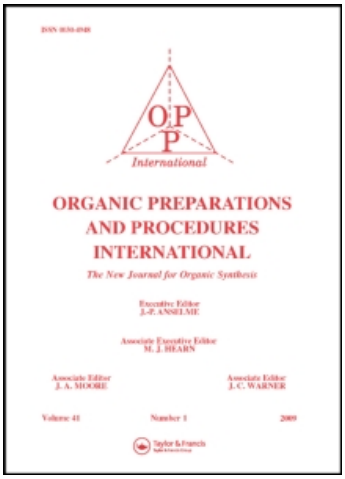

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Progress towards the Synthesis of Sordarin and its Analogs

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Introduction

Fungal infections are of small concern to healthy persons, but they can become life threatening in immunocompromised individuals, such as AIDS and cancer patients, as well as recipients of organ transplants. As a result of advances in the management of such conditions, the number of immunosuppressed subjects has been on the rise, and with it, the incidence of mycoses.[1] These infections are treatable with appropriate drugs, notable among which are the azoles,[2–4] the polyenes,[5] and the echinocandins.[6,7] Such agents act by undermining the integrity of the fungal cell membrane by binding ergosterol or inhibiting its biosynthesis.[8,9] Unfortunately, the very mechanism of action and pharmacological properties of these drugs overshadow their use on grounds of toxicity, side effects, drug-drug interaction, resistance,[10] and, for the echinocandins, lack of oral bioavailability. An unmet need in antimycotic therapy is a potent, safe, orally bioavailable agent with a novel mode of action.[11,12] A natural product known as sordarin, **1**, may be the key to such an objective.

Sandoz scientists isolated sordarin from the fungus, *Sordaria araneosa* and patented it in 1967 under the name of SL 2266 (*Figure 1*).[13] Sordarin and congeners were subsequently found in other species of filamentous fungi.[14] Unlike the foregoing drugs, the target of **1** is the so-called fungal elongation factor 2 (EF2).[15,16] Sordarin stabilizes the EF2/ribosome complex, thereby blocking translocation and inhibiting protein synthesis. Such a novel mode of action has engendered considerable interest in **1** as a possible antifungal resource. However, its activity is species-dependent. For instance, it is quite potent against *Candida*[17,18] (*Figure 1*) and *Saccharomyces cerevisiae*,[19] but it is inactive toward other fungi. Fermentation provides a reliable supply of sordarin.[20,21] A number of pharmaceutical laboratories have thus sought analogs with a broader spectrum of activity through chemical modification of the natural product.

The reaction of **1** with concentrated aqueous HCl affords a diterpenoid aglycone **2** which is termed sordaricin, and which is essentially devoid of biological activity (*Figure 2*). Its structure, together with that of sordarin, was disclosed in 1971.[22,23] Both compounds exhibit an aldehyde and a carboxylic acid in a vicinal arrangement. The tetracyclic framework

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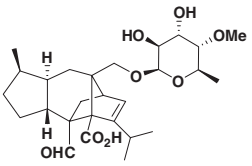


Sordarin (1)

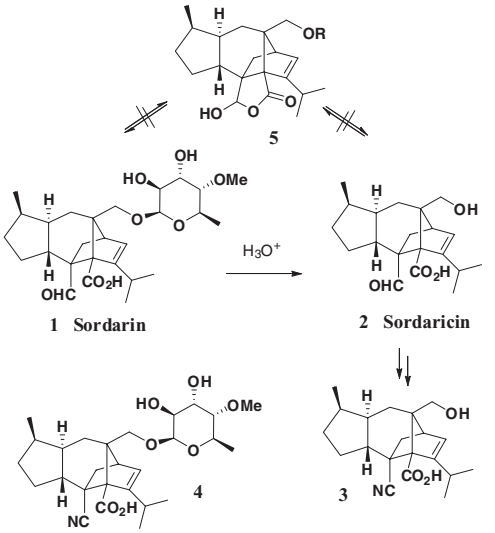
IC_{50} of sordarin against common fungi

Sordarin	*C. albicans* 2005E	*C. glabrata* 2375E	*C. neoformans* 2867E
IC_{50}	0.01 μg/mL	0.2 μg/mL	0.06 μg/mL

Figure 1
Structure of Sordarin and Activity against some *Candida* species.

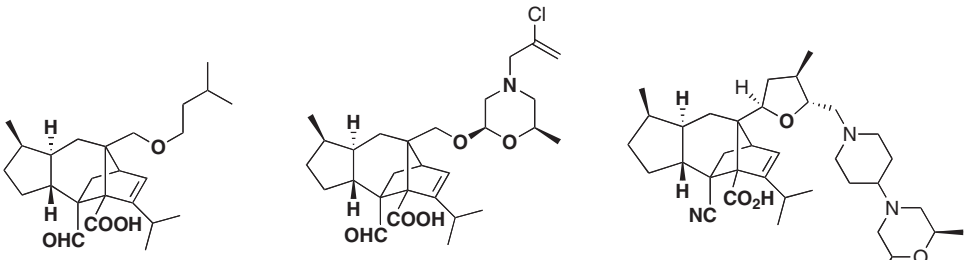
of the molecule imposes a dihedral angle of 67° between the two groups,[24] preventing equilibration with the pseudo-acid **5** (*Figure 2*). Conversion of the aldehyde into a cyano group furnishes compounds with equal or greater potency (*Figure 2*).[25]

Research groups at Merck,[25] GSK,[26,27] Bristol-Myers-Squibb,[28,29] Sankyo,[30,31] and Astellas (formerly Fujisawa)[32] have explored modifications of the glycosyl segment in



Compound	IC_{50}	Compound	IC_{50}
sordarin (**1**)	10 μg/mL	**3**	20 μg/mL
sordaricin (**2**)	>250 μg/mL	**4**	2 μg/mL

Figure 2
Structure and Activity of Sordarin and Congeners against *S. cerevisiae* YPH98.



unnamed
(Merck, ref. 25)

GW531920
(GlaxoSmithKline, ref. 27)

FR290681
(Fujisawa, ref. 32)

Figure 3
Representative Sordarin Analogs.

order to improve bioactivity. This has led to a number of analogs with increased potency and spectrum of activity. Three representative examples appear in *Figure 3*. It is worthy of note that a number of exceptionally potent Merck compounds dispense altogether with the saccharide-like unit, exhibiting a short hydrophobic chain instead.

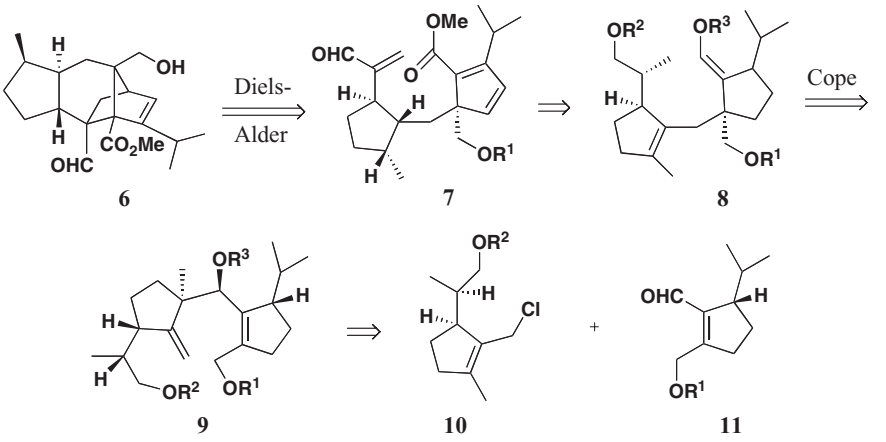
Considerably less research has been reported in regard to possible modification of the terpenoid nucleus. The potency of nitrile analogs has already been mentioned, but extensive alterations of the molecular core are significantly more challenging and arguably require a great deal of synthetic work. This review summarizes key aspects of published efforts in this area, starting with the total synthesis of sordaricin and sordarin and continuing with an outline of published research centering on congener synthesis through modification of the aglycone.

