Table II. Standard Heats of Formation of Some α- and β-Substituted Naphthalene Derivatives (gas, 298 K)

compd	$\Delta H_f°$, kcal mol^{-1}
1-methylnaphthalene[a]	27.93
2-methylnaphthalene[a]	27.75
1-(trichloromethyl)naphthalene[b]	10.90
2-(trichloromethyl)naphthalene[b]	6.15

[a] From ref 8. [b] From molecular mechanics calculations (this work).

vation shown by the reaction of **2**. In our opinion, however, another effect arising from the different steric hindrance of the two leaving groups is much more effective. In fact, groups bonded at position 4 of the quinazoline are subjected to a peri interaction with the hydrogen at position 5 as observed in naphthalene derivatives. This destabilizing interaction, effective in the initial state, should decrease in the transition state, as the leaving group is going out of the plane of the ring. This steric effect, which lowers the enthalpy of activation, should be much more important for the bulkier trichloromethyl group than for the chlorine atom.

In order to validate this hypothesis, we tried to evaluate the amount of the peri interaction of the CCl_3 and Cl groups by looking at the standard heats of formation (gas phase) of 1-substituted and 2-substituted naphthalenes, using the latter as a model compounds. Since the standard heats of formation for the (trichloromethyl)naphthalenes are not reported, we recurred to molecular mechanics calculations.[7] The standard heats of formation for α- and β-chloronaphthalene reported in literature[8] are not comparable since they refer to different physical states. Unfortunately, the MMP2 program is not parametrized for calculations on aromatic chloro derivatives. Since the heats of formation of the corresponding methylnaphthalenes are available[8] and considering that the methyl group has a lower steric hindrance than chlorine,[9] they can be used as an alternative to evaluate an upper limit for the amount of peri interaction of a chlorine atom. All these values are collected in Table II. It is evident that the peri interaction is practically negligible for the methyl group ($\Delta\Delta H_f° = 0.2$ kcal mol^{-1}) whereas it is significant for the trichloromethyl group ($\Delta\Delta H_f° = 4.7$ kcal mol^{-1}). The result of this comparison strengthens our hypothesis that the lower enthalpy of activation shown by the reaction of **1** may be due to a peri destabilizing effect.

The differences in the activation entropies are, in our opinion, more difficult to rationalize since solvation effects may play a significant role in determining these differences.

Experimental Section

Melting points are uncorrected. ^{1}H NMR measurements were obtained with a Bruker WP 80 SY instrument. Mass spectra were obtained with a Kratos MS 80 spectrometer. GLC analyses were carried out on a 5830A Hewlett-Packard instrument with a flame-ionization detector and an OV-101 column (5% on Chromosorb WHP 100-120).

TLC analyses were performed on Merck 60 F_{254} silica gel plates. Column chromatography separations were carried out on Merck 60 silica gel (70-230 mesh). The kinetic measurements were carried out spectrophotometrically, at different temperatures, in the thermostated cell compartment of a Cary 219 instrument. An excess of tetrabutylammonium hydroxide was present, so that the reactions occurred under pseudo-first-order conditions. The kinetics were followed at 308 nm, a wavelength corresponding to an absorbance maximum of the conjugated base of **3**. The second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the corresponding nucleophile concentrations. The activation parameters were obtained by using the Eyring equation.[10]

4-(Trichloromethyl)quinazoline (1) was prepared as previously described.[4]

4-Chloroquinazoline (2) was prepared from 4-hydroxyquinazoline according to a reported procedure.[11]

Reaction of 1 with Tetrabutylammonium Hydroxide. Tetrabutylammonium hydroxide (16 mL of 1.5 M aqueous solution, 24 mmol) and 3 mL of water were added at room temperature to a solution of **1** (0.376 g, 1.52 mmol) in 12.4 mL of MeCN. After about 5 min, the reaction was complete. TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of one product only. The solution was neutralized with aqueous HCl, partially evaporated, and then continuously extracted with ethyl ether for 24 h. The ether solution was dried (Na_2SO_4). Removal of the solvent left a white solid (0.175 g) that was identified as 4-hydroxyquinazoline[11] (yield 79%).

