Quassinoids: Total Synthesis of *dl*-Castelanolide

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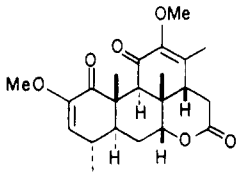
Received January 10, 1984

The total synthesis of *dl*-castelanolide (**5**) is described, which proceeds in 15.2% yield from the tetracyclic alcohol **8**, thus confirming the structural assignment made via classical methods by Geissman over ten years ago.

Many species of the botanical family Simaroubaceae have been known for over a century to contain bitter principles. Originally these bitter principles were collectively referred to as "quassin". The isolation of the individual constituents of "quassin" and the elucidation of their structures were resolved during the early sixties. It was Valenta and co-workers[1] who established by classical methods the structure and stereochemistry of quassin **1** and neoquassin **2**, which were first detected in the bitter



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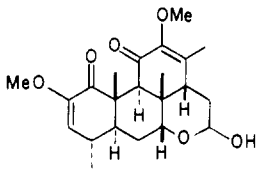

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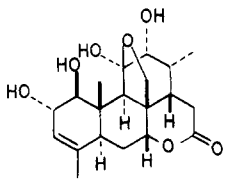
principles of *Quassia amara* in 1835.[2] It was ca. 20 years after the structural work was completed that the synthesis of quassin and neoquassin was reported.[3] Today all the closely related bitter principles of "quassin" are called quassinoids.[4]

Much attention remains focused on quassinoids[4,5] because of their potent in vivo antineoplastic activity,[6] demonstrated antimalarial properties.[7] and their ability to inhibit cell transformation.[8] At the time we initiated our synthetic studies on castelanolide, success at total synthesis in the quassinoid area remained limited to only one published account.[3] Recently Polonsky has described the transformation of the relatively abundant chaparrin **3** into castelanone **4**.[9]



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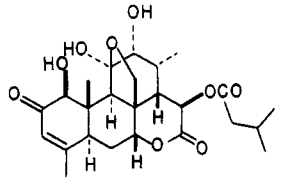

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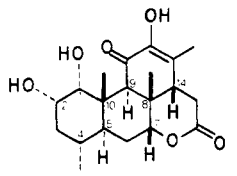
As a consequence of a detailed examination of the constituents of *Castela nicholsoni* (Simaroubaceae), a plant known to possess antiamebic activity, Geissman and coworkers isolated in the early seventies two new quassinoids, castelanolide (**5**) and chaparrolide (**6**).[10] We record below



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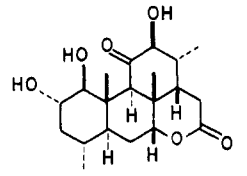

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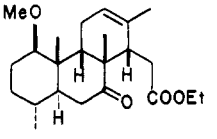
the complete details of the total synthesis of racemic castelanolide, which confirms the structural assignment put forth by Geissman over ten years ago.[11]

The location of the nine chiral centers in castelanolide coupled with its highly oxygenated carbon backbone suggested as a possible starting point the tetracyclic alcohol **8** prepared previously in connection with the total synthesis of *dl*-quassin via a four-step sequence from the known Diels–Alder adduct **7**.[3] The use of **8** in the synthesis of castelanolide ensures the proper configuration at six



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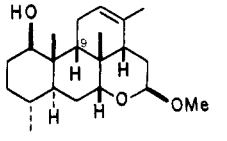

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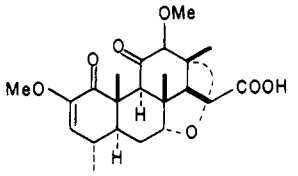
[C(4), C(5), C(7), C(8), C(10), and C(14)] of the nine chiral centers. The early structural studies on quassin by Robertson and co-workers[12] strongly suggested that the stereochemistry at C(9) in castelanolide could be established during the final stages of the synthesis since C(9) exists in its most stable configuration. This point was unequivocally established during the synthesis of quassin.[3] However, it should be noted that prior to equilibration at C(9), the D-ring δ-lactone must be in place and fully protected so as to avoid complications due to inversion of the stereocenter at C(14). For example, it has been previously shown that treatment of quassin with aqueous base at elevated temperatures gives rise to pseudoquassinolic acid **9**.[1b]



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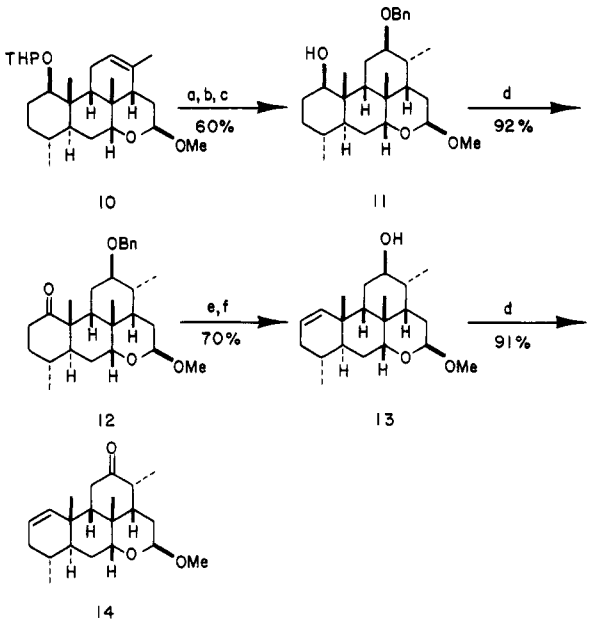
Results and Discussion

