Quassinoids. 2. Synthesis of an ABCD Ring Precursor Involving a Lactonization Induced by Iodotrimethylsilane

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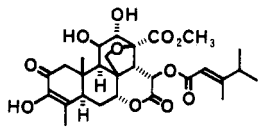
The Diels–Alder reaction of 3-formyl-4a,5,6,7,8,8aα-hexahydro-7β-(benzyloxy)-4aβ,8α-dimethylnaphthalen-2(1*H*)-one with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene in benzene at 25 °C furnished an extremely acid-labile Diels–Alder adduct, 3β-(benzyloxy)-8β-formyl-14α-methoxy-12-((trimethylsilyl)oxy)-19-nor-9β-podocarp-12-en-7-one. Stereoselective reduction of this adduct with sodium bis(2-methoxyethoxy)aluminum hydride in toluene at 0 °C and subsequent acid hydrolysis provided 3β-(benzyloxy)-7α-hydroxy-8β-(hydroxymethyl)-19-nor-9β-podocarp-13-en-12-one. An X-ray crystallographic study of the monobenzoate derivative, 3β-(benzyloxy)-7α-hydroxy-8β-((benzoyloxy)methyl)-19-nor-9β-podocarp-13-en-12-one, of the aforementioned product confirmed the relative stereochemistry of this ABC ring intermediate. Sequential treatment of this monobenzoate derivative with chloroacetic anhydride and sodium iodide furnished an α-iodo ester, 3β-(benzyloxy)-8β-((benzoyloxy)-methyl)-7α-(iodoacetoxy)-19-nor-9β-podocarp-13-en-12-one. Cyclization of this α-iodo ester using iodotrimethylsilane provided 3β-(benzyloxy)-20-hydroxy-21-nor-9β-picrasan-12-one benzoate, a tetracyclic ABCD ring progenitor of the quassinoids.

In developing a synthetic route to the quassinoids, we examined both intramolecular[1] and intermolecular Diels–Alder reactions of a dienophile incorporating the AB rings with a diene comprising a C ring progenitor. We were particularly interested in obtaining a Diels–Alder adduct that would provide suitable functionality for elaboration of the remaining D and E rings of quassinoids such as bruceantin (1). We wish to report a stereoselective synthesis of an ABC ring intermediate[2] and an interesting cyclization to an attractive ABCD ring intermediate that involves an intramolecular Reformatsky-type reaction promoted by iodotrimethylsilane.



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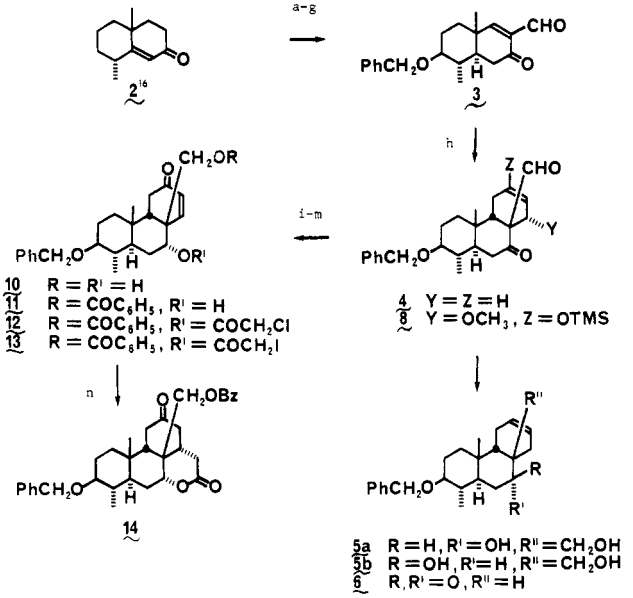
The Diels–Alder reaction of the enedione[1] **3** with 1,3-butadiene in a sealed tube at 150 °C furnished the adduct **4** shown in Scheme I. Using this adduct as a model system, we examined the stereoselective reduction of the C-7 carbonyl group to the required C-7α axial alcohol **5a**. We encountered 7β-stereoselectivity in the reduction of **4** with sodium borohydride, lithium aluminum hydride, and lithium tri-*tert*-butoxyaluminum hydride, and we noted a significant amount of retro aldol product **6** with lithium tri-*sec*-butylborohydride. Only sodium bis(2-methoxyethoxy)aluminum hydride exhibited a modest (2:1) 7α-stereoselectivity and encouraged us to employ this reducing agent to the actual system of interest.

