Acyclic diastereoselection as a synthetic route to quassinoids: A Claisen rearrangement based strategy for bruceantin

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(*E*)-3-(*p*-Chlorophenyl)-5-[2-(*p*-chlorophenyl)vinyl]isothiazole (14-*E*). To a solution of 3-(*p*-chlorophenyl)-5-methylisothiazole (**4b**, 0.5 g, 2.4 mmol) and potassium *tert*-butoxide (0.32 g, 2.9 mmol) in dry THF (20 mL) was added *p*-chlorobenzaldehyde (0.4 g, 2.9 mmol) at room temperature. The reaction mixture was stirred for 2 days. After usual workup, chromatography of the residue on silica gel gave 0.30 g (38%) of **14-*E*** as colorless solid: mp 157-158 °C; ^{1}H NMR δ ($CDCl_3$) 7.12, 7.16 (ABq, J = 16 Hz, 2 H), 7.33, 7.41 (ABq, J = 9 Hz, 4 H), 7.50 (s, 1 H), and 7.43, 7.88 (ABq, J = 8.8 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$ + CF_3CO_2H) 7.21 (s, 2 H), 7.37, 7.49 (ABq, J = 9 Hz, 4 H), 7.49 (s, 1 H), and 7.48, 7.77 (ABq, J = 8.8 Hz, 4 H); UV λ_{max} (log ϵ, MeOH) 230 (4.09), 270 (4.31), 320 nm (4.43).

Anal. Calcd for $C_{17}H_{11}NSCl_2$: C, 61.46; H, 3.34; N, 4.22. Found: C, 61.41; H, 3.35; N, 4.23.

(*Z*)-3-(*p*-Chlorophenyl)-5-[2-(*p*-chlorophenyl)vinyl]isothiazole (14-*Z*). By the method as described above, photoisomerization of **14-*E*** (55 mg, 0.17 mmol) resulted in a mixture of **14-*E*** and **14-*Z***. Thin-layer chromatographic separation of the mixture gave **14-*Z*** (32 mg) along with **14-*E*** (22 mg).

14-*Z*: mp 133.5-134 °C; ^{1}H NMR δ ($CDCl_3$) 6.80 (s, 2 H), 7.30 (s, 1 H), 7.28, 7.42 (ABq, J = 9 Hz, 4 H), 7.39, 7.78 (ABq, J = 8.8 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$ + CF_3CO_2H) 6.94, 7.34 (ABq, J = 11.7 Hz, 2 H), 7.24, 7.53 (ABq, J = 8.2 Hz, 4 H), 7.45 (s, 1 H), 7.52, 7.71 (ABq, J = 9 Hz, 4 H); UV λ_{max} (log ϵ, MeOH) 257 (4.43), 280 (4.32, shoulder), and 300 nm (4.20, shoulder).

Anal. Calcd for $C_{17}H_{11}NSCl_2$: C, 61.46; H, 3.34; N, 4.22. Found: C, 61.44; H, 3.28; N, 4.24.

Bond Switching Equilibration of 3. A solution of **3b-α** (5 mg, 0.015 mmol) in benzene-d_6 (0.4 mL) was allowed to stand at 42 °C for 1 day to result in equilibrium between **3b-α** and **3b-β**, the ratio being 58:42 evaluated from the integral value of each vinyl proton in the ^{1}H NMR spectrum. Since the mixture consisted of only two components and the spectrum of **3b-α** had been recorded, it was an easy matter to assign ^{1}H NMR signals for **3b-β** by subtraction of those of **3b-α**.

Such a bond switch was also observed for **3e** and **3d***. Therefore, by the same methodology, spectral data of **3e-β** and **3d*-β** were also easily estimated. The spectra of **3b,d*,e** obtained by the ring transformation equilibrium were superimposable upon those of the sample prepared by direct coupling reaction of **4** with the corresponding benzonitrile.

3b-β: ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3 H), 4.32 (br s, 2 H), 5.91 (s, 1 H), 7.1-7.6 (m, 7 H), 7.84 (half ABq, J = 8.1 Hz, 2 H); ^{1}H NMR δ (C_6D_6) 2.11 (s, 3 H), 3.3-3.8 (br s, 2 H), 5.65 (s, 1 H), 6.9-7.3 (overlapped with protons contained in benzene-d_6), 8.06 (half ABq, J = 8.1 Hz, 2 H).

3e-β: ^{1}H NMR δ (Me_2SO-d_6) 5.74 (s, 1 H), 5.8-6.1 (br s, 2 H), 7.46, 7.68 (ABq, J = 9.0 Hz, 4 H), 7.53 (t, J = 2.0 Hz, 1 H), 7.91 (s, 1 H), 8.07 (d, J = 2.0 Hz, 2 H); ^{1}H NMR δ (C_6D_6) 3.1-3.5 (br s, 2 H), 5.58 (s, 1 H), 6.81 (s, 1 H), 7.05-7.25 (overlapped with protons contained in benzene-d_6), 7.87 (d, J = 2.0 Hz, 2 H).

3d*-α-*Z*: ^{1}H NMR δ (benzene-d_6) 3.2-3.7 (br s, 2 H), 5.62 (s, 1 H), 7.0-7.2 (overlapped with protons contained in benzene-d_6), 7.19, 7.81 (ABq, J = 9.0 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$) 4.0-4.6 (br s, 2 H), 5.88 (s, 1 H), 7.33 (d, $^3J_{^{15}NH}$ = 3.5 Hz, 1 H), 7.38, 7.86 (ABq, J = 8.6 Hz, 4 H), 7.38, 7.48 (ABq, J = 9.0 Hz, 4 H).

Kinetic Studies. The Hitachi R-90H FT NMR instrument was used for all measurements. For each run, approximately 5 mg of **3-α** was dissolved into 0.4 mL of deuterated solvent (Me_2SO-d_6 or benzene-d_6) in a 5-mm NMR tube which was placed at the instrument probe. At appropriate intervals, the integral ratios of vinyl proton for **3b,e-α** and **3b,e-β** were monitored. In the case of **3d***, the characteristic signals of amino protons ($^{14}NH_2$ and $^{15}NH_2$) were used to monitor the reaction. The reversible first-order rate constants, k_1, were calculated from the slope of the linear plots of ln ($m/(m - x)$) vs. time (t) by using the least-squares method. The parameter m equals the mole fraction of β form at the equilibrium and x means the mole fraction of **3-β** at an appropriate time (t).[22]

Determination of Molecular Weight of 3b,d,e. The molecular weight of **3b,d,e** was determined by vapor pressure osmometry (Knauer Co.) in the range 0.005-0.020 M in benzene solution: **3b**, 340 (calcd, 327); **3d**, 343 (347); **3e**, 390 (382).

Acknowledgment. We are indebted to Mitsui Petrochemical Industries for the measurement of the molecular weight of **3b,d,e** and also to Chisso Corporation for the gift of silylating reagents. We thank professor J. C. Martin of University of Illinois (Urbana) for his valuable suggestion. A part of this work was supported by the Grant-in-Aid for Scientific Research (No. 5743006), Ministry of Education, Science and Culture of Japanese Government.

Registry No. **3a-*Z***, 95514-26-4; **3a-*Z*** (*N*-acetyl derivative), 95514-27-5; **3b-α-*Z***, 95514-28-6; **3b-β-*Z***, 95514-29-7; **3c-α-*Z***, 95514-30-0; **3c-β-*Z***, 95514-31-1; **3d-*Z***, 95514-25-3; **3d*-α-*Z***, 95514-38-8; **3d*-β-*Z***, 95514-44-6; **3e-α-*Z***, 95514-32-2; **3e-β-*Z***, 95514-33-3; **3f-α-*Z***, 95514-34-4; **3f-β-*Z***, 95514-35-5; **4a**, 13369-71-6; **4b**, 94225-34-0; **5**, 3848-36-0; **6**, 68870-58-6; **7**, 91182-87-5; **8**, 95514-22-0; **9a**, 95514-24-2; **9b**, 95514-23-1; **10a**, 95514-36-6; **10b**, 95514-37-7; **12a**, 95514-39-9; **12b**, 94225-36-2; **13b-*Z***, 95514-42-4; **13d-*Z***, 95514-40-2; **13d-*E***, 95514-47-9; **13d*-*Z***, 95514-41-3; **13e-*Z***, 95514-43-5; **14-*E***, 95514-45-7; **14-*Z***, 95514-46-8; *p*-ClC_6H_4CN, 623-03-0; $MeCOCH_2CO_2Me$, 105-45-3; *p*-$ClC_6H_4C^{15}N$, 36093-33-1; *p*-$ClC_6H_4CO^{15}NH_2$, 31656-61-8; 3-phenyl-5-methylisoxazole, 1008-74-8.

Acyclic Diastereoselection as a Synthetic Route to Quassinoids: A Claisen Rearrangement Based Strategy for Bruceantin

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Abstract: A highly stereoselective Claisen rearrangement of allyl vinyl ether **17** gives rise to β-keto ester **18** having the correct relative stereochemistry at C_8, C_9, and C_{14} of the quassinoids. Efficient, rapid assembly of rings C, D, and E is achieved. The model sets the stage for an eventual synthesis of (-)-bruceantin from keto acid **9b**.

Bruceantin (**1**) is a physiologically active quassinoid isolated from *Brucea antidysenterica Mill.*, a Simaroubaceous tree indigenous to Ethiopia, which has been utilized in the treatment of cancer.[1] The initial activity of bruceantin toward a number of cancer screens sparked interest in this substance at the National Cancer Institute (NSC 165563) and rekindled the synthetic chemists' interest in the area of quassinoids,[2] a field marked heretofore by the contributions of Dias[3] and Valenta.[4]

(1) Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1975**, *40*, 648. Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Sigel, C. W. *Ibid.* **1973**, *38*, 178.

(2) Polonsky, J. In "Progress in The Chemistry of Organic Natural Products"; Herz, W., Grisbach, H., Kirby, G. W.; Eds.; Springer-Verlag: Berlin, 1973; Vol. 30, p 102. Polonsky, J. "Chemistry and Chemical Taxonomy of the Rutales"; Waterman, P. G., Grundon, M. F.; Eds.; Academic Press: New York, 1983; p 247.

(3) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 1613, 3584.

