NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.5 Hz), 1.06 (d, 3 H, J = 6.3 Hz), 1.48–1.80 (m, 2 H), 2.08 (m, 1 H, J = 6.3 Hz), 2.66 (ddd, 1 H, J = 2.2, 6.3, 7.5 Hz), 3.40 (d, 2 H, J = 6.3 Hz), 3.63 (dd, 1 H, J = 2.2, 6.3 Hz), 3.72 (s, 3 H), 4.48, 4.49 (AB system, 2 H, J = 12.2 Hz), 7.25–7.40 (m, 5 H); ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] of **17** obtained from silyl ketene acetal **20**, δ 5.62 (≥96%, MeO, s), 5.68 (≤4%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(fod)$_3$] of **17** obtained from silyl ketene acetal **20**, δ 5.56 (≥96%, MeO, s), 5.45 (1%, MeO, s), 5.33 (≤3%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(hfc)$_3$] of **17** obtained from silyl ketene acetal **19**, δ 6.37 (≥90%, MeO, s), 6.45 (≤10%, MeO, s); ^{1}H NMR [$CDCl_3$ + Eu(fod)$_3$] of **17** obtained from silyl ketene acetal **19**, δ 6.10 (>99%, MeO, s).

Synthesis of Benzobicyclo[3.2.1]octanes Involving Inversion of Configuration via an N to O Acetyl Migration[1]

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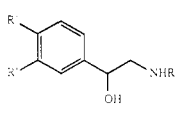
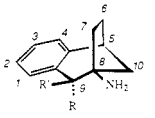
Two conformationally defined analogues of phenylethanolamine, 8-amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (**5**) and 8-amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*exo*-9-ol (**6**), have been synthesized. The benzobicyclo[3.2.1]octane skeleton was constructed by an intramolecular cyclization of 3-phenylcyclopentane-1,1-dicarboxylic acid (**10**). The sodium borohydride reduction of 8-amino-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (**12**) gave the endo alcohol **5**. The greater stability of the exo alcohol **6** compared to **5** was confirmed by AM1 calculations. The exo alcohol **6** was obtained from **5** by an N to O acetyl migration. A possible mechanism for this migration in the inversion of the stereochemistry at C-9 is discussed. Structural assignments using 2-D NMR spectra and an NOE difference spectrum are presented.

Epinephrine (**1**) is synthesized by phenylethanolamine *N*-methyltransferase (PNMT) from norepinephrine (**2**). As part of a continuing study to explore the binding requirements at the active site of PNMT for both substrates and inhibitors,[2,3] we had need of compounds **5** and **6** with the benzobicyclo[3.2.1]octane skeleton. These amines were designed as conformationally defined analogues of phenylethanolamine (**3**), a good substrate of PNMT.



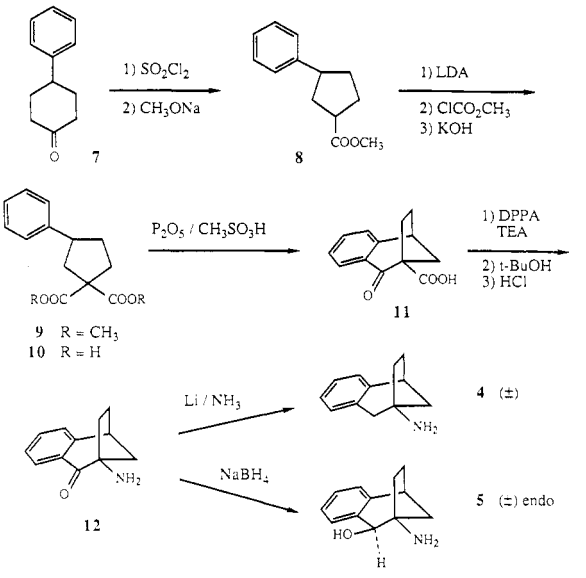
1 R = Me, R' = OH
2 R = H, R' = OH
3 R = R' = H



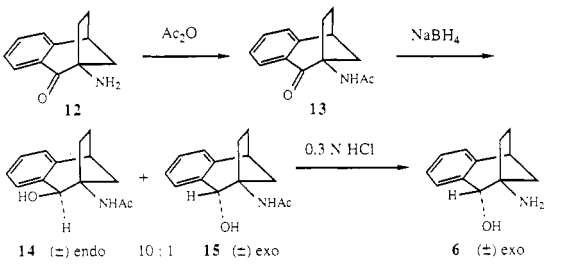
4 R = R' = H (±)
5 R = H, R' = OH (±) endo
6 R = OH, R' = H (±) exo

Although several synthetic approaches to benzobicyclo[3.2.1]octanes are available, only a few compounds with substitution at bridgehead position 8 in this ring system were known.[4,5] Entry into this ring system via rearrangement of the benzobicyclo[2.2.2]octane ring system has been studied by us[4] and by others.[6] Boger and Mullican[7] proposed a novel approach to this ring system in which the aliphatic portion was constructed prior to an aromatic annulation sequence. Considering the availability of starting material and our specific targets, we developed

Scheme I



Scheme II



(1) (a) Presented in part at the 194th National Meeting of the American Chemical Society, New Orleans, LA, Aug 30–Sept 4, 1987. (b) Paper 13 in our series "Conformationally Defined Adrenergic Agents"; for paper 12, see: Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433.

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an efficient route for the synthesis of compounds **4–6** as shown in Schemes I and II, in which an N to O acetyl migration was a key step for inversion of the stereochemistry at C-9 of **5**.

