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THE CHEMISTRY OF C-AROMATIC TAXANE DERIVATIVES ATROPISOMER CONTROL OF REACTION STEREOCHEMISTRY

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Abstract- The atropselective synthesis of tricyclo [9.3.1.$0^{3,8}$] pentadecane ring systems is reported. Substrate conformation is utilized for the stereoselective elaboration of functional groups. The conformational dynamics of intermediates are also reported.

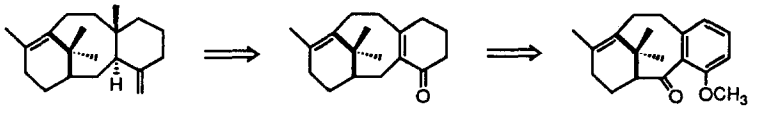
Introduction

The remarkable success of taxol in advanced clinical trials[1] has prompted an intensive effort in the synthesis of this natural product and its derivatives.[2] In 1983 we reported a type 2 intramolecular Diels-Alder entry into the taxane ring system[3]. The development of this approach for synthesis of functionalized taxane derivatives that may be of value for structure-activity studies is dependent upon the stereoselective elaboration of functionality in the tricyclo[9.3.1.$0^{3,8}$]pentadecane rings. The conformation of this novel 6-8-6 bridged-fused skeleton plays an important role in these transformations. The present work reports efforts that involve the synthetic elaboration and conformational analysis of C-aromatic taxane rings.

Results and Discussion

C-Aromatic taxane derivatives are readily available from the type 2 intramolecular Diels-Alder reaction. One approach for elaboration of these cycloadducts to the taxane natural product skeleton is outlined in Scheme 1. The strategy involves transformation of a functionalized C-aromatic ring (3) to enone 2 allowing for introduction of the C-19 methyl group.

SCHEME 1



1 2 3

C-Aromatic taxanes can adopt one of two low energy conformations. Their conformational preference and the energy barrier separating each conformer plays an important role in the synthesis of molecules possessing this ring structure[4]. Conformational analysis of C-aromatic derivatives, including the C-4 methoxy aromatic compound 3 revealed an opportunity to employ *substrate control* for the stereoselective synthesis of the tricyclic taxane skeleton (Scheme1).[5] It was anticipated that the C-19 methyl group could be delivered to the convex face of the folded endo conformation via conjugate addition to

enone **2**. Support for this approach arises from the fact that suitable functionality at C-4 (taxane numbering) results in a conformational lock of the tricyclic ring system. Furthermore, under Lewis Acid catalyzed conditions, the endo conformational isomer (cf. Scheme 2) is formed exclusively.[4] With substituents such as OCH_3 and Br at C-4 the barrier separating the conformers is in excess of 27 kcal/mole, permitting the isolation and elaboration of the desired conformation of the C-aromatic taxane tricycle.

It is important to establish if substrate conformation can be utilized to control the stereochemistry of functional group manipulations of C-aromatic intermediates, and to study the barriers and conformational preferences of the modified derivatives.

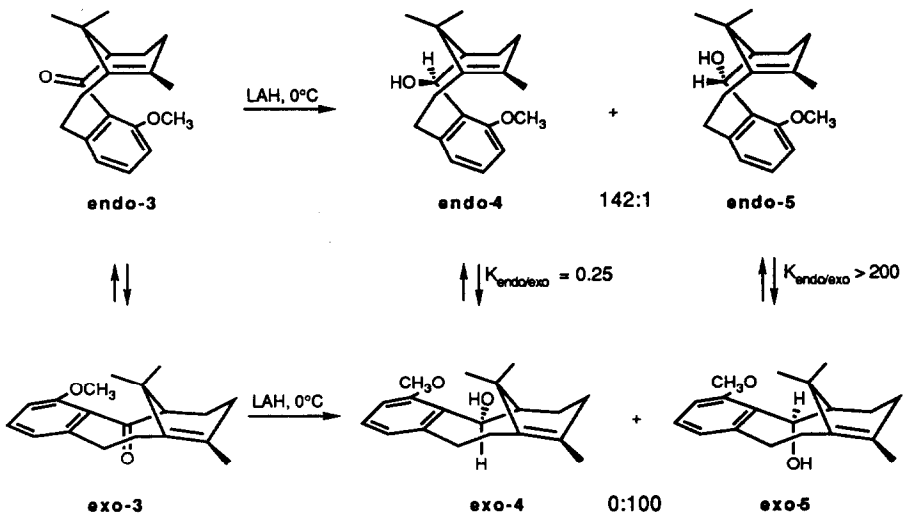
Examination of the X-ray crystal structure of the endo and exo conformers of ketone **3** reveal that opposite faces of the carbonyl group are exposed in the two conformers, and that nucleophilic attack should give rise to epimeric products. To confirm this analysis the stereochemistry of the reduction of the C-2 carbonyl was investigated (Scheme 2). Endo ketone **3** was treated with LAH (1.1 eq) in ether at 0°C. The reaction afforded a 142:1 ratio of β:α alcohols, endo-**4** and endo-**5**, as determined by gas chromatography analysis. The ^1H NMR of the β isomer is fully consistent with the assigned endo conformation. In particular, the allylic methyl singlet at 0.59 ppm establishes its proximity to the shielding region of the aromatic ring. Conversely, treatment of the exo methoxy ketone **3** (obtained through thermal equilibration/separation of pure endo material) under the same reduction conditions, afforded the α alcohol exo-**5** as the sole product. ^1H NMR analysis reveals that the alcohol retains the exo conformation. In particular, the C-16 methyl group at 0.15ppm establishes its proximity to the shielding region of the aromatic ring.

The epimeric alcohols **4** and **5** were found to exhibit intriguing conformational behavior. Under the conditions of the reduction and work-up, both epimers retain their original conformation. To establish whether the product conformation is under kinetic or thermodynamic control, and to establish, at least qualitatively, the magnitude of the barrier separating the conformational isomers, the following experiments were carried out. A chloroform solution of the endo β alcohol **4** was warmed to 35°C for 1 hour. Two compounds were obtained in a ratio of 4/1. Separation by chromatography followed by ^1H NMR analysis showed them to be the endo and exo atropisomers. The major product was verified as the exo conformer (exo-**4**) by X-ray analysis. In a similar manner, a chloroform solution of the exo α alcohol **5** was warmed to 30°C for 1 hour. HPLC analysis of the resulting solution showed only the presence of the endo isomer; the exo material could no longer be observed. This indicates that for this diastereomer the endo conformation is preferred by at least 200/1 ($\Delta G^o > 3.1$ kcal/mole).

We suggest several factors to account for these observations. Perhaps the most important is the preference for the hydroxyl group to occupy the pseudo-equatorial position on the central eight-membered ring. This preference can be reinforced by hydrogen bonding between the hydroxyl proton and the C-4 methoxy oxygen in exo-**4** and endo-**5**.
These results document the kinetic selectivities of the LAH reductions, and also confirm the initial expectations that extremely high levels of facial selectivity may be obtained based upon substrate control in the C-aromatic taxane tricyclic system. The opportunity to isolate individual isomers (atropisomers) makes this a powerful synthetic strategy in this series.

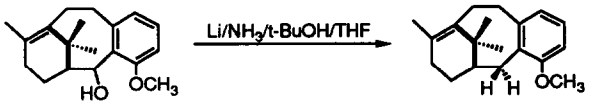
The preceding stereochemical results are important for the subsequent Birch reduction of the alcohols. Hydrogenolysis of the benzylic oxygen requires that the C-O bond must adopt a position which is parallel to the π system of the aromatic ring[6].

SCHEME 2



Examination of molecular models reveals that this situation occurs only in exo-α-alcohol **5** and the endo-β-alcohol **4**. The remaining conformational isomers have the C-2 substituent pseudo-equatorial on the eight member ring, and thus coplanar with the σ plane of the aromatic ring. Thus endo-**5** and exo-4 were not expected to undergo hydrogenolysis *providing the conformation is maintained during the course of the reduction.*

The individual benzylic alcohols were subjected to dissolving metal reduction conditions. Each alcohol was treated with lithium and ammonia in the presence of THF and t-butanol at -78°C (eq. 1). Endo-**4** and exo-**5** gave 80 and 75% yields, respectively, of the C-2 dihydro compound **6**. The remaining isomers (exo-**4** and endo-**5**) afforded complex reaction mixtures with none of the hydrogenolysis product. These results are consistent with the stereoelectronic analysis. Only those isomers with the benzylic C-O sigma bond aligned for cleavage (endo-**4** and exo-**5**) undergo hydrogenolysis. Thus, a strategy to prevent the hydrogenolysis of the α hydroxy group at C-2 emerges. The required stereochemistry coincides with the

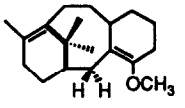


endo-4, exo-5 **6**

configuration found in the taxane natural products. Preservation of the benzylic bond depends upon securing the endo conformation and its maintenance during reduction.

Upon removal of functionality at C-2, the energy barrier separating endo and exo conformational isomers is dramatically reduced. Thus, the dihydro compound **6** undergoes conformational interconversion in solution at room temperature. At equilibrium the endo/exo ratio is 4.2 (ΔG^0 = 0.85 kcal/mole). The barrier for interconversion, as determined by measuring the coalescence temperature by ^{1}H NMR, is 22.6 kcal mole-1. This barrier is not sufficiently high enough to allow for easy separation of the two conformers at room temperature.

Interestingly, no net reduction of the aromatic ring was observed in these hydrogenolysis reactions. The reduction potential is apparently quite high, and it became apparent that harsher conditions would be required to affect this reduction. For example, treatment of the dihydro compound **6** with 60 eq. of lithium in ammonia for 24 h left starting material unchanged. Carrying out the reduction using lithium (20 eq.) in the presence of methylamine[7] and ethanol gave a low yield of the monoenol ether **7**; no dienol ether could be detected.