I. Total Syntheses of Sordaricin and of Sordarin

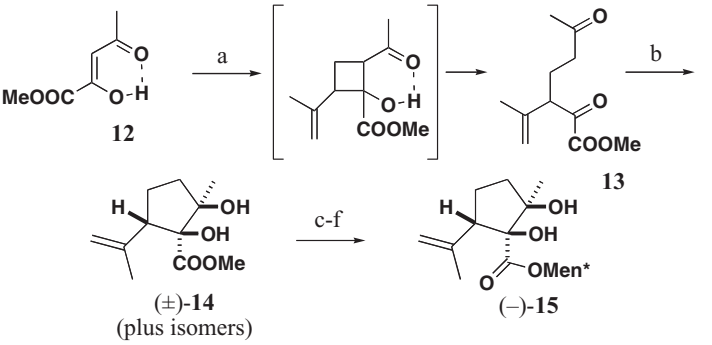
1. The Kato-Takeshita Synthesis of Sordaricin Methyl Ester

The first total synthesis of sordaricin, in the form of its the methyl ester, **6**, was achieved by the Kato-Takeshita group in 1993 (*Scheme 1*).[33] This enantioselective synthesis relied on the merger of chloride **10** and aldehyde **11** to furnish **9**. The latter was then advanced to **6** through a sequence that involved a Cope rearrangement (cf. **9** → **8**) and an intramolecular Diels-Alder reaction (**7** to **6**) as the key transformations.

The synthesis of fragments **10** and **11** evolved from a common intermediate, (−)-**15**, which was obtained by starting with a photochemical reaction of isoprene with methyl 2,4-dioxopentanoate, **12** (*Scheme 2*). Mukaiyama-type reductive cyclization of the resultant **13** furnished (±)−**14** plus two other isomers.[34] These were separated and the desired (±)−**14** was converted into a pair of diastereomeric (−)-menthyl esters. Fractional crystallization afforded (−)-**15**, which possesses the correct configuration at the carbon atom bearing the isopropenyl substituent. Ester (−)-**15** was elaborated into **17** and **21** as delineated in *Scheme 3*.[35] It is not clear how allylic alcohol **17** was further advanced to the requisite aldehyde **26**. On the basis of a later publication,[36] one may infer that the sequence employed for this purpose could be the one shown in *Scheme 4*.



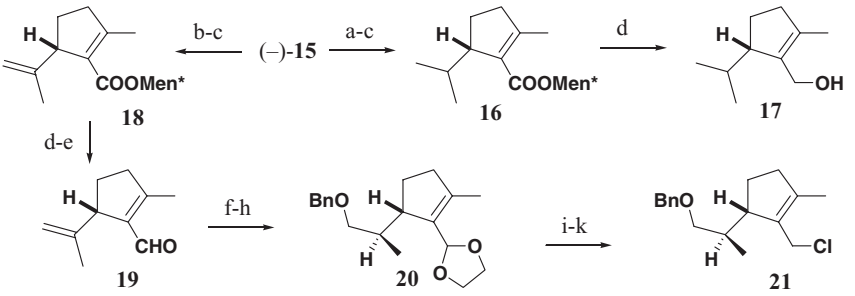
Scheme 1
The Kato-Takeshita Retrosynthetic Logic for **6**.



(a) isoprene, *hν*; (b) $TiCl_4$, Zn; (c) $CH(OMe)_3$; (d) K-alkoxide of (–)-menthol; (e) AcOH; (f) fractional crystallization.

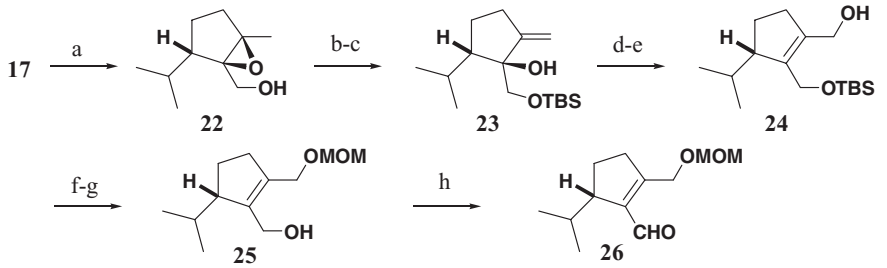
Scheme 2
Synthesis of Sordarin Precursor (–)–**15**.

The union of **21** and **26** was realized as indicated in *Scheme 5*. The reaction of chloride **21** with $CrCl_2$, prepared *in situ* by LAH reduction of $CrCl_3$, generated an organochromium derivative, which then added to aldehyde **26**[37] to furnish alcohol **28**. The stereochemical outcome of this step is consistent with a bond-forming process occurring through a tightly bound, 6-centered chair-like transition state such as **27** (formal charges omitted for clarity), wherein both donor and acceptor react from the least sterically encumbered face. This minimizes the non-bonding interactions indicated with solid arrows. *O*-Methylation of **28**, followed by thermal activation at 200°C gave **29**, as a result of a Cope rearrangement product, in 89% yield. This material was further elaborated to ester **30** by a four-step sequence that involved an ene reaction with singlet oxygen and a directed hydrogenation of a tetrasubstituted olefin as key transformations.



(a) H_2, Pd(C), 100%; (b) $CH(OMe)_3$; (c) Ac_2O, heat, 98% for **16**, 99% for **18**; (d) DIBAL, 92% for **17**, 90% for **18**; (e) MnO_2, 68%; (f) $(CH_2OH)_2$, PPTS, 91%; (g) disiamyl borane, then H_2O_2, NaOH, 83%; (h) NaH, BnCl, 76%; (i) 0.5 N aq. HCl, 72%; (j) $NaBH_4$, 96%; (k) $(COCl)_2$, 95%.

Scheme 3
The Kato-Takeshita Synthesis of **17** and **21** from Precursor (–)−**15**.



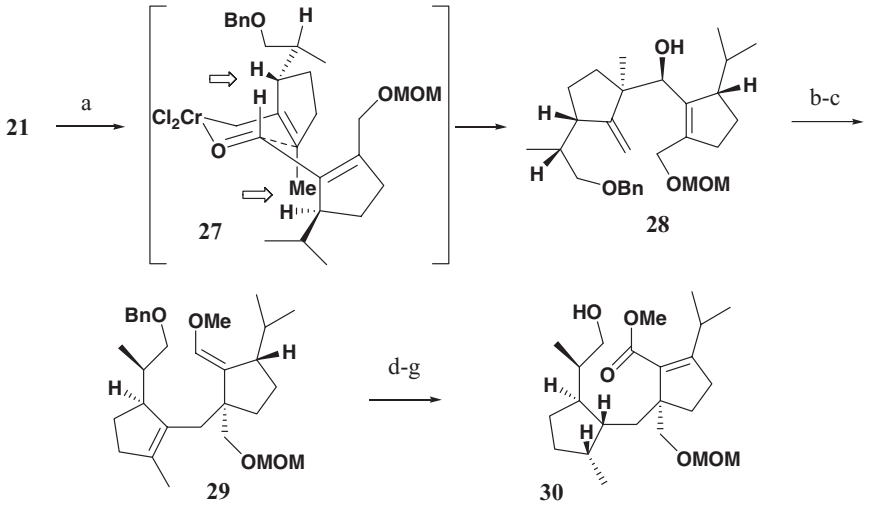
(a) Sharpless epoxidation; (b) $Al(O\text{-}iPr)_3$, toluene; (c) TBSCl, imidazole, DMF; (d) PCC; (e) $NaBH_4$; (f) MOMCl; (g) TBAF; (h) oxidation.

