Total Asymmetric Synthesis of the Putative Structure of the Cytotoxic Diterpenoid (−)-Sclerophytin A and of the Authentic Natural Sclerophytins A and B

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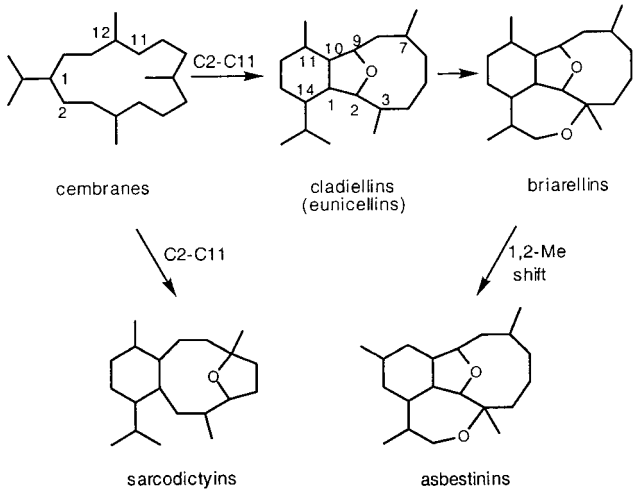
Abstract: An enantioselective synthetic route to the thermodynamically most stable diastereomer of the structure assigned to sclerophytin A (**5**) has been realized. The required tricyclic ketone **33** was prepared by sequential Tebbe−Claisen rearrangement of lactones **29** and **30**, which originated from the Diels−Alder cycloaddition of Danishefsky's diene to (5*S*)-5-(*d*-menthyloxy)-2(5*H*)-furanone (**14**). An allyl and a cyano group were introduced into the resulting adduct by means of stereocontrolled allylindation under aqueous Barbier-like conditions and by way of cyanotrimethylsilane, respectively. Following stereocontrolled nucleophilic addition of a methyl group to **33**, ring A was elaborated by formation of the silyl enol ether, ytterbium triflate-catalyzed condensation with formaldehyde, *O*-silylation, and Cu(I)-promoted 1,4-addition of isopropylmagnesium chloride. The superfluous ketone carbonyl was subsequently removed and the second ether bridge introduced by means of oxymercuration chemistry. Only then was the exocyclic methylene group unmasked via elimination. An alternative approach to the α-carbinol diastereomer proceeds by initial α-oxygenation of **37** and ensuing 1,2-carbonyl transposition. Neither this series of steps nor the Wittig olefination to follow induced epimerization at C10. Through deployment of oxymercuration chemistry, it was again possible to elaborate the dual oxygen-bridge network of the target ring system. Oxidation of the organomercurial products with O_2 in the presence of sodium borohydride furnished **72**, which was readily separated from its isomer **73** after oxidation to **61**. Hydride attack on this ketone proceeded with high selectivity from the *β*-direction to deliver (−)-**60**. Comparison of the high-field ^{1}H and ^{13}C NMR properties and polarity of synthetic **5** with natural material required that structural revision be made. Following a complete spectral reassessment of the structural assignments to many sclerophytin diterpenes, a general approach to sclerophytin A, three diastereomers thereof, and of sclerophytin B was devised. The presence of two oxygen bridges as originally formulated was thereby ruled out, and absolute configurations were properly determined. Key elements of the strategy include dihydroxylation of a medium-ring double bond, oxidation of the secondary hydroxyl in the two resulting diols, unmasking of an exocyclic methylene group at C-11, and stereocontrolled 1,2-reduction of the α-hydroxy ketone functionality made available earlier.

Introduction

Marine invertebrates are widely recognized to be an extraordinarily rich source of oxygenated 2,11-cyclized cembranoids.[2−5] The considerable structural diversity of this class of natural products has resulted in the offering of a biogenetic proposal[6] that rationalizes formation of the four related classes (Scheme 1). Of these, the cladiellins (also known as eunicellins)[7] and sarcodictyins[8] appear to be primary metabolites generated by carbon−carbon bond formation across positions C2 and C11 in cembrane precursors. They differ in the relative positioning

Scheme 1



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(1) Present address: Aventis Pharmaceuticals, Inc., 1041 U.S. Route 202/206, P.O. Box 6800, Bridgewater, NJ 08807-0800.
(2) Fenical, W. In *Marine Natural Products, Chemical and Biochemical Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; pp 174−242.
(3) (a) Coll, J. C. *Chem. Rev.* **1992**, *92*, 613. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259 and prior reports in this series.
(4) Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1992; Vol. 60, pp 1ff.
(5) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531.
(6) Stierle, D. B.; Carté, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088.

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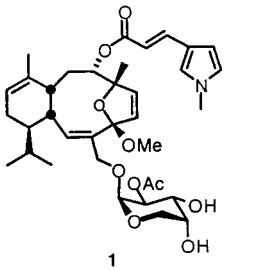
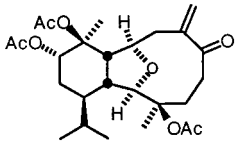
of the tetrahydrofuranyl oxygen. The briarellins[9] are the result of further oxygenation to introduce an oxepane ring, and the asbestinins[10] possess a translocated methyl substituent.

In line with their natural role to ward off predation, many of these metabolites are ichthyotoxic and molluscicidal.[8,11] Significantly, however, the range of inherent biological activity is far more expansive and includes potent antitumor activity, insect growth inhibition, antiinflammatory effects, and cell division inhibition.[5,11,12] Recently, the spotlight has been focused on eleutherobin (**1**)[13] whose capacity for inducing tubulin polymerization and microtubule stabilization[14] has attracted considerable synthetic interest.[15] Several other compounds in this large class have, on preliminary examination, exhibited cytotoxic properties that qualify them as opportune targets for de novo synthesis. Included in this group are labiatin B (**2**),[16,17] briarellin A (**3**),[10a] and sclerophytin A (**4**).[18] For example, **4** exhibits in vitro cytotoxicity against the L1210 cell line at a concentration of 1 ng/mL.



1



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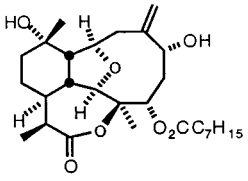

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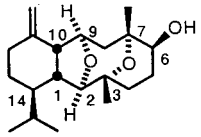
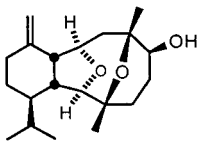


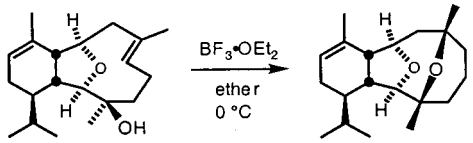
4

The total synthesis of any member of this select group represents a significant challenge to contemporary synthetic chemistry. Syntheses of eleutherobin (**1**)[15] and 7-deacetoxyalcyonin acetate[19] have been completed. More recently, we gained interest in developing an enantiocontrolled approach to the sclerophytin family that held the prospect of serving as a general route to this class of diterpenes.[20]

In line with this goal, X-ray crystallographic[7,21] and circular dichroism measurements[22] performed on structurally related compounds have made clear the fact that the resident stereocenters C1, C2, C3, C9, C10, and C14 possess the *R* configuration in common. Thus, one objective became to fuse the six-membered ring properly in cis fashion to the larger cyclodecanol unit. Beyond this, the detailed spectroscopic analysis reported by Sharma and Alam[18] for sclerophytin A was not able to define the configuration of C7 with absolute certainty because of its relatively remote location. The data can be construed to be equally compatible with the 7*R* configuration as in **5** and the absence of a second oxygenated bridge. The epimeric formulation **5** is significantly less strained than **4**[20] and conforms additionally to the low-temperature boron trifluoride-catalyzed cyclization of cladiellin **6** to **7** previously reported by Hochlowski and Faulkner.[23] Overman and Pennington have recognized the same structural ambiguities and have independently achieved a total synthesis of **5**.[24] The above considerations led us to seek a solution to the challenge of setting the two oxygen bridges anti as in **5**, as the strategy should also enable an independent synthesis of **7** to be accomplished. At the least, the structure of sclerophytin A would be established by a process of elimination.



5



6 **7**

Retrosynthetic Planning

Initial disconnection of **5** at the O−C7 bond with provision for late-stage introduction of the methylenecyclohexane func-

(7) Eunicellin was the first cladiellane to be described: Kennard, O.; Watson, D. G.; Riva di Sanseverino, L.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett.* **1968**, 2879.

(8) Sarcodictyins A−F were the first members of this subgroup to be isolated: (a) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019. (b) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 964.

(9) At 10 members, the briarellin class is a significantly smaller group than the other three: (a) Rodríguez, A. D.; Cóbar, O. M. *Tetrahedron* **1995**, *51*, 6869. (b) Rodríguez, A. D.; Cóbar, O. M. *Chem. Pharm. Bull.* **1995**, *43*, 1853.

(10) For early reports, consult: (a) Rodríguez, A. D.; Cóbar, M. O. *Tetrahedron* **1993**, *49*, 319. (b) Morales, J. J.; Lorenzo, D.; Rodríguez, A. D. *J. Nat. Prod.* **1991**, *54*, 1368.

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(13) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A.M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.

(14) Long, B. H.; Casazza, A. M.; Carboni, J.; Wasserman, A. J.; Cornell, L.; Fairchild, C. R.; Lindel, T.; Jensen, P. R.; Fenical, W. *Cancer Res.* **1998**, *58*, 1111.

