Application of Enelike Reactions of Aldehydes with Vinyl Ethers: A Stereoconvergent Synthesis of (±)-Phyllanthocin

Marco A. Ciufolini,* Shuren Zhu, and Melissa V. Deaton

Department of Chemistry, MS 60, Rice University, 6100 Main Street, Houston, Texas 77251-1892

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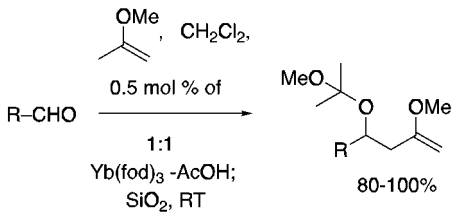
(±)-Phyllanthocin has been synthesized through a key step involving the enelike reaction of an aldehyde with 2-methoxypropene recently developed in these laboratories. This work demonstrates that our chemistry is suitable for multistep synthetic applications, and it shows that stereocontrol in the creation of the phyllanthocin structure may be achieved by thermodynamic equilibration of both peripheral stereogenic carbons.

We have recently disclosed that the 1:1 complex of $Yb(fod)_3$ and acetic acid (0.5 mol % or less) promotes an unusual enelike[1] reaction of ordinary aldehydes with those vinyl ethers that display the oxygen functionality at the central carbon of an allylic system, e.g., 2-methoxypropene (MP, Scheme 1).[2] This efficient, economical process occurs at room temperature, it requires no drastic measures to exclude air or moisture, it affords end-products in nearly quantitative yield and in high purity, and it may be easily conducted even on substantial scales.[3]

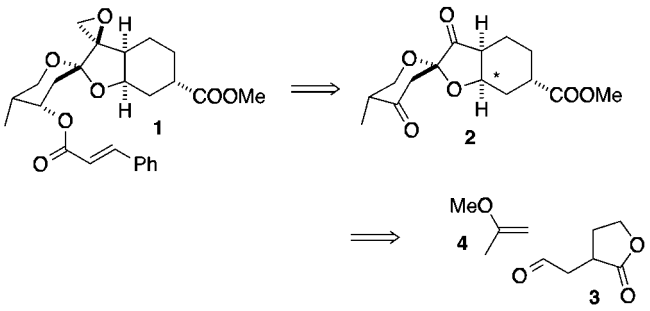
Much strategic and tactical opportunity arises as a result of this transformation. However, the potential that new methodology seems to hold *a priori* must be demonstrated in the context of a sensible synthetic exercise, because not all new preparative techniques may be capable to sustain the total synthesis of a molecule of at least medium complexity. This is especially true if such new techniques were needed at an early stage of a synthetic scheme, and indeed, new reactions are often demonstrated at a late stage of a synthetic route. Here, we describe a total synthesis of the racemate of the sesquiterpene, phyllanthocin, (±)-**1**, that utilizes this reaction as a key early step, thereby supporting the notion that the new chemistry is indeed suitable for multistep synthetic efforts.

Phyllanthocin is the methyl ester of the aglycon of the antitumor agent, phyllanthoside.[4] Both substances have elicited much attention in the synthetic arena.[5] A number of factors influenced our selection of **1** as a synthetic target. Previous syntheses of phyllanthocin had clearly revealed the difficulties associated with its deceptively simple structure and had underscored the requirement for rather sophisticated plans and techniques to build its molecular framework. As a result, a frank assessment of the power and potential of our enelike reaction would be possible. Also, phyllanthocin may surely be regarded as a molecule of medium complexity, and indeed, several published approaches to its framework have yet to be translated into a total synthesis. It thus seemed likely that the synthetic community may fully appreciate the value of a technique capable of delivering **1**.

Scheme 1



Scheme 2



With these goals in mind, we identified an advanced intermediate for **1** in the form of diketone **2** (Scheme 2), which may be envisioned to arise from the ene adduct of MP, **4**, with aldehyde **3**.[6] The starred stereogenic carbon in **2** is created through the ene process, and it is the sole nonepimerizable center in the entire molecule. At the same time, **2** displays the thermodynamic relative configuration of all stereocenters. Therefore, it seemed likely

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(1) The term "ene reaction" is used herein solely to describe the outcome of our transformation, which is more likely to be mechanistically related to Prins-type reactions. Nomechanistic implications exist in such usage.

(2) Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409.

(3) Cf. (a) Ciufolini, M. A. In *Advances in Heterocyclic Natural Products Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1996; vol. 3, p 1.

(4) Isolation: Kupchan, S. M.; LaVoie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

(5) Previous syntheses: (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. (b) Williams, D. R.; Sit, S. Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949. (c) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. (d) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420. (e) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (f) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071. (g) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1272. (h) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092. (i) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J. *J. Org. Chem.* **1987**, *52*, 3706. (j) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209. (k) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520. (l) Trost, B. M.; Kondo, Y. *Tetrahedron Lett.* **1991**, *32*, 1613. Synthetic Studies: (m) Linderman, R. J.; Viviani, F. G.; Kwochka, W. R. *Tetrahedron Lett.* **1992**, *33*, 3571. (n) Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576.

(6) Prepared in 59% overall yield by allylation of butyrolactone (LDA, THF, −78 °C, allyl bromide, 87%) followed by ozonolysis (O_3, 5:1 CH_2Cl_2/MeOH, −78 °C, then Me_2S) and chromatography (80% EtOAc/hexanes, 68%).

