Synthesis of Inhibitors of Adenosine Deaminase.[1] A Total Synthesis of *erythro*-3-(Adenin-9-yl)-2-nonanol[2] and Its Isomers from Chiral Precursors

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Received November 16, 1981

The synthesis of both isomers of EHNA[2] ("erythrohydroxynonyladenine") from D- and L-rhamnose is described. The key intermediates, (*R*)- and (*S*)-2-(benzyloxy)propanal, derived respectively from 5-*O*-benzyl-D- and -L-rhamnitol, were each condensed with hexylmagnesium bromide to give a 3:1 mixture of threo/erythro alcohols. Conversion of the threo alcohols to their methanesulfonates and displacement of the latter compounds with (adenin-9-yl)sodium, followed by debenzylation, afforded the desired erythro compounds in both series. The (2*S*,3*R*)-3-(adenin-9-yl)-2-nonanol isomer ("L-EHNA") was found >80-fold more tightly bound to calf mucosal adenosine deaminase ($K_i = 7.64 \times 10^{-10}$ M) than its 2*R*,3*S* isomer ($K_i = 6.23 \times 10^{-8}$ M). In addition, the erythro alcohols were converted to their respective threo derivatives, the 2*S*,3*S* and 2*R*,3*R* isomers, by an identical set of reactions.

In the past few years, inhibitors of adenosine deaminase (adenosine aminohydrolase EC 3.5.4.4, "ADA") have attracted considerable attention as possible co-drugs for use with certain biologically active adenine nucleosides that are of use against viruses and cancer. Of these, pentostatin[3,4] and coformycin[5] are extremely potent inhibitors of ADA, with K_i's in the range of 10^{-12}–10^{-11} M, respectively.[6] A moderately potent inhibitor, EHNA,[2] which possesses a $K_i = 1.6 \times 10^{-9}$ M (i.e., a semitight binding inhibitor)[6] may emerge as the most desirable for use in chemotherapy, owing to its lower toxicity and reversible ADA binding.[7] EHNA, as a racemic mixture, was designed and evaluated by Schaeffer and co-workers,[8] on the basis of an extensive rationale formulated over a number of years. In the present study, a synthesis of both stereoisomers of EHNA (**14b** and **16b**) from carbohydrate precursors was carried out in order to identify the bioactive enantiomer.[9,10] Herein is described that synthesis.

Results and Discussion

Chemical Synthesis. The basic synthetic strategy was to carve out the requisite C-2 chiral center from an available carbohydrate precursor and then construct the remainder of the molecule, using known principles of stereochemistry and simple chemical techniques to derive the desired stereochemistry at the second asymmetric (C-3) center. The enantiomeric, benzyl-protected propanal derivatives **7** and **8** (see Scheme I), capable of being chain-extended via organometallic reactions, were considered ideal building blocks for the compounds.

The enantiomeric aldehydes **7** and **8** were each carved, respectively, out of L- and D-rhamnose as depicted in Scheme I. 1,2:3,4-Di-*O*-isopropylidene-L-rhamnitol (**1**) was readily obtained from commercially available L-rhamnose by a two-step process[11] of (1) reduction with sodium borohydride and (2) acetonation of the resulting L-rhamnitol to give **1**. Synthesis of 1,2:3,4-di-*O*-isopropylidene-D-rhamnitol (**2**) was accomplished in three, high-yielding steps[12] from D-mannose, an inexpensive precursor. By making use of the internal symmetry afforded by the D-manno configuration (see Scheme II), one can go directly to D-rhamnitol without proceeding through the usual intermediate compounds required for the preparation of 6-deoxyhexitols. Thus D-mannose was converted to D-mannose diethyl dithioacetal (**17**), followed by Raney nickel desulfurization, to give directly D-rhamnitol (see Scheme II) that was subsequently acetonated to give the D-precursor **2**.

Benzylation of either **1** or **2** with benzyl chloride and an excess of sodium hydride in *N*,*N*-dimethylformamide afforded the 5-*O*-benzyl-1,2:3,4-di-*O*-isopropylidenerhamnitol (**3** or **4**) as a distillable liquid. Deisopropylidenation of **3** or **4** was most expeditiously carried out with the mild process that uses the volatile acid–water mixture of 9:1 trifluoroacetic acid–water[13] to give the respective 5-*O*-benzylrhamnitol (**5** or **6**) as a white, crystalline product.

The free hydroxy compound **5** or **6** was then subjected to glycol cleavage by using sodium metaperiodate at pH 6–8 to give the (*S*)- or (*R*)-2-(benzyloxy)propanal (**7** or **8**, respectively). These protected derivatives of chiral 2-hydroxypropanal were isolated as stable, distillable liquids that were found to hydrate (or alcoholate) rapidly upon exposure to moisture or solvent that contained even traces of moisture (or alcohol). Hence, difficulties were encountered in obtaining reproducible optical rotations on the anhydrous products **7** and **8**. While specific rotations at the sodium D line as high as ±60° were sometimes encountered for **7** or **8**, these values invariably fell to lower numbers when the sample was allowed to stand in moist air. A more practical procedure for determining optical rotations on the hydrated species was adopted whereby the $[\alpha]_D$ values were determined on solutions of **7** or **8** that were allowed to stand at least 6 h in 95:5 ethanol–water. This procedure gave consistent results of $[\alpha]^{20}_D$ −16.3° for **7** and $[\alpha]^{22}_D$ +16.0° for **8**, virtually assuring the optical integrity of these compounds. The addition of 1 N sodium hydroxide solution to the above solutions failed to sig-

