Articles

A Partial Synthesis of (-)-Shinjulactone H from (+)-Quassin

Hideo Nakamura, Sundar Vasudevan, Moonsun Kim, Carolyn P. Brock, and David S. Watt*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

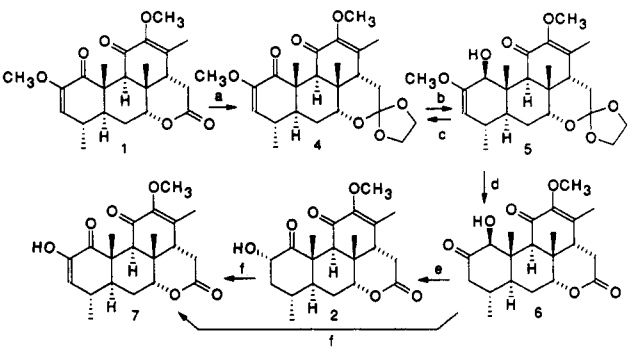
Received September 24, 1991

A partial synthesis of (-)-shinjulactone H (3) from (+)-quassin (1) required the selective manipulation of two similar *O*-methyldiosphenol groups. Protection of the δ-lactone in 1 as an ortho ester, selective reduction of the C-1 carbonyl group, hydrolysis of the resulting enol ether in the A ring, and catalytic hydrogenation of the *O*-methyldiosphenol in the C ring delivered an intermediate possessing an α-ketol group in the A ring and an α-methoxy ketone group in the C ring. Demethylation and concomitant α-ketol tautomerization in the A ring delivered (-)-shinjulactone H (3).

As part of our interest in devising a synthesis of the pentacyclic quassinoids[1,2] from a tetracyclic, commercially available precursor, (+)-quassin (1), we needed to develop procedures that would differentiate the *O*-methyldiosphenol groups in the A and C rings of 1. Success in this venture would set the stage for the application of various remote functionalization[3] reactions that would provide access to the C-8 angular methyl group and permit the introduction of the bridging tetrahydrofuran ring characteristic of the pentacyclic quassinoids.[2] As a prelude to this study, we required selective reactions for the manipulation of the two carbonyl groups at C-1 and C-11 as well as the δ-lactone in (+)-quassin (1). This task required that we differentiate between two similar *O*-methyldiosphenol groups in the A and the C rings of (+)-quassin (1). Our prior study of the partial synthesis of the tetracyclic quassinoid, picrasin B[4] (2), from (+)-quassin (1) focused on the manipulation of functionality in the A ring (Figure 1) and provided a partial solution to this problem. We now report a partial synthesis of another tetracyclic quassinoid, (-)-shinjulactone H[5] (3), that highlights the selective manipulation of the three carbonyl groups in (+)-quassin (1).

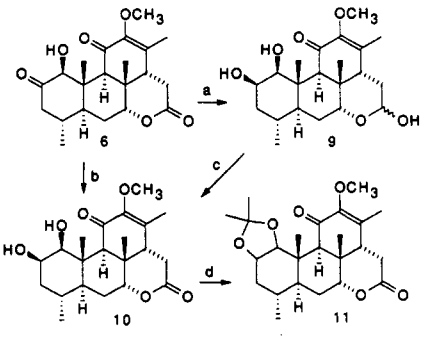
As shown in Scheme I, regioselective ketalization of the δ-lactone in quassin (1) provided the ortho ester 4. Further differentiation of the two remaining carbonyl groups involved the sodium borohydride reduction of 4 in the presence of cerium chloride to furnish the C-1β alcohol 5. The reoxidation of 5 under Swern conditions[6] returned the ortho ester 4 and confirmed the structural assignment of 5. Hydrolysis of both the enol ether functionality in the A ring and the ortho ester of 5 using pyridinium *p*-toluenesulfonate in aqueous acetone afforded "isopicrasin B" (6), an α-ketol tautomer of the natural picrasin B (2). A base-catalyzed isomerization[7] of "isopicrasin B" (6)

Scheme I[a]



[a] (a) $HOCH_2CH_2OH$, *p*-TsOH (88%); (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH (43%); (c) $(COCl)_2$, DMSO (58%); (d) PPTS, aqueous acetone (94%); (e) DBU, MeOH (44%); (f) $(COCl)_2$, DMSO, Et_3N (55%).

Scheme II[a]

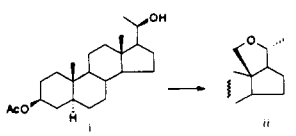


[a] (a) $NaBH_4$ (82%); (b) $NaBH(OAc)_3$ (58%); (c) Ag_2O, 70% aqueous EtOH (56%); (d) *p*-TsOH, acetone (38%).

(1) (a) Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.* **1989**, *30*, 5985. (b) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.

(2) (a) Polonsky, J. *Forts. Chem. Org. Naturst.* **1973**, *30*, 101. (b) Polonsky, J. *Ibid.* **1985**, *47*, 221. (c) Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Inter.* **1989**, *21*, 521.

(3) (a) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501. (b) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525. (c) Meystre, Ch.; Kalvoda, J.; Annex, G.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2884. The conditions described in ref 3c were successfully used to convert i to ii in 31% yield.



(4) Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.* **1989**, *30*, 5989.

(5) Ishibashi, M.; Yoshimura, S.; Tsuyuki, T.; Takahashi, T.; Matsushita, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2013.

(6) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

0022-3263/92/1957-2223$03.00/0

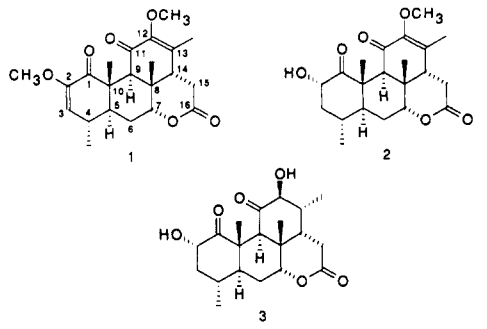


Figure 1.

