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Total Synthesis of *cis*-Sylvaticin

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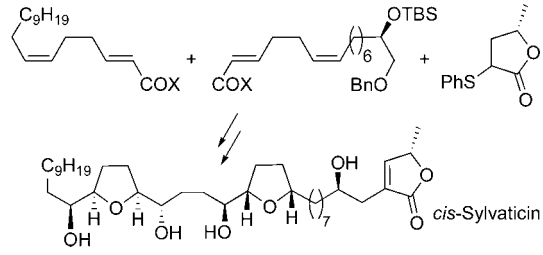
ABSTRACT



An asymmetric total synthesis of (+)-*cis*-sylvaticin is described. Key steps include the use of permanganate-mediated oxidative cyclization of 1,5-dienes to synthesize the two major fragments 2 and 3 and a catalytically efficient tethered RCM to unite these THF-containing fragments. In addition, *t*-BuP$_4$ base was found to reliably promote rapid alkylation of the butenolide precursor fragment 4.

Since the antitumor activity of the *Annonaceous* acetogenin uvaricin was reported in 1982, there has been great interest in this family of natural products, which was stimulated further by the discovery of various other biological activities.[1] The majority of acetogenins fall into three structural categories: the mono-THFs, adjacent bis-THFs and the nonadjacent bis-THFs. There have been numerous syntheses of the first two categories. However, the nonadjacent bis-THFs have received relatively less attention.[2–4]

cis-Sylvaticin is a nonadjacent bis-THF acetogenin isolated from leaf extracts of the tropical fruit tree *Rollinia mucosa*. The relative and absolute stereochemistry of the natural product was determined by McLaughlin et al. using NMR data for **1** and its Mosher ester and acetal derivatives.[5] There has been one previous total synthesis of *cis*-sylvaticin by Donohoe et al.,[3] which has provided confirmation of McLaughlin's stereochemical assignments.

We describe herein a convergent asymmetric synthesis of *cis*-sylvaticin, building the target from three fragments: two

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(1) Reviews of the chemistry and biology of *Annonaceous* acetogenins: (a) Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (b) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540. (c) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–306. (d) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087–1117. (e) Saez, J.; Sahpaz, S.; Villaescusa, L.; Hocquemiller, R.; Cavé, A.; Cortes, D. J. *Nat. Prod.* **1993**, *56*, 351–356. (f) Rupprecht, J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237–278.

(2) For representitive total syntheses of non-adjacent bis-THF acetogenins: (a) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383–3386. (b) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791. (c) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154–3157. (d) Marshall, J. A.; Jiang, H. J. *J. Org. Chem.* **1998**, *63*, 7066–7071. (e) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998**, *54*, 6329–6340.

(3) Total synthesis of *cis*-sylvaticin: Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704–13705.

(4) For representitive total syntheses of related non-adjacent THF-THP acetogenins: (a) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369–2372. (b) Zhu, L.; Mootoo, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2750–2754. (c) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. R. *J. Am. Chem. Soc.* **2003**, *125*, 14702–14703. (d) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739–5752. (e) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751–4754. (f) Hoppen, S.; Bäurle, S.; Koert, U. *Chem.−Eur. J.* **2000**, *6*, 2382–2396. (g) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279–11284.

(5) Shi, G.; Zeng, L.; Gu, Z. M.; MacDougal, J. M.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1785–1796.

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major THF-containing fragments **2** and **3**, and the known 3-phenylsulfanyl substituted lactone **4** (Figure 1).[6] The

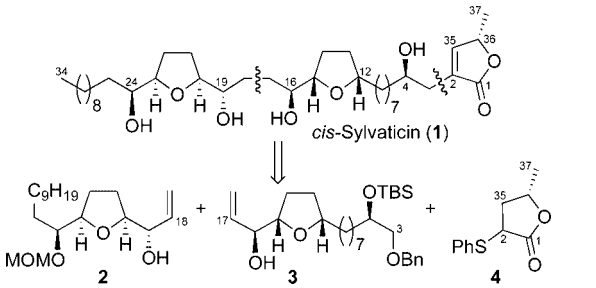
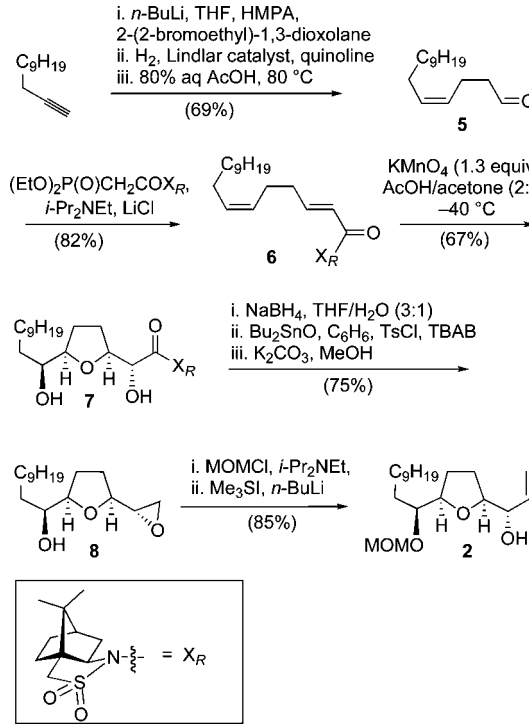