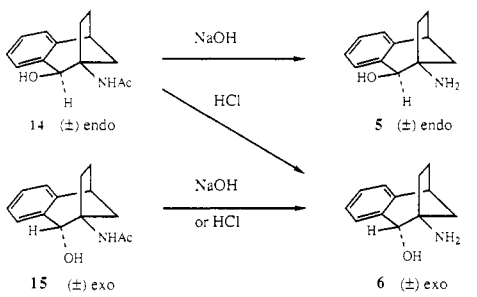
A Favorskii rearrangement on commercially available 4-phenylcyclohexanone (**7**, Scheme I) to contract the six-membered cyclohexanone ring by chlorination with sulfuryl chloride followed by treatment with sodium methoxide led to **8**. The second ester group was introduced with lithium diisopropylamide and methyl chloroformate. After hydrolysis of the diester **9**, intramolecular cyclization of the dicarboxylic acid **10** to form the benzobicyclo[3.2.1]-octane skeleton (**11**) was accomplished with P_2O_5/methanesulfonic acid according to the method of Eaton et al.[8] A modified Curtius rearrangement[9] (sequential treatments with diphenyl phosphorazidate (DPPA), *tert*-butyl alcohol, and hydrochloric acid) was used to convert the carboxyl group at bridgehead position 8 to the amino group (**12**).

Reductive removal of the carbonyl oxygen from **12** turned out to be difficult, probably due to the steric hindrance from the methano and ethano bridges. Catalytic hydrogenation (H_2/Pd–C, 50 psi) was sluggish, and a Raney nickel reduction through the dithioketal gave a complex mixture of products. Deoxygenation of **12** was accomplished by lithium/ammonia reduction according to the procedure of Hall et al.,[10] to give conformationally defined phenylethylamine **4** cleanly. That the carbonyl carbon is much more accessible by hydride from the methano bridge side than from the side of the ethano bridge in this ring system was demonstrated by the sodium borohydride reduction of ketone **12**; a product was obtained in which the ratio of the endo alcohol **5** to the exo alcohol **6** was 15:1.[11] The sensitivity of the sodium borohydride reduction to steric hindrance was noticed by Brown and Muzzio[12] in a few bicyclic systems including bicyclo[2.2.2]octanones and norbornanones. We previously observed[4] that the reductive amination of 9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-8-ol gave only the endo amine.

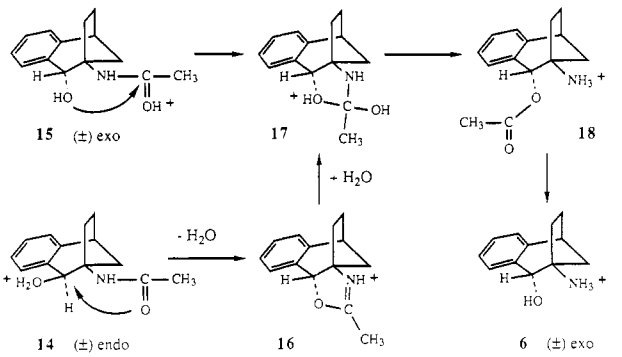
When the endo alcohol **5** was heated in 1 N HCl under reflux for 3 days, a 1:3 mixture[11] of endo and exo alcohols **5** and **6** was obtained, with the exo isomer **6** predominant. Alcohols **5** and **6** could not be separated by chromatography. As expected, the exo alcohol **6** described later gave the same 1:3 equilibrium mixture when treated with 1 N HCl. The ratio of the two isomers in the equilibrium mixture reflects the relative stability of **5** and **6**. The heats of formation calculated by the AM1 method[13] were −27.4 kcal/mol for the endo isomer **5** and −30.4 kcal/mol for the exo isomer **6**. The hydroxyl group preferentially resides at the exo position to lessen the interaction with the bridge atoms.

Taking advantage of the closeness of the amino group to the hydroxyl group in compound **5**, we felt that it would be possible to invert the stereochemistry at C-9 by applying

Scheme III



Scheme IV



an N to O acyl migration strategy to our conformationally defined benzobicyclo[3.2.1]octane system. The N to O acyl migration is a well-studied reaction in interconversion between diastereomers in several ethanolamines,[14,15] such as the norephedrines, 2-aminocyclohexanols, and 2-aminotetralols. Compound **12** was acetylated with acetic anhydride and reduced with sodium borohydride (Scheme II). A 10:1 mixture[11] of endo and exo acetamido alcohols **14** and **15** was obtained. Amides **14** and **15** could be separated by chromatography, but this was not necessary. Acid hydrolysis (0.3 N HCl) of the mixture of **14** and **15** gave a product in which the ratio of the endo alcohol **5** to the exo alcohol **6** was 1:14;[11] the stereochemistry at C-9 was inverted. The two isomeric acetamido alcohols **14** and **15** were separated and treated with acid (0.3 N HCl) or base (1 N NaOH); the inversion of the stereochemistry at C-9 occurred only when the endo isomer **14** was treated with acid (see Scheme III).

Analogous to the mechanism[15] proposed for N to O acyl migration in other ethanolamine systems, the possible mechanism of the inversion is depicted in Scheme IV. Because **14** and **15** have different geometries in the rigid benzobicyclo[3.2.1]octane system, they may go through two different pathways. For the endo isomer **14**, it is likely that the acetyl oxygen attacks the carbon bearing the hydroxyl group (C-9) and *intramolecularly* replaces the hydroxyl group, giving the exo amino alcohol **6** with *inversion* of the stereochemistry at C-9 after hydrolysis of the intermediates **16–18**. For the exo isomer **15** under the same conditions, the benzylic hydroxyl group could attack the carbonyl carbon and form the intermediate **17**. Following the hydrolysis sequence, the exo amino alcohol **6** is generated

