

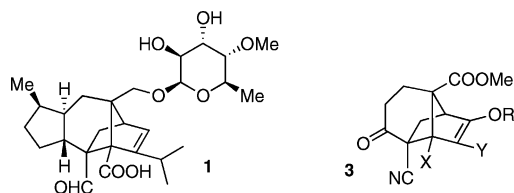
An Avenue to the Sordarin Core
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ABSTRACT



We describe a synthesis of ketones **3** (X = O–R or CN; Y = H or alkyl), which are useful building blocks for the preparation of analogs of the potent antifungal agent sordarin, **1**. Congeners of **1** constructed from **3** should permit detailed SAR investigations of the terpenoid core of the natural product.

Fungal organisms are the etiologic agents of a number of human pathologies, which become especially problematic in immunocompromised individuals such as AIDS and cancer patients.¹ Fungal infections are also of major concern in agriculture, where they can significantly reduce yields and diminish profitability.² The search for new antifungal agents thus remains a key objective both in medicine and in agricultural science.

Substances that exert antifungal action by novel mechanisms are of special interest, and noteworthy in such a context is a family of natural products known as the sordarins³ (Figure 1), which block protein synthesis by inhibiting the

fungal elongation factor 2.⁴ Sordarin, **1**, has been the focus of considerable structure–activity research, but efforts have concentrated on modification of the glycosyl unit.⁵ It is known that the aglycone of sordarins, which is termed sordaricin, **2**, may be O-alkylated to yield congeners that are endowed with activity comparable to that of the natural product;⁶ however, except for the fact that bioactivity is retained upon replacement of the CHO group in **1** with a

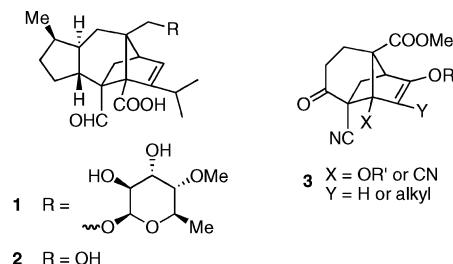


Figure 1. Sordarin (**1**), sordaricin (**2**), and ketones **3** targeted in the present study.

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CN substituent,⁶ no information is in the public domain with respect to the role of the subunits that adorn the terpenoid core (the COOH group, the isopropyl substituent, the cyclopentane ring).

A resurgence of interest in sordarins has occurred in the past few years, as attested by recent synthetic activity⁷ that nicely complements early work dating from 1993.⁸ The chemistry developed during these important efforts could surely be harnessed to furnish analogs that may clarify the function of the various segments of the sordarin core. A more practical alternative might be to focus on ketones **3**, which, arguably, could be expeditiously elaborated to sordarin analogs displaying variously modified terpenoid units. A concise avenue to **3** is presented herein, together with a discussion of unusual chemical properties observed for various synthetic intermediates.

Our approach to **3** emphasizes low cost and ease of execution, while regarding issues of absolute stereocontrol as secondary, at least at this stage. The retrosynthetic considerations adumbrated in Figure 2 identified enones **5**

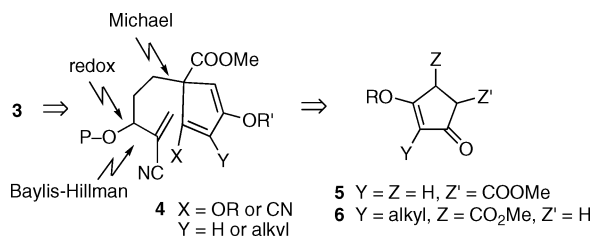
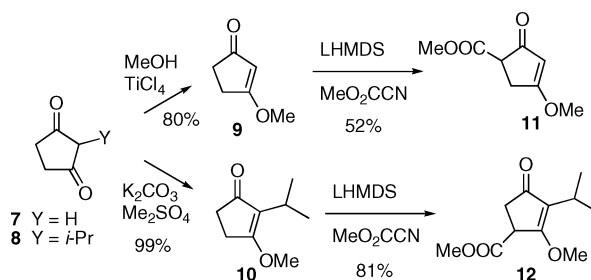


Figure 2. Retrosynthetic analysis of ketones **3**.