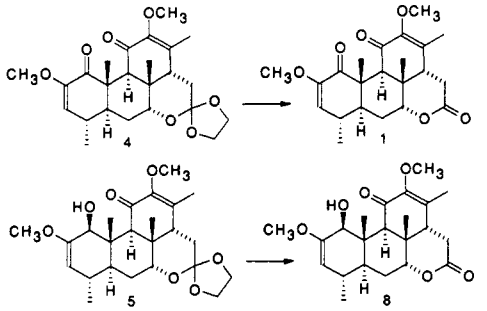


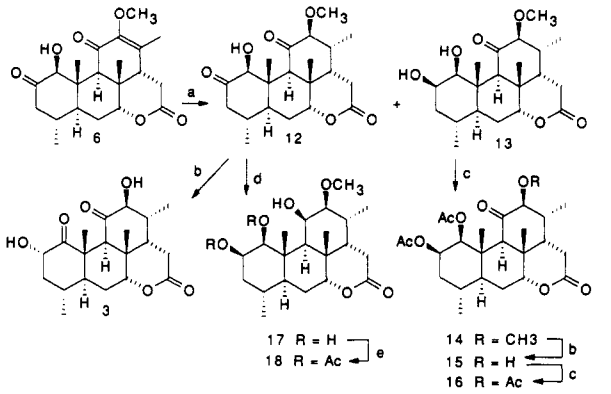
Figure 2.

furnished picrasin B (2), and Swern oxidation of either 6 or 2[1] gave the same known quassinoid, Δ^2-picrasin B (7). Finally, the selective hydrolysis of the ortho ester functionality in 4 or 5 was possible using 1,2-dichloro-4,5-dicyanoquinone in aqueous acetone to give the δ-lactone 1 or 8, respectively (Figure 2). We assume this latter process involves the acid-catalyzed hydrolysis of the ortho ester by trace amounts of the hydroquinone. An independent experiment in which the ortho ester 4 was treated with 1,2-dichloro-4,5-dicyanohydroquinone in aqueous acetone led to quassin (1) in low yield, suggesting that the combination of acid-catalyzed hydrolysis and oxidative destruction[8,9] of ethylene glycol was responsible for the good yield observed using 1,2-dichloro-4,5-dicyanoquinone.

The reduction of 6 with sodium borohydride or sodium triacetoxyborohydride[10] led to the *cis*-diol 9 as a mixture of hemiacetal isomers and to the *cis*-diol 10, respectively, shown in Scheme II. In the latter case, the hindered nature of the C-1β hydroxyl group in 6 favored direct reduction of the α-ketol to give a *cis*-diol and precluded a reduction to give the *trans*-diol in which complexation of the vicinal C-1β alcohol preceded intramolecular hydride delivery. Silver oxide oxidation of the δ-lactol 9 provided 10 and established that both had the same stereochemistry at C-1 and C-2. The conversion of 10 to the acetonide 11 also confirmed the *cis*-diol structural assignment in the A ring.

Depending on reaction conditions, the catalytic hydrogenation of 6 over platinum afforded either a mixture of

Scheme III[a]



[a] (a) H_2, PtO_2 (42% for 12; 38% for 13); (b) BBr_3, NaI, 15-crown-5 (52% for 3; 67% for 15); (c) Ac_2O, Et_3N, DMAP (78% for 14; 70% for 16); (d) $NaBH(OAc)_3$ (63%); (e) Ac_2O, Et_3N (93%).

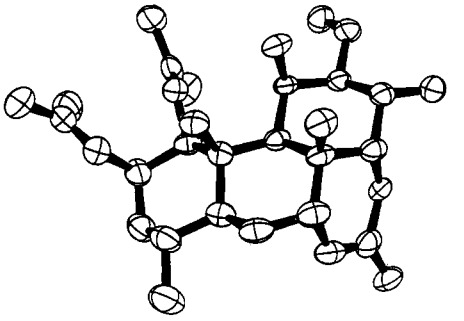


Figure 3. Perspective drawing of one of the two independent molecules in the crystal structure of 18. The shapes of the ellipsoids correspond to 50% probability contours of atomic displacement, and the hydrogen atoms have been omitted for the sake of clarity. There are no important differences between the structures of the two independent molecules.

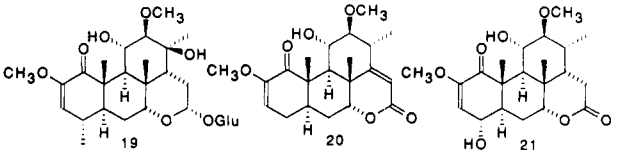


Figure 4.

the α-ketol 12 and the *cis*-diol 13 or exclusively the *cis*-diol 13, as shown in Scheme III. We assumed that reduction of the *O*-methyldiosphenol functionality in the C ring occurred from the least hindered β-face of 6 and led, following isomerization at C-12, to the diequatorial C-12β methoxy and C-13α methyl stereochemistry as indicated by the $J_{12\alpha,13\beta}$ value of 11.3 Hz. Exposure of the α-ketol 12 to boron tribromide in the presence of sodium iodide and 15-crown-5 at 25 °C led to demethylation[11] in the C ring and α-ketol isomerization in the A ring to furnish (−)-shinjulactone H (3) in 52% yield having ^{1}H NMR data in agreement with literature values.[5]

In the case of the *cis*-diol 13, an analysis of the coupling constant for H-12 ($J_{12\alpha,13\beta}$ = 11.5 Hz) confirmed the stereochemical assignments in the C ring, and the conversion of the *cis*-diol 13 to 2-epichaparrolide triacetate[12] (16) confirmed the stereochemical assignments in the A ring. Unlike the hydride reduction[13] of 11-keto steroids in which

(7) For other base-catalyzed α-ketol isomerizations, see: Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: New York, 1968; p 388f.

(8) For a related example using periodic acid, see: Walborsky, H. M.; Davis, R. H.; Howton, D. R. *J. Am. Chem. Soc.* **1951**, *73*, 2590.

