Synthetic Routes to 6,8-Dioxabicyclo[3.2.1]octyl Pheromones from D-Glucose Derivatives. 4.† Synthesis of (-)-α-Multistriatin

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The precursor for (-)-α-multistriatin (alkyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*lyxo*-hexopyranoside) may be approached from the corresponding isomeric 4-oxo-2-*C*-methyl- or 2-oxo-4-*C*-methylpyranosides by (a) methylenation followed by (b) hydrogenation. The yields in step a and stereocontrol in step b have been found to depend strongly on a number of factors including the protecting group for the C6 hydroxyl. For elaboration to the multistriatin skeleton, the glycosidic methoxyl is hydrolyzed under neutral conditions by using refluxing dimethoxyethane–water which avoids any epimerization of the C2 methyl group. The resulting glycose is treated with vinylmagnesium bromide, and the allylic alcohol obtained is oxidized with manganese dioxide. Exposure of the enone to hydrogen then leads directly to α-multistriatin.

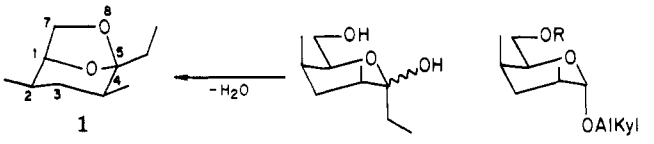
α-Multistriatin, a component of the aggregation pheromone of the elm bark beetle *Scolytus multistriatis*, was isolated, characterized, and synthesized in racemic form by Silverstein and co-workers.[1] Using a route beginning with (*R*)-glyceraldehyde, Mori showed that the absolute configuration was 1*S*,2*R*,4*S*,5*R* as shown for **1**[2] (Scheme I). Syntheses of the racemic material have been reported by Fried[3] and Barlett,[4] and a route to **1** beginning with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside has been carried out by Sum and Weiler.[5] In this paper we outline a synthesis of **1** from glucopyranosides, portions of which have appeared in preliminary form.[6]

In the accompanying papers we have outline syntheses of *exo*-brevicomin[7] and frontalin,[8] which like α-multistriatin (**1**) possesses a dioxabicyclo[3.2.1] framework. However, α-multistriatin presents the greatest challenge since it possesses the largest number (four) of chiral centers in its skeleton. Retrosynthetic analysis gives the hemiketal **2**, the hydrated form of **1**, which is drawn in the $^4C_1$ conformation in order to emphasize its relationship to alkyl α-D-glycopyranoside systems stabilized by the anomeric effect. In this contest the synthesis of α-multistriatin (**1**) would necessitate a stereoselective route to the alkyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*lyxo*-hexopyranoside (**3**). Accordingly, the preparation of this substance was our first objective.

Appropriate starting materials for preparation of **3** are the ketones **7** and **10** which have been previously obtained as exclusive products in the reactions of enones **6** and **9**, respectively, with lithium dimethylcuprate.[9] As indicated in Scheme II, hydrogenation of the corresponding alkenes **8** and **11** can lead to three (**3**–**5**) of the four possible diastereomers. Assignment of configuration to all three is thereby greatly simplified since the desired isomer **3** is obtainable from both **8** and **11**, the other diastereomers being, therefore, **4** and **5**, respectively.

Preparation of the Alkenes 8 and 11. The route begininning with enone **6** was first investigated in view of the fact that this substrate is more readily accessible than enone **9**.[9] We found that the yields obtained in the additions of lithium dimethylcuprate to enone **6** (see Scheme II) were highly dependent on the group at C6, being best with the tritylated material **6b**. In Scheme II we also

Scheme I



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indicate that differences were found in the olefination step. The low yield in the methylenation of **7a** is ascribed to the fact that under the basic conditions of the Wittig reaction, the β-hydroxy ketone was undergoing retro-aldol liberation of formaldehyde (Scheme III).[10] In the case of the benzoate ester **7c**, some hydrolysis and degradation were also occurring in view of the isolation of **8a** as a product. In the olefination step the tritylated ketone **7b** gave moderate yields of **8b**; but this substance would present a problem during the upcoming acidic cleavage of the glycosidic methoxyl, since the trityl group would be lost, with the possible formation of a 1,6-anhydro ring.[11]

The benzyl protecting group would avoid all problems noted in the foregoing paragraph, but the preparation of this material was expectedly problematic. The retro-aldol reaction (Scheme III) observed in the Witting reactions of compounds such as **6a** and **7a** would also occur if these substrates were treated with sodium hydride in order to carry out the benzylation. Benzylations have been done by using benzyl bromide and silver oxide in dimethyl formamide;[12] but application of this procedure to **6a** also caused decomposition. The problem could be averted if the monobenzyl ether **13a** (Scheme IV) could be prepared selectively, but we were only partially successful in this

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† For part 3 see ref 8.

‡ Taken in part from the M.Sc. Theses of D.E.P. (1977), B.J.F. (1979), and the Year IV Report of B.M.R. (1980) at the University of Waterloo.

(1) (a) Gore, W. E.; Pearce, G. T.; Silverstein, R. M. *J. Org. Chem.* **1975**, *40*, 1705. (b) Pearce, G. T.; Gore, W. E.; Silverstein, R. M. *Ibid.* **1976**, *41*, 2797.
(2) Mori, K. *Tetrahedron* **1976**, *32*, 1979.
(3) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469, 2475.
(4) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625.
(5) Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1978**, *56*, 2700.
(6) Fitzsimmons, B. J.; Plaumann, D. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1979**, 3925.
(7) Sherk, A. E.; Fraser-Reid, B. *J. Org. Chem.*, previous paper in this issue.
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(11) Cerny, M.; Stanek, J.; Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.
(12) Croon, I.; Lindberg, B. *Acta Chem. Scand.* **1959**, *13*, 593.
(13) Bhacca, N. S.; Horton, D.; Paulsen, H. *J. Org. Chem.* **1968**, *33*, 2484.

