Synthesis G. Forcher et al. Paper

Titanium-Mediated Cyclopropanation of Nitriles with Unsaturated Grignard Reagents: Application to the Synthesis of Constrained Lysine Derivatives

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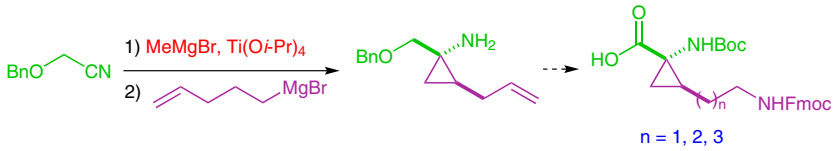


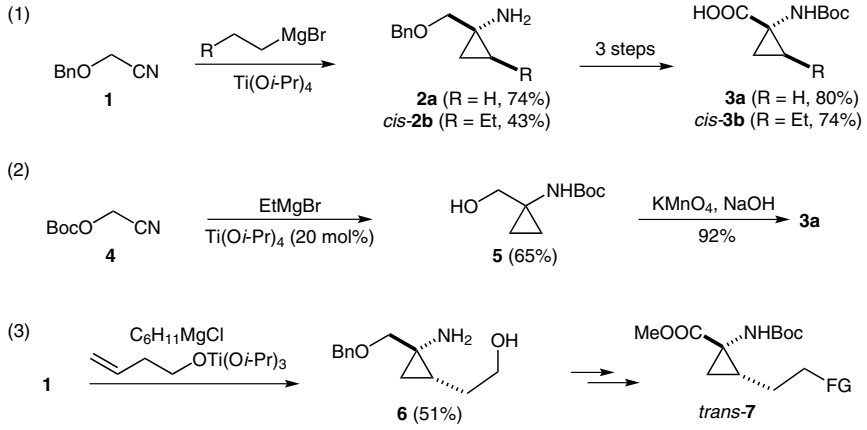
Received: 18.11.2014
Accepted after revision: 15.12.2014
Published online: 28.01.2015
DOI: 10.1055/s-0034-1379978; Art ID: ss-2014-t0705-op

Abstract A comparative study of the titanium-mediated cyclopropanation of (benzyloxy)acetonitrile and Boc-protected cyanohydrin using unsaturated Grignard reagents (but-3-enyl- and pent-4-enylmagnesium bromides) is described. The best conditions to provide the *cis* and *trans* isomers of cyclopropylamines bearing unsaturation were identified and the alkene moiety was subjected to chemical modifications, as shown by the synthesis of orthogonally protected *cis*- and *trans*-2,3-methanolysine, *cis*-2,3-methanoornithine, and *cis*-2,3-methanohomolysine.

Key words amino acids, cyclopropane, Grignard reaction, nitriles, titanium

If the conformational freedom of peptides is associated with high binding affinities, it is also considered as a major drawback in their use as suitable therapeutic agents, responsible for poor selectivity and metabolic stability.[1] The restriction of the biopolymer flexibility with tools able to control secondary structures, while retaining crucial information brought by amino acids side chains, allows its biological properties to be enhanced.[2] With this aim, many amino acids surrogates are designed to control peptide conformational space and among them both diastereomers of 2-substituted 1-aminocyclopropanecarboxylic acids (or 2,3-methanoamino acids) are of great interest.[3] Indeed, the cyclopropyl system allows simultaneous control of the conformation of the peptide backbone while the *cis*/*trans* relative configurations allow exploration of the side-chain orientations.[1a,4] 2,3-Methanoamino acid derivatives are used in drug design[5] and, for example, an important cyclopropane-containing amino acid, (1*R*,2*S*)-dehydrocoronamic acid, is the common component of a family of hepatitis C NS3 NS4 protease inhibitors.[6]

From a synthetic point of view, 2,3-methanoamino acids are prepared by a variety of methods; these were extensively reviewed in 2007.[3e] Among them, low-valent-titanium-mediated cyclopropanation reactions[7] have been found to be a valuable entry to 2,3-methanoamino acid derivatives. The Kulinkovich reaction,[8,9] i.e. the diastereoselective synthesis of cyclopropanols from carboxylic esters, was initially explored. However, several steps were generally required to convert the resulting cyclopropanols into amino acids.[10] The variant using tertiary amides[11] was more straightforward and gives a variety of amino acids accessible in a few steps;[12] the main drawback was the difficulty in separating the diastereomers obtained in the cyclopropanation step. The most recent variant using nitriles gives primary cyclopropylamines directly[13] that can be converted into amino acids in few steps. This method was successfully applied to a short synthesis of Boc-protected aminocyclopropanecarboxylic acid (ACC) **3a** and coronamic acid **3b** [Scheme 1 (1)].[14] Subsequent enhancement of the reaction using the cyano carbonate **4** and a catalytic amount of titanium(IV) isopropoxide provided **3a** in only two steps [Scheme 1 (2)].[15]



Scheme 1 Titanium-mediated synthesis of 2,3-methanoamino acid derivatives from nitriles

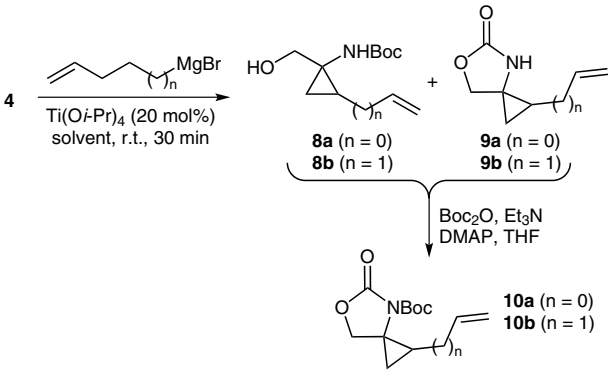
Within a project devoted to the synthesis and the biological application of functionalized constrained α-amino acids that includes their insertion in pseudotetrapeptides,[16] we have reported a new diastereoselective access to functionalized *trans*-2,3-methanoamino acids[17] based on the intramolecular ligand exchange of homoallylic alcohol to titanacyclopropane.[18] The hydroxyl side chain of the so-prepared *trans*-disubstituted cyclopropylamine **6** was further modified to afford various constrained functionalized amino acid analogues **7** [Scheme 1 (3)].[19] In order to fully understand the influence of the side chain position of amino acids derivatives incorporated in peptidomimetics, the diastereomers bearing the *cis* relative configuration are also required.[17] However they are not accessible using the previously reported method. A general access to the two isomers was thus envisioned from titanium complexes and unsaturated Grignard reagents, and the results of the study are presented here. The usefulness of this method is illustrated by the synthesis of orthogonally protected *cis*- and *trans*-2,3-methanoamino acids bearing amino groups.

The titanium-mediated cyclopropanation of *tert*-butyl cyanomethyl carbonate (**4**) and (benzyloxy)acetonitrile (**1**) was checked with two unsaturated Grignard reagents (but-3-enyl- and pent-4-enylmagnesium bromide). The results are presented in Table 1 and Table 2, respectively.

As previously reported,[15b] the cyclopropanation reaction of *tert*-butyl cyanomethyl carbonate (**4**) works well with but-3-enylmagnesium bromide (Table 1, entries 1 and 2), affording a mixture of vinyl-substituted cyclopropylamine derivatives **8a** and **9a** in good yield. This mixture was directly converted into a unique *N*-Boc-protected oxazolidinone **10a**, which can easily be transformed into **8a** using lithium hydroxide.[15b] Whereas a mixture of diastereomers was formed in diethyl ether, excellent diastereoselectivity was observed in tetrahydrofuran in favor of the *trans* isomer exclusively, which was isolated in 69% yield (entry 2). The same trend was observed with related cyano ester substrates.[20]

In contrast, subjecting cyano carbonate **4** to the cyclopropanation reaction conditions using pent-4-enylmagnesium bromide in diethyl ether gave selectively **8b** as an inseparable mixture of diastereomers (entry 3). When tetrahydrofuran was used, the obtained mixture of **8b**/**9b** was directly transformed into *N*-Boc oxazolidinone **10b** (entry 4) which was isolated in low yield and diastereoselectivity. Similar results were observed with butylmagnesium bromide,[15b] indicating no influence of the double bond on the outcome of the reaction.

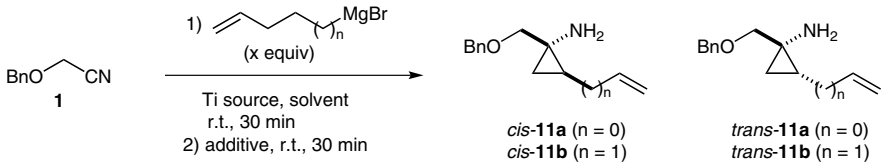
Table 1 Cyclopropanation of Nitrile **4** with Unsaturated Grignard Reagents



Entry	n	Solvent	Ratio[a] **8**/**9**	Product	Yield[b] (%)	Ratio *cis*/*trans*
1	0	Et$_2$O	2.3:1	**10a**[15b]	74	1.5:1
2	0	THF	1:5.7	**10a**[15b]	69	<1:19
3	1	Et$_2$O	1:0	**8b**	60	1:2.3
4	1	THF	1:1.5	**10b**	21	1:2.2

[a] Ratio calculated by integration of characteristic signals of **8** and **9** in the crude ^{1}H NMR.
[b] Isolated yields, diastereomeric ratio calculated from integration of crude ^{1}H NMR.

Table 2 Cyclopropanation of Nitrile **1** with Unsaturated Grignard Reagents



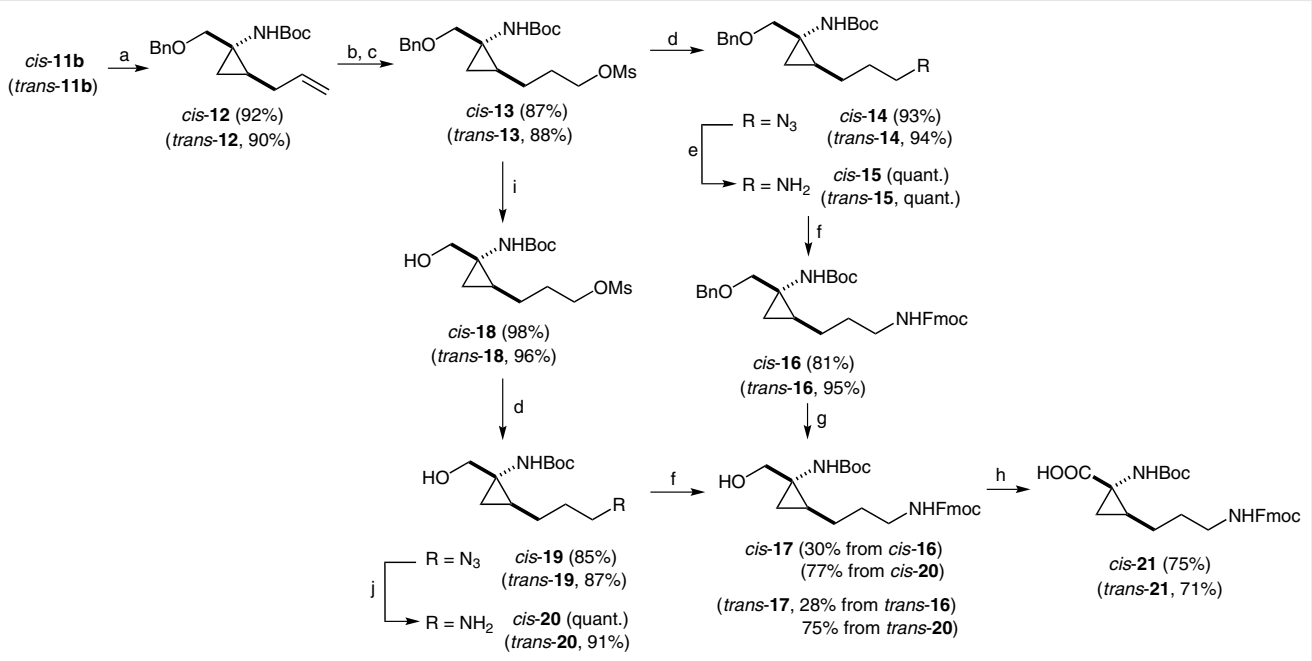
Entry	Titanium source[a]	n	x	Solvent	Additive	dr[b] *cis*/*trans*	Yield[c] (%)	
							cis-**11**	*trans*-**11**
1	$Ti(Oi\text{-}Pr)_4$	0	2	Et_2O	–	–	0	0
2	$Ti(Oi\text{-}Pr)_4$	0	2	THF	–	–	0	0
3	$Ti(Oi\text{-}Pr)_4$	1	2	Et_2O	–	2.0:1	45	22
4	$MeTi(Oi\text{-}Pr)_3$	1	1.1	Et_2O	–	2.2:1	42	19
5	$Ti(Oi\text{-}Pr)_4$ + MeMgBr	1	1.1	Et_2O	–	1.9:1	45	22
6	$Ti(Oi\text{-}Pr)_4$	1	2	THF	–	1.3:1	19[d]	16[d]
7	$Ti(Oi\text{-}Pr)_4$	1	2	THF	$BF_3{\cdot}OEt_2$ (2 equiv)	1.6:1	36	25
8	$MeTi(Oi\text{-}Pr)_3$	1	1.1	THF	–	1:1	26[d]	26[d]
9	$MeTi(Oi\text{-}Pr)_3$	1	1.1	THF	$BF_3{\cdot}OEt_2$ (2 equiv)	1.3:1	41	24

[a] Reaction conditions: **1** (1 mmol), solvent (5 mL), $Ti(Oi\text{-}Pr)_4$ (1.1 equiv), $MeTi(Oi\text{-}Pr)_3$ (1.1 equiv), or $Ti(Oi\text{-}Pr)_4$ (1.1 equiv) then MeMgBr (1 equiv), followed by alkenylmagnesium bromide.
[b] Diastereomeric ratio calculated from integration of crude ^1H NMR.
[c] Isolated yields.
[d] Ketones were also obtained as byproducts.

