Use of Cyclic β-Keto Ester Derivatives in Photoadditions. Synthesis of (±)-Norasteriscanolide

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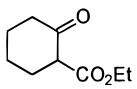
The [2 + 2] photoaddition of 2-cyclopentenones with derivatives of the cyclic β-keto ester **1** was investigated. The resultant adducts then underwent fragmentation to 5/8 fused ring systems present in terpenoid natural products such as asteriscanolide (**3**). For example, photoaddition of 2-cyclopentenone with the trimethylsilyl derivative **13** gave the head-to-head *cis-anti-cis* adduct **14**. Monomethylation and borohydride reduction of the adduct yielded lactone **19**. Cleavage of the silyl ether in **19** with fluoride ion followed by spontaneous fragmentation gave norasteriscanolide (**20**). Substrate **20**, which possesses all the stereochemical features of the natural product **3** but lacks two methyl groups, was synthesized in only four steps using this methodology.

In the de Mayo reaction, enolized β-diketones (or their enol ester derivatives) undergo photoaddition with alkenes to yield adducts which may then fragment in a retroadol reaction to give ring enlarged products.[1] We wished to investigate the participation in photoadditions of enolized alicyclic β-keto esters serving as the alkene component. It has been shown that enols of these substrates are not effective participants in photoadditions[2] so we have utilized various derivatives of an enolized β-keto ester in our study.[3] The derivatives investigated were the ethyl ether, the acetate, and the trimethylsilyl ether of enolized ethyl 2-oxocyclohexane-1-carboxylate (**1**).



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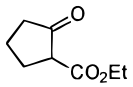

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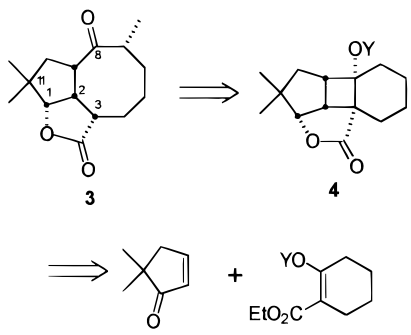
Our ultimate objective in the use of derivatives of **1** or of the cyclopentanone homolog **2**[4] is the efficient synthesis of 5/7, 5/8, or 6/7 fused ring systems which are present in many terpenoid natural products.[5] For example, a retrosynthetic analysis of our approach to the cyclooctane-containing sesquiterpene lactone asteriscanolide **3**[6] is outlined in Scheme 1. In the critical step, fragmentation of adduct **4** (Y could be H, R, COR, or SiR_3) should lead to the desired 5/8 ring system. Adduct **4** could be prepared by photoaddition of a substituted 2-cyclopentenone and a derivative of **1**. (+)-Asteriscanolide has been prepared previously by an intramolecular [4 + 4] cycloaddition,[7] and other potential approaches have been reported.[8]

Scheme 1



Results and Discussion

Before proceeding with an investigation of the cyclic β-keto ester derivatives, we examined briefly the photoaddition of **1** itself with cyclic enones. The enol form of **1** has been reported to be the major tautomer particularly in nonpolar solvents,[9] so potentially this could serve as the alkene component in a photoaddition. Irradiation of 2-cyclopentenone with an excess of **1** gave only enone dimer and none of the mixed adduct. Enone ester **5**[10] was investigated next as it is more reactive than 2-cyclopentenone in photoadditions and has less tendency to dimerize. Irradiation of **5** with an excess of either **1** or the ethyl enol ether of **1** gave in less than 10% yield the desired head-to-head adducts.[11]

In our search for a more reactive β-keto ester derivative, we converted **1** to the enol acetate **6** using isopropenyl acetate.[12] Irradiation of **6** and enone **5** gave adducts **7** (40%) and **8** (40%) (Scheme 2) along with a

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(1) (a) Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G.; de Mayo, P. *J. Org. Chem.* **1969**, *34*, 794. (b) Weedon, A. C. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: New York, 1995; Chapter 54.

