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Concise Syntheses of the Natural Products (+)-Sylvaticin and (+)-*cis*-Sylvaticin

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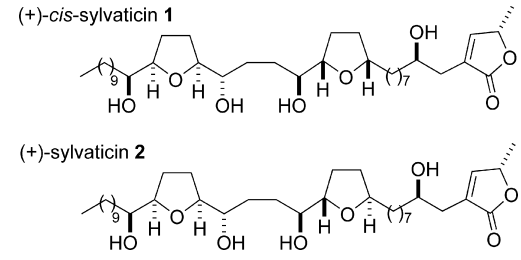
Abstract: Two concise syntheses of the natural products *cis*-sylvaticin and sylvaticin are reported, using oxidative cyclization methodology as the key step. A sequential solvolysis/hydride shift/intramolecular reduction cascade was used to establish the *trans* stereochemistry of one of the THF rings of sylvaticin.

Introduction

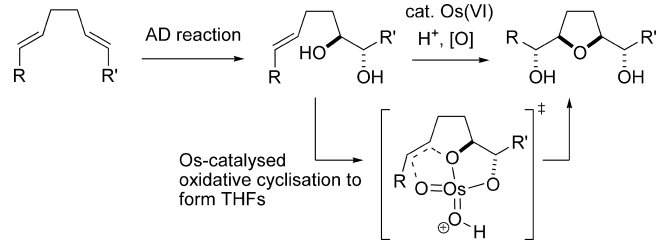
Sylvaticin and its C-12 epimer *cis*-sylvaticin belong to the nonadjacent bis-THF subclass of the annonaceous acetogenins. Sylvaticin was isolated by McLaughlin in 1990 from the dried fruits of *Rollinia sylvatica* St. Hil. (Annonaceae).[1] Subsequent isolations were reported in 1993 from *Annona purpurea* and in 1995 when it was isolated from leaf extracts of *Rollinia mucosa* (Jacq.) Baill. together with *cis*-sylvaticin, bullatalicin, and muricatetrocin B.[2,3] Both *cis*-sylvaticin and the parent sylvaticin display potent activity as antitumor agents and exhibit nanomolar cytotoxicity toward certain human solid tumor cell lines (human lung carcinoma and human pancreas carcinoma). Their mode of action is thought to include the inhibition of ATP production *via* the blockage of mitochondrial complex I. The biosynthesis of these acetogenins is thought to start from a long chain fatty acid with the terminal γ-lactone functionality initially formed with the nonadjacent bis-THF core then generated by oxidation of the unsaturated units present followed by a series of ring-opening and closing reactions.[4]

Both natural products **1** and **2** contain two nonadjacent THF rings, with sylvaticin bearing the only *trans*-ring. One THF is flanked on either side by a hydroxyl group and an alkyl chain, and the second is flanked by one hydroxyl group and an alkyl chain ending in a γ-lactone functionality with a hydroxyl group at the C-4 position (see Scheme 3 for numbering). At the outset of this work, the structures of **1** and **2** had not been verified by total synthesis, although the group of McLaughlin had performed an extremely thorough analysis of both compounds in the original isolation paper.[3] McLaughlin had also shown the precise positions of the two THF rings (and the hydroxyl groups) by EIMS of the natural products and their TMS derivatives. The relative and absolute stereochemistry was determined by various NMR techniques developed for these acetogenins and included a full analysis of their di- and tetra-Mosher ester derivatives, and the structures were finally assigned as shown in Scheme 1.

Scheme 1



Scheme 2



Previous work in our group culminated in the first synthesis of (+)-*cis*-sylvaticin in 2006;[5] with Brown and co-workers subsequently reporting a synthesis of this natural product in

