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Stereoselective Synthesis

Influence of $A^{1,3}$ Strain on the Stereochemical Outcome of Acid-Mediated Amido Cyclization in the Synthesis of 2-(4-Methoxyphenyl)-3,4-(dihydroxy)piperidines

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Abstract: The synthesis of 2-(4-methoxyphenyl)-3,4-(dihydroxy)piperidines was accomplished by using ethyl *p*-methoxycinnamate as the starting material and an acid-mediated amido cyclization reaction as the key step. This short and straightforward strategy avoids extra steps to create the chiral center and does not require a leaving group at the benzylic carbon. This study also showed that the stereochemical outcome of the cyclization reaction is influenced more by allylic 1,3-strain ($A^{1,3}$ strain) than by the participation of a neighboring group.

Introduction

Polyhydroxy pyrrolidine and piperidine alkaloids, both synthetic and of natural origin, are commonly referred to as imino- or azasugars. These compounds are selective inhibitors of glycoprocessing enzymes and potential agents for the treatment of several diseases such as diabetes, lysosomal storage disorders, viral infections, and cancer.[1] Polyhydroxy pyrrolidines, a recent addition to the class of iminosugars, have an aryl group at the C-2 position as well as interesting biological properties. Initial examples are (–)-codonopsinine (**1**) and (–)-codonopsinol (**2**, Figure 1), which were isolated from *Codonopsis clematidea*.[2] In animal tests, these compounds have exhibited antibiotic and hypotensive pharmacological activity without affecting the central nervous system.[3] (+)-Radicamine A (**3**) and (+)-radicamine B (**4**, Figure 1), which are later members of this class of compounds, were isolated by Kusano and co-workers from *Lobelia chinensis* LOUR (Campanulaceae) and exhibit glycosidase inhibitory activity.[4]

As a part of our ongoing research activity in the synthesis of iminosugars, we recently developed a new and highly stereoselective strategy that involves an acid-mediated amido cyclization reaction to synthesize of 2-aryl-substituted polyhydroxy pyrrolidines and, more specifically, the above natural products.[5] The high stereoselectivity of this approach is from the participation of adjacent acetate group to give a *trans*-dioxalonium intermediate, which undergoes an intramolecular opening by the amido nitrogen in an S_N2 mode to give the *trans*-pyrrolidines. In the absence of neighboring acetate functionality, the formation of a mixture of 1,2-*cis* and -*trans* products are observed (Scheme 1).[5c] Interestingly, the stereochemical purity at the benzylic carbon is inconsequential, unlike corresponding S_N2 cyclization reactions, because the reaction proceeds through a benzylic carbocation intermediate. Therefore, this process does not require a pure stereogenic center with a leaving group at the benzylic position and, thus, results in a short and straightforward strategy.

Herein, we report the application of the above strategy for the stereoselective synthesis of the 2-aryl-3,4-(dihydroxy)piperidines **5**, **6**, *ent*-**5**, and *ent*-**6** (Figure 1) and also our findings for the construction of the stereogenic center at the benzylic position.

2-Arylpiperidine is an important structural motif that is present in many bioactive natural products and synthetic molecules.[6] For example, CP-99,994 (**7**) and L-733,060 (**8**, Figure 1) and their related structures are neurokinen 1(NK_1) antagonists.[6] Previously, our group synthesized antagonist **8** by using ring-closing metathesis (RCM) and organocatalysis approaches.[7] However, 2-aryl-substituted polyhydroxy piperidines are gaining more importance because of their glycoprocessing enzyme inhibition activity. These molecules can be considered hybrid structures of bioactive and naturally occurring

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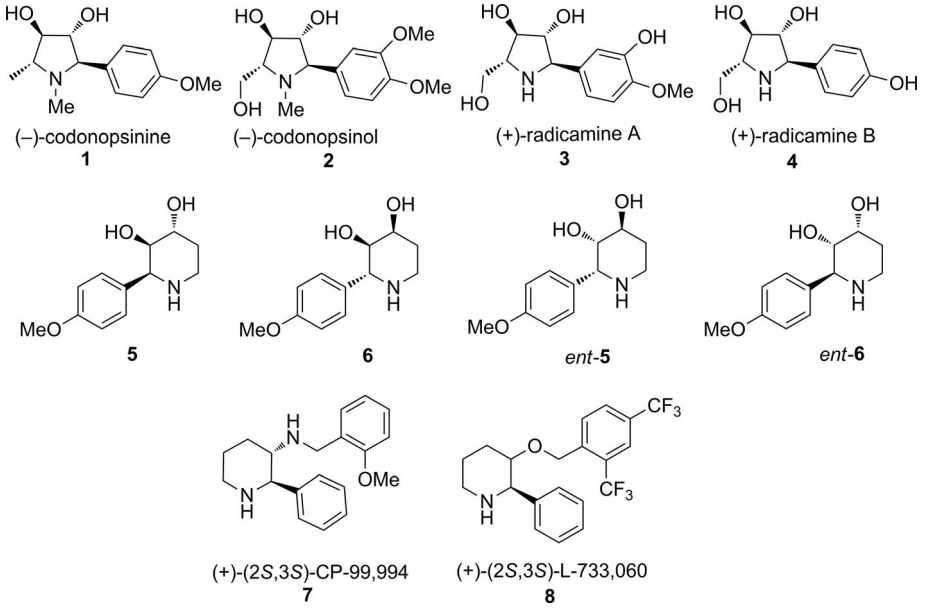
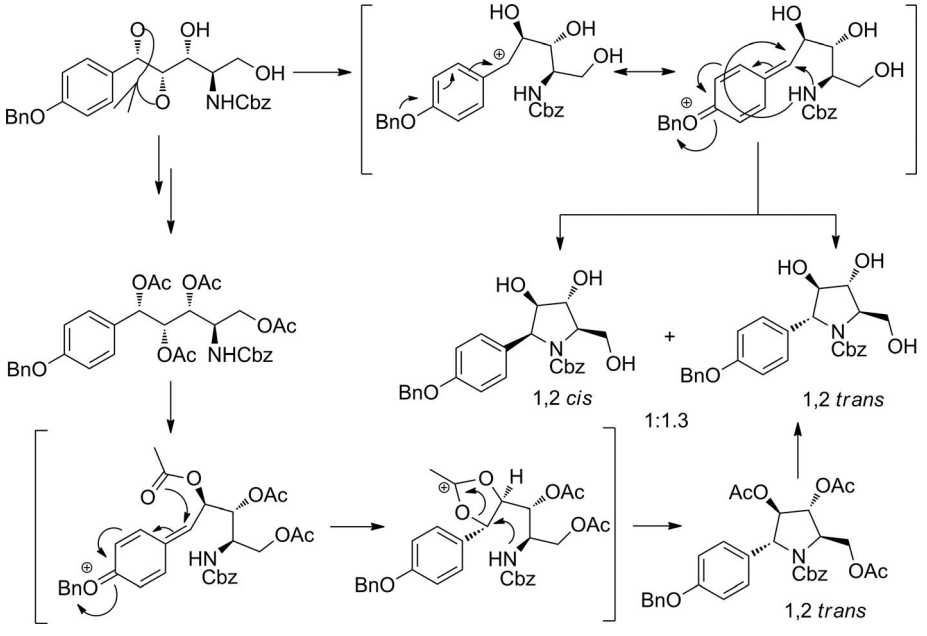


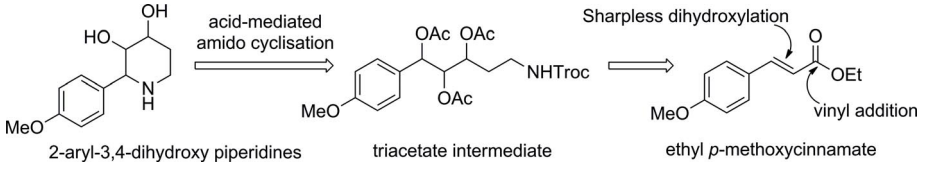
Figure 1. Some polyhydroxylated iminoalditols.



