Synthesis of Simplified Azasordarin Analogs as Potential Antifungal Agents

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ABSTRACT: A new series of simplified azasordarin analogs was synthesized using as key steps a Diels-Alder reaction to generate a highly substituted bicyclo[2.2.1]heptane core, followed by a subsequent nitrile alkylation. Several additional strategies were investigated for the generation of the key tertiary nitrile or aldehyde thought to be required for activity at the fungal protein eukaryotic elongation factor 2. This new series also features a morpholino glycone previously reported in semisynthetic sordarin derivatives with broad spectrum antifungal activity. Despite a lack of activity against *C. albicans* for these early de novo analogs, the synthetic route reported here permits more comprehensive modifications of the bicyclic core, and SAR studies that were not heretofore possible.

INTRODUCTION

The development of resistance to the relatively small number of antifungal agents in clinical use for invasive fungal infections is now of great concern. It is estimated that more than 2 million people die annually of invasive fungal infections, which can have mortality rates of >50%.[1] Additionally, fungi are estimated to destroy approximately 20% of crops worldwide. With increasing resistance observed for both clinical and agricultural antifungals, the identification of new classes of antifungals is an urgent matter.[2-4] In 1965, Sigg and Stoll from Sandoz AG submitted a patent application first describing the natural product sordarin as an antibacterial and antifungal agent.[5] First isolated from the fungus *Sordaria araneosa*,[6] sordarin has a unique tetracyclic diterpene scaffold, with a [2.2.1]heptene at its core with adjacent aldehyde and acid groups (**1**, Figure 1). Attached to the core is an unusual carbohydrate glycone, which can be replaced with a multitude of substituents via semisynthesis, leading to derivatives such as **2** (GW 471558)[7] and **3**.[8]

Importantly, the antifungal target of sordarin was later deduced by groups at Merck and Glaxo to be the ribosomal protein eukaryotic elongation factor 2 (eEF2),[9,10] a necessary component of protein synthesis which is a target presently unaddressed by current clinical antifungals. The high potency against e.g. fluconazole-resistant fungal strains and selectivity for sordarin derivatives over human eEF2 provided additional impetus for numerous pharmaceutical companies to pursue sordarin derivatives as antifungal agents. The complexity of sordarin as a synthetic target necessitated the near-exclusive pursuit of semisynthetic derivatives, since sordarin can be produced on large scales via fermentation,[11] and the natural glycone easily hydrolyzed and replaced with alternatives that imbue the derivatives with improved properties. Despite these efforts, to our knowledge no fungal eEF2 inhibitors have reached clinical stages. This manuscript describes our efforts thus far to synthesize novel analogs possessing a simplified bicyclic [2.2.1] scaffold more amenable to systematic modifications, which could lead to sordarin analogs with improved properties for clinical use.

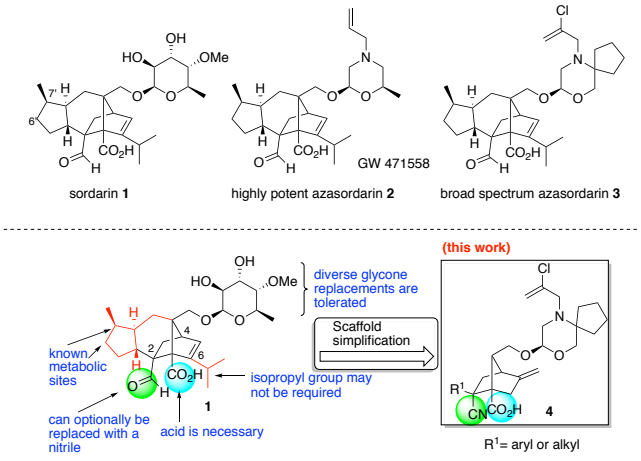


Figure 1. Sordarin and two representative azasordarin derivatives (top); known sordarin SAR and our plan for simplified analogs via scaffold simplification (bottom).

Design of Analogs

Semisynthetic replacement of the glycone of sordarin has led to several highly potent and orally active azasordarin analogs against *C. albicans* such as **2** (Figure 1),[7] as well as a few analogs with a broader spectrum of antifungal activity (e.g. **3**).[8] One liability that has been identified with certain sordarin derivatives is their unsatisfactory metabolic stabilities. Sordarin and its aglycone sordaricin are hydroxylated at the C-6 and C-7 positions by rat and mouse hepatic fractions.[12] We hypothesize that analogs with alternative scaffolds, particularly those with substituents at the "western" side that are resistant to cytochrome P-450-mediated oxidation, could maintain the

pharmacophore for antifungal activity (Figure 1, bottom left) and possess improved pharmacokinetic (PK) profiles. Previous SAR studies have suggested that the key part of the sordarin pharmacophore is the vicinal aldehyde-carboxylic acid, held within the rigid bicyclic framework in a perpendicular orientation which precludes hemiacetal formation.[13] X-ray crystal structures of eEF2 complexed with sordarin have clarified the importance of the aldehyde and acid moieties, which form 4 hydrogen bonds with bound waters and two backbone amides of eEF2 (Figure 2).[14,15] It should be noted that several potent analogs have been reported where the aldehyde has been replaced with a nitrile.[13] We reasoned that a modified bicyclo[2.2.1]heptane core could maintain a similar dihedral angle between these moieties, and permit the identification of novel analogs with comparable potencies to the natural product and its semisynthetic derivatives, but with the potential for improved PK properties. A simplified monocyclic cyclopentane with vicinal aldehyde and acid moieties was previously reported by Cuevas to possess only marginal antifungal activity.[12]

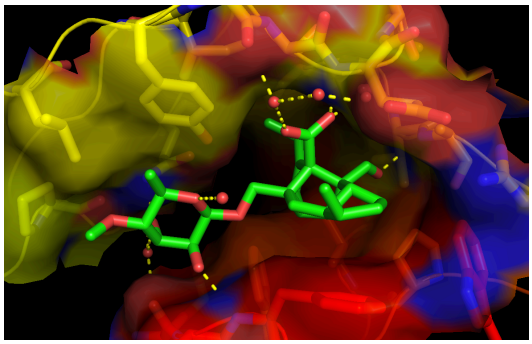


Figure 2. X-ray structure of eEF2-sordarin[14]

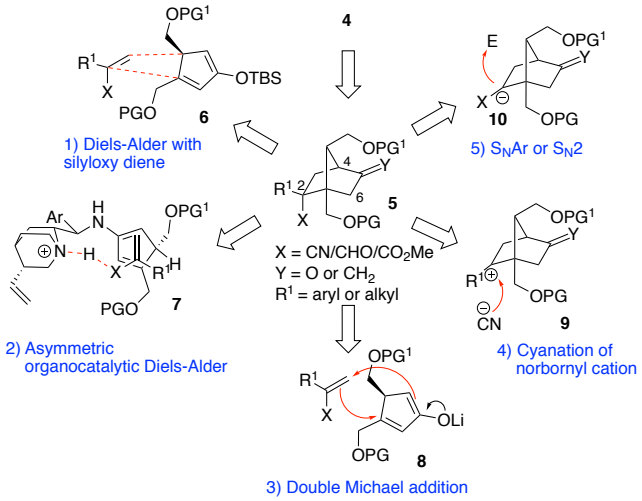
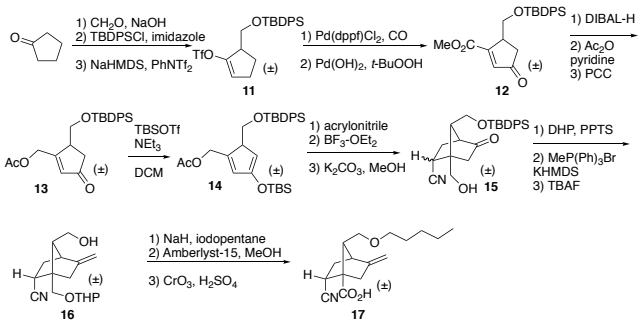


Figure 3. Proposed strategies for constructing the desired bicyclo[2.2.1]heptane core with quaternary center at C-2. PG = protecting group.

