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STEROID PHOTOCHEMISTRY

THE PHOTOCYCLOADDITION OF AN ENONE AND DIENONE TO NORBORNENE AND NORBORNADIENE

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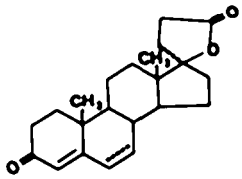
Abstract—The photocycloaddition of a steroidal 4-en-3-one and a 4,6-dien-3-one to bicyclo[2.2.1]-heptene and bicyclo[2.2.1]heptadiene has been studied. The photocycloaddition to norbornene furnished only the *trans*-4α,5β-cyclobutane, while the enone gave a mixture of *cis* and *trans*-[2+2] adducts as well as the first example of hydrogen transfer in this series to form a 4-(2-norbornanyl 1)-conjugated enone. The photocycloaddition of the dienone to norbornadiene formed the 4-(7-norbornenyl)-dienone by a 1,4-hydrogen shift as the major product, together with lesser amounts of the unrearranged *trans*-4α,5β-[2+2]-cyclobutane. On the other hand, the cycloaddition of the enone to norbornadiene yielded the 4α-(7-norbornene)-β,γ-enone as the major product; accompanied again by the unrearranged *trans*-[2+2]-adduct. In addition, the 4α,5α-*cis*-[3+2] adduct was obtained and was formed by rearrangement of the norbornenyl radical portion of the intermediate diradical.

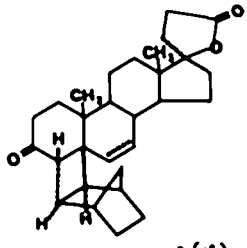
Steroidal enones readily add olefins to form cyclobutanes in a head-to-tail fashion, and quenching studies with dienes indicated that the cycloaddition occurred through the enones triplet state. In distinct contrast to simpler enones however, there was a marked absence of products derived from hydrogen transfer processes.[2] Although enones give mixtures of *cis* and *trans*-adducts, a linear dienone formed regio and stereospecifically *trans*-fused cyclobutanes, again without any evidence for hydrogen transfer reactions.[3] In suitable systems however, linear dienones are capable of H-abstraction.[4] Attempts at quenching the dienone cycloadditions using dienes led to a variety of novel adducts.[5] When non-Diels-Alder dienes were used, the distribution and structure of the adducts was characteristic of a diradical intermediate, without any evidence for a charge separation contribution.[6] The dienone diene cycloadditions could be quenched however using Ullmann's quencher,[7] 3,3,4,4-tetramethyl-1,2-diazetidine 1,2-dioxide, implicating a $\pi\pi^*$-triplet state with an energy of less than 50 Kcal/mole as the reactive state.[8] Although the *trans*-dienone [2+2]-cycloadducts are not stable to GLC,[9] thus precluding quenching studies, it is not unreasonable to assume that these adducts are also formed via the lowest excited triplet state of the dienone.

Previous studies by McCollough on the photocycloaddition of simple enones to norbornadiene (bicyclo[2.2.1]hepta-2,5-diene) were primarily concerned with the products formed from hydrogen transfer reactions.[10] These adducts were enones which were substituted at the α- or β-position with a norbornene, bonded at C-7, or a nortricyclane, and each of the cyclohexenone photocycloadditions studied formed a substantial variety of these adducts.[10] Although the [2+2]-adducts were not investigated, McCollough did obtain IR-evidence of *cis* and *trans*-fused cyclobutane adducts.[10] We would like to present our results on the photocycloaddition of steroidal 4-en-3-one **1** and 4,6-dien-3-one **2** to norbornene (bicyclo[2.2.1]hept-2-ene) and norbornadiene which describes the first hydrogen transfer reactions undergone by these chromophores in steroids, as well as the structures of the cycloadducts. The observations made on these steroids indicate that cycloadditions to norbornadiene are even more subtle than previously supposed.[10] The additions to norbornene were studied to provide reference compounds to the expectedly more complex adduct mixtures from the norbornadiene irradiations. These compounds were necessary because the majority of the norbornane NMR resonances will occur under the steroid proton resonances and will not ordinarily be observable. Since triplet cycloadditions have been amply demonstrated to proceed through a diradical intermediate,[2,11] the adducts will involve only the norbornene double bond. This is because the 2-norbornyl radical has shown to be stable and does not undergo the facile Wagner–Meerwein rearrangements so characteristic of the 2-norbornyl cations.[12,13]

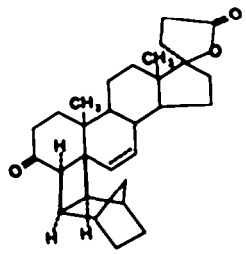
The photocycloaddition of dienone **2**, although a more complex chromophore, to norbornene yielded, as with other olefins,[3] only the *trans*-4α,5β-adduct **3** in 61% yield. The *exo*-configuration was assigned by analogy with the predominant attack by electrophiles[12] and theoretical calculations,[14] as well as similar photocycloadducts involving norbornene some of whose structures have been determined by x-ray studies.[15] *Cis*-addition of the excited enones to the olefins is assumed,[17] and, based on this, *exo*-addition, and the other spectroscopic observations, the stereochemistry about the newly formed cyclobutane rings is indicated in the formulae. The *trans*-adduct **3** proved to be remarkably stable, requiring refluxing for 16 hr in sodium methoxide solution to cause



1
2 (Δ^6)



3 (Δ^6)
5

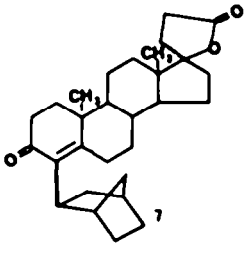


4 (Δ^6)
6

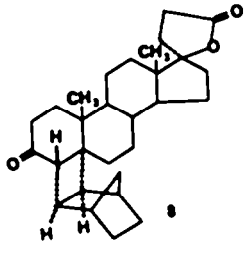
complete epimerization to the much more stable *cis*-4β,5β-adduct **4**, Hydrogenation of *trans*-**3** with Pd/C gave the dihydro-4α,5β-*trans*-adduct **5** which could be epimerized to the *cis*-4β,5β-adduct **6**, and thus these were available for comparison with the adducts of the enone **1** with norbornene.