The behavior of the unsaturated Grignard reagents toward nitrile **1** in the presence of titanium(IV) isopropoxide was also investigated (Table 2). Surprisingly, when but-3-enylmagnesium bromide was used with nitrile **1**, no trace of the expected 2-vinylcyclopropylamine **11a** was observed (entries 1 and 2), whatever the conditions used. Aminocyclopentenes could also be formed from nitriles, titanium(IV) isopropoxide, and homoallylic Grignard reagents,[20] but the expected 1-[(benzyloxy)methyl]cyclopent-3-enylamine was not detected either. Despite the complete disappearance of the starting material, this organomagnesium reagent was not suitable for the cyclopropanation of (benzyloxy)acetonitrile (**1**), showing the marked difference of reactivity between nitriles **1** and **4**.

On the other hand, the reaction of two equivalents of pent-4-enylmagnesium bromide with nitrile **1** in the presence of stoichiometric amount of titanium(IV) isopropoxide in diethyl ether afforded the expected allyl-substituted cyclopropylamine **11b** in 67% yield as a 2:1 mixture of *cis* and *trans* diastereomers (Table 2, entry 3). Fortunately, these isomers are easily separable by column chromatography [ΔR_f ~0.4 (EtOAc)], and the *cis* isomer was the major product, making this method complementary to the one using homoallylic alcohols [Scheme 1 (3)]. In order to reduce the amount of Grignard reagent, methyltitanium(IV) isopropoxide[21] was also used in the presence of only 1.1 equivalents of organomagnesium bromide (entry 4). This procedure was facilitated by the successive addition of methylmagnesium bromide (1 equiv) and the unsaturated Grignard reagent (1.1 equiv) to the mixture of titanium(IV) isopropoxide and the nitrile (entry 5), thus avoiding the preparation of methyltitanium(IV) isopropoxide. This method was reproducible on a multigram scale, and the cyclopropylamines *cis*-**11b** and *trans*-**11b** were isolated in good yields (46% and 21%, respectively). The yield of cyclopropylamines **11b** was significantly lower (35%) when the reaction was conducted in tetrahydrofuran, and two isomeric ketones, namely 1-(benzyloxy)hept-6-en-2-one and 1-(benzyloxy)-3-methylhex-5-en-2-one, were also observed, in 24% and 6% yields, respectively (entry 6). These ketones are the result of an inefficient ring contraction of the five-membered metallacycle. It was shown that Lewis acids assist the ring contraction of azatitanacyclopentene intermediates.[13] Indeed, the use of boron trifluoride–diethyl ether provided a higher yield (61%) of **11b**, but the diastereoselectivity was lower than in diethyl ether (entry 7). The same trend was observed with methyltitanium(IV) isopropoxide (entries 8 and 9).

As a result of this study, only the combination of (benzyloxy)acetonitrile (**1**) and pent-4-enylmagnesium bromide was able to furnish both the *cis* and *trans* isomers in a pure form after chromatography. The cyclopropylamines *cis*-**11b** and *trans*-**11b**, bearing an allyl substituent, are useful intermediates to access functionalized substituted 2,3-



Scheme 2 Synthesis of protected 2,3-methanolysine *cis*-**21** and *trans*-**21**. *Reagents and conditions*: (a) Boc_2O, NaOH, *t*-BuOH–H_2O; (b) $BH_3{\cdot}Me_2S$, THF then NaOH, H_2O_2; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaN_3, MeCN; (e) HCO_2NH_4, Pd/C, MeOH; (f) FmocCl, Na_2CO_3, dioxane–H_2O; (g) DDQ, CH_2Cl_2; (h) RuO_2, $NaIO_4$, CCl_4–MeCN–H_2O; (i) H_2 (3 bar), Pd/C, MeOH; (j) H_2 (3 bar), $Pd(OH)_2$/C, MeOH.

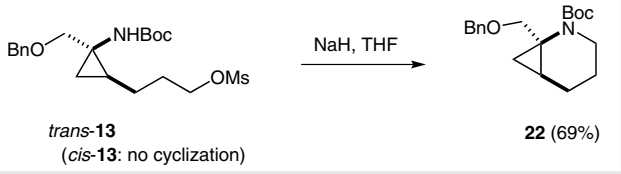
methanoamino acids. The synthesis of several orthogonally protected constrained lysine derivatives from **11b** is described.

After Boc-protection of the primary amine function, the allyl-substituted *cis*-**12** was subjected to a hydroboration–oxidation sequence followed by a treatment with mesyl chloride to afford pure mesylate *cis*-**13** in 87% yield (Scheme 2). Substitution with sodium azide in refluxing acetonitrile provided azide *cis*-**14** which was submitted to palladium-catalyzed hydrogenolysis conditions with the aim of reducing the azido function and removing the benzyl-protecting group in one step. Unfortunately, attempts using hydrogen (3 or 30 bar) or ammonium formate as a hydrogen source in the presence of palladium on charcoal (10% wt) in methanol, at room temperature or reflux failed to furnish the expected product. Only the reduction of the azide moiety occurred to lead to the amine *cis*-**15** in quantitative yields in all cases. The reluctance of the *O*-benzyl group to undergo hydrogenolysis was also reported by de Meijere et al. on similar structures,[11a] and was mainly attributed to the deactivation of the palladium surface through complexation with the free amine released in the media.

The primary amine was then protected giving *cis*-**16**. Attempts to remove selectively the benzyl group by hydrogenolysis failed, and radical debenzylation using Birch conditions led to degradation of the substrate. Only 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the alcohol *cis*-**17** but in low yield (30%). A similar pattern of reactivity was observed with the *trans* isomer and *trans*-**17** was prepared in 28% yield from *trans*-**19**. These low yields were overcome by performing the hydrogenolysis on the mesylate *cis*-**13**; the alcohol *cis*-**18** was cleanly obtained in 98% yield and the mesylate function was next displaced by the azide anion to give *cis*-**19**. Quantitative reduction and subsequent amine protection as the Fmoc carbamate furnished the alcohol *cis*-**17** which was finally transformed into the protected 2,3-aminolysine *cis*-**21** by ruthenium(IV) oxide/sodium periodate oxidation (39% overall yield from *cis*-**11**). The strategy was also validated in the *trans* series and the known carboxylic acid *trans*-**21** was similarly obtained in 32% yield from cyclopropylamine *trans*-**11**.

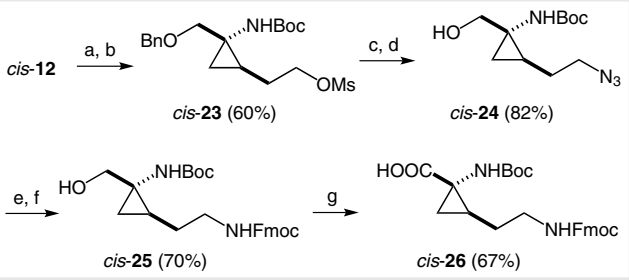
The relative configurations of *cis*- and *trans*-**11**, initially attributed by NOESY spectroscopic experiments, were further confirmed by treating the two mesylates *cis*- and *trans*-**13** with sodium hydride. Under these conditions, *trans*-**13** underwent intramolecular cyclization to the bicyclic compound **22** whereas only starting material was recovered from the *cis* isomer (Scheme 3).

Submission of the *N*-Boc cyclopropylamine *cis*-**12** to ozonolysis and subsequent reductive treatment afforded the hydroxyethyl-substituted cyclopropylamine intermediate which was subjected to mesylation to give *cis*-**23** in 60% yield (Scheme 4). The azidation–hydrogenolysis sequence developed for *cis*-**13** was applied to *cis*-**23** and an identical



Scheme 3 Cyclization of *trans*-**13**

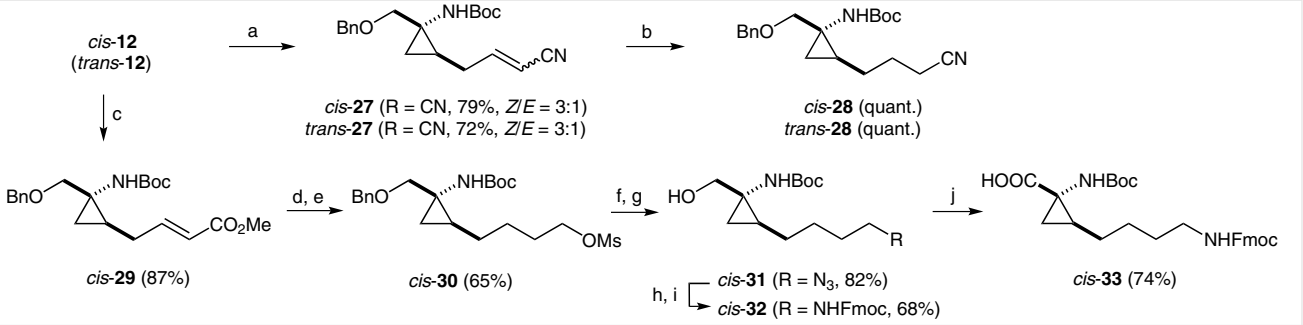
observation was made concerning the absence of O-debenzylation during the palladium-catalyzed hydrogenolysis of this analogue of **14**. Therefore, the removal of the benzyl protecting group of *cis*-**23** was carried out prior to the substitution of the mesylate by the azide moiety to give *cis*-**24** in 82% yield. Finally, a three-step sequence consisting of azide hydrogenolysis/Fmoc protection/oxidation provided the protected 2,3-methanoornithine *cis*-**26** in 47% overall yield.



Scheme 4 Synthesis of protected 2,3-methanoornithine *cis*-**26**. *Reagents and conditions*: (a) O_3, CH_2Cl_2–MeOH then $NaBH_4$; (b) MsCl, Et_3N, CH_2Cl_2; (c) H_2 (3 bar), Pd/C, MeOH; (d) NaN_3, MeCN; (e) HCO_2NH_4, Pd/C, MeOH; (f) FmocCl, Na_2CO_3, dioxane–H_2O; (g) RuO_2, $NaIO_4$, CCl_4–MeCN–H_2O.

The access to the 2,3-methanohomolysine series involved homologation of the allylic side chain of *cis*-**12** (Scheme 5). Thus, cross metathesis with acrylonitrile was envisaged to simultaneously introduce the nitrogen atom.[22] Using the 2nd generation Hoveyda–Grubbs catalyst in dichloromethane, the metathesis led to the expected alkene *cis*-**27** in 79% yield. The mixture was directly subjected to various reduction conditions inspired from recent Jubault's work on similar structures,[23] but it was not possible to remove the benzyl protecting group or to reduce the nitrile.[24] In the unique case of nitrile reduction [$Pd(OH)_2$/C, 30 bar H_2], ammonia as well as a condensation product were formed, as already observed by Maschmeyer.[25] Similar observations were made in the *trans* series, and *trans*-**28** was quantitatively obtained by hydrogenation of *trans*-**27**. Consequently, the cross-metathesis was performed with methyl acrylate to prepare unsaturated ester *cis*-**29**, which was isolated in 87% yield as the unique *E* diastereomer. Reduction using lithium aluminum hydride afforded the saturated alcohol intermediate that was directly subjected to mesylation to give *cis*-**30** in 65% yield. As described for the other analogues, palladium-catalyzed O-debenzylation followed by treatment with sodium azide provided the alcohol *cis*-**31**. Hydrogenolysis then Fmoc protection led to *cis*-**32**. Finally, the protected 2,3-methanohomolysine *cis*-**33** was isolated in 74% yield after oxidation.