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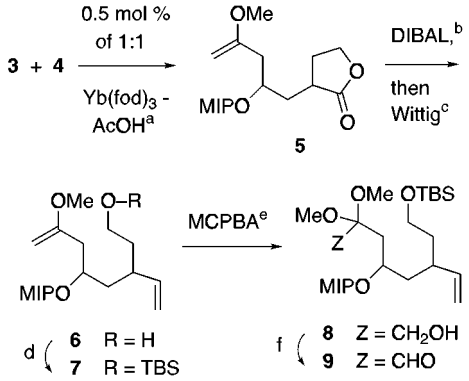
Scheme 3[a]

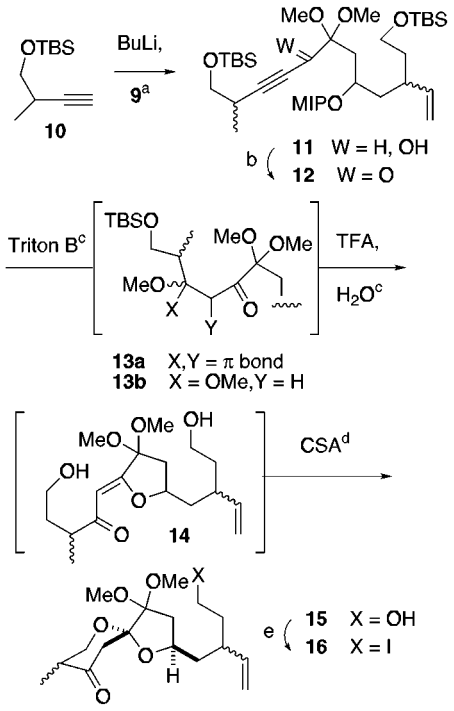


[a] (a) CH_2Cl_2, SiO_2, rt, 100%; (b) THF, −78 °C, 75%; (c) $Ph_3P{=}CH_2$, THF, rt, 79%; (d) TBS-Cl, imidazole, DMF, 0 °C, 96%; (e) 1.5 equiv; CH_2Cl_2, MeOH, K_2CO_3, 0 °C, 73%; (f) cat. TPAP, NMO, 4 Å mol sieves, CH_2Cl_2, rt, 100%. Overall 41% from **3** to **9** over six steps.

that the configuration of the starred carbon may be relayed through epimerization to the rest of the molecule,[7] in particular, to the methyl- and carbomethoxy-bearing stereocenters, thereby alleviating some of the issues presented by the stereocontrolled creation of **2**. This is in fact the case. A stereoconvergent synthesis of **2**/**1** was thus realized as follows.

Compound **5** (MIP = 2-methoxyisopropyl) emerged in 99% yield as a 1.5:1 mixture of unassigned diastereomers upon stirring a mixture of **3** and **4** in CH_2Cl_2 at room temperature in the presence of 0.2 mol % of catalyst. Notice that the presence of a lactone in **3** would probably disallow more traditional carbonyl-ene reactions.[8] For reasons that will be apparent shortly, adduct **5** was advanced to **6** through DIBAL reduction and Wittig methylenation. Silylation and treatment of the intermediate **7** with MCPBA in CH_2Cl_2/MeOH produced alcohol **8** (73%), which was oxidized to aldehyde **9** (*N*-methylmorpholine *N*-oxide ["NMO"]/cat. tetrapropylammonium perruthenate ["TPAP"], Scheme 3). The Li acetylide prepared from **10** added readily to **9** (Scheme 4), and the emerging carbinol **11** was oxidized (TPAP, 89% overall) to ynone **12**. Exposure to Triton B resulted in conjugate addition of MeOH to give a mixture of compounds **13a** and **13b**, which, without further purification, were subjected to acid-catalyzed spirocyclization to **15**.[9] It became clear later that compound **15** had arisen as a mixture of diastereomers that were epimeric at the level of the methyl and the vinyl groups, but that displayed substantially only the thermodynamic configuration of the spirocenter. This relative configuration is probably controlled by the preference of the tetrahydrofuran for the *cis* 2,5-dialkyl arrangement and by an

Scheme 4[a]



[a] (a) −78 °C, 30 min; (b) cat. TPAP, NMO, 4 Å mol sieves, CH_2Cl_2, rt, 89% a-b; (c) i. Triton B, MeOH, rt, 2 h, then ii. TFA, H2O, THF, rt, 1 h, 62%; (d) CSA, CH_2Cl_2, rt, 10 h, 71%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, then NaI, acetone, reflux, 78%. Overall 31% from **9** to **16** over six steps.

anomeric effect at the level of the pyranone unit that favors the placement of the furan oxygen at the axial position.

While exposure to DBU caused equilibration of **15** to the methyl-equatorial diastereomer, we found that this operation was best postponed. Accordingly, the free OH in **15** was converted into an iodide in preparation for ketal hydrolysis and base-promoted cyclization to a tricyclic intermediate. This latter step could not be effected cleanly when the ring C ketone was present, necessitating an intermediate $NaBH_4$ reduction of **16** to a carbinol, which fortunately required no protection. It is worthy of note that this reduction proceeded stereoselectively to give the axial alcohol **17** through equatorial delivery of hydride, in contrast with the normal behavior of $NaBH_4$. Seemingly, approach of the reducing agent to the carbonyl group from the normally more favorable axial trajectory is impeded due to molecular shape. A similar phenomenon was observed earlier and confirmed by us during reduction of late intermediate **2**. Base treatment of **17** provided exclusively the *cis*-fused isomer of tricyclic intermediate **18**, which was oxidized to **19** with RuO_4 (Sharpless conditions)[10] and esterified to a an essentially 1:1:1:1 mixture of diastereomers of **2**, described in Scheme 5 as compound **20**. The tandem oxidative cleavage of the vinyl group/carbinol oxidation was not as efficient as previously observed in simpler model compounds (cf. Scheme 8). Compensating for the disappointing yield of this step, exposure of **20** to DBU caused equilibration of the two peripheral stereogenic centers to the thermodynamic relative configuration, as apparent from a change in the isomer ratio to a substan-

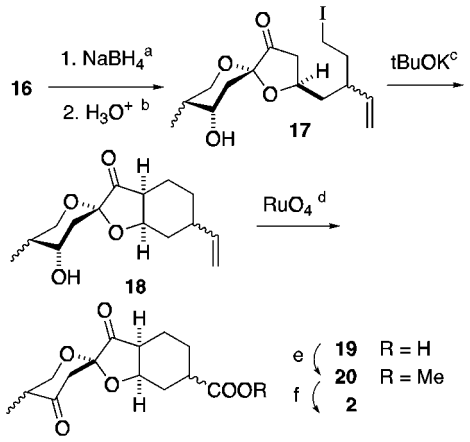
(7) This principle had been partly validated during earlier synthetic work on **1**, particularly with respect to the stereochemistry of the spiroacetal, but not for entirestereochemical array of **2**, as shown here.

