Macrolactonization–Transannular Aldol Condensation Approach to the Taxane AB Ring System

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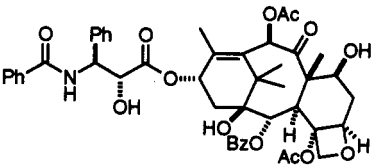
Cyclohexenone **13**, containing the fully elaborated taxane A ring, was prepared from 4,4-dimethyl-2-cyclohexenone (43% for four steps); two copper-catalyzed Grignard conjugate addition reactions on crowded dienones **8** and **11** were employed as key transformations. Elaboration of **13** to the chloro keto acid **6** was achieved via an epoxidation/regioselective chloride-mediated epoxide ring opening/Jones oxidation protocol (42% for three steps). Macrolactonization (59%) followed by chemoselective transannular aldol condensation within the resulting 11-membered bicyclic keto lactone **4** under thermodynamic control (51%) resulted in closure of the taxane B ring to afford the target 2(5*H*)-furanone **3**.

The antimitotic taxane diterpenoid, taxol (**1**),[1] has shown exceptional promise in the clinical treatment of several neoplasms,[2] most notably advanced drug-refractory ovarian[3] and breast[4] cancers. Its unique mechanism of action involves the promotion of microtubule assembly and the stabilization of these polymers.[5] The practical and ecological problems associated with the current commercial isolation of taxol from the stem bark of the Pacific yew have made the development of alternate sources an emergency priority.[6] The synthesis of taxol and related analogues constitutes an important avenue of investigation in this endeavor, and considerable progress has been made in this area.[1,7] Significantly, however, the total synthesis of taxol has not yet been reported.[8]



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Construction of the eight-membered taxane B ring is among the most challenging facets of taxane synthesis. Few direct cyclization approaches to this ring have been reported,[1,7,9] presumably because of a combination of significant enthalpic and entropic barriers to ring closure in this strained and crowded system. An attractive strategy for constructing the taxane B ring involves a *transannular* cyclization protocol. Initial closure of a macrocyclic ring should proceed without the high enthalpic barrier posed by direct closure of the taxane B ring. A subsequent transannular cyclization step within this macrocycle to close the eight-membered B ring would be free of the entropic problems inherent in a direct B ring closure reaction, since the two reactive sites for cyclization would be held proximate by the macrocyclic ring. Interestingly, few transannular approaches to the taxane skeleton have been reported. Biomimetic electrophilic transannular cyclizations within verticillene and related compounds have failed to afford the taxane skeleton.[10] Ohtsuka and Oishi successfully performed transannular acylation of a sulfoxide-stabilized carbanion derived from 12-membered lactam sulfoxide **2** in their approach to the taxane AB ring system.[11] The synthesis of **2**, however, required either 27 steps from α-ionone[11a,b] or 24 steps from 1,5-pentanediol.[11d] Since the completion of our studies outlined in this paper,

• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

(1) For recent reviews dealing with the structure, isolation, synthesis, and pharmacology of taxol and related taxane diterpenoids, see: (a) Suffness, M.; Cordell, G. A. In *The Alkaloids—Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 25, Chapter 1, pp 6–18, 280–288. (b) Blechert, S.; Guenard, D. In *The Alkaloids—Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, Chapter 6, pp 195–238. For a review on the chemistry and structure–activity of taxol, see: (c) Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1.

(2) For recent reviews of the promise of taxol as an antineoplastic agent, see: (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Rose, W. C. *Anti-Cancer Drugs* **1992**, *3*, 311. (c) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646.

(3) See, for example: (a) McGuire, W. P.; Rowinsky, E. K.; Rosenhein, M. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Int. Med.* **1989**, *111*, 273. (b) Sarosy, G.; Kohn, E.; Link, C. *et al. Proc. Am. Soc. Clin. Oncol.* **1992**, *11*, 716.

(4) Holmes, F. A.; Walters, R. S.; Theriault, R. L. *et al. J. Natl. Cancer Inst.* **1991**, *83*, 1797.

(5) Horwitz, S. B. *Trends Pharmacol. Sci.* **1992**, *13*, 134.

(6) (a) Gentry, R. *J. Natl. Cancer Inst.* **1991**, *83*, 603. (b) The commercial production of taxol *via* semisynthesis is expected to begin in 1993: Holton, R. A. *Second National Cancer Institute Workshop on Taxol and Taxus*, Sept 23–24, 1992, Alexandria, VA.

(7) For recent reviews of synthetic approaches to the taxane skeleton, see: (a) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465. (b) Paquette, L. A. In *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1992; Vol. 11 (Stereoselective Synthesis, Part G), pp 3–69.

(8) Several groups have made considerable progress toward this goal. Among the most noteworthy contributions are those of Holton (first total synthesis of a taxane natural product, *ent*-taxusin: Holton, R. A. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: San Diego, 1991; Vol. 3, pp 165–197), Wender (Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878), and Paquette (Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772. Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354).

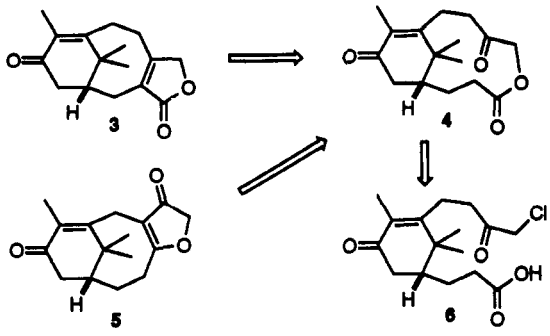
(9) For recent approaches, see: (a) Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345. (b) Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Chemistry Lett.* **1993**, 133. (c) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (d) Kataoka, Y.; Nakamura, Y.; Morihira, K.; Arai, H.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1992**, *33*, 6979. (e) Wang, Z.; Warder, S. E.; Perrier, H.; Grimm, E. L.; Bernstein, M. A. *J. Org. Chem.* **1993**, *58*, 2931.

(10) (a) Kato, T.; Takayanagi, H.; Suzuki, T.; Uyehara, T. *Tetrahedron Lett.* **1978**, *14*, 1201. (b) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3397. (c) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907.