(15) (a) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520. (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789. (c) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674. (d) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.

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(17) Ortega, M. J.; Zubía, E.; Salvá, J. *J. Nat. Prod.* **1997**, *60*, 485.

(18) Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537.

(19) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

(20) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875.

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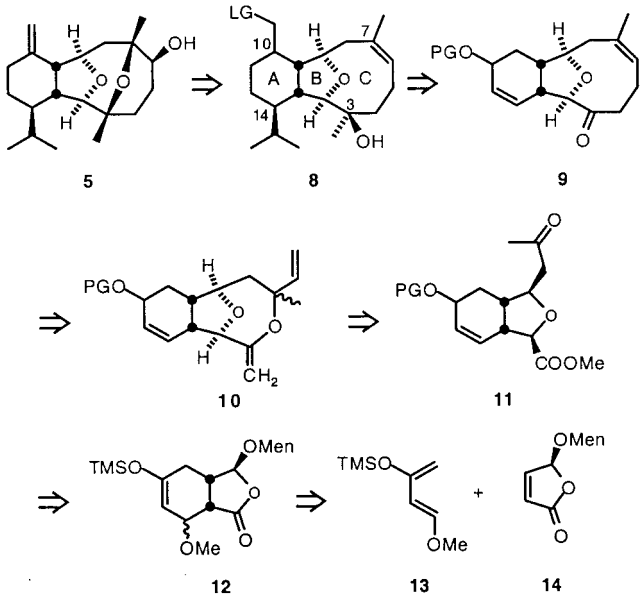
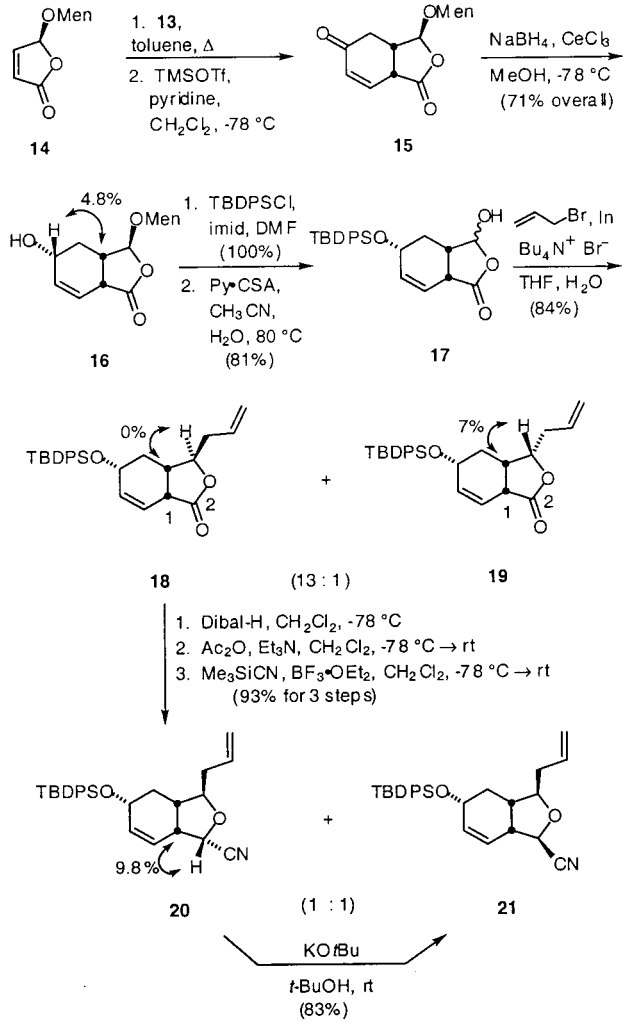
(24) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683.

Scheme 2



Scheme 3



tionality was envisioned to lead back to **8** (Scheme 2). Our expectation was that the remaining ether oxygen in this advanced intermediate would find it possible to steer the approach of Hg^{2+} to the α-surface of the unsaturated linkage by means of coordination and thereby exercise a high degree of stereoselectivity.[25] This prospectus had the useful feature that control of the course of the introduction of the C3 methyl group into **9** would extend subsequently to C7. Of comparable significance was the recognition that the global ensemble of structural features resident in **9** might be installed by Claisen rearrangement of **10**. If this were so, one could easily imagine that chemoselective vinyl anion addition to the ketone carbonyl in **11** with accompanying ring closure would deliver a tricyclic lactone, Tebbe olefination[26] of which would provide **10**. This choice of sequential steps would allow us to examine quickly the critical ring expansion that is expected to provide **9**. We were mindful from the outset, however, that the proper confluence of conformational factors had to be met to realize this objective.

Although we shall leave unspecified for the moment which of several options was to be implemented for introduction of the necessary functionality in **11**, it was recognized that a Diels–Alder cycloaddition involving Danishefsky's diene (**13**)[27] and (5*S*)-5-(*d*-menthyloxy)-2-(5*H*)-furanone (**14**)[28] could generate **12** as the matrix upon which additional structural complexity could be appended.

First Generation Synthesis. Preparation of Hydroxy Ester 27. The convergent assembly of **27** began with exploration of a direct route to keto lactone **15**. In line with the earlier report of Feringa,[28] the heating of **13** with **14** in toluene resulted in a completely regioselective cycloaddition. The appearance of two products in a ratio of 2:1, diasteromeric at the carbon bearing the methoxy group, is due to a modest endo stereoselectivity. In practice, the formation of a mixture at this point is inconsequential. As a result of the chiral auxiliary, elaboration of the cis-fused bicyclic framework occurs to set stereogenicity properly in either case, and both adducts undergo conversion to **15** under controlled conditions. The latter step, recognized to be demanding,[28] could be efficiently and reproducibly accomplished by application of Vorndam's protocol (Scheme 3).[29] These mild conditions rely on a catalytic quantity of trimethylsilyl triflate in the presence of pyridine or lutidine as the proton scavenger, instead of treatment with dilute aqueous acidic solutions.

There is no known direct method for conversion of the uncommon γ-alkoxy-γ-lactone unit of the type resident in **15** into the corresponding allylated γ-lactone as found in **18** and **19**. For our purposes, it was envisioned that addition of the allylindium reagent to a γ-hydroxy-γ-lactone of general formula **A** might well generally provide products such as **C** selectively via chelation-controlled 1,2-addition to the ring-opened β-carboxy aldehyde tautomer **B** and subsequent lactonization. When

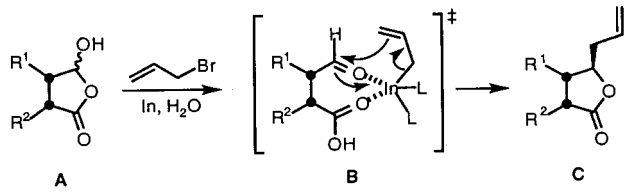
(25) (a) Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1959**, 227. (b) Henbest, H. B.; McElhinney, R. S. *J. Chem. Soc.* **1959**, 1834. (c) Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407. (d) Chamberlain, P.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1382. (e) Matsuki, Y.; Kodama, M.; Itô, S. *Tetrahedron Lett.* **1979**, 2901. (f) Giese, B.; Bartmann, D. *Tetrahedron Lett.* **1985**, *26*, 1197. (g) Pougny, J.-R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375. (h) Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Gazz. Chim. Ital.* **1984**, *114*, 193. (i) Paquette, L. A.; Bolin, D. G.; Stepanian, M.; Branan, B. M.; Mallavadhani, U. V.; Tae, J.; Eisenberg, S. W. E.; Rogers, R. D. *J. Am. Chem. Soc.* **1998**, *120*, 11603.

(26) Review: Pine, S. H. *Org. React.* **1993**, *43*, 1.

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

(28) (a) de Jong, J. C.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1247. (b) de Jong, J. C.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1990**, *31*, 3047.

(29) Vorndam, P. E. *J. Org. Chem.* **1990**, *55*, 3693.



preliminary studies involving congeners of **15** were found to be highly responsive to this neighboring carboxyl effect,[30] our interest turned to assessing the response of **17** to these Barbier-like aqueous allylation conditions. To this end, **15** was reduced under Luche conditions[31] to give predominantly (ratio of 9.6:1) the α-carbinol **16**, which was *O*-silylated and subsequently subjected to mild acidic hydrolysis. In line with previous observations, the allylindation of **17** served well to deliver a 13:1 mixture of **18** and **19**. The need to clearly distinguish these diastereomers was satisfied by means of NOE analysis. For the major product, the absence of any observable interaction between the two vicinal protons shown in the structural formula unequivocally defined it to be the required β-allyl derivative.

