

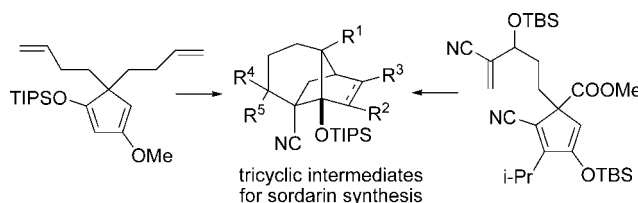
Synthetic Studies toward Sordarin: Building Blocks for the Terpenoid Core and for Analogues Thereof

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Avenues to bi- and tricyclic building blocks for the elaboration of sordarin and its analogues are described. The target molecules were obtained through inter- and intramolecular Diels–Alder reactions of a number of previously unknown cyclopentadienes. Unusual properties of 3-cyanoenones and 1-cyanocyclopentadienes have been unveiled and circumvented.

Introduction

The incessant onslaught of fungal pathogens renders the search for new antifungal agents an important priority both in medicine and in agriculture. Indeed, fungi are responsible for a number of human pathologies, especially in immunocompromised subjects (AIDS and cancer patients, recipients of organ transplants),¹ as well as for major agricultural losses.²

Antifungal agents that operate by novel mechanisms are of special interest, and in that regard, a remarkable family of natural products isolated from *Sordaria araneosa*, and known as the sordarins³ (Figure 1), have captured significant attention, given their unique mode of action. Thus, sordarin, **1**, and its congeners block protein synthesis by inhibiting the fungal elongation factor 2.⁴

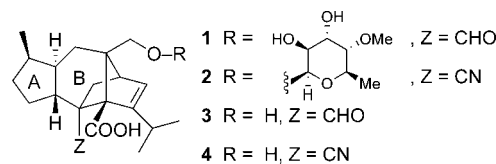


FIGURE 1. Structure of sordarin (**1**) and congeners.

The potency and selectivity of **1** have elicited considerable activity in both the biological and the chemical arena. In the latter connection, three landmark total syntheses have been recorded.⁵ In the medicinal chemistry domain, efforts have been largely confined to the glycoside segment of the molecule.⁶

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[§] Bayer CropScience SA.

(1) Cf. (a) Rupp, S. *Fut. Microbiol.* **2007**, 2, 141. (b) Klepser, M. E. *Pharmacotherapy* **2006**, 26, 68. (c) Onyewu, C.; Heitman, J. *Anti-Infect. Agents Med. Chem.* **2007**, 6, 3. (d) Richardson, M. D.; Warnock, D. W. *Fungal Infection: Diagnosis and Management*, 3rd ed.; Blackwell Publishing: Malden, MA, 2003.

(2) Cf. *Modern Crop Protection Compounds*; Kraemer, W.; Schirmer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007.

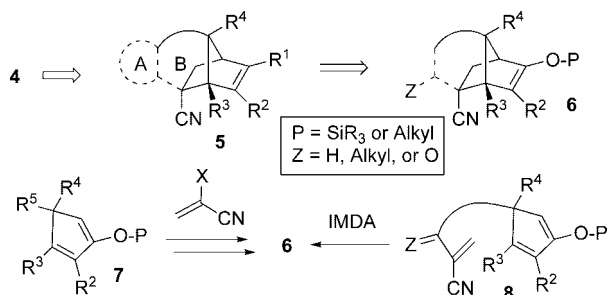
(3) (a) Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, 54, 1178, and references cited therein. Recent review (b) Liang, H. *Beilst. J. Org. Chem.* **2008**, 4, 31.

(4) (a) Justice, M. C.; Hsu, M. J.; Tse, B.; Ku, T.; Balkovec, J. M.; Schmatz, D.; Nielsen, J. J. *Biol. Chem.* **1998**, 273, 3148. (b) Capa, L.; Mendoza, A.; Lavandera, J. L.; Gomez de las Heras, F.; Garcia-Bustos, J. F. *Antimicrob. Agents Chemother.* **1998**, 42, 2694. (c) Shastry, M.; Nielsen, J.; Ku, T.; Hsu, M.-J.; Liberator, P.; Anderson, J.; Schmatz, D.; Justice, M. C. *Microbiology* **2001**, 147, 383.

(5) (a) Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002. (b) Mander, L. N.; Thomson, R. J. *Org. Lett.* **2003**, 5, 1321. (c) Mander, L. N.; Thomson, R. J. *J. Org. Chem.* **2005**, 70, 1654. (d) Kitamura, M.; Chiba, S.; Narasaka, K. *Chem. Lett.* **2004**, 33, 942. (e) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, 128, 6931.

(6) Cf. (a) Bueno, J. M.; Chicharro, J.; Fiandor, J. M.; Gomez de las Heras, F.; Huss, S. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1697. (b) Serrano-Wu, M. H.; St Laurent, D. R.; Carroll, T. M.; Dodier, M.; Gao, Q.; Gill, P.; Quesnelle, C. A.; Marinier, A.; Mazzucco, C. E.; Regueiro-Ren, A.; Stickle, T. M.; Wu, D.; Yang, H.; Yang, Z.; Zheng, M.; Zoekler, M. E.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1419, and references cited therein.

SCHEME 1



Indeed, little appears to be in the public domain concerning the structure–activity relationship of the terpenoid core. It is known that analogue **2**, wherein a cyano functionality is present in lieu of a formyl group, is essentially equipotent to **1**.⁷ It is also established that the hexose unit may be replaced by a saccharide analogue or even by a hydrophobic alkyl chain.⁷ However, the aglycone of sordarin, which is termed sordarin, **3**, is inactive.

Our involvement in the sordarin area⁸ was motivated by a desire not only to achieve a total synthesis, but also to address the structure–activity relationship of the terpenoid core. We thus launched a synthetic program that would also generate building blocks for the assembly of a diversity of analogues of sordarin nitrile, **4**. Such analogues, shown in Scheme 1 as **5**, would display diverse substituents R^1 – R^4 on the main bicyclic system and various modifications of rings A and B. Of special interest were compounds (i) amenable to the construction of diverse variants of ring A, (ii) possessing a contracted ring B or no ring B at all, (iii) such that R^4 contains an ether linkage wherein the oxygen atom is connected to the bicyclic core by a short bridge consisting of 1 and 4 carbon atoms,⁹ (iv) bearing H, or an oxygenated functionality, or a cyano substituent, in lieu of a carboxylic group, at the bridgehead position (R^3), and (v) possibly incorporating small alkyl groups or an oxygenated functionality as the R^1 substituent. Frameworks of general structure **6** satisfied such desiderata. Accessing the target molecules from cyclopentadienes **7** and **8** through bimolecular or intramolecular Diels–Alder (IMDA)¹⁰ reactions, respectively, seemed to be the best solution. At this early stage, we disregarded issues of absolute stereocontrol, focusing instead on devising an approach that would be of facile execution. All chiral compounds described herein are, therefore, racemic.

Results

Among cyclopentadienes of general structure **7**, dioxxygenated species of the type **9** and **10** (Figure 2) were regarded as especially useful for the objectives of the present work. Surprisingly, a search of the Chemical Abstracts Service database found no recorded instances of such cyclic analogues of the Danishefsky diene.¹¹ Mono-oxygenated variants such as **11** and **12** are known, but they are rare, and their Diels–Alder chemistry remains unexplored. Indeed, such compounds appear

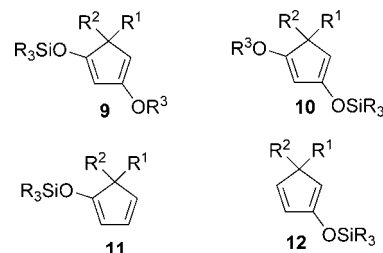
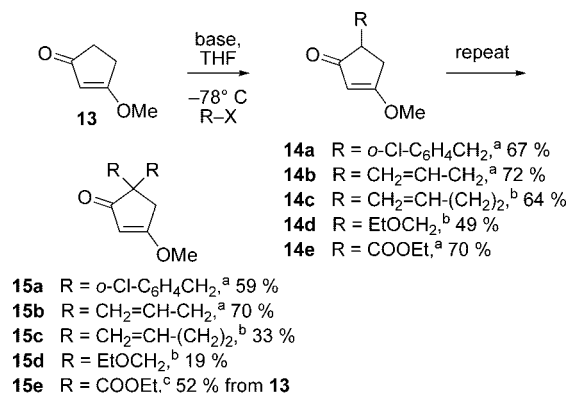


FIGURE 2. Structures of known (**11** and **12**) and yet undocumented (**9** and **10**) silyloxycyclopentadienes.

SCHEME 2^a

^a (a) Base = LDA, $R-X = o\text{-Cl-C}_6\text{H}_4\text{CH}_2\text{Br}$ (**14a**) or allyl bromide (**14b**); (b) base = LDA, DMPU as cosolvent, $R-X = 4\text{-iodo-1-butene}$ (**14c**) or chloromethyl ethyl ether (**14d**); (c) base = KHMDS (2.4 equiv), $R-X = \text{EtOOC-CN}$ (2.4 equiv), DMPU as cosolvent.

to have been employed only as nucleophiles. For instance, a cyclopentadiene such as **11** was used in a nucleophilic addition to a sulfonium salt¹² and as a terminating element in cationic olefin cyclization reactions,¹³ while one of the type **12** was added to Eschenmoser's salt during a sequence leading to the introduction of an exomethylene group,¹⁴ or hydroxyethylated by reaction with ethylene oxide/ TiCl_4 .¹⁵ Preliminary experiments thus aimed to explore the Diels–Alder reactivity of **9** and **10**.

We initially investigated some symmetrically substituted cyclopentadienes, Diels–Alder reactions of which were unaffected by issues of facial selectivity. The preparation of these dienes commenced with a double alkylation of the kinetic enolate of the known **13**¹⁶ (Scheme 2). The only point worthy of note here is that the modest yield recorded in the second alkylation of **14d** was probably due to the tendency of the corresponding enolate to undergo elimination of ethoxide ion and consequent formation of an exomethylene derivative, which probably degraded under the conditions of the reaction. Still, it was pleasing to observe that the second alkylation step produced at least some of the desired **15d**. It should also be noted that compound **15e** was prepared in one step from **13** by double acylation with the Mander reagent.¹⁷

Enol silylation of enones **15** afforded cyclopentadienes **16**–**20** (Scheme 3). These substances proved to be sensitive and prone to desilylation; therefore, they were not extensively purified prior

(7) Tse, B.; Balkovec, J. M.; Blazey, C. M.; Hsu, M.-J.; Nielsen, J.; Schmatz, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2269.