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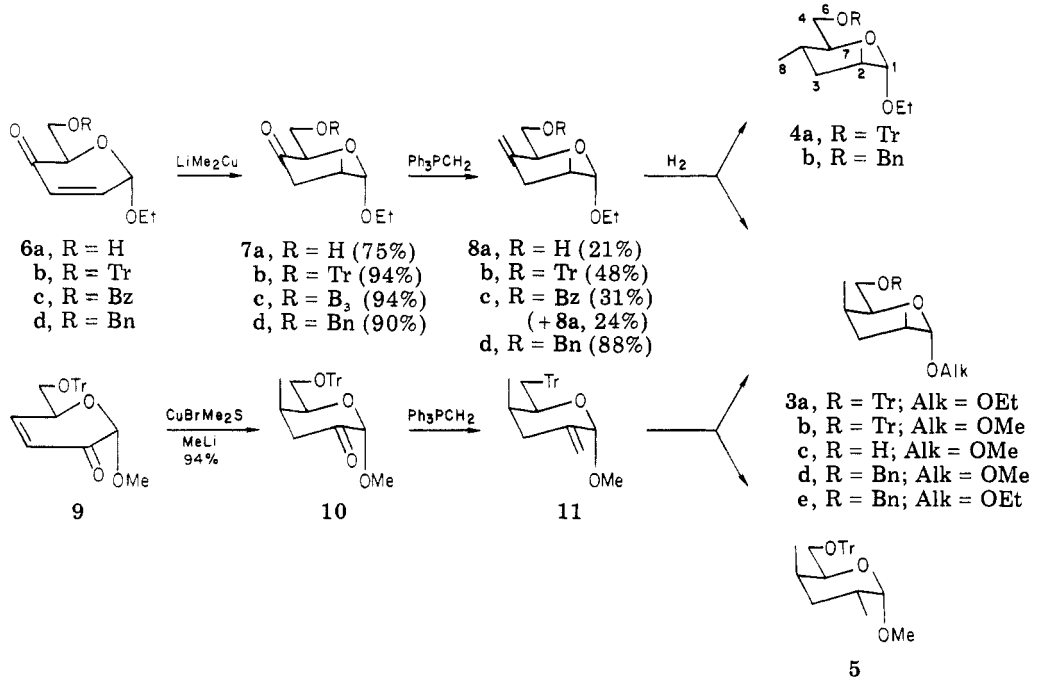
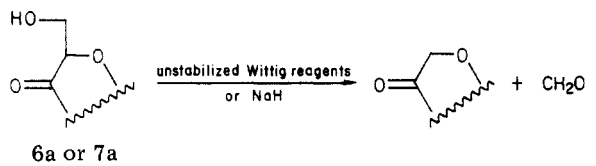
Scheme II

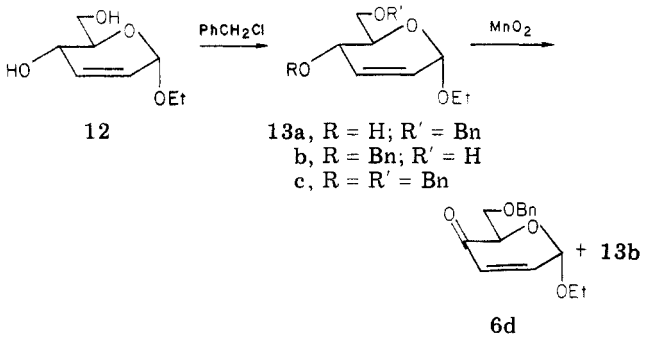


[a] Tr = CPh_3; Bz = COPh; Bn = CH_2Ph.

Scheme III



Scheme IV



endeavor. Thus treatment of the diol **12** with 1.5 equiv of benzyl bromide at low temperatures gave a 2:1 mixture of monobenzylates **13a** and **13b** in addition to some dibenzylate **13c** and unchanged diol **12**. The isomers **13a** and **13b** were not resolved, but they were readily separated from the other products by column chromatography. Oxidation of the mixture **13** (**a** and **b**) with manganese dioxide then led to the enone **6d** which was then readily separated from unchanged **13b**.

As indicated in Scheme II, conjugate addition of methyl to give ketone **7d** and the subsequent olefination to give **8d** both proceed in excellent yields.

The preparation of the isomeric alkene **11** from enone **9** is also shown in Scheme II. The ketone **10**[9] had been previously prepared by us, and the olefination step proceeded in 68% yield based on unrecovered **10**.

Hydrogenation of the Alkenes. Initially, we found that hydrogenations of the alkenes **8** or **11** were unsuccessful or difficult irrespective of the catalyst used, the nature of the protecting group, or whether the substrate was crystalline or syrupy. On the assumption that this was due to traces of phosphorus byproducts remaining from the Wittig reaction, we adopted the practice of stirring the purified alkenes (even where crystalline) first with W-8 Raney nickel in ethyl acetate prior to carrying out the hydrogenation with the catalyst of interest.

Hydrogenation of the tritylated alkenes **8b** and **11** over Raney nickel was examined first. The three diastereomers **4a**, **3a** (or **3b**), and **5** were all resolved on thin-layer chromatograms, and they could therefore be separated chromatographically, and their NMR parameters were determined (see Experimental Section).

The particular merit of approaching **3** from the isomeric alkenes **8** and **11** is appreciated by examining the ^1H NMR data reported in the Experimental Section. With "normal" α-D-hexopyranosides, diequatorial protons at C1 and C2 (as in **3**) have a small coupling constant ($J_{1,2} \approx 1$ Hz), while with the equatorial–axial arrangement (as in **5**) the magnitude is larger ($J_{1,2} \approx 4$ Hz). Had we relied solely upon these criteria in deducing the structures of the products from hydrogenation of **11**, we would have misassigned compounds **3b** and **5**, whose values for $J_{1,2}$ are 5.2 and 1.0 Hz, respectively.

The values of $J_{1,2}$ for **3a** and **3b**, 6.0 and 5.3 Hz, respectively, suggest that there is some flattening brought about by the syn diaxial interaction of the methyl substituents in **3**. This view was advanced by Weiler and Sum[5] to account for the magnitude of $J_{1,2}$ in **3b**. Alternatively, a conformational equilibrium having an appreciable amount of the $^1C_4$ conformer of **3**, as had been noted in idose systems,[14] cannot be ruled out.

The relative ratios in entries 1–3 of Table I indicate that very little stereoselectivity was obtained in the hydrogenation of the tritylated alkene **8b** on using a variety of catalysts. The benzyl analogue **8d** (entry 4) gave an excellent yield, but again the stereoselectivity was poor.

We therefore turned to the C2 *exo*-methylene derivative **11**. We were conscious of the study by Miljkovic and

(14) Miljkovic, M.; Glisin, D. *J. Org. Chem.* **1975**, *40*, 3357.