The titanium-mediated cyclopropanation reaction of nitriles using unsaturated Grignard reagents was found to be strongly dependent on the nature of the substrate and the solvent in terms of reactivity, yield, and diastereoselectivity. The most useful result was obtained from (benzyloxy)acetonitrile (**1**) and pent-4-enylmagnesium bromide, affording both the *cis* and the *trans* isomers in pure form. Although it is not diastereoselective, the simplicity of the method, using easily available substrates and reagents, and the easy separation of stereoisomers makes this method attractive for the preparation of constrained amino acids. The synthetic utility of the obtained cyclopropylamines was thus illustrated by the synthesis of orthogonally protected 2,3-methanoamino acids bearing an amino side chain with variable length, suitable for peptidic synthesis. Their incorporation in pseudopeptides and their behavior in biological media are currently under investigation.



Scheme 5 Synthesis of protected 2,3-methanohomolysine derivative *cis*-**33**. *Reagents and conditions*: (a) acrylonitrile, 2nd generation Hoveyda–Grubbs catalyst, CH_2Cl_2; (b) H_2 (30 bar), Pd/C, MeOH; (c) methyl acrylate, 2nd generation Hoveyda–Grubbs catalyst, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) MsCl, Et_3N, CH_2Cl_2; (f) H_2 (3 bar), Pd/C, MeOH; (g) NaN_3, MeCN; (h) HCO_2NH_4, Pd/C, MeOH; (i) FmocCl, Na_2CO_3, dioxane–H_2O; (j) RuO_2, $NaIO_4$, CCl_4–MeCN–H_2O.

All experiments were carried out under a N_2 atmosphere. Et_2O, THF, and CH_2Cl_2 were purified by passing through neutral alumina columns under N_2. The Grignard reagents were prepared in anhyd Et_2O or THF using the conventional method from the appropriate bromide precursors and Mg turnings, with the exception of MeMgBr and PhMgBr which were purchased in solution in Et_2O from Sigma-Aldrich. Ti(O*i*-Pr)$_4$ was purchased from Sigma-Aldrich. Nitriles **1** and **4**, as well as MeTi(O*i*-Pr)$_3$, were prepared according to known procedures.[15,23,26] Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) by using 5% ethanolic vanillin solution as stated. Column chromatography was carried out using silica gel 60 (0.040–0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 or Bruker AC-400 spectrometer relative to the residual solvent peak. IR spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer on a single-reflection diamond ATR unit. HRMS were recorded on a Waters Micromass GCT Premier spectrometer.

tert-Butyl 5-Oxo-1-allyl-6-oxa-4-azaspiro[2.4]heptane-4-carboxylate (10b)

To a solution of *tert*-butyl cyanomethyl carbonate **4** (548 mg, 3.5 mmol) and Ti(O*i*-Pr)$_4$ (210 µL, 0.7 mmol) in THF (9 mL) under argon at 0 °C was added dropwise a solution of pent-4-enylmagnesium bromide (4.3 mL, 1.70 M in Et_2O, 7.3 mmol). The solution gradually turned from clear yellow to brown. At the end of the addition (30 min), the mixture was stirred for 60 min. H_2O (13 mL) was slowly added, followed by EtOAc (5 mL) and 1 M HCl until the two layers became clear (acidic pH). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave a crude 1:1.5 mixture of amino alcohol **8b** and oxazolidinone **9b**.

To the solution of the crude mixture of **8b** and **9b** in THF (3.5 mL) was added successively Boc_2O (940 mg, 4.2 mmol), Et_3N (638 µL, 4.5 mmol), and DMAP (86 mg, 0.7 mmol). The solution was stirred at r.t. for 1 h then sat. aq NH_4Cl solution (8 mL) was added. The aqueous phase was extracted with Et_2O (3 × 7 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was purified by column chromatography (silica gel, cyclohexane–EtOAc, 90:10) to afford the Boc-oxazolidinone **10b** as a pure 1:2.2 mixture of *cis*- and *trans*-diastereoisomers (185 mg, 21% yield over two steps) as a yellow oil; R_f = 0.37 (cyclohexane–EtOAc, 80:20).

IR (neat): 2979, 2931, 1791, 1723, 1641, 1456, 1394, 1368, 1348, 1253, 1155, 1073, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.81 (m, 1 H), 5.11 (ddd, *J* = 16.1, 3.1, 1.6 Hz, 0.7 H), 5.08 (ddd, *J* = 10.3, 3.1, 1.6 Hz, 0.7 H), 5.07 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 0.3 H), 5.02 (ddd, *J* = 10.1, 3.0, 1.5 Hz, 0.3 H), 4.39 (d, *J* = 8.1 Hz, 0.3 H), 4.29 (d, *J* = 8.4 Hz, 0.7 H), 4.13 (d, *J* = 8.4 Hz, 0.7 H), 3.85 (d, *J* = 8.1 Hz, 0.3 H), 2.31–1.93 (m, 3.7 H), 1.53 (s, 2.7 H), 1.52 (s, 6.3 H), 1.04–0.96 (m, 0.3 H), 0.94–0.88 (m, 0.3 H), 0.33 (t, *J* = 6.1 Hz, 0.7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 152.8, 150.2, 149.1, 136.6, 135.8, 116.0, 115.4, 84.2, 84.1, 71.8, 65.9, 45.3, 43.8, 32.5, 31.2, 28.2, 28.1, 24.6, 17.5, 14.9, 10.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}NNaO_4$: 276.1206; found: 276.1208.

cis-2-Allyl-1-[(benzyloxy)methyl]cyclopropylamine (*cis*-11b) and *trans*-2-Allyl-1-[(benzyloxy)methyl]cyclopropylamine (*trans*-11b)

To a solution of (benzyloxy)acetonitrile **1** (4.0 g, 27.2 mmol) and Ti(O*i*-Pr)$_4$ (8.95 mL, 29.9 mmol) in Et_2O (140 mL) at r.t. under argon were successively added dropwise a solution of 2.95 M MeMgBr in Et_2O (9.22 mL, 27.2 mmol) then a solution of 0.99 M pent-4-enylmagnesium bromide in Et_2O (30.2 mL, 29.9 mmol). The solution went gradually from clear yellow to brown. At the end of the addition (ca. 30 min), the mixture was stirred for 45 min. Water (100 mL) was slowly added, followed by EtOAc (30 mL) and 1 M aq HCl until the two layers became clear (acidic pH). The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and filtered. Concentration under reduced pressure gave a crude mixture of diastereomers (1:1.9) that were separated by chromatography (silica gel, cyclohexane–EtOAc, 80:20 then EtOAc). Cyclopropylamines *trans*-**11b** (1.30 g, 22%) and *cis*-**11b** (2.66 g, 45%) were isolated as yellow oils.

trans-11b

R_f = 0.50 (EtOAc).

IR (neat): 3374, 3065, 3031, 2999, 2853, 1639, 1496, 1454, 1361, 1253, 1075 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 5 H), 5.93 (ddt, *J* = 17.2, 10.3, 6.0 Hz, 1 H), 5.14 (dq, *J* = 17.2, 1.9 Hz, 1 H), 4.98 (ddt, *J* = 10.3, 1.9, 1.5 Hz, 1 H), 4.56 (d, *J* = 10.4 Hz, 1 H), 4.53 (d, *J* = 10.4 Hz, 1 H), 3.36 (d, *J* = 9.9 Hz, 1 H), 3.26 (d, *J* = 9.9 Hz, 1 H), 2.27–2.22 (m, 2 H), 1.55 (br s, 2 H), 0.81–0.73 (m, 1 H), 0.63 (dd, *J* = 9.0, 4.8 Hz, 1 H), 0.29 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.5, 128.4, 127.6, 114.1, 79.4, 72.7, 37.3, 32.0, 21.9, 17.4.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO$: 218.1545; found: 218.1540.

cis-11b

R_f = 0.10 (EtOAc).

IR (neat): 3373, 3065, 3031, 3000, 2851, 1639, 1497, 1453, 1361, 1274, 1075 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 5.89 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1 H), 5.05 (dq, *J* = 17.1, 1.7 Hz, 1 H), 4.98 (ddt, *J* = 10.2, 1.7, 1.4 Hz, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 3.51 (d, *J* = 10.0 Hz, 1 H), 3.44 (d, *J* = 10.0 Hz, 1 H), 2.17 (m, 1 H), 1.92 (m, 1 H), 1.80 (s, 2 H), 1.04 (m, 1 H), 0.79 (dd, *J* = 9.1, 5.0 Hz, 1 H), 0.24 (dd, *J* = 6.0, 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.0, 128.5, 127.8, 127.7, 114.6, 75.3, 73.2, 37.5, 33.7, 25.0, 18.8.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO$: 218.1545; found: 218.1537.

tert-Butyl *cis*-2-Allyl-1-[(benzyloxy)methyl]cyclopropylcarbamate (*cis*-12); Typical Procedure

To a solution of the cyclopropylamine *cis*-**11b** (3.62 g, 16.7 mmol) in *t*-BuOH–H_2O (3:2, 60 mL), were successively added 3 M aq NaOH (8.3 mL, 25 mmol) and Boc_2O (11.3 g, 25 mmol). The solution was stirred for 30 min at 35 °C then water (120 mL) was added. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–Et_2O, 90:10) to afford the pure carbamate *cis*-**12** (4.88 g, 92%) as a colorless oil; R_f = 0.25 (cyclohexane–EtOAc, 90:10).

IR (neat): 3334, 3074, 3058, 2977, 2928, 1714, 1641, 1495, 1454, 1391, 1365, 1167, 1074 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H), 5.92 (ddt, *J* = 17.2, 10.2, 6.3 Hz, 1 H), 5.12 (br s, 1 H), 5.08 (ddt, *J* = 17.2, 1.7, 1.5 Hz, 1 H), 5.00 (ddt, *J* = 10.2, 1.7, 1.4 Hz, 1 H), 4.55 (d, *J* = 12.3 Hz, 1 H), 4.52 (d, *J* = 12.3 Hz, 1 H), 3.73–3.63 (m, 1 H), 3.50 (d, *J* = 10.4 Hz, 1 H), 2.34 (dt, *J* = 12.6, 6.3 Hz, 1 H), 1.94–1.86 (m, 1 H), 1.44 (s, 9 H), 1.16 (m, 1 H), 1.03 (dd, *J* = 8.6, 5.6 Hz, 1 H), 0.53 (dd, *J* = 6.4, 5.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 138.5, 137.5, 128.4, 127.7, 127.6, 115.0, 79.3, 73.2, 71.5, 36.8, 33.3, 28.5, 24.8, 18.4.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}NO_3$: 318.2069; found: 318.2062.

tert-Butyl *trans*-2-Allyl-1-[(benzyloxy)methyl]cyclopropylcarbamate (*trans*-12)

Applying the previous procedure on *trans*-**11b** (1.0 g, 4.61 mmol) afforded *trans*-**12** as a colorless oil (1.31 g, 90%); R_f = 0.25 (cyclohexane–EtOAc, 90:10).

IR (neat): 2975, 1707, 1487, 1166, 1069, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5 H), 5.92 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 1 H), 5.21 (dq, *J* = 17.2, 1.8 Hz, 1 H), 5.01 (ddt, *J* = 10.3, 1.7, 1.5 Hz, 1 H), 4.97 (br s, 1 H), 4.55 (d, *J* = 12.3 Hz, 1 H), 4.52 (d, *J* = 12.3 Hz, 1 H), 3.55 (d, *J* = 10.0 Hz, 1 H), 3.38 (d, *J* = 10.0 Hz, 1 H), 2.23 (m, 1 H), 2.11 (m, 1 H), 1.43 (s, 9 H), 1.04–0.92 (m, 2 H), 0.61–0.50 (m, 1 H).