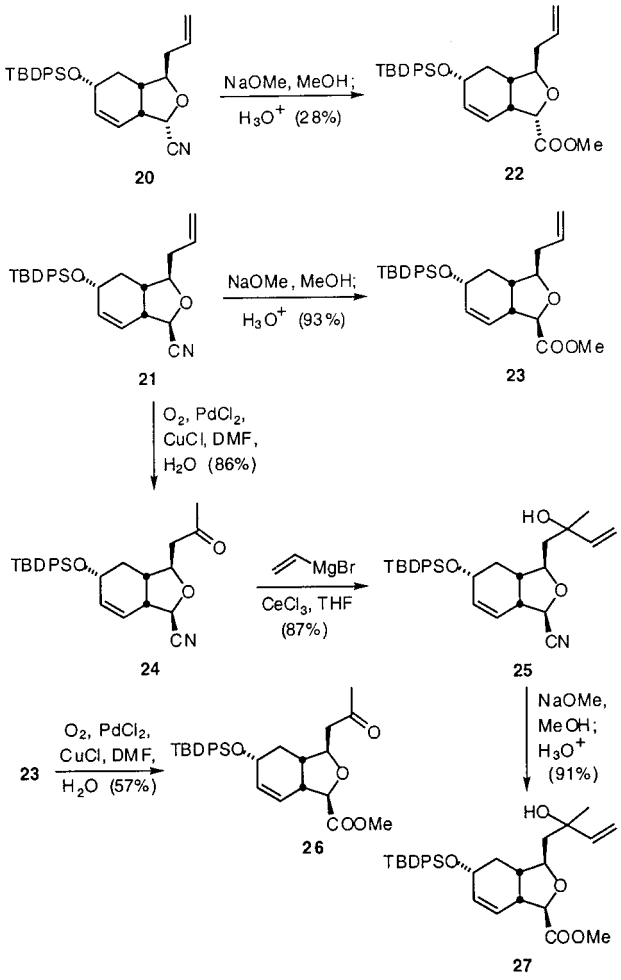
With multigram quantities of **18** in hand, attention was turned to effecting homologation at C2 as a prelude to implementation of the key Tebbe−Claisen sequence. Thus, this lactone was subjected to Dibal-H reduction, acetylation, and ultimately treatment with trimethylsilyl cyanide (TMSCN) and boron trifluoride etherate in CH_2Cl_2 at −78 °C. A 1:1 mixture of the chromatographically separable nitriles **20** and **21** was thereby obtained in excellent yield. A change to acetonitrile as solvent did not alter the stereoselectivity. Activation of the lactol in the form of its acetate prior to cyanation was found to be far more efficient than direct treatment of the lactol with TMSCN under the same conditions.[32]

At this juncture, verification that **21** was the β-isomer was offered by NOE studies and reinforced by chemical equilibration. Although introduction of the cyano substituent proved not to be stereoselective, the discovery that **20** could be efficiently converted into **21** by exposure to potassium *tert*-butoxide in *tert*-butyl alcohol constituted a major step forward.

As a direct consequence of the sensitivity of these nitriles, the task of transforming them into their respective esters without epimerization required the avoidance of conventional conditions. Ultimately, recourse was made to a one-pot two-step procedure that consisted of imidate formation with sodium methoxide in methanol[33] and mild acidic hydrolysis of the imino ethers.[34] This protocol nicely skirted the risk of potential epimerization, and proceeded in notably high yield when the CN substituent resided on the sterically noncongested β-surface of the bicyclic framework.

These findings prompted two complementary studies (Scheme 4). In the first, **21** was transformed by Wacker oxidation[35] into the keto nitrile **24**, a process which gave rise to the ester **26** through comparable processing of **23**. More significantly, addition of vinylmagnesium bromide to **24** in the presence of

Scheme 4



cerium trichloride[36] afforded **25**, which proved to be a most useful precursor to **27**. Therefore, this propitious hydrolysis sequence[37] proceeds efficiently without interference from neighboring keto or hydroxyl functionality. Where **27** is concerned, its structural framework is constituted of all the features required to advance to lactones **29** and **30**.

The Tandem Tebbe−Claisen Ring Expansion. The convenient formation of **27** permitted its exploitation as a precursor to **33**. The requisite series of transformations, summarized in Scheme 5, began with the generation of carboxylic acid **28** via saponification of **27** with lithium hydroxide and subsequent macrolactonization according to Yonemitsu's modification of the Yamaguchi protocol.[39] These relatively efficient steps

(30) Bernardelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284.
(31) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(32) (a) Brückner, C.; Holzinger, H.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2450. (b) Brückner, C.; Lorey, H.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 556.
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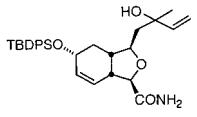
(34) Le Borgne, J. F.; Cuvigny, T.; Larchevêque, M.; Normant, H. *Synthesis* **1976**, 238.
(35) Tsuji, J. *Synthesis* **1984**, 369.

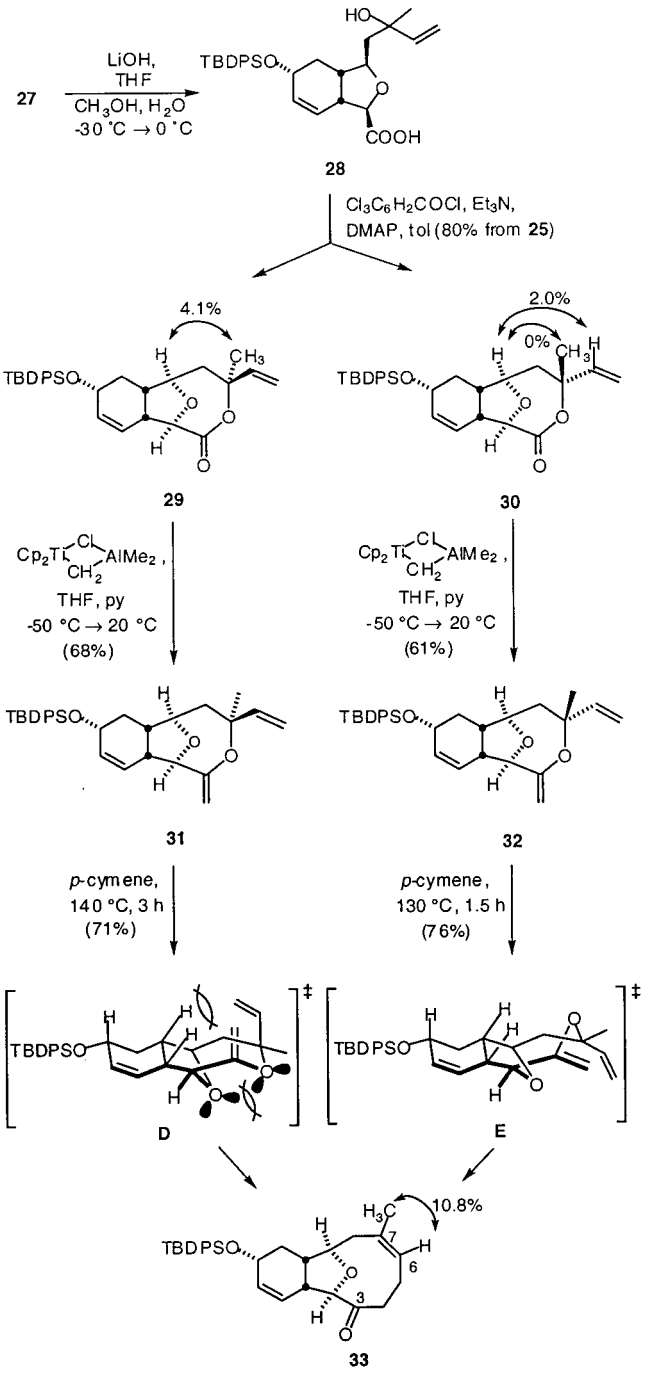
(36) The $CeCl_3$-mediated addition [Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713; Dimitrov, V.; Kostova, K.; Genov, S. *Tetrahedron Lett.* **1996**, *37*, 6787] gave better yields than the procedure involving preformation of the vinylcerate at −78 °C [Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(37) Attempts to bring about the direct hydrolysis of **25** to the carboxylic acid with 10% KOH and H_2O_2 in DMSO[38] invariably stopped at the amide stage to give *i*.



i

(38) (a) Katritzky, A.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949. (b) Sasaki, S.; Nakashima, S.; Nagatsugi, F.; Tanaka, Y.; Hisatome, M.; Maeda, M. *Tetrahedron Lett.* **1995**, *36*, 9521.

Scheme 5



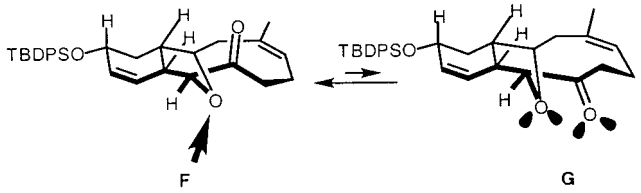
delivered a chromatographically separable mixture of lactones **29** and **30**, which were readily distinguished by NOE methods. Individual submission of these advanced intermediates to Tebbe methylenation,[26] with proper provision for the complete removal of $AlMe_3$ and $AlMe_2Cl$ during preparation of the Tebbe reagent, made available the enol ethers **31** and **32**, respectively.

In pilot experiments, the planned Claisen rearrangements[40−42] were performed by heating in *p*-cymene at 130−140 °C with monitoring of the progress of reaction by thin-layer chromatography. Despite the strain release that serves as a component of the driving force for these isomerizations, it was clearly obvious that **32** was transformed into **33** more rapidly than was **31**. In fact, after heating a 1:1 mixture of **31** and **32** at 140−150 °C for 1 h, only **31** remained unreacted. Upon closer scrutiny, the discovery was made that **32** rearranges quantitatively into **33** in just 3 h upon being heated in neat condition at 55 °C. By comparison, **31** required higher temperatures (e.g., 130 °C) for a longer period. Even under these circumstances, the conversion to **33** was incomplete, and some decomposition was evident. Ultimately, a compromise position was taken to reconcile this kinetic imbalance. Recourse to $NaBF_4$, or less preferably pyridinium camphorsulfonate, as promoter[43] allowed the sigmatropic process to be performed efficiently in refluxing toluene during a few hours.

