Conversion of Asperuloside to Optically Active Prostaglandin Intermediates

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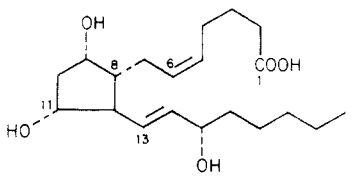
The iridoid glycoside asperuloside has been converted by both oxidative and reductive routes to optically active prostanoid intermediates. The enol ether group was oxidized to a lactone by I_2/PDC followed by in situ reduction of the iodo lactone with thiosulfate. Hydrolysis and decarboxylation then gave the 11-homologue of the Corey lactone aldehyde. Wadsworth–Emmons reaction of this added the lower side chain as expected. Alternatively, tetrahydroasperuloside was converted to a tetracyclic acetal by acid treatment. This was selectively cleaved by acetyl chloride/$TiCl_4$ to a hemiacetal which underwent Wadsworth–Emmons reaction, followed by oxidation and decarboxylation to give the same intermediate prepared by the lactone route.

The Corey disconnection of $PGF_{2\alpha}$ (1) to a dialdehyde and then differentiation of the formyl groups, as in lactone–aldehyde **2**, has been the model for many related



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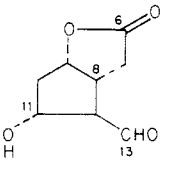

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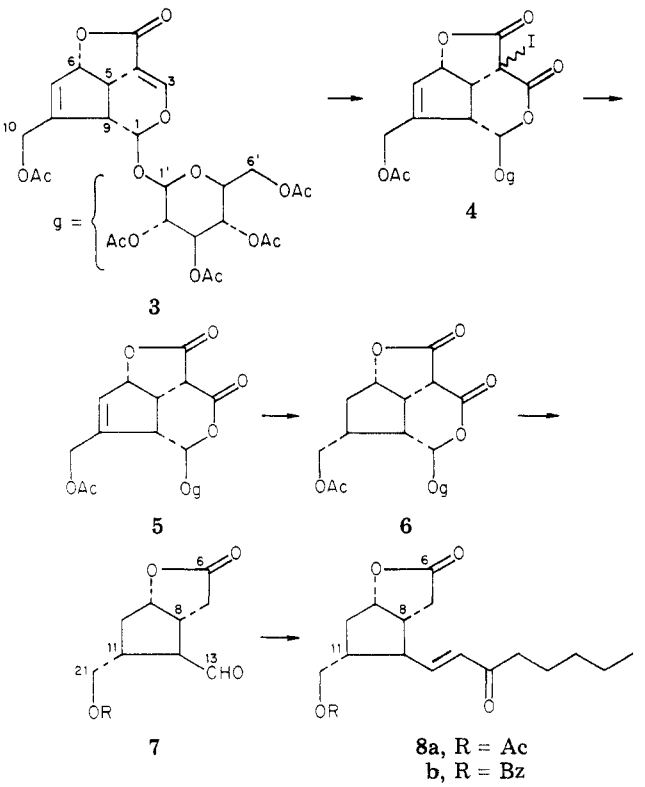
prostaglandin syntheses.[1] Hydrolysis and epimerization of the enol–acetal system characteristic of the iridoids[2] [e.g., asperuloside tetraacetate (**3**)] should give a similar dialdehyde potentially useful as an optically active prostaglandin intermediate, but unfortunately most iridoids are destroyed too rapidly by aqueous acid to allow such a direct approach.

Fortunately, removal of the offending enol double bond, either by reduction[3] or by oxidation,[4] renders the system amenable to further synthetic manipulation. We now report the efficient conversion of asperuloside tetraacetate (**3**) to prostaglandin intermediates by both oxidation (Scheme I) and reduction (Scheme II) routes.

Results and Discussion

Asperuloside. Asperuloside occurs in over 100 species of land plants[2,5] and in concentrations reported as high as 12%.[6] The most convenient source for our work has been *Coprosma repens*, an evergreen shrub available from commercial sources.[7] The crude iridoid may be isolated

Scheme I



3

4

5

6

7

8a, R = Ac
b, R = Bz

by hot acetone[8] or water extraction of either fresh or dried plant parts, followed by column chromatography if necessary. We have employed fresh plant parts, but since water, either as the extraction solvent or extracted from the plant itself, causes a fair amount of lactone hydrolysis, it has proven more convenient to acetylate the crude extract residues and isolate the tetraacetate **3** instead, 0.2–0.5% yields being obtained.

Oxidation Route (Scheme I). Oxidation of asperuloside tetraacetate with iodine and pyridinium dichromate,[9] followed by in situ reduction of the iodo lactone product (**4**) with sodium thiosulfate, gave dilactone **5** in 91% yield. Hydrogenation of the cyclopentene double bond by using rhodium on carbon in dry dioxane afforded

(1) (a) A. Mitra, "The Synthesis of Prostaglandins", Wiley, New York, 1977; (b) J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, 1977.

(2) J. M. Bobbitt and K. P. Segebarth in "Cyclopentanoid Terpene Derivatives", W. I. Taylor and A. R. Battersby, Eds., Marcel Dekker, New York, 1969.

(3) (a) M. Naruto, K. Ohno and N. Naruse, *Chem. Lett.*, 1419 (1978). (b) M. Naruto, K. Ohno, M. Naruse, and H. Takeuchi, *Tetrahedron Lett.*, 251 (1979). See also: (c) M. Naruto, K. Ohno, M. Naruse, and H. Takeuchi, *Chem. Lett.*, 1423 (1978); K. Ohno and M. Naruto, *ibid.*, 1015 (1979), 175 (1980); (d) K. Weinges, H. Eltz, and D. TranViet, *Angew. Chem., Int. Ed. Engl.*, **19**, 628 (1980); (e) W. F. Berkowitz and S. C. Choudhry, *Tetrahedron Lett.*, 1075 (1981).

(4) W. F. Berkowitz, I. Sasson, P. S. Sampathkumar, J. Hrabie, S. Choudhry, and D. Pierce, *Tetrahedron Lett.*, 1641 (1979).

(5) (a) S. R. Jensen, B. J. Nielsen and R. Dahlgren, *Bot. Not.*, **128**, 148 (1975); (b) V. Plouvier and J. Faure-Bonvin, *Phytochemistry*, **10**, 1097 (1971).

(6) V. Plouvier and M. G. Bertrand, *C. R. Hebd. Seances Acad. Sci.*, **242**, 1643 (1956).

(7) See the Experimental Section.

(8) (a) L. H. Briggs and B. F. Cain, *J. Chem. Soc.*, 4182 (1954); (b) L. H. Briggs, B. F. Cain, P. W. LeQuesne, and J. N. Shoolery, *ibid.*, 2595 (1965).

(9) R. D'Ascoli, M. D. D'Aurio, L. Nucciarelli, G. Piancatelli, and A. Scettri, *Tetrahedron Lett.*, **21**, 4521 (1980).

