addition of 25 mL of diethyl ether, a white precipitate formed. The powdery solid was filtered, washed with ether, and air dried to yield 3.63 g (87%): mp 178–183 °C; ^{1}H NMR ($CDCl_3$)[7] δ 3.82 (3 H, s, 3-OCH_3), 3.50–3.55 (3 H, m, 6-OCH_3), 2.43 (3 H, s, N-CH_3), 4.66 (1 H, s, 5α proton), 5.42 to 5.95 (2 H, m, vinylic protons).

7α-(Aminomethyl)-6,14-*endo* ethenotetrahydrothebaine Benzoic Acid Salt (4). A solution of **3** (500 mg, 1.31 mmol) in THF (6 mL, distilled from LAH) was added dropwise to a mixture of LAH (155 mg, 4.08 mmol) in THF (6 mL). The solution was refluxed for 20 h, then carefully quenched in 30 mL of 1 M H_2SO_4. The solution was made basic with 10 M NaOH and extracted 3 times with $CHCl_3$. The organic layers were combined, washed several times with 10% NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a viscous, yellow tinted oil. The oil was dissolved in ether (25 mL) and benzoic acid (0.32 g, 2.6 mmol), as a solution in 25 mL of ether, was added. The resultant white precipitate was filtered, washed with ether, and air dried to yield 493 mg of the benzoic acid salt (77%). The salt was recrystallized from methanol/ether: mp 208–214 °C; TLC (2-propyl alcohol/concentrated NH_4OH, 10:1), one product, R_f 0.42; ^{1}H NMR (D_2O)[7] δ 3.82 (3 H, s, 3-OCH_3), 3.56 (3 H, s, 6-OCH_3), 2.39 (3 H, s, N-CH_3); ^{1}H NMR ($CDCl_3$) free base, δ 4.84 (1 H, s, 5α proton), 5.60 and 5.74 (2 H, ABq, J = 8 Hz, vinylic protons). Anal. Calcd for $C_{29}H_{34}N_2O_5$: C, 70.99; H, 6.99; N, 5.71. Found: C, 70.80; H, 6.88; N, 5.51.

6-Desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (5). A solution of **3** (500 mg, 1.31 mmol) in THF (6 mL, distilled from LAH) and CCl_4 (0.5 mL, 5.2 mmol) was added dropwise to a mixture of LAH (740 mg, 19.5 mmol) in THF (6 mL). After the mixture was refluxed for 17 h, it was treated in the same manner as **4** to yield 334 mg of a white solid (74%). Recrystallization from ethanol gave colorless crystals: mp 216–218 °C; TLC (2-propyl alcohol/concentrated NH_4OH, 10:1), one product, R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 3.82 (3 H, s, 3-OCH_3), 2.37 (3 H, s, N-CH_3), 4.35 (1 H, s, 5α proton), 5.37 and 5.79 (2 H, ABq, J = 9 Hz, vinylic protons). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.91; H, 7.43; N, 7.91.

7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine Benzoic Acid Salt (6). A solution of the free base of **4** (751 mg, 2.04 mmol) in $CHCl_3$ (20 mL) was added to 1 M BBr_3 in $CHCl_3$ (20 mmol). The mixture was stirred at ambient temperature for 15 min, then quenched in 50 mL of ice cold dilute NH_4OH solution, and stirred at 0 °C for 30 min. The layers were separated, and the aqueous phase was extracted 3 times with 15-mL portions of $CHCl_3$. The $CHCl_3$ layers were combined, washed with 10% NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a light brown solid. The solid was dissolved in methanol (2 mL)/ether (20 mL), and a solution of benzoic acid (0.40 g, 3.3 mmol) in 20 mL of ether was added. The resultant precipitate was filtered, washed with ether, and air dried to yield 520 mg of a light brown solid. The salt was recrystallized from methanol–ether: mp 220–224 °C; ^{1}H NMR (D_2O)[7] δ 3.61 (3 H, s, 6-OCH_3), 2.41 (3 H, s, N-CH_3); 5.60 and 5.75 (2 H, ABq, J = 9 Hz, vinylic protons); ^{1}H NMR ($CDCl_3$) free base, δ 3.57 (3 H, s, 6-OCH_3), 2.36 (3 H, s, N-CH_3), 4.58 (1 H, s, 5α proton), 5.43 and 5.70 (2 H, ABq, J = 9 Hz, vinylic protons). Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.56; H, 6.77; N, 5.88. Found: C, 70.38; H, 6.89; N, 5.72.