(8) For outstanding reviews see: (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, Springer-Verlag: Berlin, Germany, 1986. (b) Santelli, M; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996; Ch. 2. Fortunately, our enelike reaction tolerates a good range of spectator functionality. Recent example of carbonyl-ene reaction in terpene synthesis and bibliography: Snider, B. B.; Vo, N. H.; O'Neil S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.

(9) Theoretically, an intermediate of the type **13** could have been prepared starting with addition of the kinetic enolate of 3-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-butanone to **9**. However, reaction of this enolate with **9** proceeded poorly, while addition to simple aldehydes was uneventful. The reasons for this remain unclear.

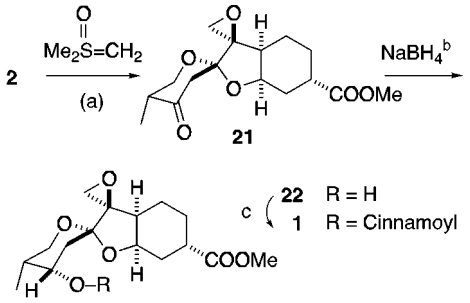
(10) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

Scheme 5[a]



[a] (a) MeOH, −10 °C; (b) HCOOH, rt, 1 h, 96% a−b; (c) tBuOK, THF, 0 °C; (d) 5 mol % $RuCl_3 \cdot 3H_2O$, 2 equiv of KIO_4, CCl_4:MeCN:H_2O (2:2:3) 35% c−d; (e) MeI, K_2CO_3, DMF, rt, 2 h; (f) DBU, THF, rt, 12 h, 60% e−f. Overall 20% from **16** to **2** over six steps.

Scheme 6[a]

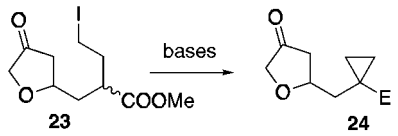


[a] (a) DMSO, rt; (b) MeOH, 0 °C, 76% a−b; (c) PhCH=CHCOCl, 4-DMAP, CH_2Cl_2, rt, 71%. Overall 54% from **2** to (±)-**1** over three steps, 1.4% from **3** to (±)-**1** over 21 steps.

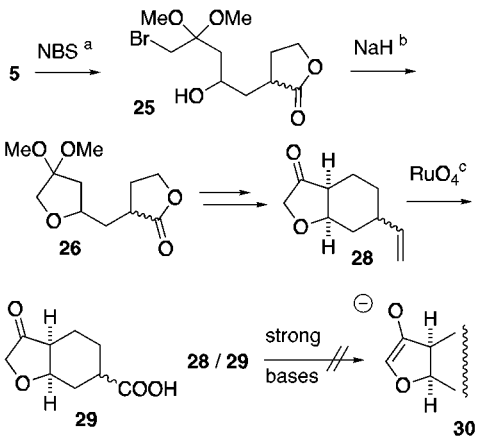
tial 1:45:2.5:1.5 in favor of the most energetically favorable **2**.[11] This intermediate was readily advanced to (±)-phyllanthocin by minor permutations/modifications of known procedures. Thus, reaction of **2** with the Corey−Chaykowsky ylide[12] proceeded efficiently to afford furanone epoxide **23**. The high degree of chemoselectivity observed in this reaction may be attributed to increased electrophilicity of the furanone vs the pyranone carbonyl, as a result of an inductive effect generated by the pair of spiroacetal oxygen substituents at the furanone α-position. The elevated stereoselectivity appears to be a consequence of molecular shape: the sulfur ylide attacks preferentially from the convex face of the strongly puckered molecule of **2**. Molecular shape is also likely to be responsible for selective formation of axial carbinol **22** upon reduction of pyranone **21** with $NaBH_4$ (12:1 diastereoselectivity).[13] Finally, cinnamoylation of **22** afforded fully synthetic (±)-**1**, mp 113−115 °C (Scheme 6).

In closing, it seems worthwhile to recount some important early observations that ultimately led to the formulation of the successful route to phyllanthocin

Scheme 7



Scheme 8[a]



[a] (a) MeOH, CH_2Cl_2, 0 °C; (b) THF−tBuOH, rt, 67% a−b; (c) cat. $RuCl_3$, KIO_4, aqueous MeCN, CCl_4, 56%.

described above. First, conversion of **5** to **7** was dictated by the propensity of model analogues of **17** wherein an ester was present in lieu of the vinyl group, e.g., **23**, to produce only cyclopropanes **24** upon base treatment under a variety of conditions (Scheme 7). This forced conversion of the ester to an alternative functionality. Consideration of overall efficiency, as well as precedent,[5a] induced us to select a vinyl unit as a latent ester group.

We also explored perhydrobenzofuranone **28** and **29** as alternative advanced intermediates for **1**. The route to these compounds also relies on our ene reaction, as briefly outlined in Scheme 8. It was hoped that formation of a kinetic enolate of the type **30** from **28** or **29** would allow connection of a forerunner to the spirocyclic segment of **1**. Unfortunately, enolization of **28**/**29** in a controlled manner was found to be extremely problematic. In particular, **28** displayed a strong inclination to undergo self-aldolization, carbonyl reduction even under Corey−Gross conditions,[14] and a miscellany of other complex transformations. While these difficulties were not entirely unexpected for an α-alkoxy ketone such as **28**,[5m,15] their gravity bordered on the extreme, and it seriously undermined our attempts to connect the future spiroacetal moiety by aldol-type operations.

Both **28** and **29** condensed in a satisfactory manner with aromatic aldehydes under aqueous basic conditions, whereupon an enolate of the type **30** presumably forms reversibly and in minute concentrations. However, nonenolizable *aliphatic* aldehydes suitable for delivery of the spiroacetal moiety of **1**, e.g., **31** and **32**, produced exceedingly poor results in this reaction. Isoxazole aldehyde **33**, a carrier of a latent variant of the desired spiro group, condensed efficiently with **29**, but the resultant **34** resisted reductive ring cleavage with $Mo(CO)_6$[16] under mild conditions, whereas more forcing conditions pro-

(11) This ratio was determined by scrutiny of the ^1H NMR spectra of **20** and **2**, hardcopies of which are provided as Supporting Information.