Scheme 1. Mechanism for acid-mediated amido cyclization (Cbz = benzyloxycarbonyl).

2-arylpyrrolidines (i.e., **1**–**4**) and polyhydroxy piperidines, such as nojirimycin and fagomine.[8]

The structural and biological importance of these 2-arylhydroxypiperidines prompted us to develop a synthetic strategy for these substances. A retrosynthetic pathway (Scheme 2) was designed that incorporated our acid-mediated amido cyclization protocol (Scheme 1) for the synthesis of compounds **5**, **6**, *ent*-**5**, and *ent*-**6**. The piperidine core skeleton was prepared from a triacetate intermediate, which was envisaged to be obtained from ethyl *p*-methoxycinnamate.



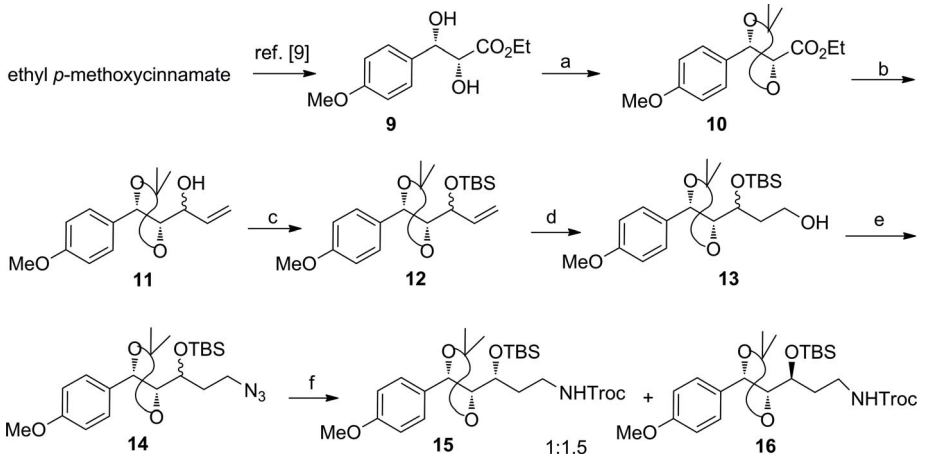
Scheme 2. Retrosynthetic pathway (Troc = trichloroethyloxycarbonyl).

Results and Discussion

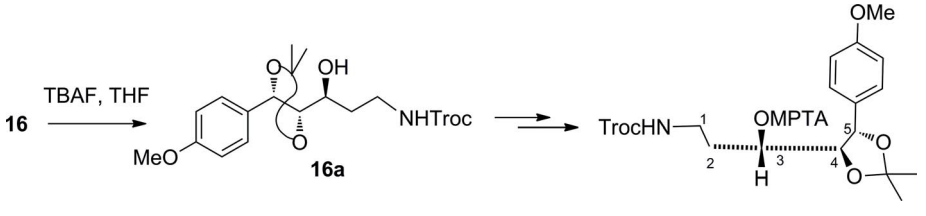
Ethyl *p*-methoxycinnamate underwent dihydroxylation by using AD-mix-α (AD = asymmetric dihydroxylation) to obtain compound **9**,[9] which upon treatment with 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of *para*-toluenesulfonic acid (*p*TsA) in CH_2Cl_2 afforded compound **10** (Scheme 3). The reduction of the ester functionality in **10** by using diisobutylaluminum hydride (DIBAL-H) gave an aldehyde, which was treated with vinylmagnesium bromide at 0 °C in tetrahydrofuran (THF) to obtain **11** as a mixture inseparable diastereomers (1:1.5 by ^{1}H NMR spectroscopy) in 69 % yield (over two steps). The allylic hydroxyl group was then protected as a *tert*-butyldimethylsilyl (TBS) ether by employing imidazole and TBSCl to give compound **12**. The hydroboration of **12** gave primary alcohol **13**, which was converted into azido derivative **14** by treatment with methanesulfonyl chloride in the presence of triethylamine followed by the addition of sodium azide in dry *N*,*N*-dimethylformamide (DMF, 77 % yield, over two steps). Compound **14** was reduced with lithium aluminum hydride (LAH), and the resulting primary amine was treated with Troc-Cl in the presence of K_2CO_3 in MeOH to give a diastereomeric mixture of **15** and **16** (1:1.5), the isomers of which were separable (Scheme 3).

The stereochemical assignment of the newly created asymmetric center was established by using a modified Mosher method (Scheme 4).[10] Thus, desilylation of major isomer **16** by treatment with tetra-*n*-butylammonium fluoride (TBAF) afforded **16a**. The synthesis of both the (*S*)- and (*R*)-methoxy(trifluoromethyl)phenylacetyl (MTPA) esters of **16a** were achieved by using MTPA acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), and the chemical shifts of the protons for both the (*S*)- and (*R*)-MTPA esters of **16a** were assigned. The equation $\Delta\delta = \delta_S - \delta_R$ was used to calculate the differences between the chemical shifts ($\Delta\delta$) of the protons adjacent to the chiral center. The protons with $-\Delta\delta$ values were placed on the left hand side of the model, and the protons with $+\Delta\delta$ values were placed on the right. This was used to determine the absolute stereochemistry of newly generated stereocenter (i.e., C-3), which was assigned the (*S*) configuration.

