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A MODEL FOR TRITERPENE SIDE-CHAIN SYNTHESIS

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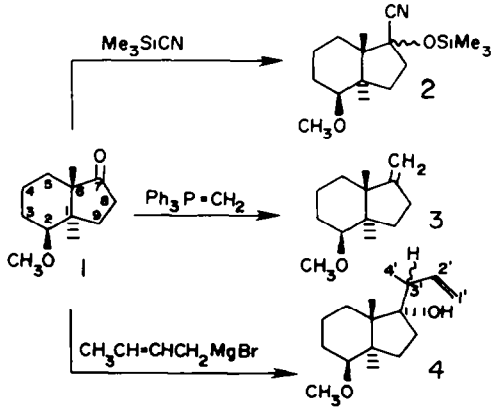
Abstract—Although the hindered CO function in *trans* - 1,6 - dimethyl - 2 - methoxybicyclo[4.3.0]nonan - 7 - one (**1**) resists nucleophilic addition and is prone to enolate formation, good yields of addition products from trimethylsilyl cyanide, methylenetriphenylphosphorane and crotyl magnesium bromide were obtained. Efforts to transform the methallyl adduct **4** from the latter reaction to a C_8H_{17} terpenoid side chain failed because of a facile Me shift in the course of dehydration of the 3°-alcohol. The nature of this rearrangement was demonstrated by conversion of rearranged olefin **5** to unsaturated ketone **11**. Introduction of the terpenoid side chain was eventually accomplished by conversion of **1** to the *E*-ethylidene derivative **13**, from there to the 7β-acetyl intermediate **17**, and finally to a mixture of side chain epimers **19** by a Wittig condensation followed by hydrogenation. Interesting stereochemical differences in reactions of **1** compared with 17-ketosteroids are noted.

Steroid side chains, especially those exhibiting chirality at C-20, have been the target of many synthesis efforts. In addition to those described in the excellent review by Piatak and Wicha,[1] several stereoselective methods based on electrocyclic and sigmatropic reactions have been reported over the past two years.[2] Despite obvious similarities to the steroids, very little attention has been directed to the construction of triterpene side chains. Thus Woodward's classical synthesis of lanosterol[3] began with cholesterol, and the existing side chain was simply maintained. The polyene cyclization approach to triterpene synthesis used by van Tamelen[4] involved construction of the side chain prior to formation of the tetracyclic skeleton.

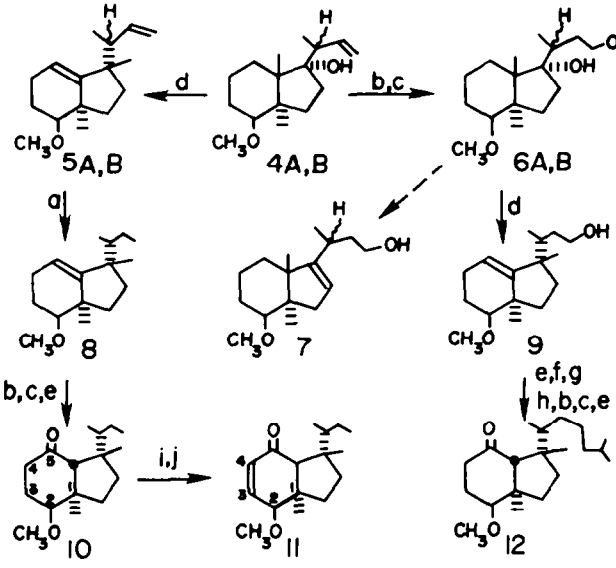
As part of our program for the synthesis of tetracyclic triterpenes, we have explored methods for introducing a branched side chain at the CO function of the useful bicyclic model compound **1**. Since this model incorporates both the angular Me substituents found at the C,D-ring fusion in triterpenes of the lanostane, euphane and cucurbitane families, we are confident that our procedures will be effective with 17-keto derivatives of these ring systems. The CO function in **1** is known[5] to be sluggish in reacting with nucleophilic reagents, and is prone to enolate formation when treated with strong bases. Consequently, we were concerned that **1** might prove exceptionally resistant to nucleophilic addition. Fortunately this is not the case, and a number of potentially useful reactions of this kind have been achieved. These include additions of trimethylsilyl cyanide, methylenetriphenylphosphorane and crotyl magnesium bromide[5,6] (Scheme 1).



Scheme 1.

