was dried over sodium sulfate and evaporated to give **5bα** as a white solid (89%).

Preparation of 5-Methyl-2-oxo-6-phenyl-4-*p*-tolyltetrahydro-1,3-oxazine ((*S*,*R*,*R*/*R*,*S*,*S*)-5bβ). To a solution of **6bα** (5 mmol) in anhydrous THF (30 mL) in an ice bath was added aluminum trichloride (0.8 g, 6 mmol) with stirring. The solution was refluxed for 15 h, then hydrolyzed with 3 N KOH, and extracted with ether. The extract was dried, filtered, and evaporated. The residue, a white solid (91%), was purified by recrystallization from *n*-hexane–chloroform (6:1): mp 232–233 °C; IR (Nujol) 3260, 1710, 820, 780, 770, 740 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.50 (d, 3 H, J = 7.5 Hz), 2.00 (m, 1 H), 2.30 (s, 3 H), 4.20 (d, 1 H, J = 9.5 Hz), 4.90 (d, 1 H, J = 9.5 Hz), 5.50 (br s, NH), 7.00–7.50 (m, 9 H); ^{13}C NMR ($DCCl_3$) δ 153.83, 138.47, 137.34, 136.55, 127.10–129.49, 84.54, 62.30, 40.55, 20.99, 12.82.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.91; H, 6.93; N, 4.53.

Preparation procedure and spectral data for compounds **5aβ**, **5cα**, and **5dβ** are included as supplementary material.

General Preparative Procedure of 1-(Carbethoxyamino)-3-propanols 6α.[8b] To a solution of **4α** (10 mmol) in anhydrous THF (40 mL) and anhydrous pyridine (5 mL) in a ice bath was added ethyl chloroformate (1.2 mL, 12 mmol) with stirring. The mixture was refluxed for 10 h, then poured onto 3 N KOH, and extracted with ether. The extract was dried over sodium sulfate and evaporated under reduced pressure. The residual 1-(carbethoxyamino)-3-propanols **6α** were purified by recrystallization from *n*-hexane–chloroform (6:1). Reaction yields and melting points are shown in Table IV.

1-(Carbethoxyamino)-2-methyl-1,3-diphenyl-3-propanol ((*S*,*R*,*S*/*R*,*S*,*R*)-6aα). Obtained from the reaction of **4aα** and ethyl chloroformate: IR (Nujol) 3400, 1700, 760, 740, 710 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.60 (d, 3 H), 1.15 (t, 3 H), 2.00 (m, 1 H), 3.40 (br s, OH) 4.00 (q, 2 H), 4.70 (m, 1 H), 4.90 (br s, NH), 5.70 (d, 1 H), 7.00–7.40 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 157.10, 143.32, 140.90, 125.32–128.53, 71.85, 60.94, 59.16, 45.30, 14.39, 10.05.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.35; N, 4.47. Found: C, 72.67; H, 7.51; N, 4.53.

Spectral data for compound **6bα** are included as supplementary material.

Reduction of 5 with $LiAlH_4$. Reduction of **5** with $LiAlH_4$ was carried out by following the procedure described for the preparation of **4** (Method A).

Reduction of 5-Methyl-2-oxo-6-phenyl-4-*p*-tolyltetrahydro-1,3-oxazine ((*S*,*R*,*S*/*R*,*S*,*R*)-5bα). Compound **4iα** (80%) was obtained.

Results from the reduction of **5aβ** and **5bβ** are included as supplementary material.

General Preparative Procedure of Tetrahydro-1,3-oxazines 8.[24] To a solution of **4** (5 mmol) in ether at room temperature was added 35–40% aqueous formaldehyde (5 mmol). The solution was stirred for 16 h at room temperature. Solvent was removed and the residue dried under reduced pressure to yield tetrahydro-1,3-oxazines **8**. Reaction yields are given in Table V.

5-Methyl-4,6-diphenyltetrahydro-1,3-oxazine ((*S*,*R*,*S*/*R*,*S*,*R*)-8aα) was obtained from the reaction of **4aα** and formaldehyde. The residue was purified by distillation: IR (film) 3360, 1600, 750, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.90 (d, 3 H, J = 7.5 Hz), 2.45 (m, 1 H), 2.80 (br s, NH), 4.00 (d, 1 H, J = 3.0 Hz), 4.45 (d, 1 H, J = 12.0 Hz), 4.65 (d, 1 H, J = 12.0 Hz), 4.70 (d, 1 H, J = 3.0 Hz), 7.00–7.70 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 141.70 141.07, 125.10–128.36, 76.21, 75.64, 58.61, 36.22, 12.83; MS, m/e 253 (M^+), 223, 209, 180, 134, 118.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.51; N. 5.53. Found: C, 80,57; H, 7.64; N, 5.67.

Spectral data for compounds **8bα** and **8bβ** are included as supplementary material.

Reduction Followed by Hydrolysis of 2-Ethyl-5-methyl-2,4,6-triphenyl-5,6-dihydro-1,3-oxazine (9). Reduction of **9** with Na/*i*-PrOH was carried out by following the procedure described for preparation of **4** (Method C). A yellow oil was obtained. The oil was solved in THF. 4 N HCl was added to the solution and the mixture heated for 7 h, treated with 3 N KOH until basic, and extracted with ether. The organic layer was dried, filtered, and evaporated. γ-Amino alcohol **4a** (81 %) was obtained as a mixture of diastereoisomers.

Separation of the Diastereoisomers of 4a. The crude product containing two isomers (γ/α = 66/34, calculated by ^1H and ^{13}C NMR) was suspended in hexane and stirred. The slurry was filtered. The hexane-insoluble solid was identified as **4aα**. From the filtrate hexane was removed and isomer **4aγ** was distilled.

(*S*,*R*,*R*/*R*,*S*,*S*)-4aγ: IR (film) 3300, 1600, 740, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.70 (d, 3 H, J = 7.5 Hz), 2.10 (m, 1 H), 3.25 (br s, NH and/or OH), 4.35 (d, 1 H, J = 3.0 Hz), 5.20 (d, 1 H, J = 3.0 Hz), 7.00–7.50 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 144.71, 143.56, 125.42–128.42, 77.25, 59.53, 45.48, 12.10.

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.87; H, 7.93; N, 5.60.

Registry No. **2a**, 85356-29-2; **2b**, 85356-31-6; **2c**, 97293-65-7; **3a**, 85356-36-1; **3b**, 85356-37-2; **3c**, 97210-88-3; **3d**, 97210-89-4; **3e**, 97210-90-7; **3f**, 97210-91-8; **3g**, 97210-92-9; **3h**, 97210-93-0; **3i**, 97210-94-1; **3j**, 97210-95-2; **4aα**, 97210-96-3; **4aβ**, 97275-75-7; **4bα**, 97210-97-4; **4bβ**, 97275-76-8; **4cα**, 97210-98-5; **4cβ**, 97275-77-9; **4dα**, 97210-99-6; **4dβ**, 97275-78-0; **4eα**, 97211-00-2; **4eβ**, 97275-79-1; **4fα**, 97211-01-3; **4fβ**, 97275-80-4; **4gα**, 97211-02-4; **4gβ**, 97275-81-5; **4hα**, 97211-03-5; **4hβ**, 97275-82-6; **4iα**, 97211-04-6; **4iβ**, 97275-83-7; **4jα**, 97211-05-7; **4jβ**, 97275-84-8; **4kα**, 97211-06-8; **4kβ**, 97275-85-9; **4lα**, 97211-07-9; **4lβ**, 97275-86-0; **4mα**, 97211-08-0; **4mβ**, 97275-87-1; **5aβ**, 97211-09-1; **5bα**, 97211-10-4; **5bβ**, 97275-88-2; **5cα**, 97234-62-3; **5dβ**, 97211-11-5; **6aα**, 97211-12-6; **6bα**, 97211-13-7; **8aα**, 97211-14-8; **8bα**, 97211-15-9; **8bβ**, 97275-89-3; **9**, 97211-16-0; CH_3COCl, 75-36-5; $ClCOCH(CH_3)_2$, 79-30-1; $ClCOC_6H_{11}$, 2719-27-9; $ClCO_2Et$, 541-41-3; PhCOCl, 98-88-4; *p*-$CH_3C_6H_4COCl$, 874-60-2; *p*-ClC_6Ch_4COCl, 122-01-0; $Ti(OEt)_4$, 3087-36-3; $B(OEt)_3$, 150-46-9; $TiCl_4$, 7550-45-0; formaldehyde, 50-00-0.

