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Total Synthesis of the Purported Structure of Sclerophytin F

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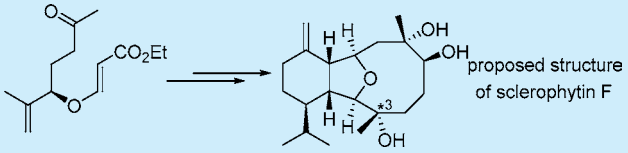
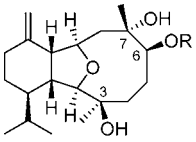
Supporting Information

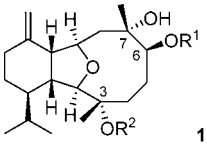
ABSTRACT: The synthesis of the compound that has been proposed to be the natural product sclerophytin F has been completed from a known vinylogous carbonate. The synthetic strategy relied upon rearrangement of a catalytically generated ylide-like intermediate to produce an oxabicyclo[6.2.1]-5-undecen-9-one and an intermolecular Diels–Alder reaction to construct the complete tricyclic core found in the natural product. Comparison of the spectroscopic data for synthetic material to that reported for sclerophytin F shows that the natural product does not have the revised structure possessing the 3*S* configuration (*) proposed previously.



The sclerophytins are polyoxygenated diterpenes of the cladiellin family of marine natural products.[1] The first members to be isolated and identified were sclerophytins A and B, which were first reported by Sharma and Alam in 1989.[2] Sclerophytin A was found to be cytotoxic with activity of 1 ng mL^{-1} against the L1210 cell line.[2] Sharma and Alam proposed that sclerophytins A and B were doubly ether-bridged compounds, but subsequent synthetic studies by the groups of Paquette and Overman demonstrated that the originally proposed structures were incorrect and that sclerophytin A is the triol **1** and sclerophytin B is the C-6 acetate **2** (Figure 1).[3,4]



1 R = H sclerophytin A
2 R = Ac sclerophytin B
3 R = Me sclerophytin F methyl ether
4 R = Et patagonicol



5 R^1 = H R^2 = Ac sclerophytin E
6 R^1 = H R^2 = H sclerophytin F
7 R^1 = H R^2 = CO*n*-Pr litophynin E
8 R^1 = Ac R^2 = CO*n*-Pr 6-acetoxy litophynin E
9 R^1 = Et R^2 = Ac 6-ethoxy sclerophytin E
10 R^1 = CO*i*-Bu R^2 = Ac 6-isovaleroyl sclerophytin E

Figure 1. Members of the sclerophytin family of cladiellin diterpene natural products.

Several other sclerophytins have been isolated (**3**–**10**, Figure 1).[5] The structures of many of these compounds were deduced by comparison of NMR data to that of sclerophytins A and B, but unfortunately they were predicated on the basis of incorrect structures assigned to sclerophytins A and B by Alam et al.[2] The exceptions to this are sclerophytin F methyl ether (**3**) and patagonical (**4**) (Figure 1), the structures of which were confirmed by X-ray crystallography.[5b,c]

In an attempt to resolve apparent inconsistencies in the structural assignments for some of the sclerophytins, Friedrich and Paquette reviewed and reanalyzed all of the spectroscopic and other data for these compounds in 2002.[6] They concluded that there are in fact two series of compounds with opposite stereochemistry at C-3 and reassigned the structures of sclerophytins E and F (**5** and **6**), litophynin E (**7**), and the 6-substituted derivatives (**8**–**10**) to have the *S* configuration at the C-3 position, as shown in Figure 1.

Sclerophytin F (**6**) was isolated from the soft coral *Sclerophytum Capitalis* and identified by Alam et al. in 1989 (Figure 1).[5a] If the structural reassignments made by Friedrich and Paquette in 2002 are correct,[6] triol **6** is a particularly important compound because it should be possible to prepare all of the other sclerophytins having the *S* configuration at C-3 (**5** and **7**–**10**, Figure 1) from this compound. Consequently, sclerophytin F became the primary target in our quest to establish the structures of members of the sclerophytin family of natural products unambiguously by direct synthesis.

Recently we reported the total syntheses of 10 cladiellin natural products, all of which have the *R* configuration at C-3.[7] We expected that a parallel synthetic strategy could be developed for the construction of sclerophytin-type cladiellin natural products having the *S* configuration at the C-3 stereocenter. We therefore decided to test our hypothesis by undertaking the total synthesis of the proposed structure of sclerophytin F (**6**) with the expectation that we would be able access the natural products **5** and **7**–**10** from the triol thereafter.