(9) An alternate mechanism would involve the formation of a charge transfer complex as discussed by Yonemitsu (Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393) and direct oxidation of the orthoester by DDQ along the lines previously described by Barton using trityl tetrafluoroborate: Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542.

(10) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T. *Ibid.* **1986**, *27*, 5939.

(11) For a related demethylation, see: Collins, J. L.; Grieco, P. A.; Gross, R. S. *J. Org. Chem.* **1990**, *55*, 5816.

(12) Spectral data was compared with natural chaparrolide: Mitchell, R. E.; Stocklin W.; Stefanovic, M.; Geissman, T. A. *Phytochemistry* **1971**, *10*, 411.

reduction from the less hindered α-face predominated, the facial selectivity in the reduction of the α-ketol **12** was uncertain because of the presence of the δ-lactone. Reduction of **12** with sodium triacetoxyborohydride proceeded with attack from the concave face and led to a triol **17** having the C-11β stereochemistry, as confirmed by X-ray crystallography[14] (Figure 3) of the corresponding 1β,2β-diacetate **18**. The C-11β stereochemistry in the triol **17** and the 1β,2β-diacetate **18** was also supported by the coupling constant $J_{9\alpha,11\alpha}$ of 3.6 Hz that contrasted with the coupling constants $J_{9\alpha,11\beta}$ of 11–11.2 Hz reported for picrasinoside G[15] (**19**), javanicin O[16] (**20**), and R[16] (**21**) (Figure 4), all of which have a C-11α hydroxyl group. The attempted remote functionalization of the C-8 (or C-10) angular methyl in the 1β,2β-diacetate **18** with lead tetraacetate[3c] failed, however, to provide a pentacyclic quassinoid.

Experimental Section

2,12-Dimethoxy-2,12-picradiene-1,11,16-trione 16-Ethylene Acetal (4). To a solution of 240 mg (0.619 mmol, 1 equiv) of (+)-quassin (**1**) (Pfaltz and Bauer) in 12 mL of benzene was added 6 mg (0.03 mmol, 0.05 equiv) of *p*-toluenesulfonic acid monohydrate and 690 μL (768 mg, 12.4 mmol, 20 equiv) of distilled ethylene glycol. The mixture was refluxed for 4 h under a Dean–Stark trap, cooled to 25 °C, diluted with EtOAc, and washed with brine. The aqueous layers were combined and reextracted with additional EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by chromatography on silica gel using 2:1 EtOAc–hexane to afford 237 mg (88%) of **4**: mp 154–156 °C; IR ($CHCl_3$) 1680 (enone C=O), 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3, C-8 CH_3), 1.10 (d, J = 6.8 Hz, 3, C-4α CH_3), 1.53 (s, 3, C-10 CH_3), 1.70–1.79 (m, 1, C-5α H), 1.86 (s, 3, C-13 vinylic CH_3), 1.90–2.50 (m, 6, C-14β H, C-4β H, C-6 CH_2, C-15 CH_2), 3.18 (s, 1, C-9α H), 3.65 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), 3.69–3.77 (m, 1, C-7β H), 4.02–4.22 (m, 4, OCH_2CH_2O), 5.27 (d, J = 2.4 Hz, 1, C-3 vinylic H); ^{13}C NMR ($CDCl_3$) δ 12.4, 14.8, 19.0, 21.4, 25.3, 31.0, 32.4, 37.8, 43.1, 45.6, 45.8, 48.0, 54.7, 58.9, 63.4, 64.5, 74.8, 116.2, 118.5, 138.3, 148.1, 148.4, 193.2 (C-2), 198.7 (C-11); HRMS calcd for $C_{24}H_{32}O_7$ 432.2149, found 432.2149.

Anal. Calcd for $C_{24}H_{32}O_7 \cdot {}^1/_2H_2O$: C, 65.29; H, 7.53. Found: C, 65.09; H, 7.59.

2,12-Dimethoxy-1β-hydroxy-2,12-picradiene-11,16-dione 16-Ethylene Acetal (5). To 590 mg (1.37 mmol, 1 equiv) of **4** in 30 mL of absolute EtOH under N_2 was added 762 mg (2.05 mmol, 1.5 equiv) of $CeCl_3 \cdot 7H_2O$. The mixture was stirred at 25 °C for 15 min and cooled to 0 °C. To this solution was added 78 mg (2.05 mmol, 6 equiv) of $NaBH_4$ in 20 mL of abs EtOH dropwise. The mixture was stirred at 0 °C for 60 min. The reaction was quenched by adding ca. 10 mL of a saturated NH_4Cl solution. The solution was concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and washed with brine. The aqueous layer was extracted with additional $CHCl_3$. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on silica gel using 2:1 EtOAc–hexane to afford 253 mg (43%) of **5** as a foam: IR (KBr) 3360 (br OH), 1661 (enone C=O), 1637 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3, C-4α CH_3), 1.02 (s, 3, C-8 CH_3), 1.14 (s, 3, C-10 CH_3), 1.50–1.90 (m, 3, C-6 CH_2 and C-5α H), 1.92 (s, 3, C-13 CH_3), 1.96–2.15 (m, 3, C-15 CH_2 and C-4β H), 2.20–2.30 (m, 1, C-14β H), 2.89 (s, 1, C-9α H), 3.55 (s, 3, OCH_3), 3.60 (s, 3, OCH_3), 3.69–3.77 (m, 1, C-7β H), 4.00–4.30 (m, 5, OCH_2CH_2O and C-3 vinylic H), 4.50 (s, 1, C-1α H), 6.66 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 11.3 15.7, 20.7, 21.7, 25.4, 29.5, 32.8, 39.3, 41.2, 42.4, 48.7, 54.6, 55.4, 59.7, 63.6, 64.7, 75.4, 77.2, 101.6, 118.1, 144.2, 148.5, 153.6, 198.7 (C-11).

Anal. Calcd for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.26; H, 7.84.

