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Synthesis of (−)-Sordarin

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Abstract: The first total synthesis of (−)-sordarin (**1**) was accomplished exploiting the following key reactions: (i) Ag(I)-catalyzed oxidative radical cyclization of a cyclopropanol derivative leading to a bicyclo-[5.3.0]decan-3-one skeleton; (ii) Pd(0)-catalyzed intramolecular allylation reaction resulting in the entire strained bicyclo[2.2.1]heptan-2-one framework of sordaricin (**2**); (iii) selective dihydroxylation of terminal alkenes by the combined use of OsO_4 and $PhB(OH)_2$; and (iv) β(1,2-*cis*)-selective glycosidation via a 1,3-anchimeric assistance from a 4-methoxybenzoyl group.

Introduction

Sordarin (**1**), isolated in 1971 as a metabolite of the fungus *Sordaria araneosa*,[1] is a potent and selective inhibitor of fungal protein synthesis.[2] Despite the high-sequence homology between the fungal and mammalian protein synthesis mechanisms, sordarin is able to selectively form the stable complex of fungal elongation factor 2 (EF-2)/a ribosomal stalk protein (P0) and prevent the release of EF-2 in the course of translation.[3] This compound exhibits potent in vitro antifungal activity against several fungi such as *Candida albicans*.[4]

As shown in Figure 1, the structure of sordarin (**1**)[5] contains a diterpene aglycon, sordaricin (**2**),[6] which has a unique tetracyclic diterpene core containing a bicyclo[2.2.1]heptene framework (norbornene system) with three successive quaternary carbon centers (C-5, C-6, C-7).[7] The molecule also has an unusual 6-deoxy-glycoside residue, which is bonded with sordaricin (**2**) through a β(1,2-*cis*)-glycoside linkage.

The characteristic biological activity and the challenging molecular architecture of sordarin (**1**) have stimulated synthetic efforts directed toward its total synthesis. While there are no reports of the synthesis of sordarin (**1**), syntheses of sordaricin (**2**)[8] have been accomplished by employing the postulated biogenetic intramolecular [4+2]-cycloaddition[9] to form the polysubstituted norbornene system.

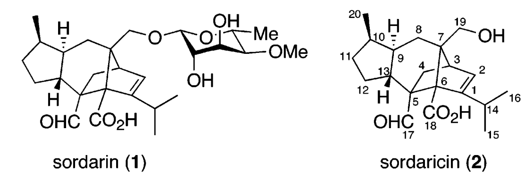

Figure 1. Molecular structures of sordarin (**1**) and sordaricin (**2**).

We have recently communicated a racemic synthesis of sordaricin (**2**),[10] based on the construction of the highly strained substituted norbornene system by a Pd(0)-catalyzed intramolecular allylation reaction.[11] Because of the interesting biological activities of sordarin (**1**), we turned our attention to the synthesis of natural sordarin and its structural analogues as well as the improvement of the synthetic route to sordaricin (**2**). Herein, we wish to report the full details of our total synthesis of (−)-sordarin (**1**).

Results and Discussion

1. Synthetic Plan. The retrosynthetic analysis for the synthesis of (−)-sordarin (**1**) is outlined in Scheme 1. The structure of sordarin (**1**) is composed of two distinct domains, sordaricin (**2**) and an unusual 6-deoxy-glycoside residue, which are linked by a β(1,2-*cis*)-glycosidic bond. Our strategy relied on the β(1,2-*cis*)-selective glycosidation of sordaricin ethyl ester **3** with fluoro sugar **4** having an acyloxy group at C-3 with the aid of a 1,3-anchimeric assistance. In turn, sordaricin ethyl ester **3** was envisaged to arise from bicyclo[2.2.1]heptan-2-one derivative **5** via the introduction of an isopropyl unit and

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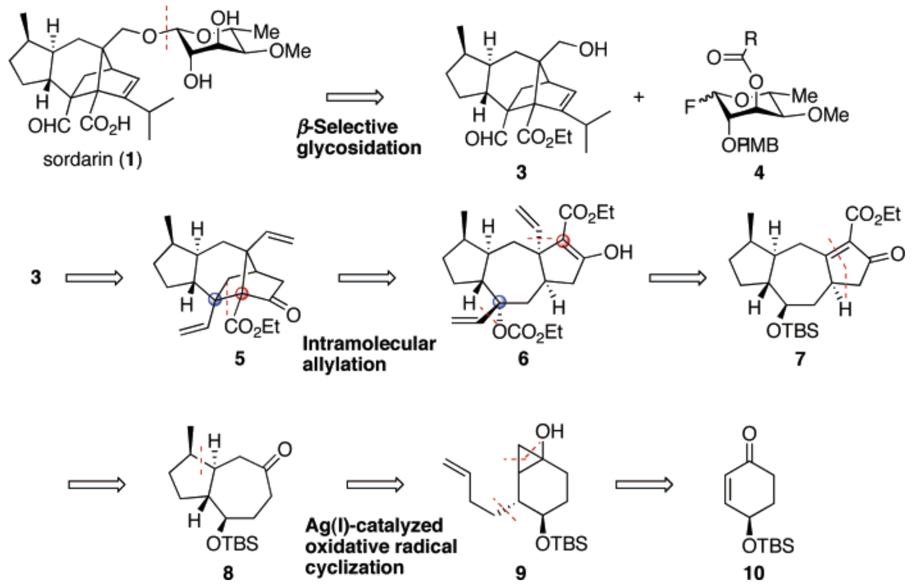
(1) Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 1178−1190.
(2) Protein synthesis is considered as one of the most attractive targets for developing novel antimicrobial agents, see: Hall, C. C.; Bertasso, A. B.; Watkins, J. D.; Georgopapadakou, N. H. *J. Antibiot.* **1992**, *45*, 1697−1699.
(3) Justice, M. C.; Hsu, M. J.; Tse, B.; Ku, T.; Balkovec, J.; Schmatz, D.; Nielsen, J. *J. Biol. Chem.* **1998**, *273*, 3148−3151.
(4) DiDomenico, B. *Curr. Opin. Microbiol.* **1999**, *2*, 509−515 and references therein.
(5) Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.
(6) It has recently become apparent that several sordaricin derivatives exhibit antifungal activities, see: Quesnelle, C. A.; Gill, P.; Dodier, M.; Laurent, D. S.; Serrano-Wu, M.; Marinier, A.; Martel, A.; Mazzucco, C. E.; Stickle, T. M.; Barrett, J. F.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 519−524.
(7) The numbers on each carbon atom of intermediates **8**, **13**, **14**, **18**, **19**, **20**, **21**, **33**, and **34** correspond to those of sordaricin (**2**).
(8) (a) Mander, L. N.; Thomson, R. J. *J. Org. Chem.* **2005**, *70*, 1654−1670. (b) Mander, L. N.; Thomson, R. J. *Org. Lett.* **2003**, *5*, 1321−1324. (c) Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002−1004.
(9) Borschberg, H. J. Ph.D. Dissertation, ETH, Zurich, Switzerland, 1975. For a review of the biogenetic intramolecular [4+2]-cycloaddition, see: (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.
(10) Kitamura, M.; Chiba, S.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 942−943.
(11) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140−145. (b) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361−4401. (c) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144−152.