(1) For a preliminary account, see: Baker, D. C.; Hanvey, J. C.; Hawkins, L. D.; Murphy, J. *Biochem. Pharmacol.* **1981**, *30*, 1159–1160.
(2) EHNA stands for "erythrohydroxynonyladenine", a name depicting the title compound, *erythro*-3-(adenin-9-yl)-2-nonanol (see ref 8).
(3) Woo, P. W. K.; Dion, H. W.; Lange, S. M.; Dahl, L. F.; Durham, L. J. *J. Heterocycl. Chem.* **1974**, *11*, 641–643.
(4) Baker, D. C.; Putt, S. R. *J. Am. Chem. Soc.* **1979**, *101*, 6127–6128.
(5) Nakamura, H.; Koyama, G.; Iitaka, Y.; Ohno, M.; Yagisawa, N.; Kondo, S.; Maeda, K.; Umezawa, H. *J. Am. Chem. Soc.* **1974**, *96*, 4327–4328.
(6) Agarwal, R. P.; Spector, T.; Parks, R. E., Jr. *Biochem. Pharmacol.* **1977**, *26*, 356–367.
(7) Shannon, W. M.; Schabel, F. W., Jr. *Pharmacol. Ther.* **1980**, *11*, 263–390.
(8) Schaeffer, H. J.; Schwender, C. F. *J. Med. Chem.* **1974**, *17*, 6–8.
(9) While Schaeffer and co-workers have demonstrated that L(+)-9-(2-hydroxypropyl)adenine and related compounds are indeed the bioactive isomers (see: Schaeffer, H. J.; Vince, R. *J. Med. Chem.* **1967**, *10*, 689–691. Schaeffer, H. J.; Johnson, R. N.; Schwartz, M. A.; Schwender, C. F. *Ibid.* **1972**, *15*, 456–458), the present work extends these findings to include EHNA and its isomers that contain two asymmetric centers.
(10) Frieden, C.; Kurz, L. C.; Gilbert, H. R. *Biochemistry* **1980**, *19*, 5303–5309.
(11) Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Weber, J. M. *J. Chem. Soc.* **1963**, 2287–2290.
(12) Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 3880–3884.
(13) Christiansen, J. E.; Goodman, L. *Carbohydr. Res.* **1968**, *7*, 510–512.

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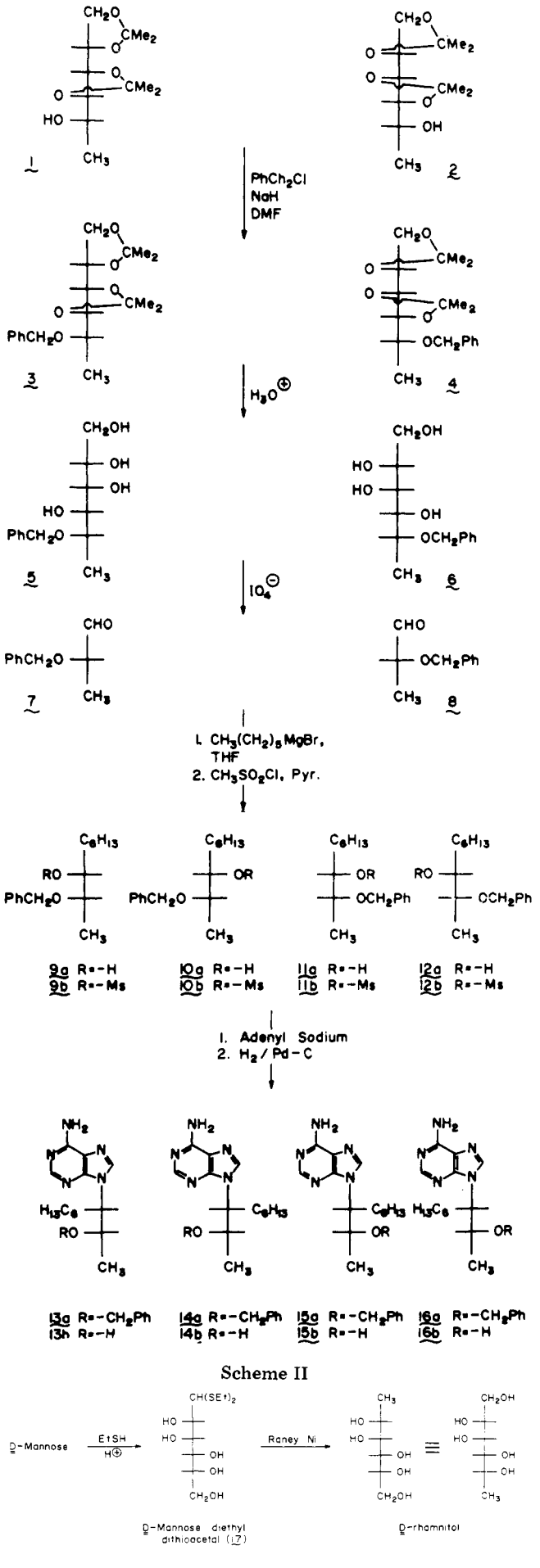
Scheme I



Scheme II

nificantly alter the $[\alpha]_D$ values, indicating that these molecules are indeed resistant to base-promoted racemization, at least in the hydrated state. Attempts to examine the enantiomeric aldehydes in the presence of the chiral shift reagent tris[3-[(trifluoromethyl)hydroxymethylene)]-(+)-camphorato]europuim(III) failed to resolve any racemic compounds. While the experiment was not conclusive, one could observe signals down to ca. 10% of **7** or **8** in a mixture of **7** and **8**. Signal overlap, even at 200 MHz, was too great to allow a quantitative determination of any possible racemate below ca. 10%.

Addition of *n*-hexylmagnesium bromide to a solution of **7** (or **8**) in dry tetrahydrofuran at ≤35 °C, followed by heating at reflux for 24 h, gave good yields of (2*S*,3*R*)-2-*O*-benzyl-2,3-nonanediol (**9a**) and (2*S*,3*S*)-2-*O*-benzyl-2,3-nonanediol (**10a**) (or the respective 2*R*,3*S* and (2*R*,3*R* isomers from **8**) in a ratio of 25:75 (i.e., erythro/threo ratio of 1:3 as determined by gas–liquid chromatography). The diastereomers **9a** and **10a** (or **11a** and **12a**) were separated by column chromatography on silica gel and were readily distinguished from one another by their ^{1}H NMR spectra and optical rotations (see Experimental Section).

Examination of the 200-MHz spectra (see Experimental Section) of the pairs of alcohols **9a** and **11a**, as well as **10a** and **12a**, revealed data supportive of erythro and threo configurations, respectively. Alcohols **9a** and **11a** showed an eight-line multiplet for H-2 and a six-line pattern for H-3, with $J_{2,3}$ = 3.4 Hz, as confirmed by spin decoupling and computer-assisted simulation experiments. Alcohols **10a** and **12a**, on the other hand, displayed for H-2 a five-line signal, with a six-line multiplet for H-3, with $J_{2,3}$ = 6.0 Hz. The broader 6-Hz coupling for H-2–H-3 (compared to $J_{2,3}$ = 3.4 Hz) has been attributed to the threo isomer in related systems of known stereochemistry.[8]

The threo/erythro ratio of 3:1 resulting from the Grignard reaction is consistent with the findings reported by Cram[14] for α-hydroxy carbonyl compounds in general, where the products were found to be predominantly those arising from α induction, i.e., attack of the nucleophile on the less-hindered face of that rotamer formed by chelation of the organometallic reagent between the hydroxyl oxygen and the oxygen of the carbonyl group. In our hands, at dry-ice bath temperatures, stereoselectivity approaching 100% in favor of the threo isomer was observed;[15] however, the conversion to product was too low for preparative utility, and the reaction was routinely carried out under prolonged reflux in tetrahydrofuran to achieve maximum conversion to the alcohols. This requirement was probably due, in part, to the competing conversion of the aldehyde to a different form (identified as a slow-migrating zone on TLC, presumably the hydrated species or, possibly, a metal chelate).