Irradiation of the enone **1** in the presence of norbornene led to a variety of adducts which could be isolated by column chromatography. The first compound so isolated was not, however a [2+2] adduct but possessed an α,β-unsaturated enone chromophore in the IR and UV. Its elemental analysis and mass spectrum indicated a mono-adduct and the absence of olefinic resonances in the NMR allowed the formulation of **7** as the 4-(2-norbornyl)-derivative of the starting enone **1**, The exo-stereochemistry was assigned for the reasons previously given. The major product (41%) isolated was the *cis*-4α,5α-[2+2] adduct **8**,[16] while a 26% yield of the *trans*-adduct **5**, identical with the sample prepared by hydrogenation of the dienone *trans*-adduct **5**, was obtained. In addition to these adducts, a small amount (2%) of a *cis*-4β,5β-adduct **9** was obtained. This was assigned the anti-configuration based on the results of McCollough et al.[17] They demonstrated, based on x-ray results, that the *trans*-isomer of a variety of cyclohexenone-cyclopentene adducts epimerize to the syn-adduct, while the *cis*-adducts possess the anti-configuration.[16,17] Among the enones studied was 3-methylcyclohexenone which serves as an excellent model for the enone **1**. This means that the 4β,5β-isomers **4** and **6**, derived from the 4α,5β-*trans*-isomers possess the syn-configuration and this is in agreement with the least sterically hindered approach of the olefin to the excited enone. The isolation of the *cis*-fused β-cyclobutane **9** indicates that, in agreement with the results of thermal reactions,[18] a small amount of cycloaddition can also occur from the β-face of the steroid in these enones.

The enone adduct **7** can be formed either directly through a 1,3-hydrogen shift or indirectly through a 1,5-hydrogen shift to form a 4-norbornyl-3-keto-5-ene adduct which isomerizes under the reaction conditions to form the conjugated enone **7**. In order to differentiate between these two possibilities the deuterated enone **13** was synthesized. The 3β-hydroxy-5-ene steroid[19] **10** was oxidized to the 3-keto-5-ene steroid **17** with buffered pyridinium chlorochromate[20] and isolated by flash chromatography[21] in 45% yield. The β,γ-unsaturated enone **11** was preferentially deuterated at C-4 by a modification of the procedure described by Ringold.[22] Although the original procedure called for refluxing the β,γ-unsaturated enone with



7



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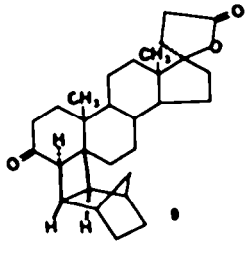

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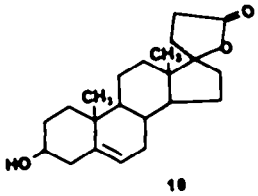
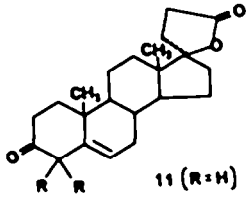
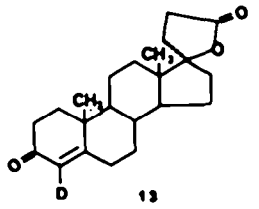


10



11 (R=H)
12 (R=D)

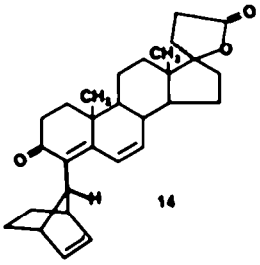


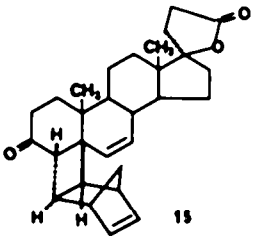
13

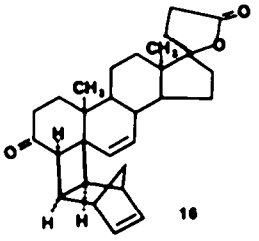
deuterium oxide in methoxyethyl ether (diglyme), under the conditions compound **11** rearranged to conjugated α,β-unsaturated enone **1** with deuterium incorporation at carbons 2, 4 and 6. However, refluxing compound **11** in 1,2-dimethoxyethane for 30 h formed the partially 4-deuterated steroid **12** which analyzed, by mass spectrometry,[23] for 35% D_1, 7.9% D_2 and only 1.2% D_3. Acid catalyzed isomerization of **12** proceeds through the dienol with specific protonation of C-6 and formed the 4-deuterated enone **13** with 44.0% D_1 and only 1.4% D_2. If the formation of the norbornyl enone **7** proceeds through initial formation of a 4-norbornyl-3-keto-5-ene adduct, analogous to the latter described additions of enones **1** and **2** with norbornadiene, then the deuterium will be lost in the conjugation to form the observed adduct **7**. If, on the other hand, the adduct **7** is formed directly through a 1,3-hydrogen shift then the deuterium will be retained in the adduct. When the deuterated enone **13** was irradiated in the same manner as enone **1** with norbornene and the adduct **7** was isolated, it was found by mass spectrometry to contain 28% D_1 and 1% D_2. Sodium methoxide catalyzed exchange on adduct **7** furnished the same deuterium incorporation results. This result indicates that, in the absence of a deuterium isotope effect, 64% of **7** is formed directly by a 1,3-hydrogen shift in the 1,4-diradical. However, since the hydrogen abstraction reaction is finely balanced with the ring forming reactions, a deuterium isotope effect probably occurs and the adduct **7** is formed exclusively through a 1,3-hydrogen shift.

