acetate/hexane. The 63:37 isolated product ratio was matched by HPLC [Chromanetics Spherisorb ODS reverse-phase column, methanol/acetonitrile/H_2O, 0.01 M NH_4SO_4, 0.005 M $(NH_4)_2CO_3$ (2:1:1)] analysis of the crude reaction product. The alkaloids had physical constants corresponding to those of the products previously reported in our synthesis using the epoxy aldehyde 7.[3]

(b) From a reaction mixture sealed in glass and heated at 210 °C for 30 min after addition of triethylamine were isolated 42% of pandoline and 24% of 20-epipandoline (70:30 product ratio by HPLC).

(c) A reaction analogous to part a but using the bromo lactol **20a** and with refluxing for 2 h after addition of triethylamine gave a 63:37 ratio of pandoline to 20-epipandoline.

(d) A reaction at 20 °C for 24 h after addition of triethylamine gave equal amounts of pandoline and 20-epipandoline.

(e) When 0.64 g (3.1 mmol) of the bromo lactol **20a** and 0.50 g (2.05 mmol) of the indoloazepine **6** in 20 mL of benzene were stirred under nitrogen at 47 °C for 72 h, most of the azepine reacted, and traces of pandoline and 20-epipandoline formed. Addition of 1 mL of triethylamine, continued stirring at 47 °C for 72 h, and a workup as under a gave 173 mg (24%) of pandoline and 282 mg (39%) of 20-epipandoline. HPLC of the crude alkaloid mixture showed a 33:67 ratio.

(f) An analogous reaction mixture stirred at 20 °C for 7 days after addition of triethylamine gave 176 mg (24%) of pandoline and 238 mg (33%) of 20-epipandoline, with a 36:64 ratio of isomers in the crude reaction product.

(g) A solution of 950 mg (3.0 mmol) of the epoxy aldehyde **7** (at least 40% pure by NMR)[3] and 400 mg (1.6 mmol) of the indoloazepine **6** in 20 mL of benzene was held at 47 °C under nitrogen for 4 days and then worked up as under a to give 110 mg (19%) of pandoline and 244 mg (42%) of 20-epipandoline. The crude reaction product showed a 31:69 HPLC ratio of these alkaloids.

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Registry No. 1, 21217-98-1; **2a**, 73824-79-0; **2b**, 73805-38-6; **6**, 66859-22-1; **7**, 80641-93-6; **8a**, 80695-59-6; **8a**·HCl, 80695-60-9; **8a** acetate, 80695-61-0; **8b**, 80695-62-1; **8b**·HCl, 80695-63-2; **8b** 3,5-dinitrobenzoate, 80641-94-7; **8b** acetate, 80695-64-3; **8b** 14-thiocarbamate, 80641-95-8; **9**, 74129-84-3; **10**, 80779-26-6; **10** acetate, 80658-38-4; **11a**, 80665-38-9; **14**, 80642-07-5; **14** hydrazone, 80642-08-6; **16**, 80658-39-5; **18**, 18374-17-9; **19**, 80642-05-3; **19** hydrazone, 80642-06-4; **20**, 80641-96-9; **22**, 80641-97-0; **22a**, 80641-98-1; **22a** hydrazone, 80641-99-2; ethyl 2-ethyl-4-pentenoate, 80642-00-8; methyl 2-ethyl-4-pentenoate, 42998-02-7; ethyl 4,5-epoxy-2-ethylpentanoate, 80642-01-9; methyl 4,5-epoxy-2-ethylpentanoate, 74121-06-5; 2-ethyl-4-pentenoic acid, 1575-73-1; 2-ethyl-4-pentenoic acid *p*-toluamide derivative, 80642-02-0; 5-chloro-2-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-03-1; methyl 4,5-dichloro-2-ethylpentanoate, 80642-04-2; 14α-methyl-*d*-norvincadifformine, 80658-40-8; 5-chloro-4-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-09-7; 5-bromo-4-ethyl-4-hydroxypentanoic acid 1,4-lactone, 80642-10-0.

