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Enantioselective synthesis of cyclopropane aminoalcohols containing quaternary stereogenic centers

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Abstract

Some title compounds have been synthesized in enantiomerically pure form starting from D- or L-glyceraldehyde as chiral precursors. A new synthesis of (+)-(*Z*)-methanohomoserine, one of the key intermediates employed, is also described. The target molecules are densely functionalized. Thus, in addition to one or two hydroxyl groups on a side-chain, an amino group is attached to a quaternary carbon of the cyclopropane ring, and the fourth substituent of such a stereogenic center contains a halogen atom, an alkyl group, or an alcohol, thioether or ester function. Some of these compounds are useful precursors in the synthesis of new cyclopropane nucleosides.

1. Introduction

Compounds containing an amine function and one or more hydroxyl groups are of great interest due either to their intrinsic properties or for use as powerful synthetic intermediates. The 1,2-aminoalcohol function is present in the widely consumed drug propanolol, a β-blocking agent, and in the structure of serine protease inhibitors.[1] Aminoalcohols bearing a cyclic moiety in their structure have been described as displaying relevant activities. Thus, for instance, chiral pyrrolidines with amino and hydroxymethyl groups inhibit α-glycosidases.[2] Six-membered ring molecules containing 1,2- and 1,3-aminoalcohol functions have been used for phosphodiester recognition allowing aminoglycoside antibiotics with activity against HIV to be designed.[3] Moreover, 1,2-, 1,3-, and, less frequently, 1,4-aminoalcohols are useful as chiral ligands for catalysts[4] or as chiral auxiliaries in asymmetric synthesis.[5] Some representantives of these different types of compounds are shown in Fig. 1. Finally, aminoalcohol molecules containing a cyclopropane ring have been employed as key intermediates in the synthesis of carbocyclic nucleosides.[6]

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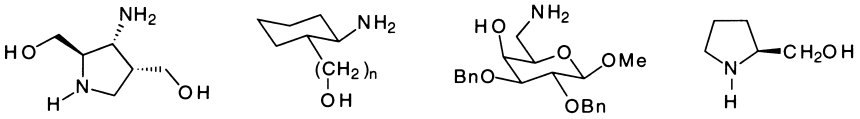


Figure 1.

In this paper we describe stereoselective synthetic routes to several types of enantiomerically pure cyclopropane aminoalcohols **1**–**4** and some conveniently protected derivatives (Fig. 2). All these compounds contain one or two hydroxyl groups and one amino group in 1,2- or 1,3-relative positions.

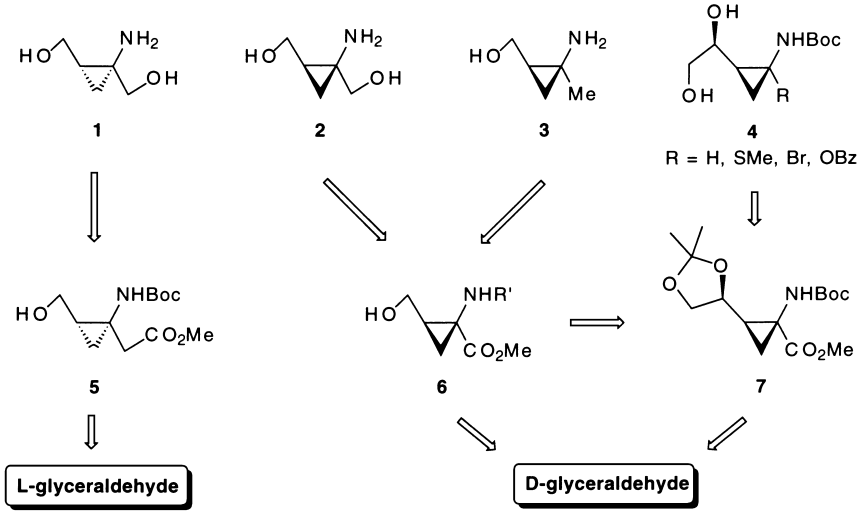


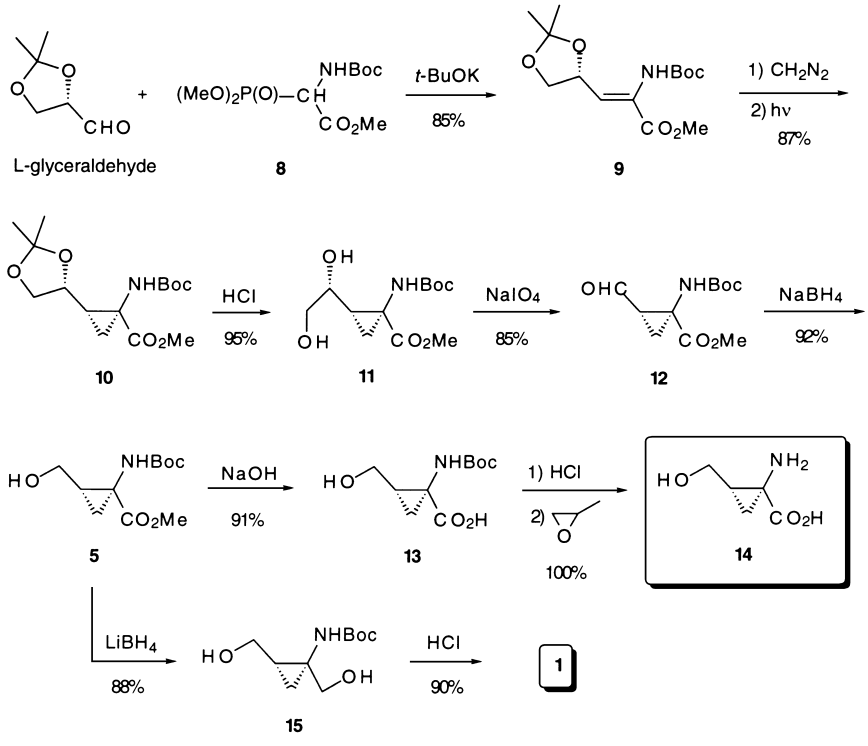
Figure 2.

Moreover, these molecules contain a quaternary carbon in the cyclopropane ring linked to an amino group and to a substituent containing different chemical functions. These structures are, therefore, densely functionalized and highly sterically constrained. *gem*-Disubstitution in conformationally restricted cyclopropane derivatives is a structural feature present in NMDA receptor antagonists related to Milnacipran®.[7] Furthermore, some *gem*-disubstituted cyclopropane carbocyclic nucleosides have been recently revealed to be potent anti-HIV agents.[8]

The syntheses achieved in this work are highly efficient and versatile, since divergent pathways from common precursors lead to different types of products. Some of these compounds have been prepared in both enantiomeric forms starting, alternatively, from (+)- and (−)-(*Z*)-methanohomoserine derivatives **5** and **6**, respectively. A new synthesis of free amino acid (+)-**14** (Scheme 1) is reported herein starting from L-glyceraldehyde as the chiral precursor. (*Z*)-Methanohomoserine is a useful precursor in the synthesis of other cyclopropane amino acids,[9] and it is also an analogue of the precursor to the plant growth hormone ethylene, being processed by the in vivo ethylene-forming enzyme (EFE) to produce allylic alcohol.[10] In addition to the free aminoalcohols, some partially protected derivatives have also been prepared, these products being convenient synthetic building blocks.

2. Results and discussion

The main targets and precursors are shown in Fig. 2. Aminoalcohol **1** as well as its *N*-Boc derivative **15** (Scheme 1) have been obtained from protected (+)-(*Z*)-methanohomoserine **5**. This product and



Scheme 1.

amino acid **14** have been synthesized from L-glyceraldehyde prepared, in turn, from L-gulonolactone.[11] The enantiomeric aminodiol **2**, aminoalcohol **3**, and some derivatives have been synthesized from **6**. Finally, the latter compound and aminoalcohols **4** result from the common precursor **7** obtained from D-glyceraldehyde.

*2.1. Synthesis of aminodiol **1** and (+)-(Z)-methanohomoserine **14***

The synthetic pathway is depicted in Scheme 1, the key common intermediate being compound **5** that, after deprotection, affords free amino acid **14** and, in addition, is susceptible of reduction to diol **15** which is the immediate precursor of aminodiol **1**.