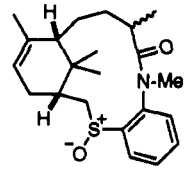
(11) (a) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203. (b) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4711, 4722. (c) Oishi, T. *Yakugaku Zasshi* **1989**, *109*, 523. (d) Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1991**, *39*, 1359.

0022-3263/93/1958-6807$04.00/0

Scheme I



Pattenden has reported an interesting, though as yet relatively low yielding, tandem radical macrocyclization–radical transannulation approach to the taxane ABC ring system.[12,13]



Central to our approach to the taxane AB ring system is the use of a *transannular aldol condensation* within the macrocyclic keto lactone 4 (Scheme I). Prior work from our group[14-16] suggested that the formation of the 11-membered keto lactone 4 from chloro keto acid precursor 6 should be possible. Preliminary studies in model systems have demonstrated the viability of preparing medium-ring carbocycles via thermodynamically controlled transannular aldol condensation reactions within macrocyclic keto lactones.[15-17] However, neither these preliminary studies nor an inspection of Dreiding models of the various possible aldolate intermediates allowed us to clearly delineate *a priori* the likely chemoselectivity of such transannular condensation chemistry within 4; formation of the desired 2(5*H*)-furanone 3 and/or the unwanted isomeric 3(2*H*)-furanone 5 were considered possible. Therefore, it remained to prepare the key macrocyclic keto lactone 4 and examine the chemoselectivity of transannulation reactions within 4. It should be noted that alternate "directed" methodology suitable for the chemoselective generation of the desired 2(5*H*)-furanone adduct 3 was available[15,16] should the thermodynamically controlled aldolization chemistry fail to afford the requisite target.

Results and Discussion

Synthesis of the key chloro keto acid intermediate 6 began with 4,4-dimethyl-2-cyclohexenone (7) (Scheme II).[18] The DDQ-mediated dehydrogenation of enone 7 to dienone 8 was accomplished (83%) by refluxing in 1,4-dioxane in the presence of 1 equiv of TsOH following a method developed for the dehydrogenation of steroidal enones.[19,20] Further elaboration of the taxane skeleton required conjugate addition chemistry on dienone 8. Given the ready accessibility of 8, surprisingly few conjugate addition reactions of this compound have been reported, presumably because of the severe steric crowding at the β-carbons. Fetizon *et al.* achieved the Michael addition of two lithium lactone enolates to 8 in 40% and 66% yields, respectively; however, Mukaiyama addition of a sterically crowded silyl enol ether to 8 under Lewis acid catalysis failed.[20b] The bis-conjugate addition of the sterically undemanding cyanide ion to 8 has also been reported.[21,22] Attempts to add nitromethane and nitroethane anions to 8 in a conjugate addition fashion gave no significant reaction.[22] Our goal was to achieve the conjugate addition to dienone 8 of an organometallic reagent bearing terminal functionality suitable for elaboration to the α-chloro ketone moiety in 6. Interestingly, no conjugate addition reactions of organometallic reagents to dienone 8 have apparently been reported. Nevertheless, the successful copper (I)-catalyzed conjugate addition of vinyl Grignard reagent to the similarly crowded 4,4-dimethyl-2-cyclopentenone[23] suggested that such chemistry might be feasible. Indeed, addition of 3-butenylmagnesium bromide (3 equiv) to dienone 8 in ether at −40°C under $(CuI{\cdot}Bu_3P)_4$ catalysis, followed by direct alkylation of the resultant enolate with CH_3I in the presence of HMPA, afforded adduct 9 in 79% yield as a 6:1 mixture of β- and α-epimers.[24] On occasion this conjugate addition–enolate methylation protocol afforded a chromatographically separable mixture of 9 and the nonalkylated conjugate addition product 10. In these cases, methylation of the kinetic enolate of 10 gave 9 in 65% yield. DDQ-mediated dehydrogenation of enone 9 in refluxing 1,4-dioxane in the presence of 1 equiv of TsOH then cleanly afforded dienone 11 in 91% yield.[25]

In order to complete assembly of the pentasubstituted taxane A ring, a second conjugate addition reaction at the sterically less crowded β-carbon in dienone 11 was required. This would achieve incorporation of a three-carbon unit with terminal functionality suitable for elaboration to the

(12) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843 (corrigendum *Ibid.* **1992**, *33*, 7448).

(13) Several other approaches to the taxane skeleton have involved transannulation (Winkler, J. D.; Sridar, V.; Siegel, M. G. *Tetrahedron Lett.* **1989**, *30*, 4943) or related macrocyclic ring contraction reactions (Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141. Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629. Yadav, J. S. *Pure Appl. Chem.* **1993**, *65*, 1349).

(14) Karim, M. R.; Sampson, P. *J. Org. Chem.* **1990**, *55*, 598.

(15) Chai, K.-B. Ph.D. Dissertation, Kent State University, 1992.

(16) Chai, K.-B.; Sampson, P. Manuscript in preparation.

(17) Karim, M. R.; Sampson, P. *Tetrahedron Lett.* **1988**, *29*, 6897.

(18) Compound 7 is commercially available. For an efficient preparation, see: Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399.

(19) Turner, A. B.; Ringold, H. J. *J. Chem. Soc. C* **1967**, 1720.

(20) The DDQ-mediated dehydrogenation of enone 7 to dienone 8 in the absence of TsOH has been reported [(a) Legler, G.; Quiring, B. *Tetrahedron* **1967**, *23*, 2683. (b) Andriamialisoa, R. Z; Fetizon, M.; Hanna, I.; Pascard, C.; Prange, T. *Tetrahedron* **1984**, *40*, 4285. (c) Zimmerman, H. E.; Hackett, P.; Juers, D. F.; McCall, J. M.; Schroder, B. *J. Am. Chem. Soc.* **1971**, *93*, 3653] though it often proceeds in only moderate yield. In our hands, prolonged refluxing of enone 7 with DDQ in anhydrous benzene or 1,4-dioxane resulted in incomplete conversion to 8. Other workers have reported similar observations: (d) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin Trans. I* **1973**, 529.

(21) (a) Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 905. (b) Neh, H.; Kuhling, A.; Blechert, S. *Helv. Chim. Acta* **1989**, *72*, 101.