Supplementary Material Available: Spectral and analytical data for compounds **2c**, **3c–j**, **4a–m**, **5aβ**, **5cα**, **5dβ**, **6aα**, **6bα**, **8aα**, **8bα**, **8bβ** (18 pages). Ordering information is given on any current masthead page.

Quassinoids. An Approach to the BCDE Rings of Bruceantin

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Received March 5, 1985

Synthesis of a model **28** for the BCDE rings of bruceantin via a BC → BCE → BCED ring strategy is presented. The sequence includes Diels–Alder reaction of methyl 3,5-hexadienoate **9** and quinone **8** derived from *o*-vanillyl alcohol, selenocyclization of hydroxy diester **22**, and lactone formation to give the BCDE system **25**. Manipulation on **25** showed the viability of its functional groups for further development in the synthetic strategy.

The quassinoids constitute a large and constantly expanding family of terpenoid bitter principles found in *Simaroubaceae*, a large botanical family of pantropical distribution.[2] Quassin (**1**) was isolated in 1973[3] and its

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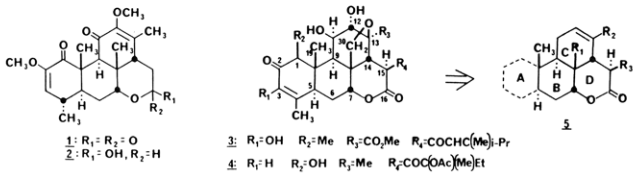


structure elucidated, together with neoquassin (**2**), in the early 1960s.[4] It has been known for some time that certain quassinoids are effective antiamoebic and antimalarial agents.[5] In addition, the leaves and roots of *Brucea antidysenterica* have been used for centuries in Ethiopia for the treatment of cancer,[6] and this has led to the isolation and characterization of a number of quassinoids which exhibit potent in vivo antineoplastic activity, among which are bruceantin (**3**)[7] and quasimarin (**4**).[8] Bruceantin is currently in clinical trials in the United States.[9]

Several general approaches to quassinoids have been reported.[10] Grieco and co-workers first accomplished an elegant total synthesis of quassin (**1**)[11] and the related castelanolide.[12] Studies specifically directed at the more complex systems containing bridging ethers such as **3** and **4** have also appeared.[13] Kraus and co-workers first reported a model of the BCDE system.[14] Kametani[15] and Ganem[16] and co-workers have accomplished models of the ABCDE system, with the latter containing the most complex functionality suitable for further elaboration. Total synthesis of **3** has not yet been reported.

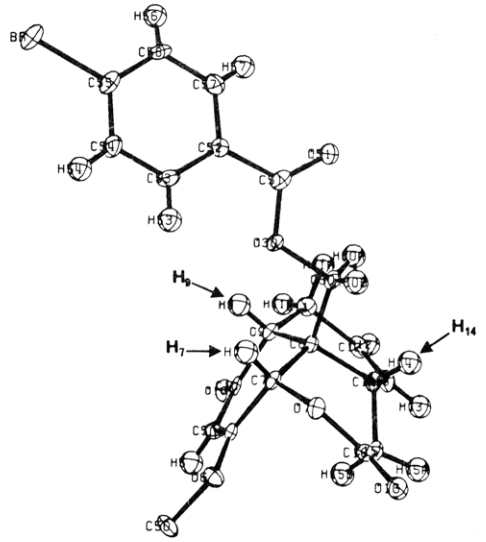
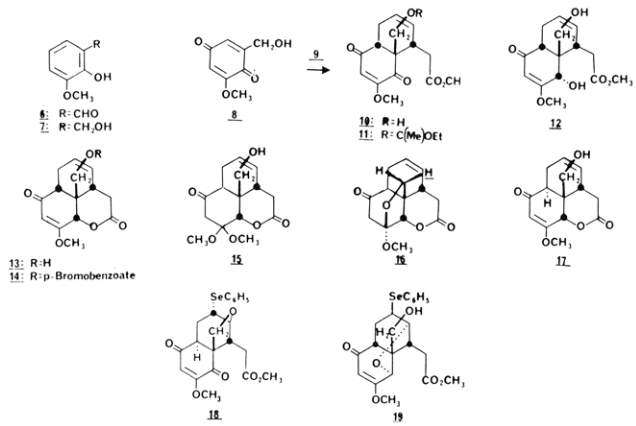


Figure 1. ORTEP diagram of **14**.

Chart I



The vast majority of the known quassinoids share a common tetracyclic carbon skeleton and a common stereochemistry within this framework. Substantial differences are found in the substitution pattern and oxidation state of the A ring of this family of natural products. However, the B, C, and D rings can be thought of as variations of the three substituents R_1–R_3 shown in formula **5**. Accordingly, we sought a general strategy in which these differences could be accommodated readily. In this paper, we report our general approach to quassinoid synthesis through its application to the specific case where $R_1 = CH_2OH$ and $R_2 = R_3 = H$ of **5** as a model for the BCDE rings of bruceantin (**3**).

Our initial efforts were directed in a BCD → BCDE strategy to synthesis of lactone **13**, as shown in Chart I. Catalytic hydrogenation of *o*-vanillin (**6**) gave phenol **7** quantitatively. Difficulties encountered in large-scale production of quinone **8** using Fremy's salt[17] were overcome by salcomine.[18] Diels–Alder reaction of quinone **8** with methyl 3,5-hexadienoate **9**[19] led in high yield to adduct **10**. No trace of any isomer could be detected by TLC or NMR (^1H or ^{13}C). Sodium borohydride reduction of **10** at 0 °C led rapidly to a mixture of hydroxy ester **12** and lactone **13**. Prolonged stirring of the mixture at room

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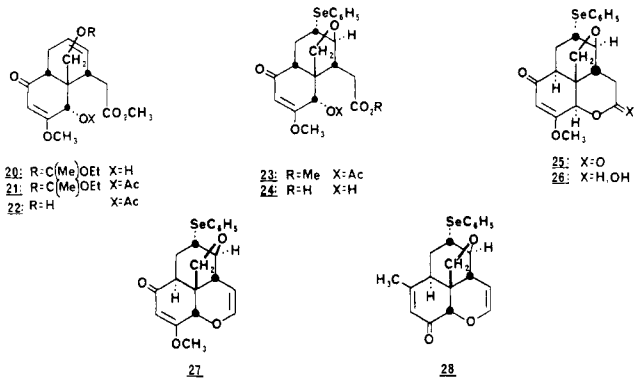
Chart II



temperature or brief stirring in the presence of dilute $NaHCO_3$ effected total conversion to the crystalline lactone **13** in an overall yield of 65% from *o*-vanillin. The stereochemical features were unambiguously established by single-crystal X-ray analysis[20] of its *p*-bromobenzoate ester **14**, shown in Figure 1, which clearly demonstrates the cis nature of all ring junctures. This was in accord with our expectation that the BC cis ring fusion would be established in the Diels–Alder reaction to give **10** and that reduction of the C-7 carbonyl had been directed to the convex face.