6-Desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine (7). A solution of **5** (550 mg, 1.55 mmol) in $CHCl_3$ (2 mL) was added to 1 M BBr_3 in $CHCl_3$ (31 mmol). The mixture was stirred at ambient temperature for 2 h, then quenched in 20 mL of ice cold, dilute NH_4OH solution, and stirred at 0 °C for 15 min. The layers were separated, and the organic phase was extracted with 1 M NaOH (20 mL). The aqueous layers were combined and concentrated to 20 mL. The pH of the concentrate was adjusted to 9.9 with NaOH. The solution was saturated with NaCl and then extracted 5 times with 15-mL portions of $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 384 mg of a light brown solid (72%): ^{1}H NMR ($CDCl_3$) δ 2.35 (3 H, s, N-CH_3), 4.33 (1 H, s, 5α proton), 5.33 and 5.72 (2 H, ABq, J = 9 Hz, vinylic protons).

7α-(Hydroxymethyl)-6,14-*endo*-ethenotetrahydrothebaine (8).[10] A solution of **2** (500 mg, 1.36 mmol) in THF (6 mL) was added dropwise to a mixture of LAH (260 mg, 6.85 mmol) in THF (6 mL). The mixture was refluxed for 8.5 h and subjected to the standard workup to yield 403 mg of a colorless, viscous oil (80%): ^{1}H NMR ($CDCl_3$) δ 3.83 (3 H, s, 3-OCH_3), 3.71 (3 H, s, 6-OCH_3), 2.36 (3 H, s, N-CH_3), 4.57 (1 H, s, 5α proton), 5.49 and 5.91 (2 H, ABq, J = 9 Hz, vinylic protons).

6-Desmethyl-7α-(hydroxymethyl)-6,14-*endo*-ethenotetrahydrothebaine (9). A solution of **2** (500 mg, 1.36 mmol), CCl_4 (0.5 mL, 5.2 mmol), and 6 mL of THF was added dropwise to a mixture of LAH (775 mg, 20.4 mmol) in THF (6 mL). The mixture was refluxed for 8.5 h and subjected to the standard workup to yield a colorless, viscous oil which by TLC (dichloromethane/methanol, 20:1) showed two products: R_f 0.26 and 0.16. The two products were separated by chromatography on silica gel. The NMR of the faster moving product was identical with **8**, while the NMR of the less mobile product indicated demethylation at the 6 position: ^{1}H NMR ($CDCl_3$)[7] δ 3.83 (3 H, s, 3-OCH_3), 2.38 (3 H, s, N-CH_3), 4.35 (1 H, s, 5α proton), δ 5.40 and 5.70 (2 H, ABq, J = 10 Hz, vinylic protons).

7α-(((*p*-Toluenesulfonyl)oxy)methyl)-6,14-*endo*-ethenotetrahydrothebaine (10).[10] To a solution of compound **8** (1.07 g, 2.91 mmol) in pyridine (15 mL, dried over NaOH) at 0 °C was added *p*-toluenesulfonyl chloride (1.11 g, 5.82 mmol). After 96 h at 5 °C, the reaction mixture was added with stirring to 300 mL of ice water upon which a pink precipitate immediately formed. The solid was filtered, washed with 400 mL of water, and air dried to yield 1.47 g of a spongy, pink solid (96%). Recrystallization from ethanol gave pink tinted needles: mp 129–130 °C; NMR ($CDCl_3$)[7] δ 3.81 (3 H, s, 3-OCH_3), 3.48 (3 H, s, 6-OCH_3), 2.45 (3 H, s, Ts-CH_3), 2.36 (3 H, s, N-CH_3), 4.53 (1 H, s, 5α proton), 5.43 and 5.61 (2 H, ABq, J = 9 Hz, vinylic protons).