Scheme I[a]



10 R = R' = H
11 R = COC_6H_5, R' = H
12 R = COC_6H_5, R' = $COCH_2Cl$
13 R = COC_6H_5, R' = $COCH_2I$

4 Y = Z = H
8 Y = OCH_3, Z = OTMS

5a R = H, R' = OH, R'' = CH_2OH
5b R = OH, R' = H, R'' = CH_2OH
6 R, R' = O, R'' = H

[a] a, $HOCH_2CH_2OH$, p-TsOH; b, $CrO_3 \cdot 2Py$; c, Li, NH_3, C_2H_5OH; d, $PhCH_2Br$, NaH; e, H_3O^+; f, $NaOCH_3$, $HCO_2C_2H_5$; g, DDQ; h, 1,3-butadiene or 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene; i, $NaAlH_2(OCH_2CH_2OCH_3)_2$, 0 °C; j, H_3O^+; k, BzCl, DMAP, Py; l, $(ClCH_2CO)_2O$, DMAP, Py-THF; m, NaI, acetone; n, TMSI, CH_3CN, −20 °C.

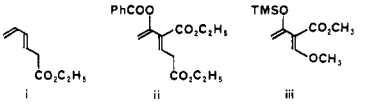
The Diels–Alder reaction of **3** with 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene[3,4] (**7**) in benzene at 25 °C

(1) For the first paper in this series, see: Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470.

(2) For recent synthetic efforts in the quassinoid area see: (a) Stojanac, N.; Sood, A.; Valenta, Z.; Stojanac, Z. *Can. J. Chem.* **1975**, *53*, 619. (b) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (c) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 1613. (d) Dailey, O. D., Jr.; Fuchs, P. L. *Ibid.* **1980**, *45*, 216. (e) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (f) Dias, J. R.; Nassim, B. *Steroids* **1980**, *35*, 405. (g) Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619. (h) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. (i) Grieco, P. A.; Ferrino, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022. (j) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *Ibid.* **1982**, *47*, 601. (k) Mandell, L.; Lee, D. E.; Courtney, L. F. *Ibid.* **1982**, *47*, 610. (l) Kraus, G. A.; Taschner, M.; Shimagaki, M. *Ibid.* **1982**, *47*, 4271. (m) Fukumoto, K.; Chihiro, M.; Shiratori, Y.; Ihara, M.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1982**, 2973.

(3) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

(4) Efforts to employ other 1,3-butadienes such as i–iii were unsuccessful.



i ii iii

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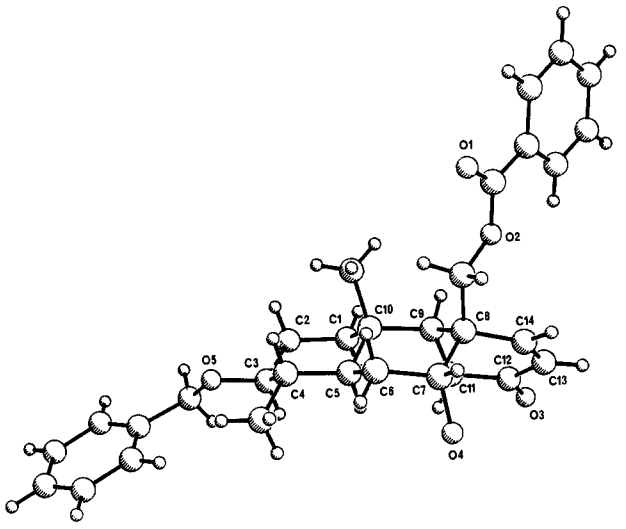
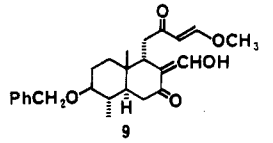


Figure 1. 3β-(Benzyloxy)-7α-hydroxy-8β-((benzoyloxy)-methyl)-19-nor-9β-podocarp-13-en-12-one (11). Each atom type has been drawn with fixed, arbitrary radius.

provided an adduct, **8**, which proved extremely sensitive to acid. Exposure of the adduct **8** to 0.005 M hydrochloric acid or silica gel led to the unexpected seco derivative **9**.