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(11) The hydrogen at C-9 in **5** (singlet, 4.80 ppm) and that in **6** (singlet, 4.24 ppm) are easily detected in their ^{1}H NMR spectra. The ratio of exo and endo isomers was obtained by integration of the H-9 signals in the ^{1}H NMR spectrum.
(12) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811.
(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. The calculations were performed on the free amines with the Quantum Chemistry Program Exchange package AMPAC (QCPE No. 506) distributed with the SYBYL software package (see ref 16).
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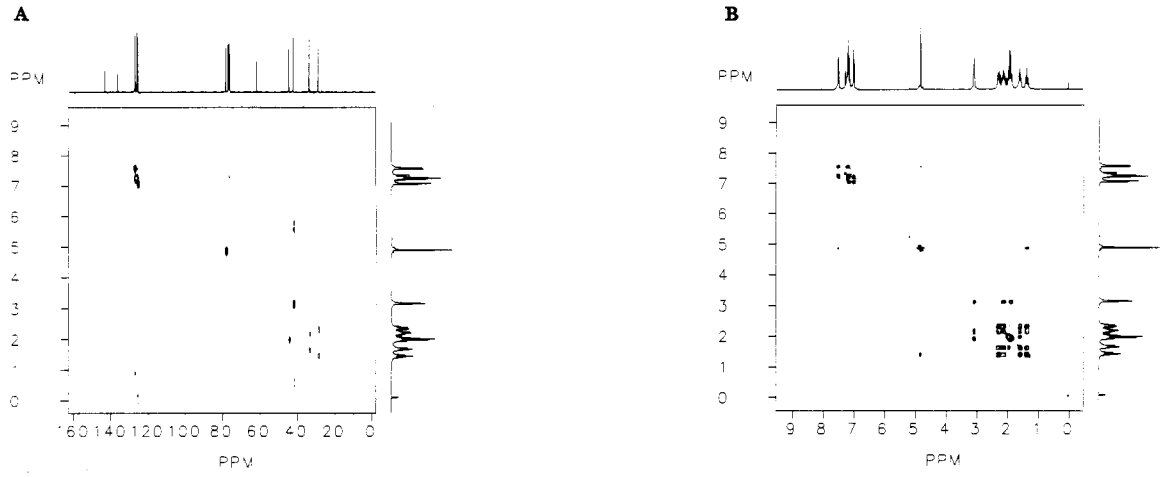

Figure 1. (A) $^{1}H-^{13}C$ heteronuclear chemical shift correlation spectrum of **5**. (B) $^{1}H-^{1}H$ homonuclear chemical shift correlation spectrum of **5**.

with *retention* of the stereochemistry at C-9. It should also be noted that the acidic conditions could direct the migration from N to O by the protonated primary amino group. Computer graphics analysis[16] showed that the shortest distances between the carbonyl carbon and the hydroxyl oxygen are 2.64 Å for the endo isomer **14** and 2.30 Å for the exo isomer **15**, which favors the mechanism shown in Scheme IV for the inversion.

Structural assignment for benzobicyclo[3.2.1]octanes usually has been carried out by deduction from reaction mechanism,[6b] by analysis of coupling constants in the ^{1}H NMR spectra,[6b,g] or by X-ray crystallography.[17] Because there is no proton on the bridgehead carbon (C-8) in **5** and **6**, analysis of proton–proton coupling constants could not be used to define the stereochemistry at C-9. Smith et al.[18] recently reported structural assignments with 2-D NMR in several rigid systems including benzobicyclo[3.2.1]octane. Because the orientation of the 9-hydroxyl group is important for our study, we independently developed a similar procedure, in which 2-D NMR techniques were combined with a nuclear Overhauser experiment. Compound **5** is used as an example to illustrate our approach.

In the ^{1}H NMR spectrum of **5**, two clearly distinguishable resonances at 4.80 ppm and 3.05 ppm were assigned to the two benzylic protons (H-9 and H-5, respectively), on the basis of their chemical shifts and coupling patterns; the chemical shifts of the protons on the methano and ethano bridges were distributed from 2.4 to 1.2 ppm. Taking advantage of the two clearly distinguishable resonances, we first distinguished the protons on the methano bridge from those on the ethano bridge according to their correlations with H-5 (3.05 ppm) by using the $^{1}H-^{1}H$ homonuclear chemical shift correlation spectrum (HOMCOR) and $^{1}H-^{13}C$ heteronuclear chemical shift correlation spectrum (HETCOR), and then we performed a nuclear Overhauser experiment to determine the closeness of H-9 (4.80 ppm) to either the proton on the methano bridge or that on the ethano bridge.

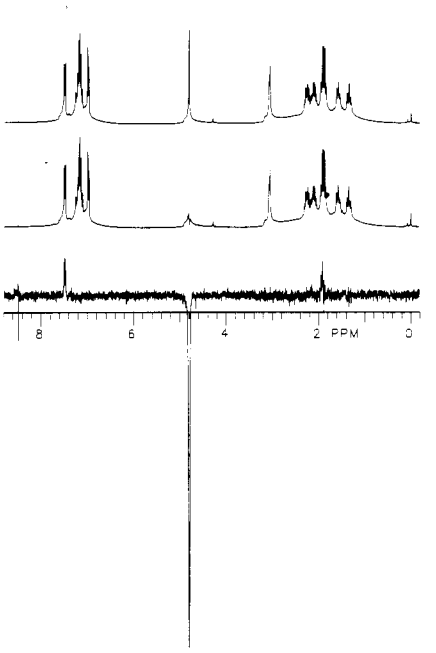

Figure 2. Nuclear Overhauser experiment on **5**. Top: proton spectrum with off resonance. Middle: proton spectrum with on resonance (4.80 ppm). Bottom: difference spectrum from subtracting the off-resonance spectrum from the on-resonance spectrum. The irradiation at 4.80 ppm enhanced the proton signals at 1.88 ppm (4%, H-10) and 7.48 ppm (5%, H-1).