Scheme 1. Retrosynthetic Analysis of Sordarin (**1**)

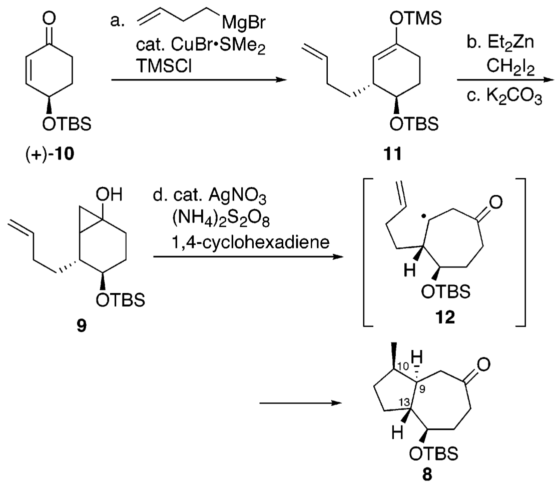


oxidative cleavages of two vinyl groups. It was anticipated that **5** would be prepared from tricyclic compound **6** by Pd(0)-catalyzed intramolecular allylation of a π-allylpalladium intermediate. Tricyclic compound **6** could be derived from bicyclic ketone **8**, which itself is prepared by the Ag(I)-catalyzed oxidative radical cyclization of cyclopropanol derivative **9** as developed in our laboratory.[12] Compound **9** was anticipated to arise from optically active (+)-4-*tert*-butyldimethylsilyloxy-2-cyclohexen-1-one (**10**).

2. Stereoselective Synthesis of Bicyclo[5.3.0]decan-3-one Compound 8. Optically active bicyclic compound **8**, incorporating the three successive chiral centers (C-10, C-9, C-13) of the *trans*-perhydroindene part of sordaricin (**2**), was prepared from optically active (+)-4-*tert*-butyldimethylsilyloxy-2-cyclohexen-1-one (**10**)[13] as summarized in Scheme 2. Thus, treatment of cyclohexenone **10** with 3-butenylmagnesium bromide in the presence of a catalytic amount of $CuBr \cdot SMe_2$, TMSCl, and HMPA in THF at −78 °C[14] produced the corresponding silyl enol ether **11** as a single stereoisomer. Cyclopropanation of this silyl enol ether **11** was carried out by using diethylzinc and diiodomethane,[15] and the resulting TMS-protected cyclopropanol was successively deprotected with a catalytic amount of potassium carbonate in methanol to afford cyclopropanol **9**. In our previous syntheseis of (±)-sordaricin (**2**),[10] bicyclo[5.3.0]-decan-3-one derivative **8** was prepared by the oxidative radical cyclization of **9** with a stoichiometric amount of manganese-(III) tris(2-pyridinecarboxylate) [$Mn(pic)_3$]. Recently, we upgraded this stoichiometric reaction to a catalytic process by the use of a $AgNO_3$–$(NH_4)_2S_2O_8$–pyridine system.[12] Treatment of **9** with a catalytic amount of $AgNO_3$, $(NH_4)_2S_2O_8$ as a reoxidant, and pyridine in the presence of 1,4-cyclohexadiene in DMF gave optically active **8** stereoselectively via the cyclization of β-keto radical intermediate **12**.

3. Synthesis of Tricyclic Compound 6. The synthetic route leading to tricyclic compound **7** is shown in Scheme 3.

Scheme 2. Stereoselective Synthesis of Bicyclo[5.3.0]decan-3-one **8**[a]

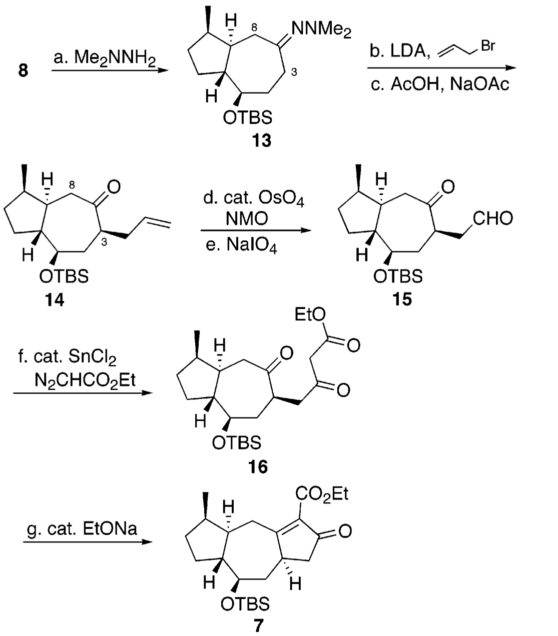


[a] Reagents and conditions: (a) 3-butenylmagnesium bromide (1.5 equiv), $CuBr \cdot SMe_2$ (0.1 equiv), TMSCl (2.0 equiv), HMPA (2.4 equiv), THF, −78 °C, 1 h, 91%; (b) Et_2Zn (1.5 equiv), CH_2I_2 (2.3 equiv), Et_2O, reflux, 13 h; (c) K_2CO_3 (0.03 equiv), MeOH, room temperature, 1 h, 82% (two steps); (d) $AgNO_3$ (0.1 equiv), $(NH_4)_2S_2O_8$ (2.4 equiv), pyridine (2.0 equiv), 1,4-cyclohexadiene (3.0 equiv), DMF, 20−25 °C, 4 h, 85%. THF = tetrahydrofuran; TMS = trimethylsilyl; HMPA = hexamethylphosphoramide; DMF = *N*,*N*-dimethylformamide.

