ORGANIC LETTERS

2003
Vol. 5, No. 8
1321−1324

Total Synthesis of Sordaricin

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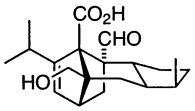
Received February 13, 2003

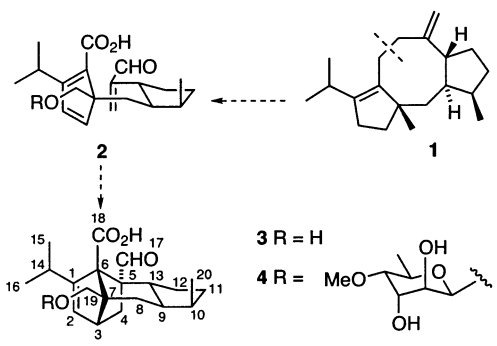
ABSTRACT



sordaricin

The total synthesis of sordaricin, the diterpene aglycone of an important class of antifungal compounds, is described. Two approaches were explored, the first of which utilized a possible biogenetic intramolecular [4 + 2] cycloaddition to form the complete carbon skeleton of the target molecule. A second approach using a tandem cycloreversion/intramolecular [4 + 2] cycloaddition sequence is also detailed.

The sordarins are an emerging class of potent antifungal compounds, of which sordarin (**4**),[1] isolated in 1971 from the ascomycete *Sordaria araneosa* Cain, is the structural prototype. The sordarins exhibit remarkable in vitro activity against a wide range of fungal pathogens such as *Candida albicans*,[2] causative agent of the common thrush infection. Additionally, sordarins show encouraging in vivo activity against several pathogenic fungi, including *Pneumocystis carnii*,[2] the major cause of lethal pneumonia among immunocompromised patients. Unlike the other major antifungals, which are targeted against fungal ergosterol biosynthesis, the sordarins are selective inhibitors of fungal protein synthesis through a specific interaction with Elongation Factor 2 (EF2),[3] a remarkable feat considering the high degree of EF2 homology (85%) between fungi and higher order Eukaryotes. The combination of potent biological activity and a novel mode of action has made the sordarins lead compounds for the development of new antifungal agents.



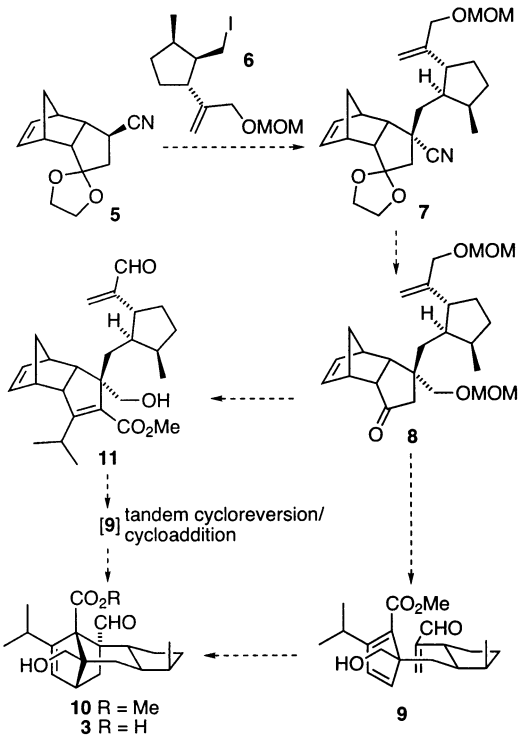
We were intrigued by the sordarins, not only because of their interesting biological activity but also because of their unusual structures[4] and possible biosynthesis. The diterpene aglycone sordaricin (**3**) has been shown to be biosynthetically derived from cycloaraneosene (**1**),[5] and it is tempting to speculate that a biogenetic route from **1** to **3** might proceed by means of an intramolecular [4 + 2] cycloaddition, such as that shown by the conversion of **2** to **3**. Two key model studies[6] showed the validity of such a postulate, by demonstrating that such an intramolecular [4 + 2] cycloaddition was possible. These reports were followed by a successful total synthesis of the methyl ester (**10**) subsequently by Kato and co-workers in which the final step was the cycloaddition **9** → **10**,[7] although **9** was not actually isolated. Our interest in sordaricin (**3**) was 2-fold: to develop a short, flexible synthesis and to conduct a thorough study of the postulated biosynthetic intramolecular [4 + 2] cycloaddition.