Scheme V

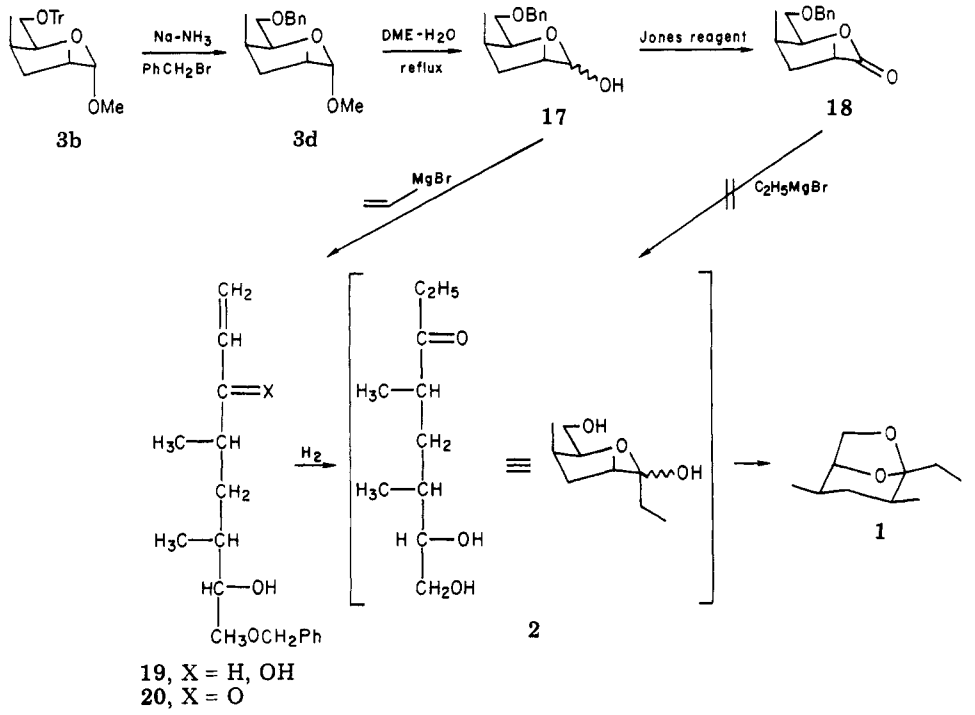
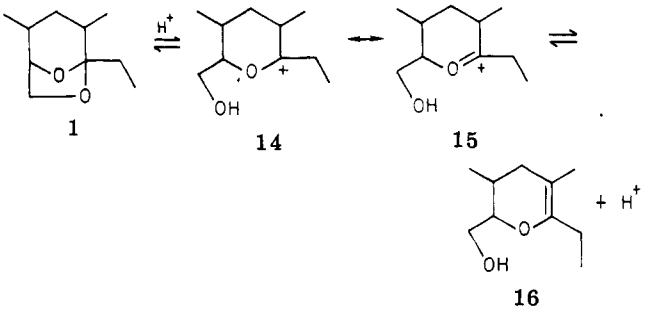


Table I. Hydrogenation[a] of Alkenes

entry	alkene	catalyst	overall yield, %	products (rel ratio)
1	8b	Ni[c]	98	3a + 4a (1.2:1)[b]
2	8b	Pt	97	3a + 4a (2.2:1)[b]
3	8b	$(Ph_3P)_3RhCl$	80	3a + 4a (2.3:1)[b]
4	8d	Pt	98	3e + 4b (2.6:1)[b]
5	11	Pt	98	3d + 5 (9:1)
6	11	Ni[c]	98	3d + 5 (4:1)

[a] Atmospheric pressure and ambient temperature. [b] GLC determination. [c] W8 Raney nickel.

Scheme VI



Glisin[14] on related C2 *exo*-methyleneglycopyranosides. These workers had found that the axial C2 methyl group was produced selectively only if the glycosidic alkoxyl group was in the β orientation, a finding which did not augur well for the formation of the desired substrate, **3**, from **11**. However, the results in entries 5 and 6 (Table I) indicate excellent stereoselectivity for the desired diasteromer. *Therefore the preferred route to the desired synthon, 3, is from the C2 methylene adduct 11 and not from the C4 alternative 8.*[5]

Transformations at the Anomeric Center. In viewing of the foregoing encouraging yields we obviously wished to proceed with the trityl-protected material **11**. However, this protecting group would also be removed in the projected acid hydrolysis of the glycosidic alkoxyl with concomitant risk of forming a 1,6-anhydro ring.[11] In order to avoid this contingency, we decided to selectively hydrolyze the trityl group from **3b**, but although this was achieved according to TLC monitors, the product **3c** apparently formed an azeotrope and codistilled with the solvent. Accordingly, the trityl group of **3b** was removed with sodium in liquid ammonia, and after the excess ammonia had been allowed to evaporate, the residue was taken up in diethyl ether and benzylated directly. This led to a 60% overall yield of **3d** (Scheme V).

The hydrolytic removal of the glycosidic methoxyl of **3d** now presented the problem. Silverstein had found that C4 of α-multistriatin was epimerized upon treatment with either aqueous or Lewis acids, giving γ-multistriatin, and he attributed this to the reversible formation of the enol ether **16** shown in Scheme VI. After some experimentation we achieved some success by treating **3d** with a 0.2% of solution of sulfuric acid in water–dioxane mixtures at room temperature for 4 days. At this time the hydrolysis was still not complete, but according to evidence of GLC monitors, longer reaction times led to epimerization.

In other studies in our laboratory we had found that activated glycosides could be hydrolyzed by boiling in water with dioxane[15] or dimethoxyethane[16] as cosolvents. Accordingly, when the glycoside **3d** was refluxed in aqueous dimethoxyethane for 3 h, the glycose **17** was isolated in 93% yield as a syrupy material. GLC analysis revealed only one component, indicating that this treatment had not caused any isomerization at C2.

It was now necessary to add a a two-carbon unit at C1 of the pyranose ring, and to this end the lactone **18** was prepared. We had hoped to add a single ethyl group which would have afforded the desired hemiketal **2**. However, in spite of ample precedent[17] we were unable to control the addition of ethylmagnesium bromide, and the tertiary alcohol was obtained.