Figure 1. Retrosynthetic analysis of *cis*-sylvaticin.

fragments **2** and **3** can be delivered by diastereoselective permangante-mediated oxidative cyclization of suitably substituted 1,5-dienes.[7] These two main THF building blocks may then be connected to provide the main backbone of *cis*-sylvaticin by olefin metathesis, facilitated by the use of a temporary silicon tether between the allylic alcohol groups.[8]

It was clear that the C18−C34 fragment **2**, which unlike **3** does not contain a remote oxygen bearing stereogenic center, would be simpler to synthesize. The required C24−C34 aldehyde **5** was prepared following a modified route reported by Carballeira,[9] which entailed: alkylation of 1-dodecyne with 2-(2-bromoethyl)-1,3-dioxolane, semihydrogenation of the triple bond and acid hydrolysis of the acetal (Scheme 1). Olefination of **5** with the (2*R*)-10,2-camphorsultam phosphonate was effected using a procedure descibed by Masamune and Roush to afford the *E*-enoyl sultam in high yield and stereoselectivity.[10] Successful permanganate-mediated oxidative cyclization of diene **6** was achieved using conditions established in our laboratory.[11] Analysis of the crude ^{1}H NMR indicated a high level of diasteroselectivity (dr = 9:1) and the major diastereoisomer **7** was isolated in 67% yield. The stereochemical assignments were made on the basis of literature precedent.[11] Reductive cleavage of the chiral auxiliary, subsequent monotosylation of the triol and treatment of the resulting sulfonate ester with base (DBU/CH_2Cl_2 or K_2CO_3/MeOH) returned the epoxide **8** in 75% yield over three steps. Formation of the epoxide ring, which would serve as a precursor to the required allylic alcohol, permitted selective protection of the C24 carbinol

Scheme 1. Synthesis of the C19−C34 Fragment **2**



as a MOM ether. To conclude the synthesis of the C18−C34 fragment **2**, the protected epoxide was converted to the allylic alcohol by an efficient reaction with trimethylsulfonium ylid.[12]

The C3−C17 fragment **3** could also be prepared using oxidative cyclization of a 1,5-diene that already contained the remote C4 secondary alcohol required in *cis*-sylvaticin. Synthesis of the fragment began with rhenium-catalyzed epoxidation of 1-bromo-8-octene,[13] followed by an alcoholytic kinetic resolution of the resulting epoxide **9** (Scheme 2). Alcoholysis in the presence of Jacobsen Co oligosalen catalyst **(*S*,*S*)-12** yielded the secondary alcohol **(*R*)-10** with excellent *ee* (HPLC),[14] while simultaneously introducing a robust C3 protecting group with excellent regiocontrol. The remaining epoxide, which was enriched in the *S*-enantiomer, was submitted to a second resolution using the enantiomeric oligosalen **(*R*,*R*)-12** to afford **(*S*)-10**, again with excellent enantio- and regioselectivities. An efficient Mitsunobu-hydrolysis sequence completed conversion of the remaining material to the benzyl ether **(*R*)-10**.

Reaction of the enantiomerically enriched bromohydrin **(*R*)-10** with an excess of lithated alkyne **13** afforded the 1,3-

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(11) (a) Hu, Y. L.; Brown, R. C. D. *Chem. Commun.* **2005**, 5636–5637. (b) Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. *J. Org. Chem.* **2002**, *67*, 8079–8085. (c) Cecil, A. R. L.; Hu, Y. L.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368–3374.

