Synthesis of 8-*epi*-castanospermine and 6,7,8-tri-*epi*-castanospermine

Yves St-Denis and Tak Hang Chan

Abstract: 8-*epi*-Castanospermine (**11**) and 6,7,8-tri-*epi*-castanospermine (**12**) were synthesized from the hydroxyproline precursor **13** which was obtained enantioselectively via an enzymatic process.

Key words: castanospermine, synthesis of, enzymatic reduction, enzymatic resolution, asymmetric synthesis.

Résumé : On a synthétisé les 8-*épi*-castanospermine (**11**) et 6,7,8-tri-*épi*-castanospermine (**12**) à partir du précurseur hydroxyproline (**13**) obtenu de façon énantiosélective par le biais d'un processus enzymatique.

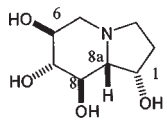
Mots clés : castanospermine, synthèse, réduction enzymatique, résolution enzymatique, synthèse asymétrique.

Introduction

Castanospermine (**1**) is a polyhydroxylated indolizidine alkaloid which has elicited much biological and chemical interest (1). It was isolated from the Australian legume *Castanospermum australe* (Moreton Bay chestnut) and has been shown to be a potent inhibitor of various glycosidases (2). It also inhibits the processing of *N*-linked glycoproteins (3). Castanospermine and its analogs have been examined as potential therapeutic agents (4) in the treatment of cancer (5) and HIV-I (6). Epimers of castanospermine, including 6-*epi*-castanospermine (**2**) (7) and 6,7-di-*epi*-castanospermine (**3**) (8), have been isolated as well. Comparison of their inhibitory activities toward different glycosidases showed that the change of stereochemistry at a single hydroxy group could alter the inhibitory properties.

Many syntheses of **1** and its modifications have been reported (9). A commonly used synthetic approach is to start with the appropriate carbohydrate precursor. Depending on the carbohydrate precursor used, epimers of castanospermine have also been synthesized. Thus, the syntheses of 6-*epi*- (**2**), 1,6-di-*epi*- (**4**), 1-*epi*- (**5**), 1,6,8-tri-*epi*- (**6**), 1,7,8-tri-*epi*- (**7**), and 1,6,7,8-tetra-*epi*-castanospermine (**8**) have all been reported (10). We recently reported on the use of the amino acid derivative (*S*)-prolinol (**9**) as the precursor for the synthesis of various isomers of 1-deoxycastanospermine (**10**) (11, 12, footnote 2). We have now extended the approach by starting with an amino acid precursor with the incorporation of the 1-hydroxy function. The results gave rise to a synthesis of 8-*epi*- (**11**) and 6,7,8-tri-*epi*-castanospermine (**12**) (13).

Structure 1.



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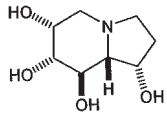

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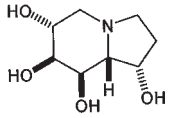

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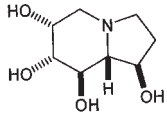

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Dedicated to Professor Stephen Hanessian on the occasion of his 65th birthday in recognition of his significant contributions to the art of organic synthesis.

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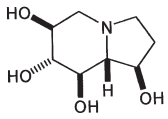
[2]Recent work by Martin et al. (12) has led to reassignment of the stereochemistry of the compounds reported by us in reference 11. The revised stereochemistries should be: compound **22aa**: 6*R*, 7*S*, 8*R*, 8a*S*; **22ab**: 6*S*, 7*R*, 8*R*, 8a*S*; **22ba**: 6*S*, 7*R*, 8*S*, 8a*S*; **22bb**:

Structure 5.



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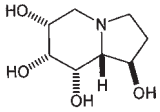

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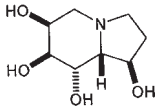

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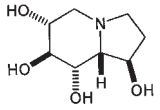

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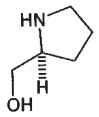

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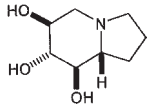
Structure 10.



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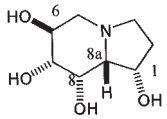
Structure 11.



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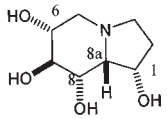
Structure 12.



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Results and discussion

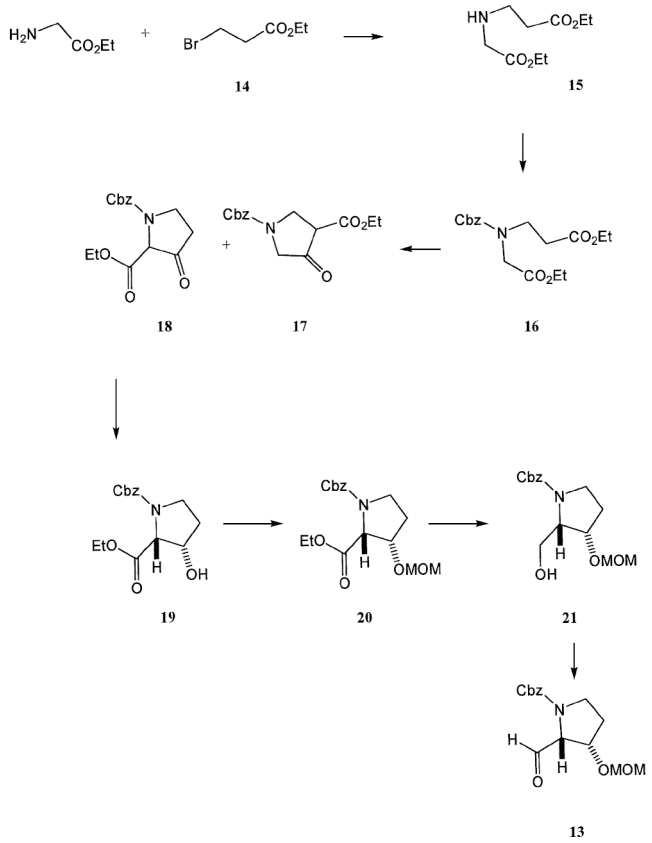
Preparation of (2*R*,3*S*)-*N*-benzyloxycarbonyl-3-methoxymethyloxypyrrolidine-2-carboxaldehyde (13)