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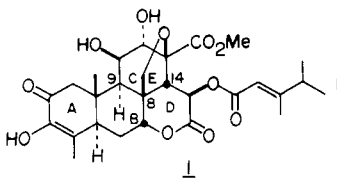
While subsequent synthetic efforts directed toward the total synthesis of quassinoids (Simaroubaceae) have emanated from the laboratories of Fuchs,[5] Watt,[6] Ganem,[7] Kraus,[8] Kametani,[9] Takahashi,[10] Heathcock,[11] and others,[12] only Grieco has reported the synthesis of members of this group—namely quassin (**2**)[13] and castelanolide (**3**).[14] No members of the bruceolides (*Brucea*) have been synthesized.



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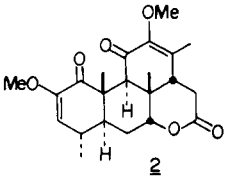

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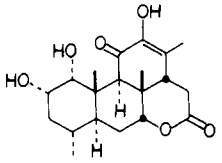

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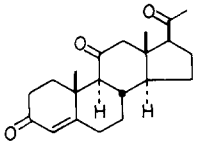

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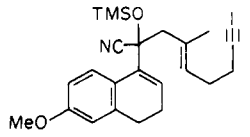
We present in this paper a synthetic approach to the pentacyclic ring system of bruceantin by a method involving acyclic diastereoselection that is contrary to the traditional course of steroid and higher terpene syntheses, in that the issue of stereochemistry is addressed prior to the formation of rings, in this instance rings C, D, and E.

Examination of quassinoids **1–3** reveals the same relative $C_{9\alpha}$, $C_{8\beta}$ stereochemistry present in the steroid nucleus, exemplified by 11-ketoprogesterone (**4**). The significant difference is the $C_{14\beta}$ configuration in the quassinoids and the $C_{14\alpha}$ configuration in the steroids. We have previously provided a solution to this problem



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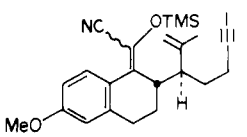

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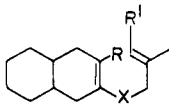

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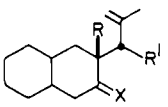

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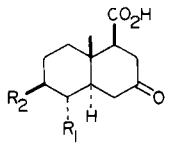
in the context of steroid syntheses,[15] wherein the $C_{8\beta}$, $C_{14\alpha}$ stereochemistry is created by virtue of the Cope rearrangement of trimethylsilylcyanohydrin (**5**), which proceeds through a chairlike transition state to provide cinnamonitriles (**6**). The correct $C_{14\beta}$ stereochemistry of the quassinoids could be created if a Cope rearrangement of structural type **5** could be induced to undergo rearrangement through a boatlike transition state, which is, however, an unlikely prospect. Since the stereochemistry at C_{14} reduces itself to a question of side chain olefin facial selectivity in the rearrangement, an operational equivalent of the boatlike transition state derived from structural type **5**, wherein the allylic side chain moiety is appended to C_9, is the rearrangement of generic structure **7**, which has the side chain allylic unit appended to a C_7 substituent, through a chairlike transition state.

The starting material chosen to test this strategy was the keto acid **9a**, which was prepared according to the procedure of McMurry.[16] Although the acid provided the necessary functionality in ring B to test the synthetic approach, ring A was left devoid of functionality. However, the functionalized keto acid **9b** has been prepared in this laboratory in optically active form in anticipation of the success of the work at hand.

Table I. Carbomethoxylation of Ketone **11a**

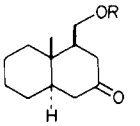
entry	base	conditions[a,b]	13	14	15
1	LDA	kinetic	1	4	
2	LDA	thermodynamic[c]	1	1	
3	NaHMDS	kinetic	1	1	
4	NaHMDS	thermodynamic	7	1	
5	KHMDS	thermodynamic	1		1.5

[a] Kinetic: 1.0 equiv of **11a** added to 1.1 equiv of R_2NM at −78 °C followed by acylation at −78 °C. [b] Thermodynamic: 1.1 equiv of **11a** added to 1.0 equiv of R_2NM at −78 °C, warm to 25 °C, cool to −78 °C followed by acylation at −78 °C. [c] Slow equilibration, incomplete.



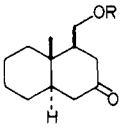
9a, $R_1 = R_2 = H$

b, R_1 = Me, R_2 = OMOM



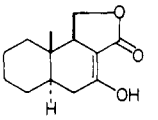
10a, R = H

b, R = CO_2Me



11a, R = TBS

b, R = MTM



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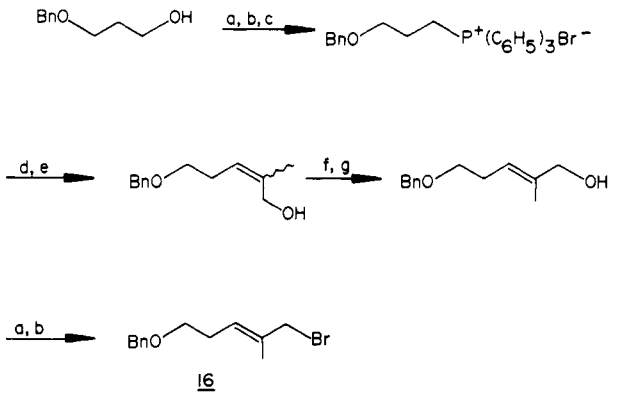
Keto acid **9a** was readily transformed into its methyl ester with diazomethane. Sequential ketalization (ethyl orthoacetate, MeOH, *p*-TsOH), reduction ($LiAlH_4$), and hydrolysis gave rise to keto alcohol **10a**. The hydroxyl group of keto alcohol **10a** was protected as either its *tert*-butyldimethylsilyl ether (TBS) or methylthiomethyl ether (MTM), two groups which were deemed to be eventually compatible with the methoxymethyl ether group of keto acid **9b**. Although both ketones **11a** and **11b** have been successfully carried on toward our objective, only a detailed description of the TBS route will be provided, since it is the method of choice.

Carbomethoxylation of ketone **11a** (dimethyl carbonate, *t*-BuOK, THF, reflux) successfully introduced the required functionality at C_8 (bruceantin numbering), but only the lactone **12** could be isolated. This material is presumably formed by initial

(4) Stojanac, N.; Sood, A.; Sojanac, Z.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 619.
(5) (a) Dailey, O. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (b) Pariza, R. P.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2306.
(6) Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470.
(7) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353.
(8) Kraus, G. A.; Tashner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271.
(9) Fukumoto, K.; Chihiro, M.; Ihara, M.; Kametani, T.; Honda, T. *J. Chem. Soc., Perkins Trans. 1* **1983**, 2569. Shisiko, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2139. Ihara, M.; Chihiro, M.; Fukumoto, K.; Kametani, T. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 373.
(10) Murae, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 941. Honda, T.; Murae, T.; Ohto, S.; Kurata, Y.; Kawaii, H.; Takahashi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 299.
(11) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawaint, T. *J. Org. Chem.* **1984**, *49*, 3264.
(12) For other contributions, see: Pfenniger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* **1981**, 4115. Mandell, L.; Lee, D. E.; Courtney, L. F. *J. Org. Chem.* **1982**, *47*, 610.
(13) Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.
(14) Grieco, P. A.; Lis, R.; Ferrino, S.; Jaw, J. Y. *J. Org. Chem.* **1982**, *47*, 601.
(15) Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1981**, 1179; *J. Am. Chem. Soc.* **1984**, *106*, 718.
(16) McMurry, J.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217. Boger, D. L. *Tetrahedron Lett.* **1978**, 17. McMurry, J.; Blaszczak, L. C.; Johnson, M. A. *Tetrahedron Lett.* **1978**, 1633.

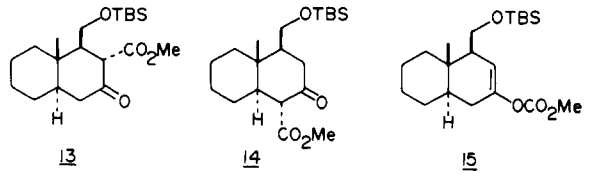
Scheme I



a) MsCl, Et_3N, CH_2Cl_2; b) LiBr, acetone; c) $(C_6H_5)_3P$; d) KHMDS, THF, $THPOCH_2COCH_3$; e) H_3O^+; f) PCC; g) $NaBH_4$

C_8-carbomethoxylation via reversible enolate formation, base promoted desilylation in refluxing THF, and eventual lactonization. This mechanism is supported by the lack of intramolecular acylation of carbonate **10b** when exposed to the reaction conditions and the formation of both lactone **12** and the desired β-keto ester when the MTM derivative **11b** was subjected to the reaction conditions.

A solution to this difficulty was realized by employing the excellent procedure of Mander,[17] which permits the acylation of lithium enolates with methylcyanoformate in THF/HMPA at −78 °C. When the ketone **11a** was added to a THF solution of LDA at −78 °C (kinetic conditions), a 1/4 ratio of β-keto esters **13** and **14**, respectively, was obtained (Table I, entry 1). Attempts to



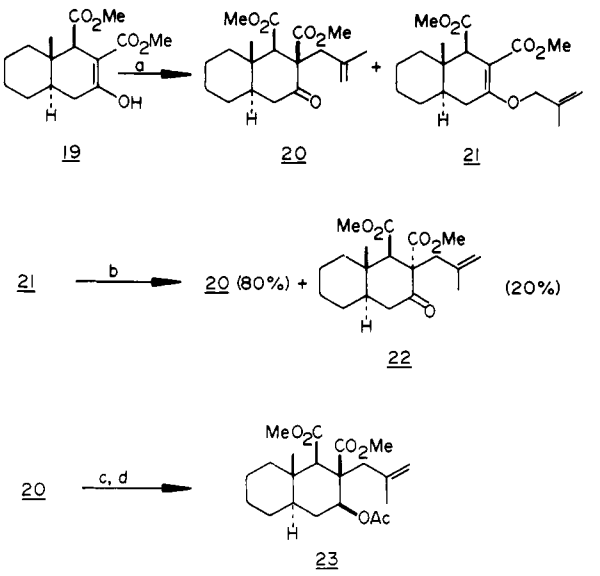
effect equilibration of the enolates (entry 2) proved unsuccessful, owing to the inordinately slow exchange of the lithium enolates. When the sodium counterion was employed (entry 3), the kinetic conditions provided a 1/1 ratio of **13** and **14**, while equilibrating conditions (entry 4) afforded a readily separable 7/1 mixture of **13**/**14**. The potassium counterion, while giving cleanly the desired enolate (entry 5), afforded both the C- and O-acylation products **14** and **15**. The structures **13** and **14** were readily assigned by ^1H NMR decoupling experiments.

