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Carbocyclic Ribosylamines: Synthesis of 5-Substituted Carbocyclic β-Ribofuranosylamines

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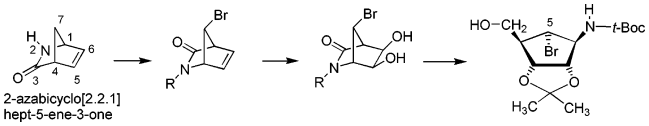
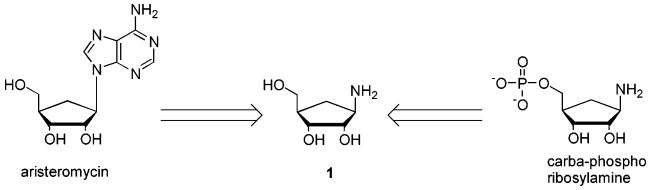
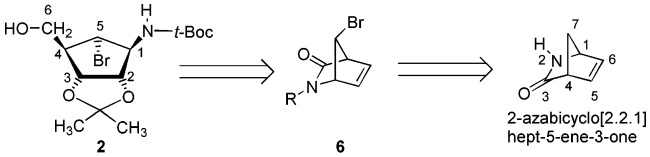


A synthesis of 5-substituted cyclopentylamine precursors for 5′-substituted carbocyclic nucleoside analogues was developed. We show that the stereochemistry of the OsO_4-catalyzed hydroxylation of an apically brominated lactam, 7-bromo-2-azabicyclo[2.2.1]hept-5-en-3-one, can be controlled through the appropriate selection of the lactam N−H protecting group. Sterically large groups direct the hydroxylation to the exo-face of the olefin, yielding hydroxylation products that can be converted into analogues of carbocyclic ribosides. Conversely, a sterically small protecting group permits OsO_4 approach from the endo-face, yielding hydroxylation products analogous to carbocyclic lyxosides. A key intermediate for carbocyclic sugar production, (1*S*,2*S*,3*R*,4*R*,5*S*)-1-(*tert*-butyloxycarbonyl)amino-5-bromo-2,3-(dimethylmethylene)dioxy-4-hydroxymethylcyclopentane, was synthesized starting from a commercially available enantiomerically pure lactam, (1*S*)-(+)-2-azabicyclo[2.2.1]hept-5-en-3-one, in seven steps in an overall yield of 21%.

Carbocyclic ribofuranosylamine (**1**),[1−5] in which a cyclopentane replaces the ribofuranose ring of the parent sugar, is a synthetic precursor for biologically active carbocyclic nucleosides, such as aristeromycin,[1−5] and for carbocyclic analogues of phosphosugar intermediates in purine biosynthesis.[6,7] It is also related to the synthetic precursors of the anti-retroviral drugs carbovir and abacavir.[8]



Numerous synthetic methods have been reported for these important compounds.[9−13] Relatively few of the available methods allow facile introduction of a substituent into the 5-position of the cyclopentane ring, and those available are either excessively long or utilize an achiral starting material and therefore require a resolution. We have developed a method to produce a 5-substituted carbocyclic amine **2** starting from 2-azabicyclo[2.2.1]hept-5-ene-3-one (**3**).[14,15] Bicyclic lactam **3** has been used previously as the precursor of the carbocyclic ribosylamine.[3,4] It is an attractive starting material, since it is commercially available both as the racemate and as either of the pure enantiomers and can be hydroxylated stereoselectively. The ready availability of inexpensive enantiomerically pure **3** is the result of efficient enzymatic resolution of the racemate.[16−18] Our synthetic strategy is based on the observation that *N*-benzyl-protected **3** can be converted into an apically substituted lactam in two steps involving bromination and dehydrobromination.[19] The apical position of bicyclic **3** corresponds to the C-5 position of the cyclopentylamine **2**. Osmium tetraoxide catalyzed cis-hydroxylation of *N*-benzyl-protected olefin **6**, however, exclusively produced the diastereomeric endo-hydroxylation product, resulting in carbocyclic analogues of lyxofuranosides. We now report that the stereochemistry of hydroxylation of brominated lactam **6** can be controlled through the appropriate selection of the nitrogen protecting group to yield exo-hydroxylation products exclusively.