Previously, we found that treatment of ketone **8** with LDA, followed by the addition of TMSCl, gave a regioisomeric mixture (1:1) of silyl enol ethers.[16] This problem was solved by applying *N*,*N*-dimethylhydrazone for stereo- and regioselective allylation at C(3) of **8** via the three-step sequence:[17] (i) conversion to *N*,*N*-dimethylhydrazone **13**, (ii) allylation of the hydrazone using LDA and allyl bromide, and (iii) hydrolysis of the hydrazone to ketone **14**. Dihydroxylation of the vinyl group of **14** using osmium tetroxide, followed by $NaIO_4$-induced oxidative cleavage, provided the corresponding aldehyde **15**, which was then converted into β-keto ester **16** by reaction with ethyl diazoacetate in the presence of tin(II) chloride.[18] Dehy-

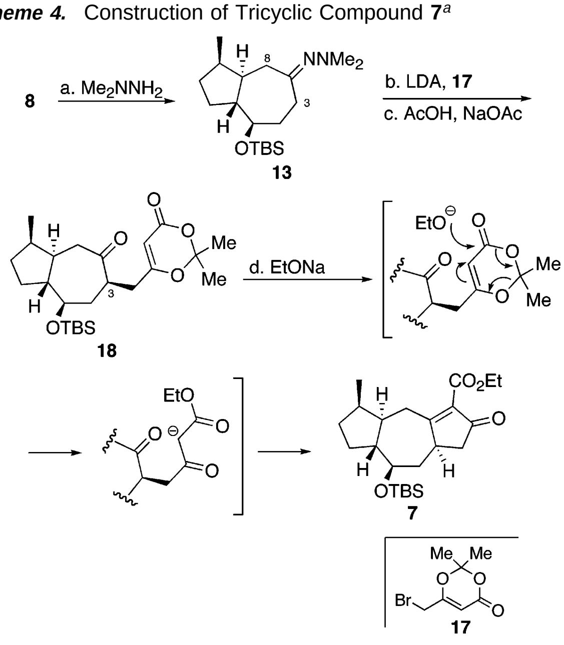
(12) Chiba, S.; Cao, Z.; El Bialy, S. A. A.; Narasaka, K. *Chem. Lett.* **2006**, *35*, 18−19.
(13) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166−173.
(14) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349−362.
(15) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323−5324.
(16) Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Ikeno, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 85−97.
(17) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3−6.

Scheme 3. Construction of Tricyclic Compound **7**[a]



[a] Reagents and conditions: (a) *N*,*N*-dimethylhydrazine (2.0 equiv), AcOH (5 drops), EtOH, room temperature; (b) LDA (1.1 equiv), then allylbromide (2.0 equiv), THF, −78 °C, 0.5 h; (c) AcOH−THF−H_2O−NaOAc (5:2:2:1 by weight), room temperature, 3 h, 85% (three steps); (d) OsO_4 (0.005 equiv), NMO (1.2 equiv), THF−H_2O, room temperature, 22 h; (e) $NaIO_4$ (2.0 equiv), THF−H_2O, room temperature, 1 h, 96% (two steps); (f) $SnCl_2$ (0.09 equiv), ethyldiazoacetate (1.6 equiv), CH_2Cl_2, room temperature, 4.5 h, then reflux, 2 h, 93%; (g) EtONa (0.3 equiv), EtOH, 0 °C, 0.5 h, 76%. LDA = lithium diisopropylamide; NMO = *N*-methylmorpholine *N*-oxide.

Scheme 4. Construction of Tricyclic Compound **7**[a]

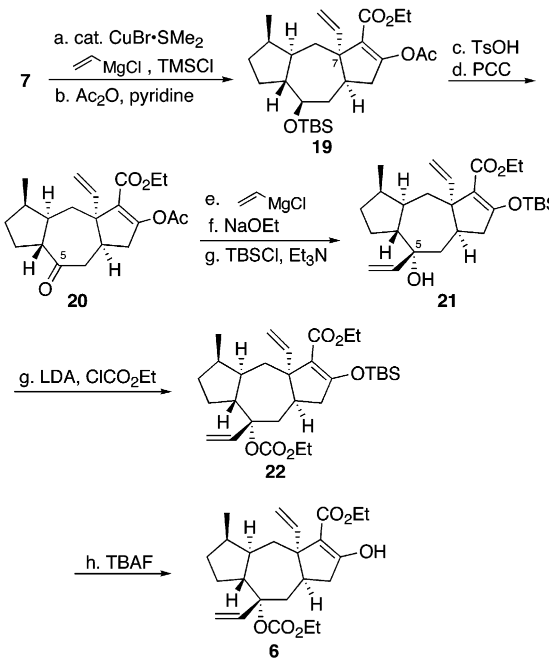


[a] Reagents and conditions: (a) *N*,*N*-dimethylhydrazine (2.0 equiv), AcOH (5 drops), EtOH, room temperature; (b) LDA (1.1 equiv), then **17** (2.0 equiv), THF, −78 °C, 1 h; (c) AcOH−THF−H_2O−NaOAc (5:2:2:1 by weight), room temperature, 3 h, 60% (three steps); (d) EtONa (2.0 equiv), EtOH, 60 °C, 0.5 h, 70%.

drative condensation of **16** catalyzed by sodium ethoxide in ethanol gave tricyclic compound **7**.

To simplify the synthesis of **7**, an alternative route was developed (Scheme 4). This improved sequence began with the reaction of lithium aza-enolate of *N*,*N*-dimethylhydrazone **13**

Scheme 5. Synthesis of Compound **6** for Palladium-Catalyzed Allylation[a]



[a] Reagents and conditions: (a) vinylmagnesium chloride (1.6 equiv), CuBr·SMe_2 (0.15 equiv), TMSCl (2.0 equiv), HMPA (4.3 equiv), THF, −78 °C, 1 h; (b) Ac_2O (2.0 equiv), DMAP (trace amounts), pyridine, room temperature, 0.5 h, 97% (two steps); (c) TsOH·H_2O (0.1 equiv), THF−H_2O, 60 °C, 15 h; (d) PCC (2.0 equiv), Celite, CH_2Cl_2, room temperature, 3 h, 90% (two steps); (e) vinylmagnesium chloride (1.9 equiv), THF, −78 °C, 1 h; (f) NaOEt (1.1 equiv), EtOH, 0 °C, 0.5 h; (g) TBSCl (1.2 equiv), Et_3N (3.0 equiv), DMAP (trace amounts), CH_2Cl_2, room temperature, 5 h, 89% (three steps); (h) LDA (1.5 equiv), $ClCO_2Et$ (1.6 equiv), THF, −78 to 0 °C, 89%; (i) TBAF (1.0 equiv), THF, 0 °C, 0.5 h, quant. DMAP = 4-dimethyl-aminopyridine; PCC = pyridinium chlorochromate; TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride.