Although silyl cyanide addition and diisobutylaluminum hydride (DIBAH) reduction of **1**[5] gave mixtures of stereoisomers at C-7, allyl and crotyl Grignard reagents add in a stereoselective fashion. Since the methallyl adduct **4** incorporates two new chiral centers, four diastereomers are possible. Chromatography, ^1H NMR and ^{13}C NMR clearly show that two stereoisomers (**A** and **B**) are formed, and subsequent dehydration indicates that this stereoisomerism lies at the 3' C of the side chain and not at C-7. Crotyl reagents of Cr,[7] Cd[8] and Zn[8] were also examined, but all proved unreactive with **1**. Although the Grignard addition tolerated a wide variation in temperature, the stereoselectivity at C-3' showed only slight improvement (*ca* 3:1) on cooling to −100°. The assignment of configuration at C-7 in the Grignard adduct **4** is based in part on the similar proton chemical shifts of the angular Me groups—a distinguishing feature in the epimeric alcohols formed by DIBAH reduction of **1**.[5,9] Molecular models also show that a 7β-alkyl substituent should be more stable than the 7α-isomer. A previously reported[18] adduct from crotyl magnesium bromide and a bicyclic ketone similar to **1**, but lacking the C-1 angular Me group (i.e. a steroid CD moiety), was assigned the opposite configuration at C-7, in keeping with the relatively low hindrance of the α-face. Furthermore, Inhoffen *et al.* found[18] that acid-catalyzed dehydration of this β-tertiary alcohol proceeded without rearrangement, in contrast to our results with adduct **4** and derived compounds.

Hydroboration of **4** followed by an alkaline peroxide work-up gave epimeric diols **6A** and **B**, which were separated easily by crystallization from ether solution. Configurations could not be assigned to these isomers, but we hoped that mild dehydration would generate epimeric olefinic alcohols **7A, B** that could then be converted to terpene side chains. However, dehydration of either **4** or **6** by the relatively mild boron trifluoride method[10] gave only the rearranged products **5** and **9** respectively (Scheme 2). The nature of this rearrangement was disclosed by conversion of these olefins to ketones **10** and **12**—the latter also requiring a chain elongation by conventional procedures. Carbonyl stretching absorption at 1700 cm^{-1} in **10** and **12** clearly indicates that this functional group is in the 6-membered ring, rather than the 5-membered ring as expected from **7**. The 1,4-relationship of the CO group to the OMe group in **10** was confirmed by a two-step dehydrogenation to **11**, which displayed a distinctive coupling of the low-field ^1H NMR signals ($J_{2,3} \approx J_{2,4} \approx 2$ Hz). All of these



Scheme 2.

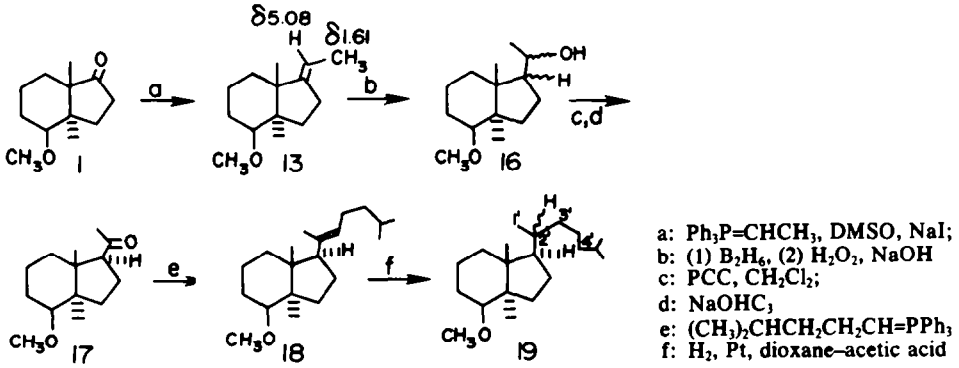
reactions were conducted with the epimeric mixture originally present in **4A,B**. Rearrangements of this kind are well known in 17-hydroxysteroids.[11]

