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STUDIES ON DIELS-ALDER REACTIONS OF 1,3,3-TRIMETHYL-2-VINYLCYCLOHEXENE WITH 2-CYCLOHEXENONES

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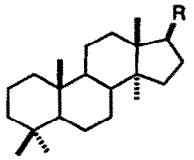
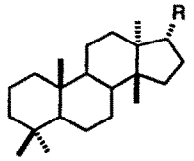
Abstract: The $ZnBr_2$-catalyzed reaction of 1,3,3-trimethyl-2-vinylcyclohexene (**4**) with 2-carbomethoxy-4,4-dimethyl-2-cyclohexenone at high pressure (12 kbar) produces the expected Diels-Alder product. However, reactions of (**4**) with the more sterically demanding dienophile (**5a**) give products of apparent Michael reaction followed by proton transfer.

Introduction.

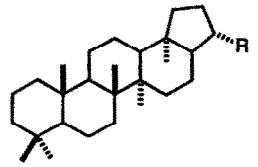
The development of synthetic approaches to tetra- and pentacyclic triterpenes, for example lanostanes **1**, euphanes **2** or hopanes **3**, and higher terpenes, has attracted considerable attention[1] over the last several decades due to the prevalence of these molecules in biological systems and, more recently, due to their potential significance in the evolution of biomembranes[2] and utility as biomarkers in fossil fuels.[3] Investigations of new approaches toward lanostanes and euphanes[4] have received particular interest due in part to the activity of some lanostane derivatives as inhibitors of lanosterol 14α-methyl demethylase[5] and as suppressors of HMG-CoA reductase activity.[4a,6] As such, these molecules are candidates for regulation of cholesterol biosynthesis. Of the new synthetic approaches to lanostane and euphane triterpenes, those based on a Diels-Alder construction of the B or C rings of the carbocyclic framework offer notable advantages in terms of convergency, versatility, ease of preparation of the precursors and the potential for enantioselective syntheses (either or both Diels-Alder components are, or should be, preparable from enantiomerically pure Wieland-Miescher ketone[7] or (*S*)-4-hydroxy-1,3,3-trimethyl-2-vinylcyclohexene[8]). Reusch[9a] has described an approach based on disconnection A in Scheme I. Valenta,[9b-c] and more recently Ourisson,[2a] have developed a strategy based on disconnection B. We have reported a synthetic approach to tricyclic diterpenes following



1, R=C_8H_{15}

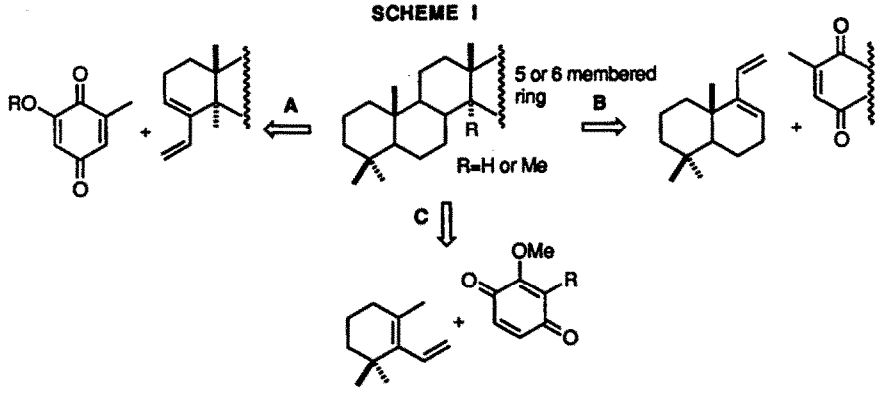


2, R=C_8H_{15}



3, R=C_3H_7

SCHEME I



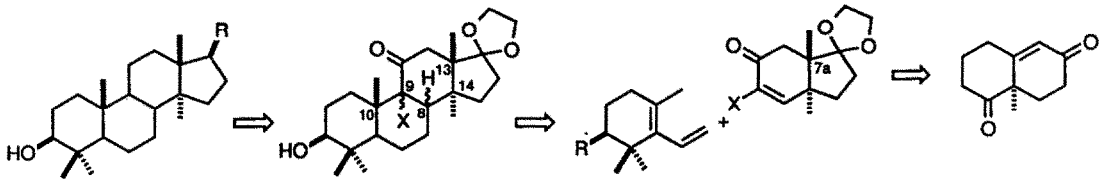
an alternate strategy outlined in disconnection C.[10] Herein we describe efforts to adapt this strategy to the synthesis of higher terpenes of the lanostane or euphane classes.

Results and Discussion.

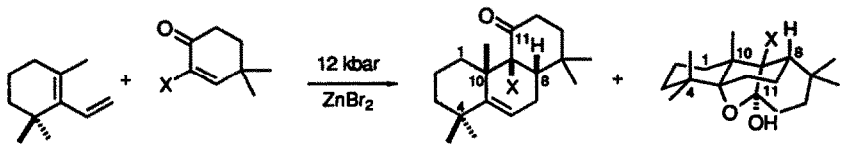
Our synthetic plan is outlined in Scheme II. The key questions encountered in evaluating this plan were 1) would the Diels-Alder reaction work in view of the steric bulk surrounding the reaction centers in both the diene **4** and the dienophile **5**, and 2) if the Diels-Alder reaction were successful, what would be the stereochemistry of the product? To obtain information pertaining to these questions, reactions involving diene **4a** and 4,4-dimethyl-2-cyclohexenones **6** were examined initially as a model system (Scheme III).[11]

The $ZnBr_2$-catalyzed reaction of 2-carbomethoxy-4,4-dimethyl-2-cyclohexenone **6a**[12] with **4a** at 12 kbar gave Diels-Alder adduct **7** in 47-63% yield accompanied by smaller amounts of **8** in 10-18% yield for a number of experiments. The latter product apparently results from acid catalyzed hydration of **7** on chromatography (SiO_2). $ZnBr_2$ was required in these high pressure experiments; no Diels-Alder products were found in its absence and other Lewis acids failed to promote the reaction at high pressure [$Yb(fod)_3$, $SnCl_4$ or $SiCl_4$ in CH_2Cl_2] or at atmospheric pressure ($TiCl_4$ or $SnCl_4$ in CH_2Cl_2 or $LiClO_4$ in Et_2O[13]).