The interesting rate difference in question can be rationalized by comparing the two chairlike transition states **D** and **E** that are presumably involved (Scheme 5). Although the adoption of these chair geometries guarantees that both enol ethers will give rise to product having a *Z* double bond, the sterically and electronically disfavored interactions that are incurred in **D** but not in **E** elevate the energy barrier with observable consequences.

The structural assignment to **33** rests on two constituent spectroscopic features. When H6 was irradiated, the signal corresponding to the neighboring methyl group showed a 10.8% NOE enhancement. The phenomenon was reciprocal. Furthermore, according to ^{13}C NMR correlations,[10b,44] the chemical shift at δ 25.4 is uniquely characteristic of a methyl substituent that is geminal to one alkyl chain and trans to another.

Setting Stereochemistry at C3. The next issue to be addressed was 1,2-addition of a methyl group to the C3 carbonyl in **33** as a prelude to a more advanced functionalization of the A ring (see **8**). From the conformational vantage point, it was considered reasonable that the carbonyl group in its medium-sized ring would prefer to be oriented to the β-face as in **F**. Note that this arrangement avoids the unfavorable electronic interactions between the two oxygenated centers that must clearly operate in the "carbonyl-down" alternative **G**. On this



basis, we predicted that addition of methyllithium to **33** would result in predominant attack from the molecular exterior to deliver **34** as the predominant or exclusive product. A strong diastereofacial bias was indeed seen, such that **34** was the only tertiary carbinol detected (Scheme 6). The important piece of stereochemical identification was once again derived from NOE

(39) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613.

(40) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

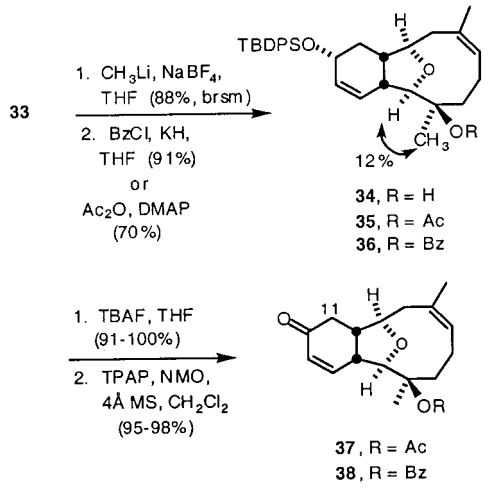
(41) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2.

(42) (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985** *107*, 7352. (b) Paquette, L. A., Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610. (c) Paquette, L. A.; Sweeney, T. J. *Tetrahedron* **1990**, *46*, 4487. (d) Friedrich, D.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 3831. (f) Paquette, L. A., Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841. (g) Paquette, L. A.; Philippo, C. M. G.; Vo, N. H. *Can. J. Chem.* **1992**, *70*, 1356.

(43) For a discussion of the catalysis of the Claisen rearrangement, consult: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(44) (a) Selover, S. J.; Crews, P.; Tagle, B.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 964. (b) Crews, P.; Kho-Wiseman, E. *J. Org. Chem.* **1977**, *42*, 2812. (c) de Haan, J. W.; van de Ven, L. J. M. *Tetrahedron Lett.* **1971**, 3965.

Scheme 6



measurements. The strong (12%) enhancement between H2 and the newly introduced methyl substituent proved particularly convincing.

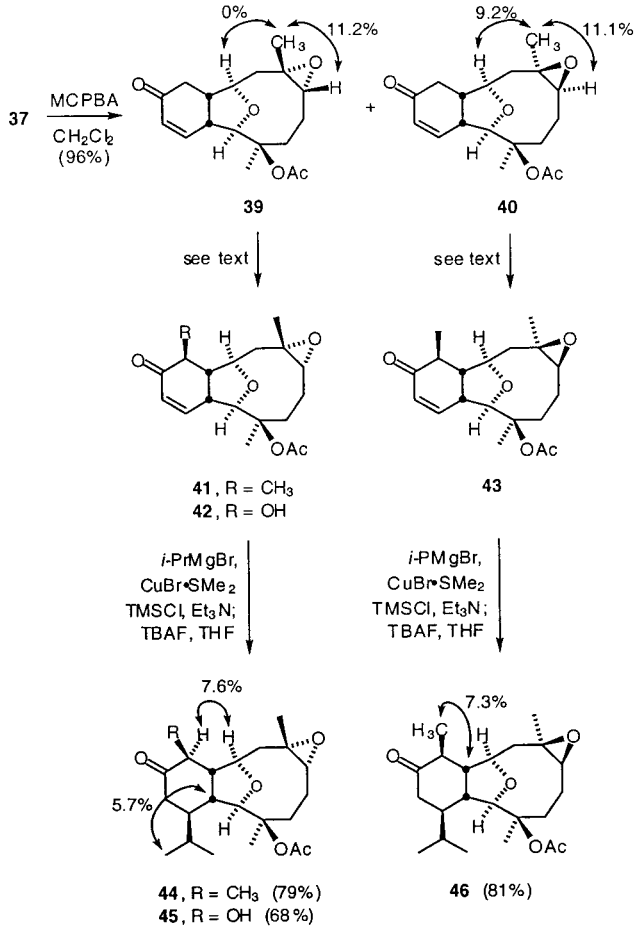
Following *O*-acetylation or benzoylation of this entity, the long-serving silyl protecting group was removed, and the allylic alcohols so formed were oxidized to ketones **37** and **38** with the perruthenate reagent.[45]

Since little precedence was available, the decision was made to briefly explore the stereochemistry of epoxidation of **37** to assess the feasibility of regiocontrolled electrophilic attack at C11. These functional group manipulations began by treating **37** with MCPBA, with resultant formation of **39** and **40** in a 2:1 ratio (Scheme 7). Thus, a modest preference for approach of the peracid to the α-surface of the medium-ring double bond was demonstrated.

Not entirely unexpected[46] were our observations that the enolate anions of these epoxy ketones are rather unreactive chemical intermediates. Following the deprotonation of **39** under kinetically controlled conditions with potassium hexamethyldisilazide in THF at −78 °C and the subsequent introduction of excess methyl iodide, isomerically pure **41** was obtained in only 45% yield (or 53% based on recovered unreacted **39**). Under comparable conditions, **40** gave rise to a 7:1 mixture of **43** and its α-methyl epimer (41%). The response of the enolate anion of **39** toward the Davis oxaziridine[47] was to deliver the α-hydroxy ketone **42** with complete stereoselectivity and somewhat more efficiently. Beyond this, intermediates **41**−**43** smoothly underwent 1,4-conjugate addition in the presence of isopropylmagnesium chloride and the copper(I) bromide−dimethyl sulfide complex to provide **44**−**46**, respectively, in good yield. A number of NOE studies supported the depicted stereochemical assignments (see formulas).

Three important points had now been established: (a) α-attack on the double bond positioned in the largest ring of these heterotricyclic frameworks is not sterically impeded; (b) electrophilic attack on the planarized enolate anion formed in either series occurs preferentially from the *β*-face, with **39** exhibiting particularly high stereoselectivity; (c) steric factors likewise control the direction of entry of the isopropyl cuprate reagent,

Scheme 7



thereby leading to the proper setting of the requisite *R* configuration at C14.

Elaboration of Ring A. As a prelude to examining the problem of setting the two anti-oxygen bridges present in the target, we hoped to complete the proper functionalization of ring A in an efficient manner. Two changes were instituted at the outset. In an effort to deter premature deacylation at C3, the acetate group was replaced with the more robust benzoate alternative. In addition, the decision was made to probe the reactivity of siloxy diene **47** as a way of facilitating alkylation at C11 (Scheme 8). The matter of generating **47** was easily resolved. To reach **48**, **47** was directly exposed to chloromethylphenyl sulfide and silver tetrafluoroborate in CH_2Cl_2 as the solvent. The alternate use of the more often utilized $TiCl_4$[48] was found to be destructive, and the milder Lewis acid $ZnBr_2$ proved inefficient. This reaction sequence furnished **48** in 55% yield for the two steps. To reach primary carbinol **49** in an efficient manner, recourse was made to 37% aqueous formaldehyde in THF with ytterbium triflate as the promoter.[49] This protocol led to the isolation of **49** in 65% yield alongside 32% of recovered enone **38**. The subsequent *O*-silylation of **49** proceeded in reduced yield because of the sensitivity of this compound to concurrent retroaldol cleavage.

