DOI: 10.1002/chem.200903490

A Flexible Approach to Azasugars: Asymmetric Total Syntheses of (+)-Castanospermine, (+)-7-Deoxy-6-*epi*-castanospermine, and (+)-1-*epi*-Castanospermine

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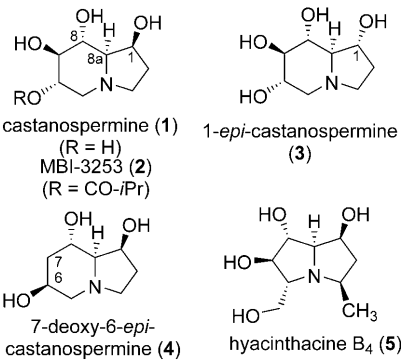
Abstract: The asymmetric total synthesis of natural azasugars (+)-castanospermine, (+)-7-deoxy-6-*epi*-castanospermine, and synthetic (+)-1-*epi*-castanospermine has been accomplished in nine to ten steps from a common chiral building block (*S*)-**8**. The method features a powerful chiral relay strategy consisting of a highly diastereoselective vinylogous Mukaiyama-type reaction with either chiral or achiral aldehydes ($\geq$95% *de*; *de* = diastereomeric excess) and a diastereodivergent reduction of tetramic acids, which allows formation of three continuous stereogenic centers with high diastereoselectivities. The method also provides a flexible access to structural arrays of 5-(α-hydroxyalkyl)tetramic acids, such as **17/34**, and 5-(α-hydroxyalkyl)-4-hydroxyl-2-pyrrolidinones, such as **18** and **25/35a**. The method constitutes the first realization of the challenging chiral synthons **A** and **D** and thus of the conceptually attractive retrosynthetic analysis shown in Scheme 1 in a highly enantioselective manner.

Keywords: alkaloids · asymmetric synthesis · Mukaiyama-type reaction · natural products · total synthesis

Introduction

Polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids, also known as azasugars, are an important class of sugar mimetic that exhibit important bioactivity.[1] Among them, castanospermine (**1**), an alkaloid[2] first isolated from the seeds of *Castanospermum australe* and then from the dried pod of *Alexa leiopetala*, has attracted considerable attention. As a powerful inhibitor of α- and β-glucosidases,[3] castanospermine (**1**) shows considerable potential as an antiviral agent in the treatment of HIV,[4] hepatitis C,[5] and HSV-1[6] infections. Castanospermine and its stereoisomers also have potential use in the inhibition of the progression of multiple sclerosis,[7] angiogenesis, cancer,[8] and diabetes.[9] MBI-3253 (celgosivir, 6-*O*-butanoyl castanospermine) (**2**), in combination with peginterferon **2b** alone (double combination therapy) or also with ribavirin (triple combination therapy) are under Phase II clinical trials for the treatment of patients with chronic HCV.[10–12] Several stereoisomers of castanospermine have also been isolated from natural sources.[13] The synthetic 1-*epi*-castanospermine (**3**)[14] was suggested to possess anti-HIV activity, and thus is a valuable synthetic target for full evaluation of its biological activity. In addition, 7-deoxy-6-*epi*-castanospermine (**4**) was isolated from the seeds of *Castanospermum australe*.[15] At the same time, these alkaloids provide a natural platform for exploring new synthetic methodologies.[16]



Numerous imaginative strategies have been developed for the enantioselective synthesis of castanospermine[16] and their stereoisomers.[14,17] However, novel, efficient, and flexi-

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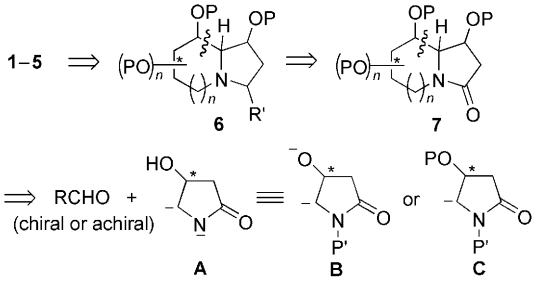
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903490.

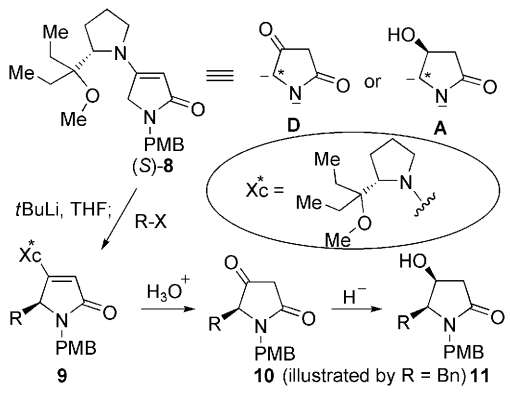
ble methods are still in high demand because of both the high biological and pharmaceutical potential of this class of compounds and the continuing discovery of new azasugars, such as hyacinthacine B_4 (**5**),[18] from natural sources. A conceptually attractive strategy for a general approach to azasugars, such as castanospermine (**1**), 1-*epi*-castanospermine (**3**), 7-deoxy-6-*epi*-castanospermine (**4**), and hyacinthacine B_4 (**5**), is illustrated retrosynthetically in Scheme 1. The



Scheme 1. Retrosynthetic analysis of polyhydroxylated alkaloids (azasugars). P = protecting group.

practical realization of this approach in a highly enantio- and diastereoselective manner has been hampered by the nonavailability of suitable synthetic methodology allowing the generation and/or stereoselective reaction of carbanions **B/C** corresponding to chiral synthon **A**.[19–21] The challenges associated with the chiral-synthon-**A**-based methodology are manifold, they include quick proton exchange of the carbanion **B**,[21] β-elimination of the carbanion **C**,[22] low stereoselective C–C bond formation[23] and access to the enantiomeric form of carbanions **B/C**.[19a,b]

In connection with a program aimed at the synthesis of 5-alkylteramic acids and 5-alkyltetramates, which are also key structural features found in many bioactive natural products,[24,25] we have been engaged in the development of enantiomerically pure tetramic acid derivative **8** as a synthetic equivalent of tetramic acid synthon **D** and 4-hydroxyl-2-pyrrolidinone 5-carbanionic synthon **A** (Scheme 2).[26,27]

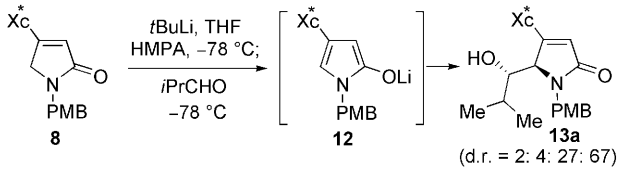


Scheme 2. Demonstration of compound **8** as a synthetic equivalent of chiral synthons **A** and **D**. PMB = *p*-methoxylbenzyl.

By starting from this building block, a highly diastereoselective and C-5 regioselective alkylation method was established for the synthesis of 5-alkyltetramic acid derivatives **9**. Further elaboration of compounds **9** to 5-alkyl-4-hydroxyl-2-pyrrolidinones **11** via the corresponding 5-alkyltetramic acids **10** validated compound **8** as a synthetic equivalent of chiral synthons **D** and **A**.[26] More recently, we reported preliminary results on the highly diastereoselective C-5 α-hydroxyalkylation of **8** and application of this method to the asymmetric synthesis of **3**.[28] We now report full details of this work. In addition, we also describe the asymmetric synthesis of **1**, an extension of the highly diastereoselective C-5 α-hydroxyalkylation of tetramic acid derivative **8** to achiral aldehydes, and the application of the latter method to the asymmetric synthesis of **4**.

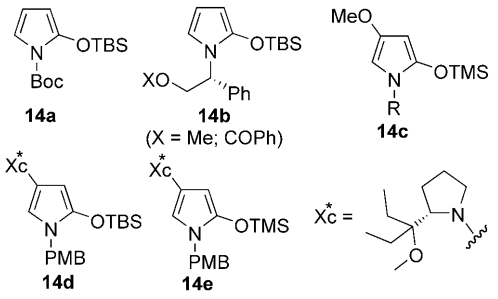
Results and Discussion

Our initial efforts have been devoted to the exploration of the use of vinylogous enolate **12**, generated[29] in situ from tetramic acid derivative **8**. Disappointedly, although the alkylation of this enolate shows excellent diastereoselectivity,[26] its reaction with *iso*-butanal gave compound **13a** as a mixture of four diastereomers in only modest selectivity with a ratio of 2:4:27:67 (Scheme 3).



Scheme 3. Reaction of vinylogous enolate **12** with *iso*-butanal. HMPA = hexamethylphosphoramide.

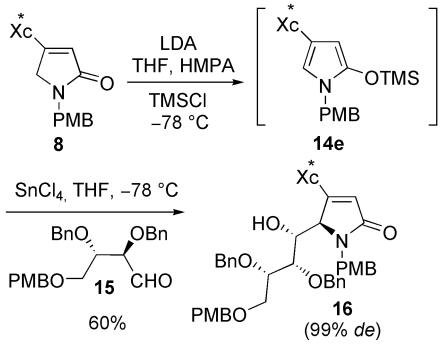
In light of the widespread use of 2-[(*tert*-butyldimethylsilyl)oxy]pyrrole (**14a**) (TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl) by Casiraghi and co-workers[30a,b,31] and



its chiral version **14b** by Royer and co-workers,[30c,31] as well as 2-trimethylsilyloxy-4-methoxypyrrole (**14c**) (TMS = trimethylsilyl)[19f,g,29] in vinylogous aldol reactions, we turned our attention to the exploration of the use of the silyl dienol

ether **14d**.[31] However, successive treatment of compound **8** with reagent system TBSOTf/2,6-lutidine and an aldehyde led only to the recovery of starting material. Thus vinylogous TMS-enol ether **14e** was chosen as a synthetic equivalent of the vinylogous enolate **12**.

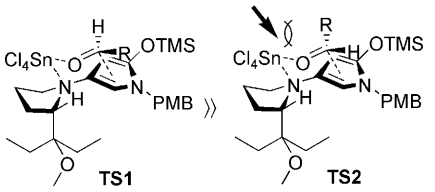
To begin the synthesis of **3**, 4-*O*-(4-methoxybenzyl)-2,3-bis(*O*-benzyl)-L-threose (**15**) was prepared according to a known procedure (cf. the Supporting Information). The vinylogous silyl enol ether **14e** was prepared in situ from tetramic acid derivative **8** by treatment with LDA in THF at −78 °C for 1 h and trapping the resultant vinylogous enolate **12** with trimethylsilyl chloride. Without isolation, the vinylogous silyl enol ether **14e** was allowed to react, in the presence of tin tetrachloride at −78 °C, with **15** for 3.5 h (Scheme 4). To our delight, the desired α-hydroxyalkylated



Scheme 4. Diastereoselective vinylogous Mukaiyama-type reaction of **14e** with chiral aldehyde **15**. LDA = lithium diisopropylamide.

product **16** was obtained as the sole product in 60% yield. Both the ^{1}H and ^{13}C NMR spectra of the product are quite complex, showing a mixture in a 2.2:1 ratio. Since HPLC analysis showed only one product in 99% *de* (*de* = diastereomeric excess), we assumed that the complex peaks appearing in both the ^{1}H and ^{13}C NMR spectra of **16** are rotameric in nature, owing to slow rotation of the chiral auxiliary. To confirm this interpretation, ^{1}H NMR spectra of **16** were recorded in [D_6]DMSO at 20 and 95 °C, respectively. The peaks from the minor isomer disappeared at 95 °C, and reappeared when the temperature returned to 20 °C. These NMR spectroscopic experiments showed that the aldol products observed in the NMR spectra are rotamers rather than diastereomers, in agreement with our previous observations.[26] This was confirmed at a later stage (**16**→**18**). A stereochemical assignment was also carried out at a later stage (vide infra), which revealed that the newly formed stereocenters are *erythro* (*anti*) and the relationship with the adjacent stereocenter is *threo* (*syn*).

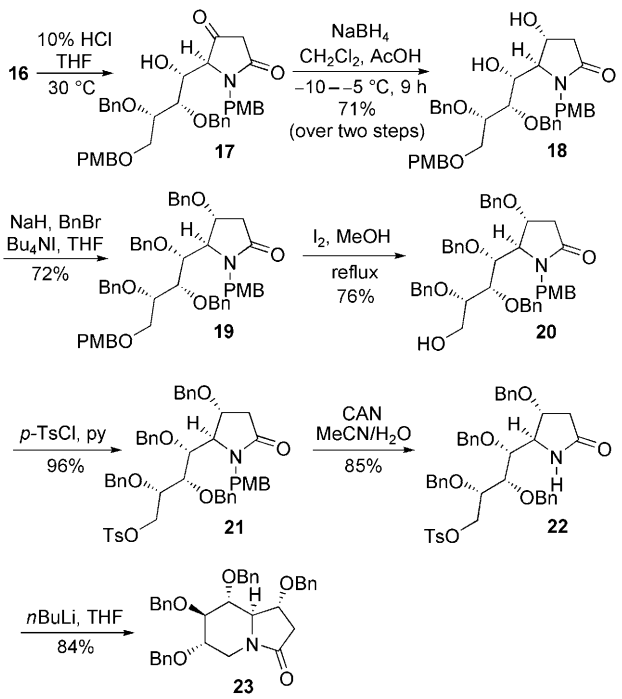
Thus the vinylogous Mukaiyama-type reaction between **14e** and **15** established the correct configurations at C-8*a* and C-8 required for the synthesis of castanospermine and its C-1 epimer. This stereoselection can be rationalized by transition-state **TS1**, which is favored over **TS2** (Scheme 5). In transition-state **TS1** or **TS2**, the *re* face of the vinylogous



Scheme 5. Possible transition states.