(12) Corey, E. J.; Chaykowsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

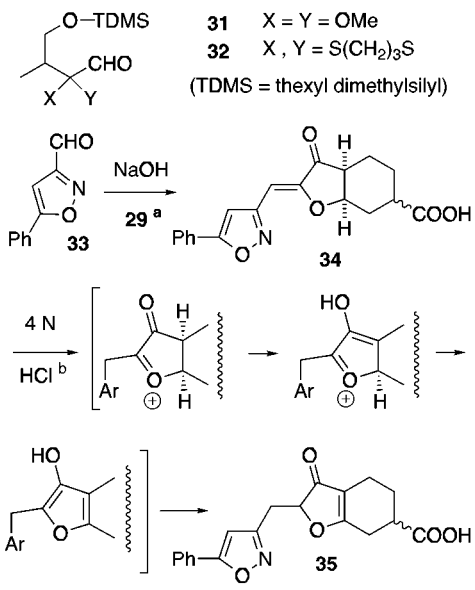
(13) While $NaBH_4$ is normally selective for the equatorial alcohol in reduction of six-membered cyclic ketones, a well-documented steric effect is responsible for the opposite selectivity in the present system (ref. 5).

(14) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(15) An excellent survey of the unpredictable behavior of α-alkoxy ketones toward enolate formation may be found in: Gleave, D. M. Doctoral Dissertation, University of Saskatchewan, 1993.

(16) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877.

Scheme 9[a]



[a] (a) Aqueous EtOH, rt, 90%; (b) EtOH, reflux, 91%.

moted complex reactions. Attempted hydration of the enone double bond in **34** with aqueous acid induced instead an interesting rearrangement to furanone **35**, wherein the enone double bond has formally migrated to a remote position inside the furanoid ring. We propose the mechanism of Scheme 9 to account for this noteworthy rearrangement. Fortunately, the merger of the future spiro and bicyclic units by the method detailed in Scheme 4 resolved all such difficulties.

In summary, this work demonstrates the viability of our enelike methodology in the synthesis of at least moderately complex organic structures.[17] Even in terms of length (23 linear steps from butyrolactone as the longest linear sequence), the present synthesis is comparable to several known alternatives (only the Burke synthesis[5c] is significantly shorter), but it starts with structurally simpler materials. This provides an indication of the synthetic potential of our enelike reaction, further applications of which will be described in due course.

Experimental Section[18]

Aldehyde 3. BuLi (2.5 M in hexane, 42 mL, 105 mmol) was added to a cold (−78 °C) solution of iPr_2NH (10.6 g, 105 mmol) in THF (200 mL, Ar). After 30 min, γ-butyrolactone (9.04 g, 105 mmol) was added. Stirring at −78 °C was continued for 45 min before addition of allyl bromide (12.7 g, 105 mmol). The reaction mixture was warmed to −20 °C, quenched with saturated aqueous $NaHCO_3$, and extracted (EtOAc). The combined extracts were dried (Na_2SO_4) and concentrated to give 11.5 g of 2-allylbutyrolactone as a colorless oil. Ozonized oxygen was bubbled through a cold (−78 °C) solution of this material in CH_2Cl_2 (150 mL) and MeOH (20 mL) containing 1.5 g of powdered $NaHCO_3$. When the reaction was completed (TLC), Me_2S (7.5 mL) was added, and the mixture was warmed to rt, washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (40% EtOAc/hexanes) to give 7.12 g (53% over two steps) of **3**, colorless, viscous oil. ^{1}H: 9.78 (t, 1H, J = 0.4 Hz), 4.38 (dt, 1H, J = 15.9, 1.9 Hz), 4.23 (ddd, 1H, J = 15.9, 2.3, 6.5 Hz), 3.06 (ddt, 1H, J = 18.7, 3.7, 0.4 Hz), 2.95 (m, 1H), 2.69 (ddt, 1H, J = 18.7, 8.2, 0.4 Hz), 2.53 (m, 1H), 1.90 (m, 1H). ^{13}C: 199.1, 178.6, 66.9, 44.2, 33.9, 28.8. IR: 3422, 1761, 1718. MS (CI): 129 (MH^+). HRMS (CI): calcd for $C_6H_9O_3$ 129.0552 (MH^+). Found 129.0551.

Ene Product 5. Silica gel (1 g) was added to a mixture of aldehyde **3** (6.5 g, 51 mmol), 2-MP (**4**, 30 mL, 6 equiv), CH_2Cl_2 (60 mL), AcOH (10 μL, 0.2 mol %), $Yb(fod)_3$ (100 mg, 0.2 mol %). After stirring at rt for 10 h, the mixture was diluted with Et_2O (200 mL), washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated to give 13.9 g (100%) of **5**, light yellow oil, 1.5:1 mixture of unassigned diastereomers. ^{1}H (C_6D_6): 4.33 (m, 1H), 4.14 (m, 1H), 3.97 (m, 1H), 3.92 (d, 1H, J = 1.7 Hz), 3.85 (d, 1H, J = 1.7 Hz), 3.70 (m, 1H), 3.52 (m 1H), 3.20 (s, 3H), 3.00 (s, 3H),2.72- 2.10 (m, 3H), 1.60 (m, 2H), 1.30 (s, 6H). ^{13}C (C_6D_6): 179.5, 161.9, 101.4, 84.1, 68.4, 66.5, 55.0, 49.4, 42.4, 36.8, 36.3, 30.6, 25.8, 25.6. IR: 1773, 1653. MS (CI): 273 (MH^+), 255, 241, 183, 73. HRMS (CI): calcd for $C_{14}H_{25}O_5$: 273.1702 (MH^+), obsd 273.1695.