Scheme 4
The Presumed Synthesis of **26** from **17** by Kato and Takeshita.

The creation of Diels-Alder substrate **32** proceeded through a sequence (*Scheme 6*) that included the hydroxylation of the enolate of **30** with molybdenum$^{(IV)}$ oxo-diperoxo (pyridine)(HMPA) complex (the "MoOPH" reagent), followed by dehydration to **31**. The oxidation state of the molecule was further upgraded through release of the TBS group, Swern oxidation of the liberated alcohol to an aldehyde, formation of the corresponding silyl enol ether, and ensuing Saegusa oxidation to enal **32**. The latter step occurred with complete regioselectivity. Heating of **32** at 40°C followed by cleavage of the MOM group afforded sordaricin methyl ester, **6**, in 2% overall yield from **21** and **26** over 16 linear steps.

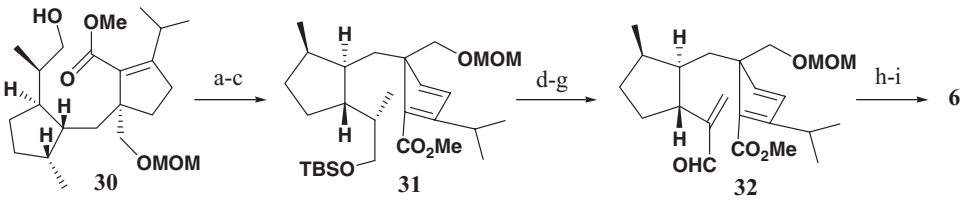
2. The Mander Synthesis of Sordaricin

A decade later, the Mander group achieved the total synthesis of sordaricin.[38,39] This work was based on model studies dating back to the early 1990′s,[40,41] and again it relied on an intramolecular [4 + 2] cycloaddition for the assembly of the bicyclo[2.2.1] subunit. *Scheme 7* delineates key aspects of the synthetic plan, which rested on the alkylation of the anion



(a) $CrCl_3$/LAH, **26**, 83%; (b) NaH, MeI, 99%; (c) xylene, 200 °C, 89%; (d) $^1O_2$; (e) AcCl/Py; (f) H_2, $Pd(OH)_2$; (g) H_2, Ir, *t*-BuOH, 58% over 4 steps.

Scheme 5
The Kato-Takeshita Preparation of Intermediate **30**.

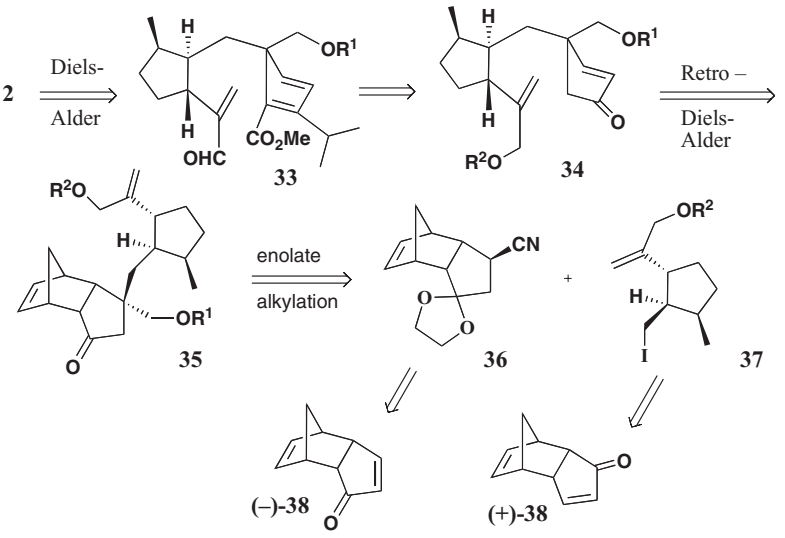


(a) imidazole, TBSCl; (b) LHMDS, MoO_5/Py, HMPA; (c) $SOCl_2$, Py, Ac_2O, 44% over 3 steps; (d) TBAF; (e) Swern ox.; (f) LHMDS, TMSCl, 26% over 3 steps; (g) $Pd(OAc)_2$; (h) benzene, 40 °C, 58% over 2 steps; (i) HOAc, H_2O, 62%.

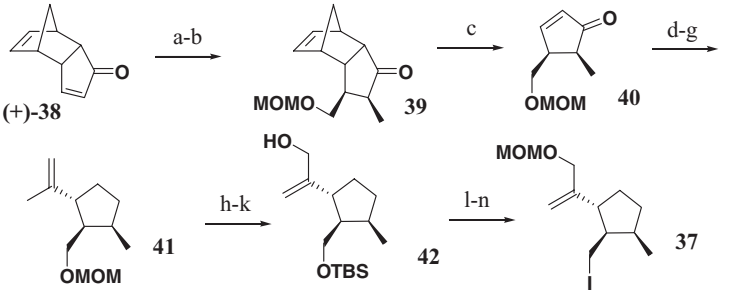
Scheme 6
The Final Steps of the Kato-Takeshita Synthesis of Sordaricin Methyl Ester.

of nitrile **36** with iodide **37**, ultimately leading to **35**. Retro-Diels-Alder reaction of the latter would reveal enone **34**, which may then progress to **33** in preparation for the crucial Diels-Alder reaction. A noteworthy aspect of this approach is that intermediates **36** and **37** are available from enantiomeric forms of enone **38**.

The preparation of **37** (*Scheme 8*) evolved from (+)−**38**, which was processed to **40** by a tandem cuprate addition—enolate alkylation, followed by retro-Diels-Alder expulsion of cyclopentadiene. A second organocopper addition to **40** followed by deoxygenation gave **41**. The subsequent hydroxylation of the isopropenyl segment of this material was envisoned to occur *via* epoxidation of the double bond followed by base-promoted rearrangement of the oxirane to an allylic alcohol. However, an unexpected complication materialized at this juncture: epoxidation of **41** even with the neutral reagent, DMDO triggered an



Scheme 7
The Mander Retrosynthetic Plan.

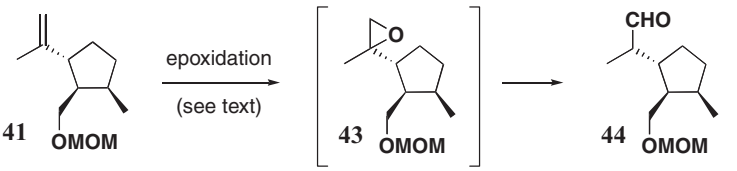


(a) $MOMOCH_2Li$, CuI, TMEDA, TMSCl; (b) MeLi, MeI, 60% a-b; (c) 180 °C, 85%; (d) isopropenyl-MgBr, CuI, 70%; (e) $NaBH_4$; (f) PhOC(S)Cl, pyridine; (g) Bu_3SnH, AIBN, 88% d-g; (h) PPTS, *t*-BuOH; (i) TBSCl, $(i\text{-Pr})_2NEt$; (j) *m*CPBA, $NaHCO_3$; (k) LICA, 49% h-k; (l) MOM-Cl; (m) TBAF; (n) I_2, Ph_3P, imidazole, 84% l-n.