Reaction of 2 with Tetrabutylammonium Hydroxide. Tetrabutylammonium hydroxide (16 mL of 1.5 M aqueous solution, 24 mmol) and 3 mL of water were added at room temperature to a solution of **2** (0.25 g, 1.52 mmol) in 12.4 mL of MeCN. After about 5 min, the reaction was complete. TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of two compounds that, after neutralization with aqueous HCl and extraction with ethyl ether, were separated by column chromatography (silica gel, 4:1 benzene/ethyl acetate and ethyl acetate). The minor product was eluted first (25 mg) [mp (CCl_4) 127-128 °C; ^{1}H NMR (CD_3COCD_3) δ 7.2-7.8 (m, 4 H, H6-H8 and CH), 8.30 (two multiplets, 1 H, H-5), 8.55 (s, 1 H, H-2), 9.35 (s, 1 H, NH); IR (Nujol) 2220 cm^{-1} (-CN stretching); mass spectrum ($(M + 1)^+$), m/e 170] and was identified as 4-(cyanomethyl)quinazoline (yield 9.7%). The main product was then eluted (170 mg) and identified as 4-hydroxyquinazoline[11] (yield 77%).

Determination of the Ratios of 3/4 for the Reaction of 2. The reaction was carried out, as reported above, at the same temperature of the kinetic runs (see Table I). After extraction with ethyl ether, the ratio of **3**/**4** was obtained by GCL analysis.

Acknowledgment. We thank Dr. Felice Grandinetti for his assistance in the molecular mechanics calculations.

Registry No. **1**, 99356-81-7; **2**, 5190-68-1; **4**, 112270-68-5; 1-(trichloromethyl)naphthalene, 37827-78-4; 2-(trichloromethyl)-naphthalene, 37827-80-8.

(7) (a) Calculations were performed by using the Allinger MMP2 molecular mechanics program.[7b] (b) Allinger, N. L.; Flanagan, H. L. *J. Comput. Chem.* **1983**, *4*, 399.

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Reductive Amination of Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione

Alan P. Marchand,* Paritosh R. Dave, N. Satyanarayana, and Benny E. Arney, Jr.

Department of Chemistry, North Texas State University, Box 5068, Denton, Texas 76203-5068

Received August 27, 1987

Sodium cyanoborohydride is a highly selective reducing agent which is stable to pH 3 in aqueous acidic solution. Its ability to preferentially reduce iminium ions in the presence of ketone or aldehyde carbonyl groups renders it suitable for use as a reagent in the reductive amination

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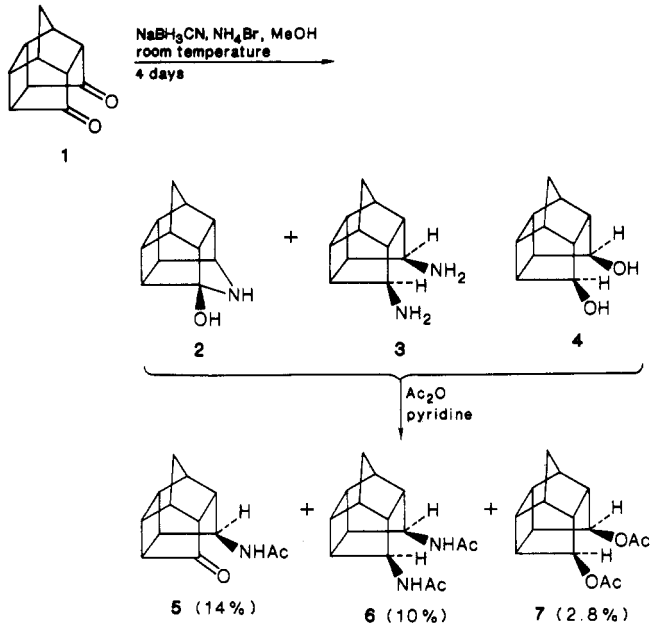
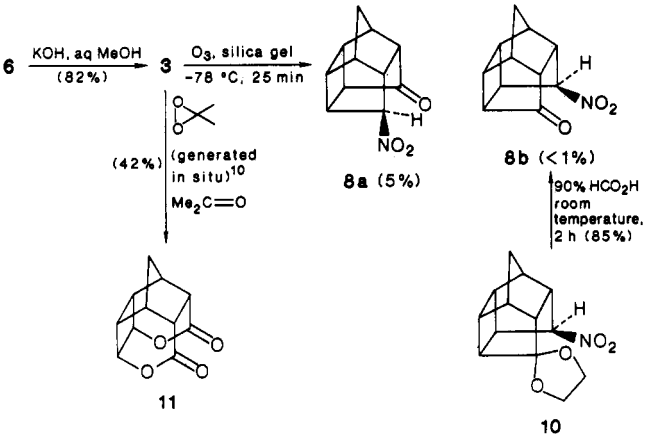
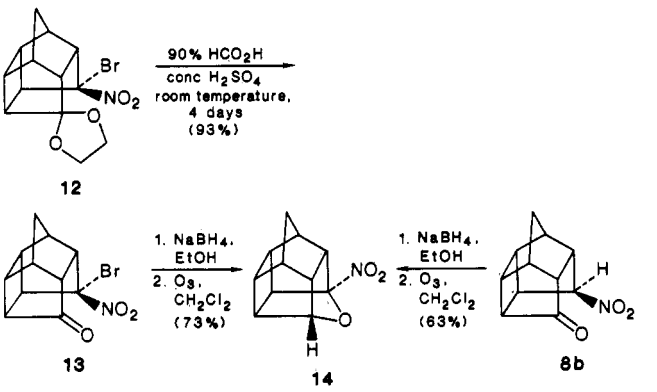
Scheme I