Wittig Product 6. DIBAL (1.5 M in toluene, 28.7 mL, 43 mmol) was added to a solution of **5** (10.5 g, 38.6 mmol) in 150 mL dry THF at −78 °C. Stirring was continued for 1 h, and then MeOH was added dropwise until bubbling stopped (**CAUTION**: flammable gases released). The mixture was diluted with Et_2O (400 mL), washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated. Chromatography (50% EtOAc/hexanes) gave 7.9 g (75%) of the lactol, colorless oil. ^{1}H (C_6D_6): 5.37 (m, 1H), 4.25 (m, 2H), 4.05 (m, 1H), 3.98 (d, 1H, J = 2.1 Hz), 3.85 (d, 1H, J = 2.1 H), 3.77 (m, 1H), 3.68 (m, 1H), 3.20 (s, 3H), 3.13 (s, 3H), 2.80 (m, 1H), 2.44−1.70 (m, 4H), 1.38 (s, 3H), 1.27 (s, 3H). ^{13}C (C_6D_6): 162.3, 104.2, 101.5, 99.2, 83.2, 69.3, 67.2, 54.8, 49.4, 43.7, 42.4, 35.0, 25.80, 25.75 ppm. IR: 3410, 1671. MS (CI): 257 ($MH^+ - H_2O$), 225, 185, 167, 141, 113, 73. HRMS (CI): calcd for $C_{14}H_{25}O_4$: 257.1753 ($MH^+ - H_2O$), obsd 257.1745. BuLi (2.5M in hexane, 24 mL, 60 mmol) was added to a suspension of $Ph_3PMe^+ I^-$ (23.6 g, 58.5 mmol) in THF (150 mL) at 0 °C, followed, 30 min later, by a solution of lactol (5.34 g, 19.5 mmol) in THF (35 mL). After stirring for 1 h, the mixture was diluted with ether (250 mL), washed with H_2O (150 mL), dried (Na_2SO_4), and concentrated. The residue was treated with petroleum ether (200 mL), the precipitate was filtered off, and the solution was concentrated. Chromatography gave 4.2 g (79%) of alcohol **6**, colorless oil. ^{1}H: 5.61 (m, 1H), 5.07 (m, 2H), 4.00 (m, 1H), 3.93 (d, 1H, J = 1.9 Hz), 3.89 (d, 1H, J = 1.9 Hz), 3.66 (m, 2H), 3.49 (s, 3H), 3.23 (s, 3H), 2.65 (dd, 1H, J = 13.5 and 4.3 Hz), 2.37 (dd, 1H, J = 14.1 and 5.7 Hz), 2.29 (dd, 1H, J = 14.1 and 5.3 Hz), 2.24 (dd, 1H, J = 13.5 and 4.7 Hz), 1.65−1.56 (m, 3H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C: 161.5, 142.7, 115.1, 101.1, 82.9, 67.7, 60.9, 54.7, 49.3, 41.3, 40.9, 38.0, 37.7, 25.3, 25.2. IR: 3406, 1658. MS (CI): 255 ($MH^+ - H_2O$), 241, 223, 209, 183, 151, 113, 73. HRMS (CI): calcd for $C_{15}H_{27}O_3$ ($MH^+ - H_2O$) 255.1960, obsd 255.1955. Anal. Calcd for $C_{15}H_{28}O_4$: C 66.14%, H 10.36%, Found: C 65.92%, H 10.34%.

Silyl Ether 7. A cold (0 °C) solution of **3** (4.2 g, 15.4 mmol), imidazole (4.2 g, 62 mmol), and TBDMSCl (2.6 g, 16.9 mmol) in 30 mL of DMF was stirred for 30 min, and then it was diluted with ether (100 mL) and washed with H_2O. The ether layer was dried (Na_2SO_4) and concentrated to a colorless oil, 5.7 g, 96% yield. ^{1}H: 5.56 (m, 1H), 5.02 (m, 2H), 4.21 (m, 2H), 3.99 (d, 1H, J = 1.5 Hz), 3.86 (d, 1H, J = 1.5 Hz), 3.59 (m, 2H), 3.21 (s, 3H), 3.14 (s, 3H), 2.89 (dd, 1H, J = 13.5 and 4.4 Hz), 2.59 (dd, 1H, J = 13.7 and 6.8 Hz), 2.37 (dd, 1H, J = 13.7 and 6.8 Hz), 2.22 (dd, 1H, J = 13.5 and 9.0 Hz), 1.42−1.35 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.91(s, 9H), 0.04 (s, 6H). ^{13}C: 162.6, 143.6, 115.3, 101.3, 83.1, 69.1, 61.4, 54.7, 49.3, 42.8, 41.9, 39.3, 37.9, 26.5, 26.1, 26.0, 18.9, −4.72 ppm. IR: 1652. MS (CI): 355 ($MH^+ - CH_3OH$), 297, 257, 165, 89. HRMS (CI): calcd for $C_{20}H_{39}O_3Si$ ($MH^+ - CH_3OH$) 355.2669, found 355.2663.

(17) For an asymmetric variant of this chemistry see: Carreira, E.; Lee, W.; Singer,R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

(18) Unless otherwise indicated: (a) NMR spectra (ppm, δ, ^{1}H = 250; ^{13}C = 62.5 MHz, 25 °C) were recorded in $CDCl_3$. Splitting: "s" (singlet), "d", "dd", etc. (doublet, doublet of doublets, etc.), "t" (triplet), "q" (quartet), "m" (multiplet), "app" (apparent), "br" (broad), or "c" (complex). (b) FTIR spectra (cm^{-1}) were obtained from films on NaCl plates. (c) Low and high res mass spectra (*m/e*) were obtained in the CI (CH_4) or EI (70 eV) mode. All sensitive reactions were carried out under Ar. MeOH: dried over 4 Å mol sieves; EtOAc, MP: dist at atm. press; CH_2Cl_2, Et_3N, iPr_2NH: dist from CaH_2 at atm press.; THF: dist from Na/Ph_2CO. Elemental analyses were performed by Galbraith-Laboratories, Knoxville, TN.

Anal. Calcd for $C_{21}H_{42}O_4Si$: C 65.24%, H 10.95%. Found: C 65.31%, H 10.90%.