Since the reaction conditions directly provide the β-keto esters without enolization,[18] the α-carbomethoxyl groups in **13** and **14** adumbrated the eventual facial selectivity of the critical [3,3]-sigmatropic rearrangement on ring B.

Prior to embarking on the O-alkylation of β-keto ester **13**, a study of the enolization of **13** and **14** was conducted. Treatment of **13** with *t*-BuOK in THF followed by acidification provided exclusively (^1H NMR, $CDCl_3$) the enol form of **13** immediately after workup. After 24 h, the keto/enol ratio of the NMR sample was 3/1, and after 2 weeks, it was at the equilibrium value of 7/1. In contrast, a sample of β-keto ester **14**, when exposed to the base/acid treatment, revealed a 1/2 keto/enol ratio immediately after workup, and only the keto form **14** after 24 h.

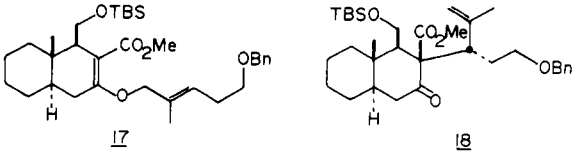
O-Alkylation of β-keto ester **13** required allylic bromide **16**, whose synthesis is outlined in Scheme I. A mixture of the (*E*)- and (*Z*)-allylic alcohol, readily prepared by the procedure of Still,[19] was isomerized to the (*E*)- isomer by successive PCC oxidation

Scheme II



a) NaH, DME; $CH_2=C(Me)CH_2Br$; b) xylene, reflux; c) $NaBH_4$, EtOH; d) Ac_2O, pyr.

to the (*E*)-unsaturated aldehyde and $NaBH_4$ reduction. The desired O-alkylation product **17** was formed in 89% yield by alkylation of the potassium enolate of β-keto ester **13** in HMPA with bromide **16** in the presence of sodium iodide. These conditions minimized C-alkylation. When an *n*-nonane solution of allyl vinyl ether **17** was heated at reflux (151 °C) for 40 h, a near quantitative yield of a single, diastereomeric rearrangement product was obtained! At this juncture, the stereochemistry was assigned on the basis of the working hypothesis formulated earlier. Not until the final assembly of rings C, D, and E could the stereochemical course of the rearrangement be ascertained.

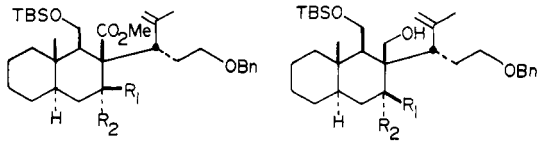


Although the relative stereochemistry at C_8, C_{14} remained in doubt, the carbomethoxylation experiments suggested that the C_8, C_{14} bond-forming reaction should occur from the α face of ring B. In preliminary studies (Scheme II), the alkylation of keto diester **19** was explored. A single C-alkylated product was obtained whose stereochemistry was confirmed by a single-crystal X-ray structure determination of the derived acetate **23**.[20] The stereochemical course of the C-alkylation is in accord with the observations of Kuehne,[21] who has investigated a similarly substituted keto ester. The O-alkylation product **21** provided 80% of the C-alkylated isomer **20** and 20% of the diastereomer **22** upon Claisen rearrangement. Bond formation from the β face of ring B in the transition state leading to **22** encounters a 1,3-diaxial interaction with the angular methyl group. This interaction would be expected to be more pronounced with the trisubstituted olefin of allyl vinyl ether **17** owing to the added interaction of the C_9–CO_2Me with the β-benzyloxyethyl moiety in the chair transition state. The boat transition state from the β face of ring B is more congested than the chair transition state.

With the appropriate carbon atom framework established, the construction of rings C, D, and E was initiated. Attempted reduction of β-keto ester **18**, or its analogue in the MTM series, with $LiAlH_4$ at room temperature over a period of 20 h gave

(17) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 5425.
(18) The reaction generates an initial aldol product. Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.*, in press.
(19) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.
(20) Relevant experimental and X-ray data are available in the supplementary material.
(21) Kuehne, M. E. *J. Org. Chem.* **1970**, *35*, 171.

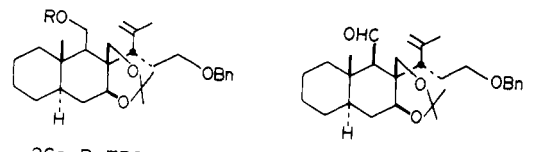
complex mixtures of reduction products, little of which was the desired diol.[22] By employing more controlled reduction conditions ($LiAlH_4$, 0 °C, 30 min), a mixture of β-hydroxy esters **24a** and **24b** was obtained in a 3.5/1 ratio, respectively. Reduction of the equatorial isomer **24a** with $LiAlH_4$ at room temperature once again gave a complex mixture while the axial isomer **24b** afforded the diol **25b**. Reduction of the β-keto ester **18** with DIBAL cleanly provided the equatorial alcohol **24a**. The equatorial alcohol was



24 25

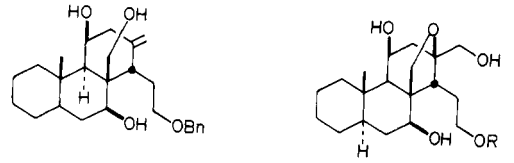
a, R_1=OH, R_2=H
b, R_1=H, R_2=OH
c, R_1=OTBS, R_2=H

clearly the culprit during the ester reduction. Accordingly, the hindered hydroxyl function required protection. This objective was realized through the aegis of *tert*-butyldimethylsilyl triflate ($TBSOT_f$).[23] Reduction of the bis-silylated ester **24c** with $LiAlH_4$ proceeded without complication, but with reward, in that concomitant, selective desilylation of the recently protected hydroxyl group was realized.[24] This reaction presumably occurs by initial reduction of the ester to the (alkoxymethylene)hydridoaluminate, which effects intramolecular, reductive desilylation of the congested silyloxy function.[25] Clearly, desilylation does not precede ester reduction, because this route would lead to the complex mixtures observed previously. Silyl transfer to the alkoxymethylene group followed by selective, bimolecular reduction is untenable because both silyl ethers would be expected to be cleaved.



26a, R=TBS
b, R=H

27

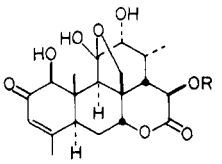


28

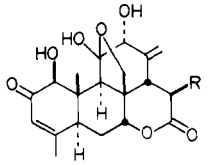
29a, R=Bn
b, R=H

Protection of the diol **25a** as its acetonide **26a** proceeded smoothly. Subsequent desilylation with n-Bu_4NF in refluxing THF afforded the primary alcohol **26b**,[26] which was readily oxidized with pyridinium dichromate[27] to provide the aldehyde **27** necessary for elaboration of ring C. Exposure of the aldehyde to stannic chloride in CH_2Cl_2 at 0 °C for 3 min accomplished the formation of ring C via a Lewis acid catalyzed ene reaction and effected the required deprotection of the diol functionality, which resulted in triol **28**. The $C_{11\beta}$–OH configuration was assigned by analogy with our previous experience in the steroid field,[15] and, more significantly, the appearance of the $C_{11\alpha}$–H as a broad singlet at δ 4.29 in its ^1H NMR spectrum required the axial hydroxyl orientation. The cyclization occurs with exceptional facility, in spite of the need for the transition state of the cyclization to have the complexed aldehyde axial, buttressed against the axial substituents at C_8 and C_{10}. Moreover, only the exocyclic olefin was observed, with no apparent capture of chloride ion.[28]

The exocyclic olefin provides a veratile functionality that could undergo reduction in a quest of the antileukemic agents glaucarubilone (**30a**) and ailanthinone (**30b**) or directly afford the methylene of agents ailanthone (**31a**) and dehydroailanthinone (**31b**). The olefin provides a convenient access to ring E of burceantin and oxidation at C_{21}. Accordingly, triol **28** was subjected to *m*-chloroperbenzoic acid oxidation, which directly provided tetracyclic triol **29a**. It has been difficult to detect any



30a, R=COCH(CH3)C2H5
b, R=CH(CH3)C2H5



31a, R=H
b, R=O2CCH(CH3)C2H5

epoxide in the reaction medium. The stereochemistry of the epoxide is not significant since both the α and β epoxides can cyclize under acidic (*m*-chlorobenzoic acid) conditions. Understandably, the α epoxide would be expected to cyclize faster than its β isomer.

Hydrogenolysis of the benzyl ether was acheived over Pd/C to afford the highly polar tetraol **29b**. Oxidation of **29b** with Jones reagent and subsequent esterification with diazomethane gave rise to diketo diester **32** without formation of lactones. Finally, at the stage of the tetracycle **32**, the stereochemistry of the Claisen rearrangement could be confirmed as having proceeded through a chairlike transition state. Irradiation of the $C_{12\alpha}$–H AB doublet at δ 2.87 (J = 16.3 Hz) caused simplification of the obscured $C_{12\beta}$–H, situated in the region δ 2.56–2.71 along with the unperturbed C_9–H (br s) and the two C_{15}–H. Irradiation of the $C_{12\beta}$–H caused collapse of the $C_{14\beta}$–H at δ 3.63 (dt, $J_{14,15}$ = 7.6 Hz, $J_{12\beta,14\beta}$ = 1.7 Hz) to a 7.6 Hz triplet, indicating the presence of W coupling between the $C_{12\beta}$–H and $C_{14\beta}$–H. In addition, all intermediates bearing ring E exhibited W coupling between the C_9–H and the distal C_{20}–H.[29]

Closure of the lactone ring remained as the final challenge of the study. Selective reduction of diketone **32** at C_7 to provide the equatorial alcohol **33a** was accomplished with high stereoselectivity with $LiAl(t\text{-}BuO)_3H$ in THF. The appearance of the $C_{7\alpha}$–H as a doublet of triplets ($J_{6\beta,7\alpha}$ = 11.7 Hz, $J_{6\alpha,7\alpha} = J_{OH,7\alpha}$ = 4.8 Hz) at δ 3.48 confirmed the assignment. Formation of the mesylate by Crossland's procedure[30] afforded **33b**, which was subjected to saponification with K_2CO_3 in aqueous methanol followed by diazomethane esterification to provide the desired pentacyclic lactone **34**. The facile displacement of the mesylate with inversion gave added credence to the assigned C_{14} stereochemistry.

