Tetrahedron Vol 44, No. 4, pp 1007 to 1014, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

A MODEL FOR TRITERPENE SIDE-CHAIN SYNTHESIS. 2

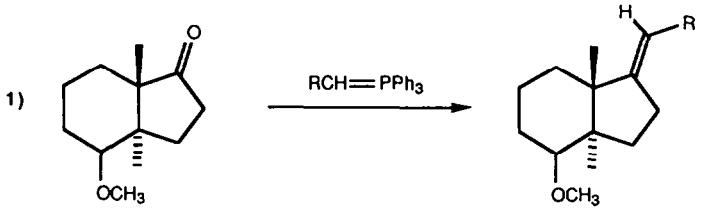
Wu-Yi Wang and William Reusch*
Department of Chemistry, Michigan State University,
East Lansing, Michigan 48824

(*Received in USA* 21 *August* 1987)

Abstract : A bicyclic model for 17-keto derivatives of triterpenes, *trans* -1,6-dimethyl-2-methoxybicyclo[4.3.0] nonan-7-one (**1**), was used to explore side-chain construction concurrent with oxidation at C-8 (triterpene C-16). Oxidation of methylene derivative **2** with selenium dioxide gave β alcohol **14**, and borohydride reduction of the corresponding ketone (**15**) led to the α epimer **16**. Each allylic alcohol (**14** and **16**) reacted stereospecifically with phenylsulfenyl chloride to give, respectively, diastereoisomeric sulfoxides **20** and **19**. The latter yielded a conjugate base that was methylated selectively to give sulfoxide **21**. Desulfuration of **21** with trimethylphosphite generated the ethylidene α alcohol **22**, and following PDC oxidation, E enone **25**.This enone was a minor product from an alternative synthesis beginning with ethylidene derivative **3**. Treatment of **3** with selenium dioxide followed by PDC gave the isomeric Z enone **24** as the major product. Reaction of **24** with lithium bis-4-methyl-3-pentenylcuprate proceeded by a facial-selective conjugate addition to the euphane CD model **26**. The E isomer **25**, under similar conditions, gave only an unresolved mixture. These results are compared with similar steroid reactions reported by Trost and Schmuff[11].

Introduction

In our previous paper on this subject[1] we used *trans*-1,6-dimethyl-2-methoxybicyclo[4.3.0]nonan-7-one (**1**) as a model for tetracyclic triterpene side-chain construction. Since this bicyclic ketone incorporates both of the angular methyl groups found at the CD-ring fusion in lanostane and euphane triterpenes, it provided a convenient substitute for the corresponding 17-keto derivatives which are not readily available[2]. Although many methods have been developed for side-chain construction starting from 17-keto steroids[3], very few of these have been applied to equivalent 14α-methyl analogs. Because the CD moiety of the tetracyclic triterpenes has a nominal C_2 symmetry axis, as does **1**, steric effects at carbon atoms 15, 16 and 17 are less easily estimated than they are in steroids. Consequently, interesting and important differences may be anticipated in the application of established methods, and were in fact observed in our earlier study[1]. In steroids and triterpenes the relative configurations at C-13 and C-17 are equivalent (ignoring mirror image relationships), but the configurational relationship at C-20 changes from the lanostanes (and steroids) to the euphanes. Useful methods for side-chain synthesis must therefore achieve selective configurational control at C-20. Reaction sequences developed by Koreeda[4] and Krief[5] on the one hand, and Midland[6] on the other, complement each other in this respect. The former generates a euphane-like side-chain, whereas the latter gives a lanostane-like structure.



1 **2** R = H **3** R = CH_3

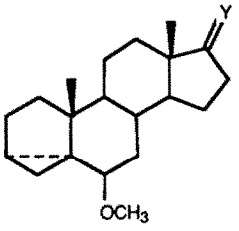
Our interest in further exploration of this subject focussed on the desirabilty of introducing functionality at C-16 concurrently with side-chain elaboration. Many naturally-occurring triterpenes, among them tumulosic acid[7], echinodol[8], kulinone[9], and holotoxin[10] have hydroxyl or carbonyl groups at this site. Since these functions can be further transformed or removed, their presence enhances the scope and flexibility of procedures that make use of their directive influence.

Recent work by Trost and Schmuff[11] has established the usefulness of C-16 functionality in facilitating steroid side-chain synthesis. Some of the compounds they studied are shown in Chart 1. As expected, these steroids showed a strong preference for α-face reactivity (**5** → **6** , **7** → **8** , **7** → **9**); but displayed variable

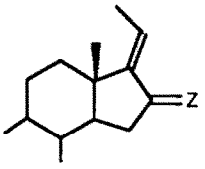
selectivity in the Mislow / Evans sulfoxide rearrangement[12] (**6** → 51% **12a** + 29% **12b** ; **8** → 26% **11**). Allyl sulfone anions derived from these sulfoxides were alkylated to give products of type **13** and also proved to be excellent Michael donors. The results we report here are interesting because, when considered in juxtaposition to the Wisconsin steroid work, they reflect the influence of a 14α-methyl group on ring D chemistry.