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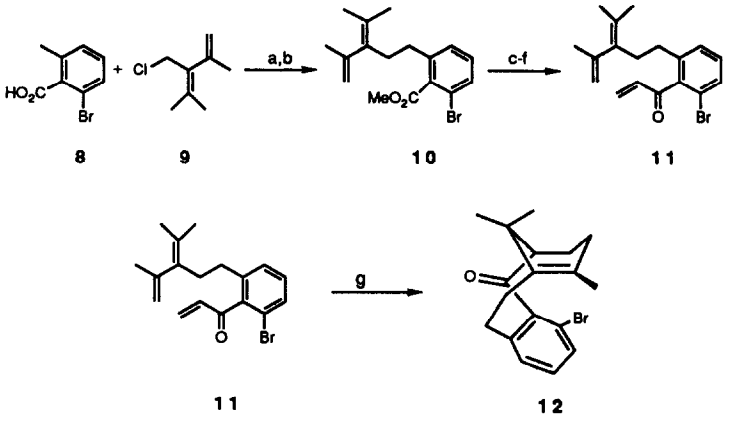
The inability of the methoxy compound to undergo smooth Birch reduction to a cyclohexenone with retention of the C-2 benzylic oxygen prompted a revision of the strategy. It seemed reasonable that an electron withdrawing group should lower the reduction potential of the aromatic nucleus and render it more susceptible to dissolving metal reduction conditions[8]. A C-4 carboxy group would not only satisfy this requirement but also provide a handle for further manipulation of the C-ring. A suitable precursor to the acid was found to be the aryl bromide **12**.

C-4 Bromide Route. A similar strategy employed for the synthesis of aromatic methoxy **3**[4] was used for the bromide (Scheme 3). Thus, treatment of the disubstituted benzoic acid **8**[9] with 2.2 eq of LDA followed by trapping of the tolyl anion with the chlorodiene **9**[3] at -78°C, and subsequent esterification with ethereal diazomethane gave the diene ester **10** in 82% yield. Transformation of the diene ester to the trienone **11** was accomplished in the following manner: (1) reduction with DIBALH, (2) oxidation of the benzyl alcohol with PCC/Celite, (3) vinylation with vinyl magnesium bromide, and (4) oxidation of the allylic alcohol with $BaMnO_4$/Celite to give after chromatography the trienone **11** in 66% yield from the diene ester.

Diels-Alder cyclization of the trienone was accomplished by Et_2AlCl catalysis to afford a single cycloadduct (endo-**12**) in 76% yield. The cycloadduct was assigned the endo conformation based on comparison of the 500 MHz ^{1}H NMR spectrum with that of endo aromatic methoxy compound **3**. The vinyl methyl group appears as a broad singlet at 0.84ppm, indicative of being in the shielding region of the aromatic ring. The endo conformation of the bromoketone is maintained in solution at room temperature. Upon warming, a slow interconversion to the exo conformer is observed. By studying the rate of approach to equilibrium at five temperatures (49.9°C to 89.6°C) the energy barrier was found to be 27.1 kcal/mole. The cycloaddition is another example of an *atropselective reaction* that generates a C-aromatic taxane ring system[4,10]. The barrier separating the conformational isomers is sufficiently large so that subsequent transformations on the aromatic cycloadduct are

expected to be controlled by the folded endo conformation, with the delivery of reagents to occur from the convex face of the molecule. This has been realized experimentally.

SCHEME 3[a]

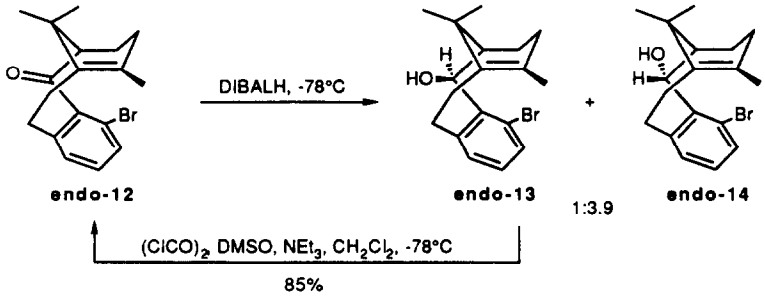


[a] (a) LDA, -78°C, then **9**, -78°C-0°C, 84%; (b) CH_2N_2, 98%; (c) DIBALH, C_7H_8, 0°C; (d) PCC/Celite, CH_2Cl_2, 23°C; (e) $CH_2CHMgBr$, THF, 0°C; (f) $BaMnO_4$, C_6H_6, 80°C, 66% from **10**; (g) Et_2AlCl, CH_2Cl_2, -78°C, 76%

Reduction of the carbonyl moiety of endo-**12** with DIBALH at 0°C gave a 2.7/1 ratio of α/β alcohols endo-**14** and -**13** (Scheme 4). This ratio was increased to 3.9/1 by lowering the reaction temperature to -78°C. The diastereomeric alcohols are easily separable via chromatography, and results in isolated yields of 71% and 16% for the α- and β– epimers, respectively. The observation that the major product was the α isomer was an unexpected result since the LAH reduction of the related aromatic endo-methoxy substrate **3** gave only a trace amount of the α isomer. Subsequent examination of the reaction of the methoxy derivative with DIBALH resulted in a 6.5/1 ratio of diastereomeric alcohols favoring the β epimer. Apparently, the stereochemical outcome of the hydride reduction of these compounds is dictated by the substituent at C-4 as well as the reducing reagent. Examination of a series of C-4 analogues reveals a linear relationship between the ratio of diastereomers and the van der Waals radius of the substituent, a result that is consistent with steric approach control[11]. Only in the case of the aryl bromide is the major product the α diastereomer, which corresponds to the C-2 configuration found in the taxane natural products.

It should be pointed out that the minor diastereomer (endo-**13**) can be oxidized using Swern conditions[12] to regenerate the endo bromoketone **12** in 85% yield. After an additional reduction step the α epimer can be obtained in a combined yield of >80% after two cycles. The structures of bromo alcohols **13** and **14** were confirmed via X-ray analysis[13] (Figure 1). The endo conformation is maintained during the course of the reduction and purification. The X-ray reveals an extremely crowded

SCHEME 4



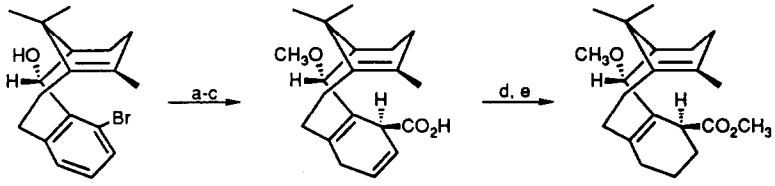
environment about the eight member ring, which assumes a distorted chair-boat conformation in both diastereomers. It is apparent that the sterically least congested environment for the C-2 hydroxy group is the pseudo-equatorial position. The barrier separating the conformational isomers of the individual epimers is sufficiently high to permit their isolation and characterization. The atropisomers of each diastereomer can be equilibrated by heating a $CDCl_3$ solution of each at 80°C for 1 hour. This produces an equilibrium mixture of the endo and exo conformers. At equilibrium, the endo isomer is preferred for the α-alcohol ($K_{endo/exo}$ = 15.3), while the exo conformer is preferred for the β-epimer ($K_{endo/exo}$ = 0.54). As in the related aromatic methoxy series the equilibrium reflects a preference for the hydroxy group to occupy the pseudo-equatorial position. However, the lower equilibrium values may reflect the absence of intramolecular hydrogen bonding in the bromine series.

Figure 1. X-ray structures of (a) endo-**13** and (b) endo-**14.**

Elaboration of the desired endo-α-alcohol was accomplished follows. Protection[14] of α alcohol **14** is readily accomplished using CH_3I/NaH to give the endo methyl ether in 99% yield (Scheme 5). A single atropisomer is obtained as shown by the presence of only three aliphatic methyl singlets and a single peak for the methoxy methyl group in the ^1H NMR. Metal-halogen exchange, followed by trapping of the aryllithium with CO_2 afforded the endo aromatic acid in 93% yield. The required endo conformation was maintained throughout both transformations.

Treatment of the aromatic acid with lithium in ammonia afforded after kinetic protonation the cyclohexadiene acid **15** in quantitative yield. ^{1}H NMR analysis of the product revealed that indeed the C-2 methoxy group remains intact, and that at room temperature in solution the molecule exists as a 2.2/1 ratio of endo/exo conformers. Introduction of two sp^3 centers on the C ring apparently lowers the conformational barrier. However, the enolate generated from the dissolving metal reduction either retains the endo conformation leading to protonation from the β- face, or if conformationally mobile at -78°C, the endo conformer must react preferentially to give **15**, since shielding by the gem-dimethyl group of the exo enolate would give predominantly the C-4 epimer[15]. The stereochemistry at C-4 was verified by X-ray analysis[13] (Figure 2). Interestingly, although the molecule is conformationally mobile at room temperature in solution, it crystallizes as a single (endo) conformer.

SCHEME 5[a]



endo-14 **15** endo-16

[a] (a) NaH, CH_3I, THF, 0°C-23°C, 99%; (b) t-BuLi, CO_2(g), Et_2O, -78°C, 93%; (c) Li/NH_3, EtOH, THF, -78°C; (d) CH_2N_2; (e) H_2, PtO_2, EtOH, 23°C, 77% from **15**

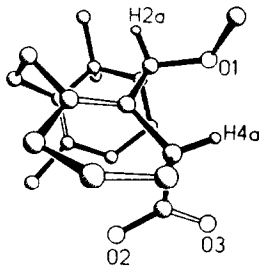


Figure 2. X-ray structure of **15**.