Our synthetic strategy (Scheme 1) involved the alkylation between iodide **6** and nitrile **5** to afford **7**. Elaboration of **7**, via **8**, would then give aldehyde **9**, which would undergo

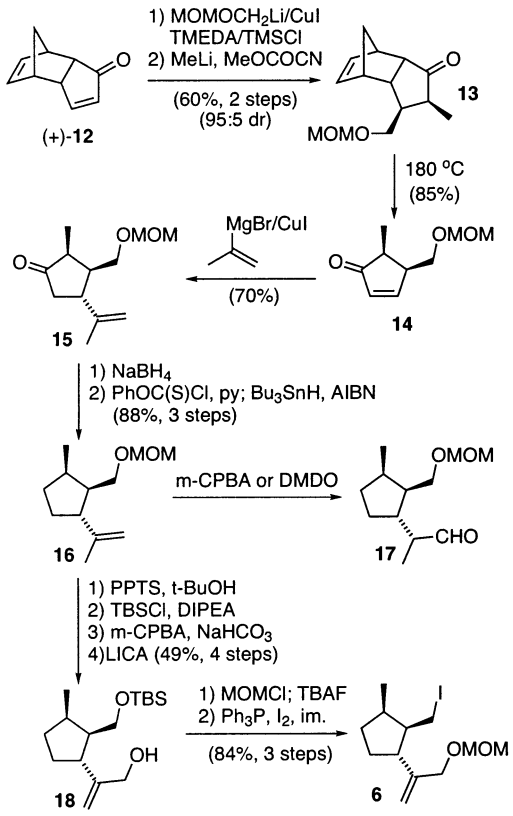
(1) Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 1178.
(2) For a review of sordarin biological activity, see: Gargallo-Viola, D. *Curr. Opin. Anti-Infect. Invest. Drugs* **1999**, *1*, 297.
(3) Justice, M. C.; Hsu, M. J.; Tse, B.; Ku, T.; Balkovec, J.; Schmatz, D.; Neilsen, J. *J. Biol. Chem.* **1998**, *273*, 3148.
(4) Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.
(5) Borschberg, H. J. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1975.
(6) (a) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595. (b) Kato, N.; Wu, X.; Takeshita, H. *Chem. Express* **1991**, *6*, 687.
(7) Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.

10.1021/ol0342599 CCC: $25.00
Published on Web 03/28/2003

Scheme 1



Scheme 2



the aforementioned intramolecular [4 + 2] cycloaddition to give us the target natural product (**3**) after demethylation. We also considered that ketone **8** might be converted into aldehyde **11**, which we hoped would undergo a tandem cycloreversion/intramolecular [4 + 2] cycloaddition to form the sordaricin carbon skeleton in a single operation. Production of the iodide **6** and nitrile **5** fragments was planned to come from (+)- and (−)-**12**,[8] respectively.

Synthesis of the iodide **6** (Scheme 2) commenced with the 1,4-addition of the cuprate derived from $MOMOCH_2Li$[9] to enone (+)-**12**, to give a silyl enol ether, which was then treated with MeLi followed by methyl iodide, to afford the *syn*-substituted tricycle **13** (60% over 2 steps, 95:5 dr). Heating **13** in 1,2-dichlorobenzene at reflux effected smooth cycloreversion to cyclopentenone **14** (85%), which upon exposure to CuI/isopropenylmagnesium bromide gave the trisubstituted cyclopentanone **15** (70%). Carbonyl deletion was next carried out over three steps, using the Barton−McCombie[10] protocol, to give the key cyclopentane **16** in good overall yield (88%). Unfortunately, all attempts to epoxidize the alkene bond present in **16** with a view to preparing **6** led to a facile [1,2] hydride shift, to form aldehyde **17**, even under the neutral conditions of dimethyl dioxirane (DMDO). However, conversion of the MOM ether **16** to the corresponding TBS ether, and subsequent treatment with *m*-CPBA gave an excellent yield of the desired epoxide, which was converted to allylic alcohol **18** (49% from **16**) upon exposure to lithium cyclohexylisopropyl amide (LICA). Allylic alcohol **18** had been prepared previously from carvone as part of an earlier study.[11] Protection of the hydroxy group as a MOM ether, followed by TBS ether removal with TBAF, gave the parent alcohol, which was readily converted into the target iodide **6** (84% over 3 steps)-using iodine/Ph_3P/imidazole.

Construction of the requisite nitrile fragment **5** (Scheme 3) was readily achieved by the 1,4-addition of KCN to enone (−)-**12**,[12] followed by ketalisation using ethylene glycol and Dowex 50-W resin (72% over 2 steps). Having achieved a synthesis of both required fragments, examination of the required alkylation was addressed. After extensive experimentation the desired product **7** could be obtained as a single diastereomer in yields between 55% and 67%, based on iodide consumption. Nitrile **7** was then reduced to the corresponding aldehyde by treatment with DIBAL-H followed by mild acidic hydrolysis using 1.0 M aqueous oxalic acid. Next, reduction of the aldehyde to the corresponding alcohol was achieved using $NaBH_4$, and protection of the hydroxyl group as a MOM ether was subsequently carried out using standard conditions (MOMCl, DIPEA, and DMAP).[13] Ketone **8** was then obtained using TsOH in

(8) For preparation of (+)- and (−)-**12**, see: (a) Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636. (b) Tanako, S.; Moriya, M.; Tanaka, K.; Ogasawara, K. *Synthesis* **1994**, 687.

