

Chapter 2

Total Syntheses of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinylogous Mukaiyama-Michael Addition.*

I. Introduction.

i. The \square -Butanolide Architecture.

The \square -butanolide architecture is a privileged motif in organic synthesis and can be found in over 13,000 natural products, some of which are shown in figure 1.¹ Kallolide is a diterpenoid and a member of the rare pseudopterane family.² Members of this family possess significant biological activity, and kallolide is an anti-inflammatory agent with activity comparable to that of indomethacin. Merrilactone A has received considerable attention in the past few years because of its role as a neurotropic agent. It is implicated in the treatment of Alzheimer's and Parkinson's diseases due to its ability to affect the maintenance and growth of neurons as well as its ability to prevent neurological death. Spiculisporic acid is a commercial surfactant that will be discussed in more detail (*vide infra*).

* A preliminary communication of this work has been published: Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

¹ The Beilstein database reports >200 natural isolates that incorporate \square -butanolide structure.

² Look, S. A.; Burch, M. T.; Fenical, W.; Zhen, Q.-T.; Clardy, J. *J. Org. Chem.* **1995**, *50*, 5741.

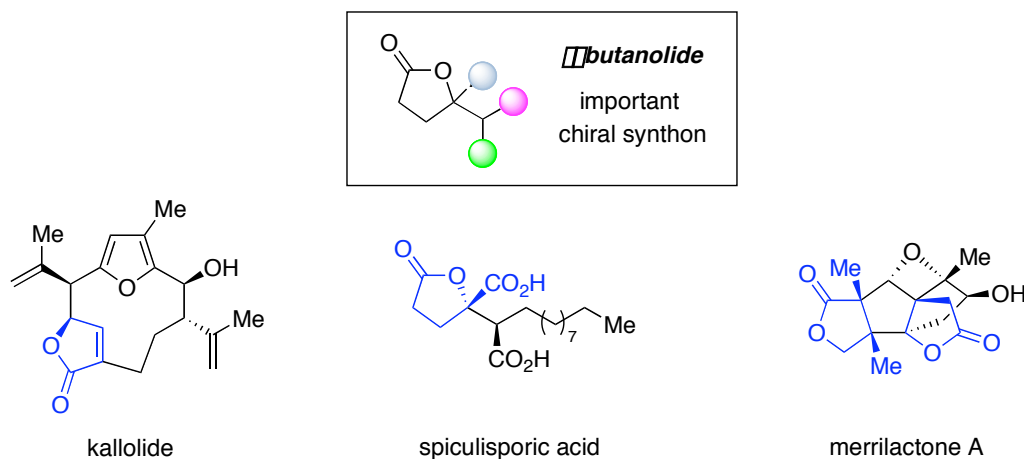


Figure 1. Butanolides in natural products.

Despite their prevalence in natural products, there are only a few methods in which γ -butanolides are commonly synthesized.³ The two most common ways are (i) lactonization of a γ -alcohol onto a carboxylic moiety (Fig. 2A) and (ii) oxidation of a siloxyfuran (Fig. 2B). An alternative strategy is the metal-catalyzed trapping of a pendant carboxylic acid onto an alkene or alkyne (Fig. 2C). The latter route is not amenable to varying functionality on the γ -system, as there are few examples of this reaction with a tetrasubstituted olefin as shown in figure 2. Within the realms of these three methods, the biggest challenge is setting the stereochemistry about the fully-substituted γ -carbon.

³ For reviews on synthesis of butenolides, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Recent Res. Dev. Syn. Org. Chem.* **2000**, 65. (b) Negishi, E.-I.; Kotor, M. *Tetrahedron* **1997**, 53, 6707. (c) Knight, D. W. *Contemporary Org. Synth.* **1994**, 1, 287.

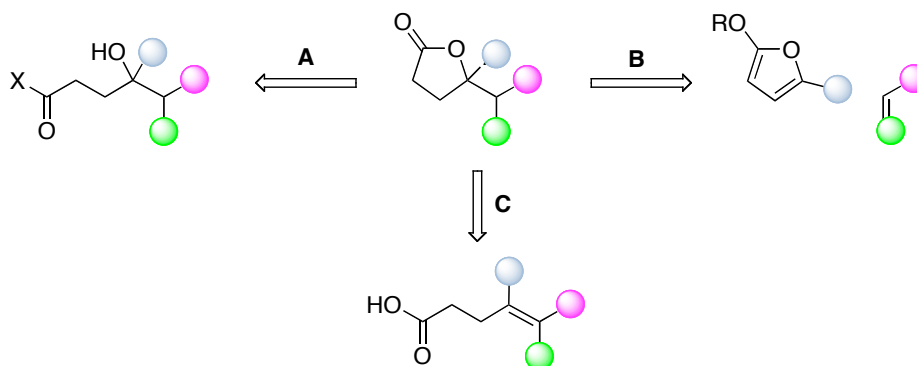
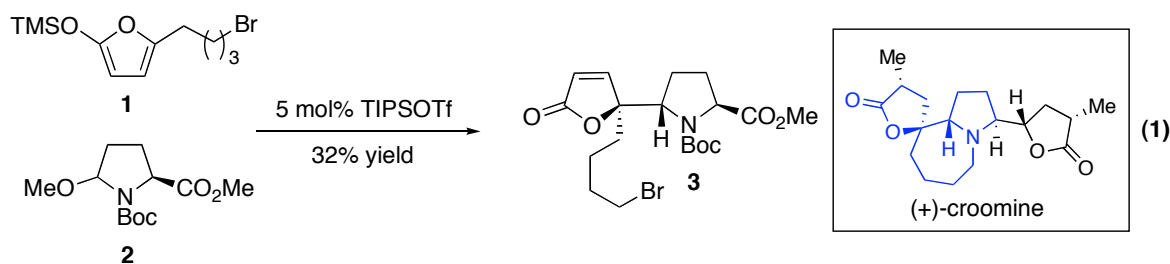


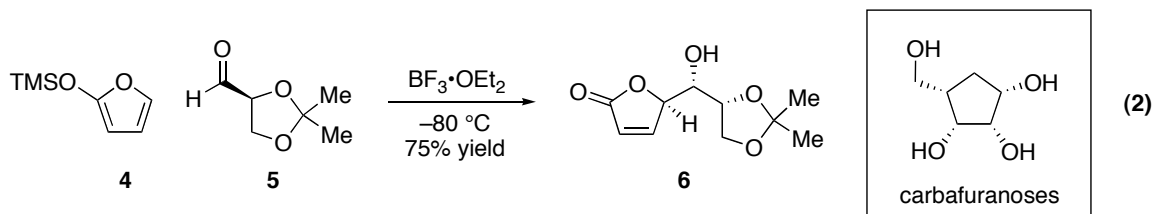
Figure 2. Syntheses of the butanolide architecture.

A variety of diastereoselective methods have been developed for the stereoselective formation of γ -butanolides. In the synthesis of (+)-croomine, Martin and co-workers reported that the addition of functionalized siloxyfuran **1** to chiral γ -methoxyamine **2** under Lewis acidic conditions affects a diastereoselective Mannich reaction to form butenolide **3** (eq. 1).⁴ Analogously, the diastereoselective Aldol reaction in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ produces a single diastereomer of butenolide **6**, which is an intermediate in the syntheses of a variety of furanose derivatives (eq. 2).⁵



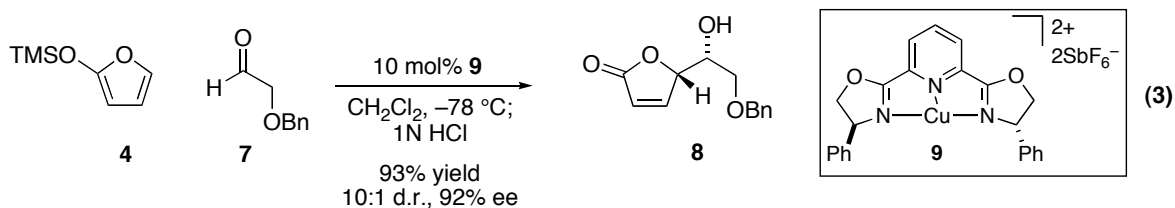
⁴ (a) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (b) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

⁵ Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070.



The catalytic coupling of siloxyfurans and aldehydes and α,β -unsaturated system using chiral Lewis acids has emerged as a preeminent strategy to generate enantioenriched butenolide structures. These are termed the Mukaiyama-Aldol and Mukaiyama-Michael reaction, respectively.

