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Article

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Building the housane: diastereoselective synthesis and characterization of bicyclo[2.1.0]pentane carboxylic acids

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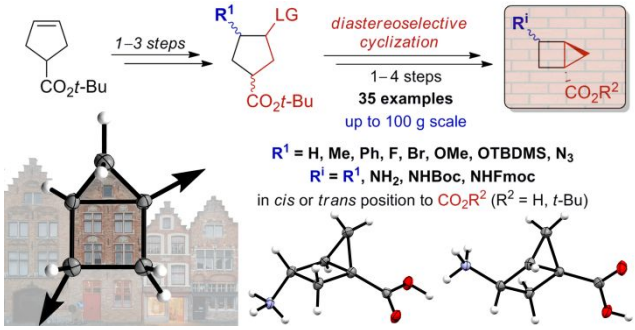
Abstract. An approach to 1,3-disubstitued bicyclo[2.1.0]pentane (housane) derivatives was developed. The method relied on LiHMDS-mediated intramolecular cyclization of trisubstitued cyclopentane carboxylates bearing a leaving group (at the C-4 position) and an additional substituent (at the C-3 atom), in turn synthesized from cyclopent-3-ene carboxylate. The synthetic sequence allowed for the preparation of both *cis*- and *trans*-1,3-disubstituted housane-1-carboxylic acids in diastereoselective manner on up to 80 g scale. In particular, bicyclic γ-amino acids – GABA analogues – were synthesized. It was shown that the bicyclo[2.1.0]pentane did not significantly affect pK_a of the corresponding derivatives and slightly increased their hydrophilicity (by 0.07–0.25 Log*P* units) as compared to cyclopentane. X-Ray diffraction studies showed that *cis*- and *trans*-1,3-disubstituted

housanes can be considered as flattened analogues of the corresponding cyclopentane derivatives with fixed envelope conformation of the five-membered ring.



Introduction

Occurrence of low-molecular-weight alicyclic scaffolds in molecular design has significantly increased over the last years,[1–3] partially due to their high relevance to the «escape from flatland» concept favoring compounds with higher sp^3 atom fraction.[4,5] Thus, cyclopropane derivatives are ubiquitous in natural[6] and synthetic[7] products with a wide range of pharmaceutical applications:[8–12] for example, 6 marketed and 26 investigational drugs contain the cyclopropane carboxylate moiety. Similarly, cyclobutane fragment is the smallest cyclic moiety which does not significantly alter chemical properties when incorporated to the target molecules.[13–16] In turn, cyclopropane- and cyclobutane-based conformational restriction is a multipurpose tool in medicinal chemistry providing enhanced potency, selectivity, and metabolic resistance of drug candidate supplemented with minimization of entropic penalty within binding to biological targets.[17]

In this view, bicyclo[2.1.0]pentane ("housane") derivatives containing both cyclopropane and cyclobutane rings in their structure are of special interest. The bicyclo[2.1.0]pentane scaffold can be considered as a constrained surrogate of cyclopentane, which has a proven track of biological relevance represented by analogues of γ-aminobutyric acid (GABA (**1**), a chief inhibitory neurotransmitter),[18–22] *e.g.* ACPD (**2,** mGluR agonist)[23–25] or eglumegad (**3**, LY354740, $mGlu_{2/3}$ orthosteric agonist) used for neuroprotection, treatment of anxiety and drug addiction (Figure 1).[26,27]

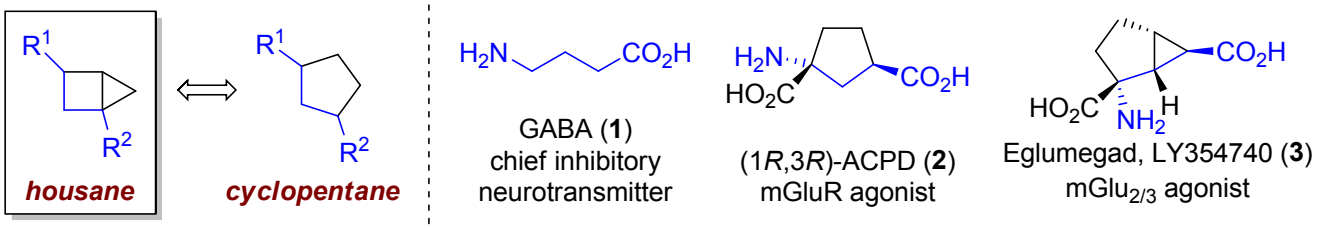
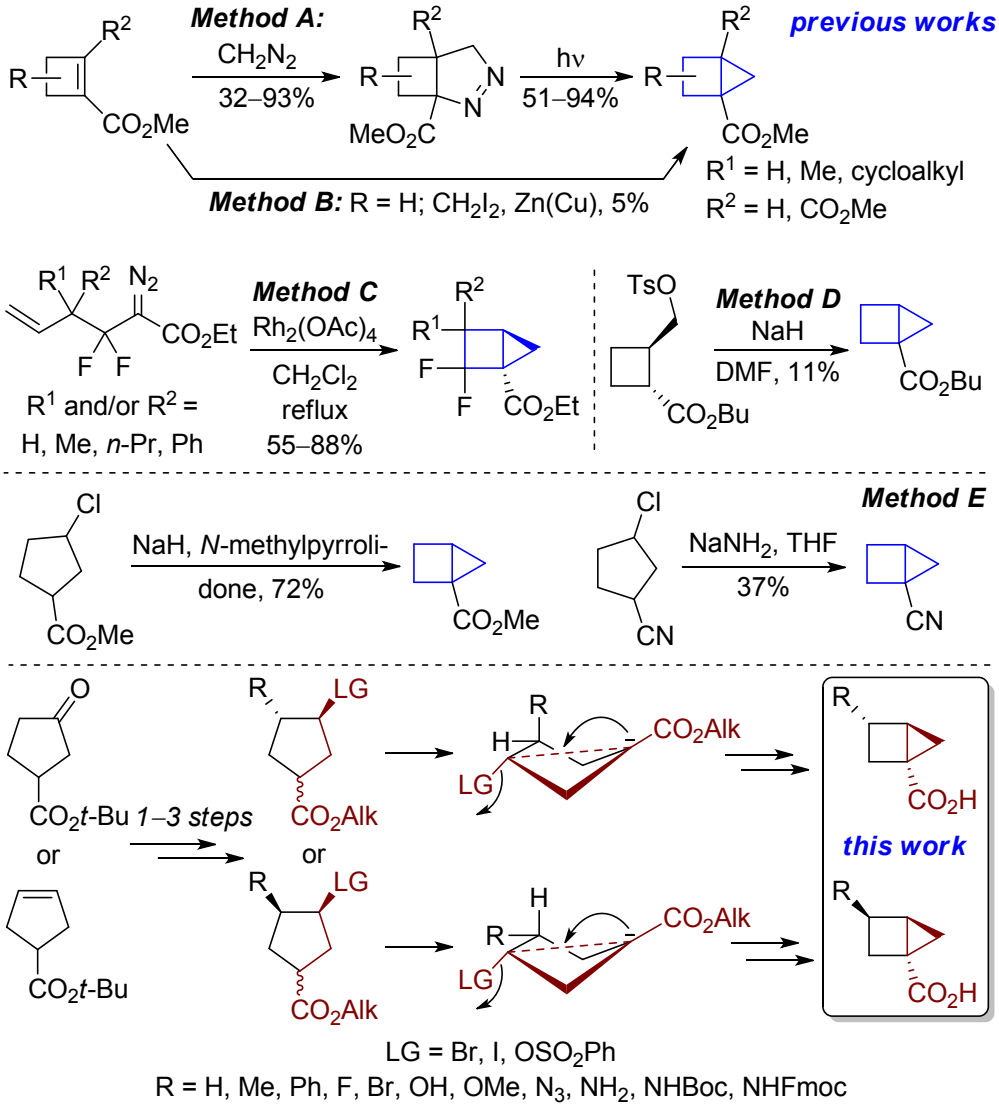


Figure 1. Housane – a conformationally constrained analogue of cyclopentane, a scaffold of high biological relevance

To date, wide application of bicyclo[2.1.0]pentane derivatives has been hampered by limited synthetic accessibility of the corresponding building blocks. In particular, the known methods for preparation of housane carboxylates relied on two-step cyclopropanation of cyclobutene carboxylates with diazomethane (Scheme 1). Rhodium-catalysed 1,3-dipolar cycloaddition led to pyrazolines, which subsequently undergo photochemical denitrogenation providing bicyclo[2.1.0]pentanes (Method **A**).[28–33] Such transformations are often accompanied with formation of significant amounts of by-products. Analogous approach relied on the Simmons–Smith reaction (Method **B**); however, the corresponding housane was obtained in extremely low yield.[34] Another method included intramolecular cyclopropanation via the decomposition of δ,ε-unsaturated β,β-difluoro-α-diazo esters (Method **C**).[35] At the same time, the only example of housane synthesis via intamolecular alkylation was performed with 2-(tosyloxymethyl)cyclobutane carboxylate; however, low yield of the target product was achieved (Method **D**).[34] Similar approach was described by Hall and co-workers for the case of 2-(chloromethyl)cyclobutanecarbonitrile, which was obtained via intramolecular cyclizations of 2-(chloromethyl)cyclobutanecarbonitrile (14% yield), 3-chlorocyclopentanecarbonitrile (37% yield), or methyl 3-chlorocyclopentanecarboxylate (72% yield) (Method **E**).[36] Several examples of substituted 2-azabicyclo[2.1.0]pentane-1-carboxylates were also synthesized via intramolecular alkylations.[37–39]

In line with our continuous efforts to synthesize advanced sp^3-enriched bicyclic building blocks for drug discovery,[40–42] in this work, we have aimed at developing of efficient and scalable diastereoselective approach to functionalized 1,3-disubstituted housanes. Our approach was similar to the method of Hall and co-workers[36] mentioned above and included anionic cyclization of appropriate trisubstituted cyclopentane derivatives. It was expected that diastereoselectivity of the cyclization of the corresponding enolate should be defined by relative configuration of the substituent R and the leaving group in the substrate; on the contrary, configuration at the center adjanced to the ester moiety should be unimportant due to flattened structure of the corresponding enolate intermediates. In addition to that, characterization of structural and physico-chemical properties of the aforementioned scaffold as a promising structural motif for medicinal chemistry was envisaged.

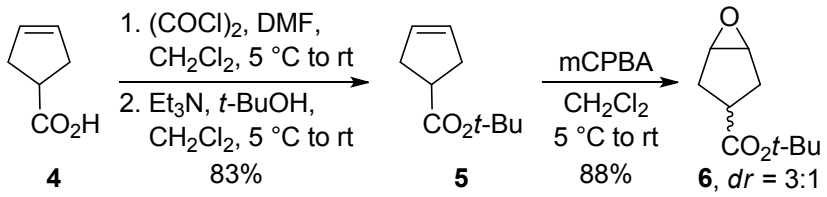


Scheme 1. Approaches to housane carboxylates (carboxylic acids)

Results and discussion

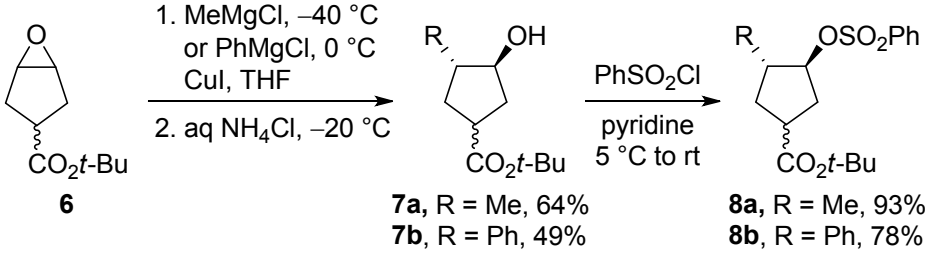
Synthesis. According to the synthetic plan shown in Scheme 1, it was anicipated that incorporation of both leaving group necessary for the cyclization step and the target substituents into the cyclopentane core could be achieved by taking an advantage of cyclopentene carboxylic acid **4**. The reaction sequence commenced with preparation of the corresponding *tert*-butyl ester **5**, which was obtained in 83% yield on up to 250 g scale (Scheme 2). Epoxydation of **5** under standard conditions (*m*-CPBA in CH_2Cl_2) gave derivative **6** in 88% yield as a diastereomeric mixture (*dr* = 3:1); this step could be also performed on large scale (up to 150 g in one run). It should be stressed out that the moderate diastereoselectivity at

this step was not important since the stereogenic center adjenced to the carboxylate moiety would undergo epimerization upon further base-promoted cyclization.



Scheme 2. Synthesis of oxirane **6**

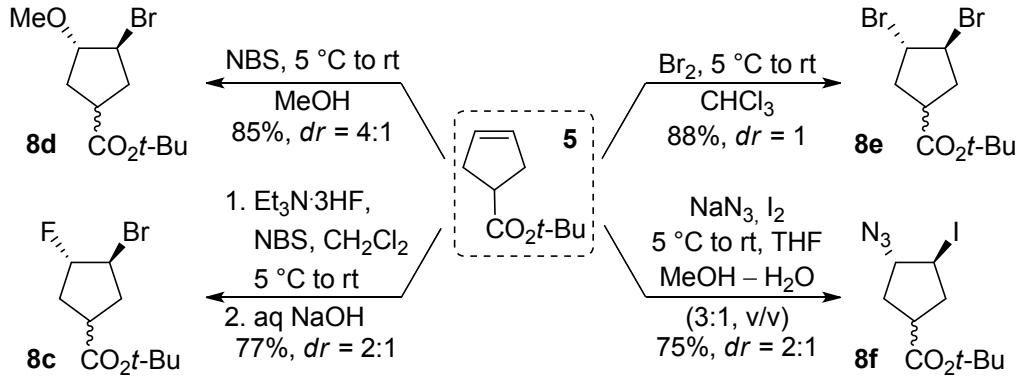
Subsequent oxirane ring opening in **6** was perfomed with MeMgCl (–40 °C) or PhMgCl (0 °C) in the presence of CuI in THF and provided *trans* alcohols **7a** and **7b** in 64% and 49% yield, respectively, on up to 100 g scale (Scheme 3). Sulfonylation of **7a** and **7b** with $PhSO_2Cl$ in pyridine gave intermediates **8a** and **8b** in 93% and 78% yield, respectively. It is important to outline that while mesylation of **7a** or **7b** was successful, cyclization of the corresponding mesylates did not proceed in all atempts and resulted in formation of an uninterpreted mixture.



Scheme 3. Synthesis of intermediates **8a** and **8b** (relative configurations are shown)

Direct introducing of other target substituents and leaving groups in *trans* relative configuration was achieved by some common electrophilic addition reactions of alkene **5**. In particular, fluorine-contaning derivative **8c** was obtained in 77% yield on up to 150 g scale via fluorobromination using $Et_3N{\cdot}3HF$ and NBS in CH_2Cl_2 (Scheme 4). Reaction of **5** with NBS in MeOH resulted in methoxy-substituted bromide **8d** (85% yield), while treatment of **5** with Br_2 in $CHCl_3$ gave dibromide **8e** in 88% yield. Azide **8f** was

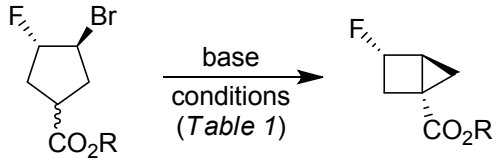
synthesized from **5** in 75% yield by the reaction with NaN_3 and I_2 in MeOH – H_2O (3:1, v/v) on up to 280 g scale. Again, diastereoselectivity of these transformations (*dr* 2:1 to 1:0) was not critical since the stereogenic center near the carboxylate moiety would undergo epimerization upon further base-promoted cyclization.



Scheme 4. Synthesis of intermediates **8c–f** (relative configurations are shown)

The cyclization step was optimized for the case of fluorinated derivative **8c**, taking an advantage of monitoring the reaction progress by ^{19}F NMR; the corresponding methyl ester or carboxylic acid were also evaluated. Our preliminary experiments relied on using the methyl ester and 2.4-fold excess of *t*-BuOK in THF (Entry 1) or 2-fold excess of *t*-BuOK in benzene (Entry 2). Unfortunately, only the traces of cyclization products were detected. Next, the reaction was performed in hexanes at 5 °C to rt, and the target housane was obtained at these conditions in diastereoselective manner, but only in 29% yield as a mixture of *tert*-butyl and methyl esters formed *via* transesterification reaction (Table 1, Entry 3). Further increase of the reaction temperature led to formation of the same mixture of esters, but in higher yield (45%, Entry 4). Thus, it was considered that *tert*-butyl ester **8c** would be more suitable for this transformation. Its reaction in the aforementioned conditions gave the target housane **9c**; unfortunately, the reaction was accompanied with the bromine elimination, and the corresponding fluorocyclopentene carboxylate was obtained as a by-product (Entry 5). Attempted cyclizations in the presence of MeONa, NaH, or DBU were also unsuccessful (Entries 6–8).

