d, J = 18 Hz), 2.36 (1 H, d, J = 18 Hz), 2.48 (2 H, d, J = 10 Hz), 2.76 (1 H, d, J = 7 Hz), 2.88 (1 H, t, J = 10 Hz), 3.68 (3 H, s); MS, m/e 250 (M^+), 235 (base), 149, 107, 91, 41. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.77; H, 8.98.

Acknowledgment. We express our appreciation to Professor Steven D. Burke (University of South Carolina) for providing the ^{1}H NMR and IR spectra and an authentic sample of the compound **20**.

Note Added in Proof. Subsequent confirmation of the structures of the compounds **5** and **9** was made respectively by comparison of their ^{1}H NMR spectra with those generously provided by Professor S. Danishefsky (Yale University) and Professor A. B. Smith, III (University of Pennsylvania).

Registry No. (±)-**1**, 74807-65-1; (±)-**2**, 84057-30-7; (±)-**5**, 78739-64-7; (±)-**6**, 84057-31-8; (±)-**7**, 84057-32-9; (±)-**7** formate, 84057-33-0; (±)-**8**, 82652-82-2; (±)-**9**, 82652-83-3; (±)-**10**, 84057-34-1; (±)-**11**, 84057-35-2; (±)-**12**, 84057-36-3; (±)-**13**, 84057-37-4; (±)-**14**, 84057-38-5; (±)-**16**, 84057-39-6; (±)-**17**, 84057-40-9; (±)-**18**, 84057-41-0; (±)-**19**, 84057-42-1; (±)-**20**, 78739-62-5; 2-cyclohexenone, 930-68-7; isobutene, 115-11-7; propargyl bromide, 106-96-7; (±)-(1R*,5S*)-6,6-dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-one, 84057-43-2; (±)-(1R*,6S*,7S*)-7-hydroxymethyl-10,10-dimethyltricyclo[4.3.2.0^{2,6}]undec-2-en-4-one, 84057-44-3.

Palladium-Assisted Macrocyclization Approach to Cytochalasins: A Synthesis of Antibiotic A26771B

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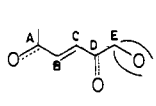
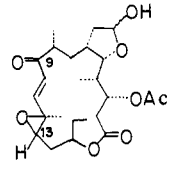
Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received June 28, 1982*

Abstract: A synthetic strategy to macrocycles possessing a γ-oxo-δ-hydroxy-, γ,δ-dihydroxy-, and γ-hydroxy-α,β-unsaturated carbonyl system derives from a palladium-catalyzed C–C bond-forming reaction. In this approach, the macrocyclization employs a β-keto sulfone as an electrofugal group and a 2-ethoxyallyl acetate as a nucleofugal group mediated by a phosphine–palladium(0) complex. In addition to facilitating anion formation and nucleophilic attack on the (π-allyl)palladium intermediate, the benzenesulfonyl group serves as a stereochemical control element which permits relay of stereochemical information between remote centers. The total synthesis of antibiotic A26771B is completed in 12 steps from 10-undecenal to illustrate the applicability of this methodology. The utility of conformational biases of large rings in synthesis and the mechanism of the macrocyclization are also discussed.

The highly oxidized structural fragment represented by formula **1** populates many naturally occurring macrocycles. For example,

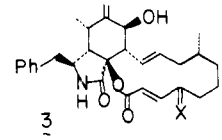


1



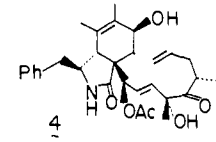
2

the aglycon **2** of the antibiotic rosaramycin possesses such a unit [C(9)–C(13)].[1] The cytochalasins, a group of fungal metabolites noted for inhibitory activity against bacteria and fungi and for unusual cytostatic activity,[2] prominently display this grouping in a richly diverse fashion as **3**–**6** illustrate. Among this family of compounds, both lactones and macrocyclic ketones are found.[3-6]



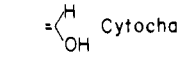
3

X=O Cytochalasin A[3]

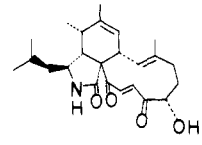


4

Cytochalasin C[4]

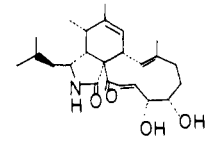


Cytochalasin B[3]



5

Aspochalasin B[5]

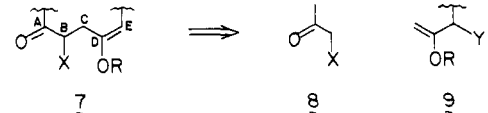


6

Aspochalasin C[5]

Furthermore, the sensitivity of the 2-ene-1,4-dione functionality as found in **3** and **5** make it desirable to introduce such a structural grouping at the final stages of synthesis. For these reasons, in searching for a general solution to these macrocycles, we focused on methods that would generate the macrocycle via C–C bond formation and simultaneously create the appropriate juxtaposition of functionality to permit the elaboration of **1** with the flexibility to adjust selectively the oxidation state at each carbon A → E.

With the goal of a general solution to this problem, we envisioned the fragment **7** as such a flexible unit. For example,



(1)

7 **8** **9**

hydrolysis and carbonyl reduction (or simple double bond reduction) followed by elimination of HX produces **3**. Hydroxylation and elimination produces **5** and with a minor modification **6**. The

(1) Ganguly, A. K.; Liu, Y. T.; Sarre, D.; Jaret, R. S.; McPhail, A. T.; Onun, K. K. *Tetrahedron Lett.* **1980**, *21*, 4699.

(2) Tamm, Ch. *Front. Biol.* **1978**, *46*, 15. For some recent examples, see: Probst, A.; Tamm, Ch. *Helv. Chim. Acta* **1981**, *64*, 2056. Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2703.

(3) Rothweiler, W.; Tamm, Ch. *Experientia* **1966**, *22*, 750. Scott, P. M.; Harwig, J.; Chen, Y.-K.; Kennedy, B. P. C. *J. Gen. Microbiol.* **1975**, *87*, 177. Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *Chem. Commun.* **1967**, 26.

(4) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc.* **1969**, 923; *Jpn. J. Antibiot.* **1969**, *22*, 170.

(5) Keller-Schierlein, W.; Kupfer, E. *Helv. Chim. Acta* **1979**, *62*, 1501. Heberle, W.; Loeffler, W.; Konig, W. A. *Arch. Microbiol.* **1974**, *100*, 73.

(6) For synthetic efforts, see: Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *96*, 5383. Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534. Bailey, S.; Thomas, E. J.; Turner, B. W.; Jarvis, J. A. J. *J. Chem. Soc., Commun.* **1978**, 474. Owens, C.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1504. Brettle, R.; Cummins, D. P. *Ibid.* **1977**, 2835. Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKengie, A. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960. Sttork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *Ibid.* **1978**, *100*, 7775. Schmidlin, T.; Tamm, Ch. *Helv. Chim. Acta* **1978**, *61*, 2096. Schmidlin, T.; Zurcher, W.; Tamm, Ch. *Helv. Chim. Acta* **1981**, *64*, 235.

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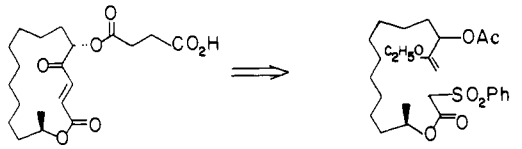
Table I. Palladium-Catalyzed Cyclizations of 11

entry	11, mmol	base, equiv	$Pd(Ph_3P)_4$, mol %	ligands, mol %	solvent[a]	time, h	concn,[b] M	yield,[c] %
1	0.13	2	7	17, dppp	THF/TOL	18	0.0032	84
2	0.20	2	7	18, dppp	THF/TOL	21	0.0040	59
3	0.48	2	6	12, dppp	THF/TOL	18	0.0054	60.5
4	0.56	2	7	13, dppp	THF	18	0.0056	59.5
5	0.17	2	6	12, dppb	THF	18	0.0034	66
6	0.73	2	6.5	13, dppb	THF	16	0.0066	58
7	1.80	2	6	12, dppb	THF	19.5	0.0090	56
8	0.45	2	6		THF	16.5	0.0045	0[d]
9	0.20	2	6	12, Ph_3P	THF	19.5	0.0041	0[d]
10	0.20	2	5.6	5.9, dppe	THF	20	0.0040	59
11	0.55	2	6	12, dppe	THF	62	0.0055	0
12	0.46	2	1.7	3.7, dppp	THF/TOL	19	0.0460	27

[a] Substrate was heated at reflux in THF with O,N-bis(trimethylsilyl)acetamide, and then added to a solution of the Pd catalyst and added ligand at reflux in either toluene or THF, as indicated. All reactions performed under argon. [b] Concentration of substrate. [c] Yield after purification by preparative TLC or medium-pressure liquid chromatography. [d] Only starting material recovered.

logical bond disconnection in **7** at B–C suggests that an allylic alkylation between a nucleophile generated from **8** and the electrophile **9** represents an excellent strategy. Furthermore, the unusual ability of palladium templates to facilitate macrocyclization via allylic alkylation imparts special interest to this strategy.[7-9] Antibiotic A26771B (**10**) was chosen as an adequate



