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Synthesis of α-Cyclopropyl-β-homoprolines†

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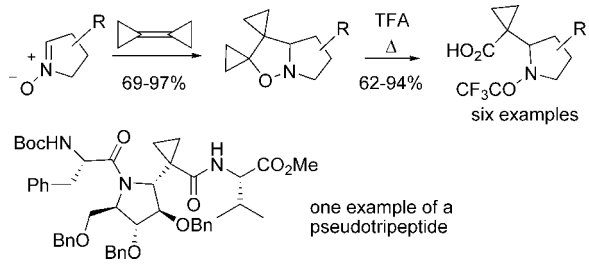

1-(2-Pyrrolidinyl)cyclopropanecarboxylic acids (α-cyclopropyl-β-homoprolines) were prepared by 1,3-dipolar cycloadditions of cyclic nitrones onto bicyclopropylidene followed by trifluoroacetic acid induced thermal fragmentative rearrangement. With the use of enantiopure pyrroline *N*-oxides derived from easily available chiral pool molecules, β-homoprolines were formed with high stereocontrol. The incorporation of one of these new cyclic β-amino acids into a simple tripeptide was also evaluated. In particular, the sterically hindered nitrogen atom of the highly substituted pyrrolidine **30** was smoothly acylated through the intermediate formation of a mixed anhydride.

Introduction

β-Amino acids are important targets in organic chemistry because of their roles as synthetic intermediates[1] and as key components of a variety of biologically active compounds[2] including peptidomimetics[3] and β-peptides.[4,5]

Of special interest are α- and β-amino acids containing a 1,1-disubstituted cyclopropane ring adjacent to the carboxyl moiety.[6] In general, the introduction of the relatively small cyclopropyl moiety significantly influences the conformational flexibility of the respective amino acid and peptides derived from it.[6] For example, the parent 1-(aminomethyl)cyclopropanecarboxylic acid (**1**) has been incorporated by Varie et al. in cryptophycin analogues with potent antitumor activity,[7] and Seebach et al. have shown that oligomers of **1** have interesting secondary structures.[8] In addition, the benzyl ester **2** is an interesting inhibitor of monoamine oxidase,[9] and other derivatives of **1** have

† Dedicated to Professor Francesco De Sarlo on the occasion of his 70th birthday.

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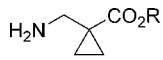
been shown to be potent binders of the α_2-δ protein[10] and have been used as direct precursors of α-methylene-γ-butyrolactones.[11]



1 R = H
2 R = Bn

Despite their high potential as building blocks in organic synthesis and tools in medicinal chemistry, β-amino acids with a cyclopropane ring in the 2-position have not been explored to a large extent, and this may be due to difficulties in preparing some of their more complex derivatives in a stereoselective manner.[12,13]

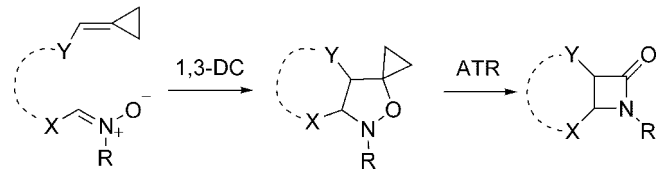
Recently, we disclosed a new general approach to β-lactams and β-amino acids based on the 1,3-dipolar cycloaddition (1,3-DC) of nitrones to methylenecyclopropane (MCP) and its derivatives, followed by fragmentative thermal rearrangement of the protonated cycloadducts (spiroCycloPropaneIsoxazolidine Acidic Thermal Rearrangement, CPI-ATR).[14] In particular, monobactams and 3,4-*cis*-fused azetidinones are produced in good yields starting from the cycloadducts of acyclic nitrones formed in an inter- or intramolecular process, respectively (Scheme 1).[14,15]

The method exploits the stereoselectivity of the cycloaddition to control the configuration of the stereocenters on the azetidinone ring, which is retained during the CPI-ATR step. Actually, the use of nitrones obtained from chiral pool precursors allowed the synthesis of optically active azetidinones with high stereocontrol.

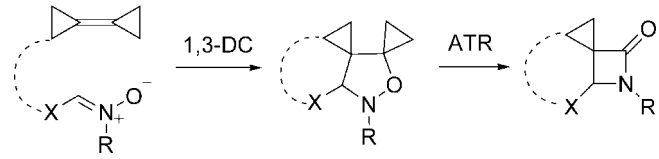
The same two-step approach could be easily extended to the synthesis of highly strained 3-spirocyclopropane-β-lactams by the use of bicyclopropylidene (BCP) as the dipolarophile in the cycloaddition step (Scheme 2).[16]

Usually, various protic acids such as TFA, *p*-TsOH, and HCl could be used to initiate the fragmentative rearrangement of 5-spirocyclopropaneisoxazolidines into β-lactams. In the case of highly reactive products, TFA was the acid of choice,

SCHEME 1. Intra- and Intermolecular Approach to Monobactams and 3,4-Fused Azetidinones by the 1,3-DC/ATR Sequence



SCHEME 2. Intra- and Intermolecular Approach to 3-Spirocyclopropane-β-lactams by the 1,3-DC/ATR Sequence



and it caused the direct formation of the stable *N*-(trifluoroacetyl)-β-amino acids by trifluoroacetolysis of the lactam bond.[17] For example, cycloadducts of pyrroline *N*-oxides did not afford the expected carbapenams but the corresponding β-homoprolines.[15b]

The practicability of the 1,3-DC/CPI-ATR approach to the synthesis of variously decorated azetidinones and β-amino acids prompted us to investigate new applications in order to establish the real scope of the process.