At this point a major concern was whether or not the Grignard process had caused any racemization of the aldehyde **7** (or **8**) or conceivably of the products **9a** and **10a** (or **11a** and **12a**). ^{1}H NMR studies conducted at 100 MHz with the chiral shift reagent as for **7** and **8** revealed no evidence of enantiomeric mixtures to a confidence level of ca. 5%, limited by inadequate signal separation and loss of resolution at higher concentrations of the europuim(III) reagent. Although these NMR studies could not be further improved, multiple experiments where the conditions of the Grignard reaction were varied (with respect to tem-

(14) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81* 2748–2755.

(15) Compare Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, 1031–1034. These authors report 100% threo products for similar systems where the reactions were conducted at −78 °C.

Table I. Hydride Reduction of (2S)-2-(Benzyloxy)-3-nonanone[a]

example	hydride reagent	addition temp, °C	% yield[b]	2S,3R isomer, % erythro	2S,3S isomer, % threo
1	borane-tetrahydrofuran	−78	85.3	14.1	85.9
2	borane-methyl sulfide	−78	43.4	19.3	80.7
3[c]	potassium tri-*sec*-butylborohydride	−78	68.8	25.4	74.6
4[d]	diisobutyl aluminum hydride	−78	89.8	28.5	71.5
5[e]	9-borabicyclo[3.3.1]nonane	5	0.8	32.7	67.3
6[f]	bis-(3-methyl-2-butyl)borane	−78	80.5	39.3	60.7
7	sodium borohydride	5	91.9	41.9	58.1
8	lithium borohydride	5	97.8	60.1	39.9
9[g]	lithium tetrahydroaluminate	−5	81.9	61.7	38.3

[a] The solvent used was freshly distilled tetrahydrofuran, except where noted otherwise. The excess reagent was decomposed, except where noted, by cautious addition of ca. 0.5 mL of methanol at room temperature. [b] Yields were based on GLC determinations; see the Experimental Section for details. [c] Used 0.5 M K-Selectride in tetrahydrofuran (Aldrich). [d] Used 20% DIBAL-H in hexane (Alfa-Ventron). [e] Used crystalline 9-BBN (Aldrich). Workup was carried out by adding ca. 0.5 mL of methanol, followed by 0.2 mL of 30% aqueous hydrogen peroxide and 0.2 mL of 1 M sodium hydroxide (Brown, H. C.; Bigley, D. B.; Arora, S. K.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 7161-7167). [f] Reagent freshly prepared from borane-tetrahydrofuran and 2-methyl-2-butene (Brown, H. C.; Krishnaumurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778-1791. [g] Workup was carried out according to the procedure of: Mićović, V. M.; Mihailović, M. L.-J. *J. Org. Chem.* **1953**, *18*, 1190.

perature, duration, and concentration of the Grignard reagent) showed that the alcohols **9a** and **11a**, as well as **10a** and **12a**, were obtained with reproducible values for specific rotations. These findings also support the lack of racemization at this stage of the synthesis.

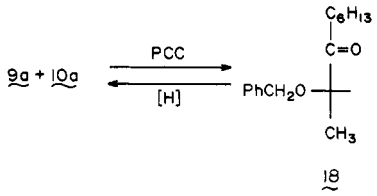
However, the above point concerning racemization was considered so crucial to the success of the entire scheme that the point was exhausively investigated by the preparation of derivatives of the alcohols **10a** and **12a** by using enantiomerically pure reagents. One such process that proved exceedingly useful was the preparation of the 3-*O*-[α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetyl] derivatives of **10a** and **12a** as described by Pirkle and Simmons.[16] These derivatives gave clear signal separations, especially at the $PhCH_2$ resonances situated at ca. δ 4.5. From these ^1H NMR spectra one could safely conclude that no racemization (i.e. ≤1%, based on observation of the signals on a 10 Hz/cm expansion, full scale, at 200 MHz) had taken place. At this point the stereochemical integrity of the alcohols **9a**–**12a** was firmly established.

Methanesulfonylation of each the diastereomeric alcohols **9a**–**12a** proceeded with methanesulfonyl chloride in pyridine to give the methanesulfonates **9b**–**12b** as syrupy liquids of limited thermal stability. ^1H NMR spectra of these compounds indicated products of high quality (see ref 22 and 23), and these were used directly in the displacement reactions described below.

The displacement of the methanesulfonyloxy group of the threo isomer **10b** (or **12b**) proceeded in *N,N*-dimethylformamide with the sodium salt of adenine to give exclusively the erythro product, (2*S*,3*R*)-3-(adenin-9-yl)-2-*O*-benzyl-2-nonanol (**14a**) [or (2*R*,3*S*-3-(adenin-9-yl)-2-*O*-benzyl-2-nonanol (**16a**) from **12b**]. The crude products were scrutinized by both TLC and ^1H NMR spectroscopy, and no evidence of diastereomeric nucleoside contaminants that would have resulted via processes other than S_N2 conversions were evident. The yields were on the order of 8–17%,[17] with considerable nonnucleoside products arising from decomposition of the mesylates accounting for the low yields.

Deprotection of the purine adducts **14a** and **16a** was accomplished by hydrogenolysis of the benzyl ether at pH 2 to give directly the EHNA isomers (2*S*,3*R*)-3-(adenin-9-yl)-2-nonanol hydrochloride (**14b**) and (2*R*,3*S*)-3-(adenin-9-yl)-2-nonanol hydrochloride (**16b**). Comparison of physical data with authentic, racemic EHNA hydrochloride[18] showed the products to be identical by TLC, HPLC, UV, IR, and ^1H NMR; **14b** and **16b** are distinguishable from one another by their specific optical rotations.[19] Again, careful examination of these products by HPLC revealed no trace of diastereomeric products (i.e., the threo product **13b** or **15b**, vide infra) that might have arisen during the displacement reaction with adeninyl sodium.

