A Free-Radical Cyclization of α-Bromo Acetals Leading to Tetracyclic 9β-Picrasanes[1]

Moonsun Kim, Raymond S. Gross, Hubert Sevestre, Norma K. Dunlap, and David S. Watt*

Department of Chemistry, Division of Medicinal Chemistry, and Lucille Parker Markey Cancer Center, University of Kentucky, Lexington, Kentucky 40506

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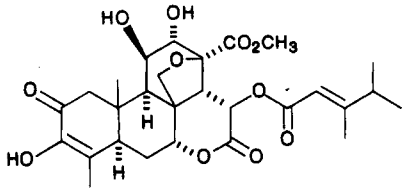
A free-radical cyclization of a tricyclic 18,19-bisnor-9β-podocarp-13-en-12-one that was derived from (*R*)-(−)-4,4a,7,8-tetrahydro-4a-methyl-2,5(3*H*,6*H*)-naphthalenedione and that possessed a C-7α (1-bromo-2-ethoxy)ethoxy group led to a tetracyclic intermediate possessing a protected 7α,16-lactol and suitable functionality for a quassinoid synthesis.

The quassinoids[2] comprise a complex family of degraded triterpenes that possess a spectrum of biological activities and represent a significant synthetic challenge.[3] Many of the quassinoids possess a δ-lactone ring as a characteristic structural feature as illustrated by bruceantin (1) and similikalactone D (2). Various synthetic procedures



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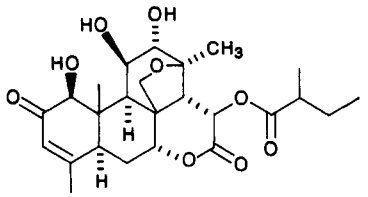

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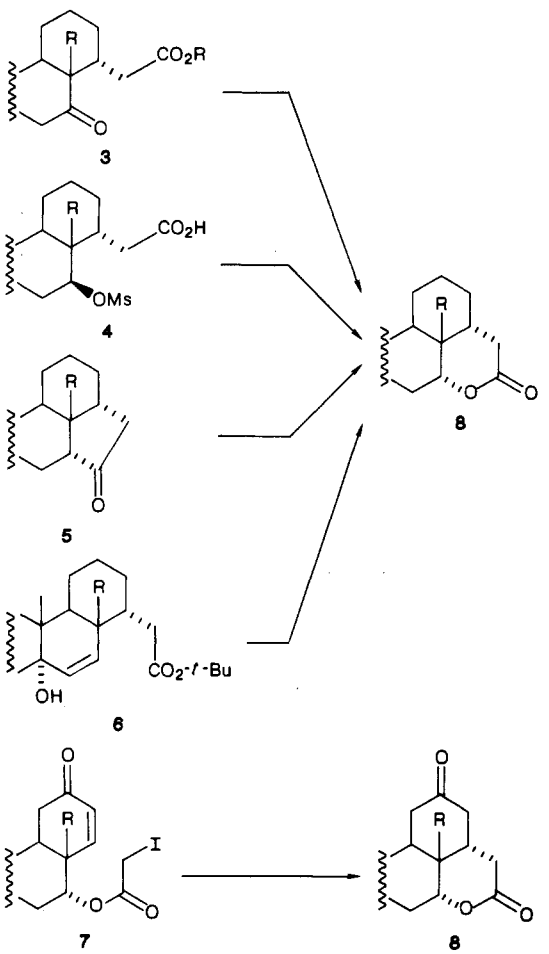
have been developed to introduce this functionality with the correct stereochemistry at both the C-7 and C-14 centers. As shown in Scheme I, these methods include the reduction of C-7 ketone **3** in the presence of a C-14α carbalkoxymethyl group in order to obtain the δ-lactone **8**,[4] the S_N2 displacement of C-7β mesylate **4** by a C-15 carboxy group,[3f,5] the Baeyer–Villiger oxidation of cyclopentanone **5**,[6] the equilibration of a C-6 ketone to introduce the correct C-7α stereochemistry,[7] the reduction of the tosylhydrazone of a 13-en-12-one,[8] and the oxidative solvolysis of allylic alcohol **6** with concomitant participation of a C-15 ester.[9] We added to this list of lactonization reactions by developing a cyclization[10] of α-iodoacetate **7**,

Scheme I



(1) This paper is 7 in a series dealing with the synthesis of quassinoids. For 6, see: Gross, R. S.; Watt, D. S. *Synth. Commun.* **1987**, *17*, 1749. Portions of this work were presented at the Colloque sur la Chimie des Terpenes in Grasse, France, April 1986.

(2) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101; **1985**, *47*, 221.

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(4) (a) Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, *21*, 1619. (b) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7587. (c) Murae, T.; Honda, T.; Ohta, S.; Kurata, Y.; Matsuo, H.; Takahashi, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 24th* **1981**, 348; *Chem. Abstr.* **1982**, *96*, 162979k. (d) Honda, T.; Murae, T.; Ohta, S.; Kurata, Y.; Kawai, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 299. (e) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601; **1984**, *49*, 2342. (f) Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539. (f) Stevens, R. V.; Vinogradoff, A. P. *J. Org. Chem.* **1985**, *50*, 4056.

(5) Shishido, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. *J. Chem, Soc., Perkin Trans. 1* **1984**, 2139.

(6) (a) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3346. (b) Fukumoto, K.; Chihiro, M.; Shiratori, Y.; Ihara, M.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1982**, *23*, 2973. (c) Fukumoto, K.; Chihiro, M.; Ihara, M.; Kametani, T.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2569.

(7) Weller, D. D.; Stirchak, E. P. *J. Org. Chem.* **1983**, *48*, 4873.

(8) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353.

(9) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264.

(10) (a) Voyle, M.; Dunlap, N. K.; Watt, D. S.; Anderson, O. P. *Ibid.* **1983**, *48*, 3242. (b) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839. (c) Demir, A. S.; Gross, R. S.; Dunlap, N. K.; Bashir-Hashemi, A.; Watt, D. S. *Ibid.* **1986**, *27*, 5567.