SCHEME II



SCHEME III



4 **6a**, X=CO_2CH_3 **b**, X=H **c**, X=S(O)Ph **d**, X=$S(O)_2$Ph **7**, X=CO_2CH_3 **8**, X=CO_2CH_3

The structure of the major product **7** is established by spectral evidence and single crystal X-ray analysis (Figure 1).[14] It is notable that in the formation of **7**, the ketone carbonyl adopts the endo orientation in the cycloaddition in spite of the steric bulk of the 4,4-dimethyl moiety. The structure of the minor product **8** is established from spectral data and chemical evidence. Mass spectral data indicates that this product is a 1:1 adduct plus H_2O and ^{13}C and ^1H NMR spectra shows one carbonyl resonance (177.0 ppm), an OH resonance (5.02 ppm) and no other sp^2 carbons or vinyl hydrogens. One carbonyl absorbance at 1698 cm^{-1} is apparent in the IR spectrum along with weak OH stretches at 3631 and 3473 cm^{-1}. In addition, a DEPT NMR experiment indicates six methyl groups (one OCH_3), seven methylene groups, one methine carbon and six quaternary carbons - two at 101.6 (C-11) and 88.0 (C-5) ppm. Finally, dehydration of **8** to **7** is apparent upon allowing a $CDCl_3$ solution of **8** to stand at room temperature over several days. Although the apparently facile hydration of **7** to **8** is remarkable, it is not without precedent.[15] Reactions of **6b-d**[16] with diene **4a** under thermal, Lewis acid catalyzed, high pressure or a combination of high pressure and Lewis acid [$ZnBr_2$, $Yb(fod)_3$, $Eu(fod)_3$, $SnCl_4$, BF_3, $TiCl_4$, $AlCl_3$, $EtAlCl_2$ or 1:1 $TiCl_4$:$Ti(OiPr)_4$] catalysis fail. Nevertheless, the formation of **7** from **4a** and **6a** indicates that Diels-Alder reactions of **4** with sterically hindered 2-cyclohexenones are feasible.

Attention was then directed toward reactions of diene **4a** with **5a** (Scheme II). The question of stereoselectivity was more difficult to address. Although we felt there was good reason to predict that cycloaddition, if successful, would occur via approach of the diene to the α-face of the enone

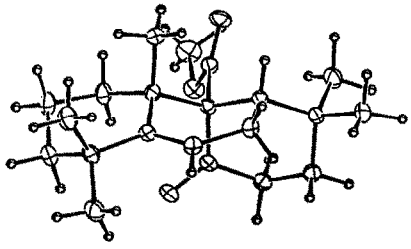


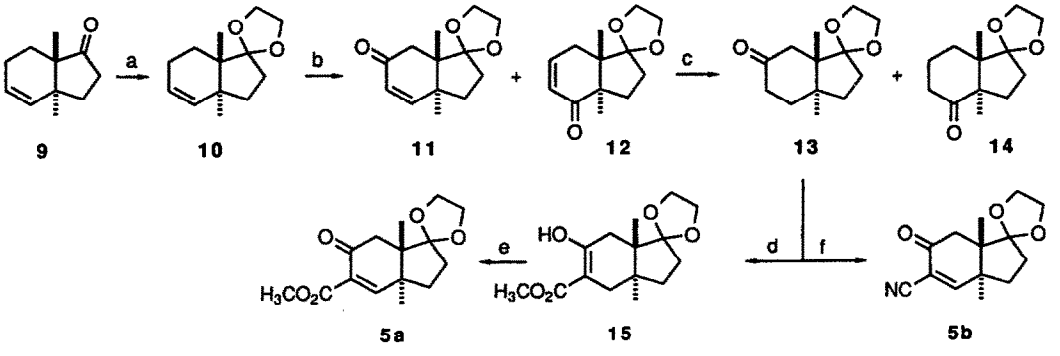
Figure 1. ORTEP drawing of **7**.

(examination of molecular models suggested that the C-7a methyl group in **5a**, i.e., the eventual C-13 methyl of the anticipated Diels-Alder product, should effectively shield the β-face of the enone), the stereochemistry at C-8 and C-9 of the desired Diels-Alder product was not of vital importance since these two centers were destined to be converted eventually to sp^2 carbons. Prediction of the orientation of the remaining stereocenter at C-10 of the product with respect to C-13 and C-14 depended upon which of the two carbonyl groups, the ketone or the ester, adopts an endo orientation in the transition state. Although the results found in the model system suggested the ketone carbonyl group should be endo, the added steric bulk of the quaternary C-7a center in the dienophile precluded a confident prediction and it was felt that the answer would await practical experience.

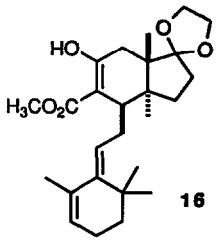
The preparation of **5a** was straightforward (Scheme IV) starting from the known *trans*-1,6-dimethylbicyclo[4.3.0]nonenone **9** which is available in five steps from the Wieland-Miescher ketone.[17] Ketalization of **9** followed by allylic oxidation with $CrO_3{\cdot}(py)_2$[18] gave a 2-3:1 mixture of enones **11** and **12**, respectively. Although partial separation of **11** from **12** could be effected by careful column chromatography, **12** could not be obtained free of **11**. However, catalytic hydrogenation of the mixture gave a mixture of **13** and **14** which were easily separable. The overall yield of **13/14** from **9** was 52%. Conversion of ketone **13** to 2-carbomethoxyenone **5a** was accomplished in 72% overall yield by standard procedures.[12,19] Cyanoketone **5b** was also prepared from **13** by the sequence 1) LDA, 2) *p*-TsCN[20] and 3) $PhSeCl/H_2O_2$.[19]

Reactions of **4a** with **5a** under the combined high pressure/Lewis acid ($ZnBr_2$) conditions gave the 1:1 adducts **16**, **17** and **18** in yields ranging from 50-78, 5-15, and 1-6%, respectively, for a number of experiments. Under similar conditions, attempted reactions of **5b** or **11** with **4a** failed. Again, $ZnBr_2$ was the Lewis acid of choice for reactions of **4a** with **5a**; reactions without it and those

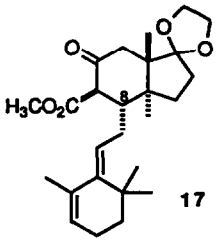
SCHEME IV



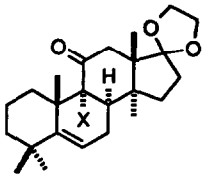
Reagents and Conditions. a) $HOCH_2CH_2OH$, *p*-TsOH, PhH, Δ, 80%; b) $CrO_3{\cdot}py_2$, CH_2Cl_2, rt, 66%; c) H_2, Pd/C, EtOAc, rt, 98%; d) NaH, $O{=}C(OCH_3)_2$, DME, Δ, 80%; e) i. PhSeCl, py, CH_2Cl_2, 0°C, ii. H_2O_2/H_2O, CH_2Cl_2, 0°C, 91%; f) i. LDA, THF, -78°C; ii. *p*-TsCN, 60%; iii. H_2O_2/H_2O, CH_2Cl_2, 0°C, 40%.