Table 1. Synthesis of 3-fluorohousane-1-carboxylic acid or its derivatives



Entry	R	Base	Solvent	Temperature	Time	Yield, %[a]
1	Me	*t*-BuOK (2.4 eq)	THF	5 °C to rt	overnight	traces[b]
2	Me	*t*-BuOK (2 eq)	benzene	5 °C to rt	overnight	traces[b]
3	Me	*t*-BuOK (2.2 eq)	hexanes	5 °C to rt	overnight	29[c]
4	Me	*t*-BuOK (2.2 eq)	hexanes	68 °C	2 h	45[c]
5	*t*-Bu	*t*-BuOK (2.2 eq)	hexanes	68 °C	2 h	31[b,d]
6	*t*-Bu	MeONa (1.15 eq)	MeOH	5 °C to rt	overnight	0
7	*t*-Bu	NaH (1.2 eq)	DMF	5 °C to rt	overnight	0
8	*t*-Bu	DBU (2.1 eq)	benzene	5 °C to rt	overnight	traces[b]
9	*t*-Bu	LDA (1.15 eq)	THF	–70 °C to rt	overnight	traces[b]
10	*t*-Bu	LDA (1.5 eq)	THF	–70 °C to rt	2 h	22[b]
11	*t*-Bu	MeLi (1.05 eq)	THF	–70 °C to rt	1 h	0
12	*t*-Bu	LiHMDS (1.1 eq)	THF	–70 °C to rt	1 h	0
13	*t*-Bu	LiHMDS (1.5 eq)	THF	–70 °C to rt	1 h	40
14	*t*-Bu	LiHMDS (2.5 eq)	THF	–70 °C to rt	1 h	71
15	H	LiHMDS (2.5 eq)[a]	THF	–70 °C to rt	1 h	0

[a] Isolated yield. [b] Estimated by ^{1}H and/or ^{19}F NMR unless noted otherwise. [c] A mixture of *tert*-butyl and methyl esters was formed via transesterification. [d] Side bromine elimination occurred, which gave the corresponding fluorocyclopentene carboxylate as a by-product

In further experiments, a series of lithium-containing bases were tested for the transformation of **8c** into **9c** (THF at –70 °C to rt). Thus, using 1.15-fold excess of LDA did not result in formation of target product (Entry 9), while 1.5-fold excess gave **9c** in low yield (22%, Entry 10). Neither 1.05-fold excess of MeLi (Entry 11) nor 1.1-fold excess of LiHMDS (Entry 12) were sufficient to achieve the required transformation. Nevertheless, increasing amount of LiHMDS finally resulted in significantly higher

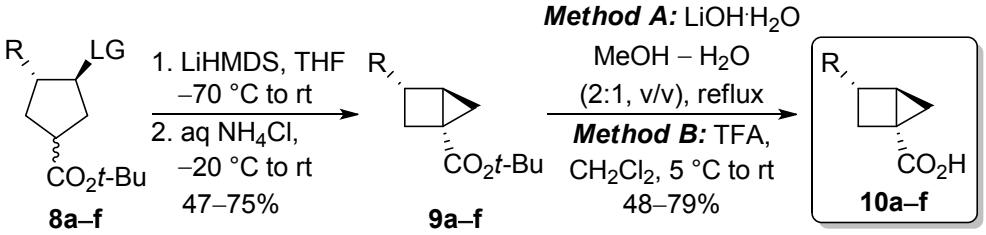
yields of **9c** (Entries 13 and 14). In particular, the best result was obtained by using 2.5-fold excess of LiHMDS, and the target housane **9c** was obtained in 71% yield (Entry 14). It should be noted that attempted synthesis of **9c** starting from the corresponding carboxylic acid instead of ester **8c** via the dianion formation was unsuccessful (Entry 15).

The optimized conditions of the cyclization step (2.5-fold excess of LiHMDS, THF, –70 °C to rt, 1 h) were applied to the series of intermediates **8a–f**, and corresponding 1,3-disubstituted housane carboxylates **9a–f** were obtained diastereoselectively in moderate to good yields (47–75% yield, Table 2). It should be outlined that cyclization of phenyl-substituted derivative **8b** into **9b** was accompanied with formation of the corresponding phenylcyclopentene by elimination of bromine atom, presumably due to energetically favorable formation of the conjugated double bond. For the preparation of bromohousane derivative **9e**, the inversed reagent addition order should be used to prevent decomposition of the product and tar formation (see the Experimental Part).

Expectedly, *cis* isomers of the 1,3-disubstituted housanes **9a–f** were obtained exclusively, which was defined by the *trans* relative configuration of the stereogenic centers at the C-3 and C-4 atoms of corresponding intermediates **8** (see also below).

Subsequent hydrolysis of *tert*-butyl esters **9a–f** was found to be somewhat challenging. Thus, common acidic cleavage of *tert*-butyl group proceeded smoothly only for the case of phenyl (**9b**) and bromo (**9f**) derivatives obtained in 58% yield on 40 g scale (Table 2, Entries 2 and 5). In other cases, however, this transformation was unruitful due to significant tar formation. Nevertheless, uncommon alkaline hydrolysis of **9** performed upon reflux in the presence of $LiOH \cdot H_2O$ in MeOH – H_2O (2:1, v/v) gave the target carboxylic acids **10** in 48–79% yield on up to 50 g scale (Entries 1, 3, 4, and 6). The presence of MeOH as the co-solvent was found to be essential; possibly, *in situ* base-catalyzed trans-esterefication occurred giving the correesponding methyl esters, followed by their alkaline hydrolisis. In the absence of MeOH, the *tert*-butyl group cleavage did not occur in all cases.

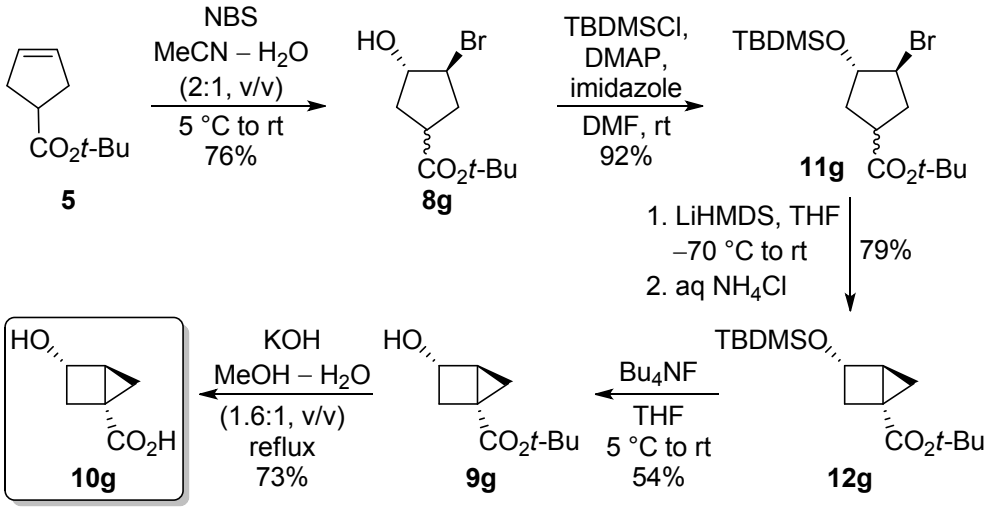
Table 2. Preparation of 3-substituted bicyclo[2.1.0]pentane-1-carboxylic acids **10**



Entry	R	Leaving group (LG)	Starting material **8**	Ester **9** (yield, %[a])	Carboxylic acid **10** (yield, %[a])	Method
1	Me	OSO_2Ph	**8a**	**9a** (65)	**10a** (79)	**A**
2	Ph	OSO_2Ph	**8b**	**9b** (50)	**10b** (58)	**B**[b]
3	F	Br	**8c**	**9c** (71)	**10c** (63)	**A**
4	OMe	Br	**8d**	**9d** (75)	**10d** (72)	**A**
5	Br	Br	**8e**	**9e** (47)	**10e** (58)	**B**
6	N_3	I	**8f**	**9f** (51)	**10f** (48)	**A**

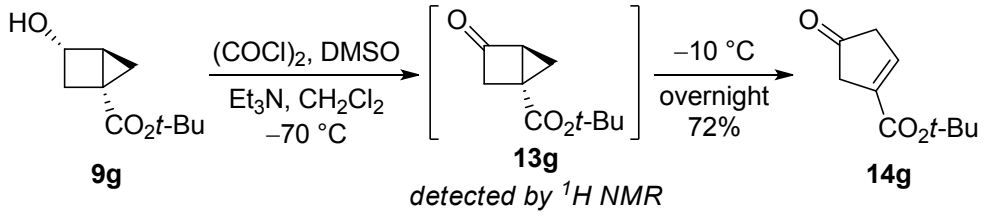
[a] Isolated yield of the products. [b] Side formation of the corresponding cyclopentene occurred

Unfortunately, an attempted preparation of the corresponding γ-hydroxycarboxylate **9g** from oxirane **6** via tandem oxirane ring opening - intramolecular cyclization by using LDA or LiHMDS resulted in significant tar formation. Thus, synthesis of **9g** relied on the aforementioned reaction sequence; however, additional protection – deprotection of the hydroxyl group were requred. Hydroxybromination of alkene **5** (providing **8g** in 76% yield) followed by treatment with TBDMSCl in the presence of DMAP – imidazole in DMF gave *O*-protected intermediate **11g** in 92% yield (Scheme 5). Subsequent cyclization of **11g** upon common conditions led to bis-protected derivative **12g** (79% yield), which was transformed into the target γ-hydroxyester **9g** via Bu_4NF-mediated silyl protective group cleavage (54% yield). Alkaline hydrolysis of the ester moiety proceeded smoothly by refluxing in MeOH – H_2O (1.6:1, v/v) in the presence of KOH, and the carboxylic acid **10g** was isolated in 73% yield on up to 25 g scale.



Scheme 5. An approach to hydroxycarboxylic acid **10g** (relative configurations are shown)

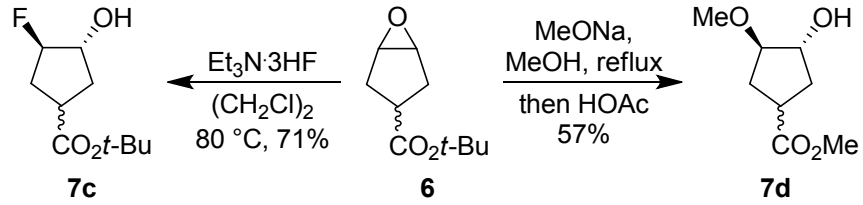
Attempted oxidation of alcohol **9g** with the Swern reagent resulted in formation of the corresponding ketone **13g** (detected by ^{1}H NMR), which was transformed exclusively into the corresponding ring-opened cyclopentenone **14g** (72% yield) upon storage at –10 °C overnight (Scheme 6).



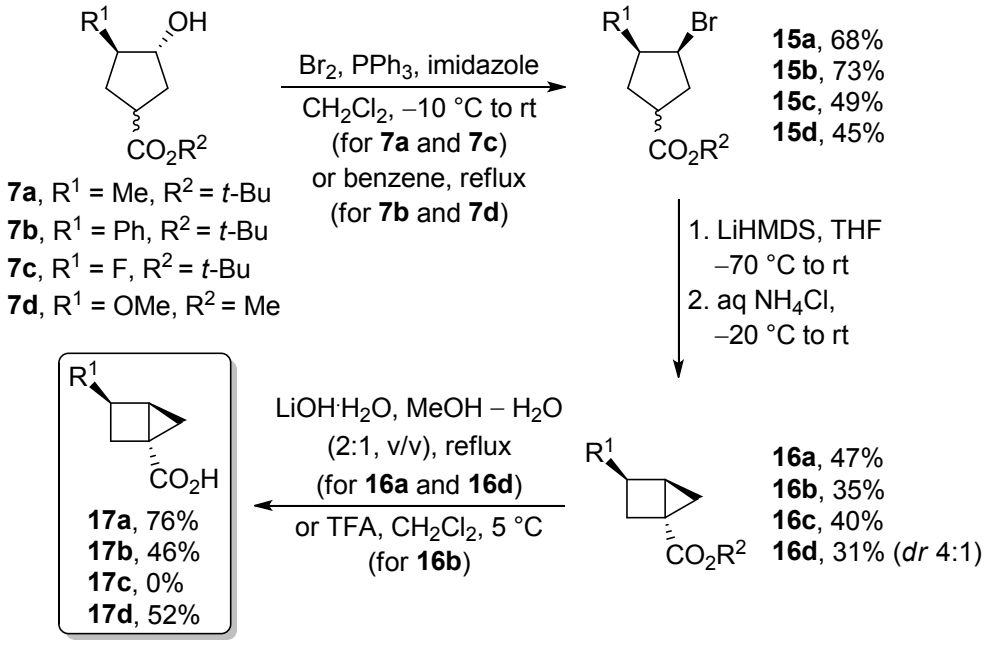
Scheme 6. Attempted synthesis of ketone **13g** (relative configurations are shown)

Next, we have aimed at the preparation of stereoisomeric 1,3-disubstituted housane derivatives with *trans* relative configuration of the corresponding substituents. It was envisaged that *trans* alcohols **7** obtained by ring opening of aforementioned oxirane **6** could be suitable intermediates for synthesis of the corresponding *cis* bromides **15** (via the Appel reaction with $Br_2 – PPh_3$) required for transformation into the target *trans* housane carboxylates **16**. Indeed, alcohols **7a** and **7b** bearing methyl and phenyl substituents, respectively, were prepared according to Scheme 3. Furthermore, reaction of **6** with $Et_3N{\cdot}3HF$ in dichloroethane at 80 °C led to fluorinated derivative **7c** in 71% yield on up to 80 g scale

(Scheme 7). Oxirane ring opening with MeONa in MeOH was implemented for the preparation of methoxy-susbtituted derivative; however, this transformation was accompanied with trans-esterification reaction, which led eclusively to the formation of methyl ester **7d** in 57% yield.



Scheme 7. Oxirane ring opening for the preparation of **7c** and **7d** (relative configurations are shown)

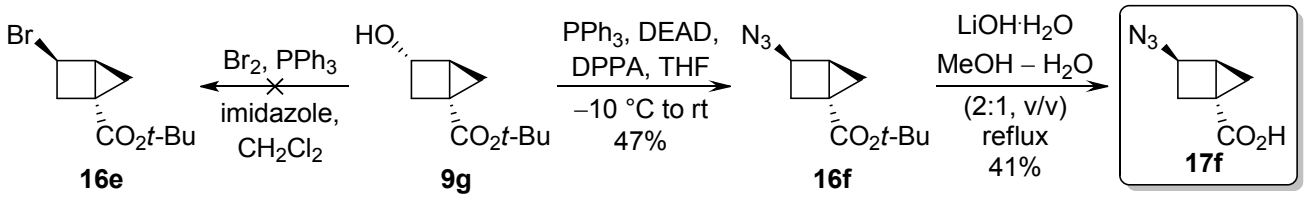


Scheme 8. Synthesis of 3-substituted bicyclo[2.1.0]pentane-1-carboxylates **16** and **17** (relative configurations are shown)

The Appel reaction was applied to *trans* alcohols **7a–d** for the preparation of *cis* bromides **15a–d** in 45–73% yield on up to 150 g scale (Scheme 8). Expectedly, cyclization of **15a–c** proceeded in diastereoselective manner and led to housanes **16a–c** in moderate yield (35–47% yield), while partial epimerization occurred in the case of **15d**, and housane **16d** was obtained in 31% yield (*dr* 4:1 ratio). Subsequent *tert*-butyl group cleavage proceeded smoothly with LiOH in MeOH – H_2O (for **16a** and

16d) or with TFA in CH_2Cl_2 (for **16b**) providing the title building blocks **17a**, **17b** and **17d** in 46–76% yield. Neither of methods was fruitful for hydrolysis of **16c** – plausible bicyclo[2.1.0]pentane ring opening occurred upon both acidic and basic conditions, and no formation of **17c** was detected.

It should be outlined that the aforementioned reaction sequence did not work for the preparation of *trans* azide **16f** (stereisomeric to **9f**); preparation of the corresponding intermediate **15f** was not fruitful in that case (the Appel reaction did not proceed due to the side Staudinger reaction). Nevertheless, preparation of azide **16f** could be achieved in 47% yield on up to 110 g scale via the Mitsunobu reaction of alcohol **9g** (PPh_3, DEAD and DPPA in THF) (Scheme 9). The corresponding azido carboxylic acid **17f** was obtained in 41% yield by cleavage of the *tert*-butyl group with $LiOH·H_2O$. Unfortunately, the Appel reaction of **9g** performed with $Br_2 – PPh_3$ did not result in the formation of *trans* γ-bromo carboxylate **16e** in all attempts (Scheme 9).

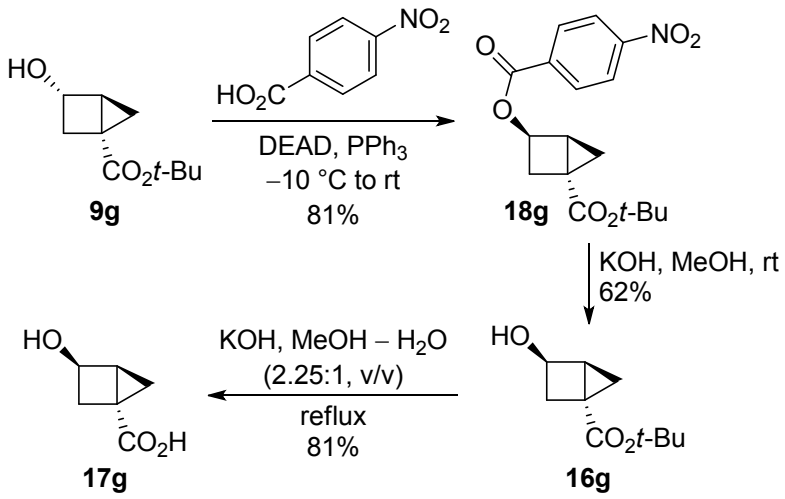


Scheme 9. Synthesis of azide **17f** (relative configurations are shown)

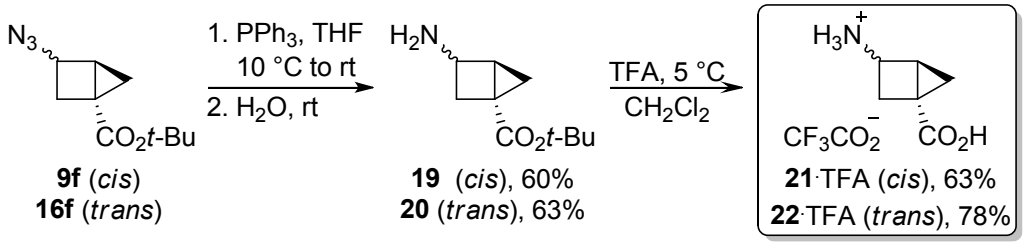
Next, we anticipated that *cis* dihydroxylation of alkene **5**, followed by monosylilation with TBDMSCl, sulfonylation and futher transformations similar to those shown in Scheme 5 could be suitable for the preparation of **17g** (a stereoisomer of **9g** with *trans* configuration of the hydroxy group to the carboxylate moiety). However, sulfonylation of the corresponding monosilyl derivative did not occur in all attemtps, presumably due to steric hindance from the bulky TBDMS group. In this view, the Mitsunobu reaction of **9g** with 4-nitrobenzoic acid, DEAD and PPh_3 was applied for the configuration inversion, and the product **18g** was obtained in 81% yield (Scheme 10). Selective hydrolysis of ortogonally protected diester **18g** with KOH in MeOH gave hydroxyester **16g** (62% yield), which was

trahsformed into the corresponding carboxylic acid **17g** in 81% yield on up to 20 g scale with KOH in MeOH – H_2O (2.25:1, v/v).