Based on McCollough's results on the photoaddition of enones to norbornadiene,[10] we expected a complex mixture from irradiation of the dienone **2** in the presence of this diene. Thus we were pleasantly surprised when the photoaddition of the dienone yielded only two major adducts and a third, as yet unidentified, minor adduct. Separation by column chromatography yielded the major product **14** and this was shown to be a dienone by its characteristic absorptions in the IR and UV. The position of attachment to the steroid was determined to be at C-4 when the C6,7-olefinic protons appeared as a doublet of doublets due to vicinal coupling and allylic coupling to the axial 8β-hydrogen.[24] The position of attachment of the steroid to the norbornene was determined by NMR using a combination of europium induced shifts and double resonance to be anti at C-7. The structural assignment was based on the presence of a one proton broad singlet whose shape is consistent with a 7-anti substituted norbornene ring, but not for a 5-substituted ring. Due to steric interactions between the norbornene ring and the B-ring of the steroid, there is restricted rotation about the steroid C-4 and the norbornene C-7 bond. Based on $Eu(Fod)_3$ studies, it was shown that the C-1 norbornene bridgehead proton is close to the steriod C-3 carbonyl group. In the anti-configuration shown in structure **14**, three norbornene protons are expected to have broad singlet signals: the two bridgehead protons and the methylene hydrogen. This is observed in the NMR spectrum of **14** in deuterobenzene, and in the Eu shift studies. Decoupling experiments between the norbornene olefinic proton signals and two of the board singlet signals confirmed that two of the broad singlets were due to the bridgehead protons. These bridgehead protons have different chemical shift and shift at different rates with $Eu(Fod)_3$. This is expected since rotation about the steroid-norbornene dond in **14** is restricted due to steric interactions. Coupling between the bridgehead protons and the methylene bridge hydrogen was also demonstrated. This coupling is one of several small couplings for both the bridgehead and the methylene C-7 hydrogens. If the diradical intermediate in the norbornadiene-dienone hydrogen transfer adduct has not rearranged but simply transferred hydrogen to form a 5-substituted norbornene, then no proton, other than the bridgehead ones, would be expected to give a singlet signal. The proton at C-5 in this adduct should have two vicinal couplings, each greater than 5Hz, to the adjacent methylene protons. The anti-configuration rather than the syn was assigned to **14** on the basis of the europium shift studies. The norbornene C-2 olefinic proton, adjacent to the faster shifting bridgehead hydrogen at C-1, shifts more slowly than the C-3 olefinic proton. In the syn configuration, it would be expected to shift more rapidly. In the anti-isomer, however, the C-2 olefinic proton has a larger H-Eu-O angle, and would be expected to shift slowly. The H–Eu–O angle for the C–3–olefinic proton is smaller, compensating for the longer C–3–proton–europium distance. The norbornene ring in dienone **14** could be selectively hydrogenated to yield the 7-norbornyl derivative. The second major product was the *trans*-fused $4\alpha,5\beta$-[2+2]-adduct **15**. The stereochemistry was proven by its epimerization to the $4\alpha,5\beta$-[2+2]-adduct **16**. To prove that compounds **15** and **16** were indeed cyclobutanes and not products derived from rearrangement of a possible norbornenyl radical,[12] the *trans*-adduct **15** was hydrogenated at 50°C. and 60 psi for 7 days to yield the *trans*-fused [2+2] adduct **5** in 82% yield, which had been obtained from the photocycloaddition of enone **1** to norbornene.

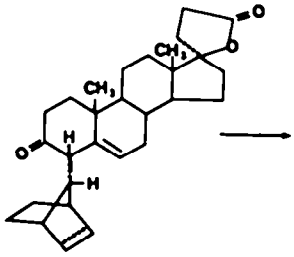
In contrast to the results obtained with dienone **2**, the addition of the enone **1** to norbornadiene gave a complex mixture of three major adducts and two very minor unidentified adducts **23** and **24**. Although unidentified, these minor products (< 2%) were neither hydrogen transfer products (enones) nor nortricyclane products. The major products of this photoaddition was the dienone **17**. The structure of this adduct was determined from its spectral data and chemical reactions. Its IR spectrum indicated an unconjugated carbonyl

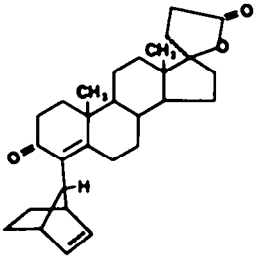

14


15

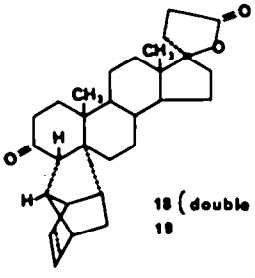

16

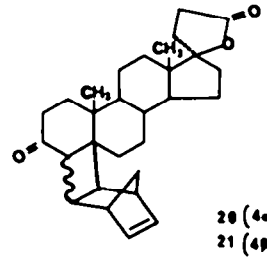
group while the NMR spectrum indicated the presence of three olefinic protons. The correct structure, a 3-keto-5-ene steroid substituted at C-4 by a norbornene group, was initally ruled out when **17** was recovered unchanged from methanolic sodium methoxide. This led us to consider that **17** was a 4α-(2-norbornadienyl)-5α-H adduct; the result of an unprecedented 1,3-hydrogen shift, analogous to the norbornene-enone **1** adduct. Inspection of models of this molecule indicated that if the norbornadiene double bond β,γ- to the ketone became conjugated with the C-3 carbonyl group, severe steric interactions would occur between the resultant norbornene ring and the steroid C6-hydrogens. The mass spectrum was in accord with either structure, indicating a weak parent and a base peak at amu 93 which is norbornadiene plus hydrogen. However consideration of the difficulty observed in epimerizing the *trans*-fused cyclobutane **3** prompted us to repeat the experiment in refluxing potassium methoxide solution. Under these conditions, adduct **17** smoothly isomerized to the α,β-unsaturated ketone **22**. The stereochemistry in compound **17** was shown to be alpha by its very strong positive chiroptical effects. To determine whether the intermediate norbornenyl radical had rearranged prior to hydrogen abstraction, the norbornene double bond in compound **17** was selectively hydrogenated to yield the dihydro-compound **25**. Isomerization in the same way as **17** yielded the conjugated enone **26**, which was distinctly different from the enone **7**. Since compound **7** was formed via the 2-norbornanyl radical, which would not be expected to rearrange,[12] the hydrogen-abstraction product **17** is a 7-(2-norbornenyl)-β,γ-enone. The *anti*-configuration was assigned by analogy with compound **14** where this orientation was demonstrated by NMR experiments. Complete hydrogenation of compounds **14** and **22** gave a mixture which was not characterized but shown by GLC on three columns to be identical, thus relating these two compounds.