Scheme III



By a process identical with that described above, the erythro methanesulfonates **9b** and **11b** were converted to their respective threo products, (2*S*,3*S*)-3-(adenin-9-yl)-2-nonanol hydrochloride (**13b**) and (2*R*,3*R*)-3-(adenin-9-yl)-2-nonanol hydrochloride (**15b**). These compounds were readily distinguished from their erythro counterparts by ^1H NMR spectroscopy, and their structures were confirmed by spectroscopic and chemical means (see Experimental Section). The stereoisomers **13b** and **15b** were distinguished on the basis of their specific optical rotations.[19]

In order to possibly increase the production of the desired erythro EHNA product by making maximum use of the erythro alcohol, a mixture of **9a** and **10a** was oxidized with pyridinium chlorochromate[20] to give the ketone (2*S*)-2-(benzyloxy)-3-nonanone (**18**), and its reduction was studied with a variety of reducing agents (see Scheme III).

(16) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239–3246.
(17) No attempts have been made to date to improve upon the yields in this displacement reaction. Change of solvent and other conditions could considerably improve the process.
(18) EHNA hydrochloride was kindly supplied by the Burroughs-Wellcome Co.
(19) After this manuscript was submitted, a report appeared (Bastian, G.; Bessodes, M.; Panzica, R. P.; Abushanab, E.; Chen, S.-F.; Stoeckler, J. D.; Parks, R. E., Jr. *J. Med. Chem.* **1981**, *24*, 1385–1388) describing an alternative, albeit more lengthy, synthesis of compounds **13b**–**16b**, indicated to be the free amines. A comparison of the $[\alpha]_D$ values (the only physical data reported) between the compounds described both herein and in ref 1 and those reported by Bastian et al. agree within experimental error whenever appropriate adjustments are made for differences in molecular weight.
(20) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

The products were examined by GLC (see Table I), with an interest in determining the highest yielding, stereoselective reduction to give the desired high threo/erythro product ratio. In this respect, borane–tetrahydrofuran was found to be most satisfactory, giving a threo/erythro ratio of 6.09:1.00 in an overall yield of 85%. It is noteworthy that the more electrophilic reducing agents (i.e., the borane and allane derivatives) more strongly favor the threo isomer than their more nucleophilic counterparts (the borohydrides and aluminum hydrides). These observations are in line with the results expected with those compounds where α induction plays a decisive role in stereoselection in the reductive process. A noted exception to the above is the reduction with the bulky potassium tri-*sec*-butylborohydride (K-Selectride), where steric factors presumably outweigh other effects in isomer selection.

Inhibition of Adenosine Deaminase. Both of the erythro products **14b** and **16b** were subjected to an assay for inhibitory activity against adenosine deaminase[21] (Sigma Type III, calf mucosal origin, pH 7.5, using adenosine as the substrate). The 2*S*,3*R* isomer **14b** (K_i = 7.64 × 10^{-10} M) was found some 81.5-fold more tightly binding than the 2*R*,3*S* isomer **16b** (K_i = 6.23 × 10^{-8} M). The biologically more potent **14b** is at least 1.8 times as active as the racemic mixture heretofore described.[6,8,10] The threo products **13b**, and **15b**, known[8] to be less tightly binding, exhibited K_i = 2.01 × 10^{-7} and 1.63 × 10^{-7} M, respectively.

Experimental Section

Evaporations, unless otherwise specified, were conducted at 40 °C under water aspirator vacuum. Melting points were determined by using a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were determined on a Perkin-Elmer 710-B spectrophotometer as neat films for liquids or as potassium bromide pellets for solids. ^{1}H NMR spectra were recorded at 100 MHz on a Varian HA-100 or at 200 MHz on a Nicolet NT-200 instrument, with chemical shifts being reported as δ units [parts per million downfield from a tetramethylsilane internal standard (δ 0.0)]; coupling constants are first-order values reported in hertz. Optical rotations were determined in 1-dm cells of 1- or 5-mL capacity by using a Perkin-Elmer Model 241 spectropolarimeter. Thin-layer chromatography (TLC) was carried out on E. Merck (catalog No. 5539) aluminum-backed silica gel 60 plates (20-μm thickness). Column chromatography was conducted at 1 atm by using E. Merck silica gel 60 (70–230 mesh, ASTM, catalog No. 7734). Chromatography solvents include the following: A, chloroform; B, 1:1 ether–hexane; C, 9:1 chloroform–methanol. Anhydrous solvents were prepared via distillation from the appropriate drying agent as follows: tetrahydrofuran, potassium benzophenone ketyl; pyridine and dichloromethane, calcium hydride; *N*,*N*-dimethylformamide, calcium hydride, 65–67 °C (ca. 20 torr). All other solvents and reagents were of "reagent" grade and were used directly as supplied.

5-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (3). To a stirred suspension of 99.6 g (2.07 mol) of a 50% oil dispersion of sodium hydride (rendered free of mineral oil by petroleum ether washing) in 100 mL of dry *N*,*N*-dimethylformamide was added dropwise 102.2 g (0.42 mol) of 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol **1** in 300 mL of dry *N*,*N*-dimethylformamide over 30 min. The reaction mixture was stirred for 24 h at room temperature, at the end of which time 58.3 g (0.46 mol) of benzyl chloride was added dropwise over a 1-h period. After being stirred for an additional 24 h at room temperature, the reaction mixture was cooled to 5 °C, and 50-mL of methanol was added dropwise over 20 min. The solvents were then evaporated to dryness at ca. 60 °C (1 torr), and the residue was suspended in 1 L of water. The aqueous suspension was extracted with three, 400-mL portions of chloroform, and the combined, organic layers were dried over magnesium sulfate and concentrated to provide a crude, golden syrup that was purified by distillation in vacuo: yield 106 g (76%); bp 139–140 °C (0.25 torr); $[\alpha]^{20}_D$ +4.0° (*c* 1, chloroform); R_f 0.9 (A); IR data (neat): 1244 (m, CH_2OCH), 1070 cm^{-1} (m, CHOC); NMR ($CDCl_3$) δ 1.25 (3 H, d, *J* = 7.4, $CHCH_3$), 1.29, 1.32 (6 H, 6 H, 2 s, CMe_2), 3.56–4.20 (6 H, m, H-1–H-5), 4.49 (1 H, d, *J* = 12, $PhCH_a$), 4.66 (1 H, d, *J* = 12, $PhCH_b$), 7.34 (5 H, m, Ph).

Anal. Calcd for $C_{19}H_{28}O_5 \cdot 0.06H_2O$: C, 67.83; H, 8.39. Found: C, 67.60; H, 8.40.

5-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-D-rhamnitol (4). By use of 7.6 g (154 mmol) of **2** and correspondingly less of the other reagents in the process as for **3**, 5.9 g (57%) of pure **4** was obtained: bp 141–142 °C (0.25 torr); $[\alpha]^{19}_D$ −3.6° (*c* 0.7, chloroform); NMR, IR, and TLC data were identical with those for **3**.