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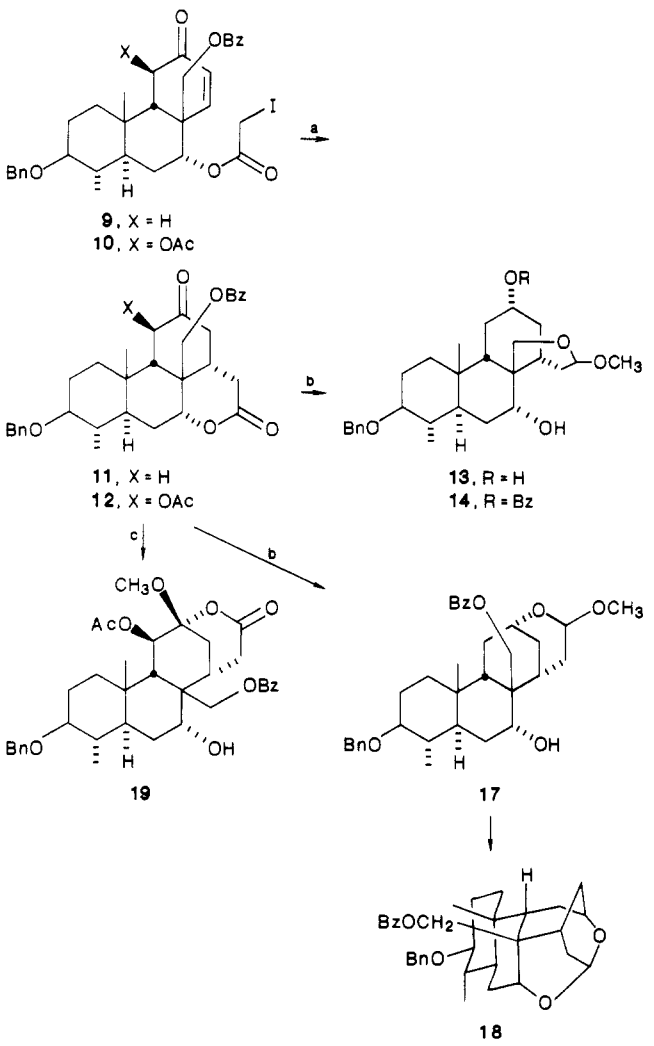
Scheme II[a]

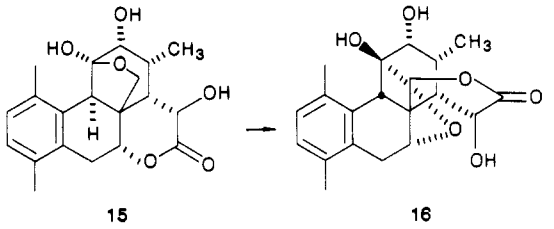


[a] (a) TMSI, Et_3N (ref 10); (b) DIBAL followed by HCl, MeOH; (c) HCl, MeOH.

which was promoted by iodotrimethylsilane. In the course of work designed to elaborate these intermediates, we found that the reduction of the δ-lactone or the C-12 ketone within a 9β-picrasane skeleton led to a number of rearrangements. Consequently, we report a direct approach for the introduction of a protected δ-lactol that did not involve the reduction of a δ-lactone[11] and that, in addition, provided intermediates suitable for an enantioselective synthesis[3h,12] of quassinoids.

We developed an approach to the racemic, tetracyclic 19-nor-9β-picrasan-12-ones[10] **11** and **12** involving the cyclization of tricyclic α-iodoacetate derivatives **9** and **10**, respectively, using iodotrimethylsilane (Scheme II). In anticipation of various base-catalyzed reactions needed for transformations elsewhere in the skeleton, we needed to convert the δ-lactone in **11** or **12** to a protected δ-lactol. However, the selective manipulation of the δ-lactone in the presence of the other carbonyl groups proved difficult as a consequence of the cis fusion of the BC rings which placed the functionality at C-7, C-12, and C-16 within close proximity. Conditions were not identified that would permit the selective reduction of the δ-lactone in **11** in the presence of the C-12 ketone and the C-20 benzoate.[13]

The complete reduction, for example, of **11** using an excess of diisobutylaluminum hydride followed by treatment with acidic methanol produced the protected 16,20-lactol **13**, reminiscent of a similar translactonization encountered in the rearrangement of glaucanol (**15**) to isoglaucanol A (**16**).[2] Exclusion of the isomeric protected



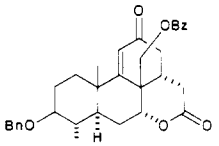
7α,16-lactol or the 12α,16-lactol was based on the conversion of **13** to a monobenzoate **14**, which did not possess the characteristic AB quartet for the C-20 (benzoyloxy)methyl group in the ^1H NMR spectrum. Under conditions where only the δ-lactone and the C-12 ketone in **11** were reduced, we encountered another transacetalization leading to the 12α,16-lactol **17** as well as the curious internal acetal **18** in poor yield. Finally, efforts to protect the C-12 ketone in **12** as a dimethoxy ketal prior to the reduction of the δ-lactone led to a translactonization of the hemiketal intermediate[14] to give the rearranged δ-lactone **19**.

These difficulties highlighted the need to develop a route to a 9β-picrasane intermediate that would avoid the need to reduce a δ-lactone in the presence of a C-12 ketone. Previous methods for the direct introduction of a protected δ-lactol that do not involve the reduction of a δ-lactone

(11) For examples of δ-lactone reductions in related systems using sodium borohydride or diisobutylaluminum hydride, see: (a) Moron, J.; Rondest, J.; Polonsky, J. *Experientia* **1966**, *22*, 511. (b) Polonsky, J.; Bourguignon-Zylber, N. *Bull. Soc. Chim. Fr.* **1965**, 2793. (c) Murae, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 941. (d) Ishibashi, M.; Tsuyuki, T.; Murae, T.; Hirota, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Ibid.* **1983**, *56*, 3683.

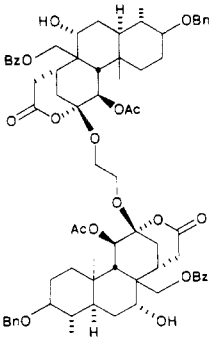
(12) For recent efforts to develop an enantioselective synthesis from chiral substrates, see: (a) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (b) Nassim, B.; Schlemper, E. O.; Dias, J. R. *Steroids* **1982**, *39*, 2926. (c) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, Y.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339. (d) Ziegler, F. E.; Hwang, K.-J., Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573.

(13) We have also examined the logical alternatives involving the inversion of the C-9β stereochemistry in tricyclic intermediates but this approach led to yet another rearrangement: Dunlap, N. K.; Gross, R. S. Watt, D. S. *Synth. Commun.*, in press. In addition, we have also prepared tetracyclic enone i (ref 10c) but found that selective manipulation of functionality in this intermediate was also problematical.