In the HETCOR spectrum (Figure 1A), the important information is that the two protons that resonate at 1.88 ppm are on the same carbon (44.78 ppm). Examination of the HOMCOR spectrum (Figure 1B) revealed that the four protons at 2.24, 2.11, 1.56, and 1.34 ppm were correlated to one another and that H-5 (3.05 ppm) was correlated with the proton at 2.11 ppm and with the protons at 1.88 ppm. Thus, the 1.88-ppm multiplet was assigned to the two protons on the methano bridge.

Irradiation at H-9 (4.80 ppm) caused a nuclear Overhauser effect (Figure 2) on one of the protons on the methano bridge (1.88 ppm). This indicated that H-9 was close to the methano bridge and the 9-hydroxyl group was close to the ethano bridge; compound **5**, therefore, was 8-amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol. The accuracy of this analysis was confirmed by X-ray crystallography.[19]

(16) The structures of **14** and **15** were analyzed with the SYBYL software package (version 3.4; Tripos Associates, St. Louis, MO). Energies were minimized by the MAXMIN (molecular mechanics) procedure by starting with the crystal structures of **5** and **6** (see ref 19). The shortest distances between carbonyl carbon and hydroxyl oxygen were measured by rotating the bond between nitrogen and C-8.

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Compounds **4–6** were evaluated for activity as substrates and inhibitors for PNMT, and full details will be reported.[20] In summary, no activity as a substrate was found for any of the three analogues. Compound **4**, a conformationally defined analogue of the half-chair conformation of 2-aminotetralin, is a less potent inhibitor of PNMT than is 2-aminotetralin but is more potent than other conformationally defined analogues in which the 2-aminotetralin is constrained in a half-boat conformation.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian XL-300 instrument operating at 300 MHz for proton and 75 MHz for carbon-13. All chemical shifts were in parts per million (ppm) downfield from tetramethylsilane. Multiplicity abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on an IBM FTIR-32 spectrometer. Mass spectra were measured on a Varian CH-5 mass spectrometer. Microanalyses were conducted at the University of Kansas or Midwest Microlab, Ltd., Indianapolis, IN. Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison Model 7924 chromatotron on Merck silica gel 60 PF254/$CaSO_4$·0.5H_2O. Bulb-to-bulb distillations were carried out by using a Kugelrohr distillation apparatus (Aldrich Chemical Co., Milwaukee, WI), and oven temperatures were recorded. Unless otherwise stated, all methanol and ethanol used were anhydrous. Hexanes refers to the mixture of hexane isomers.

Methyl 3-Phenylcyclopentanecarboxylate (8). A mixture of 4-phenylcyclohexanone (**7**, 1.53 g, 8.8 mmol), sulfuryl chloride (0.71 mL, 8.8 mmol), a trace amount of benzoyl peroxide, and carbon tetrachloride (50 mL) was heated under reflux for 5 h. Water (50 mL) was added, and the mixture was stirred for 20 min. The mixture was extracted with carbon tetrachloride, and the combined carbon tetrachloride extracts were washed with 5% $NaHCO_3$ and brine and dried over Na_2SO_4. After removal of solvent, a white solid (1.83 g, 99.9% yield) was obtained. The crude product was a mixture of *cis*- and *trans*-2-chloro-4-phenylcyclohexanone (1:3 ratio based on the integration of the H-2 signal in its ^{1}H NMR spectrum) and used directly in the following Favorskii reaction. The major isomer (*trans*-2-chloro-4-phenylcyclohexanone[21]) was purified by recrystallization from hexanes as needles: mp 83–85 °C; IR (KBr) 1717, 766, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.3 (m, 5 H), 4.31 (m, 1 H, CHCl), 3.52 (tt, J = 12, 4 Hz, 1 H), 3.18 (dt, J = 14, 6 Hz, 1 H), 2.42 (m, 3 H), 2.24 (dm, J = 14 Hz, 1 H), 1.96 (dq, J = 5, 13 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 204.17 (C=O), 143.18, 128.72, 126.89, 126.81, 59.92 (CHCl), 41.87, 36.54 (CHPh), 35.92, 33.73; mass spectrum, m/e (relative intensity) 210 (8), 208 (18, M$^+$), 173 (7), 164 (7), 155 (13), 153 (38), 145 (22), 129 (28), 104 (99), 91 (100). Anal. Calcd for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28. Found: C, 69.30; H, 6.30.

To a suspension of sodium methoxide (0.52 g, 9.7 mmol) in ether (200 mL) was added dropwise a solution of 2-chloro-4-phenylcyclohexanone (crude product obtained above, 1.83 g) in 50 mL of ether. The mixture was heated under reflux for 2 h, and then water (100 mL) was added. The aqueous mixture was extracted with ether, and the combined ether extracts were washed with water and brine and dried over Na_2SO_4. The removal of solvent gave a yellow oil, which was distilled bulb-to-bulb (110–130 °C (0.5 mm)) and purified by PCTLC with 9:1 hexanes/ethyl acetate as eluent. Ester 8[22] was obtained as a colorless oil (0.79 g, 44.1% yield from **7**): IR (neat) 3027, 2952, 2870, 1730, 1435, 1198, 1171, 754, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.15 (m, 5 H), 3.60 (s, 3 H, OCH_3), 3.13 (m, 1 H), 2.94 (m, 1 H), 2.29 (m, 1 H), 2.07 (m, 2 H), 1.88 (m, 2 H), 1.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) 176.88 (C=O), 144.77, 128.21, 126.85, 125.89, 51.56, 44.80, 42.87, 37.39, 34.48, 29.85; mass spectrum, m/e (relative intensity) 205 (5), 204 (26, M$^+$), 172 (27), 144 (100). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.09; H, 7.70.