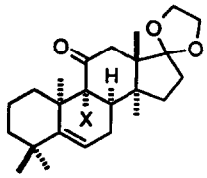
16



17



18, X=CO_2CH_3



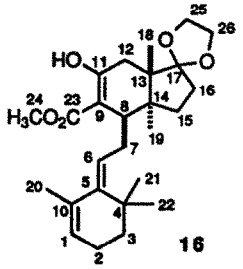
19, X=CO_2CH_3

utilizing $Zn(OTf)_2$, $Mg(OTf)_2$, $LiClO_4$, $B(OAc)_3$, $Eu(fod)_3$ or $Yb(fod)_3$ failed to give Diels-Alder products. The structure of the major product **16** is assigned from spectral data including extensive ^1H-^1H decoupling, COSY, DEPT, HETCOR, heteronuclear (^1H-^{13}C) multiple bond correlation (HMBC)[21] and ^1H-^1H NOE NMR experiments. The β-hydroxy-enone moiety is indicated by a carbonyl stretching frequency at 1650 cm^{-1} in the IR spectrum, an O-H resonance at 12.68 ppm in the ^1H NMR spectrum and ^{13}C resonances at 174.1 ppm (C-23) and 172.9 ppm (C-11). Similar spectral features are also found with compound **15** and 2-carbomethoxy-4,4-dimethylcyclohexanone.[12] The NMR data from **16** allow the unambiguous assignment of each resonance in both the ^1H and ^{13}C spectra and the data from the HMBC and NOE experiments are summarized in Figure 2 and 3. The important data include the following. The HETCOR and the HMBC experiments establish the resonances of C-12 (35.4 ppm) and C-17 (117.7 ppm) and long range coupling between these carbons and the C-18 methyl hydrogens show that the latter resonate at 1.11 ppm. Irradiation of the C-18 methyl hydrogens produce NOE enhancements of the β C-12 hydrogen and one of the C-7 hydrogens (Figure 3). Thus, C-7 and C-18 are cis. Irradiation of the C-10 allylic methyl group (C-20) gives NOE enhancements of the hydrogens at C-1 (5.31 ppm) and C-6 (5.61 ppm).

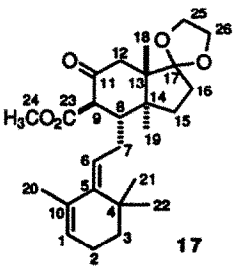
Spectral data are also used to assign the structure of **17**. Ester and ketone carbonyl groups are apparent from stretching frequencies at 1745 and 1701 cm^{-1} in the IR spectrum and from resonances at 171.3 and 207.3 ppm in the ^{13}C NMR spectrum. Again, all resonances in both the ^{13}C and ^1H NMR spectra can be assigned from the experiments mentioned above (Figure 2). The most informative datum was the H-9 resonance at 3.09 ppm with a $J_{H8\text{-}H9}$ = 10.7 Hz. Because of the trans 6/5 ring fusion, the cyclohexyl ring is expected to be fairly rigid. Of the four possible relative configurations of the C-8 and C-9 stereocenters, only the one shown has the H-8 and H-9 trans diaxial which is consistent with the observed $J_{H8\text{-}H9}$ (the other three have these protons ax-eq, eq-ax or eq-eq). Apparently the enol tautomer of **17** is disfavored due to ^{1,2}A-strain between the CO_2CH_3 group and the equatorial appendage at C-8.

All spectral data for **18** are again consistent with the structure shown. However, in order to

Figure 2. Summary of the Data from HMBC NMR Experiments on **16** and **17**.



16



17

Carbon #	Correlated Protons	Carbon #	Correlated Protons
1	3,20	13	12α,12β,8,18,19
2	1,3	14	8,7,12β,15,16,18,19
3	1,21 or 22	15	8,16,19
4	3,6, 21 or 22	16	----
5	1,3,6,7,20	17	12α,15,16,18,25,26
6	7,8	18	12α,12β
7	8	19*	8,15(both H's)
8	6,7,19	20	1
9	7,8,12α,12β	21	3,22
10	6,20	22*	
11	8,12α,12β	23	24
12	18	24	----
		25	26
		26	25

Carbon #	Correlated Protons	Carbon #	Correlated Protons
1	3,20	14*	7,12,19
2	3	15	19
3	21/22	16	----
4	3,6,21/22	17	15,16,18,25,26
5	3,7,20,21/22	18	12
6	7	19	----
7	8,9	20	----
8*	6,9,19	21*	3,22
9	7	22*	3,21
10	6,20	23	9,24
11	9,12	24	----
12*	18	25	26
13	12,18,19	26	25

*Signals too close to one another to determine all correlations accurately.

observe all of the ^{13}C resonances, the ^{13}C, COSY, DEPT, HETCOR, and HMBC NMR spectra were recorded at 323°K in $CDCl_3$. At lower temperatures, not all of the carbon signals were observed presumably because of long relaxation times due to hindered rotation. The ^{1}H and NOE NMR spectra were recorded at 297°K. Again, important spectral data include carbonyl stretching frequencies at 1740 and 1715 cm^{-1} in the IR spectrum, resonances at 208.4 and 176.5 ppm in the ^{13}C spectrum, and resonances from seven quaternary (one sp^2), nine methylene, two methine (one sp^2 and one sp^3) and six methyl (one OCH_3) carbons in the DEPT and HETCOR spectra. It is possible to

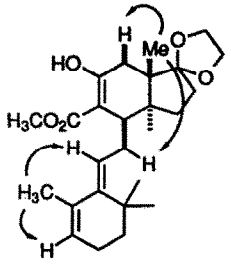


Figure 3. Summary of the ^{1}H-^{1}H NOE Data for **16**.

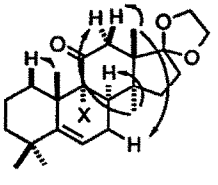
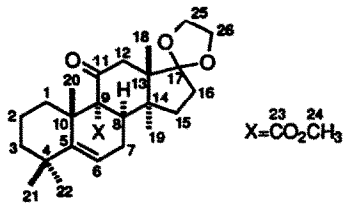


Figure 4. Summary of the ^{1}H-^{1}H NOE Data for **18**.

Figure 5. Summary of the Data from the HMBC NMR Experiments on **18**.