As described in our previous report,[16] we successfully established a synthetic route to simplified [2.2.1] bicyclic analogs of sordarin (Scheme 1). This route relied on chromatographic separation of endo/exo Diels-Alder adduct *rac*-**15** to give *endo*-**15**. Subsequent protecting group manipulation followed by Wittig reaction and Jones oxidation furnished simplified alkyl sordarin analog **17**. However, **17** failed to show antifungal activity against several strains of *C. albicans* at concentrations up to 8 μg/mL. We reasoned that this may be attributed to the lack of a complex glycone, and/or the lack of a quaternary center at C-2. Therefore, we chose to append to our scaffold a morpholine glycone previously reported in sordarin derivatives showing broad and potent antifungal activity (**3**, Figure 1).[8]

Scheme 1. Synthesis of our first-generation sordarin analogs[16]



DHP = 3,4-dihydro-2H-pyran

To construct the tertiary chiral center at C-2, we have thus far explored five strategies for preparation of key intermediates **5** that are suitable for elaboration to the desired analogs **4** (Figure 3). A Diels-Alder approach using 1,1-disubstituted alkenes could be the most convergent approach to **5**. Reactions using silyloxy diene **6** could avert undesired 1,5-hydride or alkyl shifts that are well known for cyclopentadienes,[17] but are slowed down by electron-rich diene substituents.[18] The silyloxy group is also a versatile handle for subsequent transformations, and provides the desired regioselectivity for cycloadditions, with the aldehyde/nitrile and carboxylic acid precursors on vicinal carbons in the cycloadducts. The *endo*/*exo* diastereoselectivity could also be modified by using suitable Lewis acids. The second approach uses as the key step an asymmetric organocatalytic Diels-Alder reaction reported by Jørgensen,[19] which could also provide highly enantiomerically-enriched products via the catalytic enamine intermediate **7**. This approach would also have the advantage of avoiding the need to preactivate the diene component via silylenol ether formation. The third approach also involves a formal [4+2] cycloaddition reaction, but one which could proceed via a double Michael addition mechanism. In this proposed reaction, enolate **8** could add to the dienophile to generate a second enolate, which could subsequently cyclize by adding back to the resulting enone. The fourth strategy, which depends on a prior cycloaddition reaction, is to install the nitrile on the *endo* face of the bicycle by addition of cyanide to an intermediate carbocation **9**. The fifth strategy leverages our prior cycloaddition reactions with acrylonitrile,[16] but uses a subsequent S_NAr or S_N2 substitution reaction to introduce the aryl or alkyl substituent via the *exo* face of the bicycle.

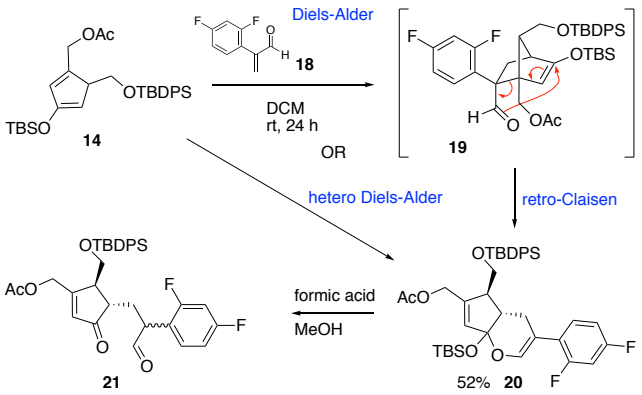
RESULTS AND DISCUSSION

1. Diels-Alder with silyloxy diene

Our initial target compounds possess a fluorinated aryl group as R^1 (**4**, Figure 1), which we hypothesize should fit into

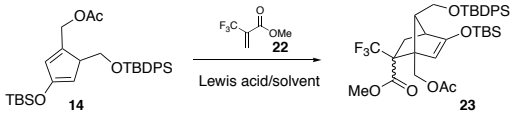
the lipophilic portion of the eEF2 binding pocket occupied by the cyclopentane ring of sordarin. The installation of such aryl substituents has proven to be challenging thus far. Our initial attempt used the 2-aryl-acrylaldehyde **18**, but instead of the desired adduct **19**, the unexpected dihydropyran **20** was obtained (Scheme 2). This product could be generated from either a retro-Claisen rearrangement of **19** or an inverse electron demand, hetero Diels–Alder reaction. Davies reported that Lewis-acid catalyzed reactions of cyclopentadiene and 2-arylacroleins generated mixtures of bicyclo[2.2.1]heptenes and dihydropyrans analogous to **19** and **20**, with the heptenes able to convert to the dihydropyrans.[20] One notable difference in our case is that the dihydropyran was the only product observed. The aldehyde-containing Diels-Alder adduct and its rearranged product are expected to be in equilibrium, with the ratio determined in part by the ring strain and extent of conjugation of the α-substituent (in this case, a fluorinated arene).[21] Silyl ketal **20** is an unstable species that decomposed to racemic aldehyde **21** upon treatment with formic acid in methanol, or after storage in the freezer (–20 °C) for a month dissolved in DCM under neutral conditions. The most straightforward way to circumvent the undesired hetero Diels-Alder reaction could be to use the nitrile or ester counterparts of **18**, but unfortunately these dienophiles failed to give any cycloadducts with **14**.

Scheme 2. Diels-Alder/Retro-Claisen or hetero-Diels-Alder reaction of enal 18



To potentially circumvent the lack of Diels-Alder reactivity of acrylates, we turned our attention to the α,β-unsaturated ester **22** with a more highly activating trifluoromethyl methyl group to decrease the LUMO level of the dienophile. The trifluoromethyl group is also a desirable substituent for our medicinal chemistry studies due to its lipophilic but metabolically stable profile. After extensive screening of different solvents and Lewis acids, we learned that diene **14** was indeed not compatible with most Lewis or Brønsted acids (e.g. trifluoroethanol, Table 1, entry 15), as reported by Gleason for a related OTBS-substituted cyclopentadiene.[18] Lewis acids that were compatible with **14** ($Mg(OTf)_2$, $Mg(ClO_4)_2$, and $Eu(hfc)_3$; entries 4, 18 and 19) didn't give any *endo* selectivity. The diastereomers were tentatively assigned based on a report by Ishihara characterizing *endo*/*exo* isomers with the same dienophile.[22] The diastereoselectivity can be tilted slightly by using different solvents; the highest *exo* selectivity was achieved in DCM (Table 1, entries 8, 9), and the most *endo* selective reaction was in hexanes (Table 1, entry 11). Due to the low tolerance of **14** to Lewis acids, we didn't pursue alternative dienophile/Lewis acid combinations to increase the proportion of the desired *endo* cycloadducts, though we anticipate that bulkier substituents than CF_3 may favor the desired *endo* cycloadducts.

Table 1. Solvent and Lewis acid screening for Diels-Alder using 22



entry	solvent	temp. (ºC)	Lewis acid[e]	endo /exo[b]	yield[c]
1	DCM	–78 to rt	$InCl_3$	N/A	decomp.
2	DCM	–78 to rt	$ZnBr_2$	N/A	decomp.
3	DCM	–78 to rt	$Yb(OTf)_3$	N/A	decomp.
4	DCM	–78 to rt	$Mg(OTf)_2$	0.75	68%
5	DCM	–78 to rt	$Zn(OTf)_2$	N/A	decomp.
6	DCM	–78 to rt	$Eu(OTf)_3$	N/A	decomp.
7	DCM	–78 to rt	K-10	N/A	decomp.
8	DCM	–78 to rt	–	0.67	83%
9	DCM	rt	–	0.71[d]	40%[d]
10	THF	rt	–	0.82	85%
11	hexanes	rt	–	1.04	96%
12	MeCN	rt	–	0.85	91%
13	acetone	rt	–	0.8	63%
14	MeOH	rt	–	0.93	86%
15	F_3CCH_2OH	rt	–	N/A	decomp.
16	$PhCF_3$	rt	–	0.83	100%
17	EtOAc	rt	–	0.78	74%
18	MeCN	rt	$Mg(ClO_4)_2$	0.87	98%
19	$CDCl_3$	rt	$Eu(hfc)_3$	0.62	trace

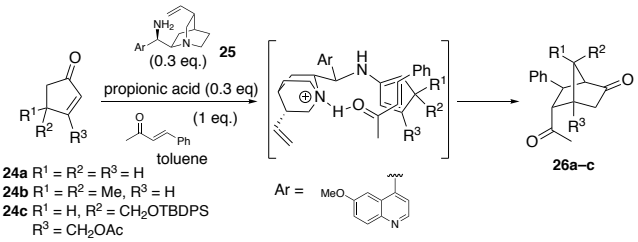
[a]Diene was washed with phosphate buffer (pH 7) before using; all experiments were run for 24 h. [b]Diastereomers were assigned based on a previously reported analog,[22] and the ratio was determined with ^{19}F NMR. [c]NMR yield using pentachloroethane as internal standard, unless otherwise specified. [d]Isolated yield. [e]1 eq. except for entry 18 (0.9 eq.) and entry 19 (0.2 eq.). decomp. = diene decomposed to **13**. K-10 = Montmorillonite K-10. $Eu(hfc)_3$ = europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. rt = room temperature (22–23 ºC).

2. Asymmetric organocatalytic Diels-Alder

In order to achieve an *endo*-selective Diels-Alder reaction and avoid the acid sensitivity of diene **14**, we examined the organocatalytic asymmetric Diels-Alder reaction reported by Jørgensen[19] The quinidine-derived amine catalyst **25** worked smoothly with cyclopentenone (Table 2, entry 1), as was reported. However, we weren't able to extend the scope to include 4-substituted cyclopentenones (entries 2, 3). When the

C-4 position of the cyclopentenone is disubstituted, the reaction didn't proceed (entry 2), likely because the transition state is disrupted by the steric repulsion between the dienamine intermediate and the dienophile. When the C-4 position is monosubstituted (**24c**), the enone was consumed, but no cycloaddition products were observed (entry 3).

