68% optical purity, $[\alpha]_D$(abs) 174°]. Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.96; H, 12.00.

Registry No. (±)-1, 69308-42-5; (+)-1, 25225-94-9; (−)-1, 74958-51-3; (±)-*exo*-2, 86022-51-7; (−)-*exo*-2, 74958-52-4; (+)-*exo*-2, 86022-54-0; (±)-4, 75768-03-5; (−)-4, 75801-50-2; (−)-*endo*-5, 75768-04-6; (+)-*exo*-6, 86087-01-6; (±)-7, 75768-02-4; (+)-7, 75801-41-1; (−)-*endo*-8, 75801-44-4; (−)-*exo*-9, 75801-47-7; (±)-10, 69308-42-5; (−)-10, 86022-55-1; (+)-10, 86022-56-2; (−)-*exo*-11, 69308-43-6; (±)-*exo*-11, 86022-52-8; (+)-*exo*-11, 86022-57-3; (±)-*endo*-12, 86022-53-9; (−)-*endo*-12, 86022-58-4; (+)-protoadamantane, 86022-59-5; HLADH, 9031-72-5.

A Novel Approach to the Synthesis of Xylomollin

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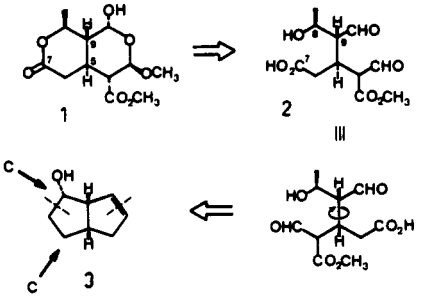
Received September 20, 1982

An approach to the natural product xylomollin (1) is described. The cis-fused bicyclo[3.3.0]octane ketone 4 was modified by the addition of one carbon and sequential cleavage of each of the carbocyclic rings to form the cis-fused bislactone 18. Treatment of 18 with zinc chloride in methanol effected cleavage of both lactone rings with reformation of a new bislactone 20, with the trans ring fusion in the natural product. Carbon NMR spectral data and assignments are provided for all intermediates.

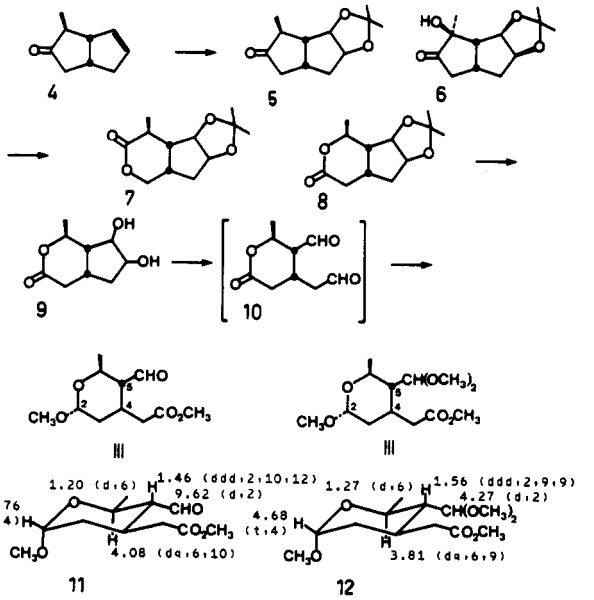
The iridoid mono- and sesquiterpenes represent interesting synthetic challenges, especially the more highly oxygenated examples such as sarracenin,[1] xylomollin,[2] and allamandin.[3] We have been involved for some time in the synthesis of these functionally rich natural products, starting from readily available *cis*-bicyclo[3.3.0]octanes. This approach has the advantage that the highly favored, cis fusion of the [3.3.0] ring fusion matches that found in all but one of the iridoids.[4] The one exception is xylomollin (1) and we were especially fascinated by the possibility that a *cis*-bicyclo[3.3.0]octane might ultimately be transformed into the trans-fused natural product. Such a sequence would formally require inversion of stereochemistry at one or the other of the bridgehead carbons, a process that could be accomplished by actual epimerization or by interconversion of the two, equal length chains attached to the lower bridgehead atom as illustrated in Scheme I. We choose the latter option both because it is stereochemically unambiguous[5] and because to our knowledge it represents a unique means of stereochemical control.

Our initial efforts were directed at a model study of the interconversion. The dialdehyde **10** was prepared from ketone **4** by the sequence shown in Scheme II. Two points concerning these transformations are worthy of note. First, while the oxidation of alkene linkage in **4** with catalytic osmium tetraoxide proceeded in high yield and with good exo face stereoselectivity (5.5:1), a small amount of the tertiary alcohol **6** was also generated, presumably by oxidation of the enolic form of the ketone. Second, Baeyer–Villager oxidation of ketone **5** led to an abnormally large amount (10%) of the lactone **7** resulting from migration of the less substituted carbon atom.