Lactone **34** requires $C_{12\alpha}$ and $C_{15\beta}$ hydroxylation in addition to reduction of the C_{12}–ketone[5] to the axial isomer. These studies

(22) In the TBS series, several unidentifiable products were formed. The NMR spectrum indicated the virtual absence of the methylene olefin and benzyl ether. In the MTM series, an aldehyde methine signal was detected, which could arise from retroaldolization of the β-hydroxy ester and proton exchange to give the aldehyde enolate. The aldehyde would be liberated upon workup.

(23) Corey, E. J.; Cho, H.; Ruecker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.

(24) This reaction was first discovered in the MTM series and was not necessarily anticipated. For the $LiAlH_4$ cleavage of an unhindered γ-silyloxy alcohol, see: Martinez, G.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. *J. Am. Chem. Soc.* **1982**, *104*, 1436.

(25) A referee has suggested the plausible alternative that a six-membered chelated aluminum species (vs. seven-membered) followed by hydride attack at silicon may account for the selectivity.

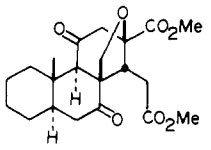
(26) Alcohol **26b** is the convergence point of the TBS and MTM series.

(27) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

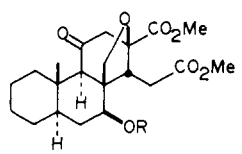
(28) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(29) W coupling between the $C_{12\beta}$–H and $C_{14\beta}$–H and the $C_{9\alpha}$ and the C_{20}–distal H has been observed in quassinoids. Lee, K.-H.; Imakura, Y.; Sumida, Y.; Wu, R.-Y.; Hall, I. H.; Huang, H.-C. *J. Org. Chem.* **1979**, *44*, 2180.

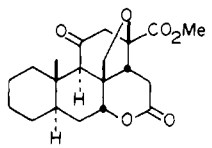
(30) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.



32



33a, R=H
b, R=Ms



34

are currently under investigation, and when completed they will be applied to the total synthesis of (−)-bruceantin via keto acid **9b**.

Experimental Section

All reactions were performed in flame-dried glassware under N_2 unless otherwise noted. Diethyl ether, dimethoxyethane, and tetrahydrofuran (THF) were distilled from benzophenone ketyl under N_2. Hexane, triethylamine, methylene chloride, hexamethylphosphoramide (HMPA), and toluene were distilled from calcium hydride. *n*-Butyllithium (Alfa-Ventron) was titrated by the method of Kofron.[31] Workup means drying (anhydrous $MgSO_4$), filtration, and concentration in vacuo.

Thin-layer chromatography was accomplished with EM Reagents precoated Silica Gel 60 F-254 TLF plates. Flash chromatography was carried out with Baker Silica Gel 60 (230–400 mesh).[32]

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 5-SX FT spectrometer in CCl_4 solution, unless otherwise indicated. Proton nuclear magnetic resonance spectra were obtained on either a JEOL FX-90Q (90 MHz) or a Bruker WM-250 (250 MHz) spectrometer. Carbon-13 nuclear magnetic spectra were obtained on a JEOL FX-90Q (22.5 MHz) or a Bruker WM-250 (62.89 MHz) spectrometer. All NMR samples employed $CDCl_3$ as internal standard.

Elemental analyses were performed by Atlantic Microlab Inc., Atlanta.

Keto Alcohol 10a. To a solution of 10.0 g (47.6 mmol) of keto acid **9a** in 50 mL of THF in an Erlenmeyer flask [**CAUTION**: The flask must be free of chips and scratches to avoid the possibility of a diazomethane explosion.] was slowly added with swirling an ethereal solution of 2.5 g (59.5 mmol) of diazomethane (from Diazald, Aldrich). Glacial acetic acid was added dropwise to destroy excess diazomethane followed by removal of solvents in vacuo to afford 10.65 g of a crude keto ester, ^1H NMR (90 MHz) δ 3.66 (s, 3 H).

The crude keto ester (47.6 mmol) in 50 mL of methanol containing 16.2 g (0.10 mol) of triethyl orthoacetate and 0.53 g (2.8 mmol) of *p*-toluenesulfonic acid was allowed to stir at 25 °C for 2 h. The solution was diluted with ether (450 mL) and successively washed with aqueous $NaHCO_3$ solution and water. Workup provided 12.6 g of crude ketal ester as a pale yellow oil: ^1H NMR (90 MHz) δ 3.61 (s, 3 H), 3.16 (s, 3 H), and 3.11 (s, 3 H).

To a stirred suspension of 3.55 g (93.3 mmol) of $LiAlH_4$ in 100 mL of ether was added dropwise a solution of 12.6 g (46.7 mmol) of the ketal ester dissolved in 50 mL of ether. After the addition was complete, stirring was continued for an additional 2 h. The reaction mixture was successively and cautiously decomposed with 3.5 mL of water, 3.5 mL of 15% aqueous NaOH, and 11 mL of water. The mixture was filtered through Celite in vacuo, and the filtrate was concentrated in vacuo to give 11.0 g of a yellow oil. The oil was dissolved in 100 mL of technical grade acetone containing 0.45 g (2.36 mmol) of *p*-toluenesulfonic acid. The solution was stirred at 25 °C for 2 h after which 5 mL of saturated aqueous $NaHCO_3$ was added, and stirring was continued for 20 min. The solvent was removed in vacuo. The residue was taken up in ether washed with water and worked up to provide 9.05 g of an oil which was purified by flash chromatography (70% EtOAc/hexane) to give 8.87 g of keto alcohol **10a** as a colorless oil (95% from keto acid **9a**): R_f 0.16 (50% EtOAc/hexane); GC/MS, m/z (rel intensity) 196 (M^+, 33), 178 (6), 165 (81), 137 (38), 109 (100); IR 3637 (s), 3541–3315 (br), 1715 cm^{-1}; ^1H NMR (250 MHz) δ 3.88 (dd, J = 10.6, 3.6 Hz, 1 H), 3.47 (br t, J = 10.0 Hz, 1 H, −HC*H*OH), 2.59 (ddd, J = 15.5, 4.5, 1.9 Hz, $C_{8\alpha}$-H), 2.26 (dd, J = 15.5, 13.0 Hz, $C_{8\beta}$-H), 2.19 (dd, J = 15.5, 13.0 Hz, $C_{6\beta}$-H), 2.10 (ddd, J = 15.0, 4.5, 1.9 Hz, $C_{6\alpha}$-H), 1.85 (dt, J = 12.8, 2.5 Hz, $C_{1\beta}$-H), 1.77–1.63 (m, 2 H), 1.58–1.43 (m, 3 H), 1.39–1.20 (m, 3 H), 1.11 (td, J = 12.8, 4.4 Hz, $C_{1\alpha}$-H), 0.97 (s, angular CH_3); ^{13}C NMR 210.8, 62.4, 51.5, 45.8, 45.1, 41.5, 38.2, 35.4, 28.5, 26.1, 21.5, 11.2 ppm.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.30.

***tert*-Butyldimethylsilyl Ether 11a.** To a solution of 9.0 g (45.9 mmol) of keto alcohol **10a** in 50 mL of CH_2Cl_2 at 25 °C was added 7.0 g (68.8 mmol) of triethylamine and 112 mg (0.92 mmol) of 4-dimethylaminopyridine. A solution of 7.6 g (50.5 mmol) of *tert*-butyldimethylsilyl chloride in 20 mL of CH_2Cl_2 was added dropwise with an addition funnel. After the mixture was stirred for 4 h, it was washed successively with 1 N HCl and water. Workup and flash chromatography (20% EtOAc/hexane) provided 12.9 g (91%) of a low-melting white solid: R_f 0.52 (20% EtOAc/hexane; mp 46 °C (neat); IR 1714 cm^{-1}; ^1H NMR δ 3.75 (dd, J = 10.0, 4.0 Hz, 1 H), 3.50 (dd, J = 10.0, 7.4 Hz, 1 H), 2.52 (ddd, J = 15.6, 4.6, 1.9 Hz, $C_{8\alpha}$-H), 2.29 (dd, J = 15.6, 13.0 Hz, $C_{8\beta}$-H), 2.18 (dd, J = 15.0, 13.0 Hz, $C_{6\beta}$-H), 2.09 (dd, J = 15.0, 4.3, 1.9 Hz, $C_{6\alpha}$-H), 1.85 (dt, J = 13.0, 2.5 Hz, $C_{1\beta}$-H), 1.76–1.21 (m, 8H), 1.08 (td, J = 13.0, 4.6 Hz, $C_{1\alpha}$-H), 0.97 (s, 3 H, angular CH_3), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.027 (s, 3 H); ^{13}C NMR 210.7, 62.5, 51.2, 45.8, 45.2, 41.6, 38.4, 35.4, 28.5, 26.2, 25.8 (×3), 21.6, 18.1, 11.4, −5.6 (×2) ppm.

Anal. Calcd for $C_{18}H_{34}SiO_2$: C, 69.61; H, 11.04. Found: C, 69.74; H, 11.09.

Keto Esters 13 and 14. To a solution of 5.0 g (16.1 mmol) of ketone **11a** in 60 mL of THF at 0 °C was added 15.5 mL (0.93 M THF, 16.4 mmol) of sodium hexamethyldisilazide[33] via syringe over 30 min. After the addition was complete, the solution was allowed to stir 7 h at 0 °C. The solution was cooled at −78 °C followed by the addition of 1.5 g (17.7 mmol) of methyl cyanoformate.[34] Stirring was continued 1 h at −78 °C. The solution was poured into water and extracted with ether. Workup and flash chromatography (5% EtOAc/hexane) gave a 7:1 mixture of keto esters **13** and **14**, respectively. **13**: R_f 0.48 (20% EtOAc/hexane); mp 81–82 °C (pentane); IR 1748, 1716 cm^{-1}; ^1H NMR δ 3.85 (dd, J = 10.9, 2.5 Hz, 1 H), 3.76 (d, J = 12.3 Hz, C_8-H), 3.74 (s, CO_2CH_3), 3.56 (dd, J = 10.9, 4.4 Hz, 1 H), 2.27 (dd, J = 13.3, 12.9 Hz, $C_{6\beta}$-H), 2.19 (dd, J = 13.3, 4.3 Hz, $C_{6\alpha}$-H), 2.02 (ddd, J = 12.3, 4.4, 2.5 Hz, C_9-H), 1.89 (dt, J = 12.5, 3.0 Hz, $C_{1\beta}$-H), 1.75 (br d, J = 12.5 Hz, 1 H), 1.66–1.45 (m, 3 H), 1.40–1.20 (m, 3 H), 1.06 (td, J = 12.5, 4.5 Hz, $C_{1\alpha}$-H), 1.06 (s, angular CH_3), 0.88 (s, 9 H), 0.02 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR 205.9, 170.3, 59.6, 56.7, 52.5, 51.4, 45.3, 44.6, 38.6, 35.7, 28.3, 26.0, 25.6 (×3), 21.4, 18.0, 12.7, −5.9, −6.2 ppm.