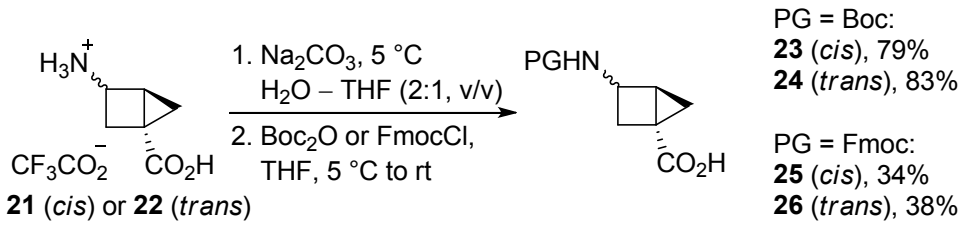
Further synthetic studies were aimed at the preparation of stereoisomeric housane-derived γ-amino acids as promising GABA analogues (Scheme 11). We took an advatage of stereoisomeric azido esters **9f** and **16f**, which were successfully reduced to the corresponding *cis* (**19**) and *trans* (**20**) amino esters with PPh_3 in THF followed by quenching with H_2O (60% and 63% yield, respectively). The corresponding amino acids **21** and **22** were obtained as trifluoroacetates by treatment of **19** and **20** with TFA in CH_2Cl_2 in 63% and 78% yields, respectively, on up to 70 g scale.



Scheme 10. Synthesis of γ-hydroxy carboxylic acid **17g** (relative configurations are shown)

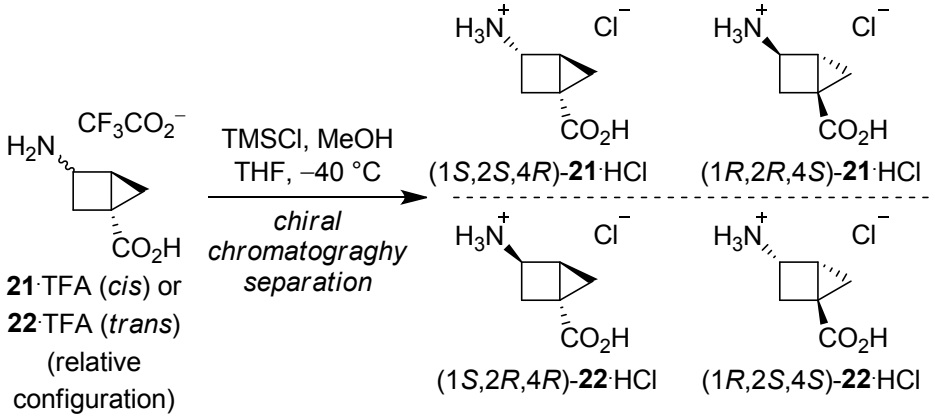


Scheme 11. Synthesis of amino acids **21** and **22** (relative configurations are shown)



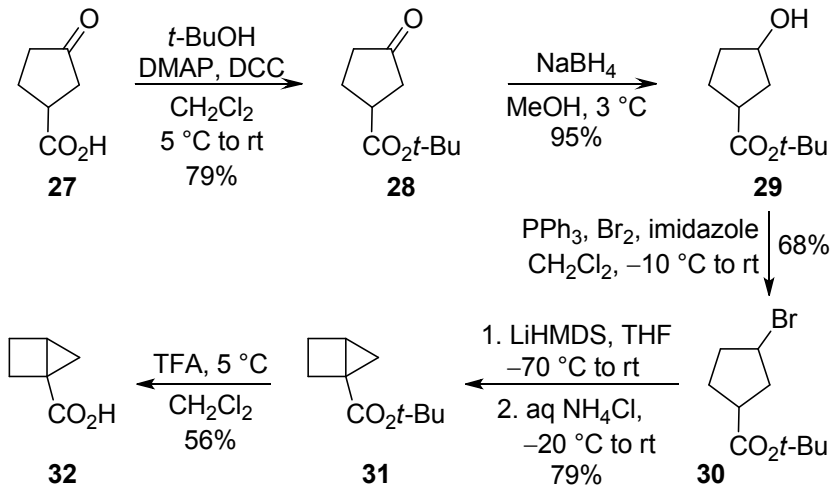
Scheme 12. Synthesis of *N*-protected amino acid derivatives **23–26** (relative configurations are shown)

N-Protected derivatives **23**–**26** were also obtained using standard procedures, taking into account possible applications in drug design and peptide synthesis (Scheme 12). Moreover, separation of enantiomers was performed for both **21** and **22** using chiral stationary phase HPLC (Scheme 13). Absolute configuration of the products obtained was established by X-Ray diffraction studies (see below).



Scheme 13. Synthesis of four amino acid hydrochlorides **21** and **22**

Finally, the aforementioned strategy was successfully applied to synthesis of the parent housane-1-carboxylic acid (**32**). The reaction sequence commenced with transformation of 3-oxocyclopentanecarboxylic acid (**27**) into the corresponding *tert*-butyl ester **28** (79% yield, Scheme 14). Further steps included reduction of **28** to alcohol **29** with $NaBH_4$ in MeOH (95% yield, *dr* = 4:1), and the Appel reaction (Br_2, PPh_3, imidazole, CH_2Cl_2), which gave **30** in 68% yield. Intramolecular LiHMDS-mediated cyclization of bromide **30** provided the target *tert*-butyl bicyclo[2.1.0]pentane-1-carboxylate **31** in good yield (79%). The protective group cleavage of **31** proceeded smoothly by using TFA in CH_2Cl_2 and led to carboxylic acid **32** in 56% yield.



Scheme 14. Synthesis of housane-1-carboxylic acid (**32**)

Physico-chemical properties. Dissociation constants (pK_a) were measured for the *cis* and *trans* housane-derived carboxylic acids, and effect of the housane core on acidity was compared to the corresponding disubstituted cyclopentanes (Figure 2). It was found that bicyclo[2.1.0]pentane scaffold bearing hydroxy (**10d**/**17d**) or methoxy (**10g**/**17g**) group at the γ position to CO_2H-moiety reduced pK_a by 0.28–0.38 units as compared to that of cyclopentanes **33–35**. However, in the case of *N*-Boc-amino derivatives, the *cis* isomer **24** was found to be slightly less acidic (by 0.09 pK_a units) then *cis*-disubstituted cyclopentane **36**, while acidity of *trans* housane **25** was comparable to that of **36**. Furthermore, pK_a value of *cis* phenyl-substituted housane **10b** was close to that of *trans* cyclopentane **37**. Unfortunately, the pK_a measurement was not successful for the case of *trans*-disubstituted housane **17b**, possibly due to the bicyclic ring system opening with alkali. The observed differences in the pK_a values described above are not significant and might be related to some subtle conformational effects. The obtained results show that the bicyclo[2.1.0]pentane scaffold might be a close mimetic of cyclopentane in terms of acid-base properties of the corresponding derivatives.

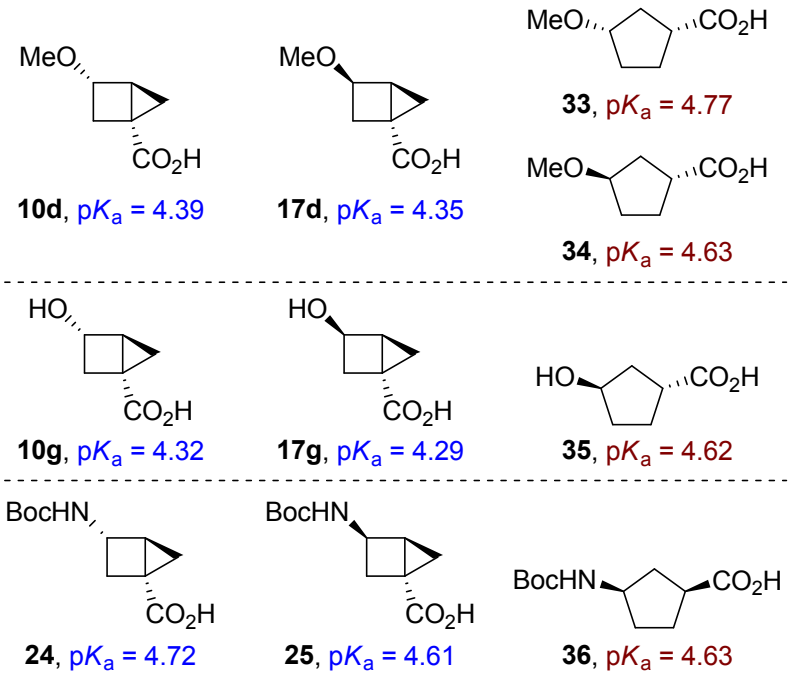


Figure 2. Measured pK_a values for the compounds **10**, **17**, and **33**–**36**

In addition to that, Log*P* were measured for phenyl-substituted housanes **10b** and **17b**, as well as for cyclopentane derivative **37** (Figure 3). In the case of *trans*-3-phenylhousane carboxylic acid **17b**, hydrophililicity increased by 0.25 Log*P* units as compared to that of **37** (Log*P* = 2.94). On the other hand, only a slight decrease of the Log*P* value (by 0.07 units) was found for the *cis* counterpart **10b**.

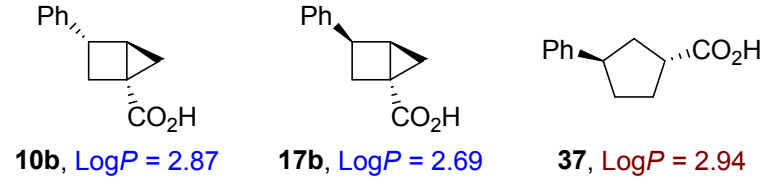


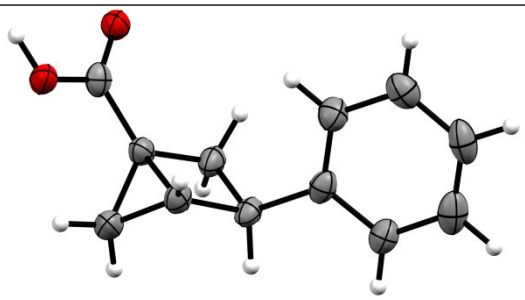
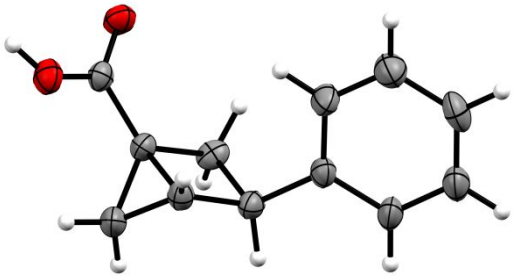
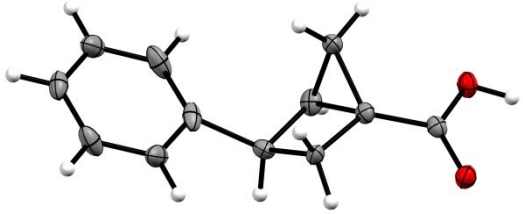
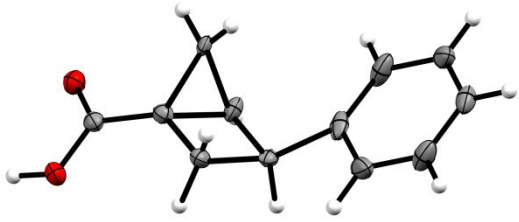
Figure 3. Measured Log*P* values for the compounds **10b**, **17b**, and **37**

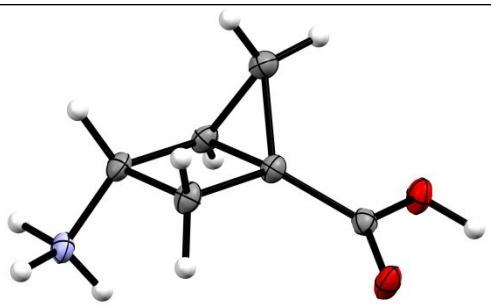
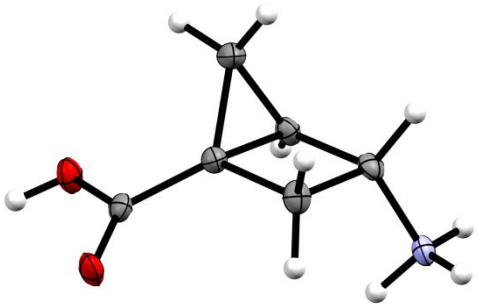
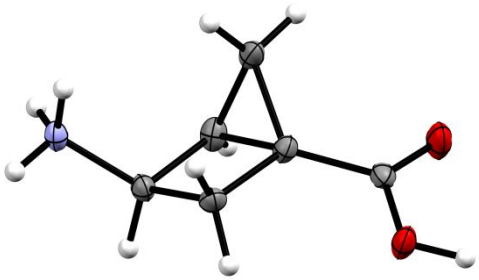
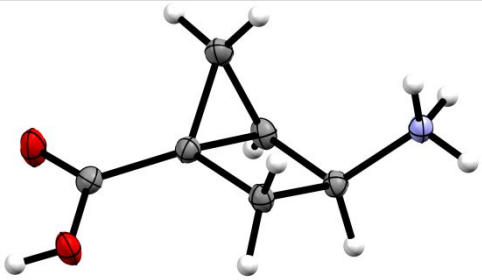
Molecular structures. X-Ray diffraction studies were performed with single crystals of housane derivatives obtained by slow evaporation of their solutions: *cis* phenyl-substituted housane carboxylic acid **10b** (in *t*-BuOMe – hexanes), its *trans* isomer **17b** (in THF), as well as amino acid hydrochlorides

(1*S*,2*S*,4*R*)-**21**·HCl·H_2O (in MeCN – EtOH), (1*R*,2*R*,4*S*)-**21**·HCl·H_2O (in MeCN – EtOH); (1*S*,2*R*,4*R*)-**22**·HCl (in MeOH), and (1*R*,2*S*,4*S*)-**22**·HCl (in MeCN – EtOH).

The crystals of (1*S*,2*S*,4*R*)-**21**·HCl·H_2O, (1*R*,2*R*,4*S*)-**21**·HCl·H_2O, (1*S*,2*R*,4*R*)-**22**·HCl, and (1*R*,2*S*,4*S*)-**22**·HCl contained single type of the conformers in the unit cell; for **10b**, two very similar conformers (A and B) were observed for each of the enantiomeric pairs, whereas for **17b**, two enantiomers (A and B) were observed at different positions resulting in crystallographic disorder (Table 3).

Table 3. Molecular geometry of the compounds **10b**, **17b**, **21**·HCl·H_2O, and **22**·HCl

#	Compound	*r*, Å	φ_1,[a] deg	φ_2,[a] deg	$\lvert\theta\rvert$, deg[b]	ORTEP diagrams[c]
1	**10b** (A)[d]	2.188	31.8	48.8	0.4	
2	**10b** (B)[d]	2.184	33.7	52.8	0.5	
3	**17b** (A)[e]	2.141	36.2	46.6	166.8	
4	**17b** (B)[e]	2.174	35.3	48.4	160.3	

5	(1*S*,2*S*,4*R*)-**21**	2.158	35.3	55.6	3.0	
6	(1*R*,2*R*,4*S*)-**21**	2.168	31.6	55.9	3.0	
7	(1*S*,2*R*,4*R*)-**22**	2.154	32.9	51.0	176.1	
8	(1*R*,2*S*,4*S*)-**22**	2.161	32.6	50.5	176.6	
9	*cis*-1,3-C5[f]	2.425	47.0	56.4	12.9	–
10	*trans*-1,3-C5[f]	2.450	46.0	67.2	150.9	–

[a] Defined according to Figure 4. [b] Since the signs of θ angle are opposite for different enantiomeric conformations, only absolute values of θ are considered. [c] Thermal ellipsoids are shown at 30% probability level. [d] Two slightly different conformers in the crystal cell. [d] Two enantiomers in the crystal cell leading to crystallographic disorder. [f] Average values for *cis*- and *trans*-1,3-disubstituted cyclopentane derivatives (from refs. 43 and 44).

To discuss geometry of the obtained derivatives, an exit vector plot (EVP)-based method was used,[43,44] which had been applied for analysis of various cyclic systems previously.[41,45–51] This approach represents the scaffold as a simplified geometrical model with so-called exit vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ starting from the ring atoms C^1 and C^3 decorated with the corresponding substituents (Figure 4). The size of the scaffold can be estimated by the distance r between the C^1 and C^3 atoms, while the plane angles φ_1 (between vectors $\boldsymbol{n_1}$ and C^1C^3), φ_2 (between vectors $\boldsymbol{n_2}$ and C^3C^1), and the torsion angle θ (defined by vectors $\boldsymbol{n_1}$, C^1C^3, and $\boldsymbol{n_2}$) can be used to describe its three-dimensionality. Exit vector plots (EVP) are obtained by depicting values of these parameters in the $r - \theta$, $\theta - \varphi_1/\varphi_2$, and/or φ_1/φ_2 plots.