The *trans* ring fusions shown for **10** and **12** are supported by suggestive but hardly compelling evidence. Hydroboration of **8** and **9** probably occurs from the less-hindered top side, giving a *trans* fused product. The secondary alcohols derived from these hydroborations were oxidized to **10** and **12** respectively, and these ketones were not epimerized by treatment with base. Furthermore, the C-2 (carbinol) proton in **10** and **12** is split into a doublet of doublets ($J_{2,3}$ = 3.7 and 7.2 Hz) in a fashion that suggests it has an equatorial orientation (i.e. the OMe group is axial), and the secondary alcohol precursor of **10** has a similar splitting pattern ($J_{2,3}$ = 3.8 and 5.2 Hz). Now the chair conformer of the *trans* isomer must have an axial OMe group; but the more favorable of the two *cis* conformers has an equatorial OMe group, and the axial C-2 proton in the latter should display a large (*ca* 12 Hz) axial:axial coupling constant. Of course, non-chair conformations of the *cis* isomer might perturb these coupling interactions in a manner that could generate the observed pattern. However, the ^{13}C chemical shifts of C-2 suggest there is little configurational or conformational change in the structures of **1** (δ83.7 ppm), **8AB** (δ81.9 and 82.0 ppm) and **10AB** (δ82.8 and 83.0 ppm) in the vicinity of the OMe group. A significant downfield shift (*ca* 4 ppm) has been noted for the transformation of an axial methoxycyclohexane to its equatorial isomer.[12]

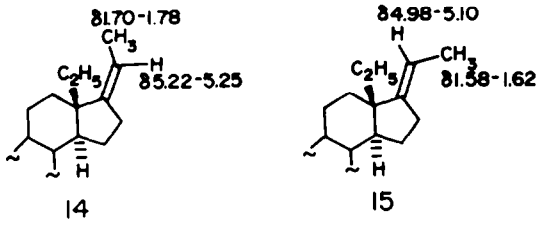
itiate the construction of several important two-carbon functionalized side chains.[13] This reaction normally gives the less-stable *Z* isomer of the 17-ethylidene steroid,[14] and subsequent transformation to pregnane derivatives has generally been straightforward. Although we were able to prepare the methylene derivative of **1** in good yield (Scheme 1), the increased bulk of the ethylidene reagent severely inhibited our initial efforts to use it in side chain construction. This problem was eventually overcome by increasing the ionic strength of the DMSO reaction medium. Thus addition of excess NaI enabled us to prepare **13** from **1** in over 60% isolated yield (Scheme 3).

In an effort to find an alternative means of elaborating the side chain, some reactions of trimethylsilyl cyanohydrin **2** with organometallic reagents were explored. In ether solution at reflux neither MeLi nor MeMgI reacted with **2**. Under more forcing conditions, both reagents attack the Si atom, and the derived cyanohydrin base decomposed to **1**.

The Wittig condensation of ethylidenetriphenylphosphorane with 17-ketosteroids has been used to in-



Scheme 3.



Scheme 4.

The ^{1}H NMR spectrum of **13** indicated that a single stereoisomer was formed in the Wittig condensation, and further suggested that this was the *E* isomer **13**—in contrast to the experience with 17-ketosteroids. The isomeric 17-ethylidene derivatives **14** and **15** have distinctive vinyl hydrogen and allylic Me chemical shifts[15] that correspond either to equivalent signals in *Z*-17-ethylidene steroids[14b] or in compound **13**. The change in olefin stereochemistry noted here presumably reflects geometrical differences in the Wittig transition states. One such difference might be that 17-ketosteroids react only at the alpha-face,[14a] whereas **1** may react with hindered nucleophiles chiefly at the beta-face. We noted earlier that small nucleophiles, such as cyanide ion, do not show significant face discrimination on adding to **1**.

The final stages of our side chain synthesis are outlined in Scheme 3. Hydroboration of **13** appears to proceed equally from both sides of the double bond, since oxidation of the derived secondary alcohols (**16**) gave an equimolar mixture of epimeric ketones. Molecular models (Dreiding) clearly indicate that the β-isomer **17** should suffer less steric crowding than its α-epimer, and treatment of this mixture with base gave crystalline **17** containing less than 5% of the α-epimer. The ^{1}H NMR spectrum of **17** displays a one-proton triplet (J = 8.5 Hz) at δ2.72 ppm in agreement with this assignment. Condensation of **17** with isohexylidenetriphenylphosphorane generated the *E* olefin **18**, as expected from recent studies by Schow and McMorris.[16] Catalytic hydrogenation of **18** then yielded a 2:1 mixture of 2′-epimers which could be separated by gas chromatography (SE-30). In principle, a configurational assignment at C-2′ might be made by comparing the distinctive ^{13}C NMR spectra of the **19** isomers with the side chain signals reported for dihydrolanosterol and euphenol.[17] In practice, however, ambiguities in the spectra interpretations prevented this from being accomplished, and we will defer the assignment until the tetracyclic ring system has been assembled.