Our preliminary synthetic studies centered around incorporating oxygen into ring C of tetracyclic compound **8** and utilizing the C(1) hydroxyl for establishing the carbon–carbon double bond between C(1) and C(2) which ultimately would serve to introduce the C(1)–C(2) vicinal glycol structural unit of castelanolide. Toward this end we set out to convert alcohol **8** into tetracyclic ketone **14** (Chart I) by introducing oxygen into the C(12) position of **8**. Tetrahydropyranylation (DHP, PPTS,[13] CH_2Cl_2) of tetracyclic alcohol **8** proceeded in 97% yield, giving rise to **10** which was subjected to hydroboration using borane in tetrahydrofuran. Subsequent oxidation with alkaline aqueous hydrogen peroxide provided the corresponding tetracyclic alcohol. The β orientation of the hydroxyl corresponds to attack by borane from the least hindered convex face of **10**. Benzylation[14] of the hindered C(12) hydroxyl followed by cleavage of the C(1) tetrahydropyranyl ether gave rise to crystalline tetracyclic alcohol **11**, mp 140–141 °C, whose structure was fully supported by its ^1H NMR spectrum. Collins oxidation of **11** provided crystalline ketone **12**, mp 150.5–152.0 °C, which set the stage for introduction of the C(1)–C(2) olefin via a two-step sequence.[15] Phosphoroylation of the enolate generated by treatment of tetracyclic ketone **12** with lithium diisopropylamide in a mixture of tetrahydrofuran–hexamethylphosphoramide afforded the corresponding phosphorodiamidate which upon exposure to lithium in ethylamine–tetrahydrofuran simultaneously cleaved the phosphorodiamidate C–O ester bond and the benzyl ether, giving rise to crystalline tetracyclic olefin **13**, mp 129–130 °C, in 70% overall yield. Collins oxidation of alcohol **13** provided ketone **14**, mp 138.5–140.0 °C, in 91% yield.

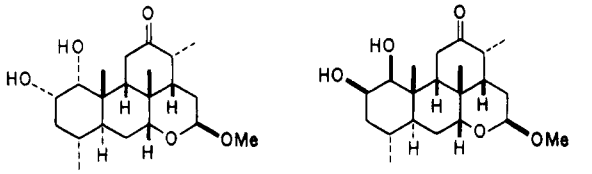
With the availability of olefin **14**, we briefly examined glycolation of the C(1)–C(2) olefin. Treatment of **14** with

Chart I[a]



[a] (a) BH_3·THF, THF, 0 °C → 25 °C, 3 h; 30% H_2O_2, 50 °C, 2 h; (b) NaH, THF, HMPA, BnBr, *n*-Bu_4NI, 55 °C, 17 h; (c) MeOH, PPTS, THF, 55 °C, 3.5 h; (d) $CrO_3(pyr)_2$, CH_2Cl_2, 25 °C; (e) LDA, THF, HMPA, −78 °C → 0 °C; $(Me_2N)_2POCl$, 0 °C (1.5 h) → 25 °C (2.0 h); (f) Li (15 equiv), $EtNH_2$–THF (2:1), *t*-BuOH (3.0 equiv), 0 °C, 1 h.

osmium tetroxide in pyridine followed by mild reduction of the osmate ester[16] provided a 1:1 mixture of glycols **15** and **16**. This result is not surprising in view of the fact



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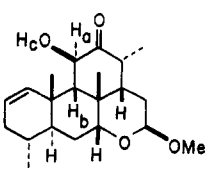
that Drieding models reveal that the C(11) β hydrogen hinders approach of the reagent from the α face of the double bond. It thus became clear that prior to glycolation of the C(1)–C(2) double bond the configuration at C(9) in **14** or its equivalent would have to be inverted. We therefore set out to introduce oxygen into the C(11) position of **14** so as to achieve the necessary inversion of configuration at C(9).

The solution to introducing oxygen into the C(11) position of **14** was made obvious by our earlier experiences in connection with the total synthesis of quassin.[3] The kinetic enolate of ketone **14** was treated with oxodiperoxy(pyridine)(hexamethylphosphoric triamide)molybdenum.[17] Workup afforded a 45% yield (77% based on recovered **14**) of crystalline hydroxy ketone **17**, mp 183–184



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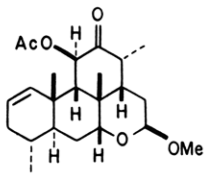
°C. The beta orientation of the hydroxyl function follows from inspection of the 220-MHz ^1H NMR spectrum of **17** in $CDCl_3$ which reveals H_a as a doublet of doublets centered at δ 4.34 with J_{ab} = 11.0 Hz and J_{ac} = 3.5 Hz. The exclusive formation of **17** was anticipated since examination of Dreiding models reveals that the bulky reagent can only interact with the enolate on the less-hindered convex face of the molecule.

That the C(11) hydroxyl was oriented β was also borne out by experiment. Acetate **18**, prepared in 94% yield by



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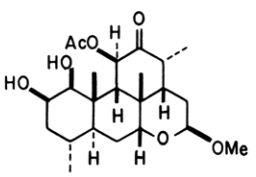

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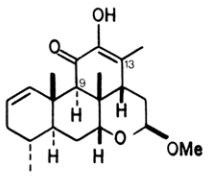
treatment of hydroxy ketone **17** with acetic anhydride in pyridine, upon osmylation gave rise to diol **19** as the sole product in 87% yield. In this case the C(11) acetoxy function completely blocks the α face of the C(1)–C(2) olefinic bond.