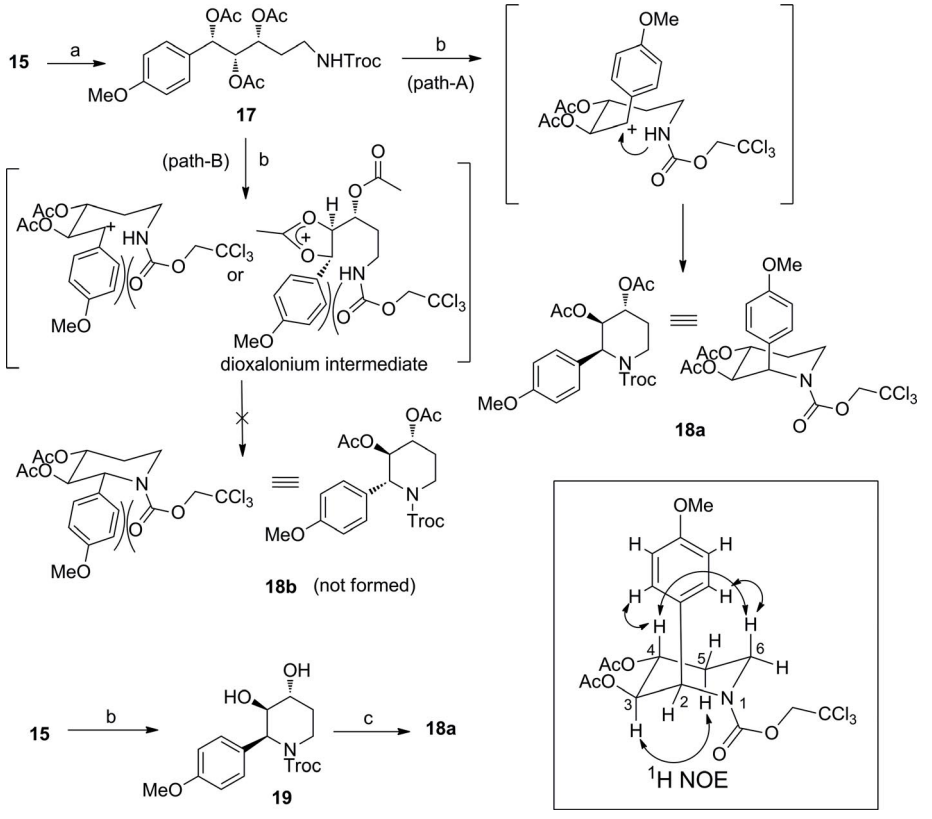
The treatment of compound **15** with 80 % AcOH in water followed by acetylation with acetic anhydride gave triacetate **17**. As predicted by our earlier observations, a subsequent acid-mediated amido cyclization of **17** in the presence of a TFA/CH_2Cl_2 mixture could yield **18b** through a *trans*-dioxalonium intermediate, in which all of the substituents are in the equatorial position (Scheme 5). Interestingly, the reaction of **17** under TFA/CH_2Cl_2 conditions exclusively gave **18a**, in which the aryl group at C-2 was in the axial position. This was confirmed by ^{1}H NOE correlations (NOE observed between the axial protons at C-4 and C-6 with the protons on the phenyl ring) and the value of the equatorial-axial coupling constant (J = 6.4 Hz) of the benzylic proton and the C-3 axial proton (Scheme 5). The predominant factor for the formation of **18a** involves allylic 1,3-strain ($A^{1,3}$ strain; path-A is sterically favored over the path-B, which encounters severe $A^{1,3}$ strain during the formation of the ring). In compounds such as **18b**, severe $A^{1,3}$ strain is known to



Scheme 3. Reagents and conditions: (a) 2,2-DMP, *p*TsA, CH_2Cl_2, room temp., 12 h, 96 %; (b) (i) DIBAL-H, THF, −78 °C, 2 h; (ii) vinylmagnesium bromide, THF, 0 °C to room temp., 2 h, 69 % (2 steps); (c) TBS-Cl, imidazole, CH_2Cl_2, room temp., 2 h, 90 %; (d) BH_3•DMS (DMS = dimethyl sulfide), THF, 0 °C to room temp., 2 h, 79 %; (e) (i) Ms-Cl (Ms = methylsulfonyl), Et_3N, CH_2Cl_2, 0 °C to room temp., 13 min; (ii) NaN_3, DMF, 80 °C, 6 h, 77 % (2 steps); (f) (i) $LiAlH_4$, THF, 0 °C to room temp., 3 h; (ii) Troc-Cl, K_2CO_3, MeOH, room temp., 30 min, 81 % (2 steps).



Scheme 4. Analysis by Mosher method.



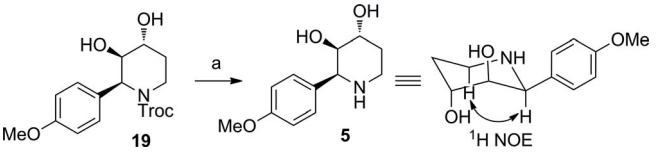
Scheme 5. Reagents and conditions: (a) (i) 80 % aqueous AcOH, room temp., 8 h; (ii) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to room temp., 6 h, 70 % (2 steps); (b) TFA/CH_2Cl_2 (1:3), 0 °C to room temp., 4 h, 78 %; (c) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to room temp., 4 h, 76 %.

occur between the *N*-carbamate and the equatorial substituent at C-2 position.[11a–11k] As a result, the cyclization reaction gave **18a**, which is devoid of $A^{1,3}$ strain between the C-2 axial and *N*-Troc groups. This explanation clearly supports that $A^{1,3}$ strain is the controlling element in the formation of the new stereocenter.

Our earlier observations have shown that the amido cyclization, in the absence of the neighboring acetate group, gives a mixture of two possible stereoisomers (1:1.3). However, treating compound **15** to the TFA/CH_2Cl_2 conditions resulted in the exclusive formation of **19**. The treatment of **19** with Ac_2O gave **18a**, the analysis of which confirmed the axial orientation of the aryl group in **19**. This further substantiated the influence of $A^{1,3}$ strain (Scheme 5).

Next, the removal of the Troc protecting group in compound **19** by using Zn in AcOH-MeOH (1:1) and heating at reflux gave compound **5**. ^1H NMR and NOE experiments of the product revealed an NOE correlation between the benzylic proton and the axial methylene proton adjacent to the nitrogen atom. This clearly indicates that a ring flip occurred to place the aryl group in the equatorial position.[12] (Scheme 6).

A similar sequence of reactions was carried out on compound **16**. The treatment of **16** with 80 % aqueous AcOH followed by acetylation of the resultant product with acetic anhydride gave triacetate compound **20**. In the presence of TFA/CH_2Cl_2 (1:3), compound **20** afforded only **21a**, which has the C-2 aryl group in the axial position (NOE observed between axial protons at C-4 and C-6 with the protons on the phenyl ring)