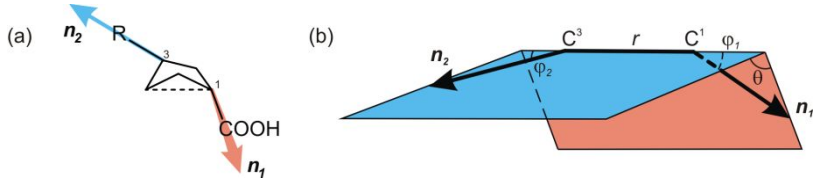


Figure 4. Definition of EVP parameters: (a) exit vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$; (b) r, φ_1, φ_2, and θ.

EVP analysis of the compounds **10b**, **17b**, **21**, and **22** showed that *cis*- and *trans*-1,3-disubstituted housane scaffolds are somewhat smaller (r = 2.141–2.188 Å) than the corresponding cyclopentanes ($r \sim 2.4$ Å); they are also slightly more flattened (θ = 0.4–3.0° and 160.3–176.6° for *cis* and *trans* isomers vs θ = 12.9° and 150.9° (on average) for *cis*- and *trans*-1,3-disubstituted cyclopentanes, respectively) (Figure 5). In the $\varphi_1 - \varphi_2$ plot, the housane derivatives are located closely to the corresponding cyclopentane-derived scaffolds, although φ_1/φ_2 values are somewhat smaller. Therefore, *cis*- and *trans*-1,3-disubstituted bicyclo[2.1.0]pentane cores can be considered as slightly distorted analogues of the corresponding cyclopentanes with fixed envelope conformation of the five-membered ring.

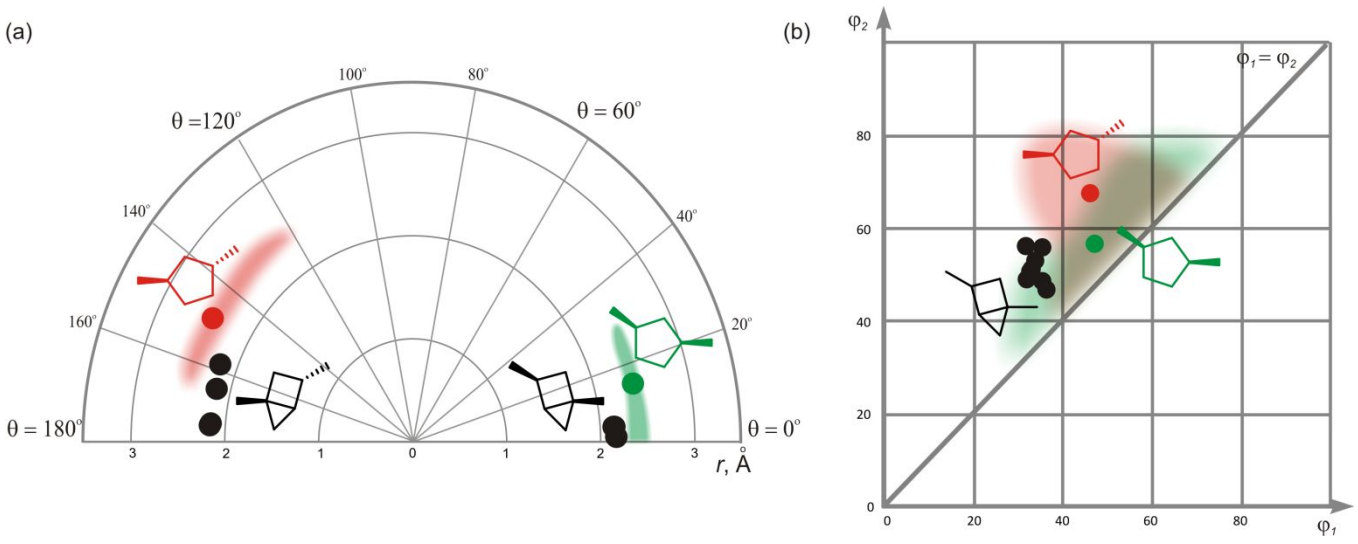


Figure 5. Geometric parameters of 1,3-disubstituted housanes and cyclopentanes shown in (a) $r - \theta$ plot (polar coordinates); (b) $\varphi_1 - \varphi_2$ plot. Fused areas and colored data points correspond to all experimentally observed and average parameter values for 1,3-disubstituted cyclopentanes, respectively;[43,44] black dots – to the values for 1,3-disubstituted housanes

Conclusions

An efficient approach to 1,3-disubstituted bicyclo[2.1.0]pentane (housane) carboxylic acids was developed, which was based on intamolecular cyclization of the corresponding trisubstituted cyclopentanes **7** or **15** bearing a *tert*-butyl carboxylate function (at the C-1 atom), a leaving group (at C-4), and an additional substituent (at C-3). In turn, these intermediates were obtained from cyclopent-3-ene carboxylic acid (**4**). Although the aforementioned cyclopentane derivatives were obtained as mixtures of two diastereomeric pairs, the overall synthetic sequences were highly diastereoselective for the preparation of either *cis*- or *trans*-1,3-disubstituted housane derivatives. The configuration of the products was defined by relative orientation of the substituents at the C-3 and C-4 atoms in the corresponding key intermediate. Similar strategy was also applied for the preparation of the parent bicyclo[2.1.0]pentane-1-carboxylic acid (**32**) from 3-oxocyclopentanecarboxylic acid (**27**).

The key step of the approach, i.e. intramolecular cyclization of intermediates **7** or **15**, required thorough optimization; the best results were obtained when 2.5-fold excess of LiHMDS in THF was

used. The overall reaction sequence was effective for the preparation of *cis*-1,3-disubstitued housanes bearing alkyl, aryl, halogene, azide, and alkoxy groups at the C-3 position; for the hydroxy group, the use of a silyl protection was necessary. For the *trans*-diastereomers, the method was somewhat less efficient and worked only for alkyl-, aryl-, fluoro-, and methoxy-substituted derivatives. Other derivatives were obtained via configuration inversion in *cis*-3-hydroxyhousane-1-carboxylate **9f**.

Synthesis of the target carboxylic acids required removal of the *tert*-butyl protective group which appeared to be somewhat challenging in some cases. The standard acidic cleavage was fruitful only for sterically hindered phenyl and bromo derivatives, whereas for other representatives, less common alkaline hydrolysis was applied. As a result, 35 housane-derived building blocks were obtained on multigram scale (up to 80 g). Moreover, γ-amino acids **21** and **22** – bicyclic GABA analogues – were obtained.

It was also shown that the bicyclo[2.1.0]pentane scaffold does not strongly affect pK_a values of the corresponding derivatives and decreases their lipophilicity as compared to cyclopentane. X-Ray diffraction studies demonstrated that *cis*- and *trans*-1,3-disubstituted housanes can be considered as slightly flattened analogues of the corresponding cyclopentanes with fixed envelope conformation of the five-membered ring. Taking into account the aforementioned properties of the title compounds, as well their accessibility on a multigram scale, they can be considered as extremely promising building blocks for organic synthesis and drug discovery, which are now readily available to chemical community. Further applications of these products might rely on probable susceptibility of the bicyclo[2.1.0]pentane scaffold towards ring opening, which was observed for some derivatives in this work. This provides possibilities for design of covalent ligands, which will be discussed in an upcoming study.

Experimental part

The solvents were purified according to the standard procedures.[52] **4**, **27**, **33–37** were purchased from commercial sources. Melting points were measured on an automated melting point system. Analytical TLC was performed using silica gel plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a

NMR spectrometer at 500 MHz for Protons, 126 MHz for Carbon-13, and 470 MHz for Fluorine-19, or at 400 MHz for Protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an LCMS instrument (chemical ionization (CI)) and GCMS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were recorded on an LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Preparative flash chromatography was performed on chromatograph using 40 g columns. CCDC 1961442 (**10b**), CCDC 1961443 (**17b**), CCDC 1961444 (**(1*S*,2*S*,4*R*)-21**), CCDC 1961445 (**(1*R*,2*R*,4*S*)-21**), CCDC 1961446 (**(1*S*,2*R*,4*R*)-22**), and CCDC 1961447 (**(1*R*,2*S*,4*S*)-22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

***tert*-Butyl cyclopent-3-enecarboxylate (5)**.[53,54] Cyclopent-3-enecarboxylic acid **4** (200 g, 1.78 mol) was dissolved in CH_2Cl_2 (2000 mL), and DMF (1 mL) was added. The mixture was cooled to 5 °C and oxalyl chloride (184 mL, 272 g, 2.14 mol) was added dropwise at 5 °C. The mixture was stirred at rt overnight, and the solvent was evaporated in *vacuo* at 45 °C. The residue was dissolved in CH_2Cl_2 (2000 mL), the solution was cooled to 5 °C, and the solution of Et_3N (495 mL, 359 g, 3.55 mol) and *t*-BuOH (395 g, 5.33 mol) in CH_2Cl_2 (500 mL) was added dropwise at 5 °C. The reaction mixture was stirred at rt overnight, then washed with 10% aq $NaHSO_4$ (2×500 mL) and brine (500 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 247 g (83%); yellowish liquid; bp 55–57 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 2H), 3.00 (quint, J = 8.2 Hz, 1H), 2.58 (d, J = 8.2 Hz, 4H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.5, 129.0, 79.9, 42.5, 36.3, 28.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{17}O_2$ 169.1229. Found 169.1231.

***tert*-Butyl 6-oxabicyclo[3.1.0]hexane-3-carboxylate (6)**. A solution of alkene **5** (150 g, 0.892 mol) in CH_2Cl_2 (3000 mL) was cooled to 5 °C. Then, *m*-CPBA (231 g, 1.34 mol) was added in portions at 5 °C, and the resulting mixture was stirred at rt overnight. The precipitate was filtered off, filtrates were

washed with 10% aq $NaHCO_3$ (4×500 mL) and brine (500 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 35 °C. The crude product was purified by distillation in *vacuo*. The compound was obtained as *ca.* 3:1 mixture of diastereomers. Yield 144 g (88%); colorless liquid; bp 72–74 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 1.5H) and 3.41 (s, 0.5H), 2.63 – 2.48 (m, 1.5H) and 2.27 (dd, *J* = 14.0, 8.0 Hz, 1.5H) and 1.85 – 1.75 (m, 2H), 1.45 – 1.39 (m, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.2 and 173.9, 80.4 and 80.2, 56.3 and 56.1, 38.9 and 38.5, 31.2 and 30.4, 28.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{17}O_3$ 185.1178. Found 184.1175. $[M+Na]^+$ Calcd. for $C_{10}H_{16}NaO_3$ 207.0997. Found 207.0997.

(3*R,4*R**)-*tert*-Butyl 3-hydroxy-4-methylcyclopentanecarboxylate (7a).** Oxirane **6** (144 g, 0.782 mol) was dissolved in THF (2800 mL), and CuI (14.9 g, 78.2 mmol) was added under argon atmosphere. The mixture was cooled to –40 °C, and 3 M MeMgCl in THF (525 mL, 1.56 mol) was added dropwise at –40 °C. The reaction mixture was stirred at rt overnight, then cooled to –20 °C and 20% aq NH_4Cl (600 mL) was added in one portion. The resulting mixture was warmed up to rt, EtOAc (3000 mL) was added, the organic layer was washed with brine (2×1000 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 3:2 of diastereomers. Yield 100 g (64%); yellowish liquid; bp 95–97 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 4.35 (quint, *J* = 2.7 Hz, 1H), 2.86 – 2.72 (m, 1H), 2.61 – 2.50 (m, 2H), 2.31 – 1.51 (m, 4H), 1.41 (s, 9H), 1.06 (d, *J* = 5.9 Hz, 3H); minor diastereomer δ 4.45 (quint, *J* = 3.4 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.43 – 2.38 (m, 2H), 2.31 – 1.51 (m, 4H), 1.39 (s, 9H), 1.04 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 177.0 and 175.7, 80.4 and 79.9, 79.7 and 79.2, 42.6 and 42.1, 41.6 and 41.2, 37.3 and 37.2, 35.7 and 35.3, 28.0 and 28.0, 18.0 and 17.9. GC/MS (EI): *m/z* = 144 $[M–H_2C=C(CH_3)_2]^+$, 185 $[M–CH_3]^+$. Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.19; H, 10.11.

(3*R,4*S**)-*tert*-Butyl 3-hydroxy-4-phenylcyclopentanecarboxylate (7b).** Oxirane **6** (120 g, 0.651 mol) was dissolved in THF (1200 mL), and CuI (13.7 g, 71.7 mmol) was added under argon atmosphere. The mixture was cooled to 0 °C, and 1 M PhMgCl in THF (717 mL, 0.717 mol) was added

dropwise at 0 °C. The reaction mixture was stirred at rt overnight, then cooled to –20 °C, and 20% aq NH_4Cl (500 mL) was added in one portion. The resulting mixture was heated to rt, and EtOAc (3000 mL) was added. Organic layer was separated, washed with brine (2×1000 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (3:1) as eluent; $R_f = 0.45$. The compound was obtained as *ca.* 5:2 mixture of diastereomers. Yield 83.7 g (49%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 7.43 – 7.24 (m, 5H), 4.23 (q, *J* = 7.4 Hz, 1H), 3.01 – 2.90 (m, 2H), 2.47 – 2.25 (m, 2H), 2.20 (s, 1H), 2.13 – 1.84 (m, 2H), 1.48 (s, 9H); minor diastereomer δ 7.26 – 7.16 (m, 5H), 4.16 – 4.09 (m, 1H), 3.12 (q, *J* = 8.2 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.47 – 2.25 (m, 2H), 2.13 – 1.84 (m, 3H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.5 and 175.3, 142.4 and 142.0, 128.6 and 128.6, 127.5 and 127.3, 126.7 and 126.5, 80.8 and 80.3, 79.9 and 78.9, 54.3 and 53.4, 41.4 and 41.4, 37.2, 35.5 and 34.7, 28.1 and 28.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{16}H_{22}NaO_3$ 285.1467. Found 285.1463.

(3*R,4*R**)-*tert*-Butyl 3-fluoro-4-hydroxycyclopentanecarboxylate (7c).** Oxirane **6** (100 g, 0.543 mol) was dissolved in dichloroethane (100 mL), and $Et_3N{\cdot}3HF$ (131 g, 0.814 mol) was added at rt (NOTE: using less concentrated solutions result in significantly increased reaction time). The mixture was stirred at 80 °C overnight, then cooled to rt, and CH_2Cl_2 (1000 mL) was added. The resulting mixture was washed with H_2O (300 ml), 10% aq K_2CO_3 (600 mL) and brine (300 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 78.7 g (71%); colorless liquid; bp 92–95 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 – 4.70 (m, 1H), 4.39 – 4.25 (m, 1H), 3.00 – 2.90 (m, 1H), 2.39 – 2.06 (m, 4H), 1.90 – 1.84 (m, 1H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.7, 98.5 (d, *J* = 178 Hz), 80.7, 75.8 (d, *J* = 27.1 Hz), 40.9 (d, *J* = 1.5 Hz), 35.0, 33.6 (d, *J* = 22.0 Hz), 27.9. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –178.8. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{17}FNaO_3$ 227.1059. Found 227.1057.

(3*R,4*R**)-Methyl 3-hydroxy-4-methoxycyclopentanecarboxylate (7d).** Na (12.8 g, 0.53 mol) was added to MeOH (2000 mL), and the mixture was refluxed for 2 h. Then, oxirane **6** (196g, 1.06 mol) was added, and the resulting mixture was refluxed overnight, and cooled to the rt. HOAc (67 g, 1.11 mol)

was added in one portion, and the resulting mixture was evaporated in *vacuo* at 45 °C. The residue was dissolved in *t*-BuOMe (1000 mL) and washed with brine (2×200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo.* The compound was obtained as *ca.* 3:2 mixture of diastereomers. Yield 106 g (57 %); colorless liquid; bp 60–62 °C / 7 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 4.19 (dt, *J* = 6.9, 3.8 Hz, 1H), 3.72 – 3.65 (m, 3H), 3.61 – 3.56 (m, 1H), 3.34 (s, 3H), 3.00 (quint, *J* = 8.6 Hz, 1H), 2.44 – 2.09 (m, 3H), 1.89 – 1.83 (m, 2H); minor diastereomer δ 4.13 (dt, *J* = 6.0, 2.9 Hz, 1H), 3.72 – 3.65 (m, 4H), 3.33 (s, 3H), 3.00 (quint, *J* = 8.6 Hz, 1H), 2.44 – 2.09 (m, 3H), 1.99 (ddd, *J* = 13.7, 9.3, 2.9 Hz, 1H) , 1.89 – 1.83 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.2, 82.7 and 82.7, 71.1 and 70.9, 52.2 and 52.1, 47.4 and 47.1, 35.0 and 34.6, 30.9 and 30.5, 28.1 and 27.7. GC/MS (EI): *m/z* = 141 $[M–OCH_3]^+$, 174 $[M]^+$. Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.51; H, 8.05.