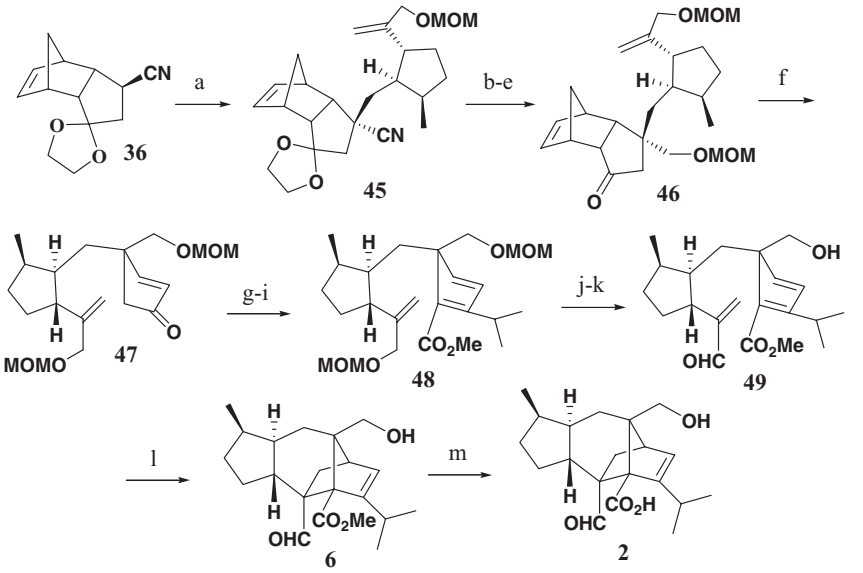
Scheme 8
The Mander Synthesis of Iodide **37**.

uncontrollable semipinacol rearrangement of the presumed intermediate **43** to aldehyde **44** (*Scheme 9*). Fortunately, the TBS-protected analog of **41** could be epoxidized without incident. This mandated a protecting group exchange at the stage of **41**. The rest of the sequence could then be executed without further incident to afford **37**.

Nitrile **36** emerged upon conjugate addition of cyanide to (−)-**38** and ketalization of the resultant product. Alkylation of the anion of **36** with **37** occurred exclusively from the convex face of the molecule and provided adduct **45** (*Scheme 10*). Conversion of the nitrile into an alcohol, MOM protection thereof, and hydrolysis of the dioxolane gave ketone **46**, which upon thermolysis (180°C) expelled cyclopentadiene and furnished enone **47**. Mander



Scheme 9
Unanticipated Semi-pinacol Rearrangement of MOM-Protected Epoxide **43**.



(a) LDA, HMPA, then **37**, 55%; (b) DIBAL; (c) $NaBH_4$; (d) MOMCl, DMAP, *i*Pr_2NEt; (e) TsOH, 90% over 4 steps; (f) 180°C, 96%; (g) LDA, MeOC(O)CN; (h) NaH, $PhNTf_2$; (i) 2-Th(CN)CuLi, *i*PrMgCl, 56% over 3 steps; (j) $MgBr_2$, 86%; (k) MnO_2, 100 %; (l) toluene, 40°C 100%; (m) *n*PrSNa, 79%.

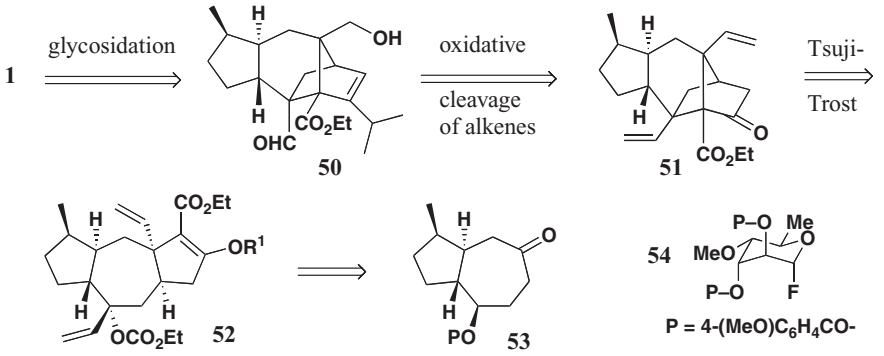
Scheme 10
The Mander Synthesis of Sordaricin.

carbomethoxylation, formation of an enol triflate and installation of the isopropyl group by an organocopper addition afforded **48**. The MOM groups were removed and the allylic alcohol was selectively oxidized with MnO_2. The emerging **49** cyclized to **6** quantitatively upon heating at 40°C. Sordaricin was obtained upon nucleophilic cleavage of the methyl ester with *n*PrSNa. Overall, sordaricin was reached in 13 steps and in 18% overall yield from intermediates **36** and **37**.

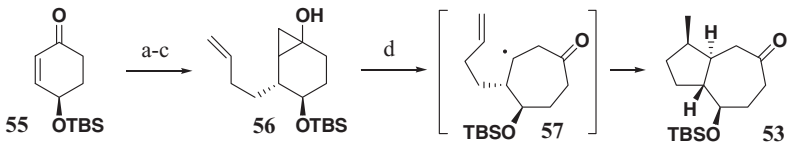
3. The Narasaka Synthesis of Sordarin

In 2004, Narasaka and collaborators described a third avenue to sordaricin,[42] this time in racemic form, and two years later the same team announced the first total synthesis of (−)-sordarin.[43] The Narasaka strategy deviates from the previous ones in that it avoided

the use of Diels-Alder chemistry to access the bicyclo[2.2.1]heptane system of the natural product, relying instead on a noteworthy intramolecular Tsuji-Trost reaction.[44] *Scheme 11* captures the essence of this elegant approach. The natural product was synthesized through a stereoselective glycosidation of sordaricin ethyl ester, **50** with glycosyl fluoride **54**. Allylic carbonate **52** served as the substrate for the intramolecular Tsuji-Trost reaction leading to **51**, which served as the forerunner of **50**. Central to the implementation of this **56** (*Scheme 12*).[45] To wit, exposure of **56** to a Mn(III) or, in this case, an Ag(I) salt, triggers a cascade of events: one-electron oxidation of the cyclopropanol, proton loss and fragmentation of the cyclopropane resulting in formation of radical **57**, cyclization thereof and reduction of the primary product of such a process to the ultimate **53** *via* H-atom transfer from a suitable donor (1,4-cyclohexadiene in this case). Enantiopure **53** was thus prepared from cyclohexenone **55**, which in turn is available in 7 steps from quinic acid.[46] Narasaka's earlier synthesis of *rac*-**50** had started with (±)−**55**, but except for the optical purity of **55**, the two routes are identical.



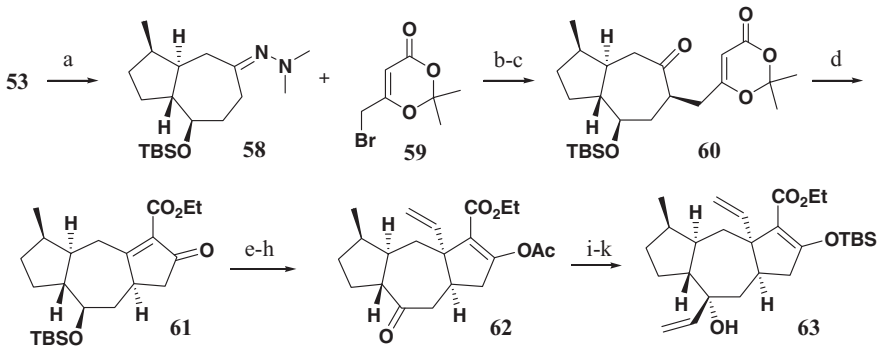
Scheme 11
The Narasaka Retrosynthetic Logic.