7α-Methyl-6,14-*endo*-ethenotetrahydrothebaine (11). Compound **10** (100 mg, 0.19 mmol) was added to LAH (75 mg, 2.0 mmol) in THF (5 mL, dried over 3-Å molecular sieves). The mixture was refluxed for 41 h and then subjected to the usual workup to yield 42 mg of a powdery brown solid (65%): ^{1}H NMR ($CDCl_3$)[7] δ 3.80 (3 H, s, 3-OCH_3), 3.49 (3 H, s, 6-OCH_3), 2.34 (3 H, s, N-CH_3), 0.79 (3 H, d, J = 7.2 Hz, 7α-methyl), 4.58 (1 H, s, 5α proton), 5.40 and 5.64 (2 H, ABq, J = 10 Hz, vinylic protons).

Acknowledgment. We thank Mallinckrodt, Inc., for their generous gift of thebaine. This work was supported by Grant DA-03319 from the National Institute on Drug Abuse and in part by a Faculty Research Grant for the California State University Foundation, Northridge.

(10) Intermediate previously reported by Bentley et al. (ref 5), but no details of synthesis or characterization were given.

Facile Stereoselective Reductions of Enediones and Cage Diketones Using $NaBH_4$–$CeCl_3$

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The use of sodium borohydride and of lithium aluminum hydride for the reduction of ketone and aldehyde carbonyl functionalities is a standard technique in synthetic organic chemistry.[1-3] Sodium borohydride is the more selective of the two reagents. Recently, Luche and co-workers have

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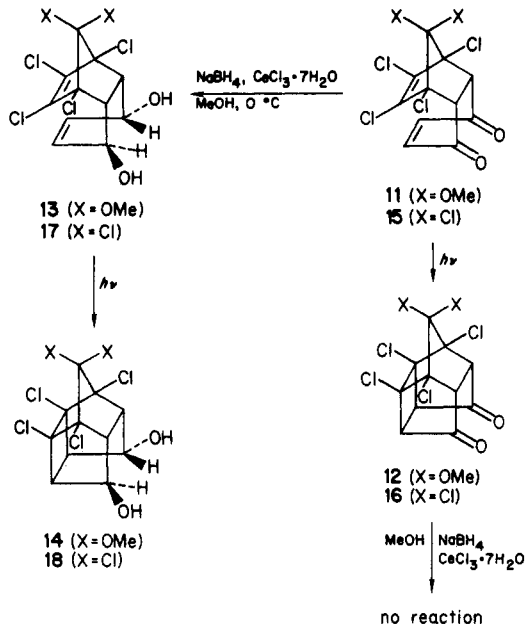
0022-3263/86/1951-1622$01.50/0

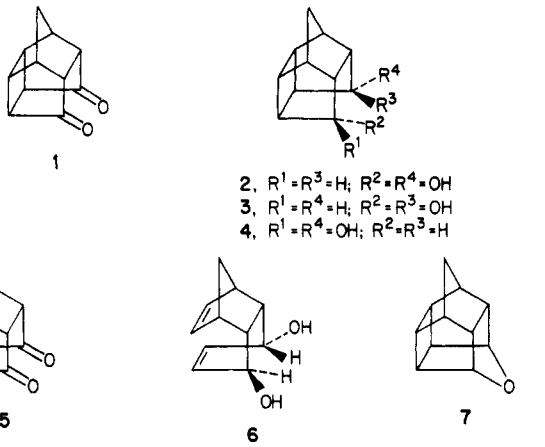
Scheme I



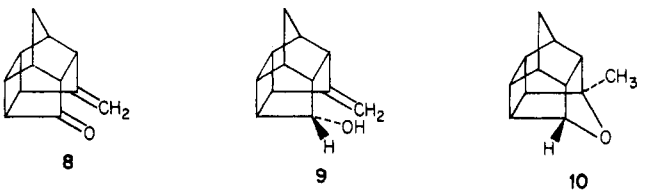
reported that alcohol solutions of sodium borohydride in combination with lanthanide halides are capable of selectively converting α,β-unsaturated ketones to allylic alcohols.[4] As part of a program designed to explore the synthesis and chemistry of functionalized pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes,[5-8] we have examined the $NaBH_4$–$CeCl_3$ reductions of some substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones, their corresponding tricyclic enedione precursors, and related compounds.