Since the stereochemistry of the 8a position of castanospermine itself corresponds to the unnatural *R*-configuration of proline, the requisite 3-hydroxylated proline precursor **13** cannot be prepared from the natural amino acids. In the literature, Sih and coworkers have used microbial enzymatic reduction or hydrolysis to prepare (2*R*,3*S*)-3-hydroxyproline derivatives (3*b*). Alternatively, Sibi and Christensen improved an already known baker's yeast reduction method to give the (2*R*,3*S*)-Boc-protected proline ester in good chemical and optical yields (14). Since the baker's yeast reduction is easy to perform, we adopted this method with modification (15) to prepare the Cbz protected compound **13** according to Scheme 1. Thus, condensation of ethyl 3-bromopropionate (**14**) with freshly prepared ethyl glycinate was accomplished in refluxing benzene to give a good yield of the *N*,*N*-disubstituted aminodiester **15**. Protection of the free amine with the Cbz group was performed to provide the carbamate **16** in good yield (16). Dieckmann cyclization of **16** using potassium *t*-butoxide in toluene afforded a 1.3:1 mixture of regioisomers **17** and **18** which could be separated by distillation and chromatography. Even though the required **18** was the minor isomer, the sequence for its preparation was nevertheless quite short and utilized cheap and readily available starting materials. Baker's yeast reduction of **18** gave the (2*R*,3*S*)-β-hydroxyester **19** in good enantioselectivity (>99% ee). For comparison purpose, sodium borohydride reduction of **18** in ethanol gave the racemic **19** as the sole diastereomer, spectroscopically identical to the enantiomerically pure compound. Many of the subsequent reactions could therefore be explored with the racemic compound first. Protection of the secondary alcohol of (+)-**19** with the MOM protecting group gave compound **20**. Reduction of **20** with lithium borohydride in ether gave a good yield of the primary alcohol **21**, which was oxidized by the Swern oxidation to the aldehyde **13** in quantitative yield.

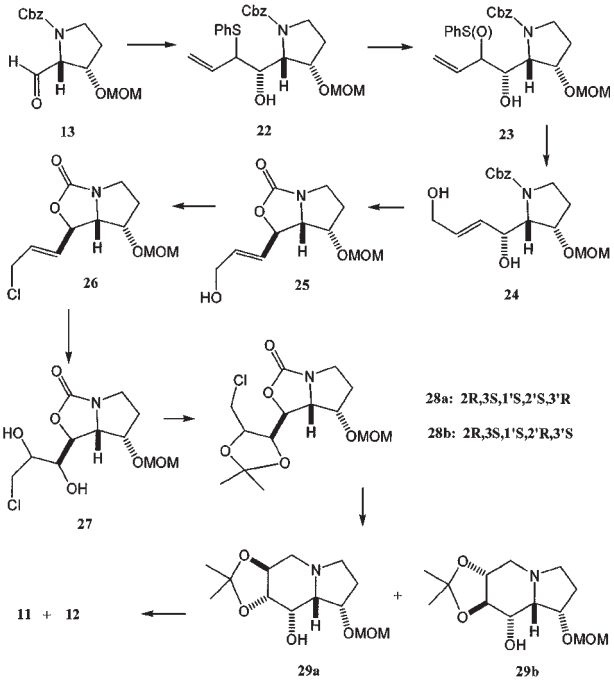
Synthesis of 8-*epi*- (11) and 6,7,8-tri-*epi*-castanospermine (12) (Scheme 2)

Coupling of **13** with the titanium reagent derived from the anion of allyl phenyl sulfide gave only one stereoisomer, **22** (17). It is interesting to compare the stereoselectivity in the present coupling with our previously reported coupling of *N*-Cbz-pyrrolidine-2-carboxaldehyde where the 3-MOM substituent was missing (11). The stereoselectivity is much higher in the present case, presumably due to the influence of the MOM group. Since it was established by Yamamoto and co-workers that the coupling reaction gave excellent erythro selectivity (17), the two newly created stereogenic centers could have either the 1′*S*, 2′*S* or the 1′*R*, 2′*R* configurations. Definitive assignment could not be made at this point. Furthermore, the stereochemistry at the carbon 2 position is of no real interest to us since it will be destroyed in the subsequent reactions. In any case, oxidation of the

Scheme 1.



Scheme 2.



sulfide **22** to the corresponding sulfoxide **23** followed by trimethyl phosphite treatment (18) gave the rearranged diol **24**. In conformity with similar rearrangements observed previously (11), the double bond in **24** was expected to have the *trans* stereochemistry. This was confirmed through the coupling constants of the olefinic protons in the bicyclic compound **25** prepared by intramolecular cyclization of **24** under basic conditions. The primary allylic alcohol function in **25** was transformed to the chloride **26** with triphenylphosphine in carbon tetrachloride (19). Hydroxylation of the double bond of **26** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (20) led to an inseparable mixture of diols **27a** and **27b**. Conversion of the diols to the corresponding acetonides allowed separation into individual compounds **28a** and **28b** in a ratio of about 5:3. Base hydrolysis of compound **28a,** the major isomer, followed by spontaneous intramolecular cyclization gave the protected indolizidine **29a**. Removal of the MOM and the isopropylidene protecting groups of **29a** under aqueous acidic conditions gave in quantitative yield the product **11** which we subsequently assigned the structure as (+)-8-*epi*-castanospermine (vide infra). Base hydrolysis of **28b**, the minor isomer, led not only to cyclization but deprotection as well to give product **12** to which the structure 6,7,8-tri-*epi*-castanospermine was assigned.