Lactam **3** can be converted into apically substituted lactam **6** in a three-step process of protection, bromination, and dehy-

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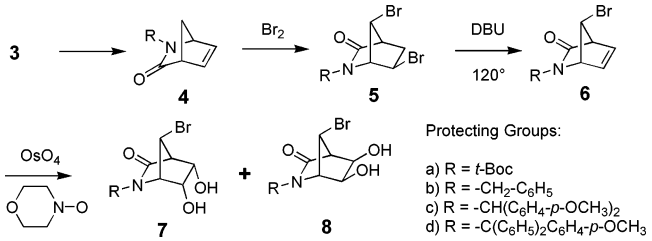
SCHEME 1



drohalogenation (Scheme 1). Previous studies of this reaction established that bromination proceeds via a carbonium ion rearrangement involving migration of the nitrogen and results in stereospecific production of the enantiomeric lactam in high yield.[19,20] The second step, dehydrohalogenation of the dibromide **5** resulting in the apically brominated **6**, was reportedly successful only if the amide N−H was protected. We therefore began our investigation by producing several *N*-protected lactams (**4a**−**4d**) and subjecting them to the conditions of bromination and dehydrohalogenation.

Carbamate nitrogen protecting groups were first evaluated and found to be unuseable. Bromination of the carbobenzyloxy (Cbz)-protected lactam **4a** resulted in a mixture of the two isomeric and unrearranged dibromides in low yield, in which there was no detectable **5**. Bromination of the *tert*-butyloxycarbonyl (*t*-Boc)-protected lactam **4** resulted in a small amount of the rearranged dibromide (**5a**, approximately 25%), accompanied by three unrearranged diastereomeric dibromides (approximately 25% each), as determined from the ^{1}H NMR. Direct bromination[21] of the unprotected lactam (**3**) produced the rearranged dibromide (**5**, R = H) in high yield, which was then protected by treatment with di-*tert*-butyl dicarbonate and DMAP to give the *t*-Boc-protected lactam dibromide (**5a**) in 80% yield. This compound was identical to the minor product obtained by direct bromination of the *t*-Boc lactam (**4a**), confirming our assignment of its structure. All attempts to dehydrobrominate *t*-Boc-protected **5a** to produce the corresponding olefin **6a**, under several basic conditions gave only tars. Electron-withdrawing substituents on the lactam nitrogen have been known to facilitate ring opening,[22] and perhaps the electron-withdrawing carbamate facilitates the cleavage of the amide bond and decomposition. It has also been reported that the unprotected lactam dibromide cannot be dehydrobrominated, probably due to the formation of the amide anion leading to decomposition.[19]

Next, we turned to *N*-alkyl derivatives for amide protection. The *N*-benzyl derivative **4b** was produced by treating **3** with benzyl bromide and KOH. Olefin **4b** was quantitatively brominated to rearranged dibromide **5b** and dehydrohalogenated at 120 °C in 1,8-diazabicycloundecene (DBU) in 70% yield as reported.[19] The 4,4′-dimethoxydiphenylmethyl group was selected for evaluation because it was reported to cleave under mild acidic conditions, similar to that for a trityl group.[23] Protection of the amide nitrogen was achieved with dimethoxydiphenylmethyl chloride in CH_2Cl_2 under phase-transfer catalysis, using powdered sodium hydroxide and potassium carbonate as the base, to give **4c** in 66% yield. Bromination of **4c** in CH_2Cl_2 at room temperature afforded the desired rearranged dibromide **5c** in 50% yield. Elimination by heating with DBU, at 120 °C gave a clean dehydrohalogenation to generate the olefin **6c** in 89% yield. Finally, protection of the pure enantiomer lactam (**3**) with monomethoxytrityl chloride (MMT-Cl) in CH_2Cl_2 under phase-transfer catalysis afforded the MMT-protected lactam (**4d**) in 63% yield. Bromination under the previously successful conditions i.e., in CH_2Cl_2 at ambient temperature, gave the rearranged dibromide (**5d**) in a very low yield (14%). The yield could be improved to 50% by using carbon tetrachloride as the solvent and further improved to 70% by including magnesium oxide as the base. This dibromide (**5d**) was cleanly dehydrobrominated by heating in DBU at 120 °C for 12 h to produce the olefin (**6d**) in 85% yield.