Anal. Calcd for $C_{19}H_{28}O_5 \cdot 1.1H_2O$: C, 64.05; H, 8.55. Found: C, 63.94; H, 8.76.

5-*O*-Benzyl-L-rhamnitol (5). To 40.0 g (0.12 mol) of 5-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (**3**) stirred at 5 °C was added dropwise 100 mL of 9:1 of trifluoroacetic acid–water over a 5-min period. The stirred reaction mixture was allowed to warm to room temperature, and the solvents were coevaporated to dryness several times with absolute ethanol at ≤30 °C. Crystallization of the resulting crude residue in hot 95% ethanol provided 23.6 g (84%) fine white needles of **5**: mp 144.5–145 °C; $[\alpha]^{27}_D$ +28.7° (*c* 1, methanol); R_f 0.1 (A); IR (KBr) 3300 (s, OH), 1290 cm^{-1} (m, COC); NMR [$(CD_3)_2SO$-d_6 + 10% D_2O] δ 1.19 (3 H, d, *J* = 5.5, $CHCH_3$), 3.35–3.65 (6 H, m, H-1–H-5), 4.42 (1 H, d, *J* = 11.7, $PhCH_a$), 4.56 (1 H, d, *J* = 11.7, $PhCH_b$), 7.25–7.40 (5 H, m, Ph).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.70; H, 7.96.

5-*O*-Benzyl-D-rhamnitol (6). By the procedure used for **5**, 5.9 g (17.5 mmol) of **4** was converted to 4.4 g (98%) of **6**: mp 144–145 °C; $[\alpha]^{27}_D$ −25.0° (*c* 2, methanol); NMR, IR, and TLC data were identical with those for **5**.

Anal. Calcd for $C_{13}H_{20}O_5 \cdot 0.75H_2O$: C, 57.87; H, 8.03. Found: C, 57.85; H, 8.15.

(2*S*)-2-(Benzyloxy)propanal (7). To a stirred suspension of 33.8 g (0.14 mol) of 5-*O*-benzyl-L-rhamnitol (**5**) in 500 mL of water (buffered to pH 7.41 with 10 mL of 1 M sodium phosphate) was added dropwise 94.9 g (0.44 mol) of sodium metaperiodate in 750 mL of water over a 1-h period at room temperature. During the oxidation process, the reaction mixture was maintained between pH 6.0 and 8.0 with the addition of 0.1 M sodium hydroxide. After being stirred for an additional 16 h, the resulting reaction mixture was extracted with five 300-mL portions of ethyl acetate. The combined organic layers were washed with one 300-mL portion of saturated, aqueous sodium chloride, dried over magnesium sulfate, and concentrated to provide a crude oil that was purified by distillation in vacuo: yield 19.7 g (84%); bp 52–54 °C (0.05 torr); $[\alpha]^{20}_D$ −16.3° (*c* 1.4, 95:5 ethanol–water); R_f 0.26 (A); IR (film) 1730 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 1.46 (3 H, d, *J* = 7, H-3), 3.86 (1 H, dq, $J_{1,2}$ = 2, $J_{2,3}$ = 7, *H*-2), 5.59 (2 H, s, $PhCH_2$), 7.32 (5 H, brs, Ph), 9.62 (1 H, d, H-1).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 65.83; H, 7.37. Found: C, 65.88; H, 7.35.

(2*R*)-2-(Benzyloxy)propanal (8). By the procedure used for **7**, 0.40 g (1.6 mmol) of **6** was converted to 0.2 g (78%) of **8**: bp 52–54 °C (0.01 torr); $[\alpha]^{22}_D$ +16.0° (*c* 1, 95:5 ethanol–water); NMR, IR, and TLC data were identical with those for **7**.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 65.83; H, 7.37. Found: C, 65.81; H, 7.46.

(2*S*,3*R*)-2-*O*-Benzyl-2,3-nonanediol (9a) and (2*S*,3*S*)-2-*O*-Benzyl-2,3-nonanediol (10a). To a stirred solution of 15.0 g (0.09 mol) of 2-(*S*)-(benzyloxy)propanal (**7**) in 200 mL of dry tetrahydrofuran under a nitrogen atmosphere was added dropwise 250 mL (0.25 mol) of freshly prepared 1.0 M *n*-hexylmagnesium bromide in dry tetrahydrofuran over a period of 30 min, keeping the temperature ≤35 °C. The mixture was then brought to reflux, and at the end of 24 h, the cooled reaction mixture was quenched by the addition of a saturated, aqueous solution of ammonium chloride (75 mL) and then poured into 100 mL of water. The aqueous suspension was extracted with four 75-mL portions of ethyl acetate, and the combined organic layers were washed with 50 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to afford a colorless oil. The

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resulting alcohols were separated by chromatography in 2-g portions over 400 g of silica gel with a 1:4 ether/*n*-hexane eluent to afford 2.7 g (12%) of **9a** and 11.2 g (49%) of **10a**, homogeneous by TLC and NMR. Samples of the separated isomers were further purified for analysis by distillation in vacuo.

Data for **9a**: bp 109–110.5 °C (0.01 torr); $[\alpha]^{20}_D$ +23.6° (*c* 1, chloroform); R_f 0.35 (B); IR (film) 3450 cm^{-1} (w, OH); NMR (C_6D_6) δ 0.86 (3 H, t, $J_{8,9}$ = 5, CH_2CH_3), 1.05 (3 H, d, $J_{1,2}$ = 6.5, H-1), 1.16–1.6 (10 H, m, H-4–H-8), 2.86 (1 H, dq, $J_{2,3}$ = 3.4, H-2), 3.25 (1 H, ddd, $J_{3,4}$ = 6, H-3), 3.83 (1 H, d, J = 12, $PhCH_a$), 3.99 (1 H, d, J = 12, $PhCH_b$), 7.06–7.36 (5 H, m, Ph).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.75; H, 10.44.

Data for **10a**: bp 114–115 °C (0.01 torr); $[\alpha]^{20}_D$ +31.3° (*c* 1, chloroform); R_f 0.41 (B); IR (film) 3400 cm^{-1} (w, OH); NMR (C_6D_6) δ 0.81 (3 H, t, $J_{8,9}$ = 6, CH_2CH_3), 1.03 (3 H, d, $J_{1,2}$ = 6, $CHCH_3$), 1.12–1.66 (10 H, m, H-4–H-8), 3.21 (1 H, dq, $J_{2,3}$ = 6, H-2), 3.43 (1 H, dt, $J_{3,4}$ = 6, H-3), 4.18 (1 H, d, J = 12, $PhCH_a$), 4.43 (1 H, d, J = 12, PhH_b), 7.0–7.24 (5 H, m, Ph).