Scheme I



Scheme II

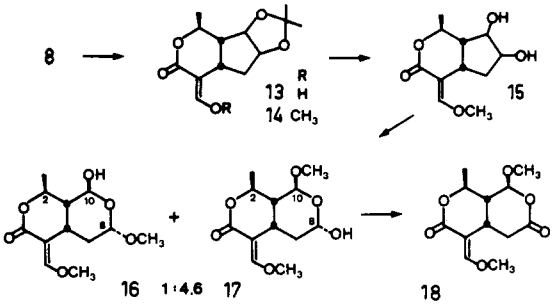


Treatment of dialdehyde **10** with acidic methanol led to a facile transformation the lactolide ester **11** as an anomeric mixture at C-2. Further conversion to the acetal **12** (again obtained as an anomeric mixture) could be achieved by prolonged treatment with the same medium. Analysis of the interproton coupling data for the major isomers of **11** and **12** led unequivocally to the assignment of the transoid relationship between the substituents at C-4 and C-5 (for **11**, $J_{4,5}$ = 10 Hz; for **12**, $J_{4,5}$ = 9 Hz). There are two independent reasons for the greater stability

(1) Miles, D. H.; Kokpol, U.; Bhattacharya, J.; Atwood, J. L.; Stone, K. E.; Bryson, T. A.; Wilson, C. *J. Am. Chem. Soc.* **1976**, *98*, 1569.
(2) Kubo, I.; Muira, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704.
(3) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477.
(4) Bobbitt, J. M.; Segebarth, K.-P. In "Cyclopentanoid Terpene Derivatives"; Taylor, W. I., Battersby, A. R., Ed.; Marcel Dekker: New York, 1969; Chapter 1.
(5) The stereochemistry originally reported for xylomollin was in error. See the following: Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S.; Helbling, A. M. "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, March, 1978; American Chemical Society: Washington, DC, 1978; ORGN 176. Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079.

0022-3263/83/1948-2511$01.50/0

Scheme III

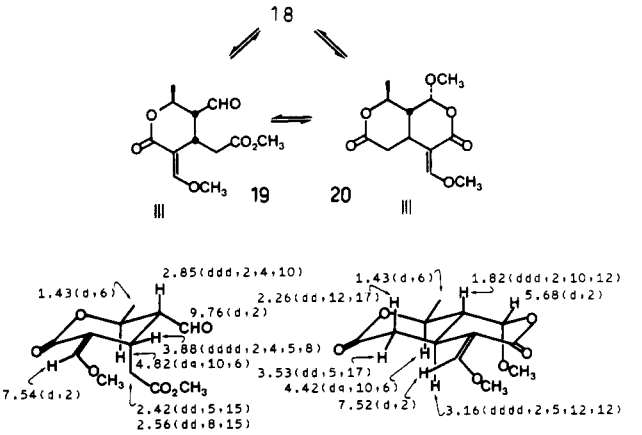


of these systems (relative to **10**) wherein the two lower, two carbon chains have been interchanged: the removal of an axial substituent otherwise present and the greater stability of the ester relative to the lactone functionality (this latter difference is responsible for the acyl–lactone rearrangement).[6]

Further progress toward the synthesis of xylomollin using either **11** or **12** would require the incorporation of one additional framework carbon atom and the oxidation of the lactolide to a lactone. For a variety of reasons we chose to add the additional carbon at an earlier stage in the sequence, as outlined in Scheme III. Methoxymethylidenation of lactone **8** was accomplished by the two-step sequence of formylation followed by O-methylation. We have depicted the *E* geometry about the double bond in **14** and the intermediates to follow, based only on the rigorous establishment of this relationship in **18** by single-crystal, X-ray structural analysis.[7] Selective deprotection of the glycol unit in **14** required carefully defined conditions to avoid concomitant removal of the methoxymethylidene group. Treatment of the crude dialdehyde resulting from periodate cleavage of glycol **15** with methanol and acid under carefully controlled conditions produced mainly the acetal hemiacetal **17** as well as the isomeric **16**. The stereochemistry created at C-8 and C-10 in both **16** and **17** is understandable, as the axial disposition of the C-10 substituent avoids congestion with the C-2 methyl group. We presume that **17** is favored because in this isomer the hydroxyl group is equatorial and thus more accessible for solvation (similar to the situation in glucose, where the anomeric effect is overcome by the same factor). This outcome was quite fortuitous since it left C-8 conveniently exposed for oxidation. For this purpose pyridinium dichromate was found to be superior to a variety of other chromium-based reagents.

The lactone **18** contains all of the stereochemical relationships and basic functionalities present in xylomollin. All that remained to be done was to effect certain disconnections between various functional groups, reconstituting them into the unique arrays found in the natural product. Toward that end we expended more effort than had been consumed in the entire sequence to this point. A wide variety of both acidic and basic reagents led to the destruction of lactone **18** without the generation of any identifiable products. However, various zinc salts were found to be effective in transforming **18** into what appears to be a thermodynamic mixture of **19** and **20**, (Scheme IV). Either of these products reverted to approximately the same mixture (1:4.5:1.4 **18**:**19**:**20**) when subjected to the same reaction conditions. The proton coupling data for **20** was fully consistent with the proposed transoid arrangement at the ring fusion. We have drawn **20** as the

Scheme IV



lactone acyclic enol ether rather than the isomeric cyclic enol ether ester on the basis of the downfield position of the methoxyl (δ 3.91 vs. 3.77 for sarracenin,[1] which has the latter system). Unfortunately, **20** is a minor component of the equilibrium mixture and separation from **18** and **19** could only be effected using a high-quality, analytical HPLC column with light loading. Thus, further progress toward the synthesis of xylomollin from **20** was not practical.

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzophenone and sodium. Skelly B (hexane) was stirred with sulfuric acid and solid sodium carbonate and distilled before use. All other solvents and reagents were used as obtained from commerical sources.