CHART I

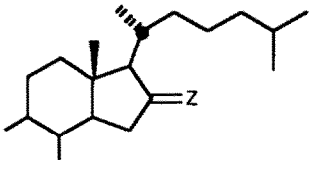
Ring D Functionalized Steroids Reported by Schmuff and Trost[11]



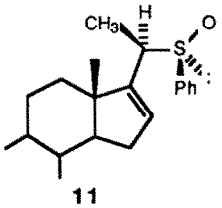
4 Y = O
5 T = CH_3CH



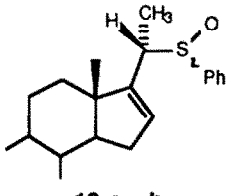
6 Z = α-OH, β-H
7 Z = O
8 Z = β-OH, α-H



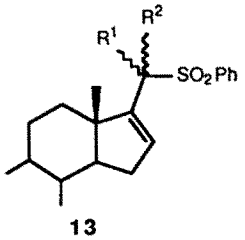
9 Z = O
10 Z = H_2



11



12 a , b

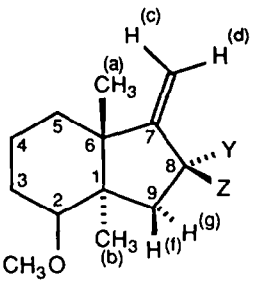


13

Results

Wittig olefination of **1** gave **2** and **3** (equation 1), as noted in our first paper in this series[1]. The ethylidene derivative **3** is formed with opposite stereoselectivity and in slightly lower yield than in the corresponding reaction of 17-keto steroids. Subsequent transformations of these olefins are described in Chart 2 and equations 2 and 3. Selenium dioxide oxidation of **2** proceeded with surprisingly high stereoselectivity to the 16β-alcohol **14**, accompanied by a small amount of enone **15**. Oxidation of **14** to **15**, followed by cerium-doped borohydride reduction, gave the α epimer **16** with equally high stereoselectivity.

Structure assignments for the epimeric alcohols **14** and **16** were made chiefly on the strength of their characteristic ^1H nmr spectra. Two factors proved to be particularly informative. First,with respect to the corresponding ketone, a hydroxyl group at C-8 (C-16 in equivalent steroid numbering) exerts a weak deshielding influence on a cis-oriented angular methyl group and a stronger shielding effect on a corresponding trans angular methyl. From data reported by Trost and Schmuff[11], the former effect is about +0.03 ppm and the latter -0.17 ppm. Perturbations induced by the shift reagent 2,2,6,6,-tetramethylheptanedionate europium magnified this effect, and aided our assignments. Second, the carbinol proton signals from these same alcohols show distinctive multiplicities that reflect differences in the dihedral angles with hydrogen atoms at C-9 (steroid C-15). Pertinent nmr data for bicyclic ketone **15** and the epimeric alcohols **14** and **16** are presented in Figure1. The chemical shift difference in the angular methyl signals (*a-b*) is +0.33 ppm for **15**, +0.53 ppm for **14** and +0.16 ppm for **16**. Using the hydroxyl shielding increments from the earlier steroid study (+0.03 and -0.17), we calculate these differences to be +0.53 for **14** and +0.13 for **16**. The assignment of methyl signals *a* and *b* is unambiguous, since *b* displays a long-range coupling to the β-hydrogen atom on C-9. Finally, the broad triplet at δ4.59 ppm in **14** (J_{app} = 7.0 Hz) and the broad doublet at δ4.78 ppm in **16** (J_{app} = 8 Hz) are due to the carbinol proton H^{θ}, and are consistent with the steroid analogs as well as molecular mechanics modeling. Parallel and equally pronounced changes were observed in the ^1H nmr spectra of alcohols **22** and **23** (vis-a-vis ketones **24** and **25**), obtained in good yield from the selenium dioxide oxidation of **3** (eq. 2).



Compound	Proton (s)	Chemical Shift	Multiplicity (J)
15 Y=Z=O	a (3)	1.25 ppm	s
	b (3)	0.92	d (J^{bf} =1Hz)
	c (1)	4.87	s
	d (1)	5.75	s
	f (1)	2.88	d,q (J^{fg} =17, J^{bf} =1)
	g (1)	1.77	d (J^{fg} =17)
14 Y= H, (e) Z=OH	a (3)	1.28	s
	b (3)	0.75	d (J^{bf} =1Hz)
	c (1)	4.78	d (J^{ce} =2)
	d (1)	5.03	d (J^{de} =1)
	e (1)	4.59	t,t ($J^{ef,eg}$ =7, $J^{ce,de}$ =1.5)
	f (1)	2.12	d,d,q (J^{fg} =12, J^{ef} =7, J^{bf} =1)
	g (1)	1.6 - 1.9	Hidden
16 Y= OH, Z=H (e)	a (3)	1.08	s
	b (3)	0.92	d (J^{bf} =1Hz)
	c (1)	4.74	d (J^{ce} =2)
	d (1)	4.95	d (J^{de} =2)
	e (1)	4.78	d,t (J^{ef} =8, $J^{ce,de}$ = 2)
	f (1)	2.65	d,t,q (J^{fg} =13, J^{ef} = 8, J^{bf} =1)
	g (1)	1.20	d (J^{fg} =13)