Cookson and co-workers have reported that sodium borohydride reduction of diketone **1** affords a mixture of two isomeric diols, **2** (endo,exo diol, mp 273–273.5 °C) and **3** (endo,endo diol, mp 276–276.5 °C).[9] In addition, the exo,exo diol **4** (mp 221–223 °C)[10] has been synthesized from the cyclopentadiene-*p*-benzoquinone endo-Diels–Alder cycloadduct, **5**, in two steps: (i) reduction of enedione **5** with diisobutylaluminum hydride to afford the corresponding diol **6** followed by (ii) photocyclization of **6** to afford **4**.

In our hands, reaction of **5** with $NaBH_4$–$CeCl_3$ in methanol at 0 °C[4] resulted in stereospecific reduction, thereby affording pure exo,exo diol **6**. Subsequent photocyclization of that diol afforded pure **4**. If we instead reduced cage diketone **1** under these conditions, the corresponding endo,endo diol **3** was formed stereospecifically. That **3** indeed possesses the endo,endo configuration was established by its ready dehydration to the corresponding cage ether **7**. Thus, an important feature of this study is our ability to produce stereospecifically either **3** or **4** from a common precursor, **5**, simply by reversing the order of the two-step synthetic sequence; (i.e., reduction of **5** followed by photocyclization affords **4**, whereas photocyclization of **5**[5] followed by reduction affords **3**).



As part of this study, we have examined the $NaBH_4$–$CeCl_3$ reduction of cage enone **8**. The reduction proceeded smoothly to afford the corresponding endo alcohol **9**. That the C–OH bond in **9** is indeed endo was established via its facile acid-catalyzed conversion into the corresponding cage ether **10**.



Interestingly, enediones **11** and **15** (Scheme I) were reduced smoothly and stereospecifically by $NaBH_4$–$CeCl_3$ to the corresponding exo,exo diols (**13** and **17**, respectively). The fact that both **13** and **17** possess the exo,exo configuration was demonstrated: (i) by the fact that each of their ^{13}C NMR spectra indicated the existence of a symmetry plane in each molecule and (ii) by the fact that intramolecular photocyclization of **13** and of **17** afforded the corresponding cage diols (**14** and **18**, respectively), neither of which could be dehydrated under conditions where the corresponding endo,endo cage diol **3** formed ether **7**.

In contrast to the behavior of **11** and **15**, the corresponding cage diketones (**12** and **16**, respectively, Scheme I) proved to be inert to $NaBH_4$–$CeCl_3$ even under forcing conditions (see Experimental Section).[11] It seems likely that the failure of **12** and of **16** to undergo reduction is a result of the steric effect of the nearby bridgehead C–Cl bonds (which effectively impede approach by the reagent to the exo faces of the 8,11-carbonyl groups in these cage molecules).

Experimental Section

Melting points and boiling points are uncorrected.

Reduction of 1 with $NaBH_4$–$CeCl_3$. Diketone **1** (348 mg, 2.0 mmol) was dissolved in a 0.4 M solution of cerium(III) chloride heptahydrate in methanol (10 mL, 4.0 mmol). The resulting solution was cooled to 0 °C by external application of an ice bath. Sodium borohydride (151 mg, 4.0 mmol) was then added at such a rate that the temperature of the reaction mixture did not rise significantly above 0 °C. The reaction mixture was analyzed by

(4) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, *601*.
(5) Marchand, A. P.; Allen, R. W. *J. Org. Chem.* **1974**, *39*, 1596.
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(7) Marchand A. P.; Kaya, R.; Baker, A. D. *Tetrahedron Lett.* **1984**, *25*, 795.
(8) Mehta, G.; Rao, K. S.; Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1984** *49*, 3848.
(9) Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062.
(10) Sasaki, T.; Eguchi, S.; Kiriyama, T.; Hiroaki, O. *Tetrahedron* **1974**, *30*, 2707.