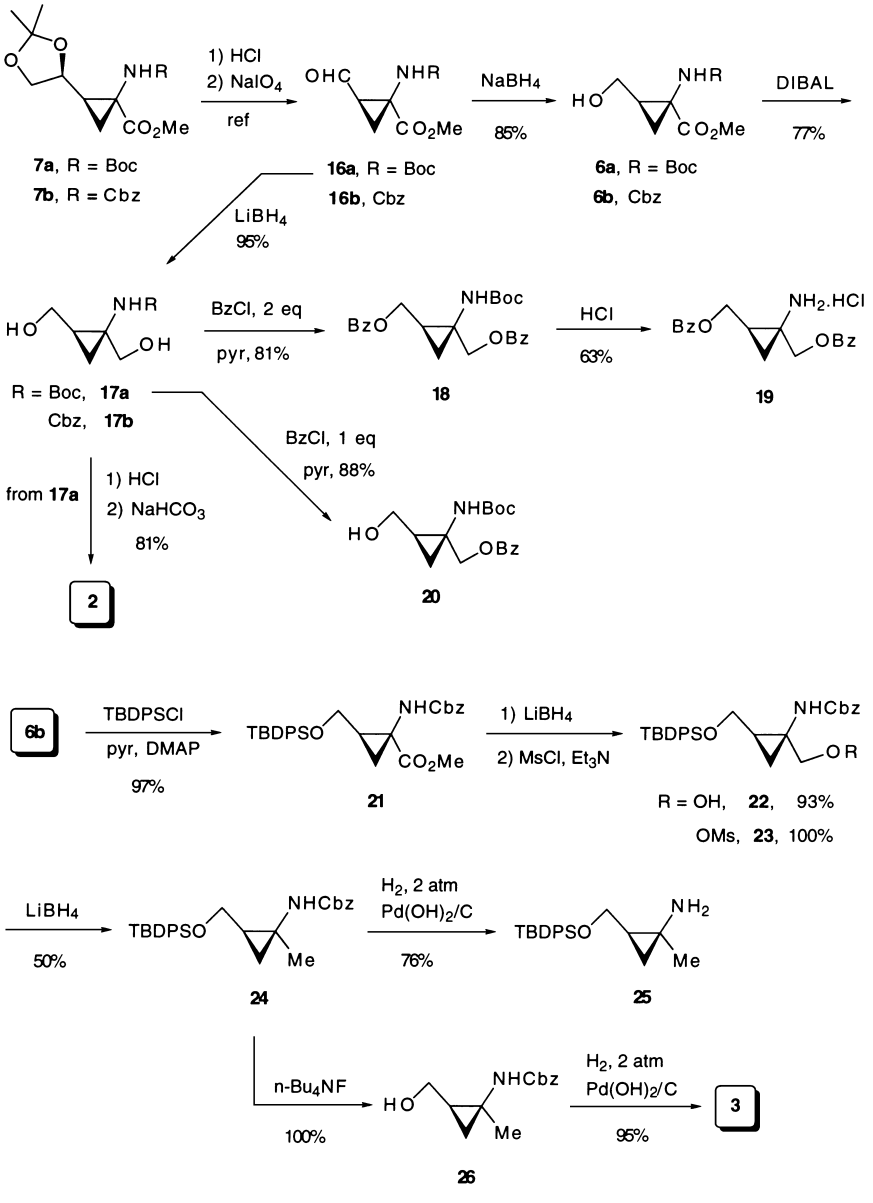
Compound **5** was prepared by using the same methodology earlier employed in our laboratory for the synthesis of its enantiomer from D-glyceraldehyde.[9] Actually, L-glyceraldehyde was condensed with phosphonate **8**,[9] in the presence of potassium *tert*-butoxide, affording aminopentenoate **9** as the major isomer (85% yield). Cyclopropanation of the double bond was accomplished by highly stereoselective 1,3-dipolar cycloaddition of diazomethane to **9** followed by photolysis of the resultant pyrazoline. In this way, cyclopropane **10** was obtained in 87% yield for the two steps. Hydrolysis of the acetonide and subsequent oxidative cleavage of diol **11** gave aldehyde **12** which was reduced to alcohol **5** with $NaBH_4$. The free amino acid **14** was prepared by saponification of the methyl ester with methanolic sodium hydroxide followed by hydrolysis of the carbamate with 1 M HCl and subsequent treatment with propylene oxide as acid captor. (+)-(*Z*)-Methanohomoserine was thus obtained in 50% overall yield from L-glyceraldehyde. It is noteworthy that this synthetic sequence competes advantageously with other methods previously described for the preparation of this amino acid.[10]

Following a divergent route, compound **5** was reduced by $LiBH_4$ giving diol **15** in 88% yield which was

deprotected by hydrolysis of the carbamate with 1 M HCl followed by treatment with sodium bicarbonate. Aminodiol **1** was thus obtained in 43% overall yield from L-glyceraldehyde.

2.2. *Synthesis of aminoalcohols **2**, **3**, and some derivatives*

The starting materials were compounds **7a**,**b** (Scheme 2) prepared from D-glyceraldehyde by using the same protocol explained above for the synthesis of **10**.



Scheme 2.

Hydrolysis of the acetonide followed by diol oxidation afforded aldehydes **16a**,**b** which were reduced to alcohols **6a**,**b**, respectively.[9] Compound **6b** is, in turn, the precursor of aminoalcohol **3**. Thus, the ester group in **6b** was reduced with DIBAL affording diol **17b** in 77% yield. Diols **17a**,**b** were also obtained

from **6a**,**b** in 95% when $LiBH_4$ was used as reducing agent. Nevertheless, the yield was improved and the synthetic sequence shortened when one-pot reduction of both aldehyde and ester groups in **16a** was achieved with $LiBH_4$, obtaining **17a** in 95% yield. Hydrolysis of the *N*-Boc group by the usual method gave free aminodiol **2** in 66% yield from **7a** (49% yield from D-glyceraldehyde).

Derivatives **18**–**20** were also prepared in order to dispose of selectively protected products. Thus, reaction of **17a** with 2.5 equivalents of benzoyl chloride in the presence of pyridine, at room temperature for 16 h, afforded **18** that led to **19** after hydrolysis with HCl. Treatment of **19** with sodium bicarbonate liberated the amine which was an unstable oil being, therefore, characterized as the hydrochloride. In addition, diol **17a** was chemoselectively monoprotected by reaction with 1 equivalent of benzoyl chloride at room temperature for 3 h to afford **20** in 88% yield, thus showing the different reactivity of the two hydroxyl groups.

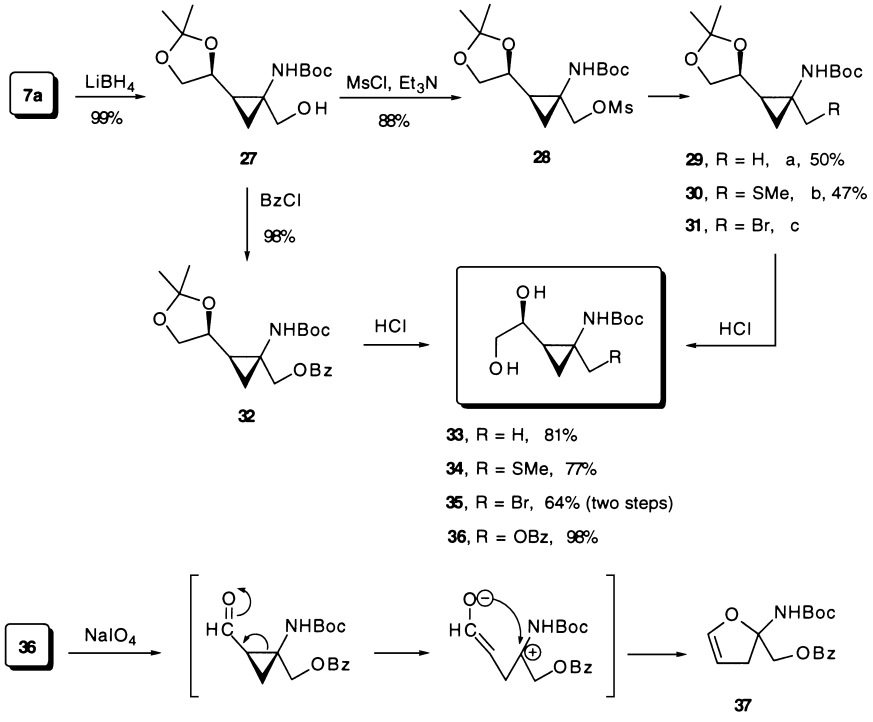
The protected (−)-(*Z*)-methanohomoserine derivative **6b** was the key intermediate in the synthesis of aminoalcohol **3**. The required chemical transformations involve reduction of the methyl ester to methyl group and deprotection of the amine. Previously, the hydroxyl group in **6** was protected as *tert*-butyldiphenylsilyl ether in almost quantitative yield. Then, ester **21** was reduced with $LiBH_4$ and the resultant alcohol **22** was converted into mesylate **23** under standard conditions with 93% yield for the two steps. The instability of this compound under the usual purification conditions forced the use of the crude product in subsequent transformations. This fact, as well as the low reactivity observed for **23**, could account for the unsatisfactory results obtained when it was reacted with several nucleophiles, and for the modest yield (50%) in its reduction to furnish **24**. Compound **24** is orthogonally protected and leads, alternatively, to products **25** and **26** in which only the amino or the hydroxyl group is free, conferring on these molecules the ability to be selectively elaborated in further transformations. Thus, hydrogenation under two atmospheres pressure, in the presence of palladium hydroxide as catalyst, gave amine **25**. On the other hand, treatment of **24** with *n*-Bu_4NF afforded alcohol **26**. Finally, reductive carbamate-removal led to the free aminodiol **3**.