Dimethyl 3-Phenylcyclopentane-1,1-dicarboxylate (9). A solution of diisopropylamine (2.04 g, 20.2 mmol) in THF (120 mL) was cooled at 0 °C, and *n*-butyllithium (7.6 mL, 1.6 M solution in hexanes, 12.2 mmol) was added dropwise. After 15 min, the cloudy solution was cooled to −78 °C. A solution of **8** (2.06 g, 10.1 mmol) in 30 mL of THF was added through a syringe. After 30 min, methyl chloroformate (2.3 mL, 30.3 mmol) was added, the stirring at −78 °C was continued for 30 min, and then the reaction mixture was allowed to warm to room temperature and quenched by the addition of 1 N HCl (50 mL). The mixture was extracted with ether, and the combined ether extracts were washed with 5% $NaHCO_3$, water, and brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by PCTLC with 9:1 hexanes/ethyl acetate as eluent, giving **9** (2.54 g, 96.0% yield) as a colorless oil: bp 145–155 °C (bulb-to-bulb distillation, 0.5 mm); IR (neat) 2953, 1732, 1435, 1269, 1157, 754, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.25 (m, 5 H), 3.75 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.17 (m, 1 H), 2.76 (dd, J = 8, 13 Hz, 1 H), 2.51 (m, 1 H), 2.36–2.09 (m, 3 H), 1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) 173.00 (C=O), 172.91 (C=O), 143.46, 128.38, 126.99, 126.29, 59.83 ($C(CO_2CH_3)_2$), 52.71 (CH_3O), 52.68 (CH_3O), 45.11 (CHPh), 42.06, 34.15, 33.81; mass spectrum, m/e (relative intensity) 262 (7, M$^+$), 231 (2), 202 (6), 171 (4), 145 (42), 143 (49), 91 (100). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.30; H, 7.22.

3-Phenylcyclopentane-1,1-dicarboxylic Acid (10). A mixture of **9** (2.06 g, 7.9 mmol), KOH (2.05 g, 36.5 mmol), methanol (10 mL), and water (10 mL) was stirred at room temperature for 12 h. The mixture was diluted with 100 mL of water and washed with ether. The aqueous solution was acidified with 6 N HCl to pH 1 and extracted with methylene chloride. The combined methylene chloride extracts were dried over Na_2SO_4 and evaporated, to yield **10** as a white solid (1.68 g, 91.5%). A small amount of the white solid (75 mg) was dissolved in 3 mL of 5% KOH and filtered. After acidification, **10** was crystallized as needles: mp 167–169 °C dec; IR (KBr) 3000 (br), 1696, 1287, 1198, 916, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6) 12.72 (br s, 2 H, COOH), 7.27 (m, 5 H), 3.08 (m, 1 H), 2.57 (dd, J = 8, 14 Hz, 1 H), 2.34 (m, 1 H), 2.25–2.0 (m, 3 H), 1.63 (m, 1 H); ^{13}C NMR (DMSO-d_6) 173.68, 173.62, 143.88, 128.34, 126.87, 126.11, 59.44, 44.51, 41.52, 33.72, 33.57; mass spectrum, m/e (relative intensity) 234 (4, M$^+$), 216 (2), 190 (20), 188 (11), 172 (15), 143 (52), 128 (19), 118 (100), 117 (58), 104 (33), 91 (38), 51 (25), 44 (87). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.78; H, 6.26.

9-Oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-8-carboxylic Acid (11). According to the procedure of Eaton et al.,[8] a mixture of P_2O_5 (10 g) and methanesulfonic acid (100 g) was stirred at room temperature for 2 h, then mixed with **10** (1.65 g, 7.0 mmol) and stirred for 4 h. The yellow reaction mixture was poured into 150 mL of ice/water with stirring. The mixture was extracted with ether (4 × 100 mL), and the combined ether extracts were dried over Na_2SO_4 and evaporated. Compound **11** (1.49 g, 97.8%) was obtained as a yellowish solid: mp 204–206 °C; IR (KBr) 3000 (br), 1711 (C=O), 1682 (C=O), 1335, 1291, 1206, 938 cm^{-1}; ^{1}H NMR (DMSO-d_6) 12.60 (s, 1 H, COOH), 7.88 (d, J = 8 Hz, 1 H), 7.60 (t, J = 7 Hz, 1 H), 7.39 (m, 2 H), 3.48 (m, 1 H, benzylic), 2.51 (m, 1 H), 2.26 (m, 2 H), 2.14 (m, 1 H), 1.60 (m, 2 H); ^{13}C NMR (DMSO-d_6) 196.50 (C=O), 172.69 (C=O), 150.33, 134.32, 128.78, 127.09, 126.98, 126.94, 63.70, 42.02, 41.45, 31.36, 26.92; mass spectrum, m/e (relative intensity) 217 (2, M$^+$ + 1), 199 (2), 172 (100), 157 (39), 153 (20), 144 (61), 131 (73), 115 (41), 103 (39). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.60. Found: C, 71.85; H, 5.80.

8-Amino-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (12). A procedure of Ninomiya et al.[9] was followed.

(20) Grunewald, G. L.; Ye, Q.; Sall, D. J.; Criscione, K. R.; Wise, B., unpublished results.