(9) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495.

(10) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(11) Robinson, R. Unpublished work.

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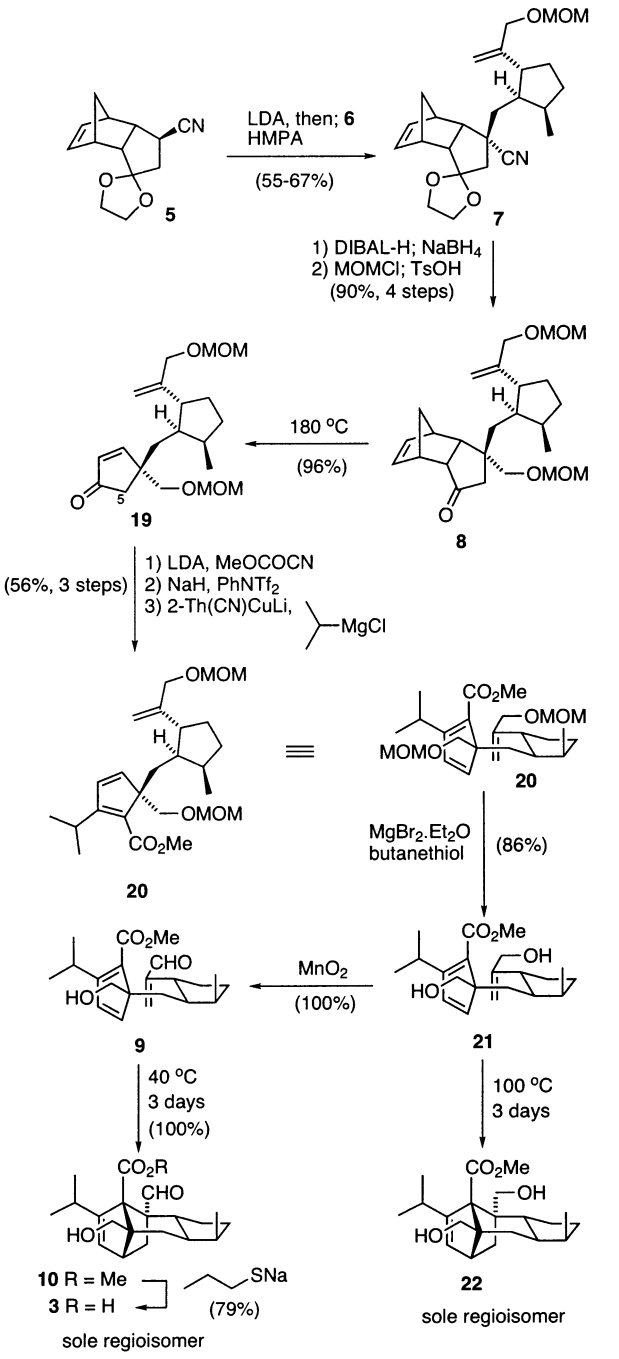
Scheme 3



acetone. This entire sequence, from **7**, could be carried out without the need for chromatography until after the final step to give a 90% overall yield of the ketone **8**. Heating **8** at 180 °C overnight effected a smooth cycloreversion, affording cyclopentenone **19** (96%). C-Acylation at C5 of **19** was carried out by enolization with LiHMDS/hexanes in ether, followed by the addition of MeOCOCN[14a] to afford the corresponding β-keto ester as a 1:1 mixture of keto and enol tautomers. The use of ether[14b] for this reaction was essential, as THF led to complete formation of the undesired enol carbonate. Next, synthesis of **20** was carried out by first converting the β-keto ester into the corresponding enol triflate, followed by the addition of the higher order cuprate derived from 2-Th(Cu)CNLi[15] and isopropylmagnesium chloride (56% over 3 steps). Removal of the MOM groups ($MgBr_2 \cdot Et_2O$, *n*-butanethiol)[16] and selective oxidation of the allylic alcohol function (MnO_2) afforded the target aldehyde **9** (86% over 2 steps). Aldehyde **9**, as expected,[7] cyclized over 3 days at 40 °C to give a quantitative yield of **10**, which could be demethylated to give sordaricin (**3**), mp 189−191 °C, $[\alpha]_D$ −55 (*c* 0.2, MeOH) [lit.[1] mp 190−191 °C, $[\alpha]_D$ −58 (*c* 0.2, MeOH)] (79% yield); spectroscopic data (^1H and ^{13}C NMR, MS, IR) were identical to those of natural material.