While the copper-catalyzed addition of isopropylmagnesium chloride to **48** could not be induced to proceed efficiently, it was found that **50** gave rise reproducibly to **52** in 90% yield. NOE measurements confirmed that the stereochemical course of this process did not differ from earlier precedent. Therefore,

(45) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

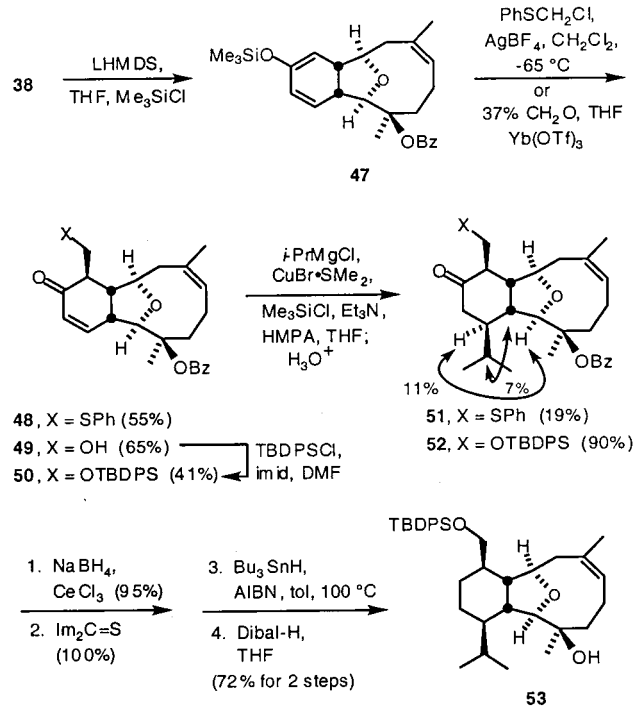
(46) For comparison, the enolate anion of **37** was found *not* to react with the Eschenmoser salt, dry formaldehyde, or tosyl cyanide.

(47) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.

(48) Paterson, I. *Tetrahedron* **1988**, *44*, 4207.

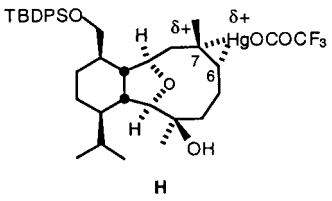
(49) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.

Scheme 8



the stage was set for deoxygenative removal of the carbonyl oxygen. This reductive maneuver was implemented in three steps consisting of Luche reduction, formation of the thiocarbonyl imidazolide, and radical reduction.[50] Subsequent removal of the benzoate functionality provided **53** in 72% yield from **52**.

Scrutiny of the Applicability of Oxymercuration Chemistry. Attainability of Prototype Sclerophytin 7. Having removed the superfluous oxygen in ring A, we next set out to conduct selected model experiments involving possible intramolecular participation during the oxymercuration of **53**. After treatment with mercuric trifluoroacetate in DMF under thermodynamic conditions,[51] the cyclized mercurials were subjected directly to the reductive action of sodium borohydride. These conditions led to the isolation of both **54** (57%) and **55** (23%) (Scheme 9). The mercurinium ion **H** that materializes upon

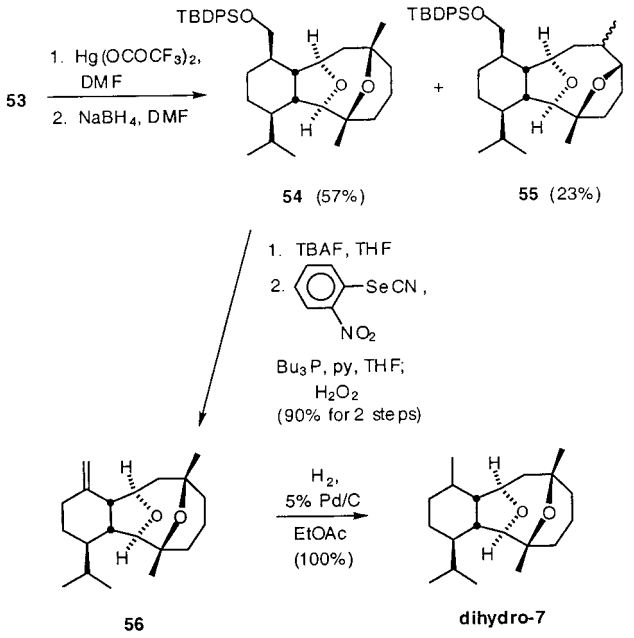


H

complexation to the α-surface of the π-bond can consequently be judged to be sufficiently unsymmetrical to position greater positive charge at C7 than at C6. In this way, formation of a pyran ring as in **54** can compete quite effectively with otherwise kinetically favored five-ring closure to deliver **55**.

The availability of **54** in this manner made possible its conversion to the exo-methylene derivative **56** by oxidative elimination of the *o*-nitrophenyl selenide derivative.[52] Hydrogenation of **56** under standard conditions furnished a diastereomeric mixture of the doubly bridged ether dihydro-**7**, whose ^{1}H NMR spectrum showed the major product to be the same substance produced earlier by Hochlowski and Faulkner[24] from the metabolite **6** of a Pacific soft coral. In a two-step sequence, they generated dihydro-7 having the same characteristic peaks δ 3.93 (br t, $J = 5$ Hz, 1 H), 3.67 (s, 1 H), 1.27 (s, 3 H), 1.06 (s, 3 H), 0.95 (d, $J = 6.8$ Hz, 3 H, 0.92 (d, $J = 6.8$ Hz, 3 H), and 0.78 (d, $J = 6.8$ Hz, 3 H).

Scheme 9



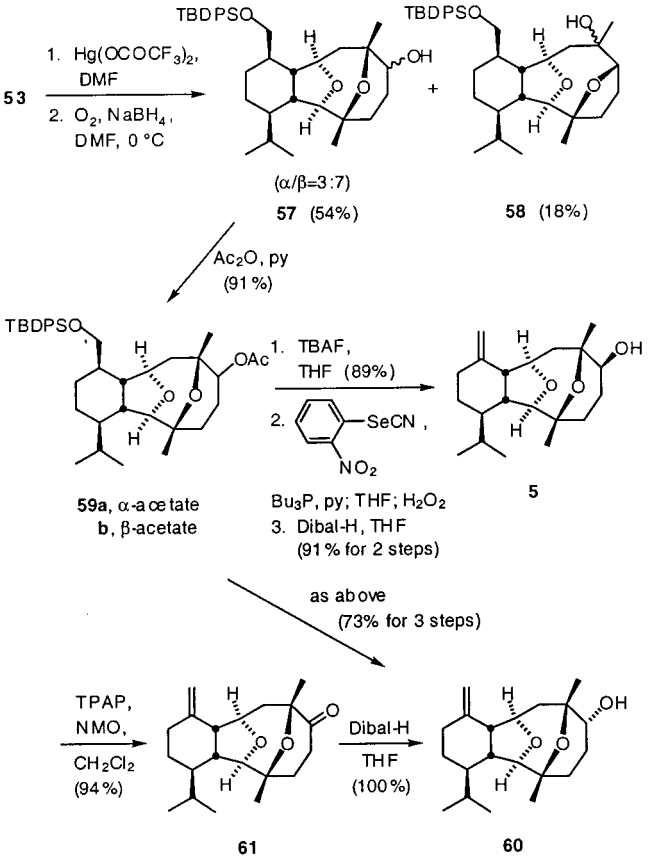
This linkup was perceived to be of direct relevance to our working assumptions regarding the synthesis of **5** by a parallel stratagem. Further, this validation constituted an endorsement for the oxymercuration as a workable means for setting the pair of ether bridges in an anti relationship.

Acquisition of 5. Following completion of the reconnaissance phase just described, we returned to the oxymercuration of **53**, but presently with oxidative demercuration ($NaBH_4$, O_2)[53] in mind. To our delight, this protocol furnished the secondary carbinol **57** (54%, $\alpha,\beta = 3{:}7$) as the major product in addition to 18% of the tertiary alcohol **58** (Scheme 10). Following acetylation of **57**, it proved convenient to separate the α- and β-epimers chromatographically. This development made feasible the subsequent independent elaboration of both **5** and **60**. Introduction of the exocyclic double bond in both epimers of **57** was accomplished by fluoride ion-induced desilylation in advance of dehydration via the *o*-nitrophenylselenocyanate[54] and Dibal-H reduction. In addition, the complementary α-isomer **60** was produced by oxidation of **5** to ketone **61** and reduction of the latter intermediate. Interestingly, hydride attack occurred from the β-direction to deliver **60** exclusively.

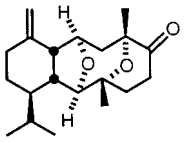
Neither targeted compound was identical to the natural substance. While **5** is dextrorotatory, sclerophytin A is not.[55] Beyond this, the significantly more polar nature of **4** commands attention. This marked difference is also reflected in the derived ketones **61** and **62**. Quite unexpected at the time was the finding that the previously unknown **62** (incorrect structure) was

(50) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(51) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876.
(52) Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem.* **1980**, *45*, 2247.
(53) Harding, K. E.; Marman, T. H.; Nam, D.-h. *Tetrahedron Lett.* **1988**, *29*, 1627 and relevant references therein.
(54) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(55) The optical rotation of natural sclerophytin A has not previously been reported: $[\alpha]_D$ −6.9 (*c* 0.087, $CHCl_3$).