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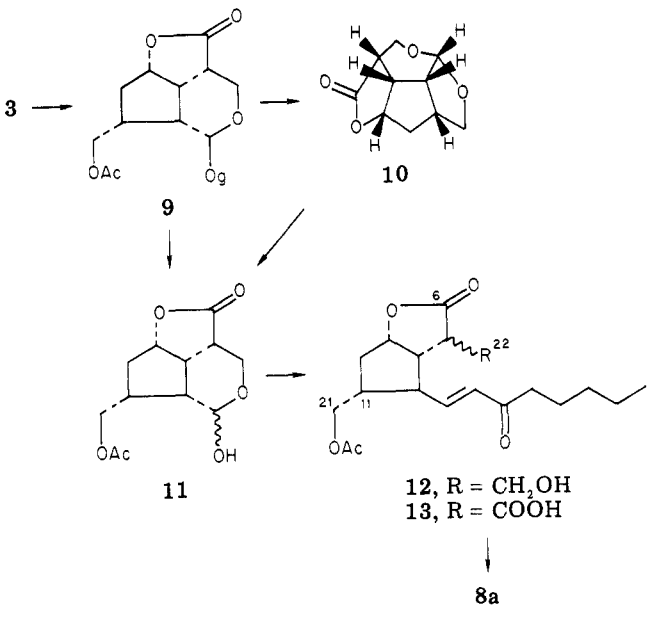
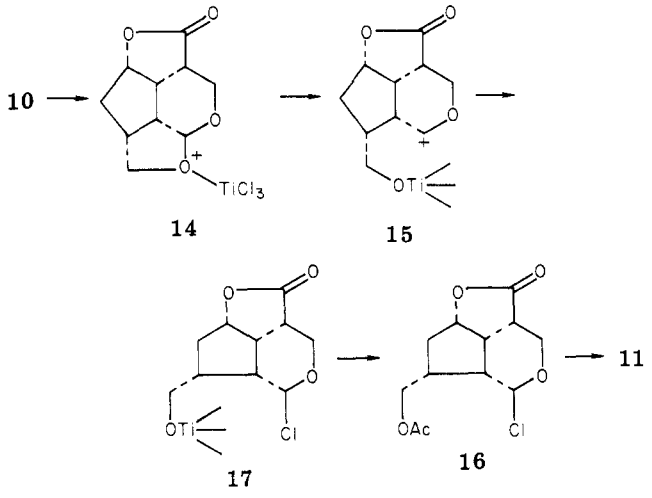
Scheme II



Scheme III



a 98% yield of one epimer (**6**). Hydrolysis of **6** in refluxing 5/1 acetic acid/water solution for 18 h gave a 61% yield of lactone–aldehyde **7**, the "11-homologue" of Corey lactone–aldehyde **2**. The long period of reflux caused selective hydrolysis of the glucose acetate groups, and free glucose was simply extracted into water. Furthermore, in the same pot, the formyl group of the aglycon was epimerized and the α-carboxy lactone was decarboxylated, while the acetate and lactone groups of the aglucon survived intact.

Wadsworth–Emmons reaction of aldehyde **7** gave an 87% yield of enone **8a**, identical with that prepared by the reduction route outlined in Scheme II.

Ohno and co-workers[3a-c] have recently converted aucubin to aldehyde **7b** and enone **8b** (R = benzoyl)[10] and then to both $PGF_{2\alpha}$ and 11-homo-$PGF_{2\alpha}$. We believe that **7a** and **8a** (R = acetyl) would serve as well.

Reduction Route (Scheme II).[3e] Hydrogenation of **3** over rhodium on carbon in ethyl acetate proceeded smoothly at room temperature and gave one major product (**9**) contaminated with several hydrogenolysis products. At lower temperatures the reaction was more selective, and by starting at −30 °C and raising the temperature slowly during 3 h to 0 °C we isolated **9** in virtually quantitative yield. TLC examination of the reaction mixture at −15 °C showed an intermediate product which eventually disappeared by −5 °C. No attempt was made to isolate the dihydro derivative.

The double-resonance, high-resolution NMR spectrum of **9** allowed assignment of the chemical shifts of H-1, H-8, and H-9, and the corresponding splitting constants, warranting the conclusion that hydrogenation occurred exclusively from the exo face to produce the structure shown.

Hydrolysis of tetrahydroasperuloside tetraacetate (**9**) by refluxing 5/1 acetic acid/water solution for 3 h gave a mixture from which aglucon **11** was isolated by column chromatography. An optimum yield of 50% was obtained by refluxing the mixture for 24 h, but a second aglucon, **10**, also began to appear in the reaction mixture. When reflux was continued for 4–12 days, hemiacetal **11** was converted entirely to acetal **10**. As with **6** (above), the glucose fragment was completely hydrolyzed to water-soluble glucose, and **10** was isolated in 86–92% yield by simple extraction. X-ray analysis of the anhdyro aglucon **10**, very kindly performed by Dr. J. Blount (Hoffmann-La Roche), confirmed the structure and stereochemistry indicated by the NMR and chemical analyses. The absolute stereochemistry characteristic of the iridoids[2] may be assumed, as no reaction has affected the bonds at C-5 or C-6.

Selective Hydrolysis of Acetal 10: Titanium Tetrachloride/Acetyl Chloride. Ohno[3b] has elegantly applied a variation of the Mukaiyama reaction to a similar anhydro aglucon prepared from aucubin, introducing thereby a precursor to the enone side chain. When we attempted a similar reaction with **10**, only **11** was isolated whether using Ohno's reagent (2-acetoxy-1-heptene) or isopropenyl acetate. On the assumption that a mechanism such as that shown in Scheme III accounted for the selective hydrolysis of the unsymmetrical acetal, **10** was treated with acetyl chloride and $TiCl_4$ in methylene chloride, resulting in a 95% yield of **11**. The fact that **11** was produced by partial hydrolysis of **9** and by selective cleavage of **10** is proof that only the five-membered ring was opened. The Mukaiyama reaction with Ohno's anhydro aglucon paradoxically resulted in opening of only the six-membered ring. The factors controlling this selective hydrolysis are thus as yet unknown.

Enone 8a. Hemiacetals have been widely used as aldehyde equivalents in Wittig-type reactions,[11] and Wadsworth–Emmons reaction of **11** gave a mixture of enones **12** in 73% yield. The mixture was oxidized by short exposure to Jones reagent, and the unstable carboxylic acid which formed was decarboxylated by refluxing in acetic acid solution, giving enone **8a** (R = acetyl) in 74% overall yield (from **12**) which was identical with that prepared by the oxidation route (Scheme I).

Evidence for the β stereochemistry of the enone side chain of **8a** comes from Ohno's observation[3b] that the vinyl protons of the α side chain epimer of **8b** (R = benzoyl) appear at δ 7.03 and 6.19, while those of the β enone epimer, ultimately converted to $PGF_{2\alpha}$, appear at δ 6.69 and 6.20. The vinyl protons of **8a** (R = acetyl) appear at δ 6.61 and 6.18. Obviously, epimerization took place during the Wadsworth–Emmons reaction of **11** and relieved the strain of the all-cis system[11d,e] inherited from the anhydro aglucon **10**.