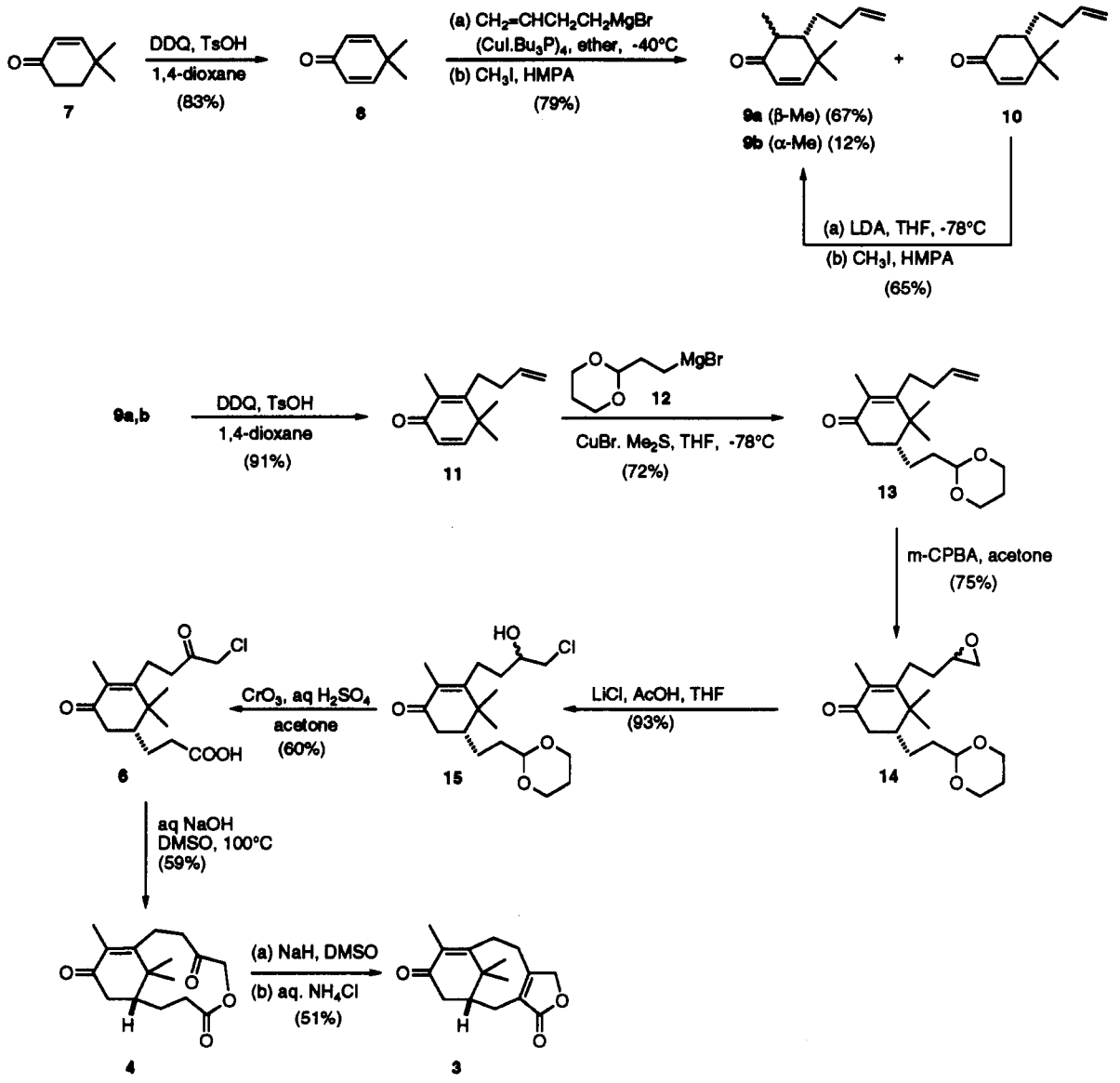
(22) Goodyear, G.; Waring, A. J. *J. Chem. Res., Miniprint* **1991**, 2937.

(23) (a) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262. (b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981**, *103*, 4647.

(24) The *trans*-stereochemistry of the major product 9a was assigned based on the typical *trans*-diaxial H_5–H_6 coupling constant (13.0 Hz). The use of various other reaction conditions during the first step led to significantly lower yields of 9 (R = CH_2=$CHCH_2CH_2$): 1.1 equiv of RMgBr, THF, −78°C (38%); 1.1 equiv of RMgBr, ether, −78 °C (45%); 2.2 equiv of RMgBr, ether, −40°C (57%).

(25) Extended refluxing of 9 with DDQ in anhydrous benzene or 1,4-dioxane in the absence of TsOH gave dienone 11 contaminated with 20–30% unreacted enone.

Scheme II



carboxylic acid function in 6. Chemoselective conjugate addition of the nitromethane anion in a closely related system[11a,b] had previously been achieved, although the reaction was very slow (65 °C, 20 days). The attempted conjugate addition of several different sulfur-stabilized carbanions to the same substrate had failed.[11a,b] Again, no organometallic-based conjugate addition reactions on substrates of this type have apparently been reported.[26] Initial attempts to add a "Rieke organocopper reagent" derived from ethyl 3-bromopropanoate using activated copper(0) [(CuI·Bu_3P)$_4$, Li, naphthalene, THF][27] to dienone 11 gave only unreacted starting material. Attention was then turned to the copper-catalyzed conjugate addition of 2-(1,3-dioxan-2-yl)ethylmagnesium bromide (12) to 11. In line with results reported by Helquist,[28] it was found that generation of Grignard reagent 12 from 2-(2-bromoethyl)-1,3-dioxane[29] under standard conditions was problematic; however, 12 was readily generated using activated Mg powder prepared from anhydrous $MgCl_2$/K according to the procedure of Rieke.[30] In contrast to earlier studies on dienone 8, conjugate addition of Grignard reagent 12 to dienone 11 under (CuI·Bu_3P)$_4$ catalysis failed under various conditions. However, employing CuBr·Me_2S as catalyst proved effective; optimum conditions required a large excess of Grignard reagent and gave 13 in 72% yield.[31] The synthesis of this fully elaborated taxane A ring (four steps, 43% overall yield) compares favorably in terms of length and overall efficiency with other approaches to the taxane A ring.[1,7,9,32]

The next phase of this work required conversion of 13 to chloro keto acid 6, the key lactonization precursor.