TMS-enol ether **14e** is blocked by the substituent of the chiral auxiliary. Thus an aldehyde approaches **14e** from the *si* face. Next, formation of a six-membered transition state favors the approach of the aldehyde by the *re* face (**TS1**) leading to the *erythro* (*anti*)-product. The reaction of **14e** with aldehyde **15** differs from examples reported by Casiraghi both in its stereoselection and also in the reaction conditions used (THF at −78 °C vs. diethyl ether at −85 °C).

The stage was now set for the synthesis of **3**. Compound **16** was treated with HCl (10% in THF) at 30 °C to give tetramic acid **17** (Scheme 6). In the presence of AcOH, reduc-



Scheme 6. Synthesis of indolizidinone **23**. CAN = ammonium cerium(IV) nitrate; TsCl = *p*-toluenesulfonyl chloride; py = pyridine.

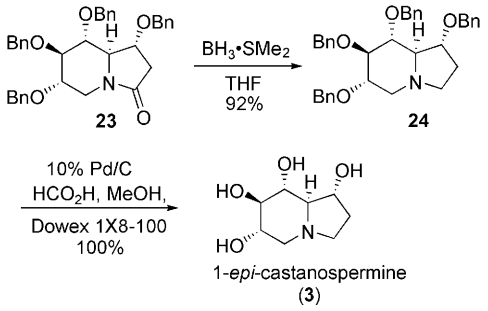
tion of this crude tetramic acid with $NaBH_4$[32] at −10 to 5 °C for 9 h gave diol **18** as the sole diastereomer as judged by ^{1}H NMR spectroscopic analysis.

The two hydroxyl groups in compound **18** were protected (NaH, BnBr, nBu_4NI) to afford the desired bisbenzylated product **19** in 72% yield. Treatment of compound **19** with I_2 in refluxing methanol[33] resulted in the selective cleavage of the *O*-PMB group and furnished primary alcohol **20** in 76%

yield. Tosylation of alcohol **20** (*p*TsCl/py) produced tosylate **21** in 96% yield. Cleavage of the *N*-PMB group under Yoshimura conditions[34] (CAN, MeCN/H_2O 9:1, 5 h, RT) gave the desired lactam **22** in 85% yield. Cyclization of **22** was undertaken by treatment with *n*BuLi in THF at −78°C for 0.5 h, then overnight at RT. The desired indolizidinone **23** was obtained in 84% yield.

The relative stereochemistry of **23** was established first by ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC experiments to identify the signals of each proton and then by NOESY experiments. These experiments showed that the vinylogous Mukaiyama-type reaction on **14e** led predominately to the *erythro* (*anti*)-isomer **16**, and that reduction (**17**→**18**) established the 4,6-*threo* (*syn*)-stereochemistry.[32]

Subsequent reduction of lactam **23** with borane dimethyl sulfide complex (BH_3•SMe_2, THF, RT, 15 h) proceeded smoothly to give indolizidine **24** in 92% yield (Scheme 7).



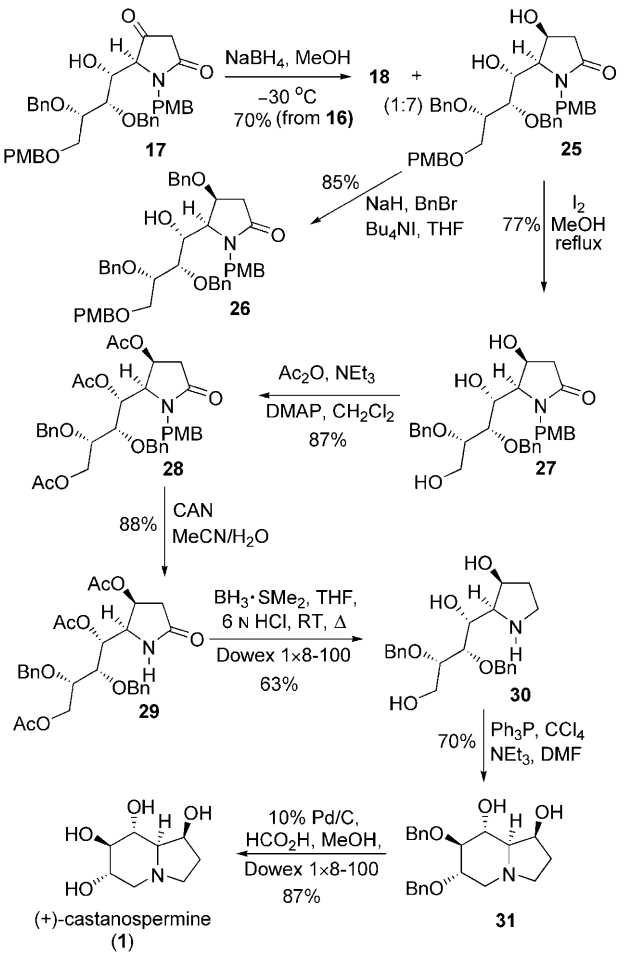
Scheme 7. Synthesis of 1-*epi*-castanospermine (**3**).

Finally, cleavage of the four benzyl groups in **24** was accomplished by 10% Pd/C-catalyzed transfer hydrogenation to give 1-*epi*-castanospermine (**3**) in quantitative yield. The physical and spectral data of the synthetic material ($[\alpha]_D^{22}=+3.8$ ($c=0.54$ in MeOH); lit.[14] $[\alpha]_D^{25}=+3.8$ ($c=0.5$ in MeOH); for the antipode: $[\alpha]_D^{22}=-4$ ($c=1.2$ in MeOH); $[\alpha]_D^{22}=-3.1$ ($c=1.86$ in MeOH)) are consistent with those reported.[14]

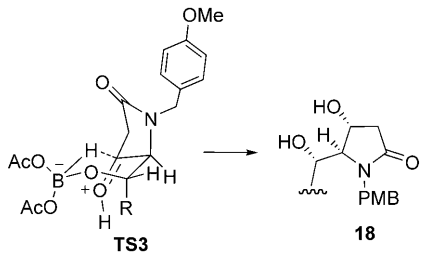
Next we turned our attention to the asymmetric synthesis of (+)-castanospermine (**1**). Reduction of tetramic acid derivative **17** with sodium borohydride ($NaBH_4$) at −30°C yielded hydroxyl lactams **18** and **25** in a ratio of 1:7 in a combined yield of 70% (Scheme 8). Such *cis* diastereoselectivity is generally observed in the reduction of tetramic acids.[35]

The stereochemical outcome of the reduction of **17** with $NaBH_4$ in HOAc/CH_2Cl_2 can be rationalized by Evans' directed-reduction model.[32] Compound **17** provides a singular situation merging an alicyclic–cyclic β-hydroxy ketone system, the hydroxyl group directed intramolecular hydride delivery via the transition state **TS3** leads to 1,3-*syn*-diol **18** (Scheme 9), which is in contrast to results seen with simple alicyclic systems.[32]

For the bisbenzylation of **25**, the conditions used in the synthesis of 1-*epi*-castanospermine (**18**→**19**) were used, but



Scheme 8. Synthesis of (+)-castanospermine (**1**). DMAP = 4-dimethylaminopyridine.



Scheme 9. Proposed stereochemical course.

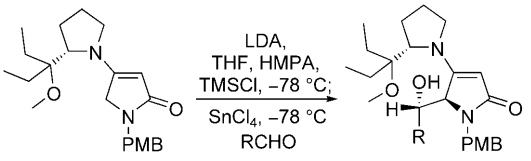
the monobenzylated product **26** was obtained in 85% yield. This difference is attributable to the steric hindrance of *cis*-**25**. To tackle this problem, an alternative approach was devised. Thus after chemoselective cleavage of *O*-PMB by refluxing an I_2-containing methanolic solution[33] of **25**, the triol **27**, obtained in 77% yield, was trisacetylated to give **28**. Treatment of the resulting tris(acetate) with ceric ammonium nitrate in MeCN/H_2O (9:1, v/v) at RT gave lactam **29** in 88% yield. One-pot conversion of lactam **29** to trihydroxypyrrolidine **30** was achieved by reduction with borane dimethyl sulfide complex (BH_3•SMe_2, THF, reflux, 12 h), fol-

lowed by treating the resulting borane–pyrrolidine complex with 6 M HCl at RT for 30 min, which with concomitant trisdeacetylation gave pyrrolidine **30** in 63% yield. The key cyclization of trihydroxylated pyrrolidine derivative **30** was performed by treatment with $PPh_3/CCl_4/NEt_3$ in DMF.[36] After 1 h reaction at RT in the dark, indolizidine **31** was formed in 70% yield. It is noteworthy that the foregoing modifications relative to the procedures developed for 1-*epi*-castanospermine were one step shorter.

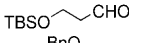
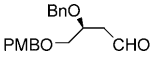
Finally, bisdebenzylation of **31** was achieved by catalytic transfer hydrogenolysis (HCO_2H, 10% Pd/C, MeOH, RT, 4 h). Filtration of the reaction mixture through ion-exchange resin Dowex 1×8–100 afforded (+)-castanospermine (**1**) in 87% yield. The physical ($[\alpha]_D^{20} = +77.5$ ($c = 0.3$ in H_2O); lit.[2a] $[\alpha]_D^{24} = +79.7$ ($c = 0.93$ in H_2O)) and spectral data of the synthetic material are consistent with those reported.[2a]

To develop a more general vinylogous Mukaiyama-type reaction based on tetramic acid derivative **8**, we next examined the coupling of the vinylogous silyl enol ether **14e**, generated in situ from derivative **8**, with achiral aldehydes. The results are summarized in Table 1. As can be seen, the α-hydroxyalkylation of **8** with achiral aldehydes (Table 1, entries 1–7) gave, in each case, only one major (**13**) of the four possible diastereomers in excellent diastereoselectivity. These results support the proposed mechanism shown in Scheme 5, namely, stereoselection of the vinylogous Mukaiyama-type reaction is governed by the chiral auxiliary and not by the chiral aldehyde.

Table 1. Results for the vinylogous Mukaiyama-type reaction of the vinylogous silyl enol ether **14e** derived from **8** with achiral aldehydes.

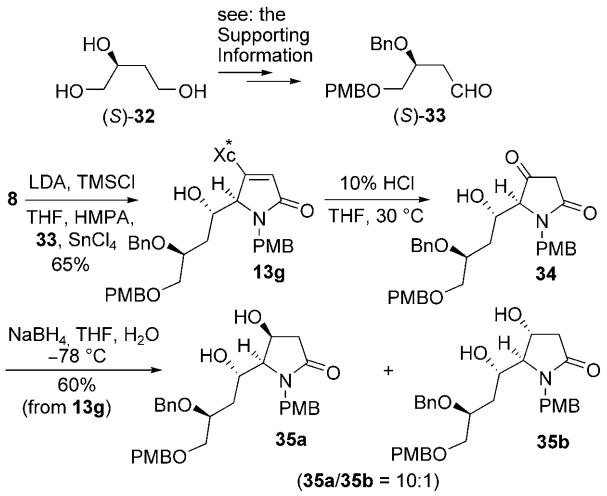


8 **13**

Entry	Aldehyde	Product	Yield [%][a]	*de*[b]
1	*i*PrCHO	**13a**	84	97
2	*n*PrCHO	**13b**	85	99
3	$nC_5H_{11}CHO$	**13c**	77	97
4	$nC_6H_{13}CHO$	**13d**	77	97
5	*c*HexCHO	**13e**	78	95
6		**13f**	69	>99
7		**13g**	65	>99

[a] Isolated yield. [b] *de* determined by HPLC analysis.

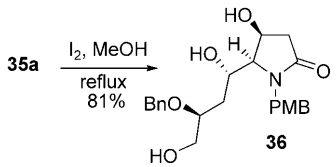
With the dual aims of confirming the stereochemistry of the vinylogous Mukaiyama-type reaction based on tetramic acid derivative **8**, and of demonstrating the synthetic value of the method, the synthesis of the azasugar **4**[15,37] was undertaken. For this purpose, the required aldehyde **33** was synthesized from the known (*S*)-butanetriol **32** (cf. the Supporting Information). By using our previously established methods, the condensation of the tetramic acid derivative **8** with aldehyde **33** gave product **13g** as the sole diastereomer in 65% yield (Scheme 10). Treatment of **13g** with a 10% HCl in THF at 30 °C afforded tetramic acid derivative **34**, which without further purification, was reduced with $NaBH_4$



Scheme 10. Vinylogous Mukaiyama-type reaction with aldehyde **33** and subsequent transformations.

(THF, H_2O) at −78 °C to give diols **35a** and **35b** in 10:1 ratio in a combined yield of 60% (Scheme 10).

The stereochemistry of the major diastereomer (**35a**) was deduced from the triol **36**, which was obtained by treating **35a** with iodine in refluxing methanol (Scheme 11). The relative stereochemistry of **36** was established by single-crystal X-ray diffraction analysis (Figure 1).