Scheme II



Scheme III



of aldehydes and ketones.[1,2] As part of an ongoing program that is concerned with the synthesis and chemistry of new, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes,[3] we have investigated the reductive amination of the title compound (**1**)[4] by using sodium cyanoborohydride in the presence of ammonium bromide.[2c]

In our hands, the reaction of **1** with sodium cyanoborohydride in the presence of ammonium bromide at pH 7.5–8.0 afforded a mixture of three products (**2**–**4**, Scheme I). One product, **2**, could be isolated in pure form via careful fractional crystallization of the product mixture (see Experimental Section). However, the remaining mixture of cage diamine **3** and cage diol **4** proved to be intractable.

Further separation was carried out on the material obtained after the crude reaction product had been acetylated via reaction with acetic anhydride–pyridine. Careful fractional recrystallization of the acetylated product mixture afforded pure *endo*-8,*exo*-11-diacetamidopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**6**, 10%). Analysis of the proton and carbon-13 NMR spectra of **6** revealed that it contains no symmetry element. Hence, of the three possible cage diamide stereoisomers (endo-8,endo-11, exo-8,exo-11, and endo-8,exo-11), only the endo-8,exo-11 isomer lacks a twofold symmetry element and, hence, must correspond to **6**.

Further purification of the acetylated product mixture via careful column chromatography afforded *endo*-11-acetamidopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**5**, 14%) and *endo*-8,*exo*-11-diacetoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**7**, 2.8%). Stereochemical assignments in **5** and in **7** are based upon analysis of their proton and carbon-13 NMR spectra, respectively.

There is considerable current interest in the synthesis and chemistry of energetic polynitropolycyclic "cage" compounds.[5] Accordingly, several potential methods have been investigated in efforts to oxidize the amino functionalities in **3** to NO_2 groups. Pure **3** could be obtained in 82% yield simply via base-promoted hydrolysis of **6**. Low-temperature ozonolysis of **3** impregnated on dry silica gel[6] afforded a mixture of isomeric cage mononitro ketones **8a** and **8b** in low yield (5% and ca. 1%, respectively; see Scheme II). Interestingly, the H-11 protons in **8a** and in **8b** absorbed at δ 4.56 and 4.65, respectively. Whereas the former resonance was a singlet, the resonance at δ 4.65 appeared as a triplet (coupled to the H-1 and H-10 protons in **8b**). The multiplicity of each H-11 signal reflects the dihedral angle dependence of vicinal coupling[7] to its respective neighboring protons. Proton NMR spectra obtained in our laboratory for other 8-substituted and 8,11-disubstituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes generally display triplet splitting for exo-8,11 protons and little or no fine structure for endo-8,11 protons.[8] On this basis, we tentatively assign the singlet at δ 4.56 to an endo-11 proton and the triplet at δ 4.65 to an exo-11

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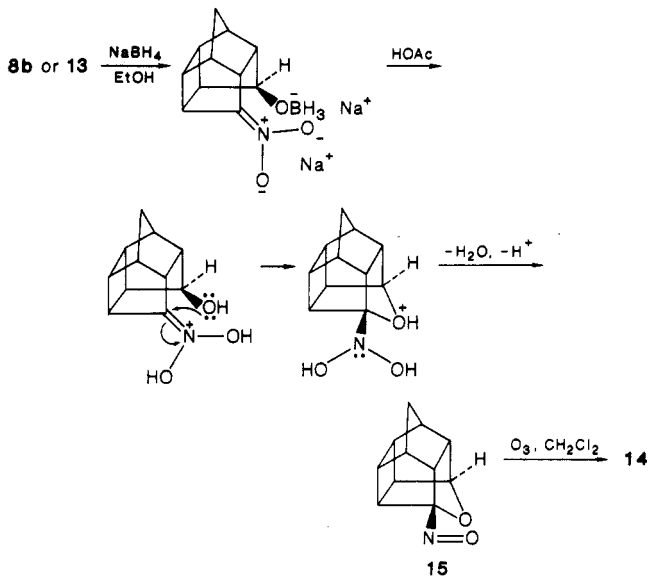
Scheme IV



proton, thereby permitting the structure assignments for **8a** and for **8b** to be made as shown in Scheme II. Independent confirmation of the structure of **8b** was obtained via hydrolysis of the corresponding ketal **10**, whose synthesis has been reported previously.[9] The spectral properties of the product of hydrolysis of **10** were in agreement with the corresponding spectra obtained in this study for **8b**.