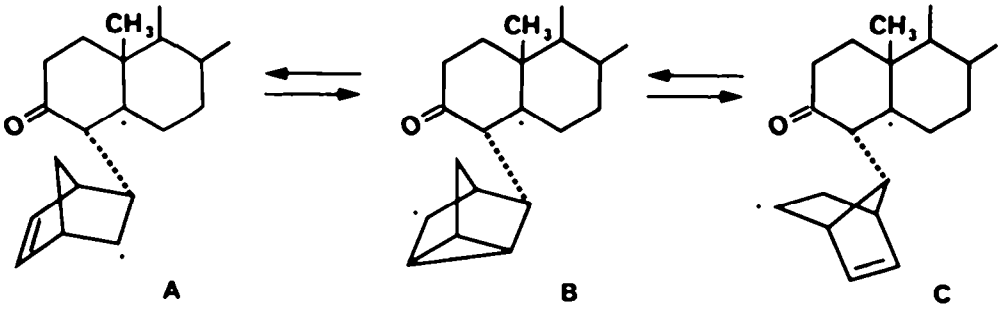

17 (double bond)
25


22 (double bond)
26

A second adduct **18**, obtained in 16% yield, contained a norbornene ring as demonstrated by resonances for two olefinic protons in its NMR spectrum, and an unconjugated cyclohexanone CO group in its IR spectrum. The stereochemistry about the newly formed bonds was determined to be alpha by the positive chiroptical effects, and when **18** was recovered unchanged from sodium methoxide solution. Since this norbornadiene enone **18** was postulated to be a cyclobutane derivative, a correlation with the enone-norbornene 4α,5α-[2+2] adduct **8** was attempted. Compound **18** was smoothly hydrogenated in dioxane over palladium on carbon to yield the dihydro-derivative **19** which was, however, distinctly different than the [2+2]-adduct **8**, indicating that rearrangment had occurred. The structure for **18** is postulated to be formed through initial exo-bonding to form the diradical **A** which bridges to form the nortricyclyl radical **B**. The cyclopropylcarbinyl radical in **B** then opens to the homoallylic radical **C** and subsequent bond formation generates **18**. All of these steps have ample literature precedents.[12,25] Bridging in diradical **A** occurs faster than bond formation and diradical **B** is not set up for facile bond formation, leaving **C** free to ring close to generate **18**. An alternative structure wherein **18** is indeed a cyclobutane but resulting from *endo*-addition of the enone to norbornadiene has not been rigidly excluded. However it is very unlikely that only an *endo*-adduct would have been isolated when *exo*-addition is the predominant reaction pathway.[12]


18 (double bond)
19


20 (4α)
21 (4β)



Additionally, *endo*-addition of enones to norbornadiene has been shown to lead to a homo-Diels-Alder adduct, and not cyclobutanes.[10]

The final major product obtained from the photocycloaddition of enone **1** to norbornadiene was obtained in 10% yield and was identified as the *trans*-fused 4α,5β-[2+2] adduct **20**. Its structure was proven by its spectral properties and its ready epimerization to the *cis*-fused 4α,5β-[2+2] adduct **21**. Hydrogenation of **20** over Pd/C yielded compound **5**, the *trans*-fused 4α,5β-[2+2] adduct of enone **1** and norbornene.

The photocycloaddition of enone **1** to both norbornene and norbornadiene was quenched by the addition of 2-methyl-1,4-butadiene (isoprene) indicating, as with previous cycloadditions, reaction occurring through the enone triplet excited state. Since the [2+2] adducts of the dienone **2** are not stable to gas chromatography, quenching studies, using the low energy quencher 3,3,4,4-tetramethyl-1,2-diazetidine 1,2-dioxide, were done using the decrease in the absorbtion maximum (λ 282 nm) of the dienone. Under these conditions, the additions to both norbornene and norbornadiene were quenched, indicating, as with the photocycloadditions to dienes, that the dienone cycloadditions occur through the triplet excited state.

DISCUSSION

In comparing the results obtained in this study with those of McCollough *et al.*,[10] the most noticeable difference is the isolation of only a single hydrogen transfer product from the steriod irradiations as opposed to a variety of such products obtained from the simpler cyclohexenones. Until this investigation, no hydrogen transfer reactions had been observed in steroid 3-keto-4-ene olefin additions. The conjugated norbornanyl enone **7** derived from steroid **1** and norbornene is formally derivable from a 1,3-hydrogen shift in the intermediate diradical. This type of transfer was hitherto unknown in enone cycloadditions. However, the deuterium labelling experiment clearly indicates the occurrence of the 1,3-shift in the direct formation of **7** via the 1,4-diradical rather than the formation of **7** through fortuitous conjugation of a β,γ-enone adduct formed by a 1,5-hydrogen shift. In agreement, and yet contrast, the hydrogen transfer product **14** formed from enone **1** and norbornadiene is the result of the rearrangment of the norbornenyl half of the intermediate diradical and subsequent abstraction of the C-6 steroid hydrogen. Inspection of models indicates that this would be the 6α-equatorial hydrogen. The final result is therefore a 1,6-hydrogen shift via a seven-membered transition state. In the intermediate diradical formed from the addition of dienone **2** to norbornadiene, the steroid C-6 hydrogen is part of an allylic radical and thus not available for abstraction. The initially formed norbornene radical does not abstract the steroid C4β-hydrogen like the enone **1**, an energetically unfavourable 1,3-shift (a four-membered transition state), but rearranges to the anti-7-substituted norbornene radical which abstracts the hydrogen in an energetically more favorable 1,4-shift. Therefore in the systems studied, we have observed 1,3; 1,4 and 1,6-hydrogen shifts where heretofore none had been observed in steroid enone and dienone additions to olefins. The apparent reason for the observance of this type of product is the bulkiness of the olefins employed. We[1,6] and others[17] have previously shown that the photocycloaddition of enones and dienones to cycloolefins and dienes employs a highly ordered transition state where the olefin orthogonally approaches the plane of the excited enone with the ring methylenes of the olefin oriented towards the CO side of the steriod. The first bond formed is 4α and the methylene group of the norbornene has substantial steric interactions with the steroid B-ring preventing free rotation about the newly formed bond. This semi-frozen conformation allows hydrogen abstraction or rearrangement and subsequent abstraction since the radical center in the norbornane (ene) residue is in close proximity to the abstractable steroid C-4 or C-6 hydrogens. A possible reason for the occurrence of the 1,3-hydrogen shift in the enone **1**-norbornene cycloaddition and its absence in the enone and dienone-norbornadiene cycloadditions is that the 2-substituted-3-norborn-5-enyl radical can rearrange whereas the 2-substituted-3-norbornyl radical cannot. If the rearrangement of the initially formed norbornenyl radical is fast compared to its hydrogen abstraction capability then the more favored 1,4 and 1,6-hydrogen abstraction processes become the exclusive enone adduct forming pathways.

The *trans*-fused cyclobutanes obtained from the enone **1** and dienone **2** and norbornadiene bear out previous suppositions that this cycloaddition is either concerted or that the second bond formation occurs much faster than the possible norbornene radical can rearrange.[2,11] It also appears that if the

diradical is an intermediate sufficiently long lived to undergo rotation about the initially formed bond, rearrangement occurs to form the [3+2]-adduct exclusively, as in the formation of the [3+2]-adduct **18** from enone **1** and norbornadiene.

EXPERIMENTAL

General. Mp pts were taken on Thomas-Hoover Uni-Melt capillary apparatus and are uncorrected. IR spectra were run in KBr and UV spectra in methanol and are not reported unless $\pi\pi^*$-absorption was observed. A Varian Associates T-60, A-60, FT-80, or HA-100 Spectrometer was used to record spectra. All spectra were recorded in $CDCl_3$ using TMS as an internal standard unless otherwise noted, and are reported as chemical shift, following by a first order analysis of the splitting pattern, coupling constant in hertz where appropriate and then the integrated signal intensity. ORD/CD curves were obtained on methanol solutions, unless otherwise noted, in a Jasco ORD/UV-5 spectrometer. Mass spectra were run on an A.E.I. MS-30 mass spectrometer. Microanalyses were performed by Searle Laboratories Microanalytical Service, under the supervision of Mr. E. Zielinski and Chromatographies were run under the direction of Mr. Robert Nicholson.