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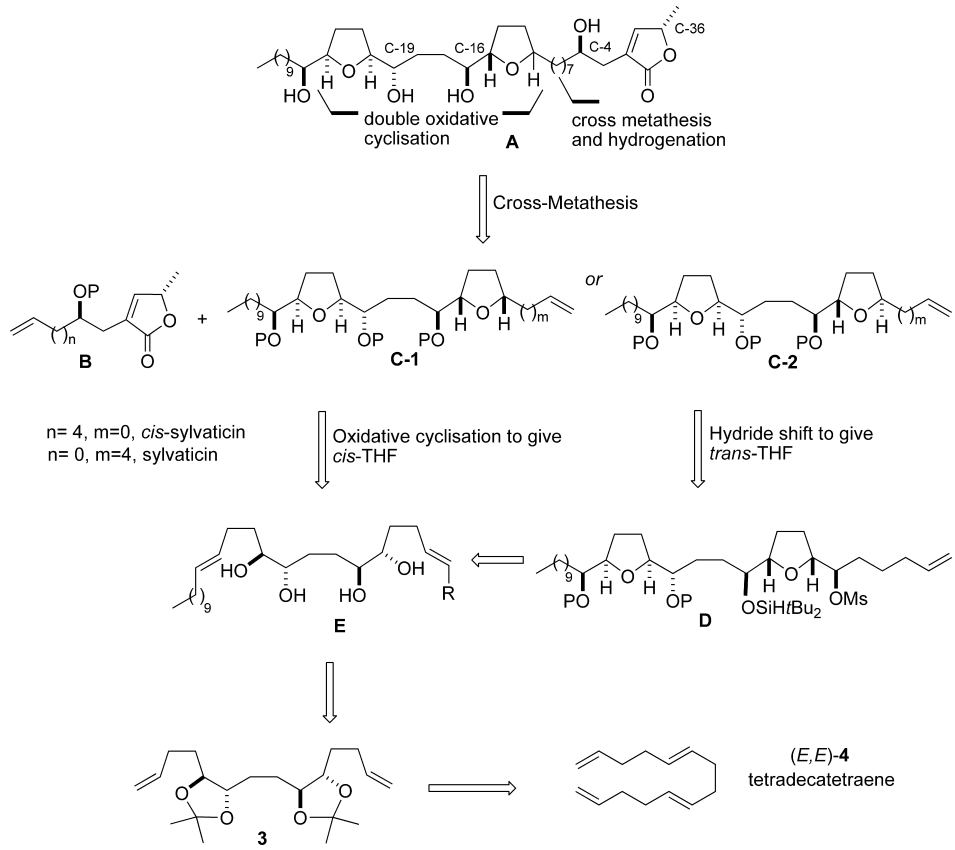
(1) Mikolajczak, K. J.; Madrigal, R. V.; Rupprecht, J. K.; Hui, Y. H.; Liu, Y. M.; Smith, D. L.; McLaughlin, J. L. *Experentia* **1990**, *46*, 324.
(2) Felicitas Cepleanu, K. O.; Hamburger, M.; Hostettmann, K.; Gupta, M. P.; Solis, P. *Helv. Chim. Acta* **1993**, *76*, 1379.
(3) Shi, G.; Zeng, L.; Gu, Z.; MacDougal, J. M.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1785.
(4) For a review see (a) Bermejo, A.; Figadére, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. (b) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1992**, *62*, 504. (c) Rupprecht, J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (d) Saez, J.; Sahpaz, S.; Villaescusa, L.; Hocquemiller, R.; Cavé, A.; Cortes, D. *J. Nat. Prod.* **1993**, *56*, 351. (e) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087. (f) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275.
(5) Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704.

10.1021/ja9049959 CCC: $40.75

Scheme 3



2008.[6] In both cases, the data from the synthetic sample exactly matched those of the natural product, thus confirming that the original assignment was correct. In addition, there are other key syntheses of related nonadjacent bis-THF annonaceous acetogenins reported in the literature.[7] Herein, we describe a full account of our studies which led to the preparation of (+)-*cis*-sylvaticin **1**, and we also report the first total synthesis of the parent natural product sylvaticin **2**.

Results and Discussion

Our strategy for forming the THF rings of these natural products relied upon the intramolecular oxidative cyclization reaction of vicinal diols onto alkenes to form *cis*-THF rings, using osmium(VI) as a catalyst and an acid as the promoter.[8] This methodology has proven to be an extremely reliable route to THFs, proceeding with complete stereospecificity for *syn*-addition across the alkene and also high stereoselectivity for the formation of *cis*-2,5-THFs, Scheme 2. Preparation of the starting diols as single enantiomers (and diastereoisomers) is readily achieved by a Sharpless AD reaction[9] of the corresponding diene. Following this AD sequence with an oxidative cyclization allows the preparation of *cis*-THFs with a high degree of control over all aspects of stereochemistry.

The three rings and nine stereocenters of *cis*-sylvaticin **1** and sylvaticin **2** pose an interesting synthetic challenge with the core *bis*-THFs of particular interest. It was proposed that this key segment **C** of both natural products could be synthesized in a very concise manner using a novel bis-oxidative cyclization reaction to introduce the two *cis*-THF rings (see **E**→**C-1**, Scheme 3). While this approach would be ideal for the construction of *cis*-sylvaticin directly, we were also intrigued by the possibility of using our recently developed hydride-shift/intramolecular reduction methodology (see **D**→**C-2**, Scheme 3) to construct the *trans*-THF ring of sylvaticin from a *cis*-THF precursor[10] and therefore enable the completion of both natural product syntheses *via* a single strategy.

In both cases, we anticipated using the reliable cross-metathesis (CM) chemistry[11] to attach the butenolide portion **B** to the bis-THF unit, as had been previously described by Lee,[12] which would allow completion of the syntheses. Analysis of likely synthetic routes meant that we were required to disconnect the chain linking the THF rings to the butenolides in different places during approaches to sylvaticin and *cis*-sylvaticin. However, it was decided that an *E,E*-tetradecatatraene

(6) Brown, L. J.; Spurr, I. B.; Kemp, S. C.; Camp, N. P.; Gibson, K. R.; Brown, R. C. D. *Org. Lett.* **2008**, *10*, 2489.

(7) (a) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 4247. (b) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066. (c) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998**, *54*, 6329. (d) Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475. (e) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154. (f) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (g) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383.