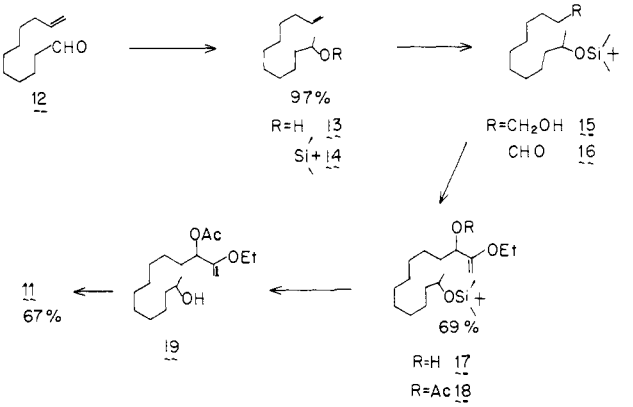
10 **11**

model[10,11] to test these concepts. An ambidofunctional group X in **8** should facilitate anion generation and subsequently serve as a leaving group for olefin formation; thus, the choice of benzenesulfonyl. A relatively poor leaving group for Y in **9** permits the precursor to be easily manipulated and its reactivity to be unmasked only at the time of cyclization. A carboxylate not only fits this description but represents an excellent type of substrate for palladium catalysis.[9] Thus, palladium-based methodology permits a rational design of synthetic strategy. In this paper, we wish to report (1) the realization of this proposal and the benefits derived from such palladium-based methodology and (2) that the combination of the properties of the benzenesulfonyl group with the conformational bias of the macrocycle permits relay of stereochemical information between distant centers. Thus, a benzenesulfonyl group can serve as a stereochemical control element.

Synthesis of the Seco Ester 11

Scheme I outlines the straightforward synthesis of **11** in 40% overall yield from 10-undecenal (**12**). Addition of methylmagnesium iodide[12] to **12** in ether gave the alcohol **13** in 99% yield. The unpurified alcohol, homogeneous by TLC and ^1H NMR, was directly silylated by using standard conditions to give **14** in 97% yield from **12** after column chromatography. Hydroboration of **14** with 1.5 equiv of disiamylborane[13] followed by oxidative workup gave the primary alcohol **15** selectively. TLC analysis showed

Scheme I. Synthesis of Cyclization Substrate 11



one major spot and NMR analysis of the crude alcohol (weight recovery 100%) failed to reveal the presence of the alternate regioisomer. While an analytical sample was prepared by preparative TLC, it was found advantageous in practice to use the unpurified alcohol in the oxidation step. Treatment with pyridinium chlorochromate in methylene chloride gave a 93% weight recovery of crude aldehyde **16**, which again was used immediately in the following reaction. Attempted purification by preparative HPLC led largely to the formation of a product tentatively identified as the aldehyde trimer. An analytical sample was prepared by medium-pressure liquid chromatography.

Addition of (1-ethoxyvinyl)lithium[14] to the crude aldehyde gave the crude allylic alcohol **17** which was immediately subjected to acetylation to provide the allylic acetate **18** in 69% overall yield from olefin **14**, after purification by column chromatography on silica gel. This sequence of four reactions was easily carried out without intermediate purification on a moderate scale.

Desilylation using tetra-*n*-butylammonium fluoride to **19** followed directly by esterification by benzenesulfonylacetic acid gave the cyclization precursor **11** in 62–67% yield from **18** after purification. Purifying **19** prior to the final acylation led to somewhat lower overall yields. Enol ether **11** exhibited a marked sensitivity to hydrolysis, especially upon attempted purification on silica gel having high activity. Thus, while successful purification could be carried out upon medium-pressure liquid chromatography on a Woelm silica gel column, attempted purification on commercial (Lobar) prepacked silica gel column led to almost exclusive hydrolysis.

Palladium Cyclization Studies

While cyclizations of simply substituted allylic acetates has been examined in our laboratories, the effect of substitution on the

(7) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867; *Tetrahedron Lett.* **1978**, 2275; *J. Am. Chem. Soc.* **1979**, *101*, 1595; **1980**, *102*, 4743.

(8) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864.

(9) For reviews, see: Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385; *Pure Appl. Chem.* **1981**, *53*, 2357.

(10) Michel, K. H.; De Marco, P. V.; Nagarajan, R. *Jpn. J. Antibiotics* **1977**, *30*, 571.

(11) (a) Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, 2633. (b) Talsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Ibid.* **1980**, 1479. (c) Asaoka, M.; Yanagida, N.; Takei, H. *Ibid.* **1980**, 4611. (d) Asaoka, M.; Abe, M.; Mukuta, T.; Takei, H. *Chem. Lett.* **1982**, 215.

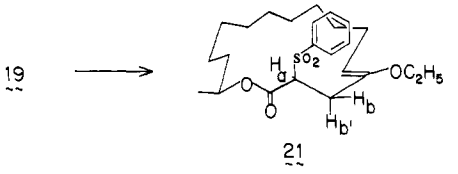
(12) Peterson, P. E.; Chevli, D. M. *J. Org. Chem.* **1974**, *39*, 3684.

(13) Brown, H. C.; Kulkarni, S. V.; Rao, C. G. *Synthesis* **1980**, 151.

(14) Boeckman, R. K., Jr.; Bruza, K. J. *J. Org. Chem.* **1979**, *44*, 4781. Baldwin, J. E.; Hofle, G. A.; Lever, O. W. *Jr. J. Am. Chem. Soc.* **1974**, *96*, 7125. Schollkopf, U.; Hunssle, P. *Liebigs Ann. Chem.* **1972**, *763*, 208.

carbons of the allyl unit remains relatively unknown. Among the possible substituents, oxygen is feared to be detrimental due to its known deceleration of the intermolecular reaction.[15] Typically a solution of the substrate and *O,N*-bis(trimethylsilyl)acetamide (*O,N*-bis) in THF was heated at reflux and then added via cannula all at once to a refluxing solution of 6 mol % tetrakis(triphenylphosphine)palladium (**20**) and 12 mol % of an auxillary phosphorus ligand in toluene or THF. No attempt was made to simulate truly high dilution conditions by slow addition of the substrate to the palladium solution. All runs were performed between 0.003–0.05 M.

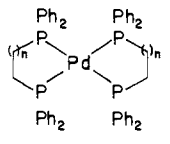
Table I summarizes the results of varying ligand, solvent, and concentration. Special note should be made that the high yield (84%) obtained in entry 1 was not reproducible; the optimum reproducible yield was 60 ± 5%, after isolation by medium-pressure liquid or preparative thick-layer chromatography. Entries 3 and 4 are included to illustrate reproducibility under nearly identical conditions. At higher substrate concentrations, a marked decrease in the yield of **21** was observed (entry 12). Whether this



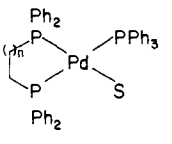
concentration dependence resulted from intermolecular alkylation competing with the desired intramolecular reaction at higher substrate concentrations is not discernable since a dimeric by-product was never isolated nor characterized. Small changes in concentration (entries 5, 6, and 7) or increases in scale (entry 7) do not lead to perceptibly different changes in yield.

As the reaction time required at elevated temperatures for complete conversion was always on the order of 16–20 h (attributable to the lowered reactivity of the 2-ethoxy-substituted allylic acetate), concern over the stability of the palladium(0) catalyst under these conditions mandated the rigorous exclusion of oxygen. To this effect, all reactions were carried out under argon; the reaction vessels were alternately evacuated (to ca. 0.5 torr) and filled with argon several times after being charged with the substrate or catalyst. By a similar technique the solvents were degassed. The use of "house nitrogen" resulted in several complete failures, with recovery of the starting material; it is strongly felt that these failures could be blamed on catalyst deactivation by trace amounts of oxygen.

Three bidentate phosphorus ligands were examined as auxillary ligands for the palladium catalyst.[7,8] The respective 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphine)butane (dppb) palladium complexes were generated in situ from 2 molar equiv of ligand and 1 molar equiv of **20**. No discernible differences were observed in the cyclization reactions using either dppp or dppb (entries 1–4 vs. entries 5–7, Table I); however, when such bidentate ligands were absent, no cyclization occurred. An unusual observation was repeatably found, however, with the dppe ligand. When 2 equiv of dppe (with respect to Pd) was used with 1 equiv of **20**, no reaction occurred under conditions similar to those used with dppp and dppb (entry 11). However, a 59% yield of **21** was obtained when only 1.05 equiv of dppe was used with respect to the amount of **20** (entry 10). These results suggest that whereas **22** (n = 1) is not a catalyst due to its stability with respect to ligand



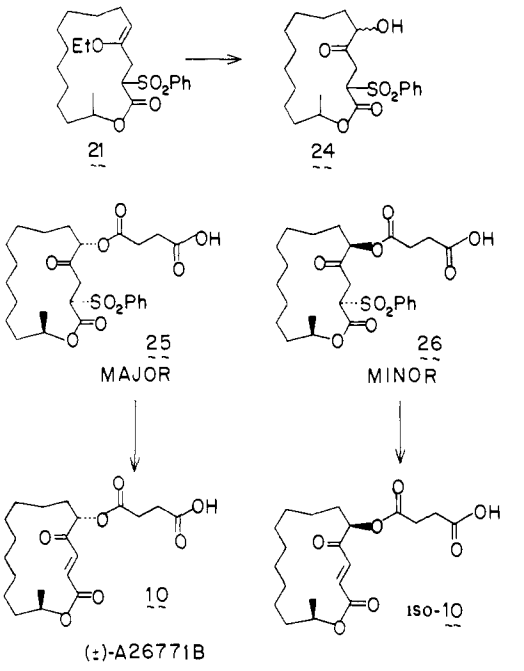
22



23

(15) Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448.

