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Total Synthesis of Cristatic Acid

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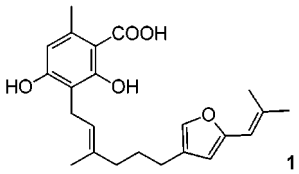
ABSTRACT



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The first total synthesis of cristatic acid 1, an antibiotic endowed with considerable activity against Gram-positive bacteria, hemolytic properties, and significant cytotoxicity, is described. Key to success are the formation of its 2,4-disubstituted furan moiety via a palladium-catalyzed alkylation of vinylepoxide 10 derived from sulfonium salt 8 and the use of SEM ethers as the protecting groups for the phenolic OH functions.

Cristatic acid **1**, a secondary metabolite isolated by Steglich et al. from the fruiting bodies of the higher mushroom *Albatrellus cristatus*,[1] exhibits an interesting range of biological properties including (i) antibiotic activity against gram-positive bacteria, (ii) strong hemolytic function, and (iii) a considerable inhibitory effect against cells of the ascites form of Ehrlich carcinoma. Notably, permethylation of **1** enhances the latter property to a significant extent but leads to a total loss of its antibacterial effect.[1] This pronounced yet hardly understood structure/activity profile renders this particular farnesyl phenol derivative an attractive target for total synthesis and makes further studies of the biological response to changes in functionality called for.

The only preparative approach toward cristatic acid reported in the literature,[2] however, reveals some significant challenges posed by this target. In particular, difficulties arise from the electron rich and hence rather labile furan moiety, which severely restricts the choice of reaction conditions once this ring is formed. Thus, the attempted total synthesis described by Joullié et al. failed because these authors were unable to find conditions for the final deprotection of the phenolic OR groups without destroying the furan.[2,3] Moreover, the sensitivity of some precursors rendered the attachment of the tether between the phenolic and the heterocyclic ring quite problematic.[2,4]

With these lessons in mind, we redesigned a synthesis which avoids such complications (Figure 1). Rather than

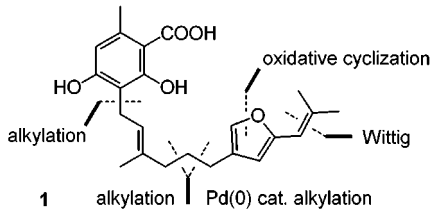

Figure 1. Retrosynthetic analysis of cristatic acid **1**.

assembling the target from the individual building blocks by alkylation of the furan, we chose to use allylic and benzylic C−C bonds within the tether as more promising sites of

(1) Zechlin, L.; Wolf, M.; Steglich, W.; Anke, T. *Liebigs Ann. Chem.* **1981**, 2099.
(2) Chiarello, J.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 41.

(3) See the following for leading references on studies towards related farnesyl phenol natural products; some of them further illustrate the difficulties arising in the final deprotection steps of the aryl ether groups: (a) Chen, K.-M.; Semple, J. E.; Joullié, M. M. *J. Org. Chem.* **1985**, *50*, 3997. (b) Safaryn, J. E.; Chiarello, J.; Chen, K.-M.; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2635. (c) Guthrie, A. E.; Semple, J. E.; Joullié, M. M. *J. Org. Chem.* **1982**, *47*, 2369. (d) Chen, K.-M.; Joullié, M. M. *Tetrahedron Lett.* **1982**, *23*, 4567. (e) Mori, K.; Takechi, S. *Tetrahedron* **1985**, *41*, 3049. (f) Mori, K.; Fujioka, T. *Tetrahedron* **1984**, *40*, 2711. (g) Saimoto, H.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 597.

(4) Only a few general methods for the preparation of 2,4-disubstituted furans are known; for a review see: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.

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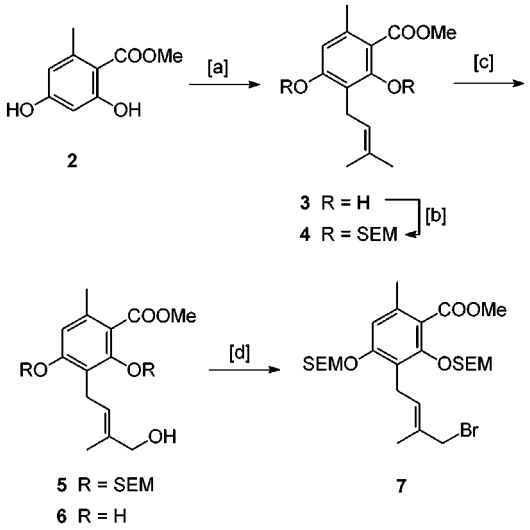
disconnection. Judicious choice of protecting groups that are labile under neutral or only slightly basic conditions should enable us to carry out the final deprotection step and therefore bring cristatic acid into reach. Summarized below is the successful reduction of these ideas to practice.