(21) The assignment of the major isomer to trans was based on the assumed chair conformation with the 4-phenyl group being equatorial and the 2-chloro atom axial. In the IR spectrum, the carbonyl absorption was observed at 1717 cm^{-1} vs 1734 cm^{-1} for the minor isomer; see: Brutcher, F. V., Jr.; Roberts, T.; Barr, S. J.; Pearson, N. *J. Am. Chem. Soc.* **1959**, *81*, 4915. In the ^{1}H NMR spectrum, the signal for H-2 was observed as a multiplet (J < 5 Hz) at 4.31 ppm vs 4.65 ppm for the minor isomer as a doublet of doublets (J = 5 Hz and 13 Hz). For more discussion on the conformation of 2-chlorocyclohexanones, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1981; pp 112–121, 460–469.

(22) Compound 8 was either the cis or the trans isomer. The second isomer was found at less than 10% and was not characterized.

Triethylamine (1.2 mL, 8.4 mmol) was added to a suspension of **11** (1.73 g, 8.0 mmol) in toluene (15 mL), followed by the addition of diphenyl phosphorazidate (1.8 mL, 8.4 mmol). After the mixture was heated at 80 °C for 2 h, *tert*-butyl alcohol (2.3 mL, 24.0 mmol) was added. The heating was continued for 20 h, and then solvent was removed under vacuum. The oily residue was mixed with 1 N HCl (50 mL) and heated under reflux overnight. The mixture was washed with ether, basified, and extracted with ether. The combined ether extracts were dried over Na_2SO_4. After removal of solvent, the residue was purified by PCTLC with methylene chloride/methanol/ammonium hydroxide (250:25:1) as eluent. **12** (0.92 g, 62.9% yield) was obtained as a white solid: mp 61–63 °C; IR (KBr) 3376, 3301, 2961, 2861, 1688, 1601, 1443, 1204, 957 cm^{-1}; ^1H NMR ($CDCl_3$) 8.06 (d, J = 8 Hz, 1 H), 7.49 (t, J = 8 Hz, 1 H), 7.33 (t, J = 7 Hz, 1 H), 7.25 (d, J = 7 Hz, 1 H), 3.44 (m, 1 H), 2.42 (m, 1 H), 1.7–2.2 (m, 6 H, NH_2 and four aliphatic protons), 1.64 (m, 1 H); ^{13}C NMR ($CDCl_3$) 202.32 (C=O), 151.06, 133.81, 129.68, 127.73, 126.72, 126.49, 67.40 (CNH_2), 47.06, 43.08 (benzylic), 33.88, 31.97; mass spectrum, m/e (relative intensity) 188 (26), 187 (100, M^+), 169 (33), 168 (33), 158 (98), 144 (50), 131 (67), 130 (67), 115 (36), 103 (27). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.28; H, 7.09; N, 7.50. **12**·HCl was made in ether with ethereal HCl and recrystallized from ethanol/ether: mp 253–254 °C. Anal. Calcd for $C_{12}H_{13}NO$·HCl: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.31; H, 5.98; N, 6.00.

8-Amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-*endo*-9-ol (5). A solution of **12** (0.77 g, 4.1 mmol) in 20 mL of absolute ethanol was cooled at 0 °C. Sodium borohydride (0.34 g, 8.9 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. Most of the solvent was removed under reduced pressure, and the residue was dissolved in 50 mL of 1 N NaOH and then extracted with methylene chloride. The combined methylene chloride extracts were dried over Na_2SO_4 and evaporated, to give **5** as a white solid (0.75 g, 98.5% yield). The white solid was dissolved in methanol, and anhydrous HCl was bubbled through the solution. After removal of solvent, **5**·HCl was recrystallized from ethanol/ether: mp 272 °C dec; IR (KBr) 3000 (br), 1605, 1514, 1455, 1269, 1053, 745 cm^{-1}; mass spectrum, m/e (relative intensity) 190 (18), 189 (95, free amine M^+), 171 (50), 170 (52), 156 (14), 143 (41), 128 (25), 115 (47), 103 (15), 91 (20), 82 (84), 77 (55), 57 (100). Anal. Calcd for $C_{12}H_{15}NO$·HCl: C, 63.85; H, 7.15; N, 6.21. Found: C, 64.10; H, 7.29; N, 6.10. A small amount of **5**·HCl was converted to free amine **5** for analysis: mp 126–128 °C; ^1H NMR ($CDCl_3$) 7.48 (d, J = 8 Hz, 1 H), 7.15 (m, 2 H), 6.97 (d, J = 6 Hz, 1 H), 4.80 (s, 1 H, C*H*OH), 3.05 (m, 1 H, benzylic), 2.60 (br s, 3 H, NH_2 and OH), 2.24 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 2 H), 1.57 (m, 1 H), 1.34 (m, 1 H); ^{13}C NMR ($CDCl_3$) 143.46, 136.84, 127.57, 127.29, 126.37, 125.86, 78.74 (CHOH), 62.18 (CNH_2), 44.80, 42.51 (benzylic), 34.04, 29.37.