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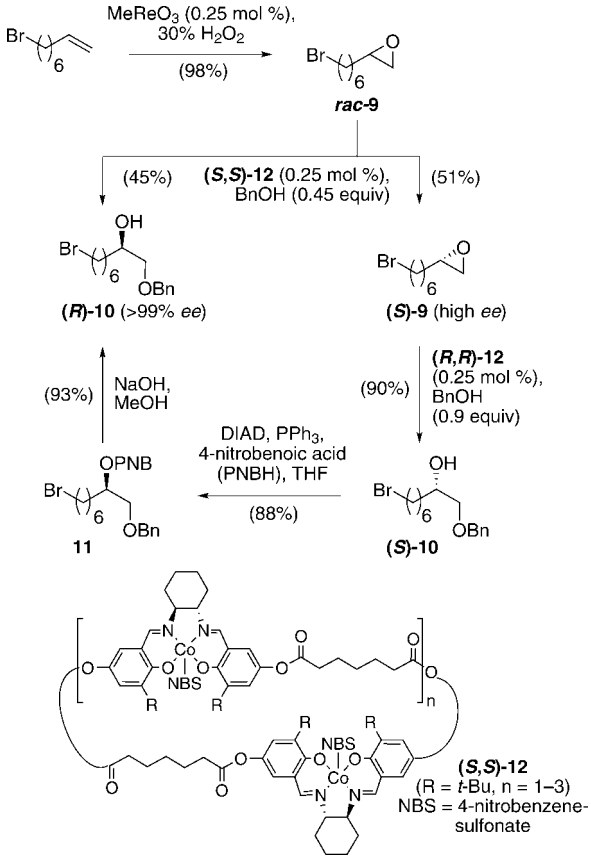
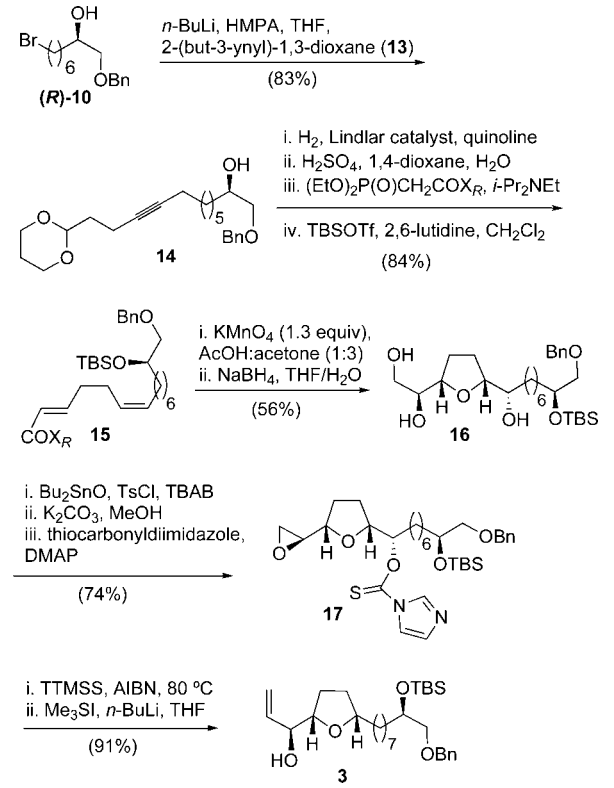
(14) (a) Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Edit.* **2002**, *41*, 1374–1377. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

Scheme 2. Synthesis of Benzyl Ether **(*R*)-10**



Scheme 3. Synthesis of Fragment C3−C17



dioxane **14** in high yield (Scheme 3). Subsequent semihydrogenation, acetal deprotection, olefination and silylation of the secondary alcohol delivered the *E,Z*-diene **15**. The key oxidative cyclization afforded a separable mixture of diastereoisomeric products (dr = 8.7:1 from isolated yields) from which the desired isomer was isolated in 61% yield. Reductive cleavage of the acylsultam functionality delivered triol **16** in high yield. At this stage the removal of the superfluous C11 hydroxyl group was addressed, requiring selective derivatization of the triol **16**. Once again, we were able to exploit epoxide formation to leave the secondary alcohol free for conversion to a thiocarbamate derivative **17**. Pleasingly, any concerns over the potential sensitivity of intermediate **17** were allayed when radical deoxygenation was found to proceed extremely effectively using *tris*(trimethylsilyl)silane (TTMSS).[15] The fragment synthesis was completed by conversion of the epoxide to the allylic alcohol **3** as described above.

Silicon-tethered RCM has been applied previously to the synthesis of nonadjacent acetogenins.[4c,16] Some of these investigations have required high catalyst loadings,[4c] and other authors have reported moderate yields for tethering and/or RCM reactions.[4b,17] An alternative strategy is to use cross metathesis (CM), although this approach typically employs an excess of one precious fragment.[18] In the present study stoichiometric sequential reaction of dichlorodi*iso*propyl silane with the left and then right-hand fragments **2** and **3** effected efficient tethering, providing that the reaction was sufficiently concentrated (~0.5 M in **2**, Scheme 4).[19] RCM with Grubbs' second generation precatalyst (10 mol %, 0.06 M in substrate) led to smooth cyclization at 75 °C (80% yield, 91% based on recovered diene), whereas at higher temperatures catalyst decomposition was observed to be a significant issue leading to the requirement of higher catalyst loadings and returning poorer yields. Exposure of the metathesis product to H_2 in the presence of 5% Pd/C (wet Degaussa type) caused the hydrogenolysis of the benzyl ether, with slower reduction of the alkene. By contrast, use of standard 5% Pd/C led to selective hydrogenation of the olefin only and $Pd(OH)_2/C$ was required to remove the protecting group. Interestingly, exposure of the metathesis product directly to H_2 in the presence of $Pd(OH)_2/C$ produced no observable reaction.