In 1999, the Evans group reported that utilization of chiral copper complex **9** catalyzed the addition of siloxyfuran **4** to β -oxyacetaldehydes **7** to furnish the enantioenriched vinylogous Mukaiyama-Aldol product **8** in excellent yield (eq. 3).⁶ While the Mukaiyama-Aldol transformation has received considerable attention within the synthetic community,⁷ the enantioselective 1,4-addition of silyl enol ethers to electron-deficient olefins was not as well studied.



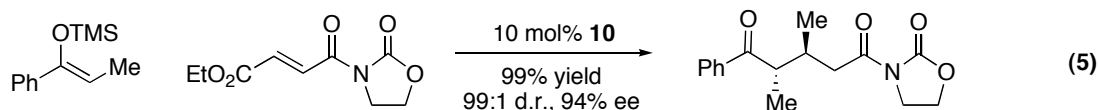
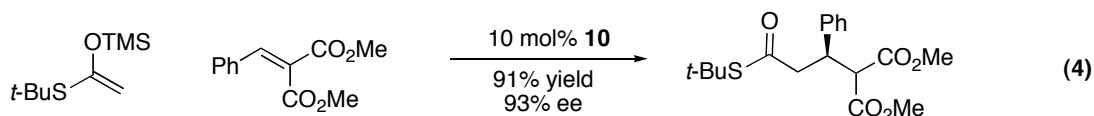
⁶ (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

⁷ For reviews that incorporate this topic, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (b) Carreira, E. M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8B2. (c) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim 2000; Chapter 8.

ii. The Mukaiyama-Michael Reaction.

Since its discovery by Mukaiyama in 1974,⁸ the Mukaiyama-Michael reaction of silyl enol ethers with α,β -unsaturated carbonyl compounds has become a powerful technique for the stereoselective formation of carbon-carbon bonds under mild reaction conditions.

Prior to this research, only electrophiles that were capable of bidentate chelation to a chiral Lewis acid complex were suitable electrophiles for the Mukaiyama-Michael addition. For example, the Evans group used copper(II) bisoxazoline **10** to catalyze the enantioselective addition of silyl enol ethers to alkylidene malonates⁹ (eq. 4) or unsaturated acyl oxazolidinones¹⁰ (eq. 5). In separate reports, Katsuki¹¹ and Desimoni¹² employed chiral Lewis acids **10** and **11** to catalyze the Mukaiyama-Michael addition of siloxyfuran **4** to acyl oxazolidinones (eq. 6 and 7).



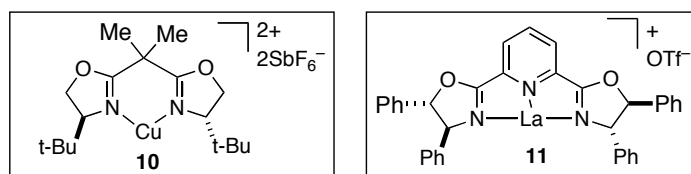
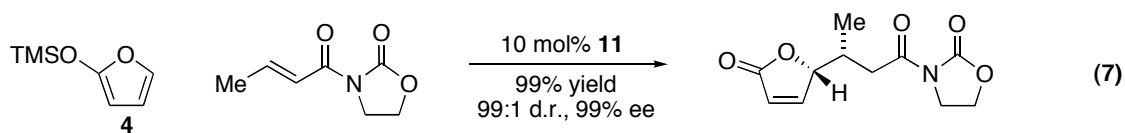
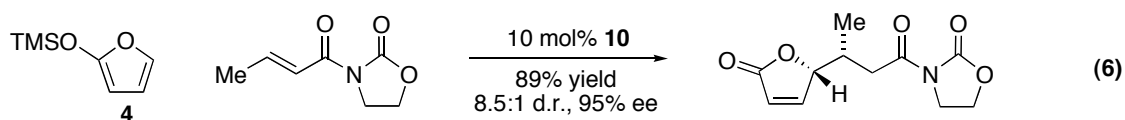
⁸ (a) Narasaki, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.

⁹ Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

¹⁰ Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

¹¹ (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (b) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568.

¹² Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *53*, 10203.



iii. Mukaiyama-Aldol versus Mukaiyama-Michael Addition.

The deficiency in enantioselective Mukaiyama-Michael reactions may be due to the propensity of Lewis acids to promote 1,2-addition to the carbonyl in preference to 1,4-addition to the α,β -unsaturated system (Fig. 3).¹³ In fact, it is documented that metal-mediated siloxyfuran additions to enals proceed in a highly selective fashion to give the Mukaiyama-Aldol product.¹⁴

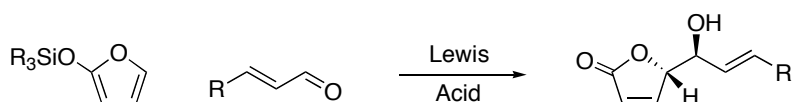
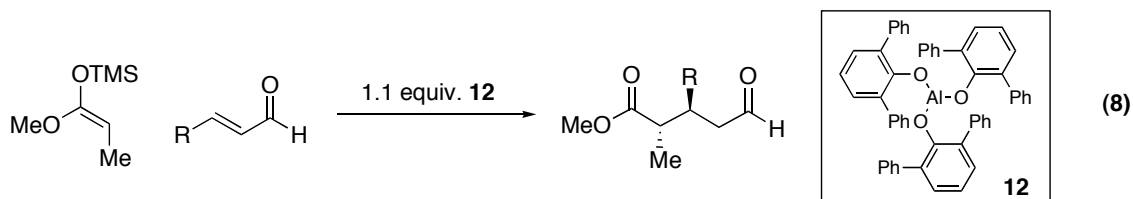


Figure 3. Lewis acids promote a Mukaiyama-Aldol addition.

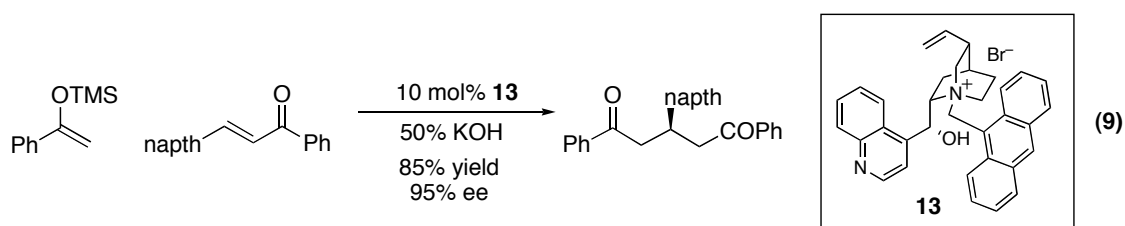
¹³ (a) Rodriguez, A. D.; Shi, J. G.; Huang, S. P. D. *J. Org. Chem.* **1998**, *63*, 4425.

¹⁴ (a) von der Ohe, F.; Bruckner, R. *Tetrahedron Lett.* **1998**, *39*, 1909. (b) von der Ohe, F.; Bruckner, R. *New J. Chem.* **2000**, *24*, 659.

To date, the only example of a metal-mediated Mukaiyama-Michael addition has been reported by the Yamamoto group, who utilized the sterically demanding aluminum acid complex **12** to promote the 1,4-addition of silyl enol ethers to enals (eq. 8).¹⁵ It is hypothesized that the steric demand imposed by the aluminum promoter partitions the reaction away from addition to the carbonyl to give the Mukaiyama-Michael product.



While metal-catalyzed reactions are mostly ineffective in this synthetic transformation, several organocatalytic approaches to the enantioselective Michael reaction have been reported. The first report was in 1975 when quinine was used to catalyze the 1,4-addition of 1,3-dicarbonyls to enones.¹⁶ Twenty-five years later, Corey demonstrated that cinchona alkaloid derivative **13** could catalyze the Mukaiyama-Michael addition of silyl enol ethers to enones with high levels of enantioselectivity (eq. 9).¹⁷



¹⁵ Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

¹⁶ Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *14*, 4057.

¹⁷ (a) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (b) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639.

II. Organocatalytic Vinylogous Mukaiyama-Michael Reaction.

During our group's studies on LUMO-lowering organocatalysis (*vide* Chapter 1), α,β -unsaturated aldehydes had been shown to be quite useful substrates in a broad range of transformations.¹⁸ It was expected that organocatalysis with chiral imidazolidinones would render the α,β -unsaturated aldehyde inert to 1,2-addition by the siloxyfuran, thus overcoming the limitations to the construction of β -butenolides imposed by Lewis acid catalysis (Fig. 3). α,β -Unsaturated iminium ions arising from chiral imidazolidinone **14** should favor 1,4-addition because of the steric constraints imposed by the catalyst framework (Fig. 4).