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After considerable experimentation to avoid the same problems that plagued the reduction of **4**, the sodium bis(2-methoxyethoxy)aluminum hydride reduction of the crude adduct in toluene at 0 °C[5] followed by acid hydrolysis furnished the 7α-alcohol **10** in 55% overall yield from the dienophile **3**. None of the epimeric 7β-alcohol was detected. We ascribe this 7α-stereoselectivity in the reduction of the Diels–Alder adduct to the additional steric bulk of the (trimethylsilyl)oxy group on the concave face of **8**. Differentiation of the primary and secondary neopentyl alcohol functionality in **10** involved the initial conversion to the monobenzoate derivative **11** using benzoyl chloride and 4-(dimethylamino)pyridine.[6] The ^1H NMR and particularly the ^{13}C NMR data (Table I) were consistent with these structural assignments, and an X-ray crystallographic determination of the crystal and molecular structure of **11** confirmed the relative stereochemistry of the seven chiral centers as shown in Figure 1. Further treatment of the monobenzoate **11** with chloroacetic anhydride followed by sodium iodide in acetone furnished the α-iodo ester **13**.

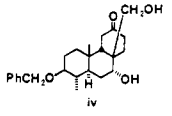
Table I. ^{13}C NMR Data[a]

carbon	10	11	12	13	14
1	26.4[b]	26.4[b]	26.2[b]	26.3[b]	26.6[b]
2	35.0[b]	34.8[b]	34.2[b]	34.4[b]	34.9[b]
3	82.9	82.7	82.5	82.7	82.7
4	44.0	44.6	44.3	44.4	43.9
5	38.3[c]	38.2	37.3[c]	37.5[c]	36.9[c]
6	31.0	30.3	27.3	27.1	26.8
7	68.8	67.7	72.2	72.0	77.5
8	47.5	46.6	45.1	45.1	39.9
9	38.7[c]	38.2	38.2[c]	38.2[c]	36.8[c]
10	36.0	36.1	36.1	36.2	35.9
11	37.5	37.5	37.0	37.3	35.0[d]
12	201.4	200.3	199.7	199.7	209.8
13	131.2	131.8	130.9	131.1	39.1[d]
14	154.6	152.4	151.2	151.3	34.6
15			40.7	−5.9	44.1[d]
16			165.7[d]	167.4[d]	171.1
C-8 CH_2	67.2	67.1	67.3	67.5	70.4
CH_2Ph	71.1	71.1	71.0	71.1	71.4
benzoate C=O		166.4	165.9[d]	165.8[d]	166.1
C-4β CH_3	23.0	23.0	22.4	22.5	22.4
C-10 CH_3	15.9	15.3	15.2	15.3	15.0
aromatic C	127.5	127.5	127.4	127.5	127.6
	127.8	127.8	127.7	127.8	127.8
	128.3	128.3	128.2	128.3	128.3
		128.6	128.5	128.6	128.8
		129.2	129.1	129.2	129.2
		129.5	129.5	129.5	129.5
		133.6	133.4	133.5	133.8
	138.6	138.7	138.5	138.6	138.6

[a] Assignments based upon distortionless enhancement polarization transfer (DEPT) experiments: Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323. [b-d] Signals may be interchanged.

An intramolecular Reformatsky reaction[7-9] of the α-chloro ester **12** or α-iodo ester **13** using either zinc or magnesium failed to furnish the desired lactone **14**. In contrast, exposure of the α-iodo ester **13** to 2 equiv of iodotrimethylsilane[10,11] in acetonitrile at −20 °C furnished the δ-lactone **14** in quantitative yield. Competitive cleavage of either the benzyl ether[12] or the lactone[13] itself was not observed at this temperature. This unusual cyclization presumably involved the initial addition of iodotrimethylsilane to the enone moiety[14] in **13** to secure the trimethylsilyl enol ether **15** bearing a 14β-iodo group on the sterically accessible, convex face. Subsequent attack by iodide ion on the α-iodo ester[15] and S_N2 displacement of the C-14β iodo group secured the δ-lactone **14**, an at-

(5) Reductions at higher temperatures than 0 °C for 1.25 h led to a 45% yield of the saturated ketone iv: IR (TF) 2919, 1700 cm^{-1}; ^1H NMR



iv

(C_6D_6) δ 0.68 (s, 3, C-10β CH_3), 1.05 (d, J = 5.9 Hz, 3, C-4α CH_3), 2.54–2.66 (m, 1, C*H*OBn), 3.02, 3.23 (AB q, J = 11.0 Hz, 2, CH_2OH), 3.89 (m, 1, C*H*OH), 4.29, 4.56 (AB q, J = 12.1 Hz, 2, CH_2Ph), 7.02–7.50 (m, 5, aromatic H); exact mass spectrum calcd for $C_{24}H_{34}O_4$, 386.2395; found, 386.2496.