Scheme 11. Synthesis of the triol **36**.

Although triol **36** could serve as an intermediate for the synthesis of **4**, its high polarity and low solubility led us to protect the hydroxyl groups by benzylation (NaH, BnBr, nBu_4NI, THF). As in the case of **25**, the monobenzylated product **37** was obtained in 85% yield and its ^1H-^{13}C HMBC spectrum showed the benzyl group was located at the C-4 hydroxyl group. The amide **40** was obtained by successive iodine-mediated selective cleavage of the *O*-PMB (I_2, MeOH, reflux),[33] bisacetylation (Ac_2O, NEt_3, DMAP, CH_2Cl_2), and cleavage of the *N*-PMB with CAN in a mixture of MeCN/H_2O (9:1). Treatment of a THF solution of amide **40** with borane–dimethylsulfide complex at reflux resulted in concomitant reduction of the amide group and cleavage of the two acetyl groups to give product **41** in 71% yield, isolated after the hydrochloride salt formation. Treat-

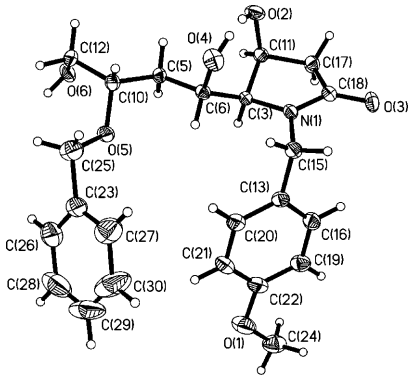
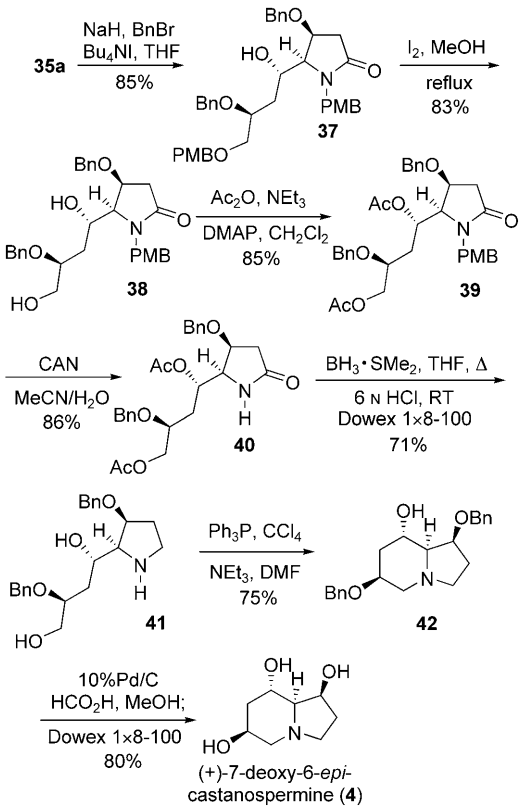


Figure 1. X-ray crystallographic structure of compound **36**.[38]

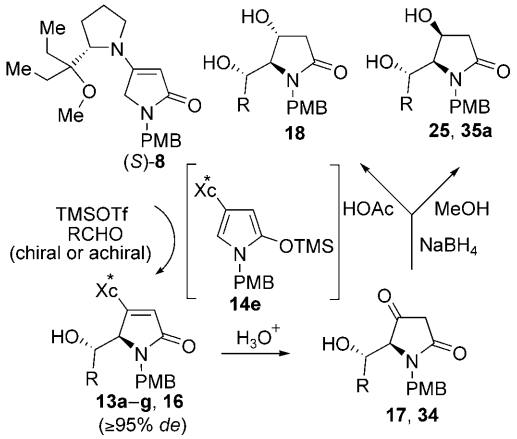
ment of amino-diol **41** with a mixture of triphenylphosphine/carbon tetrachloride/triethylamine in DMF produced the desired indolizidine **42** in 75% yield (Scheme 12). Finally, the indolizidine **42** was converted into 7-deoxy-6-*epi*-castanospermine (**4**) in 80% yield by bisdebenzylation (10% Pd/C, HCO_2H, MeOH) and chromatographic separation by using an ion-exchange resin Dowex 1×8–100. The physical and spectral data of the synthetic material ($[\alpha]_D^{20}=+17.1$ ($c=0.6$ in MeOH); lit.[15] $[\alpha]_D^{26}=+18.3$ ($c=0.712$ in MeOH)) are consistent with those reported.[15]



Scheme 12. Synthesis of 7-deoxy-6-*epi*-castanospermine (**4**).

Conclusion

Chiral nonracemic tetramic acid derivative **8** has been shown to be a suitable practical equivalent of synthons **A** and **D**, made by a highly diastereoselective, vinylogous Mukaiyama-type reaction with chiral nonracemic aldehydes. On the basis of this method, diastereo-divergent syntheses of (+)-1-*epi*-castanospermine (**3**) and (+)-castanospermine (**1**) have been achieved in ten and nine steps, in 14.7 and 13.9% overall yields, respectively, from the key building block **8**. The power of the synthon-**A**-based method has been further demonstrated by its vinylogous Mukaiyama-type reaction with achiral aldehydes and its application in the asymmetric synthesis of 7-deoxy-6-*epi*-castanospermine (**4**), achieved in ten steps with 7.8% overall yield. Tetramic acid derivative **8** thus provides, via silyl dienol ether **14e** formed in situ, the first platform for the highly diastereo- and enantioselective synthesis of structural arrays of 5-(α-hydroxyalkyl)tetramic acids, such as **17**/**34**, 5-(α-hydroxyalkyl) 4-hydroxyl-2-pyrrolidinones, such as **18**, and **25**/**35a** with two or three continuous chiral centers (Scheme 13). This constitutes the first practical fulfillment in a highly enantioselective manner of the conceptually attractive retrosynthetic analysis set out in Scheme 1.



Scheme 13. Tetramic acid derivative **8** as a versatile chiral building block for the enantio- and diastereoselective construction of hydroxylated N-containing heterocycles. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Experimental Section

General: Melting points were uncorrected. IR spectra were measured by using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

Typical procedure for the vinylogous Mukaiyama-type reactions of vinylogous silyl enol ether 14e, generated in situ from 8, with chiral, achiral, and α-achiral aliphatic aldehydes: LDA (0.41 mmol in 3 mL of THF) was added dropwise over 5 min to a solution of tetramic acid derivative **8**

(100 mg, 0.27 mmol) in anhydrous THF (3 mL) and HMPA (0.23 mL, 1.35 mmol) at −78 °C, and the resultant mixture was stirred for 1 h at −78 °C. TMSCl (0.09 mL, 0.67 mmol) was added at −78 °C and the mixture was allowed to warm to −10 °C followed by stirring for 2 h. The mixture was re-cooled to −78 °C, and aldehyde **15** (170 mg, 0.4 mmol) and $SnCl_4$ (0.4 mL, 0.81 mmol, 2 M in CH_2Cl_2) were successively added. The mixture was stirred at −78 °C for 3.5 h and then quenched with saturated $NaHCO_3$ solution (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3×15 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:2 to give (*R*)-1-(4-methoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methoxybenzyloxy)-2,3-bis(benzyloxy)-1-hydroxybutyl]-4-[(*S*)-2-(3-methoxypentan-3-yl)pyrrolidin-1-yl]-1*H*-pyrrol-2(5*H*)one (**16**) (128 mg, 60%) as a colorless oil. *de* = >99% (determined by HPLC analysis); $[\alpha]_D^{20} = +45.4$ (*c* = 2.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers, M/m 2.2:1): δ = 0.60–0.70 (m, 6H; rotamer m), 0.72–0.84 (m, 6H; rotamer M), 1.05–1.91 (m, 8H), 2.66 (s, 1H), 3.00 (s, 1H), 3.05–3.20 (m, 1H), 3.45–3.74 (m, 6H), 3.75 (s, 3H), 3.78 (s, 3H), 4.02–4.07 (m, 1H), 4.08–4.17 (m, 1H), 4.22 (d, *J* = 14.7 Hz, 1H; rotamer m), 4.30 (d, *J* = 14.7 Hz, 1H; rotamer M), 4.33–4.77 (m, 6H; two rotamers), 4.83 (s, 1H; rotamer m), 5.02 (s, 1H; rotamer M), 5.20 (d, *J* = 14.7 Hz, 1H; rotamer M), 5.31 (d, *J* = 14.7 Hz, 1H; rotamer m), 6.79 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.13–7.36 ppm (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers): δ = 7.8, 8.8, 24.5, 24.7, 25.6, 26.5, 44.8, 50.5, 52.0, 55.1, 55.2, 63.5, 66.8, 67.8, 71.8, 72.9, 73.1, 73.5, 74.4, 79.0, 81.5, 95.3, 113.7, 113.8, 127.7, 127.8, 128.1, 128.3, 128.4, 129.1, 129.6, 130.0, 130.7, 137.8, 137.9, 158.6, 159.3, 164.8, 174.0 ppm; IR (KBr): $\tilde{\nu}$ = 2934, 1634, 1591, 1513, 1245, 1034 cm^{-1}; MS (ESI): *m*/*z* (%): 793 (100) $[M+H]^+$; HRMS (ESI): *m*/*z*: calcd for $C_{48}H_{61}N_2O_8+H^+$: 793.4428; found: 793.4419.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-1-hydroxy-2-methypropyl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (13a): By following the typical procedure, the reaction of tetramic acid derivative **8** (100 mg, 0.27 mmol) with *i*PrCHO (73 μL, 0.81 mmol) gave **13a** (101 mg, 84%) as a colorless oil. *de* = 97% (determined by HPLC analysis); $[\alpha]_D^{20} = +50.2$ (*c* = 3.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70–1.01 (m, 12H), 1.33–1.97 (m, 9H), 2.50–2.80 (m, 1H), 3.17 (s, 3H), 3.22–3.33 (m, 1H), 3.64–3.73 (m, 2H), 3.78 (s, 3H), 4.05–4.10 (m, 1H), 4.10–4.19 (d, *J* = 14.9 Hz, 1H), 5.02 (s, 1H), 5.14 (d, *J* = 14.9 Hz, 1H), 6.79–6.81 (m, 2H), 7.17–7.19 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.9, 8.6, 17.7, 21.0, 24.8, 25.1, 26.0, 26.3, 29.3, 29.7, 44.7, 50.1, 53.1, 55.2, 64.6, 66.2, 76.7, 81.6, 95.3, 113.9, 129.6, 130.5, 158.7, 166.1, 174.1 ppm; IR (KBr): $\tilde{\nu}$ = 3323, 2965, 1638, 1587, 1513, 1245, 1034 cm^{-1}; MS (ESI): *m*/*z* (%): 467 (100) $[M+Na^+]$, 445 (70) $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{40}N_2O_4$: C 70.24, H 9.07, N 6.30; found: C 69.96, H 9.41, N 6.07.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-1-hydroxy-1-propyl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (13b): By following the typical procedure, the reaction of tetramic acid derivative **8** (91 mg, 0.24 mmol) with *n*-butanal (66 μL, 0.73 mmol) gave compound **13b** (91 mg, 85%) as a colorless oil. *de* = 99% (determined by HPLC analysis); $[\alpha]_D^{20} = +18.6$ (*c* = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.92 (m, 9H), 1.12–2.08 (m, 12H), 3.15 (s, 3H), 3.19–3.33 (m, 2H), 3.64–3.73 (m, 1H), 3.78 (s, 3H), 3.85–3.94 (m, 1H), 4.10 (s, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 4.99 (s, 1H), 5.01 (d, *J* = 14.8 Hz, 1H), 6.79–6.81 (m, 2H), 7.17–7.19 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 8.5, 14.1, 19.4, 24.8, 25.0, 25.8, 26.4, 31.9, 44.7, 50.0, 52.3, 55.2, 65.9, 66.0, 73.6, 81.5, 94.3, 113.9, 129.7, 130.8, 158.7, 164.7, 174.2 ppm; IR (KBr): $\tilde{\nu}$ = 3350, 2934, 1634, 1591, 1509, 1377, 1241 cm^{-1}; MS (ESI): *m*/*z* (%): 467 (50) $[M+Na^+]$, 445 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{40}N_2O_4$: C 70.24, H 9.07, N 6.30; found: C 69.97, H 9.45, N 6.00.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-1-hydroxyhexyl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (13c): By following the typical procedure, the reaction of tetramic acid derivative **8** (117 mg, 0.31 mmol) with *n*-hexanal (114 μL, 0.94 mmol) gave compound **13c** (113 mg, 77%) as a colorless oil. *de* = 97% (determined by HPLC analysis); $[\alpha]_D^{20} = +26.5$ (*c* = 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.89 (m, 9H), 1.12–2.11 (m, 16H), 3.17 (s, 3H), 3.20–3.33 (m, 2H), 3.62–3.68 (m, 1H), 3.78 (s, 3H), 3.85–3.92 (m, 1H), 4.10 (s, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 4.96 (s, 1H), 4.98 (d, *J* = 14.8 Hz, 1H), 6.81–6.83 (m, 2H), 7.21–7.23 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 8.5, 14.0, 22.5, 24.7, 25.0, 25.8, 25.9, 26.4, 29.7, 31.9, 44.7, 50.0, 52.3, 55.2, 65.9, 66.0, 73.9, 81.5, 94.2, 113.9, 129.7, 130.8, 158.7, 164.7, 174.1 ppm; IR (KBr): $\tilde{\nu}$ = 3334, 2934, 1638, 1591, 1513, 1385, 1248 cm^{-1}; MS (ESI): *m*/*z* (%): 495 (100) $[M+Na]^+$, 473 (60) $[M+H]^+$; elemental analysis calcd (%) for $C_{28}H_{44}N_2O_4$: C 71.15, H 9.38, N 5.93; found: C 70.93, H 9.78, N 5.72.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-1-hydroxyheptyl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azol-one (13d): By following the typical procedure, the reaction of tetramic acid derivative **8** (159 mg, 0.43 mmol) with *n*-heptanal (172 μL, 1.28 mmol) gave compound **13d** (160 mg, yield: 77%) as a colorless oil. *de* = 97% (determined by HPLC analysis); $[\alpha]_D^{20} = +23.7$ (*c* = 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.89 (m, 9H), 1.10–2.11 (m, 18H), 3.17 (s, 1H), 3.20–3.33 (m, 2H), 3.62–3.70 (m, 1H), 3.77 (s, 3H), 3.85–3.92 (m, 1H), 4.10 (s, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 4.96 (s, 1H), 4.98 (d, *J* = 14.8 Hz, 1H), 6.81–6.83 (m, 2H), 7.22 ppm (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 8.5, 14.0, 22.6, 24.7, 25.0, 25.8, 26.2, 26.4, 29.4, 29.8, 31.7, 44.7, 50.0, 52.4, 55.2, 66.0, 73.9, 81.5, 94.2, 113.9, 129.7, 130.8, 158.7, 164.7, 174 ppm; IR (KBr): $\tilde{\nu}$ = 3361, 2930, 1634, 1587, 1513, 1389, 1245 cm^{-1}; MS (ESI): *m*/*z* (%): 509 (80) $[M+Na]^+$, 487 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{29}H_{46}N_2O_4$: C 71.57, H 9.53, N 5.76; found: C 71.94, H 9.91, N 5.58.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-cyclohexyl(hydroxyl)methyl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (13e): By following the typical procedure, the reaction of tetramic acid derivative **8** (142 mg, 0.38 mmol) with cyclohexanecarbaldehyde (138 μL, 1.15 mmol) gave compound **13e** (143 mg, yield: 78%) as a colorless oil. *de* = 95% (determined by HPLC analysis); $[\alpha]_D^{20} = +59.4$ (*c* = 3.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.89 (m, 6H,), 1.05–1.95 (m, 19H), 2.49 (s, 1H), 3.10–3.15 (m, 1H), 3.17 (s, 1H), 3.20–3.30 (m, 1H), 3.65–3.72 (m, 2H), 3.77 (s, 3H), 4.08 (s, 1H), 4.15 (d, *J* = 14.9 Hz, 1H), 5.01 (s, 1H), 5.10 (d, *J* = 14.9 Hz, 1H), 6.81–6.83 (m, 2H), 7.17–7.19 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.8, 8.6, 24.7, 25.1, 25.9, 26.2, 26.3, 26.5, 27.6, 31.4, 38.9, 44.6, 50.1, 53.1, 55.2, 64.3, 66.1, 81.6, 95.5, 113.8, 129.6, 130.5, 158.9, 166.0, 174.0 ppm; IR (KBr): $\tilde{\nu}$ = 3342, 2930, 1638, 1587, 1245, 1034 cm^{-1}; MS (ESI): *m*/*z* (%): 507 (100) $[M+Na]^+$, 485 (50) $[M+H]^+$; elemental analysis calcd (%) for $C_{29}H_{44}N_2O_4$: C 71.87, H 9.15, N 5.78; found: C 71.34, H 9.13, N 5.41.