Anal. Calcd for $C_{20}H_{36}SiO_4$: C, 65.17; H, 9.85. Found: C, 65.26, H, 9.88.

14: R_f 0.44 (20% EtOAc/hexane); ^1H NMR (250 MHz) δ 3.76 (s, CO_2CH_3), 3.74 (dd, J = 10.0, 4.0 Hz, 1 H), 3.54 (dd, J = 10.0, 7.0 Hz, 1 H), 3.17 (d, J = 13.0 Hz, C_6-H), 2.61 (dd, J = 15.5, 4.5 Hz, $C_{8\alpha}$-H), 2.38 (dd, J = 15.5, 13.0 Hz, $C_{8\beta}$-H), 1.96–1.85 (m, 2 H), 1.80–1.70 (m, 2 H), 1.60–1.25 (m, 5 H), 1.15 (td, J = 13.0, 4.0 Hz, $C_{1\alpha}$-H), 1.01 (angular CH_3), 0.88 (s, 9 H), 0.034 (s, 3 H), 0.03 (s, 3 H).

(3-(Benzyloxy)propyl)triphenylphosphonium Bromide. To a solution of 20.0 (60.2 mmol) of 3-(benzyloxy)-1-propanol[35] in 100 mL of CH_2Cl_2 at 25 °C was added 9.1 g (90.3 mmol) of triethylamine. The solution was cooled to 0 °C, and 8.3 g (72.2 mmol) of methanesulfonyl chloride was added over a 20-min period. After the addition was complete, the reaction mixture was stirred an additional 30 min at 0 °C. Anhydrous lithium bromide (52.0 g, 0.6 mmol) in 200 mL of acetone was added, and the resulting suspension was brought to a gentle reflux for 6 h. The reaction mixture was cooled, and the acetone was removed in vacuo. The residue was taken up in ether and washed successively with water and 1 N HCl. Workup and distillation (bp 92 °C, 0.3 torr) gave 12.0 g (88%) of 3-(benzyloxy)-1-bromopropane: ^1H NMR δ 7.38–7.31 (m, 5 H), 4.54 (s, 2 H), 3.62 (t, J = 5.8 Hz, 2 H), 3.55 (t, J = 6.5 Hz, 2 H), 2.20–2.13 (m, 2 H).

A solution of 13.8 g (52.4 mmol) of triphenylphosphine and 12.0 g of the bromide in 60 mL of toluene was heated at reflux for 7 h. After the solution was cooled, the white precipitate was filtered and recrystallized

(31) Kofron, W. C.; Blaclawski, M. *J. Org. Chem.* **1976**, *41*, 1879.
(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(33) Wannagat, U.; Niederpuem, H. *Chem. Ber.* **1961**, *94*, 1540. Brown, C. A. *Synthesis* **1974**, *5*, 427.
(34) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.
(35) Eliel, E.; Badding, V. G.; Rerick, M. *J. Am. Chem. Soc.* **1962**, *84*, 2356.

(CH_3CN/ether) to give 21.8 g (85%) of the phosphonium salt: mp 152 °C; ^1H NMR δ 7.91–7.62 (m, 15 H), 7.31–7.27 (m, 5 H), 4.47 (s, 2 H), 4.02–3.84 (m, 2 H), 3.82 (t, J = 5.1 Hz, 2 H), 2.04–1.92 (m, 2 H).

5-(Benzyloxy)-2-methylhex-2(E)-en-1-ol. To a mechanically stirred suspension of 50.0 g (0.33 mol) of the phosphonium salt (vide supra) in 500 mL of THF at 0 °C was added 195 mL (0.31 mol, 1.5. M/hexane) of n-butyllithium over 30 min. The resulting dark red solution was stirred 30 min at 0 °C. The tetrahydropyranyl ether of hydroxyacetone[36] (50.0 g, 0.33 mol) was added dropwise (neat) over 20 min at 0 °C followed by stirring at 25 °C for 5 h. The reaction mixture was filtered through a pad of Celite, and solvent was removed in vacuo. The gummy residue was taken up in ether and washed with water. The ether solution (400 mL) was treated with 100 mL of a 5% solution of concentrated hydrochloric acid in methanol and allowed to stir for 20 h at 25 °C. The solution was neutralized by the addition of saturated aqueous $NaHCO_3$. The organic solvents were removed in vacuo, and the residue was diluted with ether followed by a water wash. The ether solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to 100 mL. The solution was stored at −15 °C for 20 h to crystallize triphenylphosphine oxide. The solids were removed by vacuum filtration over a pad of silica gel, and the filtrate was concentrated to provide 67 g of yellow oil.

To a CH_2Cl_2 solution (200 mL) of the oil at 25 °C was added 107.8 g (0.5 mol) of pyridinium chlorochromate[37] followed by stirring at 25 °C for 8 h. The reaction mixture was filtered through a pad of Celite, concentrated, and purified by flash chromatography (20% EtOAc/hexane) to give 45.7 g (68%) of the (E) aldehyde as a colorless oil: ^1H NMR (250 MHz) δ 9.35 (s, 1 H), 7.29–7.25 (m, 5 H), 6.49 (t, J = 6.0 Hz, 1 H), 4.48 (s, 2 H), 3.57 (t, J = 6.4 Hz, 2 H), 2.59 (q, J = 6.5 Hz, 2 H), 1.69 (s, 3 H).

To a solution of 1.58 g (41.67 mmol) of sodium borohydride in 50 mL of absolute ethanol at 0 °C was added 5.0 g (24.5 mmol) of the (E) aldehyde over 15 min. After the addition was complete, the solution was allowed to stir at 25 °C for 1 h. The solution was diluted with ether and washed with water. The aqueous washings were back extracted with ether. The combined organic phases were worked up, and the residue was purified by flash chromatography (20% EtOAc/hexane) to give 4.65 g (92%) of the (E) alcohol: ^1H NMR (250 MHz) δ 7.39–7.28 (m, 5 H), 5.45 (tq, J = 7.0, 1.2 Hz, 1 H), 4.53 (s, 2 H), 3.99 (s, 2 H), 3.51 (t, J = 6.9 Hz, 2 H), 2.38 (q, J = 6.9 Hz, 2 H), 1.69 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.79. Found: C, 75.54; H, 8.82.

3-(Benzyloxy)-1-bromo-2-methyl-2(E)-hexene (16). To a solution of 1.0 g (4.8 mmol) of 3-(benzyloxy)-2-methyl-2(E)-hexen-1-ol and 727 mg (7.2 mmol) of triethylamine in 25 mL of CH_2Cl_2 at 0 °C was added 660 mg (5.8 mmol) of methanesulfonyl chloride over 20 min. After the addition was complete, the reaction mixture was stirred an additional 30 min at 0 °C. Anhydrous lithium bromide (4.18 g, 48.0 mmol) in 25 mL of reagent grade acetone was added, and the resulting suspension was stirred at 25 °C for 2.5 h. The reaction mixture was filtered through a pad of Celite followed by in vacuo concentration of the filtrate. The residue was diluted with ether and washed with water. Workup and flash chromatography (10% EtOAc/hexane) gave 1.16 g (90%) of the bromide as a colorless oil: ^1H NMR δ 7.35–7.26 (m, 5 H), 5.66 (t, J = 7.1 Hz, 1 H), 4.52 (s, 2 H), 3.99 (s, 2 H), 3.50 (t, J = 6.8 Hz, 2 H), 2.37 (q, J = 6.7 Hz, 2 H), 1.79 (s, 3 H).

Anal. Calcd for $C_{13}H_{17}BrO$: C, 58.00; H, 6.36. Found: C, 57.79; H, 6.44.

Allyl Vinyl Ether 17. To a solution of 8.2 g (22.3 mmol) of β-keto ester **13** in 75 mL of HMPA at 25 °C was added 2.74 g (24.5 mmol) of potassium *tert*-butoxide. After solution had occurred, 4.0 g (26.7 mmol) of sodium iodide and 7.1 g (26.7 mmol) of allylic bromide **16** were added. The resulting white suspension was heated at 60 °C for 6 h. After the solution was cooled, the mixture was diluted with ether and thoroughly washed with water. The aqueous phases were back-washed with pentane. The combined organic phases were worked up and subjected to flash chromatography (5% EtOAc/hexane) to give 11.15 g (89%) of the vinyl ether as a colorless oil: R_f 0.20 (10% EtOAc/hexane); IR 1729, 1669 cm^{-1}; ^1H NMR δ 7.38–7.28 (m, 5 H), 5.47 (t, J = 7.0 Hz, vinyl H), 4.52 (s, benzyl CH_2), 4.15 (s, allyl ether CH_2), 3.78 (dd, J = 10.2, 4.7 Hz, 1 H), 3.69 (s, CO_2CH_3), 3.60 (dd, J = 10.2, 6.3 Hz, 1 H), 3.48 (t, J = 7.0 Hz, 2 H), 2.43–2.32 (m, 3 H), 2.05–1.00 (m, 11 H), 1.68 (s, vinyl CH_3), 0.88 (s, 9 H), 0.75 (s, angular CH_3), 0.02 (s, 6 H); ^{13}C NMR 169.3, 153.1, 138.4, 133.8, 128.2 (×2), 127.4 (×2), 127.3, 123.9, 113.2, 73.6, 72.7, 69.6, 60.9, 51.4, 50.9, 40.9, 38.6, 34.6, 29.8, 28.3 (×2), 26.0, 25.8 (×3), 21.8, 18.1, 13.7, 11.8, −5.6 (×2) ppm.

Anal. Calcd for $C_{33}H_{52}SiO_5$: C, 71.18; H, 9.41. Found: C, 71.18; H, 9.44.