Anal. Calcd for $C_{16}H_{26}O_2 \cdot 0.10H_2O$: C, 76.20; H, 10.47. Found: C, 76.12; H, 10.66.

(2*R*,3*S*)-2-*O*-Benzyl-2,3-nonanediol (11a) and (2*R*,3*R*)-2-*O*-Benzyl-2,3-nonanediol (12a). By the procedure for **9a** and **10a** and with correspondingly smaller quantities of reagents, 2.6 g (15.9 mmol) of (2*R*)-2-(benzyloxy)propanal (**8**) was converted to 0.80 g (20%) of **11a** and 2.1 g (54%) of **12a**.

Physical and spectral data for **11a** were identical with those for **9a**: bp 107–108 °C (0.025 torr); $[\alpha]^{18}_D$ −22.5° (*c* 1, chloroform).

Anal. Calcd for $C_{16}H_{26}O_2 \cdot 0.5H_2O$: C, 74.08; H, 10.49. Found: C, 73.80; H, 10.73.

Physical and spectral data for **12a** were identical with those of **10a**: bp 109–109.5 °C (0.025 torr); $[\alpha]^{18}_D$ −31.3° (*c* 1, chloroform).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.87; H, 10.53.

(2*S*,3*R*)-3-(Adenin-9-yl)-2-*O*-benzyl-2-nonanol (14a). (A) Mesylation of (2*S*,3*S*)-2-*O*-Benzyl-2,3-nonanediol (10a). To a stirred solution of 2.43 g (9.70 mmol) of (2*S*,3*S*)-2-*O*-benzyl-2,3-nonanediol (**10a**) in 30 mL of dry pyridine was added in one portion 1.22 g (10.67 mmol) of methanesulfonyl chloride. The mixture was stirred at room temperature for 48 h, at the end of which time the solution was poured over 100 g of ice, and the resulting suspension was extracted with three 50-mL portions of chloroform. The combined organic layers were dried over magnesium sulfate and concentrated to 3.05 g of crude **10b** as an amber oil that was used directly, without further purification, in the next step.[22]

(B) Displacement of (2*S*,3*S*)-2-*O*-Benzyl-3-*O*-methanesulfonyl-2,3-nonanediol (10b) with Adeninylsodium. To a stirred suspension of 0.11 g (2.58 mmol) of a 57% oil dispersion of sodium hydride (rendered free of mineral oil by washing in petroleum ether) in 10 mL of dry *N*,*N*-dimethylformamide was added, under a nitrogen atmosphere, 0.34 g (2.15 mmol) of adenine. The resulting suspension was stirred for 24 h at room temperature, at the end of which time 3.05 g (9.70 mmol) of **10b**, dissolved in 5 mL of *N*,*N*-dimethylformamide, was added in one portion. The mixture was stirred for 7 days at 50 °C, quenched by the addition of 5 mL of methanol, and evaporated to dryness at ca. 60 °C (1 torr). The residue was suspended in 50 mL of water and extracted with four 20-mL portions of ethyl acetate. The combined extracts were washed with 20 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated to dryness. The crude product was dissolved in 2 mL of chloroform, applied to a slurry-packed (chloroform) column of silica gel, and eluted with a linear gradient of 0–10% methanol in chloroform to give, from the appropriate fractions upon crystallization from cyclohexane, 0.35 g (10%) of pure **14a** as fine, white needles: mp 123–124 °C; $[\alpha]^{17}_D$ +78.7° (*c* 1, chloroform); R_f 0.51 (C); IR (KBr): 3100 (s, NH_2), 1670 (m, adenine), 1600 cm^{-1} (s, adenine); NMR (C_6D_6) δ 0.79 (3 H, t, $J_{8,9}$ = 6.5, H-9), 0.87 (3 H, d, $J_{1,2}$ = 6.3, H-1), 0.95–1.15 (6 H, m, H-6–H-8), 1.75–2.1 (4 H, m, H-4, H-5), 3.60–3.71 [1 H, dt (5 lines), $J_{2,3}$ = 5.2 H-2], 4.02 (1 H, d, J = 11.5, $PhCH_a$), 4.27 (1 H, d, J = 11.5, $PhCH_b$), 4.45–4.55 [1 H, m (5 lines), H-3], 5.21 (2 H, br s, NH_2), 7.06–7.35 (5 H, m, Ph), 7.75, 8.68 (2 H, 2 s, H-2, H-8).

Anal. Calcd for $C_{21}H_{29}N_5O$: C, 68.63; H, 7.95; N, 19.06. Found: C, 68.54; H, 7.97; N, 19.04.

(2*S*,3*S*)-3-(Adenin-9-yl)-2-*O*-benzyl-2-nonanol (13a). By the procedure in the foregoing section, 0.84 g (3.35 mmol) of **9a** was reacted with methanesulfonyl chloride–pyridine, and the resultant methanesulfonyl derivative **9b**[23] was converted to 85 mg (8%) of the adenine derivative **13a**, isolated as a crystalline solid: mp 149–150 °C, $[\alpha]^{19}_D$ −52.0° (*c* 1, chloroform); R_f 0.52 (C); IR (KBr) 3110 (s, NH_2), 1670 cm^{-1} (s, adenine); NMR (C_6D_6) δ 0.82 (3 H, t, $J_{8,9}$ = 6.5, H-9), 1.05 (3 H, d, $J_{1,2}$ = 6.2, H-1), 1.1–1.3 (6 H, m, H-6–H-8), 1.73 (4 H, br s, H-4–H-5), 3.95 (1 H, dq, $J_{2,3}$ = 4.0 H-2), 4.35 (1 H, d, J = 11.7, PhH_a), 4.48–4.57 [1 H, m (7 lines) H-3], 4.64 (1 H, d, J = 11.7, PhH_b), 5.59 (2 H, br s, NH_2), 7.18–7.35 (5 H, m, Ph), 8.01 (2 H, s, H-2, H-8).

Anal. Calcd for $C_{21}H_{29}N_5O$: C, 68.63; H, 7.95; N, 19.06. Found: C, 68.54; H, 8.00; N, 19.03.

(2*R*,3*S*)-3-(Adenin-9-yl)-2-*O*-benzyl-2-nonanol (16a). By the same procedure as for **14a**, but with correspondingly smaller equivs of reagents, 0.47 g (1.89 mmol) of **12a** was converted to 114 mg (16%) of **16a**, having identical physical and spectral properties with those of **14a**; $[\alpha]^{19}_D$ −78.4° (*c* 1, chloroform).