(5*R*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-5-[(*S*)-1-hydroxy-3-*tert*-butyldimethylsilanoxypropyl]-1-(4-methoxy-benzyl)-2,5-dihydro-1*H*-2-azolone (13f): By following the typical procedure, the reaction of tetramic acid derivative **8** (156 mg, 0.42 mmol) with 3-(*tert*-butyldimethylsilyloxy)propanal (237 mg, 1.26 mmol) gave compound **13f** (162 mg, 69%) as a colorless wax solild. *de* = >99% (determined by HPLC analysis); $[\alpha]_D^{20} = +35.9$ (*c* = 2.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.77–0.85 (m, 6H), 0.90 (s, 9H), 1.33–1.98 (m, 10H), 3.14 (s, 1H), 3.20–3.35 (m, 2H), 3.62–3.74 (m, 2H), 3.78 (s, 3H), 3.88–3.96 (m, 1H), 3.98 (s, 1H), 4.09 (s, 1H), 4.19 (d, *J* = 9.8 Hz, 1H), 4.30 (d, *J* = 14.5 Hz, 1H), 4.97 (s, 1H), 5.14 (d, *J* = 14.5 Hz, 1H), 6.81–6.83 (m, 2H), 7.24–7.26 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −6.0, −5.9, 7.5, 8.1, 17.7, 24.5, 24.7, 25.5, 25.6, 26.0, 30.5, 44.0, 49.4, 51.8, 54.8, 62.9, 64.0, 65.7, 74.4, 81.0, 93.8, 113.4, 129.6, 130.5, 158.2, 164.0, 173.5 ppm; IR (KBr): $\tilde{\nu}$ = 3346, 2930, 1638, 1587, 1513, 1245, 1093 cm^{-1}; MS (ESI): *m*/*z* (%) 583 (83) $[M+Na]^+$, 561 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{31}H_{52}N_2O_5Si$: C 66.39, H 9.35, N 4.99; found: C 69.79, H 9.75, N 5.05.

(*R*)-1-(4-Methoxybenzyl)-5-[(1*S*,3*S*)-4-(4-methoxybenzyloxy)-3-(benzyloxy)-1-hydroxybutyl]-4-[(*S*)-2-(3-methoxypentan-3-yl)-pyrrolidin-1-yl]-1*H*-pyrrol-2(5*H*)one (13g): By following the typical procedure, the reaction of tetramic acid derivative **8** (379 mg, 1.02 mmol) with aldehyde **33** (383 mg, 1.22 mmol) gave compound **13g** (454 mg, 65%) as a colorless oil. *de* = >99% (determined by HPLC analysis); $[\alpha]_D^{20} = +17.6$ (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68–0.83 (m, 6H), 1.20–1.99

(m, 10H), 2.98 (s, 3H), 3.14–3.31 (m, 2H), 3.47 (dd, $J=10.0$, 4.4 Hz, 1H), 3.52 (dd, $J=10.0$, 5.6 Hz, 1H), 3.57 (dd, $J=7.9$, 5.0 Hz, 1H), 3.72 (s, 3H), 3.78 (s, 3H), 3.80–3.90 (m, 1H), 4.12–4.16 (m, 1H), 4.22–4.29 (m, 1H), 4.30 (d, $J=14.7$ Hz, 1H), 4.45 (s, 1H), 4.50 (d, $J=11.5$ Hz, 1H), 4.61 (d, $J=11.4$ Hz, 1H), 4.89 (s, 1H), 5.06 (d, $J=14.6$ Hz, 1H), 6.74–6.80 (m, 2H), 6.84–6.89 (m, 2H), 7.10–7.45 ppm (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=7.7$, 8.6, 24.2, 24.8, 25.6, 26.5, 32.0, 44.4, 50.3, 52.0, 55.1, 55.2, 65.1, 66.3, 69.7, 72.2, 72.6, 73.0, 75.4, 81.4, 93.6, 113.7, 113.8, 127.7, 127.8, 128.3, 128.4, 129.2, 129.4, 129.5, 129.7, 129.9, 130.7, 138.4, 158.5, 159.2, 164.6, 174.0 ppm; IR (KBr): $\tilde{\nu}=3432$, 2949, 1634, 1590, 1501, 1248, 1100 cm^{-1}; MS (ESI): m/z (%): 709 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{41}H_{54}N_2O_7$: C 71.69, H 7.92, N 4.08, O 16.31; found: C 71.57, H 7.62, N 4.17.

(*S*)-1-(4-Methyoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methyoxybenzyl-oxy)-2,3-bis(benzyloxy)-1-hydroxybutyl]pyrrolidine-2,4-dione (17): A solution of 10% HCl (20 mL) was added to a THF (50 mL) solution of compound **16** (650 mg, 0.82 mmol). After the mixture had been stirred at 30 °C for 48 h, the mixture was extracted with ethyl acetate (3×15 mL) and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude tetramic acid derivative **17** as a colorless oil, which was used in the next step without further purification.

(4*R*,5*R*)-1-(4-Methoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methoxybenzyl-oxy)-2,3-bis(benzyloxy)-1-hydroxybutyl]-4-hydroxypyrrolidin-2-one (18): $NaBH_4$ (80 mg, 2.1 mmol) was added portionwise to a solution of the crude tetramic acid derivative **17** (446 mg, 0.70 mmol) in a mixed solvent system CH_2Cl_2 (10 mL)/AcOH (1 mL) at −25 °C. The mixture was stirred at −10 °C for 9 h and quenched with a cooled saturated solution of $NaHCO_3$ (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:1 to give **18** as a colorless solid and (375 mg, 84%) as a single diastereomer. M.p. 252–254 °C (EtOAc/PE); $[\alpha]_D^{20}=+1.2$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.88$ (s, 1H), 2.26 (dd, $J=17.4$, 2.0 Hz, 1H), 2.73 (br s, 1H), 2.78 (dd, $J=17.4$, 6.5 Hz, 1H), 3.25–3.32 (m, 1H), 3.45 (s, 1H), 3.52 (d, $J=6.4$, 4.6 Hz, 1H), 3.60 (d, $J=10.5$, 3.4 Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.81–3.84 (m, 2H), 3.86 (d, $J=15.4$ Hz, 1H), 4.30 (d, $J=11.6$ Hz, 1H), 4.36 (d, $J=11.6$ Hz, 1H), 4.38–4.42 (m, 1H), 4.43 (d, $J=11.5$ Hz, 2H), 4.61 (d, $J=11.5$ Hz, 1H), 4.64 (d, $J=11.5$ Hz, 1H), 4.92 (d, $J=15.4$ Hz, 1H), 6.81 (m, 2H), 6.87 (m, 2H), 7.10 (m, 2H), 7.18–7.38 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=40.4$, 43.3, 55.3, 65.3, 67.8, 68.4, 68.5, 73.2, 73.8, 80.8, 113.9, 114.1, 128.1, 128.3, 128.7, 129.1, 129.4, 129.7, 137.4, 159.0, 159.4, 173.9 ppm; IR (KBr): $\tilde{\nu}=3378$, 2961, 1699, 1510, 1386, 1245, 1036 cm^{-1}; MS (ESI): m/z (%): 642 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{38}H_{44}NO_8+H^+$: 642.3067; found: 642.3054.

(4*R*,5*R*)-1-(4-Methoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methoxybenzyl-oxy)-1,2,3-tris(benzyloxy)butyl]-4-(benzyloxy)pyrrolidin-2-one (19): NaH (60% in mineral oil, 26 mg, 0.65 mmol) was added to a solution of compound **18** (375 mg, 0.59 mmol) in anhydrous THF (20 mL) at −20 °C. After H_2 evolution had ceased (10 min), benzyl bromide (0.7 mL, 5.9 mmol) and tetrabutylammonium iodide (22 mg, 0.06 mmol) were added. The mixture was stirred at RT for 3 days. The reaction was quenched with H_2O (1 mL) at 0 °C and the mixture was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:2 to give compound **19** (346 mg, 72%) as a colorless oil. $[\alpha]_D^{20}=+4.5$ ($c=1.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.46$ (d, $J=17.3$ Hz, 1H), 2.81 (dd, $J=17.3$, 6.4 Hz, 1H), 3.51–3.65 (m, 6H), 3.70 (s, 3H), 3.77 (s, 3H), 4.03 (dd, $J=8.4$, 1.0 Hz, 1H), 4.21 (d, $J=6.2$ Hz, 1H), 4.23–4.33 (m, 6H), 4.37 (d, $J=12.0$ Hz, 1H), 4.44 (d, $J=11.5$ Hz, 1H), 4.53 (d, $J=12.0$ Hz, 1H), 4.64 (d, $J=10.8$ Hz, 1H), 4.71 (d, $J=11.5$ Hz, 1H), 6.67 (d, $J=8.6$ Hz, 2H), 6.79 (d, $J=8.6$ Hz, 2H), 6.98 (d, $J=8.6$ Hz, 2H), 7.12–7.35 ppm (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=38.4$, 43.1, 55.1, 55.2, 65.6, 68.8, 70.1, 72.3, 72.7, 73.0, 74.9, 75.0, 76.0, 77.8, 79.5, 113.7, 113.8, 113.9, 127.4, 127.6, 127.8, 127.9 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.1, 129.3, 129.5, 129.9, 137.7, 137.8, 138.1, 18.2, 158.8, 159.2, 173.8 ppm; IR (KBr): $\tilde{\nu}=2922$, 1688, 1610, 1509, 1451, 1245, 1093 cm^{-1}; MS (ESI): m/z (%): 844 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{52}H_{55}NO_8$: C 76.07, H 6.74, N 1.83; found: C 76.07, H 7.14, N 1.82.