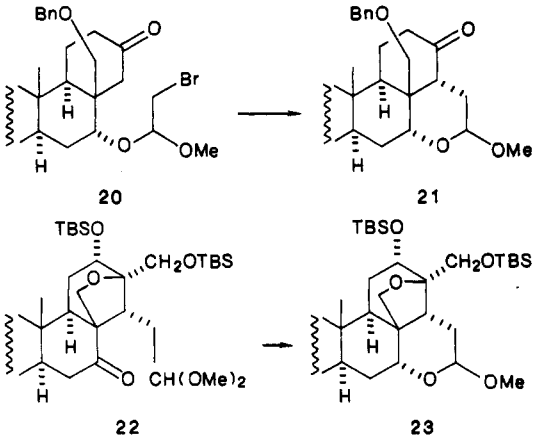
i

(14) An apparent solution to this problem would employ ethylene glycol such that the conversion of the hemiketal to the ketal would be an intramolecular process; however, the use of ethylene glycol led to the formation of rearranged lactone ii.



ii

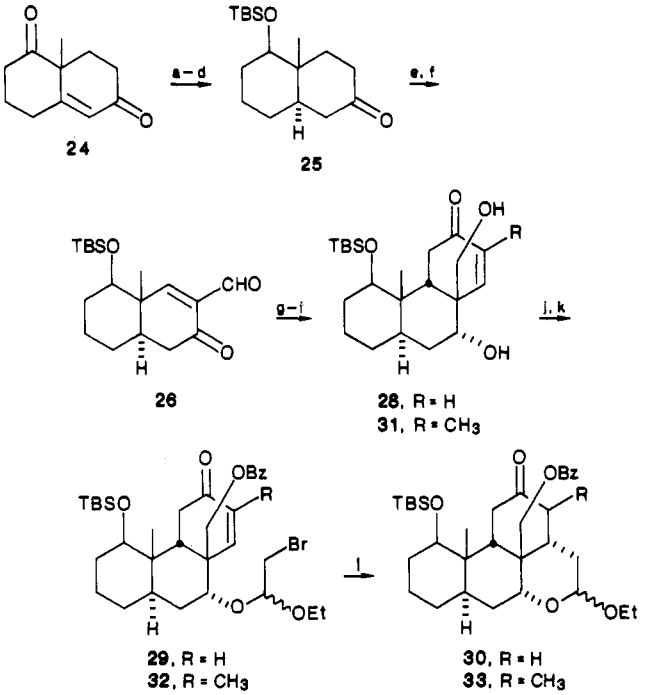
include the enolate alkylation[3a] of the bromo acetal **20** and the transacetalization[15] of ketone **22**. We developed an alternate approach that would take advantage of the methodology which we had already developed and that would also permit the development of an enantioselective synthesis.



The *R* enantiomer of the Wieland–Miescher ketone[16] **24** served admirably as a starting material for such an approach as shown in Scheme III. Application of the Hajos–Parrish procedure[17] using D-proline to 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione furnished **24** in 98% ee and in good yield. Although this procedure required the expensive D-proline catalyst, the economy of operations necessary to transform **24** to a suitable dienophile outweighed the possible use of the *S* enantiomer of **24** available from the L-proline-catalyzed cyclization. As shown in Scheme III, sodium borohydride reduction[18] of the C-2 ketone, protection using *tert*-butyldimethylsilyl chloride,[19] lithium–ammonia reduction,[20] and pyridinium chlorochromate oxidation[21] furnished the bicyclic ketone **25** having appropriately differentiated oxygen functionality and the required trans fusion of the AB rings. Conversion of **25** to the dienophile **26** involved the regioselective condensation of **25** with ethyl formate and an oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[10] or preferably with phenylselenyl chloride.[22] A Diels–Alder reaction of **26** with Danishefsky's diene (**27a**), reduction of the initial adduct with sodium bis(2-methoxyethoxy)aluminum hydride, and acid-catalyzed hydrolysis of the intermediate β-methoxy trimethylsilyl enol ether afforded the tricyclic enone **28**. Selective benzoylation of the primary hydroxyl group in **28** and *N,N*-dimethylaniline-catalyzed exchange with 1,2-dibromoethyl ethyl ether[23] provided the key intermediate **29** as a 1:1 mixture of diastereomers that could be separated by chromatography.

Recent interest in the use of free-radical-based procedures for cyclization processes[24] suggested that the reduction of an α-bromo acetal[25] would afford the desired tetracyclic adduct. The tri-*n*-butyltin hydride reduction of **29** led to the tetracyclic intermediate **30** as approximately a 2.1:1.8 mixture of C-16 epimers in 57% yield.[10] Independent cyclization of each diastereomer **29a** and **29b** led to comparable yields of one of the diastereomers of **30**. The configuration at C-16 in these diastereomers was not determined, and exposure of the mixture of diastereomers

Scheme III[a]



[a] (a) $NaBH_4$, EtOH, 0 °C, 4 h; (b) *t*-$BuMe_2SiCl$, imidazole; (c) Li, NH_3, Et_2O; (d) PCC, NaOAc, CH_2Cl_2; (e) NaH, HCO_2Et, DME, EtOH (cat.); (f) PhSeCl, $CHCl_3$, Py, followed by 30% H_2O_2; (g) CH_2=C(OTMS)CH=CHOMe (**27a**) or CH_2=C(OTMS)C(Me)=CHOMe (**27b**); (h) $NaAlH_2(OCH_2CH_2OMe)_2$, toluene; (i) 0.005 M HCl; (j) PhCOCl, DMAP, Py; (k) $BrCH_2CHBrOEt$, $PhNMe_2$, CH_2Cl_2; (l) *n*-Bu_3SnH, AIBN, benzene, 80 °C.

30 to ethanol and 10-camphorsulfonic acid did not alter the diastereomeric ratio.

Since a number of the quassinoids also possess a C-13 methyl group,[2] we sought to extend this method to the preparation of intermediates bearing this additional substituent. We employed a similar sequence using 1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene[26] (**27b**) in place of Danishefsky's diene to prepare the C-13 methyl analogue **31**. We were pleased that the overall yield of the Diels–Alder sequence leading to **31** was 85%, a significant improvement over the yield in the sequence leading to **28**. Conversion of the tricyclic material **31** to the α-bromo acetal **32** followed exactly the same sequence described earlier, but in this case, we were unable to separate the diastereomeric α-bromo acetals **32**. The free-radical cyclization of **32** furnished the desired adduct **33** in 82% yield as a mixture of diastereomers at C-16 but not C-13.

