotection. The latter steps for the preparation of bicyclic primary amines **62a** and **62b** could be performed on over 50 g scale in a single run.



Scheme 8. Synthesis of building blocks **47e** and **49e**.



Scheme 9. Synthesis of bicyclo[3.2.1]octane-derived building blocks **60a**, **60b**, **62a**, and **62b**.

In addition to that, amino acid derivatives was obtained in an analogous manner to that of bicyclo[4.1.1]octane counterparts (Scheme 10). The reaction sequence included iodoazidation of unsaturated ester **16** and further cyclization of intermediate **17c** thus obtained into 5-azidobicyclo[3.2.1]octane-1-carboxylate **18c**. Compound **18c** was subjected to catalytic hydrogenation in the presence of Boc_2O in order to obtain *N*-Boc-protected amino ester **63** (61% yield over three steps, 6 g scale). The latter derivative was used to obtain amino ester **64** (91% yield), *N*-Boc-amino acid **65** (71% yield), as well as amino acid hydrochloride **66** (61% yield from **65**).

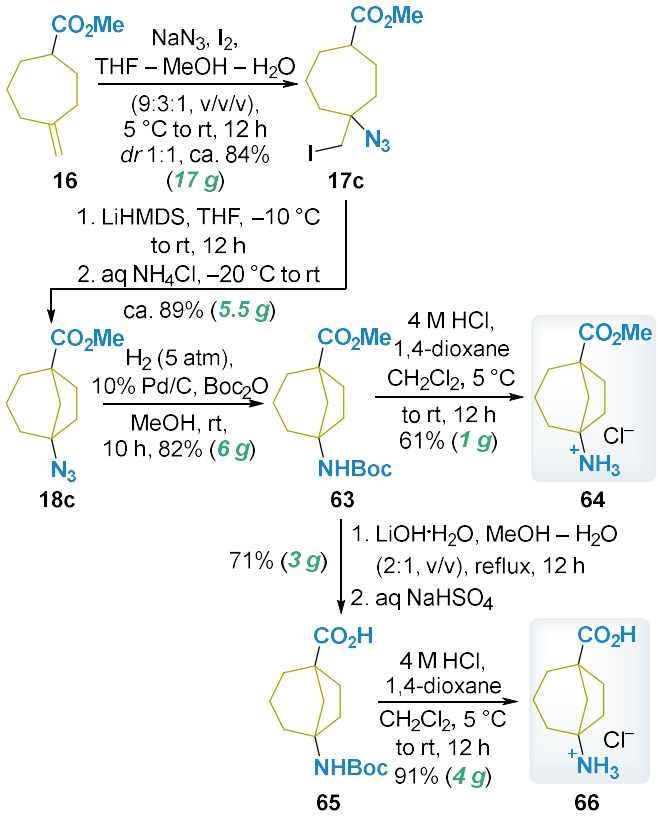
Synthesis of 1,4-disubstituted bicyclo[3.2.0]heptanes. Cyclization of vicinal *trans*-4,5-disubstituted cycloheptane carboxylates **23a** and **23b** (obtained from cycloheptene derivative **22** with *dr* 2:1) proceeded in a diastereoselective manner under the common conditions to give bicyclic compounds **24a** and **24b** (Scheme 11). After hydrolysis, carboxylic acids **67a** and **67b** were obtained in 75–89% yield on up to 16 g scale (53% and 63% yield, respectively, over three steps).

The iodoazidation – LiHMDS-mediated cyclization sequence was suitable for the diastereoselective preparation of azido ester **24c** in 66% yield on up to 75 g scale in a single run, also starting from cycloheptene derivative **22** via intermediate **24c** (Scheme 12). The following transformation of **24c** into amino ester **68** was performed via the Staudinger reaction (71% yield, 77 g scale). Compound **68** was subjected to *N*-Boc-protection (87% yield of intermediate **69**, 114 g scale), alkaline hydrolysis (for the preparation of *N*-Boc-amino acid **70** in 76% yield), and acid-mediated cleavage of the carbamate group (81% yield of amino acid **71**).

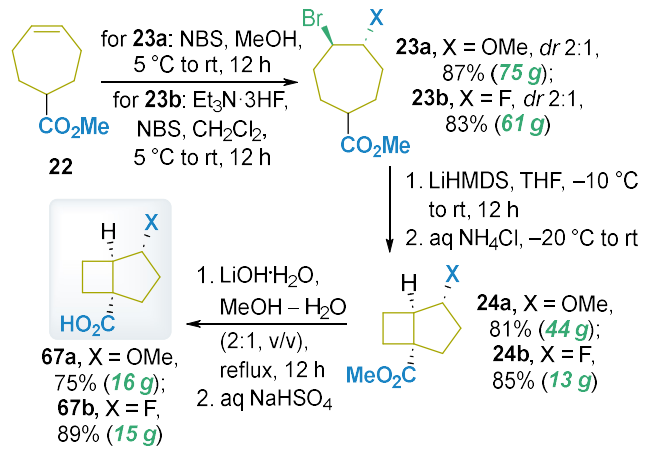
Bromohydroxylation of alkene **22** upon action of NBS in MeCN – H_2O (2:1, v/v) provided alcohol **23e** as a ca. 2:1 mixture of diastereomers in 99% yield on up to 62 g scale in a single run (Scheme 13). The subsequent treatment of compound **23e** with TBDMSCl in the presence of DMAP and imidazole in DMF gave *O*-protected intermediate **23f** in 90% yield. The cyclization of **23f** under the conditions described above provided bis-protected fused bicyclic derivative **24f** (68% yield). The cleavage of both protecting groups was achieved via the alkaline hydrolysis in the presence of $LiOH·H_2O$ in refluxing MeOH – H_2O (2:1, v/v) and gave target compound **72** in 82% yield on up to 23 g scale.