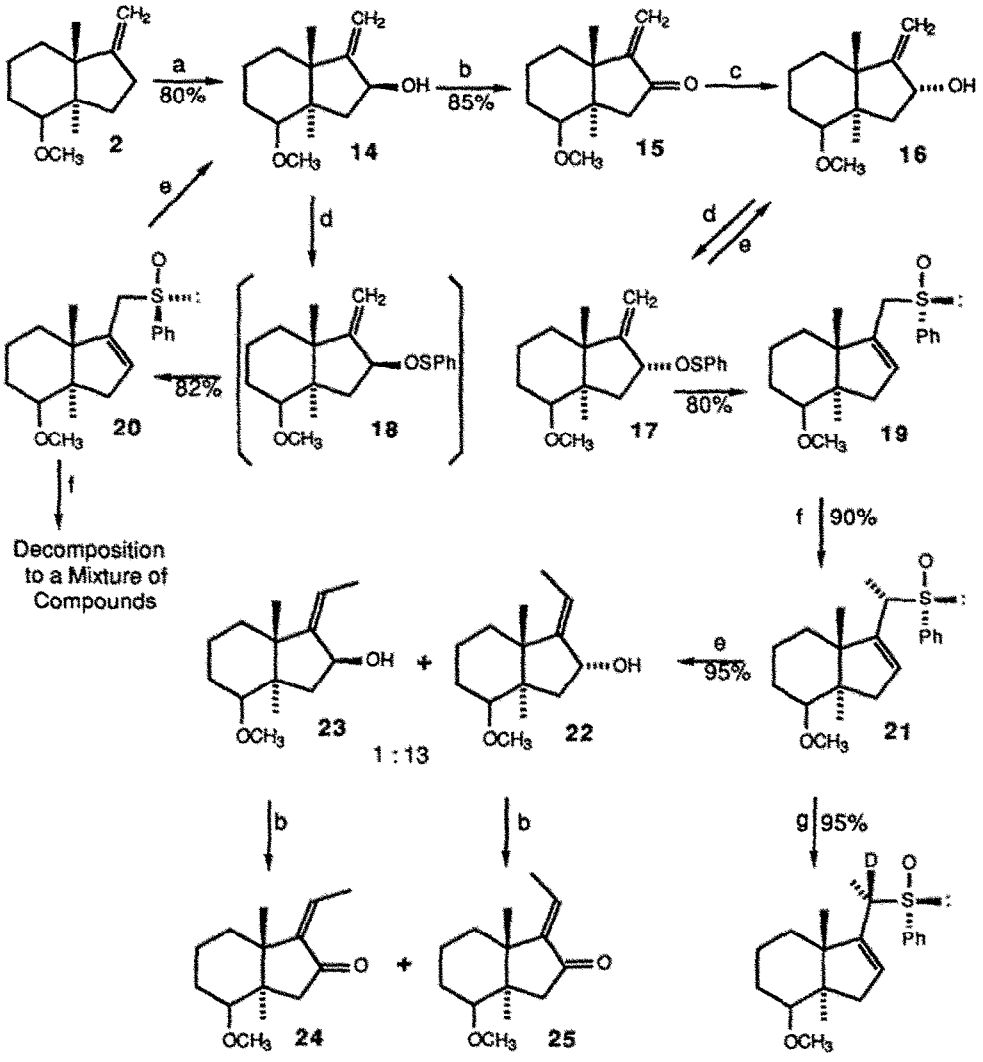
Figure 1.
Selected ^{1}H NMR Data

Because of the facility with which epimeric alcohols **14** and **16** could be prepared, we next examined their behavior in the Mislow / Evans sulfoxide rearrangement[12], anticipating that subsequent alkylation of the resulting allylic sulfoxides (or the derived sulfones) might prove effective in side-chain construction. In the event, reaction of the lithium salts from **14** and **16** with phenylsulfenyl chloride proceeded first to the corresponding sulfenate esters (**18** and **17**) followed by rearrangement to diastereomeric sulfoxides **20** and **19** respectively. Since **17** could be isolated and characterized whereas **18** was never observed, the rate of sigmatropic rearrangement of these sulfenate esters must differ markedly. Allylic sulfoxides **19** and **20** proved stable under refrigerated storage, but slowly interconverted at room temperature. A benzene solution of either isomer was converted to a 50:50 mixture of the two during one hour at reflux.

Desulfuration experiments with **19** and **20** demonstrated the stereospecificity of the rearrangement to **17** and **18** respectively,but also disclosed significant "cross-over" on heating. Thus, a methanol solution of **20** and trimethyl phosphite (2 eq.) returned the β allylic alcohol **14** in the course of two days at 25° C or 8 hr. at reflux. Similar treatment of **19** gave no reaction after two days at room temperature, but on refluxing 24 hr. yielded a 2:1 mixture of **16** and **14**. The corresponding sulfenate ester **17** gave **16** (and its methyl ether) exclusively, on treatment with trimethyl phosphite in methanol.

Sulfoxides **19** and **20** behaved very differently when their conjugate bases were reacted with methyl iodide. In the case of **19**, a good yield of a single methyl derivative ,**21**, was obtained; and this gave the α-E allylic alcohol **22** on desulfuration with methanolic trimethyl phosphite. Similar treatment of **20** (the more reactive isomer) generated a mixture from which no informative products could be isolated. Selenium dioxide oxidation of the ethylidene compound **3** gave a small amount of **22**, but the major product was the expected β-Z isomer **23** (eq. 2). Oxidation of **22** and/or **23** with PDC[16] gave the corresponding enones **25** and **24** with some interconversion. Treatment of either **24** or **25** with a trace of iodine in refluxing benzene or with potassium hydroxide in refluxing methanol generated a 1:1 equilibrium mixture of these isomers.