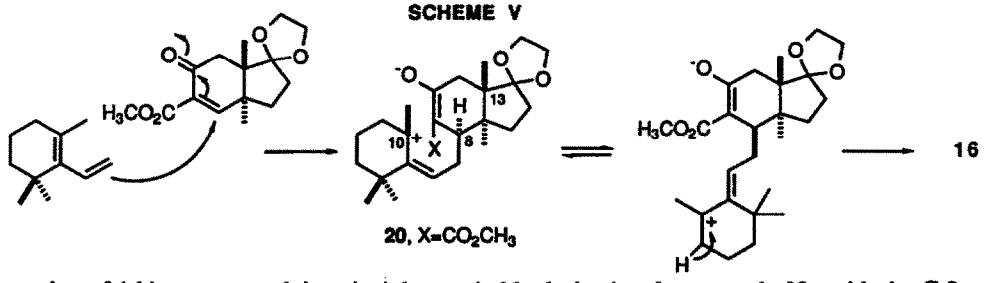


Carbon#	Correlated Protons	Carbon#	Correlated Protons	Carbon#	Correlated Protons
1	3,20	9	7,8,20	18	12
2	3	10	6,20	19	8,15
3	21/22	11	8,12	20	1
4	6,21/22	12	18	21	22
5	7,20,21/22	13	8,12,18,19	22	21
6	7,8	14	8,12,16,19	23	8,24
7	6,8	15	16,19	24	--
8	7,19	16	--	25	26
		17	18,25/26	26	25

assign most of the signals in the ^{1}H and ^{13}C NMR spectra from this data and the remaining are assigned from data obtained in the HMBC experiment which are summarized in Figure 5. Of particular importance are long range correlations between a) C-17 and the hydrogens on C-18, b) C-19 and H-8, and c) C-1 and the hydrogens on C-20. These data establish the resonances of the C-10, C-13 and C-14 methyl groups. ^{1}H-^{1}H NOE experiments (Figure 4) then clearly establish the stereochemistry of the B/C ring juncture. Coupling constants of 12 and 7 Hz to H-8 are also consistent with the structure shown. Finally, the stereochemistry at C-10 is assigned by the observation of the equatorial H-1 at 2.43 ppm as a dd with one large coupling constant (J_{gem} = 13.8 Hz) and two smaller coupling constants (≤3Hz).[10a] Molecular models of **18** suggest that this proton should be deshielded by the proximal CO_2Me. Models of **19**, with the C-10 stereocenter inverted, show that in this molecule the axial H_1 should be deshielded by the C-11 carbonyl and this signal would show two large coupling constants (J_{gem} and $J_{ax\text{-}ax}$).[10a]

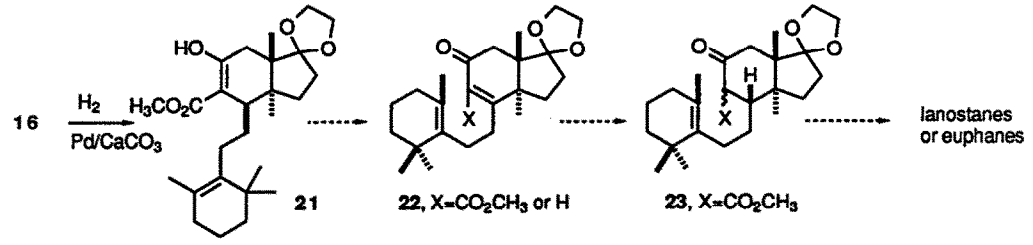
Surprisingly, although C-C bond formation between the diene **4a** and the β-carbon of the dienophile **5a** occurs in spite of the steric congestion about the β-carbon, the major product **16** and **18** result from approach of the diene to the β face of **5a** to give **20** (Scheme V). Then, in order for the C-9-C-10 bond to form, the developing B ring must adopt a twist boat conformation and severe steric interactions result between the C-10 and C-13 methyl groups. The high energy for the transition state leading from **20** to **18** allows proton transfer to give **16** to compete effectively. Although the

SCHEME V

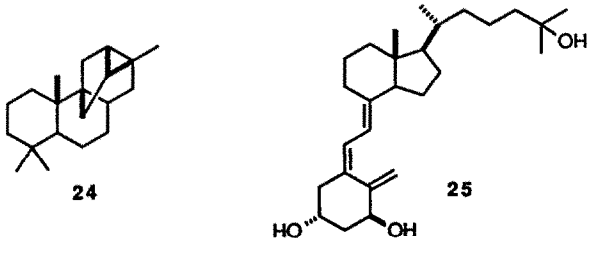


formation of **16** is unexpected, in principle, a suitable derivative, for example **23** - with the C-8 center inverted- (Scheme VI), might be induced to undergo cyclization to products possessing a lanostane or euphane structure. In preliminary experiments to explore this idea, we found that hydrogenation of **16** with 5% Pd on $CaCO_3$ as catalyst cleanly effects 1,4-reduction of the diene to give **21** in 97% yield. However, oxidation of **21** to **22** has proven troublesome.[22]

SCHEME VI



In summary, reaction of 1,3,3-trimethyl-2-vinylcyclohexene (**4a**) with 2-carbomethoxy-4,4-dimethyl-2-cyclohexenone (**6a**) gives the expected Diels-Alder product whereas reaction with the more sterically demanding dienophile **5a** gives **16** as the major product, apparently by a Michael addition of the diene to the dienophile followed by proton transfer. The former reaction is noteworthy as a potential route to helifulvane triterpenes (**24**),[23] and the latter type of process holds promise as a route to analogs of calcitriol (**25**).[24] We plan to report results of experiments to explore these possibilities at a later date.



Experimental.[25]

Diels-Alder Addition of 2-Vinyl-1,3,3-trimethylcyclohexene (4) with 2-Carbomethoxy-4,4-dimethyl-2-cyclohexenone (6a).