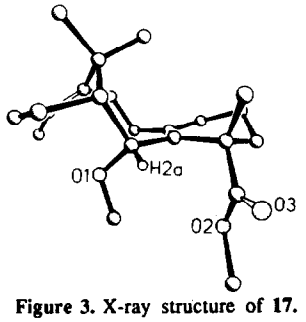
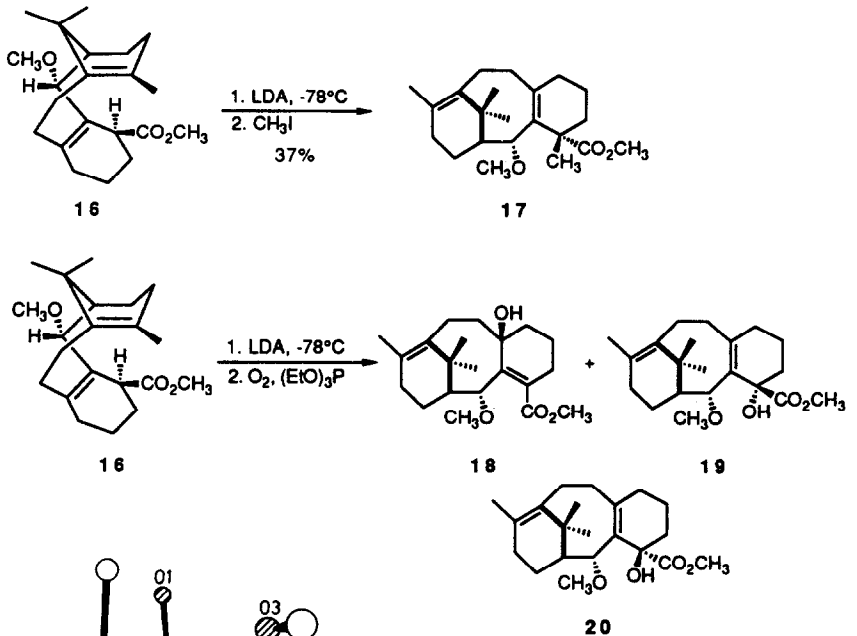


Figure 3. X-ray structure of **17**.

Success of the Birch reduction of the C-4 carboxy derivative led to an exploration of chemistry that would allow for the introduction of the angular C-19 methyl group. To this end, esterification of cyclohexadiene acid **15** with diazomethane followed by hydrogenation produced the β,γ unsaturated ester endo-**16** in 77% overall yield from the aromatic acid. At this stage there is the possibility of functionalizing either at the alpha (C-4) position or at the gamma (C-8) position via the dienolate of the ester. To determine the selectivity of this reaction, ester **16** was treated with LDA at -78°C followed by a

methyl iodide quench to afford a 37% yield of material whose ^1H NMR indicated six methyl resonances (Scheme 6). HETCOR and NOE spectroscopy experiments were inconclusive regarding the location of the newly introduced methyl group. Structural confirmation was supplied by X-ray analysis[13] which showed that alkylation occurred at C-4 to give ester **17** (Figure 3). The ORTEP plot shows that the electrophile approached from the β face of the folded endo conformation resulting in the isolation of a single diastereomer. Unlike the other crystals obtained for X-ray analysis in this series of compounds, the

SCHEME 6



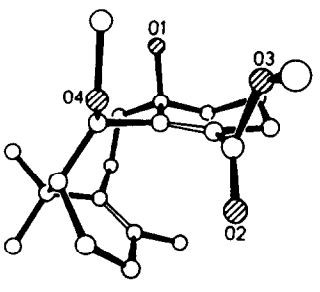


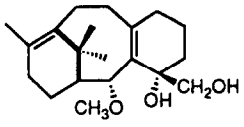
Figure 4. X-ray structure of **18**.

alkylated ester **17** crystallized in the exo form. The reasons for this is not immediately obvious, but could be the result of placing an increased number of sp^3 centers in the C ring, thereby enhancing the repulsive interactions encountered between

the A and C-rings in the endo conformation. The exo isomer is also greatly preferred in solution. At room temperature in d_2-tetrachloroethane the exo/endo ratio is 20/1 ($\Delta G°$ = 1.8 kcal/mole). Upon heating a broadening of the methyl peaks is observed, and a coalescence temperature of 126°C is obtained for the C-16 methyl group. The energy barrier for the conformational interconversion is calculated to be 21.0 kcal/mole, which is substantially lower than aryl bromide **12**.

While the alkylation of the lithium dienolate of ester **16** gives a single regio- and stereo-isomer, the results are not as straightforward when oxygen is the electrophile. Bubbling oxygen into a THF solution of the dienolate in the presence of triethyl phosphite[16] at -78°C resulted in the formation of three of the four possible hydroxyesters. ^{1}H NMR analysis of the crude reaction mixture showed the ratio of **18/19/20** to be 1/1.3/1.6. The three isomers were separated by silica gel chromatography to afford **18**, **19**, and **20** in 20, 21, and 33% yields, respectively. The structural identity of the isomers were not readily discernible via spectroscopic methods. The minor product was the only one of the three which was crystalline, and its structure was determined via X-ray analysis[13] (Figure 4). The ORTEP plot reveals a hydroxy group which occupies an axial position at C-8 on the cyclohexene ring. Additionally, it is interesting to note that the carbonyl π system is perpendicular to that of the C-3-C-4 double bond.

The product with the hydroxyl group alpha to the ester and anti to the bridge ('α,anti' isomer,**19**) was converted to diol **21** upon treatment with DIBALH at 23°C. The diol thus obtained was crystalline and X-ray analysis[13] showed the anti relationship between the C-4 hydroxy group and the methano bridge (Figure 5). The diol **21** is of interest in that it contains the C-4 substitution pattern found in taxol, i.e. an α-oxygen functionality and a β-oxymethyl group. This represents the first report of the formation of this stereocenter during the course of a synthesis of the taxane tricyclic ring system.



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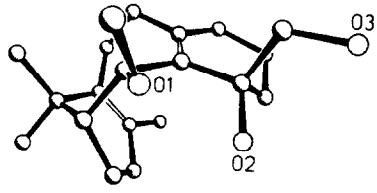

Figure 5. X-ray structure of diol **21**.

The major isomer of the hydroxylation reaction was found to have the hydroxyl group α to the carbomethoxy group and syn to the dimethylmethano bridge ("α,syn" isomer, **20**). That this is the major product is not surprising based on findings of the alkylation reaction (vide supra) and the electronic bias for dienolates to react at the α-position[17].

The alcohols **18-20** exhibit interesting conformational properties. The γ,syn isomer **18** was isolated as the endo conformer, and no evidence of the corresponding exo conformer was observed in the 500 MHz ^{1}H NMR at 23°C. The spectrum remained essentially unchanged upon heating to 50°C for 1 h[18]. The absence of the exo conformer under these conditions implies that the conformational equilibrium lies far to the side of the endo isomer, and does not represent an unusually high barrier for the interconversion. The α,anti hydroxyester **19** undergoes conformational interconversion at room temperature. ^{1}H NMR analysis of a $CDCl_3$ solution showed the endo/exo equilibrium value to be 12.5/1 ($\Delta G°$ = 1.50

kcal/mole). Heating this solution to 50°C for 1 h gave no observable change in the spectrum. The absorption assigned to the carbomethoxy methyl of the minor (exo) isomer appears 10.4 Hz downfield from that of the corresponding methoxy group in the endo conformer. The absence of coalescence of these two peaks allows us to set a lower limit on the energy barrier, which must lie between 18-23 kcal/mole, assuming chromatographic separability of the individual conformers[19].

The α,syn isomer **20** exists as a mixture of the two conformers at room temperature. At 23°C the endo/exo equilibrium value is 1.8 (ΔG° = 0.35 kcal/mole), and ^{1}H NMR coalescence experiments give a single point energy barrier of 19.0 kcal/mole for the interconversion. This experimentally observed value lends credence to the barrier estimated for the structurally similar α, anti isomer 19.

The differences in the conformational properties between the C-aromatic series (i.e., **3** and **12**) and the C-cyclohexene series is worth noting. The high barrier to interconversion is lost upon Birch reduction of the aromatic ring to generate the cyclohexadiene acid **13**, although the preference for the endo conformation is maintained. Only in the case of the C-4 alkylated ester **17** is the exo conformational isomer the preferred one. The analogous hydroxyester **20** has a slightly lower barrier to interconversion than does **17**, but still prefers to be in the endo conformation. In summary, the origin of the effect of substituents at C-4 on the dynamics of this ring system is unclear at the present time. However, of extreme importance is the fact that the γ-hydroxyester **18** exists solely in the endo conformation. This observation leads to the conclusion that the C-8 stereocenter is important for locking the C-saturated molecules in the endo conformation.

The results reported herein demonstrate the feasibility of employing substrate control to stereoselectively manipulate the tricyclic ring system found in the taxane natural products. The intermediates in this series have been shown to exhibit intriguing conformational properties, however a complete understanding of the dominant factors involved is not presently available. The information obtained from these studies is currently being utilized for the synthesis of taxane natural products.

Acknowledgment. We are grateful to NIH for support of this research.

Experimental Section

General. All reactions were conducted under a nitrogen atmosphere unless otherwise indicated. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Dichloromethane, hexane, benzene, toluene, and diisopropylamine were distilled from calcium hydride. Alkyllithium reagents were titrated with diphenylacetic acid. Infrared spectra were recorded using an Analect RFX-40 spectrophotometer using polystyrene as a standard. Proton nuclear magnetic resonance spectra were recorded on either a Bruker WM-250 (250 MHz), GE QE-300 (300 MHz), GE GN-500 (500 MHz), or a GE Omega-500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance spectra were recorded on either the WM-250, QE-300, GN-500, or the Omega-500 instruments operating at 62.9 MHz, 75.4 MHz, 125.7 MHz, and 125.7 MHz, respectively. Chemical shifts are reported as d values relative to $CHCl_3$ (7.27 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) or tetramethylsilane (0.00 ppm for both). Low resolution mass spectra were recorded on a Finnigan 4000 GC/MS/DS mass spectrometer and are recorded as mass/charge (relative percent). High resolution mass spectra were recorded on a VG 7070e high resolution mass spectrometer. Chromatographic separations were performed utilizing Merck silica gel PF 254 (230-400 mesh). Thin layer chromatographic separations were conducted on Merck silica gel 60 F254 precoated

PF 254 (230-400 mesh). Thin layer chromatographic separations were conducted on Merck silica gel 60 F254 precoated plates, utilizing appropriate visualization agents. *In vacuo* as used in the experimental section refers to evaporation of solvent or volatiles at reduced pressure using a Buchi rotary evaporator.