Herein we report a study of the CPI-ATR of several cycloadducts of cyclic nitrones onto BCP. In addition, the feasibility of using a highly functionalized α-cyclopropyl-β-homoproline as a building block in peptide synthesis was evaluated.

Results and Discussion

Usually, the reaction rate of BCP with cyclic nitrones is slow between room temperature and 60 °C, but the corresponding adducts, the 2,3-fused 4,5-(bis)spirocyclopropanated isoxazolidines, are obtained in good yields and with high diastereoselectivity.[18] At higher temperature the conversion of the reagents is faster, but the in situ transformation of cycloadducts into 4-piperidones by the well-known thermal rearrangement of 5-spirocyclopropaneisoxazolidines[19] (CPI-TR; Brandi−Guarna reaction[20]) is also observed.

The spirocyclopropaneisoxazolidine **4a** derived from the nitrone of methyl prolinate **3a**[21] was obtained under standard conditions (BCP, toluene, 60 °C, 3 d) in 69% yield (Scheme 3). Surprisingly, the corresponding *tert*-butyl ester **4b** proved

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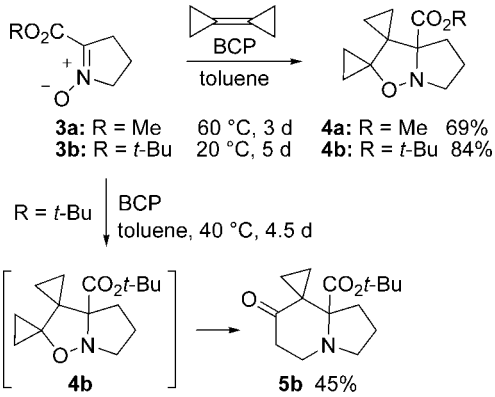
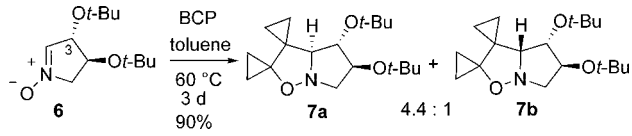
SCHEME 3



SCHEME 4



to be extremely thermally labile. In particular, a mixture of the adduct **4b** and the ketone **5b** was obtained by heating nitrone **3b**[22] and BCP at 60 °C for 2 days or at 50 °C for 1 day, and **5b** was the only product after 4.5 days at 40 °C (Scheme 3). No rearrangement was observed at room temperature, and the isoxazolidine **4b** was obtained in 84% yield by stirring the reagents at 20 °C for 5 days.

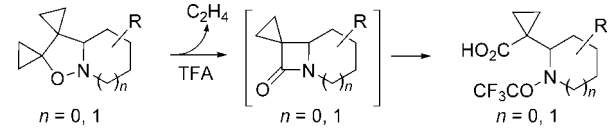
Enantiopure hydroxylated pyrroline *N*-oxide **6**,[23] easily derived from tartaric acid, reacted with BCP at 60 °C to afford the *anti*- and *syn*-(3-O*t*-Bu)-adducts **7a** and **7b** in a 4.4:1 ratio and 90% overall yield (Scheme 4). The other (bis)spiroisoxazolidines **8**−**13** used in the study were prepared as previously described.[18]

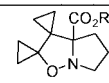
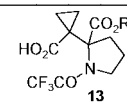
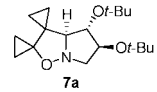
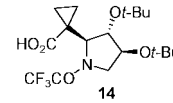
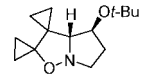
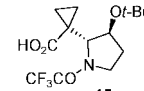
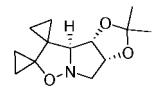
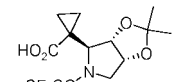
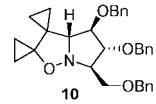
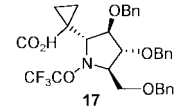
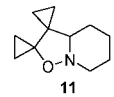
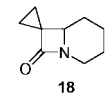
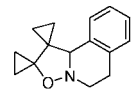
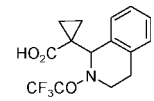
The results of the ATR of 4,5-(bis)spirocyclopropaneisoxazolidines **4** and **7**−**12** are shown in Table 1. Analogously to the monospiro-annelated 2-spirocyclopropane-pyrrolo[1,2-*b*]isoxazolidines,[15b] ATR of dispiro-fused derivatives **4** and **7**−**10** in the presence of TFA afforded α-cyclopropyl-β-homoprolines **13**−**17** (entries 1−7, Table 1). The *N*-protected amino acids were isolated in good yields (62−94%) after chromatography. The reaction could also be carried out on a 1 g scale, and microwave irradiation often provided better results than conventional heating. As in the previous cases, the intermediate carbapenames could not be detected in the reaction mixtures.

The presence of the trifluoroacetamide moiety in homoprolines **13**−**17** is evidently discernible in proton decoupled ^{13}C NMR spectra, which show the two characteristic quartets at 156−157 (J_{C-F} = 36−37 Hz) and 116−117 ppm (J_{C-F} = 287−288 Hz). A long-range C−F coupling constant is also observed between pyrrolidine C-5 carbon and the fluorine atoms (46.5−63.8 ppm, J_{C-F} = 2.6−4.0 Hz). In one case (**16**), the structure was confirmed by a single crystal X-ray analysis.