^{13}C NMR (10 MHz, $CDCl_3$): δ = 156.1, 138.6, 137.7, 128.4, 127.6, 127.5, 114.8, 79.4, 75.1, 73.1, 37.1, 32.5, 28.5, 21.7, 17.2.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}NO_3$: 318.2069; found: 318.2061.

cis-3-{2-[(Benzyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]cyclopropyl}propyl Methanesulfonate (*cis*-13); Typical Procedure

To a solution of *cis*-**12** (3.65 g, 11.5 mmol) in THF (80 mL) at 0 °C was added BH_3·Me_2S (3.83 mL, 40.3 mmol) and the mixture was stirred for 1 h at r.t. The solution was cooled to 0 °C and 12 M aq NaOH (24.0 mL, 288 mmol) and 30% aq H_2O_2 (23.0 mL, 207 mmol) were successively added carefully. The mixture was stirred for 10 min at 0 °C then water (50 mL) was added. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with sat. $Na_2S_2O_3$ solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After dissolution of the residue in CH_2Cl_2 (60 mL), the resulting solution was cooled to –10 °C and Et_3N (2.87 mL, 20.7 mmol) then MsCl (0.98 mL, 12.7 mmol) were slowly added. The mixture was allowed to warm up to r.t. and water (50 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, cyclohexane–EtOAc, 90:10 then 70:30) afforded the mesylate *cis*-**13** (4.15 g, 87%) as a colorless oil; R_f = 0.23 (cyclohexane–EtOAc, 70:30).

IR (neat): 3383, 2975, 2934, 1707, 1498, 1453, 1350, 1246, 1168, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.11 (br s, 1 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.28–4.22 (m, 2 H), 3.60 (d, *J* = 10.2 Hz, 1 H), 3.54 (d, *J* = 10.2 Hz, 1 H), 2.97 (s, 3 H), 2.00–1.85 (m, 2 H), 1.60–1.50 (m, 1 H), 1.47–1.37 (m, 10 H), 1.06 (m, 1 H), 1.00 (dd, *J* = 9.2, 5.5 Hz, 1 H), 0.50 (dd, *J* = 6.4, 5.5 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.6, 138.3, 128.4, 127.7, 126.6, 79.3, 73.2, 71.6, 69.9, 37.2, 36.7, 29.0, 28.4, 25.2, 24.9, 18.5.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}NO_6S$: 414.1950; found: 414.1958.

trans-3-{2-[(Benzyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]cyclopropyl}propyl Methanesulfonate (*trans*-13)

Applying the previous procedure on *trans*-**12** (2.10 g, 6.62 mmol) afforded *trans*-**13** as a colorless oil (2.40 g, 88%); R_f = 0.23 (cyclohexane–EtOAc, 70:30).

IR (neat): 3380, 2976, 2935, 1702, 1498, 1453, 1350, 1246, 1168, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.98 (br s, 1 H), 4.53 (s, 2 H), 4.29 (t, *J* = 6.4 Hz, 2 H), 3.50 (d, *J* = 10.1 Hz, 1 H), 3.43 (d, *J* = 10.1 Hz, 1 H), 2.99 (s, 3 H), 1.89 (quint, *J* = 6.9 Hz, 2 H), 1.72–1.63 (m, 1 H), 1.44 (s, 9 H), 1.42–1.34 (m, 1 H), 0.97–0.86 (m, 2 H), 0.54–0.48 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.1, 138.4, 128.5, 127.7, 127.6, 79.6, 75.0, 73.1, 69.9, 37.5, 37.5, 29.1, 28.4, 24.1, 22.3, 17.2.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}NO_6S$: 414.1950; found: 414.1947.

tert-Butyl *cis*-2-(3-Azidopropyl)-1-[(benzyloxy)methyl]cyclopropylcarbamate (*cis*-14); Typical Procedure

To a solution of mesylate *cis*-**13** (4.15 g, 10.0 mmol) in MeCN (100 mL) was added NaN_3 (1.63 g, 25 mmol). The solution was refluxed overnight then water (80 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration under reduced pressure afforded the pure azide *cis*-**14** (3.35 g, 93%) as a pale yellow oil; R_f = 0.64 (cyclohexane–EtOAc, 70:30).

IR (neat): 3337, 2975, 2933, 2866, 2093, 1712, 1494, 1453, 1365, 1246, 1166, 1095, 1069 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 5.10 (br s, 1 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 3.51 (d, *J* = 10.2 Hz, 1 H), 3.30 (t, *J* = 6.8 Hz, 2 H), 1.80–1.69 (m, 2 H), 1.62–1.53 (m, 1 H), 1.43 (s, 9 H), 1.35–1.25 (m, 1 H), 1.12–1.04 (m, 1 H), 1.00 (dd, *J* = 9.0, 5.4 Hz, 1 H), 0.49 (dd, *J* = 6.3, 5.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.7, 138.4, 129.8, 128.5, 127.8, 79.4, 73.3, 71.7, 51.2, 36.8, 28.8, 28.5, 26.5, 25.2, 18.6.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}N_4O_3$: 361.2240; found: 361.2234.

tert-Butyl *trans*-2-(3-Azidopropyl)-1-[(benzyloxy)methyl]cyclopropylcarbamate (*trans*-14)

Applying the previous procedure on *trans*-**13** (2.40 g, 5.8 mmol) afforded *trans*-**14** as a pale yellow oil (1.97 g, 94%); R_f = 0.50 (cyclohexane–EtOAc, 80:20).

IR (neat): 3352, 3321, 2975, 2937, 2865, 2092, 1703, 1494, 1452, 1390, 1165, 1069 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 5.02 (br s, 1 H), 4.52 (s, 2 H), 3.45 (s, 2 H), 3.32 (t, *J* = 6.7 Hz, 2 H), 1.82–1.57 (m, 3 H), 1.43 (s, 9 H), 1.39–1.20 (m, 1 H), 0.97–0.80 (m, 2 H), 0.49 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.1, 138.5, 128.5, 127.7, 127.6, 79.5, 75.1, 73.1, 51.1, 37.4, 28.8, 28.4, 25.3, 22.5, 17.2.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}N_4O_3$: 361.2240; found: 361.2235.

tert-Butyl *cis*-2-(3-Aminopropyl)-1-[(benzyloxy)methyl]cyclopropylcarbamate (*cis*-15)

To a solution of azide *cis*-**14** (3.33 g, 9.24 mmol) in MeOH (90 mL) were successively added 10% Pd/C (831 mg, 20 wt%) and ammonium formate (2.91 g, 46.2 mmol). The mixture was refluxed for 10 min then allowed to cool to r.t. After filtration through a pad of Celite and concentration under reduced pressure, the residue was taken up in EtOAc (60 mL). The organic solution was washed with 3 M aq NaOH (30 mL), then the aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic fractions were dried ($MgSO_4$) and filtered. Concentration under reduced pressure afforded the pure amine *cis*-**15** (3.09 g, quant.) as a pale yellow oil.

IR (neat): 3358, 3315, 2974, 2934, 2864, 2360, 1693, 1536, 1494, 1452, 1390, 1165, 1068 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 5.16 (br s, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 3.64 (m, 1 H), 3.50 (d, *J* = 10.2 Hz, 1 H), 2.71 (m, 2 H), 2.06 (br s, 2 H), 1.65–1.52 (m, 3 H), 1.42 (s, 9 H), 1.21–1.14 (m, 1 H), 1.11–1.04 (m, 1 H), 0.97 (m, 1 H), 0.46 (t, *J* = 5.9 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.7, 138.4, 128.4, 127.8, 127.7, 79.3, 73.2, 71.8, 41.6, 36.8, 32.8, 28.5, 26.6, 25.5, 18.7.

HRMS (CI-NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{31}N_2O_3$: 335.2335; found: 335.2345.

tert-Butyl *trans*-2-(3-Aminopropyl)-1-[(benzyloxy)methyl]cyclopropylcarbamate (*trans*-15)

Applying the previous procedure on *trans*-**14** (2.45 g, 6.8 mmol) afforded *trans*-**15** as a pale yellow oil (2.27 g, quant.).

IR (neat): 3360, 3313, 2975, 2933, 2862, 2360, 1687, 1536, 1495, 1452, 1390, 1166, 1071 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 6.04 (br s, 1 H), 4.58 (d, *J* = 12.4 Hz, 1 H), 4.51 (d, *J* = 12.4 Hz, 1 H), 3.64 (m, 1 H), 3.36–3.28 (m, 1 H), 3.87–3.76 (m, 2 H), 1.60–1.40 (m, 13 H), 0.95–0.85 (m, 2 H), 0.49 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.4, 138.7, 128.4, 127.6, 127.5, 79.0, 75.3, 73.0, 40.9, 37.3, 32.8, 28.5, 25.0, 22.7, 17.2.

HRMS (CI-NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{31}N_2O_3$: 335.2335; found: 335.2339.

tert-Butyl *cis*-1-[(Benzyloxy)methyl]-2-{3-[(9*H*-fluoren-9-ylmethoxy)carbonylamino]propyl}cyclopropylcarbamate (*cis*-16); Typical Procedure

To a solution of the amine *cis*-**15** (3.09 g, 9.24 mmol) and Na_2CO_3 (1.96 g, 18.5 mmol) in dioxane–H_2O (1:1, 90 mL) cooled to 0 °C was added FmocCl (2.51 g, 9.70 mmol). The solution was stirred overnight at r.t. and the solvents were evaporated under reduced pressure. The residue was taken up in water (40 mL) and CH_2Cl_2 (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 80:20) to afford the protected amine *cis*-**16** (4.18 g, 81%) as a pale yellow oil; R_f = 0.36 (cyclohexane–EtOAc, 70:30).

IR (neat): 3326, 2962, 2926, 2854, 1694, 1514, 1450, 1365, 1258, 1165, 1071, 1020 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (93:7 mixture of rotamers) = 8.10 (d, *J* = 7.4, 2.2 Hz, 0.14 H), 7.61 (dd, *J* = 7.2, 3.7 Hz, 1.86 H), 7.45 (t, *J* = 7.8 Hz, 0.14 H), 7.40 (t, *J* = 7.5 Hz, 1.86 H), 7.35–7.25 (m, 7 H), 5.28–5.10 (br s, 2 H), 4.54 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.41 (d, *J* = 6.9 Hz, 2 H), 4.23 (t, *J* = 6.9 Hz, 1 H), 3.66 (d, *J* = 10.2 Hz, 1 H), 3.49 (m, 1 H), 3.26–3.14 (m, 2 H), 1.72–1.63 (m, 2 H), 1.47–1.38 (m, 10 H), 1.18–1.06 (m, 1 H), 1.03–0.97 (m, 1 H), 0.92–0.84 (m, 1 H), 0.63 (t, *J* = 6.0 Hz, 0.07 H), 0.47 (t, *J* = 5.9 Hz, 0.93 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C5 or C8), 155.6 (C5 or C8), 144.0, 143.8, 141.2, 138.0, 128.3, 127.6, 127.5, 126.9, 124.9, 119.8, 79.3, 73.2, 71.5, 66.4, 47.3, 40.1, 36.9, 29.5, 28.5, 26.6, 25.5, 18.7.

HRMS (CI-NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{41}N_2O_5$: 557.3015; found: 557.3018.

tert-Butyl *trans*-1-[(Benzyloxy)methyl]-2-{3-[9*H*-fluoren-9-ylmethoxy)carbonylamino)]propyl}cyclopropylcarbamate (*trans*-16)

Applying the previous procedure on *trans*-**15** (2.13 g, 6.37 mmol) afforded *trans*-**16** as a pale yellow oil (3.38 g, 95%); R_f = 0.36 (cyclohexane–EtOAc, 70:30).

IR (neat): 3351, 3064, 2931, 2865, 1693, 1504, 1450, 1365, 1246, 1165, 1072 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (75:25 mixture of rotamers) = 8.07 (m, 0.5 H), 7.76 (d, *J* = 7.5 Hz, 1.5 H), 7.71–7.56 (m, 2 H), 7.55–7.26 (m, 9 H), 4.95 (br s, 2 H), 4.58–4.49 (m, 2 H), 4.40 (d, *J* = 6.8 Hz, 2 H), 4.23 (m, 1 H), 3.55–3.33 (m, 2 H), 3.31–3.16 (m, 2 H), 1.75–1.55 (m, 2 H), 1.50–1.34 (m, 10 H), 1.26 (m, 1 H), 0.98–0.82 (m, 2 H), 0.58 (m, 0.25 H), 0.48 (m, 0.75 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 156.6, 144.2, 144.1, 141.5, 140.9, 138.5, 130.2, 129.8, 128.5, 127.8, 127.7, 127.2, 125.2, 120.1, 79.6, 75.1, 73.2, 66.6, 47.5, 40.9, 37.5, 29.8, 28.5, 25.5, 22.8, 17.4.