Synthesis of 1,4-disubstituted bicyclo[3.1.0]hexanes. As mentioned above, bromination of unsaturated ester **25** was the key transformation for the successful synthesis of 1,4-disubstituted bicyclo[3.1.0]hexane derivatives. The reaction provided dibromide **26a** in 88% yield on up to 107 g scale in a single run (Scheme 14). The subsequent cyclization gave *cis*-4-bromobicyclo[3.1.0]hexane-1-carboxylate (**27a**) in 83% yield.

According to the initial plan, nucleophilic substitution in bromide **27a** was envisaged to introduce the required functional groups into the bicyclo[3.1.0]hexane scaffold. Indeed, the reaction of compound **27a** with KSAc in DMF apparently proceeded according to S_N2 mechanism and resulted in expected *trans*-isomeric thioacetate **73** in 89% yield (Scheme 15). Oxidative chlorination of compound **73** provided sulfonyl chloride **74**.

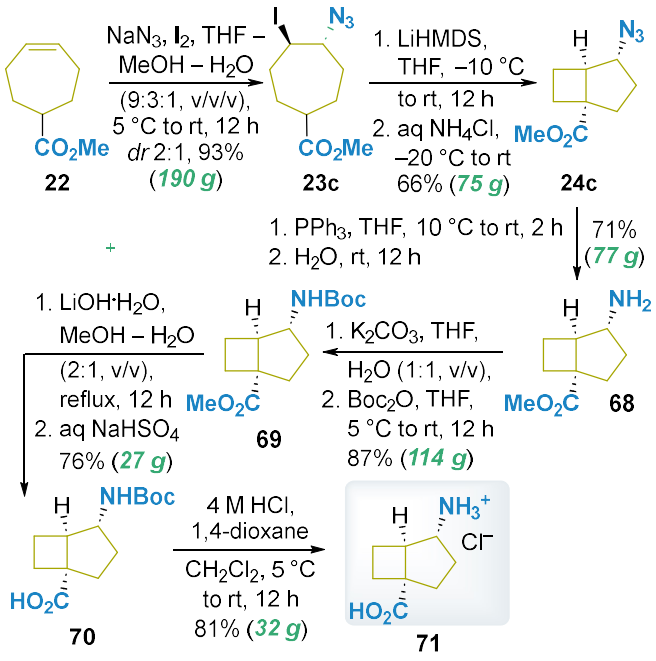


Scheme 10. Synthesis of bicyclo[3.2.1]octane amino acid derivatives **63**–**66**.

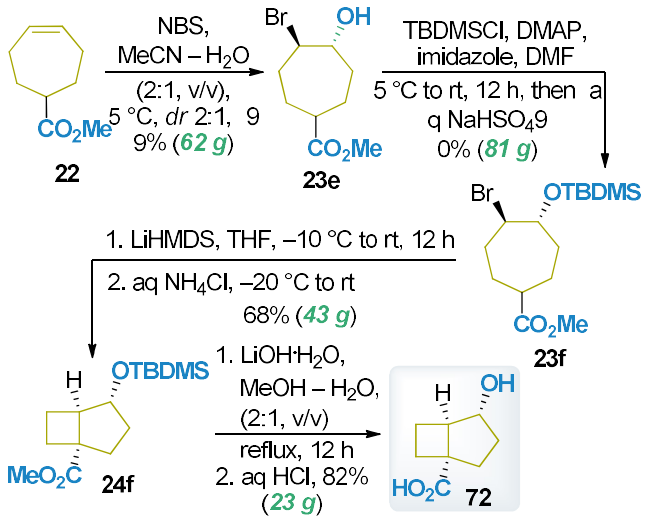


Scheme 11. Synthesis of bicyclo[3.2.0]heptane carboxylic acids **67a** and **67b** (relative configurations are shown).

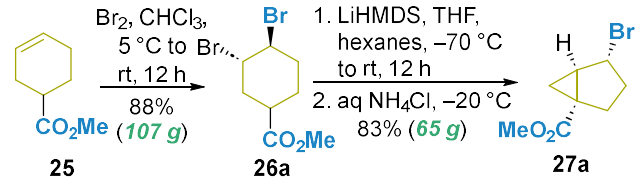
In a similar manner, the reaction of bromide **27a** with NaN_3 gave corresponding azide **75**, albeit the diastereoselectivity was somewhat lower in this case (*dr* 6:1, with *trans* isomer being the major one). After alkaline hydrolysis, diastereopure carboxylic acid *trans*-**76** was obtained. Further transformations included the catalytic hydrogenation of the azide group (for the preparation of amino acid *trans*-**77**), followed by the esterification with $SOCl_2$ and MeOH giving amino ester *trans*-**78**.