In a high pressure reaction tube were placed 2-carbomethoxy-4,4-dimethyl-2-cyclohexenone, **6a** (92 mg, 0.51 mmol), 1,3,3-trimethyl-2-vinylcyclohexene, **4** (86 mg, 0.57 mmol), followed by $ZnBr_2$ (42.3 mg, 0.19 mmol) and dichloromethane (1.2 mL). The reaction mixture was pressurized to 12 kbar for 23 hours. The reaction mixture was concentrated and flash chromatography of the residue with 10% ethyl acetate in hexane as eluent gave the Diels-Alder adduct **7** (80 mg, 47.7%) and **8** (30.4 mg, 18.1%). Recystallization of **7** from EtOAc/hexanes gave clear colorless crystals, mp 95.5-96.5°C; R_f 0.35 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) 5.17 (dd, 1H, J = 2.9, 5.3 Hz, H-6), 3.69 (s, 3H, H-17), 2.82 (m, 1H, J = 14.9, 13.9, 6.9 Hz, H-12ax), 2.82* (m, 1H, J = 9.6, 8.1 Hz, H-8), 2.25 (ddd, 1H, J = 2.9, 9.6, 19.6 Hz, H-7α), 2.14 (ddd, 1H, J = 2.2, 5.1, 14.9 Hz, H-12eq), 2.07 (ddd, 1H, J = 4.2, 12.9, 12.9 Hz, H-1ax), 1.99 (ddd, 1H, J = 5.4, 8.1, 19.6 Hz, H-7β), 1.90 (ddd, 1H, J = 5.1, 13.9, 13.9 Hz, H-13ax), 1.78 (ddd, 1H, J = 4.7, 13.1, 13.1 Hz, H-3ax), 1.64 (ddddd, 1H, J = 2.8, 3.3, 12.8, 12.9, 12.9 Hz, H-2ax), 1.50 (m, 1H, J = 13.4 Hz, H-2eq), 1.43 (dddd, 1H, J = 2.1, 2.1, 6.9, 13.7 Hz, H-13eq), 1.34 (m, 1H, J = 12.9 Hz, H-3eq), 1.16 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.97 (s, 3H), 0.84 (m, 1H, J = 12.3 Hz, H-1eq). ^{13}C NMR ($CDCl_3$, 125 MHz) 207.6 (C-11), 172.6 (ester C=O), 150.8 (C-5), 115.5 (C-6), 66.7 (quat), 51.6 (OCH_3), 45.1 (C-8), 40.39 (quat), 38.8 (CH_2), 38.6 (CH_2), 35.4 (CH_2), 34.7 (quat), 34.6 (quat), 33.4 (CH_2), 32.9 (CH_3), 31.9 (CH_3), 28.4 (two overlapping CH_3's), 25.9 (CH_2), 24.4 (CH_3), 18.4 (CH_2). IR (CCl_4) 2970, 2940, 2880, 1745, 1715, 1540, 1465, 1450, 1435, 1395, 1390, 1380, 1375, 1230, 1210, 1140, 1040 cm^{-1}. EIMS *m/z* (relative intensity) 332(M^+, 8), 273(3), 257(9), 249(7), 229(4), 217(3), 183(100), 151(98), 135(35), 105(16), 93(10), 91(20), 79(14), 69(21), 55(36), 41(63). HRMS *m/z* 332.2343 (Calcd for $C_{21}H_{32}O_3$ 332.2351). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found C, 76.08; H, 9.84.

Spectral data for **8**; oil, R_f 0.19 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) 5.02 (s, 1H, OH), 3.73 (s, 3H, OCH_3), 2.98 (ddd, 1H, J = 13, 13, 5 Hz, H-1ax), 2.34 (dd, 1H, J = 9, 9 Hz, H-8), 2.08 (dm, 1H, J = 15 Hz), 1.83 (m, 1H)*, 1.78 (m, 1H)*, 1.70 (m, 2H)*, 1.65 (m, 2H)*, 1.46 (m, 2H), 1.23 (s, 3H, CH_3), 1.09 (dm, 1H, J = 12 Hz)*, 1.04 (s, 3H, CH_3), 1.02 (m, 1H)*, 0.92 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.82 (m, 1H)*. ^{13}C NMR ($CDCl_3$, 125 MHz) 177.0 (ester C=O), 101.6 (quat, C-11), 88.02 (quat, C-5), 61.0 (quat), 51.47 (OCH_3), 46.01 (quat), 42.71 (CH), 36.38 (CH_2), 35.98 (quat), 34.94 (CH_2), 34.72 (quat), 32.53 (CH_2), 30.58 (CH_2), 29.11 (CH_3), 27.50

(overlapping CH_2 and CH_3), 26.14 (CH_3), 25.34 (CH_3), 22.22 (CH_3), 19.81 (CH_2), 18.10 (CH_2). IR ($CDCl_3$) 3631, 3473, 2939, 2874, 1699, 1426, 1319, 1264, 1012 cm^{-1}. EIMS *m/z* (relative intensity) 350(M^+, 2), 333(5), 332(8), 317(1.5), 304(2), 300(1.9), 285(1.5), 273(22), 235(13), 204(13), 203(10), 183(22), 179(26), 151(39), 139(13), 137(10), 135(19), 133(10), 55(100). (*The chemical shifts and integration of these signals were determined by HETCOR and DEPT experiments.)

Synthesis of Ketal-10.

Trans-dimethylhydrindenone **9** (1.79 g, 10.9 mmol), ethylene glycol (12.2 mL, 21.8 mmol), benzene (75 mL) and *p*-toluenesulfonic acid monohydrate (102 mg, 0.54 mmol) were placed in a round bottom flask swept with N_2. The solution was refluxed with azeotropic removal of water over 20-30 h. After cooling the mixture, most of the benzene was removed by rotary evaporation. Ether was added followed by washing the solution with 5% aqueous NaOH and brine. After drying over magnesium sulfate and filtration, the solution was concentrated. Chromatography of the resulting viscous oil on silica gel using 10% EtOAc/hexanes as eluent gave recovered starting material (0.11 g, 5.6%) and the ketal product **10** (1.81 g, 79.7%) as a colorless liquid : R_f 0.36 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) 5.74 (ddd, 1H, J = 9.8, 2.3, 2.3 Hz), 5.38 (ddd, 1H, J = 9.8, 3.1, 3.1 Hz), 3.96-3.81 (m, 4H), 2.20-2.00 (m, 5H), 1.74 (m, 1H), 1.38 (m, 1H), 1.28 (m, 1H), 1.11 (s, 3H), 1.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 135.8, 124.1, 118.8, 64.9, 63.9, 45.5, 44.7, 36.0, 31.4, 27.4, 24.3, 23.0, 19.2. IR ($CHCl_3$) 2960, 2900, 1460, 1435, 1380, 1325, 1295, 1175, 1155, 1140, 1110, 1050, 1025, 1000, 960, 920, 900 cm^{-1}. Mass spectral analysis, either CI or EI, failed to provide a M^+ for confirmation of the molecular formula.

Oxidation of 10 to 11/12.

Chromium trioxide (24 g, 0.24 mol) was added to an ice-cooled, mechanically stirred solution of pyridine (41 mL, 0.51 mol) in dichloromethane (250 mL) under nitrogen. The deep burgundy solution was stirred for 5 min and the ice bath removed. After stirring an additional 10 min, a solution of the olefin-ketal **10** (1.92 g, 9.24 mmol) in dichloromethane (10 mL) was added rapidly by syringe. A tarry precipitate immediately began to form on the sides of the flask. After stirring for 24 h at rt, the reaction mixture was decanted and the tarry deposit was washed repeatedly with dichloromethane. The combined dichloromethane solutions were evaporated to leave a dark oil which turned murky brown on dilution with ether. The solution was filtered through Celite and the yellow filtrate was washed twice with 5% aqueous HCl (75 mL), once with brine (75 mL) and then dried over magnesium