Scheme II. Conversion of Macrolide to Antibiotic A26771B



dissociation, **22** (n = 2 or 3) and **23** do dissociate a ligand to produce the coordinatively unsaturated palladium species necessary for catalytic action.

The purified macrolide was isolated as a viscous, colorless oil; analytical TLC indicated the presence of two closely spaced diastereomers, the major spot being less polar. The ratio of diastereomers was approximately 9:1, as determined by ^{1}H NMR spectroscopy, and this was invariant in all runs. Structural identification was based on ^{1}H and ^{13}C NMR, IR, MS, and elemental analysis. Selective proton decoupling experiments indicated two geminal protons at δ 2.7–2.9 (H_b and $H_{b'}$) with an apparent coupling constant of 14.5 Hz and each coupled with the vicinal proton H_a ($J_{a,b}$ = 11.7 Hz, $J_{a,b'}$ = 2.7 Hz). The methine proton signal was observed at δ 4.09 as an apparent doublet of doublets (J = 11.7 Hz, J' = 2.7 Hz). Examination of the crude residue prior to purification by 270-MHz ^{1}H NMR analysis revealed no evidence for the formation of a 14-membered enol ether. Molecular mechanics calculations indicate that the conformation depicted in **21** with the methyl group and the benzenesulfonyl group trans is 3 kcal/mol more stable than the corresponding cis isomer. The Z olefin stereochemistry[15] is assigned by ^{13}C NMR spectral analysis based upon the chemical shifts of the olefinic carbons observed at 226.6 and 149.0 ppm.[16]

Modification of Macrolide to Antibiotic A26771B

The final stages of synthesis require adjustment of the oxidation level. The question of stereochemistry of the hydroxylation was examined by consideration of the preferred conformation as depicted in **21** and derived from a molecular mechanics calculation. With the benzenesulfonyl group as a conformational anchor and stereochemical directing group, it shields the β face of the enol ether as depicted in **21**—a fact which should direct the hydroxylation to the α face—i.e., trans to the methyl group as required for antibiotic A26771B. Treatment of **21** with 1.1 molar equiv of osmium tetroxide in pyridine,[17] followed by an aqueous sodium bisulfite workup, gave α-hydroxy ketone **24** in 80–83% yield, as a 3:1 mixture of diastereomers (see Scheme II). The product, in all trials was contaminated with a small amount (<10%) of γ-hydroxy enedione, arising from elimination of benzenesulfinic acid. As attempted purification on silica gel resulted in decomposition, the unpurified mixture was in practice utilized in the subsequent reaction. ^{1}H NMR analysis indicated two sets

(16) Taskinen, E. *Tetrahedron* **1978**, *34*, 425.
(17) Schroder, M. *Chem. Rev.* **1980**, *80*, 187.

of signals occurring as doublets at δ 0.920 and 0.924, each with a coupling constant of 6.2 Hz, and in approximately a 3:1 ratio, respectively. One of the two methylene protons β to the phenyl sulfone was distinguishable; major isomer δ 3.40 (dd, J = 10 Hz, J' = 3.0 Hz, relative area = 3), and minor isomer δ 3.20 (dd, J = 18 Hz, J' = 2.9 Hz, relative area = 1). The methine proton α to the phenyl sulfone was observed at δ 4.45 (dd, J = 11.8 Hz, J' = 2.7 Hz, major) and 4.54 (dd, J = 10.7 Hz, J' = 2.9 Hz, minor). The use of a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide as an oxidant in aqueous acetone[18] gave the hydroxy ketone in 80% yield (unpurified) in a somewhat higher 4.4:1 ratio. The product was contaminated with residual (~10% by weight) *N*-methylmorpholine and only a trace amount of the elimination product.

As it was necessary to carry through unpurified **24** in the subsequent reaction, the α-hydroxy ketone obtained by the stoichiometric osmium tetroxide reaction was utilized, as the product was somewhat cleaner than that obtained in the catalytic reaction. The optimal conditions found for succinylation of **24** involved treatment of the crude alcohol with 2 molar equiv of succinic anhydride and 1 molar equiv of 4-(dimethylamino)-pyridine in methylene chloride at 25 °C for 23 h. Examination of the crude product (a yellow solid) obtained in 89% yield from **21** by ^{1}H NMR spectroscopy indicated a 3:1 mixture of two diastereomeric acid sulfones (**25**:**26**, 3:1), plus a small amount of a mixture of the two diastereomers of antibiotic A26771B (**10** and 15-iso-**10**). Under a variety of conditions, approximately 10% elimination to give **10** and 15-iso-**10** was consistently observed in the succinylation reaction. However, attempts to force this reaction to complete conversion under the conditions of the succinylation were never successful.

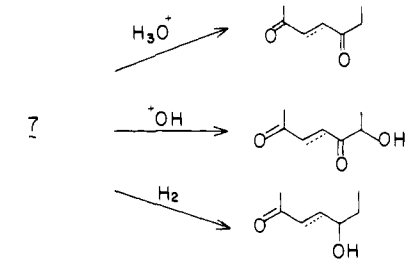
From a concentrated ethereal solution of the crude mixture, diastereomer 15-iso-**10** selectively crystallized in 23% yield from **21**. Evaporative removal of the solvent from the mother liquors led to a crystalline mass; however, selective crystallization of **25** was never achieved. The mixture was used in the elimination reaction to give (±)-A26771B, contaminated with the corresponding diastereomer.

The selective crystallization of one diastereomeric isomer of the sulfone acid allowed for the assignment of the configuration at the carbon bearing the hydroxyl group, as fluoride-induced elimination[19] of the sulfone of **26** led to the obtention of a pure sample of 15-iso-**10**. Thus, **25** correlates with the major diastereomer of the α-hydroxy ketone formed in the osmium tetroxide reaction of **21**.

While various bases such as Hunig's base and potassium carbonate led to substantial decomposition, use of dry tetrabutylammonium fluoride in THF at 0 °C led smoothly to the elimination product either as pure 15-iso-**10** from **20** or as a 3:1 mixture of **10** and 15-iso-**10** from the 3:1 mixture of **25** and **26**. The signals of the major isomer in the NMR spectrum corresponded exactly to those of an authentic sample of **10** as did the IR spectra.

Conclusions

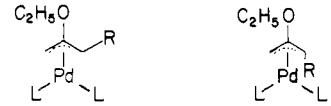
The palladium-based methodology for the construction of macrocycles remains a method to be proven. The mildness of the conditions and the ability to capitalize on C–C bond-forming reactions for the macrocycle construction create the potential for synthetic strategy not otherwise available. In that regard, it should be noted that the strongest base present in the current cyclizations is *O*,N-bis(trimethylsilyl)acetamide. The example of antibiotic A26771B illustrates a unique strategy that emanates from this palladium-based methodology. By masking the sensitive ene-1,4-dione moiety as in **7**, we can control the conditions and the timing of its unveiling. Furthermore, by use of hydrolytic, oxidative, or reductive techniques, a range of structural possibilities emerge in the form of unsaturated or saturated systems as shown in eq 2. The high efficiency observed in the palladium-catalyzed



(2)

cyclization compares very favorably to the disappointing yields obtained in macrolactonization approaches.[11a-c] This point should be particularly noteworthy with respect to cytochalasin B for which the structural features that lead to very poor results in the macrolactonization should be absent in an approach derived from this palladium-based methodology.[6]

The formation of **21** as a single isomer contaminated by a minor amount of the diastereomer which is epimeric at C(2) is noteworthy. Although either a 14- or a 16-membered ring could have formed, only the larger of the two possible rings does form in accord with all of our previous macrolactonizations.[7] While the stereochemistry of the two substituents is undoubtedly thermodynamically controlled, the exclusive formation of the Z olefin reflects the relative stability of the syn and anti (π-allyl)palladium



complexes in which the former represents the more stable one.[15] This rare ability to control the stereochemistry of enol ethers can hold promise in controlling the stereochemistry of introduction of side chains. The high stereocontrol in the cyclization reaction permits the translation of this stereochemistry in subsequent transformations—a key feature for the more elaborate naturally occurring macrolides. Indeed, even in as simple a system as **21**, the combination of its stereochemical homogeneity, the bulk of the benzenesulfonyl group, and the conformational bias of this large ring permits a good diastereoselectivity in the hydroxylation step. In this respect, we can consider the benzenesulfonyl group to play the role of a stereochemical relay in which stereochemical information is transmitted from C(15) to C(5) via C(2).[20]

The success of this cyclization with the relatively poor allylic substrate as in this case points to the likelihood of broad generality. For this electron-rich allyl system, the optimum catalyst is **23**, n = 3. While in other cases several bidentate ligands can replace dppb and even be better, it does appear that at least one bidentate ligand per palladium is desirable in all the macrocyclizations. The great success of this process encourages application of this strategy to the cytochalasin family in general and aspochalasin B in particular.