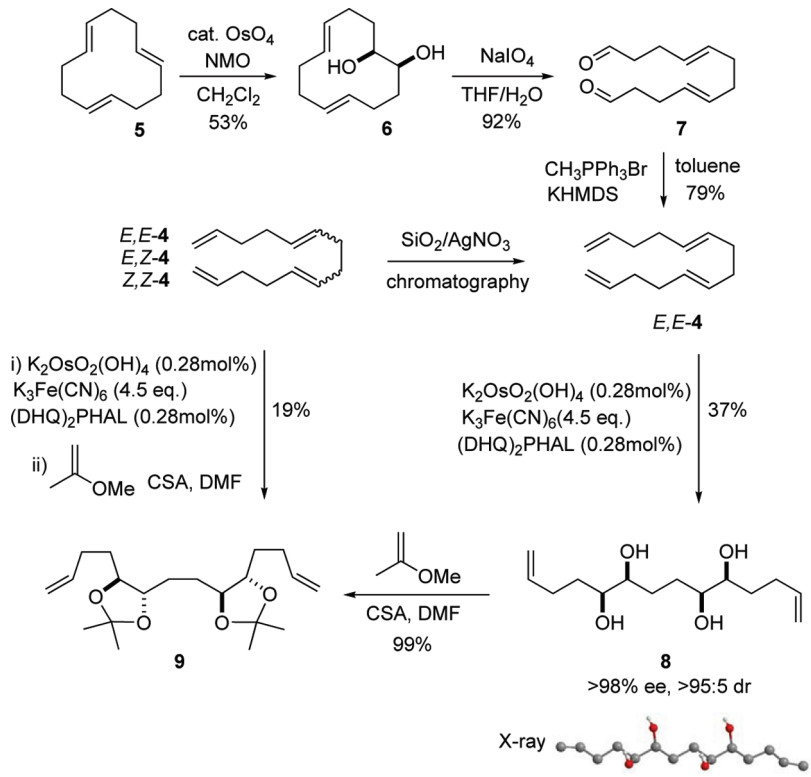
(8) (a) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 948. (b) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766. (c) Donohoe, T. J.; Churchill, G. H.; Wheelhouse (neé Gosby), K. M. P.; Glossop, P. A. *Angew. Chem., Int. Ed* **2006**, *45*, 8025. (d) Donohoe, T. J.; Wheelhouse (neé Gosby), K. M. P.; Lindsay-Scott, P. J.; Glossop, P. A.; Nash, I. A.; Parker, J. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2972.

(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(10) Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869.

(11) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

Scheme 4



(*E*,*E*-**4**) would serve as a useful starting material for both natural products syntheses. We would seek to perform regioselective AD reactions on the two internal alkene units of **4** before desymmetrizing the system by distinguishing between the two ends of the molecule.

Asymmetric Dihydroxylation of Tetraenes. The first step in the synthesis requires the asymmetric dihydroxylation of *E*,*E*-tetradecatetraene **4**. 1,5,9,13-Tetradecatetraene is commercially available but only as an approximately 1:1:1 mixture of the three possible geometric isomers, Scheme 4. Fortunately the isomers could be separated by chromatography on silica gel doped with $AgNO_3$ to yield pure *E*,*E*-1,5,9,13-tetradecatetraene, *E*,*E*-**4**. The isolated tetradecatetraene was confirmed as the *E*,*E*-isomer by the synthesis of authentic *E*,*E*-1,5,9,13-tetradecatetraene from *E*,*E*,*E*-cyclododecatriene **5** in three steps. Both sets of materials and a mixture of the two had identical NMR data.

Asymmetric dihydroxylation of *E*,*E*-**4** using $(DHQ)_2PHAL$ as the chiral ligand led to the formation of desired tetraol **8** in 37% yield, >98% ee, >95:5 dr (Scheme 4). The ee and dr were ascertained by tetra-Mosher ester formation from authentic standards of both the enantiomer of **8** (made using DHQD ligand) and the meso-tetraol (made by sequential mono-AD using DHQD and then with DHQ). The absolute stereochemistry of tetraol **8** was assigned by using the Sharpless mnemonic.[9]

Finally, an X-ray crystal structure of tetraol **8** authenticated its relative stereochemistry, Scheme 4.[13] The tetraol **8** was readily transformed into bis-acetonide **9** by reaction with vinyl-methyl ether and CSA in DMF.

The outcome of the AD reaction has its origins in the preferential oxidation of 1,2-*trans* alkenes over monosubstituted alkenes. Based upon Sharpless's rate data, a selectivity of approximately 7:1 can be expected.[12] Calculations can predict the maximum yield for the dihydroxylation of the two *trans* alkenes in *E*,*E*-**4**, assuming this 7:1 rate difference, and also that the second oxidation proceeded with the same regioselectivity as that of the first. The calculation showed a maximum theoretical yield of 42% for the formation of **8** which is close to the 37% achieved in practice.