Diverse standard attempts to epimerize the crucial C-9 of **13**, including low-temperature kinetic enolate trapping experiments, were unsuccessful. Furthermore, attack of numerous electrophilic reagents upon the C-12/13 double bond failed to give the desired D-ring product. However, reaction of **13** with catalytic sodium methoxide in methanol gave **15** in 75% yield. This was converted in 69% to ketal lactone **16** by azeotropic refluxing in benzene with catalytic *p*-TsOH. When **16** was refluxed in benzene with catalytic *p*-TsOH but without azeotrope, partial conversion was effected to the desired **17**. However, during isolation, on standing and in solution, **17** rapidly epimerized to **13**.[23]

The rapidity of epimerization of **17** and the inability to epimerize C-9 in **13** attest to the difficulty of access to the desired trans,cis BCD system, as was also found by Weller et al. on a related tricycle.[13h] This is the first report of the desired system **17**, and that it could arise here stems from the presence of the requisite trans BC stereochemistry in the precursor **16**, which was confirmed by long range *W* coupling between H-9 and one of the C-30 hydrogens in the 200-MHz ^1H NMR. Epimerization has previously been observed to accompany bridge formation. Kraus reported epimerization at C-9 (trans → cis) of a model BCE system upon bridging ketal formation between C-12 and C-10, which was utilized ingeniously for subsequent transformations,[14] and we found that *cis*-**10** led to *trans*-**18** upon treatment with (phenylseleno)phthalimide.

To circumvent the above difficulties, we turned our attention to a BCE → BCDE strategy. Sodium borohydride reduction of **10** at −40 °C afforded **12** as the sole product in 92% yield. Treatment of **12** with PhSeCl gave **19**, in which ring closure was effected through the secondary rather than the primary hydroxyl group. Protection of **10** with ethyl vinyl ether gave **11** in 91% yield, which was reduced at −40 °C to give **20** in 99% yield (Chart II). Acetylation of the secondary hydroxyl followed by aqueous acid gave hydroxy diester **22** in 78% recrystallized yield. Reaction of **22** with PhSeCl in the presence of K_2CO_3 gave **23** in 79% yield after purification. Saponification of **23** with excess sodium hydroxide led rapidly to diacid **24**, which was transformed to the desired BCDE system **25** by catalytic *p*-TsOH in refluxing benzene in 43% yield from **23**. In view of the importance of **25** in the overall strategy, a detailed ^1H NMR analysis was undertaken. Table I lists data from the 500-MHz analysis. These data, along with analyses of Dreiding models of **25** in possible cis and trans BC configurations, unequivocally confirmed the stereochemical assignment. The perspective drawing of the CD rings of **25** illustrates the relevant couplings (Figure 2).

We briefly investigated functional group manipulations on **25** to test its validity as a model for D-ring hydroxylation and as a precursor for A-ring annelation. The selenide was retained since oxidative elimination on a similar system had resulted in the initially formed C-11/12 double bond moving into conjugation with the C-10 carbonyl group. Selective reduction of **25** with lithium aluminum tri-*tert*-butoxyhydride gave lactol **26** quantitatively as a

Table I. Selenoether Lactone 25 Chemical Shifts, Coupling Constants, and Assignments from 500-MHz ^1H NMR in $CDCl_3$

chemical shift, δ	signal type	|J|, Hz	assignment[a]
2.32	dd	7, 11, 16	H-11 ax
2.35	dd		
2.42	dd	6, 16	H-11 equ
2.50	dt	5, 14	H-14
2.85	dd	2, 6, 11	H-9
2.94	dd	5, 18	H-15 equ
3.51	dd	14, 18[b]	H-15 ax
3.53	dd	2, 9[b]	$H\text{-}30_w$
3.60	dd	4, 7[c]	H-12
3.76	s		OCH_3
3.84	d	9	H-30
4.47	t	4, 5	H-13
4.69	s		H-7
5.40	s		H-5
7.22	m		Ar
7.48			

[a] Ax = axial, equ = equatorial. [b] Coupling constants were obtained from spectra recorded in 10% C_6D_6/90% $CDCl_3$, which induced chemical shifts sufficient to separate these signals. [c] Coupling constant determined after decoupling of overlying $H\text{-}15_{equ}$ signal by irradiation at δ 2.90.

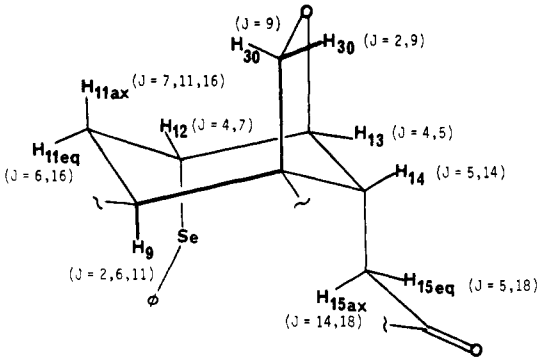


Figure 2. Perspective drawing of the CD rings of selenoether lactone **25**.

(20) Crystallographic data were obtained at 115 K with a Syntex P1 diffractometer equipped with a locally constructed low-temperature device.[21] Experimental and data handling techniques were analogous to those described previously.[22] Direct methods, difference Fourier, and least-squares refinement techniques were used in the solution of the structure. In the final refinement, positions, and anisotropic thermal parameters of all non-hydrogen atoms were refined along with the positions of the hydrogen atoms. Isotropic temperature factors of the hydrogen atoms were fixed at 2.0 Å^2.

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(23) The transience of **17** precluded its full characterization, but spectral comparison of 200-MHz ^1H NMR shows it to be consistent with C-9 rather than C-7 epimerization.

2:1 mixture of diastereomers. Dehydration of this mixture with *p*-TsOH afforded enol ether **27** in 36% yield. Although crystalline, **27** could not be separated from a minor unidentified impurity. Long-range *W* coupling between the protons at C-9 and C-30 was observed in the 200-MHz ^{1}H NMR spectrum, confirming retention of the trans BC ring juncture. Finally, treatment of **27** with methyllithium followed by dilute acid gave enone **28** in 40% yield.

Experimental Section

Infrared spectra were recorded on a Beckman IR 4210 infrared spectrophotometer. ^{1}H NMR spectra were taken on a Varian T-60 and Bruker 200- and 500-MHz spectrometers and on a 395-MHz spectrometer (designed and built by Professor Frank Anet of this department) using tetramethylsilane as an internal standard. Mass spectra were determined on an AE1-M59 spectrometer. Melting points are corrected.

***o*-Vanillyl Alcohol (7).** *The following is a modification of* the reported procedure.[24] A solution of *o*-vanillin (50 g, 329 mmol) in absolute ethanol (200 mL) was reduced at 45 psi at room temperature in the presence of Raney nickel (2 g). The reaction was complete in 2 days. The solution was filtered through Celite and concentrated in vacuo. Crystallization of the resultant oil was effected from hot benzene/hexane to afford 45.6 g (90%) of pure *o*-vanillyl alcohol **7**. Evaporation of the mother liquor to dryness and recrystallization from hot benzene/hexane afforded a second crop of 4.05 g (8%) of **7**.

Quinone 8. A solution of *o*-vanillyl alcohol **7** (20 g, 0.128 mmol) in 200 mL of dimethylformamide was stirred in the presence of salcomine (2 g, 6 mmol) for 2 days with a slow stream of oxygen bubbling through the solution. Celite (10 g) was added and the *mixture stirred for 10 min. The solvent was evaporated in vacuo,* and the finely powdered residue was placed in a Soxhlet extractor and extracted with ethyl acetate/ether (1:4) for 7 days. The collection flask was removed and the solvent evaporated in vacuo to afford 18.7 g (86%) of pure quinone **8** identical in all respects with material obtained by oxidation of **7** with Fremy's salt as described in the literature.[17]