(2) (a) Hunt, R. G.; Potter, C. J.; Reid, S. T.; Roantree, M. L. *Tetrahedron Lett.* **1975**, 2327. (b) Tokuda, M.; Watanabe, Y.; Itoh, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 905.

(3) Derivatives of *acyclic* β-carbonyl esters have been reported to undergo photoaddition with enones. (a) *Enol acetates*: Ogino, T.; Yamada, K.; Isogai, K. *Tetrahedron Lett.* **1977**, 2445. Van Audenhove, M.; Termont, D.; De Keukeleire, D.; Vandewalle, M.; Claeys, M. *Tetrahedron Lett.* **1978**, 2057. (b) *Silyl ethers*: Liu, H.-J.; Dieck-Abularach, T. *Tetrahedron Lett.* **1982**, *23*, 295.

(4) The enol acetate of **2** has been utilized in a photoaddition reaction with a substituted 2-cyclopentenone: Liu, H.-J.; Lee, S. P. *Tetrahedron Lett.* **1977**, 3699.

(5) (a) Fraga, B. M. *Nat. Prod. Rep.* **1995**, *12*, 303 and earlier reports. (b) *Total Synthesis of Natural Products*; ApSimon, J., Ed.; J. Wiley and Sons: New York, 1983, Vol. 5.

(6) San Feliciano, A.; Barrero, A. F.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A. *Tetrahedron Lett.* **1985**, *26*, 2369.

(7) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.

(8) (a) Mehta, G.; Murty, A. N. *J. Org. Chem.* **1990**, *55*, 3568. (b) Booker-Milburn, K. I; Cowell, J. K. *Tetrahedron Lett.* **1996**, *37*, 2177.

(9) (a) Rhoads, S. J.; Pryde, C. *J. Org. Chem.* **1965**, *30*, 3212. (b) Rhoads, S. J. *J. Org. Chem.* **1966**, *31*, 171.

(10) Lange, G. L.; Decicco, C.; Willson, J.; Strickland, L. A. *J. Org. Chem.* **1989**, *54*, 1805.

(11) Organ, M. G. Ph.D. Thesis, University of Guelph, 1992.

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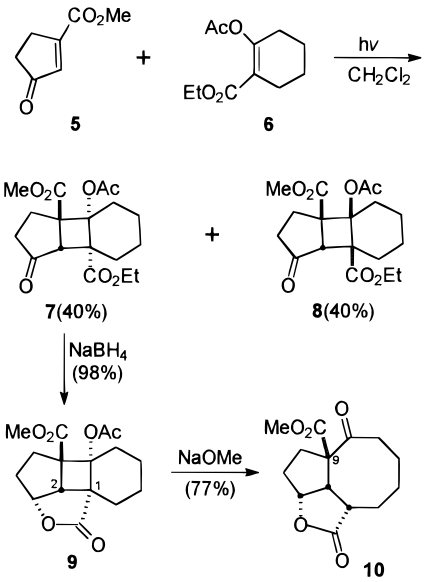
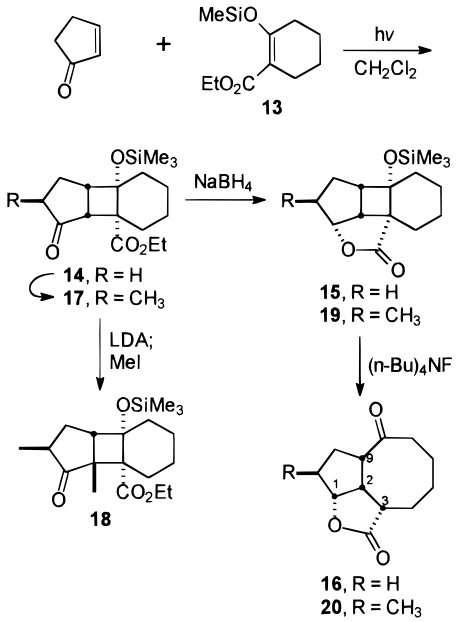
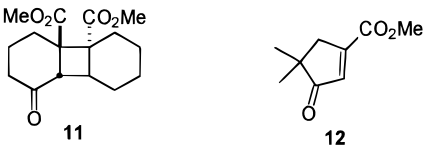
Scheme 2