We find that an acid-catalyzed ene reaction of **13** with ethylpropiolate[2c] proceeds with high stereoselectivity, but extensive elimination of the OMe group also takes place.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 237B grating spectrophotometer. PMR spectra were taken in $CDCl_3$ soln using either a Varian T-60 or a Bruker 250 MHz spectrometer, and are calibrated in ppm (δ) downfield from TMS as an internal standard. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer, or with the Bruker 250 MHz instrument. Mass spectra were taken with a Finnigan 4000 GC/MS spectrometer or, in the case of high-resolution measurements, with a Varian MAT CH-5DF spectrometer. UV spectra were recorded on a Unicom SP-800 spectrophotometer. Mps were measured on either a Hoover–Thomas apparatus (capillary tube) or on a Reichert hot-stage microscope, and are uncorrected.

Microanalyses of C and H were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

All reactions in which strongly basic reagents were used were conducted under N_2 or argon, using solvents purified by distillation from suitable drying agents in the absence of O_2.

Methallyl adducts **4A** *and* **B**

To a stirred suspension of Mg turnings (10 g, 0.417 mol) in ether (50 mL) was slowly added (6 hr) a soln of crotyl bromide (31.5 g, 0.233 mol) in ether (150 mL). The resulting metallic gray soln was stirred for 1 hr, toluene (90 mL) was added, and this soln was cooled to −78°. A soln of **1** (7.4 g, 38 mmol) in ether (50 mL) was added over 45 min and this mixture was stirred for 5 hr at −78°. After warming to room temp, sat NH_4Cl was added, and the mixture was filtered. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water, brine, and dried. Removal of solvent yeilded 9.5 g (99%) of **4A** and **B**, similar to the epimer mixture obtained in an earlier study.[5]

Trimethylsilyl cyanohydrin **2**

A soln of **1** (1.99 g, 10.2 mmol), trimethylsilylcyanide (3.9 mL, 30.5 mmol) and ZnI_2 (0.35 g) in 50 mL CH_2Cl_2 was refluxed 48 hr, cooled, filtered and evaporated. Chromatography of the dark colored residue on silica gel gave 2.8 g (93%) of **2**, which was formed as a nearly equimolar mixture of diastereomers, having a surprisingly sharp m.p. 90–92°. The properties of **2** confirm its structure: $\tilde{\nu}_{max}$ ($CHCl_3$) 1250 and 1080 cm^{-1}; ^{1}H NMR δ0.22 and 0.23 (9H, s), 1.04, 1.11, 1.12 and 1.26 (6H, all singlets), 1.3 to 2.7 (10H), 3.13 and 3.17 (1H, both multiplets), 3.27 and 3.28 (3H, s); mass spectrum (70 eV) *m/e* (rel. intensity) 295(18), 280(12), 139(84), 122(93), 71(100). (Found: C, 64.64; H, 9.85. Calc for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89%.)

Trans - 1,6 - *Dimethyl* - 7 - *methylene* - 2 - *methoxybicyclo*[4.3.0]*nonane* **3**

A soln of methylenetriphenylphosphorane (17 mmol) in DMSO (30 mL) was prepared by adding methyltriphenylphosphonium bromide (6.3 g) to a DMSO soln of dimsyl sodium at room temp. To this was added 0.574 g (2.9 mmol) of **1** in 3 mL DMSO. After 60 hr at 60°, the mixture was cooled, poured into water and extracted with hexane. The washed and dried extracts yielded 0.442 g (77%) of **3** as a clear oil: $\tilde{\nu}_{max}$ (neat) 3050, 1655 and 875 cm^{-1}; ^{1}H NMR δ0.75 (3H, s), 1.08 (3H, s), 1.1 to 2.6 (10H), 3.24 (1H, m), 3.29 (3H, s), 4.25 (1H, m), 4.31 (1H, m); ^{13}C NMR ($CDCl_3$) δ 160.74, 100.22, 84.05, 57.80, 46.85, 46.58, 29.48, 29.41, 27.60, 23.76, 23.61, 23.47, 17.66; mass spectrum (70 eV) *m/e* (rel. intensity) 194(2), 179(2), 162(87), 147(77), 71(100).