(11) (a) We have observed previously that **12** can be reduced smoothly with sodium borohydride in 95% aqueous ethanol (in the absence of cerium chloride heptahydrate) to afford the corresponding exo,endo diol along with a small amount of a hemiketal; see: Marchand, A. P.; Chou, T.-C. *Tetrahedron* **1975**, *31*, 2655. (b) Other investigators have reported that 4,4-dimethoxy-2,3,5,6-tetrabromopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione can be reduced with sodium borohydride in ethanol to afford the corresponding endo-8,exo-11-diol in 88% yield; see: Hirao, K.-I.; Kajikawa, Y.; Yonemitsu, O.; Osawa, E. *Heterocycles* **1982**, *17*, 63.

TLC 5 min after addition of the sodium borohydride had been completed; this examination revealed that no **1** remained unreacted. The reaction was then quenched via addition of water (25 mL), and the resulting mixture was then extracted with ether. The combined ether layers were washed successively with brine and then with water. The organic layer was then dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo to afford endo,endo diol **3** (320 mg, 90%). Recrystallization of the crude product from acetone afforded pure **3** as a colorless microcrystalline solid: mp 271–272 C (lit. mp 276–276.5 °C,[9] mp 273–276 °C[11]); ^{13}C NMR ($CDCl_3$) δ 34.37 (t), 38.31 (d), 39.87 (d), 42.93 (d), 45.46 (d), 71.60 (d).

Dehydration of Endo,Endo Diol 3. To a solution of compound **3** (352 mg, 2.0 mol) in dry dichloromethane (10 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The resulting mixture was stirred at room temperature for 5 h, at which time the reaction mixture was washed successively with dilute aqueous sodium bicarbonate solution, brine, and water. The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The resulting oily residue was distilled under reduced pressure; compound **7** was thereby obtained (260 mg, 81.5%) as a pale yellow oil: bp 64 °C (0.1 mm). This oil solidified upon standing for 2 days at room temperature; the resulting solid material was purified via recrystallization from acetone. Pure **7** was thereby obtained as a colorless microcrystalline solid: mp 188–190 °C, (lit.[10] mp 190–191 °C); ^{13}C NMR ($CDCl_3$) δ 36.32 (t), 40.01 (d), 42.00 (d), 44.21 (d), 47.39 (d), 73.34 (d).

Reduction of 5 with $NaBH_4$–$CeCl_3$. Enedione **5** (3.5 g, 20 mmol) was dissolved in a solution of cerium(III) chloride heptahydrate (15 g, 40 mmol) in methanol (60 mL), and its reduction with sodium borohydride (1.5 g, 40 mmol) was allowed to proceed in the manner described above for the corresponding reduction of **1**. The product was extracted into chloroform; the combined organic layers were dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. Crude diol **6** (0.84 g, 82%) was thereby obtained; recrystallization from acetone afforded pure **6** as a colorless microcrystalline solid: mp 157–158 °C (lit.[12] mp 146–148 °C). The infrared, proton NMR, and ^{13}C NMR spectra of **6** thereby obtained were in agreement with literature values.[12]

Photocyclization of an acetone solution of **6** (196 mg, 1.1 mmol) was accomplished via irradiation with a Hanovia 450-W medium pressure Hg lamp (Pyrex filter) for 14 h. The acetone solution was then filtered, and the filtrate was concentrated in vacuo, thereby affording crude exo,exo diol **4** (157 mg, 81%). Recrystallization of this material from acetone afforded pure **4** as a colorless microcrystalline solid: mp 232–233 °C (lit.[12] mp 221–223 °C). The infrared, proton NMR, and ^{13}C NMR spectra of **4** thereby obtained were in agreement with literature values.[12]