CPI-ATR of adducts **11** and **12**[18a] of six-membered ring cyclic nitrones afforded different results, and in the case of **11** the unopened azetidinone **18** could be isolated, albeit in

TABLE 1. CPI-ATR of 4,5-(Bis)spirocyclopropanated Isoxazolidines



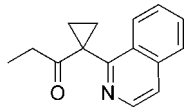
	adduct	reaction conditions[a]	product	yield (%)
	 4		 13	
1	**a**: R= Me	MeCN, 82 °C, 3 h		62
2	**b**: R= *t*-Bu	MeCN, 70 °C, 26 h		63
	 7a		 14	
3		toluene, 55-61 °C (MW),[b] 10 min		91
	 8		 15	
4		toluene, 110 °C, 2 h		51
5		toluene, 55-65 °C (MW),[b] 1 h		73
	 9		 16	
6		toluene, 55-70 °C (MW),[b] 35 min		77
	 10		 17	
7		toluene, 110 °C, 10 min		94
	 11		 18	
8		MeCN, 70 °C, 7 h		16
9		toluene, 110 °C, 3 h		19
10		MeCN, 60 °C, 21 h		24[a,c]
	 12		 19	
11		MeCN, 60 °C, 3 h		46
12		toluene, 110 °C, 30 min		41[d]
13		MeCN, 60 °C, 7 h		–[a,d]

[a] TFA (1.1−2 equiv) was used as the protic acid in all cases except in experiments 10 and 13, for which *p*-TsOH (1 equiv) was used. [b] MW irradiation power of 150 W with simultaneous cooling (CEM Discover microwave reactor with IR temperature monitoring). [c] 72% conversion. [d] In experiment 12, 1-[1-(1-isoquinolinyl)cyclopropyl]-1-propanone **20** was obtained in 7% yield in addition to the amino acid **19**, whereas in experiment 13, **20** was the only observed product (20% yield).

(22) Salvati, M.; Cordero, F. M.; Pisaneschi, F.; Bucelli, F.; Brandi, A. *Tetrahedron* **2005**, *61*, 8836–8847.

(23) (a) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748. (b) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274–5275.

poor yields (entries 8−10, Table 1). The use of *p*-TsOH gave slightly better results than TFA in the rearrangement of **11**. In either case, no formation of the corresponding ring-opened β-amino acid was observed. When the tetrahydroisoquinoline derivative **12** was heated at 60 °C in the presence of a slight excess of TFA, the *N*-trifluoroacetyl β-amino acid **19** was obtained in 46% yield (entry 11, Table 1). In close analogy to the formation of other β-homoprolines, the first product of the ATR of **12** was probably the spirocyclopropane-annelated azeto[2,1-*a*]isoquinolin-2-one, which must be more reactive than azetidinone **18** and therefore spontaneously undergoes trifluoroacetolysis under the reaction conditions. At 110 °C, protonated **12** was converted into a 6:1 mixture of **19** and the isoquinoline **20**, which had previously been obtained by the purely thermal rearrangement of **12** under neutral conditions (entry 12, Table 1).[18a] Finally, heating of **12** in the presence of *p*-TsOH led to the ketone **20** along with a complex mixture of decomposition products (entry 13, Table 1).



20

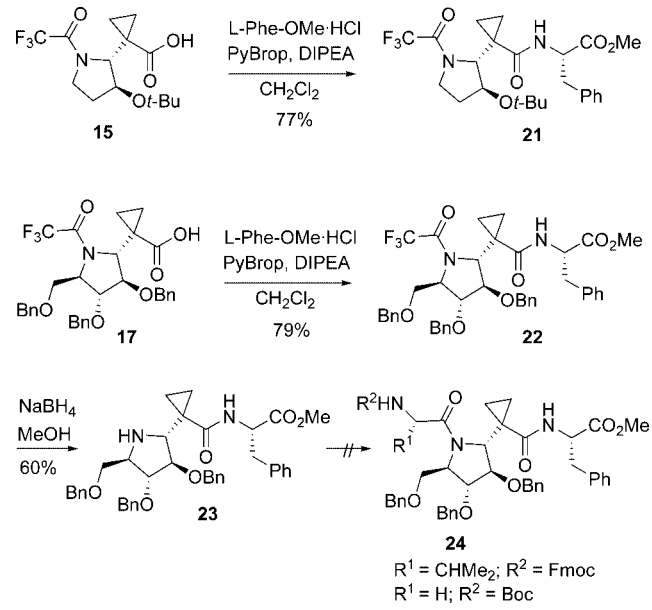
These results prove that the 1,3-DC/ATR process constitutes an easy and efficient access to the new class of α-cyclopropyl-β-homoprolines. Obviously, a possible application of these densely functionalized amino acids is in the area of peptidomimetics, provided that they can be incorporated into simple peptides. As a matter of fact, cyclic and/or sterically crowded amino acids often exhibit a rather poor reactivity in peptide couplings with natural amino acids. Accordingly, the reactivity of the synthesized β-homoprolines had to be tested.

The synthesized homoprolines have the convenient feature to be protected at the amino group, therefore they can be directly used in peptide synthesis. The carboxyl group of **15** and **17** underwent condensation with L-Phe-OMe under standard conditions, affording the pseudodipeptides **21** and **22** in 77−79% yield (Scheme 5). After removal of the trifluoroacetyl group in **22**, any attempt to couple **23** with L-Fmoc-Val and even with the less sterically demanding Boc-Gly totally failed (Scheme 5).