1β-Hydroxy-12-methoxy-12-picrasene-2,11,16-trione or "Isopicrasin B" (6). A mixture of 253 mg (0.58 mmol, 1 equiv) of **5** and 44 mg (0.18 mmol, 0.3 equiv) of pyridinium *p*-toluenesulfonate in 11 mL of acetone and 1.1 mL of H_2O was refluxed for 3 h. The mixture was cooled, concentrated, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on a preparative TLC (silica gel) plate using EtOAc to afford 207 mg (94%) of **6**: mp 208–211 °C; IR (KBr) 3430 (br OH), 1724 (lactone C=O), 1662 (enone C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 5.5 Hz, 3, C-4α CH_3), 1.17 (s, 3, C-8 CH_3), 1.23 (s, 3, C-10 CH_3), 1.60–1.90 (m, 3, C-3 CH_2 and C-5α H), 1.93 (s, 3, C-13 CH_3), 2.08–2.21 (m, 2, C-6 CH_2), 2.40–2.66 (m, 3, C-4β H and C-15 CH_2), 2.95 (s, 1, C-9α H), 3.05 (dd, J = 11.8 and 6.6 Hz, 1, C-14β H), 3.64 (s, 3, OCH_3), 3.98 (d, J = 4.2 Hz, 1, C-1α H), 4.33–4.41 (m, 1, C-7β H), 5.09 (d, J = 4.4 Hz, 1, OH); ^{13}C NMR ($CDCl_3$) δ 11.3, 15.1, 19.6, 21.9, 25.2, 30.9, 31.0, 38.1, 42.7, 45.6, 46.4, 47.9, 52.7, 59.6, 82.4, 85.6, 141.1, 148.6, 169.0 (C-16), 196.8 (C-11), 208.1 (C-2).

Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.99; H, 7.49.

2,12-Dimethoxy-1β-hydroxy-2,12-picradiene-11,16-dione (8). To a solution of 100 mg (0.23 mmol, 1 equiv) of **5** in 2.3 mL of 1:20 H_2O–acetone was added dropwise 63 mg (0.28 mmol, 1.2 equiv) of DDQ in 2.3 mL of 1:20 H_2O–acetone. The mixture was stirred at 25 °C for 45 min and passed through a neutral alumina column using acetone. The eluate was collected, concentrated, and chromatographed on a preparative TLC (silica gel) plate using EtOAc to afford 69 mg (77%) of **8**: mp 202–204 °C; IR (KBr) 3340 (br OH), 1736 (lactone C=O), 1662 (enone C=O), 1637 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.9 Hz, 3, C-4α CH_3), 1.18 (s, 3, C-8 CH_3), 1.25 (s, 3, C-10 CH_3), 1.27–1.50 (m, 1, C-5α H), 1.65–1.90 (m, 1, C-4β H), 1.95 (s, 3, C-13 CH_3), 2.05–2.20 (m, 2, C-6 CH_2), 2.38–2.58 (m, 2, C-15 CH_2), 2.66 (s, 1, C-9α H), 3.00 (dd, J = 22.5 and 12.5 Hz, 1, C-14β H), 3.57 (s, 3, OCH_3), 3.63 (s, 3, OCH_3), 3.99 (d, J = 2.3 Hz, 1, C-3 vinylic H), 4.27–4.35 (m, 1, C-7β H), 4.52 (s, 1, C-1α H), 6.42 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 11.2, 15.9, 20.6, 22.4, 25.6, 29.5, 31.4, 38.1, 41.1, 42.3, 47.0, 54.7, 55.7, 60.0, 77.03 (C-7), 82.7, 101.4, 143.5, 148.5, 153.1, 168.6 (C-16), 196.8.

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.55; H, 7.78.

12-Methoxy-1β,2β,16-trihydroxy-12-picrasen-11-one (9). To a solution of 329 mg (0.875 mmol, 1 equiv) of **6** in 17 mL of MeOH under N_2 was slowly added 66 mg (1.75 mmol, 8 equiv) of $NaBH_4$ in 18 mL of MeOH. The mixture was stirred at 25 °C for 4 h. The reaction was quenched by adding 10 mL of saturated aqueous NH_4Cl solution. The solution was concentrated, diluted with CH_2Cl_2, and washed with brine. The aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on a preparative TLC (silica gel) plate using EtOAc to afford 274 mg (82%) of **9** as a foam. The major isomer had the following spectral data: IR (KBr) 3305 (br OH), 1660 (enone C=O), 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3, C-4α CH_3), 1.12 (s, 3, C-8 CH_3), 1.31 (s, 3, C-10 CH_3), 1.91 (s, 3, C-13 CH_3), 2.39–2.47 (m, 1, C-14β H), 2.78 (s, 1, C-9α H), 3.30 (d, J = 4.0 Hz, 1, C-1α H), 3.61 (s, 3, OCH_3), 3.95–3.98 (m, 1, C-7β H), 3.98–4.02 (m, 1, C-2α H), 4.81–4.88 (m, 1, C-16 H); HRMS calcd for $C_{21}H_{32}O_6$ 362.20933, found 362.2095. The ^{13}C NMR spectrum had more than 21 lines, confirming that the product **9** was a mixture of diastereomers at C-16.

Anal. Calcd for $C_{21}H_{22}O_6 \cdot {}^1/_2CH_3CH_2OH$: C, 65.49; H, 8.74. Found: C, 65.60; H, 8.78. This analysis was repeated with similar results on two occasions.

1β,2β-Dihydroxy-12-methoxy-12-picrasene-11,16-dione (10). To a solution of 25 mg (0.66 mmol, 20 equiv) of $NaBH_4$ in 2 mL of glacial HOAc at 20 °C under N_2 was added 49 mg (0.13 mmol,

(13) Zderic, J. A.; Iriarte, J. *J. Org. Chem.* **1962**, *27*, 1756.