(6) The use of 3 equiv of benzoyl chloride and 2 equiv of 4-(dimethylamino)pyridine was particularly important; reducing the equivalents of DMAP to one led to only a 13% yield of **11**, and increasing the equivalents of benzoyl chloride to ten led to an 81% yield of the dibenzoate derivative.

(7) Rathke, M. W. *Org. React. (N.Y.)* **1975**, *22*, 423.

(8) For examples of intramolecular Reformatsky reactions see: (a) Plattner, P. A.; Heusser, H. *Helv. Chim. Acta* **1945**, *28*, 1044. (b) Hulcher, F. H.; Hosick, T. A. U.S. Pat. 3119842, 1964; *Chem. Abstr.* **1964**, *60*, 10554g. (c) Ziegler, F. E.; Condon, M. E. *J. Org. Chem.* **1971**, *36*, 3707. (d) Kosugi, H.; Uda, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 160.

(9) Dubois, J. C.; Guette, J. P.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1966**, 3008.

(10) Schmidt, A. H. *Aldrichimica Acta* **1981**, *14*, 31.

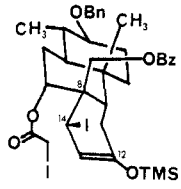
(11) A similar spirocyclization formed the basis for an elegant approach to the histrionicotoxin skeleton: Godleski, S. A.; Heacock, D. J. *J. Org. Chem.* **1982**, *47*, 4820. For other recent conjugate additions induced by TMSI, see: Marino, J. P.; Linderman, R. J. *Ibid.* **1981**, *46*, 3696. Kraus, G. A.; Gottschalk, P. *Tetrahedron Lett.* **1983**, *24*, 2727.

(12) (a) Ho, T.-L.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 774. (b) Voronkov, M. G.; Dubinskaya, E. I.; Pavlov, S. F.; Gorokhova, V. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 2355. (c) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(13) (a) Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 689. (b) Muchmore, D. C.; Dahlquist, F. W. *Biochem. Biophys. Res. Commun.* **1979**, *86*, 599. (c) Voronkov, M. G.; Komarov, V. G.; Albanov, A. I.; Kositsina, E. I.; Dubinskaya, E. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, *27*, 1692; *Chem. Abstr.* **1978**, *89*, 146971b.

(14) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1979**, 2305.

(15) For a similar dehalogenation leading to an ester enolate see: McGowan, D. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 7036.



15

tractive ABCD ring precursor to the quassinoids.

Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 spectrometer. The abbreviation TF denotes thin film. NMR spectra were determined on a JEOL 270-MHz NMR spectrometer. Mass spectra were determined on either a Varian MAT CH5, a VG-ZAB-IF, or a Kratos MS-50 mass spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

3β-(Benzyloxy)-8β-formyl-19-nor-9β-podocarp-12-en-7-one (4). A solution of 36.4 mg (0.12 mmol) of dienophile **3**, ca. 1 mL of 1,3-butadiene, and ca. 1 mg of methylene blue were heated in a sealed tube[17] at 150 °C for 64 h. After evaporation of excess 1,3-butadiene, the product was dissolved in ether, washed successively with water and brine, and dried over anhydrous magnesium sulfate. The product was chromatographed twice on silica gel in 1:3 ethyl acetate–hexane to afford 24 mg (55%) of **4**: R_f 0.54; mp 110–111 °C; IR (TF) 1722, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.17 (s, 3, C-10β CH_3), 2.77–2.94 (m, 1 C*H*OBn), 4.42, 4.64 (AB q, J = 11.2 Hz, 2, CH_2Ph), 5.59–5.89 (m, 2, vinylic H), 7.25–7.59 (m, 5, aromatic H), 9.54 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 64.1 (C-8), 71.2 (CH_2Ph), 82.5 (C-3), 122.2 (C-12 or C-13), 124.9 (C-12 or C-13), 127.6 (C_6H_5), 127.8 (C_6H_5), 128.4 (C_6H_5), 138.6 (C_6H_5), 198.9 (CHO), 206.9 (C-7); mass spectrum (70 eV), m/e (relative intensity) 366 (M^+, 0.4), 338 (28), 337 (31), 109 (20), 91 (100). Anal. ($C_{24}H_{30}O_3$) C, H.