(4*R*,5*R*)-5-[(1*R*,2*S*,3*S*)-1,2,3-Tris(benzyloxy)-4-hydroxybutyl]-4-benzyloxy-1-(4-methoxybenzyl)-2-pyrrolidinone (20): Iodine (40 mg, 1% v/v) was added to a methanolic solution (2 mL) of compound **19** (346 mg, 0.42 mmol) at 70 °C. After the mixture had been stirred at 70 °C for 96 h, the reaction was quenched with saturated $Na_2S_2O_3$ solution. The methanol was removed under reduced pressure and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic layers were separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:2 to give compound **20** (225 mg, 76%) as a colorless oil. $[\alpha]_D^{20}=-13.5$ ($c=1.7$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.52$ (d, $J=17.2$ Hz, 1H), 2.84 (dd, $J=17.2$, 5.2 Hz, 1H), 3.38 (dd, $J=8.8$, 4.3 Hz, 1H), 3.55–3.61 (m, 2H), 3.64–3.72 (m, 3H), 3.75 (s, 3H), 4.05 (d, $J=8.5$ Hz, 1H), 4.22 (d, $J=6.5$ Hz, 1H), 4.27 (d, $J=12.0$ Hz, 1H), 4.33 (d, $J=11.0$ Hz, 1H), 4.36 (d, $J=12.0$ Hz, 1H), 4.43 (d, $J=13.0$ Hz, 2H), 4.48 (d, $J=12.5$ Hz, 2H), 4.67 (d, $J=11.0$ Hz, 1H), 4.72 (d, $J=16.5$ Hz, 1H), 4.74 (d, $J=11.0$ Hz, 1H), 6.77 (d, $J=8.4$ Hz, 2H), 7.05 (d, $J=8.4$ Hz, 2H), 7.10–7.38 ppm (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=38.2$, 43.1, 55.2, 60.8, 65.7, 69.9, 71.9, 72.4, 74.9, 75.0, 76.0, 78.0, 79.7, 114.0, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.9, 137.5, 137.6, 137.7, 158.9; 173.7 ppm; IR (KBr): $\tilde{\nu}=3408$, 2930, 1669, 1513, 1459, 1248, 1093 cm^{-1}; MS (ESI): m/z (%): 724 (35) $[M+Na]^+$, 702 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{44}H_{47}NO_7+H^+$: 702.3431; found: 702.3417.

(4*R*,5*R*)-5-[(1*R*,2*S*,3*S*)-1,2,3-Tris(benzyloxy)-4-(4-methyl-benzenesulfonatebutyl]-4-benzyloxy-1-(4-methoxybenzyl)-2-pyrrolidinone (21): Pyridine (0.15 mL, 1.6 mmol), a solution of *p*TsCl (91 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (0.5 mL), and DMAP (cat.) were added successively to a solution of compound **20** (225 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (1 mL) at −8 °C. After the mixture had been stirred at −8 °C for 30 h, the mixture was diluted with CH_2Cl_2 (4 mL) and water, and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic phases were washed successively with 1 M HCl and brine (1 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatographic purification on silica gel eluting with EtOAc/PE 1:2 to give compound **21** (263 mg, 96%) as a colorless oil. $[\alpha]_D^{20}=-8.3$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.41$ (s, 3H), 2.50 (d, $J=17.3$ Hz, 1H), 2.80 (dd, $J=17.3$, 6.4 Hz, 1H), 3.49 (dd, $J=7.6$, 4.0 Hz, 1H), 3.58 (s, 1H), 3.65 (d, $J=15.2$ Hz, 1H), 3.67–3.73 (m, 1H), 3.75 (s, 3H), 3.98 (d, $J=6.8$ Hz, 1H), 4.05 (dd, $J=10.4$, 6.4 Hz, 1H), 4.15 (dd, $J=10.4$, 4.4 Hz, 1H), 4.23–4.31 (m, 4H), 4.34 (d, $J=11.2$ Hz, 1H), 4.43 (d, $J=11.6$, 1H), 4.45 (d, $J=11.6$ Hz, 1H), 4.58 (d, $J=10.8$ Hz, 1H), 4.62 (d, $J=11.2$ Hz, 1H), 4.72 (d, $J=15.2$ Hz, 1H), 6.63 (d, $J=8.4$ Hz, 2H), 6.98 (d, $J=8.4$ Hz, 2H), 7.05–7.36 (m, 22H), 7.60 ppm (d, $J=8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.6$, 38.1, 43.4, 55.2, 66.0, 69.3, 70.2, 72.6, 72.9, 74.7, 74.8, 75.6, 765, 78.8, 114.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 129.0, 129.9, 132.5, 137.4, 137.5, 137.6, 144.9, 158.9, 173.6 ppm; IR (KBr): $\tilde{\nu}=2926$, 1688, 1517, 1365, 1248, 1178, 1089 cm^{-1}; MS (ESI): m/z (%): 878 (60) $[M+Na]^+$, 856 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{51}H_{53}NO_9S$: C 71.56, H 6.24, N 1.64; found: C 71.51, H 6.62, N 1.70.

(4*R*,5*R*)-5-[(1*R*,2*S*,3*S*)-1,2,3-Tris(benzyloxy)-4-(4-methyl-benzenesulfonatebutyl]-4-benzyloxy-2-pyrrolidinone (22): CAN (849 mg, 1.55 mmol) was added to a solution of compound **21** (263 mg, 0.31 mmol) in CH_3CN (36 mL) and H_2O (4 mL), and the mixture was stirred at RT for 3 h. The reaction was diluted with H_2O (30 mL) and extracted with EtOAc (3× 25 mL). The combined organic layers were washed successively with a saturated aqueous solution of sodium bicarbonate (5 mL) and brine (5 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 2:1 to give compound **22** (192 mg, 85%) as a colorless oil. $[\alpha]_D^{20}=-25.9$ ($c=1.0$ in $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (dd, J = 17.2, 2.4 Hz, 1H), 2.41 (s, 3H), 2.43 (dd, J = 17.2, 6.8 Hz, 1H), 3.30–3.40 (m, 2H), 3.52 (dd, J = 6.0, 2.8 Hz, 1H), 3.85 (m, 1H), 4.00 (d, J = 6.8 Hz, 1H), 4.10–4.15 (m, 2H), 4.30–4.42 (m, 5H), 4.50 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 5.30 (brs, 1H), 7.11–7.36 (m, 22H), 7.70 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 37.0, 64.7, 68.9, 70.6, 72.1, 74.4, 75.0, 75.3, 77.8, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.9, 132.6, 137.2 137.6, 145.1, 175.1 ppm; IR (KBr): $\tilde{\nu}$ = 3405, 2918, 1700, 1455, 1365, 1175, 1093 cm^{-1}; MS (ESI): m/z (%): 758 (90) $[M+Na]^+$, 736 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{43}H_{45}NO_8S$: C 70.18, H 6.16, N 1.90; found: C 70.09, H, 6.56, N 1.98.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrakis(benzyloxy)hexahydro-indolizidin-3(5*H*)one (23): *n*BuLi (0.18 mL, 0.29 mmol, 1.6 M in pentane) was added to a solution of compound **22** (192 mg, 0.26 mmol) in anhydrous THF (5 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min, slowly warmed to RT, and then stirred overnight. The reaction was quenched with H_2O (2 mL) and extracted with Et_2O (3×5 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:2 to give compound **23** (124 mg, 84%) as a colorless solid. M.p. 96–98 °C (EtOAc/PE); $[\alpha]_D^{20}$ = +41.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (d, J = 18.0 Hz, 1H), 2.54 (dd, J = 18.0, 7.5 Hz, 1H), 2.62 (t, J = 11.5 Hz, 1H), 3.03 (t, J = 9.5 Hz, 1H), 3.40–3.46 (m, 1H), 3.44 (d, J = 10.0 Hz, 1H), 3.66 (t, J = 8.7 Hz, 1H), 3.77 (d, J = 7.5 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.45 (dd, J = 13.0, 5.5 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.83 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 11.5 Hz, 1H), 5.02 (d, J = 11.0 Hz, 1H), 7.20–7.38 ppm (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.4, 41.0, 66.0, 70.7, 72.8, 73.0, 75.2, 75.9, 77.8, 78.8, 86.5, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 137.5, 137.6, 137.7, 138.3, 171.3 ppm; IR (KBr): $\tilde{\nu}$ = 2923, 1698, 1454, 1092, 1069 cm^{-1}; MS (ESI): m/z (%): 586 (100) $[M+Na]^+$, 564 (60) $[M+H]^+$; HRMS: m/z: calcd for $C_{36}H_{38}NO_5+H^+$: 564.2750; found: 564.2737.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrakis(benzyloxy)octahydroindolizidine (24): BH_3·Me_2S (40 μL, 0.68 mmol) was added to a cooled (0 °C) solution of compound **23** (22 mg, 0.04 mmol) in dry THF (3 mL). The mixture was stirred at RT for 15 h and then quenched with water (2 mL) at 0 °C. The resulting mixture was stirred at 60 °C for 3 h and then extracted with CH_2Cl_2 (3×4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:5 to give compound **24** (20 mg, 92%) as a colorless solid. M.p. 103–105 °C (EtOAc/PE); $[\alpha]_D^{20}$ = +6.4 (c = 1.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77–1.85 (m, 1H), 2.00–2.12 (m, 1H), 2.20 (t, J = 10.4 Hz, 1H), 2.30 (dd, J = 9.6, 5.2 Hz, 1H), 2.51 (dd, J = 17.6, 8.8 Hz, 1H), 2.86 (t, J = 8.0 Hz, 1H), 3.20 (dd, J = 10.8, 5.4 Hz, 1H), 3.40 (t, J = 9.2 Hz, 1H), 3.55 (t, J = 4.8 Hz, 1H), 3.62–3.71 (m, 1H), 3.86–3.94 (m, 1H), 4.42 (s, 2H), 4.63 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.82 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 7.20–7.33 ppm (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4, 51.6, 53.8, 71.4, 72.1, 72.9, 74.4, 75.7, 79.3, 81.7, 82.1, 87.6, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 138.4, 138.5, 138.8, 138.9 ppm; IR (KBr): $\tilde{\nu}$ = 2926, 2854, 2799, 1613, 1352, 1097 cm^{-1}; MS (ESI): m/z (%): 550 (100) $[M+H]^+$; HRMS: m/z: calcd for $C_{36}H_{40}NO_4+H^+$: 550.2957; found: 550.2946.

(1*R*,6*S*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,6,7,8-tetraol (1-*epi*-castanospermine) (3): HCOOH (0.25 mL) was added to a mixture of compound **24** (15 mg, 0.02 mmol), 10% Pd/C (80 mg), and MeOH (2 mL) under an argon atmosphere. The suspension was stirred for 2 h and then filtered through a pad of Celite. The filter cake was washed several times with MeOH and then concentrated under reduced pressure. The residual syrup was dissolved in ethanol and stirred with Dowex 1×8–100 ion-exchange resin (80 mg) for 6 h. The mixture was filtered through Celite and the resulting filtrate was concentrated under reduced pressure to give 1-*epi*-castanospermine (**3**) (5.2 mg, quantitative) as a colorless oil. $[\alpha]_D^{20}$ = +3.8 (c = 0.5 in MeOH) (lit.[14] $[\alpha]_D^{25}$ = +3.8 (c = 0.5 in MeOH)); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.55–1.65 (m, 1H), 2.10–2.26 (m, 3H), 2.61 (q, J = 9.2 Hz, 1H), 2.89 (t, J = 8.8 Hz, 1H), 3.02 (dd, J = 11.2, 4.8 Hz, 1H), 3.10 (t, J = 8.6 Hz, 1H), 3.15–3.23 (m, 1H), 3.47 (ddd, J = 10.8, 9.2, 5.2 Hz, 1H), 4.08–4.15 ppm (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 33.9, 52.5, 56.2, 70.9, 74.3, 74.7, 74.9, 80.2 ppm; IR (KBr): $\tilde{\nu}$ = 3390, 2910, 1643, 1161, 1124, 1090 cm^{-1}; MS (ESI): m/z (%): 212 (60) $[M+Na]^+$, 190 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_8H_{16}NO_4+H^+$: 190.1079; found: 190.1074.

(4*S*,5*R*)-1-(4-Methoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methoxybenzyl-oxy)-2,3-bis(benzyloxy)-1-hydroxybutyl]-4-hydroxy-pyrrolidin-2-one (25): $NaBH_4$ (29 mg, 0.77 mmol) was added to a methanolic solution (5 mL) of the crude tetramic acid derivative **17** (163 mg, 0.26 mmol) at −30 °C. After the mixture had been stirred for 40 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL). The resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 2:1 to give two diastereoisomers **25** (102 mg, 61%; colorless oil) and **18** (14 mg, 9%; colorless oil) in a ratio of 7:1. Compound **25**: $[\alpha]_D^{20}$ = +40 (c = 1.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (dd, J = 17.3, 3.2 Hz, 1H), 2.57 (dd, J = 17.3, 7.0 Hz, 1H), 3.28 (dd, J = 5.5, 2.5 Hz, 1H), 3.60 (dd, J = 10.9, 4.9 Hz, 1H), 3.65–3.85 (m, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 3.84 (d, J = 15 Hz, 1H), 3.90–3.96 (m, 1H), 4.23–4.36 (m, 3H), 4.41 (d, J = 11.0 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 11.6, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 5.10 (d, J = 15.0 Hz, 1H), 6.72 (m, 2H), 6.87–6.89 (m, 2H), 7.02–7.04 (m, 2H), 7.15–7.36 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.0, 43.2, 55.1, 55.2, 62.0, 67.5, 68.9, 72.7, 73.2, 74.4, 78.5, 80.1, 113.8, 114.1, 127.7, 127.8, 127.9, 128.2, 128.4 (2C), 128.7, 129.2, 129.3, 129.9, 136.8, 138.1, 159.0, 159.3, 173.3 ppm; IR (KBr): $\tilde{\nu}$ = 3378, 2925, 1699, 1611, 1515, 1457, 1245, 1178, 1071 cm^{-1}; MS (ESI): m/z (%): 642 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{38}H_{43}NO_8+H^+$: 642.3061; found: 642.3055.