(a) 3-Butenylmagnesium bromide, CuBr•SMe_2, TMS-Cl, HMPA, 91%; (b) Et_2Zn, CH_2I_2; (c) K_2CO_3, MeOH, 82% b-c; (d) cat. $AgNO_3$, $(NH_4)_2S_2O_8$, 1,4-cyclohexadiene, 85%.

Scheme 12
The Narasaka Enantioselective Synthesis of Ketone **53**.

The point of departure for the main sequence of the synthesis was the regio– and diastereoslective alkylation of the anion of hydrazone **58** with dioxenone **59** (*Scheme 13*). Treatment of ensuing **60** with NaOEt promoted transesterification and consequent loss of a molecule of acetone, followed by Knoevenagel condensation. Compound **61** was obtained in 42% overall yield. Conjugate addition of vinyl magnesium chloride in the presence of CuBr, enol acetylation, selective cleavage of the TBS group and PCC oxidation afforded



(a) Me_2NNH_2, HOAc, EtOH; (b) LDA, **59**; (c) NaOAc, HOAc, THF/H_2O, 60% over 3 steps; (d) EtONa, 70%; (e) CH_2=CHMgCl, CuBr•Me_2S, TMSCl; (f) Ac_2O, Py, 97% over 2 steps; (g) TsOH, THF/H_2O; (h) PCC, DCM, 90% over 2 steps; (i) CH_2=CHMgCl, THF; (j) NaOEt, EtOH; (k) TBSCl, Et_3N, DMAP, 86% over 3 steps.

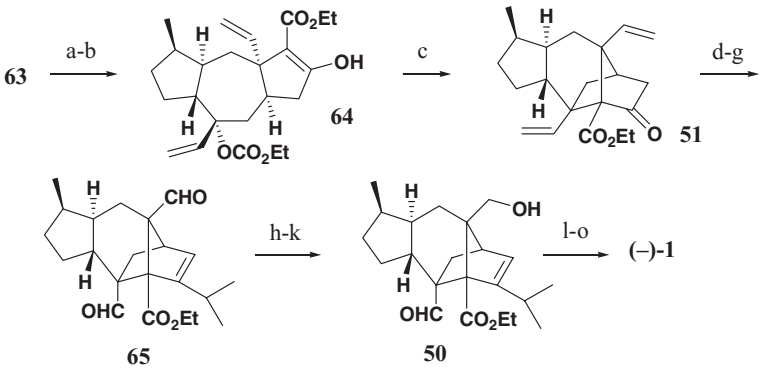
Scheme 13
The Narasaka Synthesis of Key Intermediate **63**.

62. The subsequent chemoselective addition of vinylmagnesium chloride to the ketone carbonyl proceeded diastereoselectively from the β-face. Protecting group manipulations finally surrendered the key intermediate for the synthesis: allylic alcohol **63**. The key transformation in the Narasaka synthesis of sordarin is without doubt the remarkable intramolecular Tsuji-Trost reaction of **64** (*Scheme 14*). In preparation for this step, extremely hindered alcohol **63** was converted into **64** by deprotonation with LDA and reaction of the alkoxide with ethyl chloroformate. Exposure of **64** to NaH in the presence of a catalytic amount of $Pd(PPh)_4$ surrendered **51** in 92% yield. Installation of the isopropyl group entailed enol triflation of the ketone, followed by displacement of the vinylic triflate by an isopropyl cuprate. The oxidative cleavage of the vinyl groups took place under modified Lemieux-Johnson conditions [OsO_4 and $NaIO_4$ in the presence of $PhB(OH)_2$] to reveal dialdehyde **65**. The advancement of the latter to sordaricin requires the selective reduction of the apical formyl group. However, this proved not to be possible, necessitating a more circuitous solution involving reduction of both aldehydes, selective TBS-protection of the more exposed apical carbinol, Parekh-Doering oxidation, and deprotection. Fortunately, the overall yield of **50** from **65** over the four-step sequence was a solid 77%. Fully synthetic (−)-sordarin was obtained upon Mukaiyama glycosidation of **50** with **54** and global deprotection. In summary, (−)-**1** was obtained in 6% yield from intermediate **53** over 26 steps.

II. Synthesis of Analogs of Sordarin

1. The Cuevas Sordarin Analogs

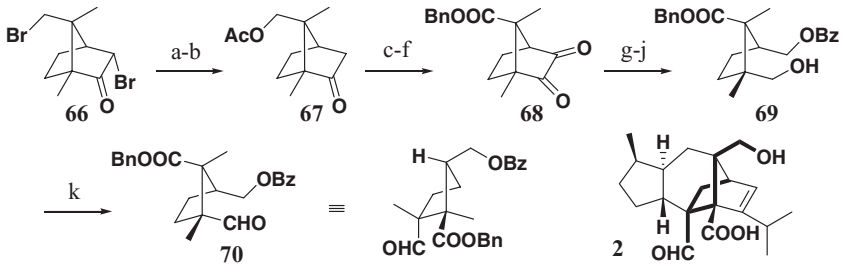
The question of whether the terpenoid core of sordarin could be simplified without significantly diminishing antifungal activity was first addressed by Cuevas *et al.*[47] These workers described a number of derivatives of substituted cyclopentane **70**, which as seen



(a) LDA, $ClCO_2Et$, THF; (b) TBAF, THF, 89% over 2 steps; (c) cat. $Pd(PPh_3)_4$, NaH, dioxane, 92%; (d) LDA, N-(5-chloro-2-pyridyl)triflimide; (e) *i*PrMgCl, 2-ThCu(CN)Li, 82% over 2 steps; (f) cat. OsO_4, NMO, $PhB(OH)_2$, DCM; (g) $NaIO_4$, THF/H_2O, 53% over 2 steps; (h) $NaBH_4$, EtOH; (i) TBSCl, imidazole, DMF; (j) SO_3•Py, Et_3N, DMSO; (k) TsOH, THF/H_2O, 77% over 4 steps; (l) **54**, $AgClO_4$, $SnCl_2$; (m) DDQ; (n) NaOEt; (o) *n*PrSNa, HMPA, 73% over 4 steps.

Scheme 14
The Narasaka Synthesis of Sordarin: the Endgame.

in *Scheme 15* nicely map onto the tetracyclic framework of sordaricin. The new substances retain aldehyde, carboxylic acid and hydroxymethyl groups as pharmacophores. Interestingly, the dihedral angle between formyl and carboxy groups in **70** is comparable to that found in **2**. The synthesis of the new cyclopentanoids started with commercial (+)−3,9-dibromocamphor, **66**, and it involved a straightforward sequence culminating with fission of camphorquinone derivative **68** and subsequent adjustment of the oxidation state of the molecule. Aldehyde **70** and its derivatives (*Figure 4*) showed unsatisfactory activity towards



(a) Zn, AcOH, 90%; (b) CsOAc, DMF, 96%; (c) LiOH, 93 %; (d) Jones reagent, 80%; (e) BnBr, DBU, 87%; (f) SeO_2, 80 %; (g) $NaBH_4$, 74%; (h) H_5IO_6; (i) $NaBH_4$, 80% h-i; (j) BzCl, DMAP, –40 °C, 44%; (k) PCC, 90%.

Scheme 15
The Cuevas Simplified Core of Sordarin.