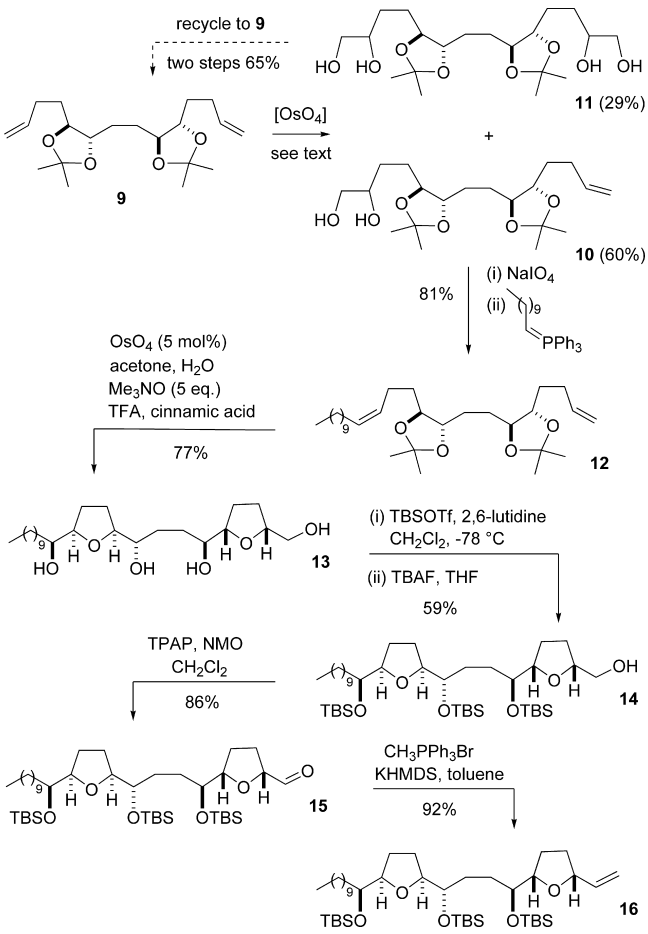
After the success of the selective double dihydroxylation, the commercially available mixture of tetradecatetraenes was subjected to the AD conditions, in the knowledge that *cis*-alkenes are dihydroxylated approximately 11 times slower than *trans* alkenes.[14] In this case the desired tetraol **8** was again isolated although the compound could not be fully purified until it was derivatized as bis-acetonide **9** (19% yield over the two steps, starting with 25 g of tetraene) which was identical to that prepared from the pure *E*,*E*-isomer of **4**. In practice, this route

(12) (a) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396. (b) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991. (c) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876. (d) Avediaaian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.

(13) Diffraction data were collected at 150 K using a Nonius Kappa-CCD area detector diffractometer ($\lambda = 0.710\,73$ Å). Cell parameters and intensity data were processed using the DENZO-SMN package (Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods in Enzymology*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: 1997; p 276), and reflection intensities were corrected for absorption effects by the multiscan method. The structures were solved by direct methods (Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122) and refined by full-matrix least squares on F using the CRYSTALS suite (Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487. Tetrgonal, $P4_12_12$; $a = 19.4191(2)$ Å, $c = 16.2612(2)$ Å, $V = 6132.12(12)$ Å^3; $Z = 16$; Data/restraints/parameters = 3090/108/413 ($R_{int} = 0.043$); R1 = 0.0365, wR2 = 0.0468 [$I > 3\sigma(I)$]. Full crystallographic results can be found in the CIF (Supporting Information). CCDC 736594.

(14) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.

Scheme 5

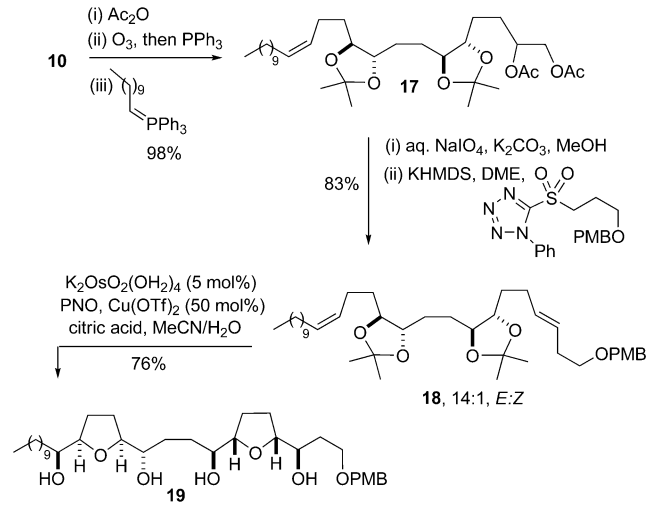


starting from the mixture of geometric isomers was used to provide material for the ensuing syntheses.

Desymmetrization and Oxidative Cyclization. The C_2 symmetrical bis-acetonide **9** was then desymmetrized by oxidation of one of its two alkene units; this was achieved by subjecting **9** to dihydroxylation conditions. However, due to the homotopic nature of the two alkenes, standard dihydroxylation conditions led to a statistical mixture of the desired compound **10**, starting material **9**, and the doubly dihydroxylated compound **11**. It was found that the yield of **10** could be increased to 60% under asymmetric dihydroxylation conditions at 0 °C. This increase in yield is likely to be due to the differential product solubility in the biphasic solvent system of the AD reaction rather than by asymmetric induction. The tetraol byproduct **11** could be recycled to **9** in 65% yield over two steps by oxidative cleavage of the two diol units to yield a bis-aldehyde followed by bis-methylenation (Scheme 5).

The oxidative cyclization precursor **12** was then prepared by oxidative cleavage of **10** to give an aldehyde, and a Wittig reaction followed using the nonstabilized ylid formed from deprotonation of commercially available undecyltriphenylphosphonium bromide with KHMDS (81% of **12** over two steps). The presence of four alkene peaks between 138.0 and 114.9 ppm in the ^{13}C NMR confirmed the formation of a second alkene unit. The complex alkene 2 H multiplet at 5.44−5.31 ppm corresponding to the disubstituted alkene could be simplified by performing a homonuclear decoupling experiment, irradiating the 2 H quartet at 2.04 ppm ($CH_3(CH_2)_8CH_2CH{=}CH$) and allowing the determination of a coupling constant, J, of 10.8 Hz between the two alkene protons; this confirms the *cis* geometry of the newly formed alkene within **12**.