Experimental Section

General Information. All reactions were run under an atmosphere of argon or, where indicated, dry nitrogen. Infrared spectra were determined on a Perkin-Elmer 267 spectrophotometer and are reported in cm^{-1}. ^{1}H NMR spectra were determined in deuteriochloroform, unless otherwise stated, on a Jeolco MH-100 (100 MHz) or a Bruker WH 270 (170 MHz) instrument. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are reported as s, singlet; d, doublet; t, triplet, q, quartet; or m, multiplet. ^{13}C NMR spectra were determined in deuteriochloroform on a Jeolco FX-200 (50.1 MHz) instrument, with chemical shifts measured relative to the center deuteriochloroform signal but reported in δ. Mass spectra were obtained at 70 eV unless otherwise noted. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle

(18) McCormmick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, 607. Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(19) Bartsch, R. A. *J. Org. Chem.* **1970**, *35*, 1023. Beltrame, P.; Biale, G.; Lloyd, D. J.; Parker, A. J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2240.

(20) Cf.: Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1974**, 3445.

Harbor, MI. Medium-pressure liquid chromatography refers to the use of either a prepacked Lobar size B column or a 2.5 × 100 cm column (column A) packed with Woelm silica gel (32–63 μm). Tetrahydrofuran was distilled from sodium benzophenone ketyl. Pyridine, dichloromethane, triethylamine, and dimethyl sulfoxide were dried by distillation from calcium hydride. Benzene, toluene, and xylenes were dried by collection of a middle cut after distillation of an ca. 25% forerun. Acetic anhydride was simply distilled before use. The products obtained were homogeneous by TLC and ^{1}H NMR analysis, unless otherwise stated.

11-Dodecen-2-ol (13). To a suspension of 1.6 g (0.66 mol) of magnesium turnings in 25 mL of ether was added 4.05 mL (9.23 g, 0.065 mol) of methyl iodide over 5 min. The exothermicity was moderated with an ice–water bath. The mixture was stirred at 25 °C for 30 min, and then a solution of 10.0 g (0.0594 mol) of 10-undecenal in 15 mL of ether was added over 10 min at a rate to maintain reflux. After addition was complete, the mixture was stirred at ambient temperature for 10 min and then cooled to 0 °C, and 25 mL of 3 N aqueous hydrochloric acid was added over 5 min. The aqueous layer was separated and extracted with 50 mL of ether. The combined ethereal layers were washed sequentially with 15 mL of saturated aqueous sodium bisulfite, 30 mL of saturated aqueous sodium bicarbonate, and 30 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 10.8 g (99%) of a light yellow liquid. TLC analysis indicated one major component, R_f 0.28 (1:1 ether/hexane). An analytical sample was obtained by column chromatography on silica gel (60–200 mesh, 35% ether/hexane) to give a colorless liquid: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.14 (d, J = 6 Hz, 3 H, CH_3), 1.25 (br s, 14 H, $(CH_2)_7$), 1.58 (s, 1 H, OH), 2.0 (m, 2 H, $CH_2C{=}C$), 3.63 (m, 1 H, CHO), 4.7–5.0 (m, 3 lines, 2 H, $H_2C{=}C$), 5.5–5.9 (m, 1 H, C=C*H*R); IR (film) 3375, 1640 cm^{-1}. The unpurified alcohol was utilized in the following reaction.

2-(*tert*-Butyldimethylsiloxy)-11-dodecene (14). A solution of 10.8 g (59 mmol) of unpurified alcohol **13**, 10.0 g (147 mmol, 2.5 molar equiv) of imidazole, and 10.6 g (70 mmol, 1.2 molar equiv) of *tert*-butyldimethylsilyl chloride in 20 mL of DMF was heated at 35 °C for 2 h. The mixture was allowed to cool to 20 °C and then poured into 100 mL of water and 100 mL of hexane. The aqueous layer was extracted with 2 × 50 mL of hexane, and the combined organic layers were washed with 50 mL of hexane and 50 mL of water followed by 50 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 18.1 g of colorless liquid. The residue was purified by column chromatography on silica gel (100% hexane, 60 cm × 5 cm column) to yield 17.3 g (97% yield based on 10-undecenal) of **14** as a colorless liquid: R_f 0.74 (hexane); ^{1}H NMR (CCl_4, 100 MHz) δ 0.20 (s, 6 H, $SiMe_2$), 0.84 (s, 9 H, *t*-Bu), 1.12 (d, J = 6 Hz, 3 H, $OCCH_3$), 1.30 (br s, 14 H, $(CH_2)_7$), 2.0 (m, 2 H, $CH_2C{=}C$), 3.6–3.9 (m, 1 H, CHO), 4.9–5.1 (m, 3 lines, 2 H, $C{=}CH_2$), 5.6–6.0 (m, 1 H, *H*C=CH_2); ^{13}C NMR ($CDCl_3$) δ −4.6 (q), 18.2 (s), 23.9 (q), 25.9 (?), 26.0 (3 carbons, q), 29.1 (t), 29.2 (t), 29.5 (t), 29.7 (t), 29.8 (t), 33.9 (t), 39.9 (t), 68.7 (d), 114.1 (t), 139.0 (d); IR (film) 2950, 2880, 1650, 1265 cm^{-1}, mass spectrum m/e (rel intensity) 298 (M^+, 0.1), 297 (0.4), 283 (M^+ − Me, 6.3), 243 (11), 241 (100), 223 (13.1); calcd for $C_{18}H_{38}OSi$, 298.2682; found, 298.2699.

Preparation of 11-(*tert*-Butyldimethylsiloxy)dodecanol (15). To 8.75 mL (7.0 g, 87.5 mmol, 10 M in borane, 1.5 molar equiv) of borane–methyl sulfide complex at −5 °C under argon was added 14.4 mL (9.5 g, 136 mmol, 2.3 molar equiv) of 2-methyl-2-butene over 10 min. The mixture was stirred at −5 °C to 0 °C for 1.5 h, 10 mL of THF was added, and the mixture was stirred an additional 1 h at 0 °C. The cold solution was added dropwise over 10 min via cannula to 17.3 g (57.9 mmol) of olefin **14** at 0 °C under argon. The mixture was stirred at 0 °C for 2 h, and 10 mL of absolute ethanol was added over 5 min, followed by the addition of 21 mL of 3 N aqueous sodium hydroxide solution. The mixture was allowed to warm to room temperature, and with care, 21 mL of 30% aqueous hydrogen peroxide was added over 30 min in ca. 1-mL portions, while maintaining the temperature of the mixture at ca. 25 °C by the use of an ice bath. Upon completion of addition, the mixture was heated at 55 °C for 30 min, cooled, and poured into 150 mL of water. The mixture was extracted with ether (3 × 75 mL), and the combined organic layers washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 19.6 g of a colorless liquid. The crude alcohol was routinely used without purification in the subsequent reaction. An analytical sample was prepared by preparative thin-layer chromatography (1:1 ether/hexane, R_f 0.30), followed by short-path distillation (bath temp 60 °C (0.01 torr)) to give a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.05 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, *t*-Bu), 1.11 (d, J = 6.1 Hz, 3 H, CH_3CH), 1.27 (br s, 17 H, $(CH_2)_8OH$), 1.57 (m, 2 H, CH_2COSi), 3.64 (t, J = 6.6 Hz, 2 H, CH_2O), 3.77 (m, 1 H, C*H*OSi); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.4, 18.1, 23.7, 25.7, 25.89 (3C), 29.4, 29.5, 29.7, 32.8, 39.7, 62.9, 68.6; IR (film) 3600–3000, 2941, 2870 cm^{-1}, mass spectrum, m/e (rel intensity) 301 (0.3), 299 (0.5), 257 (19), 159 (46), 75 (100). Anal. Calcd for $C_{18}H_{40}O_2Si$: C, 68.29; H, 12.73. Found: C, 68.40; H, 12.67.

11-(*tert*-Butyldimethylsiloxy)dodecanal (16). To a solution of 9.56 g (28 mmol) of unpurified alcohol **15** in 125 mL of methylene chloride under argon was added at once with rapid stirring 10.3 g (48 mmol, 1.7 molar equiv) of pyridinium chlorochromate. The reaction became exothermic and the solvent refluxed for ca. 2 h. The mixture was stirred a total of 3.5 h, and then 100 mL of ether was added. The mixture was stirred an additional 15 min and then filtered through a short Florisil column (60–100 mesh, 19 × 5 cm), and the column was eluted with 600 mL of ether. The filtrate was concentrated in vacuo to give 8.27 g (93% crude yield) of a light yellow liquid, which was immediately utilized in the subsequent reaction without further purification. Attempted purification by preparative high-pressure liquid chromatography led largely to the formation of a product tentatively identified as the aldehyde trimer. An analytical sample was prepared by medium-pressure liquid chromatography on silica gel (Lobar B, 5% ether/hexane) to give a colorless liquid: TLC mobility, R_f 0.39 (10% ether/hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.76 (t, J = 2.9 Hz, 1 H, CHO), 3.75 (br sextet, J = 6 Hz, 1 H, CHO), 2.42 (d of t, J = 7.3 Hz, J' = 2 Hz, 2 H, $CH_2C{=}O$), 1.63 (br quint, J = 7 Hz, 2 H, CH_2CHO), 1.27 (br s, 14 H, $(CH_2)_7$), 1.11 (d, J = 6.2 Hz, 3 H, $CH_3C{-}O$), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 6H, $OSiMe_2$); IR (film) 2710, 1724 cm^{-1}, mass spectrum, m/e (rel abundance) (no molecular ion observed) 299 (1.5, M − CH_3), 259 (1.6), 258 (13), 257 (100), 159 (20).