(26) The successful conjugate addition of Me_2CuLi to a 4,4-spiro-fused 2,5-cyclohexadienone has been reported as part of a total synthesis of β-vetivone: Bozzato, G.; Bachmann, J.-P.; Pesaro, M. *J. Chem. Soc., Chem. Commun.* **1974**, 1005.

(27) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056.

(28) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

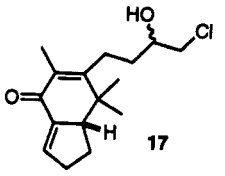
(29) Helquist used the closely related 2-(2-bromoethyl)-1,3-dioxolane in his studies.[28]

(30) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775.

(31) Use of 2.3 equiv of 12 gave 14 in only 16% yield.

(32) For some recent approaches to the taxane A ring, see: (a) Polla, M.; Frejd, T. *Tetrahedron* **1991**, *47*, 5883. (b) **1993**, *49*, 2701. (c) Pettersson, L.; Magnusson, G.; Frejd, T. *Acta Chem. Scand.* **1993**, *47*, 196. (d) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043 (corrigendum *Ibid.* **1993**, *58*, 798). (e) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117. (f) Chapuis, C.; Brauchli, R. *Helv. Chim. Acta* **1992**, *75*, 1527. (g) Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. *Tetrahedron Lett.* **1993**, *34*, 55.

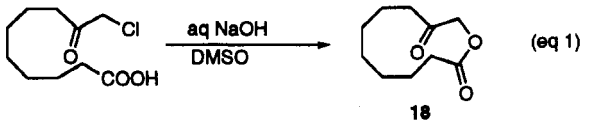
Selective epoxidation of the nonconjugated side-chain alkene in **13** (*m*-CPBA, acetone, 48 h) proceeded cleanly to afford epoxy enone **14** in 75% yield as a 1:1 mixture of two diastereomers. Completely regioselective chloride-mediated epoxide ring opening was achieved using LiCl/AcOH/THF,[33] conditions that we found to be superior to aqueous HCl/DMF in model studies.[34] The desired chlorohydrin **15** was obtained in 93% yield. Hydrolysis of the acetal moiety and oxidation of the aldehyde and secondary alcohol functionality would afford the chloro keto acid **6**. However, acid-catalyzed hydrolysis of the acetal group to the corresponding aldehyde would likely be followed by intramolecular aldol condensation leading to formation of bicyclic enone **17**.[28] Therefore, it was



17

determined that hydrolysis of the acetal should be performed under oxidative conditions. In this way, the resulting aldehyde could be rapidly oxidized to the required carboxylic acid function, precluding formation of aldol byproducts such as **17**. Using 10 equiv of Jones reagent,[35] oxidation of the secondary alcohol in **15** to the required ketone group and acetal hydrolysis with subsequent oxidation to the carboxylic acid occurred to provide the target chloro keto acid **6** in 60% yield.[36,37]

The stage was now set for lactonization to the macrocyclic keto lactone **4**. In model studies we have established that the intramolecular displacement of chloride from an α-chloro ketone by a remote carboxylate nucleophile constitutes an effective macrolactonization protocol.[14-16] A detailed kinetic investigation of the lactonization leading to simple 11-membered keto lactone **18** (eq 1) indicated



(eq 1)

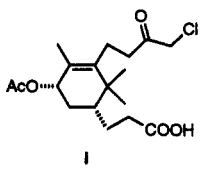
18

a low enthalpy of activation and a large negative entropy of activation for this reaction.[15,16] The increased rigidity of the chloro keto acid **6** would suggest a lower entropic barrier to ring closure than for **18**. In contrast, the significant steric crowding due to the *gem*-dimethyl moiety, and increased strain caused by the formation of a bridgehead alkene during ring closure, would raise the enthalpic barrier for the reaction leading to **4**. While the relative impact of these factors on the ease of lactonization was difficult to predict, an examination of Dreiding models suggested that this ring closure reaction should be feasible. Initial lactonization studies employed reaction conditions analogous to those that had proved useful in the closure of the simple 11-membered keto lactone **18**[14] and involved the addition of 1 equiv of 1 M aqueous NaOH in a single portion to a 1.0 mM solution of chloro keto acid **6** in a polar aprotic solvent. However, performing the reaction in refluxing acetone (8 h) or in DMSO at room temperature (4 h) led to the recovery of only unreacted starting material after workup. The required macrolactonization could only be effected by using elevated temperatures in DMSO. Reaction at 50 °C (3 h) gave keto lactone **4** in 32% yield, while performing the reaction at 100°C (3 h) afforded **4** in 55% yield (both after chromatographic purification). Optimum conditions involved the use of a multiple addition reaction. Five sequential additions of chloro keto acid **6** and 1 M aqueous NaOH to a DMSO solution at 100 °C (2.5 mM final effective substrate concentration) gave the desired macrocyclic keto lactone **4** in 59% isolated yield.

With keto lactone **4** in hand, the final transannular aldol condensation chemistry designed to close the taxane B ring was examined. We were delighted to discover that treatment of macrocyclic keto lactone **4** with dimsylsodium in *rigorously purified anhydrous* DMSO for 4 h at 90°C followed by aqueous NH_4Cl workup and chromatographic purification gave a single aldol product in 51% yield. A comparison of the ^{13}C NMR and IR spectra of this product with spectra obtained for the 3(2*H*)-furanones **19**[17] and **20**[38] and the 2(5*H*)-furanones **21**[39] and **22**[15,16] clearly indicated that the desired 2(5*H*)-furanone product **3** had been obtained (see Table I). Apparently, the most stable aldolate in this reaction is that formed by attack of the lactone enolate derived from **4** on the transannularly disposed ketone carbonyl group. No evidence was found for formation of the alternate 3(2*H*)-furanone-containing transannular condensation product **5**.