(10) Aucubin was converted to **7b** in nine steps.[3a]

(11) (a) G. Pattenden, J. E. Way, and B. C. L. Weedon, *J. Chem. Soc. C*, 235 (1970); (b) G. Pattenden and B. C. L. Weedon, *ibid.*, 1984 (1968); (c) I. T. Harrison, R. Grayshan, T. Williams, A. Semenovski, and J. H. Fried, *Tetrahedron Lett.*, 5151 (1972); (d) D. Brewster, et al., *J. Chem. Soc., Perkin Trans. 1*, 2796 (1973); (e) T. A. Eggelte, H. deKoning, and H. O. Huisman, *ibid.*, 980 (1978).

Conclusion

The conversion of iridoids to prostanoids with retention of the native substituents is an attractive route to prostaglandin analogues. In practice, one of the two methods of removing the enol double bonds, the oxidative or reductive routes described above, should be applicable to any iridoid with substituents considered desirable for incorporation into a prostaglandin analogue.

Experimental Section

Melting points were determined in open capillaries by using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Routine proton spectra were recorded at 60 MHz on a Varian EM360 instrument with Me_4Si as the internal standard. High-field spectra were obtained at Rockefeller University (220 MHz), the Southern New England High Field NMR Facility at Yale University (270 MHz), or at the University of South Carolina Magnetic Resonance Laboratory (400 MHz). NMR data are reported as parts per million (δ) downfield from Me_4Si, with the multiplicity, assignment and splitting constants in parentheses. Unless otherwise indicated, all spectra were determined in deuteriochloroform.

Infrared spectra were recorded on a Perkin-Elmer IR 598, Beckman IR 21, or Perkin-Elmer 237B and calibrated with polystyrene film. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Carbon spectra were recorded at 25 MHz on a JEOL PS/PFT-100 spectrometer at Hunter College or at 68 MHz at Yale University in deuteriochloroform with Me_4Si as an internal standard and are reported in parts per million ppm downfield from Me_4Si. Mass spectra were determined at 70 EV by using a Varian MAT CH-7 for medium resolution. The services of Dr. Frank Field of Rockefeller University, for chemical-ionization mass spectrometry, are gratefully acknowledged.

Silica gel thin-layer chromatography (TLC) was performed by using E. Merck precoated plates (5763-H, silica gel 60). Unless otherwise noted, compounds were visualized by spraying with 10% sulfuric acid in methanol and heating on a hot plate until spots developed. Analytical high-pressure liquid chromatography (HPLC) was performed with a system consisting of two 4 mm × 30 cm μ-Porasil (10 μm) silica columns (Waters 27477) or two similar Hibar-II columns (E. Merck 906006-94) in series and the following Waters components: 6000 SDS pump, U6K injector, and 401 differential refractometer detector. Analyses were performed at 2 mL/min by using 1/1 ethyl acetate/hexane (solvent I) or 2/1 ethyl acetate/hexane (solvent II) unless otherwise noted. Preparative HPLC separations were done with two silica columns in series by using a Waters Prep 500 instrument. Large-scale preparative work was done with a 10-cm column obtained from Glencoe. Solvent was delivered from a stainless-steel container under low air pressure (6 psi). "Flash" chromatography[12] was performed with E. Merck silica gel 60 (9385). Concentration of large quantities of eluent was most efficiently done with a "cyclone" circulatory evaporator (Scientific Glass Apparatus Co., Catalog No. JD9350) at water pump pressure. Final concentrations of extracts and reaction mixtures were done on a rotary evaporator at water pump pressure.

Dimethyl sulfoxide and methylene chloride were distilled from calcium hydride (Me_2SO, in vacuo) and stored over 4A molecular sieves. Dioxane was purified by passage through a column of basic alumina (Brockmann activity grade I), stored in the dark, and used within 48 h as a solvent for hydrogenation. *N*-Bromosuccinimide (NBS) was recrystallized from chloroform, dried in vacuo, and stored cold. Sodium hydride was employed as a 57% oil dispersion which was washed with dry hexane immediately before use. Sodium cyanoborohydride was purchased from Alfa Ventron (recrystallized grade). Hydrogenation catalysts were purchased from Engelhard Industries. Rhodium on carbon (5%) purchased prior to 1975 seemed superior.

Coprosma repens plant parts were purchased from Hines Wholesale Nurseries. The Strybing Arboretum (Santa Ana, CA) was also an occasional source.

Microanalyses were done by Spang Microanalytical Laboratory or Galbraith Laboratories.

Unless otherwise indicated, extracts and reaction mixtures were dried over anhydrous magnesium sulfate.

Asperuloside Tetraacetate (3): [2a*R*-(2aα,4aα,5α,7bα]-4-[(Acetyloxy)methyl]-5-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-2a,4a,5,7b-tetrahydro-2,6-dioxa-1*H*-cyclopent[*c*,*d*]inden-1-one. Asperuloside was isolated by using a variation of Duff's procedure.[13]

Roughly chopped leaves, stems, and berries (8.45 kg) of *Coprosma repens* were boiled with 30 L of water for 1 h. The liquid was decanted, and the extraction was repeated with fresh water. The combined extracts were filtered through a Celite pad and concentrated under reduced pressure in a cyclone circulatory evaporator to 3.5 L. This was slurried with 630 g of Celite 535 and further concentrated under reduced pressure on a rotary evaporator to a tan solid which was finally dried under high vacuum overnight. The resulting solid was placed on top of a partition column prepared as follows:[14] 1.8 kg of Celite 535 was mixed with 1.8 L of water saturated with 1-butanol and kept overnight to equilibrate at room temperature. This stationary phase was slurried with 1-butanol saturated with water, added to a 10-cm-diameter column, and allowed to settle while solvent flowed under a pressure of 10 psi of compressed air.

The column, with the extract-loaded Celite on top, was then eluted with 1-butanol saturated with water at a flow rate of approximately 50 mL/min at 10 psi. Asperuloside (R_f = 0.72 in 2/1 ethanol/acetone; blue spot with acid spray) appeared in fractions 12–40 (500 mL each) accompanied by asperulosidic acid (R_f = 0.83, blue spot), glucose, and various tannins. Concentration of these fractions in vacuo gave a thick brown oil. This was stirred vigorously overnight with 300 mL of acetic anhydride to convert the asperulosidic acid back to asperuloside. Pyridine (150 mL) was then added, with cooling, and the mixture was again stirred overnight at room temperature and finally poured into a mixture of 300 g ice, 200 mL water, and 25 mL of concentrated hydrochloric acid. The resulting mixture of solution and precipitate was extracted with three 250-mL portions of chloroform. These were combined, neutralized with saturated aqueous sodium bicarbonate, extracted with brine, and concentrated to 75 mL. When this was diluted with 250 mL of ether and cooled overnight in the refrigerator, 21.8 g of tan powder was deposited. A solution of the tan powder in acetone was mixed with 40 g of silica and evaporated to dryness. This silica was added to the top of a 4 × 47 cm column of silica (210 g) in 1/1 ethyl acetate/hexane, and asperuloside tetraacetate (3) was eluted, appearing in fractions 8–30 (each 250 mL). Concentration of these fractions and recrystallization of the residue from absolute alcohol gave 5.91 g (0.2%) of white crystals of 3, mp 150–151 °C (lit.[8b] mp 150 °C). This material proved to be identical with that prepared from gift samples[15] of asperuloside.

