Total Synthesis of (±)-Epoxysorbicillinol

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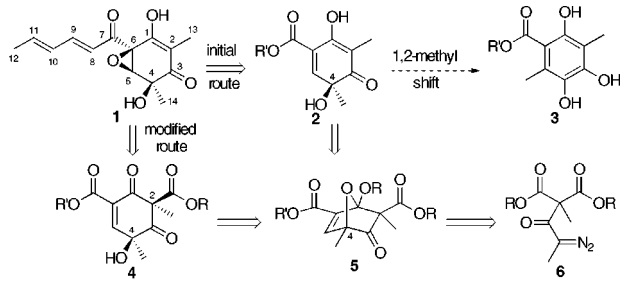
Recent interest in species of the genus *Trichoderma* as sources of unique metabolites has led to the isolation of several vertinoid polyketides. Members of this natural products class have shown interesting biological activity, including inhibiting TNF-α production and DPPH radical scavenging activity.[1] Epoxysorbicillinol (**1**) represents the first isolated vertinoid polyketide possessing an epoxide functionality.[2] Its densely functionalized chemical structure and potential for interesting biological activity led us to undertake a total synthesis of **1**.[3] Herein we report the details of this investigation.

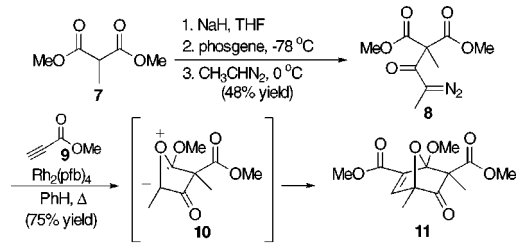
From a retrosynthetic perspective, the known propensity of the sorbyl side chain (**1**: C(7−12)) to undergo polymerization led us to target diene **2** as an advanced intermediate (Scheme 1).[4] However, as will be illustrated, it was discovered that such dienes are exceedingly prone to aromatize via a facile 1,2-methyl shift (e.g., **2** → **3**). As an added challenge, attempts to avoid this disastrous thermodynamic pitfall via protection of the C(4) hydroxyl of **2** produced substrates that were recalcitrant toward epoxidation. These difficulties dictated the development of a modified approach wherein allylic alcohol **4** served as a key intermediate. Importantly, quaternization of C(2) in **4** prevented aromatization and allowed the C(4) hydroxyl to remain free to direct epoxidation. Fortunately, both approaches (i.e., **4** → **1** and **2** → **1**) could be divergently accessed from the versatile common intermediate **5**, where the C(4) tertiary alcohol is masked intramolecularly as a cyclic acetal. Oxabicycle **5** was envisioned to arise from a rhodium-catalyzed 1,3-dipolar cycloaddition between α-diazo ketone **6** and a propiolate ester. Finally, **6** could be accessed from any number of commercially available methylmalonates.

In the forward sense, we first explored the critical metal-catalyzed carbonyl ylide cycloaddition using **8** as a model substrate (Scheme 2). To this end, deprotonation of dimethyl methylmalonate (**7**) with NaH followed by the addition of phosgene at −78 °C gave the corresponding acid chloride which, without purification, was added to an ice-cooled solution of diazoethane in ether to provide α-diazo ketone **8**.[5] Gratifyingly, exposure of **8** to catalytic $Rh_2(pfb)_4$ (1 mol %) generated intermediate carbonyl ylide **10**, which underwent smooth 1,3-dipolar cycloaddition with methyl propiolate (**9**) to afford **11** in excellent yield.[6] Interestingly, this reaction provided only a single diastereomer of **11**, the structure of which was confirmed via X-ray crystallography.