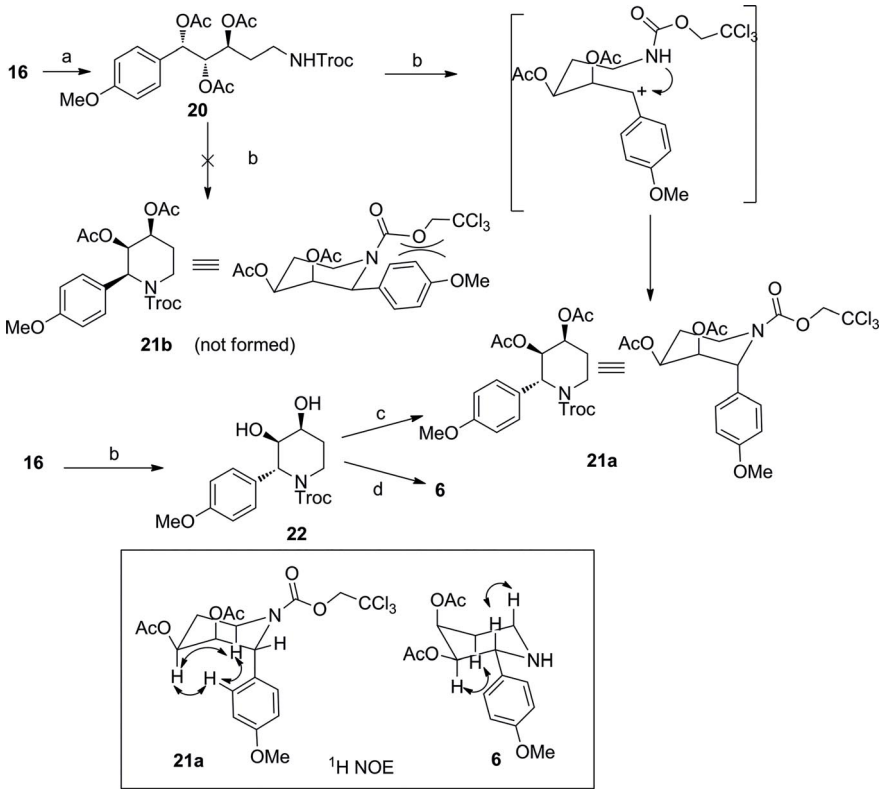


Scheme 6. Reagents and conditions: (a) Zn, AcOH/MeOH (1:1), 65 °C, 30 min, 69 %.

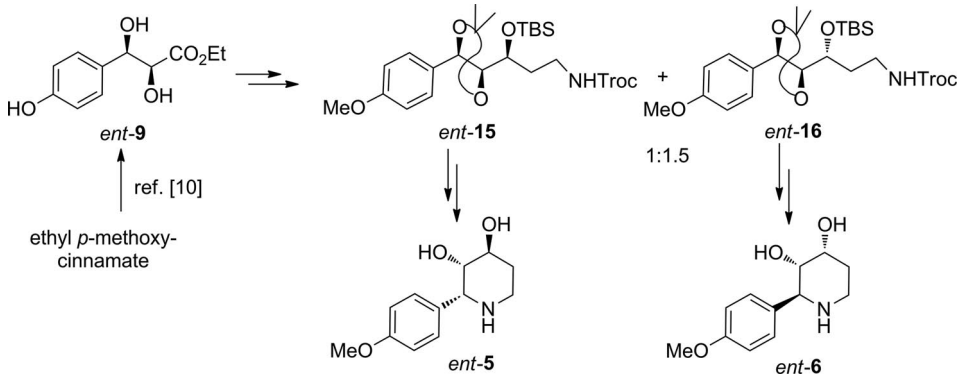
and is free of $A^{1,3}$ strain. There was no formation of **21b**, which has severe $A^{1,3}$ strain. It is interesting to note that the existing conformation of **21a** has the two bulky groups in the axial orientation, which clearly reveals that $A^{1,3}$ strain supersedes 1,3-diaxial interactions.[11l] Upon treatment with TFA/CH_2Cl_2 (1:3), compound **16** gave **22**, which upon acetylation gave **21a**. The removal of the Troc group in **22** by using Zn in AcOH-MeOH (1:1) at reflux gave **6**. The conformation of **6** was confirmed by NOE experiments and the diaxial coupling constant (J = 10.2 Hz) of benzylic proton (Scheme 7).

In addition, computational calculations were carried out, which also support the formation of **18a** and **21a** over **18b** and **21b**, respectively (detailed information is provided in Supplementary Information).

To compare the biological activity of compounds **5** and **6** with their enantiomers, *ent*-**5**, and *ent*-**6** were synthesized by using the same protocol as that used for the preparation of compounds **5** and **6**. The required β-diol compound *ent*-**9** was obtained by the dihydroxylation of ethyl *p*-methoxycinnamate using AD-mix-β[13] (Scheme 8).



Scheme 7. Reagents and conditions: (a) (i) 80 % aqueous AcOH, room temp., 8 h; (ii) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to room temp., 6 h, 70 % (2 steps); (b) TFA/CH_2Cl_2 (1:3), 0 °C to room temp., 4 h, 78 %; (c) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to room temp., 4 h, 76 %; (d) Zn, AcOH-MeOH (1:1), 65 °C, 30 min, 69 %.



Scheme 8. Synthesis of *ent*-5 and *ent*-6.

Assay of Enzyme Inhibition

The glucosidase and galactosidase inhibitory activities of compound **5**, **6**, *ent*-**5**, and *ent*-**6** were determined by measuring enzyme activity with a Perkin–Elmer Lambda 2 UV/Vis spectrophotometer equipped with temperature control and Perkin-Elmer Computerized Spectroscopy Software (PECSS). All enzyme assays were performed at 23 °C. Each experiment was repeated three times, and the results were reproducible within ±5 %. The enzymes and the corresponding substrates that were used for the assay are as the follows: α-glucosidase from yeast (4-nitrophenyl-α-D-glucopyranoside), β-glucosidase from almonds (2-nitrophenyl-β-D-glucopyranoside), α-galactosidase from green coffee beans (4-nitrophenyl-α-D-galactopyranoside), and β-galactosidase from *Kluyveromyces lactis* (4-nitrophenyl-β-D-galactopyranoside).

The *p*-nitrophenyl derivative of the substrate (1.6 mM) in phosphate buffer (0.23 M, pH = 6.8, 2.0 mL) was placed in a cuvette, and the enzyme solution (1 mg mL^{-1}, 100 μL) was added. The change in the absorbance from the release of *p*-nitrophenol was monitored at 410 nm (molar extinction coefficient at 410 nm, $\Delta\varepsilon$ = 8800 M^{-1} cm^{-1}) for 3–5 min. Similar experiments were performed in the presence of compounds **5**, **6**, *ent*-**5**, and *ent*-**6** at concentrations that varied from 1 μM to 2 mM. The IC_{50} values were calculated by nonlinear regression analysis using version 5 of Graph Pad Prism.[14] The values are reported in Table 1.

Table 1. IC_{50} values.

	IC_{50} [μM]			
	α-Glucosidase	β-Glucosidase	α-Galactosidase	β-Galactosidase
5	n.i.[a]	n.i.[a]	81	162
6	n.i.[a]	n.i.[a]	98	49
ent-**5**	196	98	n.i.[a]	n.i.[a]
ent-**6**	85	170	n.i.[a]	n.i.[a]

[a] n.i.: no inhibition (less than 50 % inhibition at 1 mM).

Compound **5** and **6** have inhibitory activity against the galactosidases, whereas compounds *ent*-**5** and *ent*-**6** show inhibitory activity against the glucosidases. To further establish these results, more analogues will need to be prepared and screened. Compounds *ent*-**5**/*ent*-**6** and **5**/**6** have shown no inhibition against the galactosidases and glucosidases, respectively, at 1 mM.

Conclusions

A highly stereoselective acid-mediated amido cyclization protocol was developed for the synthesis of 2-aryl-3,4-(dihydroxy)-piperidines. $A^{1,3}$ strain was determined to be the controlling element to determine the stereochemical outcome of the reaction. Compared with 1,3-diaxial interactions and neighboring group participation, $A^{1,3}$ strain played a larger role in the formation of the stereocenter during the cyclization.