On a large scale, 20 kg of fresh plant parts was extracted twice for 1 h with 50-gal portions of acetone. The combined extracts were concentrated and dried in vacuo to about 400 g of brown gum. Chlorophylls were extracted from 78 g of the gum by twice stirring with 500 mL of ether for 1 week. The residue was again dried in vacuo (65 g) and then acetylated as above. The crude acetylated product (58 g) was roughly chromatographed on a 5 × 15 cm column of silica by eluting with 1.5 L of ethyl acetate which gave 50 g of yellow gum upon concentration. Purification of this gum by HPLC (solvent I) followed by crystallization (absolute alcohol) gave 6.3 g (ca. 0.2%) of pure 3: mp 148–150 °C; ^{1}H NMR[16] (270 MHz) δ 2.113, 2.097, 2.045, 2.018, and 2.001 (all s, $OCOCH_3$), 5.69 (d, H-1, $J_{1,9}$ = 2.5 Hz), 7.23 (d, H-3, $J_{3,5}$ = 2.2 Hz), 3.50 (ddd, H-5, $J_{5,3}$ 2.2 Hz, $J_{5,6}$ = $J_{5,9}$ = 6.6 Hz), 5.51 (br d, H-6, $J_{6,5}$ = 6.6 Hz), 5.76 (s, H-7), 3.26 (dd, br, H-9, $J_{9,1}$ = 2.5

(12) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

(13) R. B. Duff, J. S. D. Bacon, C. M. Mundie, V. C. Farmer, J. D. Russell, and A. R. Forester, *Biochem. J.*, **96**, 1 (1965).

(14) R. V. Lemieux, *Methods Carbohydr. Chem.*, 1, 45 (1962).

(15) Samples of asperuloside were given to us by Dr. James Bobbitt of the University of Connecticut (Storrs) and by Dr. Victor Plouvier of the Museum of Natural History (Paris, France). We are very grateful for their generosity.

(16) These values are in agreement with those of H. Inouye, S. Inouye, N. Shimokawa, and M. Okigawa, *Tetrahedron Lett.*, 683 (1968).

Hz, $J_{9,5}$ = 6.6 Hz), 4.70, 4.63 (AB q, H-10AB, $J_{10A,B}$ = 14.0 Hz), 4.92 (d, H-1′, $J_{1',2'}$ = 8.1 Hz), 5.01 (dd, H-2′, $J_{2',1'}$ = 8.1 Hz, $J_{2',3'}$ = 9.6 Hz), 5.25 (dd, H-3′, $J_{3',2'}$ = 9.6 Hz, $J_{3',4'}$ = 10 Hz), 5.11 (dd, H-4′, $J_{4',3'}$ = 10 Hz, $J_{4',5'}$ = 9.6 Hz), 3.50 (ddd, H-5′, $J_{5',4'}$ = 9.6 Hz, $J_{5',6'A}$ = 4.4 Hz, $J_{5',6'B}$ = 2.2 Hz), 4.33, 4.18 (ABX, H-6′, $J_{6'A,B}$ = 12.3 Hz, $J_{6'A,5'}$ = 4.4 Hz, $J_{6'B,5'}$ = 2.2 Hz); ^{13}C NMR[17] (25 MHz) δ 170.4, 170.0, 169.9, 169.3, and 169.1 (s, all C=O), 147.7 (d, C-3), 141.4 (s, C-8), 128.7 (d, C-7), 105.4 (s, C-4), 95.9 (d, C-1), 91.7 (d, C-1′), 84.0 (d, C-6), 72.2 (d, C-3′), 72.2 (d, C-5′), 70.4 (d, C-2′), 68.1 (d, C-4′), 61.6 (t, C-10), 60.5 (t, C-6′), 43.4 (d, C-9), 36.0 (d, C-5), 20.6 (q, 5 peaks overlapping, CH_3CO); HPLC T_r (I) = 11.4 min, T_r (II) = 6.3 min; TLC (4/1 ether/ethyl acetate) R_f 0.4.

Asperuloside Tetraacetate Lactone (5): [2a*S*-(2a*α*,4a*α*,5*α*,7a*α*,7b*α*)]-4-[(Acetyloxy)methyl]-2a,4a,5,7b-tetrahydro-5-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-oxy]-1*H*-2,6-dioxacyclopent[*c*,*d*]indene-1,7(2a*H*)-dione. To a solution of 1.00 g (1.72 mmol) of asperuloside tetraacetate (3) in 20 mL of methylene chloride was added approximately 6 g of powdered molecular sieves (4A) followed by 1.31 g (3.0 equiv) of iodine.[9] After 5 min at room temperature, 4.45 g of pyridinium dichromate (7.0 equiv) was added. The reaction mixture was refluxed 6 h and then poured into 40 mL of ethyl acetate. This solution was filtered through a little anhydrous magnesium sulfate, the filter cake was washed with 50 mL of ethyl acetate, and the combined organic solutions were shaken vigorously with 100 mL of 15% aqueous sodium thiosulfate. The aqueous layer was back-washed with methylene chloride, and the combined organic layers were dried over calcium sulfate and then concentrated to a solid which was crystallized from chloroform/ether solution, giving 0.93 g (91%) of lactone 5: mp 141–142 °C; IR ($CHCl_3$) 1792, 1755 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.035, 2.022, 1.991, 1.962, and 1.931 (all s, $OCOCH_3$), 5.64 (d, H-1, $J_{1,9}$ = 3.9 Hz), 3.35 (d, H-4, $J_{4,5}$ = 10.7 Hz), 3.58 (ddd, H-5, $J_{5,4}$ = 10.7 Hz, $J_{5,6}$ = $J_{5,9}$ = 7.5 Hz), 5.43 (br d, H-6, $J_{6,5}$ = 7.5 Hz), 5.96 (s, H-7), 3.25 (m, H-9), 4.69, 4.62 (AB q, H-10A,B, $J_{10A,B}$ = 14.7 Hz), 4.83 (d, H-1′, $J_{1',2'}$ = 8.1 Hz), 4.95 (dd, H-2′, $J_{2',1'}$ = 8.1 Hz, $J_{2',3'}$ = 9.5 Hz), 5.15 (dd, H-3′, $J_{3',2'}$ = 9.5 Hz, $J_{3',4'}$ = 9.8 Hz), 5.03 (dd, H-4′, $J_{4',3'}$ = $J_{4',5'}$ = 9.8 Hz), 3.70 (ddd, H-5′, $J_{5',4'}$ = 9.8 Hz, $J_{5',6'A}$ = 4.9 Hz, $J_{5',6'B}$ = 2.0 Hz), 4.22, 4.08 (ABX, H-6′A,B, $J_{6'A,B}$ = 12.5 Hz, $J_{6'A,5'}$ = 4.9 Hz, $J_{6'B,5'}$ = 2.0 Hz); ^{13}C NMR (25 MHz) 170.7, 170.4, 170.1, 169.7, 169.6, 169.1, 162.8, 143.6, 129.7, 97.7, 97.6, 97.5, 85.8, 72.6, 71.2, 71.0, 61.7, 60.6, 45.9, 44.0, 37.9, 20.8 (5 peaks); HPLC T_r (II) = 7.9 min; TLC (4/1 ether/ethyl acetate) R_f 0.33.