Scheme 3



dimer of **5**. The head-to-head regiochemistry and *anti* stereochemistry of **7** was established by its efficient conversion to lactone **9**. The other adduct was tentatively assigned the *syn* stereochemistry depicted in **8** based on the very deshielded singlet for H-2 at 3.39 ppm.[10] Treatment of **9** with dilute methoxide resulted in transesterification of the acetoxyl group followed by a retroaldol type reaction to give the fragmentation product **10**. A comparison of this product's structure with the target asteriscanolide **3** reveals that **10** has the requisite 5/8 ring system and lactone moiety and the proper relative stereochemistry at C-1, -2, -3 and -9 but the substrate is lacking three methyl groups and has an extra methoxycarbonyl group at C-9. The plan was to remove this ester group using Krapcho methodology.[13] Attempts to either mono- or dimethylate **7** α to the ketone function using a variety of bases (LDA, NaH, KH, t-BuOK, $NaNH_2$) were uniformally unsuccessful. In a model study, adduct **11**[10] was dimethylated readily at the α-methylene site. The additional hindrance in **7** is one of several factors that may be preventing the desired alkylation. In an attempt to circumvent the methylation problem, the initial photoaddition was conducted with **6** and the dimethylated enone **12**, but none of the desired head-to-head *cis-anti-cis* adduct was isolated although other photoadducts were formed.



To investigate the photochemistry of other derivatives of **1**, the trimethylsilyl ether **13** was prepared.[3b] Photoaddition of 2-cyclopentenone with **13** gave the desired adduct **14** (Scheme 3) in a modest 35% yield (based on **13** consumed) plus a considerable amount of enone dimer. Nevertheless, the adduct was purified readily by flash chromatography. Reduction of **14** with sodium borohydride gave in high yield lactone **15**, whose formation unambiguously established the head-to-head *cis-anti-cis* structure of the adduct. Treatment of **15** with fluoride ion resulted in cleavage of the silyl ether followed by a retroaldol fragmentation to give **16**, which has all the structural features of asteriscanolide **3** but lacks the three methyl groups.

In an attempt to introduce the *gem*-dimethyl groups present at C-11 in **3**, adduct **14** was treated with LDA/MeI to give **17** in high yield. Reaction of **17** with excess LDA/MeI resulted only in a low yield of dimethylate product **18**, tentatively assigned on the basis of a methyl singlet and methyl doublet in the ^1H NMR spectrum. Surprisingly, the second methyl group was introduced at the 2-position, which would have involved an enolate double bond exocyclic to the cyclobutane ring. Attempts to generate the *gem*-dimethyl derivative using a variety of equilibrating conditions were unsuccessful. Thus we converted the monomethyl product **17** to lactone **19** and fragmentation with fluoride ion gave in high yield norasteriscanolide **20**. It is noteworthy that although **20** lacks two methyl groups present in the natural product **3**, the synthetic product was prepared in a very stereoselective manner in only four steps!

In conclusion, fragmentation of photoadducts derived from 2-cyclopentenone and the trimethylsilyl ether derivative of **1** shows promise for assembling the 5/8 ring system found in terpenoids. Preliminary results with adducts derived from 2-cyclopentenone and the TMS derivative of **2** similarly undergo facile fragmentation to give 6/7 fused ring systems.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a 200-MHz or a 400-MHz spectrometer with $CDCl_3$ as solvent and TMS as internal standard. The multiplicities of the ^{13}C resonances were determined by the attached proton test (APT), which gave positive (+) quaternary C and CH_2 signals and negative (−) CH and CH_3 signals, or by DEPT experiments. IR spectra were recorded on a FTIR spectrophotometer in CCl_4 solution using NaCl cells, and mass spectra were obtained on a high resolution spectrometer. Products were purified by flash chromatography using 230−400 mesh silica gel. A solvent mixture of EtOAc and hexanes was chosen which gave the product of interest an R_f of 0.35 on thin-layer