(4*S*,5*S*)-1-(4-Methoxybenzyl)-5-[(1*R*,2*S*,3*S*)-4-(4-methoxybenzyl-oxy)-2,3-bis(benzyloxy)-1-hydroxybutyl]-4-(benzyloxy)-pyrrolidin-2-one (26): NaH (60% in mineral oil, 16 mg, 0.39 mmol) was added in one portion to a solution of compound **25** (115 mg, 0.18 mmol) in anhydrous THF (10 mL) at −20 °C. After H_2 evolution had ceased (10 min), benzyl bromide (0.11 mL, 0.9 mmol) and a catalytic amount of tetrabutylammonium iodide were added. The mixture was warmed to RT and stirred for 3 days. The reaction was quenched with H_2O (2 mL) at 0 °C and the resulting mixture was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:2 to give compound **26** (112 mg, yield: 85%) as a colorless oil. $[\alpha]_D^{20}$ = +40 (c = 1.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 2.58 (dd, J = 17.0, 1.8 Hz, 1H), 3.34 (dd, J = 10.3, 6.2 Hz, 1H), 3.56 (dd, J = 5.3, 3.0 Hz, 1H), 3.61 (dd, J = 10.3, 3.2 Hz, 1H), 3.64–3.76 (m, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 3.91 (d, J = 15.0 Hz, 1H), 4.08 (d, J = 11.0 Hz, 1H), 4.14–4.22 (m, 2H), 4.26 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 11.4 Hz, 1H), 5.20 (d, J = 15.0 Hz, 1H), 6.71–6.77 (m, 2H), 6.82–6.87 (m, 2H), 7.36–7.04 ppm (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2, 43.2, 55.1, 55.2, 60.6, 69.5, 70.1, 71.3, 72.2, 72.9, 74.2, 75.8, 77.9, 79.9, 113.7, 114.0, 127.7 (2C), 128.1, 128.2 (2C), 128.3, 128.5, 128.6, 129.2, 129.4, 130.2, 136.5, 138.0, 138.2, 158.9, 159.1, 172.8 ppm; IR (KBr): $\tilde{\nu}$ = 3508, 2925, 2861, 1700, 1614, 1511, 1249, 1081, 1037 cm^{-1}; MS (ESI): m/z (%): 732 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{45}H_{49}NO_8+H^+$: 732.3536; found: 732.3541.

(4*S*,5*R*)-5-[(1*R*,2*S*,3*S*)-2,3-Bis(benzyloxy)-1,4-dihydroxybutyl]-1-(4-methoxybenzyl)-4-hydroxypyrrolidin-2-one (27): Iodine (100 mg, 0.39 mmol) was added to a methanolic solution (5 mL) of compound **25** (263 mg, 0.14 mmol). After the mixture had been stirred at 70 °C for 96 h, the reaction was quenched with saturated $Na_2S_2O_3$ solution. The methanol was removed under reduced pressure and the aqueous phase was extracted

with EtOAc (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 5:1 to afford compound **27** (165 mg, 77%) as a colorless oil. $[\alpha]_D^{20}=-85.4$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.46$ (dd, $J=17.3$, 2.5 Hz, 1H), 2.57 (dd, $J=17.3$, 6.8 Hz, 1H), 3.04–3.14 (m, 1H), 3.25 (dd, $J=5.3$, 2.7 Hz, 1H), 3.61 (dd, $J=5.4$, 2.6 Hz, 1H), 3.74 (s, 3H), 3.76–3.83 (m, 2H), 3.88–3.83 (m, 1H), 3.87 (d, $J=15.0$ Hz, 1H), 4.17 (d, $J=8.2$ Hz, 1H), 4.28 (d, $J=3.4$ Hz, 1H), 4.29–4.36 (m, 1H), 4.38–4.44 (m, 1H), 4.43 (d, $J=11.1$ Hz, 1H), 4.51 (d, $J=11.6$ Hz, 1H), 4.70 (d, $J=11.6$ Hz, 1H), 4.74 (d, $J=11.0$ Hz, 1H), 5.15 (d, $J=15.0$ Hz, 1H), 6.71–6.78 (m, 2H), 7.06–7.11 (m, 2H), 7.17–7.39 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=33.9$, 43.2, 55.2, 59.6, 62.4, 67.5, 67.9, 72.1, 73.9, 77.6. 79.6, 114.1, 127.8, 128.0 (2C), 128.3, 128.5, 128.6, 128.8, 129.4, 136.4, 137.8, 159.0, 173.4 ppm; IR (KBr): $\tilde{\nu}=3430$, 2931, 2871, 1673, 1512, 1453, 1246, 1074, 1028 cm^{-1}; MS (ESI): m/z (%): 522 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{30}H_{35}NO_7+H^+$: 522.2486; found: 522.2480.

(4*S*,5*R*)-5-[(1*R*,2*S*,3*S*)-2,3-Bis(benzyloxy)-1,4-diacetoxybutyl]-1-(4-methoxybenzyl)-4-acetoxypyrrolidin-2-one (28): Ac_2O (0.12 mL, 1.3 mmol), Et_3N (0.18 mL, 1.3 mmol), and a catalytic amount of DMAP were successively added to an ice-bath-cooled solution of compound **27** (137 mg, 0.26 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at RT overnight and then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) at 0°C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×8 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:1 to afford compound **28** (148 mg, 87%) as a colorless oil. $[\alpha]_D^{20}=-21.7$ ($c=2.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.97$ (s, 3H), 2.01 (s, 3H), 2.04 (s, 3H), 2.50 (dd, $J=16.7$, 8.1 Hz, 1H), 2.80 (dd, $J=16.7$, 8.5 Hz, 1H), 3.69 (td, $J_t=4.1$, $J_d=7.1$ Hz, 1H), 3.74 (s, 3H), 3.79 (d, $J=15.2$ Hz, 1H), 3.88 (dd, $J=7.7$, 2.0 Hz, 1H), 3.93 (dd, $J=11.7$, 7.0 Hz, 1H), 4.06 (dd, $J=7.7$, 3.7 Hz, 1H), 4.30 (dd, $J=11.7$, 4.3 Hz, 1H), 4.38 (d, $J=12.0$ Hz, 1H), 4.51 (d, $J=12.0$ Hz, 1H), 4.56 (s, 2H), 5.10 (d, $J=15.2$ Hz, 1H), 5.31 (q, $J=8.2$ Hz, 1H), 5.71 (dd, $J=7.7$, 2.0 Hz, 1H), 6.72–6.78 (m, 2H), 7.01–7.06 (m, 2H), 7.11–7.19 (m, 2H), 7.27–7.38 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.8$, 20.9, 21.1, 37.4, 43.2, 55.2, 57.9, 63.3, 67.8, 70.8, 72.0, 74.0, 75.6, 114.2, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 129.2, 137.3, 137.4, 159.1, 169.6, 169.8, 170.3, 170.9 ppm; IR (KBr): $\tilde{\nu}=2936$, 1743, 1698, 1513, 1370, 1229, 1075, 1038 cm^{-1}; MS (ESI): m/z (%): 648 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{36}H_{41}NO_{10}+H^+$: 648.2803; found: 648.2800.

5-(2,3-Bisbenzyloxy-1,4-diacetoxy-butyl)-4-acetoxypyrrolidin-2-one (29): CAN (729 mg, 1.33 mmol) was added to a solution of compound **28** (172 mg, 0.27 mmol) in a mixed solvent system CH_3CN/H_2O (v/v 9:1, 27 mL). The mixture was stirred at RT for 5 h and then diluted with H_2O (10 mL). The mixture was extracted with EtOAc (4×15 mL). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:1 to afford compound **29** (123 mg, 88%) as a colorless oil. $[\alpha]_D^{20}=+31.1$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.96$ (s, 3H), 1.98 (s, 3H), 2.00 (s, 3H), 2.15 (d, $J=17.6$ Hz, 1H), 2.36 (dd, $J=17.6$, 5.7 Hz, 1H), 3.61 (dd, $J=3.7$, 3.0 Hz, 1H), 3.78 (dt, $J_d=2.7$, $J_t=6.2$ Hz, 1H), 3.83 (dd, $J=10.3$, 4.5 Hz, 1H), 4.04 (dd, $J=11.4$, 6.5 Hz, 1H), 4.24 (dd, $J=11.4$, 5.3 Hz, 1H), 4.33–4.37 (m, 1H), 4.49 (d, $J=11.6$ Hz, 1H), 4.61 (d, $J=11.7$ Hz, 1H), 4.74 (d, $J=11.7$ Hz, 1H), 4.78 (d, $J=11.6$ Hz, 1H), 5.22 (dd, $J=10.3$, 4.0 Hz, 1H), 5.29 (t, $J=5.0$ Hz, 1H), 6.17 (s, 1H), 7.27–7.41 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.6$, 20.7, 20.8, 37.7, 56.9. 62.5, 66.4, 68.9, 73.0, 73.3, 74.7, 75.6, 128.1, 128.3, 128.4, 128.6 (2C), 128.9, 136.5, 136.9, 169.4, 170.0, 170.4, 174.2 ppm; IR (KBr): $\tilde{\nu}=3225$, 2920, 1740, 1703, 1370, 1230, 1100, 1035 cm^{-1}; MS (ESI): m/z (%): 528 (100) $[M+H]^+$; HRMS: m/z: calcd for $C_{28}H_{33}NO_9+H^+$: 528.2228; found: 528.2226.

(2*R*,3*S*)-2-[(1*R*,2*S*,3*S*)-2,3-Bis(benzyloxy)-1,4-dihydroxybutyl]pyrrolidin-3-ol (30): $BH_3{\cdot}SMe_2$ (0.14 mL, 1.5 mmol) was added to a solution of compound **29** (80 mg, 0.15 mmol) in dry THF (4 mL) at 0°C. The reaction was heated at reflux for 10 h and quenched carefully with MeOH (2 mL) at 0°C. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and then 6N HCl (0.5 mL) was added. The resulting mixture was stirred at RT for 30 min and then concentrated. The residue was dissolved in H_2O, passed through a column of ion-exchange resin (Dowex 1×8–100, OH^- form) eluting with water (20 mL). The eluent was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH 10:1 to afford compound **33** (37 mg, 63%) as a colorless oil. $[\alpha]_D^{20}=+26.5$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): $\delta=1.73$–1.82 (m, 1H), 1.84–1.94 (m, 1H), 2.73 (ddd, $J=10.8$, 9.5, 4.0 Hz, 1H), 2.97 (dd, $J=8.5$, 3.5 Hz, 1H), 3.06 (td, $J_t=8.1$, $J_d=10.8$ Hz, 1H), 3.74 (dd, $J=6.1$, 2.2 Hz, 1H), 3.78 (dt, $J_d=2.4$, $J_t=5.8$ Hz, 1H), 3.81–3.90 (m, 2H), 3.96 (dd, $J=8.5$, 2.1 Hz, 1H), 4.33–4.37 (m, 1H), 4.63 (d, $J=11.5$ Hz, 1H), 4.68 (d, $J=11.5$ Hz, 1H), 4.75 (d, $J=11.2$ Hz, 1H), 4.78 (d, $J=11.2$ Hz, 1H), 7.24–7.43 ppm (m, 10H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=35.5$, 45.1, 61.7, 65.6, 70.2, 73.0, 73.7, 75.1, 80.0, 81.4, 128.7, 128.9, 129.3, 129.4, 129.5, 129.6, 140.0, 140.1 ppm; IR (KBr): $\tilde{\nu}=3400$, 2930, 1635, 1450, 1395, 1060 cm^{-1}; MS (ESI): m/z (%): 388 (100) $[M+H]^+$; HRMS: m/z: calcd for $C_{22}H_{29}NO_5+H^+$: 388.2124; found: 388.2127.