Table 2. Organocatalytic Diels-Alder using cyclopentanones 24



Entry	Enone	T/t	Result
1	**24a**	60 ºC, 3 d	100% conversion to **26a**[a]
2	**24b**	60 ºC, 3 d; 100 ºC, 24 h	N.R.[a]
3	**24c**	60 ºC, 2 d	Decomposed **24c**[b]

[a]Determined by GC-MS, [b]Determined by ^{1}H NMR.

3. Double Michael addition

Inspired by Yamada's reports of stereoselective sequential Michael reactions using enolates generated from 3-alkoxycyclopentenones to generate [2.2.1] bicyclic adducts (Scheme 3),[23] we explored an analogous reaction starting from our enone **24c** and model enone **24b**. These were treated with LDA to give their corresponding lithium enolates, followed by the addition of an initial Michael acceptor. However, all enolates were unreactive in the presence of several Michael acceptors under a number of different conditions (Table 3). Despite the fact that the cyclopentanone can be smoothly deprotonated (entry 8), use of Michael acceptors with different reactivities ranging from methyl 2-(4-fluorophenyl)acrylate to acrylonitrile didn't change the result. The addition of HMPA (entries 2, 15, 11, 13) or heating (entries 10–13) were not able to initiate the desired reaction as well. Upon work up, the cyclopentenones **24b–c** were recovered. This inactivity could be explained by the lack of an electron-donating alkoxy group at C3 of **24b–c**. In the case of **24b,** the methyl group at C-4 proximal to the approaching Michael acceptor likely prevented its reaction due to steric hindrance (entries 9–11).

Scheme 3. Sequential Michael reaction reported by Yamada[23]

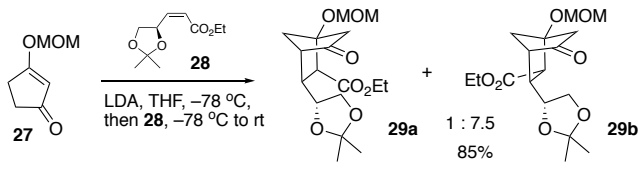
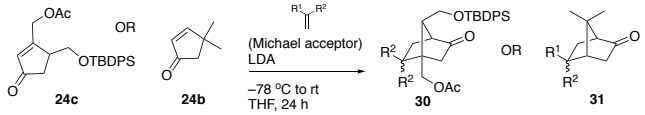


Table 3. Attempted double Michael addition



Entry	enone	Michael acceptor[b]	conditions[a]	additive	result[c]
1	**24c**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.
2	**24c**	R^1= 4-FPh, R^2= CO_2Me	A	HMPA (1 eq.)	N.R.
3	**24c**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.
4	**24c**	R^1= CF_3, R^2= CO_2Me	A	None	N.R.
5	**24c**	R^1= CF_3, R^2= CO_2Me	A	HMPA (1 eq.)	N.R.
6	**24c**	R^1= CF_3, R^2= CO_2Me	A	None	N.R.
7	**24c**	acrolein	A	None	N.R.
8	**24c**	none, quenched with D_2O	A	None	deut.[d]
9	**24c**	R^1= H, R^2= CO_2Et	A	None	N.R.
10	**24c**	R^1= 4-FPh, R^2= CO_2Me	B	None	N.R.
11	**24c**	R^1= 4-FPh, R^2= CO_2Me	B	HMPA (1 eq.)	N.R.
12	**24c**	R^1= CF_3, R^2= CO_2Me	B	None	N.R.
13	**24c**	R^1= CF_3, R^2= CO_2Me	B	HMPA (1 eq.)	N.R.
14	**24b**	R^1= H, R^2= CO_2Et	A	None	N.R.
15	**24b**	acrylonitrile	A	None	N.R.
16	**24b**	R^1= 4-FPh, R^2= CO_2Me	A	None	N.R.

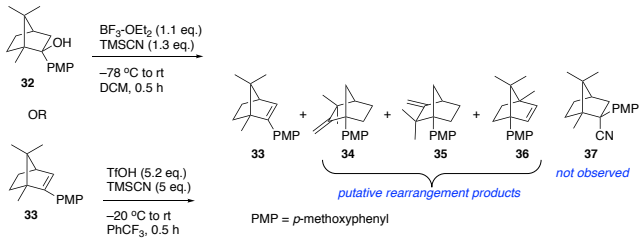
[a]Condition A: Enones were deprotonated at –78 ºC, followed by the addition of the Michael acceptor. All experiments except for entry 8 were kept at –78 ºC for 2 h, then warmed up to rt and stirred for 22 h. Entry 8 was quenched at –78 ºC after LDA deprotonation; Condition B: Enones were deprotonated at –78 ºC, followed by the addition of the Michael acceptor, then warmed up to rt and refluxed for 3h. [b]2 eq. of Michael acceptor were used in entries 1–13, each, and 1.2 eq. in entries 14–16. [c]N.R. = no reaction; [d]deut. = deuteration of α-carbon confirmed by ^{1}H NMR.

4. Hydrocyanation

We reasoned that the use of a bicyclic[2.2.1]ketone substrate could be advantageous, because it could permit the ready generation of varied aryl-containing analogs (e.g. **32**) via arylmetal 1,2-addition reactions, followed by the conversion of the resulting alcohols to nitriles via intermediate carbocations (**9**, Figure 3). However, one disadvantage of the tertiary alcohol to nitrile conversion is that it may only be high yielding for electron-rich arenes able to facilitate the S_N1-type transformation. Cyanation of a *p*-methoxylphenyl-stabilized tertiary cation has been reported with monocyclic substrates,[24-26] and there are also examples of trapping tertiary 2-norbornyl cations with nucleophiles,[27] without the extensive Wagner-Meerwein rearrangements of these non-classical carbocations.[28-30] We reasoned that an aryl substituent at the 2-position of the norbornane could inhibit rearrangements and permit trapping of the carbocation intermediate by a cyanide

nucleophile at the 2-position. We examined this strategy using model systems formed by treating camphor with 4-methoxyphenyl magnesium bromide to generate alcohol **32**, followed by acidic dehydration to generate **33**. These were separately reacted with two different acids and TMSCN (Scheme 4). Upon treatment with BF_3-OEt_2 and TMSCN, **32** quickly dehydrated and rearranged to give an inseparable mixture of dehydration product **33** and three other inseparable alkene products with GC-MS and NMR analysis consistent with Wagner–Meerwein and Nametkin rearrangements. The desired cyanation product **37** was not observed. Trapping of 2-norbornyl cation generated from **33** using TfOH and TMSCN[25] was also unsuccessful at a higher temperature (20 °C).

Scheme 4. Attempted cyanation of camphor-derived alcohol 32 and alkene 33



5. S_NAr and S_N2 substitutions

An *endo*-selective S_NAr reaction with 2-cyano-5-norbornene and aryl fluoride reported by Caron[28] suggested a promising path to desirable α-arylated nitriles (Scheme 5). In this approach, nitriles can be deprotonated with KHMDS and reacted with both electron-rich and electron-poor aryl fluorides, with **39** reported as a single (*endo*), presumably thermodynamic, diastereomer. We chose nitrile **40** to examine this approach for our application (Table 4). Under Caron's optimal conditions, **40** did not undergo the S_NAr substitution with 1,2-difluorobenzene (entry 1). When forcing conditions were applied (1,2-difluorobenzene as solvent, 115 ºC), only a trace amount of **41a** was observed via LC-MS, and most of **40** was decomposed, as followed by TLC (entry 2). We hypothesize that the substituted bridgehead next to the reaction center obstructed the approach of the arene electrophile. However, alkylation reactions were successful using iodomethane and benzyl bromide as electrophiles with quantitative conversion (entries 4, 5). Single diastereomeric products were also characterized, which we presume are the *endo* products generated from attack at the less hindered face of the nitrile anion, in accordance with Caron's report.[28]

Scheme 5. S_NAr reported by Caron[30] using 2-cyano-5-norbornene

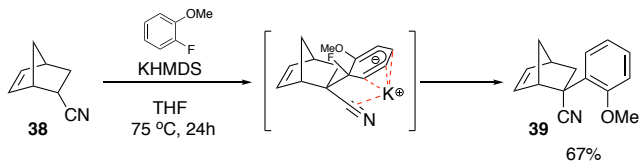
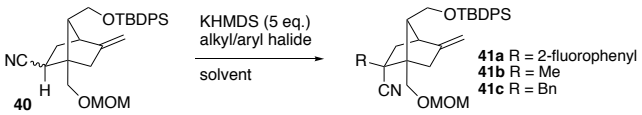


Table 4. Arylation/alkylation of secondary nitrile **40**



Entry[a]	Electrophile	Solvent	Conditions	Results
1	1,2-difluorobenzene (4 eq.)	THF	75 ºC, 12 h	N.R.[b]
2	1,2-difluorobenzene (excess)	neat	90–115 ºC, 24 h	trace **41a**[b]
3	1,2-difluorobenzene (50 eq.)	toluene	18-crown-6 (1 eq.), 100 ºC 12 h	N.R.[b]
4	MeI (45 eq.)	toluene	55 ºC, 12 h	quant. **41b**[c]
5	BnBr (5.5 eq.)	toluene	55 ºC, 12 h	quant. **41c**[c]