Procedures. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of products were dried with molecular sieves prior to concentration in vacuo. Crude products were routinely run through short columns of silica gel with an appropriate mixture of hexane and ethyl acetate. Reference to purification by HPLC unless otherwise indicated refers to the use of a Waters Prep-500 system with two silica gel cartridges. Solvent ratios are given as hexane to ethyl acetate. PLC refers to preparative layer chromatography on plates made with Merck silica gel, and μ-Porasil and Porasil-A refer respectively to the use of a Waters 3.8 mm by 30 cm high-performance column and two 1 cm by 60 cm columns packed with Porasil A. All temperatures are reported uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, AZ, and Galbraith Laboratories, Inc., Knoxville, TN.

Spectra. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on $CDCl_3$ solutions, using either a Varian HA-100 or a Nicolet 200-MHz instrument using tetramethylsilane as internal standard. ^{13}C NMR data are reported in Figure 1 and were obtained on $CDCl_3$ solutions with tetramethylsilane as standard, using either a Brucker WD-90 or a Varian FT-80A instrument. Assignments were made by using established α, β, and γ effects, our previous observations,[8] and continuous wave decoupling techniques (to distinguish between methylene and methine carbons). The methyl groups of the acetonide units were observed as distinct absorptions at average positions of 24.2 (±0.8) and 26.6 (±0.7). The quaternary carbons of the ketal units were observed in the range of 109.8–112.2. Assignments between like carbons (CH, CH_2, CH_3) differing by less than δ 3 may be interchanged. Infrared (IR) spectra were obtained on dilute, methylene chloride solutions, using a Perkin-Elmer 237B instrument. High-resolution mass spectra (HRMS) were recorded with a Dupont 21-110B instrument.

***exo*-2-Methyl-*exo*,*exo*-7,8-(isopropylidenedioxy)-*cis*-bicyclo[3.3.3]octan-3-one (5).** To a stirred mixture of 5.87 g (34.2 mmol) of *N*-methylmorpholine *N*-oxide, 120 mg (0.47 mmol) of

(6) Korte, F.; Buchell, K. H. *Angew. Chem.* **1959**, *23*, 709

(7) We are grateful to Prof. R. E. Davis, the University of Texas at Austin, for this structure determination.

(8) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

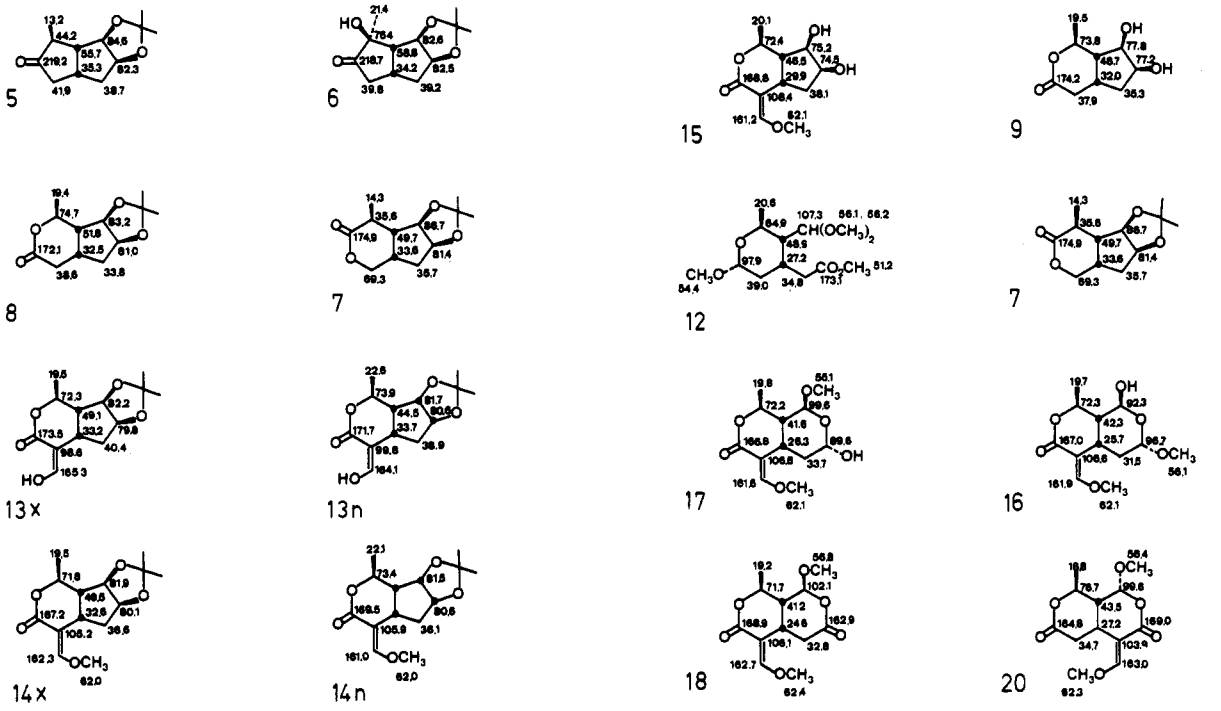


Figure 1.