*2.3. Synthesis of aminodiols **33**–**36***

Compound **7a** was the precursor of these products (Scheme 3). The synthetic goal involved specific chemical transformation of the ester group into the desired substituents, while keeping the amine and the diol functions conveniently protected.

Methyl ester in **7a** was reduced with $LiBH_4$ in nearly quantitative yield affording alcohol **27** which was reacted with mesyl chloride to produce mesylate **28**. Alternatively, reaction between **27** and benzoyl chloride gave benzoate **32** which, after hydrolysis, yielded diol **36**. Mesylate **28** was the common precursor to the target diols **33**–**35** through acetonides **29**–**31**. Thus, **28** afforded compound **29** by reduction with $LiBH_4$. In turn, thioether **30** was obtained when mesylate **28** was reacted with sodium thiomethoxide at room temperature for 20 h. On the other hand, the reaction between **28** and lithium bromide in THF was performed in order to prepare **31**, a mixture of this product along with diol **35** being unexpectedly obtained, even when both the solvent and the reactant were previously dried and experiments were run in anhydrous conditions. The mixture was treated with 5% HCl to afford compound **35** in 64% yield for the two steps.

Moreover, we tried to explore the usefulness of these diols to prepare other related compounds such as 1,2-amino acids and 1,3-aminoalcohols. However, the oxidative cleavage of the diol function by using sodium or tetra-*n*-butylammonium periodate, or ruthenium oxide, was not successful, always yielding products for which spectroscopic data revealed the absence of the cyclopropane ring and of the expected carbonyl function. The product resulting from the oxidation of **36** with sodium periodate could be isolated



Scheme 3. *Reagents*: (a) $LiBH_4$; (b) NaSMe; (c) LiBr

and purified yielding a solid, mp 93–95°C, $[\alpha]_D$=0. Its IR and ^1H and ^{13}C NMR spectroscopic data as well as the microanalysis were in accordance with the dihydrofuran structure **37** (Scheme 3). We propose the arrangement to take place at the aldehyde level, this intermediate evolving rapidly towards a zwitterionic open-chain species in which the carbocation would be stabilized by resonance with the nitrogen lone-pair. Attack of the enolate oxygen to the charged carbon led to the five-membered ring with concomitant racemization. Similar processes must occur in the attempted oxidation of substrates **33**–**35**.

3. Conclusions

Versatile synthetic strategies, through simple and efficient protocols, have been used for the preparation of a variety of cyclopropane aminoalcohols from common precursors. Since the starting materials are available in both enantiomeric forms, by using alternatively D- or L-glyceraldehyde as sources of chirality, the two enantiomeric series of products are available.

Some of the synthesized products are being evaluated for their possible biological activities and others have been used as key intermediates in the synthesis of novel cyclopropane carbocyclic nucleosides.[12]

4. Experimental

Flash column chromatography was carried out on silica gel (240–400 mesh) unless otherwise stated. Baker-silica® (40 μm) was used for the chromatography of acid-sensitive products. Melting points were determined on a hot stage and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 250

and 62.5 MHz, respectively. Electron-impact mass spectra were recorded at 70 eV. Compounds **5**, **9**–**14** were prepared following the same procedures as those previously reported for their enantiomers, whose spectroscopic data and physical constants, except specific rotation, were in good accord with the data obtained for **5**, **9**–**14**.[9] Therefore, only specific rotation and microanalysis values, for the new compounds, are given herein for these products.

*4.1. Methyl (*R*)-Z-2-*N*-tert-butoxycarbonylamino-3-(2′,2′-dimethyl-1′,3′-dioxolan-4-yl)-2-propenoate **9***

Yield: 800 mg (53%). $[\alpha]_D$=+10.9 (*c* 4.40, $CHCl_3$) (lit.[9] $[\alpha]_D$=−10.8 (*c* 2.10, $CHCl_3$) for the enantiomer). Anal. calcd for $C_{14}H_{23}O_6N$: C, 55.80%; H, 7.69%; N: 4.65%. Found: C: 55.72%; H, 7.81%; N, 4.57%.

*4.2. Methyl (1*R,*2*S,*4′*R*)-(+)-1-*N*-tert-butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-cyclopropanecarboxylate **10***

Yield: 640 mg (87% for the two steps). $[\alpha]_D$=+69.0 (*c* 1.10, $CHCl_3$) (lit.[9] $[\alpha]_D$=−68.9 (*c* 1.03, $CHCl_3$) for the enantiomer). Anal. calcd for $C_{15}H_{25}NO_6$: C, 57.13%; H, 7.99%; N, 4.44%. Found: C, 57.05%; H, 7.74%; N, 4.41%.

*4.3. Methyl (1*R,*2*S,*1′*R*)-(+)-1-*N*-tert-butoxycarbonylamino-2-(1′,2′-dihydroxyethyl)cyclopropanecarboxylate **11***

Yield: 476 mg (95%). $[\alpha]_D$=+54.3 (*c* 1.50, MeOH) (lit.[9] $[\alpha]_D$=−54.6 (*c* 1.08, MeOH) for the enantiomer). Anal. calcd for $C_{12}H_{21}O_6N$: C, 52.35%; H, 7.69%; N, 5.09%. Found: C, 52.27%; H, 7.58%; N, 4.72%.

*4.4. Methyl (1*R,*2*S*)-(+)-1-*N*-tert-butoxycarbonylamino-2-formylcyclopropanecarboxylate **12***

Yield: 341 mg (85% yield). $[\alpha]_D$=+189.0 (*c* 1.00, $CHCl_3$) (lit.[9] $[\alpha]_D$=−190.7 (*c* 0.96, $CHCl_3$) for the enantiomer). Anal. calcd for $C_{11}H_{17}O_5N$: C, 54.31%; H, 7.04%; N, 5.76%. Found: C, 54.14%; H, 6.73%; N, 5.85%.

*4.5. Methyl (1*R,*2*S*)-(+)-1-*N*-tert-butoxycarbonylamino-2-hydroxymethylcyclopropanecarboxylate **5***

Yield: 316 mg (92%). $[\alpha]_D$=+33.9 (*c* 0.80, MeOH) (lit.[9] $[\alpha]_D$=−34.1 (*c* 0.67, MeOH) for the enantiomer).

*4.6. (1*R,*2*S*)-(+)-1-*N*-tert-Butoxycarbonylamino-2-hydroxymethylcyclopropanecarboxylic acid **13***

Yield: 127 mg (91%). $[\alpha]_D$=+38.0 (*c* 1.00, MeOH) (lit.[10] $[\alpha]_D$=+37.8 (*c* 0.45, MeOH)).

*4.7. (+)-(*Z*)-Methanohomoserine **14***

Yield: 67 mg (100%). $[\alpha]_D$=+74.7 (*c* 1.05, H_2O) (lit.[10] $[\alpha]_D$=+73.8 (*c* 0.48, H_2O)).

4.8. (1R,2S)-(+)-1-N-tert-Butoxycarbonylamino-1,2-bis(hydroxymethyl)cyclopropane **15**

A 2 M solution of $LiBH_4$ in THF (2.2 mL, 5.7 mmol) was slowly added to a solution of ester **5** (175 mg, 0.7 mmol) in anhydrous THF (5 mL) at −78°C. The mixture was allowed to reach room temperature and then stirred for 18 h. The excess hydride was destroyed by slow addition of methanol, and solvents were removed at reduced pressure. The residue was dissolved in water and extracted with dichloromethane (4×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed (ethyl acetate) to afford diol **15** as a colorless oil. Yield: 137 mg (88%). $[\alpha]_D$=+18.7 (*c* 0.80, $CHCl_3$). IR (film) 3600–3100, 1685 cm^{-1}. ^1H NMR ($CDCl_3$) 0.42 (t, H_3, J=J'=5.8 Hz), 0.90 (dd, H_3, J=9.5 Hz, J'=5.8 Hz), 1.41–1.50 (complex absorption, $C(CH_3)_3$+H_2), 3.12 (t, $H_{1''a}$, J=J'=10.9 Hz), 3.36 (d, $H_{1'}$, J=11.6 Hz), 3.53 (d, $H_{1'}$, J=11.6 Hz), 3.93 (m, $H_{1''b}$), 5.31 (broad s, NH). ^{13}C NMR (methanol-d_4) 14.80 (C_3), 25.36 (C_2), 28.65 ($C(CH_3)_3$), 39.78 (C_1), 62.78 (CH_2O), 67.31 (CH_2O), 80.74 ($C(CH_3)_3$), 159.57 (CO). Anal. calcd for $C_{10}H_{19}NO_4$: C, 55.28%; H, 8.81%; N, 6.45%. Found: C, 55.20%; H, 8.83%; N, 6.28%.