(14) Crystals of **18** ($C_{25}H_{38}O_8$) were grown from EtOH–CH_2Cl_2; a = 9.400 (2) Å; b = 11.905 (1) Å, c = 12.205 (2) Å, α = 109.01 (1)°, β = 91.55 (2)°, γ = 104.02 (1)°, V = 1244.5 (4) Å^3, space group $P1$, Z = 2, D_{calcd} = 1.245 g cm^{-3} at 297 K. A total of 5717 independent reflections (a hemisphere of data having θ < 27.5°) were measured on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo Kα radiation; the 2912 reflections having $I > 2\sigma(I)$ were included in the refinement. The structure was solved using the program package DIRDIF, and was refined anisotropically (592 variables; H atoms in calculated positions) to R = 0.044.

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1 equiv) of 6 in 3 mL of glacial HOAc. The mixture was stirred for 15 h. The reaction was quenched with 2 mL of 0.5 N aqueous potassium sodium tartrate solution and stirred at 25 °C for 30 min. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, and the aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on a preparative TLC (silica gel) plate using 1:49 MeOH–$CHCl_3$ to yield 29 mg (58%) of 10 as a foam: IR (KBr) 3450 (br OH), 1684 (enone), 1733 (lactone C=O), 1637 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3, C-4α CH_3), 1.12–1.35 (m, 2, C-3 CH_2), 1.24 (s, 3, C-8 CH_3), 1.35 (s, 3, C-10 CH_3), 1.72–2.15 (m, 4, C-4β H, C-5α H and C-6 CH_2), 1.95 (s, 3, C-13 CH_3), 2.35–2.60 (m, 2, C-15 CH_2), 2.42 (s, 1, C-9α H), 2.90–3.10 (m, 1, C-14β H), 3.20 (br s, 1, OH), 3.24 (d, J = 3.9 Hz, 1, C-1α H), 3.65 (s, 3, OCH_3), 3.93–4.03 (m, 1, C-2α H), 4.26–4.34 (m, 1, C-7β H), 6.65 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 12.0, 15.6, 19.2, 23.2, 23.7, 25.1, 31.0, 38.0, 39.3, 42.7, 43.3, 47.5, 56.3, 60.0, 69.7, 79.2, 83.1, 143.6, 148.9, 169.0 (lactone C=O), 198.7 (enone C=O); HRMS calcd for $C_{21}H_{30}O_6$ 378.2042, found 378.2029.

1β,2β-Dihydroxy-12-methoxy-12-picrasene-11,16-dione 1,2-Acetonide (11). A solution of 50 mg (0.13 mmol, 1 equiv) of 10 and 5 mg (0.03 mmol, 0.2 equiv) of *p*-toluenesulfonic acid monhydrate in 13 mL of distilled acetone was refluxed under N_2 for 24 h. The mixture was cooled, and the acid was neutralized with saturated aqueous $NaHCO_3$ solution. The solution was concentrated, and the residue was extracted with EtOAc. The organic solutions were washed with brine, dried ($MgSO_4$), and chromatographed on a preparative TLC (silica gel) plate that was pretreated by developing in 1% Et_3N in ether. The plate was developed using ether to afford 21 mg (38%) of 11: mp 196–199 °C dec; IR (KBr) 1733 (lactone C=O), 1688 (enone C=O), 1647 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.7 Hz, 3, C-4α CH_3), 1.24 (s, 6, $C(CH_3)_2$), 1.15–1.45 (m, 3, C-3 CH_2 and C-5α H), 1.32 (s, 3, C-8 CH_3), 1.55 (s, 3, C-10 CH_3), 1.60–2.10 (m, 3, C-6 CH_2 and C-4β H), 1.90 (s, 3, C-13 CH_3), 2.30–2.60 (m, 2, C-15 CH_2), 2.52 (s, 1, C-9α H), 2.90–3.10 (m, 1, C-14β H), 3.67 (s, 3, OCH_3), 3.82 (d, J = 5.7 Hz, 1, C-1α H), 4.03–4.21 (m, 1, C-2α H), 4.25–4.33 (m, 1, C-7β H); ^{13}C NMR ($CDCl_3$) δ 13.0, 15.6, 20.9, 23.0, 25.9, 28.0, 28.1, 28.3, 31.7, 32.5, 37.8, 39.2, 39.7, 46.7, 56.4, 60.1, 72.9, 83.0, 84.0, 107.8, 139.1, 148.4, 169.1 (C-16), 191.0 (C-11).

Anal. Calcd for $C_{24}H_{34}O_6 \cdot 1/2CH_3CO_2CH_2CH_3$: C, 67.51; H, 8.28. Found: C, 67.51; H, 8.09. This analysis was repeated with similar results on two occasions, and an extraneous triplet (δ 1.41) and quartet (δ 3.13) were apparent in the ^1H NMR spectrum of the recrystallized material on which the analysis was performed.

1β-Hydroxy-12β-methoxypicrasene-2,11,16-trione (12). A solution of 150 mg (0.40 mmol, 1 equiv) of 6 in 10 mL of anhydrous MeOH and 10 mg of PtO_2 was stirred at 25 °C under H_2 (60 psi) for 2.5 h. The mixture was filtered through Celite, and the filtrate was concentrated. The crude product was chromatographed on a preparative TLC (silica gel) plate using 1:19 MeOH–$CHCl_3$ (two developments) to afford 57 mg (38%) of 13 (vide infra) and 64 mg (42%) of 12. An analytical sample of 12 was obtained by recrystallization from CH_2Cl_2–ether: mp >232 °C; IR (KBr) 3520 (br OH), 1740 (lactone C=O), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 6.1 Hz, 3, C-4α CH_3), 1.12 (s, 3, C-8 CH_3), 1.08 (d, J = 6.8 Hz, 3, C-13α CH_3), 1.25 (s, 3, C-10 CH_3), 1.65–1.80 (m, 2, C-5α and C-4β H), 1.80–2.15 (m, 4, C-3 and C-6 CH_2), 2.15–2.38 (m, 1, C-13β H), 2.50–2.95 (m, 3, C-15 CH_2 and C-14β H), 2.68 (s, 1, C-9α H), 3.41 (s, 3, OCH_3), 3.41 (d, J = 5.7 Hz, 1, OH), 3.55 (d, J = 11.3 Hz, 1, C-12α H), 3.80 (d, J = 5.7 Hz, 1, C-1α H), 4.36–4.41 (m, 1, C-7β H); ^{13}C NMR ($CDCl_3$) δ 10.8, 14.7, 19.5, 22.0, 25.9, 27.7, 31.3, 38.8, 40.1, 42.1, 44.2, 44.9, 46.9, 51.2, 58.5, 82.3, 85.6, 85.9, 169.8 (C-16), 206.7 (C-2), 208.2 (C-11).