3β-(Benzyloxy)-8β-(hydroxymethyl)-19-nor-9β-podocarp-12-en-7ξ-ol (5a and 5b). To 0.2 mL of toluene at 0 °C under a nitrogen atmosphere was added a solution of 10 μL of 3.46 M (0.03 mmol) of sodium bis(2-methoxyethoxy)aluminum hydride in toluene followed by 8 mg (0.02 mmol) of adduct **4** in 1 mL of toluene. The solution was stirred at 25 °C for 2.5 h and quenched with aqueous ethanol followed by 1 M hydrochloric acid. The mixture was diluted with water, and the product was extracted with ether. The ether solution was washed successively with water and brine and dried over anhydrous magnesium sulfate. The product was chromatographed on silica gel in 1:4 hexane–ethyl acetate to afford two epimeric alcohols, **5a** and **5b**.

A band (R_f 0.27) was eluted to afford 2.6 mg (31%) of **5a**: IR (TF) 3367, 2922 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.02 (s, 3, C-10β CH_3), 2.78–2.91 (m, 1, C*H*OBn), 3.43, 3.75 (AB q, J = 11.0 Hz, 3, CH_2OH), 4.02 (t, J = 6.2 Hz, 1, C*H*OH), 4.42, 4.64 (AB q, J = 11.6 Hz, 2, CH_2Ph), 5.67–5.79 (m, 2, vinylic H), 7.26–7.55 (m, 5, aromatic H); ^{13}C NMR ($CDCl_3$) δ 70.6 (CH_2OH), 71.0 (CH_2Ph), 73.7 (C-7), 83.1 (C-3), 126.1 (C-12 or C-13), 126.3 (C-12 or C-13), 127.4 (C_6H_5), 127.8 (C_6H_5), 128.3 (C_6H_5), 139.0 (C_6H_5); exact mass spectrum calcd for $C_{24}H_{34}O_3$–H_2O, 352.2420; found, 352.2392.

A band (R_f 0.34) was eluted to afford 1.3 mg (16%) of **5b**: IR (TF) 3369, 2920 cm^{-1}; ^1H NMR (C_6D_6) δ 0.87 (d, J = 6.5 Hz, 3, C-4α CH_3), 1.02 (s, 3, C-10β CH_3), 3.35, 4.13 (AB q, J = 11 Hz, 2, CH_2OH), 3.52 (dd, J = 6.5 Hz, 11 Hz, 1, C*H*OH), 4.29, 4.56 (AB q, J = 12.1 Hz, 2, CH_2Ph), 5.51–5.78 (m, 2, vinylic H), 6.95–7.50 (m, 5, aromatic H); ^{13}C NMR ($CDCl_3$) δ 69.7 (CH_2OH), 71.0 (CH_2Ph), 72.2 (C-7), 83.2 (C-3), 123.5 (C-12 or C-13), 125.0 (C-12 or C-13), 127.5 (C_6H_5), 127.8 (C_6H_5), 128.3 (C_6H_5), 138.8 (C_6H_5); exact mass spectrum calcd for $C_{24}H_{34}O_3$, 370.2529; found, 370.2496.

3β-(Benzyloxy)-19-nor-9β-podocarp-12-en-7-one (6). To 0.14 mL of 1 M (0.14 mmol) lithium tri-*sec*-butylborohydride in anhydrous THF at 0 °C under a nitrogen atmosphere was added 24 mg (0.065 mmol) of **4** in 0.6 mL of anhydrous THF. After stirring for 1.5 h at 0 °C, the reaction was quenched by the dropwise addition of 0.4 mL of 1 M hydrochloric acid. The mixture was stirred for 10 min at 0 °C, poured into water, and extracted with ether. The ether solutions were washed successively with water and brine and dried over anhydrous magnesium sulfate. The product was chromatographed on silica gel in 1:20 ethyl acetate–dichloromethane to afford 8.2 mg (38%) of **6**: R_f 0.57; IR ($CHCl_3$) 2919, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.8 Hz, 3, C-4α CH_3), 1.30 (s, 3, C-10β CH_3), 4.42, 4.64 (AB q, J = 10.8 Hz, 2, CH_2Ph), 5.47–5.70 (m, 2, CH=CH), 7.20–7.46 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 338 (2), 247 (2), 211 (4), 123 (16), 107 (14), 91 (100); exact mass spectrum calcd for $C_{23}H_{30}O_2$, 338.2242; found, 338.2249.