The synthesis was completed by conversion of the primary alcohol to the triflate, followed by nucleophilic substitution using the deprotonated γ-butyrolactone **4**. Use of KHMDS

(15) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.

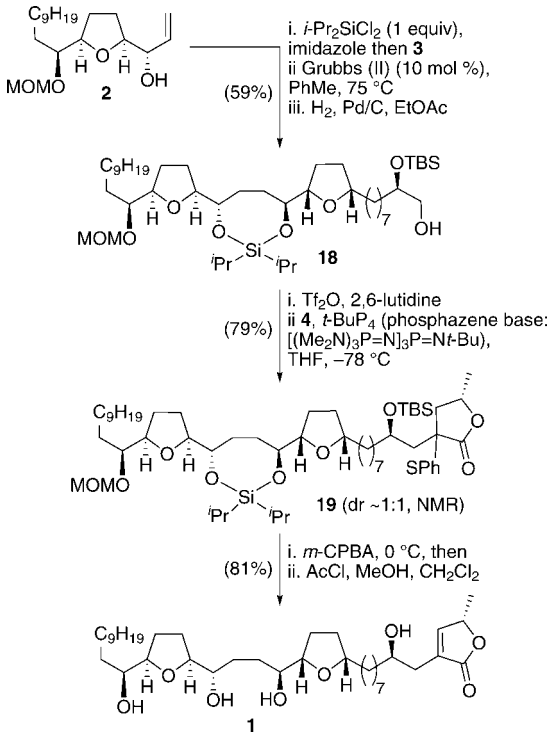
(16) For an elegant sequenced CM−tethered RCM approach see ref 2a. In this example, tethering using Ph_2SiCl_2 gave the unsymmetrical siloxane in 52%.

(17) (a) Zhu, L.; Mootoo, D. R. *Org. Lett.* **2003**, *5*, 3475–3478. (b) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154–3157.

(18) Typically a 3:1 ratio of the THF/THP-containing fragments has been used (see refs 4b and 17).

(19) Paterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *4*, 2473–2476.

Scheme 4. Final Assembly of *cis*-Sylvaticin



in the alkylation[20] met with varying success due to the observed decomposition of the anion.[21] However, use of *t*-BuP$_4$ phosphazene base gave a significantly more reactive species which underwent rapid and reproducible alkylation by the triflate in high yield. Oxidation of the phenylsulfanyl group induced a facile elimination of phenylsulfenic acid, that was followed by global deprotection to conclude the synthesis of *cis*-sylvaticin (**1**).[22,23]

In summary, the total synthesis of *cis*-Sylvaticin was completed with an overall yield of 7.8%, and a linear sequence of 21 steps. Seven of the nine stereogenic centers present in **1** were installed by permanganate-mediated oxidative cyclization reactions. The remote C4 secondary alcohol stereochemistry was established using an oligomeric Co salem catalyst to induce an efficient alcoholytic kinetic resolution of a terminal epoxide. Silicon-tethered RCM brought together the two major fragments, and a reliable protocol has been introduced for late stage coupling of the butenolide precursor using the *t*-BuP$_4$ phosphazene base. This route has yielded hundred milligramme quantities of *cis*-sylvaticin.

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Supporting Information Available: Experimental procedures and spectroscopic characterization for all compounds. This material is avaliable free of charge via the Internet at http://pubs.acs.org.

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(20) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdinsuren, B.; Nakamori, S. *Chem.−Eur. J.* **2003**, *9*, 390–399.

(21) Other researchers have reported the capricious nature of this late-stage alkylation (see ref 20). In our hands, the reaction using KHMDS as base gave the desired product on only one of three attempts. The major product of the unsuccessful reactions was the phenylsulfanyl ether. The corresponding reaction using the phosphazene base has given the desired product on every occasion.

(22) Deprotection conditions: Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035–6051.

(23) Physical data (mp 63−65 °C [Lit. 63−64 °C;[5] 59−61 °C[3]]; $[\alpha]_D$ +5.0 (*c* 0.86, $CHCl_3$) and +5.2 (*c* 0.88, CH_2Cl_2) [Lit. +5.2 (CH_2Cl_2);[5] +5.1 (*c* 0.25, $CHCl_3$[3]] and spectroscopic data for the synthetic material were in excellent accord with those reported (refs 3 and 5). Copies of the ^{1}H and ^{13}C NMR spectra for **1** can be found in the Supporting Information, along with tabulated ^{13}C NMR data for our synthetic **1** and the natural **1**.