Diels–Alder Adduct 10. A mixture of quinone **8** (3 g, 178 mmol) and diene ester **9** (3.94 g, 31.2 mmol) was heated at 55 °C for 24 h under N_2. On cooling to room temperature, a white solid precipitated. The solid was washed with ether (3 × 25 mL) and filtered and then recrystallized from ethyl acetate/hexane to afford 4.543 g (87%) of pure adduct **10**. The ether washings were distilled to recover excess diene ester. For optimization, the mother liquor from recrystallization and the residue from the ether washings were combined and concentrated in vacuo. The residue was chromatographed on Florisil (1:2 ethyl acetate/hexane) to afford an additional 0.441 g (8%) of pure adduct as white crystals: mp 125–127 °C; IR (KBr) 3500 (O–H), 1730 (C-16 C=O), 1692 (shoulder, C-7 C=O), 1675 (C-10 C=O), 1608 (C-5 C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05–2.28 (complex m, 3 H), 2.43 (t, J = 5 Hz, OH), 2.60 (br s, 1 H, allylic), 2.97 (br dd, J = 4 Hz, J = 18 Hz, 1 H, allylic), 3.44 (dd, J = 1 Hz, J = 6 Hz, 1 H, H-9), 3.62 (s, 3 H, OCH_3), 3.64 (m obscured by OCH_3 signal, 1 H, H-30), 3.80 (s, 3 H, OCH_3), 4.25 (dd, J = 5 Hz, J = 11 Hz, 1 H, H-30), 5.62 (m, 1 H, H-13), 5.72 (m, 1 H, H-12), 6.07 (s, 1 H, H-5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.20 (t, C-11), 35.73 (d, C-14), 37.88 (t, C-15), 44.08 (d, C-9), 51.88 (q, OCH_3), 55.73 (s, C-8), 56.45 (q, OCH_3), 65.12 (t, C-30), 112.84 (d, C-5), 125.52 (d, C-13), 126.70 (d, C-12), 161.56 (s, C-6), 171.54 (s, C-16), 197.50 (s, C-10), 197.81 (s, C-7); mass spectrum, calcd for $C_{14}H_{16}O_5 - CH_2O$ 264.0999, found 264.1009.

Protected Diels–Alder Adduct 11. A solution of Diels–Alder *adduct 10 (10 g, 34 mmol) in dry* CH_2Cl_2 *(100 mL) was stirred* at 0 °C under N_2 in the presence of TsOH (20 mg, 0.1 mmol). A solution of freshly distilled ethyl vinyl ether (3.5 g, 48 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture. After 20 min, solid K_2CO_3 was added and stirring continued for 10 min. The mixture was washed sequentially with saturated $NaHCO_3$, H_2O, and brine and then dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 11.335 g (91%) of crude **11** as a pale yellow oil: IR (film) 1735 (C-16 C=O), 1700 (C-7 C=O), 1675 (C-10 C=O), 1608 (C-5 C=C) cm^{-1}; ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.16 (m, 6 H, 2 CH_3 of protecting group), 2.19 (complex m, 3 H), 2.48 (br m, 1 H), 2.83 (br d, $J \sim$ 18 Hz, 1 H), 3.37–3.62 (complex m obscured by OCH_3 signal, 4 H), 3.49 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.02 (d, J = 9 Hz) and 4.18 (d, J = 9 Hz) [1 H, H-3O], 4.67 (m, 1 H, $OCH(CH_3)O$), 5.62 (m, 2 H, H-12,13), 6.13 (s, 1 H, H-5); [diastereomers, 1:1 mixture] ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.18 and 15.25, 19.51 and 19.72, 20.59 and 20.72, 36.87 and 36.98, 37.43, 44.39 and 44.53, 51.67, 53.82 and 53.92, 56.35, 61.34 and 61.82, 67.58, 100.15, 100.362, 112.21 and 112.35, 125.42 and 125.52, 127.05 and 127.12, 161.67, 171.61, 195.14 and 195.35, 198.02; [diastereomers] mass spectrum, m/e 321 (parent – CH_3CH_2O).

Diol Ester 12. Diels–Alder adduct **10** was stirred in anhydrous CH_3OH (50 mL) and cooled to −40 °C under N_2. $NaBH_4$ (0.162 g, 4.3 mmol) was added in one portion as a solid, and the reaction mixture was stirred for 30 min. Ice water was added, and the mixture was extracted into cold ethyl acetate after partitioning between cold brine/ethyl acetate. The organic layer was washed with a small volume of cold water and then brine and dried over $MgSO_4$. After filtration and concentration, there was obtained 2.42 g of **12**. This material was washed with ethyl acetate and filtered to provide 2.08 g (92%) of pure reduced **11**: mp 178 °C; IR (KBr) 3500 (O–H), 3290 (O–H), 1730 (C-16 C=O), 1622 (C-10 C=O), 1600 (C-5 C=C) cm^{-1}; ^{1}H NMR (200 MHz, CD_3COCD_3) δ 1.92 (m partly obscured by solvent, 1 H, H-11), 2.43 (m, 1 H, H-11), 2.80 (m, 4 H), 3.52 (dd partially obscured by OCH_3 signal, J = 5 Hz, J = 11 Hz, 1 H, H-30), 3.59 (s, 3 H, OCH_3), 3.62 (m obscured by OCH_3 signal, J = 5 Hz, 1 H, H-30), 3.75 (s, 3 H, OCH_3), 4.27 (t, J = 5 Hz, 1 H, OH), 4.75 (d, J = 4 Hz, 1 H, OH), 4.94 (br s, 1 H, H-7), 5.31 (s, 1 H, H-5), 5.5 (m, 2 H, H-12,13); mass spectrum, calcd for $C_{15}H_{20}O_6 - CH_3OH$ 264.0998, found 264.1001.

Cis Lactone 13. To a stirred solution of **10** (4 g, 14 mmol) in anhydrous CH_3OH (20 mL) at room temperature was added solid $NaBH_4$ (0.5 g, 13 mmol). After 30 min, 1.5 N acetic acid was added until the solution was acidic, followed by cautious addition of *half-saturated* $NaHCO_3$. *The mixture was stirred for 2 h.* A precipitate formed, which was filtered and washed with ether/ethyl acetate (1:1), affording 2.83 g (79%) of lactone **13** as a white solid. The filtrate was then extracted into CH_2Cl_2 and washed twice with H_2O and twice with brine and then dried over Na_2SO_4. After filtration and evaporation of solvent, 2 g of material was recovered. Recrystallization from hot ethyl acetate/hexane yielded an additional 0.18 g (5%) of **13** as colorless rhomboids: mp 207 °C; IR (KBr) 3380 (O–H), 1725 (C-16 C=O), 1645 (C-10 C=O), 1620 (C-5 C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.95 (br s, 1 H, OH), 2.22 (m, 1 H, H-11a), 2.43 (m, 2 H, H-9,11b), 2.50 (dd partially obscured by m, J = 5 Hz, J = 15 Hz, 1 H, H-15a), 2.80 (br s, 1 H, H-14), 2.99 (dd, J = 5 Hz, J = 15 Hz, 1 H, H-15b), 3.64 (d, J = 2 Hz, 2 H, H-30), 3.79 (s, 3 H, OCH_3), 5.08 (s, 1 H, H-7), 5.44 (s, 1 H, H-5), 5.53 (m, J = 9 Hz, 1 H, H-13), 5.98 (m, 1 H, H-12); mass spectrum; calcd for $C_{14}H_{16}O_5$ 264.0998, found 264.0996.