Preparation of 2-Ethoxy-3-acetoxy-13-(*tert*-butyldimethylsiloxy)tetradecene (18). To a solution of 12.5 mL (9.4 g, 131 mmol, 5 molar equiv) of freshly distilled ethyl vinyl ether in 25 mL of THF at −78 °C under argon was added dropwise over 5 min 18 mL (37.8 mmol, 1.4 molar equiv) of 2.1 M *tert*-butyllithium in pentane. The deep yellow mixture was stirred 10 min at −78 °C then at 0 °C for 5 min, and the solution became colorless. The mixture was cooled to −78 °C, and a solution of 8.27 g (26 mmol) of unpurified, freshly prepared aldehyde **16** in 25 mL of THF was added over 15 min. The mixture was stirred an additional 5 min and then allowed to come to room temperature. The reaction was quenched with 5 mL of saturated aqueous ammonium chloride, poured into 150 mL of water and 50 mL of saturated aqueous ammonium chloride, and extracted with ether (1 × 200, 3 × 75 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give 9.88 g (97% crude yield) of a colorless liquid. The unpurified alcohol **17** was immediately subjected to the next reaction. TLC analysis indicated one major component, **17**: R_f 0.55 (1:1 ether/hexane); ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.1 (d, J = 2 Hz, 1 H, HC=COEt syn), 4.0 (m, 1 H, C*H*OH), 3.95 (d, J = 2 Hz, 1 H, HC=COEt anti), 3.8 (q superimposed on m, 3 H, OCH_2 and CHOSi), 1.8–1.2 (m, 21 H, $(CH_2)_n$), 1.1 (d, J = 6 Hz, 3 H, CH_3COSi), 0.82 (s, 9 H, *t*-Bu), 0.04 (s, 6 H, $SiMe_2$).

A solution of 9.9 g (approximately 25 mmol) of crude alcohol **17** and 15 mL (16 g, 0.16 mol) of acetic anhydride in 60 mL of pyridine under nitrogen was stirred at 22 °C for 15 h. The mixture was poured into 1.2 L of water, and extracted with methylene chloride (1 × 250, 3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 13.7 g of a yellow oil. The residue was purified by column chromatography on silica gel (5 × 60 cm column, 5% ether/hexane + 0.02% triethylamine eluant) to give 8.33 g (78% yield, 69% from olefin **14**) of a colorless oil: TLC mobility, R_f 0.34 (10% ether/hexane); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.14 (t, J = 6.8 Hz, 1 H, CHOAc), 4.11 (d, J = 2.3 Hz, 1 H, HC=COEt syn), 3.98 (d, J = 2.3 Hz, 1 H, HC=COEt anti), 3.74 (q, J = 7.0 Hz, 2 H, OCH_2, overlapping with a m, 1 H, CHOSi), 2.07 (s, 3 H, $OCOCH_3$), 1.70 (m, 2 H, CH_2CHOAc), 1.30 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.26 (br s, 16 H, $(CH_2)_8$), 1.11 (d, J = 6.2 Hz, 3 H, CH_3COSi), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 170.0, 160.2, 82.5, 74.3, 68.5, 62.8, 39.7, 32.2, 29.6, 29.5, 29.4 (2C), 29.2, 25.8 (3C), 25.7, 25.1, 23.7, 21.1, 18.0, 14.2, −4.5, −4.8; IR ($CHCl_3$) 1730, 1688, 1632 cm^{-1}; mass spectrum, m/e (rel abundance) 428 (M^+ 0.05), 386 (0.5), 371 (16), 301 (8.8), 283 (61), 114 (100); calcd for $C_{24}H_{48}O_4Si$, 428.2209; found, 428.3340. Anal. Calcd for $C_{24}H_{48}O_4Si$: C, 67.24; H, 11.28. Found: C, 67.84; H, 11.39.

Preparation of 2-Ethoxy-3-acetoxytetradecen-13-ol (19). To a solution of 2.047 g (4.77 mmol) of silyl ether **18** in 60 mL of THF under argon was added at once 14.3 mL (14.3 mmol, 3 molar equiv Aldrich, 1 M) of tetrabutylammonium fluoride in THF. The mixture was stirred at room temperature for 69 h, poured into 100 mL of water, and extracted with ether (1 × 50, 2 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$), and concentrated in vacuo to give 1.68 g (112% by weight recovery) of a yellow viscous oil. Purification by medium-pressure liquid chromatography on silica gel (60% ether/hexane + 0.1% triethylamine eluant) of 0.828 g of the residue gave 0.532 g (72%) of a colorless viscous

oil: TLC mobility, R_f 0.34 (75% ether/hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.13 (t, J = 6.8 Hz, 1 H, CHOAc), 4.11 (d, J = 2.2 Hz, 1 H, HC=COEt syn), 3.98 (d, J = 2.2 Hz, 1 H, HC=COEt anti), 3.75 (m, 1 H), 3.73 (q, J = 7 Hz, 2 H, OCH_2), 2.08 (s, 3 H, $OCOCH_3$), 1.98 (br s, 1 H, OH), 1.70 (m, 2 H, CH_2COAc), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.28 (br s, 16 H, $(CH_2)_8$), 1.18 (d, J = 6.2 Hz, 3 H, $CHOCH_3$); ^{13}C NMR ($CDCl_3$) δ 170.0, 160.2, 82.5, 74.4, 67.9, 62.8, 39.3, 32.2, 29.5, 29.4, 29.3 (2C), 29.1, 25.6, 25.50, 23.3, 21.0, 14.1; IR ($CDCl_3$) 3600, 3300, 1730, 1655, 1630 cm^{-1}, mass spectrum m/e (rel abundance) 314 (M^+, 1.4), 272 (2), 254 (8), 102 (42), 43 (100); calcd for $C_{18}H_{34}O_3$, 314.2448; found, 314.2456.

Preparation of 2-Ethoxy-3-acetoxytetradecen-13-yl Benzenesulfonylacetate (11). Procedure A. A solution of 0.417 g (2.02 mmol, 1.2 molar equiv) of *N,N'*-dicyclohexylcarbodiimide, 0.371 g (1.85 mmol, 1.1 molar equiv) of benzenesulfonylacetic acid, 0.051 g (0.42 mmol, 0.25 molar equiv) of 4-(dimethylamino)pyridine and 0.530 g (1.68 mmol) of pure alcohol **19** in 25 mL of THF was stirred at room temperature for 41 h. The resulting heterogeneous mixture was diluted with 30 mL of ether and then filtered through a 15.2 × 1.2 cm column of silica gel, and the column was flushed with 200 mL of ether. The filtrate was concentrated in vacuo, and the resulting light yellow oil was purified by medium-pressure liquid chromatography (silica gel column A, 1:1 ether/hexane, containing 0.1% triethylamine) to give 0.575 g (69%, R_f 0.23) of **11** as a colorless, viscous oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.95 (d of m, J = 7.3 Hz, 2 H, ortho H's), 7.69 (t of t, J = 7.2 Hz, 1 H, para H), 7.58 (t of m, J = 7.5 Hz, 2 H, meta H's), 5.14 (t, J = 7.0 Hz, 1 H, CHOAc), 4.86 (sextet, J = 3.5 Hz, 1 H, CHOMe), 4.12 (s, 2 H, CH_2SO_2Ph), 4.10 (d, J = 2.2 Hz, 1 H, HC=COEt, syn), 3.99 (d, J = 2.2 Hz, 1 H, HC=COEt anti), 3.74 (q, J = 7 Hz, 2 H, OCH_2), 2.07 (s, 3 H, O_2CCH_3), 1.70 (br m, 2 H), 1.44 (br m, 2 H), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.23 (br s, 14 H, $(CH_2)_7$), 1.13 (d, J = 6.2 Hz, 3 H, $OCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 170.0, 161.7, 160.0, 138.8, 134.0, 129.0 (2C), 128.3 (2C), 82.5, 74.2, 73.6, 62.8, 61.0, 35.3, 32.1, 29.2, (2C), 29.1, 29.0, 25.0, 24.9, 21.0, 19.4, 14.1; IR ($CHCl_3$) 1740, 1670, 1640 cm^{-1}; mass spectrum, m/e (rel abundance) 496 (M^+, 4), 454 (6), 436 (4), 432 (2), 43 (100); calcd for $C_{26}H_{40}O_7S$, 496.2484; found, 496.2494. Anal. Calcd for $C_{26}H_{40}O_7S$: C, 62.88; H, 8.12; S, 6.45. Found: C, 62.77; H, 8.27; S, 6.44.

Procedure B (Use of the Crude Alcohol). A solution of 0.84 g (4.0 mmol, 1.3 molar equiv) of *N,N'*-dicyclohexylcarbodiimide, 0.752 g (3.8 mmol, 1.2 molar equiv) of benzenesulfonylacetic acid, 0.096 g (0.78 mmol, 0.25 molar equiv) of 4-(dimethylamino)pyridine and 1.23 g (crude, from 3.13 mmol of silyl ether **18**) of alcohol **19** in 25 mL of THF was stirred at room temperature for 22 h. The resulting heterogeneous mixture was diluted with 20 mL of ether and then filtered rapidly through a 15.2 × 2.5 cm column of 60–200 mesh silica gel. The column was washed well with ether, and the filtrate was concentrated in vacuo to give a light yellow oil containing a small amount of a white solid. The residue was dissolved in 6 mL of carbon tetrachloride, filtered, and concentrated in vacuo to give 1.99 g of a light yellow oil. The residue was purified by medium-pressure liquid chromatography (column A, 30% ethyl acetate/hexane + 0.05% triethylamine, 20-mL fractions) to give in fractions 39–47 inclusive 1.039 g (67% from silyl ether) of **11** as a colorless, viscous oil, homogeneous by TLC and 270-MHz NMR analysis.