In summary, a concise approach to the taxane AB ring system (nine steps from commercial material, average yield of 74% per step) has been developed. The key taxane A ring intermediate **13** was readily available in only four steps, employing two copper-catalyzed Grignard reactions on the highly crowded dienones **8** and **11** as key transformations. Elaboration of **13** to the taxane AB ring system exploited a macrolactonization–transannular aldol condensation protocol. The final product **3** contains the bridgehead double bond, and C-13 oxygenation required in the A ring of taxol and related taxane diterpenes, although it does lack the C-1 hydroxyl group present in taxol. The 2(5*H*)-furanone ring fused to the eight-membered taxane B ring in **3** should serve as a useful functional handle for elaboration of the CD ring system of the taxol skeleton. Studies in this direction are currently underway and will be reported in due course.

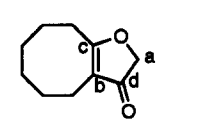
(33) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021.
(34) Chai, K.-B.; Sampson, P. *Tetrahedron Lett.* **1992**, *33*, 585.
(35) Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 604.
(36) Use of 6 equiv of Jones reagent under otherwise identical conditions gave chloro keto acid **6** in only 46% yield. The 1,3-propanediol released during acetal hydrolysis is presumably oxidized to propanedioic acid under these conditions, requiring the use of a large excess of Jones reagent.
(37) Attempts to elaborate epoxy acetal **14** into chloro keto acid **i**, which contains an α-allylic alkanoate functionality similar to that found in the A ring of taxol and related taxane diterpenes, were thwarted by hydrolytic instability of the allylic acetate functionality during elaboration of **i**. See Supplementary Material for details of this chemistry.



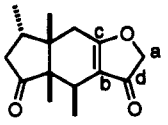
i

(38) Bernasconi, S.; Ferrari, M.; Gariboldi, P.; Jommi, G.; Sisti, M.; Destro, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1994.
(39) (a) Sun, H. H.; McEnroe, F. J.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 1903. (b) Midland, S. L.; Wing, R. M.; Sims, J. J. *J. Org. Chem.* **1983**, *48*, 1906.

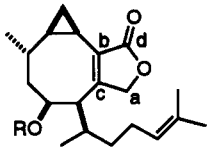
Table I. Key ^{13}C NMR and IR Spectral Data for 3(2*H*)- and 2(5*H*)-Furanone Ring Systems



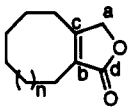
19



20



21a: R = Ac
21b: R = H



22a: n = 1
22b: n = 2
22c: n = 3

compd	^{13}C NMR chemical shift (ppm) δC_a	δC_b	δC_c	δC_d	IR: C_d=O str (cm^{-1})	lit. ref
19	74.1	115.0	191.0	202.6	1695	17
20	74.4	115.8	185.4	200.0	1700	38
21a	71.2	128.8	166.5	174.3	1735	39a
21a	71.5	128.7	166.6	174.2	1735	39b
21b	72.3	128.1	168.5	174.7	1735	39a
22a	70.8	126.3	161.4	175.5	1746	15, 16
22b	71.4	127.2	160.2	175.6	1748	15, 16
22c	71.2	126.7	160.7	176.2	1746	15, 16
3	68.6	130.8	161.7	174.9	1752	this work

Experimental Section

The following solvents and reagents were purified according to standard procedures:[40] THF (distillation from sodium/benzophenone), ether (commercial anhydrous ether stored over sodium wire), DMSO (vacuum distillation of commercial anhydrous DMSO from CaH_2), 1,4-dioxane (distillation of commercial anhydrous 1,4-dioxane from sodium), HMPA (vacuum distillation from BaO and stored over 4A molecular sieves), diisopropylamine (distillation from CaH_2), and LiCl (oven-dried at 150 °C). Commercial DDQ was purified by recrystallization from benzene. TsOH was dried by azeotropic distillation using benzene. 4,4-Dimethyl-2-cyclohexenone (7) was purchased from Aldrich Chemical Co.[18] $(CuI{\cdot}Bu_3P)_4$ was prepared according to a literature procedure.[41] *m*-CPBA was used as supplied by Aldrich Chemical Co.; 67–71% *m*-CPBA was present in each batch with the remainder *m*-chlorobenzoic acid. Other commercial reagents were used without further purification.

All reactions were performed in oven-dried (125°C) glassware with magnetic stirring under a nitrogen atmosphere (unless otherwise stated). Air- or moisture-sensitive liquids were added via syringe through a rubber septum. Reactions were typically monitored using thin-layer chromatography on commercial silica plates which were visualized by UV illumination and/or by charring with 0.5% phosphomolybdic acid in 95% ethanol. In some cases, reactions were monitored by gas chromatography on a Hewlett-Packard 5890A chromatograph equipped with a 530-μm fused silica capillary column and a flame ionization detector. Under "standard workup" conditions, the organic extracts were washed with water (three times) and brine (three times) and dried over anhydrous Na_2SO_4 and the organic solvent(s) removed *in vacuo* using a Buchi rotary evaporator. Final traces of solvent were typically removed at room temperature under high vacuum (ca. 0.5 mmHg). "Chromatography" indicates product purification by gravity column chromatography using glass columns packed with silica gel (70–230 mesh).

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. FT-IR spectral absorptions are reported in cm^{-1}; only major diagnostic bands are reported. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ solution. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane. In some cases, ^{13}C NMR assignments were based on attached proton test (APT) experiments; (–) indicates carbon atoms bearing one or three appended protons, while (+) indicates carbon atoms bearing two or no attached protons. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

4,4-Dimethyl-2,5-cyclohexadienone (8). A solution of 4,4-dimethyl-2-cyclohexenone (7) (4.00 g, 32 mmol), recrystallized DDQ (8.44 g, 37 mmol), and anhydrous TsOH (6.14 g, 32 mmol) in anhydrous 1,4-dioxane (300 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature and the volume reduced to ca. 50 mL *in vacuo*. The residue was diluted with ether (200 mL) and the resulting solution was extracted with 10% aqueous NaOH (3 × 100 mL) to remove the TsOH and hydroquinone byproduct. Standard workup afforded a red oily product (4.93 g). Kugelrohr vacuum distillation then gave 4,4-dimethyl-2,5-cyclohexadienone (8) (3.27 g, 83% yield) as a colorless liquid, bp 68–69.5°C/3.3 mmHg (lit.[20d] 77–79°C/12 mmHg). The IR,[20d] ^1H NMR,[42] and ^{13}C NMR[43] spectra were in close agreement with literature data.