Keto Ester 18. A solution of allyl vinyl ether **17** in 60 mL of n-nonane was heated at reflux for 36 h. After the reaction mixture was cooled to 25 °C, the solution was purified by flash chromatography (pentane, to remove n-nonane, then 5% EtOAc/hexane and 10% EtOAc/hexane), providing 8.73 g (86%) of the keto ester: R_f 0.47 (20% EtOAc/hexane); IR 1736, 1712, 1632 cm^{-1}; ^1H NMR (250 MHz) δ 7.34–7.26 (m, 5 H), 4.93 (s, 1 H, vinyl), 4.81 (s, 1 H, vinyl), 4.51 (d, J = 11.5 Hz, 1 H, benzyl), 4.42 (d, J = 11.5 Hz, 1 H, benzyl), 4.00 (dd, 11.0, 3.5 Hz, 1 H), 3.76 (dd, J = 11.0, 4.5 Hz, 1 H), 3.65 (s, CO_2CH_3), 3.50–3.33 (m, 2 H), 3.03 (dd, J = 11.0, 1.5 Hz, 1 H), 2.36–2.23 (m, 3 H), 2.03–1.11 (m, 11 H), 1.65 (s, vinyl CH_3), 0.90 (s, 9 H), 0.89 (s, 3 H, angular CH_3), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR 207.8, 172.4, 144.0, 138.8, 128.0 (×2), 127.4, 127.3 (×2), 127.1, 72.3, 68.7, 65.2, 60.0, 57.4, 51.5, 50.6, 44.5, 41.9, 39.3, 36.9, 29.5, 28.5, 25.7 (×3), 25.6, 21.7, 21.5, 18.0, 11.9, −5.6, −5.7 ppm.

Anal. Calcd for $C_{33}H_{52}SiO_5$: C, 71.18; H, 9.41. Found: C, 71.27; H, 9.47.

Hydroxy Ester 24a. To a solution of 8.7 g (15.6 mmol) of keto ester **18** in 80 mL of ether at 0 °C was added 25 mL (25.0 mmol, 1 M/hexane) of diisobutylaluminum hydride over 20 min. After the addition was complete, the solution was allowed to stir an additional 1.5 h at 0 °C. The reaction mixture was decomposed at 0 °C by the cautious addition of water followed by dilution with ether and washing in water, 1 N HCl, and water. The organic layer was worked up and purified by flash chromatography (5%, followed by 10% EtOAc/hexane) to give 4.99 g of the desired equatorial alcohol as a colorless oil, together with 1.5 g of recovered starting material (69% yield, based on recovered starting material): R_f 0.39 (20% EtOAc/hexane); IR 3550 (br), 1707, 1632 cm^{-1}; ^1H NMR (250 MHz) δ 7.36–7.28 (m, 5 H), 5.19 (s, 1 H, vinyl), 5.16 (s, 1 H, vinyl), 4.48 (d, J = 11.9 Hz, 1 H, benzyl), 4.42 (d, J = 11.9 Hz, 1 H, benzyl), 4.34 (d, J = 11.7 Hz, 1 H), 3.65 (s, CO_2CH_3), 3.64–3.57 (m, 2 H), 3.50–3.41 (m, 1 H), 3.39–3.29 (m, 1 H), 3.08 (dd, J = 12.2, 1.9 Hz, 1 H), 2.45–2.25 (m, 1 H), 1.90 (s, vinyl CH_3), 1.81–1.05 (m, 11 H), 0.88 (s, 9 H), 0.65 (s, angular CH_3), 0.92–0.79 (m, 2 H) 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR 146.0, 128.4 (×2), 128.2, 127.9 (×2), 127.7, 127.6, 117.1, 77.1, 74.0, 73.2, 70.1, 69.5, 60.7, 58.3, 49.7, 46.4, 45.7, 39.8, 37.6, 36.5, 30.0, 27.7, 26.2, 25.8, 25.6 (×3), 21.3, 14.8, −3.6 (×2) ppm.

Anal. Calcd for $C_{33}H_{54}SiO_5$: C, 70.92; H, 9.74. Found: C, 71.06; H, 9.78.

Diol 25a. To a solution of 5.44 g (9.75 mmol) of hydroxy ester **24a** in 80 mL of ether at 25 °C was added 1.97 g (19.5 mmol) of triethylamine. The solution was cooled to 0 °C and 3.60 g (13.64 mmol) of neat *tert*-butyldimethylsilyl trifluoromethanesulfonate[23] was added over 25 min. After the addition was complete, the solution was warmed to 25 °C and stirred an additional 2.5 h. The solution was cooled to 0 °C and 1.11 g (29.25 mmol) of lithium aluminum hydride was added, portionwise. The reaction mixture was stirred 4 h at 25 °C, cooled to 0 °C, and quenched by the sequential addition of 1.1 mL of H_2O, 1.1 mL of 15% NaOH, and 3.3 mL of H_2O. Anhydrous $MgSO_4$ was added and the mixture filtered through Celite. The solvent was removed in vacuo, and the residue was purified by flash chromatography (10% followed by 20% EtOAc/hexane) to give 3.19 g of a colorless oil, which crystallized at room temperature, along with 0.64 g of recovered starting material (70% yield based on recovered starting material): R_f 0.15 (20% EtOAc/hexane); mp (EtOAc/pentane) 120–121 °C; IR 3620 (s), 3556–3301 (br), 1647 cm^{-1}; ^1H NMR (250 MHz) δ 7.34–7.26 (m, 5 H), 5.03 (s, 1 H, vinyl), 4.85 (s, 1 H, vinyl), 4.52 (d, J = 11.9 Hz, 1 H, benzyl), 4.46 (d, J = 11.9 Hz, 1 H, benzyl), 4.17–3.92 (m, 5 H), 3.51–3.45 (m, 1 H), 3.44–3.32 (m, 1 H), 2.92 (dd, J = 11.0, 2.0 Hz, 1 H), 2.41–2.30 (m, 1 H), 2.08–1.20 (m, 15 H), 1.84 (s, vinyl CH_3), 1.11 (s, angular CH_3), 0.91 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR 145.8, 138.8, 128.2 (×2), 127.6 (×2), 127.3, 116.8, 74.6, 72.7, 70.2, 62.0. 59.7, 54.7, 50.4, 47.0, 45.6, 40.1, 37.7, 36.5, 29.7, 27.8, 26.2, 25.9 (×3), 23.0, 21.4, 18.1, 14.9, -5.5, −5.8 ppm.

Anal. Calcd for $C_{32}H_{54}SiO_4$: C, 72.40; H, 10.25. Found: C, 72.47; H, 10.26.

Acetonide Alchol 26b. A solution of 2.62 g (4.94 mmol) of diol **25a** in 15 mL of 2,2-dimethoxypropane containing 48 mg (0.25 mmol) of p-toluenesulfonic acid was stirred for 1.5 h at 25 °C. A saturated $NaHCO_3$ solution (2 mL) was added and the solution stirred an additional 10 min. The solvent was removed in vacuo, and the residue was taken up in ether and washed with water. Workup gave 2.78 g of acetonide, as a yellow oil (99% crude yield): R_f 0.68 (20% EtOAc/hexane); ^1H NMR (250 MHz) δ 7.35–7.28 (m, 5 H), 4.95 (s, 1 H, vinyl), 4.84 (s, 1 H, vinyl), 4.53 (d, J = 11.9 Hz, 1 H, benzyl), 4.43 (d, J = 11.9 Hz, 1 H, benzyl), 4.19 (d, J = 12.0 Hz, 1 H), 4.11 (dd, J = 10.4, 7.9 Hz, 1 H), 3.87 (d, J = 8.2 Hz, 1 H), 3.81 (d, J = 12.0 Hz, 1 H), 3.68 (dd, J = 10.4, 3.3 Hz, 1 H), 3.49–3.25 (m, 2 H), 1.84 (s, vinyl CH_3), 1.36

(36) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3742.

(37) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(s, 3 H, acetonide), 1.34 (s, 3 H, acetonide), 1.03 (s, angular CH_3), 0.92 (s, 9 H), 0.004 (s, 3 H), 0.001 (s, 3 H). The crude acetonide (487 mmol) was dissolved in 20 mL of THF, and 10.7 mL (10.7 mmol, 1 M/THF) of tetra-*n*-butylammonium fluoride was added. The solution was heated at reflux for 7 h and, after cooling, diluted with ether and washed with water. The aqueous layers were combined and back-extracted with ether. The combined organic extracts were worked up and purified by flash chromatography (30% EtOAc/hexane) to give 2.14 g of the alcohol as a colorless oil (95% from diol **25a**): R_f 0.1 (20% EtOAc/hexane); IR 3633 (s), 3537–3351 (br), 1632 cm^{-1}; ^1H NMR (250 MHz) δ 7.36–7.29 (m, 5 H), 4.97 (s, 1 H, vinyl), 4.85 (s, 1 H, vinyl), 4.53 (d, J = 11.9 Hz, 1 H, benzyl), 4.43 (d, J = 11.9 Hz, 1 H, benzyl), 4.13 (d, J = 12.2 Hz, 1 H), 3.88 (d, J = 12.2 Hz, 1 H), 4.14–4.10 (m, 1 H), 3.92–3.81 (m, 2 H), 3.50–3.23 (m, 2 H), 2.56 (d, J = 7.5 Hz, 1 H), 2.19–1.95 (m, 15 H), 1.85 (s, vinyl CH_3), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.11 (s, angular CH_3); ^{13}C NMR 145.3, 138.6, 128.2 (×2), 127.4 (×3), 116.2, 97.7, 72.7, 70.0, 68.7, 62.3, 61.3, 55.6, 52.6, 43.0, 42.2, 38.4, 36.2 34.1, 28.8, 28.5, 26.4 (×2), 21.9 (×2), 20.4, 13.2.