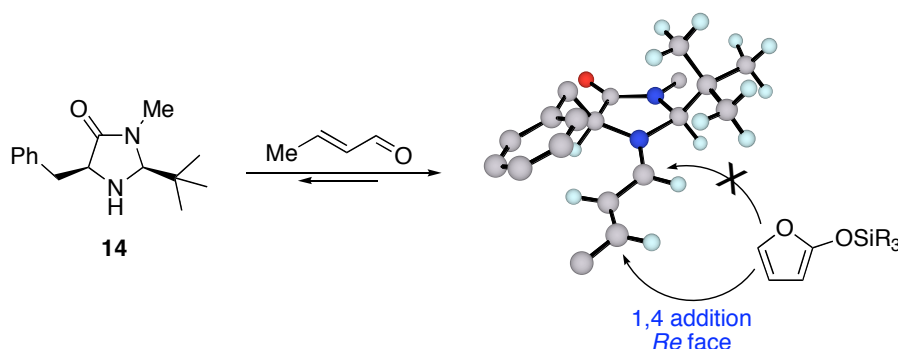


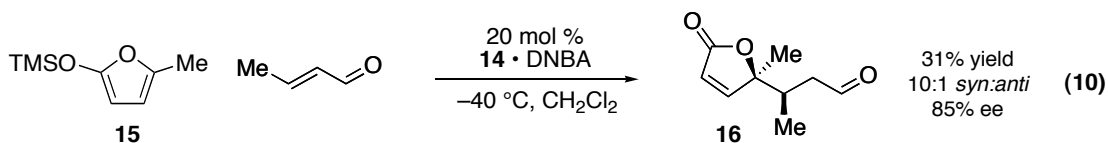
Figure 4. 1,2-addition versus 1,4-addition in the presence of chiral amines.

Additionally, the catalyst framework should enforce high levels of diastereo- and enantioselectivity in the carbon-carbon bond-forming event by shielding the *Si* face and exposing only the *Re* face towards the attack of α -nucleophiles.

¹⁸ (a) Ahrendt, K.A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (d) Austin, J. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (e) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

i. Initial Investigations into the Organocatalytic Mukaiyama-Michael.

The enantioselective organocatalytic synthesis of butenolides was first examined using siloxyfuran **15**, crotonaldehyde, and imidazolidinone **14**.¹⁹ Preliminary results demonstrated that the proposed 1,4-addition was possible with good levels of diastereo- and enantioselectivity; however, the efficiency of the reaction was poor (eq. 10).



It was believed that the catalytic cycle was being arrested by the consumption of water due to desilylation of the silyl cation intermediate **17** (Fig. 5). Therefore, there was no hydrolysis of the iminium adduct **18** and thus no turnover of catalyst.

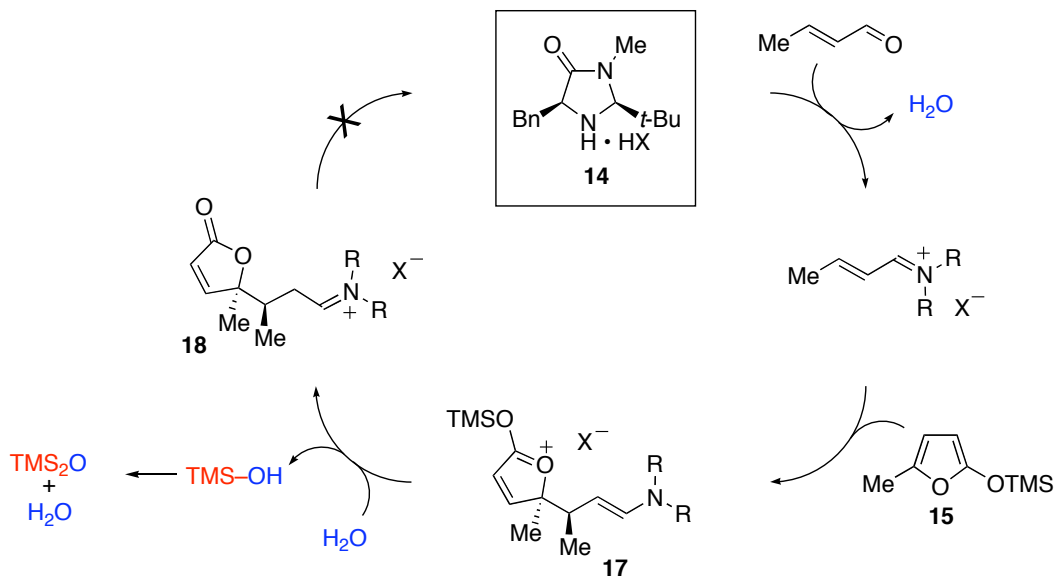


Figure 5. Consumption of water in the catalytic cycle.

¹⁹ Initial investigations were conducted by Sean P. Brown. See: Brown, S. P. Ph.D. thesis. California Institute of Technology, 2005.

It was hypothesized that the addition of a protic nucleophile to facilitate the desilylation of intermediate **17** would allow for hydrolysis of iminium **18** and complete the catalytic cycle to release desired product **16** (Fig. 6)

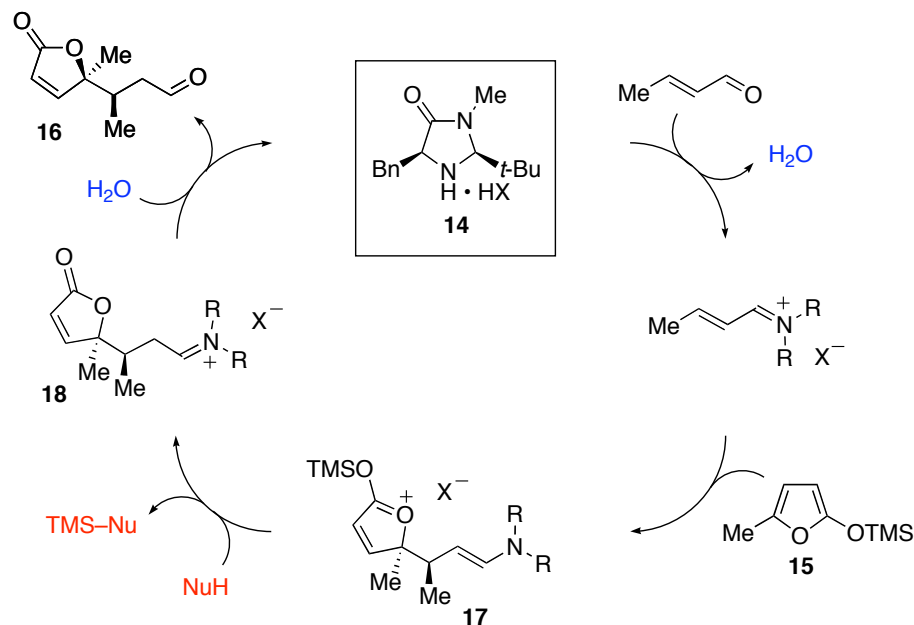


Figure 6. Restoration of the catalytic cycle by protic nucleophiles.

While a variety of protic nucleophiles were effective in scavenging the putative silyl cation intermediate (Table 1, entries 2–5), the addition of excess water provided optimal reaction efficiency (entries 5 and 6) with superior levels of diastereoselectivity and enantioselectivities greater than 90%.

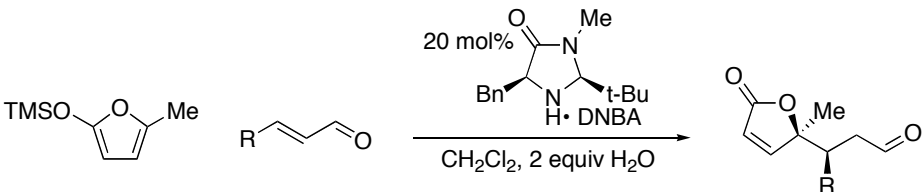
Table 1. The effect of protic sources in the organocatalytic Mukaiyama-Michael.