Cyclization of 2-Ethoxy-3-acetoxytetradecen-13-yl Benzenesulfonylacetate. General Procedure (Table I, Entry 3). A 100-mL round-bottom flask equipped with a magnetic stirrer, reflux condenser, rubber septum, and argon inlet was charged with 0.240 g (0.483 mmol) of **11**, and the system was alternately evacuated (0.06 torr) and filled with argon 3 times. Via syringe, 45 mL of dry THF was added, followed by 24 mL (0.20 g, 0.97 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide. The mixture was heated at reflux for 3 h, cooled to room temperature, and then added over 5 min via cannula to a refluxing solution of the palladium catalyst prepared in the following manner: a 250-mL flask equipped with a magnetic stirrer, rubber septum, reflux condenser, and argon inlet was charged with 0.034 g (0.029 mmol, 6 mol%) of tetrakis(triphenylphosphine)palladium(0) and 0.024 g (0.058 mmol, 12 mol%) of 1,3-bis(diphenylphosphino)propane, and the system was alternately evacuated (0.05 torr) and filled with argon 3 times. THF (45 mL) was added, and the solution was alternately evacuated (until the solvent vigorously frothed) and filled with argon (6 times). The solution was heated at reflux for 1 h, and the substrate-containing solution was added. The mixture was heated at reflux for 16 h. TLC analysis indicated the absence of **11**. The mixture was concentrated by rotary evaporation, yielding a yellow oil and a white crystalline solid. The residue was dissolved in carbon tetrachloride and filtered through a short Celite pad, and the solid washed well with carbon tetrachloride. The filtrate was concentrated in vacuo and the residue purified by medium-pressure liquid chromatography (Lobar B column, 8% ethyl acetate/hexane, containing 0.05% triethylamine) to give 0.128 g (60.5%) of **21** as a viscous, colorless oil. TLC analysis indicated a mixture of two diastereomers, the major having an R_f 0.38. ^{1}H NMR analysis indicated the ratio of diastereomers was approximately 9:1, determined by peak height measurement of the respective methyl doublet signals. (The ratio obtained here was invariant for all entries in Table I; the 270-MHz NMR spectra of the chromatographically isolated diastereomeric mixtures were virtually identical for all cases.)

21 (The ^{1}H NMR data listed are for the major diastereomer.): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.89 (dt, J = 7.2 Hz, J' = 1.4 Hz, 2 H, aromatic ortho CH), 7.69 (tt, J = 7.4 Hz, J' = 1.3 Hz, 1 H, aromatic para CH), 7.57 (tt, J = 7.4 Hz, J = 1 Hz, 2 H, aromatic meta CH), 4.84 (sextet, J = 5.7 Hz, 1 H, CHO), 4.74 (t, J = 7.6 Hz, 1 H, vinyl H), 4.09 (dd, J = 11.7 Hz, J' = 2.7 Hz, 1 H, $HCSO_2Ph$), 3.62 (q, J = 7.0 Hz, 2 H, OCH_2), 2.85 (dd, J = 14.5 Hz, $J' \simeq$ 2.7 Hz, 1 H, CH_AEtOC=C), 2.75 (m, J = 14.5 $J' \simeq$ 11.7, 1 H, CH_BEtOC=C), 2.01 (t, J = 7.1 Hz, 2 H, CH_2C=COEt), 1.23 (m, 16 H, $(CH_2)_8$), 1.18 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 0.95 (d, J = 6.2 Hz, 3 H, CH_3CO) [^{1}H decoupling data: irradiation at δ 0.95 gave 4.84 (dd, J = 7.5 Hz, J' = 5.0 Hz); irradiation at δ 2.01 gave δ 4.74 (s); irradiation at δ 2.75 and 2.85 multiplets gave δ 4.1 (s with fine coupling, i.e., partial collapse to s); irradiation at 4.09 gavz δ 2.80 (ABq, J = 14.5 Hz, 2 H); irradiation at δ 4.84 gave δ 0.95 (s); broad-band irradiation at 1–1.5 gave 2.0 (d, J = 7.5 Hz), 3.6 (s), and δ 4.84 (br s)]. ^{13}C NMR ($CDCl_3$) δ 165.0, 149.0, 137.3, 134.0, 129.4 (2C), 129.0 (2C), 116.6, 72.9, 69.1, 65.2, 34.6, 29.6, 28.2, 26.7, 26.4, 26.3, 26.1, 25.9, 23.8, 23.2, 19.3, 15.2; IR ($CHCl_3$) 1724, 1666 cm^{-1}, mass spectrum, m/e (relative intensity) 436 (M^+, 1.3), 421 (0.2), 409 (0.2), 407 (5.3), 295 (100), 265 (10.8); calcd for $C_{24}H_{36}O_5S$, 436.2274; found, 436.2281. Anal. Calcd for $C_{24}H_{36}O_5S$: C, 66.02; H, 8.31; S, 7.34. Found: C, 66.20; H, 8.07; S, 7.35.

Partial ^{1}H NMR of minor diastereomer (270 MHz, $CDCl_3$) 0.94 (d, J = 6.1 Hz), 4.16 (dd, J = 12.3 Hz, J' = 3.1 Hz). The relative ratio of the peak heights at 0.94 and 0.95 was 1:9, corresponding to the ratio of the minor to major diastereomer.

Table I, Entry 1. A solution of 0.0634 g (0.13 mmol) of **11** and 0.063 mL (0.052 g, 0.25 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)-acetamide in 20 mL of THF was heated at reflux under nitrogen for 45 min, cooled, and added via syringe over 20 min to a refluxing solution of 0.016 g (0.9 mmol, 7 mol %) of tetrakis(triphenylphosphine)palladium and 0.009 g (0.022 mmol, 17 mol %) of 1,3-bis(diphenylphosphine)-propane in 20 mL of toluene. The mixture was heated at reflux for 18 h, cooled, and concentrated in vacuo. The residue was triturated with ether, and a curdy brown precipitate formed. The solid was washed well with ether, and the ether filtrate concentrated in vacuo to yield 0.098 g of a yellow oil. The residue was purified by preparative thin-layer chromatography (silica gel 20 × 20 cm, 70% ether, 25% hexane, 5% chloroform) to give 0.0479 g (84%, R_f 0.58) of **21** as a colorless viscous oil, homogeneous by TLC and 100-MHz ^{1}H NMR.

Table I, Entry 2. A solution of 0.101 g (0.20 mmol) of **11** and 0.10 mL (0.40 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 25 mL of THF was heated at reflux under nitrogen for 3.5 h and then added over 5 min to a refluxing solution of 0.017 g (0.015 mmol, 7 mol %) of tetrakis(triphenylphosphine)palladium and 0.015 g (0.036 mmol, 18 mol %) of 1,3-bis(diphenylphosphino)propane in 20 mL of toluene. The mixture was heated at reflux for 21 h (TLC analysis after the first 90 min showed no evidence of product formation), cooled, concentrated in vacuo, and the residue triturated with ether. The solid which was formed was washed well with ether, and the ethereal washes were concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (silica gel, 40 × 20 cm, 1:1 ether/hexane). Three distinct bands visualized by UV were collected to yield 0.007 g (R_f 0.64) of an off-white crystalline solid, tentatively identified by ^{1}H NMR spectroscopy as benzenesulfinic acid, 0.0512 g (59%) (R_f 0.44) of **21** as a very light yellow viscous oil, and 0.0179 g (R_f 0.17) of a light orange oil, which consisted of several unidentified components by analytical TLC.

Table I, Entry 4. A solution of 0.280 g (0.56 mmol) of **11** and 0.28 mL (1.1 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 50 mL of THF was heated to reflux for 2 h and then added over 1 min to a refluxing solution of 0.045 g (0.039 mmol, 7 mol %) of tetrakis(triphenylphosphine)palladium and 0.0295 g (0.073 mmol, 13 mol %) of 1,3-(diphenylphosphino)propane in 50 mL of THF. The mixture was heated at reflux for 18 h, cooled, and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.1455 g (59.5%) of **21**.

Table I, Entry 5. A solution of 0.085 g (0.17 mmol) of **11** and 0.085 mL (0.34 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 25 mL of THF was heated at reflux for 1.5 h and then added over 2 min to a refluxing solution of 0.014 g (0.012 mmol, 6 mol %) of tetrakis-(triphenylphosphine)palladium and 0.0105 g (0.025 mmol, 12 mol %) of

1,4-(diphenylphosphino)butane in 25 mL of THF. The mixture was heated at reflux for 18 h, cooled, and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.0488 g (66%) of **21**.

Table I, Entry 6. A solution of 0.361 g (0.727 mmol) of **11** and 0.36 mL (1.4 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 55 mL of THF was heated at reflux for 1.0 h and then added over 5 min to a refluxing solution of 0.055 g (0.048 mmol, 6.5 mol %) of tetrakis-(triphenylphosphine)palladium and 0.040 g (0.094 mmol, 13 mol %) of 1,4-(diphenylphsophino)butane in 55 mL of THF. The mixture was heated at reflux for 16 h, cooled, and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.176 g (58%) of **21**.