4.9. (1R,2S)-(+)-1-Amino-1,2-bis(hydroxymethyl)cyclopropane **1**

A solution of **15** (120 mg, 0.5 mmol) and 1 M HCl (5 mL) in THF (5 mL) was stirred at room temperature for 8 h. Then saturated aqueous sodium bicarbonate was added to reach neutral pH and THF was removed. The aqueous solution was extracted with ethyl acetate (8×5 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure and the residue was purified by elution through a C_{18}-reverse phase cartridge using 1:1 methanol:water as eluent. In this way, pure aminodiol **1** was obtained as a colorless oil. Yield: 58 mg (90%). $[\alpha]_D$=+16.2 (*c* 1.15, MeOH). IR (film): 3500–3000 cm^{-1}. ^1H NMR (methanol-d_4) 0.96–1.09 (complex absorption, H_{3a}+H_{3b}), 1.27–1.41 (m, H_2), 3.57 (d, $H_{1'a}$, J=12.2 Hz), 3.66 (d, $H_{1'b}$, J=12.2 Hz), 3.78 (dd, $H_{1''a}$, J=11.7 Hz, J'=5.8 Hz), 4.00 (dd, $H_{1''b}$, J=11.7 Hz, J'=4.0 Hz). ^{13}C NMR (methanol-d_4) 11.33 (C_3), 22.27 (C_2), 40.97 (C_1), 59.31 (CH_2O), 65.90 (CH_2O). Anal. calcd for $C_5H_{11}NO_2$: C, 51.26%; H, 9.46%; N, 11.96%, Found: C, 51.42%; H, 9.28%; N, 11.74%.

4.10. (1S,2R)-(−)-1-N-tert-Butoxycarbonylamino-1,2-bis(hydroxymethyl)cyclopropane **17a**

This product is a colorless oil that was synthesized alternatively by reduction of alcohol **6a** or aldehyde **16a** with $LiBH_4$, following a similar protocol to that described above for the synthesis of **15** (yield 631 mg, 95%). Spectroscopic data are in good agreement with those of its enantiomer **15**. $[\alpha]_D$=−18.9 (*c* 1.05, $CHCl_3$). Anal. calcd for $C_{10}H_{19}NO_4$: C, 55.28%; H, 8.81%; N, 6.45%. Found: C, 54.99%; H, 8.91%; N, 6.74%.

4.11. (1S,2R)-(+)-1-N-Benzyloxycarbonylamino-1,2-bis(hydroxymethyl)cyclopropane **17b**

This diol is a colorless oil which was synthesized from ester **6b** by the standard procedure described above (yield: 592 mg, 94%). $[\alpha]_D$=+6.4 (*c* 2.20, $CHCl_3$). IR (film) 3650–3100, 1699 cm^{-1}. ^1H NMR ($CDCl_3$) 0.46 (t, H_3, J=J'=5.8 Hz), 0.87 (dd, H_3, J=9.5 Hz, J'=5.8 Hz), 1.33 (m, H_2), 3.09 (t, $H_{1''}$, J=J'=10.9 Hz), 3.46 (d, $H_{1'}$, J=11.7 Hz), 3.54 (d, $H_{1'}$, J=11.7 Hz), 3.85 (complex absorption, 3H), 5.04 (s, CH_2Ph), 6.07 (broad s, NH), 7.28 (s, 5H). ^{13}C NMR ($CDCl_3$) 14.54 (C_3), 25.27 (C_2), 39.24 (C_1), 61.70 (CH_2O), 67.18 (CH_2Ph), 68.06 (CH_2O), 128.07, 128.23, 128.49, 135.84 (C_{ipso}), 158.37 (CO). Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14%; H, 6.82%; N: 5.57%. Found: C, 62.15%; H, 6.98%; N, 5.42%.

4.12. (1S,2R)-(−)-1-Amino-1,2-bis(hydroxymethyl)cyclopropane **2**

A mixture of **17a** (90 mg), 5 mL of 1 M HCl and THF (5 mL) was stirred at room temperature for 8 h. Then saturated aqueous sodium bicarbonate was added to reach neutral pH. THF was removed, and the aqueous solution was extracted with ethyl acetate (8×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. Crude aminodiol **2** was purified by elution through a C_{18}-reverse phase cartridge using 1:1 methanol:water as eluent to afford pure **2** as a colorless oil (yield: 39 mg, 81%). Spectroscopic data are in good accordance with those described above for its enantiomer **1**. $[\alpha]_D$=−16.4 (*c* 1.05, MeOH). Anal. calcd for $C_5H_{11}NO_2$: C, 51.26%; H, 9.46%; N, 11.96. Found: C, 51.54%; H, 9.68%; N, 11.69.

4.13. (1S,2R)-(+)-1,2-bis(Benzoyloxymethyl)-1-N-(tert-butoxycarbonylamino)cyclopropane **18**

To an ice-cooled solution of **17a** (232 mg, 1.1 mmol) in dry dichloromethane (12 mL) anhydrous pyridine (530 μL, 6.5 mmol) and benzoyl chloride (320 μL, 2.7 mmol) was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 16 h, then dichloromethane (5 mL) was added and the solution was subsequently washed with 5% HCl (3×8 mL) and saturated aqueous sodium bicarbonate (2×8 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated at reduced pressure to afford **18** as a solid which was purified by crystallization (yield: 312 mg, 81%). Crystals, mp 126–128°C (from EtOAc/pentane). $[\alpha]_D$=+6.95 (*c* 1.15, $CHCl_3$). IR (KBr) 3500–3100, 1790, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) 0.96 (dd, H_{3b}, J=6.2 Hz, J'=5.5 Hz), 1.31 (dd, H_{3a}, J=9.5 Hz, J'=5.5 Hz), 1.44 (s, $C(CH_3)_3$), 1.57 (m, H_2), 4.02 (d, $H_{\alpha O}$, J=11.7 Hz), 4.24 (dd, $H_{\alpha O}$, J=11.7 Hz, J'=9.5 Hz), 4.56 (d, $H_{\alpha O}$, J=11.7 Hz), 4.61 (d, $H_{\alpha O}$, J=11.7 Hz), 5.91 (broad s, NH), 7.20–7.97 (complex absorption, 10H). ^{13}C NMR ($CDCl_3$) 16.38 (C_3), 22.27 (C_2), 28.32 ($C(CH_3)_3$), 36.64 (C_1), 64.10 (CH_2O), 69.42 (CH_2O), 79.83 ($C(CH_3)_3$), 128.17 (C_m), 128.33 (C_m), 129.55 (C_o), 129.61 (C_o), 129.85 (C_{ipso}), 130.52 (C_{ipso}), 132.81 (C_p), 133.04 (C_p), 155.95 (NHCO), 166.35 (CO), 166.74 (CO). MS, *m/e* (%) 326 (M−Boc, 8), 230 (8), 203 (35), 105 (PhCO, 100), 77 (Ph, 33), 57 ($C(CH_3)_3$, 100), 41 (28). Anal. calcd for $C_{24}H_{27}NO_6$: C, 67.75%; H, 6.40%; N, 3.29%. Found: C, 67.68%; H, 6.53%; N, 3.32%.

4.14. (1S,2R)-(+)-1-Amino-1,2-bis(benzoyloxymethyl)cyclopropane hydrochloride **19**

A mixture of **18** (62 mg, 0.1 mmol) and 6 M HCl (1.5 mL) in THF (1.5 mL) was stirred at room temperature overnight. The solution was evaporated to dryness to afford a solid which was purified by crystallization (yield: 30 mg, 63%). Crystals, mp 179–181°C (MeOH/ether). $[\alpha]_D$=+34.8 (*c* 1.15, MeOH). IR (KBr) 3209, 3000–2600, 1715, 1701, 1602 cm^{-1}. ^1H NMR (methanol-d_4) 1.23 (t, H_{3b}, J=7.3 Hz), 1.47 (dd, H_{3a}, J=10.2 Hz, J'=6.9 Hz), 1.97 (m, H_2), 4.23 (d, $H_{\alpha O}$, J=13.1 Hz), 4.31 (dd, $H_{\alpha O}$, J=12.8 Hz, J'=10.2 Hz), 4.73 (d, $H_{\alpha O}$, J=13.1 Hz), 4.77 (dd, $H_{\alpha O}$, J=11.7 Hz, J'=4.4 Hz), 7.29–8.03 (complex absorption, 10 H). ^{13}C NMR (methanol-d_4) 13.60 (C_3), 22.67 (C_2), 39.39 (C_1), 63.36 (CH_2O), 68.83 (CH_2O), 129.49 (C_m), 129.52 (C_m), 130.70 ($2C_o$), 130.77 ($2C_{ipso}$), 133.04 ($2C_p$), 167.52 (CO), 168.24 (CO). MS, *m/e* (%) 326 (M−36, 1), 204 (10), 203 (1), 105 (PhCO, 100), 82 (36), 77 (Ph, 42), 41 (7). Anal. calcd for $C_{19}H_{20}ClNO_4C$: 63.07%; H, 5.57%; N, 3.87%. Found: C, 62.95%; H, 5.60%; N, 3.84%.