HRMS (CI-NH_3): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{41}N_2O_5$: 557.3015; found: 557.3023.

cis-3-{2-[(*tert*-Butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropyl}propyl Methanesulfonate (*cis*-18); Typical Procedure

To a solution of the mesylate *cis*-**13** (2.05 g, 4.96 mmol) in MeOH (40 mL) was added 10% Pd/C (205 mg, 10 wt%) and the mixture was stirred at r.t. under H_2 (3 bar) for 1 h. After filtration on a pad of Celite and washing with CH_2Cl_2, the solution was concentrated under reduced pressure to afford the pure alcohol *cis*-**18** (1.57 g, 98%) as a colorless oil.

IR (neat): 3406, 2972, 2935, 1687, 1504, 1471, 1349, 1168, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H), 4.29 (dt, *J* = 9.8, 6.4 Hz, 1 H), 4.28 (dt, *J* = 9.8, 6.4 Hz, 1 H), 3.83 (d, *J* = 11.7 Hz, 1 H), 3.57 (d, *J* = 11.7 Hz, 1 H), 2.99 (s, 3 H), 2.01–1.88 (m, 2 H), 1.66 (m, 1 H), 1.55–1.47 (m, 1 H), 1.42 (s, 9 H), 1.12 (m, 1 H), 0.91 (dd, *J* = 9.3, 5.5 Hz, 1 H), 0.51 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 80.4, 69.9, 66.8, 38.6, 37.5, 29.2, 28.4, 26.3, 25.9, 18.9.

HRMS (CI-NH_3/CH_4): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{26}NO_6S$: 324.1481; found: 324.1471.

trans-3-{2-[(*tert*-Butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropyl}propyl Methanesulfonate (*trans*-18)

Applying the previous procedure on *trans*-**13** (1.64 g, 3.97 mmol) afforded *trans*-**18** as a pale yellow oil (1.23 g, 96%).

IR (neat): 3259, 2974, 2936, 2858, 1677, 1527, 1458, 1349, 1290, 1171, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (br s, 1 H), 4.27 (t, *J* = 6.3 Hz, 1 H), 4.26 (t, *J* = 6.3 Hz, 1 H), 3.72 (d, *J* = 11.1 Hz, 1 H), 3.38 (d, *J* = 11.1 Hz, 1 H), 2.99 (s, 3 H), 1.95–1.85 (m, 2 H), 1.63 (m, 1 H), 1.46–1.35 (m, 2 H), 1.42 (s, 9 H), 1.06 (m, 1 H), 0.94 (dd, *J* = 8.9, 5.7 Hz, 1 H), 0.42 (t, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 80.4, 70.5, 69.8, 39.6, 37.5, 29.1, 28.4, 24.4, 22.9, 18.2.

HRMS (CI-NH_3/CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{26}NO_6S$: 324.1481; found: 324.1475.

tert-Butyl *cis*-2-(3-Azidopropyl)-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-19); Typical Procedure

To a solution of the mesylate *cis*-**18** (1.57 g, 4.85 mmol) in MeCN (50 mL) was added NaN_3 (789 mg, 12.1 mmol). The mixture was refluxed overnight then water (40 mL) was added. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was filtered through a pad of silica gel (cyclohexane–Et_2O, 30:70) to afford the azide *cis*-**19** (1.11 g, 85%) as a pale yellow oil; R_f = 0.62 (cyclohexane–EtOAc, 30:70).

IR (neat): 3323, 2974, 2933, 2873, 2093, 1685, 1498, 1453, 1391, 1366, 1250, 1164, 1102, 1024 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16 (br s, 1 H), 3.81 (d, *J* = 11.7 Hz, 1 H), 3.63 (br s, 1 H), 3.58 (d, *J* = 11.7 Hz, 1 H), 3.31 (t, *J* = 6.7 Hz, 2 H), 1.82–1.61 (m, 3 H), 1.42–1.25 (m, 10 H), 1.10 (m, 1 H), 0.90 (dd, *J* = 9.3, 5.7 Hz, 1 H), 0.50 (br t, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 82.2, 66.8, 51.1, 38.5, 28.9, 28.4, 26.7, 26.5, 19.0.

HRMS (CI-NH_3/CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{23}N_4O_3$: 271.1770; found: 271.1775.

tert-Butyl *trans*-2-(3-Azidopropyl)-1-(hydroxymethyl)cyclopropylcarbamate (*trans*-19)

Applying the previous procedure on *trans*-**18** (1.23 g, 3.80 mmol) afforded *trans*-**19** as a pale yellow oil (897 mg, 87%); R_f = 0.55 (cyclohexane–EtOAc, 30:70).

IR (neat): 3344, 2976, 2933, 2871, 2093, 1685, 1497, 1453, 1391, 1366, 1249, 1164, 1102, 1024 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (br s, 1 H), 3.75 (br s, 1 H), 3.69 (d, *J* = 11.3 Hz, 1 H), 3.40 (m, 1 H), 3.32 (t, *J* = 6.6 Hz, 1 H), 3.31 (t, *J* = 6.6 Hz, 1 H), 1.78–1.68 (m, 2 H), 1.61 (m, 1 H), 1.42 (s, 9 H), 1.37–1.26 (m, 1 H), 1.02 (m, 1 H), 0.94 (dd, *J* = 8.9, 5.7 Hz, 1 H), 0.40 (br t, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 80.4, 70.6, 51.2, 39.5, 28.8, 28.4, 25.5, 23.1, 18.2.

HRMS (CI-NH_3/CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{23}N_4O_3$: 271.1770; found: 271.1763.

tert-Butyl *cis*-2-(3-Aminopropyl)-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-20); Typical Procedure

To a solution of the azide *cis*-**19** (1.06 g, 3.92 mmol) in MeOH (20 mL) was added $Pd(OH)_2$/C (212 mg, 10–20% $Pd(OH)_2$/C, 50% H_2O) and the mixture was stirred at r.t. under H_2 (3 bar) for 1 h. After filtration on a pad of Celite and washing with CH_2Cl_2, the solution was concentrated under reduced pressure to afford the pure amino alcohol *cis*-**20** (956 mg, quant.) as a colorless oil.

IR (neat): 3293, 2974, 2931, 2867, 1685, 1501, 1453, 1390, 1365, 1249, 1165, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.14 (br s, 1 H), 4.27 (br s, 3 H), 3.63 (m, 1 H), 3.40 (m, 1 H), 2.85 (m, 2 H), 1.75–1.40 (m, 4 H), 1.42 (s, 9 H), 1.10–0.90 (m, 2 H), 0.44 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 79.8, 69.7, 40.3, 39.3, 30.7, 28.4, 25.1, 22.7, 17.9.

HRMS (CI-NH_3/CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{25}N_2O_3$: 245.1865; found: 245.1856.

tert-Butyl *trans*-2-(3-Aminopropyl)-1-(hydroxymethyl)cyclopropylcarbamate (*trans*-20)

Applying the previous procedure on *trans*-**19** (852 mg, 3.15 mmol) afforded *trans*-**20** as a colorless oil (698 mg, 91%).

IR (neat): 3293, 2975, 2931, 2867, 1685, 1499, 1453, 1391, 1365, 1249, 1165, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.31 (br s, 1 H), 3.84 (d, *J* = 12.0 Hz, 1 H), 3.49 (d, *J* = 12.0 Hz, 1 H), 2.82 (br s, 2 H), 2.76 (t, *J* = 6.5 Hz, 2 H), 1.64–1.53 (m, 3 H), 1.45–1.35 (m, 2 H), 1.40 (s, 9 H), 1.10 (m, 1 H), 0.91 (dd, *J* = 9.4, 5.1 Hz, 1 H), 0.44 (t, *J* = 5.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 79.9, 65.6, 40.9, 39.0, 32.6, 28.4, 26.1, 26.0, 18.5.

HRMS (CI-NH_3/CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{25}N_2O_3$: 245.1865; found: 245.1857.

tert-Butyl *cis*-2-{3-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]propyl}-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-17); Typical Procedures

Procedure 1 from cis-**16**: To a solution of the benzylated alcohol *cis*-**16** (3.38 g, 6.1 mmol) in CH_2Cl_2 (60 mL) was added DDQ (4.13 g, 18.2 mmol). The mixture was stirred at r.t. for 3 d then EtOAc (100 mL) was added. The solution was washed with sat. aq $NaHCO_3$ solution (30 mL) then with water (30 mL). The combined aqueous phases were extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 80:20 then 50:50) to afford the alcohol *cis*-**17** (855 mg, 30%) as a white solid.

Procedure 2 from cis-**20**: To a solution of the amine *cis*-**20** (916 mg, 3.75 mmol) and Na_2CO_3 (797 mg, 7.52 mmol) in dioxane–water (1:1, 40 mL) cooled to 0 °C was added FmocCl (1.02 g, 3.94 mmol). The solution was stirred overnight at r.t. and solvents were evaporated under reduced pressure. The residue was taken up in water (20 mL) and CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 50:50) to afford the protected amine *cis*-**17** (1.35 g, 77%) as a white solid; mp 55 °C; R_f = 0.21 (cyclohexane–EtOAc, 50:50).

IR (neat): 3333, 2929, 1691, 1518, 1449, 1365, 1248, 1164, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 5.19 (br s, 1 H), 5.13 (br s, 1 H), 4.39 (d, *J* = 6.9 Hz, 2 H), 4.23 (t, *J* = 6.9 Hz, 1 H), 3.89 (d, *J* = 11.3 Hz, 1 H), 3.69 (br s, 1 H), 3.59 (d, *J* = 11.3 Hz, 1 H), 3.26 (m, 2 H), 1.72 (m, 2 H), 1.59 (m, 1 H), 1.45 (s, 9 H), 1.29–1.22 (m, 1 H), 1.19–1.11 (m, 1 H), 0.90 (dd, *J* = 9.2, 5.6 Hz, 1 H), 0.51 (t, *J* = 5.6 Hz, 1 H).

^{1}H NMR (400 MHz, DMSO-d_6, 363 K): δ = 7.85 (d, *J* = 7.5 Hz, 2 H), 7.67 (d, *J* = 7.5 Hz, 2 H), 7.41 (td, *J* = 7.5, 1.2 Hz, 2 H), 7.33 (td, *J* = 7.4, 1.2 Hz, 2 H), 6.81 (br s, 1 H), 6.47 (br s, 1 H), 4.32 (d, *J* = 6.7 Hz, 2 H), 4.22 (t, *J* =

6.7 Hz, 1 H), 3.56 (d, *J* = 11.5 Hz, 1 H), 3.50 (d, *J* = 11.5 Hz, 1 H), 3.05 (t, *J* = 6.6 Hz, 1 H), 3.03 (t, *J* = 6.6 Hz, 1 H), 1.56 (m, 2 H), 1.47 (m, 1 H), 1.40 (s, 9 H), 1.29–1.20 (m, 1 H), 1.00–0.92 (m, 1 H), 0.78 (dd, *J* = 9.2, 5.0 Hz, 1 H), 0.38 (dd, *J* = 6.7, 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 156.7, 144.2, 141.4, 127.8, 127.1, 125.2, 120.0, 80.5, 66.8, 66.7, 47.4, 40.8, 38.7, 29.7, 28.5, 26.9, 26.8, 19.1.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{35}N_2O_5$: 467.2546; found: 467.2549.

tert-Butyl *trans*-2-{3-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]propyl}-1-(hydroxymethyl)cyclopropylcarbamate (*trans*-17)

Applying the previous procedure 1 on *trans*-**16** (1.0 g, 1.94 mmol) afforded *trans*-**17** (253 mg, 28%)) and applying the procedure 2 on *trans*-**20** (638 mg, 2.61 mmol) afforded *trans*-**17** (908 mg, 75%) as a pale yellow oil; R_f = 0.21 (cyclohexane–EtOAc, 50:50).

IR (neat): 3341, 2970, 2931, 2861, 1738, 1692, 1537, 1510, 1463, 1448, 1366, 1231, 1217, 1165, 1046 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7.60 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 4.99 (br s, 1 H), 4.90 (br s, 1 H), 4.41 (d, *J* = 6.8 Hz, 2 H), 4.22 (t, *J* = 6.8 Hz, 1 H), 3.73 (d, *J* = 11.2 Hz, 1 H), 3.70 (br s, 1 H), 3.42 (d, *J* = 11.2 Hz, 1 H), 3.28–3.22 (m, 2 H), 1.71–1.64 (m, 2 H), 1.61–1.55 (m, 1 H), 1.40 (s, 9 H), 1.32–1.26 (m, 1 H), 1.10–1.01 (m, 1 H), 0.96 (dd, *J* = 8.7, 5.6 Hz, 1 H), 0.42 (t, *J* = 5.6 Hz, 1 H).