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.59; H, 8.01.

1β,2β-Dihydroxy-12β-methoxypicrasane-11,16-dione (13). The procedure described in the preparation of 12 was repeated using 20 mg (0.05 mmol, 1 equiv) of 6 in 5 mL of anhydrous MeOH and 5 mg of PtO_2 at 25 °C under H_2 (60 psi) for 17 h. This increased time period, relative to that used in the preparation of 12, led, after chromatography on a preparative TLC (silica gel) plate using EtOAc, to 14 mg (67%) of 13 as a foam: IR (KBr) 3440 (br OH), 1724 (lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.4 Hz, 3, C-4α CH_3), 1.05–1.10 (m, 1, C-5α H), 1.10 (d, J = 6.6 Hz, 3, C-13α CH_3), 1.14 (s, 3, C-8 CH_3), 1.20–1.27 (m, 1, C-3α H), 1.50 (s, 3, C-10 CH_3), 1.75–2.10 (m, 5, C-6 CH_2, C-3β H, C-4β H, and C-14β H), 2.29–2.35 (m, 1, C-13β H), 2.40 (s, 1, C-9α H), 2.55 (dd, J = 18.8, 12.9 Hz, 1, C-15α H), 2.84 (dd, J = 18.8, 6.8 Hz, 1, C-15β H), 2.90 (br s, 1, OH), 3.19 (d, J = 3.7 Hz, 1, C-1α H), 3.40 (d, J = 11.5 Hz, 1, C-12α H), 3.45 (s, 3, OCH_3), 3.89–3.94 (m, 1, C-2α H), 4.25 (br s, 1, OH), 4.28–4.33 (m, 1, C-7β H); ^{13}C NMR ($CDCl_3$) δ 12.3 (C-8 or C-10 CH_3), 15.1 (C-13α CH_3), 19.2 (C-4α CH_3), 23.5 (C-4), 23.6 (C-8 or C-10 CH_3), 25.8 (C-6), 27.7 (C-15), 37.4 (C-13), 39.7 (C-3), 40.2 (C-8 or C-10), 42.3 (C-8 or C-10), 43.5 (C-5), 45.2 (C-14), 56.3 (C-9), 59.7 (OCH_3), 69.8 (C-2), 80.4 (C-1), 83.0 (C-7), 86.7 (C-12), 169.7 (C-16), 214.4 (C-11); HRMS calculated for $C_{21}H_{32}O_6$ 380.2199, found 380.2191.

A vertical cross section of the HETCOR plot (see the supplementary material) along the resonances of the three C-3, C-6, and C-15 CH_2 groups indicate the chemical shifts and the J_{AB} values of the corresponding axial and equatorial hydrogens.

1β,2β-Diacetoxy-12β-methoxypicrasane-11,16-dione (14). To a solution of 27 mg (0.073 mmol, 1 equiv) of 13 in 0.2 mL of Et_3N and 0.2 mL of CH_2Cl_2 were added 0.1 mL of Ac_2O and 0.5 mg of 4-(dimethylamino)pyridine at 0 °C. The mixture was stirred at 25 °C for 22 h. The reaction was quenched with MeOH at 0 °C, and the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel using 1:3 hexane–EtOAc to afford 26 mg (78%) of 14: mp 118–118.5 °C; $[\alpha]^{19}_D$ −10.9° (c = 0.23, $CHCl_3$); IR (KBr) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.2 Hz, 3, C-4α CH_3), 1.04 (d, J = 6.6 Hz, 3, C-13α CH_3), 1.11 (s, 3, C-8 CH_3), 1.19–1.46 (m, 3, C-3 CH_2 and C-5α H), 1.57 (s, 3, C-10 CH_3), 1.75–1.89 (m, 3, C-4β H, and C-6 CH_2), 1.95 (s, 3, $COCH_3$), 2.11 (s, 3, $COCH_3$), 2.10–2.20 (m, 1, C-14β H), 2.50 (s, 1, C-9α H), 2.64 (dd, J = 19.2, 12.4 Hz, 1, C-15α H), 2.80 (dd, J = 19.2, 7 Hz, 1, C-15β H), 3.35 (d, J = 12.8 Hz, 1, C-12α H), 3.38 (s, 3, OCH_3), 4.31 (dd, J = 0.6, 2.4 Hz, 1, C-7β H), 4.66 (d, J = 4 Hz, 1, C-1α H), 5.15 (ddd, J = 0.6, 3.2, 10 Hz, 1, C-2α H); ^{13}C NMR ($CDCl_3$) δ 12.1, 15.0, 19.0, 21.3, 21.5, 23.5, 24.1, 25.4, 27.7, 38.1, 38.9, 43.5, 45.1, 53.6, 59.0, 70.2, 78.6, 82.6, 86.2, 169.6 (C-16), 170.1 (acetyl C=O), 171.4 (acetyl C=O), 207.5 (C-11).

Anal. Calcd for $C_{25}H_{36}O_8$: C, 64.64; H, 7.81. Found: C, 64.54; H, 7.84.