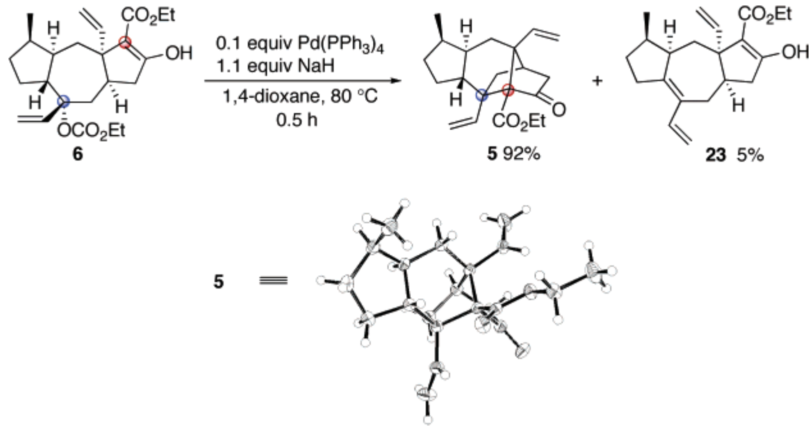
with 6-bromomethyl-2,2-dimethyl-1,3-dioxin-4-one **17**.[19] After cleavage of the *N*,*N*-dimethylhydrazone, the resulting ketone **18** was treated with sodium ethoxide in ethanol to give tricyclic keto ester **7** via deprotection of the acetonide group and successive condensation.

For the transformation of **7** to **6**, the precursor for the Pd-catalyzed intramolecular allylation, two vinyl groups were introduced as equivalents of the hydroxy methyl and formyl parts of sordaricin (**2**) (Scheme 5). Construction of the quaternary center at C(7) was accomplished via the 1,4-addition of vinylmagnesium chloride in the presence of CuBr·SMe_2 and TMSCl. Successive acetylation of the resulting enol afforded enol acetate **19**. Next, the TBS group of **19** was removed under acidic conditions, and the liberated secondary alcohol was oxidized with pyridinium chlorochromate (PCC) to ketone **20**. Addition of vinyl Grignard to the carbonyl at C(5) of **20** proceeded smoothly at −78 °C to give an allylic alcohol, and subsequent replacement of the acetyl group with TBS provided **21**. Ethoxy carbonylation of **21** and desilylation of resulting **22** with tetrabutylammonium fluoride (TBAF) gave **6**.

4. Construction of the Basic Framework of Sordaricin (2) and Synthesis of Various Bicyclo[2.2.1]heptan-2-one Derivatives. As shown in Scheme 6, construction of the bicyclo[2.2.1]-heptan-2-one framework was successfully achieved from **6** by

(18) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260.
(19) Jones, R. C. F.; Tankard, M. *J. Chem. Soc.*, *Perkin Trans. 1* **1991**, 240−241.

Scheme 6. Construction of Sordaricin Precursor **5**

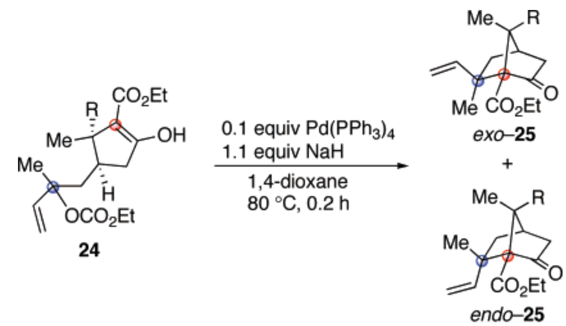


a slight modification of the original Tsuji−Trost allylation conditions.[11] When **6** was exposed to a catalytic amount of Pd(PPh_3)$_4$ and NaH, the desired intramolecular allylation furnished sordaricin precursor **5** in 92% yield along with 5% yield of β-hydride elimination product **23** as a byproduct.[20] The presence of NaH was essential for this cyclization. β-Hydride elimination product **23** was formed exclusively in the absence of NaH (the standard Tsuji−Trost reaction conditions in the case of using allylic carbonates). The structure of **5**, which contains all of the stereogenic centers of sordaricin (**2**), was secured by X-ray crystallographic analysis.[21]

Generally, bicyclo[2.2.1] systems are constructed by [4+2]-cycloadditions (Diels−Alder reactions) between cyclopentadiene derivatives and alkenes. This catalytic method has found some applicabilities as depicted in Table 1.[22] Thus, this catalytic reaction would provide a general method for the synthesis of highly substituted bicyclo[2.2.1]heptan-2-one derivatives.[23] The cyclization, however, did not proceed in a stereospecific manner, because **25b** was obtained as an *exo/endo* 5:1 mixture, even though it was carried out by using a single diastereomer of **24b** (run 3).