Experimental Section

General Methods: Moisture- and oxygen-sensitive reactions were carried out under nitrogen. All solvents and reagents were purified by standard techniques. TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness: 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) by using ethyl acetate, hexane, chloroform, and MeOH as eluents. IR spectra were recorded on a Perkin–Elmer RX-1 FTIR system. The ^1H NMR spectroscopic data were recorded at 500 and 300 MHz. The ^{13}C NMR spectroscopic data were recorded at 75, 100, and 125 MHz. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as the internal standard. The coupling constants (J) are reported in Hz. Optical rotations were measured with a Horiba-SEPA-300 digital polarimeter. Accurate mass measurements were performed on a Q STAR mass spectrometer (Applied Bio systems, USA).

Ethyl (4*R*,5*S*)-5-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (10): To a stirred solution of diol **9** (8.2 g, 34.16 mmol) in dry CH_2Cl_2 (70 mL) were added 2,2-dimethoxypropane (6.27 mL, 51.25 mmol) and *p*TsA (0.65 g, 10 mol-%) at room temperature. The reaction mixture was stirred for 12 h, cooled to 0 °C, and then neutralized by the addition of Et_3N (0.2 mL). The volatiles were removed on a rotary evaporator, and the residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 1:9) to afford compound **10** (9.18 g, 96 %) as a colorless syrup; $[\alpha]_D^{28}$ = –119.6 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1031, 1096, 1172, 1246, 1376, 1514, 1753, 2934, 2987 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.0 Hz, 3 H), 1.55 (s, 3 H), 1.61 (s, 3 H), 3.82 (s, 3 H), 4.18–4.33 (m, 3 H), 5.09 (d, J = 7.7 Hz, 1 H), 6.91 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 25.6, 26.8, 55.1, 61.2, 80.5, 81.2, 111.1, 113.8, 127.8, 129.4, 159.6, 170.2 ppm. MS (ESI): m/z = 303 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.1203; found 303.1192.

1-[(4*S*,5*S*)-5-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (11): To the stirred solution of compound **10** (9 g, 34.09 mmol) in CH_2Cl_2 (90 mL) was added DIBAL-H (25 % solution in dry toluene, 21.29 mL, 37.49 mmol) at –78 °C under nitrogen. The mixture was continuously stirred at –78 °C for 2 h. MeOH (10 mL) was then added followed by a saturated solution of sodium potassium tartarate (20 mL) and then CH_2Cl_2 (30 mL). The mixture was stirred for an additional 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL), and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to yield the aldehyde as a pale yellow liquid, which was carried onto the next step without further purification. To a solution of the crude aldehyde in dry THF (15 mL) at –5 °C under nitrogen was added vinylmagnesium bromide (33 mL, 85.22 mmol) dropwise over a period of 5 min. The solution was gradually warmed to room temperature. Upon completion, the reaction mixture was cooled to 0 °C, and a saturated aqueous NH_4Cl solution was added. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator, and the residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 2:8) to give an inseparable diastereomeric mixture of compound **11** (5.85 g, 69 %; *dr* 1:1.5 by ^1H NMR analysis) as a pale yellowish oil. IR (neat): $\tilde{\nu}_{max}$ = 772, 1031, 1169, 1245, 1374, 1513, 1612, 2851, 2922, 2985, 3075, 3459 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = 1.50 (s, 3 H), *1.51 (s, 3 H), 1.56 (s, 3 H), *1.57 (s, 3 H), ●2.19 (br. s, 2 H), 3.80 (s, 3 H), *3.81 (m, 4 H), 3.98 (dd, J = 3.6, 8.5 Hz, 1 H), *4.10 (br. s, 1 H), 4.34 (m, 1 H), 4.87 (d, J = 8.5 Hz, 1 H), *4.93 (d, J = 8.5 Hz, 1 H), ●5.14–5.17 (m, 2 H), ●5.31–5.37 (m, 2 H), ●5.71–5.83 (m, 2 H), ●6.86–6.92 (m, 4 H), ●7.28–7.32 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = *26.9, 27.3, *55.22, 55.23, *70.2, 71.7, 78.5, *79.0, 84.7, *85.1, 109.0, *109.3, 113.8, *114.0, *116.3, 117.2, 128.4, *128.8, *129.2, 129.8, 135.3, *137.5, 159.5, *159.6 ppm. MS (ESI): m/z = 287 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1232.

***tert*-Butyl{1-[(4*R*,5*S*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]allyloxy}dimethylsilane (12):** To compound **11** (5.7 g, 21.59 mmol) in dry CH_2Cl_2 (70 mL), were added TBS-Cl (6.5 g, 43.18 mmol) and imidazole (4.4 g, 64.77 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 2 h. Upon completion of the reaction (monitored by TLC analysis), water (20 mL) and CH_2Cl_2 (40 mL) were added, and the organic and aqueous layers were separated. The organic layer was washed with brine, separated, and concentrated. The residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 0.5:9.5) to afford compound **12** (7.34 g, 90 %) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 1030, 1063, 1246, 1514, 1613, 2857, 2931 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = 0.03 (s, 6 H), *0.06 (s, 6 H), *0.83 (s, 9 H), 0.91 (s, 9 H), 1.46 (s, 3 H), 1.47 (s, 3 H), *1.49 (s, 3 H), *1.51 (s, 3 H), ●3.80 (s, 6 H), *3.81 (d, J = 3.0 Hz 1 H), 3.84 (d, J = 3.0 Hz 1 H), *4.28 (m, 1 H), 4.33 (m, 1 H), *4.83 (d, J = 8.0 Hz 1 H), 4.88 (d, J = 8.0 Hz 1 H), 4.99 (d, J = 11.0 Hz 1 H), *5.18 (d, J = 11.0 Hz 1 H), *5.20 (d, J = 17.0 Hz 1 H), 5.27 (d, J = 17.0 Hz 1 H), 5.59 (m, 1 H), *5.94 (m, 1 H), ●6.83 (m, 4 H), ●7.26 (d, J = 8.0 Hz 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = *–4.9, –4.58, *–4.51, –4.4, *18.1, 18.2, 25.7, *25.8, *26.9, 27.1, *27.3, 27.3, 55.20, *55.26, *72.6, 73.3, 78.4, *78.6, *85.71, 85.75, 108.7, *108.8, 113.6, *113.7, *116.0, 116.1, *128.6, 128.8, 130.6, *130.7,

●137.5, *159.3, 159.4 ppm. MS (ESI): *m/z* = 401 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{34}O_4SiNa$ [M + Na]$^+$ 401.2119; found 401.2131.