Scheme 10



appreciably more polar than either **5** or **60**. We now recognize this to be because the structural assignment to natural **4** was misformulated by Alam and co-workers. More recently, the rightmost ether bridge in natural **4** (and by extrapolation to **62**) has been shown to be constituted instead of two tertiary hydroxyl-bearing centers.[56]

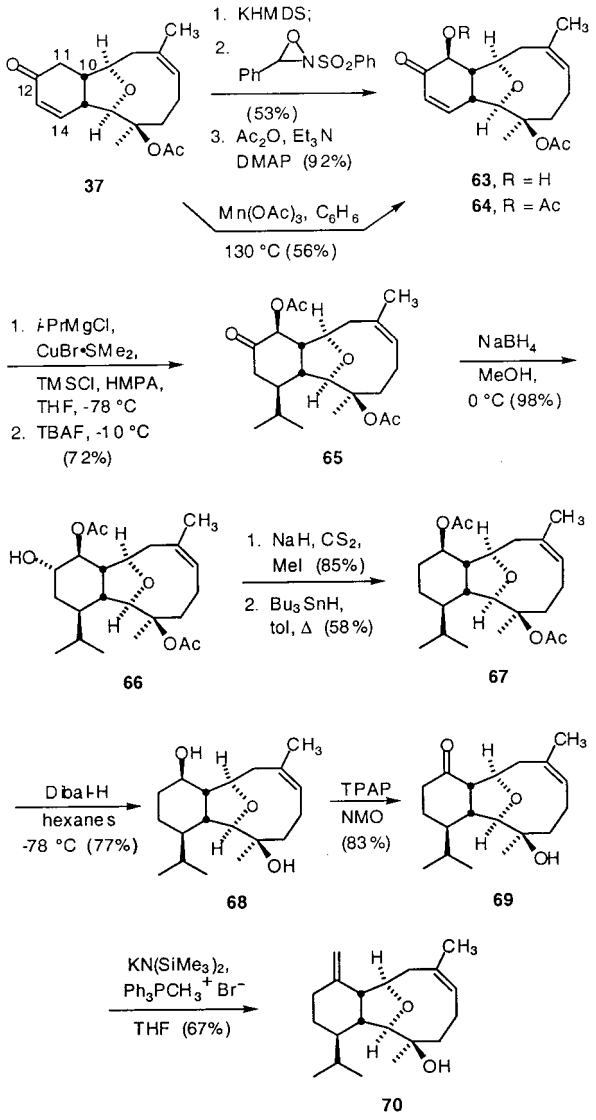


62

Alternative Synthesis of 60. Concurrent with the effort described above, an alternate and somewhat shorter route to **60** was explored. This alternative began with enantiopure ketone **37** and was designed with early migration of the C12 carbonyl to C11, concurrent with incorporation of the C14 isopropyl group from the more open β-face. In line with these objectives, the potassium enolate of **37** was generated and oxidized with the Davis oxaziridine[47] to produce α-ketol **63**, which was acetylated in turn to give **64** (Scheme 11).

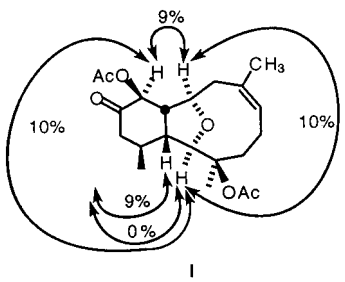
Attempts to circumvent the modest yield of this oxidative protocol prompted the examination of a Mn(III)-mediated process intended to lead directly to **64**.[57] Although roughly comparable efficiencies were realized during small-scale runs involving $Mn(OAc)_3$, recourse to larger quantities proved

Scheme 11



sufficiently unreliable in delivering **64** so as to warrant the dismissal of this alternative from further consideration.

Copper-catalyzed addition of isopropylmagnesium chloride to **64** proceeded smoothly, giving ketone **65** after fluoride ion-induced cleavage of the intermediate silyl enol ether. The stereochemical assignment to **65**, unequivocally demonstrated by a series of NOE experiments (see **I**), was consistent only with β-entry of the cuprate as before.



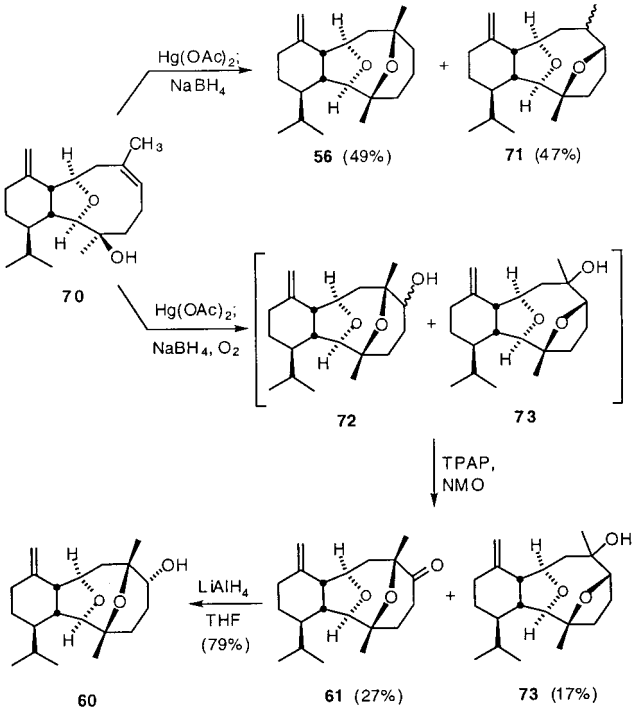
I

The acetylated nature of the hydroxyl groups in **65** presented a target of opportunity for removal of the superfluous C12 carbonyl oxygen. This goal could not be reached by possible desulfurization of a dithioacetal because of the observed high sensitivity of **65** to Lewis acids. Alternatively, its sequential

(56) (a) Friedrich, D.; Doskotch, R. W.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1879. (b) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135.

(57) (a) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839. (b) Jeganathan, A.; Richardson, S. K.; Watt, D. S. *Synth. Commun.* **1989**, *19*, 1091.

Scheme 12



treatment with sodium borohydride, conversion to the xanthate, and heating of the latter with tri-*n*-butyltin hydride[50] led uneventfully to **67**. The major carbinol formed midway in this sequence was judged to have its hydroxyl oriented to the α-face, since the geminal H11 proton exhibits two large couplings ($J_{10,11}$ = 9.9 Hz, $J_{11,12}$ = 9.4 Hz) as a necessary consequence of dual anti arrangements involving the vicinal hydrogens H10 and H12.

Progress toward the target continued with the low-temperature Dibal-H reduction of **67**, thereby producing the diol **68**. Controlled oxidation of the secondary hydroxyl in **68** with tetra-*n*-propylammonium perruthenate (TPAP),[45] in conjunction with NMO as the co-oxidant, furnished the crystalline ketone **69** in 83% yield. At this stage, it was not possible to confirm unequivocally by spectroscopic means whether epimerization may have taken place adventitiously at C10 under the basic conditions of the Wittig olefination with methylenetriphenylphosphorane required for conversion to **70**. However, by pressing forward until ultimate arrival at **60**, it was subsequently established that any concern regarding possible erosion of stereochemical integrity at this center during this particular olefination step was unwarranted.

The oxymercuration of dienol **70** proceeded chemoselectively to the trisubstituted double bond, obviously as a direct consequence of assistance provided by the C-ring hydroxyl substituent[25] (Scheme 12). Treatment of the intermediate organomercurials with sodium borohydride gave rise to the doubly bridged ethers **56** and **71** in near-comparable amounts. As before, the lack of preference for intramolecular hydroxyl capture at the tertiary olefinic center over the secondary one is believed to stem from geometrical constraints inherent to this particular structural framework. Notwithstanding, the high efficiency of this process (96% combined yield) boded well for its possible deployment in the preparation of **60**.

To this end, we investigated the possibility of the oxidative demercuration[53] of the same pair of structurally complex mercurials. The isomeric alcohols **72** and **73** were identified spectroscopically as having been formed in this reaction but proved to be exceedingly difficult to separate by chromatographic means. For this reason, the **72**/**73** mixture was directly oxidized with TPAP and NMO. The tertiary alcohol **73** was expectedly inert to these conditions and was now easily retrieved as a single diastereomer. The desired less polar ketone **61** forms without difficulty, and its availability by means of this protocol allowed for the implementation of lithium aluminum hydride reduction to furnish (−)-**60**. In line with precedent, the exclusive product was deduced to be the α-carbinol resulting from sterically controlled approach to the carbonyl group in a nonchair conformation of the C-ring.

The linear sequence beginning from **37** consisted of 13 steps. The key reactions involved carbonyl transposition in tandem with Barton deoxygenation, as complemented by intramolecular oxymercuration.

NMR Spectroscopic Analysis. The 600 MHz ^{1}H NMR spectrum of ketone **61** in $CDCl_3$ reveals the presence of two nonequivalent exocyclic methylene protons, two methine protons geminal to oxygen, three additional methines to higher field, two methyl groups attached to fully substituted carbons, and two methyls that form part of an isopropyl group (Figure 1). The combination of ^{1}H, ^{1}H COSY, and NOE difference (DPFGE method) studies provided convincing evidence for adoption of the indicated conformation. Recourse to HMBC and HSQV analyses at 150 MHz allowed for clear definition of all relevant carbon chemical shifts and specific C/H interactions. (Supporting Information).

Entirely parallel analyses of the epimeric alcohols **5** and **60** showed these reduced compounds to possess comparable three-dimensional characteristics. The coupling of H-6 to H-5α and H-5β in **5** (J = 10.7, 3.9 Hz) defined this isomer to be the β-carbinol. The α-orientation featured in **60** is met with significantly reduced spin−spin interactions (J = 3.4, 2.5 Hz) (Supporting Information). The spectrum of neither epimer compares at all favorably with that recorded for authentic scleophytin A. Particularly diagnostic of the substantive dissimilarities of the three isomers is the upfield segment of their ^{13}C NMR spectra (Figure 2).