Having successfully introduced oxygen into the C(11) position of **14**, attention was focused on inverting the configuration at C(9). Treatment of **17** with sodium methoxide–methanol in dimethyl sulfoxide[18] gave rise in 91% yield to a single crystalline diosphenol, mp 168.5–169.0 °C, having structure **20**. Isomeric diosphenol



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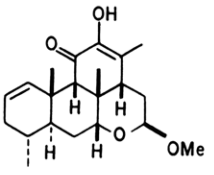

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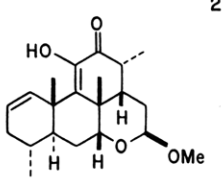

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22 was easily ruled out by examination of the 220-MHz ^1H NMR spectrum of the product, which displayed a one-proton singlet at δ 2.83 [C(9) proton] as well as a three proton singlet at δ 1.83 [C(13) methyl]. The ^1H NMR data are consistent with either structure **20** or **21**. In view of the basic conditions employed in the above reaction, coupled with our experience in the quassin series, we made the assumption that equilibration at C(9) had occurred. The structure of **20** need not be debated since this matter was unambiguously put to rest by its transformation into *dl*-castelanolide.

Prior to introduction of the C(1)–C(2) vicinal diol unit, it was elected to proceed first with unmasking the ring-D δ-lactone followed by protection of the diosphenol moiety. Hydrolysis of **20** with 10% aqueous hydrochloric acid in tetrahydrofuran followed by oxidation with Fetizon's reagent (Ag_2CO_3)[19] gave crystalline tetracyclic lactone **23**,

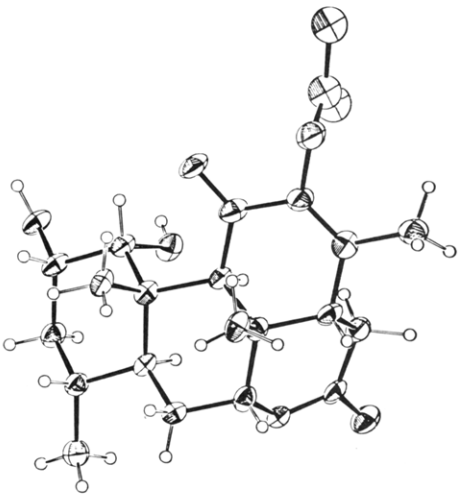
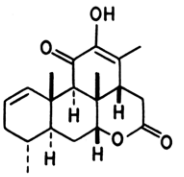


Figure 1.

mp 152–153 °C, in 81% overall yield. Protection (Ac_2O, pyridine) of the diosphenol moiety in **23** proceeded smoothly, giving rise to acetate **24** in 90% yield.



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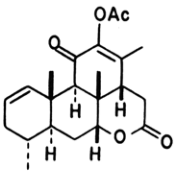
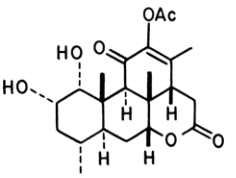


24

Oxidation of the C(1)–C(2) olefinic bond was accomplished by treatment of **24** with osmium tetroxide in pyridine followed by mild reduction ($NaHSO_3$),[16] affording (98%) crystalline racemic castelanolide monoacetate **25**, mp 207–209 °C. The α orientation of the vicinal diol unit was anticipated since one would expect osmium tetroxide to approach from the least hindered α face, away from the C(10) methyl group. Monoacetate **25** was identical by comparison of its spectral properties (^1H NMR, IR) with those of natural castelanolide monoacetate previously reported in the literature.[10]



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All that was required to complete the total synthesis of *dl*-castelanolide was cleavage of the acetate-protecting group in **25**. Treatment of **25** with potassium carbonate in methanol provided (91%) a single crystalline material, mp 135–137 °C, whose *^1H NMR spectrum was not in agreement with that previously recorded in the literature by Geissman.*[10] That the structure of the precursor monoacetate **25** was correct was unambiguously established by single-crystal X-ray analysis[20] (Figure 1). We were

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(20) Compound **25** crystallizes in space group $P\bar{1}$ with cell dimensions (at − 162 °C) of a = 9.706 (5) Å, b = 15.846 (9) Å, c = 7.330 (4) Å; α = 111.10 (2)°, β = 82.48 (3)°, and γ = 98.56 (3)°; V = 1036.51 Å^3; ρ_{calcd} = 1.302 g cm^{-3} (for Z = 2). A total of 5419 reflections were measured, of which 2600 were determined to be observable, $F_o > 2.33\sigma(F_o)$. All atoms, including hydrogens, were located and refined to final residuals of $R(F)$ = 0.0943 and $R_w(F)$ = 0.062.

indeed fortunate to be able to obtain a sample of natural castelanolide from the Geissman collection.[21] *As anticipated, our racemic sample of castelanolide was identical with the sample of the natural material by comparison of spectra* [^1H *NMR (220 MHz)*, IR] and thin-layer mobility in several solvent systems.

The total synthesis of *dl*-castelanolide was accomplished in 15 steps in 15.2% overall yield from the tetracyclic alcohol 8. The synthesis also confirms the structural assignment made by Geissman and co-workers in the early seventies.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were taken at either 90 MHz (Varian EM-390 spectrometer) or at 220 MHz as indicated. Chemical shifts are reported in δ downfield from tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer Model 298 spectrophotometer as a KBr pellet or in chloroform or carbon tetrachloride solution as indicated. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. E. Merck silica gel, 70–230 mesh, was used for column chromatography and Analtech precoated silica gel plates, 0.25-mm thickness, were used for analytical thin-layer chromatography (TLC). All solvents are reagent grade unless otherwise stated. "Dry" solvents were dried immediately before use. Dimethyl sulfoxide (Me_2SO), hexamethylphosphoramide (HMPA), pyridine, and diisopropylamine were distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Methylene chloride was dried by being passed through a column of alumina. Chromium trioxide was dried over phosphorus pentoxide.