3-(*tert*-Butyldimethylsilyloxy)-3-[(4*R*,5*S*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]propan-1-ol (13): To a solution of compound **12** (7.2 g, 19.04 mmol) in dry THF (50 mL) under nitrogen was added BH_3•DMS (2.6 mL, 28.5 mmol) at 0 °C. The reaction mixture was stirred for 3 h, and then 10 % NaOH (8 mL) followed by 30 % H_2O_2 (6 mL) was added at 0 °C. The resulting suspension was stirred for an additional 1 h and extracted with ethyl acetate (2 × 20 mL). The organic layers were separated and combined. The solvent was evaporated on a rotary evaporator to give the crude compound. Purification by chromatography on a silica gel column (20 % ethyl acetate in hexane) gave compound **13** (5.95 g, 79 % yield) as a thick syrup. IR: $\tilde{\nu}_{max}$ = 1034, 1064, 1244, 1514, 1613, 2856, 2930, 2954, 3457 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = 0.01 (s, 3 H), 0.03 (s, 3 H) *0.08 (s, 6 H), *0.85 (s, 9 H), 0.89 (s, 9 H), *1.49 (s, 6 H), 1.51 (s, 3 H), 1.55 (s, 3 H), *1.55–1.69 (m, 2 H), 1.69–1.93 (m, 2 H), ●3.52–3.76 (m, 4 H), ●3.80 (s, 6 H), ●3.88–3.09 (m, 4 H), *4.83 (d, *J* = 8.1 Hz 1 H), *6.87 (d, *J* = 1.8 Hz, 2 H), 6.90 (d, *J* = 1.8 Hz, 2 H), 7.30 (d, *J* = 2.4 Hz, 2 H), *7.33 (d, *J* = 2.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = –4.7, *–4.4, –4.3,* –4.2, *17.9, 18.1, 25.8, *26.9, *27.1, 27.3, *36.3, 36.7, *55.1, 55.2, *58.4, 59.2, 69.0, *69.4, ●79.0, ●85.2, *108.6, 108.7, 113.8, *113.9, *128.5, 128.7, 129.7, *130.3, 159.5, *159.6 ppm. MS (ESI): *m/z* = 419 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{36}O_5SiNa$ [M + Na]$^+$ 419.2224; found 419.2227.

{3-Azido-1-[(4*R*,5*S*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]propoxy}(*tert*-butyl)dimethylsilane (14): To a solution of **13** (5.8 g, 14.60 mmol) and Et_3N (4.3 mL, 29.29 mmol) in dry CH_2Cl_2 (30 mL) in an ice bath was added methanesulfonyl chloride (1.69 mL, 21.90 mmol) dropwise. After 20 min at 0 °C, the reaction was quenched by the addition of cold water, and the resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with water, dried with Na_2SO_4, and concentrated under reduced pressure to afford the corresponding mesyl derivative as a yellow oil, which was carried onto the next step without any further purification. To a stirred solution of the mesyl derivative in dry DMF (30 mL) was added NaN_3 (2.98 g, 43.80 mmol) at room temperature under nitrogen. The mixture was slowly heated to 80 °C and stirred for 2 h. After this time, the mixture was cooled to room temperature and poured into ice water (30 mL). The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purified by chromatography on a silica gel column (ethyl acetate/hexane, 1.5:8.5) afforded **14** (4.74 g, 77 %) as a yellow oil. IR (neat): $\tilde{\nu}_{max}$ = 1034, 1067, 1244, 1514, 1613, 2093, 2857, 2930, 2985 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = 0.01 (s, 3 H), 0.02 (s, 3 H) *0.04 (s, 3 H),* 0.08 (s, 3 H), *0.85 (s, 9 H), 0.89 (s, 9 H), *1.39 (s, 3 H), 1.46 (s, 3 H), 1.49 (s, 3 H), *1.51 (s, 3 H), ●1.52–1.79 (m, 4 H), ●3.17–3.37 (m, 4 H), ●3.80 (s, 6 H), ●3.81–3.88 (m, 2 H), ●3.93–4.00 (m, 2 H), *4.69 (d, *J* = 8.4 Hz, 1 H), 4.75 (d, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 4 H), 7.26 (d, *J* = 8.4 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; * minor isomer, ● major and minor isomer): δ = –4.8, –4.7, *-4.2, *18.0, 18.1, 25.8, *27.0, *27.1, 27.3, *32.5, 32.8, *47.5, 47.6, ●55.2, *68.0, 69.3, *78.7, 79.0, *84.9, 85.2, ●108.6, 113.9, *114.0, 128.5, *128.8, *129.7, 130.0, 159.60, *159.67 ppm. MS (ESI): *m/z* = 444 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{35}N_3O_4SiNa$ [M + Na]$^+$ 444.2289; found 444.2277.

2,2,2-Trichloroethyl (*R*)-3-(*tert*-Butyldimethylsilyloxy)-3-[(4*R*,5*S*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-propylcarbamate (15) and 2,2,2-Trichloroethyl (*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-[(4*R*,5*S*)-5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-yl]propylcarbamate (16): To a solution of $LiAlH_4$ (0.625 g, 16.03 mmol) in THF (20 mL) at 0 °C was added compound **14** (4.5 g, 10.68 mmol) in THF (20 mL) under nitrogen. After the reaction mixture was stirred for 1 h at 0 °C, it was quenched by the addition of H_2O (0.6 mL), 15 % aqueous NaOH (0.6 mL), and H_2O (1.8 mL). The precipitate was filtered through a pad of Celite, and the filter cake was washed with hot ethyl acetate. The filtrate was concentrated under reduced pressure to give the crude amine. To a solution of the crude residue in MeOH (25 mL) were added K_2CO_3 (4.42 g, 32.06 mmol) and Troc-Cl (2.18 mL, 16.03 mmol) dropwise at 0 °C. After the reaction mixture was stirred for 30 min at room temperature, it was concentrated under reduced pressure and diluted with ethyl acetate (50 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give a mixture of **15** and **16** as a thick syrup. Purification by chromatography on a silica gel column (ethyl acetate/hexane, 0.4:9.6) afforded **15** (1.95 g) as a colorless thick syrup followed by (ethyl acetate/hexane, 0.5:9.5) to give pure **16** (2.96 g) as a colorless thick syrup (combined yield: 4.91 g, 81 %). Data for **15**: $[\alpha]_D^{28}$ = + 9.1, (*c* = 0.77, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1036, 1064, 1243, 1514, 1740, 2856, 2929, 2953, 3349 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.49 (s, 3 H), 1.55 (s, 3 H), 1.60 (m, 1 H), 1.87 (m, 1 H), 3.16–3.29 (m, 2 H), 3.81 (s, 3 H), 3.85–3.89 (m, 2 H), 4.69 (s, 2 H), 4.79 (d, *J* = 8.0 Hz, 1 H), 5.69 (br. s, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.30 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.37, –4.34, 18.1, 25.8, 27.0, 27.3, 33.6, 37.3, 55.2, 69.6, 74.3, 79.1, 84.9, 95.7, 108.8, 114.0, 128.7, 129.5, 154.3, 159.7 ppm. MS (ESI): *m/z* = 592 [M + Na]$^+$, 594 [(M + 2) + Na]$^+$, 596 [(M + 4) + Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{38}Cl_3NO_6Na$ [M + Na]$^+$ 592.1426; found 592.1427. Data for **16**: $[\alpha]_D^{26}$ = –22.4 (*c* = 0.97, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1037, 1065, 1141, 1248, 1514, 1741, 2854, 2926, 3353 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.84 (s, 9 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 1.52–1.81 (m, 2 H), 3.19–3.31 (m, 2 H), 3.80 (s, 3 H), 3.83–3.89 (m, 2 H), 4.70 (s, 2 H), 4.79 (d, *J* = 7.5 Hz, 1 H), 5.29 (br. s, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.3, 17.9, 25.7, 27.1, 33.0, 37.9, 55.2, 70.1, 74.3, 79.4, 84.6, 95.6, 108.7, 113.9, 128.5, 130.1, 154.2, 159.5 ppm. MS (ESI): *m/z* = 592 [M + Na]$^+$, 594 [(M + 2) + Na]$^+$, 596 [(M + 4) + Na]$^+$. HRMS (ESI): calcd. for $C_{24}H_{38}Cl_3NO_6Na$ [M + Na]$^+$ 592.1426; found 592.1424.