Reduction of 8 with $NaBH_4$–$CeCl_3$. Enone **8**[13] (946 mg, 5.5 mmol) was dissolved in a 0.4 M solution of cerium chloride heptahydrate in methanol (3.7 mL, 5.5 mmol), and the reduction was allowed to proceed in the manner described above for the corresponding reduction of **1**. The product was extracted into diethyl ether; the combined organic layers were washed successively with brine and with water. The organic layer was then dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The product, **9** (817 mg, 85%), a colorless microcrystalline solid, melted sharply at 51 °C: IR (CCl_4) 3535 (s), 3050 (w), 2945 (vs), 2845 (m), 1670 (m), 1390 (s), 1180 (s), 1150 (vs), 880 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.45 (m, 2 H), 2.17–3.02 (complex m, 7 H), 3.73 (m, 1 H), 4.77 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 36.60 (t), 39.52 (d), 40.41 (d), 41.37 (d), 41.78 (d), 43.15 (d), 46.43 (d), 48.22 (d), 49.95 (d), 75.39 (d), 103.4 (t), 156.6 (s); MS (70 eV), *m/e* (relative intensity) 174.1 (molecular ion, 37.7), 108.0 (100.0).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.43; H, 7.98.

3-Methyl-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,10}$]dodecane (10). To a solution of compound **9** (200 mg, 1.15 mmol) in dry methylene chloride (10 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The resulting mixture was stirred at room temperature for 3 h, at which time the reaction mixture was washed successively with saturated aqueous sodium bicarbonate solution, brine, and water. The combined organic layers were dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue was distilled under reduced pressure, affording **10** (172 mg, 86%) as a colorless oil: bp 60 °C (1 mm); IR (neat) 2960 (vs), 2860 (s), 1378 (s), 1328 (m), 1316 (m), 1283 (m), 1110 (m), 1006 (s), 935 (m), 865 (s), 832 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.4–2.7 (complex m, 13 H); 4.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.18 (q), 41.31 (d), 41.66 (d), 43.27 (t), 43.63 (d), 44.64 (d), 45.18 (d), 48.22 (d), 55.61 (d), 58.94 (d), 85.58 (d), 93.39 (s); MS (70 eV), *m/e* (relative intensity) 174.1 (molecular ion, 34.8), 159.1 (100.0).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.88; H, 8.19.

Reduction of 11 with $NaBH_4$–$CeCl_3$. Enedione **11**[14,15] (3.46 g, 10 mmol) was dissolved in a solution of cerium chloride heptahydrate (7.5 g, 20 mmol) in methanol (35 mL), and its reduction with sodium borohydride (750 mg, 20 mmol) was allowed to proceed in the manner described above for the corresponding reduction of **1**. The product, **13** (2.1 g, 60%g), was recrystallized from ethyl acetate–hexane mixed solvent to afford a colorless microcrystalline solid: mp 167–168 °C; IR (KBr) 3400 (s), 2920 (m), 1600 (s), 1450 (s), 1400 (m), 990 (s), 890 (s), 740 cm^{-1} (s); ^1H NMR (Me_2SO-d_6) δ 2.47 (m, 4 H), 2.98 (s, 3 H), 3.07 (s, 3 H), 3.87 (s, 2 H), 5.53 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 50.1 (q), 51.4 (q), 52.1 (d), 61.9 (d), 76.6 (s), 113.8 (s), 128.5 (s), 132.8 (d); MS (70 eV), *m/e* (relative intensity) (no molecular ion), 345.0 ($[M - Cl]^+$, 0.4), 57.0 (100.0).

Anal. Calcd for $C_{13}H_{14}Cl_4O_4$: C, 41.52; H, 3.75. Found: C, 41.76; H, 3.79.

Photocyclization of an acetone solution of **13** (1.75 g, 5.0 mmol) was accomplished via irradiation with a Hanovia 450-W medium pressure Hg lamp (Pyrex filter) for 12 h. The acetone solution was then filtered, and the filtrate was concentrated in vacuo, thereby affording crude exo,exo diol **14** (1.6 g, 90%). Recrystallization of this material from ethyl acetate afforded pure **14** as a colorless microcrystalline solid: mp 279–280 °C; IR (KBr) 3400 (s), 1610 (m), 1440 (m), 1350 (s), 1210 cm^{-1} (s); ^1H NMR (Me_2SO-d_6) δ 2.62 (m, 4 H), 2.9 (s, 3 H), 3.04 (s, 3 H), 3.94 (s, 2 H), 5.70 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 50.9 (d), 51.4 (d), 52.0 (q), 52.4 (q), 68.4 (d), 78.5 (s), 78.8 (s), 102.6 (s); MS (70 eV), *m/e* (relative intensity) 345.0 ($[M - Cl]^+$, 4.7), 189.0 (100.0).