The steroids **1** and **2** were obtained from Searle Chemicals.

Irradiation of the dienone **2** *with norbornene.* A soln of **2** (10.0 g, 29.2 mmol) in 145 ml EtOAc and 45 ml of norbornene (Aldrich) was irradiated, under N_2, with a 450 watt medium pressure Hanovia mercury lamp (Pyrex filter). After 5 hr, tlc indicated most of the starting dienone had been consumed and a ppt had formed. The soln was filtered to give 650 mg of a polymer since the NMR showed neither olefinic signals nor angular Me peaks. Removal of the solvent gave an oil which was dissolved in 125 ml EtOAc, whereupon 2.75 g of photoproduct **3** crystallized. The solvent was removed and the residue was chromatographed on 1400 g of E. Merck silica. Elution with EtOAc:petroleum ether (3:7) gave an additional 3.89g of **3**, (total 6.64 g, 15.2 mmol, 61%), followed by 1.48 g of starting **2**. Compound **2** exhibits: mp 235–8° (EtOAc/petroleum ether); IR 1770 cm^{-1} (lactone), 1720 cm^{-1} (*trans*-fused cyclohexanone); NMR δ 5.95 (dd, J = 9, 1.5 Hz, 1H, C-7H), 5.67 (d, J = 9 Hz, 1H, C-6H), 3.22 (d, J = 8 Hz, 1H, 4β-H), 1.22 (s, 3H, C-19), 1.00 (s, 3H, C-18); ORD $[\phi]_{306}$ +1940°, $[\phi]_{299}$ 0°, $[\phi]_{262}$ −26,460°, a = +284; CD: $[\theta]_{289}$ +14,559°; Ms m/e 434 (37%, parent), 419 (7.9%, -CH_3), 341 (31.8%, -norbornene+H), 340 (49%, -norbornene), 66 (100%, cyclopentadiene). (Found: C, 80.35: H, 8.95. Calcd for $C_{29}H_{38}O_3$: C, 80.14: H, 8.81.)

Epimerization of **3.** A soln of **3** (1.00 g) in 75 ml MeOH was epimerized by refluxing with (NaOMe) (1.0 g) for 16 hr. Dist. water and excess HCl was added and the MeOH removed on a rotary evaporator to give 960 mg of **4** after drying. Compound **4** exhibits: mp 138-140°; IR 1780 cm^{-1}, 1705 cm^{-1}; NMR δ 5.88 (dd, J = 10, 2 Hz, 1H, C-6), 5.45 (d, J = 10 Hz, 1H), 1.00 (s, 3H, C-18), 0.93 (s, 3H, C-19); [C_6D_6] 5.72 (dd, J = 10, 2 Hz, 1H), 5.30 (dd, J = 10, ≤1 Hz, 1H), 0.83 (s, 3H), 0.78 (s, 3H); $[\alpha]_D^{24}$ -91.2° (c = 1.025%, $CHCl_3$). (Found: C, 80.06; H, 8.79. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Hydrogenation of **3.** A soln of **3** (1.00 g) in 125 ml dioxan was hydrogenated at 60 psi and 50° for 48 hr in the presence of 5% Pd/C. Filtration of the catalyst and solvent removal gave a residue which was crystallized from EtOAc/petroleum ether to give 781 mg of **5**: mp 256-7°; IR 1770 cm^{-1} (lactone), 1720 cm^{-1} (*trans*-fused cyclohexanone CO); NMR δ 3.27 (d, J = 8 Hz, 1H, C-4β), 1.13 (s, 3H, C-19), 0.92 (s, 3H, C−18); ORD $[\phi]_{304}$ +9170°, $[\phi]_{292}$ 0°, $[\phi]_{264}$ -24,450°, a = +336; CD $[\theta]_{287}$ +5320°; $[\alpha]_D^{25}$ -32.0° (C = 0.103% $CHCl_3$). (Found: C, 79.73; H, 9.58. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Epimerization of **5.** Compound **5** (1.00 g) was heated for 16 Hr in a soln of NaOMe (2.0 g) in 300 ml MeOH. The soln was cooled and dist water and excess HCl was added and the MeOH removed on a rotary evaporator. Filtration given 900 mg of **6**: mp 220° (softens) 255-8° (melts); IR 1780 cm^{-1}, 1697 cm^{-1} (*cis*-fused cyclohexanone CO); NMR δ 0.95 (s, 6H); [C_6D_6] 0.83 (s, 3H), 0.73 (s, 3H), ORD $[\phi]_{320}$-4235°, $[\phi]_{310}$ -4016°, $[\phi]_{295}$ 0°, $[\phi]_{282}$ +1135°, $[\phi]_{266}$ 0°; a = −83; CD$[\theta]_{298}$-5390°; $[\alpha]_D^{22}$ -59.9° (C = 0.108% $CHCl_3$). (Found: C, 79.62; H, 9.25. Calcd for $C_{29}H_{40}O_3$: C, 79.77; 9.23.)

Irradiation of the steroidal enone **1** *with norbornene.* A solon of **1** (10.15 g; 29.5 mmol) in 45 ml norbornene and 350 ml EtOAc was irradiated, under N_2, with a 450 watt medium pressure mercury arc (Pyrex filter) for 12 hr. The reaction was essentially complete after 4 hr, but the R_f of one of the photoproducts was very similar to **1** causing an overirradiation of *circa* 8 hr. The solvent was removed on a rotary evaporator and chromatographed on 1.5 Kg of E. Merck (Darmstadt) silica.