Aldehyde 27. To a solution of 2.1 g (4.6 mmol) of alcohol **26b** in 50 mL of CH_2Cl_2 was added 3.8 g (10.11 mmol) of pyridinium dichromate[27] at 25 °C. The reaction mixture was stirred 4 h at 25 °C and then filtered through a pad of silica gel. The filtrate was concentrated in vacuo to give 2.1 g of a light yellow oil (100% crude yield). An analytical sample was prepared by flash chromatography (20% EtOAc/hexane). R_f 0.30 (20% EtOAc/hexane); IR 1703, 1633 cm^{-1}; ^1H NMR (250 MHz) δ 10.04 (d, J = 5.0 Hz, CHO), 7.35–7.29 (m, 5 H), 4.99 (s, 1 H, vinyl), 4.84 (s, 1 H, vinyl), 4.53 (d, J = 11.8 Hz, 1 H, benzyl), 4.42 (d, J = 11.8 Hz, 1 H, benzyl), 3.97 (dd, J = 11.0, 2.0 Hz, C_7-H), 3.90 (d, J = 12.5 Hz, 1 H), 3.67 (d, J = 12.5 Hz, 1 H), 3.50–3.42 (m, 1 H), 3.34–3.23 (m, 1 H), 2.68 (dd, J = 11.0, 2.0 Hz, 1 H), 2.16–1.11 (m, 14 H), 1.82 (s, vinyl CH_3), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, angular CH_3); ^{13}C NMR 207.0, 144.5, 138.6, 128.2 (×2), 127.6, 127.4 (×2), 116.8, 98.1, 72.8, 69.6, 68.1, 64.8, 62.6, 50.5, 43.8, 43.4, 38.0, 36.4, 33.9, 28.4, 28.0, 26.8, 26.2, 22.5, 21.3, 21.1, 14.3 ppm.

Anal. Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.71; H, 9.34.

Tricyclic Triol 28. To a stirred solution of 2.05 g (4.5 mmol) of aldehyde **27** in 25 mL of CH_2Cl_2 at 0 °C was added 50 mL (5.0 mmol, 0.1 M/CH_2Cl_2) of stannic chloride. The mixture was stirred at 0 °C for 5 min. A solution of saturated $NaHCO_3$ (10 mL) was added, and stirring was continued for 5 min. The mixture was filtered through Celite, diluted with CH_2Cl_2, and washed with water. Workup and flash chromatography (50% EtOAc/hexane) provided 1.30 g of a white solid (70%): R_f 0.33 (50% EtOAc/hexane); mp 106–108 °C (EtOAc/hexane); IR 3669 (s), 3650 (s), 3630 (s), 3557–3260 (br), cm^{-1}; ^1H NMR (250 MHz) δ 7.40–7.29 (m, 5 H), 4.95 (s, 1 H, vinyl), 4.82 (s, 1 H, vinyl), 4.51 (s, 2 H, CH_2OBn), 4.29 (br s, 1 H, C_{11}), 4.24 (d, J = 12.5 Hz, 1 H, benzyl), 4.22 (d, J = 12.5 Hz, 1 H, benzyl), 3.82 (dd, J = 11.5, 4.2 Hz, $C_{7\alpha}$), 3.56–3.39 (m, 2 H), 3.19 (br s, 1 H), 3.02 (dd, J = 9.3, 3.3 Hz, 1 H, C_{14}), 2.89 (br s, 1 H), 2.41 (ddd, J = 14.4, 4.0, 2.0 Hz, 1 H, $C_{12\beta}$), 2.18 (d, J = 14.4 Hz, 1 H, $C_{12\alpha}$), 1.92–1.81 (m, 15 H), 1.11 (s, angular CH_3); ^{13}C NMR 146.3, 138.1, 128.4 (×2), 127.8 (×2), 127.7, 112.2, 75.1, 73.3, 69.7, 66.6, 65.3, 51.9, 48.5, 47.0, 44.3, 40.8, 39.4, 37.1, 34.9, 27.6, 26.6, 26.5, 21.4, 15.1 ppm.

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.19; H, 9.29.

Tetracyclic Triol 29a. To a solution of 985 mg (2.38 mmol) of triol **28** in 50 mL of CH_2Cl_2 at 25 °C was added 1.02 g (4.76 mmol) of *m*-chloroperbenzoic acid (80%). The solution was stirred 4 h at 25 °C. A saturated $NaHSO_3$ solution (5 mL) was added, and stirring was continued for 15 min. The reaction mixture was diluted with ether and washed sequentially with water, saturated $NaHCO_3$, and water. The organic layer was worked up to provide, after crystallization from THF and ether, 737 mg (72%) of the cyclic ether: R_f 0.24 (EtOAc); mp 146–147 °C (THF/ether); IR 3542 (s), 3521–3274 (br) cm^{-1}; ^1H NMR (250 MHz) 7.41–7.28 (m, 5 H), 4.54 (s, 2 H, CH_2OBn), 4.39 (d, J = 7.8 Hz, 1 H, C_{20}), 4.19 (m, br t, w/D_2O, J = 2.0 Hz, 1 H, C_{11}), 3.97 (dd, J = 7.8, 1.4 Hz, 1 H, C_{20}, W coupling to C_9), 3.67–3.46 (m, 3 H), 3.55 (d, J = 12.0 Hz, 1 H), 3.39 (d, J = 12.0 Hz, 1 H), 2.37 (m, 3 H), 1.97 (br dt, J = 12.0, 12.6 Hz, 1 H, $C_{1\beta}$), 1.76 (dd, J = 14.8, 4.7 Hz, 1 H, $C_{12\alpha}$), 1.65–1.20 (m, 13 H), 1.30 (s, angular CH_3), 0.97 (dd, J = 2.0, 1.4 Hz, 1 H, C_9), 0.92 (td, J = 12.0, 5.4 Hz, 1 H, $C_{1\alpha}$); ^{13}C NMR 137.5, 128.5 (×2), 127.9, 127.8 (×2), 84.3, 73.5, 70.3, 69.3, 69.2, 66.6, 65.5, 51.5, 50.9, 45.4, 42.4, 38.8, 37.7, 36.7, 35.7, 27.5, 26.4, 24.9, 20.9, 13.8 ppm.

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.99. Found: C, 72.44; H, 8.95.

Tetraol 29b. To a solution of 1.05 g (2.44 mmol) of triol **29a** in 30 mL of EtOAc was added 200 mg of 10% Pd/C. The suspension was vigorously stirred under a positive atmospheric pressure of hydrogen for 24 h. The reaction mixture was then filtered through Celite and the filtrate concentrated to provide 821 mg of a white solid (99%): R_f 0.03 (EtOAc); mp 109–111 °C (neat); ^1H NMR (250 MHz) δ 4.42 (d, J = 7.8 Hz, 1 H, C_{20}), 4.23 (br s, 1 H, C_{11}), 4.01 (dd, J = 7.8, 1.0 Hz, 1 H, C_{20}, W coupling to C_9), 3.85–3.66 (m, 4 H), 3.44 (d, J = 12.4 Hz, 1 H), 2.48 (br s, 1 H), 2.06–1.98 (m, 2 H), 1.84–1.20 (m, 15 H), 1.31 (s, angular CH_3), 1.16–0.92 (m, 3 H).

Diketo Diester 32. To a solution of 1.0 g (2.9 mmol) of tetraol **29b** in 50 mL of acetone at 0 °C was added 8 mL of Jones reagent (2.67 M in CrO_3) over 1 min. The solution was allowed to stir 4 h at 25 °C, after which isopropyl alcohol was added dropwise to decompose excess oxidizing agent. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a volume of 50 mL. To the solution in an Erlenmeyer flask was added 49.5 mL of ethereal diazomethane (0.36 M, 17.8 mmol; **CAUTION**: vide supra) with swirling. After addition of the diazomethane solution was complete, glacial acetic acid was added dropwise to decompose excess diazomethane. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (40% EtOAc/hexane) to provide 672 mg of a white solid (58%): R_f 0.39 (50% EtOAc/hexane); mp 150–151 °C (EtOAc/ether); IR 1735, 1709 cm^{-1}; ^1H NMR (250 MHz) δ 4.34 (d, J = 8.3 Hz, 1 H, C_{20}), 3.80 (dd, J = 8.3, 1.9 Hz, 1 H, C_{20}, W coupling to C_9), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.63 (td, J = 7.6, 1.7 Hz, 1 H, C_{14}), 2.87 (d, J = 16.3 Hz, 1 H, $C_{12\alpha}$), 2.71–2.56 (m, 4 H, including dd, J = 16.3, 1.7 Hz, $C_{12\beta}$-H), 2.23 (dd, J = 16.6, 4.0 Hz, 1 H, $C_{6\alpha}$), 2.15 (dd, J = 16.6, 15.6 Hz, 1 H, $C_{6\beta}$), 1.78–1.23 (m, 9 H), 1.25 (s, angular CH_3); ^{13}C NMR 206.6, 203.3, 170.9, 170.1, 84.4, 75.5, 60.7, 60.5, 52.7, 52.0, 47.5, 47.0, 44.0, 43.0, 38.3, 36.2, 30.9, 27.9, 25.8, 20.8, 11.0 ppm.

Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.23.

Pentacyclic Lactone 34. To a solution of 50 mg (0.13 mmol) of diketo diester **32** in 5 mL of THF at 0 °C was added 20.5 mg (0.19 mmol) of lithium hydridotri(*tert*-butoxy)aluminate. The solution was stirred for 45 min at 0 °C followed by dilution with EtOAc and washing with water, 1 N HCl, and water. Workup afforded 48.8 mg of alcohol **33a** as a white solid: R_f 0.17 (50% EtOAc/hexane); ^1H NMR (250 MHz) δ 4.27 (dd, J = 8.5, 1.7 Hz, 1 H, C_{20}, W coupling to C_9), 4.22 (d, J = 8.5 Hz, 1 H, C_{20}), 3.78 (s, 6 H, 2-CO_2CH_3), 3.48 (dt, J = 11.7, 4.8 Hz, 1 H, $C_{7\alpha}$), 3.25 (d, J = 4.8 Hz, 1 H, OH), 3.16 (dd, J = 8.4, 3.5 Hz, 1 H, C_{14}), 2.84 (dd, J = 18.1, 3.5 Hz, 1 H, $C_{15\beta}$), 2.67 (s, 2 H, C_{12}), 2.66 (dd, J = 18.1, 8.4 Hz, 1 H, $C_{15\alpha}$), 2.60 (br dt, J = 12.5, 3.0 Hz, 1 H, $C_{1\beta}$), 1.92 (d, J = 1.7 Hz, C_9-H), 1.10 (s, angular CH_3), 1.72–1.06 (m, 9 H), 0.86 (td, J = 12.5, 4.4 Hz, 1 H, $C_{1\alpha}$).