OsO_4, 12 mL of acetone, and 28 mL of water was added 4.39 g (32.4 mmol) of ketone **4**. A mildly exothermic reaction took place that was moderated by the use of a room-temperature water bath. After 12 h the reaction was terminated by the addition of 2 g of sodium bisulfite. Water (50 mL) and 2 g of Celite were aded, and the resulting slurring was filtered. The pH of the filtrate was adjusted to 7 by the addition of 2 N hydrochloric acid and the acetone present was removed in vacuo. Further aqueous acid was added until the pH was 2 and the resulting solution was saturated with sodium chloride and extracted with five 20-mL portions of ethyl acetate. The aqueous layer was concentrated to dryness and the resulting residue extracted with three 20-mL portions of ethyl acetate. The combined organics were concentrated to afford 5.3 g (96%) of crude diol: IR 3550–3400, 1738 cm^{-1}; ^1H NMR δ 1.16 (d, J = 7 Hz, 3 H), 1.2–3.2 (m, 9 H), 3.99 (t, J = 4 Hz, 1 H), 4.2–4.4 (m, 1 H). To a solution of all of the above diol in 200 mL of acetone was added 2.5 g (10.7 mmol) of camphorsulfonic acid. The reaction was stirred at room temperature for 10 min and then 10 g of sodium bicarbonate was added. The resulting slurry was filtered through approximately 10 g of silica gel and the column was washed with 50 mL of ethyl acetate. The effluent was concentrated and purified by HPLC (3:1) to afford 5.42 g (86%) of a 5.5:1 exo/endo mixture of **5** and 0.15 g (2%) of tertiary alcohol **6**, mp 155–157 °C.

For **5**: IR 1738 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1240; ^1H NMR (for the major isomer) δ 1.15 (d, J = 6 Hz, 3 H), 1.32 (s, 3 H), 1.48 (s, 3 H), 1.5–2.0 (m, 1 H), 2.0–2.6 (m, 5 H), 2.8–3.3 (m, 1 H), 4.59 (d, J = 6 Hz, 1 H), 4.83 (t, J = 6 Hz, 1 H).

For **6**: IR 3450, 3512, 1750 cm^{-1}; ^1H NMR δ 1.22 (s, 3 H), 1.35 (s, 3 H), 1.51 (s, 3 H), 1.90 (dd, J = 14, 6 Hz, 1 H), 2.03 (dt, J = 2, 14 Hz, 1 H), 2.42 (dd, J = 8, 18 Hz, 1 H), 2.4–2.55 (m, 1 H), 2.63 (ddd, J = 2, 9, 18 Hz, 1 H), 2.8–3.0 (m, 1 H), 4.66 (dd, J = 5, 5 Hz, 1 H), 4.78 (ddd, J = 2, 5, 5 Hz, 1 H); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1208. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.01. Found: C, 63.70; H, 8.26.

***exo*-2-Methyl-*exo*,*exo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (8x) and *exo*-2-Methyl-*endo*,*endo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo-[4.3.0]nonan-4-one (8n).** To a mechanically stirred solution of 6.00 g (28.5 mmol) of keto acetonides **5** (exo/endo = 9) in 100 mL of dichloromethane was added 3.6 g (1.5 equiv) of sodium bicarbonate followed by a solution of 8.8 g (4.2 mmol, 1.5 equiv) of 85% *m*-chloroperbenzoic acid in 100 mL of the same solvent dropwise over 1 h. TLC analysis after 24 h (1:1, R_f 0.52) indicated complete consumption of the starting ketones. The reaction mixture was extracted with 1 N aqueous sodium bicarbonate (100 mL) and then with brine (50 mL) and concentrated to a viscous oil. Purification by HPLC afforded 4.77 g (74%) of pure *exo*-acetonide lactone **8x** and 0.72 g (11%) of the endo isomer **8n**. There was also obtained 0.64 g (10%) of lactone **7**.

For **8x**: IR 1742 cm^{-1}; ^1H NMR δ 1.3 (s, 3 H), 1.45 (s, 3 H), 1.46 (d, J = 6 Hz, 3 H), 1.59 (ddd, J = 5, 10, 12 Hz, 1 H), 2.27 (dd, J = 7, 15 Hz, 1 H), 2.36 (dd, J = 7, 14 Hz, 1 H), 2.75 (dd, J = 7, 15 Hz, 1 H), 2.7–3.0 (m, 1 H), 4.16 (dq, J = 6, 12 Hz, 1 H), 4.35 (dd, J = 2, 6 Hz, 1 H), 4.69 (dd, J = 5, 6 Hz, 1 H); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1199. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.01. Found: C, 63.51; H, 8.13.

For **8n**: IR 1742 cm^{-1}; ^1H NMR δ 1.31 (s, 3 H), 1.47 (d, J = 6 Hz, 3 H), 1.50 (s, 3 H), 1.65–1.95 (m, 1 H), 2.05–2.75 (m, 5 H), 4.69 (q, J = 6 Hz, 1 H), 4.78 (t, J = 6 Hz, 1 H), 4.8 (t, J = 6 Hz, 1 H).

***exo*-2-Methyl-*exo*,*exo*-8,9-(isopropylidenedioxy)-4-oxa-*cis*-bicyclo[4.3.0]nonan-3-one (7).** This isomeric lactone was obtained crystalline from the separation detailed above: mp 77.5–78 °C; IR 1740 cm^{-1}; ^1H NMR δ 1.33 (s, 3 H), 1.34 (d, J = 6 Hz, 3 H), 1.48 (s, 3 H), 1.64 (septet, J = 5, 10, 14, 1 H), 2.04–2.22 (m, 1 H), 2.16 (ddd, J = 5, 8, 14 Hz, 1 H), 2.29 (dq, J = 6, 12 Hz, 1 H), 2.9 (dq, J = 6, 8, 9, 10 Hz, 1 H), 3.98 (dd, J = 9, 12 Hz, 1 H), 3.39 (dd, J = 2, 5 Hz, 1 H), 4.41 (dd, J = 6, 12 Hz, 1 H), 4.72 (dt, J = 2, 5 Hz, 1 H); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1201. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.01. Found: C, 63.89; H, 8.25.