(1*S*,6*S*,7*S*,8*R*,8a*R*)-6,7-Bis(benzyloxy)octahydroindolizine-1,8-diol (31): Triphenylphosphine (68 mg, 0.26 mmol), dry carbon tetrachloride (25 μL, 0.26 mmol), and freshly distilled triethylamine (36 μL, 0.26 mmol) were added to a solution of compound **30** (50 mg, 0.13 mmol) in dry DMF (2 mL). The mixture was stirred in the dark at RT for 1 h and then quenched with methanol (1 mL). After the mixture had been stirred for 30 min, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH 10:1 to afford compound **31** (33 mg, 70%) as a colorless oil. $[\alpha]_D^{20}=+64$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.77$ (dddd, $J=13.7$, 8.6, 8.4, 1.8 Hz, 1H), 1.89 (dd, $J=9.5$, 4.3 Hz, 1H), 2.02 (dd, $J=10.4$, 10.4 Hz, 1H), 2.08 (br s, 1H), 2.13 (dd, $J=17.6$, 8.8 Hz, 1H), 2.24 (dddd, $J=13.6$, 9.1, 7.1, 2.2 Hz, 1H), 2.50 (s, 1H), 3.10 (dt, $J_t=8.9$, $J_d=2.1$ Hz, 1H), 3.32 (dd, $J=10.6$, 5.1 Hz, 1H), 3.39 (t, $J=8.9$ Hz, 1H), 3.68–3.76 (m, 2H), 4.30–4.38 (m, 1H), 4.66 (s, 2H), 4.73 (d, $J=11.5$ Hz, 1H), 5.04 (d, $J=11.5$ Hz, 1H), 7.27–7.39 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=33.8$, 52.0, 54.4, 69.2, 70.6, 71.5, 72.6, 75.1, 79.1, 86.6, 127.7, 127.8, 127.9, 128.4, 128.6, 138.2, 138.8 ppm; IR (KBr): $\tilde{\nu}=3364$, 2998, 2940, 2875, 1660, 1100, 1079 cm^{-1}; MS (ESI): m/z (%): 370 (100) $[M+H]^+$; HRMS: m/z: calcd for $C_{22}H_{27}NO_4+H^+$: 370.2013; found: 370.2013.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,6,7,8-tetraol (castanospermine) (1): HCOOH (0.2 mL) was added to a mixture of compound **31** (28 mg, 0.076 mmol) and 10% Pd/C (40 mg) in MeOH (5 mL) under an argon atmosphere. The suspension was stirred for 4 h and then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in water and passed through a column of ion-exchange resin (Dowex 1×8–100, OH^- form) eluting with water (30 mL). The eluent was concentrated under reduced pressure to give castanospermine (**1**) (13 mg, 87%) as a colorless solid. M.p. 209–210°C (MeOH/Et_2O); $[\alpha]_D^{20}=+77.5$ ($c=0.3$ in H_2O) (lit.[2a] $[\alpha]_D^{24}=+79.7$ ($c=0.93$ in H_2O)); ^{1}H NMR (400 MHz, D_2O): $\delta=1.71$ (dddd, $J=13.9$, 8.7, 8.7, 1.8 Hz, 1H), 2.02 (dd, $J=9.9$, 4.3 Hz, 1H), 2.06 (t, $J=10.8$ Hz, 1H), 2.21 (q, $J=9.2$ Hz, 1H), 2.33 (dddd, $J=13.9$, 9.3, 7.3, 2.2 Hz, 1H), 3.08 (ddd, $J=9.2$, 9.1, 2.2 Hz, 1H), 3.18 (dd, $J=10.8$, 5.1 Hz, 1H), 3.32 (t, $J=9.1$ Hz, 1H), 3.56–3.65 (m, 2H), 4.41 ppm (ddd, $J=6.8$, 4.4, 1.8 Hz 1H); ^{13}C NMR (100 MHz, D_2O): $\delta=32.5$, 51.4, 55.2, 68.8, 69.4, 69.9, 71.2, 78.8 ppm; IR (KBr): $\tilde{\nu}=3389$, 2915, 1648, 1155, 1117, 1070 cm^{-1}; MS (ESI): m/z (%): 190 (100) $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_8H_{15}NO_4+H^+$: 190.1074; found: 190.1074.

(4*S*,5*S*)-1-(4-Methoxybenzyl)-5-[(1*S*,3*S*)-4-(4-methoxybenzyloxy)-3-(benzyloxy)-1-hydroxybutyl]-4-hydroxypyrrolidin-2-one (35a): A solution of 10% HCl (20 mL) was added to a solution of compound **13g** (647 mg, 0.94 mmol) in THF (50 mL). The mixture was stirred at 30°C for 48 h and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered,

and concentrated under reduced pressure. The residue was dissolved in THF (15 mL) and cooled to −78 °C, $NaBH_4$ (108 mg, 2.83 mmol) was added one portion, then H_2O (1 mL) was added slowly over 3 min. After the mixture had been stirred for 30 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 5:1 to give compound **35a** (275 mg, 54.4%; colorless oil) and **35b** (28 mg, 5.5%; colorless oil). Compound **35a**: $[\alpha]_D^{20}=-47$ ($c=2.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.66$ (ddd, $J=14.0$, 9.2, 2.3 Hz, 1H), 2.00 (ddd, $J=14.0$, 10.4, 2.9 Hz, 1H), 2.47 (dd, $J=17.1$, 1.5 Hz, 1H), 2.57 (dd, $J=17.1$, 5.8 Hz, 1H), 3.22 (dd, $J=4.9$, 2.9 Hz, 1H), 3.47–3.58 (m, 2H), 3.74 (s, 3H), 3.79 (s, 3H), 3.82–3.95 (m, 1H), 4.03 (d, $J=15.0$ Hz, 1H), 4.27–4.36 (m, 1H), 4.42–4.57 (m, 5H), 4.70 (d, $J=11.4$ Hz, 1H), 5.01 (d, $J=15.0$ Hz, 1H), 6.70–6.78 (m, 2H), 6.84–6.90 (m, 2H), 7.02–7.08 (m, 2H), 7.16–7.45 ppm (m, 7H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=35.9$, 41.8, 43.5, 55.2 (2C), 63.3, 66.3, 67.7, 71.9, 72.5, 73.1, 75.1, 113.8, 114.2, 127.7, 127.9, 128.2, 128.4, 129.1, 129.3. 130.0, 138.4, 159.0, 159.2, 174.4 ppm; IR (KBr): $\tilde{\nu}=3366$, 2934, 2860, 1665, 1611, 1516, 1453, 1246, 1175, 1071 cm^{-1}; MS (ESI): m/z (100): 558 $[M+Na]^+$; elemental analysis calcd (%) for $C_{31}H_{37}NO_7$: C 69.51, H 6.96, N 2.62, O 20.91; found: C 69.73, H 7.14, N 2.91.

(4*R*,5*S*)-1-(4-Methoxybenzyl)-5-[(1*S*,3*S*)-4-(4-methoxybenzyloxy)-3-(benzyloxy)-1-hydroxybutyl]-4-hydroxypyrrolidin-2-one (35b): $[\alpha]_D^{20}=-29.1$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.58$ (ddd, $J=14.2$, 8.8, 3.4 Hz, 1H), 1.72 (ddd, $J=14.2$, 9.6, 3.0 Hz, 1H), 2.25 (dd, $J=17.5$, 1.6 Hz, 1H), 2.76 (dd, $J=17.5$, 6.9 Hz, 1H), 2.80 (brs, 1H, D_2O exchangeable), 3.17–3.20 (m, 1H), 3.22 (brs, 1H, D_2O exchangeable), 3.44–3.55 (m, 2H), 3.72 (s, 3H), 3.69–3.77 (m, 1H), 3.78 (s, 3H), 3.99 (d, $J=14.3$ Hz, 1H), 3.98–4.06 (m, 1H), 4.31 (m, 1H), 4.37 (d, $J=11.5$ Hz), 4.44 (s, 2H), 4.64 (d, $J=11.5$ Hz, 1H), 4.84 (d, $J=15.0$ Hz, 1H), 6.74–6.82 (m, 2H), 6.84–6.89 (m, 2H), 7.08–7.17 (m, 2H), 7.18–7.39 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=33.4$, 41.3, 43.6, 55.2 (2C), 65.0, 71.1, 71.8, 72.2, 73.0, 75.1, 113.8, 114.1, 127.8, 127.9, 128.2, 128.4, 129.2, 129.3, 129.9, 138.2, 158.9, 159.2, 174.0 ppm; IR (KBr): $\tilde{\nu}=3392$, 2933, 1669, 1610, 1513, 1455, 1244, 1081, 1027 cm^{-1}; MS (ESI): m/z (%): 558 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{31}H_{37}NO_7$: C 69.51, H 6.96, N 2.62, O 20.91; found: C 69.32, H 7.03, N 2.81.

(4*S*,5*S*)-1-(4-Methoxybenzyl)-5-[(1*S*,3*S*)-3-(benzyloxy)-1,4-dihydroxybutyl]-4-hydroxypyrrolidin-2-one (36): Iodine (100 mg, 0.39 mmol) was added to a methanolic solution (5 mL) of compound **35a** (250 mg, 0.47 mmol). After the mixture had been stirred at 70 °C for 96 h, the reaction was quenched with saturated $Na_2S_2O_3$ solution. The methanol was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH 10:1 to afford compound **36** (157 mg, 81%) as a colorless solid. M.p. 169–170 °C (MeOH); $[\alpha]_D^{20}=-43.5$ ($c=1.0$ in MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta=1.60$ (ddd, $J=14.2$, 10.2, 2.8 Hz, 1H), 1.90 (ddd, $J=14.2$, 10.0, 2.5 Hz, 1H), 2.35 (ddd, $J=17.1$, 2.4, 0.9 Hz, 1H), 2.60 (dd, $J=17.1$, 6.0 Hz, 1H), 3.29 (dd, $J=5.1$, 3.0 Hz, 1H), 3.54 (dd, $J=11.6$, 4.8 Hz, 1H), 3.64 (dd, $J=11.6$, 4.5 Hz, 1H), 3.68 (s, 3H), 3.74 (ddt, $J_t=6.9$, $J_d=4.6$, 2.5 Hz, 1H), 3.93 (d, $J=15.0$ Hz, 1H), 4.21 (td, $J_d=10.0$, $J_t=2.8$ Hz, 1H), 4.42 (d, $J=11.1$ Hz, 1H), 4.53 (dt, $J_t=5.9$, $J_d=2.3$ Hz, 1H), 4.70 (d, $J=11.1$ Hz, 1H), 5.10 (d, $J=15.0$ Hz, 1H), 6.68–6.73 (m, 2H), 6.97–7.03 (m, 2H), 7.17–7.47 ppm (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz): $\delta=37.2$, 42.4, 44.3, 55.7, 64.6, 65.1, 67.5, 68.5, 73.5, 78.6, 115.2, 128.7, 129.1, 129.2, 129.4, 130.2, 140.2, 160.6, 176.6 ppm; IR (KBr): $\tilde{\nu}=3369$, 2934, 1661, 1459, 1248, 1077, 1042 cm^{-1}; MS (ESI): m/z (%): 438 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{23}H_{29}NO_6$: C 66.49, H 7.04, N 3.37, O 23.10; found: 66.13, H 7.24, N 3.30.

(4*S*,5*S*)-1-(4-Methoxybenzyl)-5-[(1*S*,3*S*)-4-(4-methoxybenzyloxy)-3-(benzyloxy)-1-hydroxybutyl]-4-(benzyloxy)pyrrolidin-2-one (37): Compound **35a** (740 mg, 1.38 mmol) in THF (3 mL) was added to a suspension of NaH (60% in mineral oil, 117 mg, 2.9 mmol) in THF (15 mL) at −30 °C. After the mixture had been stirred for 30 min, BnBr (0.83 mL, 6.92 mmol) and Bu_4NI (cat. amount) were added. The reaction was stirred at RT for 15 h and then quenched with saturated NH_4Cl solution (5 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3× 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:1 to afford compound **37** (735 mg, 85%) as a colorless oil. $[\alpha]_D^{20}=-2.1$ ($c=2.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.57$ (ddd, $J=13.8$, 9.8, 2.9 Hz, 1H), 1.75 (ddd, $J=13.8$, 9.7, 2.3 Hz, 1H), 2.47 (dd, $J=17.1$, 6.0 Hz, 1H), 2.65 (dd, $J=17.1$, 1.9 Hz, 1H), 3.24 (d, $J=10.2$ Hz, 1H, D_2O exchangeable), 3.35 (dd, $J=5.5$, 3.3 Hz, 1H), 3.44–3.49 (m, 2H), 3.73 (s, 3H), 3.78 (s, 3H), 3.84–3.91 (m, 1H), 3.94 (d, $J=14.9$ Hz, 1H), 4.19 (tt, $J=10.1$, 2.9 Hz, 1H), 4.28 (dt, $J_t=5.8$, $J_d=2.3$ Hz, 1H), 4.32 (d, $J=11.2$ Hz, 1H), 4.45 (d, $J=11.2$ Hz, 1H), 4.46 (s, 2H), 4.54 (d, $J=11.2$ Hz, 1H), 4.69 (d, $J=11.3$ Hz, 1H), 5.23 (d, $J=14.9$ Hz, 1H), 6.69–6.75 (m, 2H), 6.84–6.88 (m, 2H), 7.01–7.11 (m, 2H), 7.16–7.40 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=36.5$, 37.0, 43.3, 55.1, 55.2, 62.7, 66.1, 71.4, 72.1, 72.6, 72.9, 74.9, 75.3, 113.7, 114.0, 127.5, 127.8, 128.1, 128.3 (2C), 128.6, 129.2, 129.3, 130.2, 136.3, 138.6, 158.8, 159.1, 172.8 ppm; IR (KBr): $\tilde{\nu}=3506$, 2929, 2863, 1696, 1610, 1509, 1248, 1084, 1034 cm^{-1}; MS (ESI): m/z (%): 648 (100) $[M+Na]^+$; HRMS (ESI): m/z: calcd for $C_{38}H_{43}NO_7+H^+$: 626.3118; found: 626.3138.