Anal. Calcd for $C_{13}H_{14}Cl_4O_4$: C, 41.52; H, 3.75. Found: C, 41.22; H, 4.06.

Reduction of 15 with $NaBH_4$–$CeCl_3$. Enedione **15**[16] (3.7 g, 10 mmol) was dissolved in a solution of cerium chloride heptahydrate (7.5 g, 20 mmol) in methanol (50 mL), and its reduction with sodium borohydride (750 mg, 20 mmol) was allowed to proceed in the manner described above for the corresponding reduction of **1**. The product, **17** (2.1 g, 60%), was recrystallized from ethyl acetate–hexane mixed solvent to afford a colorless microcrystalline solid: mp 176–177 °C; IR (KBr) 3300 (s), 1608 (s), 1460 (s), 1270 (s), 1170 (s), 1000 cm^{-1} (s); ^1H NMR (Me_2SO-d_6) δ 2.71 (m, 2 H), 3.90 (s, 2 H), 3.99 (m, 2 H), 5.4 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 49.2 (d), 63.5 (d), 79.9 (s), 105.4 (s), 130.2 (d), 130.5 (s); MS (70 eV), *m/e* (relative intensity) (no molecular ion), 367.9 ($[M - H_2O]^+$, 0.7), 57.0 (100.0).

Anal. Calcd for $C_{11}H_8Cl_6O_2$: C, 34.33; H, 2.09. Found: C, 34.45; H, 2.23.

Photocyclization of an acetone solution of **17** (1.85 g, 5.0 mmole was accomplished via irradiation with a Hanovia 450-W medium pressure Hg lamp (Pyrex filter) for 3 h. The acetone solution was then filtered, and the filtrate was concentrated in vacuo, thereby affording crude exo,exo cage diol **18** (1.8 g, 97%). Recrystallization of this material from ethyl acetate afforded pure **18** as a colorless microcrystalline solid: mp 325 °C dec; IR (KBr) 3300–3430 (br vs,) 3000 (w), 2946 (w), 1450 (m), 1330 (s), 1102 (s), 1080 (s), 966 (s), 841 (s), 751 cm^{-1} (s); ^{13}C NMR (Me_2SO-d_6) δ 53.3 (d), 53.7 (d), 67.8 (d), 78.8 (s), 82.5 (s), 97.0 (s); MS (70 eV), *m/e* (relative intensity) (no molecular ion), 383.8 (3.7), 330.9 (100.0).

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Compound 18 could be oxidized to cage diketone 16 by using pyridinium dichromate in dimethylformamide solvent. The crude product was purified via elution chromatography (silica gel stationary phase, 20% ethyl acetate–hexane eluent), thereby affording a colorless microcrystalline solid: mp 310 °C, dec (lit.[9] mp 300 °C, dec). Authentic 16 was synthesized via intramolecular photocyclization of 15;[16] the material thereby prepared gave mp 310 °C, with decomposition. The mp of an intimate mixture of the two different samples of 16 (prepared from 18 and from 15 as described above) was undepressed.

Anal. Calcd for $C_{11}H_8Cl_6O_2$: C, 34.33; H, 2.09 Found: C, 34.29; H, 2.22.

Attempted Reduction of 12 and of 16 with $NaBH_4$–$CeCl_3$. Cage diketone 12[15] (378 mg, 1.0 mmol) was dissolved in a solution of cerium chloride heptahydrate (750 mg, 2.0 mmol) in methanol (20 mL). To this solution was added sodium borohydride (75 mg, 2.0 mmol) portionwise with stirring. The reaction mixture was then refluxed for 12 h. No reduction of 12 occurred under the conditions employed; only unreacted 12 could be recovered from these reduction attempts. Similarly, 16[9] (synthesized via intramolecular photocyclization of 15)[16] was found to be inert toward sodium borohydride–cerium chloride heptahydrate under comparable conditions.