The retrosynthetic analysis of the proposed structure of sclerophytin F (**6**) is shown in Scheme 1. Replacement of the C-6 and C-7 hydroxyl groups with an alkene along with trialkylsilyl protection of the C-3 hydroxyl group gives diene **i**. Disconnection through the exocyclic alkene and removal of a methyl group from the isopropyl substituent leads to the diketone **ii**, and conversion of the cyclic ketone into an enol ether gives the tricyclic ether **iii**. Diels–Alder disconnection of

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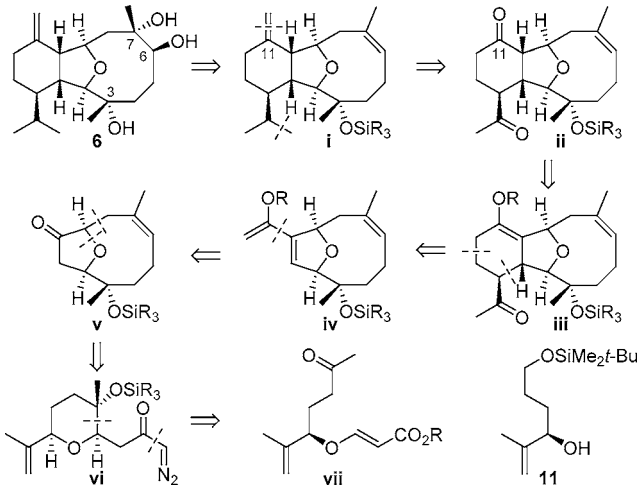
Scheme 1. Retrosynthetic Analysis of Sclerophytin F (6)



the cyclohexenyl ring in **iii** reveals the bicyclic triene **iv**. Subsequent disconnection through the conjugated alkoxy diene of **iv** reveals the bridged-bicyclic ketone **v** which in turn suggests the diazo ketone **vi** as a precursor. Further disconnections of the diazo ketone and the tetrahydropyran then lead to the vinylogous carbonate **vii**, which is analogous to intermediates used in our previous syntheses of cladiellin natural products.[7]

The novelty of the synthetic route implied by the retrosynthetic analysis shown in Scheme 1 stems from the installation of the C-3 methyl substituent at an early stage. In the case of our total syntheses of sclerophytins A and B, which have the *R* configuration at C-3, this methyl group was introduced stereoselectively at a very late stage in the synthesis. In the proposed synthesis, the C-3 methyl group would be introduced prior to formation and rearrangement of the carbenoid-derived ylide equivalent to deliver the bicyclic ketone **v**. In adopting this approach, we were aware that intermediates might behave differently in the key reaction,[7] leading to inferior yields and/or levels of diastereocontrol, and so it might be necessary to deploy completely new transformations to circumvent problems if they were to arise.

The vinylogous carbonate **12** (91−96% ee) was prepared in large quantity from the known alcohol **11**, as reported previously.[7] The alcohol **12** was converted into the aldehyde **13** by Swern oxidation (Scheme 2). Treatment of the aldehyde **13** with trimethylaluminum and Swern oxidation of the resulting alcohol delivered the methyl ketone **14**. Reductive cyclization of the ketone **14** mediated by SmI_2 then furnished an inseparable mixture (12:1) of two diastereomeric (at the 2-position) tetrahydropyranols, with the required isomer **15** predominating.[8] The diastereomers were separated by chromatography following protection of the tertiary alcohol as its *tert*-butyldimethylsilyl ether. Sequential ester cleavage, conversion of the carboxylic acid into an anhydride, and treatment with diazomethane delivered the key *α*-diazo ketone **17**.

The metal-mediated cyclization and ring-expanding rearrangement of the *α*-diazo ketone **17** to give the isomeric bridged bicyclic ethers ***E*-18** and ***Z*-18** could now be explored (Table 1). In previous work, we had investigated the metal-catalyzed reactions of the tetrahydropyranyl-substituted *α*-diazo ketone lacking a methyl substituent on the ring.[7] This work had shown that it is possible to tune the reaction to give