(1*S*,2*S*,3*R*)-1-(4-Methoxyphenyl)-5-{[(2,2,2-trichloroethoxy)-carbonyl]amino}pentane-1,2,3-triyl Triacetate (17): A solution of compound **15** (0.5 g, 0.87 mmol) in 80 % aqueous AcOH (5 mL) was stirred at room temperature for 8 h. The reaction mixture was neutralized by the addition of an aqueous 30 % ammonia solution dropwise at 0 °C. The resulting reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 4:1) to give the triol as a thick syrup. To the solution of the triol in CH_2Cl_2 (5 mL) were added Et_3N (0.74 mL, 5.27 mmol), acetic anhydride (0.40 mL, 3.91 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.01 g, 1 mol-%) at 0 °C. Upon completion of the addition, the reaction mixture was warmed to room temperature, stirred for 12 h, and diluted with chloroform (30 mL). The resulting solution was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 1.2:8.8) to afford triacetate **17** (0.33 g, 70 %) as a thick syrup; $[\alpha]_D^{28}$ = –82.9 (*c* = 0.18, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 770, 1032, 1219, 1515, 1742, 2852, 2922, 2955, 3369 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.86 (m, 2 H), 2.02 (s, 3 H), 2.05 (s, 3 H), 2.06 (s, 3 H), 2.96 (m, 1 H), 3.37 (m, 1 H), 3.80

(s, 3 H), 4.71 (s, 2 H), 4.90 (m, 1 H), 5.21 (br. s, 1 H), 5.45 (dd, *J* = 5.9, 6.4 Hz, 1 H), 5.89 (d, *J* = 6.4 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 20.8, 20.9, 37.0, 55.2, 68.9, 72.9, 74.2, 74.4, 95.5, 114.0, 127.6, 128.5, 154.4, 159.9, 169.7, 169.8, 170.8 ppm. MS (ESI): *m/z* = 564 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{26}Cl_3NO_9Na$ $[M + Na]^+$ 564.0565; found 564.0557.

(2*S*,3*R*,4*R*)-2-(4-Methoxyphenyl)-1-[(2,2,2-trichloroethoxy)carbonyl]piperidine-3,4-diyl Diacetate (18a): To a solution of compound **17** (0.1 g, 0.25 mmol) in CH_2Cl_2 (3 mL) was added TFA (1.0 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and then stirred at the same temperature for 4 h, whereupon the reaction was neutralized by the addition of $NaHCO_3$ at 0 °C. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with chloroform (2 × 20 mL). The chloroform layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 2.5:7.5) to give **18a** (0.09 g, 78 %) as a thick syrup; $[\alpha]_D^{28}$ = +112.9 (*c* = 0.51, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1043, 1239, 1370, 1425, 1513, 1714, 1741, 2851, 2921 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 1.98 (s, 3 H), 2.07 (s, 3 H), 2.18 (m, 1 H), 3.01 (dt, *J* = 2.8, 3.0 Hz, 1 H), 3.81 (s, 3 H), 4.12 (dd, *J* = 2.8, 4.1 Hz, 1 H), 4.76 (d, *J* = 11.9 Hz, 1 H), 4.86 (d, *J* = 12.0 Hz, 1 H), 5.22 (dd, *J* = 6.4, 10.0 Hz, 1 H), 5.54 (m, 1 H), 5.86 (d, *J* = 6.4 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.0, 30.1, 38.1, 55.2, 55.7, 68.5, 72.2, 75.3, 95.3, 113.9, 126.4, 127.7, 129.6, 153.4, 159.0, 169.7, 170.3 ppm. MS (ESI): *m/z* = 504 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{22}Cl_3NO_7Na$ $[M + Na]^+$ 504.0354; found 504.0344.

(2*S*,3*R*,4*R*)-2,2,2-Trichloroethyl 3,4-Dihydroxy-2-(4-methoxyphenyl)piperidine-1-carboxylate (19): To a stirred solution of compound **15** (1.20 g, 2.10 mmol) in CH_2Cl_2 (9 mL) was added TFA (3.0 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and then stirred at the same temperature for 4 h, whereupon the reaction was neutralized with $NaHCO_3$ at 0 °C. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with chloroform (2 × 20 mL). The chloroform layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 3.4:6.4) to give compound **19** (0.65 g, 78 %) as a thick syrup; $[\alpha]_D^{28}$ = +42.3 (*c* = 2.94, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1058, 1127, 1178, 1248, 1424, 1512, 1694, 2953, 3011, 3419 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *rotamer): δ = 1.65 (m, 1 H), 2.02 (m, 1 H), 3.11 (dt, *J* = 2.6, 13.7 Hz, 1 H), 3.80 (s, 3 H), 3.84 (m, 1 H), 4.01–4.21 (m, 2 H), *4.68 (s, 2 H), 4.77 (d, *J* = 16.6 Hz, 1 H), 4.80 (d, *J* = 16.6 Hz, 1 H), *5.22 (d, *J* = 6.2 Hz, 1 H), 5.66 (d, *J* = 6.2 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.2, 39.2, 55.1, 58.0, 68.4, 75.0, 75.1, 95.3, 113.7, 128.3, 129.8, 153.9, 158.7 ppm. MS (ESI): *m/z* = 420 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{18}Cl_3NO_5Na$ $[M + Na]^+$ 420.0142; found 420.0151.

(2*R*,3*R*,4*R*)-2-(4-Methoxyphenyl)piperidine-3,4-diol (5): To a stirred solution of **19** (0.45 g, 1.13 mmol) in glacial AcOH (2 mL) and MeOH (2 mL) was added Zn (0.07 g, 1.13 mmol), and the resulting mixture was heated at 65 °C for approximately 20 min under an inert atmosphere. Upon completion of the reaction, it was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give the acetic acid salt of compound **5**. The free amine was obtained by dissolving the salt in MeOH and loading the solution onto a Dowex 500WX8–200 ion-exchange resin. Elution with aqueous ammonia (26 %) afforded free base **5** (0.17 g, 69 %) as a pale yellow syrup after evaporation; $[\alpha]_D^{28}$ = +132.7 (*c* = 0.33, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 1020, 1182, 1249, 1515, 1614, 1639, 2841, 2947, 3339 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.60 (m, 1 H), 2.17 (m, 1 H), 2.99 (dd, *J* = 4.7, 12.1 Hz, 1 H), 3.16 (m, 1 H), 3.64 (br. s, 1 H), 3.78 (s, 3 H), 3.97 (d, *J* = 2.6 Hz, 1 H), 4.19 (br. s, 1 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 25.2, 41.3, 55.8, 59.0, 67.4, 71.2, 115.2, 128.7, 130.1, 161.5 ppm. MS (ESI): *m/z* = 224 $[M + H]^+$. HRMS (ESI): calcd. for $C_{12}H_{18}NO_3$ $[M + H]^+$ 224.1281; found 224.1280.