Table I, Entry 7. A solution of 0.898 g (1.808 mmol) of **11** and 0.90 mL (3.6 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 100 mL of THF was heated at reflux for 2.0 h and then added over 5 min to a refluxing solution of 0.125 g (0.108 mmol, 6 mol %) of tetrakis-(triphenylphosphine)palladium and 0.092 g (0.22 mmol, 12 mol %) of 1,4-(diphenylphosphino)butane in 100 mL of THF. The mixture was heated at reflux for 19.5 h, cooled, and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.432 g (55.5%) of **21**.

Table I, Entry 8. A solution of 0.225 g (0.453 mmol) of **11** and 0.22 mL (0.18, 0.91 mmol, 2 molar equiv) *O,N*-bis(trimethylsilyl)acetamide in 50 mL of THF was heated at reflux of 1.5 h and then added over 2 min to a refluxing solution of 0.0307 g (0.026 mmol, 6 mol %) of tetrakis(triphenylphosphine)palladium in 50 mL of THF. The mixture was heated at reflux for 16.5 h, cooled, and concentrated in vacuo. TLC and ^{1}H NMR analysis (270 MHz) indicated the absence of **21** and the presence of largely starting **11**.

Table I, Entry 9. A solution of 0.101 g (0.203 mmol) of **11** and 0.10 mL (0.40 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 25 mL of THF was heated at reflux for 1.7 h and then added over 1 min to a refluxing solution of 0.014 g (0.012 mmol, 6 mol %) of tetrakis-(triphenylphosphine)palladium and 0.0065 g (0.025 mmol, 12 mol %) of triphenylphosphine in 25 mL of THF. The mixture was heated at reflux for 19.5 h. The color went from yellow to dark brown. TLC analysis (270 MHz) indicated the absence of **21** and the presence of largely unreacted **11**.

Table I, Entry 10. A solution of 0.1006 g (0.20 mmol) of **11** and 0.10 mL (0.4 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 25 mL of THF was heated at reflux for 1.5 h and then added over 1 min to a refluxing solution of 0.013 g (0.011 mmol, 5.6 mol %) of tetrakis-(triphenylphosphine)palladium and 0.0047 g (0.012 mmol, 5.9 mol %) of 1,2-bis(diphenylphosphino)ethane in 25 mL of THF. The mixture was heated at reflux for 15 h. Since TLC analysis indicated a small amount of starting **11** still present, heating was continued for an additional 5 h; the mixture was cooled and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.0521 g (59%) of **21**.

Table I, Entry 11. A solution of 0.275 g (0.553 mmol) of **11** and 0.28 mL (1.1 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide in 50 mL of THF was heated at reflux for 2.5 h and then added over 2 min to a refluxing solution of 0.038 g (0.033 mmol, 6 mol %) of tetrakis-(triphenylphosphine)palladium and 0.026 g (0.066 mmol, 12 mol %) of 1,2-bis(diphenylphosphino)ethane in 50 mL of THF. The mixture was heated at reflux for a total of 60 h, and the color remained yellow. TLC analysis after 26 h and 60 h, and ^{1}H NMR analysis (270 MHz) after evaporative workup, indicated the absence of **21** and the presence of largely starting **11**.

Table I, Entry 12. To a solution of 0.231 g (0.465 mmol) of **11**, 0.0091 g (0.0078 mmol, 1.7 mol %) of tetrakis(triphenylphosphine)palladium and 0.0072 g (0.017 mmol, 3.7 mol %) of 1,3-bis(diphenylphosphino)-propane in 5 mL of toluene and 5 mL of THF was added 0.23 mL (0.93 mmol, 2 molar equiv) of *O,N*-bis(trimethylsilyl)acetamide. The mixture was heated to reflux for 19 h, cooled, and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography to give 0.0542 g (27%) of **21**.

Preparation of α-Hydroxy Keto Sulfone 24. Procedure A (Stoichiometric Osmium Tetroxide). A solution of 0.161 g (0.369 mmol) of **21** and 0.114 g (0.45 mmol, 1.2 molar equiv) of osmium tetroxide in 7 mL of pyridine was stirred at 25 °C for 5 h. Subsequently, 15 mL of THF and 15 mL of saturated aqueous sodium bisulfite were added, and the mixture stirred vigorously for 10 min. The mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 0.1499 g of a light brown oil, which on standing overnight turned dark brown. The residue was taken up in ether and filtered through 7.6 cm of Florisil in a pipette, and the column was washed well with ether. The filtrate was concentrated in vacuo to yield 0.130 g (83%) of a light yellow viscous oil: TLC (100% ether), R_f 0.51 (minor), 0.40, and 0.37 (^{1}H NMR analysis indicated the presence of a small amount of product resulting from elimination of benzenesulfinic acid); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.920 (d, J = 6.2 Hz, Me), 0.924 (d, J = 6.2 Hz, Me′, Me:Me′ ≃ 3.1), 1.20 (d, J = 6.2 Hz, MeCO), 1.2–1.94 (m, $(CH_2)_9$), 3.20 (dd, J = 18 Hz, J' = 2.9 Hz, OCH'_ACSO_2Ph), 3.40 (dd, J = 19 Hz, J' = 3.0 Hz, $OCCH_ACSO_2Ph$, H_A:H'_A ≃ 3:1), 3.54–3.76 (m, $OCCH_BCSO_2Ph$ and $OCCH'_BCSO_2Ph$), 4.19 (dd, J = 8 Hz, J' = 4.2 Hz, CH—OH), 4.45 (dd, J = 11.8 Hz, J' = 2.7 H, $HCSO_2Ph$), 4.54 (dd, J = 10.7 Hz, J' = 2.9 Hz, $H'CSO_2Ph$, H:H′ ≃ 3:1), 4.64 (dd, J = 7.0 Hz, J' = 6.2 Hz, $CHOH$ for enedione), 4.88 (m, 1 H, $CHMe$), 6.80 (d, J = 15.8 Hz), and 6.82 (d, J = 15.8 Hz, H═C, both diastereomers), 7.21 (d, J = 15.8 Hz) and 7.27 (d, J = 15.8 Hz, C═CH, both diastereomers), 7.54–7.88 (m, 5 H, aromatic); IR ($CHCl_3$) 3600–3050, 1727 cm^{-1}. The unpurified alcohol was utilized in the subsequent succinylation reaction.

Procedure B (Catalytic Osmium Tetroxide). To a solution of 0.0475 g (0.109 mmol) of **21** and 0.04 g (0.26 mmol, 2 molar equiv) of *N*-methylmorpholine *N*-oxide in 4 mL of acetone and 1 mL of water was added a solution of 0.7 mg (0.003 mmol, 2 mol %) of osmium tetroxide in 0.2 mL of *tert*-butyl alcohol. The mixture was stirred at 20 °C for 16 h, and then 1 mL of water, 0.15 g of Florisil, and 0.2 g sodium bisulfite were added, and the mixture rapidly stirred for 10 min and was then filtered. The solid was washed with acetone, and the combined filtrates were concentrated by rotary evaporation. To the residue was added 2 mL of saturated aqueous sodium bisulfate and 25 mL of water, and the mixture extracted with ethyl acetate (20 mL). The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate; the combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$, K_2CO_3), and concentrated in vacuo to yield 0.037 g of **24** (80%) as a light brown oil. ^{1}H NMR analysis indicated the presence of residual *N*-morpholine (estimated at 10% by weight) and only a trace of eliminated product. The relative ratio of the two diastereomeric α-hydroxy ketones was 4.4:1 (Me:Me′), determined by integration.

Preparation of Sulfone Succinate Acid (25, 26). A solution of 0.380 g (unpurified from osmium tetroxide reaction with 0.985 mmol of **21**) of α-hydroxy keto sulfone **24**, 0.197 g (1.97 mmol, 2.0 molar equiv) of succinic anhydride, and 0.120 g (0.99 mmol, 1.0 molar equiv) of 4-(*N,N*-dimethylamino)pyridine in 15 mL of methylene chloride was stirred at 25 °C for 23 h. The mixture was poured into 50 mL of water and 25 mL of saturated aqueous sodium chloride and extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 0.459 g (89% yield based on 0.985 mmol of enol ether **21**) of a yellow viscous oil, which on standing crystallized to a yellow solid. The residue was triturated with ether, and the yellow-colored impurities were dissolved, leaving a (partially) insoluble white crystalline solid. The solid was washed with 1 mL of ether and collected to give 0.108 g (21% from **21**) of one diastereomer (**26**) of the sulfone acid. The ethereal layer was concentrated in vacuo to give 0.346 g of a yellow oil. The residue was dissolved in 3 mL of ether, and on standing several days, a second crop of 0.0099 g (combined total yield of 23% from **21**) of this diastereomer was collected. The ethereal layer was concentrated in vacuo to give 0.337 g of a yellow oil. On standing several weeks, a crystallization took place; however, attempts to obtain a further separation of diastereomers **25** and **26** were unsuccessful.