1β,2β-Diacetoxy-12β-hydroxypicrasane-11,16-dione (15). To 13 mg (0.029 mmol, 1 equiv) of 14 was added 3.4 mL (1.02 mmol, 35 equiv) of 0.3 M solution of 15-crown-5 saturated with NaI in CH_2Cl_2 at 25 °C followed by 0.5 mL (0.5 mmol, 17 equiv) of 1 M solution of BBr_3 in CH_2Cl_2 at −78 °C. The mixture was stirred at 25 °C for 17 h, and the reaction was quenched with 5 mL of MeOH and 5 mL of Et_3N at 0 °C. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel using 1:3 hexane–EtOAc to afford 8.5 mg (67%) of 15: mp 124–124.5 °C; IR (KBr) 3475 (br OH), 1745 (sh, C-11 C=O), 1734 (lactone C=O), 1719 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.4 Hz, 3, C-4α CH_3), 1.09 (s, 3, C-8 CH_3), 1.13 (d, J = 6.6 Hz, 3, C-13α CH_3), 1.23–1.48 (m, 3, C-3 CH_2 and C-5α H), 1.59 (s, 3, C-10 CH_3), 1.78–2.05 (m, 5, C-6 CH_2, C-4β H, C-13β H, and C-14β H), 1.89 (s, 3, $COCH_3$), 2.11 (s, 3, $COCH_3$), 2.50 (s, 1, C-9α H), 2.66–2.96 (m, 2, C-15 CH_2), 3.32 (d, J = 4.9 Hz, 1, OH), 3.77 (dd, J = 5.1 and 10.6 Hz, 1, C-12α H), 4.29–4.37 (m, 1, C-7β H), 4.67 (d, J = 3.9 Hz, 1, C-1α H), 5.11–5.36 (m, 1, C-2α H); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.9, 18.9, 21.0, 21.3, 23.5, 24.3, 25.3, 27.6, 38.9, 40.5, 41.0, 41.8, 43.5, 45.2, 53.1, 70.3, 76.9, 78.7, 82.5, 169.5 (C-16), 170.1 (acetyl C=O), 171.5 (acetyl C=O), 210.5 (C-11); HRMS calcd for $C_{24}H_{34}O_8$ 450.2256, found 450.2257.

1β,2β,12β-Triacetoxypicrasane-11,16-dione (16). To a solution of 3 mg (6.7 μmol) of 15 in 0.1 mL of Et_3N were added 0.05 mL of Ac_2O and 0.5 mg (4 μmole) of 4-(dimethylamino)pyridine at 0 °C. The mixture was stirred at 25 °C for 15 h, and the reaction was quenched with 1 mL of MeOH at 0 °C. The mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel using 1:3 hexane–EtOAc to afford 2.3 mg (70%) of 16: mp 148–150 °C; IR (KBr) 1742 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.2 Hz, 3, C-4α CH_3), 1.02 (d, J = 6.6 Hz, 3, C-13α CH_3), 1.15 (s, 3, C-8 CH_3), 1.18–1.54 (m, 3, C-3 CH_2 and C-5α H), 1.56 (s, 3, C-10 CH_3), 1.74–1.95 (m, 4, C-6 CH_2, C-4β H and C-13β H), 1.87 (s, 3, $COCH_3$), 2.06 (s, 3,

$COCH_3$), 2.13 (s, 3, $COCH_3$), 2.34–2.50 (m, 1, C-14β H), 2.51 (s, 1, C-9α H), 2.68–2.99 (m, 2, C-15 CH_2), 4.33 (dd, J = 0.6, 3 Hz, 1, C-7β H), 4.60 (d, J = 3.7 Hz, 1, C-1α H), 4.75 (d, J = 11.7 Hz, 1, C-12α H), 5.23–5.27 (m, 1, C-2α H); HRMS calcd for $C_{26}H_{36}O_9$ 492.2362, found 492.2366.

Shinjulactone H (3). To 4 mg (0.011 mmol, 1 equiv) of **12** was added 1.05 mL (0.32 mmol, 30 equiv) of 0.3 M solution of 15-crown-5 saturated with NaI in CH_2Cl_2 at 25 °C followed by 0.16 mL (0.16 mmol, 15 equiv) of 1 M solution of BBr_3 in CH_2Cl_2 at -78 °C. The mixture was stirred at 25 °C for 16 h. The reaction was quenched with 10 mL of MeOH and 5 mL of Et_3N at 0 °C, and the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel using 1:3 hexane–EtOAc to afford 2 mg (52%) of **3**: mp 138–142 °C; $[\alpha]^{25}_D$ -15.4° (c = 0.33, absolute EtOH) [lit.[5] $[\alpha]^{21}_D$ -14° (c = 3.9, absolute EtOH)]; IR (KBr) 3642 (br OH), 1722 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.5 Hz, 3, C-4α CH_3), 1.13 (s, 3, C-8 CH_3), 1.20 (d, J = 6.8 Hz, 3, C-13α CH_3), 1.59 (s, 3, C-10 CH_3), 1.36–1.43 (m, 1, C-5α H), 1.84–2.07 (m, 5, C-3α H, C-4β H, C-6 CH_2, and C-14β H), 2.14–2.18 (m, 1, C-13β H), 2.46 (ddd, J = 3.7, 7.5, 12.9 Hz, 1, C-3β H), 2.68 (dd, J = 19, 13 Hz, 1, C-15α H), 2.85 (dd, J = 19, 6.8 Hz, 1, C-15β H), 2.93 (s, 1, C-9α H), 3.38 (d, J = 4.7 Hz, 1, C-2 OH), 3.49 (d, J = 12.8 Hz, 1, C-12 OH), 4.00 (br d, J = 10.8 Hz, 1, C-12α H), 4.31 (dd, J = 2.7, 3 Hz, 1, C-7β H), 4.77 (ddd, J = 4.3, 7.6, 11.9 Hz, 1, C-2α H); HRMS cald for $C_{20}H_{28}O_6$ 364.1888, found 364.1884.