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Registry No. 1, 2958-72-7; 3, 56143-86-3; 4, 74497-77-1; 5, 51175-59-8; 6, 101312-33-8; 7, 4378-84-1; 8, 87830-51-1; 9, 101199-19-3; 10, 101199-20-6; 11, 50874-38-9; 12, 50874-39-0; 13, 101199-21-7; 14, 101312-34-9; 15, 101312-35-0; 16, 53644-02-3; 17, 101199-22-8; 18, 101199-23-9; CeCl3, 7790-86-5; $NaBH_4$, 16940-66-2.

A Novel Synthesis of Prostaglandin D_2

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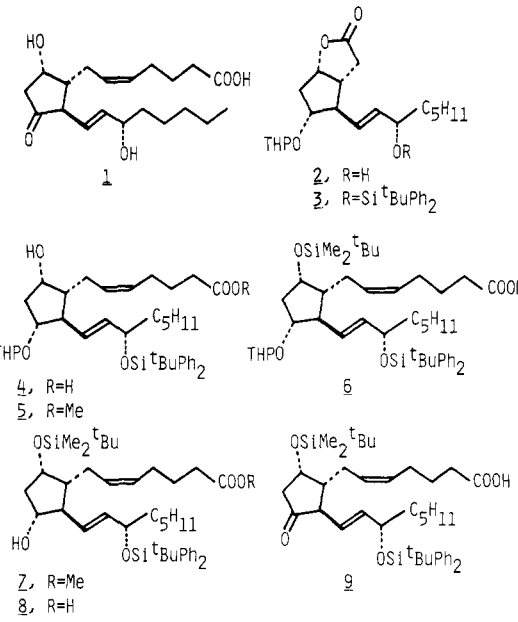
Among primary prostaglandins, recently much attention has been focused on prostaglandin D_2 (PGD_2) (1) (see Chart I) in view of its significant biological activities as a potent inhibitor of platelet aggregation and an antitumor substance.[2] A number of total syntheses of PGD_2 (1) have been reported over the past 10 years, including an elegant synthesis published recently by Noyori and his co-workers.[3] However, the regiocontrolled and short synthesis of 1 from the lactone 2, a key intermediate in a commerical prostaglandin synthesis, has never been achieved, probably owing to lack of the methodology for selective deprotection of tetrahydropyranyl ethers in the presence of silyl ethers.[4]

Chart I



In this paper we wish to report a novel synthesis of (+)-PGD_2 (1), in which the lactone 2 is regiospecifically transformed to 1 without a lengthy protection and deprotection sequence.

The lactone 2 was treated with *tert*-butyldiphenylsilyl chloride and imidazole in DMF to give 3, which, after reduction with diisobutylaluminium hydride in toluene, was subjected to the Wittig reaction using (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in THF.[5] The resulting acid 4 was treated with ethereal diazomethane, affording 5 in 87% overall yield from 2. The alcohol 5 was then converted to the disilyl ether 6 in a usual way[6] (100%).

Selective deprotection of the THP ether in the presence of two silyl ethers is the central problem in the present total synthesis. After several attempts,[7] we have found that selective deprotection proceeds nicely under the thermal conditions. Namely, heating of 6 (950 mg) in CH_3CN (19 mL) at 135 °C for 14 days (sealed tube) resulted in the formation of the desired mono ol 7 in 76% yield.[8] Hydrolysis of 7 with NaOH in aqueous methanol

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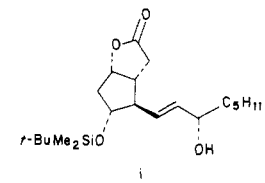
(4) Since PGD_2 is extremely labile under basic conditions, it is absolutely necessary to carry out final cleavage of the protective groups under mild acidic conditions. Therefore, the synthesis of PGD_2 starting from the lactone 2 has involved a lengthy protection and deprotection sequence. Although it appears that the lactone i is an attractive intermediate for the synthesis of PGD_2, a facile 1,5-migration of the *tert*-butyldimethylsilyl group takes place during the Wittig reaction. See: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 2607.



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(7) Recently we have reported a method for selective cleavage of THP ethers in the presence of *tert*-butyldimethylsilyl ethers by the use of alkylaluminum halides. See: Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 663. However, its application to the present case failed of success due to the faster reaction with the silyl ether at C-15 (PG numbering).

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