5. Synthesis of (−)-Sordaricin. To complete the synthesis of sordaricin (**2**) from **5**, we first adopted the strategy involving oxidative cleavage of two terminal vinyls, followed by introduction of an isopropyl unit (Scheme 7).[24] Thus, ozonolysis of (±)-**5** followed by reduction of the resulting dialdehyde proceeded smoothly to afford the corresponding diol. The resulting two

Table 1. Pd(0)-Catalyzed Synthesis of Bicyclo[2.2.1]heptan-2-ones



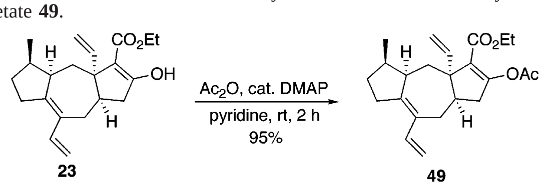
run	R (dr)[a]	yield / %[b]	*exo* : *endo*[c]
1	**24a** Me (2 : 1)	**25a** 83	3 : 2
2	**24b** vinyl (2 : 1)	**25b** 90	5 : 2
3	**24b** vinyl (1 : 0)	**25b** 89	5 : 1
4	**24c** Ph (1 : 1)	**25c** 90	5 : 3

[a] Configuration of allylic carbon in **24** was not determined. [b] Isolated yield as *endo*−*exo* mixture. [c] Stereochemistry of **25** (*exo*−*endo*) was assigned by NOESY spectroscopy.

hydroxy groups were protected as MOM (methoxymethyl) ethers to give **26**, and then the ketone was converted into enol triflate **27**. We attempted to introduce an isopropyl group onto **27** using the higher order cuprate[25] derived from lithium 2-thienylcyanocuprate [(2-Th)Cu(CN)Li][26] and isopropylmagnesium chloride, or by Pd(0)-catalyzed cross-coupling with isopropylmagnesium chloride.[27] However, the enol triflate was very unreactive, giving back only the starting material **27**. 1,2-Addition of isopropylmagnesium chloride or isopropyllithium to ketone **26** in the presence of cerium chloride[28] did not proceed at all.

We assumed that these unsuccessful results with **26** and **27** were due to the steric and electronic repulsion around the carbonyl group and the enol triflate moiety. To circumvent this problem, introduction of an isopropyl group using enol triflate **28** was examined as shown in Scheme 8. When **28** was treated

(20) The structure of **23** was confirmed by the ^{1}H and ^{13}C NMR analysis of its acetate **49**.



(21) CCDC-295066 contains the supplementary crystallographic data for compound **5**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, U.K.; fax (+44)1223-336-033; or deposit@cdc.cam.ac.uk).

(22) Synthetic schemes of the substrate **24** were depicted in the Supporting Information.

(23) There are some reports on the transition-metal catalyzed construction of bicyclo[2.2.1]heptan-2-one derivatives, see: (a) Langer, P.; Holtz, E.; Saleh, N. N. R. *Chem.-Eur. J.* **2002**, *8*, 917−928. (b) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855−2856. (c) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390−1391.

(24) This approach was carried out on racemic **5**.

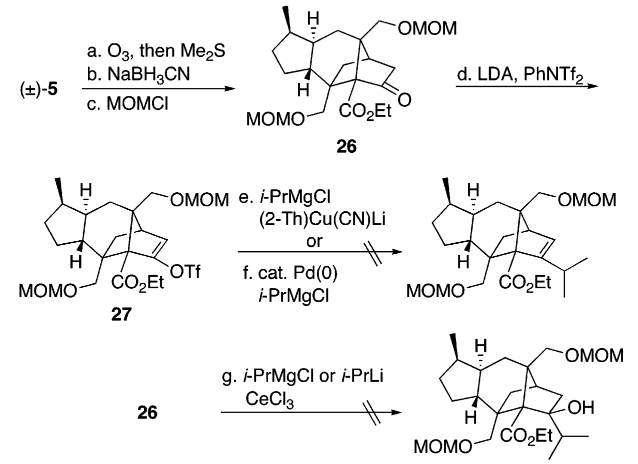
(25) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313−4316.

(26) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

(27) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.

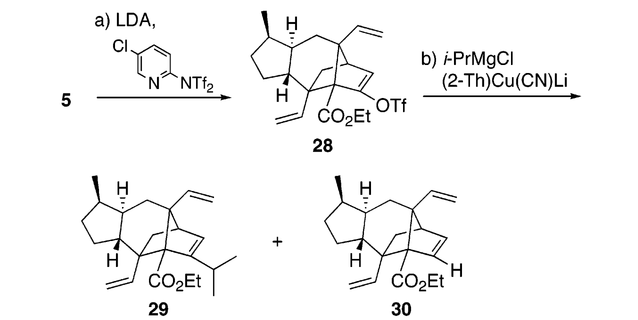
(28) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

Scheme 7. Unsuccessful Attempt To Introduce an Isopropyl Unit[a]



[a] Reagents and conditions: (a) O_3, then Me_2S (13 equiv), MeOH−CH_2Cl_2, −78 °C to room temperature, 96%; (b) $NaBH_3CN$ (2.5 equiv), THF−AcOH (10:1), room temperature, 3 h, 92%; (c) MOMCl (5.2 equiv), *i*-Pr_2NEt (6.0 equiv), CH_2Cl_2, room temperature, 2 h, 86%; (d) LDA (1.5 equiv), then $PhNTf_2$ (1.2 equiv), THF, −78 to 0 °C, 88%; (e) (2-Th)Cu(CN)Li (3.0 equiv), *i*-PrMgCl (3.0 equiv), THF−HMPA, −78 °C to room temperature, 0%; (f) $PdCl_2$(dppf) or $Pd(PPh_3)_4$ (0.1 equiv), *i*-PrMgCl (2.0 equiv), THF or Et_2O, room temperature to reflux, 0%; (g) *i*-PrMgCl or *i*-PrLi (2.0 equiv), $CeCl_3$ (2.0 equiv), THF, room temperature to reflux, 0%. MOM = methoxymethyl; Tf = trifluoromethanesulfonyl; Th = thienyl; dppf = diphenylphosphino ferrocene.

Scheme 8. Introduction of an Isopropyl Unit[a]

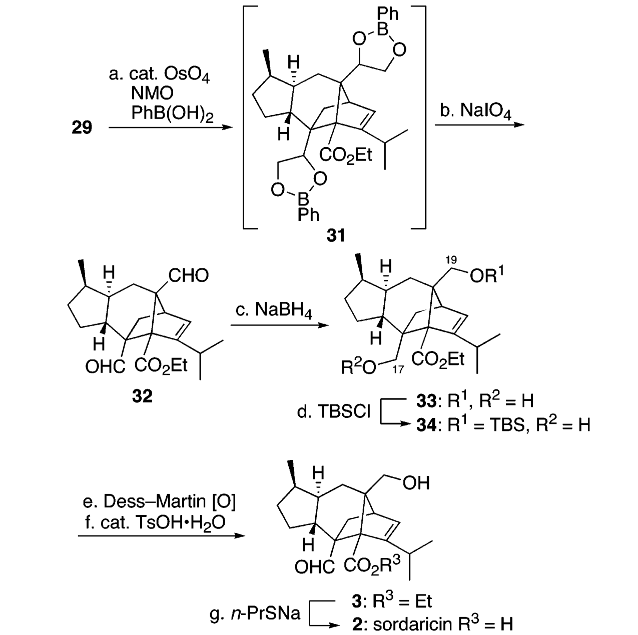


[a] Reagents and conditions: (a) LDA (1.2 equiv), then *N*-(5-chloro-2-pyridyl)triflimide (1.1 equiv), THF, −78 °C, 95%; (b) (2-Th)Cu(CN)Li (3.0 equiv), *i*-PrMgCl (3.0 equiv), THF−HMPA, −78 to −20 °C, 12 h, 86% (**29**) and 11% (**30**).

with the same higher order cuprate in the presence of HMPA,[29] the desired product **29** was isolated in 86% yield with a small amount of reduction product **30** in 11% yield.