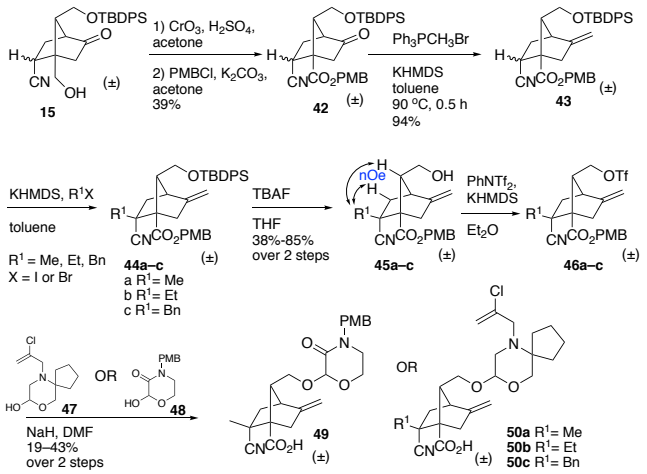
[a]To a solution of **40** (2 mg, 0.01 M) was added the indicated amount of electrophile followed by KHMDS. [b]Observed by LC-MS. [c]Estimated NMR yield using pentachloroethane as internal standard. N.R. = no reaction.

Synthesis of azasordarin analogs

We thus commenced our second-generation synthesis from the key intermediate **15**[16] we reported previously (Scheme 6). First, the bridgehead primary alcohol of **15** was oxidized to the carboxylic acid and protected using PMBCl to provide ester **42**. In previous studies, deprotonation of the carbon alpha to the ketone in a compound similar to **42** caused ring-opening through a retro-Michael pathway. In part to avoid this complication, **42** was subjected to a Wittig reaction to give olefin **43**. Normal Wittig conditions resulted in a very sluggish reaction, presumably due to steric hindrance from the TBDPS ether, however generation and reaction of the required ylide at high temperature (90 °C) yielded alkene **43** in nearly quantitative yield. The nitrile α-carbon of **43** was deprotonated by KHMDS and alkylated with three different alkyl halides to give exclusively the desired *endo* nitrile products, thus eliminating a significant weakness of our first-generation synthesis which had to rely on chromatographic separation of *endo*/*exo* diastereomers. The resulting compounds **44a–c** were treated with TBAF to give primary alcohols **45a–c**. Stereochemistry was confirmed at this stage, with nOe observed between R^1 and its two neighboring protons as shown in Scheme 6. **45a–c** were activated with $PhNTf_2$ to give triflates **46a–c**. Glycones **47** and **48** were prepared using modifications of reported protocols; though **48** has not previously been used in sordarin analogs, its ease of synthesis and similarity to other *N*-PMB morpholine-based glycones[7] inspired us to try it. Glycosidation[29] of triflates **46** with glycones **47** and **48** proceeded smoothly, and to our surprise, the PMB ester was also cleaved during these transformations to give the desired bridgehead carboxylic acids **49** and **50a–c.** These reactions proceeded in DMF but did not work in THF. **50a–c** were obtained exclusively with what we assume to be the aglycones in the equatorial positions at the anomeric carbon. This is also consistent with the increased nucleophilicity of the β-anomer of 1-*O*-lithiated pyranoses in their reactions with alkyl triflates, leading to highly selective formation of β-glycosides.[30,31] The ^1H

NMR splitting of the anomeric proton of **47** in dry $CDCl_3$ (4.94 (ddd, J = 9.0, 3.9, 2.2 Hz) is consistent with the hydroxyl group in the axial position due to the anomeric effect (the 9.0 Hz coupling is due to splitting by OH). However, the diastereomeric anomeric protons in **50a** (see expansion in NMR spectrum in Supporting Information) have larger coupling constants of 4.9 and 5.5 Hz (versus 3.9 Hz of **47**), which is more consistent with an equatorial disposition of the aglycone. Fuller and coworkers determined x-ray structures of triterpene natural product derivatives containing a morpholine-based glycone with equatorial substitution at the anomeric position, with reported coupling constants of 4.1 to 6.8 Hz.[32] Ultimately, an x-ray structure may be needed with related azasordarin analogs in the future to confirm this assignment. Since we generated racemic intermediates via this synthetic route, the final compounds **49** and **50a–c** represent an approximate 1:1 mixture of racemic diastereomers, as observed by NMR.

Scheme 6. Synthesis of azasordarin analogs



CONCLUSION

After examining numerous strategies to stereoselectively furnish the key tertiary nitrile on the bicyclo[2.2.1]heptane core, we have established a second-generation synthesis that enables the incorporation of substituents at the C-2 position. The key step was the highly *endo*-selective alkylation of bicyclic nitrile **43**, which was generated via a Diels-Alder reaction, as described in our previous report.[16] Although the synthesized analogs **49** and **50a–c** failed to show activity as isomeric mixtures against strains of *C. albicans* and *A. fumigatus* (at concentrations up to 8 μg/mL), this new synthetic route to azasordarin analogs will permit additional SAR studies not previously feasible.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents and solvents, including anhydrous solvents, were purchased from commercial vendors and used as received. Reactions were performed in ventilated fume hoods with magnetic stirring and heated in oil baths, unless otherwise noted. Reactions were performed in air, unless otherwise noted. Chilled reactions (below –10 °C) were performed in an acetone bath in a vacuum dewar, using a Neslab CC 100 immersion cooler. Unless otherwise specified, reactions were not run under N_2 atmosphere. Deionized water was purified by charcoal filtration and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane (^{1}H δ 0), or $CDCl_3$ (^{13}C δ 77.16), $(CD_3)_2CO$ (^{1}H δ 2.05, ^{13}C δ 29.84), d_6-DMSO (^{1}H δ 2.50, ^{13}C δ 39.5), or CD_3OD (^{1}H δ 3.31, ^{13}C δ 49.00). NMR data are reported as follows: chemical shifts, multiplicity (obs = obscured, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex overlapping signals); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. Filtration was performed by vacuum using VWR Grade 413 filter paper, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on Agela Technologies glass plates with 0.20 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and $KMnO_4$ stain, unless otherwise noted. Flash chromatography was performed using Biotage SNAP cartridges filled with 40-60 μm silica gel on Biotage Isolera automated chromatography systems with photodiode array UV detectors. Unless otherwise mentioned, columns were loaded with crude compounds as DCM solutions. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 x 4.6 mm, 3 μm particle size, 110 A pore size); column temperature 40 °C; 5 μL of sample in MeOH or CH_3CN at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25−95% CH_3CN/H_2O (both with 0.1% formic acid) over 5 min., then 95% CH_3CN/H_2O for 2 min. Purity was measured by UV absorbance at 210 or 254 nm. Preparative liquid chromatography was performed on a Shimadzu LC-20AP preparative HPLC with autosampler, dual wavelength detector, and fraction collector. Samples purified by preparative HPLC were loaded as DMSO solutions. Chemical names were generated and select chemical properties were calculated using either ChemAxon Marvin suite or ChemDraw Professional 15.1. NMR data were processed using either MestreNova or ACD/NMR Processor Academic Edition software. High-resolution mass spectra (HRMS) were obtained at the University of Cincinnati Environmental Analysis Service Center (EASC) with an Agilent 6540 Accurate-Mass with Q-TOF. Catalyst **25** was prepared according to a published protocol.[33]

*(7a-((Tert-butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(2,4-difluorophenyl)-4,4a,5,7a-tetrahydrocyclopenta[b]pyran-6-yl)methyl acetate (**20**).* To a solution of enal **18** (49.7 mg, 0.296 mmol) in DCM (2.7 mL) was added cyclopentadiene **14** (94.6 mg, 176 μmol) in DCM (3 mL), and the mixture was stirred at rt for 24 h. TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was concentrated and purified on a 10g SiO_2 column (30% DCM/hexanes) to give **20** (64.2 mg, 52%) as a yellow oil. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.76 – 7.60 (m, 4H), 7.52 – 7.33 (m, 6H), 7.26

(td, J = 9.0, 6.6 Hz, 1H), 7.06 – 6.90 (m, 2H), 6.78 (d, J = 1.7 Hz, 1H), 5.93 (d, J = 1.8 Hz, 1H), 4.77 (qt, J = 14.7, 1.4 Hz, 2H), 3.89 (dd, J = 10.7, 4.4 Hz, 1H), 3.80 (dd, J = 10.7, 4.7 Hz, 1H), 2.83 (s, 1H), 2.74 – 2.61 (comp, 3H), 2.03 (s, 3H), 1.05 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 170.7, 144.8, 144.0, 143.9, 136.5, 136.4, 134.3, 134.1, 132.0, 130.9, 130.9, 130.8, 130.7, 128.9, 128.8, 112.3, 107.7, 105.2, 104.9, 64.1, 62.4, 50.3, 46.9, 27.4, 26.2, 23.6, 20.8, 20.0, 18.5, –2.8. Decomposed to give **21** under LC-MS conditions (formic acid/MeOH).