Lactone Bromobenzoate Ester 14. Lactone **13** (0.1 g, 0.38 mM) was dissolved in 2 mL of dry pyridine and stirred at 0 °C. *p*-Bromobenzoyl chloride (0.25 g, 1.1 mM) was added dropwise, the ice bath was removed, and the mixture was stirred for 6 h. Water (5 mL) was added dropwise, and then the reaction mixture was extracted into CH_2Cl_2. The CH_2Cl_2 layer was separated and washed with oxalic acid and then H_2O and dried over $MgSO_4$. Evaporation in vacuo afforded a white powder, consisting of *p*-bromobenzoic acid and the desired **14**. Chromatography on silica (1:4 EtOAc/hexane) afforded 0.13 g of **14**, which was recrystallized from EtOAc/hexane to afford 0.12 g of colorless needles: mp 195–195.5 °C; IR (KBr) 1755 (benzoate C=O), 1725 (C-16 C=O), 1650 (C-10 C=O), 1625 (C-5 C=C) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35 (m, 2 H, H-11a,11b), 2.58 (m obscured by dd, 1 H, H-9), 2.58 (dd, J = 5 Hz, J = 15 Hz, 1 H, H-15a), 2.85 (br s, 1 H, H-14), 2.94 (dd, J = 5 Hz, J = 15 Hz, 1 H, H-15b), 3.75 (s, 3 H, OCH_3), 4.28 (d, J = 12 Hz, 1 H, H-30a), 4.42 (d, J = 12 Hz, 1 H, H-30b), 4.94 (s, 1 H, H-2), 5.47 (s, 1 H, H-1), 5.56 (m, 1 H, H-7), 6.03 (m, 1 H, H-6), 7.61 (d, J = 9 Hz, 2 H, Ar) 7.83 (d, J = 9 Hz, 2 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.30 (t, C-11), 34.69 (t, C-15), 35.07 (d, C-14), 39.89 (d, C-14), 45.50 (d, C-9), 56.56 (q, OCH_3), 69.10 (t, C-30), 74.47 (d, C-7), 102.48 (d, C-5), 127.39

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(Ar), 127.91 (Ar), 128.12 (Ar), 128.99 (Ar), 131.10 (d, vinyl), 132.22 (d, vinyl), 165.31 (s, C-6), 167.35 (s, C-16), 170.75 (s, benzoate C=O), 198.16 (s, C-10); mass spectrum; *m/e* 446 (parent). Crystal data: space group *P*1; $Z = 1$; lattice parameters (115 K), $a = 7.383$ (3) Å, $b = 10.280$ (3) Å, $c = 13.658$ (5) Å, $\alpha = 109.89$ (2)°, $\beta = 94.58$ (3)°, $\gamma = 108.10$ (2)°; radiation Mo Kα crystal monochromatized (0.7107 Å); crystal dimensions, 0.03 × 0.02 × 0.024 mm; absorption coefficient, 12.3 cm^{-1}, $T_{min} = 0.092$, $T_{max} = 0.95$ (correction to *I*); scan range, 1.0 below Kα_1 to 0.1 above Kα_2; scan rate, 3.0°/min; scan mode, $\theta/2\theta$; background time = scan time; observed reflections (*I* greater than 3.0*I*), 2608; $R = 0.043$, $R_w = 0.053$; error in observation of unit weight, 1.60.

Methanol Addition Adduct 15. Lactone **13** (3.19 g, 12 mmol) was added in one portion as a solid to a previously prepared solution of sodium methoxide (50 mL of anhydrous CH_3OH to which a small piece of sodium was added) and stirred at room temperature for 4 days under N_2. The mixture was acidified with 1 N HCl, and solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 and eluted through Florisil (1:2 ethyl acetate/hexane) to afford 2.73 g of crude ketal **15**. Recrystallization from ethyl acetate/hexane afforded 2.05 g (57%) of pure ketal **15**: mp 118.5–120 °C; IR (KBr) 3400 (O–H), 1740 (shoulder), 1730 (C-16 C=O), 1710 and 1700 (C-10 C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (s, 1 H, OH), 2.30 (m, 2 H), 2.65 (m, 3 H), 2.93 (m, 3 H), 3.37 (s, 3 H, OCH_3), 3.65 (dd, $J = 2$ Hz, $J = 9$ Hz, 1 H, H-30), 3.73 (s, 3 H, OCH_3), 3.85 (d, $J = 9$ Hz, 1 H, H-30), 4.37 (br s, 1 H, H-7), 5.63 (m, 2 H, H-12,13); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.39 (t, C-11), 36.98 (t, C-15), 37.57 (d, C-14), 40.93 (d, C-9), 45.02 (s, C-8), 47.03 (t, C-5), 49.90 (q, OCH_3), 51.91 (q, OCH_3), 72.53 (t, C-30), 73.26 (d, C-7), 106.53 (s, C-6), 125.97 (d, vinyl), 128.09 (d, vinyl), 173.90 (s, C-16), 208.87 (s, C-10); mass spectrum, calcd for $C_{15}H_{20}O_6 - CH_2O$ 265.1076, found 265.1047.

Ketal 16. A solution of adduct **15** (0.6 g, 2 mmol) in dry THF/benzene with *p*-toluenesulfonic acid (10 mg, 0.05 mmol) was heated to reflux under N_2. The solvent was allowed to distill away, replacing benzene as necessary, over a 2-h period. Solid $NaHCO_3$ was added and the mixture stirred for 30 min. The reaction mixture was transferred to a separatory funnel containing cold saturated $NaHCO_3$ and extracted into ethyl acetate. The organic fraction was washed well with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 0.45 g of crude **16**. Recrystallization from hot ethyl acetate/hexane provided 0.37 g (69%) of platelet-like colorless crystals of ketal **16**: mp: 209–211 °C dec; IR (KBr) 1749 (C-16 C=O), 1722 (C-10 C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (m, 1 H), 2.48 (dd partially obscured by m, $J = 4$ Hz, $J = 18$ Hz, 1 H, H-15), 2.52 (m obscured by dd, 2 H), 2.69–3.14 (complex m, 4 H), 3.34 (s, 3 H, OCH_3), 3.77 (dd, $J = 2$ Hz, $J = 9$ Hz, 1 H, H-30), 3.97 (d, $J = 9$ Hz, 1 H, H-30), 4.72 (d, $J = 1$ Hz, 1 H, H-7), 5.67 (m, 1 H, vinyl), 5.80 (m, 1 H, vinyl); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.28, 33.75, 34.34, 42.11, 42.66, 46.75, 50.49, 71.36, 78.39, 104.28, 126.60, 127.67, 170.23, 203.77; mass spectrum, *m/e* 264 (parent).

Lactone 17. Method A. A solution of methanol addition adduct **15** (38 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) and CF_3CO_2H (2 drops) was stirred at room temperature for 3 days. The solvent was evaporated in vacuo, and the resultant oil was chromatographed on Florisil (1:3 ethyl acetate/hexane) to afford 2 mg (7%) of a lower R_f fraction, crude lactone **17**.

Method B. A solution of **15** (50 mg, 0.17 mmol) in THF (25 mL) was stirred at reflux in the presence of *p*-toluenesulfonic acid (10 mg, 0.05 mmol) for 24 h. Dry toluene (75 mL) was added and the solvent allowed to distill to half the original volume. The solvent was evaporated in vacuo to afford a mixture of three compounds as an oil. The lowest R_f component was isolated by preparative TLC (SiO_2, ethyl acetate) and afforded 5 mg (11%) of lactone **17**: IR ($CHCl_3$) 3450 (O–H), 1740 (C-16 C=O), 1660 (C-10 C=O), 1622 (C-5 C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.02 (m, 1 H), 2.49 (m, 2 H), 2.84 (m, 2 H), 3.12 (br s, 1 H), 3.61 (d, $J = 11$ Hz, 1 H, H-30), 3.76 (d obscured by OCH_3 signal, 1 H, H-30), 3.78 (s, 3 H, OCH_3), 5.11 (s, 1 H, H-7), 5.49 (s, 1 H, H-5), 5.62 (m, 1 H, vinyl), 5.86 (m, 1 H, vinyl).

Method C. A solution of ketal **16** (39 mg, 0.14 mmol) was refluxed in benzene for 3 days in the presence of *p*-toluenesulfonic acid (10 mg, 0.05 mmol). The solvent was evaporated in vacuo. The lower R_f fraction was separated by preparative TLC (SiO_2, ethyl acetate) to afford 23 mg (60%) of a mixture (1:1) of lactones **13** and **17**, plus a small amount of ketal **16**.