Notes

Chiral Intermediates from Aucubin as Synthons of Modified 11-Methylprostaglandins. Assignment of Correct Structures to Two Tetrahydrodideoxyaucubins

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Current interest in the field of prostaglandins is focused on obtaining optically active intermediates without resolution. To this end many important syntheses starting from natural chiral compounds with appropiate asymmetric centers have been carried out.[2,3] In particular, one industrial research group leaded by Ohno has recently patented an original conversion of aucubin **1**, the predominant naturally occuring iridoid glucoside, to 11-deoxy-11-α-(hydroxymethyl)prostaglandin F_2 and related compounds.[4] Furthermore, Berkowitz et al.[5] have carried out two syntheses of chiral prostaglandin intermediates from aucubin and asperuloside.

With our recent interest in the iridoid chemistry,[6] we have developed new routes[7] to prostaglandin synthons from aucubin, which is easily obtained from *Aucuba japonica* and *Eucommia ulmoides*.

Our approach is outlined in Scheme I, where we describe our procedure to obtain **8** and **9** which can be considered key intermediates in obtaining, by standard procedures, modified analogues of 11-methylprostaglandins.

Our starting material was the known dideoxytetraacetylaucubin **3**,[8] obtained by Li/NH_3 reduction at −40 °C of aucubin **1** and subsequent acetylation of **2**.

To obtain compounds **4** and **5**, we used a procedure described by Berkowitz[5] which in the case of dideoxytetraacetylaucubin turned out to be very efficient. The use of anhydrous Me_2SO yielded a bromohydrin-free mixture of bromo lactones **4** which were directly reduced (Zn/AcOH) without purification to compound **5** (95% overall yield).

The key step of the reduction of the double bond in compound **5** presented much difficulty, probably because of the bulky glucose moiety.

We obtained good results by sterespecific reduction in the following manner: compound **6** (α-methyl group epimer at C_8) was obtained by PtO_2 reduction in MeOH at

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Scheme I

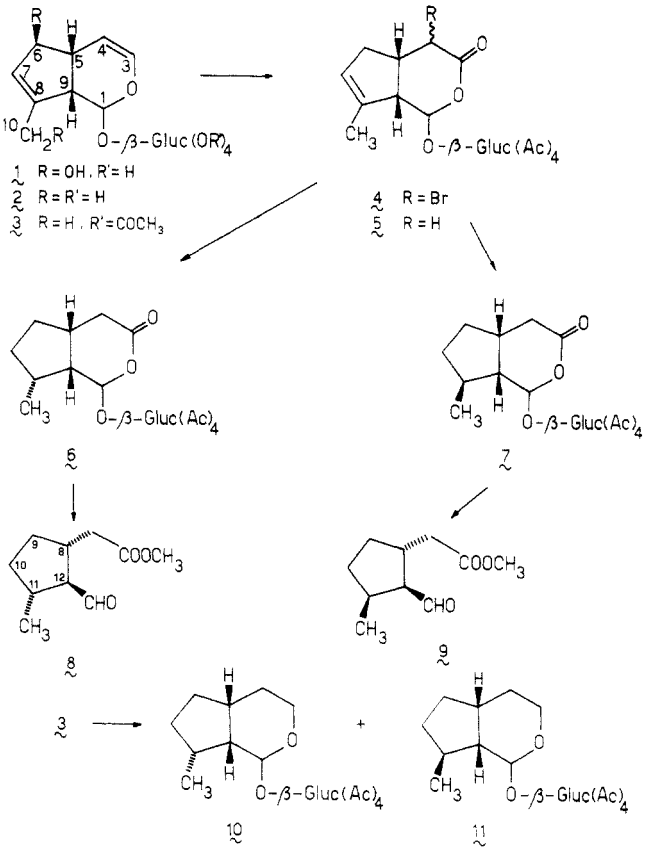

Table I. Significant ^{13}C NMR Chemical Shift Values for Compounds 6, 7, 10, and 11

	compd			
carbons	6	7	10	11
CH_3-10	15.72	18.74	18.51	19.54
C-9	43.16	47.94	43.10	49.64

4 atm, while the best conditions to obtain compound 7 (β-methyl group epimer) were use of Pd/C in MeOH at 1 atm.[9]

The exact configuration of the methyl group at the C_8 position in compounds 6 and 7 was demonstrated by ^{13}C NMR comparison with the two known[8] tetrahydrodideoxytetraacetylaucubins to which we now may assign the configurations 10 (mp 141–142 °C) and 11 (mp 90–91 °C). See Table I for selected and significant spectral data.