sulfate. Filtration and evaporation of the solvent gave a yellow oil which on chromatography gave starting material (266 mg, 13.8%) and a 2.2:1 mixture of enone-ketals **11** and **12** (1.35 g, 65.7%). Careful chromatotron chromatography with 7% ether/hexanes as eluent gave pure **11** for spectral analysis. Data for enone **11** : R_f 0.41 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 6.90 (d, 1H, J = 9.8 Hz), 5.78 (d, 1H, J = 9.8 Hz), 3.93 (m, 1H), 3.84 (m, 2H), 3.77 (m, 1H), 2.86 (d, 1H, J = 17.3 Hz), 2.14 (m, 3H), 1.90 (m, 1H), 1.53 (m, 1H), 1.29 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 201.2, 156.3, 127.0, 117.5, 65.2, 64.2, 51.2, 46.7, 43.3, 35.6, 30.9, 26.5, 20.4. IR ($CDCl_3$) 2954, 2884, 1668, 1601, 1533, 1423, 1383, 1318, 1247, 1220, 1141, 1042, 997, 908, 731, 651 cm^{-1}. EIMS *m/z* (relative intensity) 223(M^++1, 1), 207(1), 193(1), 179(2), 166(1), 147(4), 135(1), 99(95), 91(12), 86(100), 77(20), 55(31), 41(46). HRMS *m/z* 222.1259 (Calcd for $C_{13}H_{18}O_3$ - 222.1256). Data for enone **12** : R_f 0.41 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 6.75 (m, 1H), 5.91 (m, 1H), 4.0-3.75 (m, 4H), 2.79 (m, 1H), 2.2-1.5 (m, 5H), 1.26 (s, 3H), 0.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 204.7, 155.5, 126.5, 118.0, 65.0, 64.2, 45.7, 42.5, 37.0, 33.9, 32.0, 22.5, 19.4.

Reduction of Enones 11/12 to Ketones 13/14.

A mixture of enones **11** and **12** (~2.7:1, 1.86g, 8.39 mmol) were dissolved in ethyl acetate (20 mL) in a Parr hydrogenation bottle. A 10% dispersion of Pd on carbon (67 mg) was added and the suspension was placed on a Parr Hydrogenator. After 3 to 4 evacuation - hydrogen infusion cycles, the pressure was maintained at ~5 psi for 1 h. The solution was filtered through Celite and concentrated to give a residue which on careful column chromatography on silica gel with 5-7% ether/hexanes as eluent gave **13** (1.34 g, 71.5%) as a liquid and **14** (0.49 g, 26.1%) as an oil which gave clear colorless crystals on standing. Data for ketone **13** : R_f 0.29 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 3.92 (m, 1H), 3.83 (m, 2H), 3.76 (m, 1H), 2.74 (dd, 1H, J = 1.1, 15.6 Hz), 2.44 (ddd, 1H, J = 8.1, 11.3, 17.7 Hz), 2.35 (d, 1H, J = ddd, 1H, J = 1.5, 6.5, 17.7 Hz), 2.19 (ddd, 1H, J = 9.1, 9.1, 14.9 Hz), 2.11 (ddd, 1H, J = 2.4, 10.9, 10.9 Hz), 2.04 (d, 1H, J = 15.6 Hz), 1.92 (ddd, 1H, J = 6.3, 12.1, 12 Hz), 1.69 (m, 1H), 1.62 (m, 1H, J = 1.4, 8.0, 8.0 Hz), 1.51 (ddd, 1H, J = 2.4, 9.6, 9.6 Hz), 1.32 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 212.7, 117.8, 64.9, 64.2, 51.1, 45.7, 42.1, 36.69, 36.68, 33.8, 32.0, 22.6, 19.4. IR ($CDCl_3$) 2957, 2881, 1710, 1458, 1384, 1317, 1165, 1140, 1097, 1046, 948, 892 cm^{-1}. EIMS *m/z* (relative intensity) 224(M^+,>1), 209(1), 181(1), 153(1), 149(4), 140(1), 137(1), 126(1), 123(1), 113(2), 109(1), 99(100), 86(19), 55(15). HRMS *m/z* 224.1403 (Cacd for $C_{13}H_{20}O_3$ - 224.1412).

Data for ketone **14** : R_f 0.37 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 3.98-3.91 (m,

2H), 3.85-3.81 (m, 2H), 2.58 (m, 1H), 2.13 (m, 3H), 2.00 (m, 3H), 1.87 (m, 1H), 1.38 (m, 1H), 1.29 (m, 1H), 1.31 (s, 3H), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 215.4, 118.8, 65.1, 64.2, 57.2, 51.5, 35.8, 34.6, 27.7, 24.8, 22.3, 20.8, 18.9. IR ($CDCl_3$) 2964, 2881, 1713, 1462, 1424, 1386, 1342, 1315, 1295, 1139, 1094, 1048, 949, 898 cm^{-1}. EIMS *m/z* (relative intensity) 224(M^+,>1) 209(9), 140(9), 99(62), 86(100), 67(15), 55(21), 41(21). HRMS *m/z* 224.1400 (Calcd for $C_{13}H_{20}O_3$ - 224.1412).

Carbomethoxylation of 13 to 15.

To a two-necked flask fitted with a reflux condenser and magnetic stirbar was added a 50% dispersion of sodium hydride in mineral oil (284 mg, 5.92 mmol) which was then washed with hexanes (3 x 0.5 mL) and DME (1 mL) under a stream of argon. The sodium hydride was suspended in DME (4 mL) and dimethyl carbonate (1.4 mL, 16.6 mmol) was added. The reaction mixture was heated to reflux (100°C oil bath) with vigorous stirring and to the resulting hot suspension was added dropwise a solution of the keto-ketal **13** (0.47 g, 2.08 mmol) in DME (4mL). The resulting yellow heterogeneous mixture was refluxed for 3 h at 100°C and then cooled to 0°C. Dropwise addition of 10% aqueous acetic acid (4.5 mL) with constant stirring dissolved the solid mass. The reaction mixture was poured into ether, washed with saturated aqueous sodium bicarbonate, water and brine. The ether layer was dried over sodium sulfate, filtered and the filtrate concentrated to a dark yellow liquid. The crude material was loaded on to a 2 mm chromatotron plate and eluted with 9% ethyl acetate/hexane at a 1mm flow rate. Concentration of the fractions gave starting material (55.4 mg, 11.8%) and **15** as a clear yellow oil (470 mg, 80.1%). R_f 0.47 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) 12.37 (s, 1H, OH), 3.93 (m, 1H), 3.86 (m, 2H), 3.80 (m, 1H), 3.76 (s, 3H), 2.66 (d, J = 18 Hz, 1H), 2.16 (d, J = 1.5 Hz, 2H), 2.08 (m, 2H), 1.85 (d, J = 18 Hz, 1H), 1.69 (m, 1H), 1.48 (m, 1H), 1.03 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 173.5, 172.7, 118.2, 95.8, 64.9, 64.1, 51.4, 47.8, 41.5, 36.1, 34.6, 33.7, 33.6, 22.8, 18.4. IR (CCl_4) 2980, 2960, 2895, 1660, 1610, 1450, 1390, 1360, 1330, 1250, 1210, 1190, 1110, 1065, 740 cm^{-1}. EIMS *m/z* (relative intensity) 282(M^+, 7), 251(2), 237(2), 205(2), 182(3), 167(4), 150(3), 149(4), 135(3), 121(2), 113(3), 100(21), 99(100), 55(23), 41(24). HRMS *m/z* 282.1460 (Calcd for $C_{15}H_{22}O_5$ - 282.1467).