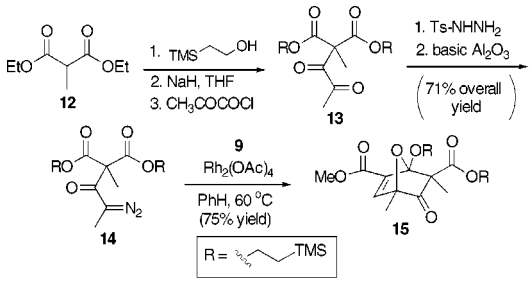
Scheme 1



Scheme 2



Scheme 3



Having established a sound method for assembly of the carbocyclic core, we turned our attention toward the synthesis of a specific bicyclic substrate that would allow us efficient access to diene **16**. After a challenging search for the proper ester protecting group, **15** was found to be a rather versatile intermediate.[7] Although the preparation of **15** was practical on a small scale using the diazotization procedure shown in Scheme 2, a more efficient synthesis which did not require the use of phosgene or diazoethane was desired for multigram scale. To this end, diethyl methylmalonate (**12**) was transesterified with 2 equiv of *β*-(trimethylsilyl)ethanol (Scheme 3). Deprotonation of the resulting diester with NaH followed by the addition of pyruvoyl chloride at −78 °C gave diketone **13**.[8] Although **13** was unstable to silica gel chromatography, treatment of the crude solution with 1 equiv of $TsNHNH_2$ followed by basic alumina gave regioselective diazotization of the desired ketone to produce α-diazo ketone **14** in excellent overall yield.[9] Optimal conditions for the cycloaddition between **14** and **9** were found using $Rh_2(OAc)_4$ in benzene

(1) (a) Warr, G. A.; Veitch, J. A.; Walsh, A. W.; Hesler, G. A.; Pirnik, D. M.; Leet, J. E.; Lin, P.-F. M.; Medina, I. A.; McBrien, K. D.; Forenza, S.; Clark, J. M.; Lam, K. S. *J. Antibiot.* **1996**, *49*, 234. (b) Abe, N.; Murata, T.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 661. (c) Abe, N.; Murata, T.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 2120.

(2) Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011.

(3) For syntheses of related natural products, see: (a) Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071. (c) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555. (d) Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem. Eur. J.* **1999**, *5*, 3651. (e) Abe, N.; Sugimoto, O.; Tanji, K.; Hirota, A. *J. Am. Chem. Soc.* **2000**, *122*, 12606.

(4) Andrade, R.; Ayer, W. A.; Mebe, P. P. *Can. J. Chem.* **1992**, *70*, 2526.

(5) A diazoethane solution was prepared by the following method: Short, R. P.; Revol, J.-M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

(6) For recent reviews of various types of carbonyl ylide cycloadditions, see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.

(7) The syntheses of several oxabicycles and their deprotection chemistry was explored and will be reported at a later date.

(8) For a preparation of pyruvoyl chloride, see: Ottenheijm, H. C. J.; Tijhuis, M. W. *Org. Synth.* **1983**, *61*, 1.

(9) This modified diazotization procedure is much more efficient than the previously described phosgene/diazoethane route and is amenable to multigram scale.

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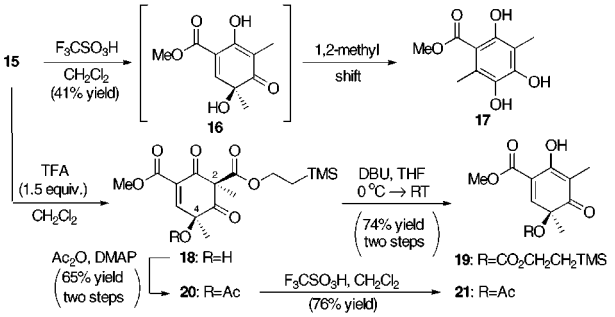
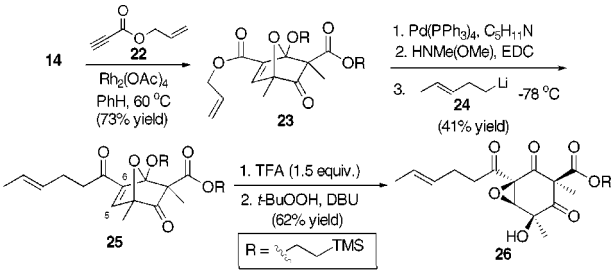
Scheme 4



Scheme 5



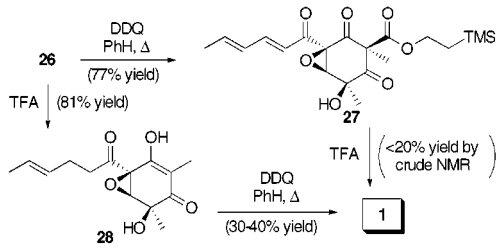
at 60 °C, thus furnishing the diastereomerically pure oxabicycle **15** in excellent yield.