4.15. (1S,2R)-(+)-1-Benzoyloxymethyl-1-N-tert-butoxycarbonylamino-2-hydroxymethylcyclopropane **20**

To an ice-cooled solution of **17a** (60 mg, 0.3 mmol) in dry dichloromethane (5 mL) anhydrous pyridine (75 μL, 0.9 mmol) and benzoyl chloride (35 μL, 0.3 mmol) was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h, then dichloromethane (5 mL) was added and the solution was subsequently washed with 5% HCl (3×8 mL) and saturated aqueous sodium bicarbonate (2×8 mL). The organic phase was dried over $MgSO_4$, the solvent was evaporated at reduced pressure and the residue was chromatographed (1:2, ethyl acetate:hexane) (yield: 78 mg, 88%). Crystals, mp 110–112°C (from EtOAc/pentane). $[\alpha]_D$=+11.3 (*c* 0.80, $CHCl_3$). IR (KBr) 3468 (N–H), 3359 (O–H), 1693 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) 0.47 (dd, H_{3b}, *J*=6.2 Hz, *J′*=5.5 Hz), 1.04 (dd, H_{3a}, *J*=9.5 Hz, *J′*=5.5 Hz), 1.42 (s, $C(CH_3)_3$), 1.60 (m, H_2), 3.16 (t, OH, *J*=*J′*=11.0 Hz), 3.75 (d, CH_2OH, *J*=11.7 Hz), 3.94 (dt, CH_2OH, *J*=*J′*=11.7 Hz, *J″*=3.6 Hz), 4.04 (d, CH_2OBz, *J*=11.7 Hz), 4.66 (d, CH_2OBz, *J*=11.7 Hz), 5.11 (sa NH), 7.43 (dd, $2H_m$, *J*=8.0 Hz, *J′*=7.3 Hz), 7.54 (dt, H_p, *J*=8.0 Hz, *J′*=1.5 Hz), 8.45 (dd, $2H_o$, *J*=7.3 Hz, *J′*=1.5 Hz). ^{13}C NMR ($CDCl_3$) 14.35 (C_3), 26.70 (C_2), 28.23 ($C(CH_3)_3$), 36.80 (C_1), 61.67 (CH_2OH), 69.35 (CH_2OBz), 81.00 ($C(CH_3)_3$), 128.38 (C_m), 129.73 (C_o), 130.11 (C_{ipso}), 133.05 (C_p), 157.41 (NHCO), 166.44 (OCOPh). MS, *m/e* (%) 322 (M+1, 49), 266 (M−PhCO, 18), 222 (M−Boc, 31), 105 (PhCO, 63), 77 (Ph, 27), 57 ($C(CH_3)_3$, 100), 41 (34). Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54%; H, 7.21%; N, 4.36%. Found: C, 63.34%; H, 7.29%; N, 4.32%.

4.16. Methyl (1S,2R)-(+)-1-N-benzyloxycarbonylamino-2-(tert-butyldiphenylsilyloxymethyl)cyclopropanecarboxylate **21**

tert-Butyldiphenylsilyl chloride (395 μL, 1.5 mmol) was added to a stirred and ice-cooled solution of **6b** (210 mg, 0.8 mmol) and dimethylaminopyridine (313 mg, 2.6 mmol) in dichloromethane (5 mL). The mixture was stirred at 0°C for 25 min and saturated aqueous NH_4Cl (5 mL) was added. Layers were separated and the organic phase was washed with water (1×8 mL) and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed (1:9 ethyl acetate:hexane) to afford pure **21** (yield: 403 mg, 97%). $[\alpha]_D$=+8.8 (*c* 3.20, $CHCl_3$). IR (film) 3600–3250, 1734 cm^{-1}. ^1H NMR ($CDCl_3$) 1.03 (s, $(CH_3)_3$), 1.03–1.22 (m, H_{3a}), 1.77 (m, H_{3b}), 1.94 (m, H_2), 3.48 (t, $H_{1'a}$, *J*=*J′*=10.7 Hz), 3.70 (s, CH_3), 4.02 (dd, $H_{1'b}$, *J*=10.7 Hz, *J′*=5.1 Hz), 5.12 (s, CH_2Ph), 7.35–7.64 (complex absorption, 15H). ^{13}C NMR ($CDCl_3$) 19.07 ($C(CH_3)_3$), 21.89 (C_3), 26.77 ($C(CH_3)_3$), 29.80 (C_2), 38.12 (C_1), 52.50 (OCH_3), 63.50 ($C_{1'}$), 66.59 (CH_2Ph), 127.75, 127.81, 127.99, 128.40, 129.84, 133.11, 135.40, 135.46, 136.37, 156.87 (NHCO), 172.92 (CO). Anal. calcd for $C_{30}H_{35}NO_5Si$: C, 69.60%; H, 6.81%; N, 2.71%. Found: C, 69.50%; H, 6.94%; N, 2.72%.

4.17. (1S,2R)-(+)-1-N-Benzyloxycarbonylamino-2-tert-butyldiphenylsilyloxymethyl-1-hydroxymethylcyclopropane **22**

Ester **21** was reduced with $LiBH_4$ following the standard procedure described above for the preparation of **15** (yield: 1.3 g, 93%). $[\alpha]_D$=+11.0 (*c* 2.00, $CHCl_3$). IR (film) 3600–3100 cm^{-1}. ^1H NMR ($CDCl_3$) 0.74 (dd, H_3, *J*=7.9 Hz, *J′*=5.8 Hz), 1.04 (s, $SiC(CH_3)_3$), 1.18 (m, H_3), 1.25 (m, H_2), 3.45 (complex absorption, CH_2OH), 3.68 (d, $H_{1'}$, *J*=11.7 Hz), 3.97 (dd, $H_{1'}$, *J*=11.7 Hz, *J′*=5.5 Hz), 5.09 (s, CH_2Ph), 5.74 (broad s, NH), 7.33–7.39 (complex absorption, 11H), 7.61–7.67 (complex absorption, 4H). ^{13}C NMR ($CDCl_3$) 17.45 (C_3), 19.08 ($SiC(CH_3)_3$), 25.55 (C_2), 26.85 ($SiC(CH_3)_3$), 39.18 (C_1), 64.05 (CH_2OSi), 66.96 (CH_2Ph), 70.15 (CH_2OH), 127.79 ($4C_o$), 128.01 ($2C_o$), 128.50 ($2C_p$), 129.83 ($4C_p$),

133.19 ($2C_{ipso}$), 135.44 (C_m), 135.52 (C_m), 158.34 (NHCO). Anal. calcd for $C_{29}H_{35}NO_4Si$: C, 71.13%; H, 7.20%; N, 2.86%. Found: C, 71.27%; H, 7.09%; N, 2.73%.

*4.18. (1*S*,2*R*)-1-*N*-Benzyloxycarbonylamino-2-*tert*-butyldiphenylsilyloxymethyl-1-methanesulfonyloxycyclopropane* **23**

Triethylamine (240 μL, 2.0 mmol) and mesyl chloride (140 μL, 2.0 mmol) were subsequently added to a stirred and ice-cooled solution of alcohol **22** (0.5 g, 1.0 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere. The mixture was stirred at 0°C for 30 min and water (8 mL) was added. Layers were separated and the aqueous phase was extracted with dichloromethane (2×8 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated at reduced pressure to afford quantitatively mesylate **23** (580 mg) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) 0.88 (t, H_3, J=J'=6.6 Hz), 1.05 (s, $C(CH_3)_3$), 1.09 (m, H_3), 1.40 (m, H_2), 2.90 (s, CH_3), 3.48 (dd, CH_2OSi, J=11.0 Hz, J'=8.7 Hz), 3.83 (d, CH_2OH, J=10.9 Hz), 4.00 (dd, CH_2OSi, J=11.0 Hz, J'=5.1 Hz), 4.58 (d, CH_2OH, J=10.9 Hz), 5.09 (s, CH_2Ph), 5.63 (broad s, NH), 7.32–7.40 (complex absorption, 11H), 7.60–7.72 (complex absorption, 4H). ^{13}C NMR ($CDCl_3$) 17.70 (C_3), 19.12 ($SiC(CH_3)_3$), 24.96 (C_2), 26.82 ($SiC(CH_3)_3$, 36.27 (C_1), 37.43 (CH_3), 63.67 (CH_2OSi), 66.75 (CH_2Ph), 74.23 (CH_2OH), 127.76 ($4C_o$), 128.01 ($2C_o$), 128.48 ($2C_p$), 129.81 ($4C_p$), 133.08 ($2C_{ipso}$), 135.38 (C_m), 135.49 (C_m), 156.24 (NHCO).