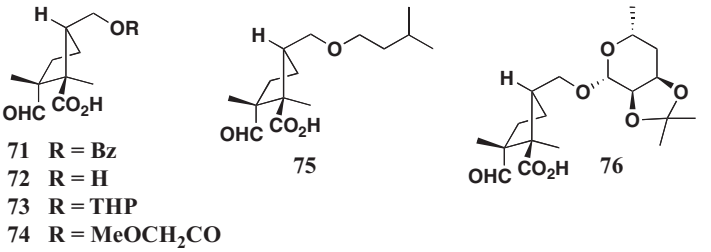


Figure 4
The Cuevas Cyclopentane Analogs of Sordarin.

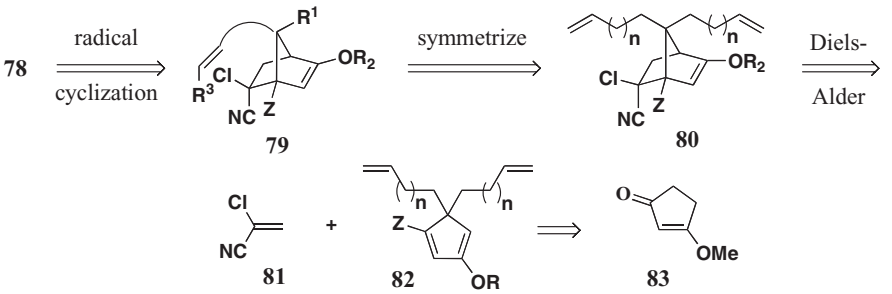
C. albicans. However, substances **71**, **73** and **76** were about 4 to 7 times more potent than (essentially inactive) sordaricin against *C. albicans* 2005E.[48]

These results indicate that simplification of the sordarin skeleton may be feasible. However, a structure-activity correlation for sordaricin is still lacking. In particular, the role and importance of the isopropyl group, carboxylic acid and tetracyclic structure are unknown. Moreover, previous total syntheses of the natural product did not explore these questions, and probably could not explore them readily, given their nature and design.

2. The Ciufolini Synthesis of Sordarin Analogs

In the early 2000's, the Bayer CropScience Company and our group launched a collaborative effort with the aim of addressing the foregoing issues. The objective of this work was to create a building block that could be elaborated into a variety of structurally simplified analogs of sordaricin. A good choice appeared to be construct **78** (*Figure 5*), wherein the oxygenated functionality in parentheses would permit additional modification of the "eastern" sector of the molecule, while group Y would enable further annulation chemistry in the "western" quadrant. Foremost objectives in planning a route to **78** were low cost and ease of execution, while issues of absolute stereocontrol were considered secondary at an initial stage.

A first generation approach to structures of the general type **78** envisioned an intramolecular radical cyclization[49] of **80** as a key step (*Scheme 16*).[50] Compounds in this



Scheme 16
Planned Avenue to Progenitor **78** of Sordarin Analogs.

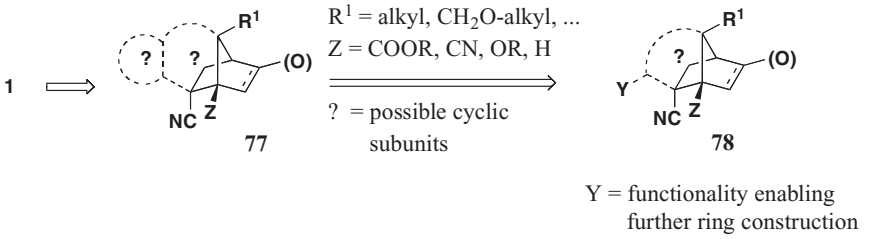
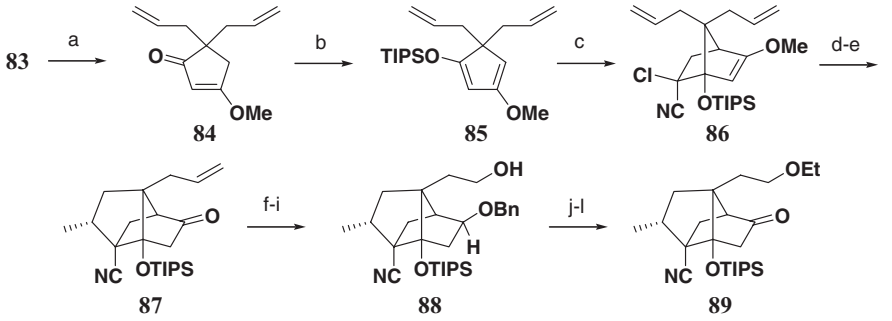


Figure 5
Sordarin Building Blocks Contemplated in Our Study.

series are accessible through a Diels-Alder reaction of 2-chloroacrylonitrile with cyclopentadienes **82**, which in turn may be prepared from **83**.

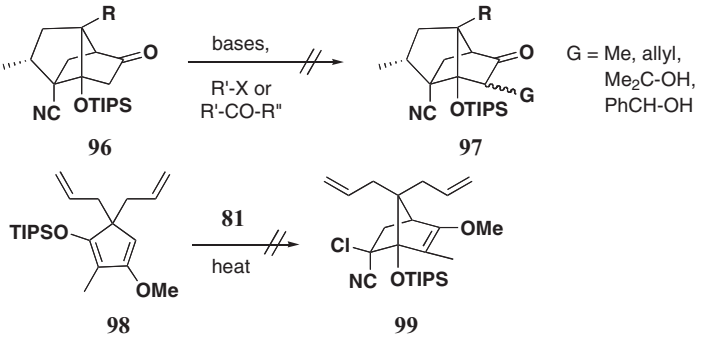
The implementation of this approach is exemplified in *Scheme 17*. Bis-allylation of **83** and enol silylation of the resultant **84** afforded cyclopentadiene **85**, which reacted with **81** the presence of K_2CO_3 to furnish **86** in 53% yield. Hydrolysis of the vinyl ether to the corresponding ketone and subsequent reaction with TMS_3SiH and AIBN produced tricyclic compound **87** (single diastereomer within the limits of 300 MHz ^{1}H NMR). The latter was then elaborated to derivatives **89** (*Scheme 17*) and **90–95** (*Figure 6*) by a straightforward sequence of reactions. Analogs **89–95** were tested against a broad range of phytopathogenic fungi. Substances **90** and **91** showed marginal efficacy at 50 ppm; however, none of the new entities were particularly potent.

The poor or marginal activity of the analogs thus obtained might have been ascribed to the absence of the bridgehead COOH group and/or of an isopropyl, or other small alkyl group, at the position adjacent to the carbonyl functionality. In the latter connection, various attempts were made to substitute the position adjacent to the carbonyl group in ketones of general structure **97** (*Scheme 18*) through alkylation or aldol reactions of the corresponding



(a) LDA, allyl bromide, repeat, 49%; (b) TIPSOTf, Hunig Base; (c) 2-chloroacrylonitrile, K_2CO_3, 53% over 2 steps; (d) 4N HCl, 96%; (e) AIBN, TMS_3SiH, 65%; (f) $NaBH_4$, 84%; (g) BnBr, NaH, 99%; (h) O_3, 99%; (i) $NaBH_4$, 93%; (j) NaH, EtI; (k) $Pd(OH)_2$, 44%; (l) Swern ox., 85%.

Scheme 17
Synthesis of Sordaricin Analog **89**.



Scheme 18
Limitations of the Initial Strategy.

enolates. All these attempts met with failure, arguably because of severe steric congestion around the nucleophilic carbon of the enolate. This induced us to investigate the possible introduction of the alkyl group in question on the starting cyclopentadiene. Unfortunately, it transpired that the presence of an extra methyl group all but extinguished Diels-Alder reactivity of cyclopentadiene such as **98**. This dissuaded us from researching dienes carrying even bulkier substituents, such as an isopropyl group.