Elution with EtOAc:benzene (5:95) gave 2.15 g (4.9 mmol, 17%) of **7**, 17β-hydroxy-4-(2′-exo-norbornan-2′-yl)3-oxoandrost-4-ene-17α-propionic acid-γ-lactone: mp 163-5° (MeOH/water); IR 1785 cm^{-1}, 1680 cm^{-1}, UV 255 nm (ϵ 13,000); NMR δ 1.17 Hz (s, 3H), 0.98 (s, 3H), [C_6D_6] 0.82 (s, 3H), 0.81 (s, 3H); ORD $[\phi]_{275}$+25,325°, $[\phi]_{256}$ 0°, $[\phi]_{236}$-28,820°, a = +541; CD $[\theta]_{256}$+43,900°; $[\alpha]_D^{24}$+89.5° (c = 0.095%, $CHCl_3$). (Found: C, 80.05; H, 9.41. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Continued elution with EtOAc:benzene (1:9) gave 5.24 g (12 mmol, 41%) **8**: mp 188-90° (ether/petroleum ether); IR 1785 cm^{-1}, 1700 cm^{-1}; NMR δ 0.92 (s, 3H), 0.78 (s, 3H), [C_6D_6] 0.80 (s, 3H), 0.60 (s, 3H); ORD $[\phi]_{310}$+5600°, $[\phi]_{293}$ 0°, $[\phi]_{268}$−8600°; a = +141; CD $[\theta]_{243}$+10,175°; $[\alpha]_D^{24}$ 25.6° (c = 0.101% $CHCl_3$); MS m/e 436 (4.3%, parent), 343 (97.6% − norbornene + H), 66 (100%, C_5H_6). (Found: C, 80.01; H, 9.18. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Elution with EtOAc:benzene (15:85) gave 264 mg (0.6 mmol, 2%) of **9**: mp 145–147°. (ether/petroleum ether), IR 1780 cm^{-1}, 1700 cm^{-1}; NMR δ 0.92 (s, 3H), 0.88 (s, 3H), [C_6D_6] 0.80 (s, 3h), 0.65 (s, 3H); ORD $[\phi]_{312}$-3275°, $[\phi]_{295}$ 0°, $[\phi]_{274}$+4280°; a = −76; CD $[\theta]_{295}$-5800°; $[\alpha]_D^{22}$-18.7° (C = 0.139%, $CHCl_3$). (Found: C, 79.67; H, 8.99. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Elution with EtOAc:benzene (1:3) gave 3.43 g (7.8 mmol, 26%) of **5**; identical with a sample prepared by hydrogenation of **3**. Epimerization of a sample of the above adduct with sodium methoxide in methanol gave a 4β,5β-cyclobutane identical with **6**.

Elution with EtOAc:benzene (1:2) returned 370 mg of starting enone **1**.

Formation of the β,γ*-enone* **11.** A soln of **10** (5.00 g, 14.5 mmol) in 75 ml CH_2Cl_2, containing 350 mg, 4.36 mmol, of suspended NaOAc was oxidized with pyridinium chlorochromate (4.7 g, 21.8 mmol) at room temp. After 3 h, the mixture was diluted with ether and filtered through Celite. The residual solid was washed with 1:1-dichloromethane-ether and finally with ether. The combined organics were evaporated and the residue flash chromatographed[21] on a 50 mm column using 1:4 EtOAc-CH_2Cl_2 to yield 2.23 g of **11**. mp128–132°.; IR 1775, 1720 cm^{-1}; NMR δ 5.35 (m, 1H), 1.21 (s, 3H), 0.99 (s, 3H); $[\alpha]_{589}^{25}$-51° [c = 0.105% ($CHCl_3$)], $[\alpha]_{365}^{25}$ + 18°. (Found: C, 76.80; H, 8.91. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83.)

C4-Deuterium exchange in β,γ*-enone* **11.** A soln of **11** (2.45 g) in 100 ml of dry distilled (from LAH) 1,2-dimethoxyethane and 10 ml of 99.9% D_2O was refluxed for 30 hr under N_2. After cooling, the soln was slowly diluted with water to yield the deuterated **12**. Mass

spectrographic analysis[23] indicated: D_0 55%, D_1 35%, D_2 7.9%, D_3 1.2%.

4-Deuterated enone **13**. A soln of C4-deuterated β,γ-enone (2.10 g) in 80 ml dry distilled 1,2-dimethoxyethane and 20 ml distilled water containing 1.0 g of *p*-toluenesulfonic acid was placed in the steam cabinet at 60° for 1.75 hr. The solon was cooled and diluted with water to yield 1.6 g of **13**. Mass spectrographic analysis[23] indicated: D_0 54.5%, D_1 44.0%, D_2 1.4%.

Irradiation of the dienone **2** *with norbornadiene*. A soln of **2** (10.0 g, 29 mmol) in 15 ml norbornadiene and 300 ml EtOAc was irradiated, under N_2, with a 450 watt medium pressure arc (Pyrex filter) for 27.5 hr. The irradiation soln was filtered from some polymeric material and the solvent removed and the residue chromatographed on 1200 g of E. Merck silica. Elution with EtOAc-benzene (1:9) gave 5.99 g of a mixture of dienone-norbornadiene adducts, followed closely by 2.27 g (6.6 mmol) of recovered dienone **2**. The remainder of material was very polar and contained no discrete spots on tlc and was not further investigated. The adduct fractions were re-chromatagraphed on 600 g of Mallinckrodt CC-7 silica and elution with EtOAc-petroleum ether (1:4) gave 1.516 g (3.5 mmol, 16%) of **14**, 17β-hydroxy-4-(7'-anti-2'-norbornen-7'-yl)-3-oxo-androsta-4,6-diene-17α-propionic acid-γ-lacatone mp 263–5° (EtOAc/ethyl ether); IR 1775 cm^{-1}, 1660 cm^{-1}, 1615 cm^{-1}, 1550 cm^{-1}, UV 291 nm (ε 20,000); NMR δ 6.50 (dd, J = 10, 2 Hz, 1H), 6.10 (m, 3H), 3.53 (broad s, 1H), 2.96 (broad s, 1H), 1.03 (s, 3H), 0.98 (s, 3H); [C_6D_6] 6.42 (dd, J = 10, 2 Hz, 1H), 6.20 (apparent t, 2H), 5.68 (dd, J = 10, 2 Hz, 1H, 3.97 (broad s, 1H), 3.10 (broad s, 1H), 2.78 (broad s, 1H), 0.80 (s, 3H), 0.68 (s, 3H); ORD $[\phi]_{310}$ + 28,500°, $[\theta]_{258}$ - 47,500°; a = + 760, CD $[\theta]_{334}$ - 6480°, $[\theta]_{288}$ + 50,760°, MS m/e 432 (parent 19.2%), 366 (12.9%, $-C_5H_6$), 341 (51.7%, $-C_7H_8$ + H), 43(100%). (Found: C, 80.66; H, 8.19. Calcd for $C_{29}H_{36}O_3$: C, 80.51; H, 8.39.)