Mechanistic and Biogenetic Considerations. A structural feature shared in common by cladiellins such as **6**, lithophynins A−D,[22c,58,59] calicophirins A and B,[60,61] and ophirin[60−63] is a trans double bond between C6 and C7. Conformational analysis of a prototype system such as **6** clearly indicates the "hydrogen down" conformer to be thermodynamically preferred relative to the "hydrogen up" arrangement **74** (Scheme 13). The nonbonded steric compression of the vinylic methyl against the C2−C9 oxygen bridge is the prime destabilizing factor. Preferential protonation of **6** would give rise to carbocation **75**, simple collapse of which with loss of a proton would deliver **7**, as observed experimentally.

In a marine environment, epoxidation of the C6/C7 double bond could transpire.[64] Attack must necessarily be relegated to the exterior of the *trans*-cyclodecene ring for the usual reasons. For **6**, this process would give rise to **76** and conceivably set

(58) Ochi, M.; Futatsugi, K.; Kotsuki, H.; Ishii, M.; Shibata, K. *Chem. Lett*. **1987**, 2207.
(59) Ochi, M.; Futatsugi, K.; Kume, Y.; Kotsuki, H.; Asao, K.; Shibata, K. *Chem. Lett.* **1988**, 1661.
(60) Ochi, M.; Yamada, K.; Shirase, H.; Kotsuki, H.; Shibata, K. *Heterocycles* **1991**, *32*, 19.
(61) Seo, Y.; Rho, J.-R.; Cho, K. W.; Shin, J. *J. Nat. Prod.* **1997**, *60*, 171.
(62) Fusetani, N.; Nagata, H.; Hirota, H.; Tsuyuki, T. *Tetrahedron Lett.* **1989**, *30*, 7079.
(63) Kashman, Y. *Tetrahedron Lett.* **1980**, *21*, 879.
(64) Solenopodins A−C are naturally occurring trans epoxy-substituted cladiellins: Bloor, S. J.; Schmitz, F. J.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1992**, *57*, 1205.

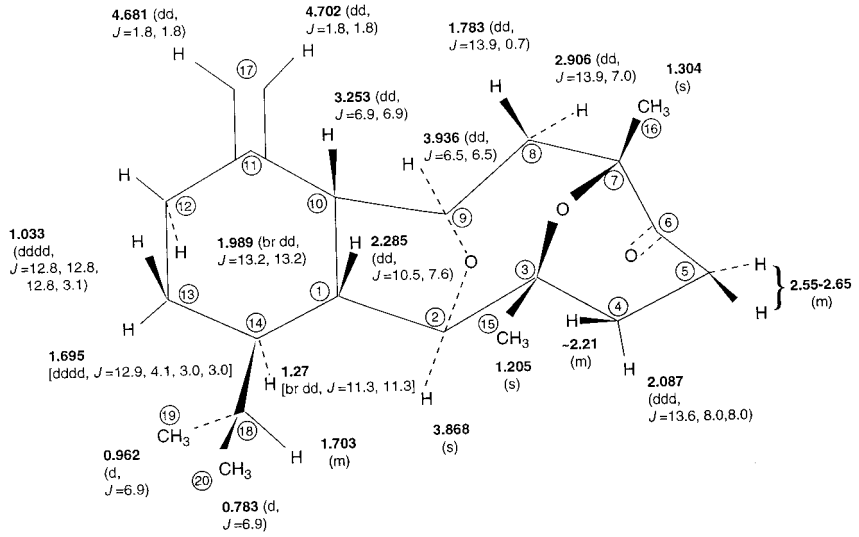


Figure 1. ^{1}H NMR assignments (δ values, 600 MHz, $CDCl_3$, J in Hz) and conformational features of ketone **61**. The values in square brackets are hidden patterns that were revealed by NOE and TOCSY methods. The numbering scheme is adapted from that reported by Sharma and Alam (ref 18).

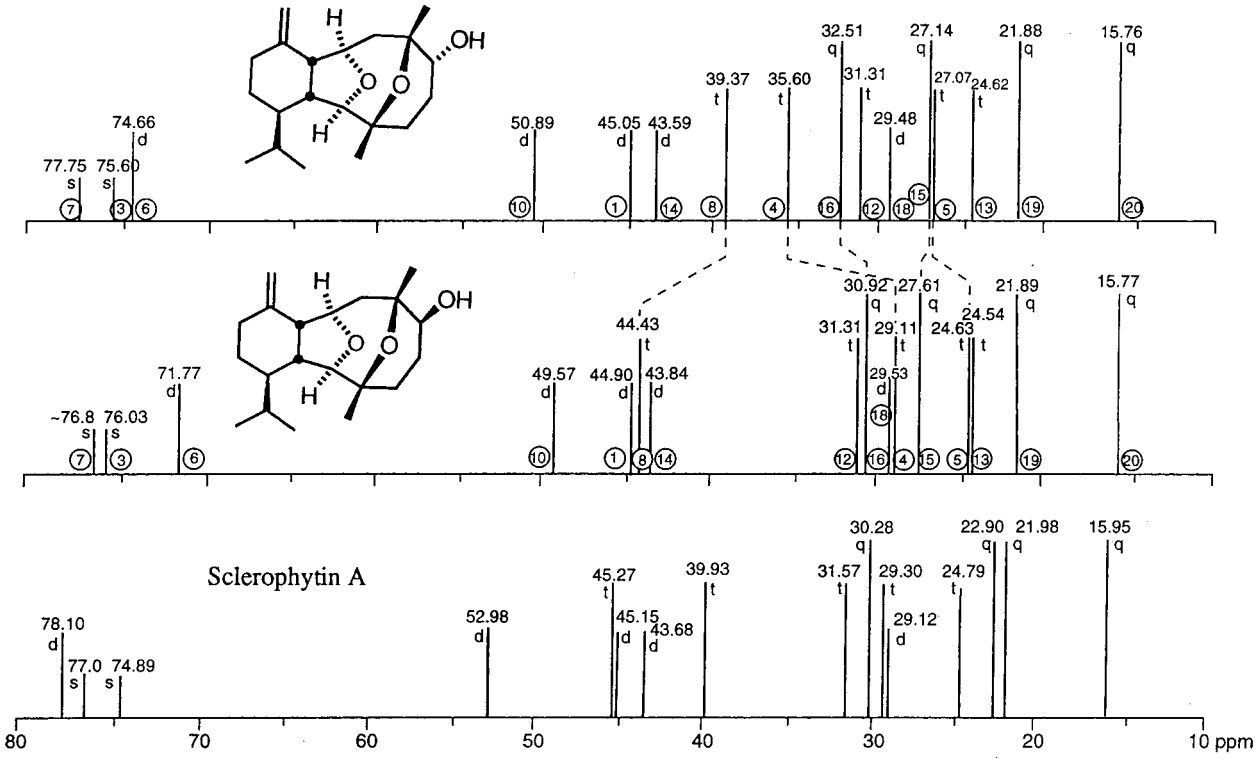


Figure 2. Comparison of the high-field sectors of the ^{13}C NMR spectra of alcohols **5** and **60** with that of authentic sclerophytin A (150 MHz, $CDCl_3$).

the stage for transannularly assisted cleavage of the oxirane ring. Proper alignment of the nucleophilic hydroxyl requires some degree of conformational rotation about the C3−C4 (and other) bonds. The net consequences of this sequence of events are the installation of two ether oxygen bridges having a syn relationship and the presence of a β-hydroxyl at C6.

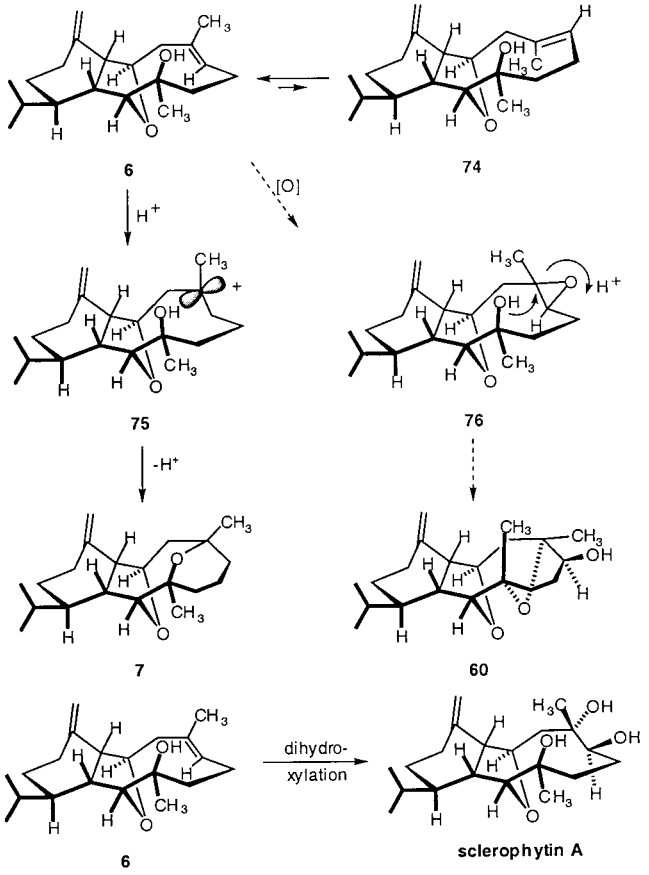
However, no substance of type **5** has yet been isolated and correctly identified.