The successful Kato and Mander syntheses of sordaricin inspired us to consider to an intramolecular Diels-Alder reaction as a means to overcome the steric barriers hampering the reaction of substituted cyclopentadienes of the type **98**.[51,52] Tricyclic compound **100** appeared to serve well the stated objectives of this program, in that it seemed to be a good point of departure for the ultimate creation of analogs **101–103** (*Scheme 19*) as well as satisfying the requirements for low cost and ease of preparation. As apparent from the *Scheme 20*, substance **100** would result upon cyclization of **105**, which in turn would be obtained through the union of three fragments: derivative **107** of readily available dione **108** plus one molecule of acrolein and one of acrylonitrile.

A model study designed to validate the planned approach was carried out starting with commercial **109** as delineated in *Scheme 21*. *O*-Methylation and Mander acylation[53]

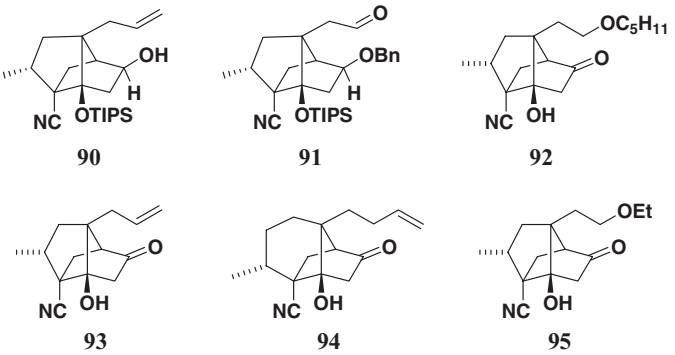
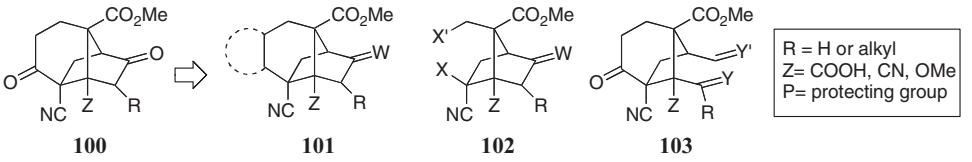
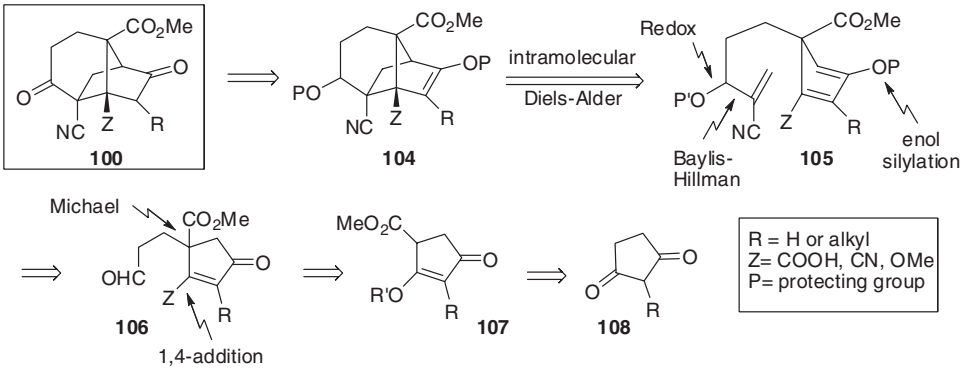


Figure 6
Sordaricin Analogs Obtained from Compound **87**.

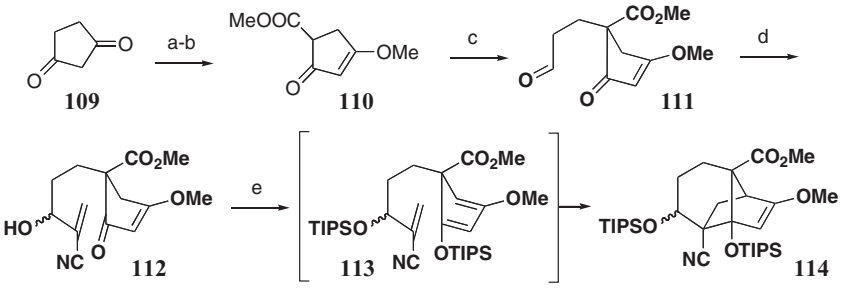


Scheme 19
Sordaricin Analogs Potentially Available from Compound **100**.



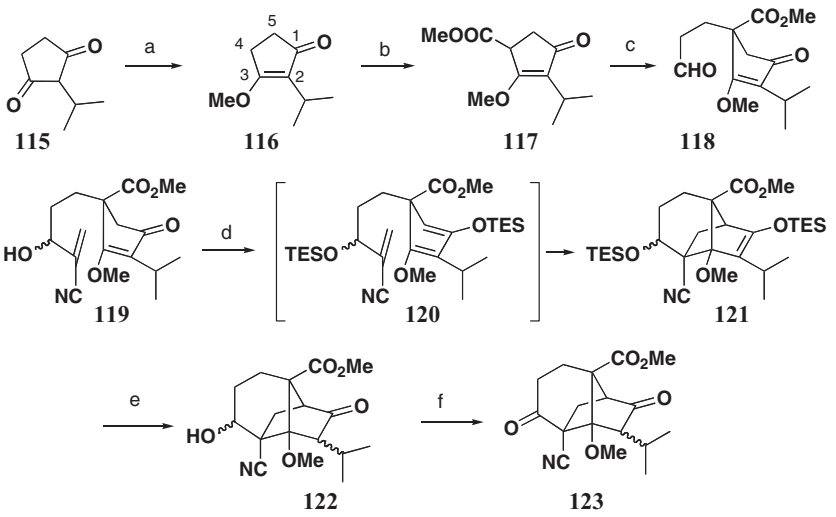
Scheme 20
Retrosynthetic Plan for Tricyclic Ketone **100**.

gave **110**,[54,55] which reacted in a Michael mode with acrolein to afford aldehyde **111**. Baylis-Hillman reaction[56,57] of the latter in neat acrylonitrile produced alcohol **112** as a ca. 1.5: 1 mixture of two unassigned alcohol diastereoisomers. Since these two isomers would ultimately be oxidized to a ketone, no effort was made to separate them at this stage. Exposure of **112** to TIPSOTf and Hünig's base produced Danishefsky-type[58,59] diene **113**, which spontaneously underwent intramolecular Diels-Alder reaction at room temperature to furnish tricyclic adduct **114** (5 steps and 18% yield from **109**).



(a) K_2CO_3, Me_2SO_4, 99%; (b) LDA, MeOC(O)CN, 52%; (c) acrolein, DBU, 99%; (d) acrylonitrile, DABCO, dr 1.5 : 1, 57%; (e) TIPSOTf, *i*Pr_2NEt, 72%.

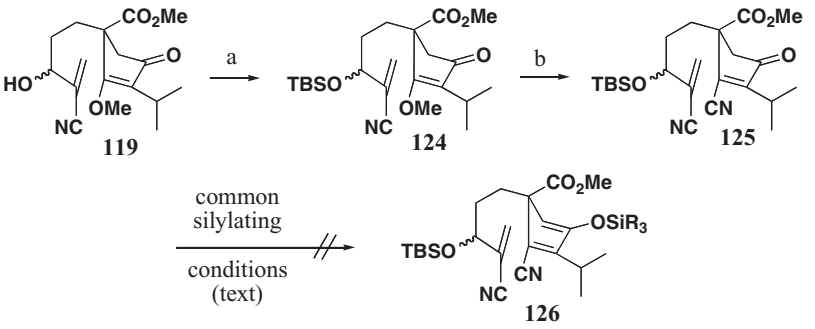
Scheme 21
Model Intramolecular Diels-Alder Reaction.