(1β,9β,16β)-16-Methoxy-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]picras-12-ene (10). A solution of tetracyclic alcohol 8 (4.20 g, 12.6 mmol) and 40 mL of dihydropyran in 40 mL of dry methylene chloride containing 316 mg (1.26 mmol) of pyridinium *p*-toluenesulfonate[13] was stirred for 2.5 h at room temperature. The solution was concentrated in vacuo and the residue was chromatographed on 100 g of silica gel. Elution with hexane–ether (9:1) provided 5.11 g (97%) of **10** as a white semisolid: R_f 0.47 (ether–hexane, 1:3); IR (CCl_4) 2940, 1460, 1437, 1370, 1318, 1280, 1254, 1195, 1177, 1155, 1125, 1107, 1054, 1040, 1020, 987, 960, 917, 862, 842 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.82 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.65 (s, 3 H), 3.34 (s, 3 H).

(1β,9β,12β,16β)-16-Methoxy-12-(phenylmethoxy)picrasan-1-ol (11). To a stirred solution of olefin **10** (11.4 g, 27.2 mmol) in 280 mL of dry tetrahydrofuran was added dropwise at 0 °C under argon over 1 h 101.8 mL of a 0.94 M solution (95.3 mmol) of diborane in tetrahydrofuran. The mixture was warmed to room temperature. After 3 h, the solution was cooled to 0 °C and 132 mL of 3 N sodium hydroxide solution was carefully added dropwise followed by 100 mL of 30% hydrogen peroxide. The solution was heated at 50 °C for 2 h. Sodium chloride was added to the cooled (room temperature) reaction flask until saturation and 500 mL of ether was added. The organic layer was separated. The aqueous layer was extracted with ether (2 × 100 mL). The combined organic extracts were washed with 10% sodium sulfite (100 mL) and brine (100 mL). After drying ($MgSO_4$) and concentrating under reduced pressure, the crude product was chromatographed on 650 g of silica gel. Elution with hexane–ether (7:3) provided 9.62 g (81%) of (1β,9β,12β,16β)-16-methoxy-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]picrasan-12-ol as a white semisolid [higher R_f isomer: R_f 0.25 (ether–hexane, 1:1); ^1H NMR (220 MHz) ($CDCl_3$) δ 0.85 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H), 1.07 (d, 3 H, J = 7.0 Hz), 1.16 (s, 3 H), 3.29 (s, 3 H), 3.34 (m, 1 H), 3.46 (m, 1 H), 3.71 (m, 2 H), 4.02 (m, 1 H), 4.46 (m, 1 H), 4.77 (d, 1 H, J = 4.5 Hz); lower R_f isomer: R_f 0.18 (ether–hexane, 1:1); IR (CCl_4) 3500, 2930, 2857, 1452, 1445, 1431, 1386, 1370, 1355, 1230, 1125, 1062, 1050, 1015 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.84 (d, 3 H, J = 6.5 Hz), 1.05 (d, 3 H, J = 7.0 Hz), 1.12 (s, 3 H), 1.16 (s, 3 H), 3.30 (s, 3 H), 3.48 (m, 2 H), 3.66 (m, 2 H), 3.92 (m, 1 H), 4.66 (br s, 1 H), 4.76 (d, 1 H, J = 4.5 Hz)] which was employed directly in the next reaction.

To a stirred solution of the above alcohols (9.62 g, 22.1 mmol) in 290 mL of dry tetrahydrofuran and 7.67 mL (44.13 mmol) of dry hexamethylphosphoramide at 0 °C under argon was added 6.52 g (154 mmol, 56.8% oil dispersion) of sodium hydride. The solution was heated to 55 °C. Freshly distilled benzyl bromide (15.7 mL, 132 mmol) was added to the reaction flask followed by 4.07 g (11.03 mmol) of tetra-*n*-butylammonium iodide. After the reaction mixture was stirred at 55 °C for 17 h, it was cooled to 0 °C. The reaction was quenched by the addition of saturated ammonium chloride solution. The reaction mixture was concentrated in vacuo and the residue was taken up in ether (500 mL) and was washed with water (100 mL) and 10% sodium sulfite solution (100 mL). After drying ($MgSO_4$) and concentrating under reduced pressure, the crude product (31 g) was purified on 1.0 kg of silica gel. Elution with hexane–ether (9:1) gave 8.72 g (75%) of (1β,9β,12β,16β)-16-methoxy-12-(phenylmethoxy)-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]picrasane as a white foam [higher R_f isomer: R_f 0.53 (ether–hexane, 1:3); ^1H NMR (220 MHz) ($CDCl_3$) δ 0.86 (d, 3 H, J = 6.5 Hz), 0.92 (d, 3 H, J = 7.0 Hz), 1.02 (s, 3 H), 1.17 (s, 3 H), 3.26 (s, 3 H), 3.36 (m, 2 H), 3.63 (m, 1 H), 3.95 (m, 3 H), 4.71 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 85.2 Hz), 4.73 (d, 1 H, J = 4.5 Hz), 7.32 (m, 5 H); lower R_f isomer: R_f 0.45 (ether–hexane, 1:3); IR (CCl_4) 2950, 2870, 1495, 1462, 1452, 1440, 1395, 1376, 1360, 1243, 1205, 1152, 1132, 1072, 1054, 1045, 1030, 971, 952, 932, 902, 888 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.84 (d, 3 H, J = 6.5 Hz), 0.91 (d, 3 H, J = 7.0 Hz), 1.13 (s, 3 H), 1.16 (s, 3 H), 3.27 (s, 3 H), 3.39 (m, 2 H), 3.88 (m, 1 H), 4.48 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 73.0 Hz), 4.75 (m, 2 H), 7.31 (m, 5 H)] which was used directly in the next reaction.