Entry	ROH	temp (°C)	time (h)	% yield	syn:anti	% ee ^{a,b}
1	none	−40	10	31	10:1	85
2	<i>i</i> -PrOH	−40	10	83	16:1	84
3	(CF ₃) ₂ CHOH	−40	10	42	10:1	83
4	phenol	−40	10	58	11:1	82
5	H ₂ O	−40	10	93	16:1	85
6	H ₂ O	−70	11	84	22:1	92

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by X-ray or nOe analysis.

ii. Scope of the organocatalytic Mukaiyama-Michael reaction.

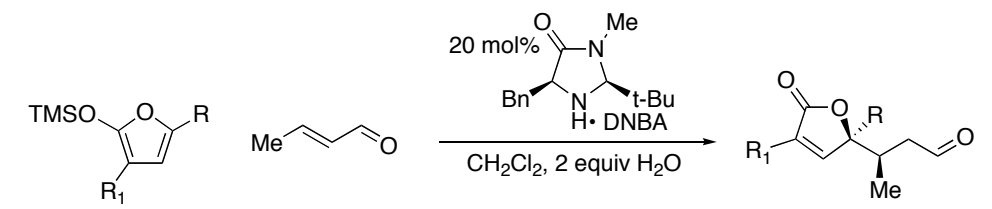
The reaction conditions developed (*vide supra*) proved to be applicable to a wide range of steric demands on the α -olefin substituent of the enal (Table 2, entries 1–4) to produce 5-(1-alkyl)-5-methylfuranones (7:1 to 31:1 *syn:anti*, 84–99% ee). Variation in the electronic nature of the enal has little influence on the sense of enantioinduction. For example, optimal levels of selectivity can be achieved with enals that do not readily participate in iminium formation (entry 6, 84% yield, 99% ee), as well as aldehydes that provide stable iminium intermediates (entry 4, 77% yield, 99% ee).

Table 2. Organocatalyzed addition of siloxyfuran into α,β -unsaturated aldehydes.


Entry	R	temp (°C)	time (h)	% yield	syn:anti	% ee ^{a,b}
1	Me	-70	11	81	22:1	92
2	<i>n</i> -Pr	-50	20	87	31:1	84
3	<i>i</i> -Pr	-20	30	80	7:1	98
4	Ph	-40	30	77	1:6	99
5	CH ₂ OBz	-70	24	86	20:1	90
6	CO ₂ Me	-60	22	84	11:1	99

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by X-ray or nOe analysis.

Significant structural variation in the siloxyfuran system can be tolerated (Table 3). The reaction appears to be quite tolerant to substitution at the 5-position of the furan (entries 1–4, 90–92% ee). While high levels of *syn* stereogenicity are available in the construction of *g*-butenolides (entries 1–4, 6), access to the *anti* diastereomer can also be realized with the appropriate choice of co-catalyst and solvent in systems that bear an electron-withdrawing substituent on the furan (entry 5, 1:7 *syn:anti*, 98% ee, 83% yield). Moreover, introduction of alkyl substituents at C(3) of the furan moiety can be accommodated without loss in stereocontrol (entry 6, 24:1 *syn:anti*, 98% ee, 73% yield).

Table 3. Organocatalyzed addition of siloxyfurans into crotonaldehyde.


Entry	R	R ₁	temp (°C)	time (h)	% yield	syn:anti	% ee ^{a,b}
1	H	H	-50	7	87	8:1	90
2	Me	H	-70	11	80	22:1	92
3	Et	H	-70	11	83	16:1	90
4	CO ₂ Me	H	-10	44	86	6:1	98 ^c
5	CO ₂ Me	H	-10	96	83	1:7	98 ^d
6	Me	Me	-65	23	73	24:1	90

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by X-ray or nOe analysis. ^c With 20 mol% catalyst•TFA in THF. ^d With 20 mol% catalyst•TfOH in CHCl₃

III. Total Syntheses of the Spiculisporic Acids.

A demonstration of the utility of this organocatalytic vinylogous Mukaiyama-Michael methodology was its use in the total synthesis of spiculisporic acid and its epimer, 5-*epi*-spiculisporic acid.

i. Background.

Spiculisporic acid **19** is a fermentation adduct isolated from the recrystallization of the precipitate formed on acidification of the culture broth of *Penicillium spiculisporum* Lehman and other *P.* species.²⁰ It is believed that the active metabolite is

²⁰ (a) Clutterbuck, P. W.; Raistrick, H.; Rintoul, M. L. *Philos. Trans. R. Soc. London, Ser. B.* **1931**, 220, 301. (b) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, 228, 828. (c) Asano, M.; Kameda, S. *J. Pharm. Soc. Jpn.* **1941**, 61, 81.

not the lactone **19** but the hydrolyzed tricarboxylic acid **19a**, secospiculisporic acid (Fig. 7).²¹

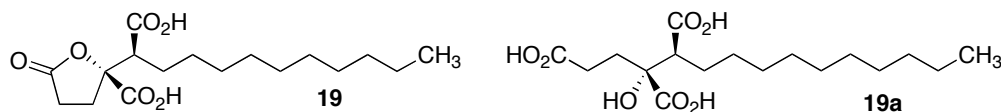


Figure 7. Spiculisporic acid and secospiculisporic acid.

Spiculisporic acid has found commercial application (i) as a biosurfactant for metal decontamination processes to remove hard, large metal cations from water²² and (ii) in fine polymer production.²³ Furthermore, it was shown that the (*n*-hexylamine) salt of spiculisporic acids **19** and **19a** change their state of molecular aggregation depending on the environmental pH: vesicles form at pH of about 6.0, lipid particles at pH of 6.3–6.6, and micelles at pH above 6.8 (Fig 8).²⁴ Because of these physiological properties, these materials have potential use as new controlled release carriers of active chemicals in the cosmetic, pharmaceutical, agricultural, and biotechnology industries.

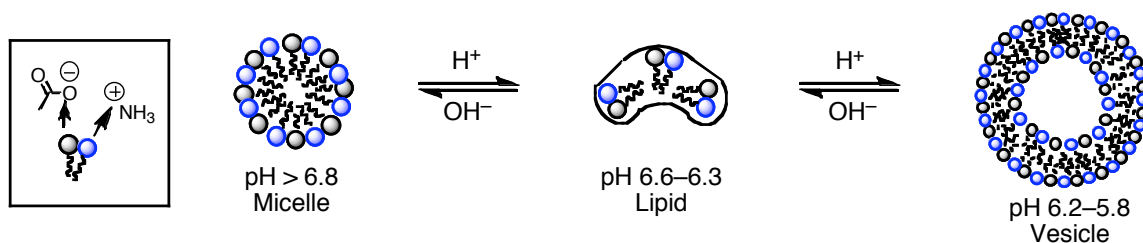


Figure 8. pH-Dependent molecular aggregation of the amine salts of spiculisporic acid.

²¹ Tabuchi, T.; Nakamura, I.; Kobayashi, T. *J. Ferment. Technol.* **1977**, *55*, 37.

²² Pekdemir, T.; Tokunaga, S.; Ishigami, Y.; Hong, H.-J. *J. Surfactants Detergents* **2000**, *3*, 43.

²³ Yamazaki, S.; Suzuki, H.; Ishigami, Y. *Kagaku Gijutsu Hokoku* **1988**, *83*, 125.

²⁴ (a) Ishigami, Y.; Zhang, Y.; Ji, F. *Chimica Oggi* **2000**, *32*; (b) Ishigami, Y.; Gama, Y.; Yamazaki, S. *J. Jpn. Oil Chem. Soc.* **1987**, *36*, 490.

To date, the only other reported enantioselective synthesis was complete by Brandaenge and co-workers in 1984.²⁵ The elaboration from D-glucose was accomplished in 22 steps and utilized none of glucose's resident stereocenters (Fig. 9)

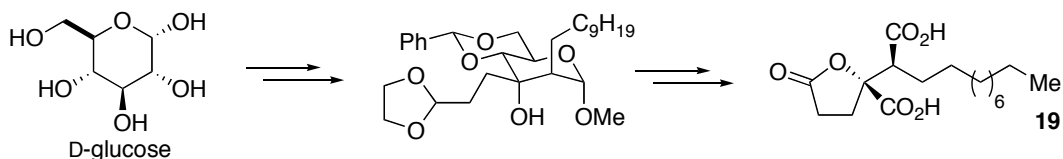


Figure 9. Brandaenge's synthesis of spiculisporic acid.

ii. Investigation of key organocatalytic Mukaiyama-Michael reaction.

As shown in figure 10, it was envisioned that the stereochemical core **20** of the natural product **19** could be constructed in one step from the organocatalytic Mukaiyama-Michael addition of siloxyfuran **21** into methyl 4-oxobutenoate (**22**).