(a) K_2CO_3, Me_2SO_4, 99%; (b) LHMDS, MeOC(O)CN, 81%; (c) acrolein, DBU, 99%; (d) acrylonitrile, DABCO, dr 1.5 : 1, 68%; (e) TESOTf, *i*Pr_2NEt, 52%, dr 52 : 48; (e) HF-Py, 100%; (f) Swern Ox., 67%.

Scheme 22
Preparation of Analog **123**.

These positive results encouraged us to transpose the chemistry to a series of compounds emanating from 2-isopropyl-1,3-cyclopentanedione, **115** (*Scheme 22*), readily prepared in large scale as described by Majetich.[60] Conversion into vinylogous ester **116** readied the molecule for Mander acylation. We estimated that in the present case it would be advantageous to introduce the requisite ester function at C-4, instead of a C-5 as seen before in *Scheme 19*. In fact, past experience indicated that the installation of a COOH equivalent on more advanced intermediates could be most readily accomplished through reaction of cyanide ion with substrates of the type **119** in a 1,4-addition–elimination mode. As determined by Koreeda,[61,62] the nature of the base utilized for the deprotonation of enones such as **116** elicits nucleophilic reactivity either at C-5 (LDA) or at C-4 (LHMDS). Presumably this is due to the formation of a kinetic enolate (i.e, at C-5 in this case) with LDA, but a thermodynamic one (C-4) with LHMDS. Indeed, deprotonation of **116** with LHMDS followed by the Mander reagent afforded **117** in 81% yield. The Michael addition of **117** to acrolein led to aldehyde **118** in quantitative yield. This sensitive compound was immediately committed to a subsequent Baylis-Hillman reaction, which, however, proceeded at an abnormally slow rate. Four days were required for complete conversion into **119**, even by operating in neat acrylonitrile. The Aggarwal catalytic system [$La(OTf)_3$ and triethanolamine as co-catalysts)[63] enabled a nine-fold rate acceleration, but at the cost of a reduced yield of **119** (50% vs. 68% chromatographed). The product was obtained as a 65:35 ratio of unassigned alcohol diastereomers, which were not separated. The formation of diene **120** upon treatment of **119** with TESOTf and Hunig base again triggered an intramolecular Diels-Alder reaction that delivered **121** as a mixture of diastereomers.



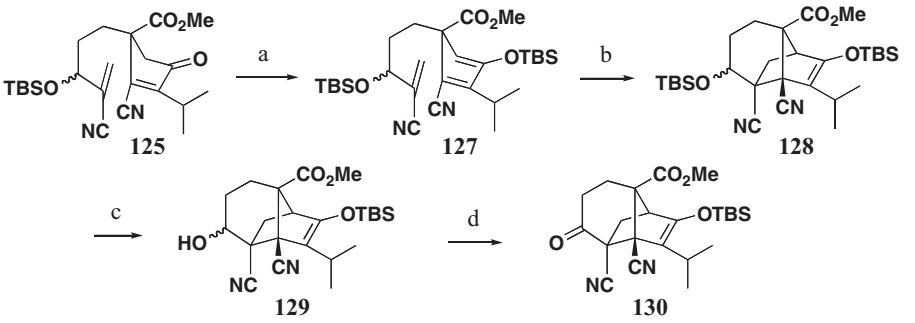
(a) TBSCl, 75%; (b) Et_2AlCN, 75%.

Scheme 23
Cyanation of **124** and Failure of the Enol Silylation of **125**.

Release of the silyl groups was best effected with HF·Pyridine complex in MeCN, and the alcohols **122** thus obtained was directly subjected to Swern oxidation to produce the tricyclic sordaricin analog **123** (1:1 mixture of isopropyl group epimers). Overall, **123** was synthesized in 19% overall yield from **115** over 7 steps.

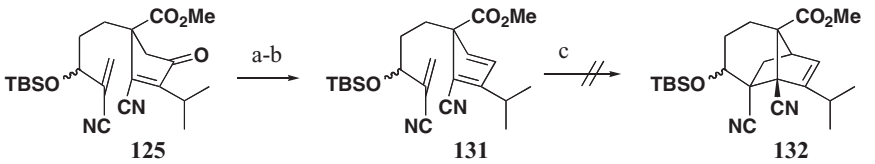
The introduction of an equivalent of the bridgehead COOH group started with silylation of alcohol **119**. Reaction of the resultant **124** with diethylaluminum cyanide (the Nagata reagent)[64] produced bis-nitrile **125** in a highly selective fashion (*Scheme 23*; no CN addition to the lateral conjugated nitrile) and in 56% yield from **119** over 2 steps. Unexpectedly, cyanoenone **125** failed to yield a silyl enol ether upon reaction with a diversity of common silylating agents. The compound was immune to the action of silyl triflates in the presence of Hünig base, and it was recovered unchanged after many such attempts. The same outcome was obtained when silyl enol ether formation was attempted under Corey-Gross (LDA, R_3SiCl),[65] Miller (TMS_2NH, TMSI),[66] and Lewis acid-promoted ($ZnCl_2$, $TiCl_4$)[67] conditions, or by use of reagents such as *N*,*O*-bis(trimethylsilyl)acetamide and *N*,*O*-bis(trimethylsilyl) trifluoroacetamide.[68,69] Fortunately, exposure of **125** to an excess of LHMDS and LiCl[70,71] in THF/HMPA, followed by addition of TBSCl, delivered diene **127** in 82% yield (*Scheme 24*). Contrary to the case of **120** and congeners, this material displayed no tendency to undergo intramolecular Diels-Alder reaction at temperatures lower than 120°C. Indeed, heating of a toluene solution at 140°C for 12 h in a sealed tube was necessary to effect conversion into **128**, which emerged as a ca. 1:1 mixture of diastereoisomers in 77% chromatographed yield. Selective deprotection of the vicinal cyanohydrin with HF·Pyridine complex and subsequent Dess-Martin oxidation produced the desired building block **130**. It should be noted that the TMS enol ether analog of **127** was too labile, while the TES or TIPS enol ethers afforded poor yields in the subsequent intramolecular Diels-Alder reaction.

It is worthy of note that diene **131**, available from **125** by Luche reduction[72] and Burgess[73] dehydration (*Scheme 25*), failed to undergo intramolecular Diels-Alder reaction at temperatures below 160°C, while above this temperature, the material decomposed. This observation, together with the obstacles encountered in the enol silylation of **125** and the



(a) LHMDS, LiCl, TBSCl, HMPA, 82%; (b) toluene, 140 °C, 77%; (c) HF-Py; (d) DMP, 50% over 2 steps.

Scheme 24
Preparation of Building Block **130**.



(a) Luche, 51%; (b) Burgess, 54%; (c) heat

Scheme 25
Failure of the Intramolecular Diels-Alder Reaction of Cyanodiene **131**.

unusually high temperature required to promote Diels-Alder cyclization of **127**, are all attributable to an unfavorable electronic effect exerted by the dienic cyano substituent.[48,49]

III. Conclusion

In conclusion, our work led to building blocks that may be useful for the preparation of analogs of sordarin exhibiting a modified terpenoid core. Congeners of **1** constructed from these intermediates should enable a detailed SAR investigation of the terpenoid core. This knowledge is likely to prove essential to the development of new antifungal agents based on a sordarin motif.

Acknowledgements

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