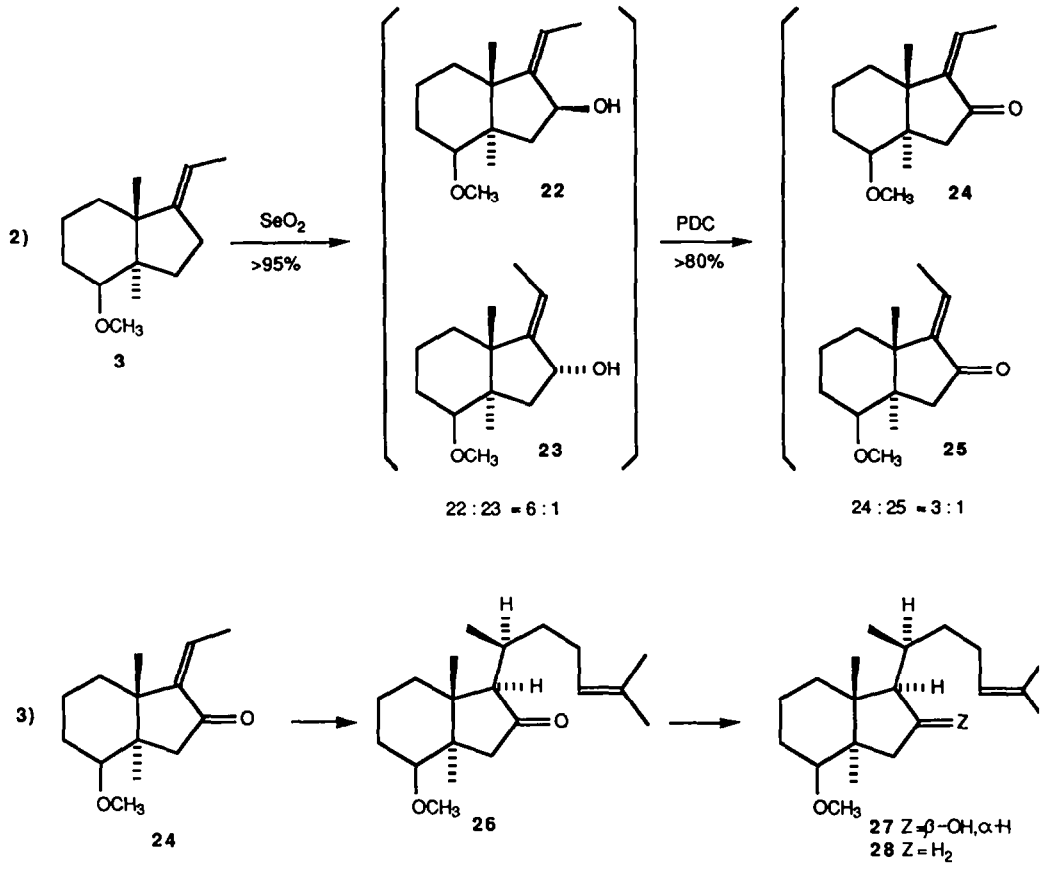
CHART 2



a) SeO_2, $tBuO_2H$; b) PDC ; c) $NaBH_4$, $CeCl_3$; d)[1] BuLi, TMEDA [2] PhSCl
e) $P(OCH_3)_3$, CH_3OH ; f) [1]LDA [2]CH_3I ; g) [1]LDA [2]D_2O

Our efforts to achieve dialkylation of sulfoxide **19** *were largely unsuccessful. Only the dimethyl derivative was obtained, and this in modest yield. The difficulty here did not lie in anion formation from* **21**, since its reaction with LDA followed by heavy water quenching gave monodeuterated **21** in high yield. Proton quenching of the same anion under presumed kinetic and thermodynamic conditions always returned **21**.

Finally, our planned side-chain synthesis was accomplished by conjugate addition of lithium bis-4-methyl-3-pentenylcuprate to **24**. Trost and Schmuff[11a] had reported good α facial selectivity in the addition of lithium diisohexylcuprate to a steroidal E enone, but we were concerned that this selectivity might be diminished with our substrate. Indeed, the E isomer **25** gave a mixture of products that was not fully characterized. The Z isomer, however, reacted cleanly to give, after base-catalysed epimerization at C-7, a single adduct **26** (*the* ^{13}C *nmr spectrum of* **26** *displayed nineteen distinct signals*). Reduction of **26** by lithium aluminum hydride gave a single alcohol, which we assigned the β *configuration* **27** *on the strength of* its characteristic ^1Hnmr spectrum[17]. Molecular mechanics calculations[15] indicate that **27** is less stable than its α epimer by 0.9 kcal/mol.



The configuration of the new chiral center in **26** (corresponding to steroid C-20) was established following Wolff-Kishner deoxygenation to **28**. In equation 3, structures **26**, **27** and **28** are drawn to match the CD moiety of the lanostane triterpenes, but in fact have the same relative configuration at the four contiguous asymmetric carbon atoms (excluding the methoxy site) as do the euphane triterpenes. From previous studies of triterpene ^{13}C nmr spectra[13] it is clear that significant chemical shift differences are observed between equivalent lanostanes and euphanes, especially for carbons 12, 16, 17, 20 and 22 ($|\Delta\delta| \geq$ 0.5ppm). Since compound **28** constitutes a racemic model of the euphane side-chain, we expected to find a correlation of appropriate ^{13}C nmr signals *vis -a-vis* those of the lanostanes. The data in Table 1 (Experimental Section) show this to be the case. Finally, **28** proved to be identical with the product from Koreeda / Krief[4,5] side-chain synthesis, as applied to **1**[14]. Preferred α face selectivity in the conjugate addition reaction is thus confirmed by this assignment.

Discussion

Molecular models (Dreiding) and molecular mechanics calculations[15] indicate that the β face of the five-membered ring in olefin **2** is less hindered than its α face, despite the quasi-C_2 symmetry of this bicyclic system. The exocyclic double bond apparently distorts the five-membered ring sufficiently to achieve the surprisingly high facial selectivities found in the selenium dioxide and sodium borohydride reactions. When this double bond is removed, as in ketone **26**, the course of hydride reduction is influenced chiefly by the adjacent side-chain substituent (the angular methyl groups have roughly equal but opposite effects).

Several intriguing differences in the behavior of our bicyclic model system *vis-a-vis* corresponding steroids are evident. To begin with, the Mislow / Evans rearrangement proved to be much more selective in this study than was observed by Trost and Schmuff in their work with steroids[11]. The reasons for this difference are not easily evaluated, and we have no explanation to offer here. As expected, the diastereoisomeric rearrangement pairs having the greater activation energy for an exo-suprafacial-sigmatropic shift[12d] (*ie.* **17** ⇄ **19**) showed significant crossover to the more facile diastereomeric reaction (**18** ⇄ **20**).

Although conjugate addition of alkyl cuprates to Z enone **24** proceeded selectively and cleanly from the α face (equation 3), as noted for a similar steroid system, an examination of E and Z isomers disclosed an interesting reversal. Thus, the steroidal E enone (**7**) gave clean α conjugate addition, whereas its Z isomer produced an intractable product mixture[11]. In our model system it was the E enone **25** that behaved poorly and gave unresolved mixtures. Once again, subtle structural factors seem to be at work here, and we do not choose to speculate further at this time.

The chief lesson to be learned from this study is that the extensive collection of methodology for steroid side-chain synthesis[3,4,5,6,11] may not be directly applicable to triterpenes and 14α-methyl steroids, particularly when reactions occur on or adjacent to ring D.