5-(3-Butenyl)-4,4,6-trimethyl-2-cyclohexenone (9). A mixture of 1,4-dibromobutane (49.65 g, 0.229 mol) and freshly redistilled HMPA (41.38 g, 0.230 mol) was heated at 200–205 °C (oil bath temperature) under nitrogen for 1 h. The product distilled out below 100 °C and was collected. Fractional distillation up a Vigreux column gave 4-bromo-1-butene (25.39 g, 82% yield), bp 96–98 °C (lit.[44] bp 98 °C): ^1H NMR δ 2.63 (dt, J = 4.5, 7.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 5.14 (m, 2H), 5.78 (m, 1H).

A solution of 4-bromo-1-butene (3.26 g, 24 mmol) in anhydrous ether (6 mL) was added to a stirred suspension of oven-dried Mg turnings (0.68 g, 28 mmol) in anhydrous ether (18 mL) via a constant addition funnel over 20 min. The resulting mixture was stirred for another 1 h to generate a gray solution containing the desired 3-butenylmagnesium bromide. This solution was then added by syringe over 20 min to a solution of freshly prepared $(CuI{\cdot}Bu_3P)_4$ (0.82 g) in anhydrous ether (4 mL) at –40 °C. The resulting purple solution was stirred for 30 min at –40 °C. Then, neat dienone 8 (1.00 g, 8.2 mmol) was added over 15 min by syringe, and the mixture was stirred for 2 h at –40 °C. HMPA (5 mL) was rapidly added to the dark blue reaction mixture, followed immediately by iodomethane (2.56 g, 18 mmol). The resulting gray solution was stirred for 20 min at –40 °C and then allowed to warm to room temperature over 90 min. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and was then extracted with ether (3 × 150 mL). The combined organic extracts were washed with 2% aqueous NH_4OH (3 × 200 mL), when standard workup afforded a crude residue (2.01 g). Chromatography (hexane–ether (2:1)) gave 5-(3-butenyl)-4,4,6-trimethyl-2-cyclohexenone (**9**) as a colorless oil (1.24 g, 79% yield). An 85:15 mixture of *trans*- and *cis*-isomers **9a** and **9b** was indicated by the ^1H and ^{13}C NMR spectral data: IR (neat) 2954, 1652, 1608, 1602 cm^{-1}; ^1H NMR major (*trans*) isomer **9a** δ 1.04 (s, 3H), 1.12 (s, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.34–1.66 (m, 3H), 2.05 (m, 1H), 2.23 (m, 1H), 2.31 (dq, J = 13.0, 6.6 Hz, 1H), 4.97 (br d, J = ca. 9 Hz, 1H), 5.02 (br d, J = ca. 18 Hz, 1H), 5.80 (m, 1H), 5.83 (d, J = 9.9 Hz, 1H), 6.59 (d, J = 9.9 Hz, 1H); minor (*cis*) isomer **9b** δ 6.53 (d, J = 10.2 Hz); all other signals overlapped with resonances due to **9a**; ^{13}C NMR major (*trans*) isomer **9a** δ 12.78 (–), 20.43 (–), 28.25 (–), 29.44 (+), 34.87 (+), 37.18 (+), 43.97 (–), 49.02 (–), 114.89 (+), 125.73 (–), 138.30 (–), 159.44 (–), 201.55 (+); minor (*cis*) isomer **9b** δ 25.03 (–), 25.91 (+), 29.05 (–), 32.86 (+), 42.24 (–), 47.33 (–), 138.10 (–), 158.10 (–); other signals overlapped with resonances due to **9a**. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.47.

3-(3-Butenyl)-2,4,4-trimethyl-2,5-cyclohexadienone (11). A solution of cyclohexenone **9** (2.00 g, 10.42 mmol, mixture of **9a** and **9b**), recrystallized DDQ (1.30 g, 5.75 mmol), and anhydrous TsOH (1.98 g, 10.4 mmol) in anhydrous 1,4-dioxane (300 mL)

(40) (a) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: London, 1980. (b) *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Furniss, B. S., et al., Eds.; Longman: London, 1978.
(41) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(42) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544.
(43) Gramlich, W. *Liebigs Ann. Chem.* **1979**, 121.
(44) Kuchibhotla, U.; Charkraborty, T. K.; Chandrasekaran, S. *Ind. J. Chem.* **1984**, *23B*, 1216.

was refluxed for 48 h. The reaction mixture was cooled to room temperature and the volume reduced to ca. 50 mL *in vacuo*. The residue was diluted with ether (200 mL), and the resulting solution was extracted with 10% aqueous NaOH (3 × 100 mL) to remove the TsOH and hydroquinone byproduct. Standard workup afforded a red oily product (2.60 g). Kugelrohr vacuum distillation followed by short-path vacuum distillation gave dienone **11** (1.80 g, 91% yield), bp 110–115 °C/0.5 mmHg: IR (Nujol) 2938, 2892, 1650, 1610, 1606 cm^{-1}; ^1H NMR δ 1.26 (s, 6H), 1.92 (s, 3H), 2.22 (m, 2H), 2.42 (m, 2H), 5.04 (br d, J = ca. 11 Hz, 1H), 5.11 (br d, J = ca. 18 Hz, 1H), 5.90 (ddt, J = 17.1, 10.2, 6.3 Hz, 1H), 6.20 (d, J = 9.9 Hz, 1H), 6.74 (d, J = 9.9 Hz, 1H); ^{13}C NMR δ 25.80, 29.93, 32.54, 40.44, 65.74, 115.03, 125.81, 131.81, 137.51, 156.73, 160.75, 189.08. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.04; H, 9.52.