(12) Damiano, J.; Geribaldi, S.; Torri, G.; Azzaro, M. *Tetrahedron Lett.* **1973**, 2301.
(13) Krapcho, P. *Synthesis* **1982**, 805.

chromatography (TLC). TLC analyses were performed on silica gel GF 254 plates with a thickness of 0.25 mm. Melting points are uncorrected

Solvents were prepared as follows: ether and THF were distilled from CaH_2 and then from sodium/benzophone ketyl, CH_2Cl_2 was distilled from CaH_2, and methanol was stored over 4A molecular sieves. Reactions sensitive to air or moisture were conducted in flame-dried flasks under an atmosphere of argon. Preparations of **5**,[10] **6**,[12] and **13**[14] have been described previously.

General Irradiation Procedures. The indicated amounts of enone and cycloalkene were placed in oven-dried 14-mm × 18-cm Pyrex irradiation tubes, and CH_2Cl_2 was added until the final enone concentration was 0.5−2.0 M. The solutions were deoxygenated with argon, and the tubes were sealed with rubber septa and irradiated using either lamp system described below. The reactions were followed by TLC and stopped when most of the enone was consumed. The solvent was removed and the crude mixture separated by flash chromatography. **Irradiation Procedure A:** The irradiation tubes were placed in a water-cooled Pyrex immersion well centered in a Rayonet RPR 208 preparative reactor with 350-nm lamps. **Irradiation Procedure B:** The irradiation tubes were held by elastic bands to the outside of a water-cooled Pyrex immersion well which was placed in a pail of ice water, and the samples were irradiated with a 450 W Hanovia lamp.

Irradiation of Methyl 3-Oxo-1-cyclopentene-1-carboxylate (5) and Ethyl 2-Acetoxycyclohexene-1-carboxylate (6). Using procedure A, a CH_2Cl_2 solution of **5** (350 mg, 2.5 mmol) and **6**[12] (2.00 g, 9.4 mmol) was irradiated for 96 h, and the reaction mixture was purified by flash chromatography (30% EtOAc/hexanes) to yield adducts **7** (349 mg, 40%) and **8** (345 mg, 40%) as clear oils: **1-ethyl 6-methyl 7α-acetoxy-2β-hydro-3-oxotricyclo[5.4.0.0^{2,6}]undecane-1α,6β-dicarboxylate (7):** ^{1}H NMR δ 4.12 (dq, J = 7.0, 1.7 Hz, 2H), 3.78 (s, 3H), 2.93 (s, 1H), 2.87 (m, 1H), 2.51 (dd, J = 17.9, 8.4 Hz, 1H), 2.40−2.15 (m, 4H), 2.10 (m, 1H), 2.05 (s, 3H), 1.82 (m, 2H), 1.63 (m, 2H), 1.43 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 217.35, 173.81, 171.91, 169.60, 80.39, 61.55, 56.40, 55.99, 52.47, 49.90, 39.20, 27.85, 26.77, 26.46, 21.32, 16.38, 16.16, 14.04; IR 2935, 2928, 1736 (br), 1450, 1225 (br), 1140 (br) cm^{-1}; EIMS 70 eV, *m/z* (rel int): 352[M]$^+$ (8.4), 292 (10.5), 264 (11), 223 (51), 204 (27), 170 (40), 119 (100), 117 (99); HRMS calcd for $C_{18}H_{24}O_7$: 352.1522, found 352.1530. **1-Ethyl 6-methyl 7β-acetoxy-2β-hydro-3-oxotricyclo[5.4.0.0^{2,6}]undecane-1β,6β-dicarboxylate (8):** ^{1}H NMR δ 4.24 (dq, J = 7.5, 3.8 Hz, 2H), 3.75 (s, 3H), 3.39 (s, 1H), 3.00 (m, 1H), 2.74 (dt, J = 13.9, 3.3 Hz, 1H), 2.40 (m, 2H), 1.96 (s, 3H), 1.95−1.35 (m, 8H), 1.32 (t, J = 7.5 Hz, 3H); IR 2948, 2862, 1744 (br), 1365, 1231, 1212, 1158, 1032 cm^{-1}.