This was possible on the basis of specific studies of methyl substitution on the cyclopentane ring[10] and several appropriate examples of ^{13}C NMR data of compounds with related structures. In particular we cite two examples in recent literature,[11,12] in which the authors compared the ^{13}C NMR chemical shifts of certain compounds having a methyl group in a cyclopentane ring cis or trans with respect to a cis ring junction. As given,[11,12] the chemical shift values of the α-methine carbon and of the methyl group in a cis relationship with a cis ring junction (CH_3 endo) are upfield with respect to the corresponding chemical shift values of the α-methine carbon and of the methyl group in a trans relationship with a cis ring junction (CH_3 exo).

Therefore, when considering compounds 6, 7, 10, and 11, the less deshielded CH_3-10 and C-9 values can be assigned to the structures with the Me group in the α configuration (CH_3 endo): for compound 6, 15.72 and 43.16 ppm; for compound 10, 18.51 and 43.10 ppm. On the other hand, the more deshielded CH_3-10 and C-9 values can be attributed to the Me group in the β configuration for compounds 7 (18.74 and 47.94 ppm) and 11 (19.54 and 49.64 ppm).[13]

The last step to compounds 8 and 9 was carried out in two different ways (MeO^-/MeOH, K_2CO_3/MeOH), both in good yields. Epimerization of the CHO group to the more stable β configuration was completed, for compound 8, in a few minutes [^1H NMR ($CDCl_3$) δ 9.56, (J = 4 Hz, d, CHO)]. For compound 9 the epimerization, which can be followed by observing the ^1H NMR resonances of aldehydic protons [δ 9.56 (J = 4 Hz, d) and 9.75 (J = 2 Hz, d)] was almost complete after 20 h.

It is noteworthy that, up to now, 9,11-deoxy-11α- or -11β-methylprostaglandins or appropriate synthons have been synthesized and that proper configurations have never been definitively assigned to compounds 10 and 11.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded on a Perkin-Elmer R-32 at 90 MHz, with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a Varian CFT-20, with chemical shifts given in parts per million from Me_4Si as an internal standard. IR spectra were run on a Perkin-Elmer Model 457.

Isolation of Aucubin. Aucubin was isolated from *Aucuba japonica* and *Eucommia ulmoides* according to the procedure described by Duff.[14] The yield of crude aucubin from fresh plant was 2%.

Preparation of Lactone 5. To a solutin of 3 (1.4 g, 2.9 mmol) in dry and distilled (CaH_2) Me_2SO was added NBS (1 g, 5.8 mmol) at room temperature with stirring under a nitrogen atmosphere. After 10 min the solution became yellow, to the reaction mixture was added water (50 mL), and the whole mixture was extracted with ether (200 mL). The etheral solution was then washed several times with water to remove the Me_2SO and then dried over Na_2SO_4. Evaporation of ether gave 4 (1.6 g) as a solid residue which was used without purificatin in the next step.

To a solution of 4 (1.6 g, 2.8 mmol) in ether (150 mL) were added with stirring acetic acid (8 mL) and then Zn (0.3 g, 5 mmol). After 10 min the reaction mixture was diluted with ether (200 mL) and washed with a solution of saturated Na_2CO_3 and water. The etheral solution, dried over Na_2SO_4 and concentrated in vacuo, yielded a solid residue of 5: 1.35 g (95% overall yield from 3); mp 132–134 °C (EtOH); ^1H NMR ($CDCl_3$) δ 5.52 (H_1, br s), 5.40 (H_7, br s), 2.59 (H_4, br d), 1.73 (CH_3-10, br s). Anal. Calcd for $C_{23}H_{30}O_{12}$: C, 55.42; H, 6.06. Found: C, 55.53; H, 6.01.