Scheme 6

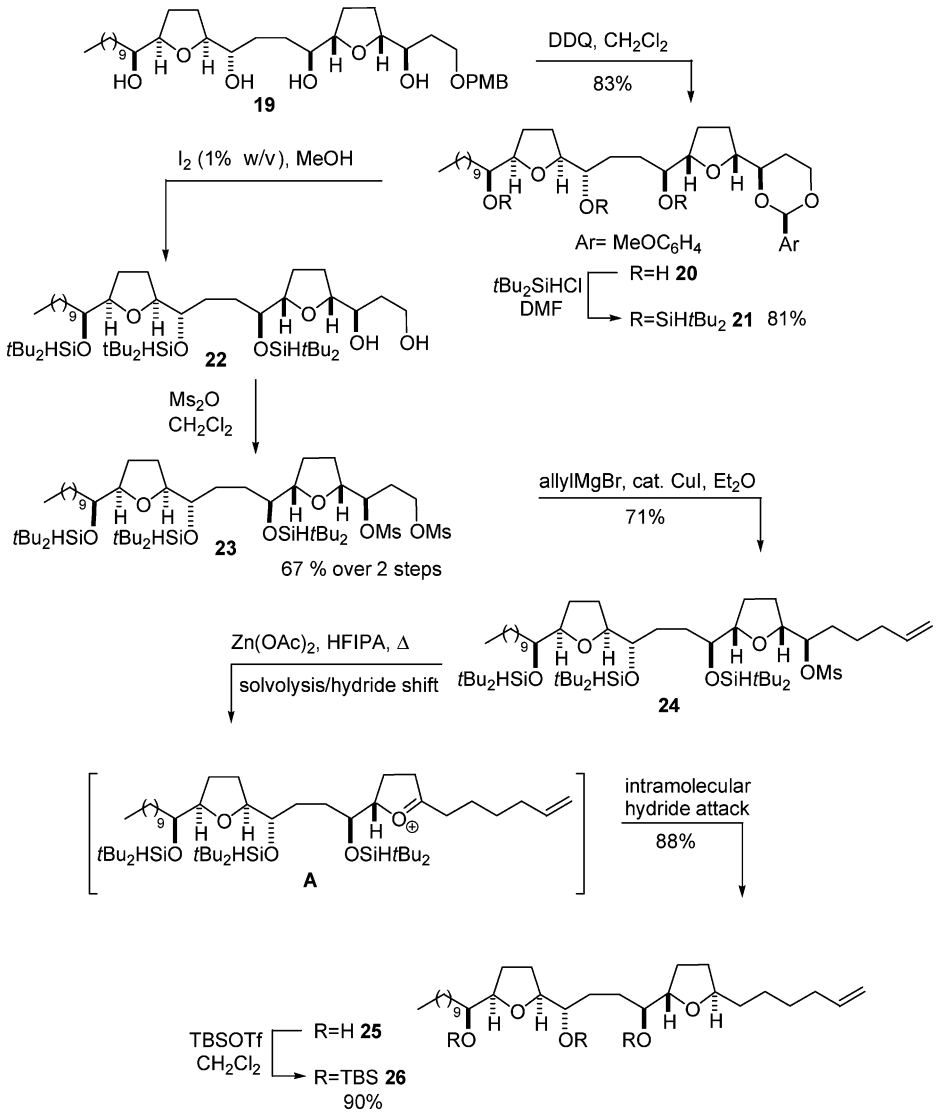


The key reaction in this synthesis of *cis*-sylvaticin is the formation of two THF rings and three stereogenic centers using a novel double oxidative cyclization reaction to access the bis-THF core of the natural product. Pleasingly, initial attempts at the oxidative cyclization of **12** afforded bis-THF **13** in a reasonable yield of 60%. The loss of alkene peaks between 5.84 and 4.99 ppm in the ^{1}H NMR showed consumption of the starting material **12**, and the peaks at 83.1, 82.9, 82.1, and 80.0 ppm in the ^{13}C NMR confirmed the formation of two THF rings in the product. However, careful inspection of the ^{1}H and ^{13}C NMR data showed the presence of a byproduct of cyclization which proved very difficult to separate from the desired bis-THF **13**. Mass spectral evidence suggested the byproduct to be an overoxidized form of **13**, and the presence of a carbonyl was confirmed by a peak at 213 ppm in the ^{13}C NMR and an absorption at 1716 cm^{-1} in the IR spectrum. We have assigned the structure of the undesired product as a ketone derived from overoxidation of product **13** at C-24. Extensive optimization of the oxidative cyclization conditions was then attempted, concentrating on promoting oxidative cyclization at the expense of overoxidation. We found that reducing the amount of TFA maximized the tetraol/ketone ratio (40:1) with the optimum conditions involving addition of the osmium in three batches over 48 h. Using this protocol, a yield of 77% of compound **13** could be obtained.