Oxidation of **3** with dimethyldioxirane (generated in situ from the reaction of acetone with oxone)[10] was attempted. To our surprise, this reaction afforded a single cage dilactone, **11**, in 42% yield. The infrared, proton NMR, and carbon-13 NMR spectra of **11** thereby produced were in agreement with those reported previously for this compound.[11]

In other work, we recently reported the synthesis of **12** (Scheme III).[9] Hydrolysis of the ketal group in **12** afforded the corresponding ketone **13**. Compounds **8b** and **13** each could be reduced via reaction with sodium borohydride in ethanol. In each case, when the reaction was quenched via addition of acetic acid, an intense blue color developed. This blue color, indicative of the presence of an intermediate nitroso compound, could be discharged via ozonolysis of a methylene chloride solution of the reduction product. Workup of the reaction mixture in each case afforded 4-oxa-3-nitrohexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (**14**, Scheme III).

A mechanism which rationalizes the formation of a nitroso-containing compound, **15**, in the sodium borohydride reduction of either **8b** or **13** is suggested in Scheme IV. Sodium borohydride functions in three different ways in these reactions: (i) It reduces the ketone groups in **8b** and in **13** stereospecifically from the exo face of the cage system, thereby affording the corresponding endo alcohol in each case. (ii) It hydrogenolyzes the carbon–bromine bond in **13**. (iii) Finally, sodium borohydride then functions as a base to generate an intermediate nitronate anion. Subsequent addition of acetic acid quenches the reaction by forming a nitronic acid which then is trapped by the neighboring endo hydroxyl group that was produced via sodium borohydride reduction of the ketone carbonyl functionality in **8b** or **13**. This unusual intramolecular trapping of a nitronic acid by the endo OH group results in the formation of the corresponding cage nitroso ether **15**.

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Experimental Section

Melting points are uncorrected.

Reaction of 1 with Sodium Cyanoborohydride–Ammonium Bromide.[2c] To a solution of diketone **1** (14.12 g, 0.081 mol) in dry methanol (300 mL) was added ammonium bromide (31.79 g, 0.325 mol). The resulting mixture was stirred at room temperature for 3 h, at which time sodium cyanoborohydride (20.4 g, 0.33 mol) was added. The reaction mixture was stirred at room temperature for 4 days and then cooled and acidified to ca. pH 3 via addition of concentrated aqueous hydrochloric acid solution. The resulting mixture was then concentrated in vacuo. Water (200 mL) was added to the residue, and the aqueous suspension was extracted with methylene chloride (3 × 50 mL). Workup of the combined organic extracts afforded unreacted **1** (3.0 g, 0.02 mol). The aqueous layer was cooled and then rendered basic to ca. pH 11 via addition of crushed potassium hydroxide pellets. Sodium chloride was then added to the aqueous layer, and the resulting mixture was extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. Thin-layer chromatographic analysis of the residue thereby obtained (6 g) indicated that this material was a mixture that contained at least three major components. This mixture was triturated with ether to remove colored impurities; colorless material (4.69 g) was thereby obtained.

This product mixture was acetylated via reaction with excess acetic anhydride–pyridine reagent. Thus, a mixture of the colorless product (4.69 g) in pyridine (40 mL) was cooled via application of an external ice bath. To the cooled mixture was added acetic anhydride (8.66 g, 0.090 mol) dropwise with stirring. After all of the acetic anhydride had been added, the ice bath was removed, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then extracted with methylene chloride, and the organic layer was washed successively with 5% aqueous hydrochloric acid solution (50 mL), 10% aqueous sodium bicarbonate solution (75 mL), and water (100 mL). The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue (2.2 g) was recrystallized from acetone, thereby affording diacetamide **6** (2.0 g, 10%) as a colorless microcrystalline solid: mp 155–157 °C; IR (KBr) 3315 (s), 1720 (vs), 1640 (vs), 1545 cm^{-1} (vs); ^1H NMR ($CDCl_3$) δ 1.10 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.66 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.96 (s, 3 H), 2.16 (s, 3 H), 2.36 (m, 4 H), 2.64 (m, 4 H), 4.06 (m, 1 H), 4.80 (m, 1 H), 7.32 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.86 (q), 24.12 (q), 34.07 (t), 35.81 (d), 37.36 (d, 39.12 (d), 40.65 (d), 42.40 (d), 43.16 (d), 44.21 (d), 44.98 (d), 48.39 (d), 72.92 (d), 168.96 (s), 169.04 (s); mass spectrum (70 eV), *m/e* (relative intensity) 260 (molecular ion, 3.1), 136 (88.3), 94 (69.4), 43 (100).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74. Found: C, 69.15; H, 7.52.