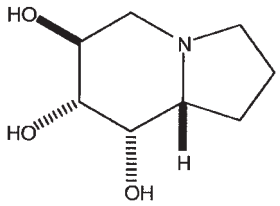
Assignment of stereochemistry

Castanospermine (**1**) itself has the 1*S*, 6*S*, 7*R*, 8*R*, and 8a*R* configurations. From the ^{1}H and ^{13}C NMR spectra of compounds **11** and **12**, it is clear that they are not identical to that of castanospermine (9*f*). In starting from the known pyrrolidinecarboxaldehyde **13**, the stereochemistries of carbons 1 and 8a (corresponding to carbons 2 and 3 of **13**) are secured as 1*S* and 8a*R* in the final products **11** and **12**. Since the dihydroxylation of double bond with osmium tetroxide has been well established to give the *cis* diol (20), the relative stereochemistry of carbons 6 and 7 in compounds **11** and **12** must be *trans*. There were two reactions in Scheme 2 which could give rise to uncertain stereochemical outcomes. The first was the conversion of **13** to **22**, which created the stereogenic carbon 8 in the final products. The stereochemistry could be either 8*S* or 8*R*. The second was that, in the hydroxylation step, the relative stereochemistry of the *cis* diol with respect to the existing stereogenic carbon 8 could be *syn* or *anti* (21). Consequently, there could be four stereochemical outcomes from Scheme 2. If, in the conversion of **13** to **22** the stereochemistry was 8*R*, then the final two products must have either 1*S*, 6*S*, 7*R*, 8*R*, 8a*R* (castanospermine **1**) or 1*S*, 6*R*, 7*S*, 8*R*, 8a*R* (6,7-di-*epi*-castanospermine **3**) stereochemistry. These two possibilities can be ruled out because the NMR spectra of neither **11** nor **12** correspond to the known **1** (9*f*) and **3** (8). If, on the other hand, in the conversion of **13** to **22** the stereochemistry was 8*S*, then the final two products must have either 1*S*, 6*S*, 7*R*, 8*S*, 8a*R* (8-*epi*-castanospermine) or 1*S*, 6*R*, 7*S*, 8*S*, 8a*R* (6,7,8-tri-*epi*-castanospermine) stereochemistry. We were able to assign compound **11** to the 8-*epi*-castanospermine structure based on comparison of the coupling constants in the ^{1}H NMR spectrum of **11** with those reported for the various stereoisomers of castanospermine (Table 1). In particular, the H6 proton has a *trans*-diaxial coupling with H7 (J = 9.5 Hz), which has a gauche coupling with H8 (J = 3.0 Hz), fully compatible with the 6*S*, 7*R*, 8*S* relative configurations of *trans*-diaxial/gauche relationship between the three protons. Martin et al. recently reported on the synthesis of 1-deoxy-8-*epi*-castanospermine (**30**) (22). The three protons

Table 1. Partial ^{1}H NMR spectra of castanospermine and epimers.

	Castanospermine (**1**)[a]	6,7-*epi*- (**3**)[b]	Compound **11**[c]	1-Deoxy-8-*epi*- (**30**)[d]
H6	3.41–3.47 (m) for H6 and H8	3.98 (dd, *J* = 1.5, 2) for H6 and H7	3.43 (ddd, *J* = 5.5, 9.5, 11.2)	3.72 (ddd, *J* = 5.2, 9.6, 10.7)
H7	3.15 (t, *J* = 9.0)	see H6	2.96 (dd, *J* = 3.0, 9.5)	3.34 (dd, *J* = 3.5, 9.6)
H8	see H6	4.08 (dd, *J* = 2, 10)	3.89 (dd, *J* = 1.0, 3.0)	3.84 (dd, *J* = 1.4, 3.5)

[a]Reference 9f.
[b]Reference 3.
[c]This work.
[d]Reference 12.



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H6, H7, and H8 in compound **30** have the same relative configurations of 6*S*, 7*R*, and 8*S* and similar coupling constants of $J_{H6–H7}$ = 9.6 Hz and $J_{H7–H8}$ = 3.5 Hz.

Experimental[3]

The assignment of the peaks for some ^{1}H and ^{13}C NMR spectra were complicated because of the geometric isomers produced by the Cbz group in compounds **16**, **18**, **19**, **20**, **21**, **13**, **22**, and **24**.

Ethyl *N*-(2-ethoxycarbonylethyl)-glycinate (15)

To a solution of freshly prepared ethyl glycinate (10.2 g, 98.4 mmol: from ethyl glycinate hydrochloride neutralized with 10 M NaOH: pH 9.5 and extracted with chloroform) in dry benzene (10 mL) was added ethyl 3-bromopropionate (**14**. 6.3 mL, 0.5 equiv.) in benzene (5 mL). A white solid formed immediately upon addition. The suspension was heated at 60°C for 5 h and poured into saturated aqueous sodium carbonate solution. The aqueous phase was extracted with chloroform (3×) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was distilled (95°C, 0.25 mm Hg) to yield **15** as a colorless oil (6.3 g, 63%). IR (neat): 3348, 2985, 1721, and 1121 cm^{-1}. ^{1}H NMR ($CDCl_3$): 4.05 (q, 2H, *J* = 7.2), 4.01 (q, 2H, *J* = 7.2), 3.27 (s, 2H), 2.76 (t, 2H, *J* = 6.6), 2.36 (t, 2H, *J* = 6.6), 1.72 (s, 1H), 1.14 (t, 3H, *J* = 7.2), 1.12 (t, 3H, *J* = 7.2). ^{13}C NMR ($CDCl_3$): 172.8, 172.6, 61.1, 60.8, 51.2, 45.1, 35.2, 14.6. MS: 204 (5), 203 (7), 174 (2), 158 (4), 130 (100), 116 (49), 84 (76), 56 (14), 42 (38).

Ethyl *N*-benzoxycarbonyl-*N*-(2-ethoxycarbonylethyl)-glycinate (16)

To a solution of **15** (3.88 g, 20.2 mmol) in dry acetonitrile (40 mL) at 0°C, under argon, was added slowly benzyl chloroformate (3.17 mL, 1.1 equiv.). The solution was stirred at 0°C for 1 h after which it was poured into water (50 mL). The phases were separated and the aqueous layer was extracted with methylene chloride (3×). The combined organic extracts were washed with 5% HCl, water, brine, and dried ($MgSO_4$). Evaporation of the solvents was followed by distillation (198°C, 0.25 mm Hg) to afford **16** as a colorless oil (5.4 g, 80%). IR (neat): 2978, 1722, and 1693 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.40–7.18 (m, 5H), 5.13 + 5.07 (2s, 2H), 4.14 + 4.11 (2q, 2H, *J* = 7.1), 4.06 (2q, 2H, *J* = 7.1), 3.59 + 3.58 (2t, 2H, *J* = 6.4), 2.64 + 2.58 (2t, 2H, *J* = 6.4), 1.22 + 1.15 (2t, 3H, *J* = 7.1), 1.21 + 1.20 (2t, 3H, *J* = 7.1). ^{13}C NMR ($CDCl_3$): 172.7 + 172.4, 170.4 + 170.3, 156.7 + 156.2, 136.8, 129.0 + 128.9, 128.5 + 128.4, 128.3 + 128.2, 68.0 + 67.8, 61.6, 61.1 + 61.0, 50.9, 45.8 + 45.0, 34.6 + 34.0, 14.6. MS: 337 (4), 229 (2), 264 (2), 220 (12), 202 (28), 91 (100).