Methyl 7α-Acetoxy-2β-hydro-3α-hydroxy-6β-(methoxycarbonyl)tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylic Acid γ-Lactone (9). To a solution of **7** (656 mg, 1.9 mmol) in dry MeOH (25 mL) at 0 °C was added $NaBH_4$ (142 mg, 3.8 mmol). The mixture was stirred at 0 °C for 15 min and then was allowed to warm gradually to rt over 1 h. MeOH was removed *in vacuo*, water (5 mL) was added to the residue, and the aqueous phase was extracted with ether (3 × 50 mL). The combined ether layers were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvent gave **9** (567 mg, 98%) as a crystalline solid: mp 114−115 °C; ^{1}H NMR δ 5.04 (dd, J = 5.4, 2.9 Hz, 1H) 3.77 (s, 3H), 3.29 (d, J = 5.4 Hz, 1H), 2.37 (dt, J = 14.8, 4.7 Hz, 1H), 2.20 (m, 3H), 2.07 (s, 3H), 1.85 (m, 2H), 1.70 (m, 4H), 1.55 (m, 1H), 1.42 (m, 1H); ^{13}C NMR δ 177.39, 172.94, 168.78, 82.99, 76.50, 60.89, 51.89, 50.64, 46.54, 34.42, 29.69, 27.63, 26.56, 20.71, 18.65, 18.37; IR 3437, 2955, 2848, 1774, 1732, 1251, 1105, 1085 cm^{-1}; EIMS 70 eV, *m/z* (rel int): 310 [M + 2]$^+$ (0.5), 307 [M − 1]$^+$ (0.4), 266 (100), 206 (16), 170 (17), 142 (35), 125 (40); HRMS calcd for $C_{16}H_{19}O_6$ 307.1181, found 307.1178.

Methyl 1β,2β,3β-Trihydro-1α-hydroxy-9β-(methoxycarbonyl)-8-oxobicyclo[6.3.0]undecane-3α-carboxylic Acid γ-Lactone (10). A mixture of lactone **9** (50 mg, 0.16 mmol) and dry MeOH (2.5 mL) was stirred at 0 °C under Ar for 10 min. To this mixture was added 1.0 M NaOMe in MeOH (180 μL, 0.18 mmol), and stirring was continued for 20 h at 0 °C. MeOH was removed *in vacuo*, saturated NH_4Cl solution (5 mL) was added to the residue, and the product was extracted with ether (3 × 20 mL). The combined ether extracts were washed with brine (5 mL) and dried ($MgSO_4$). After removal of the solvent the residue was purified by flash chromatography (30% EtOAc/hexanes) to give **10** (33 mg, 77%) as white crystals: ^{1}H NMR δ 4.99 (dt, J = 5.8, 3.7 Hz, 1H), 3.75 (s, 3H), 3.19 (dd, J = 7.0, 5.8 Hz, 1H), 2.90 (m, 1H), 2.78 (dd, J = 14.6, 7.0 Hz, 1H), 2.35−1.50 (m, 11H); ^{13}C NMR (DEPT) δ 207.1 (s), 175.6 (s), 175.1 (s), 83.6 (d), 62.1 (s), 52.5 (q), 52.3 (d), 45.6 (d), 40.8 (t), 36.8 (t), 31.3 (t), 29.5 (t), 26.5 (t), 21.1 (t); IR 2950, 2841, 1774, 1737, 1715, 1450, 1435, 1203, 1165, 1150, 1135 cm^{-1}; EIMS 70 eV, *m/z* (rel int): 266[M]$^+$ (52), 235 [M − OCH_3]$^+$ (42), 206 (63), 192 (81), 178 (77), 142 (79), 125 (100), 91 (77), 79 (65), 67 (92), 55 (86); HRMS calcd for $C_{14}H_{18}O_5$ 266.1157, found 266.1154.