12β-Methoxy-1β,2β,11β-trihydroxypicrasan-16-one (17). A solution of 11 mg (0.291 mmol, 20 equiv) of $NaBH_4$ in 1 mL of glacial HOAc at 20 °C and 22 mg (0.058 mmol, 1 equiv) of **12** in 1 mL of glacial HOAc was stirred at 20 °C under N_2 for 16 h. The reaction was quenched by adding 1 mL of 0.5 M aqueous potassium sodium tartrate, and the mixture was stirred vigorously for 1 h. The mixture was diluted with $CHCl_3$, and most of the HOAc was neutralized with saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ slution, and the aqueous layers were again extracted with $CHCl_3$. The combined $CHCl_3$ solutions were dried (Na_2SO_4), concentrated, and chromatographed on an analytical silica gel plate using 1:20 MeOH–$CHCl_3$ to afford 14 mg (63%) of **17** as a foam: IR ($CHCl_3$) 3480 (br OH), 1725 (lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.5 hz, 3, C-4α CH_3), 0.98 (d, J = 6.8 Hz, 3, C-13α CH_3), 1.05–1.40 (m, 3, C-3 CH_2 and C-5α H), 1.45 (s, 3, C-8 CH_3), 1.47 (s, 3, C-10 CH_3), 1.63–1.88 (m, 2, C-6 CH_2), 1.88–2.10 (m, 3, C-9α, C-4β H, and C-14β H), 2.10–2.40 (m, 2, C-13β and C-15α H), 2.57 (dd, J = 19, 7.3 Hz, 1, C-15β H), 2.69 (br s, 1, OH), 2.80 (br s, 1, OH), 2.93 (dd, J = 11.3, 4.2 Hz, 1, C-12α H), 3.33 (dd, J = 4.4, 3.9 Hz, 1, C-1α H), 3.44 (s, 3, OCH_3), 3.58 (d, J = 3.9 Hz, 1, C-1 OH), 3.98–4.08 (m, 1, C-2α H), 4.08–4.15 (m, 1, C-7β H), 4.77 (t, J = 3.6 Hz, 1, C-11α H); ^{13}C NMR ($CDCl_3$) δ 13.5 (CH_3), 14.5 (CH_3), 18.8 (CH_3), 23.4 (CH), 24.9 (CH_3), 26.8 (two CH_2; evidence for two carbons was obtained in the DEPT experiment where the signals were apparent at 26.95 and 26.99), 28.6 (CH), 34.7 (quaternary C), 40.3 (CH_2), 43.9 (quaternary C), 45.9 (two CH; evidence for two carbons was obtained in the DEPT experiment where the signals were apparent at 46.02 and 46.05), 46.7 (CH), 57.9 (OCH_3), 67.2 (CH), 69.8 (CH), 78.3 (CH), 82.1 (CH), 84.6 (CH), 171.6 (lactone C=O). This material resisted efforts to crystallize it and was isolated as a foam. The diacetyl derivative **18** (vide infra) was, however, crystalline and was fully characterized.

1β,2β-Diacetoxy-11β-hydroxy-12β-methoxypicrasan-16-one (18). To a solution of 59 mg (0.153 mmol, 1 equiv) of **17** in 1.5 mL of anhydrous CH_2Cl_2 at 0 °C under N_2 were added 1.5 mL of anhydrous Et_3N and 469 mg (4.59 mmol, 30 equiv) of Ac_2O. The mixture was stirred at 25 °C for 66 h. The product was concentrated and chromatographed on silica gel using 1:49 MeOH–$CHCl_3$ to afford 65 mg (93%) of **18**. An analytical sample was obtained by recrystallization from EtOAc–hexane: mp 220–221.5 °C; IR (KBr) 3480 (br OH), 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 6.5 Hz, 3, C-4α CH_3), 0.94 (d, J = 6.8 Hz, 3, C-13α CH_3), 1.15–1.65 (m, 4, C-3 CH_2, C-5α H and C-9α H), 1.52 (s, 3, C-8 CH_3), 1.54 (s, 3, C-10 CH_3), 1.65–2.05 (m, 4, C-4β H, C-6 CH_2 and C-14β H), 2.03 (s, 3, $COCH_3$), 2.08 (s, 3, $COCH_3$), 2.05–2.35 (m, 2, C-13β and C-15α H), 2.36 (br s, 1, OH), 2.56 (dd, J = 18.9, 7.1 Hz, 1, C-15β H), 2.82 (dd, J = 11.3, 3.7 Hz, 1, C-12α H), 3.32 (s, 3, OCH_3), 4.07 (t, J = 2.6 Hz, 1, C-11α H), 4.11–4.18 (m, 1, C-7β H), 4.67 (d, J = 4.2 Hz, 1, C-1α H), 5.33–5.43 (m, 1, C-2α H); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.3, 18.8, 20.8, 20.9, 24.2, 24.9, 25.9, 26.7, 28.3, 34.9, 38.6, 42.8, 45.3, 45.9, 46.4, 56.8, 66.3, 69.2, 78.5, 82.5, 84.3, 170.5 (C-16), 170.8 (acetyl C=O), 171.2 (acetyl C=O).

Anal. Calcd for $C_{25}H_{38}O_8$: C, 64.36; H, 8.21. Found: C, 64.27; H, 8.24.

Acknowledgment. We thank the National Institutes of Health (GM 36256) for their generous financial support, the University of Kentucky Research Advisory Committee, and the University of Kentucky Major Research Insturmentation Bond Program for the purchase of equipment used in this study (bond ID# 7E-8E48-25). We thank Laura Applegate for the preparation of the ortho ester **4**. We thank Professor T. Murae of the University of Tokyo for providing us with a sample of chaparrolide and its triacetate.

Registry No. **1**, 26121-56-2; **3**, 4283-48-1; **4**, 139276-56-5; **5**, 139276-57-6; **6**, 139276-58-7; **7**, 26121-57-3; **8**, 139276-59-8; **9** (isomer 1), 139276-60-1; **9** (isomer 2), 139311-85-6; **10**, 139311-86-7; **11**, 139311-87-8; **12**, 139346-55-7; **13**, 139311-88-9; **14**, 139311-89-0; **15**, 139311-90-3; **16**, 139311-91-4; **17**, 139311-92-5; **18**, 139311-93-6.

Supplementary Material Available: ^1H NMR spectra for compounds **9**, **10**, **11**, **13** (COSY), **16**, and **17**; ^{13}C NMR spectra for compounds **9**, **10**, **11**, **13** (HETCOR and DEPT), **15** (DEPT), **16** and **17** (DEPT); and full details of the X-ray structure determination (37 pages). Ordering information is given on any current masthead page.