(8) Liang, H.; Schülé, A.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett.* **2007**, *9*, 4119.

(9) Interest in such compounds was motivated by the results described in ref.

(10) The Kato (ref 5a) and Mander (ref 5b) total syntheses of **1** indeed rely on IMDA routes to the terpenoid nucleus.

(11) Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1990**, Vol. VII, 312.

(12) Kodpinid, M.; Siwapinyoyos, T.; Thebtaranonth, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4862.

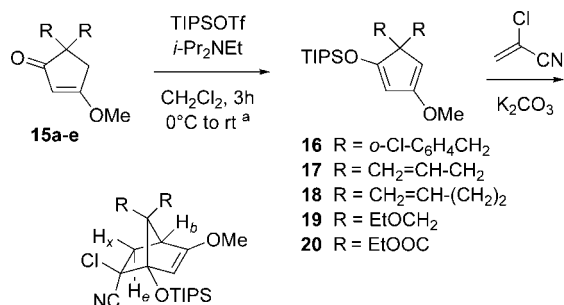
(13) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982.

(14) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380.

(15) Lalic, G.; Petrowski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583.

(16) Best made as detailed by: Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **2001**, *57*, 217.

(17) Crabtree, S. R.; Mander, L. N.; Sethi, P. S. *Org. Synth.* **1991**, *70*, 256.

SCHEME 3^a

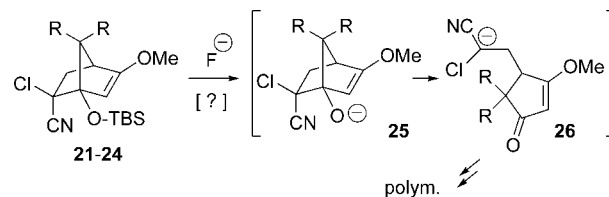
^a (a) 99% conversion for 16; 91% conv. for 17; 95% conv. for 18; 63% conv. for 19; 92% conv. for 20. (b) Toluene, 65 °C, 12 h, 53% from 15b via 17 for 21; 22% from 15c via 18 for 22. (c) Neat, 60 °C, 15 h, 40% from 15d via 19. (d) Neat, rt, 12 h, 27% from 15e via 20.

to Diels–Alder reaction. In the latter respect, TIPS enol ethers were sufficiently stable to undergo Diels–Alder reactions under purely thermal conditions, while TMS and TES ethers were labile and unsuitable for that purpose.¹⁸ Consequently, this study utilized TIPS enol ethers exclusively. The dienophile destined to combine with 16–20 would have to incorporate functionality suitable for the elaboration of ring B of sordarin-like scaffolds through ionic or radical reactions. A halogen-substituted dienophile such as 2-chloroacrylonitrile nicely satisfied this requirement. Gratifyingly, the Diels–Alder reaction of 17–20 with 2-chloroacrylonitrile proceeded normally to furnish the expected cycloadducts as single isomers, albeit in moderate yield (Scheme 3). Thus, such previously unexplored cyclopentadienes are competent in Diels–Alder reactions. On the other hand, sterically hindered diene 16 failed to react. The dienes were also inert toward less reactive dienophiles such as acrylonitrile or acrolein at temperatures up to 65 °C.¹⁹ No effort was made to promote such reactions with Lewis acid activators.

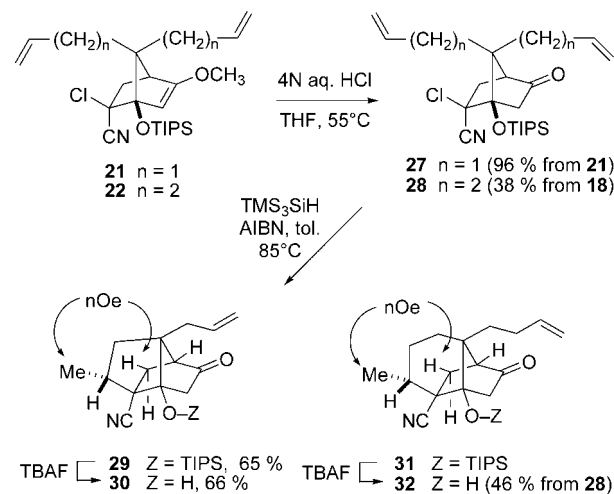
The structure of the cycloadducts was assigned as 21–24²⁰ on the following basis. First, the regioselectivity anticipated on electronic grounds²¹ found support in the diagnostic coupling constants observed between the bridgehead (H_b) proton and the neighboring *exo* (H_x) and *endo* (H_e) hydrogens (*J*_{bx} = 3–4 Hz, *J*_{be} = 0 Hz).²² We presume that these regioisomers were formed as the *endo* diastereomers (Alder rule),²³ as shown, because it seemed unlikely that the reaction might have generated exclusively *exo* cycloadducts.

Cleavage of the TIPS ether in these adducts and functionalization of the bridgehead OH group might have provided interesting sordarin analogues. However, attempted desilylation of 21–24 resulted in complete degradation. We suspect that

SCHEME 4



SCHEME 5



desilylation triggered retroaldol fragmentation of the bicyclic system and consumption of the transient 26 through a multitude of side reactions (Scheme 4). On the other hand, treatment of 21 and 22 with warm (55 °C) aqueous 4 N HCl in THF promoted only hydrolysis of the vinyl ether to furnish ketones 27 and 28 (Scheme 5). These proved to be good substrates for radical cyclization reactions leading to tricyclic sordarin building blocks 29 and 31.²⁴ As anticipated on the basis of the Beckwith model,²⁵ the reaction occurred diastereoselectively to give products wherein the configuration of the methyl-bearing stereogenic carbon coincides with that of the corresponding carbon atom of sordarin. This assignment is supported by a strong nuclear Overhauser effect observed between the methyl hydrogens and the neighboring *exo* hydrogen. Contrary to the case of 21–24, TBAF release of the TIPS group from tricyclic intermediates 29 and 31 proceeded uneventfully to give alcohols, 30 and 32.

Ozonolytic cleavage of the surviving double bond in such tricyclic systems permitted the elaboration of apical ether functionalities of the type found in a number of bioactive analogues of 1. Thus, reduction of 29 (NaBH₄, Scheme 6) provided the *exo* alcohol diastereoselectively,²⁶ which was benzylated prior to ozonolytic formation of aldehyde 35. The latter was advanced to 36–42 through conventional reaction sequences, certain aspects of which are nonetheless worthy of comment. First, debenzoylation of 37 and 38 was best accomplished with the Pearlman catalyst.²⁷ Second (Scheme 7), and contrary to the case of 29, NaBH₄ reduction of 43, obtained

(18) TMS and TES silyl ethers underwent desilylation back to the starting enones upon heating in the presence of dienophiles.

(19) An MNDO calculation (Hyperchem package) indicated that the LUMO energy of 2-chloroacrylonitrile is about 0.5 eV lower than that of acrylonitrile or acrolein.

(20) Adducts 22 and 24 were not fully characterized. For the series of compounds emanating from 22, full characterization occurred at the stage of derivative 28.

(21) This would be consequence of the electronic similarity between the cyclopentadienes in question and the Danishefsky diene (ref 11).

(22) Bowey, F. A. *Nuclear Magnetic Resonance Spectroscopy*; Academic Press: New York, NY, 1969.

(23) (a) Alder, K. *Justus Liebigs Ann* **1951**, 571, 157. Theoretical study; (b) Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1999**, 64, 6697.

(24) Compound 31 was not characterized beyond a crude ¹H NMR. In crude form, it was directly advanced to 32, which was purified and fully characterized.

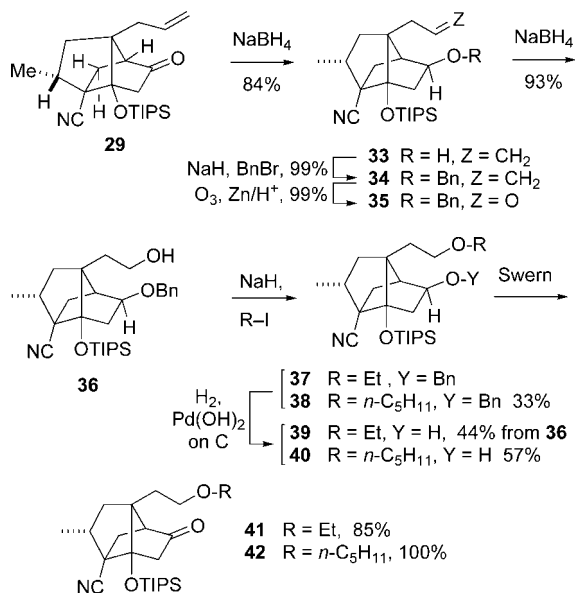
(25) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, 41, 3925.

(b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, 36, 545.

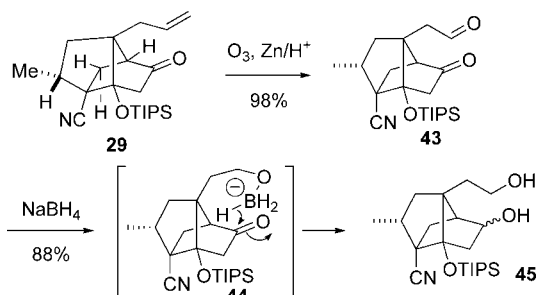
(26) As anticipated based on the behavior of the sterically similar camphor: Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, 88, 2811.

(27) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 8, 1663.

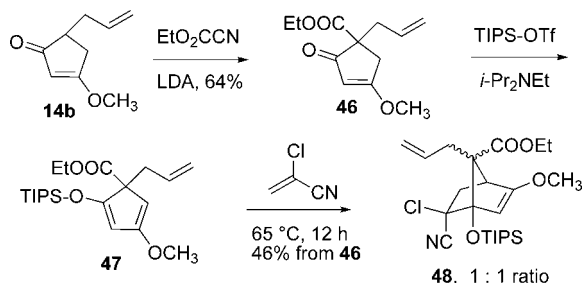
SCHEME 6



SCHEME 7



SCHEME 8

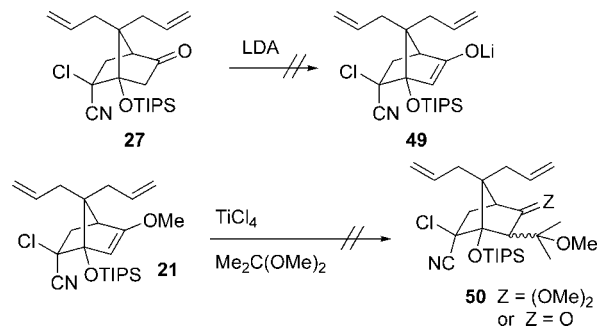


in 98% yield by ozonolysis of **29**, was nonstereoselective, leading to a mixture of epimers of alcohol **45**. We believe that rapid reduction of the formyl group leads to an intermediate such as **44**. Intramolecular hydride delivery to the keto carbonyl may now compete with the bimolecular reaction, accounting for the poor diastereoselectivity.