(3*S,4*S**)-*tert*-Butyl 3-methyl-4-((phenylsulfonyl)oxy)cyclopentanecarboxylate (8a).** A solution of alcohol **7a** (96.1 g, 0.480 mol) in pyridine (480 mL) was cooled to 5 °C, and $PhSO_2Cl$ (109 g, 0.620 mol) was added dropwise at 5 °C. The mixture was stirred at rt overnight, then evaporated in *vacuo* at 60 °C. The residue was dissolved in CH_2Cl_2 (1000 mL), the solution was washed with 10% aq $NaHSO_4$ (3×300 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (2:1) as eluent; R_f = 0.76. The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 152 g (93%); colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.55 – 7.46 (m, 2H), 4.51 – 4.41 (m, 1H), 2.81 (quint, *J* = 8.1 Hz, 1H), 2.23 – 2.02 (m, 3H), 2.01 – 1.85 (m, 1H), 1.37 (s, 9H), 1.33 – 1.19 (m, 1H), 0.85 (d, *J* = 6.1 Hz, 2H) and 0.82 (d, *J* = 6.7 Hz, 1H); minor diastereomer δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 6.8 Hz, 1H), 7.55 – 7.46 (m, 2H), 4.34 (q, *J* = 6.3 Hz, 1H), (quint, *J* = 7.1 Hz, 1H), 2.23 – 2.02 (m, 3H), 2.01 – 1.85 (m, 1H), 1.37 (s, 9H), 1.33 – 1.19 (m, 1H), 0.85 (d, *J* = 6.1 Hz, 2H) and 0.82 (d, *J* = 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.3 and 174.1, 137.1 and 137.0, 133.7 and 133.6, 129.2 and 129.1, 127.7, 89.2 and 88.3, 80.5 and 80.4, 42.0 and 40.6, 40.4 and 39.2, 35.2 and 34.8, 34.9 and 33.6, 28.0 and 28.0, 17.5 and 16.9. HRMS

(ESI-TOF) *m/z*: $[M+NH_4]^+$ Calcd. for $C_{17}H_{28}NO_5S$ 358.1688. Found 358.1686. $[M+Na]^+$ Calcd. for $C_{17}H_{24}NaO_5S$ 363.1242. Found 363.1242.

(3*R,4*S**)-*tert*-Butyl 3-phenyl-4-((phenylsulfonyl)oxy)cyclopentanecarboxylate (8b).** A solution of alcohol **7b** (110 g, 0.420 mol) in pyridine (550 mL) was cooled to 5 °C, and $PhSO_2Cl$ (97.1 g, 0.550 mol) was added dropwise at 5 °C. The mixture was stirred at rt overnight, then evaporated in *vacuo* at 60 °C. The residue was dissolved in CH_2Cl_2 (1000 mL), the solution was washed with 10% aq $NaHSO_4$ (3×300 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (2:1) as eluent; $R_f = 0.64$. Yield 132 g (78%); colorless solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.60 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.23 – 7.09 (m, 3H), 7.06 – 6.98 (m, 2H), 4.80 (q, *J* = 6.7 Hz, 1H), 3.29 – 3.20 (m, 1H), 3.03 (quint, *J* = 8.7 Hz, 1H), 2.46 – 2.35 (m, 2H), 2.22 – 2.13 (m, 1H), 1.95 – 1.87 (m, 1H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.0, 140.1, 136.3, 133.4, 129.0, 128.6, 127.6, 127.2, 126.9, 88.2, 80.8, 51.5, 42.1, 35.7, 34.9, 28.0. HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ Calcd. for $C_{22}H_{30}NO_5S$ 420.1845. Found 420.1841. $[M+Na]^+$ Calcd. for $C_{22}H_{26}NaO_5S$ 425.1399. Found 425.1399.

(3*S,4*S**)-*tert*-Butyl 3-bromo-4-fluorocyclopentanecarboxylate (8c).** Alkene **5** (110 g, 0.654 mol) was dissolved in CH_2Cl_2 (1100 mL), and $Et_3N{\cdot}3HF$ (316 g, 1.96 mol) was added at rt. The mixture was cooled to 5 °C, NBS (140 g, 0.785 mol) was added in one portion, and mixture was stirred at rt overnight. Then, reaction mixture was washed with H_2O (300 mL), 10% aq K_2CO_3 (300 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 134 g (77%); colorless liquid; bp 88–90 °C / 1 mmHg. ^1H NMR (500 MHz, $CDCl_3$): major diastereomer: δ 5.22 – 5.08 (m, 1H), 4.40 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.18 (quint, *J* = 9.4 Hz, 1H), and 2.73 – 2.47 (m, 2H), 2.33 (dd, *J* = 14.7, 7.9 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.46 (s, 9H); minor diastereomer: δ 5.26 – 5.22 (m, 1H), 4.30 – 4.23 (m, 1H), 3.08 – 3.00 (m, 1H), 2.80 – 2.74 (m, 1H), 2.73 – 2.47 (m, 1H), 2.33 (dd, *J* = 14.7, 7.9 Hz, 1H), 2.27 – 2.15 (m, 1H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.4

and 173.2, 100.0 (d, J = 181 Hz) and 99.0 (d, J = 182 Hz), 80.9 and 80.8, 52.1 (d, J = 27.9 Hz) and 49.8 (d, J = 27.0 Hz), 41.8 and 41.6, 37.5 and 37.1, 33.4 (d, J = 22.1 Hz) and 33.2 (d, J = 20.9 Hz), 28.0 and 28.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –158.4 and –165.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{17}BrFO_2$ 267.0396. Found 267.0379. $[M+Na]^+$ Calcd. for $C_{10}H_{16}BrFNaO_2$ 289.0215. Found 289.0216.

(3*S,4*S**)-*tert*-Butyl 3-bromo-4-methoxycyclopentanecarboxylate (8d).** A solution of alkene **5** (77.5 g, 0.461 mol) was dissolved in MeOH (800 mL) was cooled to 5 °C. NBS (86.1 g, 0.484 mol) was added in portions at 5 °C, resulting mixture was stirred at rt overnight, and evaporated in *vacuo* at 45 °C. The residue was dissolved in CH_2Cl_2 (700 mL), the solution was washed with brine (2×200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as *ca.* 4:1 mixture of diastereomers. Yield 109 g (85%); colorless liquid; bp 81–83 °C / 1 mmHg. ^1H NMR (400 MHz, $CDCl_3$): major diastereomer δ 4.30 – 4.22 (m, 1H), 3.99 – 3.85 (m, 1H), 3.32 (s, 1H), 3.30 (s, 2H), 3.01 (quint, J = 8.5 Hz, 1H), 2.47 (ddd, J = 14.6, 9.1, 5.9 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.18 (ddd, J = 14.6, 7.9, 2.7 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.39 (s, 9H); minor diastereomer δ 4.14 – 4.02 (m, 1H), 3.99 – 3.85 (m, 1H), 3.32 (s, 3H), 2.86 (quint, J = 8.6 Hz, 1H), 2.59 (ddd, J = 14.8, 9.1, 6.6 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.29 – 2.23 (m, 1H),1.92 – 1.82 (m, 1H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.8 and 173.7, 88.8 and 88.7, 80.6 and 80.4, 57.2 and 57.1, 52.8 and 50.9, 41.9 and 41.6, 38.0 and 37.6, 33.1 and 32.8, 28.0 and 28.0. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{11}H_{19}BrNaO_3$ 301.0415/303.0395. Found 301.0414/303.0395.

(3*S,4*S**)-*tert*-Butyl 3,4-dibromocyclopentanecarboxylate (8e)**. A solution of alkene **5** (52.0 g, 0.309 mol) in $CHCl_3$ (500 mL) was cooled to 5 °C, and Br_2 (17.5 mL, 54.3 g, 0.34 mol) was added dropwise at 5 °C. The reaction mixture was stirred at rt overnight, and washed with 10% aq Na_2SO_3 (200 mL) and brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound used in the next step without further purification (decomposed upon distillation in *vacuo* or chromatographic purification). Yield 89.2 g (88%); colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 – 4.53 (m, 1H), 4.52 – 4.40 (m, 1H), 3.24 – 3.10 (m, 1H), 2.97 – 2.88 (m, 2H), 2.52 – 2.45 (m, 1H), 2.37 (dd, J = 14.8, 8.7 Hz, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 81.0, 56.6, 54.7,

41.9, 37.4, 28.0. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{16}Br_2NaO_2$ 348.9415. Found 348.9418.

(3*S,4*S**)-*tert*-Butyl 3-azido-4-iodocyclopentanecarboxylate (8f).** Alkene **5** (186 g, 1.11 mol) was dissolved in THF (1700 mL), MeOH – H_2O (800 mL, 3:1, v/v) was added. Then, NaN_3 (252 g, 3.87 mol) was added, and the mixture was cooled to 5 °C. I_2 (701 g, 2.76 mol) was added in portions at 5 °C, and the resulting mixture was stirred at rt overnight. Then, 20% aq Na_2SO_3 (2010 mL, 3.32 mol) was added, and the mixture was extracted with *t*-BuOMe (2×100 mL). Combined organic layers were washed with brine (2×300 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 30 °C. The crude was used in the next step without further purification. Yield 281 g (75%); brown oil. The compound was obtained as *ca.* 2:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 4.35 – 4.02 (m, 2H), 3.04 (quint, *J* = 7.1 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.47 – 2.38 (m, 1H), 2.37 – 2.25 (m, 1H), 1.97 – 1.90 (m, 1H), 1.68 – 1.20 (m, 9H); minor diastereomer δ 4.35 – 4.02 (m, 1H), 4.00 – 3.90 (m, 1H), 2.89 (quint, *J* = 7.1 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.47 – 2.38 (m, 1H), 2.37 – 2.25 (m, 1H), 1.90 – 1.84 (m, 1H), 1.68 – 1.20 (m, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.3 and 173.0, 81.1 and 81.0, 70.8 and 70.8, 42.3 and 42.1, 40.1 and 39.6, 33.0 and 32.9, 28.0 and 28.0, 27.0 and 24.7. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{16}IN_3NaO_2$ 360.0185. Found 360.0182.

(3*S,4*S**)-*tert*-Butyl 3-bromo-4-hydroxycyclopentanecarboxylate (8g).** A solution of alkene **5** (150 g, 0.892 mol) MeCN – H_2O (2250 mL, 2:1, v/v) was cooled to 5 °C. NBS (168 g, 0.942 mol) was added in portions at 5 °C, the mixture was stirred at rt overnight, then evaporated in *vacuo* at 45 °C. The residue was dissolved in CH_2Cl_2 (1000 mL), the solution was washed with brine (2×300 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as *ca.* 3:2 mixture of diastereomers. Yield 180 g (76%); colorless oil; bp 111–113 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 4.56 – 4.23 (m, 1H), 4.24 – 4.12 (m, 1H), 3.10 – 3.00 (m, 1H), 2.82 – 2.06 (m, 4H), 1.90 – 1.80 (m, 1H), 1.42 (s, 9H); minor diastereomer δ 4.56 – 4.23 (m, 1H), 3.95 (q, *J* = 6.5 Hz, 1H), 3.43 (s, 1H), 2.92 (quint, *J* = 9.2 Hz, 1H), 2.82 – 2.06 (m, 3H), 1.90 – 1.80 (m, 1H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.7 and

174.1, 81.5 and 80.8, 79.7 and 79.5, 55.7 and 54.4, 41.4 and 41.1, 37.8 and 37.3, 35.0 and 34.4, 28.0 and 27.9. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{17}BrNaO_3$ 287.0259/289.0238. Found 287.0259/289.0237.

General procedure for the preparation of housanes 9a–d, 9f, 12g and 16a–d. TMS_2NH (200 mL, 154 g, 0.954 mol) was dissolved in THF (3000 mL), and the solution was cooled to –40 °C under argon atmosphere. 2.5 M *n*-BuLi in hexanes (370 mL, 0.925 mol) was added dropwise at –5 °C, the mixture was stirred at –5 °C for 30 min, and then cooled to –70 °C. The corresponding *tert*-butyl ester (0.370 mol) in THF (1 mL per 1 g of *tert*-butyl ester) was added dropwise at –70 °C, the resulting mixture was stirred at –70 °C for 30 min, and slowly warmed up to rt. Then, the mixture was cooled to –20 °C, and 20% aq NH_4Cl was added in one portion. The reaction mixture was warmed up to rt, and EtOAc was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated in *vacuo*.

(1*R,3*S**,4*R**)-*tert*-Butyl 3-methylbicyclo[2.1.0]pentane-1-carboxylate (9a).** The crude compound was purified by distillation in *vacuo*. Yield 43.8 g (65%); colorless liquid; bp 75–77 °C / 7 mmHg. ^1H NMR (500 MHz, $CDCl_3$) δ 2.00 (d, *J* = 5.7 Hz, 1H), 1.79 – 1.72 (m, 2H), 1.67 – 1.61 (m, 1H), 1.60 (t, *J* = 5.2 Hz, 1H), 1.41 (s, 9H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.14 – 1.11 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 79.6, 34.0, 31.4, 29.0, 28.1, 25.0, 23.4, 21.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{11}H_{19}O_2$ 183.1385. Found 182.1300. $[M+Na]^+$ Calcd. for $C_{11}H_{18}NaO_2$ 205.1204. Found 205.1203.

(1*R,3*S**,4*R**)-*tert*-Butyl 3-phenylbicyclo[2.1.0]pentane-1-carboxylate (9b).** The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (5:1) as eluent; R_f = 0.72. The crude compound cannot be purified by distillation in *vacuo* due to its decomposition upon heating. Yield 45.2 g (50%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 4H), 7.26 – 7.18 (m, 1H), 2.76 (dd, *J* = 5.8, 4.1 Hz, 1H), 2.44 – 2.35 (m, 2H), 2.10 (ddd, *J* = 11.4, 5.8, 0.9 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.46 (s, 9H), 1.34 (dd, *J* = 4.1, 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 145.2, 128.6, 126.6, 126.4, 80.1, 39.2, 33.0, 32.9, 28.2, 24.8, 24.5. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{16}H_{20}NaO_2$ 267.1361. Found 267.1363.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-fluorobicyclo[2.1.0]pentane-1-carboxylate (9c).** The crude compound was purified by distillation in *vacuo*. Yield 48.9 g (71%); colorless liquid; bp 42–44 °C / 1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (d, *J* = 58.4 Hz, 1H), 2.78 – 2.52 (m, 1H), 2.44 (ddd, *J* = 34.9, 12.8, 3.2 Hz, 1H), 2.02 (ddd, *J* = 16.0, 12.8, 3.8 Hz, 1H), 1.81 – 1.68 (m, 1H), 1.45 (s, 9H), 1.19 – 1.06 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.2, 87.8 (d, *J* = 197 Hz), 80.5, 33.7 (d, *J* = 21.5 Hz), 32.9 (d, *J* = 28.6 Hz), 28.0, 25.9, 22.5. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –175.7. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{15}FNaO_2$ 209.0954. Found 209.0952.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-methoxybicyclo[2.1.0]pentane-1-carboxylate (9d).** The crude compound was purified by distillation in *vacuo*. Yield 55.0 g (75%); colorless liquid; bp 51–53 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 – 3.23 (m, 1H), 3.22 (s, 3H), 2.38 (dd, *J* = 6.5, 1.9 Hz, 1H), 2.08 (dt, *J* = 11.8, 2.6 Hz, 1H), 1.81 (dd, *J* = 11.8, 4.3 Hz, 1H), 1.63 – 1.58 (m, 1H), 1.35 (s, 9H), 1.00 (dd, *J* = 4.3, 2.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.0, 80.0, 75.0, 55.2, 32.6, 32.2, 28.0, 24.9, 22.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{11}H_{19}O_3$ 199.1334. Found 199.1335. $[M+Na]^+$ Calcd. for $C_{11}H_{18}NaO_3$ 221.1154. Found 221.1150.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-azidobicyclo[2.1.0]pentane-1-carboxylate (9f).** The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (4:1) as eluent; R_f = 0.68. Yield 39.9 g (51%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 – 3.30 (m, 1H), 2.44 (dd, *J* = 6.7, 2.6 Hz, 1H), 2.34 (dd, *J* = 12.4, 2.6 Hz, 1H), 2.01 (dd, *J* = 12.4, 3.9 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.44 (s, 9H), 1.23 – 1.17 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.0, 80.7, 54.9, 31.8, 31.5, 28.0, 25.1, 23.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{15}N_3NaO_2$ 232.1062. Found 232.1063.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-bromobicyclo[2.1.0]pentane-1-carboxylate (9e).** A solution of bromide **8e** (89.0 g, 0.271 mol) in THF (1800 mL) was cooled to –70 °C under argon atmosphere. 1.1 M LiHMDS in hexanes (343 mL, 0.380 mol) was added dropwise at –70 °C. The mixture was slowly heated to rt and stirred overnight. The resulting mixture was cooled to –20 °C, and 20% aq NH_4Cl (200 mL) was added in one portion. Then, EtOAc (1000 mL) was added, organic phase was separated, washed with brine (2×500 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 31.5 g (47%), *ca*. 95% purity; colorless liquid; bp

90–92 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 – 3.67 (m, 1H), 2.73 (d, *J* = 13.0 Hz, 1H), 2.67 (d, *J* = 6.4 Hz, 1H), 2.35 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.62 (t, *J* = 6.1 Hz, 1H), 1.43 (s, 9H), 1.21 – 1.18 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.1, 80.7, 40.6, 37.2, 35.5, 28.1, 25.4, 24.8. GC/MS (EI): *m/z* = 190/192 $[M–H_2C=C(CH_3)_2]^+$, 231/233 $[M–CH_3]^+$. Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.33. Found: C, 48.34; H, 6.28; Br, 32.22.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-hydroxybicyclo[2.1.0]pentane-1-carboxylate (9g).** A solution of compound **12g** (154 g, 0.516 mol) in THF (1500 mL) was cooled to 5°C. 1 M Bu_4NF (338 g, 1.29 mol) solution in THF was added dropwise at rt. The mixture was stirred at rt overnight, dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo.* Yield 51.3 g (54%); colorless oil; bp 90–92 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 1H), 2.59 (d, *J* = 4.7 Hz, 1H), 2.37 (dd, *J* = 6.6, 1.9 Hz, 1H), 2.08 (dt, *J* = 12.0, 1.9 Hz, 1H), 1.97 (dd, *J* = 12.0, 4.1 Hz, 1H), 1.67 – 1.62 (m, 1H), 1.39 (s, 9H), 1.07 (dd, *J* = 4.7, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.5, 80.4, 67.1, 35.8, 35.5, 28.1, 24.6, 23.5. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{16}NaO_3$ 207.0997. Found 207.0994.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)bicyclo[2.1.0]pentane-1-carboxylate (12g).** The crude compound was purified by distillation in *vacuo*. Yield 87.2 g (79%); colorless oil; bp 103–105 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 4.2, 2.2 Hz, 1H), 2.35 (dd, *J* = 6.4, 2.5 Hz, 1H), 2.12 (dt, *J* = 11.5, 2.5 Hz, 1H), 1.92 (dd, *J* = 11.5, 4.2 Hz, 1H), 1.63 – 1.58 (m, 1H), 1.41 (s, 9H), 1.02 (dd, *J* = 4.6, 2.5 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.5, 79.9, 67.5, 36.1, 35.9, 28.1, 25.8, 24.3, 23.1, 18.1, –4.7. HRMS (ESI-TOF) *m/z*: $[M\text{-}Ot\text{-}Bu]^+$ Calcd. for $C_{12}H_{21}O_2Si$ 298.1964. Found 226.1970.