(15) Murae, T.; Sasaki, M.; Konosu, T.; Matsuo, H.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 3411.

(16) For a racemic synthesis using a C-1 methyl analogue of **24**, see ref 15. In addition, Mander has developed a synthesis of a C-4α carbomethoxy analogue of **24** for a projected quassinoid synthesis: Hamilton, R. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron* **1986**, *42*, 2881.

(17) (a) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1985**, *63*, 26. (b) Buchschacher, P.; Furst, A. *Ibid.* **1985**, *63*, 37.

(18) Heathcock, C. H.; Badger, R. A.; Patterson, J. W., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4133.

(19) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(20) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(21) For a review, see: Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245.

(22) Bosch, M. P.; Camps, F.; Coll, J.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

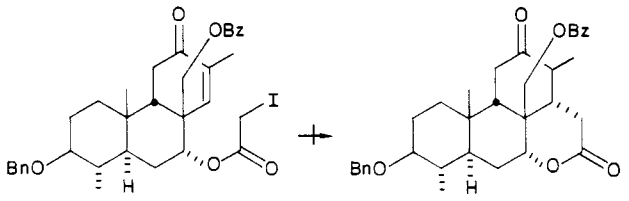
(23) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720.

(24) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.

(25) For related free-radical cyclizations of α-bromo acetals, see: (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *Ibid.* **1983**, *105*, 3741. (c) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317. (d) Hutchinson, J. H.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1987**, *28*, 1313. For a recent example of a free-radical cyclization employing an enone as an acceptor, see: Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.

(26) Danishefsky, S. J.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

Relative to the cyclization of **29**, this yield also represented a gratifying improvement in the overall yield. The free-radical cyclization process was particularly satisfying since the iodotrimethylsilane-induced cyclization of α-iodo acetate **34** had failed for the case where a C-13 methyl group was present.[10c]



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Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 or Perkin-Elmer Model 567 spectrometer. The abbreviation TF denotes thin film. NMR spectra were determined on a Varian XL-200 or Gemini 200-MHz spectrometer. Mass spectra were determined on a VG ZAB 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. Column chromatography using Macherey Nagel silica gel 60 is referred to as "chromatography on silica gel", preparative layer chromatography on Macherey Nagel silical gel F254 is referred to as "chromatography on a silica gel plate," and the drying of an organic phase over anhydrous magnesium sulfate is simply indicated by the phrase "dried".

3β-(Benzyloxy)-8β-(hydroxymethyl)-14α-(formylmethyl)-19-nor-9β-podocarpane-7α,12α-diol Methyl Acetal (13). To 11.4 mg (0.02 mmol) of **11** in 0.5 mL of dichloromethane at −78 °C under a nitrogen atmosphere was added 129 μL (0.12 mmol) of 1 M diisobutylaluminum hydride in hexane in portions at 1-h intervals. The solution was stirred for 30 min after the last addition and quenched with 0.5 mL of 1 M hydrochloric acid solution. The product was diluted with in ethyl acetate, washed with saturated sodium bicarbonate solution and brine, and dried. The crude product was dissolved in 3 mL of methanol, and 3 drops of concentrated hydrochloric acid were added. The solution was stirred at 25 °C for 1 h, diluted with ethyl acetate, washed with saturated sodium bicarbonate solution and brine, and dried. The product was chromatographed on a silica gel plate in 1:1 ethyl acetate–dichloromethane to afford 7.7 mg (81%) of **13**: IR (KBr) 3426 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3, C-10β CH_3), 0.98 (d, J = 7.3 Hz, 3, C-4α CH_3), 3.34 (s, 3, OCH_3), 3.36, 3.90 (AB q, J = 11.6 Hz, 2, C-20 CH_2O), 3.6–3.7 (m, 1, C-7β H), 4.42, 4.65 (overlapping br s and AB q, J = 11.8 Hz, 3, CH_2Ph and C-16 H), 7.27–7.35 (m, 5, Ar H); ^{13}C NMR ($CDCl_3$) δ 97.5 (C-16), 76.8 (C-7), 70.0 (C-12); mass spectrum (70 eV), m/e (relative intensity) 444 (M^+, <1), 426 (4), 414 (12), 394 (9); exact mass spectrum calcd for $C_{27}H_{40}O_5$ 444.2876, found 444.2902.

3β-(Benzyloxy)-8β-(hydroxymethyl)-14α-(formylmethyl)-19-nor-9β-podocarpane-7α,12α-diol Methyl Acetal 12α-Benzoate (14). To 7 mg (0.16 mmol) of **13** in 0.35 mL of anhydrous pyridine was added 3.8 mg (0.03 mmol) of 4-(dimethylamino)pyridine, and 6.6 mg (0.05 mmol) of benzoyl chloride. The solution was stirred for 3 h, diluted with ethyl acetate, washed with 1 M hydrochloric acid solution and brine, and dried. The crude product was chromatographed on a silica gel plate in 1:4 ethyl acetate–dichloromethane to afford 4.6 mg (53%) of **14**: ^{1}H NMR ($CDCl_3$) δ 0.98–0.99 (overlapping d and s, 6, C-4α CH_3 and C-10β CH_3), 3.35 (s, 3, OCH_3), 3.40, 4.02 (AB q, J = 13 Hz, C-20 CH_2O), 3.9–4.0 (m, 1, C-7β H), 4.41, 4.63 (AB q, J = 11.9 Hz, CH_2Ph), 4.69 (br s, 1, C-16 H), 4.95–5.10 (m, 1, C-12β H), 7.33–8.05 (m, 10, Ar H); ^{13}C NMR ($CDCl_3$) δ 166.1 (benzoate C=O), 97.4 (C-16), 74.3 (C-7), 69.9 (C-12).