(15) Radatus, B.; Fraser-Reid, B. *Can. J. Chem.* **1972**, *50*, 2909.
(16) Fitzsimmons, B. J.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1979**, *101*, 6123. Tam, T. F.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1980**, 556.
(17) See for example: Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; 1967, Vol. 1, p 442; "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 353.

The addition of vinylmagnesium bromide to glycose **17** afforded the allylic alcohol **19** in good yield, and oxidation with manganese dioxide now gave enone **20** as an amber syrup in 71% yield. After purification by preparative layer chromatography, the enone was hydrogenated over palladium, and after 6 h a slow-moving product, presumably **2** (R_f 0.05), had formed, but upon being allowed to stand for another 18 h, this gave way to a new substance (R_f 0.70). GLC and spectroscopic comparisons with authentic α-multistriatin obtained from Professor Silverstein established the authenticity of the material, and the optical rotation −19.0° was in good agreement with literature values −17.0°[1b,2] and −18.5°.[22]

Experimental Section

For "General Methods" section, see ref 7.

Ethyl 2,3-Dideoxy-2-*C*-methyl-α-D-*threo*-hexopyranosid-4-ulose (7a) and Its 6-*O*-Triphenylmethyl (7b), 6-*O*-Benzoyl (7c), and 6-*O*-Benzyl (7d) Derivatives. Conjugate addition of lithium dimethyl cuprate to the corresponding enones **6a–d** were carried out as previously described[9] by using methyllithium and cuprous iodide or tri-*n*-butyphosphine–cuprous iodide complex.

The physical constants of **7a** and **7b** have been published previously.[9]

The benzoate **7c** (yield 95%) was identified by deesterification to the known[9] **7a**: $[\alpha]^{23}_D$ +113.6° (*c* 28.9, chloroform); NMR ($CDCl_3$) δ 1.1 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.22 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 2.0–2.8 (m, 3, H-2 and H-3), 3.61 (q, 2, J_{gem} = 7 Hz, OCH_2CH_3), 4.38–4.95 (m, 3, H-5 and H-6), 4.68 (d, 1, $J_{1,2}$ = 5 Hz, H-1), 7.2–8.2 (m, 5, Ph).

For **7d**: yield 90%; R_f 0.57 [EtOAc–petroleum ether (3:7)]; $[\alpha]^{23}_D$ +40.3° (*c* 38.0, chloroform); mass spectrum, *m/e* 278 (M^+), 250 ($M^+ - CH_2CH_2$), 187 ($M^+ - PhCH_2$), 171 ($M^+ - PhCH_2O$), 157 ($M^+ - PhCH_2OCH_2$); NMR δ 1.1 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.22 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 1.8–2.6 (m, 3, H-2 and H-3), 3.78 (q, 2, J_{gem} = 7 Hz, OCH_2CH_3), 3.82 (d, 2, $J_{5,6}$ = 4 Hz, H-6), 4.25 (t, 1, $J_{5,6}$ = 4 Hz, H-5), 4.58 (s, 2, OCH_2Ph), 4.74 (d, 1, $J_{1,2}$ = 3 Hz, H-1), 7.35 (s, 5, OCH_2Ph).

Ethyl 2,3,4-Trideoxy-2-*C*-methyl-4-*C*-methylene-α-D-*threo*-hexopyranoside (8a) and Its 6-*O*-Triphenylmethyl (8b), 6-*O*-Benzoyl (8c), and 6-*O*-Benzyl (8d) Derivatives. *n*-Butyllithium was added to a stirred suspension of methyltriphenylphosphonium bromide (2.23 g, 0.0062 mol) in dry diethyl ether (50 mL) at room temperature under an argon atmosphere. After 1 h, the ketone (**7a–d**, 0.0031 mol) in diethyl ether (25 mL) was added dropwise to the reaction mixture. The reaction mixture was then allowed to stir for 6 h and then poured into a separatory funnel containing distilled water (100 mL). The ether layer was separated, washed with distilled water, and dried over magnesium sulfate. Column chromatography on silica gel then afforded the alkenes **8a–d**.

For **8a**: yield of syrupy product 21%; R_f 0.36 [ethyl acetate–petroleum ether (1:1)]; $[\alpha]^{23}_D$ +72.7° (*c* 21.3, chloroform); IR ν_{max} 3500 (OH), 3086 (terminal alkene), 1655 cm^{-1} (terminal alkene); mass spectrum, *m/e* 186 (M^+), 155 ($M^+ - HOCH_2$), 131 ($M^+ - CH_3CH_2O$); NMR δ 0.98 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.22 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 1.7–2.2 (m, 3, H-3 and OH), 2.4–2.9 (m, 1 H-2), 3.4–4.0 (m, OCH_2CH_3 and H-6), 4.3 (distorted t, 1, $J_{5,6}$ = 6 Hz, H-5), 4.53 (d, 1, $J_{1,2}$ = 3 Hz, H-1), 4.78 (br s, 1, H-8), 4.82 (br s, 1, H-8′).

For **8b**: yield 48%; recrystallized from ether, mp 119–120.5 °C; R_f 0.69 [ethyl acetate–petroleum ether (1:4)]; $[\alpha]^{23}_D$ +53.8° (*c* 11.75, chloroform); IR ν_{max} 3080 (terminal alkene), 3020 (terminal alkene), 1650 cm^{-1} (terminal alkene); NMR (220 MHz) δ 0.83 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.14 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 1.56–1.7 (m, 1, H-2), 1.72 (d, 1, H-3′), 2.27 (br d, 1, H-3), 2.91 (d, 1, $J_{5,6'}$ = 1 Hz, H-6′), 2.93 (d, 1, $J_{5,6}$ = 3 Hz, H-6), 3.11 (m, 1, *J* = 7 Hz, $OCHHCH_3$), 3.43 (m, 1, *J* = 7 Hz, $OCHHCH_3$), 3.86 (t, 1, H-5), 3.99 (d, 1, $J_{1,2}$ = 2 Hz, H-1), 4.07 (s, 1, H-8), 4.16 (s, 1, H-8), 7.28–7.66 (m, 15, phenyl). Anal. Calcd for $C_{29}H_{32}O_3$: C, 81.27; H, 7.53. Found: C, 81.13; H, 7.65.