The remaining mother liquor was concentrated in vacuo, and the residue was purified via column chromatography (silica gel stationary phase, 20% ethyl acetate–ligroin mixed solvent as eluent). Workup of the chromatographic fractions thereby obtained afforded diacetate **7** (0.60 g, 2.8%) as a viscous oil: bp 160 °C (1 mm); IR (neat) 1730 (vs), 1235 (vs), 1050 (s); ^1H NMR ($CDCl_3$) δ 1.20 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.60 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.88 (s, 3 H), 1.99 (s, 3 H), 2.19–2.75 (m, 8 H), 4.61 (m, 1 H), 5.52 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.46 (2 C, q), 35.00 (t), 36.44 (d), 38.97 (d), 39.54 (d), 40.96 (d), 42.97 (d), 44.31 (d), 45.13 (d), 46.36 (d), 74.05 (d), 77.20 (d), 170.41 (2 C, s); mass spectrum (70 eV), *m/e* (relative intensity) 262 (molecular ion, 0.2), 160 (63.2), 66 (39.5), 43 (100).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.17; H, 6.85. Found: C, 68.66; H, 7.11.

Further elution of the chromatography column with 30% ethyl acetate–ligroin mixed solvent afforded a mixture of two products, believed to be **5** and **6**. A final fraction was obtained by further elution of the column with 50% ethyl acetate–hexane mixed

solvent. Pure **5** (2.5 g, 14%) was thereby obtained as a viscous oil: bp 170 °C (1 mm); IR (neat) 3275 (vs), 1730 (vs), 1535 (vs); ^{1}H NMR ($CDCl_3$) δ 1.52 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.90 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.90 (s, 3 H), 2.32–3.32 (m, 8 H), 3.84 (m, 1 H), 6.18 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.90 (q), 36.36 (d), 37.72 (t), 41.36 (d), 41.56 (2 C, d), 42.47 (d), 45.72 (d), 50.40 (d), 51.70 (d), 52.03 (d), 170.45 (s), 220.26 (s); mass spectrum (70 eV), *m/e* (relative intensity) 217 (molecular ion, 48.1), 174 (100.0), 158 (53.4), 130 (47.2), 91 (44.0), 43 (88.2).

Anal. Calcd for $C_{13}H_{15}NO_2$: M_r 217.1103. Found (high-resolution mass spectrometry): M_r 217.1107.

3-Hydroxy-4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane (2). The crude product obtained from the reaction of **1** with sodium cyanoborohydride–ammonium bromide after basic workup (vide supra) was recrystallized from ethyl acetate. Careful, repeated fractional recrystallization from ethyl acetate eventually resulted in the isolation of pure **2** (2.0 g, 14%) as a colorless microcrystalline solid: mp 225–226 °C; IR (KBr) 3285 (m), 3075 (s), 1460 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.48 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.86 (*AB*, J_{AB} = 10.8 Hz, 1 H), 2.24–2.96 (m, 8 H), 3.58 (t, *J* = 5.0 Hz, 1 H), 4.92 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 42.07 (t), 42.10 (d), 42.49 (d), 43.50 (d), 44.95 (d), 46.09 (d), 46.20 (d), 54.36 (d), 55.56 (d), 60.99 (d), 114.78 (s); mass spectrum (70 eV), *m/e* (relative intensity) 175 (molecular ion, 39.7), 96 (100).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.26; H, 7.44.