Our approach starts from methyl orsellinate **2** which is easily accessible on a large scale in one-pot from methyl acetoacetate (Scheme 1).[5] The voluminous precipitate formed upon deprotonation of **2** with NaH in toluene reacts with prenyl bromide at 35 °C to afford compound **3** in 73% yield, which itself is a natural product isolated from the Japanese mushroom *Polyporus dispansus* ("komori-take").[6] The excellent selectivity in favor of alkylation at the C-3 position rather than the three other possible sites (C-5, O-2, O-4) in substrate **2** is remarkable. In line with the well-understood reactivity pattern of ambident nucleophiles,[7] the formation of the sodium salt of **2** is essential for this favorable outcome, whereas the corresponding potassium salt previously used in a similar context turned out to be much less appropriate.[2]

Compound **3** was then converted into the bis(2-trimethylsilylethoxy)methyl (SEM) ether **4**.[8,9] This particular protecting group was chosen in light of previous successful applications to studies on farnesyl phenol derivatives in which the final deprotections were similarly crucial.[3,10]

Scheme 1[a]



[a] (a) NaH, prenyl bromide, toluene, 35 °C, 19h, 73%; (b) SEMCl, KH, 18-crown-6 cat., THF, 5 h, rt, 84%; (c) SeO_2, t-BuOOH (70% in water), CH_2Cl_2, 5 h, rt, 61%; (d) $MeSO_2Cl$, LiBr, Et_3N, CH_2Cl_2/THF, 0 °C, 3 h, 76%.

Allylic oxidation of **4** thus formed with SeO_2 and *tert*-BuOOH delivers the required allylic alcohol **5** in good yield. An X-ray analysis of its deprotected form **6** was carried out which confirmed the attachment of the prenyl side chain at the C-3 position of the orsellinic acid and the (*E*)-configuration of the trisubstituted double bond (Figure 2).[11] Alcohol **5** was finally converted into allyl bromide **7** on treatment with mesyl chloride and LiBr in a mixed solvent system.

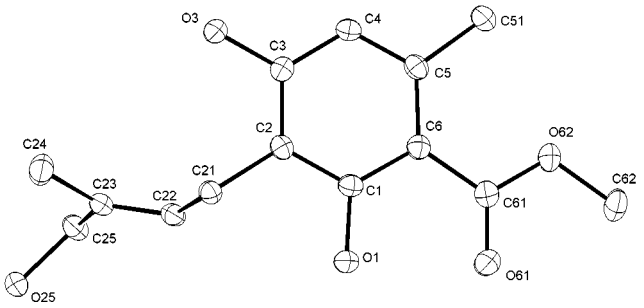
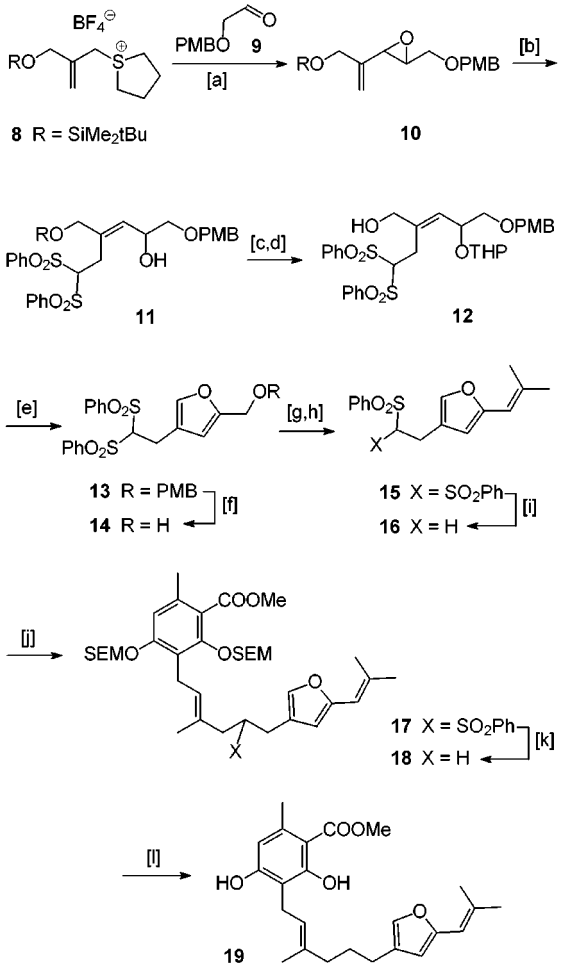


Figure 2. ORTEP diagram of the molecular structure of compound **6**. Anisotropic displacement parameter ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity. For details, see the Supporting Information. Selected bond lengths (Å) and angles (deg): O25−C25 1.4464(6), C25−C23 1.5083(18), C23−C22 1.3332(19), C22−C21 1.5077(18), C21−C2 1.5160(17), C61−O61 1.2188(18), C3−C2−C21 122.77(12), C23−C22−C21 127.30(12), C22−C23−C25 119.43(12), O61−C61−O62 120.52(12).