The remaining obstacle for the synthesis of (−)-sordaricin was selective oxidative cleavage of the two vinyl groups of **29**. Ozonolysis and OsO_4−$NaIO_4$ oxidation of **28** gave complex mixtures probably due to overoxidation of the highly reactive norbornene unit. Previously, we reported the dihydroxylation of alkenes by the combined use of OsO_4 and $PhB(OH)_2$.[30] It was assumed that if the two vinyl groups were converted into bulky phenylboronic esters, the remaining norbornene part would be shielded from the overoxidation. As depicted in Scheme 9, after treatment of **29** with a catalytic amount of OsO_4, $PhB(OH)_2$, and NMO as a reoxidant, the ^{1}H NMR spectrum of the crude mixture exhibited the formation of the desired bisphenylboronic ester **31**. Successive oxidative cleavage of the

Scheme 9. Synthesis of (−)-Sordaricin (**2**)[a]



[a] Reagents and conditions: (a) OsO_4 (0.056 equiv), NMO (3.0 equiv), $PhB(OH)_2$ (3.8 equiv), CH_2Cl_2, room temperature, 12 h; (b) $NaIO_4$ (11 equiv), THF−H_2O (1:1), 50 °C, 2 h, 53% (two steps); (c) $NaBH_4$ (3.0 equiv), EtOH, room temperature, 1 h, 95%; (d) TBSCl (1.1 equiv), imidazole (3.0 equiv), DMF, 0 °C, 3 h, 90%; (e) Dess−Martin periodinane (1.3 equiv), $NaHCO_3$ (2.3 equiv), CH_2Cl_2, room temperature, 5.5 h; (f) TsOH·H_2O (0.14 equiv), THF−H_2O (10:1), 50 °C, 12 h, 90% (two steps); (g) *n*-PrSNa, HMPA, room temperature, 12 h, 89%.

resulting phenylboronic esters with $NaIO_4$ in aqueous THF afforded dialdehyde **32** in 53% yield (two steps). Reduction of **32** with $NaBH_4$ to the corresponding diol **33** and subsequent selective protection of the less hindered C(19)-hydroxy group with TBS afforded **34**. Dess−Martin oxidation[31] of the C(17)-hydroxy group to an aldehyde, followed by desilylation with TsOH, provided sordaricin ethyl ester **3**. Finally, deethylation of ester **3** with propanethiolate[32] gave (−)-sordaricin (**2**).

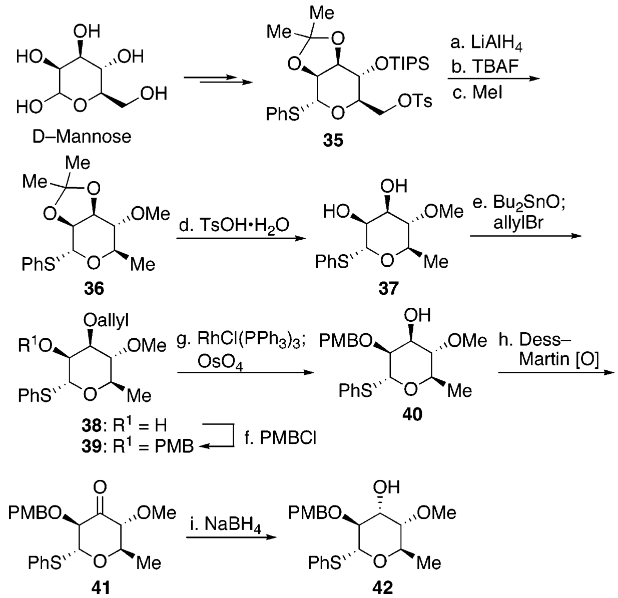
6. Construction of the Carbohydrate Unit 4. The carbohydrate fragment **4** of sordarin was prepared from D-mannose via dehydroxylation of the C-6 hydroxy and inversion of the configuration at C-3 as depicted in Schemes 10 and 11. The known tosylate **35** synthesized from D-mannose[33] was reduced with $LiAlH_4$, and the triisopropylsilyl (TIPS) was removed. Methylation of resulting alcohol led to methyl ether **36**, from which the acetonide was removed by treatment with TsOH in MeOH to give diol **37**. Tin-acetal allylation[34] of the less hindered C-3 hydroxy provided the desired C-3 allyl ether **38**. The remaining C-2 hydroxy was converted into *p*-methoxybenzyl ether **39**, and then the allyl group was removed by sequential treatment with $RhCl(PPh_3)_3$ and OsO_4/NMO furnishing alcohol **40**. Inversion at the C-3 center was realized by a two-step sequence: (i) conversion of **40** into ketone **41** by Dess−Martin oxidation and (ii) $NaBH_4$ reduction.[35]

The resulting alcohol **42** led to benzoyl ester **43a**, 4-methoxybenzoyl ester **43b**, 2,4-dimethoxybenzoyl ester **43c**, and TBS

(29) In the absence of HMPA, the desired **29** was obtained only in 58% yield along with 35% yield of the hydride adduct **30**.