Ethyl 2β,6β-Dihydro-3-oxo-7α-[(trimethylsilyl)oxy]-tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylate (14). Using procedure B, a CH_2Cl_2 solution of **13**[14] (2.00 g, 8.3 mmol) and 2-cyclopentenone (340 mg, 4.0 mmol) was irradiated for 15 h. The enone was added in 5 equal portions every 3 h over the course of the irradiation (to minimize enone dimerization). The solvent was removed and the residue purified by flash chromatography (20% EtOAc/hexanes) to give adduct **14** (134 mg, 35% based on **13** consumed) as a clear oil: ^{1}H NMR δ 4.03(q, J = 7.3 Hz, 2H), 2.80 (dt, J = 8.7, 5.2 Hz, 1H), 2.62 (m, 1H), 2.33 (d, J = 8.7 Hz, 1H), 2.20 (m, 2H), 2.00−1.40 (m, 5H), 1.18 (t, J = 7.3 Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (APT) δ 220.12 (+), 172.28 (+), 75.42 (+), 60.54 (+), 59.68 (+), 45.81 (−), 44.34 (−), 40.38 (+), 33.69 (+), 28.69 (+), 21.19 (+), 17.64 (+), 17.07 (+), 13.99 (−), 1.87 (−); IR 1737, 1255, 1180, 1150, 1120, 1105 cm^{-1}; EIMS 50 eV, *m/z* (rel int): 324[M]$^+$ (12), 279 [M − 3×(CH_3)]$^+$ (11), 250 [M − $(Si(CH_3)_3$ + H]$^+$ (24), 227 [M − $(C_5H_6O$ + $CH_3)$]$^+$ (100), 199 (49), 91 (35), 73 (71); HRMS calcd for $C_{17}H_{28}O_4Si$ 324.1757, found 324.1764.

2β,3β,6β-Trihydro-3α-hydroxy-7α-[(trimethylsilyl)oxy]-tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylic Acid γ-Lactone (15). To a solution of **14** (60 mg, 0.19 mmol) in dry MeOH (5 mL) at 0 °C was added $NaBH_4$ (14 mg, 0.37 mmol). The mixture was stirred at 0 °C for 15 min and then allowed to warm to rt over 1 h. MeOH was removed *in vacuo*, water (3 mL) was added, and the aqueous phase was extracted with ether (3 × 25 mL). The combined ether layers were washed with brine (5 mL) and dried ($MgSO_4$). After removal of the solvent the residue was purified by flash chromatography (15% EtOAc/hexanes) to give lactone **15** (44 mg, 83%) which formed crystals when stored at 0 °C: ^{1}H NMR δ 4.88 (dd, J = 5.9, 3.2 Hz, 1H), 2.76 (t, J = 5.9 Hz, 1H), 2.63 (dq, J = 8.8, 7.2 Hz, 1H), 2.24−1.20 (m, 12H), 0.10 (s, 9H); ^{13}C NMR (APT) δ 178.64 (+), 82.90 (−), 70.89 (+), 53.82 (+), 49.74 (−), 42.14 (−), 38.66 (+), 35.50 (+), 25.77 (+), 21.90 (+), 20.17 (+), 18.66 (+), 1.21 (−); IR 1773, 1446, 1355, 1256, 1174, 1141, 1130, 1120, 1020, 935 cm^{-1}; EIMS 50 eV, *m/z* (rel int): 280[M]$^+$ (2), 265 [M − CH_3]$^+$ (6), 214 (60), 199 (100), 124 (56), 91 (86), 84 (82); HRMS calcd for $C_{15}H_{24}O_3Si$ 280.1494, found 280.1492.