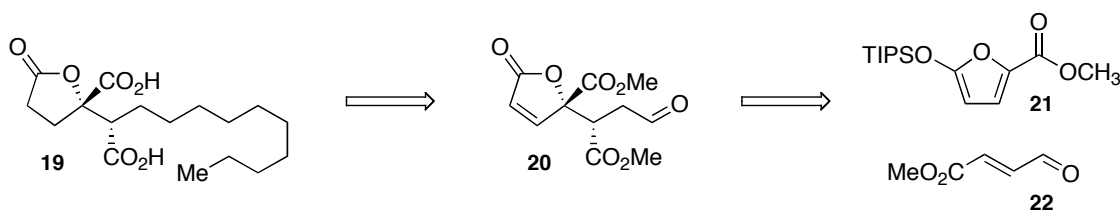


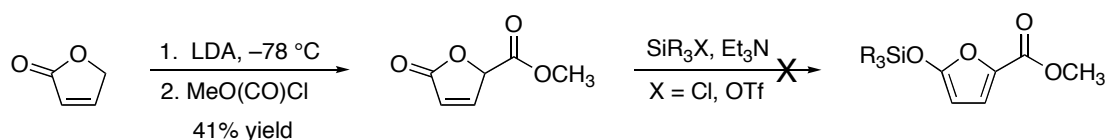
Figure 10. Retrosynthetic analysis of spiculisporic acid.

In accordance with known methodology to prepare 5-alkyl-2-siloxyfurans, alkylation at the 5-position was attempted by simple vinylogous enolate addition of 2-

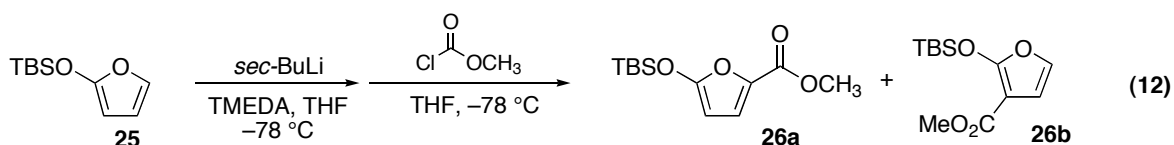
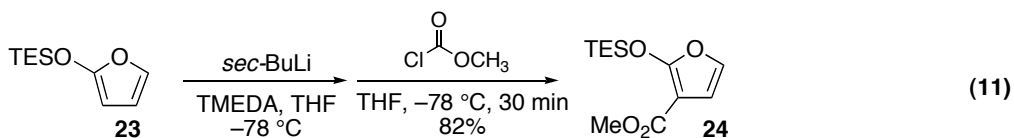
²⁵ Brandaenge, S.; Dahlman, O.; Lindqvist, B.; Maahlen, A.; Moersch, L. *Acta Chem. Scand. Ser. B* **1984**, *10*, 837.

(5*H*)-furanone to carboxylic acid derivatives (Scheme 1). Alkylation directly to the carboxylic acid with CO₂ was unsuccessful. However, analogous alkylation with methyl chloroformate proceeded with a 41% yield. Attempts to deprotonate the alkylated lactone and silylate to form the siloxyfuran were unsuccessful.

Scheme 1. Preparation of 5-carboxyl-2-siloxyfurans.

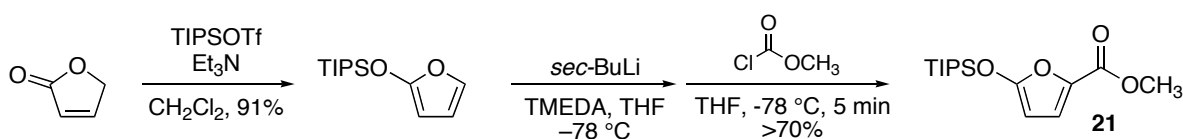


Due to the stability of the TIPS group relative to other silyl protecting groups, we were concerned about the desilylation step in the catalytic cycle. Therefore more readily desilylated furan derivatives were made. However, triethylsiloxyfuran **23** alkylated exclusively in the 3-position to afford **24** (eq. 11). Under the same conditions, *tert*-butyldimethylsiloxyfuran **8** produced with a 1:1 mixture of alkylation in the 3-position **26a** and the 5-position **26b** (eq. 12). Other alkylating reagents, such as benzyl and ethyl chloroformate, led to decomposition of the starting material.

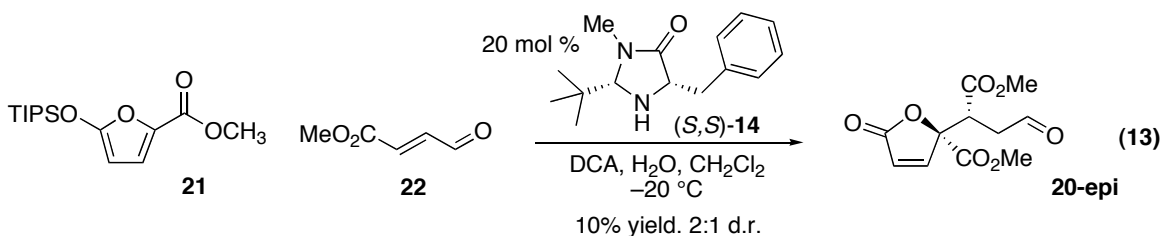


A report by Martin and co-workers in 1999 demonstrated that the 5-position of triisopropylsilylfurans could be alkylated with aryl halides.²⁶ The TIPS group sterically protects the 3-position of the furan thus exposing only the 5-position for deprotonation and subsequent alkylation. Using methyl chloroformate as the electrophile, this reaction proceeded cleanly with yields consistently above 70% (Scheme 2).

Scheme 2. Preparation of siloxyfuran **21.**



With the siloxyfuran **21** in hand, the organocatalytic step was attempted using enal **22**. Using 5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one [(*S,S*)-**14**], the reaction was conducted at -20°C with dichloroacetic acid (DCA) as the co-catalyst. A diastereoselectivity of 2:1 was observed in the proton NMR with about a 10% isolated yield of the product **20-epi** (eq. 13).²⁷

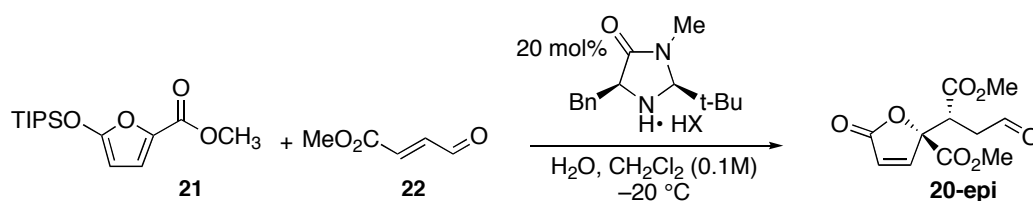


²⁶ Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

²⁷ At the start of this synthesis, the relative stereochemistry was unknown. Once the synthesis was completed, it was determined by correlation to the natural product that the original optimization series was furnishing the epimer of the desired natural product.

The limited reactivity of this system showed that the desired reaction was operative, but further optimization was still needed. Examination of the acid co-catalyst, solvent, and concentration quickly produced a more efficient and more stereoselective reaction. Stronger acid co-catalysts produced conversions over 60%, diastereoselectivities greater than 4 to 1, and enantioselectivities greater than 85% (Table 4, entries 1 and 2). Further studies were conducted with triflic acid as the co-catalyst.

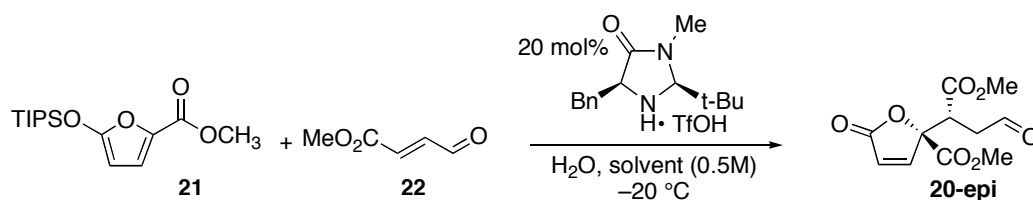
Table 4. Examination of acid co-catalyst.