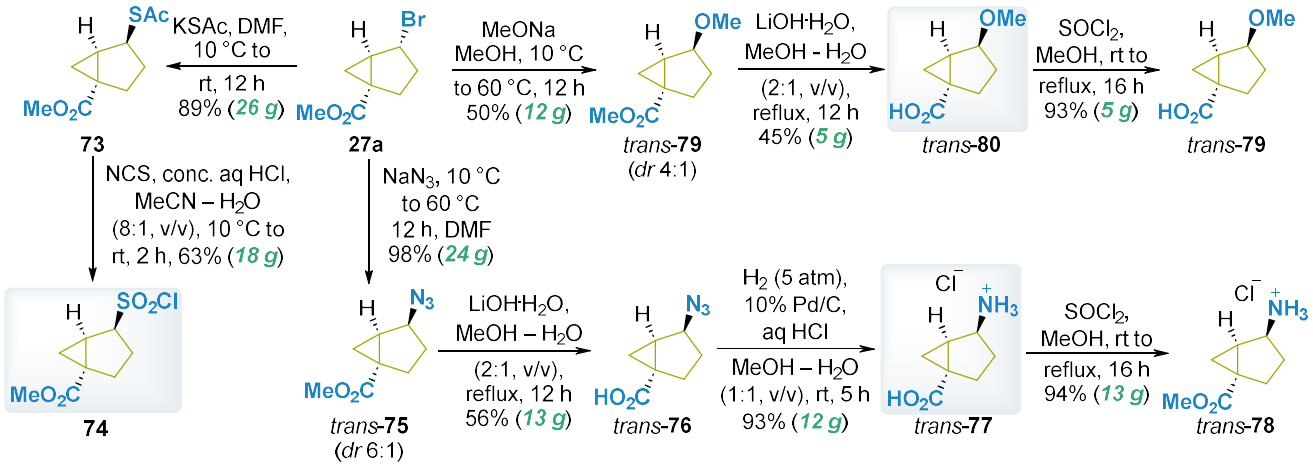
Scheme 12. Synthesis of bicyclo[3.2.0]heptane-derived amino acid **71** (relative configurations are shown).



Scheme 13. Synthesis of bicyclo[3.2.0]heptane-derived building block **72** (relative configurations are shown).



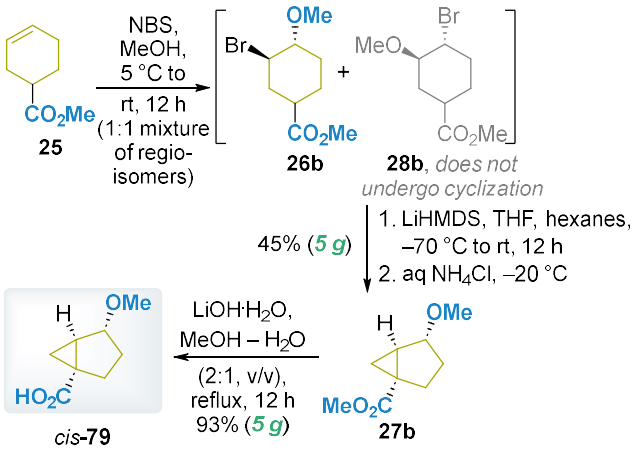
Scheme 14. Synthesis of *cis*-4-bromobicyclo[3.1.0]hexane-1-carboxylate (**27a**) (relative configurations are shown).



Scheme 15. Synthesis of *trans*-1,4-disubstiuted bicyclo[3.1.0]hexane building blocks (relative configurations are shown).

Furthermore, the reaction of bromide **27a** with sodium methoxide provided ester **79** (*dr* 4:1, with *trans* isomer being the major one). As in the previous case, pure carboxylic acid *trans*-**80** was obtained after hydrolysis of compound **79** and recrystallization. Pure *trans*-**79** could be obtained from *trans*-**80** after esterification. Unfortunately, an attempted nucleophilic substitution reaction of **26a** with cyanide ion resulted in the formation of a complex mixture, while the reaction with fluoride ion provided mostly the product of the elimination reaction (according to LC-MS and ^{1}H NMR spectra).