^{1}H NMR (400 MHz, DMSO-d_6, 363 K): δ = 7.85 (d, *J* = 7.5 Hz, 2 H), 7.66 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 6.78 (br s, 1 H), 6.31 (br s, 1 H), 4.31 (d, *J* = 6.8 Hz, 2 H), 4.22 (t, *J* = 6.8 Hz, 1 H), 3.48 (d, *J* = 11.0 Hz, 1 H), 3.34 (d, *J* = 11.0 Hz, 1 H), 3.25 (br s, 1 H), 3.02 (m, 2 H), 1.57–1.45 (m, 3 H), 1.40 (s, 9 H), 1.16–1.07 (m, 1 H), 0.89–0.82 (m, 1 H), 0.78 (dd, *J* = 8.8, 5.5 Hz, 1 H), 0.33 (t, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 156.5, 144.0, 141.3, 127.7, 127.1, 125.1, 120.0, 80.3, 70.8, 66.7, 47.4, 40.8, 39.6, 30.0, 28.4, 25.5, 23.3, 18.4.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{35}N_2O_5$: 467.2546; found: 467.2530.

cis-1-[(*tert*-Butoxycarbonyl)amino]-2-{3-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]propyl}cyclopropanecarboxylic Acid (*cis*-21);[27] Typical Procedure

To a solution of the alcohol *cis*-**17** (150 mg, 0.32 mmol) in CCl_4–MeCN–H_2O (2:2:3, 5 mL) were successively added $NaIO_4$ (413 mg, 1.93 mmol) and $RuO_2{\cdot}H_2O$ (5 mg, 0.03 mmol). The solution was stirred at r.t. for 1 h and water (3 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, 100% EtOAc) to afford the acid *cis*-**21** (115 mg, 75%) as a beige solid, which was recrystallized (CH_2Cl_2–petroleum ether); mp > 300 °C; R_f = 0.40 (EtOAc).

IR (neat): 3371, 2970, 1698, 1514, 1449, 1392, 1367, 1249, 1162, 1048 cm^{-1}.

^{1}H NMR (200 MHz, MeOH-d_4): δ = 7.89 (d, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 7.4 Hz, 2 H), 7.44–7.25 (m, 4 H), 4.33 (d, *J* = 7.1 Hz, 2 H), 4.19 (m, 1 H), 3.13 (br s, 2 H), 1.70–1.00 (m, 15 H), 0.72 (br s, 1 H).

HRMS (EI): *m*/*z* [M$^{+\bullet}$] calcd for $C_{27}H_{32}N_2O_6$: 480.2260; found: 480.2279.

Methyl *cis*-1-[(*tert*-Butoxycarbonyl)amino]-2-{3-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]propyl}cyclopropanecarboxylate

To a solution of the acid *cis*-**21** (33 mg, 0.069 mmol) in CH_2Cl_2–MeOH (7:1, 0.7 mL) was slowly added a 2 M solution $TMSCHN_2$ in hexanes (36 µL, 0.072 mmol). The solution was stirred at r.t. for 15 min then opened to the air. After evaporation of solvents under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 70:30) to afford the methyl ester (32 mg, 94%) as a colorless oil; R_f = 0.20 (cyclohexane–EtOAc, 70:30).

IR (neat): 2993, 2922, 1695, 1513, 1449, 1366, 1247, 1162, 1047 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 6.7, 0.8 Hz, 2 H), 7.60 (dd, *J* = 7.2, 0.8 Hz, 2 H), 7.40 (td, *J* = 7.2, 1.1 Hz, 2 H), 7.33 (td, *J* = 7.3, 1.4 Hz, 2 H), 5.14 (br s, 1 H), 5.02 (br s, 1 H), 4.38 (d, *J* = 6.7 Hz, 2 H), 4.21 (t, *J* = 6.7 Hz, 1 H), 3.71 (s, 3 H), 3.22 (br s, 2 H), 1.70–1.00 (m, 15 H), 0.85 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5. 156.6. 156.1, 144.2, 141.4, 127.8, 127.2, 125.2, 120.1, 80.2, 66.7, 52.5. 47.4, 40.8, 38.8, 31.6, 28.4, 27.1, 24.5, 23.6.

HRMS (CI-NH_3): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{35}N_2O_6$: 495.2495; found: 495.2462.

trans-1-[(*tert*-Butoxycarbonyl)amino]-2-{3-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]propyl}cyclopropanecarboxylic Acid (*trans*-21)[18]

Using *trans*-17 (220 mg, 0.47 mmol), the oxidation procedure described using the alcohol *cis*-17 afforded *trans*-21 as a beige solid (160 mg, 71%); mp 96–98 °C (Lit.[18] 97–98 °C); R_f = 0.40 (EtOAc).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.91 (br s, 1 H), 7.76 (d, *J* = 7.3 Hz, 2 H), 7.59 (d, *J* = 6.7 Hz, 2 H), 7.45–7.25 (m, 4 H), 5.08 (br s, 1 H), 4.53–4.29 (m, 2 H), 4.24 (m, 1 H), 3.30–3.03 (br s, 2 H), 1.80–1.22 (m, 15 H), 0.87 (m, 1 H).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 12.19 (br s, 1 H), 7.89 (d, *J* = 6.9 Hz, 2 H), 7.68 (d, *J* = 6.9 Hz, 2 H), 7.46–7.21 (m, 6 H), 4.38–4.16 (m, 3 H), 3.13–2.87 (br s, 2 H), 1.66–0.95 (m, 14 H), 0.85 (m, 1 H), 0.69 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 156.7, 144.1, 141.4, 127.8, 127.1, 125.2, 120.0, 80.2, 66.7, 47.4, 40.8, 38.2, 29.5. 28.4. 25.4, 22.8.

tert-Butyl 1-[(Benzyloxy)methyl]-2-azabicyclo[4.1.0]heptane-2-carboxylate (22)

To a solution of the mesylate *trans*-**13** (205 mg, 0.50 mmol) in THF (5 mL) cooled to 0 °C was added NaH (80 mg, 60% in oil, 2 mmol). The solution was stirred overnight at r.t. and water (5 mL) was added. The solution was acidified by the addition of 1 M aq HCl and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 95:5) to afford the bicyclic product **22** (109 mg, 69%) as a colorless oil; R_f = 0.23 (cyclohexane–EtOAc, 70:30).

IR (neat): 3063, 3003, 2972, 2931, 2860, 1691, 1496, 1477, 1453, 1390, 1363, 1164, 1092, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (70:30 mixture of rotamers) = 7.36–7.23 (m, 5 H), 4.58–4.48 (m, 2 H), 4.32 (d, *J* = 10.8 Hz, 0.3 H), 4.14 (d, *J* = 10.3 Hz, 0.7 H), 3.90 (dt, *J* = 12.7, 4.0 Hz, 0.7 H), 3.74 (m, 0.3 H), 3.26 (d, *J* = 10.8 Hz, 0.3 H), 2.92 (d, *J* = 10.3 Hz, 0.7 H), 2.75 (m, 0.3 H), 2.65 (m, 0.7 H), 1.96 (m, 1 H), 1.74 (m, 1 H), 1.58 (m, 1 H), 1.47 (s, 0.9 H),

1.45 (s, 2.1 H), 1.44 (s, 1.8 H), 1.42 (s, 4.2 H), 1.29–1.20 (m, 2 H), 0.93 (m, 0.3 H), 0.85 (m, 0.7 H), 0.51 (t, *J* = 6.3 Hz, 0.3 H), 0.43 (t, *J* = 6.3 Hz, 0.7 H).

^{1}H NMR (400 MHz, DMSO-d_6, 363 K): δ = 7.36–7.24 (m, 5 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.12 (d, *J* = 10.3 Hz, 1 H), 3.71 (m, 1 H), 2.99 (d, *J* = 10.3 Hz, 1 H), 2.61 (m, 1 H), 1.93 (m, 1 H), 1.63 (m, 1 H), 1.53 (m, 1 H), 1.41 (s, 3 H), 1.40 (s, 6 H), 1.25–1.16 (m, 2 H), 0.88 (m, 1 H), 0.41 (t, *J* = 6.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (70:30 mixture of rotamers) = 156.5 (0.7 C), 155.5 (0.3 C), 139.0 (0.3 C), 138.8 (0.7 C), 128.4 (1.4 C), 128.4 (0.6 C), 127.5 (0.9 C), 127.4 (2.1 C), 79.3 (0.7 C), 79.3 (0.3 C), 75.3 (0.7 C), 74.9 (0.3 C), 73.1 (0.3 C), 72.9 (0.7 C), 43.4 (0.3 C), 41.9 (0.7 C), 38.4 (0.3 C), 38.0 (0.7 C), 28.6 (0.7 C), 22.3 (0.3 C), 22.1 (0.3 C), 21.8 (0.7 C), 21.3 (0.7 C), 18.5 (0.7 C), 18.1 (0.3 C), 17.4 (0.7 C), 16.8 (0.3 C).

HRMS (EI): *m*/*z* [M$^{+\bullet}$] calcd for $C_{19}H_{27}NO_3$: 317.1991; found: 317.1971.

cis-2-{2-[(Benzyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]cyclopropyl}ethyl Methanesulfonate (*cis*-23)

To a solution of *cis*-**12** (1.05 g, 3.30 mmol) in CH_2Cl_2–MeOH (1:1, 33 mL) cooled to –60 °C was bubbled O_3 until blue coloration appeared; excess O_3 was removed from the flask by an argon flow. $NaBH_4$ (373 mg, 10 mmol) was added at –60 °C and the mixture was stirred overnight at r.t. Water (50 mL) was then slowly added and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude alcohol intermediate was dissolved in CH_2Cl_2 (15 mL) and the resulting solution was cooled to –10 °C. Et_3N (0.81 mL, 5.94 mmol) then MsCl (0.28 mL, 3.63 mmol) were slowly added and the mixture was allowed to warm up to r.t. Water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, cyclohexane–EtOAc, 80:20) afforded *cis*-**23** (790 mg, 60%) as a white solid; mp 81–86 °C; R_f = 0.18 (cyclohexane–EtOAc, 70:30).

IR (neat): 3410, 2978, 2941, 2902, 1691, 1497, 1395, 1350, 1248, 1169, 1076 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 5.15 (br s, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.41–4.27 (m, 2 H), 3.69 (d, *J* = 10.4 Hz, 1 H), 3.43 (d, *J* = 10.4 Hz, 1 H), 2.97 (s, 3 H), 1.79 (br s, 2 H), 1.41 (s, 9 H), 1.24–1.11 (m, 1 H), 1.11–1.00 (m, 1 H), 0.58 (t, *J* = 6.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 138.3, 128.6, 127.9, 127.8, 79.6, 73.4, 71.7, 70.0, 37.4, 36.7, 29.1, 28.5, 21.9, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{30}NO_6S$: 400.1788; found: 400.1789.

tert-Butyl *cis*-2-(2-Azidoethyl)-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-24)

To a solution of *cis*-**23** (500 mg, 1.25 mmol) in MeOH (12 mL) was added 10% Pd/C (50 mg, 10 wt%) and the mixture was stirred at r.t. under H_2 (3 bar) for 1.5 h. After filtration on a pad of Celite and washing with CH_2Cl_2, the solution was concentrated under reduced pressure to afford the debenzylated mesylate intermediate as a white solid (386 mg, quant.); mp 81–83 °C; R_f = 0.18 (cyclohexane–EtOAc, 70:30).

IR (neat): 3272, 1672, 1528, 1474, 1347, 1170, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H), 4.47–4.35 (m, 2 H), 3.93 (d, *J* = 12.0 Hz, 1 H), 3.72 (br s, 1 H), 3.52 (d, *J* = 12.0 Hz, 1 H), 3.04 (s, 3 H), 2.04–1.83 (m, 2 H), 1.43 (s, 9 H), 1.25 (m, 1 H), 0.99 (dd, *J* = 9.5 Hz, 5.6 Hz, 1 H), 0.60 (t, *J* = 5.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 80.0, 70.2, 66.0, 38.1, 37.1, 29.0, 28.3, 22.7, 18.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{23}NNaO_6S$: 332.1138; found: 332.1127.