To a solution of the alcohol in 5 mL of CH_2Cl_2 at 25 °C was added 19.2 mg (0.19 mmol) of triethylamine. The solution was cooled to 0 °C, and 17.4 mg (0.15 mmol) of methanesulfonyl chloride was added over 5 min. The solution was allowed to stir an additional 45 min at 0 °C and was then diluted with CH_2Cl_2 and washed with water. Workup gave 55.5 mg of crude mesylate **33b**: R_f 0.24 (50% EtOAc/hexane); ^1H NMR (250 MHz) δ 4.72 (dd, J = 12.0, 4.8 Hz, 1 H, $C_{7\alpha}$), 4.22 (d, J = 8.8 Hz, 1 H, C_{20}), 4.15 (dd, J = 8.8, 2.0 Hz, 1 H, C_{20}, W coupling to C_9), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.15 (s, 3 H, SO_2CH_3), 2.93 (d, J = 17.2 Hz, 1 H), 2.73–2.56 (m, 3 H), 1.95 (br s, 1 H), 1.89–1.82 (m, 1 H), 1.75–1.14 (m, 10 H), 1.10 (s, angular CH_3), 0.92–0.84 (m, 1 H).

The oily mesylate was dissolved in 5 mL of methanol and 0.5 mL of water containing 152 mg (1.1 mmol) of potassium carbonate. The mixture was heated at reflux for 5 h, and after cooling, the mixture was brought to pH 2 by the addition of 3 N HCl. The solution was diluted with EtOAc and washed with water. The water washes were back-extracted with EtOAc, and the combined organic layers were worked up and subjected to flash chromatography (40% EtOAc/hexane) to give 27.1 mg of the lactone as a white solid after recrystallization from THF/ether (59%): R_f 0.26 (50% EtOAc/hexane); mp 208–209 °C (THF/ether); IR (CH_2Cl_2) 1735, 1722 cm^{-1}; ^1H NMR (250 MHz) δ 4.61 (m, 1 H, C_7), 4.46 (d, J = 8.7 Hz, 1 H, C_{20}), 3.81 (s, 3 H, CO_2CH_3), 3.72 (dd, J = 8.7, 2.0 Hz, 1 H, C_{20}, W coupling to C_9), 3.08 (dd, J = 18.2, 6.0 Hz, 1 H, $C_{15\beta}$), 2.80 (dd, J = 18.2, 13.5 Hz, 1 H, $C_{15\alpha}$H) 2.78 (s, 2 H, C_{12}), 2.69 (dd, J = 13.5, 6.0 Hz, 1 H, C_{14}), 2.52 (dt, J = 12.2, 1.5 Hz, 1 H, $C_{1\beta}$), 2.21 (d, J = 2.0 Hz, 1 H, C_9), 1.72–1.07 (m, 9 H), 1.14 (s, angular CH_3), 0.91 (td, J = 12.2, 4.5 Hz, $C_{1\alpha}$-H); ^{13}C NMR 202.3, 169.6, 167.9, 83.0, 82.7, 74.4, 55.3, 52.9, 48.0, 46.9, 45.9, 38.5, 38.1, 36.4, 32.6, 28.8, 27.0, 26.0, 20.7, 11.6 ppm.

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.32; H, 7.26.

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performing the X-ray analysis of acetate **23**.

Registry No. 1, 41451-75-6; **9a**, 95531-75-2; **9a** (methyl ester), 95531-76-3; **9a** (methyl ester, diethyl ketal), 95531-77-4; **9b**, 95532-00-6; **10a**, 95531-78-5; **10b**, 95532-01-7; **11a**, 95532-02-8; **11b**, 95532-03-9; **12**, 95532-04-0; **13**, 95531-79-6; **14**, 95531-80-9; **16**, 95531-81-0; **17**, 95531-82-1; **18**, 95531-83-2; **19**, 95532-06-2; **20**, 95532-07-3; **21**, 95532-08-4; **22**, 95532-09-5; **23**, 95532-10-8; **24a**, 95531-84-3; **24b**, 95531-85-4; **25a**, 95531-86-5; **25b**, 95531-87-6; **26a**, 95531-88-7; **26b**, 95531-89-8; **27**, 95531-90-1; **28**, 95531-91-2; **29a**, 95531-92-3; **29b**, 95531-93-4; **32**, 95531-94-5; **33a**, 95531-95-6; **33b**, 95531-96-7; **34**, 95531-97-8; $BnO(CH_2)_3OH$, 4799-68-2; $BnO(CH_2)_3Br$, 54314-84-0; $BnO(CH_2)_3P^+(C_6H_5)_3Br^-$, 54314-85-1; (*E*)-$BnO(CH_2)_2CH{=}C(CH_3)$-$CH_2OH$, 95531-99-0; (*Z*)-$BnO(CH_2)_2CH{=}C(CH_3)CH_2OH$, 95531-98-9; (*E*)-$BnO(CH_2)_2CH{=}C(CH_3)CHO$, 95532-05-1; $THPOCH_2CO$-CH_3, 53343-13-8; $CH_2{=}C(Me)CH_2Br$, 1458-98-6.

Supplementary Material Available: X-ray positional and thermal parameters and a three-dimensional structure of acetate **23** are provided along with experimental details for the synthesis of compounds **19**, **20**, **21**, **22**, and **23** (10 pages). Ordering information is given on any current masthead page.

Polysilane High Polymers: Mechanism of Photodegradation

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Abstract: Photolysis of the high polymer $(n\text{-}C_6H_{13}MeSi)_n$ in CCl_4 leads to the formation of C_2Cl_6, indicating that the photodegradative pathway of these polymers includes the formation of silyl radicals. Photolysis of alkyl-substituted polysilane polymers, $(R_1R_2Si)_n$ (R_1 = *n*-hexyl, R_2 = Me; R_1 = R_2 = *n*-hexyl; R_1 = cyclohexyl, R_2 = Me), at 254 nm in the presence of triethylsilane gives two major products, $Et_3Si\text{-}R_1R_2SiH$ and $HR_1R_2Si\text{-}R_1R_2SiH$. Photolysis of $(n\text{-}C_6H_{13}MeSi)_n$ in the presence of ROH (R = Me; R = *n*-Pr) gives four major products, $n\text{-}C_6H_{13}(Me)Si(OH)H$, $H(n\text{-}C_6H_{13})(Me)Si\text{-}(n\text{-}C_6H_{13})(Me)SiH$, $H(n\text{-}C_6H_{13})(Me)Si\text{-}(n\text{-}C_6H_{13})(Me)SiOR$, and $(RO)(n\text{-}C_6H_{13})(Me)Si\text{-}(n\text{-}C_6H_{13})(Me)SiOR$. To explain these results, a photolytic cascade mechanism that involves both the extrusion of silylene units and the formation of silyl radical terminated polymer fragments is proposed. The photochemistry of phenyl-substituted polysilane polymers was examined and found to be considerably more complex than the photochemistry of the alkyl-substituted polymers.

Polysilane polymers, the silicon analogues of saturated linear organic polymers, possess several rather remarkable properties. The polymer backbone acts as an intense UV chromophore, and the position of the absorption maximum and the absorptivity at the absorption maximum are quite dependent upon the polymer chain length. Increasing chain length results in a marked red-shift of the absorption maxima, finally reaching a constant value in high molecular weight polymers at 300–327 nm for polyorganosilanes containing alkyl substituents and 335–360 nm for polyorganosilanes containing aryl substituents.[1] Organosilane polymers are also very photoactive under UV irradiation, with only photoscission processes occurring for alkyl-substituted polymers, and concurrent photoscission and photo-cross-linking processes being observed for polyorganosilanes with aryl and other unsaturated substituents.[1,2] The quantum efficiencies for these photoreactions in solutions are quite high, between 0.20 and 0.97, depending upon the nature of the organic substituent.[1a]

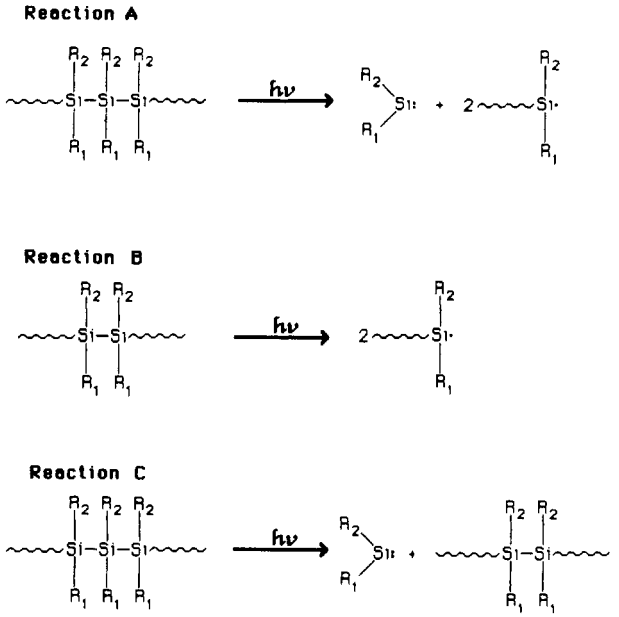
These remarkable properties are currently stimulating intense interest in these organosilane polymers as mid- and deep-UV photoresists,[2,3] as sensitive photoinitiators for olefin polymerizations,[4] as photo-cross-linked polymer precursors to β-SiC ceramics,[5] and in other applications where light sensitivity is required. In view of the unique properties of polyorganosilanes and the current interest in the photoactivity of these polymers, we have investigated the mechanism of photodegradation of polyorganosilanes.

The photochemistry of small cyclosilanes $(R_1R_2Si)_n$, n = 4–6, has been extensively investigated, and photolysis is believed to result in sequential extrusion of silylene units resulting in the formation of smaller cyclosilanes:[6]

$$(R_1R_2Si)_n \rightarrow (R_1R_2Si)_{n-1} + R_1R_2Si:$$

The photochemistry of small linear permethylpolysilanes, $(Me_2Si)_nMe$, n = 4–8, has also been studied.[6a,7] As with cyclosilanes, photolysis results primarily in the extrusion of silylenes,

Scheme I. Possible Reactions for the Photodegradation of Polysilane Polymers



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(1) (a) Trefonas, P., III; West, R.; Miller, R. D.; Hofer, D. *J. Polym. Sci., Polym. Lett. Ed.* **1983**, *21*, 823. (b) West, R.; David, L. D.; Djurovitch, P. I.; Stearley, K. L.; Srinivasan, K. S. V.; Yu, H. *J. Am. Chem. Soc.* **1981**, *103*, 1352. Zhang, X. H.; West, R. *J. Polym. Sci.* **1984**, *22*, 159. Zhang, X. H.; West, R. *J. Polym. Sci.* **1984**, *22*, 255. Zhang, X. H.; West, R. *J. Polym. Sci.* in press. Zhang, X. H.; West, R. *Polym. Commun. (Peking)*, in press.

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