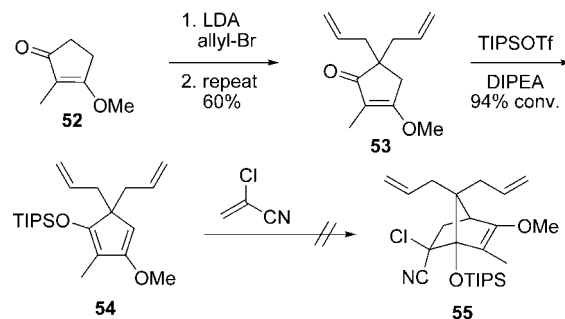
Encouraged by these results, we contemplated the possibility of inducing a facially selective Diels–Alder reactions of cyclopentadienes **7** wherein R⁴ = COOEt and R⁵ = linear alkyl. To test this hypothesis, **14b** was advanced to **46** by sequential Mander acylation¹⁷ and silyl enol ether formation (Scheme 8). However, no facial selectivity was observed in the reaction of the emerging cyclopentadiene with 2-chloroacrylonitrile, and this line of research was abandoned.²⁸

Several of the bicyclic and tricyclic compounds shown above were tested for activity against a broad range of phytopathogenic fungi. Substances **34** and **35** showed marginal efficacy at 50

SCHEME 9



SCHEME 10



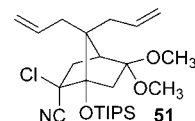
ppm; however, none of the new entities were sufficiently potent. Possible reasons for this may have been the lack of an isopropyl, other small alkyl group, at the position adjacent to the carbonyl functionality and/or the absence of the bridgehead COOH group. Concerning the first issue, we considered generating an enolate of ketone **27** to effect the desired alkylation either in the aldol or in the S_N2 mode. In practice, this proved not to be possible, because the ketone resisted deprotonation with LDA. In this respect, **27** differs from the structurally related camphor, which undergoes deprotonation normally with LDA. To wit, the documented aldol addition of the zinc enolate of camphor to acetone²⁹ was duplicated without difficulty, as was the ensuing formation of isopropylidene camphor. Evidently, the bridgehead silyloxy functionality in **27** and related ketones shields the neighboring methylene group from the action of external bases. Attempts to achieve alkylation of cycloadducts **21–24** by harnessing the nucleophilic character of the vinyl ether functionality also failed. For instance (Scheme 9), exposure of **21** to 2,2-dimethoxypropane and catalytic TiCl₄ produced none of the desired **50**.³⁰

A plausible cure for such ills was to install the desired alkyl substituent on the starting cyclopentadiene. This possibility was investigated using diene **54** (Scheme 10). Surprisingly, **54** failed to combine with 2-chloroacrylonitrile (65 °C, toluene, K₂CO₃;

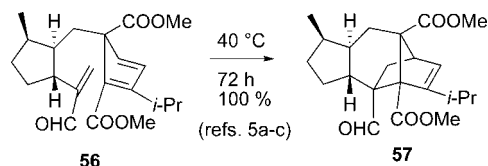
(28) Because of this disappointing outcome, compounds **47** and **48** were not purified to homogeneity or fully characterized.

(29) (a) Lightner, D. A.; Flores, M. J.; Crist, B. V.; Gawronski, J. K. *J. Org. Chem.* **1980**, *45*, 3518. (b) Schenato, R. A.; dos Santos, E. M.; Tenius, B. S. M.; Costa, P. R. R.; Caracelli, I.; Zukerman-Schpector, J. *Tetrahedron: Asymmetry* **2001**, *12*, 579. (c) Frimer, J. J.; Afri, M.; Baumel, S. D.; Gilinsky-Sharon, P.; Rosenthal, Z.; Gottlieb, H. E. *J. Org. Chem.* **2000**, *65*, 1807.

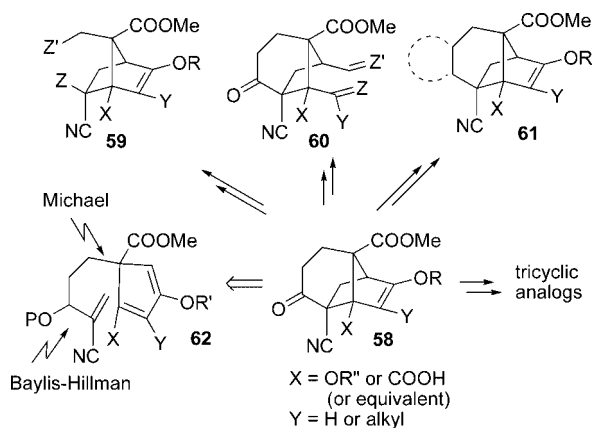
(30) This reaction furnished instead ketal **51**, which was not thoroughly characterized:



SCHEME 11



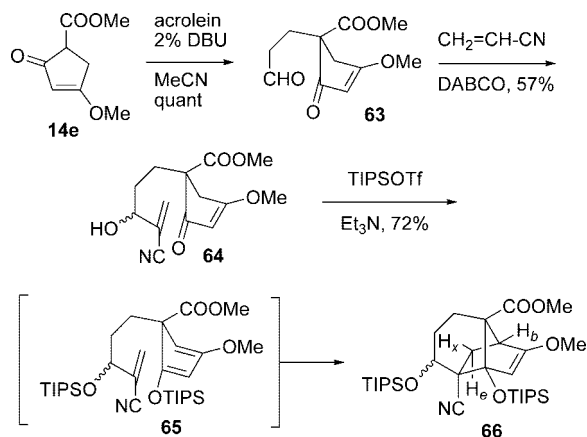
SCHEME 12



higher temperatures caused desilylation back to **53**). Given that the steric effect of a mere methyl group seemingly suffices to suppress the Diels–Alder reactivity of **54**, analogous reactions of dienes incorporating even more sterically demanding alkyls, such as an isopropyl group, were not pursued.³¹ On the other hand, pioneering work by Kato^{5a} and Mander^{5b,c} (Scheme 11) had demonstrated efficient IMDA reactions of sterically congested or electronically deactivated cyclopentadienes. We thus refocused on an IMDA approach to the assembly of building blocks for **1** displaying alkyl and bridgehead carboxy (or equivalent) groups.

Important observations by Cuevas³² suggest that the presence of at least a bicyclic system is necessary for activity. We thus concentrated on the preparation of tricyclic ketones **58** (Scheme 12), which we felt could be elaborated into a variety of sordarin congeners, including bicyclo[2.2.1]- (**59**), bicyclo[3.2.1]- (**60**), tricyclic, and tetracyclic (**61**) analogues, the latter in both the homo- and the heterocyclic series. Compounds **58** were envisioned to derive from **62**, wherein the indicated C–C bonds would be established through Michael and Baylis–Hillman reactions. To test this approach, we targeted **66** (Scheme 13), which incorporates a bridgehead oxygen functionality while lacking an alkyl substituent corresponding to the isopropyl group of **1**. Thus, the Michael addition of the known **14e**³³ to acrolein provided **63** in quantitative yield. The reaction proceeded best in the presence of 2% DBU. The use of larger amounts of base caused an apparent stalling of the reaction, resulting in diminished yields. This appears to be due to the fact that greater quantities of basic agents accelerate a competing retro-Michael fragmentation of **63**. Indeed, this aldehyde is a sensitive material that degrades easily under basic

SCHEME 13



conditions or upon contact with silica gel. Fortunately, the Michael step afforded product of excellent quality, enabling the conduct of a subsequent Baylis–Hillman reaction³⁴ without purification. The kinetics of the latter process are notoriously slow, and in fact formation of **64** required 2 days even by operating in neat acrylonitrile. The product emerged as a ca. 60:40 mixture of two unassigned alcohol diastereomers, which were not separated, since the OH group is destined to undergo ultimate oxidation to a ketone. Instead, the mixture was directly subjected to double silylation in the presence of TIPS-OTf and Hünig base (CH_2Cl_2 , 0 °C). The ¹H NMR spectra of the resultant reaction mixtures revealed the presence of nearly equimolar amounts of diene **65** and cycloadduct **66**. The latter again emerged as a single regioisomer (¹H NMR), as anticipated on the basis of bond polarization. Structure **66** was initially assigned on the basis of the coupling constants observed between protons H_x , H_e , and H_b ($J_{bx} = 4.1$ Hz; $J_{be} = 0.0$ Hz; $J_{ex} = 13.6$ Hz). However, it was also apparent that the cycloadduct had formed as a 3:1 mixture of unassigned epimers of the lateral OTIPS group. This signaled that one of the two stereoisomers of **65** (initially a 60:40 mixture of diastereomers) undergoes IMDA faster than the other. Upon standing at room temperature for 12 h, the diene component in the mixture was completely converted to the cycloadduct, which was now present as a 60:40 mixture of isomers. The sequence leading to **66** was ultimately modified by effecting the silylation step at 0 °C and then allowing the reaction mixture to stir at 25 °C for 12 h. This resulted in direct formation of a 60:40 mixture of diastereomers of **66** (72%).

The application of the same approach to the assembly of cycloadducts displaying a bridgehead COOH group, or an equivalent functionality, raised an interesting issue. Derivatization of kinetic enolates of enones **67** as seen thus far would lead to compounds **68** (Scheme 14). These could undoubtedly be advanced to structures **69** and thence to the ultimate **70**. But if one could access the thermodynamic enolates of **67** and thereby produce **71**, the preparation of an intermediate displaying an equivalent of the carboxy group at an appropriate position would be greatly facilitated. For instance, reaction of **71** with a source of cyanide ion may result in formation of **72**, which could be expeditiously converted into **70**. Fortunately, important work by Koreeda³⁵ had established that LHMDS deprotonates enones

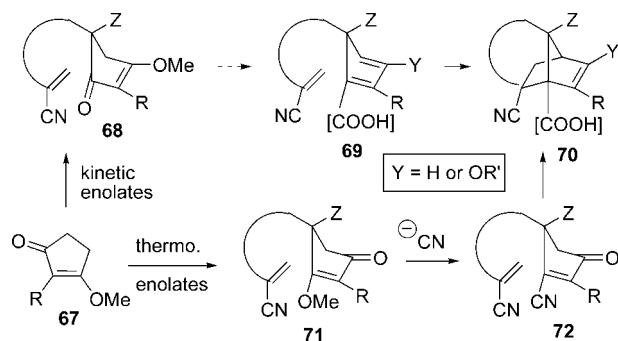
(31) Because of this failure, compound **54** was not purified to homogeneity or fully characterized.