*4.19. (1*S*,2*R*)-(+)-1-*N*-Benzyloxycarbonylamino-2-*tert*-butyldiphenylsilyloxymethyl-1-methylcyclopropane* **24**

Mesylate **23** was reduced with $LiBH_4$ according to a similar protocol to that described above for the synthesis of **15**. Crude **24** was purified by column chromatography on Baker-silica® (5:1, hexane:ether) to afford a colorless oil (yield: 240 mg, 50%). $[\alpha]_D$=+15.0 (*c* 2.70, $CHCl_3$). IR (film) 3423, 3339 (broad), 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.69 (t, H_3, J=J'=5.1 Hz), 0.85 (dd, H_3, J=8.0 Hz, J'=5.1 Hz), 1.07 (complex absorption, $C(CH_3)_3$+H_2), 1.39 (s, CH_3), 3.47 (t, CH_2OSi, J=J'=10.9 Hz,), 4.01 (dd, CH_2OSi, J=10.9 Hz, J'=5.8 Hz), 5.09 (s, CH_2Ph), 5.50 (broad s, NH), 7.35–7.43 (complex absorption, 11H), 7.60–7.68 (complex absorption, 4H). ^{13}C NMR ($CDCl_3$) 19.12 ($C(CH_3)_3$), 19.68 (C_3), 24.12 (C_2), 26.24 (CH_3), 26.85 ($C(CH_3)_3$), 33.32 (C_1), 64.91 ($C_{1'}$), 66.23 (CH_2Ph), 127.70, 127.91, 128.41, 129.73, 133.2, 135.47, 135.55, 136.76, 156.41 (NHCO). Anal. calcd for $C_{29}H_{35}NO_3Si$: C, 73.53%; H, 7.45%; N, 2.96%. Found: C, 73.50%; H, 7.84%; N, 2.75%.

*4.20. (1*S*,2*R*)-(−)-1-Amino-2-*tert*-butyldiphenylsilyloxymethyl-1-methylcyclopropane* **25**

A stirred mixture of **24** (100 mg, 0.2 mmol) and 20% $Pd(OH)_2$/C (16 mg) in methanol (10 mL) was hydrogenated under two atmospheres pressure for 24 h. The catalyst was removed by filtration through Celite and the solvent was evaporated. The residue was chromatographed on Baker-silica® giving a colorless oil (yield: 54 mg, 76%). $[\alpha]_D$=−34.6 (*c* 0.75, $CHCl_3$). IR (film) 3600, 3100 (broad) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.27 (t, H_3, J=J'=5.1 Hz), 0.47 (dd, H_3, J=9.1 Hz, J'=4.7 Hz), 0.94 (m, H_2), 1.03 (s, $C(CH_3)_3$), 1.26 (s, CH_3), 3.70 (dd, CH_2OSi, J=10.9 Hz, J'=8.4 Hz), 3.94 (dd, CH_2OSi, J=10.9 Hz, J'=5.1 Hz), 7.35–7.39 (complex absorption, 6H), 7.66–7.69 (complex absorption, 4H). ^{13}C NMR ($CDCl_3$) 18.64 ($C(CH_3)_3$), 19.20 (C_3), 26.88 ($C(CH_3)_3$), 27.18(C_2), 28.62 (CH_3), 34.32 (C_1), 64.16 ($C_{\alpha O}$), 127.59 (C_o), 129.50 (C_p), 134.19 (C_{ipso}), 135.60 (C_m). Anal. calcd for $C_{21}H_{29}NOS$: C, 74.28%; H, 8.61%; N, 4.13%. Found: C, 74.49%; H, 8.89%; N, 3.89%.

4.21. (1S,2R)-(−)-1-N-Benzyloxycarbonylamino-2-hydroxymethyl-1-methylcyclopropane ***26***

A 1 M solution of tetrabutylammonium fluoride in THF (270 μL, 0.3 mmol) was added to a solution of **24** (88 mg, 0.2 mmol) in THF (2 mL). The mixture was stirred at room temperature for 1 h, then the solvent was evaporated at reduced pressure and the residue was chromatographed (1:1, ethyl acetate:hexane) to afford pure **26** (yield: 43 mg, 100%). Crystals, mp 47–50°C (from EtOAc/pentane). $[\alpha]_D$=−19.1 (*c* 1.70, $CHCl_3$). IR (KBr) 3600–3100 (broad), 1725 cm^{-1}. ^1H NMR ($CDCl_3$) 0.34 (t, H_3, J=J'=5.8 Hz), 0.70 (dd, H_3, J=8.8 Hz, J'=5.8 Hz), 1.29 (m, H_2), 1.36 (s, CH_3), 3.08 (t, OH, J=J'=11.0 Hz), 3.50 (d, CH_2OH, J=11.0 Hz), 3.88 (dd, CH_2OH, J=11.0 Hz, J'=2.9 Hz), 5.08 (s, CH_2Ph), 5.33 (broad s, NH), 7.32 (s, 5H). ^{13}C NMR ($CDCl_3$) 16.51 (C_3), 23.85 (C_2), 28.34 (CH_3), 33.72 (C_1), 62.70 ($C_{1'}$), 67.05 (CH_2Ph), 128.03, 128.20, 128.51, 135.47, 135.96, 157.74 (NHCO). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36%; H, 7.28%; N, 5.95%. Found: C, 66.64%; H, 7.39%; N, 5.78%.

4.22. (1S,2R)-(−)-1-Amino-2-hydroxymethyl-1-methylcyclopropane ***3***

Compound **26** was hydrogenated according to the procedure described above for the preparation of **25**. Aminoalcohol **3** was purified by elution through a C_{18}-reverse phase cartridge affording an oil (yield: 22 mg, 95%). $[\alpha]_D$=−23.4 (*c* 0.55, $CHCl_3$). IR (film) 3600–3000 (broad) cm^{-1}. ^1H NMR (methanol-d_4) 0.28 (t, H_3, J=J'=5.8 Hz), 0.65 (dd, H_3, J=8.9 Hz, J'=5.8 Hz), 1.29 (m, H_2), 1.36 (s, CH_3), 3.71 (dd, J=11.7 Hz, J'=5.7 Hz), 3.96 (dd, J=11.7 Hz, J'=4.2 Hz). ^{13}C NMR (methanol-d_4) 14.93 (C_3), 22.59 (C_2), 28.01 (CH_3), 37.43 (C_1), 59.98 (CH_2O). Anal. calcd for $C_5H_{11}NO$: C, 59.37%; H, 10.96%; N, 13.85%. Found: C, 59.54%; H, 10.85%; N, 13.69%.

*4.23. (1S,2R,4′S)-(−)-1-*N*-tert-Butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-hydroxymethylcyclopropane* ***27***

Ester **7a** was reduced with $LiBH_4$ following the same procedure as that described above for the synthesis of **15** (yield: 450 mg, 99%). Crystals, mp 92–94°C (from EtOAc/pentane). $[\alpha]_D$=−60.6 (*c* 1.65, $CHCl_3$). IR (KBr) 3500–3000 (broad), 1719 cm^{-1}. ^1H NMR ($CDCl_3$) 0.82 (t, H_{3a}, J=J'=5.8 Hz), 1.03 (dd, H_{3b}, J=8.8 Hz, J'=5.8 Hz), 1.23 (complex absorption, H_2+CH_3), 1.31 (s, CH_3), 1.40 (s, $C(CH_3)_3$), 3.34 (d, CH_2OH, J=11.0 Hz), 3.75 (complex absorption, $H_{5'}$+CH_2OH), 3.84 (m, $H_{4'}$), 4.06 (dd, $H_{5'}$, J=8.0 Hz, J'=5.8 Hz), 5.08 (broad s, NH). ^{13}C NMR ($CDCl_3$) 16.76 (C_3), 25.51 (CH_3), 26.09 (C_2), 26.73 (CH_3), 28.17 ((CH_3)$_3$), 39.01 (C_1), 69.85 (CH_2OH), 70.03 ($C_{5'}$), 76.47 ($C_{4'}$), 80.57 (C(CH_3)$_3$), 108.59 ($C_{2'}$), 157.55 (NHCO). MS, *m/e* (%) 231 (M^+−56, 1), 172 (M−Boc, 29), 113 (10), 112 (12), 101 (13), 86 (33), 59 (14), 57 (100), 43 (21), 42 (25). Anal. calcd for $C_{14}H_{25}NO_5$: C, 58.52%; H, 8.77%; N, 4.87%. Found: C, 58.42%; H, 8.84%; N, 5.09%.

*4.24. (1S,2R,4′S)-(−)-1-*N*-tert-Butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-methanesulfonyloxycyclopropane* ***28***

This compound was synthesized following the same procedure as that described above for the preparation of **23**. Crude mesylate **28** was purified by crystallization (yield: 1.5 g, 88%). Crystals, mp 118–120°C (from CH_2Cl_2/pentane). $[\alpha]_D$=−42.0 (*c* 1.50, $CHCl_3$). IR (KBr) 1685 cm^{-1}. ^1H NMR ($CDCl_3$) 0.99 (m, H_{3a}), 1.20 (m, H_{3b}), 1.31 (s, CH_3), 1.42 (complex absorption, CH_3+H_2+$C(CH_3)_3$), 2.98 (s, SO_2CH_3), 3.78 (complex absorption, 3H), 4.05 (dd, $H_{5'}$, J=8.0 Hz, J'=5.8 Hz), 4.58 (d, CH_2OMs, J=10.9 Hz), 4.97 (broad s, NH). ^{13}C NMR ($CDCl_3$) 16.45 (C_3), 25.36 (CH_3), 26.65 (C_2), 26.71

(CH_3), 28.21 ($C(CH_3)_3$), 36.54 (C_1), 39.01 (CH_3SO_2), 69.82 (CH_2OH), 74.06 ($C_{5'}$), 75.91 ($C_{4'}$), 80.41 ($C(CH_3)_3$), 108.70 ($C_{2'}$), 155.34 (NHCO). MS, *m/e* (%) 345 (M^+-20, 4), 344 (16), 235 (12), 179 (100), 164 (13), 107 (18), 99 (19), 94 (15), 73 (22), 57 (98), 43 (22), 41 (22). Anal. calcd for $C_{15}H_{27}NO_7S$: C, 49.30%; H, 7.45%; N, 3.83%; S, 8.77%. Found: C, 49.64%; H, 7.55%; N, 3.77%; S, 8.48%.