Ethyl *N*-benzoxycarbonyl-3-oxopyrrolidine-2-carboxylate (18)

To a suspension of potassium *t*-butoxide (2.52 g, 1.4 eq) in dry toluene (54 mL) at 0°C, under argon, was added **16** (5.41 g, 16.0 mmol) in toluene (10 mL) over a period of 10 min. The suspension was stirred at 0°C for 30 min after which 2 mL of glacial acetic acid were added, immediately followed by a solution of sodium dihydrogen phosphate hydrate (9.1 g) in water (91 mL). The heterogeneous mixture was extracted with chloroform (3×), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in cold toluene (100 mL) and washed with cold, pH 9.5 carbonate buffer (3×). The toluene solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was distilled (Kugelrohr: oven temperature 160°C, 0.03 mm Hg) and the distillate was purified by flash chromatography over silica gel with hexanes:ethyl acetate (2:1) as eluent. Compound **18** was obtained as a colorless oil (slightly contaminated with compound **17**). IR (neat): 2978, 1741, 1712, and 1695 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.41–7.23 (m, 5H), 5.22 + 5.15 and 5.20 + 5.07 (2 AB, 2H, *J* = 8.2), 4.58 + 4.54 (2s, 1H), 4.24 (q, 2H, *J* = 4.7), 4.08 (m, 1H), 3.96 (m, 1H), 3.85 (m, 1H), 2.67 (t, 2H, *J* = 4.9), 1.28 + 1.14 (2t, 3H, *J* = 4.7). ^{13}C NMR ($CDCl_3$): 204.6, 166.4, 154.9, 136.6 + 136.4, 128.9, 128.7,

[3]For general experimental conditions, see reference 11.

128.5 + 128.4, 68.03, 65.9 + 65.8, 62.8, 42.6, 37.3 + 36.7, 14.5 + 14.4. MS: 292 (100), 248 (80), 176 (32), 158 (23).

Ethyl (2*R*,3*S*)-*N*-benzoxycarbonyl-3-hydroxypyrrolidine-2-carboxylate (19)

To a solution of sucrose (300 mg) in distilled water (4.1 mL) was added baker's yeast (200 mg). The flask was equipped with a bubble counter and the suspension was heated at 32°C for 1 h. The content of the flask was then poured into a 15 mL flask containing the keto ester **18** (0.12 g, 0.42 mmol). Stirring was continued for 24 h after which additional sucrose (300 mg) in warm (40°C) distilled water (1 mL) was added. After 48 h, celite (500 mg) was added to the mixture and the suspension was filtered through a sintered glass funnel (medium porosity). After the filtrate was washed with water, the aqueous layer was extracted with ether (3×) and the combined organic extracts were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue was purified by flash chromatography (silica gel, 3:7 hexanes:ethyl acetate) to give the optically active compound **19** (55 mg, 45%). $[\alpha]_D^{20}$ = +22.8° (*c*: 2.7 in CH_2Cl_2); lit. $[\alpha]_D^{20}$ = +21.9° (*c*: 2.0 in CH_2Cl_2)(15). IR (neat): 3378, 2978, 1741, 1701 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40–7.22 (m, 5H), (5.13 + 5.00) + 5.11 (1 AB and 1s, 2H, J_{AB} = 12.5), 4.56 (q, 1H, *J* = 6.4), 4.39 (t, 1H, *J* = 6.4), 4.19–4.06 (m, 2H), 3.66 (m, 1H), 3.49 (m, 1H), 2.02 (m, 1H), 1.23 + 1.11 (2t, 3H, *J* = 7.1). ^{13}C NMR ($CDCl_3$): 170.7 + 170.5, 155.4 + 154.9, 136.9 + 136.8, 128.9 + 128.8, 128.5, 128.4 + 128.2, 72.7 + 71.8, 67.6, 64.4 + 64.1, 61.8 + 61.7, 44.9 + 44.7, 33.2 + 32.4, 14.6 + 14.5. Exact mass calcd. for $C_{15}H_{19}NO_5$ ($M^{\cdot+}$ + H): 294.1342, found: 284.1341.

Racemic **19** was prepared by the reduction of **18** with sodium borohydride. To a solution of **18** (0.29 g, 0.72 mmol) in absolute ethanol (3.6 mL) at 0°C, under argon, was added sodium borohydride (29.8 mg, 1.1 equiv.). The solution was stirred at 0°C for 60 min after which a few drops of acetic acid were added. The solution was poured in saturated aqueous sodium bicarbonate and the aqueous layer was extracted with ether (3×). The combined organic extracts were washed with brine and dried ($MgSO_4$). After fitration, the solvents were evaporated and the residue was purified by flash chromatography to give racemic **19** (0.14 g, 66%), identical in all spectroscopic aspects with those of (+)-**19**.