To a solution of the previous mesylate intermediate (506 mg, 1.63 mmol) in MeCN (16 mL) was added NaN_3 (266 mg, 4.1 mmol). The mixture was refluxed overnight then water (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was purified by column chromatography (silica gel, cyclohexane–EtOAc, 60:40) to afford *cis*-**24** (346 mg, 82%) as a colorless oil; R_f = 0.18 (cyclohexane–EtOAc, 70:30).

IR (neat): 3500–3300, 2101, 1685, 1503, 1453, 1391, 1365, 1247, 1163, 1100, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (br s, 1 H), 3.91 (d, *J* = 11.9 Hz, 1 H), 3.69 (m, 1 H), 3.57–3.42 (m, 3 H), 1.90–1.55 (m, 2 H), 1.43 (s, 9 H), 1.25–1.10 (m, 1 H), 0.97 (dd, *J* = 9.4 Hz, 5.7 Hz, 1 H), 0.57 (dd, *J* = 6.2, 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 80.5, 66.6, 51.5, 38.6, 29.1, 28.4, 24.4, 18.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}N_4NaO_3$: 279.1428; found: 279.1435.

tert-Butyl *cis*-2-{2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]ethyl}-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-25)

To a solution of *cis*-**24** (294 mg, 1.15 mmol) in MeOH (11 mL) were successively added 10% Pd/C (74 mg, 25 wt%) and ammonium formate (360 mg, 5.75 mmol). The mixture was refluxed for 30 min then allowed to cool to r.t. After filtration through a pad of Celite and concentration under reduced pressure, the crude amine was dissolved in dioxane–H_2O (1:1, 12 mL) and Na_2CO_3 (1.96 g, 18.5 mmol) was added. The solution was cooled to 0 °C and FmocCl (327 mg, 1.26 mmol) was added. The mixture was stirred overnight at r.t. and solvents were evaporated under reduced pressure. The residue was taken up in water (10 mL) and CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 50:50) to afford *cis*-**25** (360 mg, 70%) as a white solid; mp 124–126 °C; R_f = 0.24 (cyclohexane–EtOAc, 50:50).

IR (neat): 3300, 2900, 1678, 1518, 1478, 1448, 1391, 1365, 1249, 1163, 1104, 1059, 1019 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 2 H), 7.67–7.62 (m, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 6.63 (br s, 1 H), 5.28 (br s, 1 H), 4.40–4.30 (m, 2 H), 4.20 (t, *J* = 7.1 Hz, 1 H), 3.73 (m, 1 H), 3.59 (m, 1 H), 3.49 (m, 1 H), 3.29 (m, 1 H), 2.78 (br s, 1 H), 1.95–1.75 (m, 2 H), 1.46 (s, 9 H), 1.16 (m, 1 H), 0.90 (m, 1 H), 0.48 (t, *J* = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 157.0, 144.3, 144.2, 141.4, 127.7, 127.1, 127.1, 125.4, 125.3, 120.0, 80.4, 66.7, 65.5, 47.4, 40.8, 38.5, 29.6, 28.5, 25.2, 17.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{32}N_2NaO_5$: 475.2203; found: 475.2190.

***cis*-1-[(*tert*-Butoxycarbonyl)amino)]-2-{2-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]ethyl}cyclopropanecarboxylic Acid (*cis*-26)**

To a solution of *cis*-**25** (73 mg, 0.16 mmol) in CCl_4–MeCN–H_2O (2:2:3, 2.6 mL) were successively added $NaIO_4$ (198 mg, 0.93 mmol) and $RuO_2{\cdot}H_2O$ (2.4 mg, 0.02 mmol). The solution was stirred at r.t. for 1 h and water (1.6 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc) to afford *cis*-**26** (51 mg, 67%) as a white solid; mp 65–69 °C; R_f = 0.11 (cyclohexane–EtOAc, 50:50).

IR (neat): 1692, 1507, 1449, 1392, 1336, 1249, 1160, 1103, 1048 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.5 Hz, 2 H), 7.61–7.59 (m, 2 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.26 (dt, *J* = 7.5, 1.1 Hz, 2 H), 5.98 (br s, 1 H), 5.20 (br s, 1 H), 4.39–4.31 (m, 1 H), 4.17 (t, *J* = 6.9 Hz, 2 H), 3.38–3.17 (m, 2 H), 1.93–1.82 (m, 1 H), 1.77–1.67 (m, 1 H), 1.60–1.52 (m, 1 H), 1.45 (s, 9 H), 1.36–1.33 (m, 1 H), 1.16 (ddt, *J* = 9.6, 4.8 Hz, 1 H), 0.96–0.81 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 157.1, 157.0, 144.5, 144.4, 141.4, 141.3, 127.7, 127.7, 127.3, 127.2, 125.7, 125.5, 119.9, 119.9, 80.6, 66.7, 47.5, 40.4, 31.6, 29.8, 28.4, 27.2, 22.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{30}N_2NaO_6$: 489.1996; found: 489.1985.

***tert*-Butyl *cis*-1-[(Benzyloxy)methyl]-2-(3-cyanoallyl)cyclopropylcarbamate (*cis*-27); Typical Procedure**

To a Schlenk tube filled with argon was introduced *cis*-**12** (464 mg, 1.46 mmol). After several vacuum–refill cycles, anhydrous and degassed CH_2Cl_2 (14 mL, 0.1 M/substrate) then acrylonitrile (180 µL, 2.70 mmol) were added. A solution of 2nd generation Hoveyda–Grubbs catalyst (42 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was prepared under an argon atmosphere and was transferred into the Schlenk tube. The mixture was heated at 45 °C overnight under an argon atmosphere and the green solution turned to dark red. After cooling down to r.t., ethyl vinyl ether (1 mL) was added to the mixture and the solution was concentrated under reduced pressure. The black oil was purified by column chromatography (silica gel, cyclohexane–EtOAc, 80:20) to afford *cis*-**27** as a colorless oil (394 mg, 79%, ratio *Z*/*E* 3:1); R_f = 0.34 (cyclohexane–EtOAc, 80:20).

IR (neat): 2157, 1971, 1940, 1701, 1493, 1453, 1389, 1365, 1245, 1166, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 6.81 (dt, *J* = 16.4, 6.2 Hz, 0.3 H), 6.76–6.61 (m, 0.7 H), 5.63–5.53 (m, 0.3 H), 5.33 (dt, *J* = 10.9, 1.5 Hz, 0.7 H), 5.15 (br s, 1 H), 4.58 (d, *J* = 12.2 Hz, 0.3 H), 4.55 (d, *J* = 12.2 Hz, 0.7 H), 4.51 (d, *J* = 12.2 Hz, 0.7 H), 4.49 (d, *J* = 12.2 Hz, 0.3 H), 3.68 (d, *J* = 10.5 Hz, 0.7 H), 3.63 (d, *J* = 10.5 Hz, 0.3 H), 3.49 (d, *J* = 10.5 Hz, 0.7 H), 3.44 (d, *J* = 10.5 Hz, 0.3 H), 2.60–2.47 (m, 0.7 H), 2.46–2.30 (m, 1 H), 2.20–2.13 (m, 0.3 H), 1.43 (s, 2.7 H), 1.42 (s, 6.3 H), 1.25–1.18 (m, 0.7 H), 1.17–1.12 (m, 0.3 H), 1.11–1.02 (m, 1 H), 0.63 (t, *J* = 6.2 Hz, 0.7 H), 0.57 (t, *J* = 6.0 Hz, 0.3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 157.6, 154.3, 138.2, 128.6, 127.9, 127.8, 116.1, 99.7, 79.6, 73.4, 71.5, 36.9, 31.6, 28.5, 23.8, 18.3; δ (*E*-isomer) = 157.6, 153.9, 138.1, 128.6, 127.9, 127.8, 116.1, 100.5, 79.6, 73.4, 71.4, 36.9, 32.8, 28.5, 22.9, 18.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2NaO_3$: 365.1836; found: 365.1835.

***tert*-Butyl *trans*-1-[(Benzyloxy)methyl]-2-(3-cyanoallyl)cyclopropylcarbamate (*trans*-27)**

The previous procedure was applied using *trans*-**12** (96 mg, 0.30 mmol) and afforded *trans*-**27** as a white solid (74 mg, 72%, ratio *Z*/*E* 3:1); mp 65–68 °C; R_f = 0.31 (cyclohexane–EtOAc, 80:20).

IR (neat): 2157, 1971, 1940, 1701, 1493, 1453, 1389, 1365, 1245, 1166, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5 H), 6.82 (dt, *J* = 16.4, 5.7 Hz, 0.25 H), 6.69–6.54 (m, 0.75 H), 5.66 (dt, *J* = 16.4, 1.8 Hz, 0.25 H), 5.32 (m, 0.75 H), 5.04 (br s, 0.75 H), 4.95 (br s, 0.25 H), 4.54 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 3.69 (d, *J* = 9.9 Hz, 0.75 H), 3.50 (d, *J* = 9.9 Hz, 0.25 H), 3.42 (d, *J* = 10.0 Hz, 0.25 H), 3.27 (d, *J* = 10.0 Hz, 0.75 H), 2.66–2.26 (m, 2 H), 1.44 (s, 6.75 H), 1.43 (s, 2.25 H), 1.07–0.96 (m, 1.5 H), 0.95–0.84 (m, 0.5 H), 0.64–0.52 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 156.0, 154.3, 138.3, 128.5, 127.8, 127.7, 116.0, 99.6, 79.8, 74.3, 73.2, 37.7, 30.7, 28.4, 21.4, 16.7; δ (*E*-isomer) = 156.0, 154.9, 138.2, 128.6, 127.9, 127.6, 117.7, 100.2, 79.9, 74.8, 73.3, 37.3, 31.9, 28.4, 20.0, 17.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2NaO_3$: 365.1836; found: 365.1829.

***tert*-Butyl *cis*-1-[(Benzyloxy)methyl]-2-(3-cyanopropyl)cyclopropylcarbamate (*cis*-28)**

To a solution of *cis*-**27** (100 mg, 0.29 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 10 wt%) and the mixture was stirred at r.t. under H_2 (30 bar) for 72 h. After filtration on a pad of Celite and washing with EtOAc, the solution was concentrated under reduced pressure to afford pure *cis*-**28** (102 mg, quant.) as a colorless oil; R_f = 0.27 (cyclohexane–EtOAc, 80:20).

IR (neat): 3334, 2930, 1708, 1494, 1364, 1245, 1165, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.14 (br s, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 3.60 (d, *J* = 10.1 Hz, 1 H), 3.52 (d, *J* = 10.1 Hz, 1 H), 2.39 (t, *J* = 6.9 Hz, 2 H), 1.84–1.78 (m, 2 H), 1.60–1.50 (m, 1 H), 1.49–1.42 (m, 1 H), 1.42 (s, 9 H), 1.11–1.04 (m, 1 H), 1.03–0.97 (m, 1 H), 0.51 (br t, *J* = 5.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.4, 128.6, 127.8, 119.9, 79.5, 73.3, 71.6, 36.8, 28.5, 28.3, 25.3, 24.8, 18.5, 16.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_3$: 345.2173; found: 345.2170.

***tert*-Butyl *trans*-1-[(Benzyloxy)methyl]-2-(3-cyanopropyl)cyclopropylcarbamate (*trans*-28)**

To a solution of *trans*-**27** (100 mg, 0.29 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 10 wt%) and the mixture was stirred at r.t. under H_2 (30 bar) for 72 h. After filtration on a pad of Celite and washing with EtOAc, the solution was concentrated under reduced pressure to afford pure *trans*-**28** (102 mg, quant.) as a colorless oil; R_f = 0.26 (cyclohexane–EtOAc, 80:20).

IR (neat): 3340, 2930, 1704, 1495, 1365, 1243, 1165, 1072 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 4.95 (br s, 1 H), 4.52 (s, 2 H), 3.55 (d, *J* = 9.5 Hz, 1 H), 3.37 (d, *J* = 9.5 Hz, 1 H), 2.40–2.36 (m, 2 H), 1.82–1.75 (m, 3 H), 1.43 (s, 9 H), 1.42–1.36 (m, 1 H), 0.95 (dd, *J* = 8.9, 5.3 Hz, 1 H), 0.91–0.87 (m, 1 H), 0.51 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 138.4, 128.5, 127.8, 127.7, 119.8, 79.7, 74.8, 73.2, 37.4, 28.4, 27.2, 25.4, 22.1, 17.1, 17.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_3$: 345.2173; found: 345.2172.