Scheme 2. Synthesis of *α*-Diazo Ketone 17

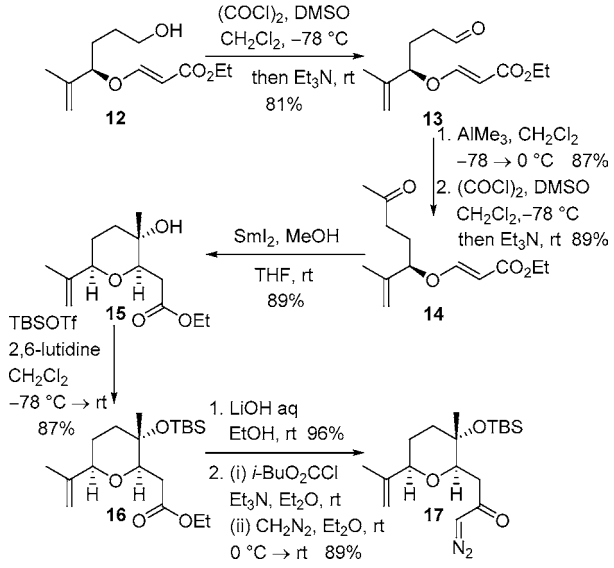
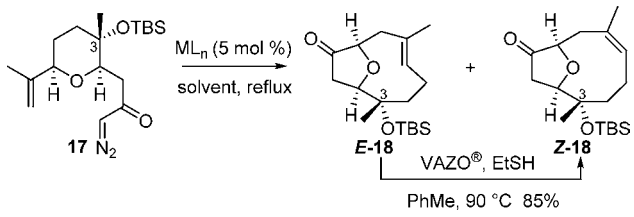


Table 1. Metal-Catalyzed Conversion of *α*-Diazo Ketone 17 into the Bridged-Bicyclic Ethers *E*- and *Z*-18



entry	catalyst	solvent	yield (%)[a]	*Z*:*E* ratio[b]
1	$Cu(hfacac)_2$	CH_2Cl_2	98	1.8:1
2	$Cu(hfacac)_2$	THF	71	1:1
3	$Cu(hfacac)_2$	PhMe	49	3:1
4	$Cu(acac)_2$	CH_2Cl_2	–	–
5	$Rh_2(OAc)_4$	CH_2Cl_2	42	7.9:1
6	$Rh_2(tpa)_4$	CH_2Cl_2	14	*Z* only
7	$Rh_2(pfm)_4$	CH_2Cl_2	61	5:1
8	$Rh_2(pfm)_4$	PhMe	31	8:1
9	$Rh_2(pfm)_4$	THF	31	*Z* only

[a]Combined isolated yield of ***E*-18** and ***Z*-18**. [b]Isomer ratios determined by ^1H NMR prior to purification. For the Rh-catalyzed reactions, filtration on alumina was done prior to NMR analysis.

predominantly the *E* or *Z* bridged-bicyclic ether product, resulting from rearrangement of an ylide-like intermediate, by altering the catalyst (ligand and/or metal) or the solvent.[9]

Various potential catalysts for the conversion of the *α*-diazo ketone **17** into the isomeric bridged bicyclic ethers ***E*-18** and ***Z*-18** were investigated, and several solvents were also screened (Table 1). The catalyst-dependence of the reaction was first probed using a variety of copper and rhodium complexes in dichloromethane at reflux. The best balance between the isomer ratio and product yield was obtained when either $Cu(hfacac)_2$ or $Rh_2(pfm)_4$ was employed as the catalyst. The use of a nonpolar solvent such as toluene resulted in an increase of the isomer ratio (favoring the *Z* isomer), but also resulted in a significant reduction in yield. An interesting observation was made when the reaction was performed in THF at reflux: the use of the copper catalyst delivered a 1:1 mixture of the products ***E*-18** and ***Z*-18**, but the *Z* isomer was obtained

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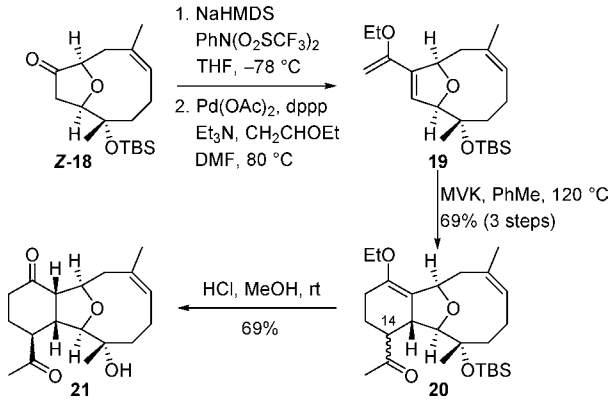
exclusively when a rhodium catalyst was employed. However, in this case the product yield for the rhodium-catalyzed reaction was inferior to that of the copper-catalyzed reaction. Interestingly, the highest yielding copper-catalyzed reactions were the least diastereoselective (entries 1 and 2, Table 1), but fortunately it was possible to isomerize the ketone ***E*-18** to give ***Z*-18** using a mixture of VAZO and a substoichiometric amount of ethanethiol in toluene.[10] In this way, the bicyclic ketone ***Z*-18** was obtained in an overall yield of 83% over two steps without intermediate purification.