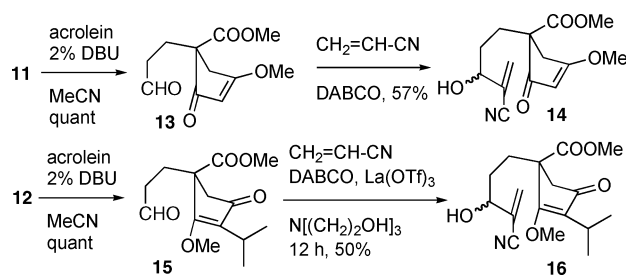
and **6** as suitable starting points for our effort. The preparation of these educts proceeded from 1,3-diones **7** and **8** (Scheme 1). Thus, **7** was converted into **9** with MeOH/TiCl₄,⁹ while **10** was best prepared by O-methylation of **8**¹⁰ with Me₂SO₄/K₂CO₃. Deprotonation of 2-unsubstituted enone **9** with LHMDS produced a kinetic enolate, which reacted with the Mander reagent¹¹ to yield the known¹² **11** (Scheme 1). In accord with Koreeda,¹³ however, the 2-substituted analog,

Scheme 1. Preparation of the Requisite Cyclopentenones



10, reacted under identical conditions to give **12**, via a thermodynamic enolate. Michael reaction of ketoesters **11** and **12** with acrolein in the presence of 2 mol % of DBU proceeded in quantitative yield (Scheme 2). Larger quantities

Scheme 2. Michael–Baylis–Hillman Avenue to Enones 14–16



of DBU promoted incomplete conversion, seemingly due to the acceleration of a competing retro-Michael expulsion of acrolein from the products. Aldehydes **13** and **15** are sensitive materials that degrade easily on silica gel. Fortunately, they emerged in a state of high purity and were utilized in the subsequent Baylis–Hillman¹⁴ step without purification. The kinetics of the latter reaction are notoriously slow. In neat acrylonitrile, **13** reacted at a reasonable rate, but **15** required more than 4 days to advance to **16** (68% chromatographed). The reasons behind the poor reactivity of **15** remain unclear. A 9-fold rate acceleration was achieved under Aggarwal conditions (La(OTf)₃ and triethanolamine as cocatalysts),¹⁵ but to the slight detriment of yield (50% chromatographed). In either case, the reaction furnished **14** and **16** as a mixture of alcohol diastereomers. However, this was inconsequential, because the alcohol in question is destined to undergo

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(11) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1990**, *70*, 256.

(12) Compound **11** is known: (a) Irie, H.; Katakawa, J.; Tomita, M.; Mizuno, Y. *Chem. Lett.* **1981**, 637. (b) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385.

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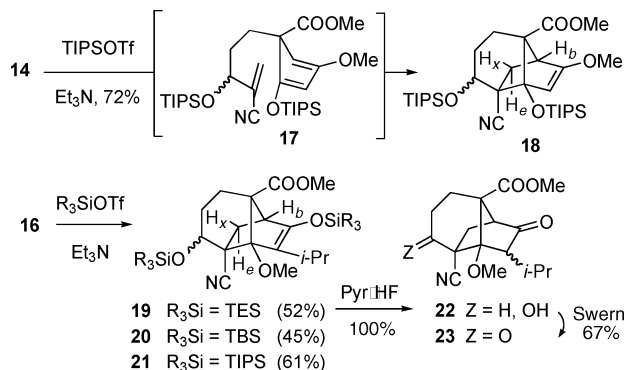
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ultimate oxidation to a ketone, thereby removing stereogenicity at the level of the associated C atom. The diastereomeric mixtures of **14** and **16** were thus advanced through the synthesis without separation.

Sordarin-like scaffolds displaying a bridgehead oxygen functionality were reached upon exposure of **14** and **16** to excess trialkylsilyl triflate/ Et_3N at room temperature. This induced formation of a presumed bis-trialkylsilyl derivative such as **17** (not isolated), which underwent a spontaneous intramolecular Diels–Alder reaction to furnish the expected adducts as mixtures of diastereomers. The transformation proceeded best when TIPS-OTf was used as the silylating agent, resulting in formation of **18** and **21** in 72% and 61% chromatographed yield, respectively. As exemplified in Scheme 3 with **19**, the use of TES-OTf in the same reaction

Scheme 3. Assembly of a Sordarin Core with Bridgehead Oxygen Functionalities



afforded a lower 52% yield. Complete regioselectivity (500 MHz ^1H NMR) was observed in all such reactions, as expected on the basis of bond polarization in both diene and dienophile units. In particular, diagnostic ^1H coupling constants were observed for the bridgehead, exo, and endo protons (cf. H_b , H_x , and H_e in **18–21**) situated on the emerging bicyclo[2.2.1]heptane system.¹⁶ The conversion of **19** to diketone **23** (mixture of *i*-Pr epimers) served to demonstrate a critical desilylation–oxidation step.