1β,2β,3β,9β-Tetrahydro-1α-hydroxy-8-oxobicyclo[6.3.0]-undecane-3α-carboxylic Acid γ-Lactone (16). To a solution of **15** (99 mg, 0.36 mmol) in dry THF (10 mL) at 0 °C was added with stirring a 0.75 M (n-Bu)$_4$NF solution in THF (0.473 μL, 0.36 mmol). The reaction was monitored by TLC, after 1 h at 0 °C water (5 mL) was added, the layers were separated, the water layer was extracted with ether (2 × 30 mL), and the combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed and the residue purified by flash chromatography (15% EtOAc/hexanes) to yield **16** (49 mg, 65%) as white crystals: mp 69.5−71 °C; ^{1}H NMR δ 4.91 (m, 1H), 3.15 (m, 2H), 2.85 (m, 1H), 2.45 (m, 3H), 2.20−1.20 (m, 9H); ^{13}C NMR (APT) δ 211.89 (+), 178.75 (+), 83.02 (−), 54.45 (−), 45.25 (−), 44.43 (+), 40.88 (−), 31.66 (+), 29.25 (+), 26.21 (+), 23.97 (+), 23.63 (+); IR 1777, 1704, 1552, 1248, 1195, 1171, 1139, 1096 cm^{-1}; EIMS 70 eV, *m/z* (rel int):

(14) (a) Ahmad, S.; Amin Khan, M.; Iqbal, J. *Synth. Commun.* **1988**, *18*, 1679. (b) Tsuji, J.; Ohashi, Y.; Minami, I. *Tetrahedron Lett.* **1987**, *28*, 2397.

208[M]$^+$ (34), 142 (17), 124 (23), 114(34), 67 (100); HRMS calcd for $C_{12}H_{16}O_{13}$ 208.1099, found 208.1111.

Ethyl 2β,4α,6β-Trihydro-4β-methyl-3-oxo-7α-[(trimethylsilyl)oxy]tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylate (17). To a solution of diisopropylamine (40 μL, 0.28 mmol) and dry THF (10 mL) in a flame-dried 25-mL round-bottomed flask at −78 °C under Ar was added a 1.6 M solution of n-BuLi in THF (173 μL, 0.28 mmol), and the solution was stirred for 30 min. A solution of **14** (45 mg, 0.14 mmol) in dry THF (2 mL) and dry HMPA (48 μL, 0.28 mmol) was transferred by cannula to the LDA solution, and stirring was continued for 30 min at −78 °C. The bath temperature was allowed to rise to −40 °C, held there for 30 min, and then reduced to −78 °C. MeI (43 μL, 0.70 mmol) was added to the solution, which was then allowed to warm to 0 °C over 2 h. The reaction was quenched with saturated NH_4Cl solution (5 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 30 mL), and the combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by flash chromatography (20% EtOAc/hexanes) gave **17** (44 mg, 95%) as a pale yellow oil: ^{1}H NMR δ 4.00 (dq, J = 7.3, 2.2 Hz, 2H), 2.81 (br q, J = 6.7 Hz, 1H), 2.39 (d, J = 8.0 Hz, 1H), 2.25 (m, 1H), 1.90−1.30 (m, 10H), 1.63 (t, J = 7.3 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (APT) δ 221.16 (+), 171.68 (+), 77.25 (+), 60.34 (+), 57.83 (+), 46.99 (−), 43.68 (−), 40.10 (−), 32.42 (+), 30.92 (+), 30.03 (+), 18.08 (+), 16.85 (+), 15.43 (−), 13.92 (−), 2.04 (−); IR 1734, 1457, 1256, 1211, 1138, 1119, 870, 847 cm^{-1}; EIMS 50 eV, m/z (rel int): 338[M]$^+$ (2), 323 [M − CH_3]$^+$ (2), 293 [M − OCH_2CH_3]$^+$ (4), 227 (35), 199 (44), 73 (100); HRMS calcd for $C_{18}H_{30}O_4Si$ 338.1913, found 338.1900.