Anal. Calcd for $C_{21}H_{29}N_5O$: C, 68.63; H, 7.95; N, 19.06. Found: C, 68.53; H, 7.99; N, 19.00.

(2*R*,3*R*)-3-(Adenin-9-yl)-2-*O*-benzyl-2-nonanol (15a). By the procedure used for **14a**, with appropriate adjustment in the quantities of reagents, 0.75 g (3.01 mmol) of **11a** was converted to 177 mg (17%) of **15a** having physical and spectral properties identical with those of **13a**; $[\alpha]^{17}_D$ +49.9° (*c* 1, chloroform).

Anal. Calcd for $C_{21}H_{29}N_5O$: C, 68.63; H, 7.95; N, 19.06. Found: C, 68.37; H, 7.99; N, 19.00.

(2*S*,3*R*)-3-(Adenin-9-yl)-2-nonanol Hydrochloride (14b). A solution of 0.12 g (0.34 mmol) of (2*S*,3*R*)-3-(adenin-9-yl)-2-*O*-benzyl-2-nonanol (**14a**) in 30 mL of 2-propanol, to which was added 1 drop of concentrated hydrochloric acid, was vigorously stirred under an atmosphere of hydrogen (ca. 50 psi) in the presence of 0.1 g of 10% palladium on charcoal for 2 days. The catalyst was filtered off by using a Celite pad, and the filtrate was again subjected to the foregoing hydrogenation conditions by using a fresh 0.1-g portion of catalyst for an additional 2 days, at the end of which time the catalyst was filtered and the solvent evaporated. The crude product was chromatographed over a 20-g column of silica gel by using 300 mL of 92.5:7.5 chloroform–methanol as the eluent. The appropriate fractions were combined, and the solvent was evaporated to give an oily product that was dissolved in 25 mL of anhydrous ether. Dry hydrogen chloride was bubbled into the solution, and the precipitated product was filtered to give **14b** as the hydrochloride salt. The precipitated material was recrystallized from ethanol–ether to give a powdery 74 mg (72%) of the crystalline salt: mp 205–207 °C dec; $[\alpha]^{20}_D$ +30.1° (*c* 0.5, ethanol); R_f 0.31 (C); IR (KBr) 3000 (br s, OH, NH_2), 1680 cm^{-1} (s, adenine); NMR [$(CD_3)_2SO$–D_2O, 9:1] δ 0.74 (3 H, t, $J_{8,9}$ = 6.3, H-9), 1.0–1.3 (6 H, m, H-6–H-8) 1.36 (3 H, d, $J_{1,2}$ = 6.3, H-1), 2.3–2.5 (4 H, m, H-4–H-5), 4.55 [1 H, dt (5 lines), $J_{2,3}$ = 5.8, H-2], 4.77–4.87 [1 H, m (7 lines), H-3], 8.53 (2 H, br s, NH_2), 8.59, 8.78 (2 H, 2 s, H-2, H-8).

Anal. Calcd for $C_{14}H_{23}N_5O \cdot 1.1HCl$: C, 52.96; H, 7.65; N, 22.06; Cl, 12.28. Found: C, 52.79; H, 7.77; N, 21.98; Cl, 12.00.

(2*R*,3*S*)-3-(Adenin-9-yl)-2-nonanol Hydrochloride (16b). By the foregoing procedure as for **14b**, 66 mg (0.18 mmol) of **16a** was hydrogenolyzed to give 41 mg (80%) of **16b**·HCl whose physical and spectral data were identical with those of **14b**; $[\alpha]^{17}_D$ −31.7° (*c* 0.5, ethanol).

Anal. Calcd for $C_{14}H_{23}N_5O \cdot HCl$: C, 53.58; H, 7.71; N, 22.32; Cl, 11.30. Found: C, 53.55; H, 7.70; N, 22.27; Cl, 11.39.

(2*S*,3*S*)-3-(Adenin-9-yl)-2-nonanol Dihydrochloride (13b). By the procedure given for **14b**, 70 mg (0.19 mmol) of **13a** was converted to 30 mg (50%) of **13b**, isolated as the dihydrochloride:

(22) Data for **10b** (or **12b**): R_f 0.45 (A); IR (film) 1353 cm^{-1} (w, sulfonate); NMR (C_6D_6) δ 0.8–1.8 (16 H, m, H-4–H-9), 2.9 (3 H, s, CH_3S_2), 3.4–4.0 (2 H, m, H-2–H-3), 4.40 (1 H, d, J = 13 Hz, $PhCH_a$); 4.48 (1 H, d, J = 13 Hz, $PhCH_b$), 7.25–7.4 (5 H, m, Ph).

(23) Data for **9b** (or **11b**): R_f 0.48 (A); IR (film) 1353 cm^{-1} (w, sulfonate); NMR (C_6D_6) δ 0.7–1.6 (16 H, m, H-1, H-4–H-9), 3.0 (3 H, s, CH_3SO_2), 3.35–3.9 (1 H, m, H-2), 4.1–4.3 (1 H, m, H-3), 4.56 (2 H, s, $PhCH_2$), 7.32 (5 H, s, Ph).

mp 195–198 °C dec; $[\alpha]^{17}_D$ −34° (c 0.25, ethanol); R_f 0.29 (C); IR (KBr) 3100 (s, OH, NH_2), 1710 (s, adenine), 1600 cm^{-1} (m, adenine); NMR [$(CD_3)_2SO$–D_2O, 9:1] δ 1.0–1.4 (9 H, m, H-6–H-9), 1.25 (3 H, d, $J_{1,2}$ = 6.3, H-1), 1.95–2.05, 2.3–2.45 (4 H, m, H-4, H-5), 4.48 (1 H, dt, $J_{2,3}$ = 3.5, H-2), 4.78–4.88 [1 H, m (8 lines), H-3], 8.39 (2 H, br s, NH_2), 8.65, 8.79 (2 H, 2 s, H-2, H-8).

Anal. Calcd for $C_{14}H_{23}N_5O$·2.0HCl: C, 45.90; H, 6.88; N, 19.12; Cl, 19.35. Found: C, 45.87; H, 6.89; N, 19.11; Cl, 19.28.

(2*R*,3*R*)-3-(Adenin-9-yl)-2-nonanol Dihydrochloride 15b. By the procedure of **14b**, 163 mg (0.44 mmol) of **15a** was converted to 30 mg (22%) of **15b**, isolated as the dihydrochloride; physical and spectral data were identical with those of **13b**; $[\alpha]^{20}_D$ +33.5° (c 0.25, ethanol).