Oxidation of 15 to 5a.

Phenylselenyl chloride (834 mg, 4.3 mmol) was placed in a two-necked flask with a magnetic stirbar under argon and dissolved in dichloromethane (7 mL). The red solution was cooled to 0°C and pyridine (0.3 mL, 3.7 mmol) was added resulting in a yellow solution which was stirred for 10 min.

A solution of the keto-ester **15** (0.48 g, 1.7 mmol) in dichloromethane (4 mL) was added dropwise and the reaction mixture stirred for 4 h. The reaction mixture was transferred to a separatory funnel and washed twice with 1M aqueous HCl (2 x 2.5 mL) and then with water. The dichloromethane layer was then transferred to a flask and cooled to 0°C. Aqueous hydrogen peroxide (30%, 1 mL) was added and the mixture stirred for 10 min followed by addition of a second aliquot of aqueous hydrogen peroxide (1 mL). The reaction mixture turned colorless and was washed with aqueous sodium bicarbonate and dried over sodium sulfate. Filtration and concentration of the filtrate gave a crude product which was chromatographed on a 2 mm silica gel chromatotron plate with a 1 mm flow rate of 20% ethyl acetate/hexanes as eluent to give **5a** (435 mg, 91%) as a light yellow oil. Crystallization from ethyl acetate/hexanes gave clear, colorless crystals, mp 55-56°C (EtOAc/hexanes); R_f 0.09 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.70 (s, 1H), 4.00-3.76 (m, 4H), 3.79 (s, 3H), 2.93 (d, 1H, J = 17.8 Hz), 2.25 (d, 1H, J = 17.8 Hz), 2.18 (m, 2H), 2.01 (m, 1H), 1.63 (m, 1H), 1.34 (s, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) 195.4, 165.3, 161.9, 129.7, 117.2, 65.2, 64.3, 52.1, 50.5, 46.8, 43.6, 35.5, 30.8, 25.7, 20.6. IR (CCl_4) 2954, 2885, 1735, 1679, 1435, 1351, 1321, 1283, 1251, 1202, 1154, 1112, 1035 cm^{-1}. CIMS *m/z* (relative intensity) 281(M^++1, 98), 266(11), 250(5), 249(28), 193(4), 100(10), 99(35), 87(14), 86(100), 55(5). EIMS *m/z* (relative intensity) 249(6), 205(2), 99(65), 91(12), 86(100), 77(12), 69(11), 59(13), 55(33), 53(17), 43(19), 41(30). HRMS *m/z* 280.1310 (Calcd for $C_{15}H_{20}O_5$ - 280.1311). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.23.

High Pressure Reaction of 1,3,3-trimethyl-2-vinylcyclohexene (4) with Enone 5a.

In two high pressure reaction tubes were placed equal amounts of 1,3,3-trimethyl-2-vinylcyclohexene, **4** (158.5 mg total, 1.05 mmol), and carbomethoxyenone **5a** (419 mg total, 1.5 mmol) followed by anhydrous $ZnBr_2$ (202 mg total, 0.895 mmol) and dichloromethane (6.0 mL). The tubes were sealed and pressurized to 12 kbar for 23 hours. The reaction mixtures were combined, concentrated and the residue chromatographed on a 4 mm SiO_2 plate at 2 mm flow rate with 8% (350 mL) and then 22% (200 mL) ethyl acetate/hexanes as eluent to give **16** (352 mg, 78%), **17** (61.0 mg, 13.5%) and **18** (6.1 mg, 1.4%). Data for **16** : R_f 0.41 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 12.68 (s, 1H, OH), 5.61 (m, 1H, H-1), 5.31 (dd, 1H, J = 5.4, 5.4 Hz, H-6), 3.91 (m, 1H, H-25/H-26), 3.85 (m, 1H, H-25/H-26), 3.79 (m, 1H, H-25/H-26), 3.74 (s, 3H, OCH_3), 3.70 (m, 1H, H-25/H-26), 2.91 (ddd, 1H, H-7), 2.68 (d, 1H, J = 17.9 Hz, H-12α), 2.42 (m, 2H, H-7, H-8), 2.07 (m, 4H, H-2, H-16), 2.00 (m, 1H, H-15), 1.88 (d, 1H, J = 17.9 Hz, H-12β), 1.82 (m, 3H, J = 1.3 Hz, H-20), 1.46 (m, 2H, H-3), 1.41 (m, 1H, H-15), 1.15 (s, 6H), 1.14 (s, 3H), 1.11 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$, 125

MHz) 174.1 (C-23), 172.9 (C-11), 141.3 (C-5), 133.3 (C-10), 128.7 (C-6), 125.1 (C-1), 117.7 (C-17), 100.7 (C-9), 64.8 (C-25), 63.9 (C-26), 51.6 (OCH_3), 48.5 (C-13), 46.9 (C-8), 44.8 (C-14), 40.1 (C-3), 36.1 (C-16), 35.4 (C-12), 34.6 (C-4), 31.8 (C-7), 31.3 (C-15), 27.9 (C-21 or 22), 27.1 (C-19 or 21), 26.8 (C-19 or 21), 22.9 (C-2), 21.9 (C-20), 20.7 (C-18). IR (CCl_4) 2960, 2940, 2900, 1650, 1605, 1465, 1450, 1390, 1380, 1360, 1325, 1250, 1215, 1190, 1110, 1065, 920 cm^{-1}. EIMS *m/z* (relative intensity) 430(M^+,7), 399(4), 294(5), 281(55), 249(79), 193(13), 161(13), 149(12), 121(19), 113(14), 105(22), 99(100), 91(32), 86(30), 79(19), 69(25), 55(55). UV (MeOH, nm) λ (ϵ): 236(19,100), 243(22,200), 251(20,200).