Ethyl (2*R*,3*S*)-*N*-benzoxycarbonyl-3-methoxymethyloxypyrrolidine-2-carboxylate (20)

To a solution of the alcohol (+)-19 (0.14 g, 0.48 mmol) in methylene chloride (4.8 mL) at 0°C, under argon, was successively added diisopropylethylamine (0.25 mL, 3 equiv.) and chloromethyl methyl ether (0.11 mL, 3 equiv.). The solution was stirred at rt for 24 h after which it was poured into 5% HCl. The aqueous phase was extracted with methylene chloride (3×) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash chromatography on silica gel with 1:1 hexanes:ethyl acetate as eluent to give compound **20** as a colorless oil (0.15 g, 92%). $[\alpha]_D^{20}$ = –18.4° (*c*: 1.1 in $CHCl_3$). IR (neat) : 2957, 1746, 1701 cm^{-1}. ^1H NMR ($CDCl_3$): 7.42–7.20 (m, 5H), (5.14 + 5.02) + 5.11 (AB + s, 2H, J_{AB} = 12.2), (4.68 + 4.60) + (4.66 + 4.58) (2 AB, 2H, *J* = 6.9), 4.21–4.07 (2q, 2H, *J* = 7.1), 3.70 (m, 1H), 3.49 (m. 1H), 3.34 + 3.33 (2s, 3H), 2.10 (m, 2H), 1.25 + 1.14 (2t, 3H, *J* = 7.1). ^{13}C NMR ($CDCl_3$): 170.0 + 169.9, 155.2 + 154.8, 136.9, 128.9 + 128.8, 128.5 + 128.4, 128.2, 96.1, 76.7 + 76.0, 67.6, 62.6 + 62.3, 61.5 + 61.4, 56.2, 44.8 + 44.6, 31.0 + 30.2, 14.7 + 14.6. Exact mass calcd. for $C_{17}H_{23}NO_6$ ($M^{\cdot+}$ + H): 338.1605, found: 338.1604.

(2*S*,3*S*)-*N*-Benzoxycarbonyl-2-hydroxymethyl-3-methoxymethyloxypyrrolidine (21)

To a solution of the ester **20** (0.84 g, 2.48 mmol) in ether (25 mL) at 0°C, under argon, was added lithium borohydride (0.12 g, 2.2 eq) and the suspension was stirred at 0° for 4 h. Acetic acid (1 mL) was then added to destroy the excess hydride and the solution was poured in saturated aqueous sodium bicarbonate solution. The phases were separated and the aqueous phase was extracted with ether (2×). The combined organic phase was washed with brine and dried ($MgSO_4$). Filtration and evaporation of the solvent was followed by flash chromatography (silica gel, 4:6 hexanes:ethyl acetate) of the residue to give alcohol **21** as a colorless oil (0.53 g, 72%). $[\alpha]_D^{20}$ = +44.7° (*c*: 1.1 in $CHCl_3$). IR (neat): 3450, 2948, 2888, 1704 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40–7.22 (m, 5H), 5.12 (s, 2H), 4.71–4.58 (m, 2H), 4.32 (q, 1H, *J* = 5.3), 3.96 (m. 1H), 3.89–3.75 (m, 2H), 3.51 (t, 2H, *J* = 6.8), 3.36 (s, 3H), 3.27 (bs, 1H), 1.98 (t, 2H, *J* = 6.8). ^{13}C NMR ($CDCl_3$): 156.9, 136.9, 129.0, 128.6, 128.4, 96.2, 77.8, 67.7, 63.4, 63.2, 56.3, 45.1, 30.6. Exact mass calcd. for $C_{15}H_{21}NO_5$ ($M^{\cdot+}$ + H): 296.1499, found: 296.1498.

(2*R*,3*S*)-*N*-Benzoxycarbonyl-3-methoxymethyloxypyrrolidine-2-carboxaldehyde (13)

Dimethyl sulfoxide (49.3 µl, 2.84 equiv.) was slowly added to a solution of oxalyl chloride (30.1 µl, 1.41 equiv.) in methylene chloride (2 mL) under argon at –78°C. The colorless solution was stirred for 15 min after which a solution of the alcohol **21** (72.2 mg, 0.24 mmol) in methylene chloride (1 mL) was added dropwise over a period of 5 min. A white precipitate was formed and the suspension was stirred for 1 h. Triethylamine (0.17 mL, 5 equiv.) in methylene chloride was added and the solution was allowed to slowly warm to room temperature. The mixture was diluted with methylene chloride (10 mL) and washed successively with 5% HCl, water, brine, and dried ($MgSO_4$). Evaporation of the solvent under vacuum gave a pale brown oil which was purified by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) to give the aldehyde **13** as a pale yellow oil (70.0 mg, 98%). $[\alpha]_D^{20}$ = +70.4° (*c*: 1.1 in $CHCl_3$). IR (neat): 2958, 2888, 1736, 1701 cm^{-1}. ^1H NMR ($CDCl_3$): 9.53 + 9.44 (2d, 1H, *J* = 2.5), 7.42–7.21 (m, 5H), 5.14 + 5.09 (2s, 2H), 4.72–4.51 (m, 3H), 4.27 + 4.21 (2dd, 1H, *J* = 2.5, 5.7), 2.75–3.60 (m, 2H), 3.29 (s, 3H), 2.16–1.80 (m, 2H). ^{13}C NMR ($CDCl_3$): 200.2 + 200.1, 155.7 + 154.8, 136.8 + 136.6, 129.0, 128.6, 128.5 + 128.4, 95.8, 79.4 + 78.3, 68.4 + 68.0, 67.8, 56.3, 45.7 + 45.1, 31.5 + 30.9. Exact mass calcd. for $C_{15}H_{19}NO_5$ ($M^{\cdot+}$ + H): 294.1342, found: 294.1341.

(2*R*,3*S*,1′*S*,2′*S*)-*N*-Benzoxycarbonyl-2-(1′-hydroxy-2′thiophenyl-3′-butenyl)-3-methoxymethyloxypyrrolidine (22)