A stirred solution of 8.72 g (16.58 mmol) of the above tetrahydropyranyl ethers in 145 mL of anhydrous methanol and 70 mL of dry tetrahydrofuran containing 416 mg (1.66 mmol) of pyridinium *p*-toluenesulfonate[13] was heated at 55 °C for 3.5 h. The solution was cooled to room temperature and concentrated in vacuo. The residue was chromatographed on 400 g of silica gel. Elution with hexane–ether (4:1) provided 7.04 g (96%) of crystalline **11**, mp 140–141 °C: R_f, 0.51 (ether–hexane, 1:1); IR (CCl_4) 3620, 3480, 2940, 2920, 2890, 2860, 1455, 1448, 1370, 1354, 1233, 1130, 1085, 1051, 1028, 998, 980, 950, 927, 902, 881 cm^{-1}; NMR (220 MHz) (CCl_4) δ 0.86 (d, 3 H, J = 6.5 Hz, C(4) methyl), 0.98 (d, 3 H, J = 7.0 Hz, C(13) methyl), 1.00 (s, 3 H), 1.14 (s, 3 H), 3.20 (s, 3 H, OCH_3), 3.30 (m, 1 H), 3.57 (br s, 2 H), 4.43 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 84.1 Hz, benzylic protons), 4.61 (m, 1 H, C(16) proton), 7.27 (m, 5 H). An analytical sample was prepared by recrystallization from hexane–ether; mp 140–141 °C. Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.98; H, 9.56. Found: C, 76.12, H, 9.40.

(9β,12β,16β)-16-Methoxy-12-(phenylmethoxy)picrasan-1-one (12). Dry pyridine (9.95 mL, 124 mmol) and 150 mL of dry methylene chloride were added to a 500-mL three-necked flask equipped with a mechanical stirrer under argon. The stirred solution was cooled to 0 °C, and 6.18 g (61.8 mmol) of dry chromium trioxide was added. After 30 min at 0 °C, dry Celite (31 g) was added and the mixture was warmed to room temperature followed by the addition of 1.82 g (4.12 mmol) of alcohol **11** in 10 mL of dry methylene chloride. The reaction was quenched by the addition of 31 g of sodium bisulfate monohydrate. After 10 min, the mixture was diluted with 200 mL of ether and filtered through a silica gel/Celite/$MgSO_4$ pad. The filter pad was washed thoroughly with ether. Concentration under reduced pressure afforded crude ketone (1.88 g), which was purified on 60 g of silica gel. Elution with hexane–ether (3:1) afforded 1.67 g (92%) of crystalline **12**: mp 150.5–152.0 °C; R_f 0.53 (ether–hexane, 1:1); IR (CCl_4) 2940, 1700, 1446, 1370, 1352, 1233, 1130, 1050, 1027, 988, 966, 929, 877 cm^{-1}; ^1H NMR (220 MHz) (CCl_4) δ 0.99 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.03 (d, 3 H, J = 7.0 Hz, C(13) methyl), 1.10 (s, 3 H), 1.18 (s, 3 H), 2.27 (dt, 1 H, J = 5, 16 Hz), 2.44 (ddd, 1 H, J = 5, 10, 16 Hz), 3.20 (s, 3 H, OCH_3), 3.60 (br s, 1 H), 4.35 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 122.4 Hz, benzylic protons), 4.60 (s, 1 H, C(16) proton), 7.1–7.4 (m, 5 H). An analytical sample was prepared by recrystallization from methylene chloride–ether, mp 150.5–152 °C. Anal. Calcd for $C_{28}H_{40}O_4$: C, 76.33; H, 9.15. Found: C, 76.34; H, 8.98.

(21) A sample of natural castelanolide was kindly provided by Professor Robert V. Stevens (UCLA).

(9β,12β,16β)-16-Methoxy-12-(phenylmethoxy)picras-1-en-1-ol Tetramethylphosphorodiamidate. Diisopropylamine (103 μL, 0.740 mmol) and 1.0 mL of dry tetrahydrofuran was added to a dry 10-mL, two-necked flask under argon. The stirred solution was cooled to −78 °C and 296 μL of a 2.33 M (0.691 mmol) solution of *n*-butyllithium in hexane was added dropwise. A solution of 217 mg (0.493 mmol) of ketone **12** in 1.0 mL of dry tetrahydrofuran containing 400 μL of dry hexamethylphosphoramide was added dropwise to the LDA solution. After addition was complete, the reaction was warmed to 0 °C where stirring was continued for 30 min prior to the addition of 400 μL (2.71 mmol) of bis(dimethylamino)phosphorochloridate. After 1.5 h at 0 °C, the temperature was warmed to 25 °C (2 h). The reaction was quenched by the addition of 2 mL of a saturated ammonium chloride solution. After concentration under reduced pressure, the residue was taken up in 50 mL of ether and washed with 10 mL of water. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product (480 mg) was purified on 10 g of silica gel. Elution with ethyl acetate afforded 218 mg (77%) of crystalline (9β,12β,16β)-16-methoxy-12-(phenylmethoxy)picras-1-en-1-ol tetramethylphosphorodiamidate: IR ($CHCl_3$) 2970, 2915, 1670, 1460, 1380, 1370, 1313, 1195, 1147, 1065, 1039, 1006, 932, 922, 907, 892, 838, 812 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.91 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.40 (d, 3 H, J = 7.0 Hz, C(13) methyl), 1.13 (s, 3 H), 1.30 (s, 3 H), 2.55 (d, 6 H, J = 10.5 Hz), 2.57 (d, 6 H, J = 10.5 Hz), 3.31 (s, 3 H, OCH_3), 3.38 (m, 1 H), 3.71 (s, 1 H), 4.55 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 113.3 Hz, benzylic protons), 4.77 (m, 1 H, C(16) proton), 5.11 (d, 1 H, J = 5 Hz, C(2) olefinic proton), 7.2–7.5 (m, 5 H). An analytical sample was prepared by recyrstallization from methylene chloride–ether, mp 176–177 °C. Anal. Calcd for $C_{32}H_{51}N_2O_5P$: C, 66.87; H, 8.94; N, 4.87; P, 5.39 Found: C, 67.05; H, 8.82; N, 4.80; P, 5.49.