(5-(((Tert-butyldiphenylsilyl)oxy)methyl)-4-(2-(2,4-difluorophenyl)-3-oxopropyl)-3-oxocyclopent-1-en-1-yl)methyl acetate (***21***). To a solution of **20** (9.9 mg, 14 μmol) in MeOH (1 mL) in a 4 mL vial was added formic acid (50 μL, 1.2 mmol). After 5 min., TLC (10% EtOAc/hexanes) indicated complete consumption of **21**, so the reaction mixture was concentrated and purified by chromatography on a silica gel packed pipette (10–20% EtOAc/hexanes) to give aldehyde **21** (1:1 diastereomeric mixture, 6.0 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, J = 1.4 Hz, 1H), 9.58 (t, J = 1.0 Hz, 1H), 7.66 – 7.49 (comp, 8H), 7.48 – 7.33 (comp, 12H), 7.25 – 7.15 (m, 1H), 7.02 (td, J = 8.5, 6.2 Hz, 1H), 6.89 – 6.74 (comp, 4H), 6.11 (q, J = 1.7 Hz, 1H), 6.06 (q, J = 1.7 Hz, 1H), 5.01 (d, J = 17.2 Hz, 1H), 4.92 (d, J = 17.4 Hz, 1H), 4.83 – 4.73 (m, 2H), 4.27 (dd, J = 9.4, 5.3 Hz, 1H), 3.95 (dd, J = 8.2, 5.6 Hz, 1H), 3.77 (dd, J = 10.4, 4.0 Hz, 1H), 3.64 (dd, J = 10.5, 6.2 Hz, 1H), 3.59 (d, J = 5.0 Hz, 3H), 2.73 – 2.58 (m, 3H), 2.38 (ddd, J = 13.9, 9.9, 5.3 Hz, 1H), 2.21 – 2.14 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.05 – 1.94 (m, 1H), 1.84 (ddd, J = 14.5, 9.4, 5.6 Hz, 1H), 1.01 (s, 9H), 0.97 (d, J = 2.6 Hz, 9H). HRMS (ESI$^+$): calcd for $C_{34}H_{36}F_2NaO_5Si$ [M+Na]$^+$ 613.2198; found 613.2207.

Methyl 1-(acetoxymethyl)-5-((tert-butyldimethylsilyl)oxy)-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (***23***). To a solution of cyclopentadiene **14** (10 mg, 18.7 μmol) in DCM (0.4 mL) was added methyl 2-(trifluoromethyl)acrylate (**22**) (4.6 μL, 37.4 μmol) in 1 mL DCM, and the mixture was stirred at rt for 24 h. TLC indicated complete consumption of the starting material (20% EtOAc/hexanes), so the mixture was concentrated and purified by chromatography on a Pasteur pipette packed with silica gel (4% EtOAc/hexanes) to give cycloadduct **23** (1:1.4 diastereomeric mixture, 5.2 mg, 40%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.55 (comp, 6H), 7.46 – 7.32 (comp, 8H), 4.56 – 4.02 (comp, 5H), 3.76 (s, 3H), 3.71 (s, 2H), 3.63 (dd, J = 10.2, 5.0 Hz, 1H), 3.51 (dd, J = 10.1, 5.0 Hz, 1H), 2.92 – 2.76 (m, 3H), 2.59 (d, J = 13.0 Hz, 1H), 2.50 (ddd, J = 21.3, 9.2, 5.0 Hz, 2H), 2.19 (dd, J = 12.9, 3.5 Hz, 1H), 1.91 (d, J = 12.5 Hz, 1H), 1.77 (d, J = 2.0 Hz, 6H), 1.03 (d, J = 4.3 Hz, 18H), 0.93 (d, J = 3.1 Hz, 18H), 0.16 (d, J = 7.6 Hz, 5H), 0.12 (d, J = 13.8 Hz, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.52, –64.24. ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.8, 169.0, 162.6, 162.3, 135.7, 135.6, 133.9, 133.8, 133.8, 133.7, 129.7, 127.8, 99.6, 97.4, 62.9, 62.6, 61.8, 61.1, 60.5, 60.0, 59.5, 58.4, 52.9, 52.9, 47.4, 46.4, 34.6, 34.5, 27.0, 25.7, 20.6, 19.4, 18.1, 0.2, –4.5, –4.6. HRMS (ESI$^+$): calcd for $C_{36}H_{50}F_3O_6Si_2$ [M+H] 691.3098; found 691.3111.

(1S,2S,4R)-2-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (***32***)[34] *and (1S,4R)-2-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene* (***33***). [35] To a solution of (*R*)-camphor (219 mg, 1.44 mmol) in THF (7 mL) was added anhydrous cerium(III) chloride (355 mg, 1.44 mmol). The mixture was sealed under N_2 and stirred for 0.5 h, then 0.5 M (4-methoxyphenyl)magnesium bromide in THF (3.2 mL, 1.58 mmol) was added. The resulting yellow solution was stirred for 0.5 h at rt, then quenched with NH_4Cl (5 mL). GC-MS indicated the organic layer contained a mixture of **32**, **33** and unreacted starting material. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (25 g SiO_2 column, 0–7% EtOAc/hexanes) to give **32** (131 mg, 35%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H), 2.28 (d, J = 13.8 Hz, 1H), 2.18 (ddd, J = 13.9, 4.2, 3.0 Hz, 1H), 1.89 (t, J = 4.3 Hz, 1H), 1.78 (s, 1H), 1.77 – 1.64 (m, 1H), 1.26 (s, 3H), 1.24 – 1.11 (m, 2H), 0.92 – 0.90 (m, 3H), 0.90 (s, 3H), 0.89 – 0.78 (m, 1H). **33** was also obtained (41 mg, 12%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 5.90 (d, J = 3.3 Hz, 1H), 3.80 (s, 3H), 2.36 (t, J = 3.5 Hz, 1H), 1.93 (ddt, J = 11.6, 8.7, 3.7 Hz, 1H), 1.70 – 1.61 (m, 1H), 1.33 – 1.22 (m, 1H), 1.13 – 1.05 (comp, 4H), 0.88 (s, 3H), 0.81 (s, 3H).

7-(((Tert-butyldiphenylsilyl)oxy)methyl)-1-((methoxymethoxy)methyl)-5-methylenebicyclo[2.2.1]heptane-2-carbonitrile (***40***). To a solution of **15** (110 mg, 0.254 mmol) in $CHCl_3$ (5 mL) was added dimethoxymethane (224 μL, 2.54 mmol) and P_2O_5 (500 mg, 1.76 mmol).[36] The mixture was sealed under N_2 and stirred for 10 min. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, the mixture was filtered through Celite and concentrated, and the intermediate MOM ether was used directly in the next step. To a solution of methyltriphenylphosphonium bromide (272 mg, 0.762 mmol) in toluene (5 mL) sealed under N_2 was added KHMDS (0.5 M in toluene, 1.52 mL, 0.762 mmol). The mixture was heated to 90 °C for 30 min., then the intermediate MOM ether was added (in toluene, 5 mL). The mixture was stirred at 90 °C for 10 min., after which time TLC (40% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was filtered through Celite, concentrated, and loaded as a toluene solution onto a 10 g SiO_2 column, and purified by chromatography (5–10% EtOAc/hexanes) to give alkene **40** (1:0.7 diastereomeric mixture, 75 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.58 (comp, 7H), 7.49 – 7.31 (comp, 10H), 4.98 (t, J = 2.5 Hz, 1H), 4.93 – 4.87 (m, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 4.65 – 4.57 (m, 1H), 4.57 – 4.49 (m, 2H), 3.90 (d, J = 10.1 Hz, 1H), 3.73 (d, J = 10.1 Hz, 1H), 3.70 – 3.61 (m, 1H), 3.59 – 3.43 (comp, 4H), 3.35 (s, 2H), 3.24 (s, 3H), 3.09 (ddd, J = 12.0, 5.0, 2.5 Hz, 1H), 2.85 (d, J = 4.3 Hz, 1H), 2.75 (q, J = 5.8, 5.2 Hz, 1H), 2.47 (dd, J = 17.1, 2.1 Hz, 1H), 2.28 (dd, J = 12.3, 4.3 Hz, 1H), 2.23 – 1.96 (comp, 5H), 1.89 (dd, J = 12.6, 9.4 Hz, 1H), 1.69 (dd, J = 12.5, 5.0 Hz, 1H), 1.05 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.5, 135.7, 135.7, 135.7, 135.6, 133.6, 133.5, 133.4, 133.2, 129.9, 129.8, 127.9, 127.8, 127.8, 127.8, 121.5, 121.1, 107.1, 106.6, 96.9, 96.6, 69.4, 66.3, 61.1, 61.1, 55.5, 55.4, 53.1, 52.9, 52.8, 47.6, 38.0, 35.4, 34.9, 34.5, 33.7, 32.4, 26.9, 19.3, 19.3. HRMS (ESI$^+$): calcd for $C_{29}H_{37}NNaO_3Si$ [M+Na]$^+$ 498.2440; found 498.2452.