(1*S*,2*S*,3*S*)-1-(4-Methoxyphenyl)-5-{[(2,2,2-trichloroethoxy)carbonyl]amino}pentane-1,2,3-triyl Triacetate (20): A solution of compound **16** (0.40 g, 0.70 mmol) in 80 % aqueous AcOH (5 mL) was stirred at room temperature for 8 h. The reaction mixture was neutralized by the dropwise addition of an aqueous 30 % ammonia solution at 0 °C. The resulting reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 4:1) to give the triol as a thick syrup. To the solution of the triol in CH_2Cl_2 (5 mL) were added Et_3N (0.6 mL, 4.21 mmol), acetic anhydride (0.32 mL, 3.15 mmol), and DMAP (0.01 g, 1 mol-%) at 0 °C. Upon completion of the addition, the reaction was warmed to room temperature, stirred for 12 h, and then diluted with chloroform (30 mL). The resulting mixture was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 1.1:8.9) to afford triacetate **20** (0.26 g, 76 %) as a thick syrup; $[\alpha]_D^{28}$ = –97.6 (*c* = 0.25, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 772, 1033, 1220, 1516, 1743, 2582, 2922, 3367 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.78 (m, 2 H), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 2.90 (m, 1 H), 3.38 (m, 1 H), 3.80 (s, 3 H), 4.68 (s, 2 H), 4.74 (m, 1 H), 5.24 (br. s, 1 H), 5.41 (t, *J* = 3.3, 8.4 Hz, 1 H), 5.83 (d, *J* = 8.4 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 20.8, 20.9, 31.3, 36.9, 55.2, 69.1, 74.1, 74.4, 74.6, 77.5, 95.5, 114.2, 127.4, 128.8, 154.4, 160.1, 169.7, 170.1, 170.6 ppm. MS (ESI): *m/z* = 564 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{21}H_{26}Cl_3NO_9Na$ $[M + Na]^+$ 564.0565; found 564.0558.

(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-1-[(2,2,2-trichloroethoxy)carbonyl]piperidine-3,4-diyl Diacetate (21a): To the solution of compound **20** (0.09 g, 0.22) in CH_2Cl_2 (12 mL) was added TFA (4 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred at the same temperature for 4 h, whereupon the reaction was neutralized with $NaHCO_3$ at 0 °C. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with chloroform (2 × 20 mL). The chloroform layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 2.5:7.5) to give **21a** (0.08 g, 78 %) as a thick syrup; $[\alpha]_D^{28}$ = –166.9 (*c* = 0.32, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 714, 749, 1046, 1241, 1514, 1712, 2852, 2925, 3020 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71 (m, 1 H), 2.03 (s, 3 H), 2.13 (s, 3 H), 2.32 (m, 1 H), 3.01 (t, *J* = 13.1 Hz, 1 H), 3.81 (s, 3 H), 4.34 (d, *J* = 13.5 Hz, 1 H), 4.63–5.01 (m, 3 H), 5.66 (br. s, 1 H), 5.91 (br. s, 1 H), 6.93 (d, *J* = 8.9 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.0, 25.3, 39.0, 55.3, 58.1, 68.8, 75.1, 95.5, 114.5, 126.6, 127.3, 154.5, 159.0, 170.3, 170.3 ppm. MS (ESI): *m/z* = 504 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{19}H_{22}Cl_3NO_7Na$ $[M + Na]^+$ 504.0354; found 504.0345.

2,2,2-Trichloroethyl (2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-(4-methoxyphenyl)piperidine-1-carboxylate (22): To the stirred solution compound **16** (2.00 g, 3.5 mmol) in CH_2Cl_2 (12 mL) was added TFA (4 mL) dropwise at 0 °C. The reaction mixture was warmed to room

temperature and stirred at the same temperature for 4 h, whereupon the reaction was neutralized with $NaHCO_3$ at 0 °C. The resulting mixture was filtered through a pad of Celite, and the filter cake was washed with chloroform (2 × 20 mL). The chloroform layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column (ethyl acetate/hexane, 3.5:6.5) to afford **22** (1.08 g, 78 %) as a thick syrup; $[\alpha]_D^{28}$ = –25.2 (*c* = 0.58, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1035, 1061, 1123, 1179, 1248, 1431, 1512, 1692, 2853, 2928, 3396 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.67 (m, 1 H), 1.98 (m, 1 H), 2.95 (dt, *J* = 3.0, 13.5 Hz, 1 H), 3.81 (s, 3 H), 3.84 (m, 1 H), 4.20–4.28 (m, 2 H), 4.54 (m, 1 H), 4.83 (m, 2 H), 5.65 (br. s, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.17 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * rotamer): δ = 27.6, 39.2, 55.2, 59.7, 66.4, 69.9, 75.1, *77.1, 95.4, *113.9, 114.2, 127.2, *127.3, 127.5, 155.3, 158.7 ppm. MS (ESI): *m/z* = 420 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{18}Cl_3NO_5Na$ $[M + Na]^+$ 420.0142; found 420.0151.

(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)piperidine-3,4-diol (6): To a stirred solution of **22** (0.80 g, 2.05 mmol) in glacial AcOH (3 mL) and MeOH (3 mL) was added Zn (0.12 g, 2.05 mmol), and the resulting mixture was heated at 65 °C for approximately 20 min under an inert atmosphere. Upon completion of the reaction, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give the acetic acid salt of compound **6**. The free amine was obtained by dissolving the salt in MeOH and loading the solution onto a Dowex 500WX8-200 ion-exchange resin. Elution with aqueous ammonia (26 %) afforded free base **6** (0.31 g, 69 %) as a colorless liquid after evaporation; $[\alpha]_D^{28}$ = –24.5 (*c* = 0.38, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 1026, 1081, 1247, 1439, 1514, 1612, 2849, 2921, 3358 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 1.89–1.94 (m, 2 H), 2.84 (m, 1 H), 3.11 (m, 1 H), 3.70 (dd, *J* = 2.8, 10.2 Hz, 2 H), 3.79 (s, 3 H), 3.87 (d, *J* = 10.2 Hz, 1 H), 4.11 (br. s, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 7.36 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 32.1, 40.9, 55.8, 60.8, 68.9, 73.3, 115.0, 130.4, 130.5, 161.1 ppm. MS (ESI): *m/z* = 224 $[M + H]^+$. HRMS (ESI): calcd. for $C_{11}H_{16}NO_4$ $[M + H]^+$ 224.1281; found 224.1284.

Compounds *ent*-**5** and *ent*-**6** were prepared from *ent*-**9** by using the same procedures as described for compounds **5** and **6**.

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