Hydroxy Ester 19. A heterogeneous solution of hydroxy ester **12** (0.96 g, 3.25 mmol) in ethyl acetate (75 mL) was stirred at −25 °C under N_2. To this was added a solution of benzeneselenenyl chloride (0.65 g, 3.4 mmol) in ethyl acetate (30 mL) dropwise. After 1 h, the reaction mixture was filtered to remove undissolved starting material (0.16 g, 0.53 mmol), then washed well with H_2O, followed by brine, and dried over $MgSO_4$. Filtration and evaporation in vacuo afforded 1 g of crude product mixture. The mixture was chromatographed through Florisil (1:1 ethyl acetate/hexane) to afford in the third fraction, 0.12 g (8%) of hydroxy ester **19** as an oil: IR (film) 3420 (O–H), 1730 (C-16 C=O), 1650 (C-10 C=O), 1620 (C=C) cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ 1.96–2.23 (complex m obscured by solvent signal, 2 H), 2.41 (dd, $J = 11$ Hz, $J = 16$ Hz, 1 H), 2.73–2.94 (complex m, 3 H), 3.45–3.82 (complex m obscured by 2 OCH_3 signals, 4 H), 3.67 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.16 (s, 1 H, H-7), 4.27 (d, $J = 2$ Hz, 1 H, H-13), 5.26 (s, 1 H, H-5), 7.32 (m, 3 H, Ar), 7.57 (m, 2 H, Ar); mass spectrum, *m/e* 452 (parent).

Protected Hydroxy Ester 20. A solution of **11** (11 g, 30 mmol) in anhydrous CH_3OH (100 mL) was stirred at −40 °C under N_2. To this was added $NaBH_4$ (1.85 g, 31 mmol) as a solid, and stirring was continued for 30 min. Ice water was added, and the mixture was stirred for an additional 20 min, allowing the temperature to approach 0 °C. The mixture was added to cold brine and extracted into ethyl acetate. The organic layer was washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo was effected without heating to afford 11 g (30 mmol, 99%) of protected hydroxy ester **20** as a pale yellow oil: IR (film) 3300 (O–H), 1730 (C-16 C=O), 1655 (C-10 C=O), 1610 (C-5 C=C) cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) [diastereomers] δ 1.14 (t, $J = 7$ Hz, 3 H, CH_2CH_3), 1.26 (d, $J = 5$ Hz, 3 H, CH_2CH_3), 2.04 (m obscured by solvent signal, 1 H, H-11a), 2.45 (m, 1 H, H-11b), 2.80 (m, 3 H), 3.32–3.82 (complex m obscured by OCH_3 signal, 6 H), 3.60 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.70 (m, 1 H, $OCH(CH_3)O$), 4.86 (s, 1 H, H-7), 5.32 (s, 1 H, H-5), 5.80 (m, 2 H, H-12,13); ^{13}C NMR (50 MHz, $CDCl_3$) [diastereomers] δ 15.28, 19.61 and 19.86, 26.30, 33.16 and 33.75, 38.12, 43.46, 51.50 and 51.57, 56.49, 61.69 and 61.76, 68.34 and 68.48, 69.76 and 69.93, 74.13, 100.29, 101.64 and 101.96, 125.17, 127.91, 173.10, 173.13 and 174.00, 197.81; mass spectrum, *m/e* 323 (parent − CH_3CH_2O).

Hydroxy Diester 22. A solution of protected hydroxy ester **20** (11 g, 29 mmol) in dry CH_2Cl_2 (100 mL) was stirred at room temperature under N_2 in the presence of triethylamine (13 g, 129 mmol) and 4-(dimethylamino)pyridine (0.385 g, 3.1 mmol). To this was added acetic anhydride (13 g, 127 mmol), and stirring was continued for 2 h. Methanol (10 mL) was added dropwise, the solution was stirred for an additional 10 min, and then the solvent was evaporated in vacuo. The resultant oil was taken up in ether and washed sequentially with 1 N oxalic acid, H_2O, $NaHCO_3$, and H_2O and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 11.3 g of crude diprotected ester **21** as an oil. This oil was taken up in CH_3OH (50 mL) and stirred at room temperature with 1 N HCl (2 mL) for 1 h. The solution was added to brine and extracted into ethyl acetate. The ethyl acetate fraction was washed with water and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 9.2 g of crude hydroxy ester **22**. Recrystallization from ethyl acetate/hexane afforded 7.25 g (78%) of pure **22**: mp 149.5–150.5 °C; IR (KBr) 3400 (O–H), 1735 (2 ester C=O), 1635 (C-10 C=O), 1605 (C-5 C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.06 (dd, $J = 12$ Hz, $J = 15$ Hz, 1 H, H-15), 2.10 (m obscured by dd, 1 H), 2.19 (s, 3 H, CH_3), 2.30 (br m, 1 H, allylic), 2.61 (dd, $J = 3$ Hz, $J = 15$ Hz, 1 H, H-15), 2.78 (br m, 1 H), 2.89 (br m, 1 H, allylic), 2.95 (d obscured by m, $J = 6$ Hz, 1 H), 3.33 (d, $J = 12$ Hz, 1 H, H-30), 3.58 (d partially obscured, $J = 12$ Hz, 1 H, H-30), 3.66 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 5.44 (s, 1 H, H-5), 5.50 (br d, $J = 10$ Hz, 1 H, vinyl), 5.64 (br d, $J = 10$ Hz, 1 H, vinyl), 6.30 (br s, 1 H, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.62 (t, C-11), 20.69 (q, acetate CH_3), 34.03 (d, C-14), 38.26 (t, C-15), 42.42 (d, C-9), 47.55 (s, C-8), 51.64 (q, OCH_3), 56.66 (q, OCH_3), 63.87 (t, C-30), 68.76 (d, C-7), 102.75 (d, C-5), 125.52 (d, vinyl), 127.05 (d, vinyl), 171.06 (s, C-6), 171.16 (s, acetate C=O), 172.96 (s, C-16 C=O), 197.78 (s, C-10 C=O); mass spectrum, calcd for $C_{17}H_{22}O_7$ 338.1366, found 338.1381.

Ether Diester 23. A solution of **22** (7 g, 20 mmol) in dry CH_2Cl_2 (100 mL) was stirred at −50 °C under N_2 in the presence of finely ground anhydrous K_2CO_3 (14 g, 0.1 mol). To this was added dropwise a solution of benzeneselenenyl chloride (4.5 g, 24 mmol) in dry CH_2Cl_2 (40 mmol). The reaction mixture was stirred for 4 h, then diluted with CH_2Cl_2 (100 mL), and filtered. The filtrate was washed well with cold H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo provided 9 g of crude **23**, which was recrystallized from ethyl acetate/hexane to afford 7.8 g (79%) of pure colorless crystals: mp 194–196 °C; IR (KBr) 1740 and 1725 (2 ester C=O), 1640 (C-10 C=O), 1608 (C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3 H, CH_3), 2.39 (2 overlapping t, J = 9 Hz, J = 16 Hz, 1 H, H-11), 2.55–3.06 (complex m, 5 H), 3.55 (dt, J = 4 Hz, J = 9 Hz, 1 H, H-12), 3.65 (s, 3 H, OCH_3), 3.66 (d obscured by OCH_3 signal, J = 8 Hz, 1 H, H-30), 3.72 (s, 3 H, OCH_3), 3.87 (d, J = 8 Hz, 1 H, H-30), 4.67 (t, J = 4 Hz, 1 H, H-13), 5.55 (d, J = 1 Hz, 1 H, H-5), 5.99 (s, 1 H, H-7), 7.24 (m, 3 H, Ar), 7.53 (m, 2 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.55, 22.04, 32.54, 38.95, 39.37, 47.96, 48.14, 51.71, 56.66, 66.57, 73.85, 78.88, 103.62, 127.53, 129.13, 130.96, 133.77, 169.74, 170.37, 171.93, 195.42; mass spectrum, calcd for $C_{23}H_{26}O_7Se$ 494.0844, found 494.0849.