Anal. Calcd for $C_{26}H_{30}O_{16}$: C, 52.17; H, 5.05. Found: C, 51.95; H, 5.07.

Asperuloside Tetraacetate Iodo Lactone (4): 4-[(Acetyloxy)methyl]-7a-iodo-4a,5,7a,7b-tetrahydro-5-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxy]-2,6-dioxacyclopent-[*c*,*d*]indene-1,7(2a*H*)-dione. The preceding reaction was performed as above, except after the reaction mixture was filtered through magnesium sulfate, it was concentrated to a gray powder which was crystallized twice from chloroformate/ether, affording iodo lactone 4: 24% yield; mp 209–211 °C dec; IR ($CHCl_3$) 1780, 1755 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.095, 2.055, 2.055, 2.009, and 1.981 (all s, $OCOCH_3$), 5.22 (d, H-1, $J_{1,9}$ = 8.5 Hz), 3.62 (dd, H-5, $J_{5,6}$ = 5.9 Hz, $J_{5,9}$ = 9.2 Hz), 4.24 (dd, H-6, $J_{6,5}$ = 5.9 Hz, $J_{6,7}$ = 2.4 Hz), 6.14 (br s, H-7), 3.22 (dd, H-9, $J_{9,1}$ = 8.5 Hz, $J_{9,5}$ = 9.2 Hz), 4.68, 4.77 (AB q, H-10A,B, $J_{10A,B}$ = 16.4 Hz), 4.86 (d, H-1′, $J_{1',2'}$ = 8.1 Hz), 5.02 (dd, H-2′, $J_{2',1'}$ = 8.1 Hz, $J_{2',3'}$ = 9.8 Hz), 5.18 (dd, H-3′, $J_{3',2'}$ = $J_{3',4'}$ = 9.8 Hz), 5.05 (dd, H-4′, $J_{4',3'}$ = $J_{4',5'}$ = 9.8 Hz), 3.71 (ddd, H-5′, $J_{5',4'}$ = 9.8 Hz, $J_{5',6'A}$ = 5.4 Hz, $J_{5',6'B}$ = 2.2 Hz), 4.20, 4.10 (ABX, H-6′A,B, $J_{6'A,B}$ = 12.2 Hz, $J_{6'A,5'}$ = 5.4 Hz, $J_{6'B,5'}$ = 2.2 Hz); HPLC T_r (I) = 10.4 min; TLC (4/1 ether/ethyl acetate) R_f 0.43.

Anal. Calcd for $C_{26}H_{29}O_{16}I$: C, 43.11; H, 4.03; I, 17.52. Found: C, 43.37; H, 4.08; I, 17.73.

Dihydroasperuloside Tetraacetate Lactone (6): [2a*S*-(2a*α*,4a*α*,4a*α*,5*α*,7a*α*,7b*α*)-4-[(Acetyloxy)methyl]-5-[(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxy]-1*H*-2,6-dioxahexahydrocyclopent[*c*,*d*]indene-1,7(2a*H*)-dione. A mixture of 2.00 g (3.36 mmol) of asperuloside tetraacetate lactone (5) and 2.00 g of 5% rhodium on carbon in 500 mL of purified dioxane was hydrogenated at 1 atm until hydrogen uptake ceased (1.2 equiv, 4 h). After filtration of the catalyst, a little decolorizing carbon was added and then filtered off through a Celite pad. Concentration of the filtrate gave 1.97 g (98%) of colorless oil showing one spot on TLC. Crystallization of the oil from chloroform/ether gave 1.85 g (92%) of white needles of dihydro lactone 6: mp 186.5–187 °C; IR ($CHCl_3$) 1790, 1752 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.019, 1.987, 1.982, 1.962, and 1.924 (all s, $OCOCH_3$), 5.49 (d, H-1, $J_{1,9}$ = 6.3 Hz), 3.59 (d, H-4, $J_{4,5}$ = 10.7 Hz), 3.32 (ddd, H-5, $J_{5,4}$ = 10.7 Hz, $J_{5,6}$ = $J_{5,9}$ = 8.1 Hz), 5.00 (m, H-6, overlaps H-4′, coupled with peaks at δ 3.32, 2.43, and 1.67), 2.43 (ddd, H-7A, $J_{7A,B}$ = 14.9 Hz, $J_{7A,8}$ = 8.7 Hz, $J_{7A,6}$ = 6.8 Hz), 1.67 (ddd, H-7B, $J_{7B,A}$ = 14.9 Hz, $J_{7B,8}$ = 5.1 Hz, $J_{7B,6}$ = 10.5 Hz), 2.55 (m, H-8, overlaps H-9, coupled with peaks at δ 4.25, 4.04, 2.55, 2.43, and 1.67), 2.55 (m, H-9, overlaps H-8, coupled with peaks at δ 5.49), 4.25, 4.04 (each dd, H-10A,B, $J_{10A,B}$ = 11.6 Hz, $J_{10A,8}$ = $J_{10B,8}$ = 6.5 Hz), 4.83 (d, H-1′, $J_{1',2'}$ = 8.1 Hz), 4.91 (dd, H-2′, $J_{2',1'}$ = 8.1 Hz, $J_{2',3'}$ = 9.5 Hz), 5.13 (dd, H-3′, $J_{3',2'}$ = $J_{3',4'}$ = 9.5 Hz), 5.01 (m, H-4′, overlaps H-6, coupled with peaks at δ 5.13 and 3.67), 3.67 (dt, H-5′, $J_{5',4'}$ = 10.0 Hz, $J_{5',6'}$ = 3.9 Hz), 4.14 (d, H-6′, $J_{6',5'}$ = 3.9 Hz); HPLC T_r (II) = 11.4 min; TLC (4/1 ether/ethyl acetate) R_f 0.66.

Anal. Calcd for $C_{26}H_{32}O_{16}$: C, 52.00; H, 5.37. Found: C, 51.81; H, 5.37.

A similar preparation, using 2.00 g (3.36 mmol) of 5 and 2.00 g of 5% rhodium on alumina in 500 mL of purified dioxane and hydrogenation at 1 atm of H_2 for 3 h, gave after chromatography on a 15-cm silica column (eluted with 1/1 ethyl acetate/hexane) and crystallization from chloroform/ether 1.53 g (77%) of the same dihydro lactone 6.