Entry	HX	pKa	conversion (%)	<i>syn:anti</i>	% ee ^{a,b}
1	TfOH	−14	63	5.9:1	85
2	HCl	−8	63	4.3:1	86
3	TFA	−0.25	44	2.5:1	80
4	DCA	1.29	49	1:1.2	58
5	DBA	1.48	48	1:1.1	66
6	2,4-DNBA	1.86	48	1:1.3	59
7	2-NBA	2.21	35	1:1.6	34
8	MCA	2.87	29	1:1.3	32

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by correlation to the natural product.

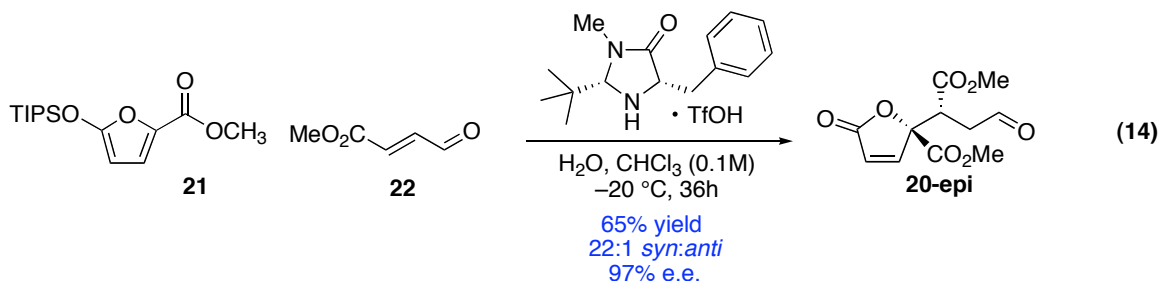
A survey of a variety of solvents revealed that non-polar solvents complimented the use of more acidic co-catalysts, now producing a highly diastereoselective and enantioselective reaction (Table 5, entries 2–4).

Table 5. Examination of solvent with triflic acid as the co-catalyst.

Entry	Solvent	conversion (%)	<i>syn:anti</i>	% ee ^{a,b}
1	CH_2Cl_2	69	5.2:1	86
2	CHCl_3	63	12.3:1	92
3	CCl_4	29	19.6:1	92
4	toluene	51	19.8:1	92
5	hexanes	24	5.1:1	78
6	pentanes	17	4.3:1	76
7	cyclohexane	20	8.3:1	81
8	THF	56	6.7:1	92
9	dioxane	64	14.5:1	92

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by correlation to the natural product.

The optimal reaction parameters for the addition of furan **21** into methyl ester aldehyde **21** employ trifluoromethanesulfonic acid (TfOH) as the co-catalyst in chloroform. When the concentration of the system was decreased from 0.5M to 0.1M at $-20\text{ }^\circ\text{C}$, the diastereoselectivity and enantioselectivity increased. These conditions ultimately provided an efficient reaction with superior levels of diastereo- and enantioselectivity (eq. 14).



iii. Completion of 5-*epi*-spiculisporic acid.

After the successful enantioselective synthesis of the vinylogous Michael adduct **20-*epi***, completion of the synthesis required olefination of the aldehyde, hydrogenation of the olefins, and deprotection of the methyl esters to afford the natural product. Although the olefination seemed to be a straightforward proposal, initial studies showed that the olefination product was quite elusive. It appears that the aldehyde is in a sterically protected environment, as larger reagents like Wittig reagents (octyl or methyl) and Julia-Kocienski phenyl-sulfone reagents²⁸ were unsuccessful (Fig. 11).

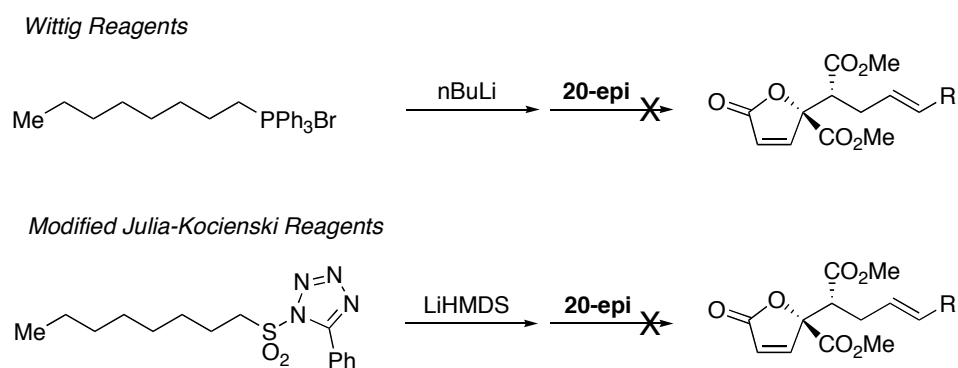


Figure 11. Unsuccessful strategies for olefination.

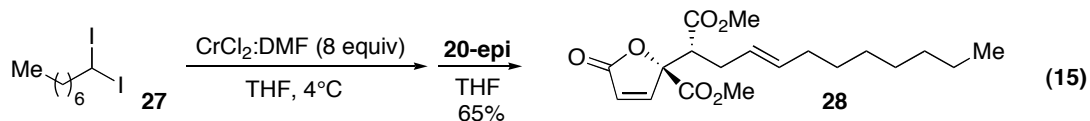
Takai and co-workers reported an olefination using 1,1-diiodoalkanes in the presence of chromium(II) to effect alkene formation.²⁹ 1,1-diiodooctane (**27**) was synthesized by literature procedure.¹ Takai olefination under standard conditions³⁰ gave desired product **28**, although the reaction was inefficient giving no more than 30% yields.

²⁸ Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett*. **1998**, 26.

²⁹ Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 953.

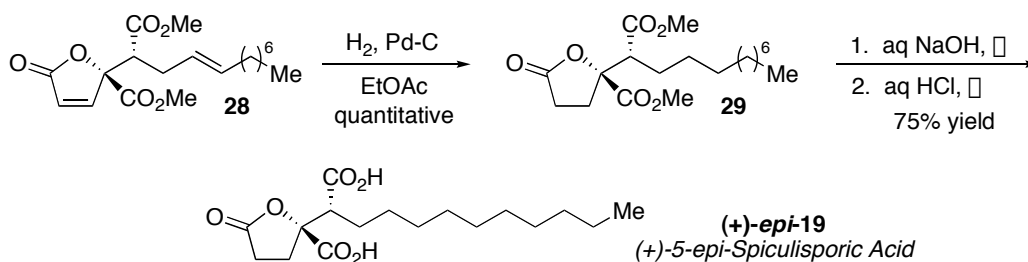
³⁰ (a) Martinez, A. G.; Alvarez, R. M.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *Synthesis* **1987**, 49. (b) Martinez, A. G.; Alvarez, R. M.; Gonzalez, S. M.; Subramanian, L. R.; Conrad, M. *Tetrahedron Lett.* **1992**, *33*, 2043.

An increase in temperature and equivalents of chromium quickly revealed a more efficient system to afford the olefinated product **28** in a 65% isolated yield (eq. 15).



Completion of the synthesis is outlined in scheme 3. Hydrogenation of both olefins of butanolide **28** proceeded smoothly in ethyl acetate at room temperature to afford butanolide **29**. Finally, saponification of the esters in the system (including the butanolide) followed by selective reclosure of the butanolide under acidic conditions provided good yield of the product. However, the final product was determined to be (+)-5-*epi*-spiculisporic acid [(+)-*epi*-**19**], as all of the characterization data was similar to the natural product, but significant differences in the chemical shifts in the ^1H and ^{13}C NMRs were observed.

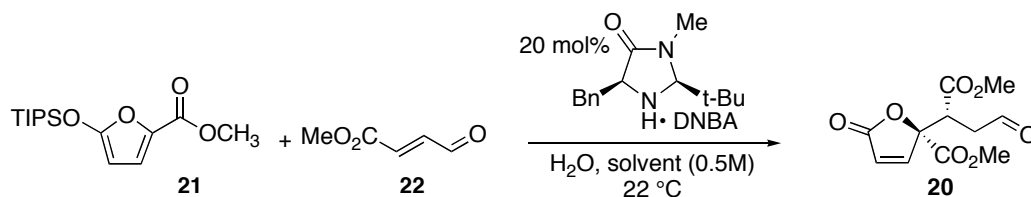
Scheme 3. Completion of (+)-5-*epi*-spiculisporic acid.



iv. Reassessment of the Organocatalytic Step.

In the initial synthesis of **20-epi**, it was demonstrated that the effect of the solvent on the diastereoselectivity of the reaction was critical (Table 6).

Table 6. Examination of solvents in the presence of weaker acidic co-catalysts.