(1*R,3*R**,4*R**)-*tert*-Butyl 3-methylbicyclo[2.1.0]pentane-1-carboxylate (16a).** The crude compound was purified by distillation in *vacuo*. Yield 31.7 g (47%); colorless liquid; bp 41–43 °C / 1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 – 2.50 (m, 2H), 2.26 – 2.17 (m, 1H), 1.44 – 1.42 (m, 1H), 1.42 (s, 9H), 1.26 – 1.22 (m, 1H), 1.16 – 1.09 (m, 1H), 0.81 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 79.6, 30.9, 29.3, 28.1, 25.8, 21.7, 19.4, 15.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{11}H_{19}O_2$ 183.1385. Found 183.1388.

(1*R,3*R**,4*R**)-*tert*-Butyl 3-phenylbicyclo[2.1.0]pentane-1-carboxylate (16b).** The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent; $R_f = 0.42$. The compound cannot be purified by distillation in *vacuo* due to its decomposition upon heating. Yield 31.6 g (35%), *ca*. 95% purity; yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 5H), 3.84 – 3.75 (m, 1H), 2.99 (t, *J* = 10.8 Hz, 1H), 2.65 – 2.55 (m, 1H), 1.77 (dd, *J* = 11.3, 4.5 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.48 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.6, 142.2, 128.2, 126.8, 125.7, 80.1, 34.6, 29.4, 29.3, 28.2, 22.8, 21.0. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{16}H_{20}NaO_2$ 267.1361. Found 267.1366.

(1*R,3*R**,4*S**)-*tert*-Butyl 3-fluorobicyclo[2.1.0]pentane-1-carboxylate (16c).** The crude compound was purified by distillation in *vacuo*. Yield 27.6 g (40%); colorless liquid; bp 74–76 °C / 7 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (ddt, *J* = 56.2, 8.2, 3.6 Hz, 1H), 2.72 (tdd, *J* = 13.0, 7.1, 2.6 Hz, 1H), 2.63 – 2.45 (m, 1H), 1.76 – 1.69 (m, 1H), 1.68 – 1.63 (m, 1H), 1.59 – 1.53 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.1 and 171.0, 80.8 (d, *J* = 216 Hz), 80.7, 31.8 (d, *J* = 25.4 Hz), 30.8 (d, *J* = 31.6 Hz), 28.0, 20.0 (d, *J* = 13.1 Hz), 19.2. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –175.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{16}FO_2$ 187.1134. Found 187.1161. $[M+NH_4]^+$ Calcd. for $C_{10}H_{19}FNO_2$ 204.1400. Found 204.1401. $[M+Na]^+$ Calcd. for $C_{10}H_{15}FNaO_2$ 209.0954. Found 209.0934.

(1*R,3*R**,4*S**)-Methyl 3-methoxybicyclo[2.1.0]pentane-1-carboxylate (16d).** The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 2:1 of diastereomers. Yield 17.9 g (31%); colorless liquid; bp 65–67 °C / 7 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (dt, *J* = 8.0, 3.7 Hz, 0.67H) and 3.39 – 3.35 (m, 0.33H), 3.71 – 3.64 (m, 3H), 3.31 (s, 1H) and 3.18 (s, 2H), 2.70 – 2.65 (m, 0.67H) and 2.24 (dt, *J* = 11.7, 2.6 Hz, 0.33H), 2.55 – 2.53 (m, 0.67H) and 1.95 (dd, *J* = 11.7, 4.2 Hz, 0.33H), 1.81 – 1.77 (m, 0.33H) and 1.59 – 1.45 (m, 1.67H) and 1.22 – 1.18 (m, 0.33H), 1.67 – 1.59 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.3 and 173.1, 75.1 and 68.5, 55.3 and 54.9, 51.6, 33.3 and 30.6, 32.2 and 30.3, 24.1 and 23.2, 19.0. GC/MS (EI): *m/z* = 125 $[M–OCH_3]^+$, 156 $[M]^+$. Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.79; H, 8.07.

(1*R,3*S**,4*R**)-3-Methylbicyclo[2.1.0]pentane-1-carboxylic acid (10a).** *tert*-Butyl ester **9a** (63.8 g, 0.350 mol) was dissolved in MeOH – H_2O (690 mL, 2:1, v/v), and $LiOH·H_2O$ (15.9 g, 0.380 mol) was

added in one portion. The mixture was refluxed overnight, then cooled to rt and evaporated in *vacuo* at 55 °C. The residue was dissolved H_2O (200 mL), washed with *t*-BuOMe (2×200 ml), $NaHSO_4$ (60.6 g, 0.505 mol) was added to aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (25 mL). Yield 34.8 g (79%); colorless crystals; mp 42–44 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 2.59 – 2.52 (m, 1H), 2.44 (td, J = 10.8, 1.6 Hz, 1H), 2.29 – 2.20 (m, 1H), 1.38 – 1.33 (m, 1H), 1.31 (dd, J = 4.3, 2.9 Hz, 1H), 1.09 (dd, J = 10.8, 4.3 Hz, 1H), 0.78 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.9, 33.6, 31.5, 28.7, 24.9, 22.4, 21.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_7H_{11}O_2$ 127.0759. Found 127.0755.

(1*R,3*S**,4*R**)-3-Phenylbicyclo[2.1.0]pentane-1-carboxylic acid (10b).** TFA (292 mL, 436 g, 3.82 mol) was added to CH_2Cl_2 (1000 mL), and the solution was cooled to 5°C. *tert*-Butyl ester **9b** (93.4 g, 0.382 mol) was added, the mixture was stirred at 5°C for 30 min, then evaporated in *vacuo* at 55 °C. The residue was diluted with benzene (200 mL), and the solution was evaporated in *vacuo* at 55 °C. The crude compound was recrystallized from MeCN (70 mL). Yield 41.7 g (58%); yellow solid; mp 110–113 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.38 – 7.29 (m, 4H), 7.23 (t, J = 7.0 Hz, 1H), 2.80 (t, J = 5.3 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.19 (ddd, J = 11.4, 4.2, 1.9 Hz, 1H), 2.08 (dd, J = 11.4, 6.0 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.44 (dd, J = 4.2, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.4, 145.3, 129.0, 126.9, 126.8, 38.6, 33.0, 32.4, 24.5, 23.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{13}O_2$ 189.0916. Found 189.0909.

(1*R,3*S**,4*S**)-3-Fluorobicyclo[2.1.0]pentane-1-carboxylic acid (10c).** *tert*-Butyl ester **9c** (61.1 g, 0.328 mol) was dissolved in MeOH – H_2O (900 mL, 2:1, v/v), and $LiOH{\cdot}H_2O$ (20.6 g, 0.492 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 55 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 mL), $NaHSO_4$ (78.6 g, 0.640 mol) was added to aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (60 mL). Yield 26.9 g (63%); beige crystals; mp

60–61 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 4.62 (ddd, J = 58.8, 3.7, 1.4 Hz, 1H), 2.63 (ddd, J = 9.5, 7.0, 2.3 Hz, 1H), 2.21 (ddd, J = 34.9, 12.6, 2.3 Hz, 1H), 2.02 (ddd, J = 16.2, 12.6, 3.7 Hz, 1H), 1.67 – 1.60 (m, 1H), 1.31 (dt, J = 4.9, 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 173.6, 88.35 (d, J = 194 Hz), 33.7 (d, J = 20.8 Hz), 32.7 (d, J = 28.4 Hz), 25.1, 22.4 (d, J = 4.4 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –174.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_6H_8FO_2$ 131.0508. Found 131.0500.

(1*R,3*S**,4*S**)-3-Methoxybicyclo[2.1.0]pentane-1-carboxylic acid (10d).** *tert*-Butyl ester **9d** (66.7 g, 0.340 mol) was dissolved in MeOH – H_2O (1050 mL, 2:1, v/v), and LiOH·H_2O (17.3 g, 0.413 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 55 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 mL), $NaHSO_4$ (61.8 g, 0.515 mol) was added to the aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (45 mL). Yield 34.8 g (72%); beige powder; mp 43–44 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 3.30 (dd, J = 4.2, 2.2 Hz, 1H), 3.20 (s, 3H), 2.49 – 2.44 (m, 1H), 1.97 (dt, J = 11.6, 2.5 Hz, 1H), 1.83 (dd, J = 11.6, 4.3 Hz, 1H), 1.62 – 1.55 (m, 1H), 1.19 (dd, J = 4.3, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.3, 74.7, 55.1, 32.6, 32.1, 24.0, 22.8. HRMS (ESI-TOF) *m/z:* $[M–H]^–$ Calcd. for $C_7H_9O_3$ 141.0552. Found 141.0554.

(1*R,3*S**,4*S**)-3-Bromobicyclo[2.1.0]pentane-1-carboxylic acid (10e).** TFA (205 g, 1.79 mol) was added to CH_2Cl_2 (300 mL), and the solution was cooled to 5 °C. *tert*-Butyl ester **9e** (93.4 g, 0.380 mol) was added, the mixture was stirred at 5 °C for 30 min, then evaporated in *vacuo* at 55 °C. The residue was diluted with benzene (200 mL), and the solution was evaporated in *vacuo* at 55 °C. The crude compound was recrystallized from MeCN (30 mL). Yield 41.9 g (58%); colorless crystals; mp 109–110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 3.99 (dt, J = 4.7, 2.2 Hz, 1H), 2.72 (dt, J = 6.7, 2.2 Hz, 1H), 2.56 – 2.53 (m, 1H), 2.40 (ddd, J = 12.8, 4.7, 1.9 Hz, 1H), 1.55 (ddt, J = 7.0, 4.7, 2.2 Hz, 1H),

1.41 (dt, J = 4.7, 2.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 173.5, 42.3, 37.2, 35.3, 24.6, 24.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_6H_8BrO_2$ 190.9708. Found 190.9702.

(1*R,3*S**,4*S**)-3-Azidobicyclo[2.1.0]pentane-1-carboxylic acid (10f).** *tert*-Butyl ester **9f** (60.0 g, 0.287 mol) was dissolved in MeOH – H_2O (900 mL, 2:1, v/v), and $LiOH·H_2O$ (24.1 g, 0.574 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 35 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 ml), and $NaHSO_4$ (72.3 g, 0.602 mol) was added to the aqueous solution, which was extracted with EtOAc (3×200 mL). Organic layer was washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 35 °C. The crude compound was recrystallized from *t*-BuOMe (60 mL). Yield 21.1 g (48%); colorless powder. ^1H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 3.48 (dd, J = 4.8, 2.7 Hz, 1H), 2.53 (dd, J = 6.9, 2.5 Hz, 1H), 2.13 (dt, J = 12.1, 2.7 Hz, 1H), 2.00 (dd, J = 12.1, 4.9 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.35 (dd, J = 4.9, 2.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.5, 54.7, 31.6, 31.4, 24.0, 22.8. HRMS (ESI-TOF) *m/z*: $[M–H]^-$ Calcd. for $C_6H_6N_3O_2$ 152.0460. Found 152.0463.

(1*R,3*S**,4*S**)-3-Hydroxybicyclo[2.1.0]pentane-1-carboxylic acid (10g).** *tert*-Butyl ester **8e** (45.0 g, 0.244 mol) was dissolved in MeOH – H_2O (520 mL, 1.6:1, v/v), and KOH (15.1 g, 0.277 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 55 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 mL), $NaHSO_4$ (35.2 g, 0.293 mol) was added to the aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (35 mL). Yield 22.8 g (73%); colorless solid; mp 127–129 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 5.37 (s, 1H), 3.55 – 3.50 (m, 1H), 2.27 (dd, J = 6.7, 2.5 Hz, 1H), 1.92 (dt, J = 11.4, 2.5 Hz, 1H), 1.84 (dd, J = 11.4, 4.2 Hz, 1H), 1.55 – 1.50 (m, 1H), 1.13 (dd, J = 4.2, 2.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 174.7, 65.8, 36.1, 35.1, 23.3, 23.3. HRMS (ESI-TOF) *m/z*: $[M–H]^-$ Calcd. for $C_6H_7O_3$ 127.0395. Found 127.0394.

(3*S,4*S**)-*tert*-Butyl 3-bromo-4-((*tert*-butyldimethylsilyl)oxy)cyclopentanecarboxylate (11g).** Bromoalcohol **8g** (231 g, 0.872 mol) was dissolved in DMF (1200 mL), and TBDMSCl (144 g, 0.959

mol), DMAP (10.6 g, 87.2 mmol) and imidazole (67.5 mL, 83.0 g, 1.22 mol) were added at rt. The mixture was stirred at rt overnight, then poured into H_2O (1000 mL), and extracted with EtOAc (800 mL). Organic phase was washed with brine (4×400 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was used in the next step without further purification. Yield 304 g (92%); colorless oil. The compound was obtained as a mixture of *ca.* 7:3 of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 – 4.32 (m, 0.3H) and 4.32 – 4.28 (m, 0.7H), 4.09 (dt, J = 6.7, 3.4 Hz, 0.7H) and 3.96 (q, J = 5.8 Hz, 0.3H), 3.04 (quint, J = 8.3 Hz, 0.7H) and 2.97 (quint, J = 8.6 Hz, 0.3H), 2.68 – 2.59 (m, 1H), 2.45 – 2.36 (m, 1H), 2.28 – 2.18 (m, 1H), 1.87 – 1.80 (m, 1H), 1.46 (s, 2.7H) and 1.45 (s, 6.3H), 0.89 (s, 2.7H) and 0.88 (s, 6.3H), 0.11 – 0.05 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.1 and 174.0, 80.5 and 80.3, 80.1, 56.5 and 54.6, 41.5 and 41.3, 37.4 and 36.7, 36.2 and 35.7, 28.0 and 28.0, 25.7 and 25.7 and 25.7, 18.0 and 17.9, –4.7 and –4.9. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{16}H_{31}BrNaO_3Si$ 401.1124/403.1103. Found 401.1121/403.1102.

***tert*-Butyl 4-oxocyclopent-1-enecarboxylate (14g).** Oxalyl chloride (1.95 mL, 2.89 g, 22.9 mmol) was dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to –70 °C. DMSO (HPLC grade, 2.77 mL, 3.05 g, 39.1 mmol) was added dropwise at –70 °C, and the resulting mixture was stirred at 30 min. A solution of alcohol **9g** (3.00 g, 16.3 mmol) in CH_2Cl_2 (30 mL) was added dropwise at –70 °C, the reaction mixture was stirred at –70 °C for 30 min, and Et_3N (11.3 mL, 8.23 g, 81.4 mmol) was added at –70 °C. The resulting mixture was stirred at –70 °C for 30 min, then warmed up to rt, washed with H_2O (2×20 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 2.13 g (72%); yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (t, J = 2.1 Hz, 1H), 2.80 – 2.76 (m, 2H), 2.51 – 2.46 (m, 2H), 1.51 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 209.2, 166.2, 163.4, 137.3, 82.4, 35.6, 27.9, 27.4. GC/MS (EI): *m/z* = 182 $[M]^+$. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.79; H, 7.61.

(3*S,4*R**)-*tert*-Butyl 3-bromo-4-methylcyclopentanecarboxylate (15a).** Alcohol **7a** (80.1 g, 0.400 mol) was dissolved in CH_2Cl_2 (800 mL), and PPh_3 (115 g, 0.440 mol) and imidazole (26.6 mL, 32.7 g, 0.480 mol) were added under argon atmosphere. The resulting mixture was cooled to –10 °C, and Br_2 (22.6 mL, 70.2 g, 0.440 mol) was added dropwise at –10 °C. The mixture was stirred at rt overnight,

10% aq Na_2SO_3 (200 mL) was added, organic layer was separated, washed with 10% aq $NaHSO_4$ (200 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The residue was suspended in hexanes (200 mL), the precipitate was filtered off, and filtrate was evaporated in *vacuo* at 45 °. The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 3:2 of diastereomers. Yield 71.6 g (68%); yellowish liquid; bp 75–78 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (quint, J = 3.5 Hz, 0.4H) and 4.34 (quint, J = 2.8 Hz, 0.6H), 3.11 – 3.01 (m, 0.4H) and 2.81 – 2.72 (m, 0.6H), 2.62 – 2.50 (m, 1.2H) and 2.43 – 2.38 (m, 0.8H), 2.02 – 1.71 (m, 3H), 1.41 (s, 5.4H) and 1.39 (s, 3.6H), 1.06 (d, J = 6.0 Hz, 1.8H) and 1.03 (d, J = 6.4 Hz, 1.2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.4 and 174.3, 80.3 and 80.2, 63.3 and 60.8, 42.5 and 41.8, 41.1 and 40.9, 40.4 and 40.0, 34.3 and 34.3, 28.0 and 28.0, 17.5 and 17.5. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{11}H_{19}BrNaO_2$ 285.0466/287.0446. Found 285.0464/287.0445.