The second fragment required for the assembly of cristatic acid was prepared from the functionalized sulfonium salt **8** which had previously been used in our laboratory as a versatile building block for the synthesis of heterocyclic natural products of different complexity.[12,13] Deprotonation with *tert*-BuLi at low temperature and reaction of the resulting sulfur ylide with 2-(4-methoxybenzyl)oxyacetaldehyde **9**[14] affords epoxide **10** in 62% yield (Scheme 2). Treatment of this compound with catalytic amounts of Pd(PPh$_3$)$_4$ and dppe selectively activates its vinyloxirane entity.[15] The resulting alkoxide deprotonates admixed bis(phenylsulfonyl)methane which then attacks the π-allyl

(5) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272. See also the Supporting Information for a multigram synthesis of this compound.
(6) Ishii, N.; Takahashi, A.; Kusano, G.; Nozoe, S. *Chem. Pharm. Bull.* **1988**, *36*, 2918.
(7) (a) Le Noble, W. J. *Synthesis* **1970**, 1. (b) Gompper, R. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 560.
(8) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(9) Silyl ethers instead of SEM groups were ruled out for the reason given in ref 19.
(10) Saimoto, H.; Kusano, Y.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 1607.
(11) For details see the Supporting Information.
(12) Furans: (a) Fürstner, A.; Gastner, T.; Rust, J. *Synlett* **1999**, 29. (b) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (c) Fürstner, A. *Synlett* **1999**, 1523.
(13) Pyrroles: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944. (c) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (d) Fürstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281.
(14) Prepared by alkylation of 2-butene-1,4-diol with *p*-MeOC$_6$H$_4$CH$_2$-Cl in the presence of NaH (DMF, *n*-Bu$_4$NI cat., rt, 77%) and cleavage of the resulting product with OsO_4 cat./$NaIO_4$ (pyridine/Et_2O/H_2O, rt, 77%) in analogy to a procedure described in: Garner, P.; Park, J. M. *Synth. Commun.* **1987**, *17*, 189.
(15) For leading references on Pd(0)-catalyzed reactions of vinyloxiranes, see: (a) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (c) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940. (d) Review: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

Scheme 2[a]



[a] (a) (i) *t*-BuLi, THF, 10 min, −78 °C; (ii) aldehyde **9**, −78 → 0 °C, 62%; (b) $(PhO_2S)_2CH_2$, $Pd(PPh_3)_4$ cat., dppe cat., THF, 14 h, rt, 98%; (c) 3,4-dihydro-2*H*-pyran, pyridinium tosylate cat., CH_2Cl_2, 0 °C → rt, 4h, 91%; (d) *n*-$Bu_4NF{\cdot}3H_2O$, THF, 50 °C, 16h, 95%; (e) (i) MnO_2, CH_2Cl_2, rt, 3 h; (ii) aqueous HCl, EtOAc, rt, 12 h, 87%; (f) DDQ, CH_2Cl_2/H_2O (20/1), 7 h, 0 °C; (g) MnO_2, CH_2Cl_2, 3 h, rt; (h) $Ph_3P{=}C(CH_3)_2$, THF, 0 °C, 14 h, 57% (over steps f−h); (i) Al(Hg), aqueous THF, 3 h, rt, 96%; (j) (i) *n*-BuLi, 0 °C, THF, 5 min; (ii) allyl bromide **7**, HMPA, −78 → 0 °C, 2 h; (k) Na(Hg), MeOH, Na_2HPO_4, 0 °C → rt, 5 h, 55% (over steps j−k); (l) *n*-$Bu_4NF{\cdot}3H_2O$, HMPA, 50 °C, 12 h, 60%.

palladium complex to afford product **11** in almost quantitative yield; this compound encodes the furan ring in its 1,4-dihydroxy skeleton.[16] Temporary protection of the allylic alcohol group as a THP acetal followed by cleavage of the primary -OTBDMS ether with *n*-Bu_4NF cleanly affords compound **12**. Subsequent oxidation with MnO_2 in CH_2Cl_2 and treatment of the resulting enal with aqueous HCl delivers the required 2,4-disubstitued furan **13** in excellent yield.