Accordingly, no evidence exists to support the epoxidative pathway. The possibility does exist that a dihydroxylative option transforms **6** into sclerophytin A. In this case, exo attack would directly set the diol configuration at C6 and C7.

The synthetic strategy developed in the present investigation involves intermediates characterized by a cis C6/C7 double bond. Oxymercuration likewise proceeds from exterior attack on this π-surface with subsequent intramolecular backside attack. Adherence to this mechanistic paradigm serves to invert the absolute configuration at C6. With these facts now deduced, it remains to determine why Nature does not opt to proceed via **76** to **5**.

Access to Authentic Sclerophytins A and B. A detailed reexamination of sclerophytin B by NMR[56a] has resulted in revised structural assignments for sclerophytins A and B. In light of this critical study, the structural motif resident in **52** was considered to be well suited to a targeted synthesis of both **84** and **85**. Therefore, this functionalized cycloalkene was subjected to dihydroxylation. Under conditions involving catalytic quantities of OsO_4 with NMO as the stoichiometric reagent,

Scheme 13



overoxidation occurred, and the products proved difficult to separate. Attempts to control the stereochemical outcome with the AD-mix formulations[65] led to anticipated results. While the β-reactant gave rise predominantly to **78**, the α-form led to no visible reaction. In the final analysis, recourse was made to the use of a molar equivalent of OsO_4, since it furnished diols **77** and **78** efficiently in a 1:1.5 ratio (Scheme 14). The reversed bias observed above during the epoxidation of related systems is noted. The ease of chromatographic separation of **77** from **78** and their concomitant production in reasonable amounts ultimately made possible the acquisition of all four possible sclerophytin-like triols. The important distinction between **77** and **78** rests on NOESY measurements performed on both diastereomers. In particular, the strong correlation noted for **78**, but absent in the spectra of **77**, defined rather unequivocally the configuration at C-7.

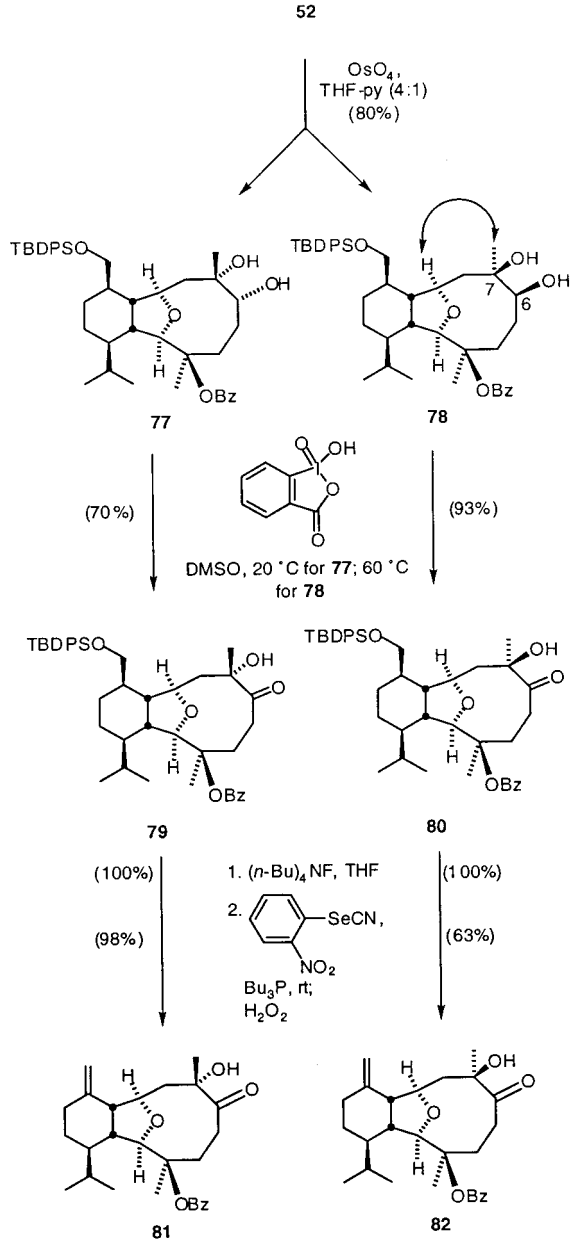
The oxidation of these diols to their respective α-hydroxy ketones **79** and **80** was satisfactorily accomplished in DMSO with *o*-iodoxybenzoic acid (IBX), a reagent purported to lack the capability of engaging in cleavage of the glycolic C−C bond.[66] This reaction serves two purposes. First, it sets the stage for intentional introduction of the hydroxyl configuration at C-6 in the final synthetic targets. Second, one gains the tactical advantage of "protecting" the C-6 hydroxyl, since this functionality, if left unmasked, is not compatible with the ensuing dehydration in ring A.[67]

(65) (a) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org Chem.* **1992**, *57*, 2768.

(66) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(67) Gallou, F. unpublished findings.

Scheme 14



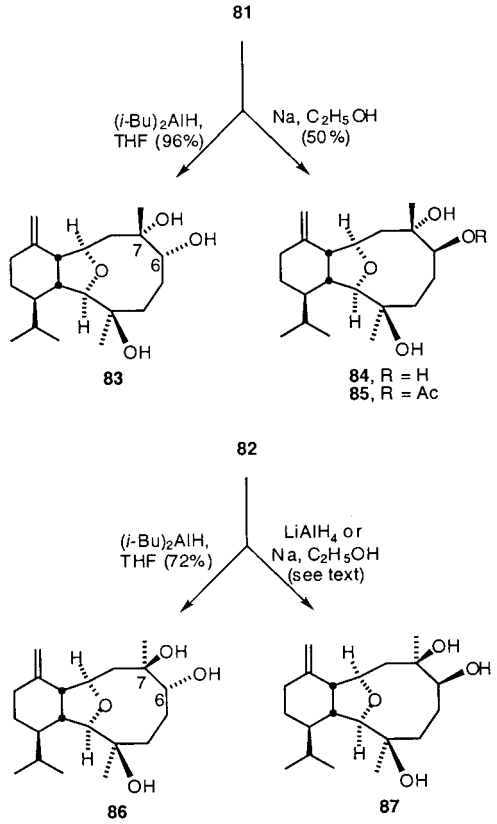
Following the desilylation of **79** and **80**, the resulting diols were carried directly into the Grieco process.[68] While both substrates formed the *o*-nitrophenylselenide at roughly comparable rates, the relative ease of selenoxide elimination proved to be markedly distinctive. When the C-7 hydroxyl configuration was β as in **80**, several hours at room temperature were sufficient to introduce the exocyclic double bond in **82** (63%). Placement of the remote C-7 hydroxyl on the α-surface eventuated instead in the formation of an appreciably more stable selenoxide intermediate. Overnight heating at 50 °C furnished **81** with enhanced efficiency (98%).

The final transformations, removal of the benzoate functionality and reduction of the ketone carbonyl, were expected to be accomplishable in a single laboratory operation (Scheme 15). The use of diisobutylaluminum hydride for this purpose resulted in the conversion of **81** to the *cis*-α-triol **83,** and of **82** to the

(68) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(69) Results in square brackets obtained from NOED and sel-TOCSY experiments.

Scheme 15



trans-triol **86**. Consequently, this reagent attacks from the β-direction irrespective of the hydroxyl configuration preexisting at C-7. This is not so with lithium aluminum hydride. In this case, **81** is again transformed into **83** while **82** leads to **87**. However, the yields are less satisfactory and studies involving this reagent were discontinued, although the consequences of kinetic control when **81** is involved were already quite apparent. For this reason, we turned to sodium in ethanol, a dissolving metal process recognized for its ability to proceed via thermodynamic control. Indeed, these conditions resulted in the introduction of a β-hydroxyl at C-6 in both stereoisomeric series, with **81** giving rise to authentic sclerophytin A (**84**).

The polarities of the four end products hold interest. In the 7α-OH subset, sclerophytin A (**84**) is more polar than epimer **83**. This trend is reversed in the 7β-OH series, with *cis*-isomer **87** being more polar than its *trans* counterpart **86**. Thus, the 6β-OH (2°) compounds are the more polar irrespective of 7-OH (3°) configuration.

The synthetic **84** generated in this investigation was spectroscopically identical to the original isolate in every detail. In addition, its optical rotation, $[\alpha]^{D}_{20}$ −2.7 (*c* 0.11, $CHCl_3$) was weakly negative in a manner similar to that recorded for the authentic material, $[\alpha]^{D}_{20}$ −6.9 (*c* 0.087, $CHCl_3$). This evidence, together with the ease with which **84** can be acetylated to give sclerophytin B (**85**), reduces the known existence of any octocoral-derived 2,11-cyclized cembranoids that contain two ether bridges to a very small number. Furthermore, **83**, **86**, and **87** are not identical to any other reported sclerophytin or analogue thereof. In the least, they have not yet been uncovered.

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Supporting Information Available: Experimental procedures and spectral characterization of all intermediates and particularly synthetic and natural sclerophytins A and B, together with detailed structural mapping of ketone **61** and alcohols **5** and **60** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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