Anal. Calcd for $C_{14}H_{23}N_5O$·2HCl: C, 45.90; H, 6.88; N, 19.12; Cl, 19.35. Found: C, 45.92; H, 6.89; N, 19.12; Cl, 19.31.

(2*S*)-2-(Benzyloxy)-3-nonanone (18). To a stirred solution of 5.60 g (22.5 mmol) of a mixture of (2*S*,3*R* or *S*)-2-*O*-benzyl-2,3-nonanediols (**9a** and **10a**) in 250 mL of anhydrous dichloromethane was added 7.30 g (33.7 mmol) of pyridinium chlorochromate (Aldrich) in one portion. After being stirred for 10 h at 25 °C, the mixture was poured over a 200 g column of dry silica gel, and the column was eluted with 1 L of 1:1 methanol–chloroform. The solvents were evaporated, and the resulting crude oil was distilled in vacuo to give 4.0 g (72%) of **18**: bp 125–126 °C (0.25 torr); $[\alpha]^{18}_D$ −32.0° (c 1.2, chloroform); R_f 0.56 (A); IR (film) 1730 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 0.7–1.6 (9 H, m, H-6–H-9), 1.30 (3 H, d, $J_{1,2}$ = 6.3, H-1), 3.93 (1 H, q, H-2), 4.55 (2 H, s, $PhCH_2$), 7.2–7.45 (5 H, m, Ph).

Anal. Calcd for $C_{16}H_{24}O_2$·0.6H_2O: C, 74.15; H, 9.80. Found: C, 74.12; H, 9.38.

General Procedure for the Reduction of (2*S*)-2-(Benzyloxy)-3-nonanone (18) with Various Hydride Reducing Agents. (A) Reduction. To a stirred solution of 0.03 g (0.12 mmol) of (2*S*)-2-(benzyloxy)-3-nonanone (**18**) in 2 mL of tetrahydrofuran (exception: sodium borohydride was used with absolute methanol as the solvent) maintained at the indicated temperature (see Table I for specific conditions) and under nitrogen atmosphere was added 0.12 mmol of the appropriate hydride reducing agent. After warming to room temperature, the mixture was stirred for 24 h, at the end of which time the excess hydride was decomposed by using the indicated reagent(s) (see Table I). The mixture was filtered through Celite, and the filtrate was diluted to exactly 10 mL with tetrahydrofuran.

(B) Gas–Liquid Chromatographic (GLC) Analysis. Quantitative GLC analysis of each reaction mixture was carried out by using a Research Specialties Co. Model 600 GLC apparatus, equipped with a hydrogen flame-ionization detector and a 0.3 × 185-cm glass column packed with 3.5% Emulfor on 80–120-mesh Chromosorb W (nitrogen carrier gas at ca. 20 mL min^{-1}) at a 190 °C column temperature. The percent yield and 2*S*,3*R* to 2*S*,3*S* (erythro/threo) product composition were determined by comparison of peak heights and known standards of both (2*S*,3*R*)-2-*O*-benzyl-2,3-nonanediol (**9a**) and (2*S*,3*S*)-2-*O*-benzyl-2,3-nonanediol (**10a**). Results are tabulated in Table I.

(2*S*,3*S*)-2-*O*-Benzyl-3-*O*-(+)-[α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetyl]nonanediol and (2*R*,3*R*)-2-*O*-benzyl-3-*O*-(+)-[α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetyl]nonanediol were prepared according the established procedure[16] by using 330 mg (1.0 mmol) of (+)-α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetic trifluoroacetic anhydride[16] and 144 mg (0.6 mmol) of (2*S*,3*S*)-2-*O*-benzyl-2,3-nonanediol (**10a**) or 61 mg (0.2 mmol) of (2*R*,3*R*)-2-*O*-benzyl-2,3-nonanediol (**12a**). The products were purified via liquid chromatography over 50 g of silica gel, eluting with 2:3 chloroform/*n*-hexane). Very viscous oils of each were obtained: R_f 0.32 (1:1 chloroform/*n*-hexane); mass spectrum, calcd for $M^+ \cdot$ *m/e* 566.2644, found *m/e* 566.2630 and 566.2632, respectively, for the derivative of **10a** and the derivative of **12a**. NMR spectra were consistent with the proposed structures.

Acknowledgment. R. B. Jarrell and R. Pajares, III, are thanked for some experimental work. This work was supported, in part, by the National Institutes of Health (Grant CA-26465) and the University of Alabama Research Grants Committee. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The NMR spectrometer was purchased under a grant from the National Science Foundation. L.D.H. gratefully acknowledges the Graduate School of The University of Alabama for the award of a research fellowship.

Registry No. 1, 3969-60-6; 2, 81408-31-3; 3, 4697-98-7; 4, 81408-32-4; 5, 4613-16-5; 6, 81408-33-5; 7, 81445-44-5; 8, 81445-45-6; 9a, 81408-34-6; 9b, 81408-35-7; 10a, 81408-36-8; 10b, 81408-37-9; 11a, 81408-38-0; 11b, 81408-39-1; 12a, 81408-40-4; 12b, 81408-41-5; 13a, 81408-42-6; 13b·2HCl, 81408-43-7; 14a, 81408-44-8; 14b·HCl, 81408-45-9; 15a, 81408-46-0; 15b·2HCl, 81408-47-1; 16a, 81408-48-2; 16b·HCl, 81408-49-3; 17, 6748-69-2; 18, 81408-50-6; (2*S*,3*S*)-2-D-benzyl-3-*O*-(+)-[α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetyl]nonane, 81408-51-7; (+)-α-[1-(9-anthryl)-2,2,2-trifluoroethoxy]acetic trifluoroacetic anhydride, 81408-52-8.

A New Class of *D*-Heteroergolines: Total Synthesis and Resolution of a 9-Oxaergoline, 4,6,6a,8,9,10a-Hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine

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Received January 8, 1982

Synthesis of the 9-oxaergoline ring system, 4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine, is presented. Both the C/D cis and the C/D trans isomers were prepared. Resolution of the C/D trans isomer afforded (−)-*trans*-6-ethyl-9-oxaergoline, **15**, which has the same configuration as the natural ergolines, namely, 6a*R*,10a*R*, and possesses potent dopamine agonist properties.

The ergot alkaloids, metabolic products of the parasitic fungus *Claviceps*, represent a widely studied structural class of compounds possessing a range of important biological properties.[1-4] The majority of the ergots contain the tetracyclic ergoline ring system, **16**.[5] The extended trans arylethylamine[6] substructure, contained within this rigid tetracyclic framework, has been viewed as the key element responsible for the interaction of these compounds

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