Base-Promoted Hydrolysis of 6. A mixture of diacetamide **6** (1.0 g, 3.8 mmol) and 25% aqueous potassium hydroxide solution (containing 1.72 g, 30.7 mmol of KOH) in 95% aqueous ethanol (8.5 mL) was refluxed for 6 h. The reaction mixture was then cooled to room temperature. Water (60 mL) was added, and the resulting mixture was extracted with methylene chloride (3 × 30 mL). The combined organic extracts were washed with water (40 mL). The organic layer was then dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate, thereby affording the corresponding cage diamine (**3**, 0.56 g, 82%) as a colorless microcrystalline solid: mp 210–211 °C; IR (KBr) 3335 (s), 3275 (m), 1600 (m), 1525 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.12 (*AB*, J_{AB} = 10.5 Hz, 1 H), 1.66 (*AB*, J_{AB} = 10.5 Hz, 1 H), 2.34–2.41 (m, 4 H), 2.62–2.68 (m, 4 H), 3.20 (dd, J_1 = 2.9 Hz, J_2 = 3.1 Hz, 1 H), 3.72 (dd, J_1 = 2.9 Hz, J_2 = 3.1 Hz, 1 H), 4.30 (br s, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.22 (d), 39.38 (s), 39.49 (s), 39.96 (s), 41.58 (s), 43.06 (s), 45.63 (s), 46.09 (s), 46.34 (s), 51.91 (s), 72.07 (s); mass spectrum (70 eV), *m/e* (relative intensity) (no molecular ion), 159.1056 [$C_{11}H_{13}N$, $(M - NH_3)^+$, 18.1].

Ozonolysis of 3.[6] To a solution of cage diamine **3** (1.0 g, 5.7 mmol) in dry methylene chloride (75 mL) was added silica gel (50 g) that had been activated by prior prolonged heating at 850 °C followed by cooling to ambient temperature under nitrogen. The resulting mixture was concentrated in vacuo, and the dry residue was cooled to −78 °C via application of an external dry ice–acetone bath. Ozone was passed over the dry residue for 25 min. The cold bath then was removed, and the reaction mixture was allowed to warm slowly to ambient temperature. The reaction mixture was extracted with methylene chloride (150 mL), and the extract was concentrated in vacuo. The residue was purified via column chromatography (silica gel stationary phase, 10% ethyl acetate–ligroin mixed solvent as eluent). The forerun thereby collected was discarded, and the chromatography column was further eluted with with 20% ethyl acetate–ligroin mixed solvent. Pure **8a** (59 mg, 5%) was thereby obtained as a colorless microcrystalline solid: mp 136–137 °C; IR (KBr) 1715 (vs), 1535 (vs), 1375 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.72 (*AB*, J_{AB} = 10.8 Hz, 1 H), 1.95 (*AB*, J_{AB} = 10.8 Hz, 1 H), 2.48–2.92 (m, 6 H), 3.25–2.45 (m, 2 H), 4.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 36.80 (d), 37.47 (t), 41.01 (d), 42.11 (d), 42.98 (d), 43.56 (d), 46.55 (d), 51.13 (d), 52.28 (d), 87.06 (d), 214.90 (s); mass spectrum (70 eV), *m/e* (relative intensity) 205 (molecular ion, 14.1), 159 (29.8), 131 (100).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.32; H, 5.79.

Continued elution of the chromatography column with 50% ethyl acetate–ligroin mixed solvent afforded pure **8b** (10 mg, 1%) as a colorless microcrystalline solid: mp 200–201 °C; IR (KBr) 1720 (s), 1524 (s), 1370 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.55 (*AB*, J_{AB} = 12 Hz, 1 H), 1.95 (*AB*, J_{AB} = 12 Hz, 1 H), 2.35–3.5 (m, 8 H), 4.65 (t, *J* = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.09 (d), 37.84 (t), 38.18 (d), 42.11 (d), 42.14 (d), 42.27 (d), 45.70 (d), 48.76 (d), 50.80 (d), 83.72 (d), 213.66 (s); mass spectrum (70 eV), *m/e* (relative intensity) 205 (molecular ion, 8.3), 159 (22.0), 131 (47.0), 91 (100).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.62; H, 5.42.

Hydrolysis of 10. A suspension of **10**[9] (100 mg, 40.0 mmol) in 90% formic acid (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in methylene chloride (25 mL). The organic solution was washed sequentially with 10% aqueous sodium bicarbonate solution (3 × 25 mL) and with water (25 mL), dried (anhydrous magnesium sulfate), and filtered, and the filtrate was concentrated in vacuo. The solid residue was recrystallized from methylene chloride–hexane mixed solvent. Pure **8b** (75 mg, 85%), mp 200–201 °C, was thereby produced; this compound proved to be identical in all respects with the corresponding material that had been prepared via ozonolysis of **3** (vide supra).