8-Amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (4). According to the procedure of Hall et al.,[10] ammonia (about 50 mL) was distilled into a flask filled with 10 mL of THF and 3 mg (0.06 mg-atom) of cobalt metal. Lithium wire (0.10 g, six pieces, 14.4 mg-atom) was washed with hexanes and added to the mixture by pieces. **12** (125 mg, 0.67 mmol) in 10 mL of THF was added to the blue solution by drops. The whole was stirred under reflux for 4 h. Ammonium chloride (about 2 g) was added in portions to discharge the blue color, and then the ammonia was allowed to evaporate. The reaction mixture was dissolved in 50 mL of 1 N NaOH and extracted with ether. The combined ether extracts were dried over Na_2SO_4 and evaporated. The residue was distilled bulb-to-bulb (110 °C (0.5 mm)), to yield **4** (96 mg, 82.4%) as a colorless oil: IR (neat) 3349, 3015, 2934, 2861, 1601, 1455, 745 cm^{-1}; ^1H NMR ($CDCl_3$) 7.08 (m, 4 H), 3.12 (m, 1 H, benzylic), 3.00 (d, J = 16 Hz, 1 H, benzylic), 2.89 (d, J = 16 Hz, 1 H, benzylic), 2.13 (m, 1 H), 1.6–1.9 (m, 5 H), 1.52 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) 144.17, 134.45, 128.86, 126.51, 125.81, 125.74, 57.93 (CNH_2), 47.96, 44.94, 43.07, 37.71, 35.55; mass spectrum, m/e (relative intensity) 174 (9), 173 (48, M^+), 158 (14), 144 (100), 128 (13), 115 (22), 91 (10), 82 (27). **4**·HCl was made in ether with ethereal HCl and recrystallized from ethanol/ether as needles: mp 252–255 °C. Anal. Calcd for $C_{12}H_{15}N$·HCl: C, 68.72; H, 7.69; N, 6.68. Found: C, 69.01; H, 7.94; N, 6.71.

8-Acetamido-9-oxo-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene (13). A mixture of **12** (0.68 g, 3.6 mmol) and acetic anhydride (10 mL) was stirred at room temperature for 1 day. After removal of excess acetic anhydride under vacuum, the residue was purified by PCTLC with 1:1 hexanes/ethyl acetate as eluent. Amide **13** (0.82 g, 98.5% yield) was obtained as a colorless oil. Bulb-to-bulb distillation (115–135 °C (0.2 mm)) gave a white solid: mp 111–113 °C; IR (KBr) 3318, 2952, 1707, 1651, 1541, 1458, 1304, 1252, 1210, 947, 783, 698 cm^{-1}; ^1H NMR ($CDCl_3$) 8.06 (d, J = 8 Hz, 1 H), 7.52 (t, J = 7 Hz, 1 H), 7.34 (t, J = 7 Hz, 1 H), 7.27 (d, J = 8 Hz, 1 H), 7.10 (br s, 1 H, NH), 3.44 (t, J = 5 Hz, 1 H), 3.14 (dd, J = 5, 12 Hz, 1 H), 2.81 (t, J = 11 Hz, 1 H), 2.54 (m, 1 H), 2.07 (s, 3 H, CH_3), 1.94 (d, J = 11 Hz, 1 H), 1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) 197.48 (benzylic C=O), 169.34 (amide C=O), 150.48, 134.13, 128.33, 127.93, 126.58, 126.41, 67.75 (CNH), 42.03 (benzylic), 41.68, 30.82, 27.23, 24.01 (CH_3); mass spectrum, m/e (relative intensity) 230 (5), 229 (9, M^+), 186 (30), 170 (42), 158 (27), 152 (21), 144 (15), 131 (21), 115 (17), 43 (100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.50; H, 6.90; N, 6.04.

8-Acetamido-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (14) and 8-Acetamido-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*exo*-9-ol (15). Sodium borohydride (0.37 g, 9.9 mmol) was added to a solution of **13** (0.57 g, 2.5 mmol) in absolute ethanol (20 mL) cooled at 0 °C. The mixture was stirred at room temperature for 1 h and then evaporated under reduced pressure. The residue was dissolved in 100 mL of water and extracted with methylene chloride. The combined methylene chloride extracts were dried over Na_2SO_4 and evaporated, giving a mixture of **14** and **15** as a thick oil (0.56 g; 10:1 ratio according to ^1H NMR). The two isomers in the oil were separated by PCTLC with 20:1 methylene chloride/methanol as eluent, and both were white solids. 8-Acetamido-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*endo*-9-ol (**14**, 0.48 g, 83.5% yield) was the major isomer: mp 151–152 °C; IR (KBr) 3285 (br), 2940, 1642, 1555, 1046, 752 cm^{-1}; ^1H NMR ($CDCl_3$) 7.49 (d, J = 8 Hz, 1 H), 7.16 (m, 2 H), 6.98 (d, J = 7 Hz, 1 H), 6.7 (br s, 1 H, NH or OH, exchangeable with D_2O), 5.8 (br s, 1 H, NH or OH, exchangeable with D_2O), 5.13 (s, 1 H, C*H*OH), 3.07 (m, 1 H), 2.69 (m, 1 H), 1.9–2.3 (m, 6 H, aliphatic protons including CH_3), 1.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) 172.38 (C=O), 142.74, 136.45, 128.12, 127.36, 126.68, 125.70, 77.88 (CHOH), 65.52 (CNH), 42.45, 40.88 (benzylic), 33.71, 27.37, 23.59 (CH_3); mass spectrum, m/e (relative intensity) 232 (11), 231 (46, M^+), 213 (33), 188 (10), 185 (9), 172 (94), 157 (42), 154 (36), 144 (95), 129 (40), 115 (50), 57 (62), 43 (100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.98; H, 7.15; N, 6.06. The minor isomer was 8-acetamido-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*exo*-9-ol (**15**, 0.04 g, 7.0% yield): mp 185–186 °C; IR (KBr) 3413 (br), 2935, 1655, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) 7.40 (m, 1 H), 7.25 (m, 2 H), 7.07 (m, 1 H), 6.11 (br s, 1 H, NH), 4.73 (s, 1 H, C*H*OH), 3.18 (m, 1 H, benzylic), 2.6 (br s, 1 H, OH), 2.36 (t, J = 11 Hz, 1 H), 1.9–2.2 (m, 6 H, aliphatic protons including CH_3), 1.56 (m, 2 H); ^{13}C NMR ($CDCl_3$) 170.38 (C=O), 143.13, 135.11, 130.56, 128.45, 126.72, 126.65, 74.61 (CHOH), 63.54 (CNH), 41.71 (benzylic), 35.00, 33.52, 29.97, 24.23 (CH_3); mass spectrum, m/e (relative intensity) 232 (3), 231 (15, M^+), 213 (22), 188 (5), 185 (7), 171 (44), 154 (23), 143 (51), 128 (38), 115 (55), 91 (14), 77 (27), 57 (49), 43 (100); HRMS calcd for $C_{14}H_{17}NO_2$ m/e 231.1259, found 231.1270.