$LiAlH_4$ Reduction of Endo Methoxy Ketone 3. To a solution of endo 3 (50 mg, 0.2 mmole) in ether (100 mL) at 0°C was added $LiAlH_4$ (20 mg, 0.6 mmole). The reaction was stirred for two h and was worked up at 0°C by addition of H_2O (20 µl) NaOH (20 ml, 10%), H_2O (60mL) and $MgSO_4$ (0.5g). The solution was filtered quickly and solvent removed *in vacuo* using an ice bath. Chromatography (silica gel: 230/400, 1:1, CH_2Cl_2/hexane) gave endo alcohol **4** (54 mg, 90%). A cholorform solution of endo alcohol (54 mg) was warmed to 35°C for 30 min (endo:exo; 1:4). Chromatography (silica gel: 230/400, 1:1 CH_2CL_2/hexane, R_f exo = 0.3, R_f endo = .33) gave exo alcohol **4** (11 mg).

endo-3,4,5,6,7,8-Hexadehydro-2α-hydroxy-4-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$] pentadec-11-ene (endo-4). FTIR ($CDCl_3$, cm^{-1}) 3580 (OH), 1575 , 1245 , 1015 . ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (t, 1H, ArH), 6.8 (m, 2H, ArH), 4.28 (m, 2H, CHOH), 3.88 (s, 3H, OCH_3), 2.8-1.8 (m, 9H), 1.75 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 0.15 (s, 3H, CH_3);^{13}C NMR (62.89 MHz, $CDCl_3$) δ 158.5, 142.4, 139.5, 132.6, 128.2, 128.1, 124.5, 109.8, 74.4, 55.7, 52.4, 38.4, 37.4, 31.1, 30.3, 28.7, 26.6, 20.1, 19.75 ; HRMS (EI, 70 eV), calc'd for $C_{19}H_{26}O_2$ (M^+) 286.1932, observed (M^+) 286.1929.

exo-3,4,5,6,7,8-Hexadehydro-2α-hydroxy-4-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$]pentadec-11-ene (exo-4). m.p. 115-117°C. FTIR ($CDCl_3$, cm^{-1}) 3590 (OH), 1575 , 1245, 1015 ;^1H NMR (250 MHz, $CDCl_3$) δ 7.05 (t, 1H, ArH), 6.80 (m, 2H, ArH), 5.65 (d, 1H, OH), 3.8 (s, 3H, OCH_3), 3.81 (m, 1H, CHOH), 2.8-1.2 (m, 9H), 1.60 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.59 (s, 3H, CH_3); HRMS (EI, 70 eV), calc'd for $C_{19}H_{26}O_2$ (M^+) 286.1932, observed (M^+) 286.1927.

$LiAlH_4$ Reduction of Exo Methoxy Ketone 2. To a solution of exo **2** (60 mg, 0.2 mmole in ether (100 mL) at 0°C was added $LiAlH_4$ (25 mg, 0.7 mmole). The reaction stirred for one h at 0°C and the reaction was quenched at 0°C by slow addition of H_2O (25 µl) NaOH (25µl, 10%) H_2O (75 µl) and $MgSO_4$ (~500 mg). Rapid filtration followed by removal of solvent *in vacuo* using an ice bath gave after flash chromatography (silica gel: 230/400, 1:1, CH_2Cl_2/pentane, R_f exo = .4, R_f endo = .45) exo alcohol **5** (58 mg, 95%). A chloroform solution of exo alcohol **5** (58 mg) was warmed to ~35°C for 15 min (endo: exo, >200:1) to give exclusively the endo alcohol **5** (58 mg).

exo-3,4,5,6,7,8-Hexadehydro-2β-hydroxy-4-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$]pentadec-11-ene (exo-5). FTIR ($CDCl_3$, cm^{-1}) 3500 (OH), 2880, 1580, 1230, 1020 ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.12 (t, 1H, ArH), 6.75 (m, 2H, ArH), 5.45 (m, 1H, CHOH), 3.88 (s, 3H, OCH_3), 3.3 (m, 1H, OH), 2.9-1.9 (m, 9H), 1.80 (s, 3H, CH_3), 0.9-0.5 (s, 3H, CH_3), 0.28 (s, 3H, CH_3); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 156.8, 140.7, 132.2, 128.6, 127.9, 126.0, 109.6, 107.4, 72.8, 56.2, 47.7, 38.5, 31.0, 30.8, 30.3, 26.9, 25.1, 22.4, 19.9; . HRMS (EI, 70 eV), calc'd for $C_{19}H_{26}O_2$ (M^+) 286.1932, observed (M^+) 286.1913.

endo-3,4,5,6,7,8-Hexadehydro-2β-hydroxy-4-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$]pentadec-11-ene (endo-5). FTIR ($CDCl_3$, cm^{-1}) 3500 (OH), 2850 , 1550, 1190, 1040; ^1H NMR (250 MHz, $CDCl_3$) δ 7.0 (d, 1H, J = 7.8 Hz, ArH), 6.8 (d, 2H, J = 7.85 Hz, ArH), 5.4 (d, 1H, J = 10.7 Hz, CHOH), 4.78 (d, 1H, J = 10.7 Hz, OH), 3.9 (s, 3H, OCH_3), 2.9-1.2 (m, 9H), 1.4 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.55 (s, 3H, CH_3); ^{13}C

NMR (62.89 MHz, $CDCl_3$) δ 156.9, 141.7, 132.3, 131.9, 131.2, 127.1, 124.8, 109.9, 73.5, 55.8, 55.2, 37.6, 35.2, 30.4, 29.8, 29.7, 25.1, 20.1, 17.9; HRMS (EI, 70 eV) calc'd for $C_{19}H_{26}O_2$ (M^+) 286.1932, observed (M^+) 286.1923.

Birch Reduction of Endo Alcohol 4. Synthesis of 3,4,5,6,7,8-Hexadehydro-4-methoxy-12,15,15-trimethyltricyclo- [9.3.1.$0^{3,8}$]pentadec-11-ene (6). To a solution of endo alcohol **4** (120 mg, 0.42 mmole) in ether (6 mL), t-butanol (6 mL) and NH_3 (12 mL) was added Li (80 mg, 12 mmole, ~25 equivalents). The solution (deep blue) stirred for 3 h. After addition of MeOH (5 mL) the ammonia was allowed to evaporate and the residue was taken up in ether (50 mL) and H_2O (10 mL). The aqueous layer was separated and washed with ether (3 x 20 mL). The ether layers were combined and dried ($MgSO_4$), solvent was removed *in vacuo* to give after chromatography (silica gel: 70/230, petroleum ether, R_f = 0.7) the C-2 dihydro compound **6** (91 mg, 80%) (endo: exo, 3.6:1).

(Endo and Exo both observable) FTIR ($CDCl_3$, cm^{-1}) 3220, 1575 , 1240, 1020; ^1H NMR (250 MHz, $CDCl_3$) δ 7.1 (t, 1H, exo ArH), 6.95 (t, 1H, endo ArH), 6.75 (m, 2H, endo and exo ArH), 3.81 (s, 3H, exo OCH_3), 3.78 (s, 3H endo OCH_3), 3.05 (m, 1H), 2.8-1.8 (m, 10H), 1.8 (s, 3H, CH_3), 1.35 (m, 1H), 1.32 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.6 (s, 3H, CH_3), 0.2 (s, 3H, CH_3); ^{13}C NMR (62.89 MHz, $CDCl_3$) (exo and endo) δ 158.2, 157.2, 143.8, 143.1, 139.7, 131.9, 131.5, 131.1, 130.9, 126.8, 126.4, 125.8, 123.5, 123.4, 108.7, 108.5, 55.8, 55.7, 45.0, 43.2, 39.5., 38.9, 37.5, 35.1, 32.8, 30.6, 30.1, 29.9, 29.7, 28.9, 28.6, 27.5, 25.3, 25.0, 21.4, 20.4 ; HRMS (EI, 70 eV), calc'd for $C_{19}H_{26}O$ (M^+) 270.1983, observed (M^+) 270.1972.

Birch Reduction of Exo Alcohol 5. Synthesis of 6. Exo alcohol **5** was reduced in a manner similar to endo alcohol **4**. A solution of exo alcohol **5** (50 mg, 0.2 mmole) in THF (3 mL) was added to Li (10 mg, ~20 equivalents) NH_3 (10 mL) and t-butanol (3 mL). The blue solution stirred for 1 h and then went clear. The reaction was worked up by addition of methanol (5 mL) followed by evaporation of ammonia and ether extraction to yield after chromatography (230/400; petroleum ether, R_f = .8) the C-2 dihydro compound **6** (38 mg, 75%).

Reduction of the C2 dihydro compound 6. Synthesis of 4-methoxy-12,15,15-trimethyl-tricyclo[9.3.1.$0^{3,8}$]pentadec-3,11-diene (7). A solution of **6** (200 mg, 0.7 mmole) in methylamine (20 mL) and THF (2 mL) was treated with Li (75 mg, 10 eq.) and ethanol (0.5 mL). The reaction stirred for 1 h and solvent was removed *in vacuo*. The residue was dissolved in ether (50 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with ether (2 x 25 mL). The ether layers were combined and dried ($MgSO_4$). Solvent was removed *in vacuo* to give after chromatography (silica gel: 230/400, 1:10, CH_2Cl_2/petroleum ether, R_f = .35) enol ether **7** (50 mg, 26%).

FTIR (NaCl, cm^{-1}) 2900, 1660, 1242 , 1048; ^1H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3H, OCH_3), 2.70 (d of d, 1H), 2.45 (m, 1H), 2.3-1.5 (m, 14H), 1.54 (s, 3H,CH_3), 1.4 (m, 2H), 1.28 (s, 3H, CH_3), 1.0 (s, 3H, CH_3); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 146.4, 135.9, 129.2, 122.5, 55.7, 48.5, 39.7, 37.6,. 36.1, 34.3, 31.8, 29.6, 28.8, 28.7, 25.5, 23.8, 23.0, 21.2, 18.0 ; HRMS (EI, 70 eV), calc'd for $C_{19}H_{30}O$ (M^+) 274.2296, observed (M^+) 274.2285.