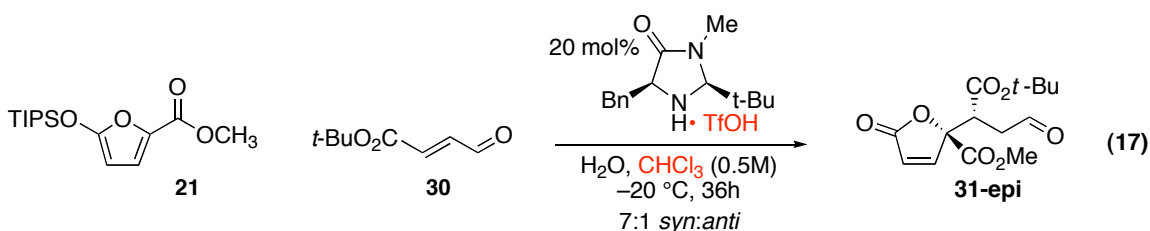
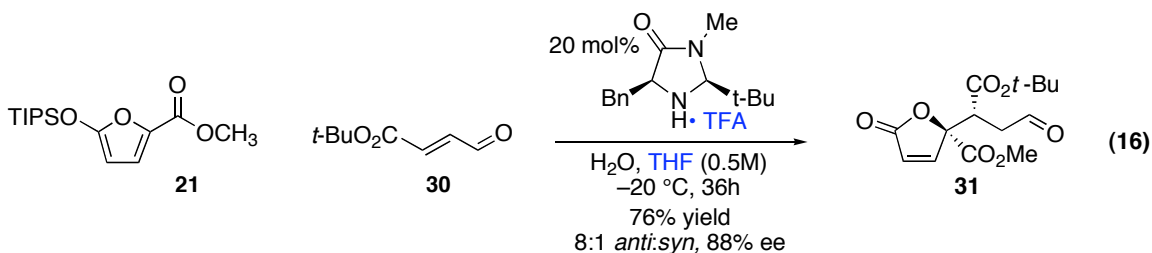
Entry	Solvent	conversion (%)	<i>anti:syn</i>	% ee ^{a,b}
1	CH ₂ Cl ₂	30	1:1.3	33
2	CHCl ₃	14	1:1.1	12
3	CCl ₄	10	1:2.0	15
4	toluene	16	1:1.2	34
5	hexanes	4	1:1.4	41
6	pentanes	2	1:2.0	44
7	THF	31	2.0:1	28
8	dioxane	43	3.0:1	−3.2
9	CH ₃ CN	30	1.1:1	20
10	Et ₂ O	30	2.4:1	33
11	DMF	24	1:1.3	−11
12	MeOH	27	1.4:1	49
13	DMSO	15	1.5:1	−2.3
14	CH ₃ NO ₂	41	1:1.3	53

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by correlation to the natural product.

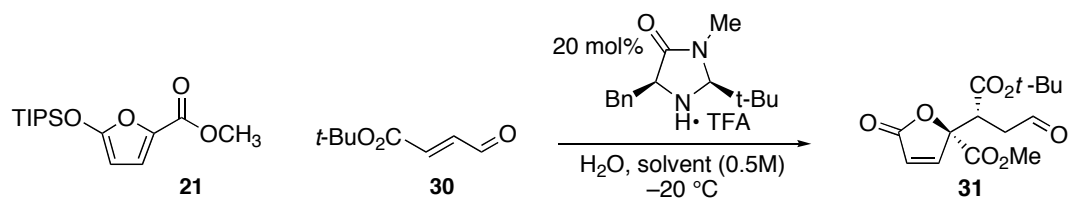
The opposite sense of diastereoiduction was obtained with reasonable enantioselectivities in the presense of weaker acids (Table 4, entries 4–8). After reexamining weaker acid co-catalysts under a variety of conditions, the diastereoselectivity in the *anti* direction remained poor. More polar solvents, however,

increased the bias toward the *anti* diastereomer while maintaining a noticeable level of enantioselectivity (Table 6, entries 7, 10, and 12, 2:1 to 3:1 *anti:syn*).

To test the effect of the steric contribution of the enal on the incoming trajectory of the nucleophile, the Michael acceptor was then changed from the methyl ester aldehyde **22** to the *tert*-butyl ester aldehyde **30**. The first reaction with enal **30** in THF with TFA as the co-catalyst gave the highest preference for the *anti* diastereomer seen thus far (eq. 16, 8:1 d.r.). Interestingly, under the previous optimal conditions, a 7:1 ratio of *syn* to *anti* was still observed (eq. 17). A postulated explanation of this is provided in section III of this chapter.



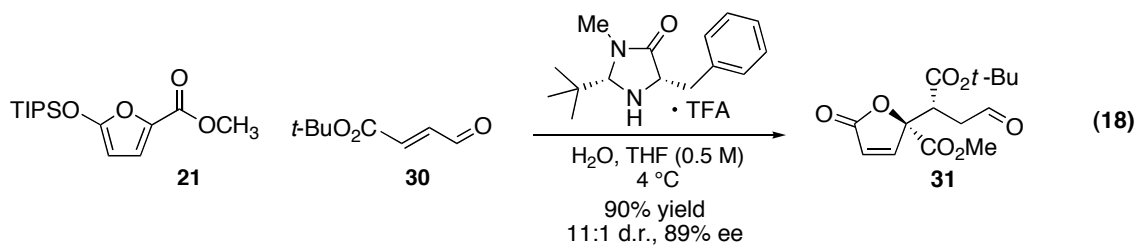
A solvent screen with enal **30** showed that while chlorinated solvents provided selectivity for the *syn* product (Table 7, entries 1 and 2), more polar solvents like THF and ether imparted high levels of *anti* selectivity (Table 7, entries 3 and 5).

Table 7. Effect of polar solvents on diastereoselectivity of adduct 31.

Entry	Solvent	conversion (%)	<i>anti:syn</i>	% ee ^{a,b}
1	CHCl ₃	34	1:2.5	35
2	CH ₂ Cl ₂	49	1:1.1	40
3	THF	50	9.4:1	86
4	dioxane	23	5.7:1	87
5	Et ₂ O	43	8.2:1	83
6	CH ₃ CN	70	3.1:1	78
7	MeOH	44	4.5:1	84
8	EtOH	70	5.3:1	85
9	DMSO	29	3.3:1	65
10	H ₂ O	19	1.9:1	77

^a Stereoselectivities determined by chiral GLC analysis. ^b Absolute and relative configuration assigned by correlation to the natural product.

The optimal conditions for the *anti* selective vinylogous Mukaiyama-Michael addition of siloxyfuran **21** are given in equation 18. After increasing the temperature and concentration of the reaction, the *anti* adduct **31** was isolated in a 90% yield with good levels of diastereo- and enantioselectivity (11:1 d.r., 89% ee).

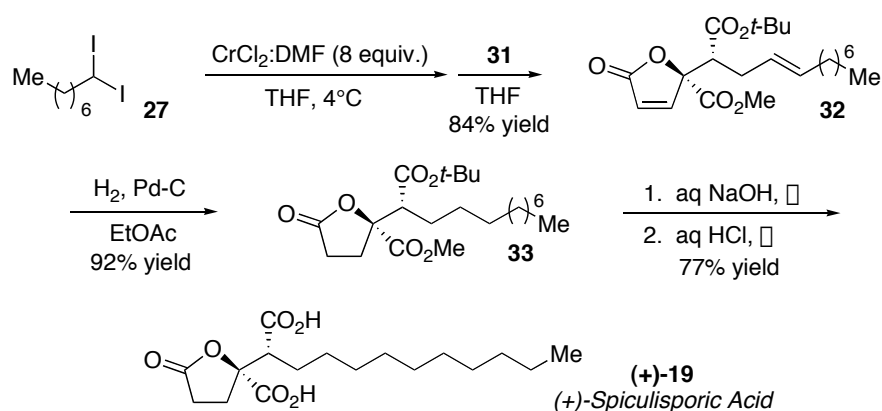


v. Completion of spiculisporic acid.

The remainder of the synthesis of spiculisporic acid was completed as described

above (*vide infra*). Takai olefination and hydrogenation was followed by saponification and acid-assisted reclosure of the butanolide to furnish the correct diastereomer of the natural product **(+)-19** (Scheme 4), with 54% overall yield for the five-step linear sequence. However, the optical rotation of the synthetic material was opposite to that observed for the natural product. Thus, the same sequence reported here was repeated with the opposite enantiomer of the imidazolidinone catalyst to prepare the matching enantiomeric series of (–)-spiculisporic acid.³¹

Scheme 4. Completion of (+)-spiculisporic acid.