Hydroxy Acid 24. A solution of **23** (3 g, 6 mmol) in CH_3OH (50 mL) was stirred at room temperature. To this was added a solution of 1 N NaOH (10 mL) in CH_3OH (20 mL), and stirring was continued for 2 h. The solution was acidified to pH 1 with 1 N HCl and then added to brine and extracted into ethyl acetate. The organic fraction was washed with H_2O and then extracted with 0.5 N $NaHCO_3$ (40 mL). The aqueous layer was reacidified to pH 1 with 1 N HCl and extracted into ethyl acetate. The organic fraction was washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 2.3 g of a white solid. This was washed twice with ethyl acetate to afford 1.6 g (63%) of pure hydroxy acid **24**: mp 189 °C; IR (KBr) 3300 (br, O–H), 1720 (CO_2H), 1590–1640 (C=O and C=C) cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ 2.38 (m, 2 H), 2.74–3.02 (complex m, 4 H), 3.56 (m, 2 H, H-12,30), 3.65 (d, J = 8 Hz, 1 H, H-30), 3.72 (s, 3 H, OCH_3), 4.15 (s, 1 H, H-7), 4.59 (t, J = 4 Hz, 1 H, H-13), 5.23 (d, J = 1 Hz, 1 H, H-5), 7.33 (m, 3 H, Ar), 7.79 (m, 2 H, Ar); mass spectrum; m/e 420 (parent − H_2O).

Selenoether Lactone 25. Hydroxy acid **24** (1.6 g, 3.7 mmol) was dissolved in a minimum of dry THF (10 mL). Dry benzene and TsOH (915 mg, 0.08 mmol) were added, and the solution was brought to reflux with stirring in a Dean–Stark apparatus under N_2. The first 20 mL of distillate was discarded, and the reaction was permitted to run 12 h. The reaction mixture was cooled, then added to a cold solution of 0.02 N $NaHCO_3$, and stirred for 15 min. The benzene layer was separated. The aqueous layer was extracted with ethyl acetate. The benzene and ethyl acetate fractions were combined and washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 1.2 g of ether lactone **25**. This was washed with cold ethyl acetate to afford 0.9 g (57%) of pure **25**. An additional 0.1 g (6%) of pure material was isolated from the ethyl acetate and recrystallized from ethyl acetate/hexane: mp 229–231 °C dec; IR (KBr) 1740 (lactone C=O), 1660 (C-10 C=O), 1620 (C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (m, 2 H), 2.56 (dt, J = 6 Hz, J = 14 Hz, 1 H, H-14), 2.96 (m obscured by d, 1 H, H-9), 3.05 (dd, J = 5 Hz, J = 18 Hz, 1 H, H-15), 3.62 (complex m, 3 H, H-7,15,30), 3.76 (s, 3 H, OCH_3), 3.84 (d, J = 9 Hz, 1 H, H-30), 4.53 (t, J = 4 Hz, 1 H, H-12), 4.76 (s, 1 H, H-7), 5.47 (s, 1 H, H-5), 7.30 (m, 3 H, Ar), 7.53 (m, 2 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.16 (t, C-11), 29.60 (t, C-15), 36.73 (d, C-14), 41.20 (d, C-9)8, 42.76 (s, C-8), 43.01 (d, C-12), 56.56 (q, OCH_3), 72.05 (t, C-30), 78.08 (d, C-13), 79.50 (d, C-7), 104.35 (d, C-5), 128.16 (d, Ar), 129.54 (d, Ar) 133.77 (d, Ar), 166.66 (s, C-6), 168.63 (s, C-16), 196.91 (s, C-10); mass spectrum, calcd for $C_{20}H_{20}O_5Se$ 240.0476, found 420.0478.

Lactol 26. To a stirred solution of $LiAlH_4$ (1.4 mg, 0.36 mmol) in dry ether (6 mL) at 0 °C under N_2 was added t-BuOH (0.1 mL, 1.1 mmol) dropwise. Stirring was continued for 15 min, the ice bath was removed, and the precipitate was allowed to settle. The ether was removed by syringe and replaced with dry THF (4 mL). The solution was stirred for 5 min to effect dissolution of the precipitate. This solution was then added dropwise to a stirred solution of ether lactone **25** (75 mg, 0.18 mmol) in dry THF (5 mL) at 0 °C under N_2 and stirred for 15 min. A 1.5 N HCl solution (1 mL, 1.5 mmol) was then added dropwise, and the mixture was stirred an additional 15 min. The mixture was then added to brine and extracted into CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 72 mg (94%) of an approximately 2:1 mixture of lactols **26** as an oil: IR (film) 3580 (sh, O–H, 3400 (br, O–H), 1650 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) [diastereomers, ~2:1] δ 2.08–2.50 (series of complex m, partially obscured by solvent signal, 4 H), 3.12 (m, 1 H), 3.59 (complex m, 4 H) 3.74 (2 s, 4 H, OCH_3, OH), 4.06 (s, minor) and 4.41 (s, major) [1 H, H-7], 4.45 (m, minor) and 5.48 (br s, major) [1 H, H-16], 5.35 (s, 1 H, H-5), 7.34 (m, 3 H, Ar), 7.59 (m, 2 H, ar); mass spectrum, m/e 422 (parent).

Vinyl Ether 27. A solution of lactols **26** (0.6 g, 1.4 mmol) in dry benzene (75 mL) was refluxed overnight under N_2 in the presence of TsOH (10 mg, 0.05 mmol) in a Dean–Stark apparatus. After the mixture cooled, solid K_2CO_3 was added, and the mixture was stirred for 15 min. The mixture was then added to brine and extracted with ethyl acetate. The organic fraction was washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 0.7 g of crude material, which was chromatographed on Florisil (1:3 ethyl acetate/hexane) to afford 0.2 g (36%) of vinyl ether **27** and a minor contaminant. Recrystallization from ethyl acetate/hexane afforded pale yellow rhomboids of vinyl ether **27** but failed to remove the unidentified material: mp 129 °C and 165 °C; IR ($CHCl_3$) 1670 (C-14 C=O), 1635 (C=O), 1618 (C-5 C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.21 (m, 1 H, H-11), 2.76 (dt, J = 2 Hz, J = 14 Hz, 1 H, H-11), 2.95 (dd, J = 3 Hz, J = 7 Hz, 1 H, H-9), 3.20 (dt, J = 2 Hz, J = 10 Hz, 1 H, H-14), 3.46 (dd, J = 3 Hz, J = 9 Hz, 1 H, H-30), 3.74 (s, 3 H, OCH_3), 3.82 (m obscured by d, 1 H, H-12), 3.84 (d, J = 9 Hz, 1 H, H-30), 4.09 (s, 1 H, H-7), 4.14 (m, 1 H, H-13), 4.99 (dd, J = 2 Hz, J = 6 Hz, 1 H, H-15), 5.47 (s, 1 H, H-5), 6.52 (dd, J = 3 Hz, J = 6 Hz, 1 H, H-16), 7.27 (m, 3 H, Ar), 7.53 (m, 2 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.47 (2°, C-11), 34.55 (4°, C-8), 34.90 (3°, C-14), 35.63 (3°, C-9), 43.80 (3°, C-12), 56.35 (1°, OCH_3), 69.28 (3°, C-13), 71.36 (2°, C-30), 73.57 (3°, C-7), 100.22 (3°, C-15), 103.62 (3°, C-5), 127.64 (3°, Ar), 129.26 (4°, Ar), 129.33 (3°, Ar), 133.67 (3°, Ar), 144.03 (3°, C-16), 170.75 (C-6), 199.79 (C-10); mass spectrum, m/e 404 (parent).