Preparation of Lactone 6. A solution of lactone 5 (0.5 g, 1 mmol) in 50 mL of MeOH and 0.1 g of PtO_2 was hydrogenated at 25 °C and 4 atm of H_2 for 1 h. The reaction mixture was filtered and evaporated to yield 6: 0.45 g (90%); mp 144–146 °C (EtOH); ^1H NMR ($CDCl_3$) δ 5.56 (H_1, d, J = 2 Hz), 2.06, 2.00, and 1.97 ($OCOCH_3$, s, 12 H), 1.08 (CH_3, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) 99.02, 97.06, 72.87, 72.35, 71.00, 68.35, 61.90, 43.16, 37.11, 35.46, 33.77, 33.28, 32.90, 20.60, 15.72 ppm. Anal. Calcd for $C_{23}H_{32}O_{12}$: C, 55.19; H, 6.44. Found: C, 55.28; H, 6.37.

Preparation of Lactone 7. A solution of lactone 5 (0.3 g, 0.6 mmol) in 40 mL of MeOH and a catalytic amount of 10% PD on activated charcoal was hydrogenated at 25 °C and atmospheric

(9) It is noteworthy that the catalytic effect we found without previous suggestion was reported by F. Murai and M. Tagawa [*Chem. Pharm. Bull.* 28(6), 1730 (1980)] in the reduction of similar iridoid glucosides, which could represent a more general useful phenomenon.

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pressure until absorption ceased (1 h). The reaction mixture, filtered and evaporated, gave a residue (0.3 g) which, purified by crystallization from EtOH, yielded **7** as a white solid: mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 5.42 (H_1, br s), 2.1, 2.02, and 2.0 ($OCOCH_3$, s, 12 H), 1.28 (CH_3, d, J = 2 Hz; ^{13}C NMR ($CDCl_3$) 100.38, 97.25, 72.84, 72.35, 70.99, 68.26, 61.89, 47.94, 38.27, 34.76, 34.36, 33.68, 33.21, 20.60, 18.74 ppm. Anal. Calcd for $C_{23}H_{32}O_{12}$: C, 55.19; H, 6.44. Found: C, 55.25; H, 6.41.

Methanolysis of Lactone 6 to 8. A solution of **6** (0.2 g, 0.4 mmol) in anhydrous MeOH was stirred at room temperature under a nitrogen atmosphere. To this solution was added dried K_2CO_3 (0.2 g, 1.4 mmol). After 10 min the reaction was completed, and the solution was carefully neutralized with 0.1 N HCl. The methanol was then removed in vacuo at 35 °C, and the resulting aqueous solution was extracted several times with ether (100 mL). Evaporation of the ethereal solution extracts, dried over Na_2SO_4, gave **8**: 55 mg (75%); an oil; ^{1}H NMR ($CDCl_3$) δ 9.56 (CHO, d, J = 4 Hz), 3.63 ($COOCH_3$, s), 1.05 (CH_3, d, J = 6 Hz); IR (CCl_4) 2700, 1750, 1730 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.27; H, 8.69.

Methanolysis of Lactone 7 to 9. A solution of lactone **6** (0.2 g, 0.4 mmol) in anhydrous MeOH was stirreed at room temperature under a nitrogen atmosphere. To this solution was added dried K_2CO_3 (0.2 g, 1.4 mmol), and the reaction was completed in 20 h. The reaction mixture was worked up as described above for **8**, yielding **9**: 50 mg (70%); an oil; ^{1}H NMR ($CDCl_3$) δ. 9.56 (CHO, d, J = 4 Hz), 3.63 ($COOCH_3$, s), 1.26 (CH_3, d, J = 2 Hz); IR (CCl_4) 2700, 1750, 1735 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.68.

Preparation of Compounds 10 and 11. Compounds **10** and **11** were prepared according to the procedure described by Birch.[8] For compound **10**: mp 140–142 °C (lit. mp 141–142 °C); ^{13}C NMR ($CDCl_3$) 94.75, 94.49, 72.76, 71.58, 71.00, 68.28, 61.68, 58.57, 43.10, 33.19, 32.61, 32.29, 29.89, 27.05, 20.18, 18.51 ppm. For compound **11**: mp 89–90 °C (lit. mp 90–91 °C) ^{13}C NMR ($CDCl_3$) 95.08, 94.88, 73.13, 71.90, 71.32, 68.69, 62.06, 58.89, 49.68, 33.52, 32.94, 31.19, 30.22, 27.37, 20.51, 19.54 ppm.