3-(3-Butenyl)-5-[2-(1,3-dioxan-2-yl)ethyl]-2,4,4-trimethyl-2-cyclohexenone (13). Freshly cut potassium (7.58 g, 194 mmol) and anhydrous $MgCl_2$ (10.19 g, 107 mmol) were refluxed in anhydrous THF (70 mL) for 3 h. After the mixture was cooled to room temperature, 2-(2-bromoethyl)-1,3-dioxane (16.16 g, 82.8 mmol) was added to the resulting dark gray suspension over 6 min. The reaction mixture was mechanically stirred for 30 min to allow complete generation of Grignard reagent **12**, and the reaction mixture was then cooled to −78°C. A solution of CuBr·Me_2S complex (4.29 g, 20.6 mmol) in dimethyl sulfide (13 mL) was added over a period of 5 min with mechanical stirring, and the reaction mixture was stirred at −78°C for 2 h. A solution of dienone **11** (1.86 g, 9.78 mmol) in anhydrous THF (2 mL) was added over 3 h by syringe pump, and the mixture was stirred at −78°C for 10 h and then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with ether (3 × 200 mL). Standard workup afforded a crude yellow oil (2.62 g). Chromatography (ethyl acetate–hexane (1:4)) gave enone **13** (2.15 g, 72% yield): IR (Nujol) 2968, 2883, 1672, 1631, 1228 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.22 (s, 3H), 1.79 (s, 3H), 2.16–2.36 (m, 5H), 2.56 (dd, J = 16.8, 3.9 Hz, 1H), 3.85 (m, 2H), 3.97 (m, 2H), 4.85 (t, J = 3.9 Hz, 1H), 5.02 (br d, J = ca. 10 Hz, 1H), 5.08 (br d, J = ca. 17 Hz, 1H), 5.88 (ddt, J = 17.1, 10.2, 5.7 Hz, 1H), plus several multiplets between δ 1.1–1.9 (7H); ^{13}C NMR δ 11.65, 20.37, 24.18, 25.75, 30.29, 31.98, 32.79, 38.73, 40.17, 43.96, 64.86, 64.91, 104.45, 114.94, 130.98, 137.60, 164.42, 198.55. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.54. Found: C, 74.42; H, 9.48.

3-(3,4-Epoxybutyl)-5-[2-(1,3-dioxan-2-yl)ethyl]-2,4,4-trimethyl-2-cyclohexenone (14). Alkene acetal **13** (0.2022 g, 0.66 mmol) was added to a stirred solution of *m*-CPBA (0.1981 g, 0.87 mmol, 70.6% *m*-CPBA) in acetone (20 mL) at 0 °C, and the resulting mixture was allowed to stand at room temperature for 48 h. The reaction mixture was diluted with ether (100 mL) and washed with saturated aqueous $NaHSO_3$ (3 × 50 mL) and saturated aqueous $NaHCO_3$ (5 × 50 mL). Standard workup gave a crude oil (0.2311 g). Chromatography (hexane–ether (1:1)) gave epoxy acetal **14** (0.1590 g, 75% yield) as a 1:1 mixture of two diastereomers: IR ($CHCl_3$) 2986, 1663, 1621, 1201 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.206 (s)/1.213 (s) (3H), 1.78 (s, 3H), 2.21 (dd, J = 16.8, 11.7 Hz, 1H), 2.35 (dd, J = 12.0, 5.4 Hz, 1H), 2.43 (dd, J = 12.6, 5.1 Hz, 1H), 2.53 (*ABX* (overlapping signal), 1H), 2.56 (dd, J = 3.9 Hz, second coupling constant not measurable due to overlapping signals, 1H), 2.80 (t, J = 4.4 Hz, *ABX*, 1H), 2.98 (m, AB*X*, 1H), 3.85 (m, 2H), 3.96 (m, 2H), 4.85 (t, J = 4.2 Hz, 1H), plus several multiplets between δ 0.8–2.0 (9H); ^{13}C NMR δ 11.57, 20.32/20.36, 24.15, 25.75, 26.83/26.97, 29.70, 31.63/31.67, 31.95, 38.71, 40.29, 43.94, 46.91/46.99, 51.98/52.02, 64.86, 64.92, 104.44, 131.18, 163.62/163.72, 198.55. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.76; H, 9.42.

3-(4-Chloro-3-hydroxybutyl)-5-[2-(1,3-dioxan-2-yl)ethyl]-2,4,4-trimethyl-2-cyclohexenone (15). Glacial acetic acid (0.17 mL, 2.79 mmol) was added to a solution of epoxy acetal **14** (0.3002 g, 0.93 mmol) and anhydrous LiCl (0.0633 g, 1.49 mmol) in anhydrous THF (1.6 mL) at room temperature. After being stirred for 10 h, the reaction mixture was diluted with water (20 mL) and extracted with ether (3 × 50 mL). Standard workup gave a crude oil (0.5324 g) which was purified by chromatography (hexane–ether (1:1)) to give chlorohydrin acetal **15** (0.3264 g, 93% yield) as a 1:1 mixture of two diastereomers: IR (Nujol) 3400–3120 (br), 2926, 2872, 1658, 1605, 1126, 947 cm^{-1}; ^1H NMR δ 1.040 (s)/1.123 (s) (3H), 1.216 (s)/1.220 (s) (3H), 1.785 (s)/1.791 (s) (3H), 3.52 (dd, *ABX*, 1H), 3.65 (dd, *ABX*, 1H), 3.86 (*ABX*, overlapping signal, 1H) (J_{AB} = 11.3 Hz, J_{AX} = 6.3 Hz, J_{BX} = 4.2 Hz), 3.85 (m, 2H), 3.97 (m, 2H), 4.85 (t, J = 4.5 Hz, 1H), plus several multiplets between δ 1.1–2.7 (14 H); ^{13}C NMR δ 14.83, 20.47, 24.38, 25.43, 28.32, 29.66, 31.35, 32.43, 39.33, 40.42, 42.48, 50.39, 64.83, 64.93, 72.39, 104.72, 130.98, 163.64, 198.73. Anal. Calcd for $C_{19}H_{31}ClO_4$: C, 63.58; H, 8.70; Cl, 9.88. Found: C, 63.54; H, 8.68; Cl, 9.90.