Oxidation of 3 with Dimethyldioxirane. Dimethyldioxirane was generated in situ by using the procedure described by Murray and Jeyaraman.[10] Thus, a solution of oxone (69.13 g, 112.4 mmol) in water (380 mL) was added dropwise with stirring to a mixture of diamine **3** (0.93 g, 5.3 mmol), acetone (25 mL, 34 mmol), and phosphate buffer (KH_2PO_4–Na_2HPO_4, pH 7.6). A 1 N solution of aqueous potassium hydroxide was added simultaneously at such a rate that the pH of the reaction mixture was maintained continuously in the range 7.5–8.0. The reaction mixture was stirred for 2 h after the addition had been completed. The resulting mixture was extracted with methylene chloride (3 × 75 mL). The combined organic extracts were washed with water (2 × 50 mL), then dried (anhydrous magnesium sulfate), and filtered, and the filtrate was concentrated in vacuo. The residue was recrystallized from acetone, thereby affording pure **11** (0.45 g, 42%) as a colorless microcrystalline solid, mp 347–350 °C (lit.[11] mp 348–352 °C). The infrared, ^{1}H NMR, and ^{13}C NMR spectra of this material agreed with spectral data reported for **11** by Surapaneni and Gilardi.[11]

Acid-Promoted Hydrolysis of 12. A suspension of **12**[9] (15.0 g, 45.7 mmol) in 90% formic acid (200 mL) that contained concentrated sulfuric acid (2 mL) was stirred at room temperature for 4 days. The progress of the hydrolysis was monitored by TLC. The reaction mixture was diluted with ice–water (600 mL) and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed sequentially with 10% aqueous sodium bicarbonate solution (100 mL) and with water (3 × 100 mL). The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo to afford a tan solid. This material was recrystallized from ether–hexane mixed solvent, thereby affording pure **13** (12.1 g, 93%) as a colorless microcrystalline solid: mp 183–184 °C; IR (KBr) 1733 (vs), 1546 (vs), 1355 (s), 1336 (s), 1090 (s), 791 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.64 (*AB*, J_{AB} = 11.7 Hz, 1 H), 1.98 (*AB*, J_{AB} = 11.7 Hz, 1 H), 2.59 (m, 1 H), 2.77 (m, 1 H), 2.85 (m, 1 H), 2.94 (m, 1 H), 3.26 (m, 1 H), 3.35 (m, 1 H), 3.39 (m, 1 H), 3.54 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 35.7 (d), 36.9 (t), 42.4 (d), 43.7 (d), 44.0 (d), 46.1 (d), 47.9 (d), 52.6 (d), 56.7 (d), 95.2 (s), 210.5 (s).

Anal. Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55. Found: C, 46.53; H, 3.49.

Sodium Borohydride Reduction of 8b. A solution of **8b** (750 mg, 3.65 mmol) in absolute ethanol (50 mL) was cooled to 0 °C via application of an external ice bath. A solution of sodium borohydride (280 mg, 7.40 mmol) in 70% aqueous ethanol (20 mL) was then added with stirring. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched via gradual addition of glacial acetic acid (15 mL), which resulted in the formation of an intense blue color. The reaction mixture was concentrated in vacuo, and the residual blue solid was partitioned between water (100 mL) and methylene chloride (100 mL). The organic layer was washed with water (2 × 50 mL), dried (anhydrous magnesium sulfate), and filtered. The clear blue filtrate was cooled via application of an external ice bath. Ozone was passed through the cooled solution until the solution became colorless. The reaction was judged to be complete when the blue color failed to reappear after the flow of ozone had been stopped. The reaction mixture was concentrated in vacuo, and the residue was purified by recrys-

tallization from absolute ethanol. Pure **14** (466 mg, 63%) was thereby obtained as colorless platelets: mp 120.0–120.5 °C; IR (KBr) 1549 (vs), 1382 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.64 (*AB*, J_{AB} = 10.8 Hz, 1 H), 2.01 (*AB*, J_{AB} = 10.8 Hz, 1 H), 2.8–3.3 (m, 8 H), 4.97 (t, *J* = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 41.3 (d), 42.8 (d), 43.3 (t), 44.6 (d), 44.9 (2 C, d), 49.6 (d), 54.7 (d), 59.1 (d), 84.7 (d), 121.2 (s); mass spectrum, *m/e* (relative intensity) (no molecular ion), 159 (100).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.30; H, 5.47.

Sodium Borohydride Reduction of 13. A suspension of **13** (3.00 g, 10.6 mmol) in 95% aqueous ethanol (300 mL) was cooled to 0 °C via application of an external ice–salt bath. To the vigorously stirred suspension was added a solution of sodium borohydride (2.0 g, 52 mmol) in 60% aqueous ethanol (50 mL). The resulting mixture was stirred for 5 min, at which time the external cold bath was removed. The reaction mixture was then stirred at room temperature for 2 h. The reaction was quenched via gradual addition of glacial acetic acid (15 mL), which resulted in the production of an intense blue color. Workup of the reaction mixture followed by ozonolysis as described above for the corresponding reaction of **8b** afforded pure **14** (1.55 g, 73%). The material thereby obtained was identical in all respects with that obtained previously via sodium borohydride reduction of **8b** followed by ozonolysis (vide supra).