Enone 28. A solution of vinyl ether **27** (0.2 g, 0.49 mmol) in dry THF was stirred under N_2 at −20 °C. A 1.21 M solution of CH_3Li (0.8 mL, 0.97 mmol) in hexane was added dropwise, and the mixture was stirred for 1 h. The cold bath was removed and the mixture brought to room temperature, then 1 N HCl (1.5 mL, 1.5 mmol) was added dropwise, and stirring was continued for 1 h. The reaction mixture was added to brine and extracted into ethyl acetate. The organic fraction was washed with H_2O and then brine and dried over Na_2SO_4. Filtration and evaporation in vacuo afforded 0.17 g of crude **28**, which was chromatographed through Florisil (1:3 ethyl acetate/hexane) to afford 96 mg of crude product mixture. Recrystallization of enone **28** from ethyl acetate/hexane afforded 74.5 mg (40%) of colorless rhomboids, containing a minor contaminant. A third recrystallization failed to remove the contaminant: mp 142 °C; IR (film) 1660 (C-16 C=C), 1635 (C=O), 1615 (C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.79 (br t, J = 2 Hz, J = 12 Hz, 1 H, H-11a), 2.01 (br s, 3 H, CH_3), 2.78 (2 overlapping dd, J = 3, 11, 14 Hz, 1 H, H-11b), 3.12 (dt partially obscured by m, J = 2 Hz, J = 10 Hz, 1 H, H-11b), 3.12 (dt partially obscured by m, J = 2 Hz, J = 10 Hz, 1 H, H-14), 3.17 (m obscured by dt, 1 H, H-9), 3.39 (dd, J = 2 Hz, J = 9 Hz, 1 H, H-30), 3.73 (s, 1 H, H-7), 3.87 (obscured by d, 1 H, H-12), 3.89 (d, J = 9 Hz, 1 H, H-30), 4.13 (dd, J = 2 Hz, J = 6 Hz, 1 H, H-13), 4.94 (dd, J = 2 Hz, J = 6 Hz, 1 H, H-15), 5.95 (d, J = 1 Hz, 1 H, H-5), 6.56 (dd, J = 2 Hz, J = 6 Hz, 1 H, H-16); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.14 (q, CH_3), 28.45 (t, C-11), 31.67 (d, C-14), 34.79 (d, C-9), 36.04 (s, C-8), 43.87 (d, C-12), 61.99 (t, C-30), 69.35 (d, C-13), 77.66 (obscured by $CDCl_3$ signal, C-7), 100.02 (d, ar), 145.17 (d, C-16), 162.26 (s, C-10), 192.16 (s, C-6); mass spectrum, m/e 388 (parent).

Acknowledgment. We are indebted to the National Science Foundation (NSF CHE81-15444) and the National Institutes of Health (CA 25675) for financial support; 500-MHz NMR spectra were determined at the Southern

California Regional NMR Facility at the California Institute of Technology (supported by NSF Grant CHE 79-16324A1). We thank D. Busby and S. Pitzenberger for obtaining proton NMR spectra and K. Fang for high-resolution mass spectra. We are extremely grateful to Dr. F. A. L. Anet for use of his 395-MHz NMR spectrometer and for stimulating discussions on analysis of selenoether lactone **25** and editorial advice. We also thank Dr. C. E. Strouse and L. Goldsmith for technical assistance and X-ray analysis of *p*-bromobenzoate **13**.

Registry No. **6**, 148-53-8; **7**, 4383-05-5; **8**, 50827-57-1; **9**, 40338-61-2; **10**, 97654-83-6; **11** (isomer 1), 97654-84-7; **11** (isomer 2), 97654-98-3; **12**, 97654-85-8; **13**, 97654-86-9; **14**, 97654-87-0; **15**, 97654-88-1; **16**, 97654-89-2; **17**, 97718-46-2; **19**, 97654-90-5; **20** (isomer 1), 97654-91-6; **20** (isomer 2), 97718-47-3; **21** (isomer 1), 97654-92-7; **21** (isomer 2), 97718-48-4; **22**, 97654-93-8; **23**, 97654-94-9; **24**, 97654-95-0; **25**, 97673-90-0; **26** (isomer 1), 97654-96-1; **26** (isomer 2), 97718-49-5; **27**, 97654-97-2; **28**, 97673-91-1; ethyl vinyl ether, 352-93-2; *p*-bromobenzoyl chloride, 586-75-4.

Supplementary Material Available: A table of atomic positions and thermal parameters of lactone **14** and a discussion of the ^1H NMR analysis of selenoether lactone **25** at 200 and 500 MHz, including a table and spectra (11 pages). Ordering information is given on any current masthead page.

A New Class of Chiral Smectic Liquid Crystals: Substituted Biphenylylcyclohexylideneethanones Having an Axial Chirality

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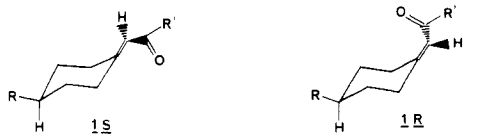
Received December 4, 1984

The introduction of a chiral cyclohexylideneethanone unit in a potential mesomorphic structure leads to the first family of optically active liquid crystals having an axial chirality. Racemic compounds **2** were synthesized by a Wittig-type coupling between β-keto phosphonates **6** (R^1 = *n*-C_5H_{11}) and substituted cyclohexanone **7** (R^2 = H, CH_3, *t*-Bu, OCH_3, O-*n*-C_5H_{11}, CO_2Et, $OCOC_6H_4CN$, $OCOC_6H_4Cl$). The optically active molecules **12** were prepared by a new route using the asymmetric coupling of a carbanion α to a chiral sulfoxide **9** (R^2 = *n*-C_5H_{11}, CH_2OEt) and a substituted biphenyl acid chloride (Ar = R′$C_6H_4C_6H_4$ with R′ = *n*-C_5H_{11}, CH_3O, *n*-$C_8H_{17}O$, CN) followed by a stereospecific pyrolytic elimination of the sulfoxide moiety. Derivatives containing only one aromatic ring were not mesomorphic in contrast to those having a biphenyl system.

Although optically active liquid crystals, mostly cholesteric, have been known for a long time,[1] the chirality has always been introduced by the way of one or more asymmetric centers, generally located in a side chain. There are no reports on any attempt to synthesize optically active liquid crystals having a molecular asymmetry,[13] although these molecules could be of interest in many applications such as dopants for nematic displays.

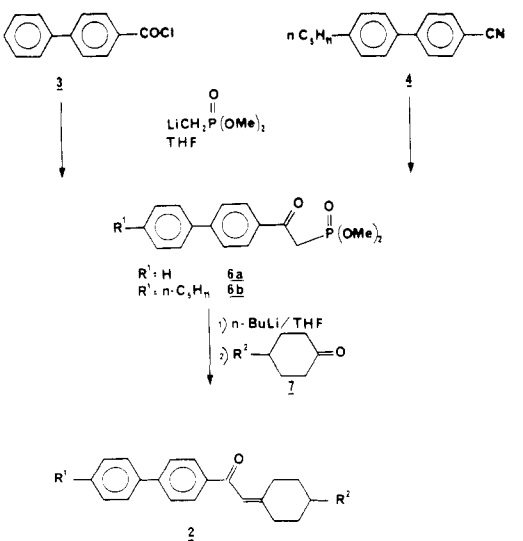
In the present work, we describe a new class of chiral liquid crystals having an axial chirality due to the presence of the chiral moiety cyclohexylideneethanone **1**.[14]



1S **1R**

These molecules which appeared to be chiral smectics or cholesteric (at room temperature in some cases) were synthesized in both racemic and optically active forms by two different routes. The optically active molecules were obtained from the asymmetric coupling of a carbanion α to a chiral sulfoxide group and substituted biphenyl acid chloride, followed by a stereospecific pyrolytic elimination of the sulfoxide moiety. This chirality transfer is a new methodology to prepare chiral cyclohexylideneethanones. However the unexpected photochemical unstability of these compounds did not allow a complete characterization of their mesomorphic phase.

Scheme I



Synthesis of Racemic Liquid Crystals 2

Because of the well-known ability of properly substituted biphenyls to give liquid crystals we chose to prepare first racemic type **2** molecules containing a biphenyl moiety (Scheme I).

The main step of the synthesis is the condensation of the β-keto phosphonates **6** with 4-substituted cyclo-

(1) (a) Kelker, H., Katz, R. "Handbook of Liquid Crystals"; Verlag Chemie: Weinheim/Berstr., West Germany, 1980; and references cited therein. (b) Gray, G. W.; Windsor, P. A. "Liquid Crystals and Plastic Crystals"; Wiley: New York, 1974; and references cited therein.

0022-3263/85/1950-4062$01.50/0