For **8c**: yield of syrup 31% (plus 8a, 24%); R_f 0.60 [ethyl acetate–petroleum ether (3:7)]; NMR δ 1.0 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.22 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 1.8–2.3 (m, 2, H-3), 2.45–3.0 (m, 1, H-2), 3.35–4.05 (m, 4, H-6 and OCH_2CH_3), 4.6 (br s, 2, H-1 and H-5), 4.9 (br s, 2, H-8), 7.2–8.2 (m, 5, phenyl).

Hydrolysis of **8c** with methanol/water/triethylamine (5:4:1) for 8 h gave **8a**.

For **8d**: yield of syrup 88%; R_f 0.66 [ethyl acetate–petroleum ether (1:9)]; $[\alpha]^{23}_D$ +67.8° (*c* 41.3, chloroform); IR ν_{max} 1655 cm^{-1} (terminal alkene); mass spectrum, *m/e* 276 (M^+), 231 ($M^+ - CH_3CH_2O$), 230 ($M^+ - CH_2CH_2 - H_2O$), 199 ($M^+ - Ph$), 155 ($M^+ - PhCH_2OCH_2$); NMR δ 0.95 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.22 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 1.6–2.2 (m, 3, H-3, H-2), 3.3–4.0 (m, 4, H-6, OCH_2CH_3), 4.4 (br t, 1, H-5), 4.53 (s, 2, OCH_2Ph), 4.53 (d, 1, H-1), 4.78 (br s, 2, H-8), 7.3 (s, 5, OCH_2Ph).

Methyl 3,4-Dideoxy-4-*C*-methyl-6-*O*-(triphenylmethyl)-α-D-*threo*-hexopyranosid-2-ulose (10). The title compound has been prepared in 83% yield from enone **9**[18] by the addition of $LiMe_2Cu$ generated from methyllithium and cuprous iodide. The alternative procedure below has been found to give better yields.

Dimethyl sulfide–copper bromide[19] (17 g, 0.078 mmol) was suspended in dry diethyl ether (600 mL). The flask was then evacuated and filled with argon, the mixture was cooled to −78 °C, and methyllithium (0.156 mol) was added. The reaction mixture was allowed to warm until clear and was then cooled back to −78 °C. A solution of carbohydrate enone **9**[18] (16 g, 0.039 mol) in dry diethyl ether (150 mL) was added. After 0.5 h the reaction mixture was allowed to warm to −40 °C and was maintained at this temperature for an additional 0.5 h. The reaction mixture was washed with distilled water (4 × 300 mL). Column chromatography using 10% EtOAc in petroleum ether gave 15.69 g (94% yield) of product.

Methyl 2,3,4-Trideoxy-4-*C*-methyl-2-*C*-methylene-6-*O*-(triphenylmethyl)-α-D-*threo*-hexopyranoside (11). The Witting olefination of ketone **10** was carried out as described for ketones **7a–d**. The product, **11**, was isolated by chromatography on silica gel using 5% EtOAc in petroleum ether and was recrystallized from diethyl ether: mp 137–139 °C; R_f 0.33 [ethyl acetate–petroleum ether (1:19)]; $[\alpha]^{23}_D$ +48.2° (*c* 14.6, chloroform); NMR δ 0.68 (d, 3, $J_{4,8}$ = 6.7 Hz, H-8), 1.29 (m, 1, H-4), 1.95–2.20 (m, 1, H-3ax), 2.6–2.9 (m, 1, H-3eq), 2.95 (d, 1, $J_{5,6'}$ = 5.6 Hz, H-6), 3.25 (d, 1, $J_{5,6}$ = 6.7 Hz, H-6′), 3.47 (s, 3, OCH_3), 4.13–4.40 (m, 1, H-5), 4.84 (s, 2, H-7, H-7′), 4.95 (s, 1, H-1), 7.1–7.7 (m, 15, phenyl). Anal. Calcd for $C_{28}H_{30}O_3$: C, 81.13; H, 7.29. Found: C, 81.10; H, 7.27.

Methyl 2,3,4-Trideoxy-2,4-di-*C*-methyl-6-*O*-(triphenylmethyl)-α-D-*lyxo*- (3b) and -α-D-*arabino*-hexopyranoside (5). Alkene 11 (250 mg, 0.60 mmol) was dissolved in ethyl acetate (25 mL) and stirred with W-8 Raney nickel for 4 h to remove traces of phoshorus-containing impurities. The mixture was filtered, the catalyst to be investigated was added, and hydrogenation was allowed to proceed at atmospheric pressure and room temperature until TLC indicated completion. TLC in ethyl acetate–petroleum ether (1:19) indicated two products with R_f 0.27 and 0.23 whose ratio could be judged from the intensities of the C2 CH_3 signals at 0.97 and 1.1 ppm, respectively, in the 220-MHz spectra.

With W-8 Raney nickel as the catalyst, the ratio of **3a** and **5** in the crude mixture was 4:1, and the material recovered after chromatography weighed 224 mg.

With PtO_2 as catalyst the ratio of **3a** and **5** was 9:1, and the material recovered after chromatography weighed 248 mg.

For **3b**: mp 138–140 °C; $[\alpha]^{23}_D$ +29.1° (*c* 11.2, chloroform) (lit.[5] mp 140–142 °C; $[\alpha]_D$ +27.0°); R_f 0.23 [ethyl acetate–petroleum ether (1:19)]; NMR (220 MHz) δ 0.70 (d, 3, $J_{4,8}$ = 7.0 Hz, H-8's), 0.75 (complex m, 2, H-3a, H-3e), 0.97 (d, 3, $J_{2,7}$ = 7.0 Hz, H-7's), 1.74 (complex m, 2, H-2, H-4), 3.09 (dd, 1, $J_{5,6}$ = 4.5 Hz, $J_{6,6}$ = 10.0 Hz, H-6), 3.30 (dd, 1, $J_{5,6}$ = 8.0 Hz, H-6′), 3.51 (s, 3, OCH_3), 4.11 (complex m, 1, H-5), 4.29 (d, 1, $J_{1,2}$ = 5.0 Hz, H-1), 7.18–7.59 (complex m, 15, phenyl). Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.73; H, 7.74. Found: C, 80.74; H, 7.74.