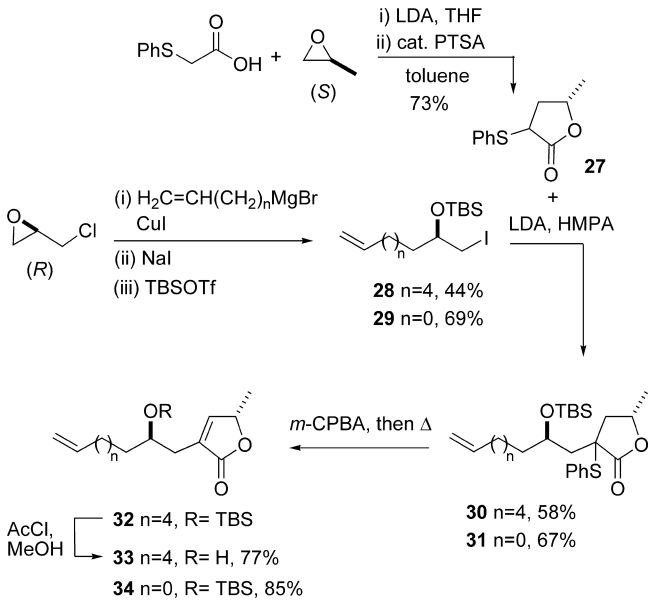
To prepare the bis-THF core for the Wittig reaction, oxidation of the primary alcohol to the aldehyde was required. Unfortunately, attempts to carry out this transformation directly from **13** failed. However, this problem could be overcome by simple protecting group manipulation; tetra-TBS protection of **13** followed by monodeprotection of the least sterically hindered primary TBS group with TBAF led to the formation of alcohol **14** in 59% yield over these two steps, Scheme 5. Oxidation of **14** with TPAP proceeded smoothly to give aldehyde **15** in 86% yield.[15] We then followed literature precedent from Lee[12] who used cross metathesis (CM) as an efficient tactic for joining related compounds in the synthesis of Annonaceous acetogenins. In preparation, aldehyde **15** was methylenated under Wittig conditions to afford alkene **16**.

(15) (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (b) Lenz, R.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291.

Scheme 7



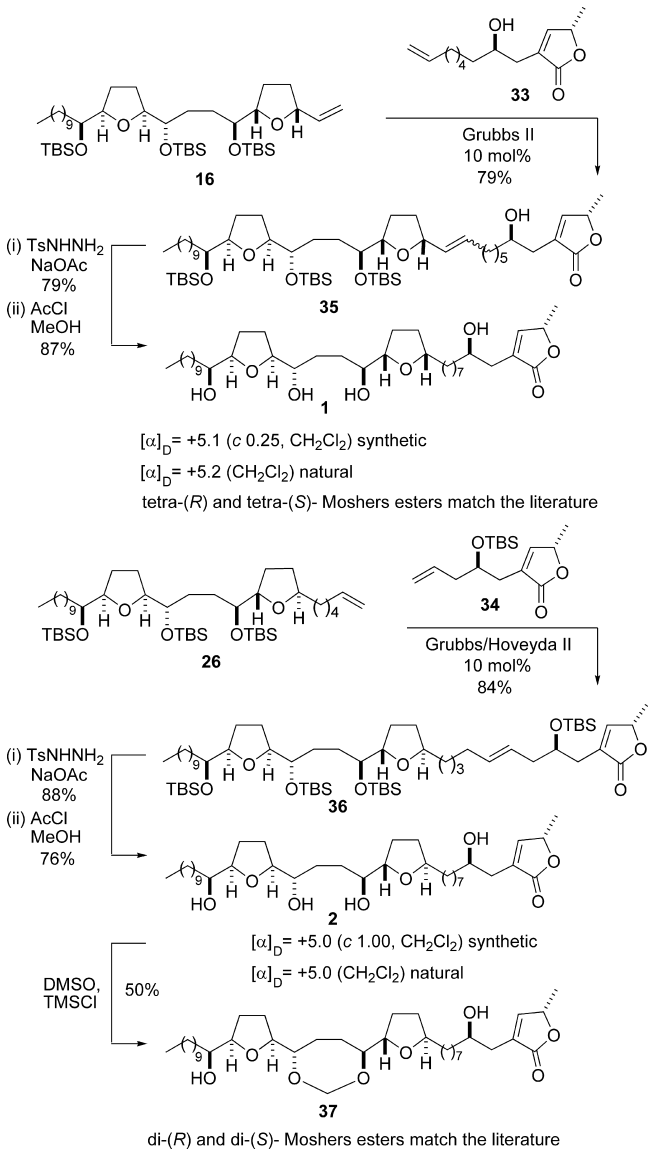
Scheme 8



Desymmetrization and Oxidative Cyclization for the Synthesis of Sylvaticin. The synthesis of sylvaticin also required desymmetrization of bis-alkene **9** so that the two alkenes could be modified in sequence; this was achieved from diol **10**, Scheme 6. Instead of periodate cleavage, as before, protection of the diol as its bis-acetate allowed us to selectively cleave the remaining alkene using ozonolysis followed by a Wittig reaction with a nonstabilized ylid, to yield *cis*-alkene **17** as the sole alkene isomer from the reaction. We then turned our attention to the other end of the molecule and proceeded to cleave the diol derived from hydrolysis of bis-acetate **17** with basic sodium periodate. The resultant aldehyde was subjected to olefination using the Kocienski variant of the Julia reaction,[16] which gave *trans* alkene **18** in good yield and with 14:1 selectivity for the *E*-isomer. A series of ^{1}H NMR experiments on compound **18** (and precursors to it) allowed us to assign the two ^{3}J values across the alkene units as 11 and 15 Hz, respectively, which confirms the stereochemcial assignment as shown.