The results from catalyst screening experiments demonstrate that the presence of the methyl substituent on the ring of the substrate **17** has a profound influence on the stereochemical outcome of the key cyclization reaction. In no case could the *E* isomer be obtained as the major product, a finding that contrasts with what had been observed during cyclization of the substrate lacking the methyl substituent on the ring, where the corresponding *E* isomer could be obtained as the major product simply by using an appropriate rhodium catalyst.[7a]

The next challenge was construction of the complete tricyclic core of sclerophytin F (Scheme 3). To this end, the ketone ***Z*-**

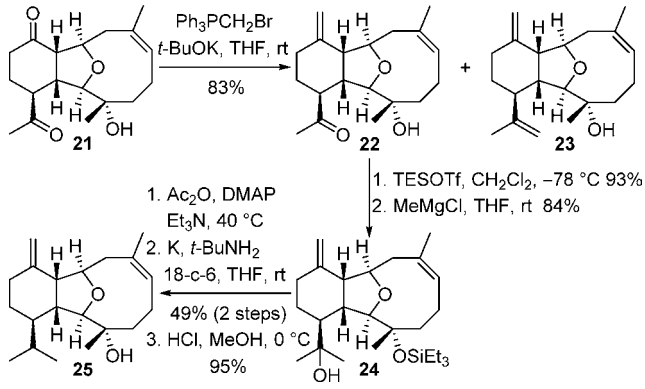
Scheme 3. Construction of the Tricyclic Core



18 was converted into an enol triflate that was then subjected to Heck coupling[11] with ethyl vinyl ether to give the diene **19**. Intermolecular thermal Diels–Alder cycloaddition of the diene **19** with methyl vinyl ketone in a sealed tube afforded the tricyclic enol ether **20** as a mixture (1:1) of *exo* and *endo* diastereomers (at C-14). Attempted base-mediated epimerization adjacent to the methyl ketone failed, probably as a consequence of the bulky C-3 silyloxy group blocking access to the proton at C-14, and so the TBS protecting group was removed in order to facilitate epimerization. Pleasingly, one-pot hydrolysis of the enol ether, cleavage of the silyl ether, and epimerization at C-14 were observed upon treatment of tricyclic enol ether **20** with hydrochloric acid. The solid diketone **21** was obtained as a single diastereomer in good yield, and the relative stereochemistry was confirmed by X-ray analysis.[12]

Further functionalization of the tricyclic core structure was necessary to install the required substituents. Selective Wittig methylenation of the diketone was possible, furnishing a separable mixture (5:1) of the methyl ketone **22** and the double methylenation product **23** (Scheme 4). Protection of the tertiary alcohol as a TES ether followed by treatment of the methyl ketone with MeMgCl afforded the tertiary alcohol **24**. The hydroxyl group was then removed by acetylation of the alcohol and treatment of the resulting acetate with potassium in

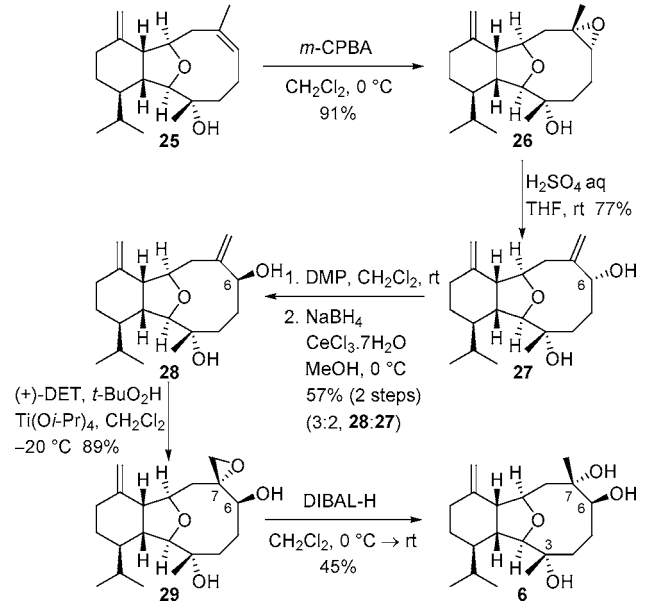
Scheme 4. Synthesis of the Tertiary Alcohol 25



the presence of [18]crown-6 and *t*BuNH$_2$ in THF, following a procedure described by Barton et al. and used by us and by Kim et al. during the synthesis of related cladiellin natural products.[7,13] Finally, the silyl ether was cleaved under aqueous acidic conditions to deliver the advanced intermediate **25**.