Hydroxylation of olefin **6** with osmium tetraoxide produces the *cis*-glycol **7** or **8**, with the stereoselectivity governed by approach of the reagent from the least sterically hindered face. Osmium tetroxide-catalyzed *cis*-hydroxylation of the *N*-benzyl-protected olefin (**6b**) led exclusively to the undesired *endo*-diol (**7b**). This was due to the fact that the bulky bromide moiety blocks the exo-face of the olefin, while the endo-face is easily accessible to the bulky catalyst. This was in contrast with the results obtained with the 7-unsubstituted bicyclic lactam **3**, in which the catalytic oxidation of the double bond gave the *exo*-diol (**8**, R = H) exclusively.[3,4] Catalytic cis-hydroxylation of *N*-diphenylmethyl-protected **6c**, on the other hand, gave a mixture of *endo*- and *exo*-*cis*-diols (**7c**, **8c**, respectively) in a ratio of 65% endo to, 35% exo with an overall yield of 100%. The increased steric bulk of the protecting group was beginning to shield the endo-face of the olefin and alter the stereoselectivity of the hydroxylation. The assignment of structures for the exo- and endo-isomers was made by comparison of ^{1}H NMR with compound (**7b**). The compound exhibiting resonances and couplings similar to that of **7b** was assigned structure **7c**, while the other isomer was assigned structure **8c**.

Since the exo-isomer was desired for our target compounds, we sought to improve the yield of this isomer by using a bulkier protecting group that would prevent OsO_4 approach from the endo-face of the olefin and favor production of the *exo*-diol. Monomethoxytrityl protection was selected, since it would also afford easy deprotection after hydroxylation, without opening the bicyclic ring. Catalytic cis-hydroxylation by refluxing with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) in H_2O/acetone/*tert*-butyl alcohol for 36 h gave complete conversion of **6d** to a single product **8d** in 90% yield, identified as the *exo*-diol by NMR. Confirmation of this stereochemistry was sought by X-ray crystallography, but suitable crystals of **8d** could not be obtained. However, another intermediate at a later stage in the synthesis (**10**) was identified by X-ray crystallography as the *exo*-diol (see the following text). We believe that even though the apical bromide hindered approach of the osmium reagent to the exo-face of the olefin (**6d**), the presence of the even larger MMT-group on the nitrogen blocks access of the reagent to the endo-face even more. A three-dimensional model (not shown) shows

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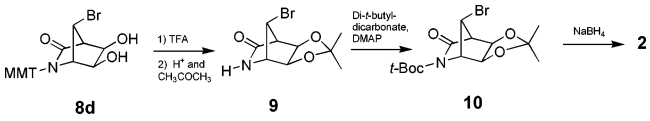
SCHEME 2



that the propeller shape of the three aromatic groups positions one of the aromatic rings of the trityl protecting group right below the endo-face of the olefin, thus shielding that face to approach of the OsO_4 from that direction. This interpretation is supported by the fact that the hydroxylation of **6d** requires more drastic conditions, e.g. higher temperature and longer reaction time as compared to the hydroxylation in case of benzyl-protected compound (**6b**).

Treatment of the diol **8d** with trifluoroacetic acid (TFA) in methylene chloride at room temperature for 2 h produced the deprotected lactam (Scheme 2), which was converted to the acetonide **9** (trifluoroacetic acid in acetone) in quantitative yield. Lactam **9** was reprotected as the *t*-Boc lactam (**10**) in 82% yield. To verify stereochemistry, the structure of **10** was established by X-ray crystallography (see Figure 1, Supporting Information). Sodium borohydride reduction and cleavage of the lactam in methanol at room temperature yielded the ring-opened alcohol **2**.

Compound **2** has all its carbons functionalized with groups in the appropriate stereochemical relationship for synthesis of C-5 substituted carbocyclic ribofuranoside analogues. The bromo group at the C-5 position can work as an excellent nucleofuge for substitution with a number of nucleophilic substituents, thus making this compound a versatile and key intermediate.