Methyl-6-bromo-2-[4-methyl-3-(methylethenyl-3-pentenyl)]benzoate (10). To a 250 mL flask was added THF (87 mL) and diisopropylamine (5.93 mL, 42.2 mmol). The solution was cooled to -78°C and n-butyllithium (16.6 mL, 2.5M in hexanes, 41.5 mmol) was added. After 20 min, a solution of acid **8** (2.51 g, 11.7 mmol) in THF (90 mL) was added via cannula over 30 min. The cannula was rinsed with THF (10 mL). The solution was stirred for 2 h whereupon the chlorodiene **9** (1.86 g, 12.9 mmol) was added neat. After 2.5 h at -78°C and 0.5 h at ambient temperature the reaction

solution was poured into a solution of 30 mL 5% HCl/30 mL saturated aqueous NH_4Cl. The layers were separated and the aqueous layer extracted with ether (3x50 mL). The combined organics were washed with 5% HCl (2x50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid. Flash chromatography (40% ether in petroleum ether) afforded 3.15 g (84%) of white solid. Treatment of the acid with ethereal diazomethane afforded a quantitative yield of the methyl ester. FTIR (NaCl, cm^{-1}): 3068, 2950, 1740, 1630, 1590, 1560, 1440, 1272, 1139, 1098, 1050, 951, 888; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38(dd, J=4, 9 Hz, 1H, ArH), 7.20(m, 1H, ArH), 4.99(m, 1H, vinyl), 4.60(m, 1H, vinyl), 3.93(s, 3H, CO_2CH_3), 2.57(m, 2H, $ArCH_2CH_2$), 2.32(m, 2H, $ArCH_2CH_2$), 1.79(s, 3H, CH_3), 1.68(s, 3H, CH_3), 1.64(s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.21, 145.9, 141.4, 135.5, 135.1, 130.3, 129.7, 128.1, 126.1, 118.9, 113.4, 52.2, 33.1, 32.8, 22.5, 21.5, 19.3; LRMS (CI, isobutane (relative intensity)): 339(100), 337(84); LRMS (EI, 70 eV (relative intensity)): 338(3), 336(3), 306(4), 304(4), 109(100); HRMS (EI, 70 eV): calc. for $C_{17}H_{21}{}^{79}BrO_2$ 336.0718, found 336.0725; calc. for $C_{17}H_{21}{}^{81}BrO_2$ 338.0699, found 338.0705.

6-Bromo-2-[4-methyl-3-(methylethenyl-3-pentenyl)]benzyl Alcohol. The bromo diene ester prepared previously (488 mg, 1.5 mmol) was dissolved in toluene (1.5 mL) and added to a solution of DIBALH (1.5M in toluene, 2.0 mL, 3.0 mmol) in toluene (0.6 mL) at 0°C. An aliquot (1 mL) of toluene was used as a rinse. Monitoring via TLC (20% ether in petroleum ether) showed no starting material after 20 min. The reaction was diluted with ether (10 mL) and sodium fluoride added (504 mg). After stirring 30 min the reaction was poured into sat. NaCl, the organics separated and the aqueous extracted with ether (4x50 mL). The organics were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 460 mg (quantitative yield) of clear oil. The oil was carried on to the next step without further purification. FTIR (NaCl, cm^{-1}): 3400(Br, OH), 3070, 2915, 1632, 1590, 1565, 1440, 1372, 1120, 1008, 890, 775, 735; ^1H NMR (250 MHz, $CDCl_3$): δ 7.43(dd, J=1.5, 7.6 Hz, 1H, ArH), 7.16(dd, J=1.5, 7.6 Hz, 1H, ArH), 7.08(t, J=7.6 Hz, 1H, ArH,), 5.03(m, 1H, vinyl), 4.84(d, J=6.2 Hz, 2H, $ArCH_2O$), 4.66(m, 1H, vinyl), 2.78(m, 2H, $ArCH_2CH_2$), 2.36(m, 2H, $ArCH_2CH_2$), 2.11(t, J=6.2 Hz, 1H, OH), 1.83(d, J=0.80 Hz, 3H, CH_3), 1.70(s, 3H, CH_3), 1.67(s, 3H, CH_3); ^{13}C NMR (75.5 MHz, CDCl3): δ 146.1, 144.1, 137.0, 135.4, 130.6, 129.3, 129.1, 126.0, 125.6, 113.5, 61.4, 33.5, 32.6, 22.6, 21.6, 19.4; LRMS (EI, 70 eV (relative intensity)): 310(40), 308(35), 292(62), 290(61), 277(52), 275(46), 67(100); HRMS (EI, 70 eV): calc. for $C_{16}H_{21}{}^{79}BrO$ 308.0776, found 308.0783; calc. for $C_{16}H_{21}{}^{81}BrO$ 310.0755, found 310.0753.

6-Bromo-2-[4-methyl-3-(methylethenyl-3-pentenyl)]benzaldehyde. The crude benzyl alcohol diene (460 mg, 1.5 mmol) was diluted with CH_2Cl_2 (10 mL) and a powdered mixture of PCC (625 mg, 2.9 mmol) and Celite (625 mg) added. The reaction was stirred at room temperature for 2.5 h then filtered through a bed of Florisil with copious ether washings. Concentration *in vacuo* yielded 439 mg of oil which was carried on without further purification. FTIR (NaCl, cm^{-1}): 3070, 2915, 2759, 1705, 1582, 1449, 1183, 1130, 889, 773; ^1H NMR (300 MHz, CDCl3): δ 10.49(s, 1H, RCHO), 7.49(m, 1H, ArH), 7.25(m, 2H, ArH), 5.00(m, 1H, vinyl), 4.61(m, 1H, vinyl), 2.92(m, 2H, $ArCH_2CH_2$), 2.33(m, 2H, $ArCH_2CH_2$), 1.83(s, 3H, CH_3), 1.68(s, 3H, CH_3), 1.66(s, 3H, CH_3); ^{13}C NMR (75.5 MHz, CDCl3): δ 194.1, 146.8, 146.1, 135.4, 133.4, 131.9, 131.5, 130.7, 127.4, 126.2, 113.5, 32.9, 32.4, 22.6, 21.7, 19.5.

1-[6-Bromo-2-[4-methyl-3-(methylethenyl-3-pentenyl)phenyl]-2-propen-1-ol. To the crude diene aldehyde (437 mg) in THF (2 mL) was added vinylmagnesium bromide (3 mL, 1M in THF, 3 mmol) at 0°C. This stirred for 1h then was poured into sat. NH_4Cl (50 mL), extracted with ether (3x50 mL), the organics combined, dried ($MgSO_4$), filtered, and

concentrated *in vacuo* to yield 550 mg of oil which was carried on without further purification. FTIR (NaCl, cm^{-1}): 3440(Br, OH), 3070, 2910, 1628, 1588, 1561, 1449, 1369, 1115, 982, 888, 772; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40(dd, J=1, 7.8 Hz, 1H, ArH), 7.17(dd, J=1, 7.8 Hz, 1H, ArH), 7.06(t, J=7.8 Hz, 1H, ArH), 6.22(ddd, J=4, 10, 17 Hz, 1H, $HC{=}CH_2$), 5.87(s, 1H, CHOH), 5.24(dd, J=1.7, 10 Hz, 1H, $HC{=}CH_2$), 5.20(dd, J=1.7, 4 Hz, 1H, $HC{=}CH_2$), 5.00(m, 1H, vinyl), 4.63(m, 1H, vinyl), 2.91(m, 1H, OH), 2.79(m, 2H, $ArCH_2$), 2.33(m, 2H, $ArCH_2CH_2$), 1.81(s, 3H, CH_3), 1.69(s, 6H, $2xCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 146.2, 144.1, 138.7, 138.0, 135.7, 131.3, 130.0, 128.8, 125.7, 123.2, 115.2, 113.4, 73.3, 67.8, 33.5, 32.4, 22.7, 21.5, 19.5; LRMS (CI, isobutane, (relative intensity)): 337(2), 335(5), 319(91), 317(95), 83(100); LRMS (EI, 70 eV (relative intensity)): 318(2), 316(2), 67(100); HRMS (EI, 70 eV): calc. for $C_{18}H_{23}{}^{79}BrO$ 334.0932, found 334.0928; calc. for $C_{18}H_{23}{}^{81}BrO$ 336.0912, found 336.0936.