***exo*,*exo*-2,3-Dihydroxy-*exo*-9-methyl-8-oxa-*cis*-bicyclo-[4.3.0]nonan-7-one (9).** To a solution of 1.00 g (4.42 mmol) of lactone acetonide **8x** in 30 mL of methanol was added 0.2 g (0.88 mmol, 0.2 equiv) of camphorsulfonic acid. The reaction was stirred at room temperature for 16 h and then the acid was neutralized by the addition of 0.82 g of sodium bicarbonate. After 20 min of additional stirring the reaction was concentrated and the residue was extracted with five 10-mL portions of ethyl acetate. The resulting solution was dried and then concentrated to afford 0.56 g (70%) of diol pure by spectral and elemental analysis: IR 3575, 3550, 1742 cm^{-1}; ^1H NMR δ 1.49 (d, J = 6 Hz, 3 H), 1.9–2.4 (m, 4 H), 1.55 (d, J = 6 Hz, 1 H), 1.74 (t, J = 4 Hz, 1 H), 2.3–2.65 (m, 2 H), 2.7–3.0 (m, 1 H), 3.19 (dd, J = 6 Hz, 1 H), 3.35 (q, J = 6 Hz, 1 H); HRMS calcd for $C_9H_{14}O_4$ 186.0892, found 186.0894. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.15; H, 7.44.

Methyl ((2α,4β,5α,6β)- and (2α,4α,5β,6α)-2-Methoxy-5-formyl-6-methyltetrahydropyran-4-yl)acetate (11). To a solution of 320 mg (1.72 mmol) of lactone diol **9** in 35 mL of water

was added 370 mg (1.74 mmol) of sodium periodate. The reaction was stirred at room temperature for 1 h and then concentrated to dryness. The residue was taken up in 10 mL of methanol and 300 mg (1.3 mmol) of camphorsulfonic acid was added. After 0.5 h the reaction mixture was neutralized by the addition of 1 mL of 1 N aqueous sodium bicarbonate, and the volatile solvents were removed in vacuo. The residue was partitioned between dichloromethane and water. The organic layer was concentrated to afford 360 mg of crude product. Purification was effected by HPLC (Porasil A, 1 cm × 1 m, 1:1), providing aldehyde **11** as a 3:1 α:β anomeric mixture at C-2 but otherwise pure by spectral analysis: IR 2855, 2730, 1725 cm^{-1}; ^1H NMR (major isomer) δ 1.20 (d, J = 6 Hz, 3 H), 1.46 (ddd, J = 2, 10, 12 Hz, 1 H), 1.92 (ddd, J = 2, 4, 14 Hz, 1 H), 2.0–2.4 (m, 2 H), 2.5–3.0 (m, 1 H), 2.36 (dd, J = 5, 16 Hz, 1 H), 3.40 (s, 3 H), 3.68 (s, 3 H), 4.08 (dq, J = 6, 10 Hz, 1 H), 4.76 (dd, J = 2, 4 Hz, 1 H), 9.62 (d, J = 4 Hz, 1 H), (minor isomer, distinct adsorptions) δ 1.30 (d, J = 6 Hz, 3 H), 3.52 (s, 3 H), 4.44 (dd, J = 2, 10 Hz, 1 H), 9.66 (d, J = 4 Hz, 1 H).

Methyl ((2α,4β,5α,6β)- and (2α,4α,5β,6α)-2-Methoxy-5-(dimethoxymethyl)-6-methyltetrahydropyran-4-yl)acetate (12). To a solution of 170 mg (0.64 mmol) of crude aldehyde **11** (prepared as described above) in 10 mL of methanol was added 150 mg (0.65 mmol) of camphorsulfonic acid. The reaction was stirred at room temperature for 1 h and then quenched by the addition of 0.5 mL of 1 N aqueous sodium bicarbonate. The mixture was then diluted with water and extracted with three 10-mL portions of dichloromethane. The combined organic extracts were concentrated to 174 mg (85%) of acetal lactolide **12** as a 3:1 α:β anomeric mixture at C-2 but otherwise pure by both spectral and elemental analysis: IR 1730 cm^{-1}; ^1H NMR (major isomer) δ 1.27 (d, J = 6 Hz, 3 H), 1.56 (ddd, J = 2, 9, 9 Hz, 1 H), 1.63 (m, 2 H), 2.34 (dd, J = 6, 14 Hz, 1 H), 2.4–2.6 (m, 1 H), 2.66 (dd, J = 4, 14 Hz, 1 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.40 (s, 3 H), 3.67 (s, 3 H), 3.81 (dd, J = 6, 9 Hz, 1 H), 4.27 (d, J = 2 Hz, 1 H), 4.68 (d, J = 4, 1 H), (minor isomer, distinct adsorptions) δ 1.43 (d, J = 6 Hz, 3 H), 3.41 (s, 3 H), 3.47 (s, 3 H), 4.32 (dd, J = 2, 9 Hz, 1 H); (on the mixture) HRMS calcd for $C_{13}H_{24}O_6$ 276.1573, found 276.1565. Anal. Calcd for $C_{13}H_{25}O_6$: C, 56.51; H, 8.75. Found: C, 56.57; H, 8.71.