(32) (a) Cuevas, J. C.; Martos, J. L. *Tetrahedron Lett.* **1998**, 39, 8553. (b) Cuevas, J. C.; Lavandera, J. L.; Martos, J. L. *Bioorg. Med. Chem. Lett.* **1999**, 9, 103.

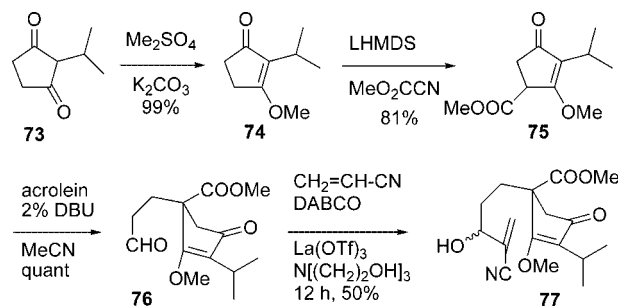
(33) (a) Irie, H.; Katakawa, J.; Tomita, M.; Mizuno, Y. *Chem. Lett.* **1981**, 637. (b) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, 22, 4385. Prepared in 52% yield by reaction of **13** with LHMDS followed by MeO_2COCN .

(34) Reviews: (a) Ciganek, E. *Org. React.* **1997**, 51, 201. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, 103, 811. (c) Awad, L.; Demange, R.; Zhu, Y.-H.; Vogel, P. *Carb. Res.* **2006**, 341, 1235.

SCHEME 14

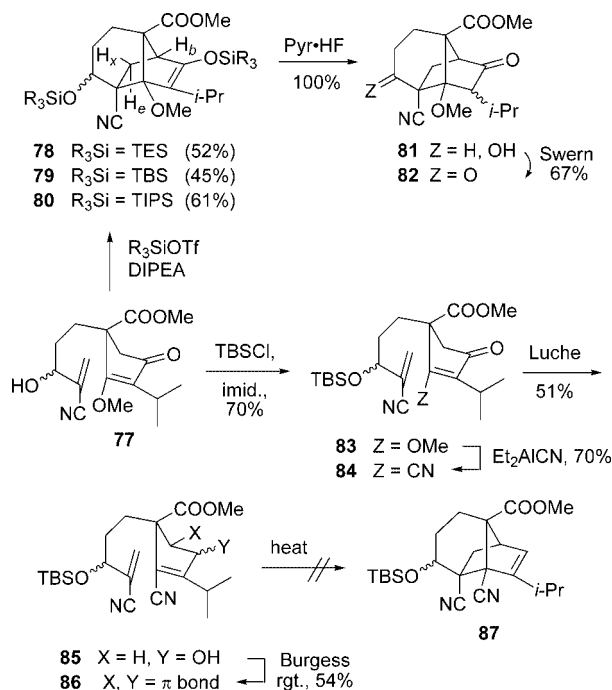


SCHEME 15



67 in which R = alkyl to furnish thermodynamic enolates. Accordingly, the known **73**³⁶ was converted into **74**, which upon exposure to LHMDS followed by MeO₂C–CN indeed afforded a product, **75** (81%), formally ensuing through acylation of the thermodynamic enolate (Scheme 15). The Michael addition of **75** to acrolein proceeded as expected, but for reasons that remain unclear, the subsequent Baylis–Hillman reaction of the resultant **76** was abnormally slow. Several days were required to convert the substrate into a nearly 50:50 mixture of alcohol diastereomers of **77** (68% chromatographed yield) under the conditions previously employed for **63** (neat acrylonitrile, DABCO). Aggarwal conditions (La(OTf)₃ and triethanolamine as cocatalysts)³⁷ enabled a 9-fold rate acceleration, but at the cost of a reduced yield of **77** (50% chromatographed). The product was obtained as a 65:35 ratio of unassigned alcohol diastereomers. We were now in a position to evaluate the effect of the isopropyl group on the IMDA reaction of a silyl enol ether derivative of **77**, and to that end, the compound was subjected to double silylation as detailed earlier. Cycloadducts **78–80** were obtained without incident.³⁸ In accord with previous findings, TIPS ethers performed most efficiently in this step (Scheme 16). Furthermore, desilylation of **78** proceeded efficiently to furnish **81** as a mixture of isopropyl epimers. Swern oxidation³⁹ of the alcohol surrendered diketone **82**, thereby demonstrating a critical desilylation–oxidation step. More importantly, treatment of the TBS ether⁴⁰ of **77** with diethylaluminum cyanide (Nagata reagent)⁴¹ afforded dinitrile **84**. Luche reduction⁴² of the enone

SCHEME 16



and dehydration of the intermediate **85** with the Burgess reagent⁴³ produced **86**.

Distressingly, compound **86** resisted IMDA reaction at temperatures as high as 160 °C, above which it decomposed. This behavior contrasts with that of **56**, which cyclizes easily and with the correct regioselectivity⁴⁴ to give **57**. In either case, electron-withdrawing groups are present on both the dienic and the dienophilic segments of the molecule. Consequently, the failure of **86** to undergo IMDA reaction is not imputable solely to an electronic incompatibility between diene and dienophile. It is known that cyclic cyanodienes are poor components of Diels–Alder reactions.⁴⁵ On the other hand, 1-cyanocyclopentadiene seems to be more reactive than acyclic cyanodienes in that it combines with tetracyanoethylene (admittedly a highly reactive dienophile) even at –25 °C.⁴⁶ Consequently, an IMDA of a cyanocyclopentadiene such as **86** was expected to be even more facile. We surmised that the failure of this reaction might be due to an abnormal lowering of the HOMO energy of the diene operated by the cyano substituent. An indication that this may be the case emerges from the fact that the Hammett σ values for a CN group are more positive than those of a COOMe group.⁴⁷ However, lack of knowledge about the ρ value for the IMDA reaction in question disallows an accurate evaluation of the effect that this may have on overall kinetics. The matter was thus addressed computationally⁴⁸ using COOMe- and CN-

(42) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, 103, 5454.

(43) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, 90, 4744.

(44) The cyclopentadiene unit in **86** lacks an oxygen substituent that might direct formation of the correct regioisomer of the adduct. However, **56** produces **57** only (Scheme 11 and ref 5c). More significantly, 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). Thus, we anticipated good regioselectivity in the IMDA cyclization of **86**.

(45) Snyder, H. R.; Poos, G. I. *J. Am. Chem. Soc.* **1950**, 72, 4104.

(46) Banert, K.; Koehler, F.; Meier, B. *Tetrahedron Lett.* **2003**, 44, 3781.

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

(48) Calculations were carried out with the Hyperchem package, available from Hypercube, Inc. (www.hyper.com).

(35) (a) Koreeda, M.; Liang, Y.; Akagi, H. *J. Chem. Soc., Chem. Commun.* **1979**, 449. (b) Koreeda, M.; Liang, Y. *Tetrahedron Lett.* **1981**, 22, 15.

(36) Majetich, G.; Song, J.-S.; Ringold, C.; Nemeth, G. A.; Newton, M. G. *J. Org. Chem.* **1991**, 56, 3973, and refs cited therein.

(37) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, 63, 7183.

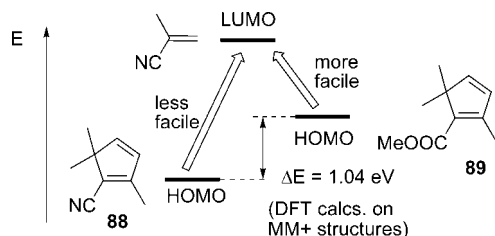
(38) The structure of these molecules again rests on the coupling constants between protons H_e, H_x and H_b (J_{bx} = 4.4 Hz; J_{be} = 0 Hz; J_{ex} = 13.1 Hz).

(39) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 3, 165.

(40) Protection of **77** as, e.g., a TES ether furnished intermediates that reacted poorly in subsequent steps.

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

SCHEME 17



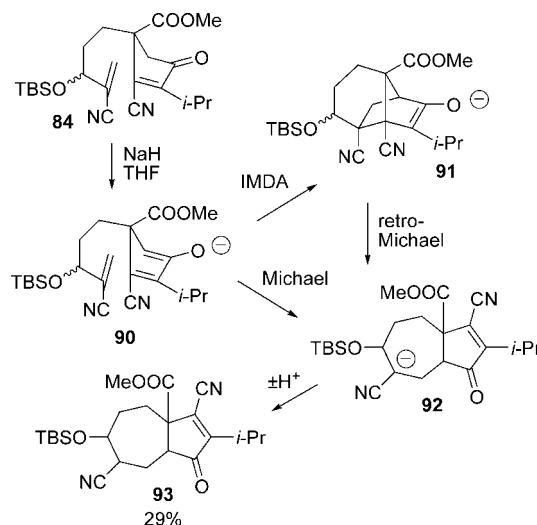
substituted cyclopentadienes **88** and **89** (Scheme 17) as better tractable mimics of the actual systems. Semiempirical calculations detected insignificant differences in the FMO energies for the two molecules.⁴⁹ However, DFT calculations (6-31G*) carried out on MM+-optimized structures revealed that the HOMO energy of **88** is about 1 eV lower than that of the ester analogue. This may account for the problematic reaction of **86**. A plausible way to circumvent such unfavorable electronic properties was to attempt the reaction with a silyl enol ether derivative of **84**. The silyloxy substituent was anticipated to raise the HOMO energy of the diene system, thereby enhancing its reactivity.