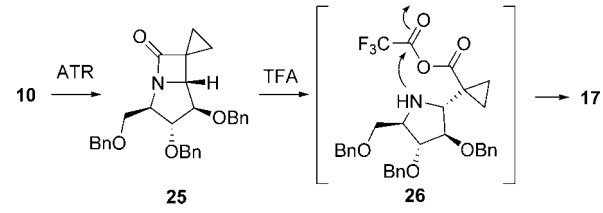
This failure is probably due to the pyrrolidine substituents that sterically interfere with the accessibility of the nitrogen atom. By analogy with the formation of **17**, which presumably involves the initial formation of a mixed anhydride by trifluoroacetolysis of carbapenam **25** followed by O−N trifluoroacetyl shift (Scheme 6),[17] the N-acylation should be easily available through an intramolecular approach. Participation of a transitional mixed anhydride was also postulated in the N-acylation of pyroglutamic acid under mild conditions.[24,25]

To test this hypothesis, a suitable mixed anhydride was necessary. The trifluoroacetamide group in **17** was hydrolyzed to obtain the unprotected amino acid **27**. Deprotonation of **27** with *N*-methylmorpholine (NMM) and treatment with the

SCHEME 5



SCHEME 6



active ester **A**, generated in situ from L-Boc-Phe-OH, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **28**), and NMM,[26] by heating at 60 °C for 30 min under microwave irradiation, gave amide **29** in 70% yield after chromatographic purification (Scheme 7). As expected, no formation of the homodimer of the deprotected amino acid **27** was observed. The formation of the mixed anhydride **B** could not be directly observed, but the success of N-acylation of the unprotected amino acid clearly supports the existence of such intermediate[24,25] and indicates that a 6-*exo-trig* cyclization in **B** is stereoelectronically viable.

Finally, the coupling of **29** with L-Val-OMe under standard conditions afforded the pseudotripeptide **30** in satisfactory yield of 47%.

Conclusions

In conclusion, the 1,3-DC/ATR two-step process has been applied to several cyclic nitrones using BCP as dipolarophile. Six-membered ring nitrones afforded cyclopropanated β-lactams or β-homopipecolic acids in moderate yields, whereas pyrroline *N*-oxides gave α-cyclopropane-β-homoprolines in good overall yields.

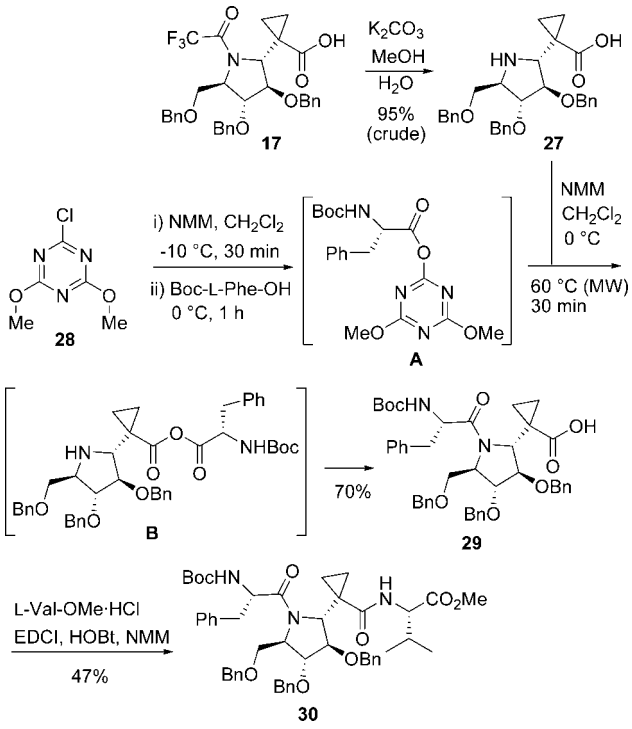
Particularly interesting was the use of enantiopure hydroxylated pyrroline *N*-oxides for the selective synthesis of highly functionalized β-amino acids. The tribenzyloxy derivative **23** could not be directly coupled at the nitrogen with natural amino acids, but this problem was nicely overcome by performing an intramolecular N-acylation through the intermediate formation

(24) Imaki, K.; Niwa, H.; Sakuyama, S.; Okada, T.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1981**, *29*, 2699–2701.

(25) For a recent approach to dipeptides of hindered α-amino acids through the formation of a transient anhydride and related reactions, see: Brown, Z. Z.; Schafmeister, C. E. *J. Am. Chem. Soc.* **2008**, *130*, 14382–14383, and references therein.

(26) (a) Kamiński, Z. J. *Synthesis* **1987**, 917–920. (b) Kamiński, Z. J. *Biopolymers (Pept. Sci.)* **2000**, *55*, 140–164.

SCHEME 7



of a mixed anhydride. In particular, the successful incorporation of the highly functionalized and sterically encumbered amino acid **27** into the pseudotripeptide **30** suggests that the synthesized α-cyclopropane-*β*-homoprolines can be used as building blocks in the synthesis of peptidomimetics.

Experimental Section

1-[2-(Methoxycarbonyl)-1-(trifluoroacetyl)-2-pyrrolidinyl]cyclopropanecarboxylic Acid (13a). A mixture of **4a** (30 mg, 0.13 mmol) and TFA (0.016 mL, 0.20 mmol) in CH_3CN (3 mL) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (petroleum ether/AcOEt/TFA = 1:1:0.01) to give **13a** (26 mg, 62%) as a waxy solid. R_f = 0.35. ^{1}H NMR (400 MHz, CD_3OD): δ 3.98−3.90 (m, 1H; 5-H_a), 3.78−3.70 (m, 1H; 5-H_b), 3.70 (s, 3H; OCH_3), 2.64−2.48 (m, 2H; 3-H), 2.11−1.88 (m, 2H; 4-H), 1.37−1.15 (m, 3H; *c*-Pr), 1.00−0.94 (m, 1H; *c*-Pr) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ 175.8 (s; CO_2H), 172.2 (s; CO_2Me), 157.2 (q, J_{C-F} = 36.4 Hz; *C*OCF_3), 117.6 (q, J_{C-F} = 287.2 Hz; CF_3), 74.1 (s; C-2), 53.2 (q, CH_3), 50.5 (tq, J_{C-F} = 3.9 Hz; C-5), 38.5 (t; C-3), 28.1 (s; *c*-Pr), 24.7 (t; C-4), 15.7 (t; *c*-Pr), 14.0 (t; *c*-Pr) ppm. IR (KBr): υ 3031, 2955, 1788, 1733, 1698, 1448, 1436, 1238, 1153 cm^{-1}. MS (ESI): 308.3 [M − H]$^-$. $C_{12}H_{140}F_3NO_5$ (309.24): calcd C 46.61, H 4.56, N 4.53; found C 46.72, H 4.81, N 4.36.