(9β,12β,16β)-16-Methoxypicras-1-en-12-ol (13). To a solution of 68 mg (9.73 mmol) of lithium in ca. 25 mL of dry ethylamine (dried by prior sequential distillation from potassium hydroxide and sodium/lithium) cooled to 0 °C was added 373 mg (0.649 mmol) of (9β,12β,16β)-16-16-methoxy-12-(phenylmethoxy)picras-1-en-1-ol tetramethylphosphorodiamidate in 13 mL of dry tetrahydrofuran containing 183 μL (1.95 mmol) of dry *t*-butyl alcohol. The reaction was stirred for 40 min at 0 °C and 1 h at reflux. The reaction was quenched by the addition of 10 mL of a saturated ammonium chloride solution. The ethylamine was evaporated by a stream of air, and the residue was taken up in 100 mL of ether and 20 mL of water. The aqueous layer was extracted with 50 mL of ether, and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product (238 mg) was chromatographed on 10 g of silica gel. Elution with hexane–ether (7:3) afforded 196 mg (90%) of crystalline **13**: mp 129–130 °C; R_f 0.57 (ether–hexane, 2:1); IR (CCl_4) 3620, 3460, 2960, 2920, 2828, 1460, 1380, 1367, 1244, 1195, 1139, 1060, 1028, 1004, 987, 970, 938, 908, 890, 883, 868 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.93 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.06 (d, 3 H, J = 7.0 Hz, C(13) methyl), 1.12 (s, 3 H), 1.15 (s, 3 H), 3.30 (s, 3 H, OCH_3), 3.68 (m, 1 H), 3.73 (br s, 1 H), 4.77 (d, 1 H, J = 5 Hz, C(16) proton), 5.41 (dd, 1 H, J = 5, 11 Hz, C(2) olefinic proton), 5.48 (d, 1 H, J = 11 Hz, C(1) olefinic proton). An analytical sample was prepared by recrystallization from methylene chloride–ether, mp 129–130 °C. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41, H, 10.24. Found: C, 75.59; H, 10.03.

(9β,16β)-16-Methoxypicras-1-en-12-one (14). Dry pyridine (1.39 mL, 17.25 mmol) and 30 mL of dry methylene chloride were added to a dry 100-mL, three-necked flask equipped with a mechanical stirrer under argon. The stirred solution was cooled to 0 °C, and 862 mg (8.62 mmol) of dry chromium trioxide was added. After 30 min, dry Celite (4.3 g) was added and the reaction flask was warmed to room temperature prior to addition of 192 mg (0.575 mmol) of alcohol **13** in 3 mL of dry methylene chloride. The reaction was stirred for 30 min at room temperature. The reaction was quenched by the addition of 4.3 g of sodium bisulfate monohydrate. The mixture was diluted with 50 mL of ether and filtered through a silica gel/Celite/$MgSO_4$ pad. The filter pad was washed thoroughly with ether. Concentration under reduced pressure afforded crude ketone (192 mg), which was purified on 6 g of silica gel. Elution with hexane–ether (7:3) provided 174 mg (91%) of crystalline **14**: mp 138.5–140.0 °C; R_f 0.60, (ether–hexane), 1:1); IR (CCl_4) 3015, 2960, 2910, 2818, 1720, 1464, 1450, 1417, 1398, 1392, 1379, 1371, 1243, 1191, 1143, 1130, 1060, 1037, 1022, 1004, 990, 980, 969, 946, 935, 910, 844, 867 cm^{-1}; NMR (220 MHz) (CCl_4) δ 0.93 (m, 6 H, C(4) and C(13) methyls), 1.13 (s, 3 H), 1.26 (s, 3 H), 2.73 (m, 1 H), 3.24 (s, 3 H, OCH_3), 3.75 (s, 1 H, C(7) proton), 4.63 (d, 1 H, J = 5 Hz, C(16) proton), 5.38 (s, 2 H, C(1) and C(2) olefinic protons). An analytical sample was prepared by recrystallization from hexane–ether; mp 138.5–140 °C. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.07; H, 9.78.