For **5**: R_f 0.27 [ethyl acetate–petroleum ether (1:19)]; $[\alpha]^{23}_D$ +50.1° (*c* 2.7, chloroform); NMR δ 0.70 (d, 3, $J_{4,8}$ = 6 Hz, H-8), 1.1 (d, 3, J_{27} = 7 Hz, H-7), 1.50–2.10 (m, 4, H-2, H-3, H-4), 3.2

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(m, 2, H-6, H-6'), 3.50 (s, 3, OCH_3), 3.9–4.6 (br, 1, H-5), 4.45 (s, 1, $J_{1,2} \simeq 1.0$ Hz, H-1), 7.1–7.7 (m, 15, phenyl).

Ethyl 2,3,4-Trideoxy-2,4-di-*C*-methyl-6-*O*-(triphenylmethyl)-α-D-*lyxo*-(3a) and -α-D-*arabino*-hexopyranoside (4a). As in the case of **11** (vide supra), alkene **8b** was first treated with W-8 Raney nickel prior to the hydrogenation. In all cases the crude product mixture, analyzed by GLC, showed two products, **3a** and **4a**, whose retention times were 6.75 and 5.06 min, respectively. Hydrogenation using W-8 Raney nickel gave a 98% yield, and the ratio of **3a** and **4a** was 1:2:1. When PtO_2 was the catalyst the ratio was 2:2:1. Hydrogenation using freshly prepared $(Ph_3P)_3RhCl$[20] in dry, distilled benzene turned out to be very slow, requiring 4–5 days. The ratio of isomers was 3:1.

For **3a**: mp 115–118 °C; R_f 0.23 [ethyl acetate–petroleum ether (1:19)]; $[\alpha]^{23}_D$ +17.2° (*c* 119, chloroform); NMR (220 MHz) δ 0.70 (d, 3, $J_{4,8}$ = 7.2 Hz, H-8's), 0.96 (d, 3, $J_{2,7}$ = 7.0 Hz, H-7's), 0.82–1.16 (complex m, 2, H-3a, H-3e), 1.27 (t, 3, J = 7.2 Hz, OCH_2CH_3), 1.71 (complex m, 2, H-2, H-4), 3.11 (dd, 1, $J_{5,6}$ = 4.5 Hz, $J_{6,6}$ = 10.2 Hz, H-6), 3.30 (dd, 1, $J_{5,6}$ = 8.0 Hz, H-6'), 3.56 (complex m, 1, $OCHH'CH_3$), 4.05 (complex m, 1, $OCHH'CH_3$), 4.15 (m (ddd), 1, H-5), 4.41 (d, 1, $J_{1,2}$ = 6.0 Hz, H-1), 7.18–7.59 (complex m, 15, phenyl). Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.87; H, 7.89.

For **4a**: mp 120–121 °C; R_f 0.32 [ethyl acetate–petroleum ether (1:19)]; $[\alpha]^{23}_D$ +27.2° (*c* 46.3, chloroform); NMR (220 MHz) δ 0.59 (d, 3, $J_{4,8}$ = 6.5 Hz, H-8's), 1.08 (d, 3, $J_{2,7}$ = 7.0 Hz, H-7's), 1.24 (t, 4, J = 7.2 Hz, OCH_2CH_3, H-3a), 1.33 (complex m, 1, H-3e), 1.64 (complex m, 1, H-2), 1.82 (complex m, 1, H-4), 3.11 (dd, 1, $J_{5,6}$ = 3.5 Hz, $J_{6,6}$ = 10.0 Hz, H-6), 3.26 (dd, 1, $J_{5,6}$ = 2.2 Hz, H-6'), 3.49 (complex m, 2, $OCHH'CH_3$, H-5), 3.84 (complex m, 1, $OCHH'CH_3$), 4.57 (s, 1, $J_{1,2} \simeq 1.0$ Hz, H-1), 7.17–7.55 (complex m, 15, phenyl). Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.55; H, 7.93.

Alkyl 6-*O*-Benzyl-2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*lyxo*-hexopyranosides 3d and 3e. (a) Hydrogenation of alkene **8d** in dioxane over PtO_2 at room temperature afforded a 98% yield of a mixture of **3e** and its isomer **4b**. GLC (isothermal at 150 °C) showed two components with retention times of 8.25 and 12.0 min in a 2:6:1 ratio, respectively. However, the mixture was not resolved on TLC in several solvent systems.

(b) The tritylated di-*C*-methylpyranoside **3b** (600 mg, 1.44 mmol) was dissolved in dimethoxyethane (60 mL) and cooled to −40 °C, and liquid NH_3 (~60 mL) was condensed into the flask. Small pieces of clean Na metal were added until the blue color persisted, and after 1 h further, solid NH_4Cl was added in portions until the color was discharged. The mixture was allowed to warm to room temperature, and the NH_3 was blown away with a stream of dry N_2. The residue was taken up in dry ether (100 mL) and the solution was then filtered under gravity and dried ($MgSO_4$). (The alcohol **3c** was evident on TLC but it was not isolated.) To the dried filtrate were added NaH (4.2 mmol), $PhCH_2Br$ (0.84 mL, 7.2 mmol), and *n*-Bu_4NI (399 mg, 1.08 mmol), and the mixture was stirred under argon for 72 h. Wet diethyl ether was added to destroy excess NaH, and then the material was recovered in the usual way. Column chromatography using ethyl acetate–petroleum ether (1:19) afforeded **3d** (34.3 mg) as a syrup: R_f 0.20 [ethyl acetate–petroleum ether (1:19)]; $[\alpha]^{23}_D$ +47.2° (*c* 55.4, chloroform); mass spectrum, *m/e* 264 (M^+), 233 ($M^+ - CH_3O$), 173 ($M^+ - PhCH_2$), 143 ($M^+ - PhCH_2OCH_2$), 112 ($M^+ - CH_3O - PhCH_2O$); high-resolution mass spectrum for *m/e* 143 ($C_8H_{15}O_2$), calcd *m/e* 143.1246, found *m/e* 143.1243; NMR δ 0.9 (m, 3, H-8), 1.0 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.4–2.0 (m, 4, H-2, H-3, H-4), 3.45 (s, 3, OCH_3), 3.55 (m, 2, H-6, H-6'), 4.1 (m, 1, H-5), 4.3 (d, 1, $J_{1,2}$ = 5 Hz, H-1), 4.55 (s, 2, OCH_2Ph), 7.35 (s, 5, OCH_2Ph).