(3*S,4*S**)-*tert*-Butyl 3-bromo-4-phenylcyclopentanecarboxylate (15b).** Alcohol **7b** (158 g, 0.600 mol) was dissolved in CH_2Cl_2 (1600 mL), and PPh_3 (236 g, 0.900 mol) and imidazole (49.8 mL, 61.3 g, 0.900 mol) were added under argon atmosphere. The mixture was cooled to –10 °C, and Br_2 (46.4 mL, 144 g, 0.900 mol) was added dropwise at –10 °C. The mixture was stirred at rt overnight, then 10% aq Na_2SO_3 aq solution (400 ml) was added. Organic layer was washed with 10% aq $NaHSO_4$ (400 mL) and brine (400 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The residue was suspended in hexanes (400 mL), the precipitate was filtered off, and filtrate was evaporated in *vacuo* at 45 °C. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent; R_f = 0.57. The compound was obtained as a mixture of diastereomers. Yield 142 g (73%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.30 – 7.23 (m, 3H), 4.68 (t, J = 4.7 Hz, 1H), 3.27 (dt, J = 12.0, 5.6 Hz, 1H), 3.05 – 2.97 (m, 1H), 2.85 – 2.73 (m, 2H), 2.65 (td, J = 12.6, 9.4 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.51 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.0, 139.8, 128.1, 128.0, 126.9, 80.7, 59.0, 51.3, 42.2, 40.0, 30.8, 28.1. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{16}H_{21}BrNaO_2$ 347.0623. Found 347.0621.

(3*S,4*R**)-*tert*-Butyl 3-bromo-4-fluorocyclopentanecarboxylate (15c).** Alcohol **7c** (85.8 g, 0.420 mol) was dissolved in benzene (850 mL), and PPh_3 (163 g, 0.620 mol) and imidazole (34.4 mL, 42.2 g,

0.620 mol) were added. Then, Br_2 (31.9 mL, 99.0 g, 0.620 mol) was added dropwise at rt, the resulting mixture was refluxed overnight, cooled to rt, and 10% aq Na_2SO_3 (400 mL) was added. The resulting mixture was stirred for 10 min, and EtOAc (850 mL) was added. Organic layer was washed with 10% aq $NaHSO_4$ (200 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The residue was suspended in hexanes (300 mL), the precipitate was filtered off, and filtrate was evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 6:1 of diastereomers. Yield 55.0 g (49%); colorless liquid; bp 80–82 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 – 4.76 (m, 1H), 4.23 – 4.06 (m, 0.14H) and 4.01 – 3.85 (m, 0.86H), 3.11 – 3.00 (m, 0.14H) and 2.80 – 2.69 (m, 0.86H), 2.49 – 2.13 (m, 4H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.3 and 172.6, 94.4 (d, J = 185 Hz) and 93.3 (d, J = 185 Hz), 81.0, 48.5 (d, J = 18.3 Hz), 48.2 (d, J = 19.3 Hz), 40.9 and 40.7, 36.4 and 36.1, 33.7 (d, J = 21.7 Hz), 33.2 (d, J = 22.6 Hz), 28.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –179.6 and –182.3. HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ Calcd. for $C_{10}H_{20}BrFNO_2$ 284.0661. Found 284.0661. $[M+Na]^+$ Calcd. for $C_{10}H_{16}BrFNaO_2$ 289.0215. Found 289.0213.

(3*S,4*R**)-Methyl 3-bromo-4-methoxycyclopentanecarboxylate (15d).** Alcohol **7d** (121 g, 0.695 mol) was dissolved in benzene (1200 mL), PPh_3 (273 g, 1.04 mol) and imidazole (57.6 mL, 70.8 g, 1.04 mol) were added at rt. Br_2 (53.6 mL, 166 g, 1.04 mol) was added dropwise at rt, the mixture was refluxed overnight, then cooled to rt. 10% aq Na_2SO_3 (600 mL) was added, and the resulting mixture was stirred for 10 min. Then, EtOAc (1000 mL) was added, organic layer was separated, washed with 10% $NaHSO_4$ (300 mL) and brine (400 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The residue was suspended in hexanes (300 mL), the precipitate was filtrated off, and the solution was evaporated in *vacuo* at 45 °C. The compound was used in the next step without further purification (an attempted distillation in *vacuo* as well as chromatographic purification led to decomposition of compound). The compound was obtained as a mixture of *ca.* 3:1 of diastereomers. Yield 74.1 g (45%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (q, J = 4.2 Hz, 0.25H) and 4.36 – 4.31 (m, 0.75H), 4.06 – 3.93 (m, 1H), 3.70 (s, 3H), 3.40 – 3.34 (m, 3H), 3.18 (quint, J = 9.1, 8.7 Hz, 1H), 2.58 (ddd, J = 14.8, 9.3, 5.8 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.34 – 2.25 (m, 1H), 1.99 (ddd, J = 14.5, 7.4, 3.2 Hz, 1H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 175.1, 88.6 and 82.3, 57.4 and 57.2, 54.0 and 52.6, 52.1 and 52.0, 40.5 and 38.4, 37.6 and 36.8, 33.1 and 31.4. GC/MS (EI): *m/z* = 157 $[M–Br]^+$, 205/207 $[M–OCH_3]^+$, 236/238 $[M]^+$. Anal. Calcd. for $C_8H_{13}BrO_3$: C, 40.53; H, 5.53; Br, 33.70. Found: C, 40.41; H, 5.62; Br, 33.72.

(1*R,3*R**,4*S**)-*tert*-Butyl 3-azidobicyclo[2.1.0]pentane-1-carboxylate (16f).** Alcohol **9g** (200 g, 1.09 mol) was dissolved in THF (2000 mL), and PPh_3 (312 g, 1.19 mol) was added. The mixture was cooled to –10 °C, and DEAD (187 mL, 207 g, 1.19 mol) was added dropwise at –10 °C, and the solution was stirred at –10 °C for 30 min. Then, DPPA (257 mL, 327 g, 1.19 mol) was added dropwise at –10 °C The mixture was stirred at rt overnight, then evaporated in *vacuo* at 35 °C. Next, *t*-BuOMe (400 mL) was added, and the resulting mixture was cooled to –20 °C. The precipitate was filtered off and washed with *t*-BuOMe (50 ml), filtrate was evaporated in *vacuo* at 35 °C. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (4:1) as eluent; R_f = 0.55. Yield 107 g (47%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 – 4.13 (m, 1H), 2.77 (ddt, *J* = 11.8, 9.4, 2.1 Hz, 1H), 2.57 – 2.44 (m, 1H), 1.63 (td, *J* = 9.1, 6.6, 3.9 Hz, 2H), 1.50 – 1.47 (m, 1H), 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 171.2, 80.7, 50.9, 30.5, 29.3, 28.1, 21.3, 19.7. GC/MS (EI): *m/z* = 136 $[M–O\textit{t}\text{-Bu}]^+$, 181 $[M–N_2]^+$, 194 $[M–CH_3]^+$. Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.04; H, 7.60; N, 19.77.

(1*R,3*R**,4*S**)-*tert*-Butyl 3-hydroxybicyclo[2.1.0]pentane-1-carboxylate (16g).** Ester **18g** (134 g, 0.402 mol) was dissolved in MeOH (1300 mL), and KOH (27.1 g, 0.482 mol) was added in one portion. The mixture was stirred at rt overnight, then evaporated in *vacuo* at 45 °C. The residue was dissolved in *t*-BuOMe (1000 mL), washed with brine (2×200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C (NOTE: if EtOAc was used instead of *t*-BuOMe, the partial transesterification occurred, and the corresponding acetyl alcohol was isolated with alcohol **16g** in 1:3 ratio). The crude compound was purified by distillation in *vacuo*. Yield 45.9 g (62%); colorless oil; bp 90–92 °C / 1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (dt, *J* = 8.5, 3.8 Hz, 1H), 2.69 – 2.64 (m, 1H), 2.48 – 2.44 (m, 1H), 2.30 (s, 1H), 1.53 (ddd, *J* = 6.7, 4.5, 2.0 Hz, 1H), 1.46 – 1.44 (m, 2H), 1.40 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz,

$CDCl_3$) δ 172.4, 80.4, 60.9, 33.4, 32.6, 28.0, 19.5, 18.9. GC/MS (EI): *m/z* = 111 $[M–Ot\text{-}Bu]^+$, 128 $[M–H_2C{=}C(CH_3)_2]^+$. Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.10; H, 8.48.

(1*R,3*R**,4*R**)-3-Methylbicyclo[2.1.0]pentane-1-carboxylic acid (17a).** *tert*-Butyl ester **16a** (55.0 g, 0.302 mol) was dissolved in MeOH – H_2O (750 mL, 2:1 v/v), and $LiOH{\cdot}H_2O$ (19.0 g, 0.453 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 55 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 ml). $NaHSO_4$ (72.5 g, 0.604 mol) was added to aqueous solution, then it was extracted with EtOAc (3×200 ml), Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, filtrated and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (30 mL). Yield 28.9 g (76%); beige solid; mp 64–67 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 2.60 – 2.52 (m, 1H), 2.44 (td, *J* = 10.8, 1.6 Hz, 1H), 2.29 – 2.18 (m, 1H), 1.40 – 1.33 (m, 1H), 1.31 (dd, *J* = 4.3, 2.9 Hz, 1H), 1.09 (dd, *J* = 10.8, 4.3 Hz, 1H), 0.78 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.6, 30.6, 29.2, 25.7, 20.7, 19.4, 16.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_7H_{11}O_2$ 127.0759. Found 127.0752.

(1*R,3*R**,4*R**)-3-Phenylbicyclo[2.1.0]pentane-1-carboxylic acid (17b).** TFA (354 mL, 527 g, 4.62 mol) was added to CH_2Cl_2 (1100 mL), and the solution was cooled to 5 °C. *tert*-Butyl ester **16b** (113 g, 0.462 mol) was added at 5 °C, and the mixture was stirred at 5 °C for 30 min. Then the solution was evaporated in *vacuo* at 55 °C, the residue was diluted with benzene (200 mL), and the resulting solution was evaporated in *vacuo* at 55 °C. The crude compound was recrystallized from MeCN (80 mL). Yield 40.0 g (46%); colorless solid; mp 177–178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.38 – 7.28 (m, 4H), 7.23 (t, *J* = 7.0 Hz, 1H), 2.80 (t, *J* = 5.3 Hz, 1H), 2.42 (d, *J* = 6.4 Hz, 1H), 2.19 (ddd, *J* = 11.2, 4.2, 1.9 Hz, 1H), 2.08 (dd, *J* = 11.5, 6.0 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.44 (dd, *J* = 4.2, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.4, 142.3, 128.5, 127.1, 126.1, 34.4, 29.4, 29.0, 21.7, 21.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{12}H_{13}O_2$ 189.0916. Found 189.0911.

(1*R,3*R**,4*S**)-3-Methoxybicyclo[2.1.0]pentane-1-carboxylic acid (17d).** *tert*-Butyl ester **16d** (22.0 g, 0.141 mol) was dissolved in MeOH – H_2O (300 mL, 2:1, v/v), and $LiOH{\cdot}H_2O$ (8.87 g, 0.211 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in

vacuo at 55 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 mL), $NaHSO_4$ (27.1 g, 0.226 mol) was added to the aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (45 mL). Yield 10.4 g (52%); beige powder; mp 53–54 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 3.91 (dt, J = 8.3, 3.6 Hz, 1H), 3.06 (s, 3H), 2.48 – 2.44 (m, 1H), 1.50 – 1.39 (m, 1H), 1.39 – 1.22 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 68.3, 54.9, 32.1, 29.9, 19.8, 18.9. HRMS (ESI-TOF) *m/z*: $[M–H]^-$ Calcd. for $C_7H_9O_3$ 141.0552. Found 141.0557.

(1*R,3*R**,4*S**)-3-Azidobicyclo[2.1.0]pentane-1-carboxylic acid (17f).** *tert*-Butyl ester **16f** (80.0 g, 0.382 mol) was dissolved in MeOH – H_2O (1200 mL, 2:1, v/v), and $LiOH·H_2O$ (32.1 g, 0.764 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 35 °C. The residue was dissolved in H_2O (200 mL), washed with *t*-BuOMe (2×200 ml), and $NaHSO_4$ (72.3 g, 0.602 mol) was added to the aqueous solution, which was extracted with EtOAc (3×200 mL). Organic layer was washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 35 °C. The crude compound was recrystallized from *t*-BuOMe (70 mL). Yield 28.1 g (48%); colorless powder. Yield 24.1 g (41%); colorless powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 4.37 (dt, J = 9.0, 4.2 Hz, 1H), 2.71 – 2.64 (m, 1H), 2.58 (ddd, J = 6.8, 4.7, 2.6 Hz, 1H), 1.59 – 1.50 (m, 2H), 1.43 (dd, J = 4.7, 2.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.4, 50.8, 30.4, 29.2, 20.3, 19.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_6H_8N_3O_2$ 154.0617. Found 154.0615. $[M+Na]^+$ Calcd. for $C_6H_7N_3NaO_2$ 176.0436. Found 176.0434.

(1*R,3*R**,4*S**)-3-Hydroxybicyclo[2.1.0]pentane-1-carboxylic acid (17g).** *tert*-Butyl ester **16g** (32.2 g, 0.174 mol) was dissolved in MeOH – H_2O (325 mL, 2.25:1, v/v), and KOH (10.8 g, 0.192 mol) was added in one portion. The mixture was refluxed overnight, then cooled to rt, and evaporated in *vacuo* at 55 °C. The residue was dissolved in H_2O (100 mL), washed with *t*-BuOMe (2×200 mL), $NaHSO_4$ (25.2 g, 0.210 mol) was added to aqueous solution, which was extracted with EtOAc (3×200 mL). Combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C.

The crude compound was recrystallized from MeCN (20 mL). Yield 18.1 g (81%); brownish solid.; mp 43–44 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 4.88 (s, 1H), 4.19 (dt, J = 8.6, 3.9 Hz, 1H), 2.50 – 2.46 (m, 1H), 2.46 – 2.38 (m, 1H), 1.47 (dd, J = 4.2, 2.7 Hz, 1H), 1.43 – 1.34 (m, 1H), 1.29 (dd, J = 11.4, 3.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.5, 59.9, 33.5, 33.3, 19.1, 18.4. HRMS (ESI-TOF) *m/z*: $[M–H]^-$ Calcd. for $C_6H_7O_3$ 127.0395. Found 127.0400.

(1*R,3*R**,4*S**)-*tert*-Butyl 3-((4-nitrobenzoyl)oxy)bicyclo[2.1.0]pentane-1-carboxylate (18g).** Alcohol **9g** (48.7 g, 0.264 mol) was dissolved in THF (500 mL), and PPh_3 was added (86.7 g, 0.330 mol). The mixture was cooled to –10 °C, and DEAD (51.8 mL, 57.5 g, 0.330 mol) was added dropwise at –10 °C The mixture was stirred at –10 °C for 30 min, and *p*-nitrobenzoic acid (55.1 g, 0.330 mol) in THF 100 mL) was added dropwise at –10 °C. The resulting mixture was stirred at rt overnight, then evaporated in *vacuo* at 45 °C. The residue was diluted in *t*-BuOMe (200 mL) and the mixture was cooled to –20 °C. The precipitate was filtered off, washed with *t*-BuOMe (50 mL), and filtrate was evaporated in *vacuo* at 45 °C. The crude compound which was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent; R_f = 0.41. Yield 71.3 g (81%); colorless solid; mp 112–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H), 5.32 (dt, J = 8.3, 3.7 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.75 – 2.70 (m, 1H), 1.77 (dd, J = 12.5, 2.9 Hz, 1H), 1.73 – 1.69 (m, 1H), 1.54 (dd, J = 4.8, 2.6 Hz, 1H), 1.46 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.0, 164.1, 150.6, 135.3, 130.7, 123.5, 80.8, 65.3, 31.2, 29.9, 28.1, 21.6, 19.6. LC/MS (CI): *m/z* = 334 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.59; H, 5.51; N, 4.11.

(1*R,3*S**,4*S**)-*tert*-Butyl 3-aminobicyclo[2.1.0]pentane-1-carboxylate (19).** A solution of azide **9f** (150 g, 0.717 mol) in THF (1500 mL) was cooled to 10 °C, and PPh_3 (210 g, 0.800 mol) was added in portions at 10 °C. The mixture was stirred at rt for 2 h, and H_2O (387 mL, 387 g, 21.5 mol) was added to the mixture in one portion. The resulting mixture was stirred at rt overnight, most of THF was evaporated in *vacuo* at 40 °C, and the residue was dissolved in 20% aq $NaHSO_4$ (645 mL, 1.08 mol). The aqueous solution was washed with *t*-BuOMe (2×500 mL), then K_2CO_3 (168 g, 1.22 mol) was added in portions, and the solution was extracted with CH_2Cl_2 (2×500 mL). Combined organic layers were

washed with brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 78.8 g (60%); yellowish liquid; bp 55–57 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (dd, *J* = 5.0, 3.3 Hz, 1H), 2.26 – 2.13 (m, 1H), 1.97 (dd, *J* = 11.7, 5.0 Hz, 1H), 1.85 (dt, *J* = 11.7, 2.8 Hz, 1H), 1.66 – 1.61 (m, 1H), 1.52 (s, 2H), 1.41 (s, 9H), 1.15 – 1.05 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.7, 80.0, 47.6, 36.7, 35.1, 28.1, 24.2, 23.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{18}NO_2$ 184.1338. Found 184.1330.