Summary of Spectral Data. Seco-derivative 9: IR (TF) 1682, 1636, 1617, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 3, OCH_3), 5.58 (d, J = 12.4 Hz, 1, COC*H*=CH), 7.59 (d, J = 12.4 Hz, 1, COCH=C*H*), 8.62 (s, 1, C*H*OH), 14.53 (s, 1, CHO*H*); exact mass spectrum (70 eV), m/e (relative intensity) 394 (9), 352 (3), 149 (14), 91 (100). This material deteriorated rapidly and a satisfactory elemental analysis was not obtained. This material also failed to display a parent ion in the exact mass spectrum and, hence, an exact mass determination was not possible.

3β-(Benzyloxy)-7α-hydroxy-8β-(hydroxymethyl)-19-nor-9β-podocarp-13-en-12-one (10). A solution of 125 mg (0.4 mmol) of dienophile **3** and 153 mg (0.89 mmol, 2.2 equiv) of 1-methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (**7**) in 1 mL of anhydrous benzene was stirred at 25 °C for 6.5 h. The ^1H NMR ($CDCl_3$) displayed signals characteristic of the desired adduct **8**: δ 0.21 (s, 9, $Si(CH_3)_3$), 0.76 (s, 3, C-10β CH_3), 0.99 (d, J = 6.5 Hz, 3, C-4α CH_3), 2.82–2.95 (m, 1, C*H*OBn), 3.13 (s, 3, OCH_3), 4.29 (d, J = 6.5 Hz, 1, C*H*OCH_3), 4.44, 4.66 (AB q, J = 11.3 Hz, 2, CH_2Ph), 4.91 (m, 1, vinylic H), 7.24–7.50 (m, 5, aromatic H), 9.80 (s, 1, CHO). To 1.14 mL of 0.42 M (0.48 mmol) sodium bis(2-methoxyethoxy)aluminum hydride in toluene at 0 °C under a nitrogen atmosphere was added the crude adduct **8** in 1.5 mL of toluene. After stirring for 15 min at 0 °C, the solution was diluted with 40 mL of THF and quenched with 2.5 ml of 1 M hydrochloric acid. The mixture was stirred at 25 °C for 1.25 h, poured into 250 mL of water, and extracted with ether. The ether solutions were dried over anhydrous magnesium sulfate, concentrated, and dissolved in 10 mL of 1:4 0.005 M aqueous hydrochloric acid–THF. The solution was stirred at 25 °C for 1 h, poured into water, and extracted with 1:1 ethyl acetate–ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The product was chromatographed on silica gel in ethyl acetate to afford 85 mg (55%) of **10**: R_f 0.19; mp 148–149 °C; IR (KBr) 3359, 3274, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.06 (s, 3, C-10β CH_3), 2.47–2.75 (m, 2, $COCH_2$), 2.75–2.92 (m, 1, C*H*OBn), 3.62, 3.82 (AB q, J = 11.4 Hz, 2, CH_2OH), 4.02 (m, 1, C*H*OH), 4.40, 4.62 (AB q, J = 11.3 Hz, 2, CH_2Ph), 6.16 (d, J = 10.3 Hz, 1, C-13 vinylic H), 6.91 (d, J = 10.3 Hz, 1, C-14 vinylic H), 7.26–7.40 (m, 5, aromatic H); ^{13}C NMR ($CDCl_3$) δ 67.2 (CH_2OH), 68.8 (C-7), 71.1 (CH_2Ph), 82.9 (C-3), 127.6 (C_6H_5), 127.8 (C_6H_5), 128.3 (C_6H_5), 138.7 (C_6H_5), 131.2 (C-13), 154.7 (C-14), 201.4 (C-12). Anal. ($C_{24}H_{32}O_4$) C, H.

Repetition of this sequence using 2.0 g of dienophile **3** and 2.4 g of diene **7** in 20 mL of benzene for 9 h followed by 2.2 mL of 3.46 M sodium bis(2-methoxyethoxy)aluminum hydride and followed by aqueous acid gave 1.3 g (53%) of diol **10** by direct crystallization from the crude product in 1:2:2 hexane–ether–ethyl acetate.