6-*O*-Benzyl-2,34-trideoxy-2,4-di-*C*-methyl-D-*lyxo*-hexopyranose (17). The glycoside **3d** (240 mg, 0.84 mmol) was dissolved in dimethoxyethane (45 mL) and distilled water (15 mL), and the resulting solution was boiled under reflux for 3 h. After cooling, the solution was extracted with CH_2Cl_2, and processing in the usual way afforded **17** (222 mg, 95%) as a syrup: R_f 0.15 [ethyl acetate–petroleum ether (1:4)]; $[\alpha]^{23}_D$ +16.2° (*c* 47.5, chloroform); IR ($CHCl_3$) 3410 cm^{-1}; mass spectrum, *m/e* 250 (M^+), 232 ($M^+ - H_2O$), 143 ($M^+ - PhCH_2O$), 129 ($M^+ - PhCH_2OCH_2$); NMR δ 0.82 (d, 3, J = 6 Hz, H-8), 0.95 (d, 3, $J_{2,7}$ = 7 Hz, H-7), 1.2–2.2 (m, 4, H-2, H-3, H-4), 3.4–4.2 (m, 4, H-5, H-6, OH), 4.5 (br s, 2, OCH_2Ph), 4.8 (br d, 1, H-1), 7.3 (s, 5, Ph).

Ethyl 6-*O*-Benzyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (6d). Ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranoside[21] (**12**; 500 mg, 2.9 mmol), benzyl bromide (0.7 mL, 4 mmol), and sodium hydride (100 mg, 4 mmol) were dissolved in dry tetrahydrofuran (50 mL) and kept in a refrigerator at −10 °C for 4 days. The solvent was evaporated, and the crude material was eluted down a silica gel column to yield the dibenzyl alkene **13c** (10 mg, 0.9%), the diol **12** (200 mg, 39%), and a mixture of the monobenzyl ethers **13a,b** (315 mg, 41%). GLC analysis showed two peaks: **13a**, 7.69 min, 67%; **13b**, 7.31 min, 33%. However, these were not resolved on TLC. The mixture of the monobenzylated alcohols (300 mg, 1.1 mmol) was dissolved in methylene chloride (40 mL), and active manganese dioxide[23] (1 g) was added. The reaction mixture was stirred at room temperature, and the progress of the reaction was followed on TLC. After 12 h a considerable amount of starting material was still present [R_f 0.44 (ethyl acetate-petroleum ether, 1:1)], but a new, higher running compound was also observed (R_f 0.87). The reaction mixture was filtered through Celite to remove the manganese dioxide and the solvent evaporated. The residue was eluted down a silica gel column to yield the enone **6d** (90 mg, 30%) and unchanged starting material (150 mL). GLC analysis of the latter showed a retention time of 7.31 min, and since further exposure to manganese dioxide caused no change, its structure is confirmed as **13b**. For **6d**: R_f 0.87 [ethyl acetate–petroleum ether (1:1)]; $[\alpha]^{32}_D$ −13.6° (*c* 29.8, chloroform); IR ($CHCl_3$) 1700 (C=O), 1640 cm^{-1} (alkene); UV (EtOH) λ_{max} 224 nm (ε 11 650); mass spectrum, *m/e* 262 (M^+), 141 ($M^+ - PhCH_2OCH_2$); NMR δ 1.23 (t, 3, J_{vic} = 7 Hz, OCH_2CH_3), 3.85 (q, 2, OCH_2CH_3), 3.91 (d, 2, J_{56} = 4 Hz, H-6), 4.6 (s, 2, OCH_2Ph), 4.6 (t, 1, $J_{5,6}$ = 4 Hz, H-5), 5.3 (d, 1, $J_{1,2}$ = 3 Hz, H-1), 6.1 (d, 1, $J_{2,3}$ = 10 Hz, H-3), 6.85 (dd, 1, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 7.4 (s, 5, Ph).

8-(Benzyloxy)-4,6-dimethyl-3-oxo-1-octen-7-ol (20). Into a dry three-necked flask equipped with a dry ice condenser, a rubber septum, and an argon atmosphere were placed magnesium turnings (0.50 g, 20 mmol), a few crystals of iodine, and dry tetrahydrofuran (10 mL). The solution was heated to reflux, and vinyl bromide (1.5 mL, 20 mmol) was added. After 15 min the deep orange color had been discharged and replaced by a pale green solution. Once the magnesium had reacted completely, the solution was allowed to cool down, compound **17** (500 mg, 2 mmol) in dry tetrahydrofuran (10 mL) was slowly added, and the reaction was followed on TLC. After 2 h aqueous ammonium chloride was slowly added to destroy the Grignard reagent. The solution was poured into a separatory funnel and extracted with methylene chloride. Upon evaporation of the solvent, the residue was purified by elution down a silica gel column to give **19** (425 mg, 76%) which exhibited the following spectral properties: R_f 0.43 [ethyl acetate–petroleum ether (bp 30–60 °C) (1:1); syrup; $[\alpha]^{23}_D$ −2.6° (*c* 32.7, chloroform); IR 3450 (OH), 3080 (terminal alkene), 1650 cm^{-1} (terminal alkene); mass spectrum, *m/e* 261 ($M^+ - OH$), 243 ($M^+ - H_2O - OH$), 169 ($M^+ - H_2O - PhCH_2$), 157 ($M^+ - PhCH_2OCH_2$), 139 ($M^+ - H_2O - PhCH_2OCH_2$); NMR δ 0.85 (br d, 6, J_{vic} = 7 Hz, $2CH_3$, overlapping), 1.4–2.0 (m, 4, H-4, H-5, H-6), 2.85 (br s, 2, OH), 2.2–4.0 (m, 4, H-3, H-7, H-8), 4.44 (s, 2, OCH_2Ph), 5.08 (d, 1, $J_{1(cis),2}$ = 12 Hz, H-1), 5.14 (d, 1, $J_{1(trans),2}$ = 15 Hz, H-1), 5.5–6.2 (m, 1, H-2), 7.32 (s, 5, phenyl).