Corey Aldehyde–Lactone Homologue 7a. Hydrolysis of 6: 5-[(Acetyloxy)methyl]-4-formyl-2*H*-hexahydrocyclopenta[*b*]furan-2-one. A solution of 0.500 g (0.83 mmol) of dihydroasperuloside tetraacetate lactone (6) in 100 mL of 5/1 acetic acid/water was refluxed (116 °C) for 18 h, concentrated to about 10 mL, and poured 90 mL of water. The aqueous mixture was extracted with five 20-mL portions of methylene chloride which were combined, dried, and concentrated onto 3 g of silica. This solid was placed on a column (2.5 cm o.d.) of silica (45 g) packed in 5/1 ether/ethyl acetate and eluted with the same solvent. Concentration of the appropriate fractions gave 0.114 g (64%) of the decarboxylated aglucon 7a as a pale yellow oil: IR ($CHCl_3$) 1775, 1735 cm^{-1}; ^{1}H NMR (60 MHz) δ 2.08 (s, $OCOCH_3$), 9.75 (br s, CHO), 5.00 (m, H-9), 4.15 (m, H-10A,B), 3.15–1.9 (m, 7 H); HPLC T_r (I) = 8.6 min; TLC (4/1 ether/ethyl acetate) R_f 0.23.

Anal. Calcd for $C_{11}H_{14}O_5 \cdot H_2O$: C, 54.09; H, 6.60. Found: C, 54.09; H, 6.64.

Enone 8a: (3a*R*,4*S*,5*R*,6a*S*)-Hexahydro-5-(acetoxymethyl)-4-[(*E*)-3-oxo-1-octenyl]-2*H*-cyclopenta[*b*]furan-2-one. Into a suspension of 21.4 mg (0.883 mmol) of sodium hydride in 4.0 mL of dry dimethoxyethane (DME, distilled from lithium aluminum hydride) under a nitrogen atmosphere was injected a solution of 0.210 g (0.95 mmol) of dimethyl 2-oxoheptylphosphonate in 1.0 mL of dry DME. Stirring was continued for 1 h while a voluminous white precipitate formed. This was cooled in an ice bath, and a solution of 0.1000 g (0.442 mmol) of aldehyde 7a in 1.0 mL of dry DME was injected. Stirring was continued for 30 min with ice cooling, followed by 2.5 h at room temperature. The reaction mixture was neutralized with glacial acetic acid (120 μL) and concentrated directly onto 2.5 g of silica gel. This was placed on top of a column (2.9 cm diameter) of silica (45 g) packed in 1/1 ethyl acetate/hexane and eluted with the same solvent. Appropriate fractions (7–16, 25 mL each) were combined and concentrated to yield 0.125 g (87%) of enone 8a as a pale yellow oil, identical in all respects with that prepared by Scheme II: IR ($CHCl_3$) 1760, 1740, 1695, 1630 cm^{-1}; ^{1}H NMR (250 MHz) δ 2.024 ($OCOCH_3$), 2.31–2.77 (m, H-7, H-10), 1.82 (m, H-8), 4.97 (sextet, H-9), 2.23 (m, H-11, H-12), 6.61 (dd, H-13, $J_{13,12}$ = 8.5 Hz, $J_{13,14}$ = 15.4 Hz), 6.18 (d, H-14), 2.52 (t, H-16, $J_{16,17}$ = 7.4 Hz), 1.60 (tt, H-17, $J_{17,16}$ = $J_{17,18}$ = 7.4 Hz), 1.28 (m, H-18, H-19), 0.89 (t, H-20, $J_{20,19}$ = 6.8 Hz), 4.12, 3.97 (ABX, H-21, $J_{A,B}$ = 11.4 Hz, $J_{21A,11}$ = 5.2 Hz, $J_{21B,11}$ = 4.4 Hz); HPLC T_r (I) = 7.3 min; TLC (4/1 ether/ethyl acetate) R_f 0.55; $[\alpha]^{25}_D$ −28° ($CHCl_3$) [lit.[3a] 7b (benzoate) $[\alpha]^{25}_D$ −25° ($CHCl_3$)].

(17) These assignments are consistent with those recorded for asperuloside. See F. Bailleul, P. Delaveau, A. Rabaron, M. Plat, and M. Koch, *Phytochemistry*, **16**, 723 (1977). See also L.-F. Tietze, U. Niemeyer, P. Marx, and K.-H. Glusenkamp, *Tetrahedron*, **36**, 1231 (1980).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.06; H, 8.13. Found: C, 67.14; H, 8.14.

Tetrahydroasperuloside Tetraacetate (9): (2a*S*,4*R*,5*S*,7a*S*,7b*S*)-5-(β-D-Glucopyranosyloxy)-4-(hydroxymethyl)-1*H*-2,6-dioxaoctahydrocyclopent[*c*,*d*]inden-1-one. Rhodium on carbon (5%, 13.9 g) was mixed with a solution of 14.13 g (24.3 mmol) of asperuloside tetraacetate (**3**) in 2 L of ethyl acetate (distilled) at −30 °C and hydrogenated at 1 atm for 3 h, while the temperature was allowed to rise slowly to 0 °C. Filtration and concentration gave 15.4 g of quite pure **9** as a white foamy solid. Recrystallization of this material from absolute ethanol gave 11.3 g (80%) of pure **9**, mp 148–149 °C. The crude product was quite suitable for hydrolysis to **10**. The catalyst was reuseable at least three times with little loss of activity.

9: IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR (270 MHz) δ 2.093, 2.056, 2.039, 2.039, and 2.016 (all s, $OCOCH_3$), 5.40 (s, H-1), 4.05, 3.88 (AB q, H-3, $J_{A,B}$ = 12.1 Hz), 2.63 (dd, H-4, overlaps H-8), 3.74 (ddd, H-5, $J_{5,9}$ = 10.7 Hz, J = 7.0 Hz), 5.04 (m, H-6, overlaps H-2′), 2.19, 1.95 (m, H-7A,7B), 2.57 (m, H-8, overlaps H-4, coupled to peaks at δ 4.19, 3.85, 2.35, 2.19, and 1.95), 2.35 (dd, H-9, $J_{9,5}$ = 10.7 Hz, $J_{9,8}$ = 8.1 Hz), 4.19, 3.85 (ABX, H-10A,B, J_{AB} = 11.7 Hz, $J_{10A,8}$ = 7.0 Hz, $J_{10B,8}$ = 5.5 Hz), 4.82 (d, H-1′, $J_{1',2'}$ = 8.1 Hz), 5.04 (m, H-2′, overlaps H-6), 5.23 (dd, H-3′, $J_{3',2'} = J_{3',4'}$ = 9.6 Hz), 5.11 (dd, H-4′, $J_{4',3'} = J_{4',5'}$ = 9.6 Hz), 3.74 (ddd, H-5′, $J_{5',4'}$ = 9.6 Hz, $J_{5',6'A}$ = 4.4 Hz, $J_{5',6'B}$ = 2.2 Hz), 4.29, 4.12 (ABX, H-6′A,B, J_{AB} = 12.5 Hz, $J_{6'A,5'}$ = 4.4 Hz, $J_{6'B,5'}$ = 2.2 Hz); HPLC T_r (II) = 6.6 min; TLC (4/1 ether/ethyl acetate) R_f 0.35.