(1*R,3*R**,4*S**)-*tert*-Butyl 3-aminobicyclo[2.1.0]pentane-1-carboxylate (20).** A solution of azide **16f** (227 g, 1.08 mol) in THF (2300 mL) was cooled to 10 °C, and PPh_3 (312 g, 1.19 mol) was added in portions at 10 °C. The mixture was stirred at rt for 2 h, and H_2O (586 mL, 586 g, 32.5 mol) was added to the mixture in one portion. The resulting mixture was stirred at rt overnight, most of THF was evaporated in *vacuo* at 40 °C, and the residue was dissolved in 20% aq $NaHSO_4$ (976 ml, 1.62 mol). The aqueous solution was washed with *t*-BuOMe (2×700 mL), then K_2CO_3 (300 g, 2.17 mol) was added in portions, and the solution was extracted with CH_2Cl_2 (2×700 mL). Combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 125 g (63%); yellow crystals; mp 42–43 °C; bp 54–56 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (dt, *J* = 8.9, 4.2 Hz, 1H), 2.71 (ddd, *J* = 11.6, 9.7, 1.8 Hz, 1H), 2.44 – 2.34 (m, 1H), 1.52 – 1.48 (m, 1H), 1.40 (s, 9H), 1.34 – 1.21 (m, 2H), 1.22 – 1.03 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 80.0, 42.9, 33.8, 32.9, 28.1, 19.8, 18.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{18}NO_2$ 184.1338. Found 184.1328.

(1*S,2*S**,4*R**)-4-Carboxybicyclo[2.1.0]pentan-2-aminium 2,2,2-trifluoroacetate (21).** TFA (276 mL, 411 g, 3.61 mol) was added to CH_2Cl_2 (700 mL), and the mixture was cooled to 5 °C. *tert*-Butyl ester **20** (66.1 g, 0.361 mol) was added, the mixture was stirred at 5 °C for 30 min, and evaporated in *vacuo* at 55 °C. The residue was diluted with benzene (200 mL), and the solution was evaporated in *vacuo* at 55 °C. The crude compound was recrystallized from MeCN (100 mL). Yield 54.8 g (63%); colorless powder; mp 167–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.32 (s, 3H), 3.10 – 3.03 (m, 1H), 2.44 (dd, *J* = 6.7, 2.4 Hz, 1H), 2.17 (dt, *J* = 12.1, 2.7 Hz, 1H), 1.95 (dd, *J* = 12.1, 4.8 Hz,

1H), 1.65 – 1.54 (m, 1H), 1.39 (dd, *J* = 4.8, 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 173.5, 158.8 (q, *J* = 31.4 Hz), 117.6 (q, *J* = 306 Hz), 44.9, 30.0, 29.5, 23.8, 22.2. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ –74.1. LC/MS (CI): *m/z* = 128 $[M–CF_3CO_2H+H]^+$. Anal. Calcd. for $C_8H_{10}F_3NO_4$: C, 39.84; H, 4.18; N, 5.81. Found: C, 40.03; H, 3.96; N, 5.82.

(1*S,2*R**,4*R**)-4-Carboxybicyclo[2.1.0]pentan-2-aminium 2,2,2-trifluoroacetate (22).** TFA (418 mL, 624 g, 5.47 mol) was added to CH_2Cl_2 (1100 mL), and the mixture was cooled to 5 °C. *tert*-Butyl ester **20** (100 g, 0.547 mol) was added, the mixture was stirred at 5 °C for 30 min, then evaporated in *vacuo* at 55 °C. The residue was diluted with benzene (200 mL), and the solution was evaporated in *vacuo* at 55 °C. The crude compound was recrystallized from MeCN (150 mL). Yield 103 g (78%); colorless powder; mp 180–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 7.93 (s, 3H), 3.95 – 3.88 (m, 1H), 2.63 (ddd, *J* = 11.9, 9.9, 2.0 Hz, 1H), 2.48 – 2.44 (m, 1H), 1.77 (dd, *J* = 5.2, 2.6 Hz, 1H), 1.59 (dd, *J* = 11.9, 4.1 Hz, 1H), 1.54 – 1.48 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 173.1, 158.9 (d, *J* = 31.7 Hz), 117.5 (q, *J* = 299 Hz), 28.2, 27.1, 20.8, 18.9. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ –74.3. LC/MS (CI): *m/z* = 128 $[M–CF_3CO_2H+H]^+$. Anal. Calcd. for $C_8H_{10}F_3NO_4$: C, 39.84; H, 4.18; N, 5.81. Found: C, 39.69; H, 3.85; N, 5.58.

(1*R,3*S**,4*S**)-3-((*tert*-Butoxycarbonyl)amino)bicyclo[2.1.0]pentane-1-carboxylic acid (23).** Amino acid **21** (28.4 g, 0.118 mol) was dissolved in H_2O – THF (300 mL, 2:1, v/v), and $NaHCO_3$ (39.6 g, 0.472 mol) was added. The solution was cooled to 5 °C, and Boc_2O (28.4 mL, 26.9 g, 124 mmol) in THF (100 mL) was added dropwise to the mixture at 5 °C. The mixture was stirred at rt overnight, then *t*-BuOMe (300 mL) was added. Organic layer was separated, and $NaHSO_4$ (100 g, 0.832 mol) was added to aqueous layer, which was extracted with *t*-BuOMe (2×300 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (50 mL). Yield 21.2 g (79%); white powder; mp 152–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.45 (d, *J* = 4.3 Hz, 1H), 3.23 – 3.14 (m, 1H), 2.28 (d, *J* = 6.3 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.84 (dd, *J* = 11.5, 5.2 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.38 (s, 9H), 1.22 (dd, *J* = 4.3, 2.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 174.4, 155.5, 78.3, 45.6, 33.2,

31.7, 28.7, 23.3, 23.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{11}H_{17}NNaO_4$ 250.1055. Found 250.1052.

(1*R,3*R**,4*S**)-3-((*tert*-Butoxycarbonyl)amino)bicyclo[2.1.0]pentane-1-carboxylic acid (24).** Amino acid **22** (31.6 g, 0.131 mol) was dissolved in H_2O – THF (300 mL, 2:1, v/v), and $NaHCO_3$ (44.0 g, 0.524 mol) was added. The solution was cooled to 5 °C, and Boc_2O (31.7 mL, 30.1 g, 0.138 mol) in THF (100 mL) was added dropwise to the mixture at 5 °C. The mixture was stirred at rt overnight, then *t*-BuOMe (300 mL) was added. Organic layer was separated, and $NaHSO_4$ (112 g, 0.933 mmmol) was added to aqueous layer, which was extracted with *t*-BuOMe (2×300 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was recrystallized from MeCN (55 mL). Yield 24.8 g (83%); white powder; mp 140–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.05 (d, J = 7.8 Hz, 1H), 4.16 – 4.02 (m, 1H), 2.59 (t, J = 10.8 Hz, 1H), 2.44 – 2.39 (m, 1H), 1.55 – 1.49 (m, 1H), 1.43 – 1.37 (m, 2H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.2, 155.1, 78.2, 31.0, 30.6, 28.7, 19.8, 19.3. HRMS (ESI-TOF) *m/z*: $[M–H]^–$ Calcd. for $C_{11}H_{16}NO_4$ 226.1079. Found 226.1090.

(1*R,3*S**,4*S**)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)bicyclo[2.1.0]pentane-1-carboxylic acid (25).** Amino acid **21** (26.0 g, 0.108 mol) was dissolved in H_2O – THF (300 mL, 2:1, v/v), and $NaHCO_3$ (36.2 g, 0.431 mol) was added. The solution was cooled to 5 °C, and FmocCl (29.2 g, 0.113 mol) in THF (100 mL) was added dropwise to the mixture at 5 °C. The mixture was stirred at rt overnight, then *t*-BuOMe (300 mL) was added, and organic layer was separated. 36% aq HCl (66 mL, 0.650 mol) was added to aqueous layer, which was extracted with *t*-BuOMe (2×300 mL). Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by flash chromatography (5 bar) on silica gel using gradient hexanes – *t*-BuOMe as eluent. Yield 12.8 g (34%); white crystals; mp 180–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.96 – 7.90 (m, 1H), 7.89 (d, J = 7.7 Hz, 2H), 7.71 (d, J = 7.7 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 4.30 (d, J = 6.9 Hz, 2H), 4.24 – 4.19 (m, 1H), 3.30 – 3.23 (m, 1H), 2.31 (d, J = 4.9 Hz, 1H), 2.14 (d, J = 11.9 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.59 – 1.50 (m, 1H), 1.30 –

1.19 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.3, 156.0, 144.3, 141.2, 128.0, 127.5, 125.6, 120.5, 79.6, 65.8, 47.2, 45.9, 33.1, 31.6, 27.3, 23.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{21}H_{20}NO_4$ 350.1392. Found 350.1390.

(1*R,3*R**,4*S**)-3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)bicyclo[2.1.0]pentane-1-carboxylic acid (26).** Amino acid **22** (20.0 g, 82.9 mmol) was dissolved in H_2O – THF (300 mL, 2:1, v/v), and $NaHCO_3$ (34.8 g, 414 mmol) was added. The solution was cooled to 5 °C, and FmocCl (22.5 g, 87.0 mmol) in THF (100 mL) was added dropwise to the mixture at 5 °C. The mixture was stirred at rt overnight, then *t*-BuOMe (300 mL) was added, and organic layer was separated. 18% aq HCl (118 ml, 0.58 mol) was added to aqueous layer, which was extracted with *t*-BuOMe (2×300 mL). Combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by recrystallized from MeCN (20 ml). Yield 11.0 g (38%); white solid; mp 178–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.68 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 4.30 (d, J = 6.8 Hz, 2H), 4.19 (t, J = 6.8 Hz, 1H), 4.10 (s, 1H), 2.61 (t, J = 10.8 Hz, 1H), 2.49 – 2.40 (m, 2H), 1.52 (s, 1H), 1.47 – 1.34 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 174.1, 155.7, 144.3, 141.2, 128.1, 127.5, 125.6, 120.6, 65.7, 47.2, 41.4, 30.7, 30.5, 20.0, 19.4. HRMS (ESI-TOF) *m/z*: $[M–H]^-$ Calcd. for $C_{21}H_{18}NO_4$ 348.1236. Found 348.1250.

***tert*-Butyl 3-oxocyclopentanecarboxylate (28).**[55] A solution of acid **27** (25.0 g, 0.195 mmol) in CH_2Cl_2 (500 mL) was cooled to 5 °C, and *t*-BuOH (123 g, 1.66 mol), DMAP (2.38 g, 19.5 mmol) were added in portions at 5 °C. The mixture was stirred for 5 min, then DCC (42.3 g, 0.205 mol) was added in portions at 5 °C, and the resulting mixture was stirred at rt overnight. The solid was filtered off, and organic layer was washed with 10% $NaHSO_4$ (200 mL) and brine (200 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. Yield 28.4 g (79%); colorless liquid; bp 70–72 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (quint, J = 7.5 Hz, 1H), 2.47 – 2.29 (m, 3H), 2.25 – 2.02 (m, 3H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 216.8, 173.5, 80.9, 41.9, 41.1, 37.3, 27.9, 26.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{17}O_3$ 185.1178.

Found 185.1176. $[M+NH_4]^+$ Calcd. for $C_{10}H_{20}NO_3$ 202.1443. Found 202.1441. $[M+Na]^+$ Calcd. for $C_{10}H_{16}NaO_3$ 207.0997. Found 207.0998.

***tert*-Butyl 3-hydroxycyclopentanecarboxylate (29).**[56] A solution of ketone **28** (20.5 g, 0.111 mol) was MeOH (200 mL) was cooled to 3 °C, and $NaBH_4$ (2.10 g, 55.6 mmol) was slowly added in portions at 3 °C. The mixture was stirred at 3 °C for 30 min, then H_2O (300 mL) was added, and the resulting mixture was evaporated in *vacuo* at 55 °C. The residue was dissolved in EtOAc (300 mL) and washed with brine (100 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 4:1 of diastereomers. Yield 19.7 g (95%); colorless liquid; bp 97–99 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 – 4.39 (m, **0**H), 4.31 – 4.24 (m, 1H), 3.05 – 2.88 (m, 1H), 2.88 – 2.66 (m, 1H), 2.00 – 1.86 (m, 4H), 1.83 – 1.71 (m, 2H), 1.45 (s, 7H), 1.43 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.6, 80.7, 73.7 and 73.5, 43.0 and 42.7, 39.2 and 38.6, 35.7 and 34.9, 28.0 and 28.0, 27.9 and 27.4. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{18}NaO_3$ 209.1154. Found 209.1153.

***tert*-Butyl 3-bromocyclopentanecarboxylate (30).** Alcohol **29** (16.2 g, 86.9 mmol) was dissolved in CH_2Cl_2 (160 mL), PPh_3 (25.1 g, 95.7 mmol) and imidazole (5.76 mL, 7.08 g, 0.104 mol) was added at rt under argon aatmosphere. The mixture was cooled to –10 °C, and Br_2 (4,93 mL, 15.3 g, 95.7 mmol) was added dropwise at –10 °C. The reaction mixture was stirred at rt overnight, and 10% aq Na_2SO_3 (40 mL) was added. The organic layer was separated, washed with 10% aq $NaHSO_4$ (40 mL) and brine (40 mL), dried over Na_2SO_4, and evaporated in *vacuo* at 45 °C. The residue was suspended in hexanes (40 mL), the solid was filtered off, and filtrate was evaporated in *vacuo* at 45 °C. The crude compound was purified by distillation in *vacuo*. The compound was obtained as a mixture of *ca.* 5:2 of diastereomers. Yield 14.8 g (68%); colorless liquid; bp 80–83 °C / 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (quint, J = 3.5 Hz, 0.72H) and 4.24 (quint, J = 6.0 Hz, 0.28H), 3.13 – 3.00 (m, 0.72H) and 2.76 – 2.65 (m, 0.28H), 2.50 – 2.43 (m, 0.28H) and 2.32 – 2.25 (m, 1.72H), 2.22 – 2.04 (m, 3H), 1.92 – 1.83 (m, 1H), 1.42 (s, 2.58H) and 1.41 (s, 6.42H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.0 and 174.0, 80.4 and 80.4, 52.8 and 49.5, 43.5 amd 42.7, 41.3 and 40.8, 37.6 and 37.4, 28.0, 27.5 and 27.5. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{10}H_{17}BrNaO_2$ 271.0310. Found 271.0309.

***tert*-Butyl bicyclo[2.1.0]pentane-1-carboxylate (31).** The crude compound was purified by distillation in *vacuo*. Yield (79%); colorless liquid; bp 65–67 °C / 7 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (td, *J* = 11.0, 4.0 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.08 (td, *J* = 11.2, 5.2 Hz, 1H), 1.60 – 1.54 (m, 2H), 1.42 (s, 9H), 1.30 (dt, *J* = 11.2, 5.2 Hz, 1H), 1.12 – 1.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 79.7, 28.1, 26.9, 25.5, 24.2, 22.4, 20.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{10}H_{17}O_2$ 169.1229. Found 169.1223.

Bicyclo[2.1.0]pentane-1-carboxylic acid (32).[36,57] TFA (4.55 mL, 6.78 g, 59.4 mmol) was added to CH_2Cl_2 (10 mL), and the mixture was cooled to 5 °C. *tert*-Butyl ester **30** (1.00 g, 5.94 mmol) was added, and the mixture was stirred at 5 °C for 30 min. Then, the solution was evaporated in *vacuo* at 55 °C, the residue was diluted with benzene (2 mL), and the solution was evaporated in *vacuo* at 55 °C. The crude compound was purified by distillation in *vacuo*. Yield 373 mg (56%); colorless liquid; bp 79–81 °C / 1 mmHg.

General procedure for the preparation of amino acid hydrochlorides. MeOH (50.9 mg, 1.59 mmol) solution in THF (5 mL) was cooled to 5 °C, TMSCl (181 mg, 1.67 mmol) was added dropwise 5 °C, and the resulting mixture was stirred for 30 min. The corresponding amino acid trifluoroacetate **21** or **22** (366 mg, 1.52 mmol) was suspended in THF (5 mL), and the mixture was cooled to –40 °C. The mixture of MeOH, TMSCl in THF was added dropwise to the suspension of **21** or **22** at –40 °C, and the reaction mixture was stirred for 30 min. Then, the mixture was filtered, the precipitate was washed with *t*-BuOMe (2×5 mL), and dried in *vacuo*. The crude compound was recrystallized from MeCN (2 mL).

***cis*-4-Carboxybicyclo[2.1.0]pentan-2-aminium chloride ((1*S*,2*S*,4*R*)-21 or (1*R*,2*R*,4*S*)-21).** Yield 189 mg (76%); colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.55 (s, 3H), 3.14 – 2.92 (m, 1H), 2.47 – 2.39 (m, 1H), 2.29 – 2.07 (m, 1H), 1.94 (dd, *J* = 12.1, 5.0 Hz, 1H), 1.75 – 1.50 (m, 1H), 1.39 (dd, *J* = 4.7, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.5, 44.7, 30.0, 29.5, 23.8, 22.8. HRMS (ESI-TOF) *m/z*: $[M–Cl]^+$ Calcd. for $C_6H_{10}NO_2$ 128.0706. Found 128.0707. *m/z*: [M–HCl+]$^+$ Calcd. for $C_6H_{10}NNaO_2$ 150.0531. Found 150.0525.

***trans*-4-Carboxybicyclo[2.1.0]pentan-2-aminium chloride ((1*S*,2*R*,4*R*)-22 or (1*R*,2*S*,4*S*)-22).** Yield 191 mg (77%); colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (br s, 1H), 8.09 (s, 3H),

3.87 (dt, J = 9.6, 4.4 Hz, 1H), 2.61 (ddd, J = 11.9, 9.6, 1.9 Hz, 1H), 2.49 – 2.37 (m, 3H), 1.89 (dd, J = 5.2, 2.6 Hz, 1H), 1.63 (dd, J = 11.9, 4.0 Hz, 1H), 1.55 – 1.37 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.1, 40.7, 28.1, 27.2, 20.9, 19.1. HRMS (ESI-TOF) *m/z*: [M–HCl+]$^+$ Calcd. for $C_6H_{10}NO_2$ 128.0706. Found 128.0706. *m/z*: [M–HCl+]$^+$ Calcd. for $C_6H_{10}NNaO_2$ 150.0531. Found 150.0524.

Supporting Information includes copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF), and crystallographic information files (CIF). This material is available free of charge at http://pubs.acs.org.

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