Closely following **14** came 0.430 g (1 mmol, 4%) of an adduct: mp 267-9° (EtOAc/ether), IR 1770 cm^{-1}, 1695 cm^{-1} NMR δ 6.35 (q, 1H), 6.10 (m, 1H), 5.73 (m, 2H), 3.83 (broad s, 1H), 1.03 (s, 3H), 0.95 (s, 3H), ORD (dioxane) $[\phi]_{315}$ - 4255°, $[\phi]_{292}$ 0°, $[\phi]_{275}$ + 1300°, $[\phi]_{258}$ 0°, a = - 56, CD $[\theta]_{298}$ - 5185°; MS m/e 432 (parent, 42.8%), 366 (15.2%, $-C_5H_6$), 341 (38.2%, $-C_7H_8$ + H), 92 (100%, C_7H_8). (Found: C, 80.59; H, 8.45. Calcd for $C_{29}H_{36}O_3$: C, 80.51, H, 8.39.)

Immediately after this adduct came 0.776 g (1.8 mmol, 8%) of **15**: mp 165–7° (MeOH/water); IR 1770 cm^{-1}, 1730 cm^{-1}, NMR δ 6.03 (t, 2H), 5.77 (q, 2H), 3.05 (d, J = 8 Hz, 1H), 1.31 (s, 3H), 1.03 (s, 3H); CD $[\theta]_{297}$ + 10,325°, MS m/e 432 (35.1%), 366 (40.2%, $-C_5H_6$), 341 (63.4%, $-C_7H_8$), 92 (100%, C_7H_8). (Found: C, 80.52; H, 8.28. Calcd for $C_{29}H_{36}O_3$: C, 80.51; H, 8.39.)

PMR and Eu studies on trienone **10**. The structure for **10** was based mainly on the presence of a one proton broad singlet signal, whose shape is consistent for a 7-norbornene proton but not for a 5-proton. Due to steric interactions, there is restricted rotation about the steroid-norbornene bond. Based on Eu(fod)$_3$ studies, it was shown that the 1-hydrogen in the norbornene residue is close to the steroid C3-carbonyl group. The two bridgehead (1 and 4) and 7-norbornenyl hydrogens were readily observed in dueteriobenzene solon. Decoupling experiments between the norbornene olefinic protons and the downfield singlets indicated which were the two bridgehead protons and the 7-proton. However, these coupling are one of several small couplings for all three protons. For a 5-norbornenyl group, no proton other than the two bridgehead protons would be expected to give a singlet. The 5-proton should have two vicinal couplings, each ≥ 5 Hz to the adjacent methylene protons.[24] The antisubstitution was determined by a europium shift study when the olefinic proton adjacent to the faster shifting bridgehead proton shifted more slowly than the other olefinic proton. In the *syn* isomer, it would be expected to shift more rapidly. In the *anti*-isomer, however, the olefinic proton adjacent to the faster moving bridgehead proton has a large H–Eu–O angle and would be expected to shift slowly. The H-Eu–O angle for the other olefinic, more remote, proton is smaller, thus compensating for the longer europium-hydrogen distance.

Epimerization of **15**. The *trans*-adduct **15** (97 mg) was suspended in 10 ml MeOH and 250 mg NaOMe added. The mixture was stirred overnight. Dil HCl was added and the MeOH removed on a rotary evaporator. The white ppt was filtered off and dried to 92 mg of **16**: mp 240–2°, IR 1775 cm^{-1}, 1697 cm^{-1}; NMR δ 5.5–6.2 (m, 4H), 3.15 (broad s, 1H), 3.02 (broad s, 1H), 1.00 (s, 6H); MS m/e 432 (Parent, 10.1%), 366 (36.6%, $-C_5H_6$), 341 (9.3%, $-C_7H_6$ + H), 92 (100%, C_7H_8). (Found: C, 77.03; H, 8.23. Calcd for $C_{29}H_{36}O_3 H_2O$: C, 77.30, H, 8.50.)

Hydrogenation of the trans-adduct **15**. 100 mg of **15** were dissolved in 100 ml dioxane with 20 mg 5% Pd/C and heated to 50° under 60 psi of hydrogen for 7 days. The catalyst was removed and the solvent evaporated. Recrystallization from EtOAc-hexane gave 82 mg in two crops. The hydrogenation product was identical to the *trans*-fused adduct **5**.

Selective hydrogenation of the norbornene double bond in **10**. To a soln of **10** (281 mg) in 40 ml dioxan, 5% Pd/C, 30 mg, was added and the mixture stirred magnetically. Hydrogen was introduced at rt and atmospheric pressure and one equivalent was consumed in 7 min. The soln was filtered from catalyst and then reduced to a small volume when crystallization commenced. After diluting with ether and filtering 205 mg (73%) of the dihydro derivative was obtained: mp 295–300°, IR 3020 cm^{-1}, 1775, 1660, 1615; UV 291 nm (ε 20,000); NMR δ 6.58 (dd, 1H), 6.03 (dd, 1H), 2.92 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H); $[\alpha]_D^{25}$ + 69.9°[c = 0.103% ($CHCl_3$)] (Found: C, 79.82; H, 8.78. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Irradiation of the steroidal enone **1** *with norbornadiene*. A soln of **1** (10.0 g; 29 mmol) in a soln of 150 ml and 40 ml norbornadiene was irradiated under N_2 for 3.5 hr with a 450 watt medium pressure mercury lamp (Pyrex filter). The solvents were removed and the residue chromatographed on 1500 g of E. Merck silica and 11 fractons were collected. Elution with EtOAc/petroleum ether (1:4) gave two fractions containing 1.96 g (4.52 mmol, 16%) of the *cis*-adduct **18**: mp 134–40°, EtOAc-petroleum ether); IR 1780 cm^{-1} (lactone), 1700 cm^{-1} (cyclohexanone); NMR δ 6.15 (dd, J = 6, 3 Hz, 1H), 5.90 (dd, J = 6, 3 Hz 1H) 3.08 (broad s, 1H, norbornene C1 or C7), 2.90 (broad s, 1H, norbornene C1 or C7); 0.97 (s, 6H, C18 and C19); ORD $[\phi]_{310}$ + 5185°, $[\phi]_{278}$ 0°, a = + 52, CD $[\theta]_{296}$ + 5450°, MS m/e 434 (parent 1.4%), 343(3.5%, $-C_7H_7$) Compound **18** could be recovered unchanged from a NaOMe in MeOH soln. (Found: C, 80.35, H, 8.88 Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.