*4.25. (1*S*,2*R*,4′*S*)-(−)-1*-N-tert-*Butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-methylcyclopropane* ***29***

Mesylate **28** was reduced with $LiBH_4$ according to the standard procedure (yield: 150 mg, 50%). Crystals, mp 80–81°C (from CH_2Cl_2/pentane). $[\alpha]_D=-80.0$ (*c* 1.00, $CHCl_3$). IR (KBr) 1691 cm^{-1}. ^1H NMR ($CDCl_3$) 0.71 (t, H_{3a}, $J=J'=5.8$ Hz), 0.82 (dd, H_{3b}, $J=8.8$ Hz, $J'=5.8$ Hz), 0.96 (m, H_2), 1.31 (s, $2\times CH_3$), 1.40 (s, CH_3), 1.41 (s, $C(CH_3)_3$), 3.69 (m, $H_{5'}$), 3.79 (t, $H_{5'}$, $J=J'=7.3$ Hz), 4.10 (dd, $H_{4'}$, $J=8.0$ Hz, $J'=5.8$ Hz), 4.76 (broad s, NH). ^{13}C NMR ($CDCl_3$) 18.33 (C_3), 23.72 (C_2), 25.48 (CH_3), 26.83 (CH_3), 28.27 ($C(CH_3)_3$), 28.51 (CH_3), 33.49 (C_1), 70.21 ($C_{5'}$), 77.50 ($C_{4'}$), 79.41 ($C(CH_3)_3$), 108.14 ($C_{2'}$), 155.37 (NHCO). MS, *m/e* (%) 214 (M^+-57, 156 (12), 101 (28), 96 (19), 70 (43), 57 (100). Anal. calcd for $C_{14}H_{25}NO_4$: C, 61.97%; H, 9.29%; N, 5.16%. Found: C, 61.98%; H, 9.41%; N, 5.04%.

*4.26. (1*S*,2*R*,4′*S*)-(−)-1*-N-tert-*Butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-(methylthiomethyl)cyclopropane* ***30***

A solution of sodium thiomethoxide (122 mg, 1.7 mmol) in anhydrous THF (5 mL) was added to a solution of mesylate **28** (426 mg, 1.2 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 20 h. Then the solvent was removed, the residue was poured into water (20 mL), and the resulting solution was extracted with dichloromethane (5×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The residue was chromatographed (1:2, ethyl acetate:hexane) to furnish pure **30** (yield: 173 mg, 47%). Crystals, mp 87–88°C (from CH_2Cl_2/pentane). $[\alpha]_D=-58.0$ (*c* 1.35, $CHCl_3$). IR (KBr) 1687 cm^{-1}. ^1H NMR ($CDCl_3$) 0.84 (t, H_{3a}, $J=J'=5.8$ Hz), 0.96–1.14 (complex absorption, H_2+H_{3b}), 1.30 (s, CH_3), 1.40 (complex absorption, $CH_3+C(CH_3)_3$), 2.11 (s, SCH_3), 2.31 (d, $H_{\alpha S}$, $J=13.9$ Hz), 3.10 (d, $H_{\alpha S}$, $J=13.9$ Hz), 3.67–3.83 (complex absorption, $2H_{5'}$), 4.07 (dd, $H_{4'}$, $J=8.0$ Hz, $J'=5.8$ Hz), 5.04 (broad s, NH). ^{13}C NMR ($CDCl_3$) 16.80 (SCH_3), 17.86 (C_3), 25.51 (CH_3), 26.86 (C_2), 27.92 (CH_3), 28.30 (($CH_3)_3$), 37.50 (C_1), 42.00 (CH_2SMe), 70.03 ($C_{5'}$), 77.00 ($C_{4'}$), 79.97 ($C(CH_3)_3$), 108.43 ($C_{2'}$), 155.40 (NHCO). Anal. calcd for $C_{15}H_{27}NO_4S$: C, 56.75%; H, 8.57%; N, 4.41%; S, 10.10%. Found: C, 56.59%; H, 8.65%; N, 4.33%; S, 9.83%.

*4.27. (1*S*,2*R*,4′*S*)-(−)-1-Benzoyloxymethyl-1*-N-tert-*butoxycarbonylamino-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane* ***32***

A solution of alcohol **27** (680 mg, 2.4 mmol), benzoyl chloride (345 μL, 3.0 mmol), and anhydrous pyridine (570 μL, 7.1 mmol) in dry dichloromethane (16 mL) was stirred under a nitrogen atmosphere at room temperature for 1 h. The reaction mixture was washed with saturated aqueous ammonium chloride (2×10 mL) and the organic phase was dried over $MgSO_4$. The solvent was evaporated at reduced pressure and the residue was chromatographed (1:3, ether:hexane) (yield: 907 mg, 2.3 mmol). Crystals, mp 94–96°C (from ether/pentane). $[\alpha]_D=-29.1$ (*c* 1.55, $CHCl_3$). IR (KBr) 1717, 1684 cm^{-1}. ^1H NMR ($CDCl_3$) 0.94 (t, H_{3a}, $J=J'=5.8$ Hz), 1.24 (complex absorption, H_2+H_{3b}), 1.28 (s, CH_3), 1.41 (s, $C(CH_3)_3$), 1.43 (s, CH_3), 3.82 (ac, 2H), 4.06 (d, CH_2OBz, $J=11.7$ Hz), 4.12 (dd, $H_{\alpha O}$, $J=8.0$ Hz, $J'=5.8$ Hz), 4.57 (d, CH_2OBz, $J=11.7$ Hz), 4.93 (s, NH), 7.42 (t, $2H_m$, $J=J'=7.3$ Hz), 7.54 (t, H_p, $J=J'=7.3$

Hz), 8.01 (d, 2H$_o$, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) 16.29 (C_3), 25.46 (CH_3), 26.46 (CH_3), 26.85 (C_2), 28.26 (C(CH_3)$_3$), 36.74 (C_1), 68.80 (CH_2OBz), 70.02 ($C_{5'}$), 76.47 ($C_{4'}$), 80.10 (C(CH$_3$)$_3$), 108.56 ($C_{2'}$), 128.34 (2C$_m$), 129.62 (2C$_o$), 129.95 (C$_{ipso}$), 133.02 (C$_p$), 155.30 (NHCO), 166.25 (CO). Anal. calcd for $C_{21}H_{29}NO_6$: C, 64.43%; H, 7.47%; N, 3.58%. Found: C, 64.72%; H, 7.25%; N, 3.55%.

*4.28. (1*S*,2*R*,1′*S*)-1*-N-tert-*Butoxycarbonylamino-2-(1′,2′-dihydroxyethyl)-1-methylcyclopropane* **33**

HCl (5%=four drops) was added to a solution of **29** (157 mg, 0.6 mmol) in methanol (8 mL) and the mixture was stirred at room temperature for 90 min. The reaction mixture was evaporated to dryness and the residue was crystallized (yield: 110 mg, 0.5 mmol). Crystals, mp 87–89°C (from CH_2Cl_2/pentane). $[\alpha]_D$=−31.1 (*c* 1.15, $CHCl_3$). IR (KBr) 3650–3000 (broad), 1693 cm^{-1}. ^{1}H NMR (acetone-d_6) 0.71–0.82 (complex absorption, 2H$_3$), 1.27 (s, CH$_3$), 1.38 (complex absorption, H$_2$+C(CH$_3$)$_3$), 3.26 (m, H$_{5'}$), 3.61 (t, H$_{5'}$, J=J'=5.8 Hz,), 4.00 (m, H$_{4'}$), 6.24 (broad s, NH). ^{13}C NMR (acetone-d_6) 18.15 (C_3), 23.94 (C_2), 28.12 (C(CH_3)$_3$), 28.53 (CH_3), 33.94 (C_1), 66.55 ($C_{5'}$), 72.00 ($C_{4'}$), 79.52 (C(CH$_3$)$_3$), 156.48 (NHCO). Anal. calcd for $C_{11}H_{21}NO_4$: C, 57.12%; H, 9.15%; N, 6.06%. Found: C, 57.48%; H, 9.38%; N, 5.89%.