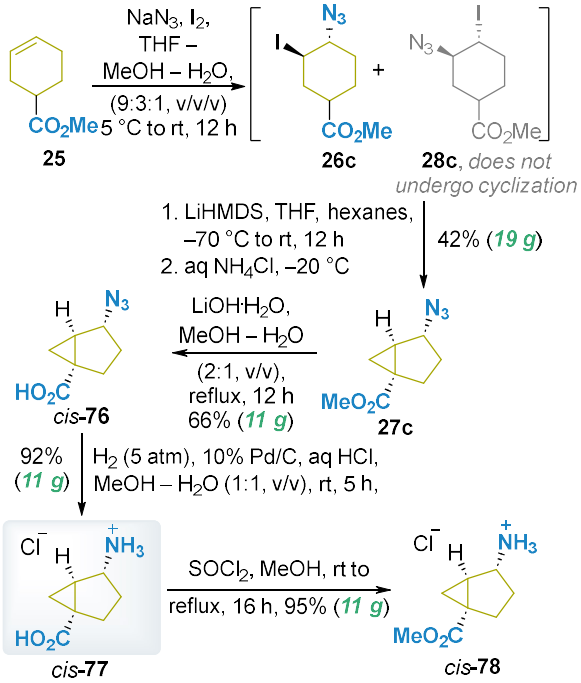
To obtain *cis*-isomeric 1,4-disubstituted bicyclo[3.1.0]hexane derivatives, selectivity of the intramolecular enolate alkylation shown in Scheme 2 was exploited. Thus, methoxybromination of compound **25** gave ca. 1:1 mixture of regioisomers **26b** and **28b**, and only one of them (**26b**) underwent cyclization into bicyclic derivative **27b** (Scheme 16). The latter compound was obtained in 45% yield (5 g scale) after chromatographic purification. Hydrolysis of ester **27b** gave carboxylic acid *cis*-**79** 93% yield.



Scheme 16. Synthesis of building block *cis*-**76** (relative configurations are shown).

In a similar manner, azidoiodination of compound **25** was used to obtain bicyclic azide **27c** (42% yield, 19 g scale) (Scheme 17).

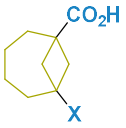
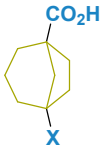
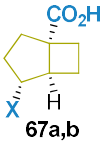
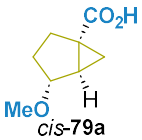
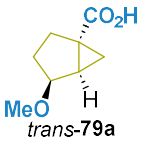
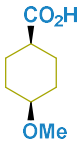
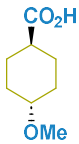
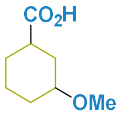
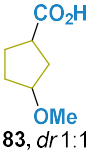
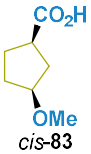
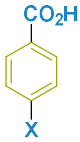
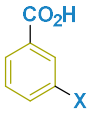
After alkaline hydrolysis of compound **27c** and further catalytic hydrogenation of resulting intermediate *cis*-**76** (66% yield), *cis* isomer of amino acid **77** was obtained (92% yield, 11 g scale, as hydrochloride). Esterification of *cis*-**77** provided amino ester *cis*-**78** (95% yield ,11 g scale, as hydrochloride).



Scheme 17. Synthesis of amino acid *cis*-**77** and its derivative *cis*-**78** (relative configurations are shown).

Physicochemical properties. The pK_a measurements were performed with methoxy-substituted carboxylic acids described in this work (**38a**, **47a**, **60a**, **67a**, *cis*-**79**, and *trans*-**79**), known benzene isostere **80**, cycloalkane derivatives **81**–**83**, and methoxybenzoic acids **84a**, **85a** according to the previously reported protocol[29] (Table 2).

Table 2. Physicochemical parameters values of model derivatives studied in this work (measured at 22 °C)

Entry	Carboxylic acid[a]	pK_a (X = OMe)	Log$P$[b] (X = OMe)	Log$P$[b] (X = F)
1	 **38a,b**	4.00±0.05	2.31±0.01	2.60±0.04
2	 **47a,b**	4.23±0.04	1.83±0.01	2.35±0.02
3	 **60a,b**	4.30±0.02	2.06±0.02	2.43±0.04
4	 **67a,b**	4.44±0.03	2.43±0.03	2.11±0.01
5	 *cis*-**79a**	4.57±0.03	1.56±0.07	–
6	 *trans*-**79a**	4.38±0.05	1.55±0.06	–
7	 **80**	4.40±0.03	2.02±0.01	–
8	 *cis*-**81**	4.53±0.07	2.01±0.03	–
9	 *trans*-**81**	4.37±0.02	2.06±0.01	–
10[c]	 **82**, *dr* 1:1	4.20±0.05	2.07±0.02	–
11[c]	 **83**, *dr* 1:1	4.32±0.04	1.88±0.01	–
12	 *cis*-**83**	4.40±0.05	1.81±0.01	–
13	 **84a,b**	4.68±0.10	2.70±0.05	2.26±0.03
14	 **85a,b**	3.79±0.04	2.82±0.02	2.68±0.06

[a] Relative configurations are shown.

[b] Measured for anilide derivatives.

[c] The compound was available as a mixture of diastereomers and was used in this form.

The obtained pK_a values for all saturated carboxylic acids varied in the range of 4.0–4.6 units and were between the corresponding values for *m*- and *p*-methoxybenzoic acids (3.8 and 4.7, respectively). The length and number of through-bond pathways between the methoxy and carboxy moieties was the main factor determining the compound's acidity. Thus, the compound **38b** having two C–CH_2–C units between the above functional groups was most acidic among the non-aromatic representatives (pK_a = 4.0). These results confirm that inductive electronic effect is the most important factor defining the compound's acidity in the series studied. Nevertheless, stereoelectronic effects also had a considerable impact on the pK_a value. For example, the compounds with *cis* orientation of the methoxy and carboxy groups were by 0.1–0.2 pK_a units slightly less acidic than the *trans* counterparts (compare the data for the *cis*- and *trans*-isomers of **79a**, **81**, or **83**). One of the reasons behind this might be destabilization of the negatively charged form for the *cis* isomers due to unfavorable dipole moment orientations.