To our complete surprise, **84** was recovered unchanged upon countless attempts to achieve enol silylation under a variety of conditions,⁵⁰ even by the application of the Corey–Gross method.⁵¹ The behavior of **84** stood in strident contrast to that of other cyanoenones, such as 4-oxo-2-pentene-carbonitrile, which are reported to undergo enol silylation without incident.⁵²

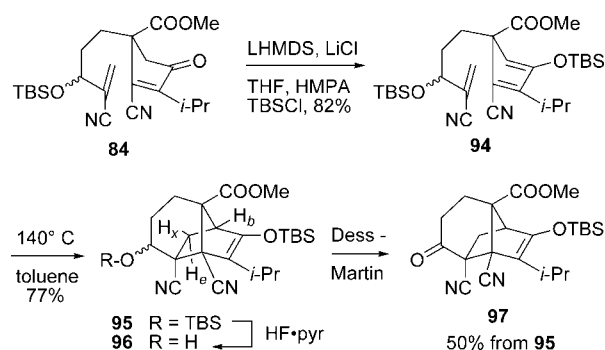
The reasons for such a failure are mystifying. We posited that **84** might suffer from an inherent barrier to enolization. To address this hypothesis, the compound was treated with NaH in THF, whereupon it was slowly converted into a mixture of products containing **93** (mixture of diastereomers, 29% yield, chrom.) as the major component (Scheme 18). This material clearly results from a formal intramolecular Michael addition of the enolate of the enone to the lateral conjugated nitrile. Of course, we cannot exclude the possible occurrence of a dienolate Diels–Alder reaction followed by retro-Michael fragmentation (cf. **90** to **91** to **92**). While the latter step would be disfavored on stereoelectronic grounds (it corresponds to an anti-Baldwin retro-5-endotrig process),⁵³ the significant release of strain associated with the breakup of the bicyclo[2.2.1] system may well overcome such barriers.

Regardless, the formation of **93** proved that the enolate of **84** is indeed accessible. Given the “enormous mechanistic complexity” of ketone deprotonation,⁵⁴ it was imprudent to formulate simplistic explanations as to why enol silylation of **84** failed. On the other hand, the foregoing observations were consistent with an insufficient kinetic reactivity of the base employed for deprotonation. A practical way to circumvent such

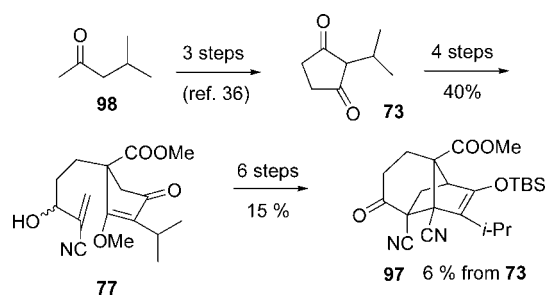
SCHEME 18



SCHEME 19



SCHEME 20



difficulties was to harness the so-called “LiX effect”,⁵⁵ that is, the ability of lithium halides to enhance the kinetic reactivity of amide bases. Indeed, exposure of **84** to an excess⁵⁶ of LHMDS and LiCl in THF–HMPA, in the presence of TBSCl, delivered the long-sought **94** in 82% yield (Scheme 19).⁵⁷ In contrast to its congeners, diene **94** displayed no inclination whatsoever to cyclize to **95** at room temperature: cyclization

(49) Numerical results are provided as Supporting Information.

(50) Over a range of temperatures, compound **84** was immune to the action of 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), 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).

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

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

(53) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.

(54) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

(55) (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.

(56) 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.

(57) The corresponding TMS enol ether was too labile, while the TES enol ether afforded poor yields in the subsequent IMDA.

had to be forced by heating a toluene solution of **94** in a sealed tube at 140 °C for 12 h. Fortunately, the expected **95** was obtained as a single regioisomer, but as a 50:50 mixture of epimers of the lateral OTBS group, in 77% chromatographed yield. We consider the reluctance of **94** to undergo IMDA reaction as another manifestation of the HOMO-lowering influence of the CN substituent. As seen earlier for similar compounds, the diagnostic coupling constants observed for protons H_c , H_x , and H_b ($J_{bx} = 3.9$ Hz; $J_{be} = 0$ Hz; $J_{ex} = 13.5$ Hz) support the structure of the new cycloadduct. Treatment of **95** with pyridine–HF induced only release of the nonenolic TBS group. The resultant mixture of diastereomeric alcohols **96** underwent smooth Dess–Martin oxidation to **97** (single isomer), thereby achieving the preparation of a building block for sordarin analogues wherein a cyano group replaces the bridgehead COOH functionality. We believe that intermediates of the type **97** are the key to the exploration of the structure–activity relationship of the terpenoid core of **1**. In addition they may possibly be useful for a total synthesis of the natural product.

In conclusion, this work has established avenues to intermediates that could serve as building blocks for the synthesis of sordarin and congeners. In the process, the preparation and the Diels–Alder reactivity of a number of previously unknown cyclopentadienes have been explored. Unusual properties of cyano-substituted enones and cyclopentadienes have been unveiled and circumvented. The successful sequence leading to tricyclic ketone **97** requires 10 steps from the known dione **73** (available in 3 steps from methyl isobutyl ketone, **98**),³⁶ and it proceeds in an overall yield of 6%. Investigations aiming to improve the synthesis of compounds such as **97** and to elaborate them to sordarin and its analogues continue in our laboratory.

Experimental Section⁵⁸

Representative Procedure for the Alkylation of 13 with Reactive Electrophiles: 5-Allyl-3-methoxy-2-cyclopenten-1-one (14b). A 2.5 M solution of *n*-BuLi in hexanes (10.7 mL, 26.8 mmol) was added dropwise to a cold (–40 °C) solution of dry diisopropylamine (3.8 mL, 26.8 mmol) in anhydrous THF (36 mL), with good stirring under Ar. The mixture was allowed to warm slowly to –10 °C, then it was cooled to –78 °C. A solution of **13** (2.5 g, 22.3 mmol) in dry THF (8 mL) was introduced dropwise, and the mixture was stirred at –78 °C for an additional 30 min after all of the ketone had been added. Neat allyl bromide (4.8 mL, 55.8 mmol) was then introduced dropwise, and the mixture was stirred for an additional 2 h at –78 °C. The solution was then allowed to warm to 0 °C and treated with water (5 mL). The THF was removed in vacuo, and the aqueous residue was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with saturated aq NaCl solution, dried (MgSO₄), and evaporated. Chromatographic purification of the residue (30% EtOAc in cyclohexane) gave 2.4 g (16.1 mmol, 72%) of product. ¹H NMR: 5.73 (m, 1H); 5.27 (t, 1H, $J = 1.1$); 5.05 (m, 2H); 3.82 (s, 3H); 2.69 (ddd, 1H, $J = 17.5, 7.1, 1.1$); 2.57 (m, 2H); 2.32 (ddd, 1H, $J = 17.5, 2.6, 1.1$); 2.17 (m, 1H). ¹³C NMR: 207.5; 190.4; 135.6; 117.4; 104.1; 59.0; 44.9; 35.8; 34.2. MS (CI): 153 [M + H]⁺. HRCIMS: calcd for C₉H₁₃O₂ 153.0916, found 153.0913.

5,5-Diallyl-3-methoxy-2-cyclopenten-1-one (15b). A 2.5 M solution of *n*-BuLi in hexanes (7.4 mL, 18.6 mmol) was added dropwise to a cold (–40 °C) solution of dry diisopropylamine (2.6 mL, 18.6 mmol) in anhydrous THF (23 mL), with good stirring under Ar. The mixture was allowed to warm slowly to –10 °C, then it was

cooled to –78 °C. A solution of the above compound (2.4 g, 15.5 mmol) in dry THF (8 mL) was introduced dropwise, and the mixture was stirred at –78 °C for an additional 30 min after all of the ketone had been added. Neat allyl bromide (3.4 mL, 38.8 mmol) was then introduced dropwise, and the mixture was stirred for an additional 2 h at –78 °C. The solution was then allowed to warm to 0 °C and treated with water (5 mL). The THF was removed in vacuo, and the aqueous residue was extracted with EtOAc (3 × 40 mL). The combined extracts were washed with saturated aq NaCl solution, dried (MgSO₄), and evaporated. Chromatographic purification of the residue (15% EtOAc in cyclohexane) gave 2.1 g (10.9 mmol, 70%) of product. ¹H NMR: 5.63 (m, 2H); 5.24 (t, $J = 1.0$, 1H); 5.05 (m, 4H); 3.81 (s, 3H); 2.43 (d, $J = 1.0$, 2H); 2.36 (ddt, $J = 13.6, J = 6.5, J = 1.3$, 2H); 2.15 (dd, $J = 13.6, J = 8.2$, 2H). ¹³C NMR: 208.5; 189.0; 133.2; 118.2; 103.6; 58.4; 50.4; 41.2; 36.9. MS (CI): 193 [M + H]⁺. IR: 1695, 1597. HRCIMS: calcd for C₁₂H₁₇O₂ 193.1229, found 193.1230.

Representative Procedure for Alkylation of 13 with Less Reactive Electrophiles: 5-(1-Buten-4-yl)-3-methoxy-2-cyclopenten-1-one (14c). A 2.3 M solution of *n*-BuLi in hexanes (14.0 mL, 32.7 mmol) was added dropwise to a cold (–40 °C) solution of dry diisopropylamine (4.6 mL, 32.7 mmol) in anhydrous THF (39 mL), with good stirring under Ar. The mixture was allowed to warm slowly to –10 °C, then it was cooled to –78 °C. A solution of **13** (2.5 g, 21.8 mmol) and dry DMPU (10.5 mL, 87.1 mmol) in dry THF (5 mL) was introduced dropwise, and the mixture was stirred at –78 °C for an additional 40 min after all of the ketone had been added. A second portion of DMPU (10.5 mL, 87.1 mmol) was added, and the mixture was stirred for another 5 min. Neat 4-iodo-1-butene (19.8 g, 109 mmol) was then injected, and the mixture was stirred for an additional 3 h, during which time it was allowed to warm to 0 °C. The solution was treated with water (5 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with saturated aq NaCl solution, dried (Na₂SO₄), and evaporated. Chromatographic purification of the residue (40% EtOAc in cyclohexane) gave 2.3 g (13.9 mmol, 64%) of product. ¹H NMR: 5.78 (m, 1H); 5.30 (s, 1H); 5.00 (m, 2H); 3.84 (s, 3H); 2.75 (dd, $J = 17.8, J = 7.1$, 1H); 2.51 (m, 1H); 2.29 (dd, $J = 17.8, J = 3.0$, 1H); 2.12 (m, 2H); 1.97 (m, 1H); 1.45 (m, 1H). ¹³C NMR: 208.2; 190.2; 138.2; 115.6; 104.1; 59.0; 45.3; 35.1; 31.8; 31.0. MS (EI): 166 M⁺, 151, 112. HREIMS: calcd for C₁₀H₁₄O₂ 166.0994, found 166.0994.