Ethyl 4α,6β-Dihydro-2β,4β-dimethyl-3-oxo-7α-[(trimethylsilyl)oxy]tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylate (18). An LDA solution was prepared as described above for the preparation of **17** using diisopropylamine (80 μL, 0.56 mmol), and 1.6 M n-Bu Li in THF (346 μL, 0.56 mmol) in dry THF (10 mL). Crude **17** (47 mg, 0.14 mmol), which was assumed to be completely monomethylated, in HMPA (48 μL, 0.28 mmol) and THF (2mL) was added to the LDA solution and stirred at −78 °C for 30 min. The bath temperature was allowed to rise to -40 °C, held there for 30 min, and cooled again to −78 °C. Methyl iodide (86 μL, 1.4 mmol) was added, and the solution was allowed to warm to 0 °C over 2 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and worked up and purified as described for **17** to give dimethylated adduct **18** (11 mg, 22% over two alkylation steps) as a yellow oil: ^{1}H NMR δ 4.09 (dq, J = 7.4, 5.3 Hz, 2H), 2.75 (br q, J = 7.8 Hz, 1H), 2.47 (dd, J = 8.9, 2.6 Hz, 1H), 2.23 (ddd, J = 12.6, 8.9, 3.2 Hz, 1H), 2.00−1.30 (m, 9H), 1.23 (t, J = 7.4 Hz, 3H), 1.15 (s, 3H), 1.08 (d, J = 7.8 Hz, 3H), 0.11 (s, 9H).

2β,3β,4α,6β-Tetrahydro-3α-hydroxy-4β-methyl-7α-[(trimethylsilyl)oxy]tricyclo[5.4.0.0^{2,6}]undecane-1α-carboxylic Acid γ-Lactone (19). Using the procedure described for the preparation of lactone **15**, a solution of **17**, (51 mg, 0.15 mmol) in MeOH (5 mL) was reduced with $NaBH_4$ (11 mg, 0.30 mmol). Workup and purification gave **19** (31 mg, 70%) as white crystals: mp 74−75 °C; ^{1}H NMR δ 4.53 (d, J = 5.9 Hz, 1H), 2.85 (dd, J = 7.4, 5.9 Hz, 1H), 2.71 (dt, J = 9.2, 7.4 Hz, 1H), 2.49 (dq, J = 7.3, 6.7 Hz, 1H), 2.20−1.20 (m, 10H), 0.78 (d, J = 7.3 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (APT) δ 179.04 (+), 87.59 (−), 71.22 (+), 53.53 (+), 49.16 (−), 42.45 (−), 41.36 (−), 39.41 (+), 29.43 (+), 26.40 (+), 20.82 (+), 19.25 (+), 16.82 (−), 1.72 (−); IR 1771, 1544, 1248, 1200, 1138, 1091 cm^{-1}; EIMS 50 eV, m/z (rel int): 294[M]$^+$ (1), 279[M − CH_3]$^+$ (3), 249 (2), 214 (51), 199 (100), 124(42), 73(56); HRMS calcd for $C_{16}H_{26}O_3$-Si 294.1651, found 294.1666.

1β,2β,3β,9β,11α-Pentahydro-1α-hydroxy-11β-methyl-8-oxobicyclo[6.3.0]undecane-3α-carboxylic Acid γ-Lactone (20). To a solution of **19** (29 mg, 0.10 mmol) in dry THF (10 mL) at 0 °C was added a 0.75 M solution of (n-Bu)$_4$NF in the THF (132 μL, 0.10 mmol). After stirring the solution for 1 h at 0 °C, water (5 mL) was added, the layers were separated, the water layer was extracted with ether (2 × 30 mL), and the combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by flash chromatography (15% EtOAc/hexanes) gave **20** (21 mg, 97%) which solidified at 0 °C but melted at rt: ^{1}H NMR δ 4.30 (t, J = 7.5 Hz, 1H), 3.35 (m, 1H), 3.10 (m, 1H), 2.60−1.60 (m, 8H), 1.45−1.15 (m, 4H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (APT) δ 212.85 (+), 178.55 (+), 88.56 (−), 48.75 (−), 47.59 (−), 45.63 (+), 41.72 (−), 39.16 (−), 32.77 (+), 30.16 (+), 26.67 (+), 22.99 (+), 17.13 (−); IR 1773, 1700, 1534, 1161, 1132, 1107 cm^{-1}; EIMS 50 eV, m/z (rel int): 222[M]$^+$ (23), 124(19), 81(100); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1260.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for **7-9**, **10**, and **14−20** are provided (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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