6-Bromo-2-[4-methyl-3-(methylethenyl-3-pentenyl)]phenyl Vinylketone (11). The crude allylic diene alcohol (549 mg) was dissolved in dry benzene (24 mL) and a powdered mixture of $BaMnO_4$ (3.72 g, 15 mmol) and Celite (3 g) added. The suspension was then heated to reflux for 8.5h at which point TLC monitoring showed complete reaction. Filtering through a bed of Celite, concentration *in vacuo*, and flash chromatography (30% CH_2Cl_2 in petroleum ether) yielded 305 mg of pale yellow oil. This represents an isolated yield of 63% for four steps based on the diene ester. FTIR (NaCl, cm^{-1}): 3075, 2915, 1669, 1448, 1401, 1262, 953, 891, 779, 752, 722; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41(dd, J=4, 5 Hz, 1H, ArH), 7.20(s, 1H, ArH), 7.18(d, J=1.6, 1H, ArH), 6.59(dd, J=10, 17.5, 1H, vinyl), 6.13(dd, J=0.7, 10, 1H, vinyl), 5.94(dd, J=0.7, 17.5, 1H, vinyl), 4.94(m, 1H, vinyl), 4.55(m, 1H, vinyl), 2.45(m, 2H, $ArCH_2CH_2$), 2.25(m, 2H, $ArCH_2CH_2$), 1.75(d, J=0.9 Hz, 3H, CH_3), 1.65(s, 3H, CH_3), 1.60(s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 197.4, 145.8, 141.7, 139.4, 137.2, 135.1, 132.7, 130.1, 129.9, 128.2, 128.1, 126.2, 118.5, 113.5, 33.1, 32.3, 22.4, 21.5, 19.4; LRMS (CI, isobutane, (relative intensity)): 335(100), 333(84); LRMS (EI, 70 eV (relative intensity)): 334(2), 332(2), 67(100); HRMS (EI, 70 eV): calc. for $C_{18}H_{21}{}^{79}BrO$ 332.0776, found 332.0777; calc. for $C_{18}H_{21}{}^{81}BrO$ 334.0755, found 334.0749.

endo-4-Bromo-2-oxo-3,4,5,6,7,8-hexadehydro-12,15,15-trimethyltricyclo[9.3.1.0^{3,8}]-pentadec-11-ene (12). To a 1L flask was added trienone **11** (2.48 g, 7.4 mmol) and CH_2Cl_2 (190 mL). After cooling to -78°C diethylaluminum chloride (5.8 g, 25% weight solution in hexanes, 12 mmol) was added over 1 min. The yellow solution was stirred for 8 min whereupon the solution was added via syringe to a 0°C solution of saturated aqueous $NaHCO_3$ (500 mL). The quenching took 4 min. Saturated aqueous sodium potassium tartrate (40 mL) was then added, and the solution stirred for 15 min while warming to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (5x75 mL). The combined organics were washed with brine (150 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid. Flash chromatography (10% ether in petroleum ether) afforded 1.70 g of pure cycloadduct. The impure fractions were combined and triturated with hexanes at 0°C to give a white solid, which was combined with the pure material from the column to give a total of 1.89 g (76%) of white solid. FTIR(KBr, cm^{-1}): 2966.6, 2916.9, 1673.6, 1471.0, 1457.7, 1389.4, 1187.7, 971.56, 938.52, 780.25, 761.54; ^1H NMR(500 MHz, $CDCl_3$): δ 7.36(dd, J=1, 8 Hz, 1H, ArH), 7.09(dd, J=1, 8 Hz, 1H, ArH), 7.00(t, J=8 Hz, 1H, ArH), 2.67(m, 5H), 2.37(m,1H), 2.27(m, 1H), 2.04(m, 1H), 1.69(m, 1H), 1.31(s, 3H, CH_3), 1.13(s, 3H, CH_3), 0.84(d, J=0.4 Hz, 3H, CH_3); ^{13}C NMR(125.7 MHz, $CDCl_3$): δ 212.0(C), 145.5(C), 139.1(C), 132.4(C), 131.3(C), 130.3(CH), 129.8(CH), 128.6(CH), 116.5(C), 62.6(CH), 37.6(C), 33.7(CH_2),

28.8(CH_3), 28.7(CH_2), 27.4(CH_2), 24.4(CH_3), 20.5(CH_3), 18.7(CH_2); HRMS (EI, 70 eV): calc. for $C_{18}H_{21}{}^{79}BrO$ 332.0776, found 332.0780; calc. for $C_{18}H_{21}{}^{81}BrO$ 334.0755, found 334.0745.

endo-4-Bromo-2α-hydroxy-3,4,5,6,7,8-hexadehydro-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}]pentadec-11-ene (endo-14). To a 100 mL flask was added bromoketone (2.01 g, 6.02 mmol), toluene (15 mL), and CH_2Cl_2 (10 mL). After cooling to -78°C DIBALH (18 mL, 1.5M in toluene, 27 mmol) was added over 6 min. This was stirred for 3 h at -78°C, then quenched into a biphasic solution of ether (50 mL) and saturated sodium potassium tartrate (50 mL). After 30 min the layers were separated, and the aqueous layer extracted with ether (3x50 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid. ^1H NMR showed the ratio of a/b (14/13) alcohols to be 3.9/1. Flash chromatography (10% ether in petroleum ether) afforded 1.43 g (71%) of a alcohol, and 0.33 g (16%) of b alcohol. FTIR(KBr, cm^{-1}): 3247.2, 2896.3, 1465.0, 1438.7, 1428.4, 1388.1, 1120.9, 1103.9, 1041.4, 1028.6, 795.97, 726.41; ^1H NMR(500 MHz, $CDCl_3$): δ 7.43(dd, J=1.3, 4.1 Hz, 1H, ArH), 7.10(dd, J=1.3, 7.5 Hz, 1H, ArH), 6.89(t, J=7.5 Hz, 1H, ArH), 4.91(d, J=9.5 Hz, 1H, CHOH), 3.41(d, J=9.5 Hz, 1H, OH), 2.81(m, 1H), 2.74(m, 1H), 2.67(m, 1H), 2.42(m, 1H), 2.07(m, 2H), 1.90(m, 2H), 1.52(m, 1H), 1.42(s, 3H, CH_3), 1.04(s, 3H, CH_3), 0.54(s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 143.6(Q), 142.1(Q), 133.5(CH), 131.6(Q), 130.6(Q), 130.2(CH), 127.4(CH), 119.3(Q), 72.7(CH), 54.8(Q), 37.3(Q), 35.5(CH_2), 30.0(CH_2), 29.5(CH_3), 27.6(CH_2), 24.8(CH_3), 19.6(CH_3), 17.9(CH_2); HRMS (EI, 70 eV): calc. for $C_{18}H_{23}{}^{79}Br$ O334.0932, found 334.0924; calc'd for $C_{18}H_{23}{}^{81}BrO$ 336.0912, found 336.0935.

endo-4-Bromo-2β-hydroxy-3,4,5,6,7,8-hexadehydro-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}]pentadec-11-ene (endo-13). FTIR (KBr, cm^{-1}): 3351.8(Br, OH), 3303.4, 2957.6, 1465.2, 1444.6, 1389.5, 1172.2, 1088.8, 1034.7, 777.71, 740.35, 728.07, 687.44; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42(dd, J=1.4, 8.0 Hz, 1H, ArH), 7.11(dd, J=1.3, 7.4 Hz, 1H, ArH), 6.91(t, J=7.8 Hz, 1H, ArH), 5.68(dd, J=3.2, 4.4 Hz, 1H), 3.80(ddd, J=7.5, 11.8, 12.8 Hz, 1H), 2.73(ddd, J=2.6, 5.4, 12.9 Hz, 1H), 2.58(m, 3H), 1.61(d, J=3.2 Hz, 1H, OH), 1.60(s, 3H, CH_3), 1.47(m, 1H), 1.06(s, 3H, CH_3), 0.59(s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 144.6(Q), 140.9(Q), 132.2(Q), 131.7(CH), 130.1(Q), 128.2(CH), 124.7(Q), 80.3(CH), 51.0(CH), 38.1(Q), 34.2(CH_2), 31.7(CH_3), 30.2(CH_2), 27.6(CH_2), 26.1(CH_3), 20.6(CH_2), 19.5(CH_3). HRMS (EI, 70 eV): calc'd for $C_{18}H_{23}{}^{79}BrO$ 334.0932, found 334.0902; calc'd for $C_{18}H_{23}{}^{81}BrO$ 336.0913, found 336.0927.

Swern oxidation of β alcohol endo-13. To a 25 mL flask containing CH_2Cl_2 (4.5 mL) at -78°C was added oxalyl chloride (0.18 mL, 2.1 mmole). A solution of DMSO (0.20 mL, 2.8 mmole) in CH_2Cl_2 (1 mL) was then added dropwise over 3 min. After 20 min. a solution of alcohol endo-13 (0.275 g, 0.82 mmole) in CH_2Cl_2 (4.5 mL) was added over 4 min. The syringe was then washed with 1 mL CH_2Cl_2. The solution was stirred for 20 min. at -78°C at which point triethylamine (0.6 mL, 4.3 mmole) was added in one portion. This was stirred at -78°C for 20 min, then an additional 20 min. at ambient temperature. The solution was cooled to 0°C and 10 mL saturated $NaHCO_3$ solution added. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organics were washed with 5% HCl (2x20 mL), water (1x20 mL), saturated aqueous NaCl solution (1x20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow solid. This crude material was combined with 90 mg of another batch and then purified via flash chromatography (30/70 CH_2Cl_2/petroleum

ether) to give 0.31 g (85% combined yield) of white solid which was identical (^{1}H & ^{13}C NMR) to the endo bromoketone **12** obtained from the cycloaddition.

endo-4-Bromo-2α-methoxy-3,4,5,6,7,8-hexadehydro-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}]pentadec-11-ene. To a 100 mL flask was added NaH (0.42 g, 50 weight% dispersion in oil, 8.78 mmol) and THF (5 mL). After cooling to 0°C, a solution of the alcohol (1.43 g, 4.26 mmol) in THF (10 mL) was added over 3 min. The syringe was rinsed with THF (2x4 mL). After 5 min at 0°C methyl iodide (2.5 mL, 40.2 mmol) was added in one portion. This stirred for 5 h while allowing the temperature to slowly rise to 23°C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer extracted with ether (4x25 mL). The combined organics were washed with 0.5% sodium bisulfite (50 mL), water (2x50 mL), brine (50 mL), dried (MgSO4), and concentrated *in vacuo* to give a white solid. Flash chromatography (7.5% ether in petroleum ether) afforded 1.47 g (99%) of white solid. FTIR (NaCl, cm^{-1}): 2973, 2897, 1468, 1442, 1433, 1373, 1206, 1186, 1111, 1093, 11080, 1039, 777. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J=8.0 Hz, 1H), 7.11 (dd, J=7.4 , 0.9 Hz, 1H), 6.90 (t, J=7.7 Hz, 1H), 4.44 (s, 1H), 3.09 (s, 3H), 2.85 (dd, J=13.6, 6.7 Hz, 1H), 2.77 (m, 2H), 2.46 (m, 2H), 2.08 (m, 2H), 1.90 (m, 1H), 1.52 (ddd, J=15.0, 10.5, 4.4 Hz, 1H), 1.43 (s, 3H), 1.05 (s, 3H), 0.56 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 144.6, 139.4, 134.1, 132.3, 130.7, 130.3, 127.4, 119.7, 82.1, 56.4, 53.4, 37.3, 35.6, 30.1, 29.7, 26.0, 25.1, 19.9, 18.4. LRMS (EI, 70eV (relative intensity)): 350 (M+2, 1.4), 348 (1.5), 318 (2.3), 316 (2.4), 303 (3.1), 301 (3.1), 275 (6.6), 273 (6.4), 248 (1.1), 194 (33.7), 133 (100). HRMS (EI, 70eV): calc'd for $C_{19}H_{25}{}^{79}BrO$ 348.1089, found 348.1113; calc'd for $C_{19}H_{25}{}^{81}BrO$ 350.1068, found 350.1080.