To a solution of allyl phenyl sulfide (0.35 g, 15 equiv.) in dry THF (10.5 mL) at –78°C, under argon, was added

n-butyllithium (2.0 M in pentane, 1.16 mL, 1.5 equiv.) and the solution was stirred at 0°C for 30 min. It was then brought back to –78°C and titanium (IV) isopropoxide (0.69 mL, 1.5 equiv.) was added slowly. After 10 min, aldehyde **13** (0.45 g, 1.55 mmol) in THF (5 mL) was added over a period of 10 min. The solution was stirred for 10 min and warmed up at 0°C for 30 min. It was then poured into 5% HCl and extracted with ether (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Evaporation of the solvent followed by flash chromatography (silica gel, 1:1 hexanes:ethyl acetate) gave the product **22** as a colorless oil (0.49 g, 72%). $[\alpha]_D^{20}$ = +50.2° (*c*: 1.1 in $CHCl_3$). IR (neat): 3424, 2948, 2893, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): 7.54–7.09 (m, 10H), 6.06 (m, 1H), 5.12 (s, 2H), 5.06 (d, 1H, *J* = 10.7), 4.90 (d, 1H, *J* = 17.2), 4.63 (s, 2H), 4.60 (m, 1H), 4.26 (q, 1H, *J* = 6.0), 4.14 (bs, 1H), 3.95 (d, 1H, *J* = 9.6), 3.66–3.42 (m, 2H), 3.33 (s, 3H), 2.15–1.84 (m, 2H). ^{13}C NMR ($CDCl_3$): 158.2, 136.7, 134.9, 133.4, 129.1, 128.7, 128.6, 127.6, 126.0, 118.5, 96.4, 77.1, 72.8, 68.0, 63.1, 56.8, 56.5, 45.3, 30.8. Exact mass calcd. for $C_{24}H_{29}NO_5S$ ($M^{\cdot+}$ + H): 444.1846, found: 444.1845.

(2*R*,3*S*,1′*R*)-*N*-Benzoxycarbonyl-2-(1′,4′-dihydroxy-2′-butenyl)-3-methoxymethyloxypyrrolidine (24)

To a solution of the hydroxysulfide **22** (0.49 g, 1.11 mmol) in methylene chloride (11.1 mL) at 0°C under argon was added *m*-chloroperoxybenzoic acid (0.27 g, 1.4 equiv.) and the solution was stirred for 60 min. It was then dissolved in ether, washed with saturated aqueous sodium bicarbonate solution (2×), dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was dissolved in dry methanol (11.1 mL) and trimethyl phosphite (0.65 mL, 5 equiv.) was added slowly. After 2 h of stirring at 60°C, the methanol was evaporated and the thick residual oil was purified by flash chromatography (silica gel, 2:8 hexanes:ethyl acetate, then ethyl acetate as eluents) to give the allylic alcohol **24** (0.28 g, 71%). $[\alpha]_D^{20}$ = +31.2° (*c*: 1.5 in $CHCl_3$). IR (neat): 3450, 2948, 2888, 1704, 1671 cm^{-1}. ^1H NMR ($CDCl_3$): 7.42–7.21 (m, 5H), 5.96–5.70 (m, 2H), 5.12 (s, 2H), 4.67 (s, 2H), 4.51 (m, 1H), 4.29 (m, 1H), 4.21–3.88 (m. 3H), 3.62–3.43 (m, 2H), 3.37 (s, 3H), 3.29 (m, 1H), 3.16 (bs, 1H), 2.20–1.91 (m, 2H). ^{13}C NMR ($CDCl_3$): 157.3, 136.9, 131.8, 131.0, 129.0, 128.6, 128.4, 97.0, 78.2, 72.1, 67.8, 63.2, 56.4, 45.5, 30.9. Exact mass calcd. for $C_{18}H_{25}NO_6$ ($M^{\cdot+}$ + H): 352.1761, found: 352.1760.

(2*R*,3*S*,1′*R*)-1,1′-*N*,*O*-Carbonyl-2-(1′,4′-dihydroxy-2′-butenyl)-3-methoxymethyloxypyrridine (25)

To a solution of the allylic diol **24** (0.21 g, 0.61 mmol) in 2-propanol:water (2:1, 6.1 mL) was added finely powdered potassium carbonate (0.17 g, 2 equiv.) and the solution was heated at 65°C for 15 h. The solvent was evaporated and the residue purified by flash chromatography (silica gel, ethyl acetate) to give the product **25** as a colorless oil (0.11 g, 77%). $[\alpha]_D^{20}$ = +99.6° (*c*: 1.1 in $CHCl_3$). IR (neat): 3436, 2946, 2895, 1751, 1674 cm^{-1}. ^1H NMR ($CDCl_3$): 5.96 (dt, 1H, *J* = 4.0, 15.5), 5.83 (dd, 1H, *J* = 6.5, 15.5), 5.04 (dd, 1H, *J* = 3.6, 6.5), 4.63 (AB, 2H, *J* = 7.0), 4.13 (d, 2H, *J* = 4.0), 4.08 (td, 1H, *J* = 0.9, 3.6), 3.62 (t, 1H, *J* = 3.6), 3.54 (ddd, 1H, *J* = 7.8, 9.5, 10.8), 3.32 (s, 3H), 3.19 (ddd, 1H, *J* = 2.1, 9.6, 10.8), 2.83 (bs, 1H), 2.25 (dddd, 1H, *J* = 0.9, 2.1, 7.8, 14.1), 1.92 (dddd, 1H, *J* = 3.6, 9.5, 9.6, 14.1). ^{13}C NMR ($CDCl_3$): 162.2, 134.5, 127.6, 95.5, 75.5, 75.4, 69.4, 62.3, 56.3, 44.2, 32.6. Exact mass calcd. for $C_{11}H_{17}NO_5$ ($M^{\cdot+}$ + H): 244.1186, found: 244.1185.

(2*R*,3*S*,1′*R*)-1,1′-*N*,*O*-Carbonyl-2-(1′hydroxy-4′-chloro-2′-butenyl)-3-methoxymethyloxypyrrolidine (26)

To a solution of the allylic alcohol **25** (0.11 g, 0.47 mmol) in a mixture of carbon tetrachloride:methylene chloride (4:1, 6.0 mL) were added successively finely powdered potassium carbonate (0.13 g, 2 equiv.) and triphenylphosphine (0.31 g, 2.5 equiv.) and the solution was stirred at 60°C for 8 h. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 2:8 hexanes:ethyl acetate) affording the chloride **26** (83.9 mg, 70%) as a pale yellow oil. $[\alpha]_D^{20}$ = +87.7° (*c*: 1.5 in $CHCl_3$). IR (neat): 2965, 2895, 1751 cm^{-1}. ^1H NMR ($CDCl_3$): 6.06–5.84 (m, 2H), 5.06 (dd, 1H, *J* = 3.6, 5.1), 4.65 (AB, 2H, *J* = 7.0), 4.11 (td, 1H, *J* = 1.1, 3.6), 4.05 (d, 2H, *J* = 6.2), 3.62 (t, 1H, *J* = 3.6), 3.58 (ddd, 1H, *J* = 7.9, 9.5, 11.0), 3.33 (s, 3H), 3.22 (ddd, 1H, *J* = 2.2, 9.7, 11.0), 2.28 (dddd, 1H, *J* = 1.1, 2.2, 7.9, 14.1), 1.93 (dddd, 1H, *J* = 3.6, 9.5, 9.7, 14.1). ^{13}C NMR ($CDCl_3$): 161.8, 131.7, 129.9, 95.5, 75.6, 74.4, 69.1, 56.4, 44.3, 43.9, 32.5. Exact mass calcd. for $C_{11}H_{16}NO_4Cl$ ($M^{\cdot+}$ + H): 262.0847, found: 262.0846.