5,5-Bis(1-buten-4-yl)-3-methoxy-2-cyclopenten-1-one (15c). A 2.3 M solution of *n*-BuLi in hexanes (5.6 mL, 13.0 mmol) was added dropwise to a cold (–40 °C) solution of dry diisopropylamine (1.9 mL, 13.0 mmol) in anhydrous THF (17 mL), with good stirring under Ar. The mixture was allowed to warm slowly to –10 °C, then it was cooled to –78 °C. A solution of the above compound (1.8 g, 10.9 mmol) and dry DMPU (5.2 mL, 43.4 mmol) in dry THF (5 mL) was introduced dropwise, and the mixture was stirred at –78 °C for an additional 40 min after all of the ketone had been added. A second portion of DMPU (5.2 mL, 43.4 mmol) was added, and the mixture was stirred for another 5 min. Neat 4-iodo-1-butene (9.9 g, 54.2 mmol) was then injected and the mixture was stirred for an additional 3 h, during which time it was allowed to warm to 0 °C. The solution was treated with water (3 mL), and the THF was removed in vacuo. The aqueous residue was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with saturated aq NaCl solution, dried (Na₂SO₄), and evaporated. Chromatographic purification of the residue (40% EtOAc in cyclohexane) gave 792 mg (3.6 mmol, 33%) of product. ¹H NMR: 5.76 (m, 2H); 5.28 (s, 1H); 4.96 (m, 4H); 3.84 (s, 3H); 2.49 (s, 2H); 1.94 (m, 4H); 1.61 (m, 4H). ¹³C NMR: 209.9; 189.6; 138.6; 115.0; 104.6; 59.0; 51.1; 39.1; 36.6; 28.9. MS (CI): 221 [M + H]⁺. HRCIMS: calcd for C₁₄H₂₁O₂ 221.1542, found 221.1544.

5,5-Bis(carbomethoxy)-3-methoxy-2-cyclopenten-1-one (15e). A solution of **13** (506 mg, 4.5 mmol) in dry THF (2 mL) was added dropwise to a cold (–78 °C) solution of KHMDS (commercial 0.5 M solution in toluene, 10.7 mL, 5.4 mmol) in dry THF (7 mL).

(58) Unless otherwise indicated, NMR spectra were recorded from CDCl₃ solutions and IR spectra were obtained from thin films deposited on NaCl plates. More detailed experimental protocols are provided as Supporting Information.

After all of **13** had been added, the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, then dry DMPU (0.6 mL, 4.5 mmol) was injected, followed by neat ethyl cyanoformate (0.5 mL, 5.4 mmol; **CAUTION: source of highly toxic HCN**). The mixture was stirred for 75 min at $-78\text{ }^{\circ}\text{C}$, then a second portion of KHMDS (0.5 M solution in toluene, 9.0 mL, 4.5 mmol) was added, and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for another 30 min. Dry DMPU (0.6 mL, 4.5 mmol) was injected, followed by neat ethyl cyanoformate (0.5 mL, 5.4 mmol). The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h, then it was allowed to warm to rt, and it was finally quenched with water (4 mL). The THF was evaporated, and the residue was extracted with EtOAc ($3 \times 20\text{ mL}$). The combined extracts were washed with saturated aq NaCl solution, dried (MgSO_4), and evaporated. Chromatographic purification of the residue (30% EtOAc in cyclohexane) furnished 491 mg (1.9 mmol, 42%) of product. ^1H NMR (C_6D_6): 5.28 (s, 1H); 4.30–4.12 (m, 4H); 3.88 (s, 3H); 3.24 (s, 2H); 1.28 (t, $J = 7.2$, 6H). ^{13}C NMR: 197.7; 172.3; 171.7; 91.1; 73.5; 59.2; 51.3; 27.4; 13.4. MS (CI): 257 $[\text{M} + \text{H}]^+$. HRMS: calcd for $\text{C}_{12}\text{H}_{16}\text{O}_6$ $[\text{M} + \text{Na}]^+$ 279.0845, found 279.0843.

Representative Procedure for the Preparation of Siloxycyclopentadienes: 5,5-Diallyl-1-triisopropylsilyloxy-3-methoxy-1,3-cyclopentadiene (17). Neat TIPSOTf (4.4 mL, 16.3 mmol) was added to a cold ($0\text{ }^{\circ}\text{C}$) solution of enone **15b** (2.4 g, 12.6 mmol) and DIPEA (3.5 mL, 20.1 mmol) in dry CH_2Cl_2 (50 mL), with good stirring under Ar. The cold bath was removed, and the solution was stirred for 3 h at rt, then it was diluted with a 3:1 mixture of pentane and CH_2Cl_2 . The colorless precipitate that appeared was filtered off, and the filtrate was sequentially washed with saturated aq NaHCO_3 and with saturated aq NaCl solutions, then dried (MgSO_4) and evaporated. The oily residue consisted (^1H NMR) of a mixture of **17** and starting enone in a 91:9 ratio. The mixture was used as such for the following step. The desired **17** possessed the following spectral characteristics. ^1H NMR (C_6D_6): 5.83 (m, 2H); 5.20 (d, $J = 1.9$, 1H); 5.15–5.00 (m, 4H); 4.32 (d, $J = 1.9$, 1H); 3.37 (s, 3H); 2.40 (m, 4H); 1.15–0.90 (m, 21H). ^{13}C NMR (C_6D_6): 167.4; 160.7; 136.1; 116.9; 101.6; 92.3; 55.9; 55.4; 40.6; 18.5; 13.0. MS (CI): 405 $[\text{M} + \text{C}_4\text{H}_9]^+$; 349 $[\text{M} + \text{H}]^+$. HRCIMS: calcd for $\text{C}_{21}\text{H}_{37}\text{O}_2\text{Si}$ 349.2563, found 349.2562.

5,5-Bis(1-buten-4-yl)-1-triisopropylsilyloxy-3-methoxycyclopent-1,3-diene (18). Neat TIPSOTf (1.1 mL, 4.1 mmol) was added to a cold ($0\text{ }^{\circ}\text{C}$) solution of the enone **15c** (687 mg, 3.1 mmol) and DIPEA (0.9 mL, 5.0 mmol) in dry CH_2Cl_2 (12.5 mL), with good stirring under Ar. The cold bath was removed, and the solution was stirred for 2 h at rt, then it was diluted with a 3:1 mixture of pentane and CH_2Cl_2 (30 mL). The colorless precipitate that appeared was filtered off, and the filtrate was sequentially washed with saturated aq NaHCO_3 and with saturated aq NaCl solutions, then dried (MgSO_4) and evaporated. The oily residue consisted (^1H NMR) of a mixture of **18** and starting enone in a 95:5 ratio. The mixture was used as such for the following step. The desired **18** possessed the following spectral characteristics. ^1H NMR (C_6D_6): 5.89 (m, 2H); 5.20 (d, 1H, $J = 2.0$); 5.11 (dd_{app}, $J = 17.0$, $J = 2.0$, 1H); 4.99 (dd_{app}, $J = 10.2$, $J = 2.2$, 1H); 4.15 (d, $J = 2.0$, 1H); 3.38 (s, 3H); 2.25–2.00 (m, 4H); 1.75 (m, 4H); 1.15–0.85 (m, 21H). ^{13}C NMR (C_6D_6): 166.9; 160.1; 140.2; 114.5; 101.7; 92.3; 55.9; 55.8; 36.1; 29.7; 18.5; 13.1. MS (CI): 377 $[\text{M} + \text{H}]^+$. HRCIMS: calcd for $\text{C}_{23}\text{H}_{41}\text{O}_2\text{Si}$ 377.2876, found 377.2878.

Representative Procedure for the Bimolecular Diels–Alder Reaction: 7,7-Bis(allyl)-6-exochloro-6-endocyano-1-triisopropylsilyloxy-3-methoxybicyclo[2.2.1]hept-2-ene (21). A solution of **17** (5.2 mmol) and 2-chloroacrylonitrile (1.3 mL, 15.7 mmol; **CAUTION: cancer suspect agent**) in dry toluene (10 mL) containing suspended solid K_2CO_3 (100 mg) was stirred at $65\text{ }^{\circ}\text{C}$ for 12 h. The mixture was filtered over Celite and evaporated. Chromatography of the residue (5% EtOAc in cyclohexane) furnished 1.2 g (2.8 mmol, 53% over 2 steps) of **21**. ^1H NMR (C_6D_6): 6.18 (m, 1H); 5.66 (m, 1H); 5.10–4.96 (m, 4H); 4.64 (d, $J = 1.6$, 1H); 3.09 (s, 3H); 2.75 (dd, $J = 14.0$, $J = 7.5$, 1H); 2.62 (ddd_{app}, $J = 15.1$, $J = 9.1$, $J =$

1.6, 1H); 2.60 (dd, $J = 14.4$, $J = 3.7$, 1H); 2.40 (dd, $J = 14.0$, $J = 7.5$, 1H); 2.32 (dd, $J = 15.1$, $J = 9.1$, 1H); 2.06 (d, $J = 3.7$, 1H); 1.65 (d, $J = 14.3$, 1H); 1.3–1.1 (m, 21H). ^{13}C (C_6D_6): 163.8; 135.5; 135.1; 119.9; 117.9; 117.8; 98.8; 98.2; 65.9; 64.5; 56.3; 46.4; 44.4; 36.7; 36.4; 18.8; 14.2. IR: 2323. MS (CI): 492 $[\text{M} + \text{C}_4\text{H}_9]^+$; 436 $[\text{M} + \text{H}]^+$; 400 $[\text{M} - \text{Cl}]^+$. HRCIMS: calcd for $\text{C}_{24}\text{H}_{39}\text{ClNO}_2\text{Si}$ 436.2439, found 436.2436.

7,7-Bis(allyl)-2-exochloro-2-endocyano-1-triisopropylsilyloxy-bicyclo[2.2.1]heptan-5-one (27). A solution of **21** (708 mg, 1.6 mmol) in THF (12 mL) containing 4 N aq HCl (5.8 mL) was stirred at $45\text{ }^{\circ}\text{C}$ for 105 min, then it was cooled to rt and diluted with diethyl ether (30 mL). The organic phase was separated and sequentially washed with saturated aq NaHCO_3 and saturated aq NaCl solutions, then it was dried (Na_2SO_4) and evaporated to provide 658 mg (96%) of colorless crystalline **27**, mp $58\text{--}59\text{ }^{\circ}\text{C}$. ^1H NMR (C_6D_6): 6.17 (m, 1H); 5.52 (m, 1H); 5.08–4.99 (m, 4H); 3.03 (m, 1H); 2.65 (m, 1H); 2.56–2.42 (m, 3H); 2.25 (dd, $J = 15.5$, $J = 9.5$, 1H); 1.98 (dd, $J = 14.0$, $J = 6.0$, 1H); 1.88 (d, $J = 5.5$, 1H); 1.55 (m, 1H); 1.1–1.0 (m, 21H). ^{13}C NMR (C_6D_6): 205.4; 134.4; 133.1; 119.7; 118.7; 119.5; 90.1; 64.6; 55.7; 54.1; 46.5; 40.4; 36.1; 34.2; 18.6; 14.0. IR: 2359, 1754, 1637. MS (CI): 422 $[\text{M} + \text{H}]^+$. HRCIMS: calcd for $\text{C}_{23}\text{H}_{37}\text{ClNO}_2\text{Si}$ 422.2282, found 422.2281.