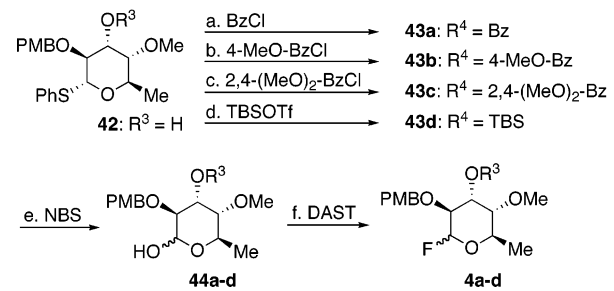
(30) Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* **1988**, 1721−1724.
(31) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(32) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459−4462.
(33) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; Suzuki, H.; Flyaktakidou, K. C.; Baudoin, O.; van Delft, F. L. *Chem.-Eur. J.* **2000**, *6*, 3095−3115.
(34) David, S.; Thieffry, A.; Veyrieres, A. *J. Chem. Soc.*, *Perkin Trans. 1* **1981**, 1976−1801.

Scheme 10. Construction of Carbohydrate Part **4**[a]



[a] Reagents and conditions: (a) $LiAlH_4$ (1.3 equiv), THF, reflux, 7 h; (b) TBAF (1.1 equiv), THF, room temperature, 1 h; (c) NaH (1.2 equiv), MeI (3.0 equiv), DMF, room temperature, 2 h, 87% (three steps); (d) ethylene glycohol (1.4 equiv), TsOH•H_2O (0.1 equiv), MeOH, 50 °C, 12 h, 87%; (e) Bu_2SnO (1.1 equiv), toluene, reflux, 3 h; allylBr (1.5 equiv), Bu_4NI (0.2 equiv), reflux, 3 h, 95%; (f) NaH (1.1 equiv), PMBCl (1.3 equiv), Bu_4NI (0.2 equiv), DMF, 50 °C, 1 h, 93%; (g) $RhCl(PPh_3)_3$ (0.03 equiv), DABCO (1.5 equiv), EtOH−H_2O (10:1) reflux, 1 h, then OsO_4 (0.05 equiv), NMO (1.2 equiv), acetone−H_2O (10:1), room temperature, 2 h, 82% (two steps); (h) Dess−Martin periodinane (1.5 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2, room temperature, 4 h, 81%; (i) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 0.5 h, 76% (dr = 25:1); DABCO = 1,4-diazabicyclo[2.2.2]octane.

Scheme 11. Construction of Carbohydrate Parts **4**[a]



[a] Reagents and conditions: (a) BzCl (2.0 equiv), DMAP (trace amounts), pyridine, room temperature, 2 h, 92%; (b) 4-MeO−BzCl (3.0 equiv), DMAP (trace amounts), pyridine, room temperature, 2 h, 99%; (c) 2,4-$(MeO)_2$−BzCl (2.0 equiv), DMAP (trace amounts), pyridine, room temperature, 12 h, 81%; (d) TBSOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), room temperature, 2 h, 98%; (e) NBS (1.5 equiv), acetone−H_2O (10:1), room temperature, 1 h, 95% (**44a**), 96% (**44b**), 68% (**44c**), and 95% (**44d**); (f) DAST (1.5 equiv), CH_2Cl_2, 0 °C, 0.2 h. NBS = *N*-bromosuccinimide; DAST = (diethylamino)sulfur trifluoride.

ether **43d**, respectively (Scheme 11). Phenyl thioglycosides **43a−d** were converted into lactols **44a−d** by the action of NBS in aqueous acetone, and then exposure to (diethylamino)sulfur trifluoride (DAST) led to the rapid conversion to the desired glycosyl fluorides **4a−d**.

7. *β*(1,2-*cis*)-Selective Glycosidation: Model Study. We expected that the desired *β*-selective glycosidation would be realized by a 1,3-anchimeric assistance[36,37] from the acyloxy group at C-3 (Scheme 12).

A model reaction was examined with neopentyl alcohol (**45**) as the glycosyl acceptor and glycosyl fluorides **4** under

Scheme 12. 1,3-Anchimeric Assistance

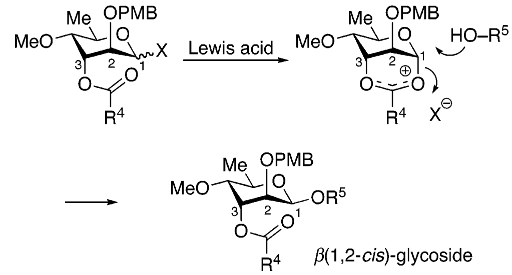
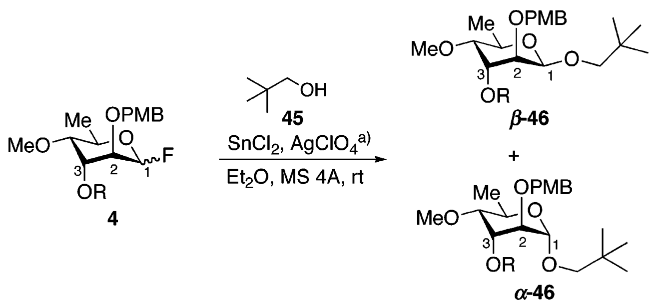
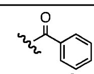
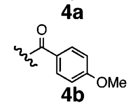
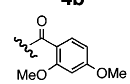


Table 2. Glycosidation of Neopentyl Alcohol (**45**)

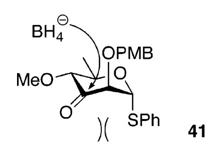


run	R	time / h	yield / %[b]	*β* : *α*[c]
1	 **4a**	1.5	**46a** 92	2.5 : 1
2	 **4b**	1.5	**46b** 92	3 : 1
3	 **4c**	5	**46c** 69	2.5 : 1
4	$SiMe_2$(*t*-Bu) **4d**	1	**46d** 80	1.5 : 1

[a] Three equivalents of neopentyl alcohol and 1.1 equiv of $SnCl_2$ and $AgClO_4$ were used. [b] Isolated yield. [c] Determined by NOESY measurement.

Mukaiyama conditions[38] ($SnCl_2$, $AgClO_4$ in Et_2O) (Table 2). In the case of glycosyl fluoride **4a** having a benzoyl group at C-3 (run 1), the coupling reaction proceeded smoothly to afford *β*- and α-anomers **46a** in 92% yields with 2.5:1 (*β*:α) selectivity.

(35) The hydride attack occurred from the opposite side of the bulky thiophenyl group at C-1, which occupies an axial position (shown below). The configuration of **42** was readily assigned by inspection of the 1,2-coupling constant.