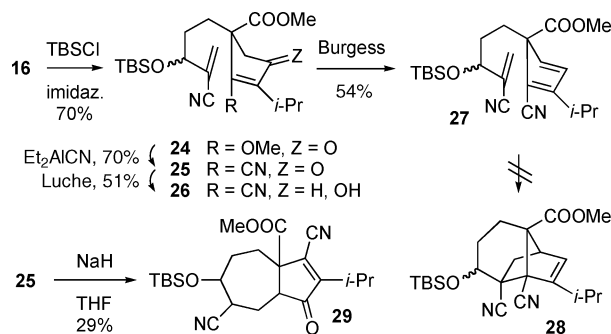
Educts suitable for the synthesis of congeners of **3** that exhibit a bridgehead CN group were obtained from **16** upon protection of the secondary alcohol as a TBS ether¹⁷ and reaction with diethylaluminum cyanide¹⁸ (Scheme 4). The resultant **25** was then advanced to **27**, which we wished to convert to **28** by an intramolecular Diels–Alder reaction. The presence of an electron-withdrawing CN group on both diene and dienophile units of **27** was not a concern *per se*: an electronically similar cycloaddition proceeds easily¹⁹ and with the correct regioselectivity.²⁰ A potentially more serious obstacle was the notoriously poor Diels–Alder reactivity of

(16) For example, for **18**, $J_{\text{bx}} = 4.1$ Hz; $J_{\text{be}} = 0$ Hz; $J_{\text{ex}} = 13.6$ Hz. For **20**, $J_{\text{bx}} = 4.4$ Hz; $J_{\text{be}} = 0$ Hz; $J_{\text{ex}} = 13.1$ Hz. See Supporting Information for full details.

(17) Protection as a TES ether resulted in intermediates that reacted poorly in the steps delineated in Scheme 5.

(18) Nagata, W.; Yoshioka, M. *Org. React.* **1984**, 25, 255.

Scheme 4. Chemistry of Cyanoenones



cyanodienes.²¹ In spite of our hope that the intramolecular nature of the reaction would overcome kinetic barriers, **27** proved to be stable up to 160 °C, above which temperature it decomposed.

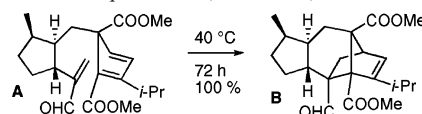
The reluctance of **27** to cyclize to **28** contrasts with the facile reaction of the corresponding ester-substituted cyclopentadiene,¹⁹ suggesting that the HOMO energy of **27** must be significantly lower than that of its ester-substituted relative. Semiempirical methods detected no appreciable differences in energies between the frontier molecular orbitals (FMOs) of the COOMe- and CN-substituted cyclopentadienes shown in Table 1,²² even though the Hammett σ

Table 1. Calculated Orbital Energies (eV)

		EH / MM*	MNDO	AM1	PM1	DFT (6-31G*)
	LUMO	−9.67	−0.58	−0.41	−0.51	+6.50
	HOMO	−12.23	−9.43	−9.35	−9.48	+4.29
	LUMO	−9.54	−0.23	−0.41	−0.63	+6.15
	HOMO	−12.11	−9.43	−9.30	−9.46	+3.31

values for a CN group are more positive than those of a COOMe group.²³ However, DFT calculations (6-31G*)

(19) The reaction in question is (refs 7a,b, 8):



(20) The cyclopentadiene unit in **27** lacks an oxygen substituent that might direct formation of the correct regioisomer of the adduct. However, **A** produces **B** only (ref 18), consistent with the fact that 2,4-pentadienoic acid reacts with acrylic acid to give a cycloadduct that displays vicinal COOH groups (Davalian, D.; Garratt, P.; Koller, W.; Mansuri, M. *J. Org. Chem.* **1980**, 45, 4183). On this basis, we anticipated good regioselectivity in the Diels–Alder cyclization of **27**.

(21) Snyder, H. R.; Poos, G. I. *J. Am. Chem. Soc.* **1950**, 72, 4104. However, 1-cyanocyclopentadiene may be more reactive than other cyanodienes, in that it combines with tetracyanoethylene (admittedly a highly reactive dienophile) even at −25 °C: Banert, K.; Koehler, F.; Meier, B. *Tetrahedron Lett.* **2003**, 44, 3781.