Anal. Calcd for $C_{26}H_{34}O_{15}$: C, 53.24; H, 5.50. Found: C, 53.48; H, 5.83.

Hemiacetal Aglucon 11. Hydrolysis of 9 to 4-[(Acetyloxy)methyl]-5-hydroxy-1*H*-2,6-dioxahexahydrocyclopent[*c*,*d*]inden-1,7(2a*H*)-one. A solution of 4.5 g (7.7 mmol) of tetrahydroasperuloside tetraacetate (**9**) in 200 mL of acetic acid and 40 mL of water was heated to 90 °C during a period of 1 h and then maintained at 90–100 °C for an additional 1.5 h. The mixture was then concentrated, and the foamy white solid residue (4.4 g) was chromatographed on a 25 × 1.5 cm column of silica gel with 2/3 methylene chloride/ethyl acetate as the eluant. Concentration of fractions 17–19 (20 mL fractions) gave 703 mg (36%) of hemiacetal **11**, mp 140–145 °C. Two recrystallizations from ethyl acetate gave 195 mg of analytical sample: mp 147–148 °C; IR ($CHCl_3$) 3590 (sharp), 3450 (br), 1770, 1738, cm^{-1}; ^1H NMR (Me_2SO-d_6, 60 MHz) δ 2.03 ($OCOCH_3$), 6.87 (br s, OH), 5.15 (d, H-1, J = 8 Hz), 4.93 (m, H-6), 4.48 (dd, H-10A, J_{AB} = 10 Hz, $J_{10A,8}$ = 4 Hz), 3.62, 4.14 (ABX, H-3A,B, J_{AB} = 11 Hz, $J_{3A,4}$ < 2 Hz, $J_{3B,4}$ = 7 Hz), 3.9–2.2 (m, remaining H); TLC (2/3 methylene chloride/ethyl acetate) R_f 0.26.

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.35; H, 6.29. Found: C, 55.98; H, 6.46.

Tetracyclic Acetal 10: (2a*R*,4*S*,4a*S*,5*S*,7a*S*,7b*R*)-Octahydro-2*H*,5*H*-1,4,7-trioxacyclopent[*j*,*k*,*l*]-*as*-indacen-5-one. A solution of 14.72 g (25.1 mmol) of tetrahydroasperuloside tetraacetate (**9**) in 360 mL of 5/1 acetic acid/water was refluxed for 12 days and then concentrated to a brown gum. This was dissolved in a mixture of 200 mL of chloroform and 400 mL of water. The aqueous layer was extracted with two 200-mL portions of chloroform. The combined organic layers were washed with water, dried, decolorized with carbon, and concentrated to 4.76 g (97%) of white solid, mp 103–106 °C. This was crystallized from chloroform/ether to give 4.23 g (86%) of tetracyclic acetal **10**, mp 111–113 °C. One further recrystallization raised the melting point to 113–114 °C: IR ($CHCl_3$) 1773 cm^{-1}; mass spectrum, m/e (relative intensity) 196 (M^+, 20), 128 (100); $[\alpha]^{25}_D$ −65° ($CHCl_3$); TLC (2/3 methylene chloride/ethyl acetate) R_f 0.37.

X-ray Analysis.[18] All-cis structure **10** was confirmed. The crystals were trigonal, space group $P3_2$ or $P3_1$ with a = 11.469 (2) Å, c = 5.956 (1) Å, and d_{calcd} = 1.440 g cm^{-3} for Z = 3 ($C_{10}H_{12}O_4$). The intensity data were measured on a Higher-Watts diffractometer (Ni filtered K_α radiation, θ–2θ scans, pulse height discrimination). A crystal measuring approximately 0.12 × 0.12 × 0.6 mm was used for data collection. A total of 608 reflections were measured for θ < 57°, of which 578 were considered to be observed [$>2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[19] and was refined by a full-matrix least-squares method. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms. The hydrogen atoms were included in the structure factor calculation, but their parameters were not refined. The final discrepancy indices are R = 0.031 and R_w = 0.035 for the 578 observed reflections. The final difference map has no peaks greater than ±0.1 e A^{-3}.

Hemiacetal Aglucon 11. Cleavage of 10 with Titanium Tetrachloride/Acetyl Chloride. To an ice-cooled and stirred solution of 1.000 g (5.1 mmol) of tetracyclic acetal **10** in 80 mL of dry methylene chloride under argon was added 4.6 mL (13 mmol, 2.5 equiv) of a 20% solution of acetyl chloride in dry methylene chloride. This was followed by 7.0 mL (6.5 mmol, 1.25 equiv) of titanium tetrachloride dissolved in 20 mL of dry methylene chloride, added dropwise during 10 min. The pale yellow reaction mixture was stirred cold for an additional 45 min and then quenched by addition of 5 g of solid potassium carbonate followed by 100 mL of methylene chloride and 2 mL of water. Stirring was continued for 2 h while a chunky precipitate of titanium dioxide formed and carbon dioxide evolved. The organic layer was decanted, and the residue was boiled with 10 mL of ethyl acetate. The combined organic layers were then dried and concentrated to 1.24 g (95%) of white solid hemiacetal, mp 122–128 °C. Recrystallization from ethyl acetate gave 1.08 g (83%) of pure **11** (mp 144–147 °C), identical by TLC, IR, NMR, and mixture melting point with the hemiacetal prepared by partial hydrolysis of **9**.

Enone (12) from Wadsworth–Emmons Reaction of 11: 5-[(Acetoxy)methyl]-3-(hydroxyethyl)-4-[(*E*)-3-oxo-1-octenyl]-2*H*-hexahydrocyclopenta[*b*]furan-2-one. *N*-Butyllithium (10.4 mL of a 1.6 M hexane solution, 16.7 mmol) was added dropwise to 20 mL of dry dimethyl sulfoxide (Me_2SO) under a nitrogen atmosphere, and the resulting mixture was stirred for 20 min. To this solution of dimsyl anion was added, dropwise in 5 min, 3.6 mL (3.9 g, 17.3 mmol) of dimethyl 2-oxoheptylphosphonate, followed, after stirring for 15 min, by a solution of 0.7424 g (2.83 mmol) of hemiacetal **11** in 9 mL of dry Me_2SO. The temperature of the reaction mixture was raised to 50 °C during a 0.5-h period and then maintained at 50–55 °C for 3 h with stirring. The reaction mixture was then cooled to room temperature, quenched by addition of 3.4 mL of glacial acetic acid, and poured into 100 mL of water. The aqueous mixture was extracted with three 75-mL portions of methylene chloride which were combined and washed with 75 mL of water. The aqueous layer was back-extracted with 50 mL of methylene chloride which was combined with the organic extracts, dried, and concentrated to a brown gum. This was further dried in vacuo at 100–110 °C, leaving a 1.409 g of brown gum which was chromatographed on a column of silica (23 × 3.8 cm) by eluting with 2/1 ethyl acetate/hexane. After 250 mL of forerun, 600 mL of eluent was collected and concentrated to give 734 mg (74%) of yellow gum, a mixture of epimeric enones **12A** and **12B**: HPLC (II) major component (A) T_r = 6.6 min, minor (B) T_r = 8.3 min (A/B ratio ca. 8/1).