Obviously but still notably, switching to saturated ring systems allowed eliminating resonance effects responsible for higher acidity of *m*-methoxybenzoic acid (pK_a = 3.8) and lower – of the *p*-isomer (pK_a = 4.7).

Log*P* measurements were performed for anilides of the above carboxylic acids using the standard shake-flask method (Table 2).[29] In addition to that, anilides of corresponding fluorine-substituted carboxylic acids **28b**, **47b**, **60b**, **67b**, as well as *p*- and *m*-fluorobenzoic acids **84b**, **85b** were included in this part of the study (since lipophilicity is a more complex phenomenon, and it is preferable to have more data points here). For the methoxy-substituted series, it was found that the bicyclic derivatives were considerably less lipophilic than their aromatic counterparts (Log*P* = 1.55–2.43 *vs* 2.70–2.82, respectively). Furthermore, the bicyclic compounds had somewhat lower Log*P* value than the corresponding monocylic analogs with the same number of carbon atoms or even those having one less carbon atom (i.e., **79a**/**83** or **47**/**81** anilide pairs). This interesting effect has been already precedented in the literature;[38,39] together with our results, these data suggest that it might have a general nature.

For the bicyclic compounds, increasing the number of carbon atoms typically resulted in higher Log*P* values, but this effect was not general. In particular, for methoxy-substituted derivatives, the lipophilicity increased in the following series:

[3.1.0] (*6*) < [2.2.1] (*7*) < [2.2.2] (*8*) ≈ [3.2.1] (*8*) < < [4.1.1] (*8*) < [3.2.0] (*7*)

(the numbers correspond to the lengths of the bridges (square brackets) and the total number of the carbon atoms (round brackets) in the bicyclic system). In other words, bicyclo[3.2.0]-heptane-derived anilide of **67a** was an outlier with higher Log*P* value.

Notably, the corresponding fluorine-substituted derivatives were somewhat more lipophilic than methoxy-substituted ones, but the general Log*P* trend remained nearly the same:

[3.2.0] (*7*) < [2.2.1] (*7*) < [3.2.1] (*8*) < [4.1.1] (*8*).

Again, bicyclo[3.2.0]heptane-derived anilide of **67b** was an outlier, with lower Log*P* value this time. We believe that somewhat higher flexibility of the bicyclo[3.2.0]heptane scaffold might be responsible for the observed differences. Since the dipole moment of the C–F bond is directly attached to the ring system, the polarity fluorinated derivatives should be more sensitive to the molecular geometry variations.

Another interesting feature is related to the Log*P* values of stereoisomeric anilides of **79a**, **81**, and **83**: the differences were negligible for the methoxy-substituted series. This is contrary to the behavior of monocyclic fluorinated compounds studied previously,[40,41] which might be again related to the higher sensitivity of organofluorine derivatives polarity to the molecular geometry changes.

The lipophilicity of anilides derived from *m*- and *p*-fluorobenzoic acids (**84b** and **85b**) should be also commented. Both compounds were less lipophilic than the corresponding methoxy derivatives, and this effect was more significant for the *p*-isomer (Log*P* = 2.68 and 2.26, respectively). We address this feature to the resonance effects increasing the overall dipole moment of the molecule. These results show that benzene derivatives are not necessarily less lipophilic than their saturated counterparts in the series studied, and fine effects of the functional groups should be also taken into account.

The Craig-type pK_a – Log*P* plot for the methoxy-substituted compound series is shown in Figure 1. These generalized data show that the bicyclic scaffolds studied in this work allow fine-tuning acidity of cycloalkane and benzene derivatives upon isosteric replacements within a range of *ca*. 0.6 pK_a units. In addition to that, the compound's lipophilicity can be also varied within a range of *ca*. 0.9 Log*P* units (and is likely to be decreased, especially for the case of benzene replacement).

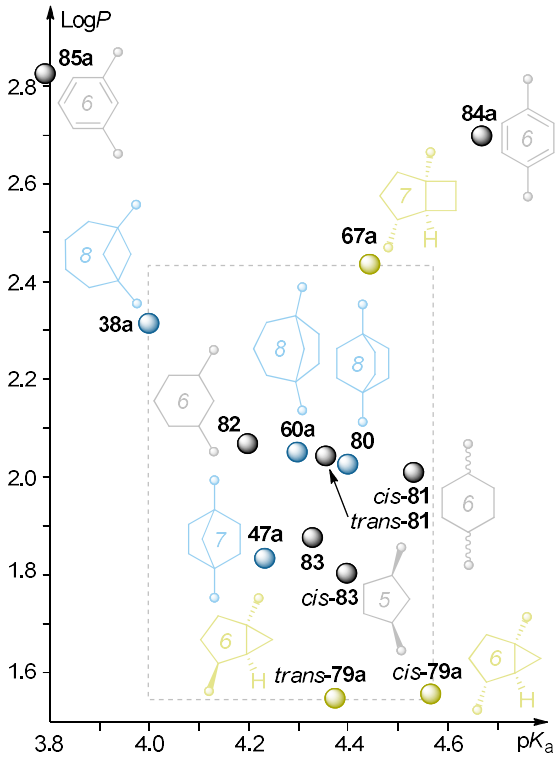


Figure 1. pK_a – Log*P* plot for methoxy-substituted carboxylic acids and their derivatives studied in this work (the numbers inside the rings correspond to the number of carbon atoms in the scaffold).