endo-4-Carboxy-3,4,5,6,7,8-hexadehydro-2α-Methoxy-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}] pentadec-11-ene. To the aryl bromide (0.765 g, 2.19 mmol) in ether (70 mL) at -78°C was added *t*-butyllithium (5.4 mL, 1.0M in pentane, 5.4 mmol) to give a clear yellow solution. This stirred for 8 min at which point anhydrous CO_2 (sublimed through a $K_2CO_3/CaSO_4$ drying tube) was bubbled into the flask. After 45 min at -78°C, the solution was allowed to warm to room temperature and CO_2 addition continued for 30 min. The solution was quenched with saturated aqueous NH_4Cl (30 mL), and acidified to pH 1 with 5% HCl. The layers were separated and the aqueous extracted with CH_2Cl_2 (3x25 mL). The combined organics were washed with brine, dried ($MgSO_4$),and concentrated *in vacuo*. Flash chromatography (40% ethyl acetate in petroleum ether) afforded 0.63 g (92%) of acid. FTIR (KBr, cm^{-1}): 3000.2 (br, CO_2H), 2895, 2650, 1695, 1463, 1303, 1098. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J=7.8 Hz, 1H), 7.30 (dd, J=1.5, 7.5 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 4.45 (s, 1H), 3.32 (s, 3H, OCH_3), 2.96 (d, J=6.7 Hz, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.50 (m, 1H), 1.45 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.51 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 210.9, 141.0, 139.1, 133.5, 133.1, 131.8, 130.6, 130.3, 126.7, 82.7, 57.9, 51.2, 37.4, 35.4, 29.6, 29.3, 27.7, 24.9, 19.7, 17.5. LRMS (EI, 70eV (relative intensity)): 314 (4), 282 (32), 267 (16), 249 (22), 239 (57), 226 (78), 221 (100), 133 (72). HRMS (EI, 70 eV): calc'd for $C_{20}H_{26}O_3$ 314.1882, found 314.1870.

4α-Carbomethoxy-2α-methoxy-3,5,6,8-tetradehydro-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}] pentadec-11-ene (15). Anhydrous ammonia was condensed into a 50 mL 2-neck flask with a CO_2/acetone condensor at -78°C until the flask was approximately half full. Lithium wire (0.045 g, 6.5 mmol) was then added to give an immediate blue color. This stirred for 15 min at -78°C at which point the acid (0.40 g, 1.27 mmol) in anhydrous ethanol (3 mL) and THF (4 mL) was rapidly added. After 1 min, the solution turned colorless, and an additional 15 mg of lithium was added to restore the blue

color. After 5 min at -78°C the solution turned colorless. NH_4Cl (2.5 g, 4.7 mmol) was added, and the ammonia allowed to evaporate over 1 h. H_2O (15 mL) was added, and the solution acidified with 5% HCl. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (6x25 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid. The ^1H NMR shows the compound to be a 2.2:1 mixture of conformational isomers. Solutions of the acid autooxidize on standing in air to regenerate the aromatic acid. The material was directly esterified with ethereal diazomethane to afford 0.41 g (99%) of the methyl ester. FTIR (NaCl, cm^{-1}): 2938, 1742, 1433, 1387, 1279, 1191, 1156, 1092. ^1H NMR (500 MHz, $CDCl_3$): δ 5.98 (m, 1H, vinyl), 5.82 (m, 1H, vinyl), 4.26 (m, $HCCO_2Me$), 3.85 (s, 1H, CHOMe), 3.66 (s, 3H, CO_2CH3), 3.19 (s, 4H, CH_3+H), 2.87 (m, 1H), 2.68-2.48 (m, 4H), 2.20 (m, 2H), 2.07 (m, 1H), 2.02-1.70 (m, 3H), 1.55 (s, 3H, CH_3), 1.38 (m, 1H), 1.35 (s, 3H, CH_3), 1.04 (s, 3H, CH_3): ^{13}C NMR (125.7 MHz, $CDCl_3$): major conformer δ 173.6, 136.4, 131.9, 130.6, 128.3, 124.9, 121.9, 82.7, 57.3, 51.8, 50.5, 42.8, 37.3, 36.1, 35.6, 28.8, 28.4, 27.6, 24.9, 20.3, 18.1: minor conformer δ 173.4, 134.9, 134.1, 131.6, 130.5, 125.0, 87.3, 56.6, 51.9, 48.4, 47.9, 38.2, 34.3, 32.4, 31.2, 30.9, 27.4, 26.6, 22.1, 19.8. LRMS (EI, 70eV (relative intensity)): 330 (2), 298 (7), 239 (33), 220 (14), 183 (30), 169 (23), 135 (48), 121 (73) 91 (100). HRMS (EI, 70 eV): calc'd for $C_{21}H_{30}O_3$ 330.2195, found 330.2189.

endo-4α-Carbomethoxy-3,8-didehydro-2α-methoxy-12,15,15-trimethyltricyclo-[9.3.1.0^{3,8}]pentadec-11-ene (endo-16). To a 100mL flask was added ethanol (10 mL) and PtO_2 (0.146 g, 0.6 mmol). The flask was evacuated and then purged with hydrogen. This was repeated three times, and the solution stirred under a hydrogen atmosphere for 5 min. The crude diene ester (1.32 g, 3.99 mmol) was dissolved in ethanol (15 mL) and added to the reaction flask over 4 min. A 5 mL aliquot of ethanol was used as a rinse. The reaction was stirred at room temperature for 1 h then filtered through a bed of Celite which was washed with copious amounts of ethyl acetate. The filtrate was concentrated *in vacuo* to yield an opaque oil. Flash chromatography (10% ether in petroleum ether) afforded 1.01 g (76%) of a clear oil. FTIR (NaCl, cm^{-1}): 3006, 2935, 1737, 1459, 1366, 1345, 1192, 1154. ^1H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 1H, CHOMe), 3.65 (s, 3H, CO_2CH_3), 3.53 (d, J=6 Hz, 1H, $CHCO_2Me$), 3.21 (s, 3H, OCH_3), 2.54 (m, 1H), 2.22-1.64 (m, 1H), 1.64-1.55 (m and s, 4H, s=CH_3), 1.42 (m, 1H), 1.36 (s, 3H, CH_3), 1.20 (m, 1H), 1.05 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 175.3 (Q), 138.1 (Q), 131.7 (Q), 131.5 (Q), 130.6 (Q), 82.9 (CH), 57.5 (CH_3), 51.2 (CH_3), 50.6 (CH), 37.9 (CH), 37.3 (CH), 35.6 (CH_2), 31.9 (CH_2), 28.2 (CH_2+CH_3), 27.4 (CH_2), 27.3 (CH_2), 25.0 (CH_3), 20.1 (CH_3), 18.2 (CH_2). LRMS (EI, 70 eV (relative intensity)): 332 (5), 300 (17), 285 (9), 257 (32), 225 (21), 197 (92), 121 (80), 91 (100). HRMS (EI, 70 eV): calc'd for $C_{21}H_{32}O_3$ 332.2351, found 332.2347.

Alkylation of the βγ-unsaturated ester 16. Synthesis of 4α-carbomethoxy-2α-methoxy-4β,12,15,15-tetramethyltricyclo[9.3.1.0^{3,8}]pentadec-11-ene (17). To an LDA solution (0.42M, 3 mL, 1.26 mmole) at -78°C was added a solution of ester **16** (0.142g, 0.43 mmole) in THF (2 mL). This stirred for 45 min at which point methyl iodide (5 mL) was added. After stirring at -78°C for 15 min the solution was poured into saturated NH_4Cl. Extraction with ether, drying ($MgSO_4$), and concentration *in vacuo* yielded a yellow oil. Radial chromatography (7% ether in petroleum ether) afforded 55 mg (37%) of the a-alkylated meterial. FTIR (KBr, cm^{-1}): 2940, 1729, 1464, 1385, 1377, 1238, 1189, 1166, 1136, 1108; ^1H NMR (500 MHz, C_6D_6): δ 3.67 (d, 1H, J=6 Hz, H_2), 3.38 (s, 3H, CO_2CH_3), 3.25 (ddd, 1H, J=2, 12, 12 Hz, H_{10}), 3.15 (s, 3H, OCH_3), 2.74 (ddd, 1H, J=3, 5, 13 Hz, H_9), 2.46 (dd, 1H, J=10, 17 Hz, H_{13}), 2.32 (dd, 1H,

J=12, 13 Hz, H_9), 2.24 (ddd, 1H, J=4, 10, 17 Hz, H_{13}), 2.15-2.00 (m, 4H), 1.89 (m, 1H, H_7), 1.84 (s, 3H, H_{18}), 1.76 (m, 1H, H_{14}), 1.68 (ddd, 1H, J=2,5, 12 Hz, H_{10}), 1.44 (s, 3H, H_{19}), 1.33 (s, 3H, H_{16}), 1.23 (s, 3H, H_{17}); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7 (Q), 138.9 (Q), 135.0 (Q), 130.0 (Q), 129.5 (Q), 86.2 (Q), 56.6 (CH_3), 51.5 (CH_3), 50.6 (CH), 47.6 (Q), 38.1 (Q), 35.9 (CH_2), 34.8 (CH_2), 33.9 (CH_2), 31.4 (CH_3), 31.0 (CH_2), 28.5 (CH_3), 27.3 (CH_2), 23.6 (CH_3), 22.8 (CH_2),19.8 (CH_3), 19.1 (CH_2); HRMS (EI, 70 eV): calc'd for $C_{22}H_{34}O_3$ 346.2508, found 346.2517.