Representative Procedure for Radical Cyclization: Compound 29. A solution of AIBN (757 mg, 4.6 mmol) and tris(trimethylsilyl)silane (5.2 mL, 16.9 mmol) in dry degassed toluene (5 mL) was added dropwise over 45 min to a hot ($85\text{ }^{\circ}\text{C}$) solution of **27** (6.5 g, 15.4 mmol) in dry degassed toluene (30 mL). The resulting mixture was stirred at $85\text{ }^{\circ}\text{C}$ for an additional 2 h, then it was cooled and evaporated. Chromatography of the residue (5% EtOAc in pentane) provided 3.8 g (9.9 mmol, 65%) of colorless crystalline **29**, mp $73\text{--}74\text{ }^{\circ}\text{C}$. ^1H NMR (C_6D_6): 5.35 (m, 1H); 4.93 (m, 2H); 2.91 (m, 1H); 2.75 (d, $J = 18.2$, 1H); 2.29 (dd, $J = 18.2$, $J = 1.4$, 1H); 2.13 (dd, $J = 13.6$, $J = 6.8$, 1H); 1.96 (d, $J = 5.9$, 1H); 1.82 (dd, $J = 13.4$, $J = 7.7$, 1H); 1.50 (m, 2H); 1.05 (m, 22H); 0.77 (d, $J = 6.7$, 3H); 0.65 (m, 1H). ^{13}C NMR (C_6D_6): 206.6; 133.7; 120.8; 118.1; 89.4; 56.9; 54.2; 49.7; 41.1; 37.3; 35.2; 34.3; 25.2; 18.6; 13.7; 12.8. IR: 2234, 1759, 1640. MS (CI): 388 $[\text{M} + \text{H}]^+$. HRCIMS: calcd for $\text{C}_{23}\text{H}_{38}\text{NO}_2\text{Si}$ 388.2672, found 388.2676.

Compound 30. A solution of **29** (1.0 g, 2.6 mmol) and TBAF (2 g, 6.5 mmol) in THF (10 mL) was stirred at rt for 2 h, then it was partitioned between ether (30 mL) and water (5 mL). The organic phase was separated, and the aqueous one was extracted with more ether. The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was rapidly filtered over silica gel (30% EtOAc in pentane) to give 395 mg (66%) of colorless crystalline **30**, mp $97\text{--}98\text{ }^{\circ}\text{C}$. ^1H NMR (C_6D_6): 5.39 (m, 1H); 4.89 (m, 2H); 2.93 (s, 1H); 2.78 (m, 1H); 2.64 (d, $J = 18.0$, 1H); 2.06 (dd, $J = 18.0$, $J = 1.0$, 1H); 2.01 (dd, $J = 14.0$, $J = 7.5$, 1H); 1.91 (d, $J = 6.7$, 1H); 1.68 (dd, $J = 14.0$, $J = 7.5$, 1H); 1.46 (m, 2H); 1.07 (dd, $J = 14.0$, $J = 2.0$, 1H); 0.72 (d, $J = 7.0$, 3H); 0.55 (dd, $J = 13.0$, $J = 8.0$, 1H). ^{13}C NMR (C_6D_6): 207.9; 133.9; 120.8; 118.0; 87.4; 55.5; 55.2; 49.1; 40.9; 37.3; 34.0; 33.8; 24.9; 12.7. IR: 3458, 2239, 1749, 1638. MS (CI): 288 $[\text{M} + \text{C}_4\text{H}_9]^+$; 232 $[\text{M} + \text{H}]^+$; 214 $[(\text{M} - \text{H}_2\text{O}) + \text{H}]^+$. HRCIMS: calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ 232.1338, found 232.1331.

2-Isopropyl-3-methoxycyclopent-2-en-1-one (74). Neat Me_2SO_4 (4.5 g, 36.0 mmol; **CAUTION: toxic, corrosive, cancer suspect agent**) was added at rt to a vigorously stirred suspension of **73** (5.0 g, 36.0 mmol) and K_2CO_3 (4.5 g, 36.0 mmol) in acetone (60 mL). The mixture was then heated to $60\text{ }^{\circ}\text{C}$ for 8 h with continued stirring, then it was cooled and concentrated. The residue was partitioned between EtOAc (10 mL) and aq 1 M NaOH (15 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc ($3 \times 30\text{ mL}$). The combined extracts were washed with brine (30 mL), dried (MgSO_4), and concentrated. Chromatography of the residue (25% EtOAc/hexanes) gave 5.5 g (35.0 mmol, 99%) of **74** as an oil. ^1H NMR: 3.91 (s, 3H); 2.73 (sept, $J = 7.0$, 1H); 2.62 (m, 2H); 2.39 (m, 2H); 1.11 (d, $J = 7.0$, 6H). ^{13}C NMR: 204.8; 184.6; 125.8; 56.5; 33.8; 24.4; 23.1; 20.4.

IR: 1682, 1621. HRCIMS: calcd for $C_9H_{15}O_2$ [M + H]⁺ 155.1072, found 155.1078.

4-Carbomethoxy-2-isopropyl-3-methoxycyclopent-2-en-1-one (75).

A solution of **74** (306 mg, 2 mmol) in THF (2 mL) was added dropwise to a cold (−78 °C) solution of LHMDS (2.1 mL of commercial 1 M THF solution, 2.1 mmol, diluted in additional 2 mL of THF), and the mixture was stirred at −78 °C for 2 h. Neat MeOCCN (160 μ L, 2 mmol; **CAUTION: source of toxic HCN**) was injected, and the solution was stirred −78 °C for 30 min. The reaction was quenched at −78 °C by addition of aq 1 N HCl (4 mL; **CAUTION: formation of HCN**), allowed to warm to rt, and extracted with EtOAc (3 \times 15 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. Chromatography of the residue (50:50 EtOAc/hexanes) gave 340 mg (81%) of **75** as an oil. ¹H NMR: 3.90 (s, 3H); 3.83 (dd, *J* = 7.6, 2.3, 1H); 3.78 (s, 3H); 2.79 (dt, *J* = 6.7, 1H); 2.72 (d, *J* = 7.4, 1H); 2.47 (dd, *J* = 17.8, 2.3, 1H); 1.14 (d, *J* = 6.8, 6H). ¹³C NMR: 202.2; 179.5; 172.1; 128.1; 57.4; 53.2; 42.7; 39.3; 23.4; 20.2. IR: 1736, 1702, 1620. HRCIMS: calcd for $C_9H_{17}O_4$ [M + H]⁺ 213.1127, found 213.1131.

Aldehyde 76. Neat DBU (13 μ L, 87 μ mol) was added to a cold (0 °C) solution of **75** (920 mg, 4.3 mmol) and acrolein (308 μ L, 4.6 mmol; **CAUTION: toxic, cancer suspect agent**) in MeCN (9 mL). The mixture was stirred at 0 °C for 30 min, then at rt for 4 h, and finally it was concentrated. The residue was treated with aq saturated NH₄Cl (20 mL) and extracted with EtOAc (4 \times 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated to afford crude **76** (1.1 g, 95%), which was used without further purification. ¹H NMR: 9.76 (s, 1H); 3.99 (s, 3H); 3.74 (s, 3H); 2.99 (sept, *J* = 6.8, 1H); 2.69 (d, *J* = 17.8, 1H); 2.48 (m, 1H); 2.32–2.28 (m, 3H); 2.23 (d, *J* = 17.7, 1H); 1.23 (dd, *J* = 7.1, 4.3, 6H). ¹³C NMR: 202.8; 200.9; 180.2; 173.6; 126.6; 59.7; 53.1; 52.2; 45.3; 39.0; 26.1; 24.5; 20.7; 20.4. IR: 1730, 1692, 1611. HRCIMS: calcd for $C_{14}H_{21}O_5$ [M + H]⁺ 269.1389, found 269.1390.

Nitrile 77. A solution of **76** (65 mg, 242 μ mol), DABCO (27 mg, 242 μ mol), triethanolamine (16 μ L, 121 μ mol), and La(OTf)₃ (7 mg, 12 μ mol) in acrylonitrile (0.5 mL; **CAUTION: cancer suspect agent**) was stirred at rt for 11 h, then it was concentrated. The residue was taken up with aq saturated NaHCO₃ (20 mL) and extracted with EtOAc (3 \times 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. Chromatography of the residue (50:50 EtOAc/hexanes) gave a ca. 60:40 mixture of diastereomers of **77** (39 mg, 50%) as an oil. ¹H NMR: 6.04 (d, *J* = 10.2, 2H); 4.29 (m, 1H); 4.01 (d, *J* = 3.0, 3H); 3.71 (s, 3H); 3.01 (m, 1H); 2.69 (dd, *J* = 17.8, 3.5, 1H); 2.30 (d, *J* = 17.7, 1H); 2.05–1.98 (m, 2H); 1.75–1.50 (m, 2H); 1.24 (m, 6H). ¹³C NMR: 203.7; 181.1; 180.8; 174.1; 174.0; 130.7; 126.9; 126.8; 126.7; 117.4; 117.3; 72.0; 71.5; 59.9; 59.8; 52.7; 45.4; 45.3; 30.3; 30.1; 29.3; 28.8; 24.6; 20.9; 20.8. IR: 3367, 2223, 1732, 1688, 1606. HRCIMS: calcd for $C_{17}H_{24}NO_5$ [M + H]⁺ 322.1654, found 322.1654.