1-[2-(*tert*-Butoxycarbonyl)-1-(trifluoroacetyl)-2-pyrrolidinyl]cyclopropanecarboxylic Acid (13b). A mixture of **4b** (53 mg, 0.20 mmol) and TFA (0.03 mL, 0.39 mmol) in MeCN (3 mL) was heated at 70 °C for 26 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (petroleum ether/AcOEt = 2:1) to give **13b** (22 mg, 63%) as a waxy solid. R_f = 0.14. ^{1}H NMR (400 MHz): δ 3.97−3.89 (m, 1H; 5-H_a), 3.66 (dt, J = 7.0, 10.1 Hz, 1H; 5-H_b), 2.55−2.44 (m, 2H; 3-H), 2.06−1.86 (m, 2H; 4-H), 1.45−1.36 (m, 3H; *c*-Pr), 1.43 (s, 9H; CH_3), 1.10−1.03 (m, 1H; *c*-Pr) ppm. ^{13}C NMR (50 MHz): δ 178.5 (s; CO_2H), 168.6 (s; CO_2t-Bu), 155.8 (q, J_{C-F} = 36.5 Hz; *C*OCF_3), 116.2 (q, J_{C-F} = 287.8 Hz; CF_3), 82.8 (s; CMe_3), 72.7 (s; C-2), 49.0 (tq, J_{C-F} = 4.0 Hz; C-5), 37.5 (t; C-3), 27.7 (q, 3C; CH_3), 27.4 (s; *c*-Pr), 23.8 (t; C-4), 16.0 (t; *c*-Pr), 14.7 (t; *c*-Pr) ppm. IR: υ 2979, 2932, 1726, 1699, 1602, 1456, 1370, 1237, 1214, 1151 cm^{-1}. MS (EI): *m*/*z* (%) 351 (0.1, M$^+$), 278 (4), 250 (41), 232 (80), 204 (20), 182(15), 136 (14), 69 (24), 57 (100). HRMS: calcd for $C_{15}H_{19}F_3NO_5$ [M − H]$^-$ 350.12098, found 350.12058.

1-[(2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-1-(trifluoroacetyl)pyrrolidinyl]-cyclopropanecarboxylic Acid (14). A mixture of **7a** (50 mg, 0.16 mmol) and TFA (19 μL, 0.24 mmol) in toluene (4.0 mL) in a sealed vial was irradiated in a microwave reactor using an irradiation power of 150 W (with simultaneous cooling) at 55−61 °C for 10 min. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (pentane/AcOEt/TFA = 4: 1: 0.01) to give **14** (58 mg, 91%) as a pale yellow oil. R_f =0.30. $[\alpha]^{24}_D$ = +10.1 (*c* 0.78, $CHCl_3$). ^{1}H NMR (400 MHz): δ 4.19−4.15 (m, 2H; 2-H, 3-H), 3.94−3.87 (m, 1H; 5-H_a), 3.85−3.79 (m, 1H; 4-H), 3.55 (dd, J = 11.0, 4.8 Hz, 1H; 5-H_b), 1.56−1.49 (m, 1H; *c*-Pr), 1.44−1.37 (m, 1H; *c*-Pr), 1.36−1.28 (m, 1H; *c*-Pr), 1.23 (s, 9H; *t*Bu), 1.19 (s, 9H; *t*Bu), 1.08−1.01 (m, 1H; *c*-Pr) ppm. ^{13}C NMR (100 MHz): δ 180.2 (s; CO_2H), 156.4 (q, J_{CF} = 36.3 Hz; *C*OCF_3), 116.3 (q, J_{CF} = 288.1 Hz; CF_3), 78.3 (d; C-3), 75.4 (d; C-4), 75.1 (s; *t*Bu), 74.5 (s; *t*Bu), 66.5 (d; C-2), 53.2 (tq; J_{CF} = 3.1 Hz; C-5), 28.9 (q, 3C; CH_3), 28.3 (q, 3C; CH_3), 24.2 (s; *c*-Pr), 18.3 (t; *c*-Pr), 15.4 (t; *c*-Pr) ppm. IR ($CDCl_3$): υ 2959, 2933, 2871, 2254, 1730, 1690, 1464, 1367, 1190 cm^{-1}. MS (EI): *m*/*z* 395 (0.3, M$^+$), 338 (1), 296 (15), 282 (2), 264 (10), 240 (51), 222 (20), 128 (16), 100 (24), 57 (100). $C_{18}H_{28}F_3NO_5$ (395.41): calcd C 54.68, H 7.14, N 3.54; found C 54.96, H 7.16, N 3.32.