3β-(Benzyloxy)-7α-hydroxy-8β-((benzoyloxy)methyl)-19-nor-9β-podocarp-13-en-12-one (11). To 77.7 mg (0.202 mmol) of diol **10** in 4 mL of anhydrous pyridine at 0 °C under nitrogen atmosphere was added 49.3 mg (0.404 mmol, 2 equiv) of 4-(dimethylamino)pyridine and 85.1 mg (0.606 mmol, 3 equiv) of benzoyl chloride.[6] The solution was stirred at 25 °C for 15 h. After stirring for 15 min, the product was diluted with ethyl acetate, washed successively with aqueous 1 M hydrochloric acid and brine, and dried over anhydrous magnesium sulfate. The product was

(16) (a) Still, W. C.; VanMiddlesworth, F. L. *J. Org. Chem.* **1977**, *42*, 1258. (b) Marshall, J. A.; Schaeffer, D. J. *Ibid.* **1965**, *30*, 3642. (c) Caine, D.; Tuller, F. N. *Ibid.* **1969**, *34*, 222. (d) Ayer, W. A.; Browne, L. M.; Fung, S. *Can. J. Chem.* **1976**, *54*, 3276.

(17) Sealed tubes were prepared by washing successively with water, acetone, ethanol, and ether, soaking the tube in ether–trimethylsilyl chloride, washing with ether, and finally, drying in an oven at ca. 90 °C for 1 h. We thank Professor R. H. Schlessinger for the details of this procedure.

chromatographed on silica gel in 1:1 ethyl acetate–dichloromethane to afford 96.7 mg (98%) of **11**: R_f 0.65; mp 168.5–170 °C; IR (KBr) 3398, 1708, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.08 (s, 3, C-10β CH_3), 2.58–2.95 (m, 3, $COCH_2$ and C*H*OBn), 4.01 (m, 1, C*H*OH), 4.34, 4.62 (AB q, J = 11 Hz, 2, CH_2OBz), 4.42, 4.64 (AB q, J = 11.6 Hz, 2, CH_2Ph), 6.25 (d, J = 10.3 Hz, 1, C-13 vinylic H), 6.89 (d, J = 10.3 Hz, 1, C-14 vinylic H), 7.26–8.01 (m, 10, aromatic H); ^{13}C NMR ($CDCl_3$) δ 67.2 (*C*H_2OBz), 67.8 (C-7), 71.2 (*C*H_2Ph), 82.8 (C-3), 152.5 (C-14), 166.5 (*C*OPh), 200.3 (C-12); mass spectrum (70 eV), m/e (relative intensity) 488 (0.01), 397 (13), 259 (20), 151 (25), 107 (45), 105 (70), 91 (100). Anal. ($C_{31}H_{36}O_5$) C, H.

X-ray Structure Determination. For **11**, $C_{31}H_{36}O_5$, a small crystal (0.35 × 0.25 × 0.20 mm^3) exhibited extinction conditions consistent with $C2/c$ (No. 15) or Cc (No. 9); the structure was solved and refined in $C2/c$. At −130 °C, a = 39.91 (1) Å, b = 7.190 (2) Å, c = 19.764 (8) Å, β = 117.60 (3)°, and Z = 8. Of 4588 reflections examined on the Nicolet R3m diffractometer (3.5° < 2θ < 50° and k, l, ≥ 0), 3132 unique observed ($I > 1.2\sigma(I)$) reflections were used for structure refinement. Refinement of the structural parameters (anisotropic thermal parameters for all non-hydrogen atoms, hydrogen atoms at idealized positions) gave R = 0.072, R_w = 0.085, and 1.57 for the standard deviation for an observation of unit weight. The highest peak in a final difference electron density map had a height of only 0.52 e Å^{-3}.

3β-(Benzyloxy)-8β-((benzoyloxy)methyl)-7α-(chloroacetoxy)-19-nor-9β-podocarp-13-en-12-one (12). To 151 mg (0.885 mmol, 5 equiv) of chloroacetic anhydride and 21.6 mg (0.177 mmol, 1 equiv) of 4-(dimethylamino)pyridine in 1.0 mL of anhydrous pyridine in at 0 °C under a nitrogen atmosphere was added 86.4 mg (0.177 mmol) of monobenzoate **11** in 1.25 mL of anhydrous pyridine. The mixture was stirred for 7 h at 0 °C. The product was diluted with 100 mL of ethyl acetate, washed successively with 1 M hydrochloric acid solution, water, saturated sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The product was chromatographed on preparative layer Macherey–Nagel silica gel plates in 2:25 ethyl acetate–dichloromethane to afford 83.9 mg (84%) of **12**: R_f 0.79; mp 151.5–152.5 °C (from dichloromethane–hexane); IR (KBr) 1741, 1715, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 5.7 Hz, 3, C-4α CH_3), 1.16 (s, 3, C-10β CH_3), 3.98 (s, 2, $COCH_2Cl$), 4.3–4.8 (m, 4, two overlapping AB q for CH_2Ph, CH_2OBz), 5.39 (m, 1, C-7α H), 6.18 (d, J = 10.3 Hz, 1, C-13 vinylic H), 6.77 (d, J = 10.3 Hz, 1, C-14 vinylic H), 7.2–8.1 (m, 10, aromatic H).