4-Methoxybenzyl-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-oxobicyclo[2.2.1]heptane-1-carboxylate (***42***). CrO_3 (525

mg, 5.25 mmol) was dissolved in H_2O (2 mL). To the solution was added concentrated H_2SO_4 (0.45 mL), to give Jones reagent (2.5 mL). To a solution of alcohol **15** (767 mg, 1.769 mmol) in acetone (20 mL) in a 50 mL round bottom flask at 0 °C was added Jones reagent (1.77 mL, 4.42 mmol), and the mixture was stirred for 30 min. at rt. TLC (40% EtOAc/hexanes) showed complete consumption of the starting material, so the mixture was quenched with MeOH (5 mL). Na_2SO_4 was added and the mixture was filtered through Celite, and the mother liquor was condensed to a green residue. The crude was dissolved in DCM (10 mL) and passed through a 10 g silica gel pad, eluting with 80% EtOAc/hexanes. The resulting eluent was concentrated to give a crude yellow oil, which was dissolved in acetone (20 mL) in a 50 mL flask. To this solution was added PMBCl (360 µL, 2.65 mmol), K_2CO_3 (1.222 g, 8.84 mmol) and TBAI (13.1 mg, 0.0354 mmol). The mixture was stirred for 24h at rt, after which time LC-MS indicated incomplete consumption of the starting material. Additional PMBCl (0.200 mL, 1.47 mmol) was added, and the mixture was stirred for another 24 h, after which time LC-MS showed complete conversion to the desired product. The mixture was filtered through Celite, concentrated, and purified by chromatography on a 10 g SiO_2 column (0–40% EtOAc/hexanes) to give ester **42** (388 mg, 39% over 3 steps) as a, colorless oil (1:1 diastereomeric mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.51 (comp, 8H), 7.48 – 7.31 (comp, 12H), 7.19 (dd, *J* = 14.1, 8.7 Hz, 4H), 6.81 (dd, *J* = 8.7, 1.8 Hz, 4H), 5.18 – 4.92 (comp, 4H), 3.89 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.78 (s, 6H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.55 – 3.46 (m, 1H), 3.04 – 2.83 (comp, 4H), 2.82 – 2.75 (m, 2H), 2.69 – 2.59 (m, 2H), 2.46 (ddd, *J* = 13.7, 11.8, 4.9 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.28 (dt, *J* = 13.8, 4.8 Hz, 1H), 2.16 – 2.06 (m, 2H), 1.79 (dd, *J* = 13.6, 5.4 Hz, 1H), 1.00 (d, *J* = 4.6 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 209.7, 169.6, 169.4, 159.9, 135.7, 135.6, 132.6, 132.5, 130.5, 130.2, 130.1, 130.0, 128.8, 128.0, 127.9, 127.0, 127.0, 119.9, 119.2, 114.2, 114.1, 67.7, 60.7, 60.5, 55.6, 55.4, 54.5, 52.4, 51.7, 51.3, 43.8, 39.7, 35.2, 33.9, 29.7, 29.0, 26.8, 19.2. HRMS (ESI$^+$): calcd for $C_{34}H_{37}NNaO_5Si$ $[M+Na]^+$ 590.2339; found 590.2352.

*4-Methoxybenzyl-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (**43**).* To a solution of methyltriphenylphosphonium bromide (18.9 mg, 0.0528 mmol) in dry toluene (1 mL) sealed under N_2 atmosphere was added KHMDS (0.5 M in toluene, 106 µL, 0.0528 mmol), and the mixture was heated at 90 °C for 30 min. To the reaction was added **42** (5.0 mg, 8.8 µmol) in toluene (0.5 mL), and the mixture was stirred for 10 min. at the same temperature. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel packed pipette (5–10% EtOAc/hexanes) to give alkene **43** (4.7 mg, 94%) as a colorless oil (1:1 diastereomeric mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.53 (comp, 8H), 7.48 – 7.30 (comp, 12H), 7.17 (dd, *J* = 11.9, 8.7 Hz, 4H), 6.87 – 6.74 (comp, 4H), 5.14 – 4.90 (m, 6H), 4.82 (s, 1H), 4.78 (s, 1H), 3.99 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.79 (d, *J* = 1.1 Hz, 6H), 3.66 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.56 – 3.35 (m, 3H), 3.06 (d, *J* = 4.2 Hz, 1H), 2.87 (d, *J* = 4.1 Hz, 1H), 2.83 (dd, *J* = 9.3, 5.1 Hz, 1H), 2.73 (s, 2H), 2.59 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.47 (d, *J* = 17.1 Hz, 1H), 2.35 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.30 – 2.11 (m, 3H), 1.97 (dd, *J* = 12.6, 9.3 Hz, 1H), 1.69 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.03 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 159.9, 148.3, 147.9, 135.8, 135.7, 133.6, 133.4, 130.4, 130.2, 130.0, 129.9, 129.8, 127.9, 127.9, 127.8, 127.5, 127.5, 121.1, 120.6, 114.2, 114.1, 107.8, 67.3, 61.1, 60.9, 56.9, 56.5, 56.5, 55.5, 53.0, 48.4, 47.5, 38.3, 36.0, 35.5, 34.8, 34.5, 33.5, 29.9, 27.0, 19.5, 19.4. HRMS (ESI$^+$): calcd for $C_{35}H_{39}NNaO_4Si$ $[M+Na]^+$ 588.2546; found 588.2564.

*4-Methoxybenzyl-2-cyano-7-(hydroxymethyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (**45a**).* To a solution of **43** (57.3 mg, 101 µmol) in toluene (1 mL), sealed under N_2, was added iodomethane (63.0 µL, 1.01 mmol), followed by KHMDS (0.5 M in toluene, 0.61 mL, 0.30 mmol). The mixture was stirred at rt for 3 h, after which time TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was quenched with saturated aqueous NH_4Cl (1 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and used directly in the next step. To a solution of this intermediate (**44a**) (49.0 mg, 84.5 µmol) in THF (1 mL) was added a solution of TBAF (1.00 M in THF, 127 µL, 0.127 mmol) at 0 ºC, and the mixture was removed from the ice bath and stirred at rt for 2 h. LC-MS indicated that some of the desired PMB ester product had been hydrolyzed to the carboxylic acid. The mixture was concentrated, then 1 N aqueous HCl (2 mL) was added, and the solution was extracted with EtOAc (3 x 2 mL). The combined organics were dried over Na_2SO_4, concentrated, and re-dissolved in acetone (3 mL). To the solution was added PMBCl (9.2 µL, 0.0676 mmol), K_2CO_3 (14.0 mg, 0.101 mmol), and 5 to 10 crystals of TBAI, and the mixture was stirred for 24 h at rt. TLC (100% EtOAc) indicated that the carboxylic acid was consumed. The mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel-packed Pasteur pipette, (30–40% EtOAc/hexanes), to give **45a** (15.9 mg, 55%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 11.9 Hz, 1H), 5.01 (t, *J* = 2.6 Hz, 1H), 4.87 (t, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 3.76 – 3.63 (m, 1H), 3.60 – 3.44 (m, 1H), 3.10 (d, *J* = 8.4 Hz, 1H), 2.98 (dq, *J* = 17.5, 2.0 Hz, 1H), 2.68 – 2.54 (m, 2H), 2.32 (t, *J* = 6.4 Hz, 1H), 2.12 – 1.97 (m, 1H), 1.84 (dd, *J* = 12.4, 3.6 Hz, 1H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 159.9, 147.1, 134.9, 130.5, 130.4, 129.7, 128.7, 127.8, 127.2, 123.4, 114.1, 114.1, 114.1, 114.0, 107.9, 67.4, 60.3, 60.2, 55.4, 50.8, 47.5, 45.0, 41.5, 36.2, 24.5. HRMS (ESI$^+$): calcd for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$ 364.1525; found 364.1530.

*4-Methoxybenzyl-2-cyano-2-ethyl-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (**45b**).* **43** (20.0 mg, 33.7 µmol) was treated following the procedure of **45a** using EtI instead of MeI. **45b** was obtained in 4.6 mg, 38% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 5.02 (t, *J* = 2.6 Hz, 1H), 4.86 (t, *J* = 2.2 Hz, 1H), 3.81 (d, *J* = 0.5 Hz, 3H), 3.70 (dd, *J* = 11.7, 7.4 Hz, 1H), 3.60 – 3.43 (m, 1H), 3.12 – 2.94 (m, 2H), 2.70 – 2.52 (m, 2H), 2.31 (t, *J* = 6.4 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.50 – 1.34 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 159.9, 147.2, 130.4, 127.2, 122.2, 114.1, 107.9, 67.3, 60.7, 60.3, 55.4, 51.3, 47.8, 47.7, 41.8, 36.6, 29.3, 8.9. HRMS (ESI$^+$): calcd for $C_{21}H_{25}NNaO_4$ $[M+Na]^+$ 378.1681; found 378.1687.