Data for **17** : R_f 0.28 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) 5.62 (m, 1H, H-1), 5.24 (dd, 1H, J = 7.9, 5.4 Hz, H-6), 3.93 (m, 1H, H-25), 3.83 (m, 2H, H-25/H-26), 3.77 (m, 1H, H-26), 3.67 (s, 3H, OCH_3), 3.09 (d, 1H, J = 10.7 Hz, H-9), 2.76 (d, 1H, J = 16.1 Hz, H-12), 2.58 (ddd, 1H, J = 10.7, 8.0, 4.9 Hz, H-8), 2.45 (ddd, 1H, J = 15.3, 5.4, 4.9 Hz, H-7), 2.39 (ddd, 1H, J = 15.3, 8.0, 7.9 Hz, H-7), 2.14 (d, 1H, J = 16.1 Hz, H-12), 2.12 (m, 2H, H-16), 2.04 (m, 2H, H-2), 1.78 (s, 3H, H-20), 1.64 (m, 2H, H-15), 1.45 (m, 2H, H-7), 1.26 (s, 3H, H-19), 1.19 (s, 6H, H-21 or H-12), 1.10 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$, 125 MHz) 207.3 (C-11), 171.3 (C-23), 143.9 (C-5), 133.5 (C-10), 125.8 (C-1), 123.7 (C-6), 117.5 (C-17), 64.9 (C-25 or 26), 64.1 (C-25 or 26), 60.8 (C-9), 52.0 (OCH_3), 51.8 (C-13), 45.4 (C-8), 45.0 (C-14), 44.9 (C-12), 40.4 (C-3), 36.3 (C-16), 34.6 (C-4), 33.4 (C-15), 32.1 (C-7), 28.5 (C-21 or C-22), 27.9 (C-21 or C-22), 22.8 (C-2), 21.8 (C-20), 18.7 (C-18), 17.4 (C-19). IR ($CDCl_3$) 2970, 2940, 2900, 2860, 1745, 1705, 1440, 1360, 1345, 1320, 1300, 1225, 1160, 1110, 1050, 1020, cm^{-1}. EIMS *m/z* (relative intensity) 430(M^+,6), 398(1), 315(3), 281(20), 249(27), 183(50), 121(18), 107(14), 99(100), 86(27), 69(27), 55(27), 43(27), 41(22). HRMS *m/z* 430.2734 (Calcd for $C_{26}H_{38}O_5$ - 430.2719).

Data for **18** : R_f 0.31 (20% EtOAc/hexane); ^1H NMR ($CDCl_3$, 500 MHz, 297°K) 5.89 (dd, 1H, J = 4.1, 7.1 Hz, H-6), 3.89-3.79 (m, 2H, H-25/26), 3.81-3.75 (m, 2H, H-25/26), 3.64 (s, 3H, OCH_3) 2.96 (d, 1H, J = 15.9 Hz, H-12), 2.68 (dd, 1H, J = 6.7, 11.8 Hz, H-8), 2.43 (ddd, 1H, J = 13.8 Hz, H-1eq), 2.22 (m, 2H, H-7), 2.11 (d, 1H, J = 15.9 Hz, H-12), 2.10 (m, 2H, H-16), 2.00 (m, 1H, H-15), 1.64 (m, 1H, H-2), 1.49 (ddd, 1H, 3.7, 5.1, 13.8 Hz, H-2), 1.38 (m, 1H, H-3 and m, 1H, H-15), 1.28 (m, 1H, H-1ax), 1.24 (s, 3H, H-20), 1.19 (s, 3H, H-19), 1.18 (m, 1H, H-3), 1.14 (s, 3H, H-21 or 22), 1.13 (s, 3H, H-21 or 22), 1.06 (s, 3H, H-18). ^{13}C NMR ($CDCl_3$, 125 MHz, 323°K) 208.4 (C-11), 176.5 (C-23), 153.7 (C-5), 122.1 (C-6), 117.8 (C-17), 66.7 (C-9), 64.9 (C-25 or 26), 64.0 (C-25 or 26), 52.7 (C-8), 51.9 (OCH_3), 51.2 (C-13), 47.2 (C-12), 45.7 (C-14), 45.4 (C-10), 37.9 (C-3), 35.9 (C-16), 35.7 (C-1), 35.3 (C-4), 33.5 (C-21 or 22), 32.5 (C-21 or 22), 31.6 (C-15), 27.6 (C-7), 27.2 (C-19), 25.7 (C-20), 19.9 (C-18), 17.7 (C-2). IR (CCl_4) 3000, 2960, 2895, 1740, 1715, 1470, 1390, 1225, 1155, 1110, 1060, 920 cm^{-1}.

EIMS *m/z* (relative intensity) 430(M^+,57), 383(2), 281(10), 261(4), 258(2), 249(6), 244(6), 221(4), 167(11), 155(12), 135(21), 105(16), 99(100), 86(68), 79(20), 69(28), 41(46). HRMS *m/z* 430.2751 (Calcd for $C_{26}H_{38}O_5$ - 430.2719).

Reduction of Diene 16 to 21.

To a solution of keto-ester **16** (275 mg, 0.64 mmol) in absolute ethanol (29 mL) in a thick walled Parr hydrogenation bottle was added 5% palladium on calcium carbonate (390 mg). The suspension was fitted onto a Parr Hydrogenator and shaken for 12 h at 52 psi H_2. The reaction mixture was filtered through a Celite plug in a pasteur pippette and the clear filtrate was evaporated on a rotary evaporator to yield **21** (261 mg, 95%) as a clear liquid: R_f 0.41 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 12.67 (s, 1H, OH), 3.93, 3.85 (m, 2H, H-25/26), 3.79 (s, 3H, OCH_3), 3.85, 3.78 (m, 2H, H-25/26), 2.70 (d, 1H, J = 17.7 Hz, H-12α), 2.25 (m, 1H, H-8), 2.23 (m, 1H), 2.19 (m, 2H), 2.05 (m, 1H), 2.00 (m, 1H), 1.95 (m, 2H), 1.85 (m, 1H, J = 17.7 Hz, H-12β), 1.61 (s, 3H, H-20), 1.58 (m, 2H), 1.55 (m, 1H), 1.45 (m, 2H), 1.35 (m, 1H), 1.12 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H),. ^{13}C NMR ($CDCl_3$, 125 MHz) 174.3, 172.4, 137.5, 127.2, 117.8, 101.6, 64.8, 63.9, 51.6, 48.3, 45.5, 45.0, 40.0, 36.1, 35.5, 34.8, 32.9, 32.2, 31.12, 31.09, 28.9, 28.5, 26.4, 20.9, 20.1, 19.5. IR (CCl_4) 2927, 1645, 1605, 1440, 1381, 1369, 1349, 1316, 1179, 1097, 1052, 950, 908 cm^{-1}. EIMS *m/z* (relative intensity) 432(M^+,1), 400(1), 303(1), 281(22), 249(24), 155(19), 99(83), 84(57), 69(13), 49(100), 41(26). HRMS *m/z* 432.2865 (Calcd for $C_{26}H_{40}O_5$ - 432.2876).

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