The missing isobutenyl side chain was installed by deprotection of the PMB ether of **13** with DDQ,[17] oxidation of the resulting alcohol **14** with MnO_2 in CH_2Cl_2 and subsequent Wittig reaction of the ensuing unstable aldehyde with $Ph_3P{=}C(CH_3)_2$ under standard conditions. This sequence was carried through without rigorous purification of the intermediates and provides the desired product **15** in 57% overall yield. Recrystallization from ether gave a sample suitable for X-ray analysis (Figure 3) which confirms the structural integrity of this key compound.[11]

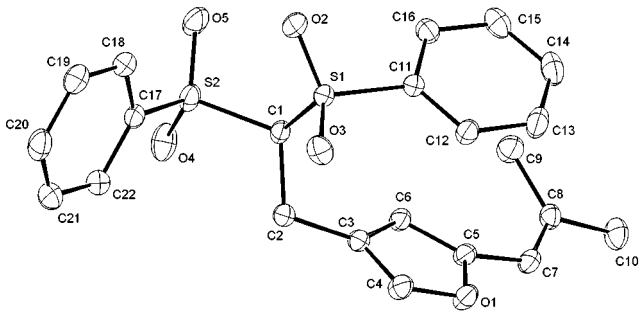


Figure 3. ORTEP diagram of the molecular structure of compound **15**. Anisotropic displacement parameter ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): C7−C8 1.3438(18), C7−C5 1.4517(18), C5−O1 1.3785(15), O1−C4 1.3679(16), C3−C4 1.3536(18), C3−C6 1.4385(17), C5−C6 1.3649(17), C2−C3 1.5004(17), C1−C2 1.5369(17), C1−S1 1.8313(13), C1−S2 1.8161(12), C1−C2−C3 111.38 (10), C5−C7−C8 126.82(12), O1−C5−C7 114.32(10), C6−C5−C7 136.29(12), C6−C3−C2 126.46(11). For details, see the Supporting Information.

Because attempted reductive metalation of **15** with lithium naphthalenide and in situ alkylation of the resulting species with bromide **7** turned out to be low yielding,[18] we decided to proceed in a stepwise manner. Thus, one of the sulfone groups of **15** was first cleaved off by treatment with Al(Hg) in aqueous THF. The resulting monosulfone **16** was then deprotonated with *n*-BuLi, and the alkylation of the resulting organolithium intermediate with bromide **7** was carried out at low temperature in the presence of HMPA as cosolvent.[19] The remaining $PhSO_2$ group in crude **17** thus obtained was removed by means of Na(Hg) in buffered MeOH as the reaction medium,[20] providing product **18** in 55% yield over both steps.

Although earlier studies on related farnesyl phenols had suggested that SEM ethers were suitable protecting groups that can be removed under conditions mild enough to

(16) Compounds **10**−**12** are obtained as mixtures of stereoisomers. Since all of them converge into product **13**, the synthesis depicted in Scheme 2 was carried out with these mixtures and no attempts were made to isolate the individual isomers.

(17) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885. (b) At this point it is essential to have chosen a PMB group rather than a simple Bn ether as the protecting group for the benzylic alcohol. All attempts to cleave the corresponding benzyl ether failed to afford the desired product **14**. For example, attempted hydrogenation over Pd/C reduces the furan ring without cleaving the benzyl ether.

(18) Yu, J.; Cho, H.-S.; Chandrasekhar, S.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett*. **1994**, *35*, 5437.

(19) Note that attempted alkylations of the metalated sulfone with an allyl bromide analogous to **7** carrying -OTBDMS instead of -OSEM groups gave the desired compound in less than 5% yield.

(20) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett*. **1976**, 3477.

preserve labile functionalities,[3g,8,10] our initial attempts to unmask cristatic acid were quite unrewarding.

Specifically, the protocol using P_2I_4 in CH_2Cl_2 gave none of the desired product but readily decomposed the starting material.[10] Attempted deprotection with *n*-Bu_4NF in THF led to the regioselective cleavage of the SEM group at O-4 but did not touch the second one at all even under forcing conditions.[8] An improved method recommended by Lipshutz et al.,[21] employing *n*-Bu_4NF in DMPU, essentially led to the same outcome and gave only tiny amounts of the desired product. Good results, however, were obtained with *n*-Bu_4NF in HMPA at 50 °C.[22] Under these conditions we were able to isolate cristatic acid as its methyl ester **19** in a respectable 60% yield. This completes the first total synthesis of this interesting bioactive target. The analytical and spectroscopic data are in full agreement with those reported in the literature.[11]

Further studies on the synthesis and biological evaluation of heterocyclic natural products are in progress and will be reported in due course.[23]

Acknowledgment. Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz program) and the Fonds der Chemischen Industrie is acknowledged with gratitude. We thank Dr. C. W. Lehmann for the X-ray analysis of compounds **6** and **15**.

Supporting Information Available: Full experimental details together with analytical and spectroscopic data of all new compounds. Details concerning the X-ray structures of compounds **6** and **15**. This material is available free of charge via the Internet at http://acs.pubs.org.

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(21) Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149.

(22) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417.

(23) For previous studies on bioactive heterocycles from our laboratory, see: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (b) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468. (c) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215. (d) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329. (e) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637. (f) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773. (g) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275. (h) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738.