Diols **6A** *and* **B**

To a soln of **4** (8 g, 32 mmol), obtained by Grignard addition to **1**[5] at −78°, in 70 mL THF at 0° was added a soln of diborane in THF (32 mmol) over a period of 20 min. After stirring for 30 min at 0°, the cooling bath was removed and the stirring continued for 1.5 hr at room temp. Sufficient water was added to quench the excess diborane, followed by 3N NaOH (12 mmol) and 30% H_2O_2 (120 mmol). After stirring for 18 hr the THF was removed and the residue was extracted with ether. The ether extracts were washed with water and brine, and dried. Removal of the solvent yielded a viscous oil which was recrystallized from ether to yield **6A**, 1.6 g (19%) m.p. 142.5–144.5° and **6B**, 4.82 g (56%) m.p. 118–119°.

Compound **6A**. $\tilde{\nu}_{max}$ ($CHCl_3$) 3590 and 3370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ0.99 (3H, d, 6.8 Hz), 1.14 (3H, s), 1.17 (3H, s), 1.2–2.2 (15H), 3.12 (1H, br. s), 3.28 (3H, s), 3.55 to 3.85 (2H, m); ^{13}C NMR ($CDCl_3$) δ87.22, 86.06, 60.39, 58.04, 49.59, 49.38, 38.27, 34.32, 30.42, 28.78, 26.89, 23.25, 18.82, 18.12, 14.48; mass spectrum (70 eV) *m/e* (rel. intensity) 252(2) M–H_2O, 194(21), 165(15), 147(32), 129(72), 122(87), 111(100).

Compound **6B**. $\tilde{\nu}_{max}$ (CCl_4) 3590 and 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ0.93 (3H, d, 6.8 Hz), 1.13 (3H, s), 1.17 (3H, s), 1.2 to 2.1 (15H), 3.13 (1H, br. s), 3.28 (3H, s), 3.55 to 3.82 (2H, m); ^{13}C NMR ($CDCl_3$) δ87.15, 86.18, 60.65, 58.06, 49.57, 49.26, 38.19, 37.91, 36.17, 30.55, 28.10, 26.85, 23.32, 18.87, 18.07, 14.48; mass spectrum (70 eV) *m/e* (rel. intensity) 220(2) M–(H_2O + CH_3OH),

194(31), 165(27), 147(68), 129(100), 122(93), 111(70). (Found (**6A**): C, 70.80; H, 11.21; Found (**6B**): C, 71.14; H, 11.17. Calc for $C_{16}H_{30}O_3$: C, 71.10; H, 11.19%.)

Unsaturated alcohol **9A** *and* **B**

A soln of **6B** (2.6 g, 9.6 mmol) in benzene (40 mL) and THF (10 mL) was heated to 50° (oil bath temp) and BF_3-etherate (1.5 mL, 12 mmol) was added. After stirring for 35 min at 50°, the soln was poured into ice-water, extracted with ether, and the combined ether extracts were then washed with brine and dried. Removal of the solvent followed by column chromatography (silica gel, 25% EtOAc/hexane) of the crude product yielded 1.97 g (81%) of **9B**: $\tilde{\nu}_{max}$ (CCl_4) 3610, 3400 and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.85 (3H, d, J = 6.8 Hz), 0.97 (3H, s), 0.98 (3H, s), 1.1–2.2 (11H), 2.6 (1H, s, OH), 3.21 (1H, br. s), 3.33 (3H, s), 3.5 to 3.8 (2H, m), 5.23 (1H, br. s); ^{13}C NMR ($CDCl_3$) δ151.65, 116.84, 81.83, 61.87, 57.23, 48.21, 46.08, 37.81, 35.09, 33.15, 30.90, 26.33, 25.49, 20.77, 20.24, 15.53; mass spectrum (70 eV) *m/e* (rel. intensity) 252(1), 220(1), 179(11), 147(90), 121(100), 105(40).

An identical procedure was used to dehydrate **6A** to **9A**, which exhibited very similar physical properties.

Oxidation of **9** *and subsequent conversion to* **12**

To a suspension of pyridinium chlorochromate (0.5 g, 2.3 mmol) in CH_2Cl_2 (3 mL) was added a soln of **9** (0.39 g, 1.5 mmol) in CH_2Cl_2 (2 mL). After stirring for 1 hr the mixture was diluted with ether and filtered through a short column of Florisil. Removal of the solvent yielded 0.3329 g (86%) of a clear oil which appeared pure by TLC and NMR. The aldehyde product is unstable and was used immediately after purification.