8β-[(Benzoyloxy)methyl]-3β-(benzyloxy)-14α-(formylmethyl)-19-nor-9β-podocarpane-7α,12α-diol Methyl Acetal (17). To 10.8 mg (0.02 mmol) of **11** in 0.5 mL of dichloromethane at −78 °C under a nitrogen atmosphere was added 42 μL (0.04 mmol) of 1 M diisobutylaluminum hydride in hexane. The solution was stirred at −78 °C for 4.5 h and quenched with 0.5 mL of 1 M hydrochloric acid solution. The product was dissolved in ethyl acetate, washed successively with saturated sodium bicarbonate solution and brine, and dried. The crude product was dissolved in 3 mL of methanol, and 3 drops of concentrated hydrochloric acid were added. The solution was stirred at 25 °C for 1 h, diluted with ethyl acetate, washed successively with saturated sodium bicarbonate solution and brine, and dried. The product was chromatographed on a silica gel plate in 1:1 ethyl acetate–dichloromethane to afford 2.4 mg (22%) of **17**: ^{1}H NMR ($CDCl_3$) δ 1.03–1.05 (overlapping d and s, 6, C-4α CH_3 and C-10β CH_3), 3.38 (s, 3, OCH_3), 3.61, 4.18 (AB q, J = 5.7 Hz, 2, C-20 CH_2O), 4.42, 4.65 (AB q, J = 11.5 Hz, 2, CH_2Ph), 4.87 (t, J = 1, C-16 H), 7.34–8.01 (m, 10 Ar H); exact mass spectrum calcd for $C_{33}H_{41}O_5$ (M^+ − OCH_3) 517.2954, found 517.2978.

11β-Acetoxy-8β-[(benzoyloxy)methyl]-3β-(benzyloxy)-14α-(carboxymethyl)-12β-methoxy-9β-podocarpane-7α,12α-diol 12α-Lactone (19). A mixture of 36 mg (0.06 mmol) of **12**, 3 mL of methanol, 1.5 mL of dichloromethane, and 4 drops of concentrated hydrochloric acid was stirred for 4.5 h. The mixture was diluted with ethyl acetate, washed with sodium bicarbonate solution and brine, and dried. The product was chromatographed on a silica gel plate in 1:2 ethyl acetate–dichloromethane to afford 17 mg (44%) of **19**: mp 176.5–178 °C; IR (KBr) 3448, 1735, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.5 Hz, 3, C-4α CH_3), 1.09 (s, 3, C-10β CH_3), 2.17 (s, 3, $OCOCH_3$), 3.62 (s, 3, OCH_3), 4.00, 4.74 (AB q, J = 13.2 Hz, 2, C-20 CH_2O), 4.18 (br s, 1, C-7β H), 4.42, 4.62 (AB q, J = 11.9 Hz, 2, CH_2Ph), 5.19 (br s, 1, C-11α H), 7.30–8.07 (m, 10 Ar H); exact mass spectrum calcd for $C_{36}H_{45}O_9$ 621.3054, found 621.3070.

(*R*)-1,2,3,4,8,8a-Hexahydro-1β-hydroxy-8aβ-methyl-6-(7*H*)-naphthalenone. To 6 g (33.7 mmol) of **24** in 30 mL of absolute ethanol was added 318 mg (8.4 mmol, 0.25 equiv) of sodium borohydride in 50 mL of absolute ethanol dropwise at 0 °C under a nitrogen atmosphere. The addition was completed over a 3-h period, and the mixture was stirred for an additional 1 h at 0 °C. The reaction was quenched by adding acetic acid until the violet color changed to yellow. After the solvent was evaporated, the crude product was extracted by using chloroform. The chloroform solution was washed with brine, dried, and concentrated to afforde 5.52 g (92%) of enone alcohol: IR (TF) 3450, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3, C-10β CH_3), 3.50 (m, 1, C*H*OH), 5.80 (s, 1, C-6 vinylic H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.49; H, 9.02.

(*R*)-1β-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,8,8a-hexahydro-8aβ-methyl-6(7*H*)-naphthalenone. To 5.3 g (29.4 mmol) of enone alcohol in 10 mL of *N,N*-dimethylformamide was added 5 g (73.5 mmol, 2.5 equiv) of imidazole followed by 6.66 g (44.1 mmol, 1.5 equiv) of *tert*-butyldimethylsilyl chloride under a nitrogen atmosphere at 25 °C. The mixture was stirred for 20 h. The crude product was diluted with ether, washed with water and brine, and dried. The crude product was chromatographed on silica gel in 1:3 ethyl acetate–hexane to afford 7.33 g (85%) of enone TBS ether: $[\alpha]_D$ −80.5° (*c* 5.90 g/100 mL, toluene); IR (KBr) 1670, 1255, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 and 0.06 (two s, 6, $SiCH_3$), 0.90 (s, 9, $SiC(CH_3)_3$), 1.17 (s, 3, C-10β CH_3), 3.36 (m, 1, C*H*OTBS), 5.78 (s, 1, C-6 vinylic H).

Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.26; H, 10.31.

(*R*)-1β-[(*tert*-Butyldimethylsilyl)oxy]-1,2,3,4,4aα,5,6,7,-8,8a-decahydro-8aβ-methyl-6β-naphthalenol. To 1.65 g (0.23 mol, 17 equiv) of lithium in 300 mL of anhydrous liquid ammonia was added 3.9 g (13.2 mmol) of enone TBS ether in 120 mL of anhydrous ether. The mixture was stirred for 1.5 h under a nitrogen atmosphere, and absolute ethanol was added until the blue color was discharged. The ammonia was allowed to evaporate at 25 °C, and 150 mL of water was added. The mixture was extracted with ether, washed with brine, dried, and concentrated to give 3.66 g (93%) of alcohol TBS ether: IR (TF) 3300, 1480, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6, $SiCH_3$), 0.80 (s, 3, C-10β CH_3), 0.85 (s, 9, $SiC(CH_3)_3$), 3.15 (m, 1, C-7 CH), 3.55 (m, 1, C-1 C*H*OTBS).

Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.28; H, 11.45.

(*R*)-1β-[(*tert*-Butyldimethylsilyl)oxy]-8aβ-methyl-1,2,3,4,4aα,5,8,8a-octahydro-6(7*H*)-naphthalenone (25). To

3.9 g (18.1 mmol, 1.5 equiv) of pyridinium chlorochromate, 2 g of Celite, and 20 mg (0.24 mmol, 0.02 equiv) of sodium acetate in 30 mL of distilled dichloromethane was added 3.6 g (12.1 mmol) of alcohol TBS ether in 5 mL of dichloromethane. The mixture was stirred for 4.5 h at 25 °C under a nitrogen atmosphere. The dichloromethane solution was decanted, diluted with 25 mL of ether, and filtered through Celite. The residue in the funnel was washed with 100 mL of ether. The crude product was chromatographed on silica gel by using 1:2 ethyl acetate–hexane to give 3.42 g (96%) of **25**: IR (TF) 1720, 1255, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, $SiCH_3$), 0.90 (s, 9, $SiC(CH_3)_3$), 1.05 (s, 3, C-10β CH_3), 3.25 (m, 1, C*H*OTBS).

Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.94; H, 10.94.

(*R*)-1β-[(*tert*-Butyldimethylsilyl)oxy]-7-formyl-8aβ-methyl-1,2,3,4,4aα,5,8,8a-octahydro-6(7*H*)-naphthalenone. To 158 mg (6.6 mmol, 2 equiv) of sodium hydride was added 17.9 mL (218 mmol, 66 equiv) of ethyl formate. The mixture was stirred for 1 h at 0 °C, and 1.00 g (3.30 mmol) of **25** in 13 mL of 1,2-dimethoxyethane and a few drops of ethanol were added. The mixture was stirred for 30 min at 0 °C and 12 h at 25 °C. The reaction was quenched by adding saturated ammonium chloride solution. The crude product was extracted from ether, washed with brine, dried, and concentrated to afford 1.03 g (96%) of hydroxymethylene ketone: ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, $SiCH_3$), 0.80 (s, 3, C-10β CH_3), 0.90 (s, 9, $SiC(CH_3)_3$), 3.30 (m, 1, C*H*OTBS), 8.60 (s, 1, C=C*H*OH), 14.5 (s, 1, CHO*H*).

(*R*)-1β-[(*tert*-Butyldimethylsilyl)oxy]-7-formyl-1,2,3,4,4aα,8a-hexahydro-8aβ-methyl-6(5*H*)-naphthalenone (26). To 1.10 g (5.68 mmol, 1.65 equiv) of phenylselenium chloride in 60 mL of anhydrous chloroform was added 0.6 mL of pyridine. The mixture was stirred for 30 min at 0 °C, and 1 g (3.38 mmol) of hydroxymethylene derivative in 10 mL of chloroform was added. The mixture was stirred for 8 h at 0 °C and washed with 10% hydrochloric acid solution. The chloroform layer was cooled to 0 °C, and 1.2 mL of 30% hydrogen peroxide solution was added in four portions at 10-min intervals. To this solution was added 10 mL of water, and the mixture was stirred for 10 min. The chloroform layer was separated, and the aqueous layer was extracted with chloroform. The combined chloroform solutions were washed with saturated sodium bicarbonate and brine and dried. The crude product was chromatographed on silica gel by using 1:3 ethyl acetate–hexane to afford 695 mg (72%) of **26**: mp 76–78 °C; IR (TF) 2980, 2880, 1680, 1610, 1260, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 and 0.15 (2 s, 6, $SiCH_3$), 0.90 (s, 9, $SiC(CH_3)_3$), 1.10 (s, 3, C-10β CH_3), 2.40 (m, 2, C-6 CH_2), 3.40 (m, 1, C*H*OTBS), 8.00 (s, 1, C-9 vinylic H), 10.10 (s, 1, CHO).

Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.94; H, 9.41.

1β-[(*tert*-Butyldimethylsilyl)oxy]-7α-hydroxy-8β-(hydroxymethyl)-18,19-bisnor-9β-podocarp-13-en-12-one (28). A solution of 161 mg (0.5 mmol) of **26** and 214 μL (1.1 mmol, 2.2 equiv) of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**27a**) in 1.7 mL of anhydrous benzene was stirred at 25 °C for 18 h under a nitrogen atmosphere. The mixture was diluted with 0.3 mL of anhydrous toluene and slowly added to 1.3 mL of 1.16 M (1.5 mmol, 3 equiv) sodium bis(2-methoxyethoxy)aluminum hydride in toluene at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched by the slow addition of a solution of 2.76 mL of 1 M hydrochloric acid solution in 6.9 mL of THF. The mixture was stirred for 15 min at 25 °C, poured into brine, and extracted with ethyl acetate. The organic phase was dried, concentrated, and dissolved in 6.25 mL of THF. To the solution was added 1.56 mL of 0.005 M aqueous hydrochloric acid solution, and the mixture was stirred for 18 h at 25 °C. The solution was poured into brine, extracted with ethyl acetate, and dried. The product was chromatographed on a silica gel plate by using 8:1 ethyl acetate–hexane to afford 112 mg (58%) of **28**: $[\alpha]^{25}_D$ −53.7° (*c* 4.7 g/100 mL, dichloromethane); mp 177–179 °C; IR (KBr) 3450, 3250, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 and 0.10 (2 s, 6, $SiCH_3$), 0.84 (s, 9, $SiC(CH_3)_3$), 1.05 (s, 3, C-10β CH_3), 2.40–2.80 (m, 3, C-9 CH and C-11 CH_2), 6.20 (d, J = 10.5 Hz, 1, C-14 vinylic H), 6.75 (d, J = 10.5 Hz, 1, C-13 vinylic H).

Anal. Calcd for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.70. Found: C, 67.01; H, 9.71.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-7α-hydroxy-18,19-bisnor-9β-podocarp-13-en-12-one. To a solution of 749 mg (1.90 mmol) of **28** in 19.0 mL of anhydrous pyridine was added 551 μL (4.75 mmol, 2.5 equiv) of benzoyl chloride and 371 mg (3.04 mmol, 1.5 equiv) of 4-(dimethylamino)pyridine at 0 °C. The mixture was stirred for 16 h at 25 °C. The crude product was extracted by using ethyl acetate, washed with water and 1 M hydrochloric acid solution and brine, dried, and concentrated. The crude was chromatographed on silica gel by using 1:1 ethyl acetate–hexane to afford 777 mg (82%) of benzoate: IR (TF) 3380, 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 and 0.10 (2 s, 6, $SiCH_3$), 0.84 (s, 9, $SiC(CH_3)_3$), 1.05 (s, 3, C-10β CH_3), 2.60–2.90 (m, 3, C-9β CH and C-11 CH_2), 4.45 (s, 2, C-8 CH_2OH), 6.25 (d, J = 10.5 Hz, 1, C-14 vinylic H), 6.65 (d, J = 10.5 Hz, 1, C-13 vinylic H), 7.40–7.95 (m, 5, Ar H).