With multigram quantities of **15** readily available, a series of studies investigating the removal of both (trimethylsilyl)ethyl groups to produce diene **16** was begun (Scheme 4). Although attempts with fluoride failed, it was eventually discovered that exposure of **15** to triflic acid effected complete deprotection; however, the desired diene (**16**) was unstable, undergoing aromatization via a 1,2-methyl shift to give **17** as the only isolable product.[10,11] In an effort to more delicately manipulate **15**, it was found that the cyclic acetal could selectively be opened using 1.5 equiv of TFA to provide allylic alcohol **18**, a manipulable intermediate wherein the quaternary center at C(2) prevented aromatization. To maintain protection against aromatization, the C(4) tertiary alcohol was masked prior to removal of the C(2) carboalkoxy group. Although this could be performed in a standard two-step protection/deprotection sequence (**18** → **21**), it was discovered that both manipulations could be performed in a single step by means of a base-promoted acyl migration that furnished carbonate **19**.

Unfortunately, numerous attempts to epoxidize **19**, **20**, and **21** failed, and it soon became clear that a successful epoxidation would require a free C(4) alcohol.[12]

In an effort to address the remaining epoxidation issue and facilitate installation of the sorbyl side chain, a revised route was developed (Scheme 5) wherein allyl propiolate (**22**) was used as a dipolarophile in the cycloaddition with **14** to furnish oxabicycle **23**. Facile deprotection of allyl ester **23** with catalytic $Pd(PPh_3)_4$ and piperidine, coupling to Weinreb's amine, followed by the addition of 1 equiv of 3-pentenyllithium (**24**) produced ketone **25**, a compound possessing the complete carbon framework of epoxysorbicillinol.[13,14] The incorporation of **24** had the benefit of delaying introduction of the α,β-unsaturation into the side chain, thus preventing polymerization problems and allowing the selective epoxidation of the C(5,6) double bond.[15] Exposure of **25** to 1.5 equiv of TFA opened the cyclic acetal to furnish an alcohol which, upon treatment with *t*-BuOOH and catalytic DBU, underwent smooth conversion to a single diastereomer of epoxy alcohol **26**.

Scheme 6



At this point only decarboalkoxylation and oxidation of the side chain were required to complete the synthesis.[16] To this end, treatment of **26** with DDQ effected the desired dehydrogenation to yield **27** with the completed side chain in place (Scheme 6). Deprotection of (trimethylsilyl)ethyl ester **27** by treatment with excess TFA afforded the natural product (**1**), albeit in very poor yield by crude NMR. Fortunately, reversing the order of the final two steps proved to be a much better route to **1**. Treatment of **26** with excess TFA provided enol **28** in excellent yield. The presence of the epoxide appeared to prevent aromatization even under these highly acidic conditions. Finally, treatment of **28** with DDQ furnished **1** in 30−40% yield.

In summary, we have completed the first total synthesis of (±)-epoxysorbicillinol (**1**) in 13 steps, starting from commercially available diethyl methylmalonate (**12**). A key step in this synthesis utilizes a novel 1,3-dipolar cycloaddition between an α-diazo ketone and a propiolate ester. During the course of this work, a synthetic route was developed that simultaneously avoided a disastrous thermodynamically favored aromatization, allowed a fastidious epoxidation to occur, and prevented polymerization of the side chain. Efforts toward the completion of an asymmetric synthesis of **1** using an appropriate enantioenriched rhodium catalyst for the cycloaddition are currently underway.

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Supporting Information Available: Spectral and experimental data pertaining to all new illustrated compounds and isolable intermediates generated en route but not illustrated; X-ray data for **11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Specifically, tetrabutylammonium fluoride and HF/pyridine failed to generate **16**.

(11) Elix, J. A.; Wardlaw, J. H. *Aust. J. Chem.* **1996**, *49*, 539. Spectroscopic verification of **17** was kindly provided by Professor Elix via personal communication.

(12) A separate series of experiments (see Supporting Information) showed that substrates such as **18** with the C(4) alcohol unprotected and the C(2) quaternary center in place were easily epoxidized to provide diastereomerically pure epoxides.

(13) For a preparation of 1-iodo-3-pentene from α-methylcyclopropanemethanol, see: Hrubiec, R. T.; Smith, M. B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 109.

(14) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

(15) Products derived from the addition of **24** to the ketone or ester were not found. This observed selectivity for the amide is likely due to steric factors.

(16) Attempts to isomerize an alkynyl group to produce the sorbyl side chain were unsuccessful.