Diastereomer 26: mp 152.0–153.2 °c (ethyl acetate/pentane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (d, J = 6.4 Hz, 3 H, Me), 1.19, 1.25, and 1.30 (br singlets, 12 H, $(CH_2)_6$), 1.55 (m, 2 H), 1.74 (m, 2 H), 1.90 (m, 2 H, $CH_2CO_2CCH_2CH_2CO_2H$), 2.75 (s, 4 H, succinate CH_2CH_2), 3.15 (dd, J_{gem} = 18.6 Hz, J' = 2.3 Hz, 1 H, $OCCH_ACSO_2Ph$), 3.63 (dd, J_{gem} = 18.8 Hz, J' = 11.6 Hz, 1 H, $OCCH_BCSO_2Ph$), 4.43 (dd, J = 11.8 Hz, J' = 2.4 Hz, 1 H, $CHSO_2Ph$), 4.86 (m, 1 H, $MeCH$-O), 5.11 (dd, J = 8.0 Hz, J' = 3.8 Hz, 1 H, $OCCHO_2CR$), 7.0 (very br s, 1 H, CO_2H), 7.59 (t with additional coupling, J = 7.4 Hz, 2 H, meta), 7.71 (t with additional coupling, J = 7.4 Hz, 1 H, para), 7.91 (d with additional coupling, J = 6.8 Hz, 2 H, ortho); ^{13}C NMR ($CDCl_3$) δ 205.0, 176.3, 171.4, 165.2, 137.6, 134.3, 129.1 (2C), 128.9 (2C), 79.2, 73.1, 65.3, 35.6, 35.1, 30.3, 29.0, 28.7, 27.0, 26.3 (2C), 26.1, 25.2, 23.4, 21.4, 19.4; IR ($CHCl_3$) 3400–3000, 1732, 1725 cm^{-1}; mass spectrum (no molecular ion), m/e (rel intensity) 424 (0.7), 282 (3), 255 (16), 183 (8), 165 (8), 55 (100). Anal. Calcd for $C_{26}H_{36}O_9S$: C, 59.52; H, 6.92; S, 6.11. Found: C, 59.65; H, 6.74; S, 6.15.

Diastereomer 25 (data taken on ca. 3:1 **25**:**26** mixture): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, J = 6.2 Hz, 3 H), 1.27 (m, ca. 12 H), 1.89 (m, 3 H), 2.69 (s, 4 H, succinate), 3.28 (dd, J_{gem} = 18.2 Hz, J' = 2.9 Hz, 1 H), 3.4–3.5 (m, 1 H), 4.46 (dd, J = 11.5 Hz, J' = 2.8 Hz, 1 H), 4.86 (m, 1 H), 5.16 (t, J = 4.8 Hz, 1 H); IR ($CHCl_3$) 3450–3000, 1732 cm^{-1}.

Preparation of 15-iso-10. To a solution of 0.0097 g (0.018 mmol) of crystalline **26** in 2 mL of THF at 0 °C was added 0.05 mL (0.05 mmol, 2.5 molar equiv) of a 1.0 M solution of tetrabutylammonium chloride in THF. The mixture was stirred at 0 °C for 30 min, 10 mL of water was added, and the mixture was extracted with ethyl acetate (1 × 10 mL, 2 × 5 mL). The combined organic layers were washed with water (2 × 15 mL), followed by saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 0.0065 g (94%) of a colorless oil. TLC and ^1H NMR analysis indicated the succinylated α-hydroxy enedione, with the same TLC mobility as authentic A26771B (10% MeOH/$CHCl_3$, R_f 0.385); however, the vinyl proton chemical shift was slightly shifted. An analytical sample was prepared by taking up the oil in a minimum of acetone and triturating with a large amount of water to give a white amorphous solid: ^1H NMR (270 MHz, $CDCl_3$) (all signals identical with A26771B except for vinyl resonances) δ 1.30 (d, J = 6.3 Hz, ca. 3 H), 1.2-1.4 (br m, ca 14 H), 1.61 (m, 2 H), 1.87 (m, 2 H), 2.75 and 2.77 (m, with 2 s, 4 H), 5.09 (m, with 4 sharp lines, 1 H), 5.36 (t, J = 5.5 Hz, 1 H), 6.76 (d, J = 15.8 Hz, 1 H), 7.16 (d, J = 15.8 Hz, 1 H), 10-11 (br s, 1 H, CO_2H); IR ($CHCl_3$) 3600-3000, 1744, 1736, 1722, 1713 cm^{-1}; mass spectrum of **10**, 15-iso-**10** mixture m/e (rel intensity) (no molecular ion observed) 293 (0.2), 281 (0.2), 231 (0.9), 181 (3.9) 119 (8), 69 (44), 44 (100).

Preparation of 10. According to the procedure given above, 0.0415 g (0.08 mmol) of a 3:1 **25**:**26** mixture was treated with 0.3 mmol of tetrabutylammonium fluoride in THF, at room temperature for 3 h, to give, after aqueous workup, 0.0295 g (95%) of a colorless oil, which solidified on standing. Addition to acetone (1 mL) and 25 mL of water produced the precipitation of a 3:1 mixture of pure **10**:15-iso-**10** as a white solid, mp 112-116 °C. The ^1H NMR signals for **10** were superimposable on the 270-MHz ^1H NMR spectrum of authentic A26771B. TLC analysis in 5% methanol/chloroform, 10% methanol/chloroform, and 100% ethyl acetate had identical mobilities with the natural product. Attempted recrystallization from ethyl acetate/hexane was unsuccessful.

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Registry No. (±)-**10**, 77449-88-8; (±)-15-iso-**10**, 84026-48-2; **11**, 83999-33-1; **12**, 112-45-8; (±)-**13**, 83999-34-2; (±)-**14**, 83999-35-3; (±)-**15**, 83999-36-4; (±)-**16**, 84009-44-9; **17**, 83999-37-5; **18**, 83999-38-6; **19**, 83999-39-7; (±)-**21** (isomer 1), 83999-40-0; (±)-**21** (isomer 2), 84026-49-3; (±)-**24** (isomer 1), 84009-45-0; (±)-**24** (isomer 2), 84048-16-8; (±)-**25**, 83999-41-1; (±)-**26**, 84026-50-6; ethyl vinyl ether, 109-92-2; benzenesulfonylacetic acid, 3959-23-7; succinic anhydride, 108-30-5.

Total Synthesis of the Paniculides

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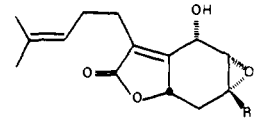
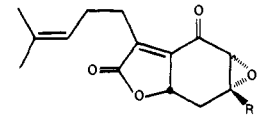
Abstract: In this, a full account, we disclose the first total synthesis of paniculides A-C (**1-3**), three highly oxygenated sesquiterpenes isolated in 1968 by Overton et al. from hypocotyl and stem tissue cultures of *Andrographis paniculata*. Our approach, which is both highly efficient and stereocontrolled and furthermore serves to confirm for the *first time* the structural assignments of the paniculides, begins with the facile photochemical [2 + 2] cycloaddition of enones **12** and **13** to 1,1-diethoxyethylene. Application of the Kochi-McMurry $Pb(OAc)_4$-induced oxidative decarboxylation on the derived carboxylic acid **9a** and the Saegusa protocol on **9b** afforded bicyclic ketones **8a** and **8b**, respectively, the concave-convex nature of which provides the needed stereochemical bias required to introduce the epoxide oxygen. Toward the latter end, reduction ($NaBH_4/CeCl_3$) of each followed by *m*-CPBA oxidation led to a 3:1 mixture of epoxy lactones. Protection of the C(15)-hydroxyl of the major lactone in each case (i.e., **6a** and **6b**) as the triethylsilyl (TES) ether and alkylation with 2-methyl-5-iodo-2-pentene gave **22a** and **22b**, respectively. Final introduction of the C(6,7) unsaturation via the Reich-Sharpless oxidative elimination protocol and removal of the TES protecting group afforded racemic paniculide A and B, respectively. Oxidation of the C(8)-hydroxyl in both cases then afforded paniculides C (**3**) and D (**4**), the latter a likely, albeit as yet unknown, natural product. The overall efficiency to paniculides A and B from enones **12** and **13**, respectively, was 5.5 and 3.6%. Finally, two significant observations emanated from this venture. First, potassium amide bases [i.e., $KN(SiMe_3)$] are more effective in the deprotonation of highly oxygenated systems than the corresponding lithium amide bases. Second, the utility of diphenyl diselenide as an electrophile can be greatly improved simply by oxidation of the selenenylation reaction mixture prior to workup.

Introduction and Background

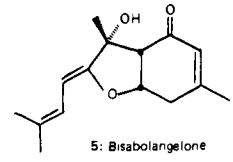
In 1968, during the course of phytochemical studies of callus cultures derived from *Andrographis paniculata* Nees,[1,2] Overton et al. at the University of Glascow disclosed the isolation of three highly oxygenated sesquiterpenoids termed paniculides A, B, and C (**1-3**, respectively) that were related to bisabolangelone (**5**).[3] Structural assignments were based on elemental composition data, in conjunction with spectroscopic properties including ^1H and ^{13}C NMR as well as mass spectrometric fragmentation patterns. Interestingly, while these novel sesquiterpenoids have been known for well over a decade, their structures at the outset of our work had yet to be confirmed either by X-ray analysis or by total synthesis. Indeed, to the best of our knowledge, there has been only one report concerning construction of the basic carbocyclic skeleton; this is the work of Jacobi at Wesleyan.[4]



1: Paniculide A, R = Me
2: Paniculide B, R = CH_2OH



3: Paniculide C, R = CH_2OH
4: Paniculide D, R = Me



5: Bisabolangelone

(1) Allison, A. J.; Butcher, D. N.; Connolly, J. D.; Overton, K. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1493.
(2) Butcher, D. N.; Connolly, J. D. *J. Exp. Bot.* **1971**, *22*, 314.
(3) Novotny, L.; Samek, Z.; Sorm, F. *Tetrahedron Lett.* **1966**, 3541.

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