Alcohol 8. Purified MCPBA (2.3 g, 13.5 mmol) in CH_2Cl_2 (7 mL) was added to a cold (0 °C) mixture of silyl ether **7** (3.5 g, 9 mmol), powdered K_2CO_3 (200 mg), dry MeOH (5 mL), and CH_2Cl_2 (20 mL). After 2 h of vigorous stirring, the mixture was diluted with CH_2Cl_2 (50 mL), washed (1 N aqueous NaOH), dried (Na_2SO_4), and concentrated. Chromatography gave 2.85 g (73%) of **8** as a colorless oil. ^{1}H: 5.50 (m,1H), 5.05 (m, 2H), 4.12 (m,1H), 3.90 (dd, 1H, J = 12.0 and 9.5 Hz), 3.76 (dd, 1H, J = 12.0 and 5.3 Hz), 3.63 (m, 2H), 3.19 (s, 3H), 3.12 (s,3H), 3.03 (s,3H), 2.19−1.93 (m, 4H), 1.77−1.38 (m, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C: 142.0, 115.7, 101.9, 101.4, 68.4, 62.4, 60.6, 49.0, 48.1, 40.0, 38.8, 37.9, 37.5, 36.7, 26.0, 25.4, 25.2, 18.3, −5.22. IR: 3462, 1638. MS (EI): 403 ($MH^+ - CH_3OH$), 331, 313, 255, 185, 155, 129, 73. HRMS (EI): calcd for $C_{21}H_{43}O_5Si$ ($MH^+ - CH_3OH$) 403.2880, obsd 403.2876. Anal. Calcd for $C_{22}H_{46}O_6Si$: C 60.79%, H 10.67%. Found: C 60.63%, H 10.63%.

Aldehyde 9. Alcohol **8** (3.5 g, 8.1 mmol) in CH_2Cl_2 (10 mL) was added at rt to a slurry of NMO (1.9 g, 16.1 mmol), TPAP (100 mg, 0.3 mmol), and 4 Å mol sieve (1.8 g) in CH_2Cl_2 (100 mL). After stirring for 2 h, the mixture was filtered (Celite) and concentrated. The resulting dark oil was treated with hexane (30 mL), and the dark ppt was filtered off. Concentration of the filtrate gave 3.5 g (100%) of the sensitive aldehyde, light yellow oil. ^{1}H (C_6D_6): 9.29 (s, 1H), 5.39 (m, 1H), 4.94 (m,2H), 3.88 (m, 1H), 3.53 (m, 2H), 3.12 (s, 3H), 3.03 (s, 3H), 3.02 (s, 3H), 2.19−1.91 (m, 4H), 1.59−1.24 (m, 3H), 1.38 (3, 3H), 1.18 (s, 3H), 0.93 (s, 1H), 0.01 (s, 6H). ^{13}C (C_6D_6): 197.1, 142.9, 115.8, 101.9,101.6, 67.6, 60.9, 50.1, 48.9, 48.8, 40.6, 39.6, 38.7, 38.3, 26.5, 25.6, 25.3, 18.8, −4.9. IR: 1751, 1669. MS (CI): 401 ($MH^+ - CH_3OH$), 375, 343, 311, 179, 115, 73. HRMS (CI): calcd for $C_{21}H_{41}O_5Si$ ($MH^+ - CH_3OH$) 401.2723, obsd 401.2715. Anal. Calcd for $C_{22}H_{44}O_6Si$: C 61.07%, H 10.25%. Found: C 61.40%, H 10.10%.

Alkyne 10. A solution of commercial 2-methyl-1,3-propanediol (8.1 g, 90 mmol), TBDMS-Cl (13.6 g, 90 mmol), and imidazole (6.8 g, 100 mmol) in DMF (80 mL) was stirred at 0 °C for 30 min and then it was diluted with ether (250 mL), washed with water, dried (Na_2SO_4), and concentrated. Chromatography (10% EtOAc/hexane) gave 8.6 g (47% yield, colorless oil) of the mono-TBS ether derivative. This material (8.5 g, 42 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with PDC (23.5 g, 1.5 equiv) at rt. After 4 h, the mixture was filtered and concentrated, and the residue was chromatographed (20% EtOAc/hexane) to give 6.9 g (81% yield, colorless oil) of the expected aldehyde. A solution of this aldehyde in CH_2Cl_2 (20 mL) was introduced into a cold (0 °C) preformed slurry of Corey−Fuchs reagent, which had been prepared by the addition of a solution of CBr_4 (22.7 g, 68.4 mmol) in CH_2Cl_2 (40 mL) into a cold (0 °C) suspension of Zn powder (4.5 g, 68.7mmol) and Ph_3P (17.9g, 68.3 mmole) in CH_2Cl_2 (200 mL), followed by stirring for 20 min. The reaction mixture was stirred at rt for 1 h, and then it was poured into petroleum ether (1 L), filtered to remove the precipitate, and concentrated to give the dibromo olefin (oil). A cold (−78 °C) solution of this oil in THF (60 mL) was treated with BuLi (2.5 M in hexane, 28 mL, 70 mmol), and after 30 min the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The ether extract was concentrated and the residue chromatographed (100% hexane) to give 4.3 g (63% over two steps) of alkyne **10** as a colorless oil. ^{1}H: 3.70 (dd, 1H, J = 9.5, 5.3 Hz), 3.46 (dd, 1H, J = 9.5, 7.1 Hz), 2.56 (m, 1H), 2.03 (d, 1H, J = 2.4 Hz), 1.18 (d, 1H, J = 6.7 Hz), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C: 86.6, 69.2, 67.3, 29.2, 26.1, 18.5, 17.4, −5.2.