EXPERIMENTAL SECTION

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere using solvents distilled from appropriate drying agents. Small-scale chromatographic separations were accomplished with the use of 2-mm silica plates (Merck F-254, 20 X 20 cm). Larger scale separations were effected by flash chromatography[18] (40-63-nm silica gel, Merck 9385). Melting points were determined on either a Thomas-Hoover capillary melting point apparatus or a Reichert hot stage microscopic apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Mass spectra (MS) were obtained with a Finnigan 4000 GC/MS spectrometer. Proton magnetic resonance spectra (^{1}HNMR) were taken in deuterochloroform solution with either a Varian T-60 or a Bruker WM 250 spectrometer and are calibrated in parts per million (δ) from tetramethylsilane (Me_4Si) as an internal standard. Carbon magnetic resonance spectra (^{13}CNMR) were recorded on a Bruker WM 250 spectrometer at 69.8 MHz,using deuterochloroform as solvent, and are calibrated in parts per million (δ) from TMS as an internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, MI. High resolution mass spectra were measured by the Michigan State University, Department of Biochemistry, Mass Spectroscopy Facility, East Lansing, MI.

Oxidation of 2 to 14 and 15: A 100 mg sample of trans-1,6-dimethyl-7-methylene-2-methoxybicyclo[4.3.0] nonane **2**, prepared from ketone **1** by Wittig methylenation, was dissolved in 5 mL methylene chloride, and added dropwise to a stirred solution of 0.23 mL (4 eq.) t-butyl hydroperoxide (90%) and 28.6 mg (0.5 eq.) selenium dioxide in 10 mL methylene chloride maintained at 15°C. Following a 22h reaction period, this solution was washed with aqueous base (10% sodium hydroxide) and brine. A light yellow oil (118 mg) remained after evaporation of the solvent, and ^{1}Hnmr showed this to be a 4:1 mixture of allylic alcohol **14** and the corresponding ketone **15**. This was readily separated into its components by flash chromatography on silica gel. If enone **15** is desired it may be produced in 90% yield by a one-pot operation in which 1.5 eq. of pyridinium dichromate (PDC)[16] is added to the reaction solution 6h before workup. Characteristic properties,**14:** IR (neat) 3602, 1470, 1375, 1315, 1200, 1135, 1085, 880 cm^{-1}; ^{1}Hnmr δ0.75(3H,d,J=1Hz), 1.28 (3H,s), 1.4 to 2.0 (8H), 2.12 (1H, ddq, J=12, 7 and 1Hz), 3.20(1H,m), 3.31(3H,s), 4.59(1H,tt,J=7 and 1Hz), 4.78 (1H,d,J=1Hz), 5.03(1H,d,J=1Hz)ppm; ^{13}Cnmr δ163.8, 104.9, 83.1, 73.7, 57.8, 46.3, 45.6, 40.4, 29.1, 24.6, 24.2, 23.2 and 17.3 ppm; mass spectrum, m/e (rel. intensity) 210(0.6), 192(0.6), 177(3), 160(12), 145(36), 71(80), 41(100). Anal. calcd. for $C_{13}H_{22}O_2$: C,74.24; H.10.54. Found: C,74.33; H.10.50. **15**: IR(neat) 2830, 1725, 1650, 1270,1130, 1085, 890 cm^{-1}; ^{1}Hnmr δ0.92(3H,d,J=1 Hz), 1.25(3H,s), 1.6 to 2.0(6H), 1.77 (1H,d,J-17Hz), 2.88 (1H,dq,J=17 and 1Hz), 3.28(1H,m), 3.31(3H,s), 4.87(1H,s), 5.75(1H,s)ppm; ^{13}Cnmr δ207.8, 155.9, 110.0, 81.7, 57.6, 45.6, 44.8, 42.5, 28.2, 24.4 (overlapping signals), 22.8, 17.3 ppm; mass spectrum, m/e (rel. intensity) 208(8), 193(2), 176(9), 165(3), 161(15), 148(17), 135(44), 107(19), 71(78), 55(54), 41(100). Anal. Calcd. for $C_{13}H_{20}O_2$:C,74.98; H_1, 9.68. Found: C, 74.74; H, 9.72.

Reduction of Enone 15 to Allylic Alcohol 16: To a solution of 82 mg enone **15** (0.39 mmol) in 1 mL methanol was added 147 mg of cerrous chloride heptahydrate (1 eq.), followed by slow addition with stirring of 12 mg sodium borohydride (33 eq.). After 5 min., during which time hydrogen evolves, the reduction was quenched by addition of water and then extracted with ether. The washed and dried extracts yielded 74 mg of a colorless oil, which crystallized on rubbing, mp. 71.0 to 72.5° C. Characteristic properties of **16**: IR 3605, 3070, 1450, 1370, 1250, 1195, 1075, 875 cm^{-1} ; ^{1}Hnmr δ0.92(3H,d,J=1 Hz), 1.08(3H,s), 1.20(1H,d,J=13Hz), 1.2 to 1.9(7H), 2.65(1H,ddq,J=13, 8 and 1Hz), 3.23 (1H,m), 3.29(3H, s), 4.74(1H,d,J=2Hz), 4.78(1H,dt,J=8 and 2Hz), 4.95(1H,d,J=2 Hz) ppm; ^{13}Cnmr δ165.0, 101.3, 83.l, 72.2, 57.6, 47.4, 45.5, 40.6, 28.9, 24.6, 24.1, 23.2, 16.9 ppm; mass spectrum, m/e (rel. intensity) 210(1), 178(12), 163(31), 145(29), 121(50), 107(39), 93(35), 79(36), 71(100), 55(57), 41(90). Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.27; H, 10.59.