Acknowledgment. We thank S. L. Frachey and F. Piccioni for accurate measurement of ^{1}H NMR and ^{13}C NMR spectra.

Registry No. **3**, 19467-17-5; **4**, 80359-98-4; **5**, 80359-99-5; **6**, 80360-00-5; **7**, 80408-21-5; **8**, 80360-01-6; **9**, 80408-22-6; **10**, 80408-23-7; **11**, 80408-24-8.

Reaction of Trifluoroacetic Acid with Alcohols, Phenols, Ethers, and Their Sulfur Analogues

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When bituminous coal is treated with trifluoroacetic acid (TFA) at 72 °C it forms a powder having greatly reduced sulfur and ash contents. This report describes the reaction chemistry of TFA with pure substances having functional groupings that would be anticipated for bituminous coal.[1,2]

Results and Discussion

The importance of trifluoroacetate derivatives of biochemical and organic substances has been well established.[3,4] The derivatives are normally formed by the addition of trifluoroacetic anhydride or trifluoroacetyl chloride to the substrate or by the in situ generation of the acid anhydride from trifluoroacetic acid (TFA) and a dehydrating agent, e.g., tetraphosphorus decaoxide.[5] The formation of trifluoroacetic acid esters would be anticipated from the reaction of the acid with an alcohol or phenol. The practical need for a nonreversible reaction dictates for many acids the use of the acid chloride or the acid anhydride; however, a number of esters have been isolated in this study without the use of these reagents. Quantitative yields of the ethyl, *n*-butyl, benzyl, methyl, and 2-naphthyl esters are obtained by refluxing the hydroxyl compound with commercial TFA. A notable exception is that phenol requires the addition of tetraphosphorus decaoxide to the reaction mixture. The phenol ester is the most rapidly hydrolyzed of the esters isolated in this study.

The cleavage of benzyl and of *tert*-butyl ethers by TFA has been noted;[6-8] however, the general use of this reagent for cleaving ether linkages has not been demonstrated. Several ethers have been found to cleave in this study. The most probable reaction route would have an oxonium ion intermediate since TFA is a very strong acid; K_a = 0.5 in acetic acid[9] (eq 1). The complex then decomposes with

$$CF_3CO_2H + n\text{-}C_4H_{10}OC_2H_5 \rightarrow [n\text{-}C_4H_{10}O(H)C_2H_5][O_2CCF_3] \quad (1)$$

cleavage of the ether linkage. The decomposition products can form by a substitution process or by elimination (eq 2 and 3). The initially formed substances then undergo

$$[n\text{-}C_4H_{10}O(H)C_2H_5][O_2CCF_3] \rightarrow n\text{-}C_4H_{10}OH + C_2H_5O_2CCF_3 \quad (2)$$

$$[n\text{-}C_4H_{10}O(H)C_2H_5][O_2CCF_3] \rightarrow n\text{-}C_4H_{10}OH + C_2H_4 + CF_3CO_2H \quad (3)$$

their characteristic reactions including polymerization, addition, and esterification. In this specific reaction the major products are the ethyl and *n*-butyl esters of TFA.

Ethyl and diphenyl ethers do not cleave in a sealed tube at temperatures up to 180 °C; however, *n*-butyl ethyl ether cleaves at 72 °C to form the ethyl and *n*-butyl esters of TFA.

Bis(1-phenylethyl) ether cleaves to initially form an alcohol and an ester (eq 4). The alcohol then splits out

$$[C_6H_5CH(CH_3)]_2O + CF_3CO_2H \rightarrow C_6H_5CH(CH_3)OH + C_6H_5CH(CH_3)OC(O)CF_3 \quad (4)$$

a molecule of water to form styrene which polymerizes. The water hydrolyses the ester to give TFA and additional alcohol which loses water. Therefore the overall reaction becomes that of eq 5.

$$[C_6H_5CH(CH_3)]_2O \xrightarrow{TFA} (C_6H_5CHCH_2)_x + H_2O \quad (5)$$

Benzyl ether reacts to form poly(phenylene methylene) analogous to the reaction of benzyl alcohol with concentrated sulfuric acid.[10] The TFA reaction can take place via an oxonium complex which decomposes to form benzyl alcohol and an ester which then undergo further reactions.

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