Ynone 12. BuLi (2.5 M in hexane, 1.0 mL, 2.5 mmol) was added to a cold (−78 °C) solution of alkyne **10** (464 mg, 2.34 mmol) in THF (5 mL, Ar). After stirring for 20 min, a solution of aldehyde **9** (714 mg, 1.65 mmol) in THF (3 mL) was added, and after 1 h, the reaction was quenched (saturated aqueous $NaHCO_3$) and extracted with EtOAc. The extracts were dried (Na_2SO_4) and concentrated, and the crude alcohol **11** was submitted to TPAP oxidation using the same protocol described above for **8**. Chromatography (20% EtOAc/hexanes) provided 920 mg (89% over two steps) of ynone **12**, colorless oil. ^{1}H: 5.56 (m,1H), 5.05 (m, 2H), 4.08 (m, 1H), 3.62−3.55 (br, 4H), 3.19 (s, 3H), 3.17 (s, 3H), 3.10 (s, 3H), 2.76−2.52 (m, 2H), 2.37−1.97 (m, 3H), 1.78−1.55 (m, 3H), 1.59 (s, 3H), 1.44 (s, 3H), 1.11 (d, 3H, J = 5.4 Hz), 0.99 (s, 9H), 0.03 (s, 6H). ^{13}C: 183.4, 143.1, 115.8, 103.1, 102.1, 96.4, 82.2, 67.7, 66.9, 61.2, 50.0, 49.4, 48.8, 41.3, 39.6, 39.3, 38.4, 30.3, 26.51, 26.47, 25.13, 25.10, 18.8, 16.9, 14.6, −4.8, −4.9. IR: 2220, 1689. MS (CI): 597 ($MH^+ - CH_3OH$), 555, 539, 403, 313, 185, 73. HRMS (CI): calcd for $C_{32}H_{61}O_6Si_2$ ($MH^+ - CH_3OH$) 597.4007, obsd 597.3997.

Spiroketal 15. A mixture of ynone **12** (145 mg, 0.23 mmol), MeOH (4 mL), and benzyltrimethylammonium hydroxide ("Triton B", 40 wt % in MeOH, 1.2 equiv) was stirred at rt for 10 h, and then it was diluted with ether (25 mL) and washed (H_2O). The ether layer was dried (Na_2SO_4) and concentrated, and the crude product **13** was dissolved in THF (3 mL)/water (1.2 mL). Neat TFA (0.7 mL) was slowly added, and 2 h later the mixture was neutralized (saturated aqueous $NaHCO_3$) and extracted (CH_2Cl_2). The extracts were dried (Na_2SO_4) and concentrated to give 47 mg (62% over two steps) of diol **14**. To a solution of this diol in dry CH_2Cl_2 (4 mL) was added CSA (5 mg). After 12 h at rt, the mixture was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated to give 34 mg (71%) of **15**. ^{1}H: 5.54 (m, 1H), 5.01 (m, 2H), 4.10−3.98 (m, 2H), 3.74−3.59 (m, 3H), 3.38 (s, 3H), 3.23 (s, 3H), 2.87−2.35 (m, 4H), 2.16 (m, 1H), 1.78−1.46 (m, 5H), 0.98 (d, 3H, J = 6.6 Hz). ^{13}C: 207.0, 141.9, 116.1, 108.8, 106.9, 74.8, 73.1, 65.5, 60.9, 50.5, 49.4, 47.2, 44.7, 38.4, 37.9, 36.0, 9.2. IR: 3458, 2936, 1717, 1454, 1387, 1325, 1287, 1173, 130, 1063, 982, 920. MS (EI): 297 ($MH^+ - CH_3OH$), 265, 200, 185, 155, 127, 115, 101, 88. HRMS (EI): calcd for $C_{16}H_{25}O_5$ ($MH^+ - CH_3OH$) 297.1702, obsd 297.1695.

Furanone 17. To a cold (0 °C) solution of **15** (135 mg, 0.41 mmol) and Et_3N (280 μL, 5 equiv) in CH_2Cl_2 (7 mL) was added MsCl (40 μL, 1.2 equiv). After 30 min, the mixture was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated. The crude mesylate and NaI (200 mg, 1.3 mmol) in acetone (10 mL) was refluxed for 7 h and then cooled, filtered (Celite), and partitioned between ether (20 mL) and water (10 mL). The ether layer was dried (Na_2SO_4) and concentrated. Flash chromatography gave 138 mg (78% over two steps) of iodide **16**. ^{1}H: 5.40 (m, 1H), 5.09 (m, 2H), 4.04−3.97 (m, 2H), 3.77−3.72 (m, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.20 (m, 1H), 3.07 (m, 1H), 2.65 (m, 2H), 2.47−2.37 (m, 2H), 2.11 (m, 1H), 1.90−1.61 (m, 5H), 0.99 (d, 3H, J = 6.5 Hz). ^{13}C: 206.9, 140.1, 116.7, 108.0, 107.0, 74.6, 65.5, 50.6, 49.4, 47.2, 44.9, 42.6, 38.8, 38.6, 36.0, 9.2, 4.6. IR: 1729. MS (EI): 407 ($MH^+ - CH_3OH$), 386, 371, 330, 197, 183, 115, 101. HRMS (EI): calc for $C_{16}H_{24}O_4I$ ($MH^+ - CH_3OH$) 407.0719, found 407.0712. Powdered $NaBH_4$ (50 mg, 1.3 mmol) was added to a cold (0 °C) solution of **16** (113 mg, 0.26 mmol) in MeOH (5 mL) and THF (0.5 mL). After 30 min, the reaction was quenched (saturated aqueous NH_4Cl) and extracted (EtOAc). The extracts were dried (Na_2SO_4) and concentrated. The crude product was dissolved in HCOOH (0.8 mL). After 1 h, the solution was neutralized (saturated aqueous $NaHCO_3$) and extracted (CH_2Cl_2). The extracts were dried (Na_2SO_4) and concentrated to give 100 mg (96% over two steps) of furanone **17**, colorless oil. ^{1}H: 5.50 (m, 1H), 5.15 (m, 2H), 4.47 (m, 1H), 3.89 (m, 1H), 3.83−3.61 (m, 2H), 3.27 (m, 1H), 3.07 (m, 1H), 2.69−2.58 (m, 1H), 2.49−2.39 (m, 1H), 2.28 (m, 1H), 2.08−1.72 (m, 7H), 0.95−0.90 (m, 3H). ^{13}C: 207.2, 140.1, 117.3, 98.9, 73.8, 67.5, 62.4, 42.5, 40.1, 39.2, 38.1, 35.1, 35.4, 13.3, 4.7. IR: 1762, 1649. MS (EI): 395 (MH^+), 377, 366, 294, 263, 236, 195, 154, 131, 109. HRMS (EI): calcd for $C_{15}H_{22}O_3I$ ($MH^+ - H_2O$) 377.0614, obsd 377.0608. Anal. Calcd for $C_{15}H_{23}O_4I$: C 45.70%, H 5.88%. Found C 45.94%, H 5.92%.