3-[3-(4-Chloro-3-oxobutyl)-2,4,4-trimethyl-5-oxo-1(6)-cyclohexenyl]propanoic Acid (6). A solution of 10.0 equiv of Jones reagent (a mixture of CrO_3 (0.5947 g), water (2.7 mL), and concd H_2SO_4 (0.55 mL)) was added to a solution of chlorohydrin acetal **15** (0.2132 g, 0.58 mmol) in acetone (100 mL) at 0 °C. After being stirred at room temperature for 12 h the reaction mixture was diluted with water (100 mL) and extracted with ether (3 × 100 mL). Standard workup gave a crude oil (0.2038 g). Crystallization from ether–hexane (1:10) at −50°C afforded pure chloro keto acid **6** (0.1117 g, 60%) as a white solid, mp 133–135 °C: IR (Nujol) 3402–2500 (br), 2928, 2882, 1743, 1674, 1646, 1603, 953 cm^{-1}; ^1H NMR δ 1.06 (s, 3H), 1.21 (s, 3H), 1.15–1.45 (br m, 2H), 1.75 (s, 3H), 1.70–1.85 (m, 1H), 1.90–2.10 (m, 1H), 2.23 (dd, J = 16.8, 8.0 Hz, 1H), 2.31 (dd, J = 16.2, 11.7 Hz, 1H), 2.42–2.65 (m, 4H), 2.76 (m, 1H), 4.10 (s, 2H); ^{13}C NMR δ 11.61, 20.12, 24.15, 24.87, 25.50, 31.85, 38.24, 38.33, 40.27, 43.25, 47.87, 131.61, 163.19, 178.64, 198.24, 201.46. Anal. Calcd for $C_{16}H_{23}ClO_4$: C, 61.05; H, 7.36; Cl, 11.26. Found: C, 61.02; H, 7.34; Cl, 11.27.

12,14,14-Trimethyl-5-oxobicyclo[8.3.1]tetradeca-12-ene-3,6,11-trione (4). (i) Via Single Addition Protocol. Aqueous NaOH (1 M, 64 μL, 0.064 mmol) was added in one portion to a stirred solution of chloro keto acid **6** (20.4 mg, 0.064 mmol) in DMSO (128 mL) at 100 °C and the solution stirred at that temperature for 3 h. The reaction mixture was partitioned between water (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (7 × 100 mL). The combined ether extracts were washed with water (5 × 400 mL). Completion of a standard workup gave a crude colorless oil (23.5 mg). Chromatography (hexane–ether (1:1)) gave keto lactone **4** (9.8 mg, 55% yield): IR (Nujol) 2993, 2842, 1749, 1682, 1643, 1602 cm^{-1}; ^1H NMR δ 1.23 (s, 3H), 1.25 (m, 3H), 1.31 (s, 3H), 1.64 (s, 3H), 2.1–2.7 (m, 6H), 2.7–3.1 (m, 2H), 4.27 (d, J = 12.9 Hz, 1H), 4.96 (d, J = 12.9 Hz, 1H); ^{13}C NMR δ 25.12, 27.31, 27.64, 29.70, 30.43, 31.59, 38.41, 38.76, 39.51, 44.11, 69.33, 134.26, 159.91, 172.61, 197.89, 206.35. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.01; H, 7.94.

(ii) Via Multiple Addition Protocol. Aqueous NaOH (1 M, 60 μL, 0.06 mmol) was added in one portion to a stirred solution of chloro keto acid **6** (20 mg, 0.06 mmol) in DMSO (132 mL) at 100°C, and the solution was stirred at that temperature for 2 h. An additional aliquot of chloro keto acid **6** (20 mg, 0.06 mmol) in DMSO (4 mL) was then added to the same reaction mixture, followed after 30 min. by the addition of more 1 M aqueous NaOH (60 μL, 0.06 mmol). This sequence of additions was repeated at 2-h intervals until a total of five aliquots of chloro keto acid **6** (total 100 mg) and 1 M aqueous NaOH (total 300 μL) had been added. The reaction mixture was then stirred for another 2 h at 100 °C and cooled to room temperature. The reaction mixture was partitioned between water (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (7 × 100 mL). The combined ether extracts were washed with water (5 × 300 mL). Completion of a standard workup gave a crude oil (0.1873 g). Chromatography (hexane–ether (3:1)) afforded keto lactone **4** (36.5 mg, 59% yield).

5-Oxa-11,14,14-trimethyltetracyclo[8.3.1.0^{3,7}]tetradeca-3(7),10-diene-4,12-dione (3). A suspension of powdered sodium hydride (15 mg, 0.63 mmol, 98%) in rigorously dried DMSO (10 mL) was heated at 70 °C with stirring for 1 h. A solution of keto lactone **4** (12.5 mg, 0.045 mmol) in rigorously dried DMSO (2 mL) was added to this clear solution using a syringe pump over 4 h. The color of the solution initially became yellow, and after 2 h it was brown. After the addition was complete, the reaction mixture was heated at 90 °C for another 2 h. Saturated aqueous NH_4Cl (5 mL) was added, and heating was continued for an additional 1 h. The volume of the reaction mixture was reduced to ca. 4 mL by short-path vacuum distillation (35–60 °C/0.5 mmHg), and the residue was then allowed to cool to room

temperature. The residue was diluted with water (20 mL) and extracted with ether (5 × 30 mL). Standard workup afforded a crude yellow oil. Chromatography (hexane–ether (5:1)) afforded the desired 2(5*H*)-furanone **3** (5.9 mg, 0.023 mmol, 51%): IR ($CHCl_3$) 2929, 2853, 1752, 1696, 1620, 1613 cm^{-1}; ^1H NMR δ 1.06 (s, 3H), 1.21 (s, 3H), 1.40 (m, 1H), 1.75 (s, 3H), 2.18–2.35 (m, 2H), 2.46 (dd, J = 8.7, 5.7 Hz, 1H), 2.50–2.60 (m, 3H), 2.75 (br t, J = ca. 8 Hz, 2H), 4.40 (d, J = 13.2 Hz, 1H), 5.11 (d, J = 12.9 Hz, 1H); ^{13}C NMR δ 26.85, 28.38, 29.24, 30.50, 31.18, 34.14, 36.38, 38.47, 42.76, 68.60, 130.84, 139.44, 161.72, 166.24, 174.85, 197.01. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.76; H, 7.82.

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Supplementary Material Available: Discussion and experimental details (with ^1H NMR, ^{13}C NMR, and IR spectral data, and elemental analyses) for the formation of enones **9** and **10** and for the attempted preparation of chloro keto acid **i** from epoxy acetal **14** *via* allylic alcohol **iii** and allylic acetate **iv** (5 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 the ACS; see any current masthead page for ordering information.