Experimental Section

(1*S*)-*N*-(*p*-Anisyldiphenylmethyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (4d). To a solution of the lactam (1*S*)-(+)-2-azabicyclo[2.2.1]-hept-5en-3-one (10 g, 91.74 mmol) in CH_2Cl_2 (400 mL) were added finely powdered sodium hydroxide (13 g) and potassium carbonate (10 g) followed by benzyl tributylammonium bromide (1 g). The mixture was stirred with a magnetic stirring bar and *p*-anisylchlorodiphenylmethane (56 g, 183.48 mmol) was added dropwise as a solution in methylene chloride (200 mL). The mixture was then stirred at room temperature for 22 h. The mixture was filtered through a short column of silica gel and the filtrate concentrated and purified by flash column chromatography on silica gel using hexanes−ethyl acetate as the eluent to give a white solid (22 g, 63%). An analytically pure sample was obtained by HPLC purification on a silica gel column: mp 63.2−63.8 °C; TLC R_f 0.27 (silica gel, hexanes−ethyl acetate, 70:30), R_f 0.56 (silica gel, hexanes−ethyl acetate, 50:50); ^{1}H NMR ($CDCl_3$) δ 2.04 (d, J = 7.6 Hz, 1H), 2.50 (d, J = 7.6 Hz, 1H), 3.28 (s, 1H), 3.78 (s, 3H), 4.41 (s, 1H), 5.93 (dd, J = 5 Hz, 2 Hz, 1H), 6.17 (dd, J = 5 Hz, 3.5 Hz, 1H), 6.80 (d, J = 9 Hz, 2H), 7.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 55.2, 55.6, 57.0, 64.0, 73.6, 112.9, 126.5, 126.5, 127.6, 128.0, 128.6, 128.7, 130.3, 134.6, 134.7, 139.0, 143.2, 158.2, 177.1; MS *m*/*z* 381 (M^+, EI), 404 (MNa^+, MALDI). Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.73; H, 6.41; N, 3.48.

(1*S*,6*R*,7*S*)-*N*-(*p*-Anisyldiphenylmethyl)-2-azabicyclo[2.2.1]-heptan-6,7-dibromo-3-one (5d). To a solution of *N*-(*p*-anisyl-diphenylmethyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (21 g, 55 mmol) in carbon tetrachloride (300 mL) was added magnesium oxide (10 g) and the slurry was stirred well. A solution of bromine (8.80 g, 55 mmol) in carbon tetrachloride (200 mL), which had been stirred with magnesium oxide and filtered, was added dropwise over a period of 2 h, and the mixture was allowed to stir at room temperature for 18 h The mixture was then filtered to remove the solids and the filtrate evaporated. The residue was purified by flash column chromatography on silica gel using hexanes−ethyl acetate as the eluent to give a white solid (21 g, 70.5%): mp 95.8−96.5 °C; TLC R_f 0.52 (silica gel, hexanes−ethyl acetate, 70:30); ^{1}H NMR ($CDCl_3$) δ 2.63 (m, 2H), 2.95 (s, 1H), 3.81 (s, 3H), 3.87 (d, J = 7.5 Hz, 1H), 4.25 (s, 1H), 4.46 (s, 1H), 6.85 (d, J = 9 Hz, 2H), 7.20 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 33.3, 41.9, 48.4, 54.7, 55.3, 69.1, 113.4, 127.4, 128.1, 128.9, 130.5, 134.3, 142.5, 142.6, 158.8, 171.6; MS *m*/*z* 539, 541, 543 (M^+, Br_2 isotope pattern, EI), 562, 564, 566 (MNa^+, Br_2 isotope pattern, MALDI). Anal. Calcd for $C_{26}H_{23}Br_2NO_2$: C, 57.69; H, 4.28; N, 2.59. Found: C, 57.72; H, 4.45; N, 2.37.