(16) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

Scheme 9



The pivotal double oxidative cyclization was then attempted on diene **18**, using our recently developed conditions which avoid the use of osmium(VIII) by utilizing pyridine-*N*-oxide as a mild reoxidant.[6] In addition, we have also found that previous conditions that required a low pH for cyclization (usually with the addition of TFA) can be replaced by Lewis acidic conditions and operate at a much higher pH. These new mild conditions were essential for the successful cyclization of **18** whereby the pH (ca. 4) was low enough to allow *in situ* deprotection of the two acetals and subsequent double oxidative cyclization to **19**, while retaining the PMB group.[17]

The next sequence of reactions was aimed at installing the tBu$_2$SiH protecting group on the C-16 hydroxyl so that it can participate in hydride transfer to an oxo-carbenium ion at a later stage, *vide infra*. To do this, the PMB group was oxidized with DDQ and the resulting oxo-carbenium ion was captured by the proximal alcohol to generate the six-membered acetal **20**, Scheme 7.[18] This tactic left the remaining three hydroxyl groups at C-24, C-19, and C-16 untouched, and these were derivatized as a silicon-hydride based silyl ether under standard conditions (**20**→**21**). Next, reaction with mild acid, generated by the action of iodine in methanol,[19] promoted selective removal of the acetal, while leaving the silicon-based protecting groups intact. This protecting group manipulation enabled us to activate each of the newly unmasked alcohols **22** as a mesylate derivative, **23**. The fate of each of the two OMs functionalities within **23** is different: the primary OMs group is destined to be used to chain extend the carbon skeleton so that it can ultimately be attached to the butenolide fragment by cross metathesis; the secondary OMs group is intended to intitiate a hydride shift/directed ionic hydrogenation sequence that is designed to remove oxygen functionality at C-11 and form a *trans* 2,5-disubstituted THF ring at the same time. Preliminary studies clearly showed that it was easiest to chain extend at the primary center before attempting hydride shift/directed reduction. Therefore, bis-mesylate **23** was reacted with allylmagnesium bromide in the presence of catalytic Cu(I), in diethylether at −20 °C, Scheme 7. The conditions for this transformation had to be carefully optimized so as to prevent double displacement by the organocuprate with **24** being isolated in 71% yield. Finally, the solvolysis of the remaining mesylate within **24** in hexafluoroisopropanol (HFIPA) was attempted in the presence of zinc acetate. Based on our previous methodology, we have evidence that this reaction sequence is initiated by a hydride shift/expulsion of the OMs group, to generate oxa-carbenium ion **A**. This is subjected to an intramolecular ionic hydrogenation, whereby the Si−H bond from the appended ROSiHtBu$_2$ group attacks the oxa-carbenium ion from the lower face as drawn in an intramolecular fashion.[10] Pleasingly, the reaction worked as planned to generate the *trans*-THF ring **25** in 88% yield. Despite extensive experimentation the conditions required to effect this transformation always gave an amount of desilylated material, and eventually we opted to extend the reaction time (to 48 h) so that all three of the silyl "protecting groups" were removed. As a direct consequence of this, three OTBS groups were then added at this stage (**26**) so that the synthesis could be continued unimpeded.

Synthesis of the Butenolide Fragment and Completion of the Syntheses. The butenolide fragment was prepared from two commercially available building blocks, namely epichlorohydrin and propylene oxide, following the general route described by Lee.[12] The commercial nature of these two starting materials means that we can readily prepare any stereochemical isomer of the CM precursor.

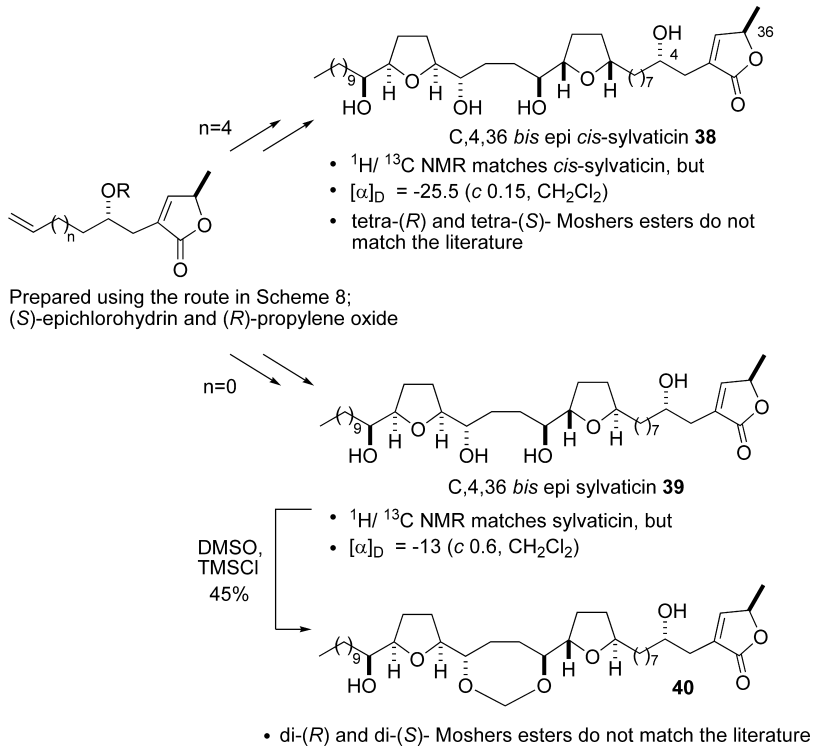
Thus, opening of (*S*)-(−)-propylene oxide with the dianion of (phenylthio)acetic acid gave lactone **27** in 73% yield as a 1:1 mixture of enantiopure diastereomers, Scheme 8. Lactone **27** was then deprotonated with LDA and quenched with iodides **28** and **29** (themselves derived from (*R*)-epichlorohydrin in three steps) as the electrophile to afford **30** and **31**, each as a 3:1 mixture of diastereomers. Alkenes **32** and **34** were then prepared by oxidation/elimination of the thiophenyl group, and in accordance with literature precedent, the elimination process was completely regioselective. For operational reasons, it was