Methyl (*E*)-4-{*cis*-2-[(Benzyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]cyclopropyl}but-2-enoate (*cis*-29)

To a Schlenk tube filled with argon was introduced *cis*-**12** (969 mg, 3.05 mmol). After several vacuum–refill cycles, anhydrous and degassed CH_2Cl_2 (27.5 mL) then methyl acrylate (2.76 mL, 30.5 mmol) were added. A solution of 2nd generation Hoveyda–Grubbs catalyst (96 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was prepared under an argon atmosphere and was transferred into the Schlenk tube. The mixture was heated at 45 °C overnight under an argon atmosphere; the green solution became dark red. After cooling to r.t., ethyl vinyl ether (1 mL) was added to the mixture and the solution was concentrated under reduced pressure. The black solid was purified by column chromatography (silica gel, cyclohexane–EtOAc, 90:10) to afford *cis*-**29** as a white solid (1.0 g, 87%); mp 51–54 °C; R_f = 0.37 (cyclohexane–EtOAc, 80:20).

IR (neat): 1720, 1684, 1649, 1499, 1365, 1247, 1164, 1090, 1070, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 7.03 (dt, *J* = 15.7, 6.4 Hz, 1 H), 5.91 (d, *J* = 15.7 Hz, 1 H), 5.14 (br s, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 3.72 (s, 3 H), 3.71 (d, *J* = 10.4 Hz, 1 H), 3.41 (d, *J* = 10.4 Hz, 1 H), 2.54–2.41 (m, 1 H), 2.07–1.96 (m, 1 H), 1.42 (s, 9 H), 1.20–1.13 (m, 1 H), 1.12–1.04 (m, 1 H), 0.56 (t, *J* = 5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 155.6, 147.9, 138.2, 128.5, 127.8, 121.4, 79.5, 73.3, 71.6, 51.5, 36.8, 31.6, 28.5, 23.5, 18.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}NNaO_5$: 398.1938; found: 398.1954.

4-{*cis*-2-[(Benzyloxy)methyl]-2-[(*tert*-butoxycarbonyl)amino]cyclopropyl]butyl Methanesulfonate (*cis*-30)

To a solution of *cis*-**29** (665 mg, 1.77 mmol) in THF (30 mL) cooled at 0 °C was added $LiAlH_4$ (107 mg, 2.83 mmol). After 15 min at 0 °C the mixture was stirred at r.t. for 2 h. The excess of $LiAlH_4$ was destroyed by addition of EtOAc (6 mL) then water (0.6 mL). The resulting suspension was stirred for 15 min and Na_2SO_4 was added. After filtration on a pad of Celite and washing with EtOAc, the solution was concentrated under reduced pressure to afford the pure saturated alcohol (616 mg, quant.) as a colorless oil; R_f = 0.11 (cyclohexane–EtOAc, 80:20).

IR (neat): 3397, 2929, 2862, 1694, 1495, 1453, 1389, 1247, 1166, 1070, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 5.15 (br s, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 3.67–3.50 (m, 3 H), 3.53 (d, *J* = 10.1 Hz, 1 H), 1.82 (br s, 1 H), 1.65–1.54 (m, 2 H), 1.54–1.45 (m, 2 H), 1.45–1.37 (m, 10 H), 1.24–1.16 (m, 1 H), 1.13–1.03 (m, 1 H), 0.97–0.91 (m, 1 H), 0.45 (t, *J* = 5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.5, 128.5, 127.8, 127.7, 79.4, 73.3, 71.9, 62.9, 36.8, 32.5, 29.1, 28.5, 27.0, 25.7, 18.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{31}NNaO_4$: 372.2145; found: 372.2141.

The crude alcohol intermediate was dissolved in CH_2Cl_2 (12 mL) and the resulting solution was cooled to –10 °C. Et_3N (434 µL, 3.19 mmol) then MsCl (151 µL, 1.95 mmol) were slowly added and the mixture was allowed to warm up to r.t. Water (16 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, cyclohexane–EtOAc, 80:20) afforded *cis*-**30** (491 mg, 65%) as a colorless oil; R_f = 0.21 (cyclohexane–EtOAc, 70:30).

IR (neat): 3392, 2973, 2932, 2863, 1708, 1495, 1351, 1245, 1168, 1073 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 5 H), 5.13 (br s, 1 H), 4.55 (d, *J* = 12.2 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.20 (t, *J* = 6.6 Hz, 2 H), 3.62 (d, *J* = 9.9 Hz, 1 H), 3.49 (d, *J* = 9.9 Hz, 1 H), 2.97 (s, 3 H), 1.78–1.73 (m, 2 H), 1.59–1.54 (m, 3 H), 1.42 (s, 9 H), 1.20–1.13 (m, 1 H), 1.10–1.02 (m, 1 H), 0.99–0.96 (m, 1 H), 0.46 (t, *J* = 5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 138.5, 128.5, 127.7, 79.3, 73.2, 71.8, 70.1, 37.5, 36.8, 29.0, 28.7, 28.5, 25.5, 18.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{34}NO_6S$: 428.2101; found: 428.2103.

***tert*-Butyl *cis*-2-(4-Azidobutyl)-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-31)**

To a solution of the mesylate *cis*-**30** (462 mg, 1.08 mmol) in MeOH (10 mL) was added 10% Pd/C (46 mg, 10 wt%) and the mixture was stirred at r.t. under H_2 (3 bar) for 1.5 h. After filtration on a pad of Celite and washing with CH_2Cl_2, the solution was concentrated under reduced pressure to afford the debenzylated mesylate intermediate as a colorless oil (367 mg, quant.); R_f = 0.13 (cyclohexane–EtOAc, 70:30).

IR (neat): 3389, 2933, 1683, 1503, 1348, 1248, 1166, 1024 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.22 (br s, 1 H), 4.20 (t, *J* = 6.5 Hz, 2 H), 3.77 (d, *J* = 11.5 Hz, 1 H), 3.77–3.60 (br s, 1 H), 3.50 (d, *J* = 11.5 Hz, 1 H), 2.97 (s, 3 H), 1.80–1.72 (m, 2 H), 1.71–1.61 (m, 1 H), 1.58–1.51 (m, 2 H), 1.39 (s, 9 H), 1.32–1.22 (m, 2 H), 1.10–1.02 (m, 1 H), 0.87 (dd, *J* = 9.2, 5.5 Hz, 1 H), 0.47 (t, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 80.2, 70.1, 66.8, 38.5, 37.4, 28.9, 28.8, 28.4, 26.8, 25.5, 18.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{27}NNaO_6S$: 360.1451; found: 360.1451.

To a solution of the previous mesylate intermediate (367 mg, 1.08 mmol) in MeCN (10.5 mL) was added NaN_3 (176 mg, 2.7 mmol). The mixture was refluxed overnight then water (6 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was purified by column chromatography (silica gel, cyclohexane–EtOAc, 70:30) to afford *cis*-**31** (252 mg, 82%) as a colorless oil; R_f = 0.31 (cyclohexane–EtOAc, 60:40).

IR (neat): 3329, 2975, 2932, 2862, 2092, 1682, 1495, 1454, 1391, 1365, 1247, 1164, 1101, 1024 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.11 (br s, 1 H), 3.80 (d, *J* = 10.2 Hz, 1 H), 3.61 (br s, 1 H), 3.60 (d, *J* = 10.2 Hz, 1 H), 3.27 (t, *J* = 6.8 Hz, 2 H), 1.73–1.59 (m, 3 H), 1.58–1.48 (m, 2 H), 1.42 (s, 9 H), 1.27 (dt, *J* = 14.7, 7.1 Hz, 1 H), 1.09 (ddd, *J* = 14.7, 9.0, 6.0 Hz, 1 H), 0.89 (dd, *J* = 9.0, 6.0 Hz, 1 H), 0.50 (t, *J* = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 80.4, 67.0, 51.5, 38.6, 29.1, 28.7, 28.5, 27.0, 26.8, 19.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{24}N_4NaO_3$: 307.1753; found: 307.1741.

***tert*-Butyl *cis*-2-{4-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino]butyl}-1-(hydroxymethyl)cyclopropylcarbamate (*cis*-32)**

To a solution of *cis*-**31** (252 mg, 0.89 mmol) in MeOH (8.5 mL) were successively added 10% Pd/C (25 mg, 10 wt %) and ammonium formate (279 mg, 4.43 mmol). The mixture was refluxed for 30 min then allowed to cool to r.t. After filtration through a pad of Celite and concentration under reduced pressure, the crude amine was dissolved in

dioxane–H_2O (1:1, 9.2 mL) and Na_2CO_3 (1.51 g, 14.3 mmol) was added. The solution was cooled to 0 °C and FmocCl (252 mg, 0.975 mmol) was added. The mixture was stirred overnight at r.t. and the solvents were evaporated under reduced pressure. The residue was taken up in water (7.5 mL) and CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 70:30) to afford *cis*-**32** (360 mg, 68%) as a colorless oil that crystallizes upon standing; mp 52–54 °C; R_f = 0.26 (cyclohexane–EtOAc, 50:50).

IR (neat): 3326, 2973, 2930, 2859, 1693, 1515, 1478, 1449, 1391, 1366, 1245, 1164, 1101, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.5 Hz, 2 H), 7.58 (d, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.29 (dt, *J* = 7.5 Hz, 1.0 Hz, 2 H), 4.97 (br s, 1 H), 4.82 (br s, 1 H), 4.41 (d, *J* = 6.8 Hz, 2 H), 4.24 (t, *J* = 6.8 Hz, 1 H), 3.79 (d, *J* = 11.7 Hz, 1 H), 3.61 (d, *J* = 11.7 Hz, 1 H), 3.31 (s, 1 H), 3.23–3.13 (m, 2 H), 1.62–1.55 (m, 2 H), 1.54–1.48 (m, 3 H), 1.44 (s, 9 H), 1.37–1.30 (m, 1 H), 1.13–1.06 (m, 1 H), 0.88 (dd, *J* = 9.5, 5.5 Hz, 1 H), 0.48 (dd, *J* = 6.5, 5.5 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.8, 156.7, 144.2, 141.4, 127.8, 127.2, 125.2, 120.1, 80.4, 67.0, 66.7, 47.4, 40.9, 38.6, 29.6, 29.1, 28.5, 27.1, 26.7, 19.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{36}N_2NaO_5$: 503.2514; found: 503.2516.

cis-1-[(_tert_-Butoxycarbonyl)amino]-2-{4-[(9_H_-fluoren-9-ylmethoxycarbonyl)amino]butyl}cyclopropanecarboxylic Acid (_cis_-33)

To a solution of *cis*-**32** (100 mg, 0.21 mmol) in CCl_4–MeCN–water (2:2:3, 3.5 mL) were successively added $NaIO_4$ (267 mg, 1.24 mmol) and $RuO_2·H_2O$ (3.3 mg, 0.02 mmol). The solution was stirred at r.t. for 1 h and water (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc 100%) to afford *cis*-**33** (76 mg, 74%) as a white solid; mp >300 °C; R_f = 0.32 (EtOAc).

IR (neat): 3326, 2930, 2868, 1694, 1514, 1450, 1392, 1366, 1246, 1160, 1102, 1049, 1024 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.5 Hz, 2 H), 7.57 (dd, *J* = 7.5, 0.9 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.28 (dt, *J* = 7.5, 1.2 Hz, 2 H), 5.26 (br s, 1 H), 4.89 (br s, 1 H), 4.40 (d, *J* = 6.8 Hz, 2 H), 4.20 (t, *J* = 6.8 Hz, 2 H), 3.19–3.10 (m, 2 H), 1.65–1.57 (m, 2 H), 1.56–1.57 (m, 4 H), 1.44 (s, 9 H), 1.32–1.24 (m, 2 H), 0.94–0.82 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 156.8, 156.7, 144.1, 141.4, 127.8, 127.2, 125.2, 120.1, 80.4, 66.8, 47.4, 41.0, 38.8, 32.0, 29.4, 28.4, 26.6, 26.3, 23.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{34}N_2NaO_6$: 517.2312; found: 517.2309.

Acknowledgment

We gratefully acknowledge the 'Agence Nationale de la Recherche' (ANR BLAN07-2_194466), the 'Centre National de la Recherche Scientifique', the 'Région Pays-de-la-Loire' and the 'Ministère de l'Enseignement Supérieur et de la Recherche' for Ph.D. and postdoc fellowships. We also thank A. Durand, P. Gangnery, F. Legros, and E. Mebold for technical assistance and analyses.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379978.

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