Compound 80. Neat TIPSOTf (190 μ L, 710 μ mol) was added to a cold (0 °C) CH₂Cl₂ (1.3 mL) solution of **77** (104 mg, 320 μ mol; 50:50 mixture of diastereomers) and Hünig base (140 μ L, 810 μ mol). The solution was warmed to rt and stirred for 12 h, then it was diluted with a 3:1 mixture of pentane/CH₂Cl₂ (10 mL), resulting in precipitation of a colorless solid which was filtered off. The filtrate was washed with aq saturated NaHCO₃ (3 mL), dried (Na₂SO₄), and concentrated. Chromatography of the residue (5:95 EtOAc/hexanes) gave 123 mg (61%) of a mixture of diastereomers of **80** as a colorless oil. ¹H NMR: 4.57 (dd_{app}, *J* = 8.6, 6.1, 1H); 4.41 (t, *J* = 8.3, 1H); 3.91 (s, 3H); 3.77 (s, 3H); 3.64 (s, 3H); 3.59 (s, 3H); 2.75–2.65 (m, 2H); 2.58 (m, 2H); 2.49–2.42 (m, 2H); 2.16 (d, *J* = 12.9, 2H); 2.05–1.80 (m, 6H); 1.75–1.40 (m, 2H); 1.34 (d, *J* = 6.7, 12H); 1.23–1.00 (m, 21H). ¹³C NMR: 173.8; 156.6; 154.4; 124.2; 123.9; 123.8; 122.9; 94.8; 94.2; 75.9; 69.8; 66.6; 66.1; 56.8; 56.5; 52.1; 51.9; 49.9; 49.2; 48.8; 42.5; 33.4; 27.8; 27.7; 26.5; 25.5; 25.1; 22.7; 21.3; 20.6; 18.3; 13.5; 12.9. IR:

2324, 1745, 1645. HRCIMS: calcd for $C_{35}H_{64}NO_5Si_2$ [M + H]⁺ 634.4323, found 634.4322.

Ketone 83. A solution of **77** (800 mg, 2.5 mmol), imidazole (253 mg, 3.7 mmol), DMAP (30 mg, 245 μ mol), and TBSCl (747 mg, 5 mmol) in dry DMF (2 mL) was stirred at 60 °C for 11 h, then it was cooled to rt, diluted with saturated aq NH₄Cl (20 mL), and extracted with EtOAc (3 \times 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. Chromatography of the residue (gradient 0 to 25% EtOAc/hexanes) gave 758 mg (70%) of a nearly 60:40 mixture of diastereomers of **83** as a light yellow oil. ¹H NMR: 5.98–5.89 (m, 2H); 4.30–4.20 (m, 1H); 3.98–3.93 (m, 3H); 3.72 (s, 3H); 3.01–2.91 (m, 1H); 2.66 (dd, *J* = 17.5, 4.2, 1H); 2.26 (dd, *J* = 17.5, 6.6, 1H); 1.95–1.82 (m, 2H); 1.56–1.43 (m, 2H); 1.22 (dd, *J* = 6.9, 4.3, 6H); 0.90 (s, 9H); 0.06–0.04 (m, 6H). ¹³C NMR: 202.5; 179.8, 179.7; 173.5; 129.6; 126.6; 126.5; 126.4; 116.8; 99.5; 72.0; 71.8; 59.2; 59.1; 52.6; 52.0; 45.0; 44.9; 30.5; 30.3; 28.0; 27.6; 25.5; 24.1; 24.0; 20.3; 19.97; 19.95; 17.95; −4.96; −4.98; −5.16; −5.18. IR: 2223, 1736, 1619. HRESIMS: calcd for $C_{23}H_{38}NO_5Si$ [M + H]⁺ 436.2516, found 436.2519.

Cyanoenone 84. Commercial Et₂AlCN solution (1.0 M in toluene, 3.3 mL, 3.3 mmol; **CAUTION: source of toxic HCN**) was added at rt to a stirred solution of **83** (729 mg, 1.7 mmol, 60:40 mixture of diastereomers) in dry benzene (15 mL). The mixture was stirred at rt for 1.5 h, then it was quenched with 1 M NaOH (4 mL; **CAUTION: exothermic reaction, formation of cyanide**) and concentrated. The residue was taken up with aq saturated NaHCO₃ (20 mL) and with EtOAc (20 mL). The organic phase was recovered, and the aqueous phase was further extracted with EtOAc (3 \times 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. The residue was chromatographed (25:75 EtOAc/hexanes) to give 508 mg (70%) of a nearly 60:40 mixture of diastereomers of **84** as a light yellow oil. ¹H NMR: 6.05–5.95 (m, 2H); 4.35–4.25 (m, 1H); 3.85–3.77 (m, 3H); 3.07 (dd, *J* = 19.0, 3.0, 1H); 3.01–2.95 (m, 1H); 2.37 (dd, *J* = 19.0, 3.0, 1H); 2.25–2.15 (m, 1H); 1.85–1.45 (m, 3H); 1.30–1.23 (m, 6H); 0.95–0.85 (m, 9H); 0.12–0.05 (m, 6H). ¹³C NMR: 203.1; 171.6; 171.5; 161.8; 161.7; 136.0; 135.9; 130.5; 126.3; 126.1; 117.0; 116.9; 113.8; 113.7; 71.9; 71.7; 53.7; 53.6; 43.8; 43.6; 31.5; 31.3; 31.0; 30.6; 26.7; 25.9; 25.8; 20.2; 20.1; −4.60; −4.8. IR: 2225, 1726. HRESIMS: calcd for $C_{23}H_{34}N_2O_4Si$ [M + Na]⁺ 453.2183, found 453.2186.

Silyl Enol Ether 94. Commercial LHMDS solution (1.0 M in THF, 0.3 mL, 0.3 mmol) was slowly added to a cold (−78 °C), stirred solution of **84** (133 mg, 0.3 mmol), LiCl (347 mg, 8.7 mmol), and TBSCl (924 mg, 6.2 mmol) in dry THF (2 mL) and HMPA (0.7 mL; **CAUTION: cancer suspect agent**). The mixture was stirred at −78 °C for 30 min, then it was heated to 50 °C. An additional five portions of LHMDS (1.0 M in THF, each portion 0.3 mL, 0.3 mmol) were added at regular intervals over 8 h. Finally, the mixture was cooled, carefully quenched with aq saturated NH₄Cl (2 mL), and concentrated. The residue was partitioned between EtOAc (20 mL) and aq saturated CuSO₄ (20 mL), the organic phase was recovered, and the aqueous phase was extracted with EtOAc (3 \times 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. The residue was chromatographed (1:9 EtOAc/hexanes) to give 138 mg (82%) of a ca. 50:50 mixture of diastereomers of diene **94** as a light yellow oil. ¹H NMR: 6.00–5.95 (m, 2H); 5.36–5.30 (m, 1H); 4.30–4.20 (m, 1H); 3.74–3.70 (m, 3H); 3.09–2.85 (m, 1H); 2.26–2.08 (m, 1H); 2.02–1.80 (m, 2H); 1.72–1.47 (m, 1H); 1.34–1.25 (m, 6H); 1.03–0.84 (m, 18H); 0.37–0.02 (m, 12H). ¹³C NMR: 172.3; 172.2; 171.0; 170.8; 157.4; 156.5; 131.3; 128.0; 127.9; 118.3; 116.7; 116.6; 114.6; 114.5; 113.4; 73.8; 73.5; 54.6; 54.3; 32.2; 31.1; 29.6; 29.3; 27.1; 27.0; 21.9; 21.8; 21.6; 21.5; 21.4; 21.3; 19.5; −3.3; −3.4; −3.5; −3.7. IR: 2209, 1736. HRESIMS: calcd for $C_{29}H_{48}N_2O_4Si_2$ [M + Na]⁺ 567.3054, found 567.3050.

Cycloadduct 95. A solution of **94** (80 mg, 147 μ mol) in dry toluene (1 mL) was stirred at 140 °C in a 20 mL glass pressure

vessel for 12 h, then it was cooled to rt and applied to a silica silica gel column (10 g). Elution (gradient 0 to 15% EtOAc/hexanes) gave 62 mg (77.5%) of a nearly 50:50 mixture of diastereomers of **95** as a light yellow oil. ^1H NMR: 4.43–4.32 (m, 1H); 3.76–3.66 (m, 3H); 2.85–2.78 (m, 1H); 2.65–2.49 (m, 2H); 2.26–1.89 (m, 3H); 1.81 (dd, $J = 12.0, 4.0$, 1H); 1.62 (d, $J = 12.0$, 1H); 1.24 (d, $J = 8$, 3H); 1.15 (d, $J = 8$, 3H); 0.98–0.86 (m, 18 H); 0.21–0.09 (m, 12H). ^{13}C NMR: 172.1; 171.7; 158.1; 157.9; 120.7; 120.9; 119.8; 120.5; 116.4; 116.7; 72.9; 70.1; 67.1; 66.8; 52.1; 52.0; 51.3; 50.4; 50.0; 38.2; 32.9; 29.5; 26.7; 26.4; 25.6; 25.3; 22.0; 22.5; 20.4; 20.3; 17.7; 17.8; –3.7; –3.6; –4.2; –4.5; –4.96; –4.94. IR: 2210, 1739. HRESIMS: calcd for $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}_4\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 567.3053, found 567.3050.

Tricyclic Ketone 97. Commercial HF–pyridine complex (70% HF, 0.9 mL) was added to a cold (0 °C), stirred solution of **95** (91 mg, 167 μmol) in MeCN (3 mL). The mixture was stirred for 6 h, during which time it was allowed to warm to rt, and then quenched with aq saturated NaHCO_3 (2 mL) and concentrated. The residue was partitioned between EtOAc (15 mL) and more aq saturated NaHCO_3 (20 mL). The organic phase was recovered, and the aqueous phase was extracted with more EtOAc (3×10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO_4), and concentrated. The crude product was oxidized without further purification. Thus, a solution of above alcohol and Dess–Martin periodinane (73 mg, 172 μmol) in CH_2Cl_2 was stirred at room

temperature for 3 h, then it was concentrated. Chromatography of the residue (gradient 5% to 10% EtOAc/hexanes) gave **97** (36 mg, 50% over two steps) as a colorless oil. ^1H NMR: 3.78 (s, 3H); 3.05 (d, $J = 3.9$, 1H); 2.90–2.68 (m, 2H); 2.62 (sept, $J = 7.0$, 1H); 2.47 (dd, $J = 13.5, 3.9$, 1H); 2.29–2.18 (m, 1H); 2.10 (d, $J = 3.5$, 1H); 2.04–1.90 (m, 1H); 1.30 (d, $J = 6.8$, 3H); 1.17 (d, $J = 6.8$, 3H); 0.96 (s, 9H); 0.26 (s, 3H); 0.23 (s, 3H). ^{13}C NMR: 198.8; 170.9; 156.7; 120.7; 116.3; 115.8; 66.5; 59.6; 57.1; 52.9; 52.7; 36.6; 31.2; 27.2; 25.6; 23.6; 22.1; 20.8; –3.3; –3.9. IR: 2359, 1734, 1646. HRESIMS: calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_4\text{Si}$ $[\text{M} + \text{H}]^+$ 429.2206, found 429.2210.

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Supporting Information Available: Experimental procedures and characterization data; detailed results of calculations; NMR spectra of several compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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