*4-Methoxybenzyl-2-benzyl-2-cyano-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (**45c**).* **43** (20.0 mg, 33.7 μmol) was treated following the procedure of **45a** using BnBr instead of MeI. **45c** was obtained in 12 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (comp, 5H), 7.23 – 7.13 (m, 2H), 6.96 – 6.82 (m, 2H), 5.28 (d, *J* = 11.8 Hz, 1H), 5.11 (d, *J* = 11.8 Hz, 1H), 4.97 (t, *J* = 2.6 Hz, 1H), 4.84 (t, *J* = 2.1 Hz, 1H), 3.77 (d, *J* = 0.9 Hz, 4H), 3.63 – 3.49 (m, 1H), 3.18 (s, 1H), 3.09 (d, *J* = 17.7 Hz, 1H), 2.75 – 2.55 (comp, 4H), 2.46 (t, *J* = 6.4 Hz, 1H), 2.07 (dd, *J* = 13.1, 4.3 Hz, 1H), 1.56 (d, *J* = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 160.0, 147.0, 134.2, 130.6, 130.5, 128.6, 127.7, 127.2, 122.7, 114.2, 107.9, 67.4, 61.0, 60.3, 55.4, 51.4, 47.7, 47.1, 41.2, 41.0, 36.5. HRMS (ESI$^+$): calcd for $C_{26}H_{27}NNaO_4$ $[M+Na]^+$ 440.1838; found 440.1841.

*6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-ol (**47**).* To a solution of (1-aminocyclopentyl)methanol[37] (3.10 g, 26.9 mmol) in EtOH (100 mL) was added 2,2-dimethoxyacetaldehyde (60% in water, 4.47 mL, 29.6 mmol). The mixture was stirred at rt for 18 h, after which time crude NMR indicated complete conversion to the intermediate imine. The mixture was quenched with 50 mL 1 N aq. NaOH followed by 50 mL H_2O, then extracted with DCM (3 x 100 mL). The combined organics were dried over Na_2SO_4, filtered, concentrated, and redissolved in Et_2O (100 mL) in a flask sealed under N_2. $LiAlH_4$ (1.02 g, 26.9 mmol) was added, and the mixture was stirred at rt for 30 min. The reaction was quenched by adding EtOAc (50 mL) and saturated aqueous Rochelle's salt (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to give a colorless oil. The intermediate amine was dissolved in EtOH (60 mL) and 2,3-dichloroprop-1-ene (1.05 mL, 11.4 mol), $NaHCO_3$ (2.00 g, 23.8 mol) and NaI (114 mg, 0.763 mmol) were added. The mixture was heated to 80 °C under N_2 atmosphere for 18 h, after which time crude NMR indicated about 10% conversion to the desired product. Additional NaI (1.14 g, 7.63 mmol), $NaHCO_3$ (2.00 g, 23.8 mol), 5 to 10 crystals of TBAI and 2,3-dichloroprop-1-ene (0.1 mL, 1.09 mmol) were added. The mixture was refluxed at 87 °C under N_2 atmosphere for 24 h, after which time crude NMR indicated about 80% conversion. The mixture was heated to 100 °C for another 2 h, then filtered through Celite and concentrated to a yellow oil, which was dissolved in conc. HCl (60 mL). The mixture was then refluxed at 105 °C under N_2 atmosphere for 2 h, the solvent was evaporated, and 6 N NaOH (30 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organics were washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by chromatography (10–40% EtOAc/hexanes) to give **47** (390 mg, 22% overall yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (app q, *J* = 1.2 Hz, 1H), 5.30 (app q, *J* = 1.0 Hz, 1H), 4.94 (ddd, *J* = 9.0, 3.9, 2.2 Hz, 1H), 3.82 (d, *J* = 9.1 Hz, 1H), 3.69 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.25 (dd, *J* = 11.4, 0.7 Hz, 1H), 3.16 (dt, *J* = 15.0, 1.3 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 2.69 (dd, *J* = 11.6, 2.2 Hz, 1H), 2.46 (dd, *J* = 11.6, 3.9 Hz, 1H), 1.86 – 1.30 (comp, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 114.2, 91.5, 69.4, 66.0, 56.4, 52.8, 31.7, 28.4, 25.9, 25.8. HRMS (ESI$^+$): calcd for $C_{11}H_{19}ClNO_2$ [M+H] 232.1104; found 232.1106.

*2-Hydroxy-4-(4-methoxybenzyl)morpholin-3-one (**48**).*[38] A solution of 50 wt% aqueous glyoxylic acid (9.14 g, 99.3 mmol) in THF (20 mL) was heated to reflux, then 2-(4-methoxybenzylamino)ethanol[39] (6.00 g, 33.1 mmol) was added over 30 min, and the reaction was refluxed for another 2 h. THF was distilled off under atmospheric pressure while maintaining a constant volume by simultaneous addition of water (20 mL). The mixture was cooled to rt, then placed in an ice bath for 30 min., where the product crystallized. The solids were filtered with a Buchner funnel, washed with water, and then dried under vacuum at 60 °C for 24 h to give **48** (3.6 g, 46%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.0 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 2H), 5.34 (s, 1H), 4.91 (s, 1H), 4.65 (d, *J* = 14.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.30 – 4.18 (m, 1H), 3.80 (s, 3H), 3.78 – 3.74 (m, 1H), 3.42 (td, *J* = 11.2, 10.6, 3.9 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H).

*2-Cyano-7-(((-4-(4-methoxybenzyl)-3-oxomorpholin-2-yl)oxy)methyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (**49**).* **45a** (6.0 mg, 17.6 μmol) was treated following the same procedure of **50a** using **48** instead of **47**, **49** was obtained in 1.5 mg, 19% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.18 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.10 – 4.95 (m, 1H), 4.94 – 4.80 (m, 1H), 4.63 (t, *J* = 15.7 Hz, 1H), 4.37 (t, *J* = 16.0 Hz, 1H), 4.24 – 3.89 (m, 2H), 3.72 – 3.60 (m, 1H), 3.42 (td, *J* = 12.4, 11.7, 4.8 Hz, 1H), 3.09 (d, *J* = 12.6 Hz, 1H), 2.93 – 2.75 (m, 2H), 2.44 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 9.9 Hz, 1H), 2.03 – 1.82 (m, 2H), 1.58 (s, 0H), 1.45 (s, 3H), 1.36 – 1.13 (comp, 5H). ^{13}C NMR (151 MHz, CD_3OD) δ 174.1, 174.0, 166.3, 166.2, 160.9, 160.9, 150.0, 150.0, 130.7, 130.6, 129.2, 124.8, 124.8, 115.2, 115.1, 108.4, 108.2, 97.9, 97.0, 91.7, 67.8, 67.6, 67.0, 60.8, 57.9, 57.9, 50.0, 49.7, 46.6, 46.4, 46.1, 45.9, 42.6, 37.3, 33.1, 30.6, 30.5, 30.3, 30.2, 28.1, 26.9, 25.1, 25.0, 23.8. HRMS (ESI$^+$): calcd for $C_{24}H_{28}N_2NaO_6$ $[M+Na]^+$ 463.1845; found 463.1855, HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 8.10 min.

*7-(((-6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (**50a**).* To a solution of **45a** (18.0 mg, 52.7 μmol) and $PhNTf_2$ (20.7 mg, 58.0 μmol) in Et_2O (1 mL), sealed under N_2 and at –50 °C, was added KHMDS (0.5 M in toluene, 211 μL, 105 μmol), and the mixture was stirred at the same temperature for 10 min. TLC indicated complete consumption of the starting material (40% EtOAc/hexane). The mixture was quenched with aq. NH_4Cl (1 mL) at the same temperature, then extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give the crude triflate, which was used directly in the next step. To a solution of **47** (6.1 mg, 26 μmol) in DMF (0.2 mL) was added NaH (60% in mineral oil, 3.4 mg, 88 μmol) at 0 °C. The mixture was stirred at rt for 15 min., then a solution of the crude triflate in DMF (0.1 mL) was added. The mixture was stirred at rt for 1 h, after which time LC-MS indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by preparative HPLC to give **50a** (3.3 mg, 43%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 – 5.50 (m, 2H), 5.31 (d, *J* = 1.2 Hz, 2H), 5.11 – 5.02 (m, 2H), 4.94 (s, 2H), 4.59

(dd, *J* = 4.9, 2.7 Hz, 1H), 4.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.08 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.68 (d, *J* = 7.8 Hz, 2H), 3.59 (dd, *J* = 11.1, 3.8 Hz, 2H), 3.38 – 3.17 (m, 3H), 3.04 (d, *J* = 5.5 Hz, 5H), 2.97 (s, 1H), 2.84 (d, *J* = 3.9 Hz, 1H), 2.79 (d, *J* = 4.0 Hz, 1H), 2.72 – 2.64 (comp, 3H), 2.60 (d, *J* = 2.7 Hz, 1H), 2.44 (ddd, *J* = 11.7, 9.3, 5.1 Hz, 2H), 2.16 – 2.30 (comp, 12H, presumably obs w/ H_2O), 2.13 (dd, *J* = 12.6, 2.3 Hz, 2H), 1.89 (dt, *J* = 12.7, 3.8 Hz, 2H), 1.59 (d, *J* = 10.5 Hz, 6H), 1.51 (d, *J* = 1.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 172.4, 147.2, 147.1, 140.1, 140.0, 123.4, 123.3, 113.3, 113.1, 108.6, 108.5, 98.7, 98.2, 70.8, 70.3, 68.1, 65.6, 65.5, 65.5, 65.3, 59.5, 59.5, 57.0, 56.9, 52.1, 52.0, 48.2, 48.1, 47.7, 47.6, 44.9, 44.9, 41.9, 41.8, 41.0, 36.2, 36.2, 29.9, 29.8, 25.8, 25.7, 25.0, 25.0, 22.9, 14.3. HRMS (ESI^+): calcd for $C_{23}H_{32}ClN_2O_4$ [M+H] 435.2051; found 435.2060; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 7.30 min.