(17) Donohoe, T. J.; Winship, P. C. M.; Walter, Daryl, S. *J. Org. Chem.* **2009**, in press (DOI: 10.1021/jo901243y).

(18) (a) Oikaw, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889. (b) Kim, C. Y.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019.

(19) (a) Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827. (b) Wahlstrom, J. L.; Ronald, R. C. *J. Org. Chem.* **1998**, *63*, 6021.

Scheme 10



beneficial to remove the TBS group from compound **32**, and this was accomplished with acid in methanol giving **33** in 77% overall yield from **30**.

In each case, two fragments **33** and **34** could then be joined to the bis-THF unit using CM methodology, Scheme 9. As suggested by Lee, 4 equiv of alkenes **33** and **34** were used in each metathesis cross-coupling reaction to ensure that alkenes **16** and **26** did not homodimerize (all are terminal alkenes of type I and therefore prone to homodimerization).[11,12] Pleasingly, the metathesis reaction of **16** with **33** proceeded to give **35** and homodimerized **33** which could be recycled into the CM reaction to good effect. The synthesis of (+)-*cis*-sylvaticin **1** was then completed in two final steps, which comprised diimide reduction of the more symmetrical and electron-rich double bond,[20] followed by acid deprotection of the three TBS groups. Likewise, the synthesis of (+)-sylvaticin was accomplished using a related protocol, *via* **36**, which furnished the natural product **2** in good overall yield. This work represents a short route to these two natural products, and it is noteworthy that *cis*-sylvaticin was completed in just 13 steps from commercially available tetraene **4** and that sylvaticin required 19 steps to complete.

Verification of the Structures of *cis*-Sylvaticin and Sylvaticin. It was essential that we were able to match the data from synthetic **1** and **2** with those reported by McLaughlin and so confirm the structures of these two natural products. Our first observations were that the ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ of the synthetic material were indeed a very good match with the literature data (see Supporting Information). Moreover, the tetra-(*R*) and tetra-(*S*)-Mosher esters of *cis*-sylvaticin **1** were also in accord with the data reported by McLaughlin. The derivatization of sylvaticin was also undertaken according to the procedure reported in the isolation paper. Formation of a cyclic formaldehyde acetal **37** was accomplished with DMSO and TMSCl to give a derivative that was also shown to match the data in the literature. Finally, formation of the di-(*R*) and di-(*S*)-Mosher ester derivatives of compound **37** provided material with NMR data that matched the original data.

However, Curran has recently shown that following the synthesis of a library of stereoisomers of the mono-THF acetogenin murisolin, a number of the stereoisomers possessed identical ^{1}H and ^{13}C NMR data to those of the natural product,[21] a problem that is typical of the acetogenin family and has also been observed by Brown during studies on *cis*-solamin.[22] As a result of these reports, thorough proof that both of our synthetic compounds were actually the natural products was deemed necessary.

Of particular concern to us was the relationship between the stereogenic centers of the butenolide fragment (C-4 and C-36) and those of the corresponding bis-THF unit. Fortunately, our synthetic approach enabled the formation of the butenolide metathesis precursors with any of the four possible configurations. These could then be coupled by CM and the final spectra compared to those of the natural material.

Preliminary results in the *cis*-sylvaticin series showed that the C-4,36 bis-epidiastereosiomer of *cis*-sylvaticin **38** had identical NMR data to those of *cis*-sylvaticin itself (although its $[\alpha]_D$ was different, see Scheme 10). Derivatives which differed at only C-4 or C-36 were distinguishable and different from the natural product and were therefore discounted. Finally, preparation of the tetra-Mosher ester derivatives of both *cis*-

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sylvaticin **1** and the C-4,36 bis-epimer **38** produced a set of compounds that clearly showed the original assignment to be correct.

A similar sequence on the C-4,36 bis-epimer of sylvaticin **39** (which had NMR but not specific rotation data that matched the literature) gave a derivative **40** that also had a poor match of its di-(*R*) and di-(*S*)-Mosher esters. We can conclude from these studies that the relative and absolute stereochemistry of *cis*-sylvaticin and sylvaticin are as shown in Scheme 1 and were correctly assigned by McLaughlin in the original isolation paper.[3]

To conclude, we have reported efficient and concise routes to two natural products and described here the first total synthesis of sylvaticin. The key step in our route is the double oxidative cyclization of a protected tetraol onto a diene unit that forms two rings in one reaction with a high degree of stereoselectivity. Moreover, the *trans*-THF ring of sylvaticin was prepared by utilizing a one-pot hydride shift/intramolecular oxo-carbenium ion reduction protocol.

Extensive derivatization of the products and stereoisomers thereof has shown clearly that the original assignment of stereochemistry, as reported by McLaughlin, was indeed correct.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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