Acknowledgment. We gratefully acknowledge the assistance of Dr. Sanjay Basak with the characterization of **14**. We thank the U.S. Army Armament Research and Development Center, Picatinny Arsenal, NJ (Contract DAAA21-86-C-0091), the Air Force Office of Scientific Research (Grant AFOSR-84-0085), the Robert A. Welch Foundation (Grant B-963), and the North Texas State University Faculty Research Committee for financial support of this study.

Registry No. **1**, 2958-72-7; **2**, 34052-35-2; **3**, 112482-28-7; **4**, 56143-85-2; **5**, 112482-29-8; **6**, 112482-30-1; **7**, 112571-23-0; **8a**, 112482-31-2; **8b**, 112571-24-1; **10**, 111933-65-4; **11**, 80707-70-6; **12**, 111933-64-3; **13**, 112482-32-3; **14**, 112482-33-4.

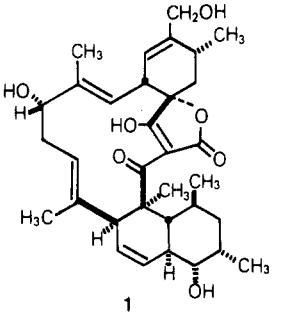
Preparation of the Chiral Hydronaphthalene Fragment of Kijanolide and Tetronolide

Kei Takeda, Tatsuya Kobayashi, Ko-ichi Saito, and Eiichi Yoshii*

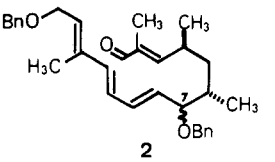
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Received September 10, 1987

In the course of their synthetic study on kijanolide (**1**)[1] and the related natural products tetronolide[2] and chlorothricolide,[3] Marshall and his co-workers have introduced an efficient method for the construction of the *trans*-octalin fragments that utilizes intramolecular Diels–Alder cyclization of conjugated aldehydes which proceeds in a highly endo-selective manner.[4] Of particular interest is the result obtained with a C(7) epimeric mixture of racemic tetraenal **2**.[5] Treatment of **2** with Me_2AlCl at low temperature afforded a 1:1 mixture of the carbinyl epimers **3a,b** in high yield, and it was suggested that a diastereomerically homogeneous sample of **2** with the correct configuration (7*S*) would produce compound **3b** exclusively. This paper records an asymmetric synthesis of **13** and **15**, optically active analogous of **3b** which have two different O-protecting groups, according to the method of Marshall. This result, together with our previous achievements in the syntheses of the spirotetronic acid fragments[6] and a macrocyclic model,[7] would make a great advance in the total synthesis of **1** and tetronolide.



1



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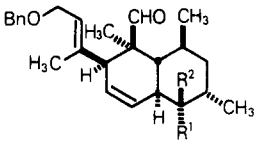

3a R^1 = H, R^2 = OBn
3b R^1 = OBn, R^2 = H

To establish the three chiral centers in the Diels–Alder precursors **11** and **12**, we employed the trideoxy sugar **4**[8] as the starting material. Desilylation of compound **4** followed by Swern oxidation of the resulting alcohol **5** gave aldehyde **6**. Horner–Emmons reaction of **6** with the phosphonate **8**, which was prepared from 4-(benzyloxy)-2-methyl-2(*E*)-butenal (**7**)[5] as outlined in Scheme I, afforded the *E,E,E* triene **9** as the only isolable diastereomer in 55% overall yield from **4**. Use of more readily available methyl 6-(diethylphosphono)-3-methyl-2(*E*),4(*E*)-hexadienoate[9] in the condensation with **6** resulted in formation of an inseparable mixture of the terminal double bond isomers. The functionalized pyranoside **9** was then treated with aqueous acetic acid in THF to give a sensitive lactol, which was immediately allowed to react with $Ph_3P{=}C(Me)COOEt$ in refluxing acetonitrile to give tetraenoate **10** (46% for the two steps). This compound was transformed into MOM- and TBS-protected tetraenals (**11** and **12**), respectively, by conventional three-step procedures, O protection followed by reduction (i-Bu_2AlH)/oxidation (pyridinium chlorochromate (PCC)).

Treatment of **11** with 1.0 equiv of Me_2AlCl in CH_2Cl_2 at −80 to −40 °C produced a mixture of cycloadducts, from which the desired octalin (−)-**13** and its diastereomer **14** were isolated by silica gel MPLC in 65% and 22% yields, respectively. The structures of these endo-mode adducts (trans ring juncture) were assigned by high-field ^1H NMR

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