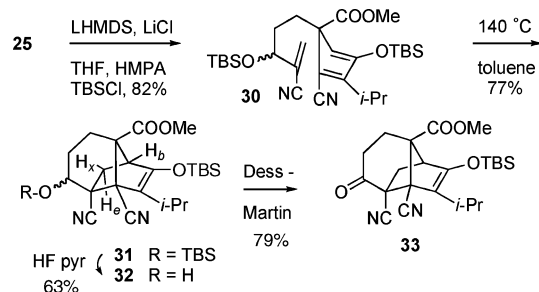
(22) These molecules are computationally more tractable mimics of the actual systems. Calculations were carried out with the Hyperchem package, available from Hypercube, Inc. (www.hyper.com).

(23) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, New York, 2001; pp 368 ff.

carried out on MM⁺-optimized structures revealed a much lower HOMO energy for the cyano compound relative to its ester analog ($\Delta E \approx 1$ eV), thereby accounting for the problematic reaction of **27**.

A plausible cure for the above problem was to induce Diels–Alder cyclization of a more reactive enol silyl ether derivative of **25**, as seen earlier in Scheme 3. But in sharp contrast to **14–16**, cyanoenone **25** proved to be fiercely resistant to enol silylation,²⁴ even under Corey–Gross²⁵ conditions. Such a reluctance to form a silyl enol ether was mystifying in light of the reportedly uneventful O-silylation of 4-oxo-2-pentene-carbonitrile.²⁶ In order to determine whether inherent barriers exist to the enolization of **25**, the compound was treated with NaH in THF. This led to a product **29** of intramolecular Michael reaction (29%; Scheme 4), signaling that the enolate in question is, after all, accessible, and that the failure of the foregoing silylation reactions was attributable to an insufficient kinetic reactivity of the base employed for the deprotonation of the substrate.²⁷ Accordingly, **25** was exposed to the action of LHMDS (excess)²⁸ and LiCl²⁹ in THF–HMPA, in the presence of TBSCl. Compound **30** thus emerged in 82% yield³⁰ (Scheme 5). In yet another manifestation of the HOMO-lowering

Scheme 5. Assembly of a Sordarin Core with a Bridgehead Cyano Functionality



influence of the CN substituent, siloxy diene **30** exhibited no proclivity whatsoever to undergo intramolecular Diels–Alder reaction at room temperature. This behavior contrasts with that of its congeners of the type **17**. Indeed, cyclization required heating at 140 °C for 12 h (toluene, pressure tube, 77% chromatographed). Fortunately, product **31** emerged as a single regioisomer (¹H NMR).³¹ The target ketone, **33**, was easily reached from **31** upon treatment with pyridine–HF complex, which induced selective release of the TBS group from the secondary alcohol and uneventful Dess–Martin oxidation of the emerging **32**. This achieved the construction of a sordarin precursor in which a CN group substitutes for the bridgehead carboxy functionality of **1**.

We believe that ketones of the type **23** and **33** are quite valuable for a study of the structure–activity relationship of the terpenoid segment of sordarin. The straightforward approach to these intermediates presented herein should facilitate the search for new antifungal agents of interest in human medicine as well as in agrochemical technology.

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

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(31) For **31**, $J_{\text{bx}} = 3.9$ Hz; $J_{\text{be}} = 0$ Hz; $J_{\text{ex}} = 13.5$ Hz.

(24) Trialkylsilyl halides/tertiary amines in the presence of Lewis acids (Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807), trialkylsilyl triflates (Review: Bach, T.; Brummerhop, H. *J. Prakt. Chem.* **1999**, *341*, 410), bis(trimethylsilyl) acetamide (Cameron, D. W.; Feutrell, G. I.; Perlmutter, P. *Tetrahedron Lett.* **1981**, *22*, 3273) or bis(trimethylsilyl) trifluoroacetamide (Fattori, D.; de Guchteneere, E.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 7415), or TMSI/HMDS (Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 73), over a range of temperatures, had no effect on **25**: the enone was recovered unchanged from all such reactions.

(25) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(26) Hosokawa, T.; Aoki, S.; Murahashi, S. *Synthesis* **1992**, 558.

(27) The “enormous mechanistic complexity” of ketone deprotonation (Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571) invites prudence in formulating simplistic explanations for the observed phenomena.

(28) A significant excess of Li-base was essential in the present case, even though excess base may actually inhibit enolization – at least in the case of esters: Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.

(29) It is well established that lithium halides enhance the reactivity of organolithium species (the “LiX effect”): (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202. (c) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533. (d) Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385. (e) Pratt, L. M.; Newman, A.; St. Cyr, J.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* **2003**, *68*, 6387.

(30) The corresponding TMS enol ether was too labile, while the TES enol ether afforded poor yields in the subsequent intramolecular Diels–Alder reaction.