1-[(2*R*,3*S*)-3-*tert*-Butoxy-1-(trifluoroacetyl)pyrrolidinyl]cyclopropanecarboxylic Acid (15). A mixture of **8** (570 mg, 2.4 mmol) and TFA (0.28 mL, 3.6 mmol) in toluene (49.5 mL) in a sealed vial was irradiated in a microwave reactor using an irradiation power of 150 W (with simultaneous cooling) at 55−65 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give **15** (567 mg, 73%) as a colorless solid. R_f = 0.27. Mp 111−112 °C. $[\alpha]^{24}_D$ = +24.6 (*c* 0.61, $CHCl_3$). ^{1}H NMR (400 MHz): δ 4.46 (dt, J = 4.9, 6.1 Hz, 1H; 3-H), 3.92−3.84 (m, 1H, 5-H_a), 3.80−3.71 (m, 1H, 5-H_b), 3.58 (d, J = 4.7 Hz, 1H; 2-H), 2.24 (dddd, J = 12.8, 6.7, 6.1, 4.5 Hz, 1H; 4-H_a) 1.85−1.76 (m, 1H, 4-H_b), 1.52 (ddd, J = 9.8, 7.6, 4.7 Hz, 1H; *c*-Pr), 1.42−1.36 (m, 1H; *c*-Pr), 1.32−1.24 (m, 1H; *c*-Pr), 1.21 (s, 9H; CH_3), 1.14 (ddd, J = 9.3, 7.7, 4.2 Hz, 1H; *c*-Pr) ppm. ^{13}C NMR (50 MHz): δ 179.6 (s; CO_2H), 156.0 (q, J_{C-F} = 36.2 Hz; *C*OCF_3), 116.3 (q, J_{C-F} = 287.8 Hz; CF_3), 74.5 (s; CMe_3), 74.3(d; C-3), 68.4 (d; C-2), 46.5 (tq, J_{C-F} = 3.5 Hz; C-5), 34.2 (t; C-4), 28.6 (q, 3C; CH_3), 23.7 (s; *c*-Pr), 17.7 (t; *c*-Pr), 15.1 (t; *c*-Pr) ppm. IR (KBr): υ 3600−2800, 2985, 1720, 1687, 1447, 1397, 1203, 1141, 1000, 758, 613 cm^{-1}. MS (EI): *m*/*z* 323 (0.3, M$^+$), 267 (9), 250 (6), 198 (23), 156 (14), 69 (14), 57 (100). $C_{14}H_{20}F_3NO_4$ (323.31): calcd C 52.01, H 6.24, N 4.33; found C 52.18, H 6.09, N 4.43.

1-[(3a*S*,4*S*,6a*R*)-2,2-Dimethyl-5-(trifluoroacetyl)tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]cyclopropanecarboxylic Acid (16). A mixture of **9** (50 mg, 0.21 mmol) and TFA (24 μL, 0.32 mmol) in toluene (5.2 mL) in a sealed vial was irradiated in a microwave reactor using an irradiation power of 150 W (with simultaneous cooling) at 55−70 °C for 35 min. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (pentane/Et_2O = 2:3) to give **16** (52 mg, 77%) as a uncolored crystalline solid. Crystallization from diethyl ether and petroleum ether afforded crystals suitable for X-ray analysis. R_f = 0.32. Mp 117−118 °C. $[\alpha]^{24}_D$ = +7.4 (*c* 0.57, $CHCl_3$). ^{1}H NMR (400 MHz): δ 4.98 (pseudo t, J = 5.4 Hz, 1H; 6a-H), 4.91 (dd, J = 6.1, 1.3 Hz, 1H; 3a-H), 4.14 (dd, J = 12.3, 5.0 Hz, 1H; 6-H_a), 3.95 (br d, J = 12.3 Hz, 1H; 6-H_b), 3.72 (br s, 1H; 4-H), 1.77 (ddd, J = 9.5, 7.6, 4.9 Hz, 1H; *c*-Pr), 1.59 (ddd, J = 9.9, 7.5, 4.9 Hz, 1H;

c-Pr), 1.40 (s, 3H; CH_3), 1.38 (ddd, J = 9.9, 7.6, 4.3 Hz, 1H; *c*-Pr), 1.32 (s, 3H; CH_3), 1.15 (ddd, J = 9.5, 7.5, 4.3 Hz, 1H; *c*-Pr) ppm. ^{13}C NMR (100 MHz): δ 179.8 (s; CO_2H), 156.9 (q, J_{C-F} = 36.9 Hz; $COCF_3$), 116.3 (q, J_{C-F} = 287.8 Hz; CF_3), 112.0 (s; C-2), 83.7 (d; C-3a), 80.1 (d; C-6a), 70.8 (d; C-4), 53.4 (tq, J_{C-F} = 3.3 Hz; C-6), 26.8 (q, 3C; CH_3), 26.1 (s; *c*-Pr), 24.7 (q, 3C; CH_3), 17.8 (t; *c*-Pr), 16.3 (t; *c*-Pr) ppm. IR: ν 3500, 3400−2600, 2992, 1693, 1448, 1384, 1253, 1206, 1154 cm^{-1}. MS (EI): *m*/*z* 323 (0.9, M^+), 308 (100), 266 (14), 248 (64), 202 (69), 196 (30), 135 (22), 67 (23), 57 (57). $C_{13}H_{16}F_3NO_5$ (323.27): calcd C 48.30, H 4.99, N 4.33; found C 48.01, H 5.08, N 4.00.