(1*S*,7*S*)-*N*-(*p*-Anisyldiphenylmethyl)-2-azabicyclo[2.2.1]hept-7-bromo-5-en-3-one (6d). A mixture of *N*-(*p*-anisyldiphenylm-ethyl)-2-azabicyclo[2.2.1]heptan-6,7-dibromo-3-one (21 g, 38.8 mmol) and DBU (30 mL) was heated at 125 °C in an oil bath for 18 h. Upon cooling, the reaction mixture was diluted with methylene chloride (300 mL) and extracted with dilute HCl solution. The organic layer was evaporated in vacuo and purified by flash column chromatography on silica gel using hexanes−ethyl acetate as the eluent to give the pure product as a white solid (15 g, 84%): mp 81.5−82.2 °C; TLC R_f 0.52 (silica gel, hexanes−ethyl acetate, 70:30); ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 1H), 3.80 (s, 3H), 4.51 (s, 1H), 4.74 (s, 1H), 6.18 (dd, J = 5.0 Hz, 1.65 Hz, 1H), 6.26 (m, 1H), 6.80 (d, J = 9 Hz, 2H), 7.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 55.2, 61.6, 65.9, 68.9, 74.3, 113.2, 126.9, 127.9, 128.5, 130.2, 132.9, 134.1, 137.3, 142.6, 158.5, 172.4; MS *m*/*z* 459, 461 (M^+, Br isotope pattern, EI), 482, 484 (MNa^+, Br isotope pattern, MALDI). Anal. Calcd for $C_{26}H_{22}BrNO_2$: C, 67.83; H, 4.82; N, 3.04. Found: C, 67.97; H, 5.07; N, 3.00.

(1*S*,4*S*,5*R*,6*S*,7*S*)-*N*-(*p*-Anisyldiphenylmethyl)-2-azabicyclo-[2.2.1]heptan-7-bromo-5,6-diol-3-one (8d). To a solution of *N*-(*p*-anisyldiphenylmethyl)-2-azabicyclo[2.2.1]hept-7-bromo-5-en-3-one (500 mg, 1.09 mmol) in acetone (15 mL) was added water (10 mL) followed by *tert*-butyl alcohol (5 mL) to give a clear solution. *N*-Methylmorpholine *N*-oxide (495 mg, 3.6 mmol) was then added with stirring followed by a solution of OsO_4 (50 mg, 0.20 mmol) in *tert*-butyl alcohol (2.5 mL), and the mixture was heated at reflux for 24 h. Solvents were evaporated in vacuo, and the residue was purified by flash column chromatography on silica gel using hexanes−ethyl acetate as the eluent to give a white solid (480 mg, 90%): mp 194.1−194.3 °C; TLC R_f 0.09 (silica gel, hexanes−ethyl acetate, 70:30), R_f 0.51 (silica gel, hexanes−ethyl acetate, 50:50); ^{1}H NMR ($CDCl_3$) δ 2.81 (d, J = 7.5 Hz, 1H), 2.88 (d, J = 7.5 Hz, 1H), 3.13 (s, 1H), 3.80 (s, 3H), 4.22 (m, 2H), 4.37 (m, 1H), 4.53 (t, J = 6.8 Hz, 1H), 6.84 (d, J = 9 Hz, 2H), 7.20 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 47.3, 55.2, 59.2, 67.7, 70.1, 73.4, 113.3, 127.4, 128.0, 128.9, 128.9, 130.6, 134.2, 142.3, 158.7, 170.0; MS *m*/*z* 493, 495 (M^+, Br isotope pattern, EI), 516, 518 (MNa^+, Br isotope pattern, MALDI). Anal. Calcd for $C_{26}H_{24}BrNO_4$: C, 63.17; H, 4.89; N, 2.83. Found: C, 63.15; H, 5.07; N, 2.67.

(1*S*,4*S*,5*R*,6*S*,7*S*)-2-Azabicyclo[2.2.1]heptan-7-bromo-5,6-(dimethylmethylene)dioxy-3-one (9). Trifluoroacetic acid (1 mL) was added to a solution of the diol (**8d**) (250 mg, 0.5 mmol) in methylene chloride (15 mL) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo, acetone was added, and the mixture was stirred for 30 min at room temperature. The solvent was then evaporated and methanol (2 mL) added to give white solids. The mixture was filtered, yielding a pure product as white solid (65 mg, 49%). The filtrate was evaporated and the residue purified by flash column chromatography on silica gel using hexanes−ethyl acetate to give an additional quantity of pure product (55 mg, 41.5%), resulting in isolation of a total of 120 mg (90.5%): mp (dec) 170.2−170.5 °C; TLC R_f 0.21 (silica gel, hexanes-ethyl acetate, 50:50), R_f 0.40 (silica gel, hexane−ethyl acetate, 30:70); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.67 (s, 3H), 3.19 (s, 1H), 4.15 (s, 1H), 4.39 (s, 1H), 4.79 (dd, J =

14.8 Hz, 3.8 Hz, 2H), 6.24 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 23.7, 24.2, 44.8, 53.0, 59.7, 78.4, 82.5, 115.4, 173.3; MS *m*/*z* 246, 248 ($M^+ -$ Me, Br isotope pattern, EI). Anal. Calcd for $C_9H_{12}BrNO$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.08; H, 4.54; N, 5.22.