8-Amino-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocyclohepten-*exo*-9-ol (6). Acid Hydrolysis of the Mixture of 14 and 15. A mixture (194 mg, 0.84 mmol) of **14** and **15** from $NaBH_4$ reduction of **13** was heated under reflux in 50 mL of 0.3 N HCl for 18 h and then diluted with 50 mL of water. The mixture was washed with ether, then basified, and extracted with methylene chloride. The combined methylene chloride extracts were dried over K_2CO_3 and evaporated, to give a white solid (120 mg, 81.7%). The white solid was dissolved in methanol, and anhydrous HCl was bubbled through the solution. After removal of solvent, **6**·HCl was recrystallized from ethanol/ether: mp 225–226 °C; mass spectrum, m/e (relative intensity) 190 (13), 189 (91, free amine M^+), 171 (52), 170 (57), 156 (16), 143 (58), 128 (45), 115 (61), 103 (13), 91 (18), 82 (52), 77 (38), 57 (100). Anal. Calcd for $C_{12}H_{15}NO$·HCl: C, 63.85; H, 7.15; N, 6.21. Found: C, 63.78; H, 7.32; N, 6.00. A small amount of **6**·HCl was converted to free amine **6** for analysis: mp 143–145 °C; ^1H NMR ($CDCl_3$) 7.40 (d, J = 5 Hz, 1 H), 7.20 (m, 2 H), 7.06 (d, J = 5 Hz, 1 H), 4.24 (s,

1 H, CHOH), 3.17 (m, 1 H, benzylic), 2.4 (br s, 3 H, NH_2 and OH), 2.10 (m, 1 H), 1.98 (m, 1 H), 1.68 (m, 1 H), 1.51 (m, 3 H); ^{13}C NMR ($CDCl_3$) 143.58, 135.96, 130.53, 128.08, 126.47, 126.41, 76.91 (CHOH), 61.04 (CNH), 42.95, 39.05, 34.15, 34.00.

NMR Measurements. The exchangeable protons were removed with D_2O. Homonuclear and heteronuclear chemical shift correlation spectra (HOMCOR and HETCOR) were run with standard Varian software. The NOE difference spectrum was determined with the decoupler placed first well off resonance and then on resonance. The low-power decoupler was used, and the attenuation was maintained as high as possible as just to saturate the resonance. Subtraction of the second FID from the first was done with the standard add-subtract routine, and the transformation was performed.

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Synthesis of *C*-Glucosides by Reactions of Glucosyl Halides with Organocuprates

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Lithium dimethylcuprate reacts with *trans*-2-chloro-6-methyltetrahydropyran (1) via nucleophilic substitution predominantly with inversion of configuration to afford *cis*-2,6-dimethyltetrahydropyran (2). Similarly, lithium dialkylcuprates displace protected α-glucosyl bromides (5) with inversion to afford the β-*C*-glucosides, β-1-alkyl-1,5-anhydroglucitols (6). In contrast, Grignard reagents gave mixtures of α- and β-*C*-glucosides 6 and 7, while organolithium reagents gave only elimination to 9.

α-Halo ethers have considerable utility in synthetic organic chemistry because of their high reactivity toward carbon nucleophiles.[1] Cyclic α-halo ethers are particularly attractive potential substrates for asymmetric induction in carbon–carbon bond formation. Thus axially disposed 2-halotetrahydropyrans (i.e. 1) are readily prepared since the anomeric effect[2] constrains the halogen atom to the axial orientation. If nucleophilic displacement by a carbon nucleophile with inversion of configuration ensues, stereospecific formation of the equatorially substituted product will result. Recently we exploited the reaction between *trans*-2-chloro-6-methyltetrahydropyran (1) and malonate anion, which occurred with nearly complete inversion of configuration, as the key step in a stereoselective synthesis of a civet constituent.[3] We hve also explored the reaction of a 2-chlorotetrahydrothiophene with several organometallic reagents during our synthesis of biotin.[4]

In the present investigation, we sought to determine whether organometallic reagents would react with 2-halotetrahydropyrans with inversion of configuration via an S_N2-like mechanism. If such displacements exhibited significant S_N1 or single-electron transfer character, however, the desired selective inversion of configuration would not be achieved. α-Halo ethers have frequenlty been reported to undergo substitution via an S_N1 mechanism in which the intermediate cation is stabilized by the adjacent oxygen.[2,5] Radical intermediates adjacent to oxygen are also stabilized.[6] Thus, the normal propensity of organolithium and Grignard reagents to displace halides via a single-electron transfer mechanism, with erosion of stereoselectivity,[7] would be expected to be particularly severe in α-halo ethers. Accordingly, we recently observed that organolithium and Grignard reagents attack a cyclic α-halo thio ether from the less hindered face, presumably via a single electron transfer process.[4]

The *C*-glycosides[8] represent one significant group of natural products that have been prepared by reactions between protected α-glycosyl halides and organometallic reagents.[9] Substitution with inversion is required for preparation of naturally occurring *C*-glycosides which generally possess the 1-β configuration. However Grignard,[10] organolithium,[11] and organocadmium[12] reagents

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