Anal. Calcd for $C_{29}H_{42}SiO_5$: C, 69.84; H, 8.49. Found: C, 70.00; H, 8.56.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-7α-[(2-bromo-1-ethoxy)ethoxy]-18,19-bisnor-9β-podocarp-13-en-12-one (29). To a solution of 244 mg (0.49 mmol) of the monobenzoate ester of **28** in 9.8 mL of anhydrous dichloromethane at 0 °C were added 217 mg (1.72 mmol) of *N*,*N*-dimethylaniline and 230 mg (1.72 mmol) of 1,2-dibromoethyl ethyl ether. The mixture was stirred at 25 °C for 20 h. The crude product was extracted by using ethyl acetate, washed with 1 M hydrochloric acid solution and brine, and dried. The crude product was chromatographed on a silica gel plate by using 1:2 ethyl acetate–hexane to afford 268 mg (84%) of **29** as a 1:1 mixture of separable diastereomers.

R_f 0.38: mp 165–170 °C; IR (KBr) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.13 (2 s, 6, $SiCH_3$), 0.80 (s, 9, $SiC(CH_3)_3$), 1.04 (s, 3, C-10β CH_3), 1.10 (t, J = 7, Hz, 3, CH_2CH_3), 2.6–2.8 (m, 3, C-9β CH and C-11 CH_2), 3.30 (m, 2, CH_2Br), 3.50 (m, 2, CH_2CH_3), 3.70 (m, 1, C*H*OTBS), 3.82 (m, 1, C-7 CH), 4.40 and 4.56 (AB q, J = 11.0 Hz, 2, C-8 CH_2OH), 4.70 (m, 1, acetal CH), 6.18 (d, J = 10.5 Hz, 1, C-14 vinylic H), 6.65 (d, J = 10.5 Hz, 1, C-13 vinylic H), 7.40–8.00 (m, 5, Ar H).

R_f 0.41: mp 127–132 °C; IR (KBr) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.13 (2 s, 6, $SiCH_3$), 0.80 (s, 9, $SiC(CH_3)_3$), 1.04 (s, 3, C-10β CH_3), 1.20 (t, J = 7 Hz, 3, CH_2CH_3), 2.6–2.8 (m, 3, C-9β CH and C-11 CH_2), 3.21 (m, 2, CH_2Br), 3.55 (q, J = 7 Hz, 2, CH_2CH_3), 3.7–3.8 (m, 2, C*H*OTBS and C-7 CH), 3.95 and 4.50 (AB q, J = 12.0 Hz, 2, C-8 CH_2OBz), 4.55 (t, J = 6.0 Hz, 1, acetal CH), 6.18 (d, J = 10.5 Hz, 1, C-14 vinylic H), 6.65 (d, J = 10.5 Hz, 1, C-13 vinylic H), 7.40–7.95 (m, 5, Ar H).

Anal. Calcd for $C_{33}H_{49}BrSiO_6$: C, 61.00; H, 7.60. Found: C, 60.84; H, 7.65.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-14α-(formylmethyl)-7α-hydroxy-18,19-bisnor-9β-podocarpan-12-one Ethyl Acetal (30). To a solution of 20 mg (0.031 mmol) of **29** as a mixture of diastereomers in 1.55 mL of benzene were added 0.5 mg (0.003 mmol, 0.1 equiv) of azobis(isobutyronitrile) and 10.1 mg (0.038 mmol, 1.25 equiv) of tri-*n*-butyltin hydride. The mixture was refluxed for 6 h, and the reaction was quenched with methyl iodide. The mixture was diluted with ethyl acetate, washed with brine, and dried. The crude product was chromatographed on a silica gel plate by using 1:3 ethyl acetate–hexane to afford 10.1 mg (57%) of **30**. On one occasion, the individual diastereomers of **29** were cyclized independently in order to obtain pure samples of each of the diastereomers of **30**. We were unable to separate the mixture of diastereomers of **30** by chromatography.

From the R_f 0.38 diastereomer of **29**, we obtained the first diastereomer of **30**: IR (TF) 1720, 1265, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.10 (2 s, 6, $SiCH_3$), 0.81 (s, 9, $SiC(CH_3)_3$), 1.05 (s, 3, C-10β CH_3), 1.22 (t, J = 7 Hz, 3, CH_2CH_3), 2.20 (m, 2, C-11 CH_2), 3.42 (m, 1, C*H*OTBS), 3.66 (m, 2, CH_2CH_3), 4.05 (m, 1, C-7 CH), 4.28 and 4.51 (AB q, J = 11 Hz, 2, C-8 CH_2OBz), 4.84 (m, 1, acetal CH), 7.40–7.95 (m, 5, Ar H); exact mass calcd for $C_{31}H_{45}SiO_5$ $[M - C_2H_5O]^+$ 525.3038, found 525.3037.

From the R_f 0.41 diastereomer of **29**, we obtained the second diastereomer of **30**: IR (TF) 1720, 1265, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 and 0.10 (2 s, 6, $SiCH_3$), 0.81 (s, 9, $SiC(CH_3)_3$), 1.05 (s, 3, C-10β CH_3), 1.22 (t, J = 7 Hz, 3, CH_2CH_3), 2.20 (m, 2, C-11 CH_2), 2.50 (m, 1, C-14 CH), 2.68 (m, 1, C-13 CH_2), 2.85 (q, 1, J = 4, 16 Hz, C-9β CH), 3.60 (m, 3, CH_2CH_3 and C-7 CH), 3.94 (m,

1, CHOTBS), 4.33 and 4.45 (AB q, J = 12 Hz, 2, C-8 CH_2OBz), 4.50 (m, 1, acetal CH), 7.40–8.06 (m, 5, Ar H); exact mass calcd for $C_{29}H_{41}SiO_6$ [M – C_4H_9]$^+$ 513.2673, found 513.2670.

8β-[(*tert*-Butyldimethylsilyl)oxy]-7α-hydroxy-8β-(hydroxymethyl)-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one (31). The same procedure described for the preparation of **28** was repeated using 161 mg (0.50 mmol) of **26** and 212 μL (1.1 mmol, 2.2 equiv) of 1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene[26] (**27b**) followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride and acid-catalyzed hydrolysis to afford, after chromatography on a silica gel plate using 8:1 ethyl acetate–hexane, 169 mg (83%) of **31**: $[\alpha]^{25}_D$ –64.7° (c 1.7 g/100 mL, dichloromethane); mp 215–218 °C; IR (KBr) 3400, 1640, 1240, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.10 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.01 (s, 3, C-10β CH_3), 1.84 (s, 3, C-13 vinylic CH_3), 2.35–2.80 (m, 3, C-9β CH and C-11 CH_2), 6.46 (s, 1, C-14 vinylic H).