(1*S*,4*S*,5*R*,6*S*,7*S*)-*N*-*tert*-Butyloxycarbonyl-2-azabicyclo[2.2.1]-heptan-7-bromo-5,6-(dimethylmethylene)dioxy-3-one (10). DMAP (800 mg, 6.68 mmol) followed by di-*tert*-butyl dicarbonate (3.65 g, 16.70 mmol) was added to a solution of the acetonide bromolactam (**9**) (1.75 g, 6.68 mmol) in methylene chloride (30 mL) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by flash column chromatography on silica gel using hexanes−ethyl acetate (90:10) as the eluent to give white crystalline solid (2.0 g, 82.7%): mp 163.1−163.6 °C; TLC R_f 0.46 (silica gel, hexanes−ethyl acetate, 70:30); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.52 (s, 9H), 1.67 (s, 3H), 3.32 (s, 1H), 4.33 (t, J = 1.3 Hz, 1H), 4.67 (d, J = 5.7 Hz, 1H), 4.75 (s, 1H), 4.77 (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.2, 27.9, 42.0, 55.2, 62.8, 78.2, 81.1, 84.6, 115.1, 147.6, 167.9; MS *m*/*z* 362, 364 (MH^+, Br isotope pattern, EI), 384, 386 (MNa^+, Br isotope pattern, MALDI). Anal. Calcd for $C_{14}H_{20}BrNO_5$: C, 46.42; H, 5.56; N, 3.87. Found: C, 46.37; H, 5.58; N, 3.83.

(1*S*,2*S*,3*R*,4*R*,5*S*)-1-(*tert*-Butyloxycarbonyl)amino-5-bromo-2,3-(dimethylmethylene)-dioxy-4-hydroxymethylcyclopentane (2). Methanol (20 mL) was added to *N*-*tert*-butyloxycarbonyl-2-azabicyclo[2.2.1]hept-7-bromo-5,6-diol-3-one-5,6-acetonide (900 mg, 2.49 mmol) and the mixture was warmed at 35 °C on a water bath for 5 min for complete dissolution. The solution was allowed to cool to room temperature and sodium borohydride (188 mg, 4.98 mmol) was added all at once. Stirring was continued for 1 h at room temperature, at which point TLC indicated completion of the reaction. The mixture was neutralized with a glacial acetic acid−methanol mixture, the solvents were evaporated, the residue was stirred with chloroform and filtered. The filtrate was purified by flash column chromatography on silica gel using hexanes−ethyl acetate as the eluent to give a white solid (700 mg, 77%): mp 116.6−117.1 °C; TLC R_f 0.11 (silica gel, hexanes−ethyl acetate, 70:30), R_f 0.44 (silica gel, hexanes−ethyl acetate, 50:50); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.45 (s, 9H), 1.53 (s, 3H), 1.69 (br, 1H), 2.34 (m, 1H), 3.85 (m, 3H), 4.30 (m, 1H), 4.58 (m, 2H), 5.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.3, 28.3, 48,9, 54.3, 60.3, 66.1, 78.1, 80.2, 81.0, 113.3, 155.1; MS *m*/*z* 365, 367 (M^+, Br isotope pattern, EI), 388, 390 (MNa^+, Br isotope pattern, MALDI). Anal. Calcd for $C_{14}H_{24}BrNO_5$: C, 45.91; H, 6.60; N, 3.82. Found: C, 45.88; H, 6.64; N, 3.78.

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Supporting Information Available: Experimental details includes the following: (1) experimental procedures for synthesis of **4a**, bromination of **4a**, synthesis of **4c**, **5c**, **6c**, **7c**, **8c**, and (2) crystallographic information and data files (CIF) for compound **10**. This material is available free of change via the Internet at http://pubs.acs.org.

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