Structural characterization. To evaluate molecular geometry of the proposed scaffolds, X-Ray diffraction studies were performed with amino acid derivatives **44**, **70**, *cis*-**86**, and *trans*-**86** (Figure 2, *A*). For the corresponding bicyclo[2.2.1]heptane, -[3.2.1]- and -[2.2.2]octane, and benzene derivatives, three-dimensional structures were generated using the Conformer tool of Marvin package.[42] For further discussions, exit vector parameter (EVP)-based method was used,[43,44] which had been applied by our group for analysis of various cyclic systems previously[45–51] and is being adopted by a wider chemical community.[25,27,52–54] The basic idea of this approach is simulating the functional groups mounted onto the scaffold by two exit vectors. Carbon atoms of the (bi)cyclic ring system bearing the functional groups are used as the starting points of these vectors, whereas the direction is defined by the attached bonds (Figure 2, *A*). Relative orientation of two exit vectors can be described by four geometric parameters *r*, φ_1, φ_2, and θ as shown in Figure 2, *B*. For flattened structures, the absolute value of θ tends to be close to 0° or 180°, whereas for linear ones, the φ_1/φ_2 angles are equal to 0°.

Exit vector plots depicted in $r - \theta$ *and* $\theta - \varphi_1/\varphi_2$ coordinates and containing the data for the studied bicyclic scaffolds are shown in Figure 3 and Table 3). It is apparent that geometrically, bridged bicyclic systems synthesized in this work (i.e., bicyclo[2.2.1]heptanes, bicyclo[4.1.1]- and -[3.2.1]octanes) are close mimetics of *m*- and (to lesser extent) *p*-disubstituted benzene, as well as *cis*-1,3-disubstituted cyclohexane scaffold (all located in the β region of exit vector plots). *cis*-Isomeric bicyclo[3.2.0]heptane and especially -[3.1.0]hexane scaffolds are found on the other side of

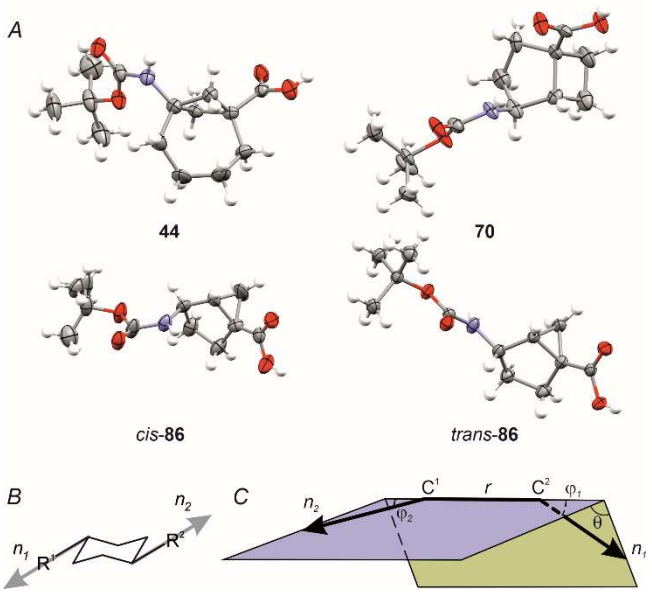
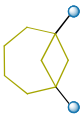
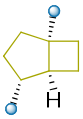
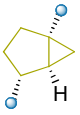
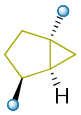
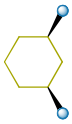
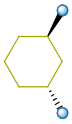
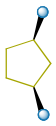
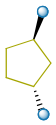
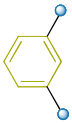


Figure 2. (*A*) Molecular structures of compounds **44**, **70**, *cis*-**86**, and *trans*-**86** according to X-Ray diffraction studies (thermal ellipsoids are shown at 50% probability level). (*B*) Definition of exit vectors $\boldsymbol{n}_1$ and $\boldsymbol{n}_2$ (1,4-disubstituted cyclohexane scaffold is taken as an example). (*C*) Definition of geometric parameters r, φ_1, φ_2, and θ.

Table 3. Geometric parameters r, φ_1, φ_2, and θ of the scaffolds studied in this work.

Entry	Scaffold	r, Å	φ_1, °[a]	φ_2, °	θ, °[b]
1		2.17	42	42	1
2		2.23	21	21	0
3		2.40	30	30	0
4		2.48	73	53	19
5		2.39	72	40	41
6		2.44	39	38	121
7		2.70	0	0	N/D[d]
8[c]		2.97	70	24	4
9[c]		2.96	30	28	177
10[c]		2.52	36	34	5
11[c]		2.53	82	35	116
12[c]		2.42	56	47	13
13[c]		2.45	67	46	151
14		2.85	0	0	N/D[d]
15		2.46	30	30	0

[a] Since the choice of φ_1 and φ_2 is deliberate, we set $\varphi_1 \geq \varphi_2$.