Hydroxylation of the βγ-unsaturated ester 16. To a 10mL flask containing dry THF was added diisopropylamine (0.17 mL, 1.20 mmol). This was cooled to -78°C, and n-butyllithium (0.80 mL, 1.5M in hexanes, 1.20 mmol) added. After stirring for 20 min, a solution of ester **16** (0.1011 g, 0.30 mmol) in THF (0.3mL) was added and the syringe rinsed with 0.3mL THF. This was allowed to stir for 2 h whereupon triethylphosphite (0.23 mL, 1.33 mmol) was entered. Oxygen was then bubbled through the solution for 35 min. The solution was allowed to warm to 0°C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted ether (3x15 mL), and the combined organics washed with 5% HCl (2x25 mL), water (25mL), brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. ^1H NMR analysis of the crude mixture showed the ratio of a,syn/ a,anti/g,syn isomers to be 1.6/1.3/1. Flash chromatography (solvent gradient: 15% ether in petroleum ether to 60% ether in petroleum ether) yielded 31.6 mg (30%) of a,syn isomer **20** as a 1.8/1 mixture of conformational isomers, 22.3 mg (21%) of a,anti isomer **19**, and 18.8 mg (18%) of g,syn isomer **18**.

4-Carbomethoxy-8β-hydroxy-2α-methoxy-12,15,15-trimethyltricyclo[9.3.1.$0^{3,8}$]-pentadeca-3,11-diene (18). FTIR (NaCl, cm^{-1}): 3467, 2985, 2970, 2897, 2864, 2833, 1712, 1460, 1442, 1433, 1252, 1207, 1134, 1093, 1076, 1009, 958, 721. ^1H NMR (500 MHz, $CDCl_3$): δ 3.99 (t, J= 1.5 Hz, 1H, CHOMe), 3.69 (s, 3H, CO_2CH_3), 3.15 (s, 3H, OCH_3), 2.53 (ddd, J= 5.5, 10.7, 14.0 Hz, 1H), 2.24 (m, 5H), 2.05 (m, 3H), 1.95 (dd, J=3.2, 7.0 Hz, 1H), 1.77 (m, 5H), 1.60 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 172.7 (C=O), 140.0 (Q), 133.2 (Q), 130.9 (Q), 128.0 (Q), 80.4 (CHOMe), 72.3 (Q, C-OH), 57.3 (CO_2CH_3), 54.5 (CH, bridgehead), 51.2 (OCH_3), 38.9 (CH_2), 37.4 (CH_2), 36.4 (Q, CMe_2), 30.7 (CH_3), 28.5 (CH_2), 28.0 (CH_2), 25.7 (CH_3), 23.1 (CH_2), 21.6 (CH_3), 17.9 (CH_2), 16.6 (CH_2). LRMS (CI, isobutane (relative intensity)): 349 (M+1, 40), 331 (12.5), 317 (70), 300 (19), 200 (100), 109 (2.6). HRMS (CI, isobutane): calc'd for $C_{21}H_{33}O_4$ (M+1) 349.2376, found 349.2399.

4β-Carbomethoxy-3,8-didehydro-4α-hydroxy-2α-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$] pentadec-11-ene (19). FTIR (NaCl, cm^{-1}): 3498, 2999, 2927, 2868, 1728, 1462, 1452, 1432, 1389, 1369, 1259, 1232, 1205, 1190, 1171, 1126, 1097, 1036, 1011. ^1H NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 1H, CHOMe), 3.73 (s, 3H, CO_2CH_3), 3.66 (s, 1H, OH), 3.17 (s, 3H, OCH_3), 2.57 (dt, J=6.2, 12.6 Hz, 1H), 2.32 (dt, J=6.3, 12.9 Hz, 1H), 2.24-2.19 (m, 2H), 2.15-2.08 (m, 2H), 1.99-1.92 (m, 2H), 1.77-1.50 (m, 7H), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 177.9, 137.2, 135.2, 131.7, 130.9, 83.3, 74.2, 57.2, 52.2, 48.2, 36.6, 35.5, 32.5, 30.9, 28.2, 28.0, 24.6, 21.0, 18.7, 18.4. LRMS (CI, isobutane (relative intensity)): 349 (M+1, 0.15), 331 (3.3), 317 (2.6), 299 (100), 285 (4.62), 2.57 (3.7), 161 (2.9) 139 (12.5). HRMS (EI, 70 eV): calc'd for $C_{21}H_{32}O_4$ 348.2292, found 348.2208.

4α-Carbomethoxy-3,8-didehydro-4β-hydroxy-2α-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$]pentadec-11-ene (20). FTIR (NaCl, cm^{-1}): 3514, 3001, 2935, 1722, 1462, 1444, 1387, 1367, 1267, 1234, 1169, 1119, 1103, 1076, 1061, 999, 735. ^1H NMR (500 MHz, $CDCl_3$): δ 5.21 (s, endo OH), 4.14 (s, endo

CHOMe), 3.74 (s, endo CO_2CH_3), 3.73 (s, exo CO_2CH_3), 3.36 (s, exo OH), 3.33 (s, endo OCH_3), 3.25 (d, J=6.2 Hz, exo CHOMe), 2.90 (s, exo OCH_3), 2.56 (dt, J=12.8, 6.1 Hz), 2.32-1.48 (m), 1.56 (s, CH_3), 1.50 (s, CH_3), 1.37-1.33 (m), 1.31 (s, CH_3), 1.17 (s, CH_3), 1.04 (s, CH_3), 0.97 (s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.2 &177.0 (C=O), 141.1 (Q), 139.9 (Q), 135.4 (Q), 134.5 (Q), 131.5(Q), 130.5 (Q), 130.1 (Q), 128.4 (Q), 86.4 (exo CHOMe), 84.8 (endo CHOMe), 76.2 (Q, exo C-OH), 75.5 (Q, endo C-OH), 57.2 (endo CO_2CH_3), 56.4 (exo CO_2CH_3), 52.8 (exo OCH_3), 51.9 (endo OCH_3), 51.1 (exo bridgehead CH), 47.7 (endo bridgehead CH) 38.1 (Q), 37.3 (CH_2), 36.75 (CH_2), 36.72 (Q), 36.0 (CH_2), 33.9 (CH_2), 31.3 (CH_3), 31.1 (CH_2), 29.6 (CH_3), 28.2 (CH_3), 28.0 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 24.7 (CH_3), 22.6 (CH_2), 20.8 (CH_3), 19.9 (CH_3), 18.7 (CH_2), 17.8 (CH_2). LRMS (CI, isobutane (relative intensity)): 349 (M+1, 1.4), 331 (14.1), 299 (100), 285 (6.9), 257 (2.9), 195 (6.9), 139 (7.0). HRMS (EI, 70 eV): calc'd for $C_{21}H_{32}O_4$ 348.2292, found 348.2306.

3,8-Didehydro-4α-hydroxy-4β-hydroxymethyl-2α-methoxy-12,15,15-trimethyltricyclo-[9.3.1.$0^{3,8}$]pentadec-11-ene (21). To a 10 mL flask was added the hydroxyester **19** (9.4 mg, 0.027 mmol) and toluene (0.5 ml). This was cooled to 0°C and DIBALH (0.15ml, 1.0M in toluene, 0.15 mmol) added. The solution was stirred for 45 min at 0°C, then warmed to room temperature and stirred for an additional 1.5 h. After recooling to 0°C, saturated aqueous sodium potassium tartrate (0.5 mL) was added, and the solution stirred for 45 min. Ether (10 mL) was added, and the layers separated. The aqueous layer was extracted with ether (4x10 mL), and the combined organics washed with brine (25 mL), dried (MgSO4), and concentrated *in vacuo*. Flash chromatography (20% petroleum ether in ether) afforded 4.2 mg (49%) of the diol. A crystal suitable for X-ray analysis was grown by slow evaporation of ethanol. FTIR (NaCl, cm^{-1}): 3439, 2999, 2931, 2833, 1462, 1389, 1371, 1342, 1207, 1088, 1076, 1034, 993, 719. ^1H NMR (500 MHz, $CDCl_3$): δ 4.51 (s, 1H, OH), 4.12 (s, 1H, CHOMe), 3.55 (d, J=11.1 Hz, 1H), 3.41 (t, J=10.6 Hz, 1H), 3.35 (s, 3H, OCH_3), 2.59 (m, 1H), 2.33-2.06 (m, 7H), 2.00-1.89 (m, 3H), 1.85-1.67 (m, 4H), 1.53 (s, 3H, CH_3), 1.41 (td, J=5.8, 13.3 Hz, 1H), 1.31 (s, 3H, CH_3), 1.06 (s, 3H, CH_3). ^{13}C NMR (125.7 MHz, d_6-benzene): δ 137.6, 133.5, 131.8, 130.6, 85.2, 76.0, 67.9, 56.6, 47.6, 36.6, 34.8, 30.4, 30.2, 29.8, 28.10, 28.05, 24.4, 21.3, 18.0, 17.6. LRMS (EI, 70eV (relative intensity)): 320 (0.02), 302 (9.8), 289 (33.6), 270 (17.5), 257 (90), 241 (10.6) 187 (44.9), 168 (67.7), 91 (94.0), 55 (100). HRMS (EI, 70eV): calc'd for $C_{20}H_{32}O_3$ 320.2351, found 320.2365.

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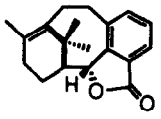
14. Less hardy protecting groups proved to be incompatible towards subsequent chemical transformations. There is a high propensity for the C-4 carboxyl derivatives to undergo spontaneous lactonization to give i. This lactone does not successfully undergo Birch reduction.



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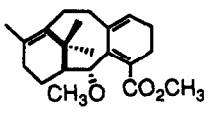

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19. The upper limit (23 kcal/mole) is the minimum value required for isolability of conformational rotamers. M. Oki, *Top. Stereochem.* **1983**, *14*, 1.