The following six fractions gave 6.64 g (15.3 mmol, 53%) of **17**: mp 214–17°, (ether/petroleum ether); IR 1780 cm^{-1}, 1720 cm^{-1} (cyclohexanone), NMR δ 6.28 (t with secondary splitting, 2H), 5.43 (broad S, 1H), 1.13 (s, 3H, C-19), 0.98 (s, 3H, C-18); ORD $[\phi]_{310}$ + 14,340°, $[\phi]_{294}$ 0°, $[\phi]_{270}$ - 16,340°, $[\phi]_{254}$ - 15,025°, a = + 307, CD $[\theta]_{295}$ + 5600°, MS m/e 434 (parent, 1.6%), 93 (100%). (Found: C, 80.20; H, 8.94. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

The following fraction was a mixture and was discarded. The next two fractions gave 605 mg of an oil from which 262 mg (0.6 mmol, 2%) of **23** could be crystallized: mp 194–97°, (MeOH/water); IR 1780 cm^{-1}, 1700 cm^{-1}; NMR δ 6.43 (dd, J = 5.5, 2.5 Hz, 1H), 5.75 (m, 1H), 3.75 (broad s, 1H), 1.06 (s, 3H), 0.92 (s, 3H), [C_6D_6] 6.50 (dd, J = 5.5, 2.5 Hz, 1H), 5.67 (m, 1H, 3.53

(broad s, 1H), 0.80 (s, 3H), 0.75 (s, 3H); ORD (dioxane) $[\phi]_{322}$ −2955°, $[\phi]_{296}$ 0°, $[\phi]_{278}$ +1350°; a = −43; CD $[\theta]_{298}$ −880°; $[\alpha]_D^{21}$ −42.4° (c = 0.122% in $CHCl_3$). (Found: C, 80.11; H, 8.66. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Continued elution gave three fractions with 640 mg from which 310 mg (0.7 mmol, 2%) of **24** could be crystallized from MeOH-water: mp 122–27°; IR 1780 cm^{-1}; NMR δ 6.06 (m, 2H), 0.93 (s, 6H);[C_6D_6] 6.00 (m, 2H), 0.82 (s,6H); ORD (dioxane)$[\phi]_{312}$ −3925°, $[\phi]_{298}$ 0°, $[\phi]_{278}$ +3370°; a = −73; CD $[\theta]_{300}$ −6285°; $[\alpha]_D^{21}$ −49.1° (c = 0.143% in $CHCl_3$). Found: C, 80.11; H, 8.91. Calcd for $C_{29}H_{38}O_3$: c, 80.14; H, 8.81.)

Elution with EtOAc/petroleum ether gave four fractions yielding 1.27 g (2.9 mmol, 10%) of **20**: mp 159–61°. (acetone/water); IR 1780 cm^{-1}, 1725 cm^{-1}; NMR δ 6.08 (t, 2H), 1.12 (s, 3H), 0.93 (s, 3H); [C_6D_6] 5.95 (m, 2H), 0.88 (s, 3H), 0.83 (s, 3H); ORD (dioxane) $[\phi]_{312}$ +7950°, $[\phi]_{296}$ 0°, $[\phi]_{265}$ −15,470°; a = +235; CD $[\theta]_{294}$ +15650°; $[\alpha]_D^{21}$ −32.7° (c = 0.125% in $CHCl_3$). (Found: C, 80.16; H, 8.69. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Epimerization of **20**. The *trans*-fused **17** (258 mg) was added to a solution of 1.0 g NaOMe in 150 ml MeOH and the mixture heated until the compound dissolved. After 19 hr, dil HCl was added and the MeOH removed. The ppt was filtered off and dried to 231 mg of **21**: mp 144–9°; IR 1780 cm^{-1}, 1700 cm^{-1}; NMR δ 6.00 (m, 2H), 1.02 (s, 3H), 0.93 (s, 3H); [C_6D_6] 5.92 (m, 2H), 0.83 (s, 3H), 0.78 (s, 3H); $[\alpha]_D^{21}$ −43.3° (c = 0.120% in $CHCl_3$). (Found: C, 80.17; H, 8.50. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Hydrogenation of **18**. A soln of **15** (174 mg) in 19.5 ml dioxane was hydrogenated at rt and atmospheric pressure in the presence of 5% Pd/C. After 22 hr, one equivalent had been absorbed and the mixture was filtered and the solvent removed. The residue was crystallized from MeOH-water to yield 165 mg of **19**: mp 227–9°; IR 1775 cm^{-1}, 1695; NMR δ 0.95 (s, 3H, C18), 0.87 (s, 3H, C19); $[\alpha]_D^{25}$ +80° [C = 0.098% ($CHCl_3$)]. (Found: C, 79.47; H, 8.88. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Hydrogenation of the trans-cyclobutane **20**. A soln of **20** (180 mg) in 50 ml THF was hydrogenated over 200 mg of 5% Pd/C for 6 hr. Filtration and evaporation of the solvent gave 175 mg of trans-adduct **5**, which was identical with that obtained from **1** and norbornene.

Base catalyzed conjugation of the β,γ-enone **14**. (a) Compound **17** (253 mg) was dissolved in 25 ml MeOH and then 250 mg NaOMe were added. After stirring at rt overnight, the mixture was diluted with distilled water to give a soln of the sodium salt of the γ-hydroxy acid. This soln was made acidic with conc HCl and the lactone collected. After drying, 239 mg of **17** were recovered. (b) To a soln of 210 mg of **17** in 50 ml absolute MeOH, was added 1 g t-BuOK and the resulting light yellow soln was refluxed under argon for 16 hr. Work-up as in part a yielded 192 mg of the conjugated **22**: mp 206–10°: IR 1775 cm^{-1}, 1680, 1665, 1580; UV 253.5nm (ε 10,750); NMR δ 612 (m, 2H), 3.38 (broad s, 1H), 3.03 (broad s, 1H), 1.14 (s, 3H), 0.98 (s, 3H); $[\alpha]_{589}^{25}$ +84° [C = 0.128% ($CHCl_3$)], $[\alpha]_{365}^{25}$ −73°. (Found: C, 80.03; H, 8.69. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81.)

Selective hydrogen of dienone **14** *to the enone* **26**. A soln of **17** (202 mg) was hydrogenated in THF over 10% Pd/C until one equivalent was consumed when uptake ceased. Filtration and evaporation of the solvent gave 196 mg of **25**: mp 201–3° C.; IR 1775 cm^{-1}, 1720; NMR δ 5.50 (m, 1H), 1.12 (s, 3H), 0.97 (s, 3H). (Found; C, 79.76; H,9.00. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

Base catalyzed conjugation of enone **25**. A soln of **25** (175 mg) in 50 ml MeOH was refluxed with t-BuOK in the same manner as **14** to yield the conjugated **26**: mp 183–6°; UV 253.5 nm (ε10,500); IR 1780 cm^{-1}, 1665, 1575; NMR δ 1.15 (s, 3H), 0.98 (s, 3H); $[\alpha]_{589}^{25}$ +68° [C = 0.128% ($CHCl_3$)], $[\alpha]_{365}^{25}$ −89°. (Found: C, 79.43; H, 9.15. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23.)

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