A soln of sec-BuBr (0.5 mL, 4.6 mmol) in ether (5 mL) was slowly added to a suspension of Mg turnings (0.131 g, 5.4 mmol) in ether (10 mL). The resulting metallic gray soln was stirred for 30 min, and then a soln of the above aldehyde (0.333 g, 1.3 mmol) in ether (7 mL) was added over a 20 min period. After stirring this mixture for 30 min, water was added and the soln was extracted with ether. The ether extracts were washed, dried and evaporated to yield 0.348 g (85%) of the adduct alcohol as a clear oil.

A mesylate derivative, prepared in 95% yield by reaction of the adduct with methane sulfonyl chloride in pyridine, was reduced by LAH in refluxing THF. Chromatography of the crude product on silica gel gave the methoxy olefin precursor of **12** in 67% yield plus 20% of regenerated adduct. Hydroboration of this methoxy olefin with freshly-prepared diborane in ether, followed by an alkaline H_2O_2 workup and oxidation with pyridinium chlorochromate in CH_2Cl_2 gave **12** in 78% yield. The product from **9B** (**12B**) proved to be configurationally pure: $\tilde{\nu}_{max}$ (CCl_4) 1695 cm^{-1}; ^1H NMR δ0.86 (3H, d, 6.5 Hz), 0.87 (6H, d, 6.5 Hz), 0.90 (3H, s), 1.12 (3H, s), 1.15–2.50 (17H), 3.1 (1H, d of d, 7 Hz and 3.5 Hz), 3.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ214.22, 82.90, 65.66, 57.09, 51.88, 48.05, 42.99, 39.39, 37.21, 35.39, 33.18, 32.24, 29.62, 28.05, 26.39, 22.86, 22.60, 22.05, 19.83, 14.75; mass spectrum (70 eV) *m/e* (rel. intensity) 308(3), 276(8), 195(100), 163(90), 121(86).

Dienes **5A** *and* **B**

These diastereomeric dienes were prepared in two ways: (1) Dehydration of **4A,B** by the BF_3 procedure used to prepare **9A,B**, (2). Addition of a crotyl aluminum–aluminum bromide soln to **1**, as described below.

To a stirred suspension of 1.25 g Al powder in 10 mL ether was added 0.3 g mercuric chloride and 1 mL (9.7 mmol) of crotyl bromide. An additional 6 mL (58 mmol) crotyl bromide in 20 mL ether was added dropwise over a 75 min period, and the resulting soln was stirred for 3 hr. A soln of **1** (3 g, 15 mmol) in 20 mL ether was then added dropwise, and this mixture was quenched with water following a 5.5 hr period. After filtering, washing and evaporating the organic soln, chromatography (silica gel) yielded 2.82 g (79%) of the **5A,B** mixture: $\tilde{\nu}_{max}$ (CCl_4) 1630 cm^{-1}; ^1H NMR δ0.90–1.01 (9H), 1.05–2.30 (9H), 3.21 (1H, m), 3.34 (3H, br. s), 4.95 (2H, m), 5.22 (1H, m), 5.8 (1H, m); mass spectrum (70 eV) *m/e* (rel. intensity) 234(1), 202(1), 179(17), 147(100), 121(20), 105(26).

Diastereomeric olefins **8A,B**

Hydrogenation of **5A,B** (0.53 g, 2.28 mmol) in EtOH soln containing 97 mg Pd-C (10%) was effected under 40 psi H_2. The dihydro products **8A,B** were isolated in 99% yield: $\tilde{\nu}_{max}$ (CCl_4) 1640 cm^{-1}; ^1H NMR δ0.81–0.96 (12H), 1.0–2.2 (11H), 3.19 (1H, m), 3.33 (3H, br. s), 5.21 (1H, m); ^{13}C NMR shows 31 signals, including δ152.33, 116.6, 116.5, 82.05 and 81.94 ppm; mass spectrum (70 eV) *m/e* (rel. intensity) 236(2), 204(3), 179(14), 147(100), 121(82), 105(25). The high volatility of this substance interfered with its microanalysis. Three independent carbon–hydrogen determinations gave a C/H ratio of 6.926 ± 0.045; calculated ratio for $C_{16}H_{28}O$ is 6.918.