[b] Absolute values are given.

[c] Average values for the cycloalkane scaffolds are retrieved from ref. [43].

[d] For the scaffolds with colinear orientation of exit vectors, the θ angle is undefined.

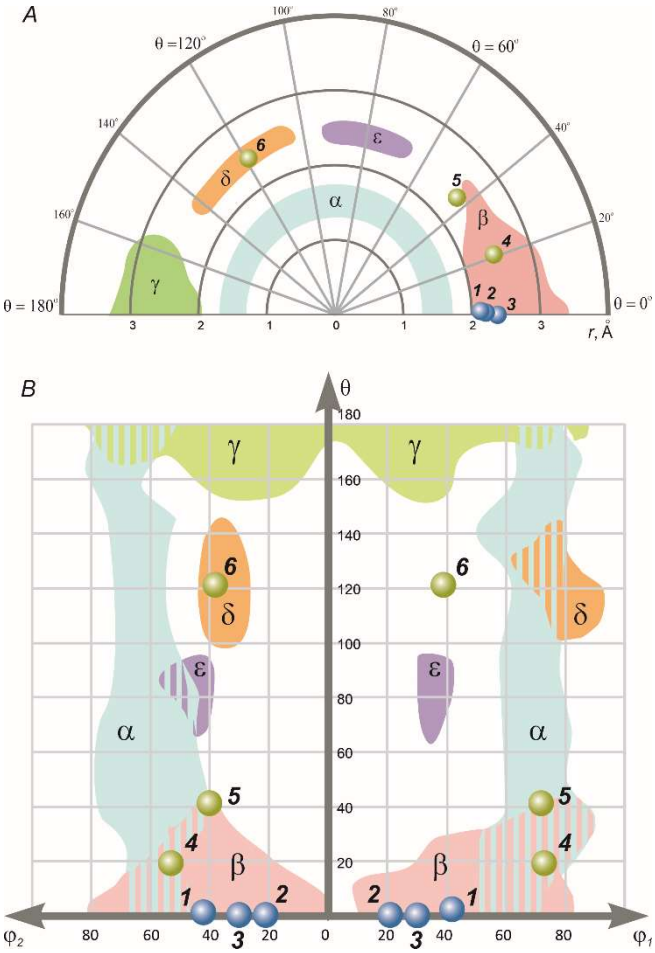
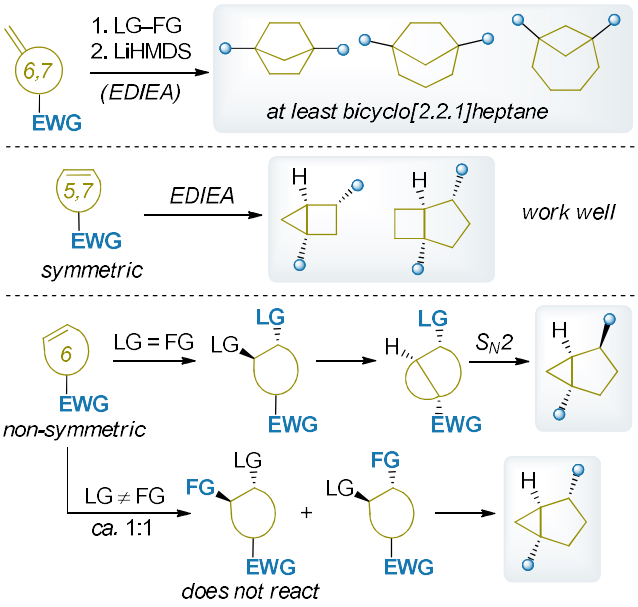


Figure 3. Bicyclic scaffolds synthesized in this work shown in $r-\theta$ (*A*) and $\theta-\varphi_1/\varphi_2$ (*B*) coordinates. Bold italic numbers corresponds to entry numbers in Table 3: ***1*** – bicyclo[4.1.1]octane, ***2*** – bicyclo[2.2.1]heptane, ***3*** – bicyclo[3.2.1]-octane, ***4*** – bicyclo[3.2.0]heptane, ***5*** and ***6*** – *cis*- and *trans*-isomeric bicyclo[3.1.0]hexanes. For the definition of EVP regions α–ε, see ref. [44].

the β EVP region; they can be considered as three-dimensional analogs of *cis*-1,3-disubstituted cyclohexanes and cyclopentanes. Finally, the *trans* isomer of 1,4-disubstituted bicyclo[3.1.0]hexane scaffold demonstrates a close resemblance to *trans*-1,3-disubstituted cyclohexane and (to a lesser extent) cyclopentane scaffolds (all located in the δ EVP region).