***exo*-2-Methyl-5-(hydroxymethylene)-*exo*,*exo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (13x).** To an ice-cooled solution of anhydrous potassium *tert*-butoxide (6.03 g, 53.9 mmol, 5.5 equiv) in 30 mL of ether was added with mechanical stirring a solution of lactone **8** (2.21 g, 9.7 mmol) in 130 mL of the same solvent. Freshly distilled methyl formate (14 mL) was then added all at once with continued stirring. The cooling bath was then removed and after 12 h at room temperature TLC analysis (1:1, R_f 0.35) indicated complete conversion. The reaction mixture was extracted with two 100-mL portions of water. The combined aqueous layers were acidified to pH 2 with 40 mL of 2 N HCl and then the pH was adjusted to 6 with solid sodium bicarbonate. This solution was saturated with sodium chloride and then extracted with five 100-mL portions of dichloromethane. The aqueous layer was then concentrated to dryness and extracted with 100 mL of the same solvent. The combined organic layers were concentrated to afford 2.3 g (93%) of crude product that was recrystallized from ethyl acetate to 2.04 g (82%) of white crystals: mp 167–168 °C; IR 3500 (br), 1662, 1610 cm^{-1}; ^1H NMR δ 1.31 (s, 3 H), 1.48 (s, 3 H), 1.5 (d, J = 6 Hz, 3 H), 1.73 (ddd, J = 2, 2, 12 Hz, 1 H), 2.0–2.26 (m, 2 H), 3.22 (q, J = 6 Hz, 1 H), 4.45 (sextet, J = 6 Hz, 1 H), 4.29 (d, J = 6 Hz), 4.68 (t, J = 6 Hz, 1 H), 7.32 (d, J = 12 Hz, 1 H), 12.48 (d, J = 12 Hz, 1 H); HRMS calcd for $C_{13}H_{18}O_5$ m/e 254.1154, found 254.1153. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.20; H, 6.93.

***exo*-2-Methyl-5-(hydroxymethylene)-*endo*,*endo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (13n).** This material was prepared as described above for the exo,exo isomer in 48% yield from endo,endo lactone **8n**: mp 114–115 °C; IR 3400 (br), 1660, 1608 cm^{-1}; ^1H NMR δ 1.26 (s, 3 H), 1.35 (s, 3 H), 1.49 (d, J = 6 Hz), 2.0–2.2 (m, 3 H), 3.05 (dq, J = 6, 6, 2 Hz, 1 H), 4.6–4.8 (m, 2 H), 4.78 (dq, J = 5, 6 Hz), 7.26 (dd, J = 2, 12 Hz, 1 H), 12.7 (d, J = 12 Hz, 1 H); HRMS calcd for $C_{13}H_{18}O_5$ m/e 254.1154, found 254.1156.

***exo*-2-Methyl-5-(methoxymethylene)-*exo*,*exo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (14x).** Potassium hydride was obtained from 0.108 g of 23.6% oil dispersed material (0.64 mmol, 1.1 equiv) by washing with two portions of pentane and drying in vacuo. To this material was added 5 mL of freshly distilled hexamethylphosphoric triamide (HMPA) and 0.13 mL (1.4 mmol, 2.4 equiv) of dimethyl sulfate followed by the dropwise addition of 0.148 g (0.58 mmol) of lactone **13x** as a solution in 0.5 mL of HMPa, all with efficient mechanical stirring. After 30 min a second, equal size portion of potassium hydride was added dropwise as a suspension in 0.5 mL of HMPA. After a further 20 min TLC analysis (1:1, R_f 0.79) indicated complete conversion. Saturated aqueous sodium bicarbonate solution (1 mL) was then added followed by partitioning of the reaction between 10 mL of ether and 10 mL of water. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were dried with molecular sieves and concentrated. Recrystallization of this material from ethyl acetate afforded 152 mg (97%) of pure α-(methoxymethylene) lactone **14x**: mp 127–128 °C; IR 1700, 1624, 1125, 1108 cm^{-1}; ^1H NMR δ 1.31 (s, 3 H), 1.47 (d, J = 6 Hz, 3 H), 1.5 (s, 3 H), 1.54 (ddd, J = 6, 12, 14 Hz, 1 H), 2.12 (dd, J = 7, 12 Hz, 1 H), 2.49 (dd, J = 7, 14 Hz, 1 H), 3.4 (quintet of d, J = 2, 7, 7, 12 Hz, 1 H), 3.93 (s, 3 H), 4.05 (sextet, J = 6, 12 Hz, 1 H), 4.4 (d, J = 6 Hz, 1 H), 4.7 (t, J = 6 Hz, 1 H), 7.57 (d, J = 2 Hz, 1 H); HRMS calcd for $C_{14}H_{20}O_5$ m/e 268.1311, found 268.1311. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.78; H, 7.66.

***exo*-2-Methyl-5-(methoxymethylene)-*endo*,*endo*-8,9-(isopropylidenedioxy)-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (14n).** This material was prepared as described above for the exo,exo isomer except that sodium hydride and methyl iodide were used for methylation of the *endo,endo*-hydroxymethylene lactone **13n** (30% yield): IR 1699, 1620 cm^{-1}; ^1H NMR δ 1.29 (s, 3 H), 1.44 (s, 3 H), 1.47 (d, J = 6 Hz, 3 H), 1.7–2.5 (m, 3 H), 3.16 (dq, J = 2, 8 Hz, 1 H), 3.91 (s, 3 H), 4.5–4.9 (m, 3 H), 7.47 (d, J = 2 Hz, 1 H).