12A: IR ($CHCl_3$) 3520, 1773, 1742, 1660, 1640 cm^{-1}; ^1H NMR (60 MHz) δ 6.69 (dd, H-13, $J_{13,14}$ = 16 Hz, $J_{13,12}$ = 7 Hz), 6.15 (d, H-14, $J_{14,13}$ = 16 Hz), 5.00 (m, H-6), 4.07 (br s, CH_2OAc), 3.87 (br s, CH_2OH), 2.07 (s, $OCOCH_3$), 0.90 (t, H-20, $J_{20,19}$ = 5 Hz). The IR and NMR spectra of the major and minor components were virtually identical.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 64.75; H, 8.01. Found: C, 64.64; H, 8.09.

Oxidation of 12 and Decarboxylation of 13 To Give 8a. A solution of 173.6 mg (0.49 mmol) of enone **12** (**A** and **B**) in 5 mL of acetone was injected during 10 s into a refluxing solution of Jones reagent[20] (4 mL) in 16 mL of acetone. The reaction mixture was refluxed for and additional 50 s, quenched with excess (10 mL) 2-propanol, poured into 200 mL of water, and extracted with four 100-mL portions of ether. The combined organic extracts were dried and concentrated to 168 mg (91%) of crude carboxylic

(18) Private communication from Dr. John Blount, Hoffmann-La Roche, Inc., Nutley, NJ, to whom we are deeply grateful. Atomic parameters are given as supplementary material.

(19) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **A27**, 368 (1971).

(20) E. J. Eisenbraun, "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 310.

acid 13 which was decarboxylated without further purification.

The crude acid 13 was a mixture of two components: TLC (ethanol) R_f 0.57 (major), 0.88 (minor). Both components dissolved in 5% aqueous sodium bicarbonate and reappeared in the organic extract after acidification with hydrochloric acid: IR ($CHCl_3$) 3680, 3618 (both sharp), 3450 (br), 1740 (br), 1630 cm^{-1}; ^1H NMR (60 MHz) δ 7.07 (br s, D_2O labile, COOH[21]), 6.63 (m, H-13), 6.23 (d, H-14, $J_{14,13}$ = 16 Hz), 5.15 (m, H-9), 4.3–2.2 (m, remaining H), 2.07 (s, $OCOCH_3$), 1.30 (m, H-18, 19), 0.92 (m, H-20).

Decarboxylation of 13. A solution of crude carboxylic acid 13 (168 mg, 0.46 mmol) in 100 mL of glacial acetic acid was refluxed for 3.5 h and then concentrated to a brown gum. This was dissolved in 10 mL of methylene chloride and filtered through a 2.5-cm column of silica in a sintered-glass funnel. The silica was washed with 100 mL each of methylene chloride and ethyl acetate, which were combined with the original organic filtrate and concentrated to 115.3 mg (78%) of a colorless, viscous oil which showed one spot on TLC (1/1 ethyl acetate/hexane), R_f 0.52, and one peak on HPLC T_r (I) = 7.3 min. IR and NMR spectra of this enone (8a) were identical with those of the sample prepared above, and the two samples were indistinguishable on HPLC (I).

(21) There are several examples of such uncharacteristic carboxyl group chemical shifts, due to intramolecular hydrogen bonding perhaps: C. J. Pouchert and J. R. Campbell, Eds., "The Aldrich Library of NMR Spectra", Aldrich Chemical Co., Milwaukee, WI, 1974. Vol. 2, Spectra No. 174B (δ 6.0), 171C (δ 7.3), 171B (δ 8.3), 170A (δ 8.5).

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Registry No. 3, 18842-95-0; 4, 80447-72-9; 5, 80447-73-0; 6, 80447-74-1; 7a, 80447-75-2; 8a, 78323-84-9; 9, 80482-91-3; 10, 78323-80-5; 11, 78323-81-6; 12 (isomer 1), 78323-82-7; 12 (isomer 2), 78342-14-0; 13, 78323-83-8.

Supplementary Material Available: Lists of atomic parameters, bond lengths, and bond angles and a diagram of the structure (4 pages). Ordering information is given on any current masthead page.

Copper(I) Catalysis of Olefin Photoreactions. 10. Synthesis of Multicyclic Carbon Networks by Photobicyclization

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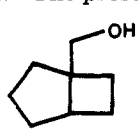
The synthetic utility of copper-catalyzed photobicyclization for construction of tricyclic ring systems is explored. UV irradiation of several monocyclic β- and γ-(4-pentenyl)allyl alcohols in the presence of copper(I) trifluoromethanesulfonate (CuOTf) generates tricyclic cyclobutylcarbinyl alcohols. Efficient syntheses are reported for both 1- and 2-(hydroxymethyl)tricyclo[4.2.1.$0^{3,9}$]nonanes, as well as 2-(hydroxymethyl)tricyclo[4.3.1.$0^{3,10}$]decane, and for 3-(hydroxymethyl)tricyclo[5.3.0.$0^{1,4}$]decane (7). Solvolytic ring expansion of 7 and subsequent catalytic hydrogenation produces tricyclo[6.3.0.$0^{1,5}$]undecane, a ring system found in the sesquiterpenes isocomene and pentalenic acid.

Construction of a complex multicyclic carbon network is often a key challenge in the total synthesis of a natural product. To be of synthetic value, new methods of carbon skeletal construction must tolerate reactive functionality required in the final product or needed to facilitate transformations of synthetic intermediates. In the previous paper of this series[1] we reported that copper(I) trifluoromethanesulfonate (CuOTf) catalyzes clean and efficient [$2_\pi + 2_\pi$] photobicyclization of β- and γ-(4-pentenyl)allyl alcohols to produce bicyclo[3.2.0]heptyl derivatives, e.g., 1 and 2. The present study explores the applicability of



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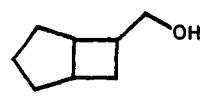

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these new reactions for elaboration of complex tricyclic ring systems. Besides obvious potential applications for the total synthesis of natural products which incorporate a bicyclo[3.2.0]heptyl array,[2] such photobicyclizations may be of value for construction of other important multicyclic ring systems. Thus, the photoproducts are cyclobutylcarbinyl alcohols which may be useful intermediates for generating, via ring expansion,[3] tricyclic ring systems such as 5 from 3 via 4 or 8 from 6 via 7. Derivatives of 5 are important intermediates for total synthesis of gibberellic acids (n = 5)[4] and the alkaloids veatchine and garryine (n = 6),[5] and the sesquiterpenes isocomene[6] and pentalenic

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