Preparation of Sulfenate Ester 17 and Sulfoxide 19: A 92 mg sample of alcohol **16** (0.44 mmole) was dissolved in 10 mL THF, cooled to -78°C, and treated with 0.5 mL of 1.3M n-butyl lithium (hexane solution). This mixture was stirred *ca.* 15 min., 0.1 mL of tetramethylethylenediamine (TMEDA) was added, and this was followed by slow addition of phenylsulfenyl chloride (107 mg, 0.74 mmol.). Lithium chloride precipitated as the reaction mixture was warmed to -45°C; and following a 1 h reaction period, it was quenched by cold aqueous ammonium chloride. Ether extraction and the usual workup gave 200 mg of an orange oil, which proved to be chiefly the sulfenate **17**. On standing, this isomerized to sulfoxide **19** which was purified by chromatography. At room temperature **19** isomerized slowly to a 1:1 mixture of **19** and **20**.

Characteristic properties of **17**: ^{1}Hnmr δ0.91(3H,br s), 1.01(3H,s), 2.57(1H,dd,J=14 and 8Hz), 3.18(1H,m), 3.23(3H,s), 4.70(1H,d,J=8Hz), 4.79(1H,s), 5.17(1H,s), 7.40 to 7.64(5H)ppm. Characteristic properties of **19**: IR 1460, 1445, 1375, 1265, 1200, 1180, 1080, 1030, 880, 690 cm^{-1}; ^{1}Hnmr δ1.03(3H,s), 1.16(3H,s), 1.6 to 1.9(7H), 2.70(lH,d,J=14.5Hz), 3.25(1H,m), 3.31(3H,s), 3.40(1H,d,J=15Hz), 3.54(1H,d,J=15 Hz), 5.57(1H,br s), 7.5 to 7.7(5H) ppm; ^{13}Cnmr δ145.0, 142.3, 131.8, 131.2, 129.5, 124.7, 83.2, 58.9, 57.7, 50.1, 49.0, 37.8, 26.8, 24.9, 23.1, 22.4, 17.6 ppm; mass spectrum (70 eV) a molecular ion (m/e 318) was not observed. Strong fragment ions were found at m/e 161 ($C_{10}H_9S$), 119, 105, 91, 77, 71 and 55.

Preparation of Sulfoxide 20: A 77 mg sample of allylic alcohol **14** (1.34 mmol) was dissolved in 10 mL THF, cooled to -78°C, and treated with 0.4 mL of 1.3 M n-butyl lithium (hexane solution). Following a 15 min reaction period,to the stirred solution was added 0.1 mL TMEDA and then 107 mg of phenylsulfenyl chloride (0.74 mmol). Lithium chloride precipitated as the reaction mixture was warmed to -45°C and 30 min later the reaction was quenched by addition of cold aqueous ammonium chloride. Ether extraction and the usual workup gave *ca.* 330 mg of an orange oil. Flash chromatography of this product gave 84 mg (82%) of sulfoxide **20**, as a colorless oil. Characteristic properties of **20**:^{1}Hnmr δ0.93(3H,s), 1.09(3H,s), 1.1 to 1.8(7H), 2.68(H,d,J=15Hz), 3.25(1H,m), 3.29(3H,s), 3.52(1H,d,J=13Hz), 3.59(1H,d,J=13Hz), 5.48(1H,brs), 7.5 to 7.7(5H) ppm; ^{13}Cnmr δ142.0, 131.1, 130.4, 129.0, 124.6, 124.2, 83.1, 57.7, 57.8, 50.1, 49.3, 38.4, 26.7, 24.7, 23.1, 22.3, 17.5 ppm; mass spectrum (70 eV) a very weak molecular ion (m/e 318) was observed. Strong fragment ions were found at m/e 161, 149, 119, 105, 91, 77, 71 and 55.

Methylation of Sulfoxide 19 to Generate 21: A solution of lithium diethylamide in THF was prepared by adding 1.1 eq. of n-butyl lithium (1.3 M in hexane) to a stirred solution of diethyl amine (0.08 mL, 0.77 mmol) in 5 mL THF. To this stirred solution at -78°C was added 85 mg of sulfoxide **19** (0.27 mmol). The resulting orange solution was warmed to -45°C briefly, recooled to -78°C, mixed with 0.1 mL TMEDA and finally treated with 0.1 mL of methyl iodide (6 eq.). The reaction mixture was slowly warmed to -45°C, held there for 2 h, and finally quenched by the addition of cold aqueous ammonium chloride solution. Ether extraction in the usual manner yielded 80 mg of a light yellow oil, which proved to be the desired **21**. Characteristic properties of **21**: IR (neat) 1460, 1448, 1375, 1265, 1200, 1090, 1035, 1025, 880, 790 cm^{-1}; ^{1}Hnmr δ0.95(3H,s), 1.12(3H,d,J=8Hz), 1.21(3H,s), 1.4 to 1.8(7H), 2.75(1H,d,J=15Hz), 3.32(3H,s), 3.34(1H,br s), 3.47(1H,q,J=8Hz), 5.36(1H,br s), 7.4 to 7.6(5H)ppm.

Oxidation of 3 by Selenium Dioxide followed by PDC: A solution of selenium dioxide (26.4 mg, 0.24 meq) and t-butyl hydroperoxide (0.2l mL, 90%) in 10 mL methylene chloride was added dropwise to a stirred solution of ethylidene derivative **3** (100 mg, 0.5 meq) in 10 mL of the same solvent. Following a 44 h reaction period, the reaction mixture was diluted with 20 mL methylene chloride, and washed with aqueous sodium hydroxide (10%), water and brine. The dried organic extracts yielded 110 mg of a colorless oil on evaporation. This proved to be a 6:1 mixture of **22** and **23**. Characteristic properties, **22:** ^{1}Hnmr δ0.71(3H,d,J=1Hz), 1.24(3H,s), 1.74(3H,d,J=7Hz), 1.4 to 2.0(8H), 2.12(1H,ddd,J=12, 7 and 1Hz), 3.19(1H,t,J=2Hz), 3.31(3H,s), 4.80(1H,br t,J=7Hz), 5.16(1H,qd,J=7 and 2Hz)ppm. **23**: ^{1}Hnmr δ0.99(3H,d,J=1Hz), 1.14(3H,s), 1.71(3H, dd J=7 and 2Hz), 1.5 to 2.1(8H), 2.56(1H,ddq,J=9, 4 and 1Hz), 3.20(1H,br t,J=3Hz), 3.27(3H,s), 4.59(1H,d quint,J=9 and 2Hz), 5.44(1H,qd,J=7 and 2Hz)ppm.