***exo*-2-Methyl-5-(methoxymethylene)-*exo*,*exo*-8,9-dihydroxy-3-oxa-*cis*-bicyclo[4.3.0]nonan-4-one (15).** To a solution of **14** (2.00 g, 7.40 mmol) in 15 mL of methanol and 50 mL of water was added 6.2 mL (5 equiv) of 6 N aqueous hydrochloric acid. After 3 h TLC analysis (see above) indicated complete conversion. The reaction was terminated and the product isolated exactly as described above in method A to afford 1.55 g (92%) of pure diol **15**: IR 3550 (br), 1700, 1622 cm^{-1}; ^1H NMR δ 1.41 (d, J = 6 Hz, 3 H), 1.59 (ddd, J = 5, 7, 14 Hz, 1 H), 2.17 (ddd, J = 5, 7, 9 Hz, 1 H), 2.37 (ddd, J = 2, 8, 14 Hz, 1 H), 3.49 (qt, J = 2, 7, 8, 9 Hz, 1 H), 3.88 (s, 3 H), 3.92 (dd, J = 5, 7 Hz, 1 H), 4.1 (dt, J = 2, 5 Hz, 1 H), 4.44 (dq, J = 6, 7 Hz, 1 H), 7.38 (d, J = 2 Hz, 1 H); HRMS calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.1000. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.65; H, 7.13.

***exo*-2-Methyl-5-(methoxymethylene)-*endo*-8-hydroxy-*exo*-10-methoxy-3,9-dioxa-*cis*-bicyclo[4.4.0]decan-4-one (17).** To a solution of 101 mg (0.44 mmol) of diol **15** in 45 mL of water was added, with stirring, 105 mg (1.1 equiv) of sodium periodate. After the reaction mixture had been stirred for 1 h at room temperature, TLC analysis (EtOAc, R_f 0.3) indicated complete consumption of the diol. The reaction solution was concentrated to dryness and then a solution of 85 mg (0.3 mmol) of camphorsulfonic acid in methanol was added. The resulting solution was stirred at room temperature and the reaction carefully monitored by TLC to prevent overreaction and production of the bisacetal. After approximately 1.5 h, two new components (R_f 0.48 and 0.53) had replaced the starting bishemiacetal. The reaction was stopped at this point by the addition of 0.4 mL of 1 N aqueous sodium bicarbonate. The solvents were removed in vacuo and the resiude was extracted with five 5-mL portions of ethyl acetate. Concentration of the combined organics afforded 119 mg (96%) of crude material from which 88 mg (71%) of hemiacetal could be obtained directly by crystallization for ethyl acetate–hexane, mp 134.5–135 °C. The resiude from the supernatent was separated by HPLC (μ-Porasil, 1:1) into 20 mg (16%) of the isomeric **16** and a further 4 mg (74% total) of the desired hemiacetal **17**.

For **17**: IR 3560, 1700, 1620 cm^{-1}; ^1H NMR δ 1.43 (d, J = 6 Hz, 3 H), 1.46 (ddd, J = 10, 10, 13 Hz), 1.73 (ddd, J = 1, 5, 10 Hz, 1 H), 2.13 (ddd, J = 3, 5, 13 Hz, 1 H), 3.25–3.4 (m, 1 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 4.7 (dq, J = 6, 10 Hz, 1 H), 4.78 (d, J =

1 Hz, 1 H), 5.17 (ddd, J = 3, 7, 10 hZ, 1 H), 7.52 (d, J = 1 Hz, 1 H); HRMS calcd for $C_{12}H_{18}O_6$ 258.1103, found 258.1109. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03. Found: C, 55.69; H, 6.81.

For **16**: IR 3550, 1700, 1625 cm^{-1}; ^1H NMR δ 1.44 (d, J = 6 Hz, 3 H), 1.52 (m, 3 H), 3.2–3.6 (m, 1 H), 3.48 (s, 3 H), 3.91 (s, 3 H), 4.75 (dq, J = 6, 10 Hz, 1 H), 5.05 (dd, J = 3, 10 Hz, 1 H), 5.4 (t, J = 1.5 hZ, 1 H), 7.55 (d, J = 1 Hz, 1 H).

***exo*-2-Methyl-5-(methoxymethylene)-*exo*-10-methoxy-3,9-dioxa-*cis*-bicyclo[4.4.0]decane-4,8-dione (18).** To a stirred solution of 195 mg (0.756 mmol) of hemiacetal **17** in 15 mL of purified dichloromethane (washed with sulfuric acid and aqueous carbonate and then distilled) was added all at once 1.70 g (4.53 mmol, 6 equiv) of freshly prepared pyridinium dichromate. The orange mixture was stirred vigorously at room temperature and monitored by TLC (EtOAc, R_f 0.60). After approximately 40 h, conversion to the lactone was complete and the reaction was then diluted with 30 mL of ether and filtered through a short column of silica gel. The column was washed with 30 mL of ethyl acetate, and the combined filtrates were concentrated. Recrystallization of the resulting white solid from ethyl acetate–hexane afforded 180 mg (93%) of pure lactone: mp 130–131 °C; IR 1750, 1700, 1620 cm^{-1}; ^1H NMR δ 1.49 (d, J = 6 Hz, 3 H), 2.09 (ddd, J = 3, 7, 9 Hz, 1 H), 2.43 (dd, J = 9, 18 Hz, 1 H), 3.08 (d, J = 8, 18 Hz, 1 H), 3.4–3.65 (m, 1 H), 3.59 (s, 3 H), 3.94 (s, 3 H), 4.48 (dq, J = 6, 9 Hz, 1 H), 5.19 (d, J = 3 Hz, 1 H), 6.56 (d, J = 2 Hz, 1 H); HRMS calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0953. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.46; H, 6.35.