There is some speculation as to whether the [4 + 2] cycloaddition detailed here is involved in the biosynthesis of the sordarins. Cyclization of **9** proceeded slowly at temperatures as low as 10 °C, indicating that it is not necessary for the reaction to be enzyme-activated. However, these experiments do not prove the absence of enzyme involvement.[17] Interestingly, cyclization of diol **21** gave **22** as the only regioisomer, but in order to achieve a significant rate of reaction heating at 100 °C (3 days) was required, indicating that oxidation at C17 most likely precedes cyclization in the putative biosynthetic pathway.

The slower rate of cyclization relative to that of the aldehyde **9** is consistent with frontier orbital considerations;[18] taking the reaction between 2,4-pentadienoic acid with either acrylic acid or propene as appropriate models for the sordaricin intermediates, it is apparent that the more favorable orbital interactions are between the HOMO of the diene and the LUMO of either dienophile.[19] Then the ΔE for the HOMO of 2,4-pentadienoic acid and the LUMO of acrylic acid is 10.01 eV, while the energy gap to the LUMO of propene is 11.21 eV,[20] thus indicating that the latter process should proceed more slowly.

Investigation into the possible tandem cycloreversion/intramolecular [4 + 2] cycloaddition approach to sordaricin (**3**) began with the previously described ketone **8** (Scheme 4). Installation of the requisite carboxy and isopropyl groups was achieved in a manner similar to that detailed for the synthesis of **20** from **19** (see Scheme 3), to give **23** (69% over 3 steps). Removal of the MOM groups ($MgBr_2 \cdot Et_2O$, butanethiol)[16] followed by oxidation (MnO_2) afforded the target aldehyde **8** (92% from **23**). In the event, heating **8** in 1,2-dichlorobenzene at 180 °C for 1 h gave an inseparable 4:1 mixture of the desired product **10** and a second compound tentatively identified as the regioisomer *iso*-**10** (76% com-

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(17) For a recent publication providing evidence of an enzyme-assisted cycloaddition, see: Johansson, M.; Köpcke, B.; Anke, H.; Sterner, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 2158.

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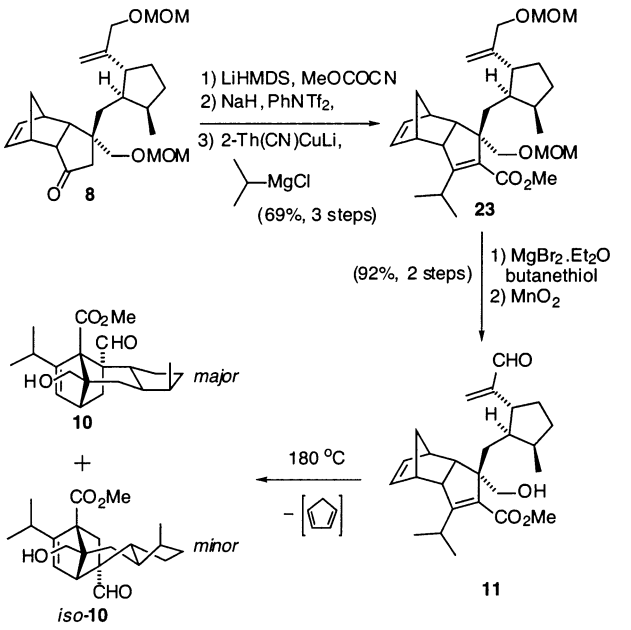
(19) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

(20) Values taken from Smith, M. B. *Organic Synthesis*; McGraw-Hill: Singapore, 1994; pp 1104−1109.

Scheme 4



bined yield). Further experimentation did not lead to any improvement in the product ratio.

In summary, an enantioconvergent total synthesis of sordaricin (**3**) has been achieved in 26 steps (longest linear sequence) from (+)-**12** in 3% overall yield, using (−)- and (+)-**12** as starting materials for key fragments **5** and **6**, respectively. This synthesis was predicated on the postulated biogenetic intramolecular [4 + 2] cycloaddition as a key step in constructing the carbon framework. A second approach to **3** utilized a tandem cycloreversion/intramolecular [4 + 2] cycloaddition as a key step but was somewhat less efficient in giving the target compound. Full details of these, and other, experiments will be reported in due course.

Acknowledgment. We thank the ANU Graduate School (Graduate School Scholarship to R.J.T), the Research School of Chemistry (Alan Sargeson Merit Award to R.J.T), and Dr. Jim Balkovec (Merck) for an authentic sample of sordaricin.

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

OL0342599