(9β,11β,16β)-11-Hydroxy-16-methoxypicras-1-en-12-one (17). Diisopropylamine (109 μL, 0.778 mmol) and 2.0 mL of dry tetrahydrofuran were added to a dry 10-mL two-necked flask under argon. The stirred solution was cooled to −78 °C, and 321 μL (0.748 mmol) of *n*-butyllithium in hexane was added dropwise followed by the addition (5 min) of a solution of 199 mg (0.599 mmol) of ketone **14** in 2.0 mL of dry tetrahydrofuran. After 20 min at −78 °C, the solution was warmed to −10 °C and 390 mg (0.898 mmol) of oxodiperoxy(pyridine)(hexamethylphosphoric triamide)molybdenum[17] was added at once by means of an L-shaped tube which was fitted with the calculated amount of reagent at the start of the experiment. The solution rapidly became yellow-green and after about 1 min was brown in color. After 5 min at −10 °C the reaction mixture was quenched with 2 mL of a saturated sodium sulfite solution. The flask was warmed to room temperature and 3 mL of water was added to give two homogeneous layers. After 15 min the layers were separated and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product (250 mg) was chromatographed on 15 g of silica gel. Elution with hexane–ether (3:1) afforded 82 mg (41%) of recovered **14**. Continued elution afforded 94 mg (45%, 77% based on recovered starting material) of crystalline **17**: mp 183–184 °C; R_f 0.45 (ether–hexane, 1:1); IR ($CHCl_3$) 3600, 3460, 3000, 2955, 2910, 2835, 1720, 1450, 1375, 1140, 1050, 1030, 997, 960, 937 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.94 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.07 (d, 3 H, J = 7.0 Hz, C(13) methyl), 1.20 (s, 3 H), 1.31 (s, 3 H), 3.04 (m, 1 H), 3.09 (d, 1 H, J = 3.5 Hz, OH), 3.30 (s, 3 H, OCH_3), 3.76 (br s, 1 H, C(7) proton), 4.34 (dd, 1 H, J = 3.5, 11.0 Hz, C(11) proton), 4.61 (t, 1 H, J = 4.5 Hz, C(16) proton), 5.36 (dd, 1 H, J = 5.5, 10.5 Hz, C(2) olefinic proton), 5.96 (d, 1 H, J = 10.5 Hz, C(1) olefinic proton). An analytical sample was prepared by recrystallization from methylene chloride–ether; mp 183–184 °C. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.34; H, 9.09.

(16β)-12-Hydroxy-16-methoxypicrasa-1,12-dien-11-one (20). To a stirred solution of 377 mg (1.08 mmol) of hydroxy ketone **17** in 800 μL of dry dimethyl sulfoxide and 16 μL of anhydrous methanol under argon was added 644 mg (11.9 mmol) of sodium methoxide. After the reaction mixture was stirred at 55 °C for 1 h, the temperature was raised to 95 °C where stirring was continued for 1.5 h. The reaction was cooled to room temperature and 25 mL of water was added. The product was isolated by extraction with ethyl acetate (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with hexane–ether (17:3) afforded 340 mg (91%) of crystalline **20**: mp 168.5–169.0 °C; R_f 0.56 (ether–hexane, 1:2); IR ($CHCl_3$) 3460, 3000, 2960, 2940, 2830, 1685, 1650, 1443, 1392, 1365, 1294, 1269, 1200, 1182, 1051, 1030, 1000, 990, 900 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.06 (s, 3 H), 1.17 (s, 3 H), 1.83 (s, 3 H, C(13) methyl), 2.30 (dd, 1 H, J = 5.0, 11.0 Hz, C(14) proton), 2.83 (s, 1 H, C(9) proton), 3.37 (s, 3 H, OCH_3), 3.66 (br s, 1 H, C(7) proton), 4.85 (d, 1 H, J = 4.0 Hz, C(16) proton), 5.42 (br d, 1 H, J = 10.0 Hz, C(2) olefinic proton), 6.17 (s, 1 H, OH), 6.48 (d, 1 H, J = 10.0 Hz, C(1) olefinic proton). An analytical sample was prepared by recrystallization from hexane–ether; mp 168.5–169.0 °C. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.00; H, 8.58.

12-Hydroxypicrasa-1,12-diene-11,16-dione (23). A solution of 26 mg (0.075 mmol) of diosphenol **20** and 500 μL of tetrahydrofuran containing 300 μL of 10% hydrochloric acid solution was heated at reflux for 1 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in 40 mL of ether and was washed with 20 mL of saturated sodium bicarbonate solution. The ether layer

was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo, leaving 31 mg of crude lactol which was dissolved in 10 mL of benzene under argon. Silver carbonate[19] (800 mg, 48% by weight) was added and the stirred reaction mixture was heated at reflux for 2.5 h. After being cooled to room temperature, the reaction mixture was filtered through a Celite pad. The filter pad was washed thoroughly with ether. Concentration under reduced pressure left 30 mg of crude product which was purified on 3 g of silica gel. Elution with hexane–ether (7:3) gave 20 mg (91%) of crystalline **23**: mp 152–153 °C; R_f 0.33 (ether–hexane, 2:1); IR ($CHCl_3$) 3450, 2963, 2918, 2837, 1722, 1685, 1655, 1443, 1390, 1378, 1367, 1341, 1315, 1290, 1275, 1188, 1130, 1032, 1002, 992, 910 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.91 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.20 (s, 6 H), 1.89 (s, 3 H, C(13) methyl), 2.62 (s, 1 H, C(9) proton), 2.95 (dd, 1 H, J = 5.0, 16.0 Hz), 4.34 (br t, 1 H, J = 3 Hz, C(7) proton), 5.46 (br d, 1 H, J = 10 Hz, C(2) olefinic proton), 6.20 (s, 1 H, OH), 6.41 (d, 1 H, J = 10 Hz, C(1) olefinic proton). An analytical sample was prepared by recrystallization from hexane–ether; mp 152–153 °C. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.82; H, 7.87.