1-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]-1-(trifluoroacetyl)pyrrolidinyl]cyclopropanecarboxylic Acid (17). A mixture of **10** (1 g, 2.01 mmol) and TFA (0.23 mL, 2.98 mmol) in toluene (50 mL) was heated at 110 °C for 10 min. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel (petroleum ether/AcOEt = 3:1) to give **17** (1.1 g, 94%) as a yellow oil. The NMR analysis revealed the presence of two conformers; only signals corresponding to the major one are given. R_f = 0.24. $[\alpha]^{21}_D$ = −10.2 (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, major conformer): δ 7.44−7.25 (m, 15 H; Ph), 5.08 (br s, 1H; 2-H), 4.71−4.44 (m, 7H; OCH_2Ph, 5-H), 4.14 (br s, 1H; 4-H), 4.04 (br s, 1H; 3-H), 3.71 (pseudo t, J = 9.4 Hz, 1H; C*H*HOBn), 3.57 (dd, J = 9.2, 5.3 Hz, 1H; C*H*HOBn), 1.50−1.42 (m, 3H; *c*-Pr), 0.93−0.84 (m, 1H; *c*-Pr) ppm. ^{13}C NMR (100 MHz, major conformer): δ 180.48 (s; CO_2H), 157.2 (q, J_{C-F} = 37.1 Hz; $COCF_3$), 137.4 (s; Ph), 137.2 (s; Ph), 136.9 (s; Ph), 128.5−127.6 (d, 15C; Ph), 116.1 (q, J_{C-F} = 288.2 Hz; CF_3), 84.5 (d; C-3), 82.7 (d; C-4), 73.2 (t; OCH_2Ph), 71.6 (t; OCH_2Ph), 71.3 (t; OCH_2Ph), 69.2 (t; CH_2OBn), 65.3 (d; C-2), 63.8 (dq, J_{C-F} = 2.6 Hz; C-5), 25.5 (s; *c*-Pr), 18.7 (t; *c*-Pr), 14.5 (t; *c*-Pr) ppm. IR: ν 3033, 2928, 2867, 1691, 1455, 1204, 1155, 1099 cm^{-1}. MS (EI): *m*/*z* (%) 583 (0.04, M^+), 492 (5), 386 (51), 354 (6), 253 (7), 181 (13), 91 (100). $C_{32}H_{32}F_3NO_6$ (583.59): calcd C 65.86, H 5.53, N 2.40; found C 65.76, H 5.83, N 2.32.

1-{(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]pyrrolidinyl}cyclopropanecarboxylic Acid (27). K_2CO_3 (4.368 g, 31.61 mmol) was added to a solution of **17** (1.274 g, 2.18 mmol) in H_2O/MeOH (8.7 mL/21.7 mL) cooled at 0 °C. The mixture was heated at 60 °C for 20 h and then concentrated under reduced pressure, and a solution of $KHSO_4$ (9.045 g, 66.42 mmol) in H_2O (200 mL) was added at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, **27** (1.007 g, 95%) was obtained as a colorless solid that was pure enough to be used in the next step of the synthesis without further purification. An analytically pure sample was obtained by flash chromatography on silica gel (AcOEt/MeOH = 10:1). R_f = 0.10. Mp 136−137 °C. $[\alpha]^{23}_D$ = −14.3 (*c* 1.12, EtOH). ^{1}H NMR (400 MHz): δ 7.38−7.22 (m, 15H; Ph), 4.62−4.40 (m, 6H; OCH_2Ph), 4.16−4.07 (m, 1H; 3-H), 3.88−3.82 (m, 1H; 4-H), 3.67−3.41 (m, 3H; 5-H, CH_2OBn), 2.79−2.70 (m, 1H; 2-H), 1.55−1.45 (m, 1H; *c*-Pr), 1.18−1.07 (m, 1H; *c*-Pr), 0.95−0.86 (m, 1H; *c*-Pr), 0.73−0.63 (m, 1H; *c*-Pr) ppm. ^{13}C NMR (50 MHz): δ 177.3 (s; CO_2H), 137.2 (s; Ph), 136.9 (s; Ph), 136.8 (s; Ph), 128.33 (d, 2C; Ph), 128.29 (d, 2C; Ph), 128.2 (d, 2C; Ph), 128.0 (d, 2C; Ph), 127.93 (d, 1C; Ph), 127.89 (d, 3C; Ph), 127.7 (d; Ph), 127.5 (d, 2C; Ph), 84.0 (d; C-3), 81.5 (d; C-4), 73.3 (t; OCH_2Ph), 73.2 (t; OCH_2Ph), 72.5 (t; OCH_2Ph), 66.4 (t; CH_2OBn), 66.1 (d; C-2), 60.3 (d; C-5), 21.0 (s; *c*-Pr), 16.6 (t; *c*-Pr), 14.5 (t; *c*-Pr) ppm. MS (EI): *m*/*z* = 488 (M^+, 1), 396 (16), 366 (62), 230 (8), 169 (16), 126 (15), 91 (100). IR ($CDCl_3$): ν 3032, 2927, 2867, 1725 1605, 1497, 1454, 1364, 1265, 1092 cm^{-1}. $C_{30}H_{33}NO_5$ (487.59): calcd C 73.90, H 6.82, N 2.87; found C 73.50, H 6.77, N 2.50.