Anal. Calcd for $C_{23}H_{40}SiO_4$: C, 67.60; H, 9.87. Found: C, 67.66; H, 9.92.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-7α-hydroxy-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one. The procedure described for the preparation of the monobenzoate ester of **28** was repeated using 128 mg (0.31 mmol) of **31**, 90 μL (0.78 mmol) of benzoyl chloride, and 60 mg (0.50 mmol) of 4-(dimethylamino)pyridine to afford, after chromatography on a silica gel plate using 1:1 ethyl acetate–hexane, 143 mg (90%) of the monobenzoate of **31**: $[\alpha]^{25}_D$ –76.8° (c 3.23 g/100 mL, dichloromethane); mp 143–146 °C; IR (TF) 3500, 1725, 1660, 1270, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.09 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.02 (s, 3, C-10β CH_3), 1.84 (s, 3, C-13 vinylic CH_3), 2.58–2.90 (m, 3, C-9β CH and C-11 CH_2), 3.65–3.78 (m, 2, C-7α OH and C-7 CH), 3.80 (m, 1, C-1 CH), 4.40 (s, 2, C-8 CH_2OBz), 6.37 (s, 1, C-14 vinylic H), 7.36–7.98 (m, 5, Ar H).

Anal. Calcd for $C_{30}H_{44}SiO_5$: C, 70.27; H, 8.65. Found: C, 70.32; H, 8.68.

8β-[(Benzoyloxy)methyl]-7α-[(2-bromo-1-ethoxy)ethoxy]-1β-[(*tert*-butyldimethylsilyl)oxy]-13-methyl-18,19-bisnor-9β-podocarp-13-en-12-one (32). The procedure described for the preparation of **29** was repeated using 140 mg (0.27 mmol) of the monobenzoate ester of **31**, 128 μL (0.96 mmol) of 1,2-dibromoethyl ethyl ether, and 121 μL (0.96 mmol) of *N*,*N*-dimethylaniline to afford, after chromatography on a silica gel plate using 1:3 ethyl acetate–hexane, 166 mg (93%) of **32** as a 1:1 inseparable mixture of diastereomers: $[\alpha]^{25}_D$ –55.9° (c 5.94 g/100 mL, dichloromethane); IR (KBr) 1725, 1665, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.12 (2 s, 6, $SiCH_3$), 0.82 (s, 9, $SiC(CH_3)_3$), 1.02 and 1.04 (s, 3, diastereomeric C-10β CH_3), 1.1–1.26 (m, 3, CH_2CH_3), 1.78 and 1.80 (s, 3, diastereomeric C-13 vinylic CH_3), 2.58–2.92 (m, 3, C-9β CH and C-11 CH_2), 4.22–4.58 (m, 2, C-8 CH_2OBz), 4.22–4.58 and 4.64–4.70 (m, 1, diastereomeric acetal CH), 6.35 (s, 1, C-14 vinylic H), 7.38–8.00 (m, 5, Ar H); exact mass calcd for $C_{30}H_{42}BrSiO_6$ [M – C_4H_9]$^+$ 605.1937, found 605.1935.

8β-[(Benzoyloxy)methyl]-1β-[(*tert*-butyldimethylsilyl)oxy]-14α-(formylmethyl)-7α-hydroxy-13-methyl-18,19-bisnor-9β-podocarpan-12-one Ethyl Acetal (33). The procedure described for the preparation of **30** was repeated using 160 mg (0.24 mmol) of **32**, 79 μL (0.390 mmol) of tri-*n*-butyltin hydride, and 4 mg (0.024 mmol) of azobis(isobutyronitrile), which were refluxed for 16 h, to afford, after chromatography on a silica gel plate using 1:3 ethyl acetate–hexane, 115 mg (82%) of **33** as a 3:2 inseparable mixture of diastereomers: $[\alpha]^{25}_D$ –48.0° (c 1.38 × 10^{-1} g/100 mL, toluene); IR (TF) 1725, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.06 (2 s, 6, $SiCH_3$), 0.79 (s, 9, $SiC(CH_3)_3$), 0.96 and 0.99 (d, J = 6.7 Hz, 3, diastereomeric C-13 vinylic CH_3), 1.03 and 1.04 (s, 3, diastereomeric C-10β CH_3), 1.19 (m, 3, CH_2CH_3), 3.44 and 3.92 (m, 1, diastereomeric CHOTBS), 3.60–3.68 (m, 2, CH_2CH_3), 3.62 and 4.06 (m, 1, diastereomeric C-7 CH), 4.24–4.58 (m, 2, C-8 CH_2OBz), 4.24–4.58 and 4.78–4.84 (m, 1, diastereomeric acetal CH), 7.40–8.10 (m, 5, Ar H); exact mass calcd for $C_{30}H_{43}SiO_6$ [M – C_4H_9]$^+$ 527.2831, found 527.2829.

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Molecular Armatures. Synthesis and Structure of Tröger's Base Analogues Derived from 4-, 2,4-, 3,4-, and 2,4,5-Substituted Aniline Derivatives[1]

Irving Sucholeiki,† Vincent Lynch, Ly Phan, and Craig S. Wilcox*†

Department of Chemistry, University of Texas, Austin, Texas 78712

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The preparation of biomimetic systems designed to mimic natural receptor sites and enzymic active sites requires the development of new synthetic strategies for preparing large molecules with predictable and well-defined shapes. In this paper a number of derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocines are prepared. The scope and limitations of the reaction of formaldehyde with aniline derivatives are examined. The molecules prepared have potential value as conformationally restricted armatures for the construction of biomimetic molecular systems. A crystallographic study reveals that the molecules are folded and that the angle formed by the two aryl rings ranges from 88° to 104°. Sulfonamides, bromides, alcohols, and amines can be introduced as side-chain substituents in these systems.

Introduction

Enzymic catalysis and molecular complexation are a sine qua non of life. The study of enzymes and of molecular interactions is based on analytical and abstractive processes.[2] Investigations of enzyme models and biomimetic experiments exemplify the abstractive approach to new knowledge.[3,4] This approach requires the investigator to

† Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

(1) Number 7 in a series on the Chemistry of Synthetic Receptors and Functional Group Arrays.

(2) Nagel, E. *The Structure of Science*; Harcourt, Brace and World: New York, 1961.

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