Methoxy ketones **10A,B**

To a cold (0°) soln of **8A,B** (0.23 g, 0.97 mmol) and BF_3-etherate (2.6 mL) in 10 mL ether was added a suspension of 0.4 g LAH (10.7 mmol) in 15 mL ether. This mixture was stirred for 4 hr, quenched with water and oxidized with alkaline H_2O_2. The organic extracts yielded 0.24 g (98%) of an alcohol, exhibiting low-field ^1H NMR signals at δ3.0 (1H, m), 3.3 (3H, s) and 3.95 (1H, m).

This alcohol in CH_2Cl_2 soln (2 mL) was added to a stirred suspension of pyridinium chlorochromate (0.45 g) in 5 mL CH_2Cl_2. Following a 3 hr period, this soln was diluted with ether, filtered and evaporated. Chromatography of the residue on silica gel yielded 0.14 g (60%) of **10**: $\tilde{\nu}_{max}$ (neat) 1695 cm^{-1}; ^1H NMR δ0.85 to 0.95 (9H), 1.13 (3H, s), 1.2 to 2.5 (12H), 3.1 (1H, d of d, 7.5 and 3.8 Hz), 3.37 (3H, s); ^{13}C NMR shows 34 signals, including δ214.32, 214.13, 82.97 and 82.90; mass spectrum (70 eV) *m/e* (rel. intensity) 252(9), 220(23), 195(100), 163(89), 121(83).

Methoxy enone **11**

A soln of **10** (0.14 g, 0.55 mmol) in 1 mL dry THF was added to a stirred soln of lithium diisopropylamide (1.1 mmol) in 5 mL THF at −78°. This mixture was warmed to 0°, a 0.14 g portion diphenyl disulfide (0.64 mmol) was added and the resulting soln was stirred 4 hr at room temp. After quenching with cold 10% HCl, it was extracted with ether, washed and dried. The crude product residue was then dissolved in MeOH (8 mL), cooled to 0° and treated with an aqueous solution of sodium periodate (0.134 g, 0.63 mmol). This oxidation was stirred for 14 hr, then filtered, evaporated and taken up in xylene. A small amount of $CaCO_3$ was added to the xylene soln, which was then refluxed for 12 hr. Filtration, followed by chromatography of the crude product (silica gel) yielded 92 mg of a mixture of **11** and **10** (roughly 2:1). Spectroscopic features characteristic of **11** are: $\tilde{\nu}_{max}$ (neat) 1670 cm^{-1}; ^1H NMR δ0.70 (3H, s), 0.85 to 0.95 (6H), 1.20 (3H, s), 1.20 to 2.5 (8H), 3.47 (3H, s), 3.65 (1H, t, 2 Hz), 6.0 (1H, d of d, 10.2 and 2.0 Hz), 6.75 (1H, d of d, 10.3 and 2.0 Hz); mass spectrum (70 eV) *m/e* (rel. intensity) 250(1), 218(4), 193(23), 161(22), 98(100).

Ethylidene derivative **13**

A soln of ethylidenetriphenylphosphorane (25 mmol) in DMSO (60 mL) was prepared by adding ethyltriphenylphosphonium bromide (9.5 g) to a DMSO soln of dimsyl sodium (25 mmol) at room temp. After the resulting red soln had stirred for 30 min, 7.6 g (51 mmol) anhyd NaI was added, followed by a soln of 1.0 g (5.1 mmol) of **1** in 5 mL DMSO. This mixture was heated at 60° for 65 hr, cooled, poured into water and extracted with hexane. The washed and dried extracts gave an oil, which was chromatographed (silica gel) to yield 0.65 g (63%) of **13** and 0.25 g (25%) of recovered **1**. Spectroscopic properties of **13**: ^1H NMR δ0.82 (3H, s), 1.16 (3H, s), 1.61 (3H, d of d of d, 7.1, 2.0 and 1.5 Hz), 1.0 to 2.5 (10H, excluding CH_3), 3.23 (1H, m), 3.28 (3H, s), 5.08 (1H, q of t, 7.1 and 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ149.14, 112.53, 84.18, 57.78, 47.71, 47.68, 31.98, 29.24, 28.89, 23,95, 23.47, 22.02, 17.86, 12.73; mass spectrum (70 eV), *m/e* (rel. abund.) 208(7), 176(67), 161(51), 71(100). (Found: C, 80.62; H, 11.53. Calc for $C_{14}H_{24}O$: C, 80.71; H, 11.61%.)