*4.29. (1*S*,2*R*,1′*S*)-1*-N-tert-*Butoxycarbonylamino-2-(1′,2′-dihydroxyethyl)-1-(methylthiomethyl)cyclopropane* **34**

HCl (5%=four drops) was added to a solution of **30** (90 mg, 0.3 mmol) in methanol (8 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness and the residue was chromatographed (ethyl acetate) (yield: 57 mg, 77%). Crystals mp 99–101°C (from CH_2Cl_2/pentane). $[\alpha]_D$=−12.0 (*c* 0.68, $CHCl_3$). IR (KBr) 3500–3100 (broad), 1692 cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.95–1.04 (complex absorption, 2H$_3$+H$_2$), 1.42 (s, C(CH$_3$)$_3$), 2.17 (s, SCH$_3$), 2.60 (d, H$_{\alpha S}$, J=14.0 Hz), 2.83 (d, H$_{\alpha S}$, J=14.0 Hz), 3.51 (m, H$_1'$), 3.70 (m, 2H$_{2'}$), 5.41 (broad s, NH). ^{13}C NMR ($CDCl_3$) 16.76 (SCH$_3$), 18.48 (C_3), 27.99 (C_2), 28.29 ((*C*H$_3$)$_3$), 38.08 (C_1), 42.43 (CH_2SMe), 66.54 ($C_{5'}$), 71.59 ($C_{4'}$), 80.08 (C(CH$_3$)$_3$), 155.93 (NHCO). Anal. calcd for $C_{12}H_{23}NO_4S$: C, 51.96%; H, 8.36%; N, 5.05%; S, 11.56%. Found: C, 51.86%; H, 8.58%; N, 4.89%; S, 11.71%.

*4.30. (1*S*,2*R*,1′*S*)-1-Bromomethyl-1*-N-tert-*butoxycarbonylamino-2-(1′,2′-dihydroxyethyl)cyclopropane* **35**

A mixture of mesylate **28** (375 mg, 1.0 mmol) and lithium bromide (175 mg, 2.0 mmol) in THF (15 mL) was stirred at room temperature for 4 days. The solvent was removed, the residue was poured into water and the resultant aqueous solution was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The residue was poured into methanol (10 mL) and 5% HCl (4 drops) was added. The solution was stirred at room temperature for 20 min, then evaporated to dryness. The residue was chromatographed (ethyl acetate) to afford diol **35** as a solid (yield: 253 mg, 64%). Crystals, mp 95–96°C (from MeOH/CH_2Cl_2/pentane). $[\alpha]_D$=−23.0 (*c* 1.00, $CHCl_3$). IR (KBr) 3700–3100 (broad), 1692 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.15–1.19 (complex absorption, 2H$_3$+H$_2$), 1.42 (s, C(CH$_3$)$_3$, 2.55 (complex absorption, 2H$_{\alpha Br}$,), 3.45–3.70 (complex absorption, H$_{1'}$+2H$_{2'}$), 5.44 (broad s, NH). ^{13}C NMR ($CDCl_3$) 20.48 (C_3), 28.27 (C(*C*H$_3$)$_3$), 30.71 (C_2), 39.09 (C_1), 42.48 (CH_2Br), 66.47 ($C_{5'}$), 71.47 ($C_{4'}$), 80.53 (C(CH$_3$)$_3$), 155.69 (NHCO). Anal. calcd for $C_{11}H_{20}BrNO_4$: C, 42.59%; H, 6.50%; N, 4.52%; Br, 25.76%. Found: C, 42.62%; H, 6.57%; N, 4.53%; Br, 25.59%.

*4.31. (1*S*,2*R*,1′*S*)-(−)-1-Benzoyloxymethyl-1-*N-tert-*butoxycarbonylamino-2-(1′,2′-dihydroxyethyl)-cyclopropane* ***36***

Following the same procedure as that described above for the synthesis of **34**, diol **36** was obtained as a solid (yield: 742 mg, 98%). Crystals, mp 124–126°C (from CH_2Cl_2/pentane). $[\alpha]_D$=−24.7 (*c* 1.00, $CHCl_3$). IR (KBr) 3600–3100 (broad), 1722, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) 1.01 (t, H_{3a}, J=J'=5.1 Hz), 1.18–1.29 (complex absorption, H_2+H_{3b}), 1.41 (s, $C(CH_3)_3$), 2.15 (s, OH), 2.35 (broad s, OH), 3.35 (m, H), 3.70 (complex absorption, 2H), 4.32 (s, CH_2OBz), 5.28 (broad s, NH), 7.43 (t, 2H_m, J=J'=7.3 Hz), 7.56 (t, H_p, J=J'=7.3 Hz), 8.03 (d, 2H_o, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) 17.10 (C_3), 27.91 (C_2), 28.58 (C(*C*H_3)$_3$), 37.42 (C_1), 67.42 ($C_{5'}$), 70.08 (CH_2OBz), 72.27 ($C_{4'}$), 79.12 (*C*$(CH_3)_3$), 129.31 (2C_m), 130.35 (2C_o), 131.41 (C_{ipso}), 133.71 (C_p), 156.52 (NHCO), 166.75 (CO). Anal. calcd for $C_{18}H_{25}NO_6$: C, 61.52%; H, 7.17%; N, 3.99%. Found: C, 61.15%; H, 7.29%; N, 3.81%.

*4.32. 2-Benzoyloxymethyl-2-*N-tert-*butoxycarbonylamino-2,3-dihydrofuran* ***37***

Sodium periodate (40 mg, 3.0 mmol) was added in small portions to a solution of diol **36** (100 mg, 0.3 mmol) in THF–water (3.5+1.5 mL). The mixture was stirred at room temperature for 15 min, then evaporated to dryness. The residue was poured into water (5 mL) and the aqueous solution was extracted with dichloromethane (4×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed. The residue was chromatographed (1:3, ether:hexane) to afford **37** as a solid (yield: 47 mg, 51%). Crystals, mp 93–95°C (from ether/pentane). IR (KBr) 3385, 1724, 1625 cm^{-1}. ^1H NMR ($CDCl_3$) 1.41 (s, $C(CH_3)_3$), 2.74 (dt, H_3, J=16.1 Hz, J'=J''=2.20 Hz), 3.01 (d, H_3, J=16.1 Hz), 4.45 (d, CH_2OBz, J=11.7 Hz), 4.57 (d, CH_2OBz, J=11.7 Hz), 4.95 (d, H_4, J=2.20 Hz), 5.50 (broad s, NH), 6.29 (d, H_5, J=2.20 Hz), 7.41 (t, 2H_m, J=J'=7.3 Hz), 7.54 (t, H_p, J=J'=7.3 Hz), 8.00 (d, 2H_o, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) 28.21 (C(*C*H_3)$_3$), 37.46 (C_3), 66.30 (CH_2OBz), 80.41 (*C*$(CH_3)_3$), 93.40 (C_2), 99.17 (C_4), 128.31 (2C_m), 129.45 (C_{ipso}), 129.70 (2C_o), 133.19 (C_p), 144.08 (C_5), 153.53 (NHCO), 166.08 (CO). Anal. calcd for $C_{18}H_{25}NO_6$: C, 63.94%; H, 6.63%; N, 4.39%. Found: C, 64.21%; H, 6.44%; N, 4.51%.

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References

1. Occhiato, E.; Jones, J. B. *Tetrahedron* **1996**, *52*, 4199.
2. Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem*. **1999**, *64*, 498.
3. Hendrix, M.; Alper, P. B.; Priestley, E. S.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 95.
4. (a) Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett*. **1987**, *28*, 6263. (b) Genow, M.; Dimitrov, V.; Ivanova, V. *Tetrahedron: Asymmetry* **1997**, *22*, 3703. (c) Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc*. **1996**, *118*, 5502.
5. (a) Eliel, E. L.; He, X.-C. *J. Org. Chem*. **1990**, *55*, 2114. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835. (c) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett*. **1999**, *40*, 819.
6. (a) Csuk, R.; von Scholz, Y. *Tetrahedron* **1994**, *50*, 10431. (b) *Ibid.* **1995**, *51*, 7193. (c) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem*. **1995**, *60*, 5236. (d) Lee, M. G.; Du, J. F.; Chun, M. W.; Chu, C. K. *Ibid*. **1997**, *62*, 1991.

7. (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamasihita, K.; Matsuda, A. *J. Org. Chem*. **1996**, *61*, 915. (b) Shuto, S.; Ono, S.; Hase, Y.; Ueno, Y.; Noguchi, T.; Yosihi, K.; Matsuda, A. *J. Med. Chem*. **1996**, *39*, 4844.
8. Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem*. **1998**, *41*, 1284.
9. (a) Jiménez, J. M.; Rifé, J.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1849. (b) *Ibid*. **1996**, *7*, 537.
10. Pirrung, M. C.; Dunlop, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. These authors prepared (+)-(*Z*)-methanohomoserine in 27% yield from (+)-(*S*)-epichlorohydrine.
11. Hubschwerlen, C. *Synthesis* **1986**, 962.
12. Rifé, J.; Ortuño, R. M. *Org. Lett*. **1999**, *1*, 1221.