The oxygen functionality at C-6 was introduced by subjecting the diene **25** to regio- and stereoselective epoxidation using *m*-CPBA (Scheme 5). Treatment of the resulting epoxide **26** with

Scheme 5. Completion of the Synthesis of the Proposed Structure of Sclerophytin F (6)



aqueous H_2SO_4 resulted in rearrangement to give the allylic alcohol **27** with the *R* configuration at C-6.[14] A two-step oxidation–reduction sequence was then employed to invert the configuration of the stereocenter at C-6 and deliver the diol having the *S* configuration at this position, as proposed for sclerophytin F. Luche reduction of the enone, produced by Dess-Martin oxidation of the allylic alcohol **27**, delivered a separable mixture (3:2) of diastereomeric alcohols **28** and **27**. Finally, the C-7 hydroxyl group was introduced by using a Sharpless asymmetric epoxidation reaction to afford the crystalline epoxide **29**, the structure of which was confirmed by X-ray crystallography (Figure 2). Reductive opening of this epoxide at the terminal position using DIBAL-H then delivered

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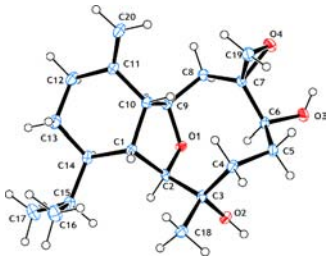

Figure 2. X-ray crystal structure of the epoxide **29**.

the triol **6**, which corresponds to the structure of sclerophytin F that had been proposed by Friedrich and Paquette.[6]

Although the $[\alpha]_D$ for the synthetic triol **6** was in close agreement with that reported for sclerophytin F, the ^1H and ^{13}C NMR data for the two compounds were significantly different.[15] This finding demonstrates that the relative configuration at one or more of the stereogenic centers (C3, C6, or C7) has been reassigned incorrectly by Friedrich and Paquette.[6]

The first synthesis of the proposed structure of sclerophytin F has been achieved in 24 steps from the known enantioenriched alcohol **12**. The strategy developed in our laboratory has now proved to be efficient for the synthesis of cladiellin systems having either the *S* or *R* configuration at C-3. The introduction of the C-3 methyl group early in the synthesis has influenced several key steps such as the rearrangement of the ylide-like intermediate as well as the epimerization at the C-14 position. Spectroscopic data for the final triol **6** does not correspond to those reported for sclerophytin F, and so the structure of the natural product proposed by Friedrich and Paquette is clearly incorrect. We are currently in the process of synthesizing the three other triols that are diastereomeric at positions C-6 and C-7. The syntheses of these compounds and their relationship to sclerophytin F will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details plus spectroscopic and other data for compounds **14**–**29** and **6**, plus X-ray data (CIF files) for diketone (±)-**21**, diol **27**, and epoxide **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(12) Crystals of racemic diketone **21** suitable for X-ray diffraction could be obtained, allowing confirmation of the relative stereochemistry. Nonracemic **21** having a high ee did not deliver crystalline material suitable for X-ray analysis.

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(14) X-ray crystallography confirmed the stereochemistry of the diol **27**. See Supporting Information.

(15) Differences between ^{13}C NMR data for sclerophytin F and triol **6** were particularly obvious. The ^{13}C NMR signals reported for the natural product and their deviation from those of triol **6** are as follows: ($CDCl_3$) δ 147.6 (+1.5), 109.3 (+1.4), 91.9 (+4.9), 86.6 (+9.2), 80.1 (+4.7), 78.2 (+3.1), 77.0 (+3.1), 52.9 (+5.1), 45.8 (+0.6), 45.4 (+3.1), 43.9 (+3.4), 35.9 (+2.7), 31.4 (+1.1), 30.5 (+0.7), 29.1 (−0.3), 24.7 (−3.8), 23.2 (−1.6), 22.3 (−0.4), 21.9 (−0.3), 15.7 (−5.0).

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