3β-(Benzyloxy)-8β-((benzoyloxy)methyl)-7α-(iodoacetoxy)-19-nor-9β-podocarp-13-en-12-one (13). A mixture of 237 mg (0.420 mmol) of α-chloroacetate **12** and 1.26 g (0.84 mmol, 20 equiv) of sodium iodide in 7 mL of acetone was refluxed for 8 h. The mixture was evaporated to dryness under a nitrogen stream, diluted with water and 20% dichloromethane–ether, and extracted. The organic solutions were washed successively with water and brine and dried over anhydrous magnesium sulfate. The product was chromatographed on preparative layer Macherey–Nagel silica gel in 1:30 ethyl acetate–dichloromethane to afford 252 mg (92%) of **13**: R_f 0.30; mp 125–126.5 °C (from ether–dichloromethane); IR (KBr) 1725 (sh), 1715, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.16 (s, 3, C-10β CH_3), 3.61 (s, 2, $COCH_2I$), 4.3–4.8 (m, 4, two overlapping AB q for CH_2Ph, CH_2OBz), 5.30 (m, 1, C-7α H), 6.20 (d, J = 10.3 Hz, 1, C-13 vinylic H), 6.76 (d, J = 10.2 Hz, 1, C-14 vinylic H), 7.2–8.1 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 656 (<1), 565 (63), 467 (22), 439 (18), 380 (50), 349 (48), 257 (100). Anal. ($C_{33}H_{37}IO_6$) C, H.

3β-(Benzyloxy)-20-hydroxy-21-nor-9β-picrasan-12-one Benzoate (14). To 10 mg (0.0152 mmol) of α-iodoacetate **13** in 0.4 mL of anhydrous acetonitrile at −20 °C under a nitrogen atmosphere was added 6.1 mg (0.0305 mmol, 2 equiv) of iodotrimethylsilane. The color of iodine was immediately noted. The mixture was stirred for 3 h at −20 °C and quenched with 0.5 mL of 1 M hydrochloric acid solution. The product was diluted with ethyl acetate, washed successively with 0.5 M sodium thiosulfate solution and brine, and dried over anhydrous magnesium sulfate. TLC displayed only two spots: desired product and S_8 derived from the thiosulfate wash. The product was chromatographed on a 20 × 20 cm analytical Merck silica gel plate in 1:10 ethyl acetate–dichloromethane to afford 8.1 mg (100%) of **14**: R_f 0.30; mp 230.5–232 °C (from dichloromethane–hexane); IR (KBr) 1739, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 5.9 Hz, 3, C-4α CH_3), 1.20 (s, 3, C-10β CH_3), 4.4–4.8 (m, 5, CH_2Ph, CH_2OBz, C-7αH), 7.2–8.1 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 530 (0.7), 439 (84), 317 (99), 299 (49), 261 (85), 181 (51), 169 (63), 131 (82), 119 (100). Exact mass spectrum calcd for $C_{33}H_{38}O_6$, 530.2669; found, 530.2688. Anal. ($C_{33}H_{38}O_6$) C, H.

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Registry No. (±)-**3**, 84132-46-7; (±)-**4**, 86863-37-8; (±)-**5a**, 86863-38-9; (±)-**5b**, 86863-39-0; (±)-**6**, 86863-40-3; **7**, 59414-23-2; (±)-**9**, 86863-41-4; (±)-**10**, 86863-42-5; (±)-**11**, 86863-43-6; (±)-**12**, 86863-44-7; (±)-**13**, 86863-45-8; (±)-**14**, 86863-46-9; 1,3-butadiene, 106-99-0; iodotrimethylsilane, 16029-98-4.

Supplementary Material Available: Tables related to the structure of **11**: Table 1, atomic coordinates for the non-hydrogen atoms; Table 2, bond lengths; Table 3, bond angles; Table 4, anisotropic thermal parameters; Table 5, hydrogen atom coordinates; and a copy of Figure 1 showing the atom labeling scheme used in the crystallographic work (6 pages). Ordering information is given on any current masthead page.