Conclusions

Electrophilic double bond functionalization – intramolecular enolate alkylation (*EDIEA*) sequence is an efficient approach for the construction of disubstituted bicyclo[m.n.k]alkane scaffolds starting (where k = 0 or 1) from the appropriate unsaturated cyclic carboxylic acids derivatives (i.e., esters or nitriles) (Scheme 18). The scope of the substrates with exocyclic double bonds (leading to bridged bicyclic ring systems) is limited by the size of the scaffold formed. Thus, bicyclo[2.2.1]heptane (formed from 4-methylenecyclohexane carboxylate) is the smallest ring system that can be constructed using this approach, albeit with moderate yield. Symmetric five- and seven-membered cycloalkenecarboxylic acid derivatives work well in the *EDIEA* sequence, giving the corresponding fused bicyclo[m.n.0]alkanes.



Scheme 18. Summary of the electrophilic double bond functionalization – intramolecular enolate alkylation (*EDIEA*) sequence scope and limitations

With non-symmetric substrates having an endocyclic double bond (e.g., cyclohexene derivative), regioselectivity of the first step becomes an issue. Luckily, the cyclization step is highly selective in this case. Therefore, using a symmetric modification for the electrophilic addition step (e.g., bromination) followed by regioselective intramolecular enolate alkylation and nucleophilic substitution can an approach to obtain *trans*-isomeric derivatives of the corresponding fused bicyclic system (i.e., bicyclo[3.1.0]hexane). On the other hand, non-symmetric electrophilic functionalization can be also used since only one of the regioisomeric addition products undergoes the cyclization at the second step. In this way, *cis* stereoisomers of the above scaffold can be synthesized.

The developed method was amendable for multigram synthesis of mono- and bifunctional bicyclo[4.1.1]- and -[3.2.1]octane, bicyclo[2.2.1]- and -[3.2.0]heptane, bicyclo[3.1.0]hexane, and bicyclo[2.1.0]pentane (housane; previous work) derivatives, including fluorinated amines and carboxylic acids, amino acids, monoprotected diamines, and many other building blocks for medicinal chemistry.

The above bicyclic scaffolds can allow fine-tuning acidity of cycloalkane and benzene derivatives upon isosteric replacements in a range of 0.6 pK_a units. In addition to that, the compound's lipophilicity can be varied in a ca. 0.9 Log*P* unit range; it is likely to be decreased or affected insignificantly. For both parameters, the conjugation effects present in the aromatic series are eliminated.

According to exit vector parameter (EVP) analysis, bicyclo[2.2.1]-heptanes, bicyclo[4.1.1]- and -[3.2.1]octanes are close structural analogs of *m*- and (to lesser extent) *p*-disubstituted benzene, as well as *cis*-1,3-disubstituted cyclohexane scaffold (Figure 4). Fused *cis*- and *trans*-isomeric bicyclo[3.m.0]alkanes (m = 1 or 2) can be used as three-dimensional mimetic of *cis*- and *trans*-1,3-disubstituted cycloalkanes (C_5/C_6), respectively. Of course, a wider range of isosteric replacements can be also envisaged for the synthesized bicyclic derivatives.

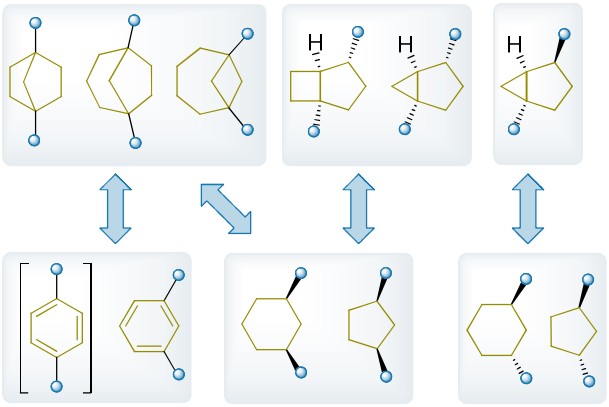


Figure 4. Potential for isosteric replacements using saturated bicyclic ring systems described in this work.

The title bicyclic benzene and cycloalkane isosteres have now become readily available to the scientific community, and with their physicochemical and structural characteristics known, we believe that these and similar ring systems accessible through the *EDIEA* reaction sequence will find their wider application in early drug discovery in the nearest future.

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Conflict of Interest

Most authors are employees, trainees, or consulting scientists of Enamine Ltd. that offers the building blocks described in this paper in the company's catalog.

Keywords: bicyclic compounds • saturated compounds • acidity • lipophilicity • isosteres • enolate alkylation

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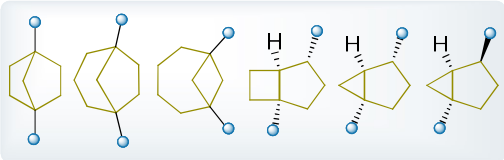
Bicyclic Compounds



☑ *EDIEA sequence*
☑ *multigram synthesis*
☑ *pK_a, LogP evaluation*
☑ *exit vector analysis*
☑ *potential benzene & cycloalkane isosteres*

Electrophilic double bond functionalization – intramolecular enolate alkylation sequence (*EDIEA*) is an efficient approach to bicyclic fused and bridged mono- and bifunctional building blocks. The method is applicable for the multigram preparation of the target compounds, which is illustrated by synthesis of over 50 building blocks on up to 150 g scale. Physicochemical and structural parameters of the title scaffolds illustrate their utility as promising benzene and cycloalkane isosteres and provide a rationale for fine-tuning the compound's properties during drug optimization.

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