1-((2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]-1-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoyl}pyrrolidinyl)cyclopropanecarboxylic Acid (29). A solution of CDMT (102 mg, 0.58 mmol) and NMM (0.067 mL, 0.58 mmol) in anhydrous CH_2Cl_2 (0.1 mL) was stirred at −10 °C for 30 min. Boc-L-phenylalanine (154 mg, 0.58 mmol) was added at 0 °C, the reaction mixture was stirred for 1 h, and then a solution of **27** (236 mg, 0.48 mmol) and NMM (107 μL, 0.98 mmol) in anhydrous CH_2Cl_2 (0.2 mL) was added at 0 °C. The reaction mixture was then heated in the microwave reactor (50 W, 60 °C) for 30 min, cooled to rt, and diluted with CH_2Cl_2. The solution was sequentially washed with a 10% aqueous solution of $KHSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (toluene/Et_2O = 2:1) to afford **29** (248 mg, 70%) as a colorless oil. The NMR analysis revealed the presence of two conformers. R_f =0.22. $[\alpha]^{21}_D$ = −21.5 (*c* 0.65, EtOH). ^{1}H NMR (400 MHz, mixture of conformers): δ 7.41−6.90 (m, 20H; Ph), 5.45 (d, J = 8.9 Hz) and 5.36 (br d, J = 8.2 Hz, 1H, N*H*Boc), 4.95−4.86 and 4.80−4.70 (m, 2H; C*H*CH_2Ph, 2-H), 4.66−4.28 (m, 6 H; OCH_2Ph), 4.27−3.58 (m, 4H; 3-H, 4-H, 5-H, C*H*HOBn), 3.05−2.84 (m, 3H; $CHCH_2Ph$, C*H*HOBn), 1.50−0.75 (m, 4H; *c*-Pr), 1.39 and 1.38 (s, 9H; *t*Bu) ppm. ^{13}C NMR (50 MHz, major conformer): δ 178.5 (s; CO_2H), 172.4 (s; N*C* = O), 154.5 (s; NCO_2tBu), 138.2 (s; Ph), 137.8 (s; Ph), 137.3 (s; Ph), 135.5 (s; Ph), 129.4−126.8 (d, 20C; Ph), 87.1 (d; C-3), 82.9 (d; C-4), 79.6 (s; *t*Bu), 72.9 (t; OCH_2Ph), 71.04 (t; OCH_2Ph), 70.98 (t; OCH_2Ph), 66.6 (t; CH_2OBn), 64.3 (d; C-5), 62.4 (d; C-2), 53.8 (d; N*C*HCH_2Ph), 40.9 (t; NCH*C*H_2Ph), 29.6 (s; *c*-Pr), 28.3 (q, 3C; *t*Bu), 15.6 (t; *c*-Pr), 14.7 (t; *c*-Pr) ppm. MS (ESI): 735 (MH^+); IR ($CDCl_3$): ν 3432, 3032, 2928, 1706, 1641, 1497, 1455, 1368, 1166, 1098 cm^{-1}. $C_{44}H_{50}N_2O_8$ (734.88): calcd C 71.91, H 6.86, N 3.81; found C 71.66, H 7.12, N 4.07.

Methyl (2*S*)-2-({[1-((2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-[(benzyloxy)methyl]-1-{(2*S*)-2-[(*tert*-butoxycarbonyl) amino]-3-phenylpropanoyl}pyrrolidinyl)cyclopropyl]carbonyl}amino)-3-methylbutanoate (30). NMM (0.042 mL, 0.38 mmol) was added to a solution of **29** (70 mg, 0.09 mmol) and L-valine methyl ester hydrochloride (32 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C. After 30 min, HOBt (26 mg, 0.19 mmol) and EDCI (36 mg, 0.19 mmol) were added at 0 °C, and the mixture was stirred at rt for 5 h. The reaction mixture was sequentially concentrated, diluted with AcOEt, washed with a saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4 filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (toluene/Et_2O = 5:1) to afford **30** (38 mg, 47% yield) as a colorless oil. The NMR analysis revealed the presence of two conformers. R_f = 0.29. $[\alpha]^{23}_D$ = −137.1 (*c* 0.49, EtOH). ^{1}H NMR (400 MHz, mixture of conformers): δ 8.46−8.32 and 7.83−7.74 (m, 1H; NH_{Val}), 7.38−7.04 (m, 20H; Ph), 5.45 (br d, J = 9.6 Hz) and 5.22−5.16 (m, 1H, N*H*Boc), 4.97−4.86 (m, 1H; C*H*CH_2Ph), 4.62−4.25 (m, 8 H; 3-H, NHC*H*$CHMe_2$, OCH_2Ph × 3), 4.23−3.93 (m, 3H; 2-H, 4-H, 5-H), 3.80−3.60 (m, 1H; C*H*HOBn), 3.77 and 3.62 (br s, 3H; OMe), 3.09−2.73 (m, 3H; $CHCH_2Ph$, C*H*HOBn), 2.31−2.14 (m, 1H; C*H*Me_2), 1.44−0.62 (m, 4H; *c*-Pr), 1.40 and 1.37 (br s, 9H; *t*Bu), 0.99 (br d, J = 6.8 Hz) and 0.97 (d, J = 6.9 Hz, 6H; CHMe_2) ppm. ^{13}C NMR (50 MHz, major conformer): δ 173.8 (s; CO), 172.7 (s; CO), 172.4 (s; CO), 154.8 (s; NCO_2tBu), 138.2 (s, 2C; Ph), 137.2 (s; Ph), 135.1 (s; Ph), 129.4−126.8 (d, 20C; Ph), 87.4 (d; C-3), 83.3 (d; C-4), 79.8 (s; *t*Bu), 72.8 (t; OCH_2Ph), 70.9 (t, 2C; OCH_2Ph), 66.5 (t; CH_2OBn), 64.2, 64.5 (d; C-2, C-5), 58.1(d; N*C*H$CHMe_2$), 53.5 (d; N*C*HCH_2Ph), 51.8 (q; OCH_3), 41.6 (t; NCH*C*H_2Ph), 30.6 (s; *c*-Pr), 30.0 (d; *C*HMe_2), 28.2 (q, 3C; *t*Bu), 19.1 (q; CH*C*H_3), 18.2 (q; CH*C*H_3), 14.1 (t; *c*-Pr), 9.9 (t; *c*-Pr) ppm. MS (ESI): 848 (MH^+), 870 [$(M + Na)^+$], 886 [$(M + K)^+$]. IR ($CDCl_3$): ν 3673, 3433, 3307, 3032, 2969, 2932, 1740, 1699,

1641, 1498, 1367, 1167, 1098 cm^{-1}. $C_{50}H_{61}N_3O_9$ (848.03): calcd C 70.81, H 7.25, N 4.96; found: C 71.21, H 7.08, N 4.68.

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Supporting Information Available: Experimental procedures, characterization data for compounds **4a**, **4b**, **5b**, **7a**, **7b**, **18**, **19**, **21**, **22**, and **23**. ^1H and ^{13}C NMR spectra for all new compounds. X-ray crystallographic analysis of **16** (CCDC 722377). This material is available free of charge via the Internet at http://pubs.acs.org.

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