Without further characterization, the mixture of allylic alcohols **22** and **23** was dissolved in 15 mL DMF and treated with 0.29 mg of PDC. Following a 5h reaction period, the mixture was diluted with water and extracted thoroughly with methylene chloride. Evaporation of the dried extracts gave 86 mg of a light colored oil, which proved to be a 3:1 mixture of **24** and **25**. Characteristic properties, **24**: mp 67 to 69°C; IR 1708, 1640, 1435, 1190, 1075, 870 cm^{-1}; ^{1}Hnmr d0.92(3H,d,J=1Hz), 1.21(3H,s), 1.5 to 2.1(6H), 1.72(1H,d,J=17Hz), 2.07(3H,d,J=7Hz), 2.84(1H,br d,J=17Hz), 3.24(1H,m), 3.30(3H,s), 5.52(1H,q,J=7Hz)ppm; ^{13}Cnmr δ 209.3, 147.3, 127.6, 81.9, 57.5, 46.2, 45.7, 42.5, 28.4, 25.3, 24.2, 22.6, 17.3, 13.6 ppm; mass spectrum, m/e (rel. intensity) 222(5), 207(6), 175(11), 149(21), 119(10), 105(15), 71(100), 55(27). **25**: IR 1720, 1650, 1450, 1375, 1200, 1123, 1080, 875 cm^{-1}; ^{1}Hnmr δ0.92(3H,d,J=1Hz), 1.28(3H,s), 1.6 to 2.1(6H), 1.75(3H,d,J=8Hz), 1.72(1H,d,J=17Hz), 2.80 (1H,dq,J=17 and 1Hz), 3.24(1H,m), 3.27(3H,s), 6.39(1H,q,J=7Hz) ppm; ^{13}Cnmr δ207.2, 147.l, 126.2, 81.8, 57.6, 46.4, 44.6, 42.7, 29.9, 24.8, 23.3, 22.4, 17.4, 12.5 ppm; mass spectrum, m/e (rel. intensity) 222(3), 207(1), 149(13), 121(7), 107(19), 85(19), 71(100), 55(39).

Desulfuration Experiments: In general, a solution of the sulfoxide to be examined (*ca.* 0.2 to 1.0 mmol) in 5 to 10 mL methanol was mixed wtih 2.0 to 2.5 equivalents of trimethylphosphite. Reactions were conducted at room temperature and at reflux for periods ranging from 8 h to several days. Isomer **20** proved more reactive than **19,** and was converted to the corresponding alcohol (**14**) at room temperature. The refluxing conditions required to desulfurate **19** caused some isomerization of the allylic alcohol product (**16**:**14**=2:1). Less isomerization was found in the corresponding reaction of methyl derivative **21** (**22**:**23**=13:1). Yields of desulfurated products were good (70%) to excellent (>95%).

Addition of lithium bis-4-methyl-3-pentenylcuprate to 24: Freshly purified cuprous bromide-dimethyl sulfide complex (256 mg, 4 eq.) was slurried in 3 mL ether, cooled to -78°C and mixed with freshly prepared 4-methyl-3-pentyl lithium. An initially formed yellow precipitate slowly dissolved when the reaction mixture was warmed to -45°C to give a gray-brown solution. An ether solution of enone **24** (50 mg, 0.23 mmol) was added slowly, and this mixture was stirred 1.5 h at -45°C followed by 1h at -20°C. After quenching the reaction mixture with aqueous ammonium chloride, it was extracted with ether. The ether extracts yielded 90 mg of an oil, which appeared to be a mixture of isomeric adducts. Treatment of this product with methanolic potassium hydroxide followed by flash chromatography gave 40 mg (59%) of pure **26**, as a colorless oil. Characteristic properties of **26**: IR 1730, 1450, 1370, 1080, 860 cm^{-1}; ^{1}Hnmr δ1.07(3H,d,J=lHz),

1.09(3H,d,J=6Hz), 1.15(3H,s), 1.61(3H,s), 1.69(3H,s), 1.2 to 1.9(10H), 2.10(1H, br d, J=5Hz), 2.2 to 2.3(2H,m), 2.67(1H, d, J=21Hz), 3.22(1H,m), 3.30(3H,s), 5.09(1H, br t, J=5Hz) ppm; ^{13}Cnmr δ219.9, 130.8, 124.6, 83.2, 61.1, 57.7, 46.3, 44.3, 43.0, 37.1, 30.9, 30.1, 25.7, 25.5, 24.0, 22.6, 18.7, 18.2, 17.4 ppm.

Reduction of 26 to alcohol 27: To a solution of 16 mg of ketone **26** in 5 mL of THF was added 0.5 mL of a 0.1M solution of lithium aluminum hydride in THF. This mixture was stirred for 40 min at 0°C, quenched by addition of water and then extracted with ether. The washed and dried extracts yielded 20 mg of a colorless oil, which was purified by flash chromatography. A 15 mg sample of **27** was obtained: ^{1}Hnmr δ0.83(3H,br s), 1.01(3H,d,J=7Hz), 1.17(3H,s), 1.3 to 2.0(14H), 1.60(3H,s), 1.68(3H,s), 3.14(1H,m), 3.30(3H,s), 4.43(1H,br q,J=7Hz), 5.09(1H,br t,J=5Hz) ppm; mass spectrum(70eV), m/e (rel. intensity) very weak molecular ion at 308, 293(9), 276(1), 259(1), 181(23), 149(100).