Diketo Ester 2. A THF solution of t-BuOK (67 mg, 0.60 mmol) was added to a cold (0 °C) solution of furanone **17** (80 mg, 0.20 mmol) in THF (4 mL, Ar atm). After 30 min, the reaction was neutralized (saturated aqueous NH_4Cl) and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated, and the crude tricyclic compound **18** was dissolved in a mixture of CCl_4 (2 mL), CH_3CN (2 mL), H_2O (3 mL), KIO_4 (150 mg, 3 equiv), and $RuCl_3$ (3 mg, 0.05 equiv). This biphasic mixture was stirred vigorously for 2 h at rt, and then it was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to give 20 mg (35% over two steps)

of acid **19**. A mixture of this crude acid (14 mg, 0.05 mmol), THF (0.5 mL), powdered K_2CO_3 (10 mg), and MeI (12 μL, 4 equiv) was stirred at rt for 4 h, and then it was diluted with ether (5 mL), washed with H_2O, dried (Na_2SO_4), and concentrated to give a mixture of four diastereomers of **2**. A solution of this material and DBU (50 μL) in 1 mL of dry THF was stirred overnight, and then it was diluted with EtOAc, washed (saturated aqueous NH_4Cl), and concentrated. Prep TLC provided 9 mg (60% over two steps) of diketo ester **2**. ^{1}H: 4.54 (m, 1H), 4.01 (dd, 1H, J = 11.1 and 7.2 Hz), 3.79 (dd, 1H, $J_1 = J_2$ = 11.1 Hz), 3.70 (s, 3H), 3.01 (d, 1H, J = 14.5 Hz), 2.83−2.74 (m, 2H), 2.60−2.46 (m, 3H), 2.35 (d, 1H, J = 14.5 Hz), 2.04−1.71 (m, 4H), 1.03 (d, 3H, J = 6.6 Hz). ^{13}C: 208.2, 205.2, 175.7, 102.9, 72.1, 66.8, 52.1, 46.2, 45.0, 42.4, 36.7, 29.2, 26.3, 23.2, 9.3. IR: 1766, 1723. MS: 296 (M^+), 265, 185, 140, 111. HRMS (EI): calcd for $C_{15}H_{20}O_6$ 296.1260, obsd 296.1252. Anal. Calcd for $C_{15}H_{20}O_6$: C 60.80%, H 6.80%. Found C 60.71%, H 6.80%.

(±)−Phyllanthocin 1. To a solution of ester **2** (5 mg, 17 μmol) in DMSO (0.3 mL) was added a solution of dimethyloxosulfonium methylide in DMSO (1.2 equiv). After 15 min, the mixture was quenched (saturated aqueous NH_4Cl) and extracted with ether (10 mL). The extracts were washed with water, dried (Na_2SO_4), and concentrated. A cold (0 °C) solution of the resulting crude epoxide **21** in MeOH (1 mL) and THF (0.1 mL) was treated with powdered $NaBH_4$ (5 mg, 0.13 mmol), and after 30 min, it was quenched with saturated aqueous NH_4Cl and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to give 4 mg (76% over two steps) of alcohol **22**. A solution of this alcohol in 2 mL of CH_2Cl_2 containing DMAP (10 mg, 6 equiv) and cinnamoyl chloride (7 mg, 3 equiv) was refluxed for 4 h and then washed (H_2O) and concentrated. Preparative TLC provided and recrystallization (1:9 ether/hexane) gave a 71% yield of (±)-phyllanthocin, colorless prisms, mp 113−115 °C. ^{1}H: 7.77 (d, 1H, J = 15.9 Hz), 7.56−7.52 (m, 2H), 7.40−7.36 (m, 3H), 6.49 (d, 1H, J = 15.9 Hz), 5.09 (br q, 1H, J = 2.7 Hz), 4.39 (dd, 1H, J = 6.5 and 3.8 Hz), 4.02 (dd, 1H, $J_1 \approx J_2$ = 11.3 Hz), 3.45 (dd, 1H, J = 11.3 and 4.5 Hz), 3.28 (s, 3H), 2.95 (AB q, 2H, J = 13.2 and 5.4 Hz), 2.42 (tt, 1H, J = 11.9 and 3.4 Hz), 2.23 (br d, 1H, J = 14.5 Hz), 2.04 (dd, 1H, J = 15.2 and 2.8 Hz), 1.98−1.85 (m, 2H), 1.72 (ddd, 1H, J = 3.6, 12.3, 14.7 Hz), 1.63 (dd, 1H, J = 15.3 and 3.2 Hz), 1.60−1.37 (m, 2H), 1.33−1.19 (m, 2H), 0.88 (d, 3H, J = 7.0 Hz). ^{13}C: 176.1, 166.9, 144.5, 134.8, 130.0, 128.8, 128.0, 118.9, 101.9, 72.7, 71.1, 70.0, 63.4, 51.2, 50.2, 38.7, 37.0, 34.4, 33.1, 26.5, 22.4, 12.8. IR: 1736, 1709, 1643. MS (EI): 442 (M^+), 411, 392, 294, 263, 182, 148, 131, 113. HRMS (EI): calcd for $C_{25}H_{30}O_7$ (M^+) 442.1992, obsd 442.1987. Anal. Calcd for $C_{25}H_{30}O_7$: C 67.86%, H 6.83%. Found C 67.78%, H 6.80%.

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Supporting Information Available: Hardcopy spectra of compounds **20** and **2** before and after equilibration (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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