Compound **19** (350 mg, 1.3 mmol) was dissolved in methylene chloride (25 mL) and manganese dioxide[23] (2.5 g) was added. The reaction mixture was stirred vigorously for 6 h and filtered through a Celite pad, and the solvent was evaporated. The pale amber syrup proved to be **20** (247 mg, 71%) which showed the following spectral data: R_f 0.54 [ethyl acetate–petroleum ether (bp 30–60 °C) (1:1)]; syrup; $[\alpha]^{23}_D$ +17.1° (c 23.3, chloroform); IR 3550 (OH), 3080 (terminal alkene), 1685 (C=O), 1625 cm^{-1} (alkene); UV (EtOH) λ_{max} 213 nm (ε 10 900); mass spectrum, *m/e* 276 (M^+), 258 ($M^+ - H_2O$), 231 ($M^+ - H_2O - CH_2CH_2$), 169 ($M^+ - PhCH_2O$), 157 ($M^+ - H_2O - PhCH_2$), 155 ($M^+ - PhCH_2OCH_2$); NMR δ 0.87

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(d, 3, J_{vic} = 7 Hz, CH_3), 1.07 (d, 3, J_{vic} = 7 Hz, CH_3), 1.4-2.0 (m, 3, H-5, H-6), 2.2 (br s, 1, OH), 2.85 (m, 1, H-4), 3.3 (s, 2, H-8), 3.4-3.8 (m, 1, H-7), 4.55 (br s, OCH_2Ph), 5.71 (dd, 1, $J_{1(cis),2}$ = 5 Hz, $J_{1(trans),2}$ = 9 Hz, H-2), 6.32 (d, 1, $J_{1(cis),2}$ = 5 Hz, H-1), 6.38 (d, 1, $J_{1(trans),2}$ = 9 Hz, H-1), 7.35 (s, 5, phenyl); high-resolution mass spectrum *m/e* 155 ($C_9H_{15}O_2$), calcd *m/e* 155.1090, found *m/e* 155.1093.

(-)-α-Multistriatin (1). The enone **20** (119 mg, 0.43 mmol) was dissolved in absolute ethanol (20 mL), and a catalytic amount of 10% palladium on charcoal was added carefully to the solution. The reaction mixture was stirred under a hydrogen atmosphere. After 6 h a new compound with R_f 0.05 [ethyl acetate-petroleum ether (3:7)] had been formed. However, within 18 h this was replaced by a compound with R_f 0.70 which was identical with authentic multistriatin. The solution was filtered through Celite and reduced in volume to about 10 mL. This was poured into a separatory funnel, and ether was added. The ether was washed several times to remove the ethanol present, dried over sodium sulfate, and blown off. The residue was purified on preparative TLC to give 1 (53 mg, 77%).

GLC of the product (isothermal 100 °C) showed a peak at 1.3 min which coincided precisely with authentic α-multistrain when coinjected: $[\alpha]^{23}_D$ -19.0° (c 1.2, chloroform); R_f 0.70 [ethyl acetate-petroleum ether (bp 30-60 °C) (3:7)]; mass spectrum, *m/e* 170 (M^+), 140 ($C_9H_{16}O^+$), 128 ($C_7H_{12}O_2$), 96 ($C_7H_{12}^+$), 86 ($C_5H_{10}O^+$), 71 ($C_4H_7O^+$); NMR δ 0.81 (d, 6, $J_{2,11}$ = 7 Hz, $J_{4,12}$ = 7 Hz, H-11, H-12), 0.92 (t, 3, $J_{9,10}$ = 7 Hz, H-10), 1.4-2.2 (m, 6, H-2, H-3, H-4), 3.68 (m, 1, H-7), 3.82 (d, 1, H-8'), 4.14 (m, 1, H-1).

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Registry No. (-)-**1**, 59014-03-8; **3a**, 73657-02-0; **3b**, 68880-95-5; **3d**, 80516-19-4; **3e**, 73656-96-9; **4a**, 73679-59-1; **4b**, 73679-57-9; **5**, 73679-58-0; **6d**, 73657-05-3; **7a**, 66149-53-9; **7b**, 66149-54-0; **7c**, 80516-20-7; **7d**, 80516-21-8; **8a**, 80516-22-9; **8b**, 73656-99-2; **8c**, 80516-23-0; **8d**, 80516-24-1; **9**, 35303-94-7; **10**, 66149-56-2; **11**, 73656-98-1; **12**, 23339-15-3; **13a**, 80516-25-2; **13b**, 58871-17-3; **13c**, 39798-87-3; **17**, 80516-26-3; **18**, 80516-27-4; **19**, 80516-28-5; **20**, 73657-04-2.

New Syntheses of Coumarins

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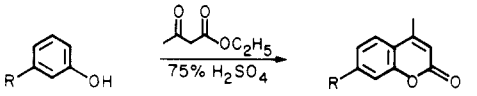
New, versatile coumarin syntheses have been developed which are based on the Claisen rearrangement of allylic or propargylic aryl ethers in which the allylic or propargylic α-carbon is further oxygenated. One proceeds by first ester exchange to the aryl dialkyl orthoacrylate which then thermally rearranges. Hydrolytic treatment gives the *o*-hydroxydihydrocinnamic acid from which the coumarin is obtained by ring closure and dehydrogenation. In parallel fashion, an orthopropiolate may be used, eliminating the dehydrogenation step. These processes have the advantage of avoiding the drastic acid conditions and orientation limitations of previous coumarin syntheses. They have been applied to syntheses in good yields of coumarins obtainable by previous methods in very poor yield or not at all.

The coumarin subunit is of interest because it is found in many natural products displaying diverse biological activities. The range of compounds includes antifungals,[1] anticoagulants,[2] compounds active against psoraris,[3] and carcinogens.[4] There have been many synthetic routes to the coumarins,[5,6] including the Perkin,[7] Knoevenagel,[8] Reformatsky,[9] and Pechmann[10] reactions. However, the Pechmann reaction has been the most widely applied method since it proceeds from simple and readily available educts. One can obtain in good yield coumarins substituted in either the pyrone or benzene ring or in both. The reaction, however, is dependent on the substituents on the phenol, on the condensing agent, and on the β-keto ester. For example, resorcinol (**1**) with 75% sulfuric acid and



1, R = OH
3, R = H

2, R = OH; 96%
4, R = H; 3%

ethyl acetoacetate gave 7-hydroxy-4-methylcoumarin (**2**) in 96% yield, while phenol (**3**) itself, when treated in an analogous fashion, afforded 4-methylcoumarin (**4**) in only 3% yield.[10] To avoid some of the adverse orienting effects and the harsh acid conditions of the Pechmann reaction, various other three-carbon moieties have been substituted for the β-keto ester component with some modest degree of success.[5,6]

With the objective of overcoming these deficiencies and difficulties, we have explored new routes to the coumarin ring system. The methods we have developed and now

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