Deoxygenation of 26 to 28. To a solution of 33 mg of ketone **26** in ethylene glycol (2.2 mL) was added 232 mL of 80% hydrazine hydrate followed by 232 mg of potassium carbonate. This mixture was heated at gentle reflux for 1.5h, cooled and a distillation head was fitted in place of the reflux condenser. The reaction mixture was heated to 220°C for 10 min, and the moisture formed on the walls of the distillation condenser was removed by a methanol rinse. This procedure was repeated until no condensed water beads were observed. The reaction mixture was then heated for 10 min at 230°C, cooled and partitioned in a two phase mixture of hexane (15 mL) and 4N hydrochloric acid (35 mL). The washed and dried hexane extracts yielded 38 mg of a light oil, which on flash chromatography gave 25 mg of pure **28**. ^{1}Hnmr δ0.85(3H,d,J=6Hz), 0.86(3H,br s), 1.00(3H,s), 1.2 to 2.0(16H), 1.60(3H,s), 1.67(3H,s), 3.17(1H,m), 3.28(3H,s), 5.09(1H,t,J=6Hz)ppm; ^{13}Cnmr δ130.8, 125.3, 85.5, 57.7, 51.0, 48.9, 43.9, 35.4, 34.8, 33.4, 30.0, 29.2, 26.9, 25.7, 24.8, 23.6, 23.2, 18.9, 17.8, 16.6 ppm; mass spectrum (25 eV), m/e (rel. intensity) 292(1), 277(4), 260(20), 179(23), 147(58), 122(100), 107(52), 71(80), 55(11); High resolution MS: Calculated for $C_{20}H_{36}O$, 292.27660. Found, 292.2759.

TABLE I

Selected ^{13}CNMR Chemical Shifts for Lanosterol[13c], Euphol[13c] and 28

Carbon Atom[a,b]	Chemical Shift[c] in : Lanosterol	Euphol	28
16	30.7	29.7	29.2
17	50.3	49.6	48.9
20	36.7	35.3	34.9
22	36.2	35.7	35.4

a Triterpene numbering

b A comparative value for C-12 is omitted, since the methoxy group in **28** causes a large pertubation at this site.

c Parts per million from internal tetramethylsilane

Acknowledgements: We thank Mr. Ernest Oliver for assistance in obtaining mass spectra.

References and Notes

1. J.Gibson and W.Reusch, *Tetrahedron*, **39**, 55 (1983).
2. a) W.Kreiser and W. Ubrich, *Justus Liebigs Ann. Chem.*,1199 (1976)
   b) M. Audouin and J.Levisalles, *Tetrahedron*, **39**, 2799 (1983).
3. a) D.M.Piatak and J.Wicha, *Chem. Rev.*, **78**, 199 (1978)
   b) J.Redpath and F.J.Zeelen, *Chem. Soc. Rev.*, **12**, 75 (1983).
4. M.Koreeda and N.Koizumi,*Tetrahedron Lett.* 1641 (1978).
5. J.R.Schauder and A.Krief,*ibid*, **23**, 4389 (1982).
6. M.M.Midland and Y.C.Kwon, *J. Am. Chem. Soc.*, **105**, 3725 (1983).
7. L.A.Cort, R.Gascoigne, J.Holker, B.J.Ralph, A.Robertson and J.J.H.Simes, *J. Chem. Soc.*, 3713 (1954).
8. F.T.Bond, D.Fullerton, L.A.Sciuchetti and P.Catalfomo, *J. Am. Chem. Soc.*, **88**, 3882 (1966).
9. C.-K.Chang and F.C.Chiang, *Tetrahedron*, **29**, 1911 (1973).
10. A.Kelecom, D.Daloze and B.Tursch, *ibid*, **32**, 2313 and 2353 (1976).
11. a) N.R.Schmuff and B.M.Trost, *J. Org. Chem.*, **48**, 1404 (1983).
    b) B.M.Trost and N.R.Schmuff, *J. Am. Chem. Soc.*, **107**, 396 (1985).
12. a) P.Bickart, F.Carson, J.Jacobus, E.Miller and K.Mislow,*J. Am. Chem. Soc.*, **90**, 4869 (1968).
    b) R.Tang and K.Mislow, *ibid*, **92**, 2100 (1970).
    c) D.A.Evans, *Acct. Chem. Res.*,**7**, 147 (1974).
    d) V.Rautenstrauch, *Chem. Commun.*, 526 (1970).
13. a) G.Lucas, F.Khuong-Huu, C.Bennett, B.Bucwalter and E.Wenkert, *Tetrahedron Lett.*, 3515 (1972).
    b) S.A.Knight, *Tetrahedron Lett.*, 83 (1973).
    c) A.Ben Harref and J.-P.Lavergne, *Bull. Soc. Chim. Fr.*, 965 (1985).
14. a) H.Ok, PhD Thesis, Michigan State University, E.Lansing, MI, **1986**.
    b) The Koreeda / Krief side-chain synthesis has been shown to proceed identically with steroids and a lanostane derivative[5].
15. a) MM2 calculations were run on an IBM-AT computer using programs distributed by Serena Software, Box 3076, Bloomington, IN 47402. These programs were adapted from the original MM programs of Allinger[15b] by J.J.Gajewski and K.E.Gilbert.
    b) U.Burkert and N.L.Allinger, *Molecular Mechanics ACS Monograph* **177** (Amer. Chem. Soc., Washington, 1982).
16. E.J. Corey and G.Schmidt, *Tetrahedron Lett.*, 399 (1979).
17. D.Lavie, Y.Shvo, O.R.Gottlieb and E.Glotter, *J. Org. Chem.*, **28**, 1790 (1963).
18. W.C.Still, M.Kahn and A.Mitra, *J.Org.Chem.*,**43**, 2923 (1978).