(4*S*,5*S*)-1-(4-Methoxybenzyl)-4-(benzyloxy)-5-[(1*S*,3*S*)-3-(benzyl-oxy)-1,4-dihydroxybutyl]pyrrolidin-2-one (38): Iodine (100 mg, 0.39 mmol) was added to a methanolic solution (5 mL) of compound **37** (337 mg, 0.54 mmol). After the mixture had been stirred at 70 °C for 96 h, the reaction was quenched with saturated $Na_2S_2O_3$ solution. The methanol was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (10:1) to afford compound **38** (225.6 mg, 83%) as a colorless solid. M.p. 183–185 °C (EtOAc); $[\alpha]_D^{20}=-2.7$ ($c=2.3$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.60$–1.75 (m, 2H), 2.15 (brs, 1H, D_2O exchangeable), 2.50 (dd, $J=17.1$, 6.0 Hz, 1H), 2.67 (dd, $J=17.1$, 1.8 Hz, 1H), 3.32 (brs, 1H, D_2O exchangeable), 3.36 (dd, $J=5.5$, 3.4 Hz, 1H), 3.44–3.57 (m, 1H), 3.74 (s, $3H_3$), 3.70–3.83 (m, 2H), 3.96 (d, $J=14.9$ Hz, 1H), 4.22–4.11 (m, 1H), 4.31 (dt, $J_t=5.9$, $J_d=2.5$ Hz, 1H), 4.35 (d, $J=11.2$ Hz, $1H_2$), 4.51 (d, $J=11.3$ Hz, 1H), 4.57 (d, $J=11.2$ Hz, 1H), 4.62 (d, $J=11.3$ Hz, 1H), 5.23 (d, $J=14.9$ Hz, 1H), 6.67–6.81 (m, 2H), 7.04–7.11 (m, 2H), 7.21–7.44 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=36.0$, 37.0, 43.4, 55.2, 62.8, 64.2, 66.3, 71.5, 72.4, 74.9, 114.0, 127.8 (2C), 128.2 (2C), 128.5, 128.7, 129.3, 136.2, 138.2, 158.9, 172.8 ppm; IR (KBr): $\tilde{\nu}=3451$, 2933, 1664, 1516, 1450, 1244, 1069, 1026 cm^{-1}; MS (ESI): m/z (%): 528 (100) $[M+Na]^+$; HRMS (ESI): m/z: calcd for $C_{30}H_{35}NO_6+H^+$: 506.2543; found: 528.2425.

(4*S*,5*R*)-5-[(1*S*,3*S*)-3-Benzyloxy-1,4-bis(acetoxy)butyl]-1-(4-methoxybenzyl)-4-benzyloxypyrrolidin-2-one (39): DMAP (cat. amount), Ac_2O (0.21 mL, 2.2 mmol), and Et_3N (0.30 mL, 2.2 mmol) were added successively to an ice-bath-cooled solution of compound **38** (363 mg, 0.72 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at RT overnight and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 1:1 to afford compound **39** as a colorless oil (417 mg, 85%). $[\alpha]_D^{20}=-39.2$ ($c=1.7$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.82$–1.96 (m, 2H), 2.02 (s, 3H), 2.04 (s, 3H), 2.51–2.60 (m, 1H), 2.64 (dd, $J=16.7$, 8.7 Hz, 1H), 3.57–3.67 (m, 1H), 3.76 (s, 3H), 3.78 (dd, $J=8.3$, 1.4 Hz, 1H), 3.84 (d, $J=14.8$ Hz, 1H), 4.04 (dd, $J=11.7$, 5.2 Hz, 1H), 4.20–4.31 (m, 2H), 4.43 (d, $J=11.2$ Hz, 1H), 4.51 (d, $J=12.0$ Hz, 1H), 4.58 (d, $J=12.0$ Hz, 1H), 4.60 (d, $J=11.2$ Hz, 1H), 5.19 (d, $J=14.8$ Hz, 1H), 5.64–5.71 (m, 1H), 6.74–6.81 (m, 2H), 6.98–7.09 (m, 2H), 7.20–7.36 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=20.8$, 21.2, 32.9, 37.2, 44.2, 55.2, , 60.8, 65.6, 70.2, 72.1, 72.2, 72.7, 73.3, 114.1, 127.4, 127.7, 127.8, 128.06, 128.1, 128.3, 128.4, 128.5, 129.2, 137.2, 138.0, 159.1, 170.2, 170.7, 172.0 ppm; IR (KBr): $\tilde{\nu}=1738$, 1692, 1513, 1252, 1200,

1026 cm^{-1}; MS (ESI): *m/z* (%): 590 (100) $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{30}H_{35}NO_6+H^+$: 590.2754; found: 590.2777.

(4*S*,5*R*)-5-[(1*S*,3*S*)-3-Benzyloxy-1,4-bis(acetoxy)butyl]-4-benzyl-oxypyrrolidin-2-one (40): CAN (1.62 g, 2.95 mmol) was added to a solution of **39** (350 mg, 0.59 mmol) in a mixed solvent system CH_3CN/H_2O (v/v 9: 1, 60 mL). The mixture was stirred at RT for 5 h and then diluted with H_2O (10 mL). The mixture was extracted with EtOAc (4×15 mL). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/PE 2:1 to afford compound **40** (239 mg, 86%) as a colorless oil. $[\alpha]_D^{20}=-24.5$ ($c=1.5$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.88$ (ddd, $J=14.5$, 10.0, 3.0 Hz, 1H), 1.98 (s, 1H, 3H), 2.02 (s, 1H, 3H), 2.02–2.09 (m, 1H), 2.45 (dd, $J=17.1$, 5.7 Hz, 1H), 2.52 (dd, $J=17.1$, 7.5 Hz, 1H), 3.65 (dtd, $J_d=7.7$, 3.1, $J_t=4.6$ Hz, 1H), 4.00–4.09 (m, 2H), 4.24 (dd, $J=11.7$, 4.4 Hz, 1H), 4.41 (td, $J_d=7.3$, $J_t=6.1$ Hz, 1H), 4.45 (d, $J=11.3$ Hz, 1H), 4.51 (d, $J=11.8$ Hz, 1H), 4.55 (d, $J=11.8$ Hz, 1H), 4.61 (d, $J=11.3$ Hz, 1H), 5.42–5.48 (m, 1H), 6.18 (s, 1H), 7.20–7.39 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=20.8$, 21.0, 32.8, 36.6, 59.7, 65.4, 70.7, 72.0 (2C), 73.2, 74.2, 127.6, 127.7, 127.8, 128.1, 128.3, 128.4, 137.1, 137.8, 170.3, 170.8, 175.0 ppm; IR (KBr): $\tilde{\nu}=3217$, 2925, 1736, 1699, 1368, 1232, 1096, 1037 cm^{-1}; MS (ESI): *m/z* (%): 492 (100) $[M+Na]^+$; HRMS (ESI): *m/z*: calcd for $C_{26}H_{31}NO_7+H^+$: 470.2179; found: 470.2189.

(1*S*,3*S*)-3-(Benzyloxy)-1-[(2*S*,3*S*)-3-(benzyloxy)pyrrolidin-2-yl]butane-1,4-diol (41): $BH_3{\cdot}SMe_2$ (0.36 mL, 3.8 mmol) was added to a solution of compound **40** (178 mg, 0.38 mmol) in dry THF (5 mL) at 0°C. The reaction was heated at 60°C for 10 h and then quenched with MeOH (2 mL) at 0°C. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and 6N HCl (0.5 mL) was added. After the mixture had been stirred at RT for 30 min, the volatile solvent was removed under reduced pressure. The residue was dissolved in H_2O and passed through a column of ion-exchange resin (Dowex 1×8–100, OH^- form) eluting with water (40 mL). The eluent was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (10: 1) to afford pyrrolidine **41** (127 mg, 71%) as a colorless oil. $[\alpha]_D^{20}=+33.8$ ($c=1.1$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.65$ (ddd, $J=14.6$, 10.1, 4.6 Hz, 1H), 1.84–1.97 (m, 2H), 2.01 (dddd, $J=13.6$, 7.8, 5.4, 2.2 Hz, 1H), 2.33 (brs, 3H, D_2O exchangeable), 2.80 (dd, $J=5.4$, 4.8 Hz, 1H), 2.90 (ddd, $J=11.1$, 8.8, 5.4 Hz, 1H), 3.20 (ddd, $J=11.1$, 7.9, 6.8 Hz, 1H), 3.56 (dd, $J=11.3$, 4.3 Hz, 1H), 3.74–3.83 (m, 2H), 4.07 (ddd, $J=10.0$, 5.6, 2.3 Hz, 1H), 4.21 (dt, $J_t=4.9$, $J_d=2.2$ Hz, 1H), 4.36 (d, $J=11.5$ Hz, 1H), 4.59 (d, $J=11.5$ Hz, 1H), 4.60 (s, 2H), 7.26–7.38 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.5$, 37.9. 44.5, 64.5, 66.7, 68.4, 70.8, 72.1, 77.4, 81.0, 127.7, 127.8 (2C), 127.9 (2C), 128.1, 128.4 (2C), 128.6 (2C), 137.4, 138.4 ppm; IR (KBr): $\tilde{\nu}=3397$, 2926, 1637, 1454, 1392, 1065 cm^{-1}; MS (ESI): *m/z* (%): 372 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{22}H_{29}NO_4+H^+$: 372.2175; found: 372.2188.

(1*S*,6*S*,8*S*,8*aS*)-1,6-Bis(benzyloxy)octahydroindolizin-8-ol (42): Triphenylphosphine (97 mg, 0.37 mmol), dry carbon tetrachloride (35 μL, 0.37 mmol), and freshly distilled triethylamine (51 μL, 0.37 mmol) were added to a solution of pyrrolidine **41** (68 mg, 0.18 mmol) in dry DMF (2 mL). The mixture was stirred in the dark at RT for 1 h and then quenched with methanol (1 mL). After the mixture had been stirred for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH 20:1 to afford indolizidinol **42** (48 mg, 75%) as a colorless oil. $[\alpha]_D^{20}=+64.7$ ($c=0.9$ in $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): $\delta=1.35$ (ddd, $J=13.4$, 11.4, 3.3 Hz, 1H), 1.78 (dd, $J=9.3$, 4.7 Hz, 1H), 1.85–2.14 (m, 4H), 2.35 (dddd, $J=13.3$, 4.7, 2.7, 2.1 Hz, 1H), 3.11 (t, $J=7.9$ Hz, 1H), 3.26 (td, $J_d=12.1$, $J_t=1.9$ Hz, 1H), 3.73–3.78 (m, 1H), 4.17–4.29 (m, 2H; H-1), 4.49 (d, $J=12.2$ Hz, 1H), 4.54 (d, $J=11.8$ Hz, 1H), 4.59 (d, $J=12.2$ Hz, 1H), 4.61 (d, $J=11.8$ Hz, 1H), 7.19–7.44 ppm (m, 10H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=30.7$, 38.7, 54.5, 56.2, 64.4, 71.5, 72.3, 74.7, 75.4, 79.0, 128.4, 128.5, 128.8 (2C), 128.9 (2C), 129.2 (2C), 129.3 (2C), 140.2, 140.4 ppm; IR (KBr): $\tilde{\nu}=3389$, 2918, 2859, 2797, 1614, 1349, 1131, 1065 cm^{-1}; MS (ESI): *m/z* (%): 354 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{22}H_{27}NO_3+H^+$: 354.2069; found: 354.2086.

(+)-7-Deoxy-6-*epi*-castanospermine (4): HCOOH (0.3 mL) was added to a suspension of compound **42** (25 mg, 0.07 mmol), 10% Pd/C (20 mg), and MeOH (2 mL) under an argon atmosphere. The suspension was stirred for 4 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in water and passed through a column of ion-exchange resin (Dowex 1×8–100, OH^- form) and eluted with water (20 mL). The eluent was concentrated under reduced pressure to give **4** (10 mg, yield: 80%) as a colorless oil. $[\alpha]_D^{20}=+17.1$ ($c=0.6$ in MeOH) (lit.[15] $[\alpha]_D^{26}=+18.3$ ($c=0.712$ in MeOH)); ^1H NMR (400 MHz, CD_3OD): $\delta=1.35$ (ddd, $J=13.2$, 11.5, 3.0 Hz, 1H), 1.62 (dd, $J=9.3$, 4.0 Hz, 1H), 1.64–1.72 (m, 1H), 2.02–2.19 (m, 4H), 3.02 (td, $J_d=11.6$, $J_t=2.2$ Hz, 1H), 3.07–3.13 (m, 1H), 3.96–4.01 (m, 1H), 4.07 (ddd, $J=11.45$, 9.30, 4.86 Hz, 1H), 4.29–4.33 ppm (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=33.6$, 40.8, 53.5, 58.9, 63.9, 67.7, 71.7, 75.4 ppm; IR (KBr): $\tilde{\nu}=3395$, 2923, 1648, 1164, 1120, 1070 cm^{-1}; MS (ESI): *m/z* (%): 174 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_8H_{15}NO_3+Na^+$: 196.0950; found: 196.0941.

Acknowledgements

The authors are grateful to the NSF of China (20832005) and the National Basic Research Program (973 Program) of China (grant no. 2010CB833200) for financial support.

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[38] CCDC-767994 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: December 20, 2009
Published online: April 8, 2010