(2*R*,3*S*,1′*S*,2′*S*,3′*R*)- and (2*R*,3*S*,1′*S*,2′*R*,3′*R*)-1,1′-*N*,*O*-Carbonyl-2-(1′,2′,3′-trihydroxy-4′-chlorobutanyl)-3methoxymethyloxypyrrolidine (27a and 27b)

To a solution of the chloride **26** (83.9 mg, 0.32 mmol) in a mixture of acetone:water:*t*-butanol (6:3:1, 2.0 mL) were added successively *N*-methylmorpholine-*N*-oxide (45.1 mg, 1.2 equiv.) and osmium tetroxide (15.0 mg, 0.05 equiv.). The orange solution was stirred at room temperature for 3 h, after which 2 mL of a solution-suspension of magnesium silicate and sodium hydrosulfite (1.2 g and 0.1 g respectively in 8 mL of water) was added. The slurry was filtered through celite and the cake was rinsed with acetone. The solvents were evaporated and the dark residual oil was purified by flash chromatography (silica gel, ethyl acetate) to provide a mixture of the products **27a** and **27b** (2:1 by NMR, 94.8 mg, 99%). IR (neat): 3335, 2952, 1751 cm^{-1}. ^1H NMR ($CDCl_3$): 4.83–4.59 (m, 3H), 4.09 (m, 2H), 3.95 (m, 1H), 3.86 (m, 1H), 3.77–3.46 (m, 5H), 3.32 (s, 3H), 3.27 (m, 1H), 2.29 (m, 1H), 2.01 (m, 1H). ^{13}C NMR ($CDCl_3$): **27a**: 162.1, 95.7, 76.1, 75.5, 71.1, 70.8, 66.1, 56.3, 45.8, 44.0, 33.0; **27b**: 162.0, 95.5, 76.4, 75.3, 72.1, 71.6, 66.0, 56.3, 45.8, 44.0, 32.8. Exact mass calcd. for $C_{11}H_{18}NO_6Cl$ ($M^{\cdot+}$ + H): 296.0902, found: 296.0901.

(2*R*,3*S*,1′*S*,2′*S*,3′*R*)- and (2*R*,3*S*,1′*S*,2′*R*,3′*S*)-1,1′-*N*,*O*-Carbonyl-2-(1′hydroxy-2′,3′-*O*-isopropylidene-4′-chlorobutanyl)-3-methoxymethyloxypyrrolidine (28a and 28b)

To a solution of the diol mixture **27a** and **27b** (94.8 mg, 0.32 mmol) in dry acetone (3.2 mL) at room temperature under argon were added 2,2-dimethoxypropane (0.20 mL, 5 equiv.) and camphorsulfonic acid (5.2 mg, 0.05 equiv.). The solution was stirred for 15 h at room temperature and heated at 40°C for 1 h after which a few drops of conc. ammonium hydroxide were added. The solvent was evaporated and the residue was taken up in ethyl acetate. The organic solution

was washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography (silica gel, 6:4 hexanes:ethyl acetate) purification gave **28a** (51.0 mg, 48%) and **28b** (31.7 mg, 29%) separately, for a combined yield of 77%. Compound **28a** (white solids): mp 74–76°C. $[\alpha]_D^{20}$ = +50.8° (*c*: 1.0 in $CHCl_3$). IR ($CHCl_3$): 2980, 1751 cm^{-1}. ^1H NMR ($CDCl_3$): 4.70 + 4.62 (AB, 2H, *J* = 7.0), 4.60 (dd, 1H, *J* = 3.2, 8.3), 4.21 (ddd, 1H, *J* = 3.8, 5.2, 7.0), 4.13 (td, 1H, *J* = 0.9, 3.2), 4.05 (dd, 1H, *J* = 7.0, 8.3), 3.88 (t, 1H, *J* = 3.2), 3.80 (dd, 1H, *J* = 3.8, 11.8), 3.65 (dd, 1H, *J* = 5.2, 11.8), 3.59 (ddd, 1H, *J* = 7.8, 9.5, 10.8), 3.34 (s, 3H), 3.26 (ddd, 1H, *J* = 2.1, 9.8, 10.8), 2.32 (dddd, 1H, *J* = 0.9, 2.1, 7.8, 14.1), 1.98 (dddd, 1H, *J* = 3.2, 9.5, 9.8, 14.1), 1.44 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$): 162.0, 112.1, 96.3, 80.8, 79.4, 76.5, 76.4, 67.7, 57.2, 45.7, 45.1, 33.5, 28.6, 28.4. Exact mass calcd. for $C_{14}H_{22}NO_6Cl$ ($M^{\cdot+}$ + H): 336.1215, found: 336.1214.