12-(Acetyloxy)picrasa-1,12-diene-11,16-dione (24). To a solution of diosphenol **23** (140 mg, 0.424 mmol) in 3 mL of dry pyridine at room temperature was added 400 μL (4.24 mmol) of acetic anhydride. After 1.25 h, the reaction mixture was diluted with 150 mL of methylene chloride, washed with saturated copper sulfate solution (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue (160 mg) was chromatographed on 10 g of silica gel. Elution with hexane–ether (3:7) gave 141 mg (90%) of crystalline **24**: mp 160–161 °C; R_f 0.45 (ether); IR ($CHCl_3$) 3020, 2960, 2910, 2870, 2830, 1760, 1730, 1690, 1665, 1440, 1372, 1345, 1330, 1296, 1274, 1180, 1116, 1080, 1028, 1003, 990, 930, 915, 904, 883 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.20 (s, 3 H), 1.30 (s, 3 H), 1.83 (s, 3 H, C(13) methyl), 2.25 (s, 3 H, acetyl methyl), 2.61 (s, 1 H, C(9) proton), 2.96 (dd, 1 H, J = 4.5, 17 Hz), 4.37 (t, 1 H, J = 2.5 Hz, C(7) proton), 5.43 (ddd, 1 H, J = 2.0, 5.0, 10.0 Hz, C(2) olefinic proton), 6.34 (d, 1 H, J = 10.0 Hz, C(1) olefinic proton). An analytical sample was prepared by recrystallization from methylene chloride–ether: mp 160–161 °C. Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 70.85; H, 7.80.

(1α,2α)-12-(Acetyloxy)-1,2-dihydroxypicras-12-ene-11,16-dione (25). To a stirred solution of olefin **24** (29 mg, 0.078 mmol) in 500 μL of dry pyridine at room temperature under argon was added 21.8 mg (0.086 mmol) of solid osmium tetraoxide. After 25 min the brown complex that had separated was decomposed by the addition of 500 μL of pyridine and a solution of 81 mg of sodium bisulfite in 800 μL of water. Stirring for 1 h at room temperature gave a light brown solution which was taken up in 50 mL of ethyl acetate. The organic layer was washed with saturated copper sulfate solution (2 × 25 mL), water (25 mL), and brine (25 mL). Concentration of the dried ($MgSO_4$) organic layer in vacuo left 50 mg of a residue which was chromatographed on 3 g of silica gel. Elution with hexane–ethyl acetate (3:7) afforded 31 mg (98%) of crystalline racemic monoacetate **25**: mp 207–209 °C; R_f 0.43 (ethyl acetate); IR ($CHCl_3$) 3500, 3000, 2960, 2930, 1755, 1725, 1690, 1665, 1447, 1400, 1376, 1350, 1300, 1280, 1182, 1120, 1032, 990, 952, 920, 820 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 0.89 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.05 (s, 3 H), 1.30 (s, 3 H), 1.83 (s, 3 H, C(13) methyl), 2.24 (s, 3 H, acetyl methyl), 2.94 (dd, 1 H, J = 7.0, 18 Hz), 3.39 (s, 1 H, C(9) proton), 3.99 (m, 1 H, C(2) proton), 4.30 (br s, 1 H, C(7) proton), 4.49 (d, 1 H, J = 2.5 Hz, C(1) proton). An analytical sample was prepared by recrystallization from methylene chloride–ether mp 207–209 °C. Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.21; H, 7.48.

***dl*-Castelanolide (5).** To a stirred solution of monoacetate **25** (32 mg, 0.078 mmol) in 5 mL of anhydrous methanol was added 50 mg of anhydrous potassium carbonate. After 15 min, 50 mL of methylene chloride was added and the solution was washed with 3% hydrochloric acid (20 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). After drying over anhydrous sodium sulfate, the organic layer was concentrated in vacuo and the residue was chromatographed on 1 g of silica gel. Elution with ethyl acetate afforded 26 mg (91%) of crystalline racemic castelanolide **5**; mp 135–137 °C; R_f 0.32 (hexane–ethyl acetate, 2:3); IR (KBr) 3500, 3400, 1935, 1860, 1730, 1685, 1655, 1445, 1390, 1235, 1125, 1040, 955, 918 cm^{-1}; NMR (220 MHz) (acetone-d_6) δ 0.89 (d, 3 H, J = 6.5 Hz, C(4) methyl), 1.10 (s, 3 H), 1.23 (s, 3 H), 1.85 (s, 3 H, C(13) methyl), 2.96 (dd, 1 H, J = 5, 18 Hz), 3.48 (s, 1 H, C(9) proton), 3.96 (m, 1 H, C(2) proton), 4.36 (br s, 1 H, C(7) proton), 4.52 (d, 1 H, J = 2.5 Hz, C(1) proton). An analytical sample was prepared by recrystallization from chloroform, mp 135–137 °C. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.87; H, 7.73.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute and, in part, by G. D. Searle and Co. We are grateful to Professor Giovanni Vidari for numerous discussions during the early stages of this work and Drs. J. C. Huffman and K. Folting for carrying out a single-crystal X-ray analysis of monoacetate **25**.

Out-of-Ring Claisen Rearrangements are Highly Stereoselective in Pyranoses: Routes to *gem*-Dialkylated Sugars[1]

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Received November 7, 1983

The Claisen rearrangement has been evaluated as a means for stereoselective creation of functionalized geminal substituents at C-2 and C-3 of hexopyrano systems. C-2 and C-3 keto sugars react with Wittig reagents to give α,β-unsaturated esters, one geometric isomer being obtained in each case. Reduction of the ester and trans vinylation with ethyl vinyl ether leads to allyl vinyl ethers which are thermolyzed in refluxing benzonitrile. The oxy-Cope rearrangement proceeds with complete stereoselectivity, the folding pattern being always from the β-face of the pyranose ring. Thus, the acetaldehyde moiety ends up axially oriented at C-2 and equatorially oriented at C-3. These stereochemical results are not affected by neighboring oxygen substituents nor by the presence or absence of an anomeric alkoxyl functionality.

In connection with a number of syntheses under way in our laboratory we need to be able to convert a secondary alcohol of a sugar residue into a functionalized *gem*-dialkyl center, e.g., I → III. Pathways involving α-alkylation of

0022-3263/84/1949-2347$01.50/0