Conversion of olefin **13** *to ketone* **17**

A soln of **13** (0.182 g, 0.88 mmol) in 10 mL THF was treated with 2 mmol borane-THF complex, as a 1 M THF soln. After 3 hr

at room temp, this reaction was quenched with water and oxidized by alkaline H_2O_2 (10 mmol of 30% H_2O_2 in 3N NaOH). Extraction with ether gave, after washing, drying and evaporating the extracts, 0.186 g (93%) of **16**. A CH_2Cl_2 soln (2 mL) of these alcohols was then added to a stirred suspension of pyridinium chlorochromate (0.355 g, 1.65 mmol) in 3 mL CH_2Cl_2. After 1.5 hr, this mixture was diluted with ether, filtered through a short silica gel column and evaporated. The resulting oil (164 mg) was considered to be an equimolar mixture of **17** and its α-epimer because of the distinctive NMR signals due to the tertiary α-protons: δ2.73 ppm, triplet, J = 8.3 Hz and 2.55 ppm, doublet of doublets, J = 9.1 and 4.4 Hz.

Treatment of an EtOH soln (3 mL) of these epimeric ketones with NaOEt (93 mg) in EtOH, followed by chromatography of the darkened product, gave 0.122 g (65%) of pure **17**: $\tilde{\nu}_{max}$ 1705 cm^{-1}; ^1H NMR δ0.91 (3H, s), 0.92 (3H, s), 1.0 to 2.0 (10H), 2.07 (3H, s), 2.75 (1H, t, 8.3 Hz), 3.2 (1H, m), 3.26 (3H, s); ^{13}C NMR ($CDCl_3$) δ209.96, 84.48, 60.56, 57.72, 49.24, 45.46, 32.56, 31.42, 29.33, 23.52, 23.11, 20.61, 18.38, 17.75; mass spectrum (70 eV) *m/e* (rel. intensity) 224(5), 209(2), 192(25), 177(11), 149(100). (Found: C, 75.42; H, 10.98. Calc for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%.)

Preparation of olefin **18**

A soln of isohexylidenetriphenylphosphorane (3.48 mmol) in DMSO (10 mL) was prepared by reacting isohexyltriphenylphosphonium bromide (1.49 g) with a dimsyl sodium soln. To the red soln of this Wittig reagent was added a soln of **17** (0.195 g, 0.87 mmol) in 3 mL DMSO, and this mixture was heated at 60° for 18 hr. The cooled mixture was then quenched with water, extracted with hexane, and the extracts worked up to give a light colored oil. Chromatography (silica gel) yielded 0.1 g (40%) of **18**: ^1H NMR δ0.82 (3H, s), 0.88 (6H, d, 6.5 Hz), 0.91 (3H, s), 1.0 to 2.5 (16H, excluding CH_3), 1.6 (3H, d, 0.8 Hz), 3.18 (1H, m), 3.28 (3H, s), 5.17 (1H, t, 7.0 Hz); mass spectrum (70 eV) *m/e* (rel. intensity) 292(2), 260(3), 179(8), 138(60), 122(63), 95(100). (Found: C, 82.24; H, 12.29. Calc for $C_{20}H_{36}O$: C, 82.13; H, 12.41%.)

Hydrogenation of **18** *to* **19**

To a soln of **18** (39 mg, 0.13 mmol) in a 50:1 dioxane/AcOH mixture was added 10 mg PtO_2, and the resulting suspension was stirred under H_2 for 4 hr. An additional 10 mg catalyst was added and the stirring was continued another 5 hr. Filtration and evaporation yielded 35 mg (89%) of the saturated ether **19**, which proved to be a 2:1 mixture of side chain epimers by GLC analysis. Spectroscopic properties of **19**: ^1H NMR δ0.85 to 0.88 (12H), 0.99 (3H, s), 1.0–2.1 (19H), 3.16 (1H, m), 3.27 (3H, s); ^{13}C NMR ($CDCl_3$): δ85.67, 85.74, 57.97, 57.90, 51.85, 51.31, 49.12, 49.05, 44.11, 44.05, 39.75, 36.64, 35.74, 35.31, 33.51, 29.51, 28.27, 28.21, 27.14, 24.29, 24.08, 23.88, 23.82, 23.48, 23.05, 22.96, 22.85, 22.76, 19.16, 18.91, 18.07, 17.99, 16.86, 16.60; mass spectrum (70 eV) *m/e* (rel intensity 294(1), 279(1), 262(4), 154(18), 122(100).

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