Compound **28b** (white solids): mp 153–155°C. $[\alpha]_D^{20}$ = +66.1° (*c*: 1.6 in $CHCl_3$). IR ($CHCl_3$): 2997, 1751 cm^{-1}. ^1H NMR ($CDCl_3$): 4.77 (dd, 1H, *J* = 1.8, 3.4), 4.71 + 4.63 (AB, 2H, *J* = 7.0), 4.40 (ddd, 1H, *J* = 4.4, 6.6, 7.5), 4.11 (td, 1H, *J* = 0.9, 3.4), 4.08 (dd, 1H, *J* = 1.8, 7.5), 3.91 (t, 1H, *J* = 3.4), 3.73 (dd, 1H, *J* = 4.4, 11.4), 3.62 (dd, 1H, *J* = 6.6, 11.4), 3.40 (ddd, 1H, *J* = 8.0, 9.5, 10.9), 3.34 (s, 3H), 3.31 (ddd, 1H, *J* = 2.1, 9.8, 10.9), 2.32 (dddd, 1H, *J* = 0.9, 2.1, 8.0, 14.3), 1.97 (dddd, 1H, *J* = 3.4, 9.5, 9.8, 14.3), 1.43 (s, 6H). ^{13}C NMR ($CDCl_3$): 171.1, 112.1, 96.4, 81.8, 76.7, 76.5, 74.1, 67.1, 57.3, 45.4, 45.3, 33.5, 28.6, 27.9. Exact mass calcd. for $C_{14}H_{22}NO_6Cl$ ($M^{\cdot+}$ + H): 336.1215, found: 336.1214.

(1*S*,6*S*,7*R*,8*S*,8a*R*)-1-Methoxymethyloxy-6,7-*O*-isopropylidene-8-hydroxyindolizidine (29a)

To a solution of the chloride **28a** (51.0 mg, 0.15 mmol) in a mixture of methanol:water (1:1, 2 mL) was added sodium hydroxide (18.3 mg, 3 equiv.) and the solution was stirred at 85°C for 18 h. The solvents were evaporated and the solid residue was extracted with chloroform. The chloroform solution was evaporated to give the aminoalcohol **29a** as a waxy solid (41.0 mg, 98%). $[\alpha]_D^{20}$ = +50.6° (*c*: 0.83 in $CHCl_3$). IR ($CHCl_3$): 3450, 2986 cm^{-1}. ^1H NMR ($CDCl_3$): 4.67 + 4.59 (AB, 2H, *J* = 7.1), 4.54 (bs, 1H), 4.46 (m, 1H), 4.35 (td, 1H, *J* = 4.2, 10.2), 3.49 (dd, 1H, *J* = 4.2, 9.3), 3.36 (s, 3H), 3.33 (m, 1H), 3.19 (t, 1H, *J* = 8.4), 2.25–2.12 (m, 4H), 1.95 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$): 111.5, 95.1, 83.2, 77.9, 77.7, 71.3, 68.4, 66.4, 54.0, 51.7, 32.5, 27.4, 27.1. Exact mass calcd. for $C_{13}H_{23}NO_5$ ($M^{\cdot+}$ + H): 274.1655, found: 274.1654.

(1*S*,6*S*,7*R*,8*S*,8a*R*)-1,6,7,8,-Tetrahydroxyindolidine (8-*epi*-castanospermine, 11)

A solution of compound **29a** (41.0 mg, 0.15 mmol) in a 4:4:2 mixture of 6 M HCl:water:tetrahydrofuran was stirred for 15 h after which the solvents were evaporated. The residue was dissolved in methanol and stirred for 1 h with Amberlyst A-26 ion exchange resin (OH^- form). Filtration followed by evaporation of the methanol gave a brownish solid which was purified by flash chromatography (silica gel, 70:20:5:5 chloroform:methanol:water:NH_4OH; spray reagent: $KMnO_4$–NaOH in water) affording the tetraol **11** as an off white solid in quantitative yield (28.4 mg). It had a melting point of 190–192°C. $[\alpha]_D^{20}$ = +44.4° (*c*: 1.3 in H_2O). IR (KBr): 3450 cm^{-1}. ^1H NMR (D_2O): 4.07 (ddd, 1H, *J* = 2.1, 4.5, 6.5), 3.89 (dd, 1H, *J* = 1.2, 3.0), 3.43 (ddd, 1H, *J* = 5.5, 9.5, 11.2), 3.09 (ddd, 1H, *J* = 4.4, 9.0, 10.0), 3.07 (dd, 1H, *J* = 5.5, 11.2), 2.96 (dd, 1H, *J* = 3.0, 9.5), 2.70 (d, 1H, *J* = 4.5), 2.45 (ddd, 1H, *J* = 7.9, 10.0, 10.1), 2.23 (t, 1H, *J* = 11.2), 1.87 (dddd, 1H, *J* = 4.4, 6.5, 10.1, 14.3), 1.31 (dddd, 1H, *J* = 2.1, 7.9, 9.0, 14.3). ^{13}C NMR (D_2O): 76.2, 73.1, 71.8, 69.8, 67.9, 56.0, 53.8, 35.4. Exact mass calcd. for $C_8H_{15}NO_4$ ($M^{\cdot+}$ + H): 190.1080, found: 190.1079.

(1*S*,6*R*,7*S*,8*R*,8a*R*)-1,5,7,8-Tetrahydroxyindolizidine (6,7,8-tri-*epi*-castanospermine, 12)

The same experimental procedures for the conversion of compound **28a** to **29a** were followed by starting with compound **28b**. The deprotection of the MOM ether group as well as the isopropylidene occurred during the cyclization. The reaction time was 36 h. The purification procedures for **11** were followed but with 70:24:3:3 chloroform:methanol:water:NH_4OH as eluent for the flash chromatography (silica gel) to give compound **12** in 65% yield. $[\alpha]_D^{20}$ = –7.3° (*c*: 1.0 in H_2O). IR (KBr): 3500 cm^{-1}. ^1H NMR (D_2O): 4.00 (ddd, 1H, *J* = 2.4, 4.8, 7.1), 3.55 (t, 1H, *J* = 4.3), 3.27 (t, 1H, *J* = 4.8), 3.14 (q, 1H, *J* = 4.2), 2.79–2.59 (m, 2H), 2.46–2.31 (m, 2H), 2.17 (m, 1H), 1.71 (dddd, 1H, *J* = 3.8, 7.1, 9.5, 14.0), 1.21 (dddd, 1H, *J* = 2.4, 8.8, 8.8, 14.0). ^{13}C NMR (D_2O): 74.5, 72.7, 72.6, 71.2, 68.07, 56.9, 55.0, 34.7. Exact mass calcd. for $C_8H_{15}NO_4$ ($M^{\cdot+}$ + H): 190.1080, found: 190.1079.

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