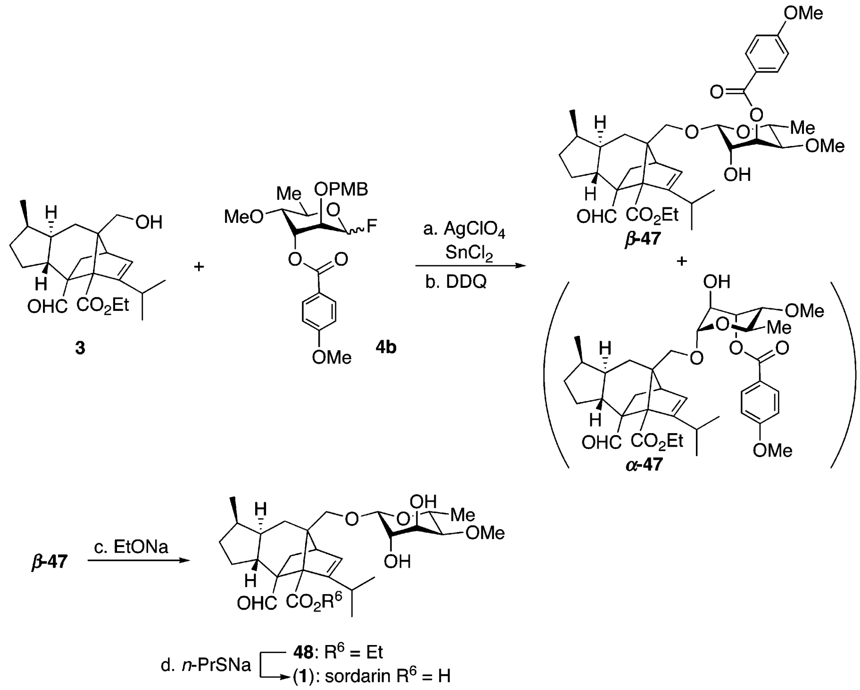


(36) There are some reports on the synthesis of *β*-2-deoxyribonucleosides using the 1,3-anchimeric assistance, see: (a) Mukaiyama, T.; Uchiro, H.; Hirano, N.; Ichikawa, T. *Chem. Lett.* **1996**, 629−630. (b) Mukaiama, T.; Hirano, N.; Nishida, M.; Uchiro, H. *Chem. Lett.* **1996**, 99−100. (c) Young, R. J.; Shaw-Ponter, S.; Hardy, G. W.; Mills, G. *Tetrahedron Lett.* **1994**, *35*, 8687−8690. (d) Lavallee, J. F.; Just, G. *Tetrahedron Lett.* **1991**, *32*, 3469−3472. (e) Ichikawa, Y.; Kubota, H.; Fujita, K.; Okauchi, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 845−852.

(37) Wiesner et al. reported the synthesis of *β*-2-deoxyglycosides by the anchimeric assistance of a *N*-methylurethane group and a 4-methoxybenzoyl group, see: Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300−314. However, Binkley et al. suggested that the anchimeric assistance from the C-3 position was not the dominating characteristic of glycosyl donors having an acyloxy group at the C-2 position, see: Binkley, R. W.; Koholic, D. J. *J. Carbohydr. Chem.* **1988**, *7*, 487−489.

(38) Mukaiyama, T.; Murai, Y.; Sonoda, S. *Chem. Lett.* **1981**, 431−432.

Scheme 13. Synthesis of (−)-Sordarin (**1**)[a]



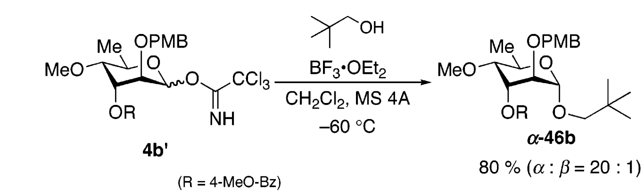
[a] Reagents and conditions: (a) **4b** (1.5 equiv), $AgClO_4$ (1.6 equiv), $SnCl_2$ (1.6 equiv), MS 4A, Et_2O, room temperature, 4 h; (b) DDQ (1.5 equiv), CH_2Cl_2−H_2O (10:1), room temperature, 2 h, 79% (***β*-47**) and 12% (**α-47**) (two steps); (c) EtONa (1.0 equiv), EtOH, room temperature, 4 h, 97%; (d) *n*-PrSNa, HMPA, room temperature, 12 h, 95%.

A slight improvement of the selectivity (β:α = 3:1) was observed by using 4-methoxybenzoate **4b** (run 2).[39,40] Introduction of a 2,4-dimethoxybenzoyl group lowered the yield (69%) and the β:α ratio (2.5:1) (run 3). Glycosidation with the comparatively bulky TBS-protected donor **4d** (run 4) gave low selectivity (β:α = 1.5:1).

8. Total Synthesis of Sordarin. Completion of the total synthesis of sordarin (**1**) is shown in Scheme 13. β(1,2-*cis*)-Selective glycosidation of sordaricin ethyl ester **3** with glycosyl fluoride **4b** by the Mukaiyama's method gave the desired coupling products with good selectivity (β:α = 6.5:1) judged by ^{1}H NMR spectroscopy of the diastereomeric mixtures. Successive deprotection of the PMB ether by treatment with DDQ led to the isolation of β- and α-anomers **47** in 79% and 12% yields, respectively. This better selectivity was probably due to not only 1,3-anchimeric assistance from the 4-methoxybenzoyl group, but also the steric effect of the rather bulky sordaricin ethyl ester **3**. Finally, removing the 4-methoxybenzoyl group of ***β*-47** using EtONa in EtOH, followed by deethylation of sordarin ethyl ester **48** with propanethiolate, gave sordarin (**1**). The physical and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, R_f, and HRMS) and biological activity[41] of synthetic sordarin matched those of an authentic sample.

(39) When this reaction was examined in CH_3CN instead of Et_2O, **α-47b** was preferentially obtained in 46% yield with 1:3 (β:α) selectivity.

(40) Interestingly, in the case of trichloroimidate **4b′** as a glycosyl donor, α-selective glycosidation proceeded to give **46b** in 80% yield with 1:20 (β:α) selectivity.



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Supporting Information Available: Experimental procedures, compound characterization, ^{1}H NMR spectra of selected compounds, and a CIF file giving crystallographic data for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA060408H

(41) Synthetic sordarin was tested for fungal growth inhibition in *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. neoformans*.