*7-(((-6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-ethyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (**50b**).* Following the same procedure of **50a** using **45b** (5.6 mg, 16 μmol) instead of **45a**, **50b** was obtained (1.5 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 - 5.52 (m, 2H), 5.30 (s, 2H), 5.10 - 5.05 (m, 2H), 4.94 (s, 2H), 4.61 - 4.56 (m, 1H), 4.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.08 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.81 (d, *J* = 1.0 Hz, 1H), 3.68 (d, *J* = 7.0 Hz, 2H), 3.58 (dd, *J* = 11.0, 4.5 Hz, 2H), 3.32 (t, *J* = 9.2 Hz, 1H), 3.23 (dd, *J* = 16.4, 11.1 Hz, 2H), 3.13 – 2.96 (comp, 6H), 2.86 (s, 1H), 2.80 (s, 1H), 2.71 – 2.56 (m, 2H), 2.49 – 2.35 (comp, 4H), 2.07 – 1.97 (m, 1H), 1.95 (t, *J* = 3.1 Hz, 5H), 1.92 – 1.78 (m, 2H), 1.69 – 1.45 (comp, 16H, presumaby obs w/ H_2O), 1.28 (s, 1H), 1.15 – 1.04 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 147.2, 147.2, 140.1, 140.1, 133.8, 114.1, 113.3, 113.1, 108.6, 108.5, 98.8, 98.1, 76.9, 70.8, 70.2, 65.7, 65.5, 65.5, 65.3, 57.0, 56.9, 52.1, 52.0, 48.6, 48.0, 47.8, 47.8, 41.7, 41.6, 40.9, 37.1, 36.7, 36.7, 36.1, 32.1, 29.9, 29.8, 29.5, 29.5, 27.4, 25.8, 25.8, 25.8, 25.7, 22.9, 14.3. HRMS (ESI^+): calcd for $C_{24}H_{34}ClN_2O_4$ [M+H] 449.2207; found 449.2225; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 7.06 min.

*2-Benzyl-7-(((-6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (**50c**).* Following the same procedure of **50a** using **45c** (7.8 mg, 19 μmol) instead of **45a**, **50c** was obtained (1.9 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.27 (comp, 10H), 5.57 (s, 1H), 5.53 (s, 1H), 5.30 (s, 2H), 5.01 (d, *J* = 7.5 Hz, 2H), 4.89 (s, 2H), 4.64 – 4.58 (m, 1H), 4.57 – 4.50 (m, 1H), 4.25 – 4.08 (m, 1H), 3.70 (dd, *J* = 20.1, 11.3 Hz, 2H), 3.59 (t, *J* = 10.7 Hz, 2H), 3.32 (t, *J* = 9.0 Hz, 1H), 3.26 (d, *J* = 11.1 Hz, 1H), 3.20 (dd, *J* = 12.3, 6.3 Hz, 2H), 3.14 – 2.96 (comp, 6H), 2.84 (s, 1H), 2.77 (s, 1H), 2.72 (d, *J* = 12.0 Hz, 1H), 2.69 – 2.63 (m, 2H), 2.62 (d, *J* = 0.7 Hz, 1H), 2.45 (ddd, *J* = 16.5, 12.8, 7.4 Hz, 5H), 2.14 – 2.02 (m, 2H), 1.57 (comp, 20H, presumably obs w/ H_2O). HRMS (ESI^+): calcd for $C_{29}H_{35}ClN_2O_4$ [M+H] 511.2364; found 511.2370; HPLC (Phenomenex Gemini C_{18}) (25% (0-1.5 min.) - 95% (3.5-10 min), MeCN/H_2O; flow rate, 1.0 mL/min). RT= 8.27 min.

*General procedure for Diels-Alder reaction using **22** (**Table 1**).* A solution of the indicated amount of Lewis acid and methyl 2-(trifluoromethyl)acrylate (2.3 μL, 18.7 μmol) in the indicated solvent (0.5 mL) was sealed under N_2 and cooled to –78 °C. **14** (5.0 mg, 9.4 μmol) in the indicated solvent (0.2 mL) was then added by syringe, and the mixture was stirred and gradually warmed up to –30 °C over 1 h. In an aluminum foil wrapped Dewar flask, the mixture was stirred for 24 h at rt. The mixture was filtered through a PTFE syringe filter, concentrated, and dissolved in 0.6 mL $CDCl_3$ containing pentachloroethane (1.1 μL, 9.4 umol). ^{1}H and ^{19}F NMR analysis was then conducted.

*Representative procedure for organocatalytic Diels-Alder reaction using cyclopentanones (**Table 2**).* To a solution of **25**[33] in toluene (0.2 M, 0.36 mL) and propionic acid (5.4 μL, 0.07 mmol), was added cyclopent-2-en-1-one (20 μL, 0.24 mmol). (*E*)-4-phenylbut-3-en-2-one (17.5 mg, 0.12 mmol) was added, and the mixture was sealed under N_2 and heated to 60 °C The experiments were monitored by GC-MS after 24 h.

*General procedure for double Michael addition (**Table 3**).* **24a** or **24b** (14.0 μmol) was sealed under N_2, dissolved in THF (0.5 mL), and cooled to 0 °C. LDA (1.37 M in heptane, 10.2 μL, 14.0 μmol) was added, and HMPA (2.4 μL, 14 μmol) was optionally added. The mixture was cooled to –78 °C and the indicated amount of Michael acceptor in THF (0.5 mL) was added by syringe. The mixture was stirred for 2 h, then warmed up to rt and stirred for another 22 h. The reaction was quenched with saturated NH_4Cl solution (1 mL) and extracted with EtOAc (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated prior to ^{1}H NMR and LC-MS analyses.

*Attempted cyanation of camphor-derived alcohol **32** and alkene **33** (**Scheme 4**).* To a solution of **32** (17.4 mg, 66.8 μmol) in DCM (0.7 mL) sealed under N_2 and cooled to –78 °C was added TMSCN (10.6 μL, 84.9 μmol), followed by the addition of boron trifluoride etherate (8.8 μL, 72 μmol), which caused the colorless solution to turn yellow. The mixture was stirred at –78 °C for 15 min., then warmed to rt. The reaction was stirred for another 15 min., then it was quenched with sat. aq. $NaHCO_3$ (1 mL). The organic phase was separated and the aqueous phase was extracted with DCM (3 x 1 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated prior to to GC-MS and ^{1}H NMR analysis.

Alternatively, $PhCF_3$ (0.5 mL) was sealed under N_2, cooled to –20 °C, and TfOH (18.8 μL, 0.21 mmol) and TMSCN (25.8 μL, 0.21 mmol) were added. After 5 min., **33** (10 mg, 0.04 mmol) in $PhCF_3$ (0.5 mL) was added dropwise at the same temperature. The mixture was allowed to warm to rt and stirred for 0.5 h. The reaction was quenched with aqueous NaOH (1 M, 1 mL), extracted with ethyl acetate (3 x 1 mL), dried over Na_2SO_4, filtered, and concentrated prior to GC-MS and ^{1}H NMR analysis.

*General procedure for aryl/alkylation of secondary nitrile **40** (**Table 4**).* To a solution of **40** (2.5 mg, 5.3 μmol) in the indicated solvent (0.5 mL) sealed under N_2 was added the indicated amount of electrophile. KHMDS (0.5 M in toluene, 52.6 μL, 0.026 mmol) was then added. The mixture was heated at the indicated temperature for the indicated time. The reaction was worked up by washing with 1 N HCl (0.5 mL) and extracting with EtOAc (3 x 0.5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a crude product which was dissolved in $CDCl_3$ containing pentachloroethane (5.26 μmol), prior to ^{1}H NMR analysis.

ASSOCIATED CONTENT

^{1}H and ^{13}C NMR spectra and LC-MS traces of select reactions and new compounds.

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Notes

A patent application including this work has been submitted.

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