Methyl ((4α,5β,6α)-2-Oxo-3-(methoxymethylene)-5-formyl-6-methyltetrahydropyran-4-yl)acetate (19). To a solution of 10 mg (0.04 mmol) of bislactone **18** in 8 mL of methanol was added 38.6 mg (6 equiv) of anhydrous zinc chloride with stirring at room temperature. After 2 h the reaction solution was concentrated (<30 °C) and the residue was partitioned between 3 mL of dichloromethane and 2 mL of water. The aqueous layer was saturated with sodium chloride and extracted with four 2-mL portions of the same solvent. The combined organic layers were concentrated and separated by HPLC (μ-Porasil, 1:1) to the following: 1 mg (10%) of starting material, 4.6 mg (46%) of aldehyde **19**, and 1.4 mg (14%) of trans-fused lactone **20**.

For **19**: IR 1735, 1710, 1625 cm^{-1}; ^1H NMR δ 1.43 (d, J = 6 Hz, 3 H), 2.42 (dd, J = 5, 15 Hz, 1 H), 2.56 (dd, J = 8, 15 Hz, 1 H), 2.85 (ddd, J = 2, 4, 10 Hz, 1 H), 3.66 (s, 3 H), 3,88 (dddd, J = 2, 4, 5, 8 Hz, 1 H), 3.93 (s, 3 H), 4.82 (dq, J = 6, 10 Hz, 1 H), 7.54 (d, J = 2 Hz, 1 H), 9.76 (d, J = 2 Hz, 1 H); HRMS calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0953.

***trans*-(1α,2β,10α)-2-Methoxy-3,9-dioxa-5-(methoxymethylene)-10-methylbicyclo[4.4.0]decane-4,8-dione (20).** This material was quite pure as isolated from the above reaction and could be crystallized from ethyl acetate–hexane with essentially quantitative recovery, affording a sample with the following: mp 121.5–122 °C; IR 1740, 1720, 1630, 1025 cm^{-1}; ^1H NMR δ 1.43 (d, J = 6 Hz, 3 H), 1.82 (ddd, J = 2, 10, 12 Hz, 1 H), 2.26 (dd, J = 12, 17 Hz, 1 H), 3.16 (dddd, J = 2, 5, 12, 12 Hz, 1 H), 3.52 (s, 3 H), 3.53 (dd, J = 5, 17 Hz, 1 H), 3.91 (s, 3 H), 4.42 (dq, J = 10, 6 Hz, 1 H), 5.68 (d, J = 2 Hz, 1 H), 7.57 (d, J = 2 Hz, 1 H); HRMS calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0940. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.12; H, 6.42.

Acknowledgment is gratefully made to the Robert A. Welch Foundation (Grant No. F 626) and the National Institutes of Health (Grant No. GM 29195) for financial support of this research.

Registry No. 1, 61229-34-3; 4, 63641-33-8; *exo*-2-methyl-*exo*,*exo*-7,8-dihydroxy-*cis*-bicyclo[3.3.0]octan-3-one, 86046-52-8; 5 (isomer 1), 86046-53-9; 5 (isomer 2), 86116-86-1; 6, 86046-54-0; 7, 86046-55-1; 8 (isomer 1), 86046-56-2; 8 (isomer 2), 86116-87-2; 9, 86046-57-3; 11 (isomer 1), 86046-58-4; 11 (isomer 2), 86046-59-5; 12 (isomer 1), 86046-60-8; 12 (isomer 2), 86046-61-9; 13 (isomer 1), 86046-62-0; 13 (isomer 2), 86116-88-3; 14 (isomer 1), 86046-63-1; 14 (isomer 2), 86116-89-4; 15, 86046-64-2; 16, 86046-65-3; 17, 86046-66-4; 18, 86046-67-5; 19, 86046-68-6; 20, 86046-69-7; acetone, 67-64-1; methyl formate, 107-31-3.

Effect of Meta and Para Substituents on the Stannous Chloride Reduction of Nitrobenzenes in Aqueous Ethanol[1]

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Received September 30, 1982

The rate of reduction of 24 meta- and para-substituted nitrobenzenes with $SnCl_2$ catalyzed by HCl in ethanol–water (90:10 v/v) at 30 °C has been measured iodometrically. The rate is expressed as $v = k[ArNO_2][SnCl_2][HCl]_{st}^{0.5}$, suggesting that the sole active reducing species is $SnCl_3^-$ and the dissociation of HCl is very small. The effect of meta and para substituents in which the solvation of the substituent is taken into account was examined with the Hammett equation, which gave a ρ value of 2.1 ± 0.1. Yukawa–Tsuno and Taft equations, in which resonance and inductive effects are separated, are also discussed.

Only a few kinetic studies have been reported in the HCl-catalyzed reduction of aromatic nitro compounds to amines with stannous chloride.[4-7] Goldschmidt et al.[4] have reported that the reduction of water-soluble nitrobenzenes ($ArNO_2$) in aqueous solution obeys the rate equation 1,

$$v = k_1[ArNO_2][SnCl_2][Cl^-] = k_1[ArNO_2][SnCl_2][HCl]_{st} \quad (1)$$

where $[\ ]_{st}$ means the stoichiometric concentration. The equation suggests a mechanism that involves $SnCl_3^-$:

$$SnCl_2 + Cl^- \overset{\text{fast}}{\rightleftharpoons} SnCl_3^- \text{ (equilibrium constant } K_2) \quad (2a)$$

$$ArNO_2 + SnCl_3^- \xrightarrow[k_2]{\text{slow}} ArNO + SnOCl_3^- \quad (2b)$$

$$ArNO \xrightarrow{\text{fast}} ArNHOH \xrightarrow{\text{fast}} ArNH_2 \quad (2c)$$

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0022-3263/83/1948-2515$01.50/0