IV. Proposed Explanation for the Change in Diastereoselectivity.

As shown in equations 14 and 18, by altering the conditions of the organocatalytic Mukaiyama-Michael reaction of siloxyfuran **21** into □,□-unsaturated aldehydes, the sense of diastereoinduction can be completely turned over to favor either the *anti* or *syn*

³¹ The Supporting Information reports the enantiomeric series for (–)-spiculisporic acid (–)-5-*epi*-spiculisporic acid using (*S,S*)-*tert*-butyl benzyl imidazolidinone catalyst (*S,S*)-**14**.

diastereomer with high levels of enantioselectivity using a single enantiomer of the imidazolidinone catalyst **14**. It is impossible to aver the exact reason; however, a look at the different possible transition states may give insight for this diastereodivergence.

i. Approach of the nucleophile onto the iminium system.

It has been proposed in the literature that Mukaiyama-Michael additions onto an α,β -unsaturated system can occur through an open transition state, preferably through an antiperiplanar approach of the nucleophile.² As shown in figure 12, there are six possible approaches of siloxyfuran **21** onto the iminium system.

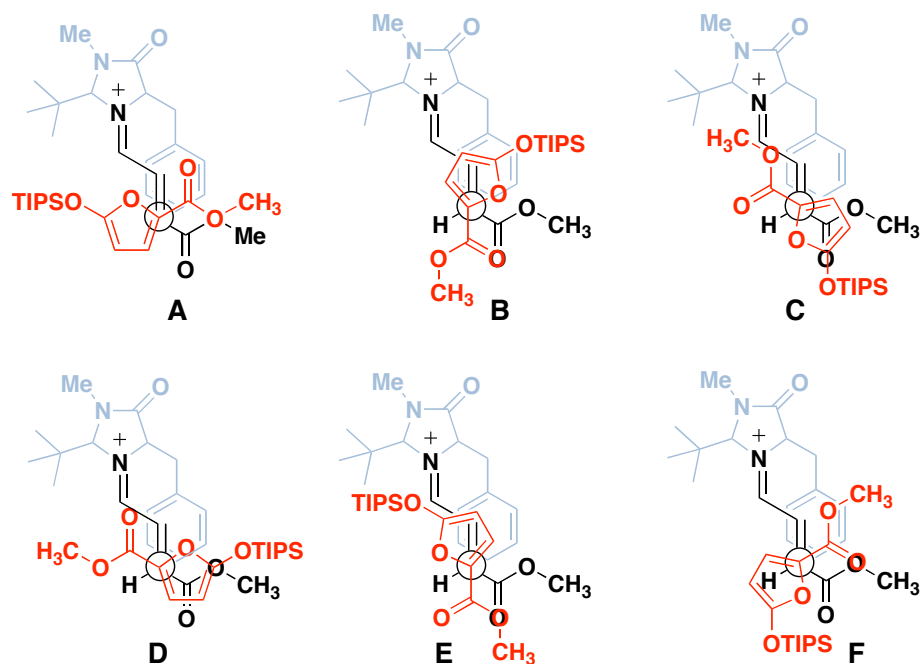
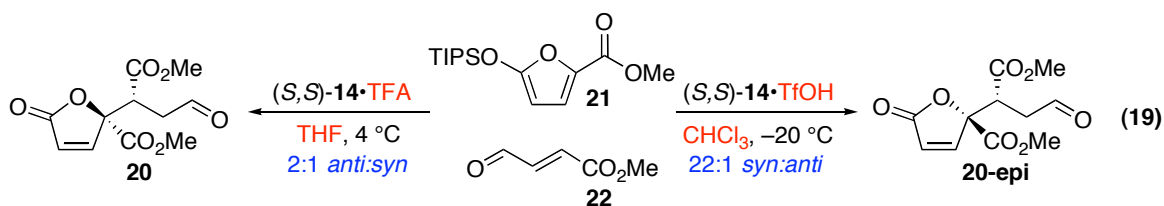


Figure 12. Possible transition states for organocatalytic Mukaiyama-Michael.

Transition states **A–C** will provide the *syn* diastereomer of the butenolide adduct while **D–F** provide the *anti* diastereomer. The furan moiety may prefer to be oriented over the hydrogen of the enal in order to avoid a steric interaction in the transition state. This would suggest that transition states **A** and **F** could be contributing to the preferred orientation. For the following analyses of each reaction under both sets of optimized conditions (TfOH/CHCl₃ or TFA/THF), only transition states like **A** and **F** will be presented.

ii. *Mukaiyama-Michael into methyl-4-oxobutenoate (22).*



As shown in equation 19, the addition of siloxyfuran **21** proceeded with excellent levels of diastereocontrol to favor the *syn* product **20-epi B** (22:1 *syn:anti*). When a less acidic co-catalyst was employed in combination with a more polar solvent, the *anti* diastereomer **20** was slightly favored (2:1 *anti:syn*).

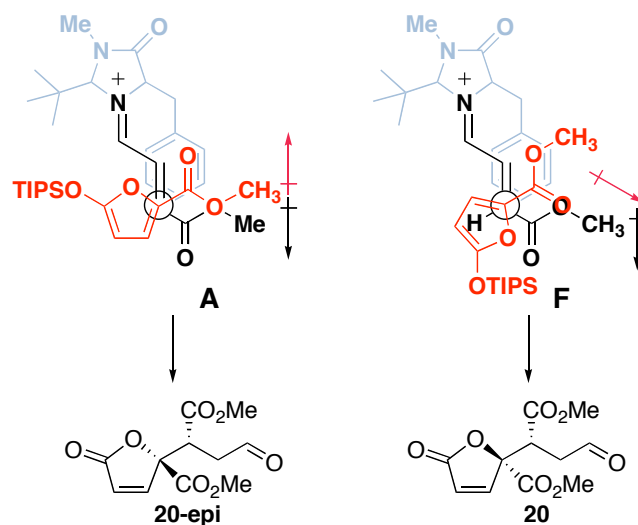
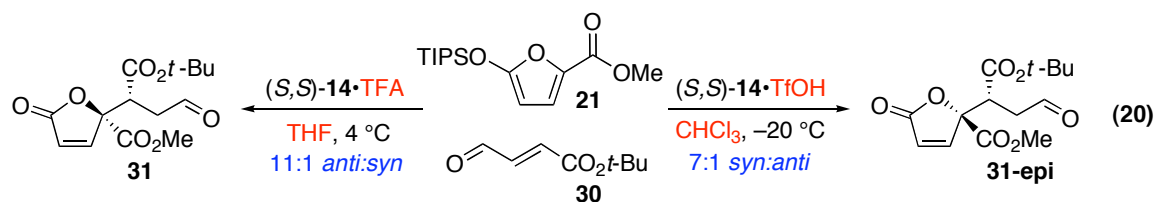


Figure 13. Dipole interactions in the transition state.

Transition state **A** (Fig. 13) may be preferred because it (i) minimizes steric interactions, (ii) has the nucleophile arranged in an antiperiplanar fashion onto the iminium, and (iii) minimizes the net dipole of the siloxyfuran (Fig. 12, red dipole arrow) and the iminium (Fig. 12, black dipole arrow). A non-polar solvent should reinforce this propensity to minimize the dipoles, whereas a more polar solvent should be more accommodating to a net charge. It is hypothesized that the non-polar solvent CHCl_3 favors transition state **A**, thus explaining the formation of the *syn* product **20-epi** with high diastereoselection (eq. 19). A more polar solvent like THF, meanwhile, could provide stabilization for transition state **F**, thus resulting in a slight preference for the *anti* product **20** that is observed.

iii. *Mukaiyama-Michael into tert-butyl-4-oxobutenoate (30).*



As shown in equation 20, the addition of siloxyfuran **21** to *tert*-butyl enal **30** proceeded with moderate levels of diastereocontrol to deliver the *syn* product **31-epi** when a TfOH/CHCl₃ co-catalyst/solvent combination was used (7:1 *syn:anti*). The same conditions with the methyl ester enal **22** provided a much larger preference for the *syn* product (eq. 19, 22:1 *syn:anti*). Conversely, when a less acidic co-catalyst was employed with a more polar solvent, the *anti* diastereomer **20** was now favored with good levels of diastereoselectivity (eq. 20, 11 to 1 *anti:syn*).

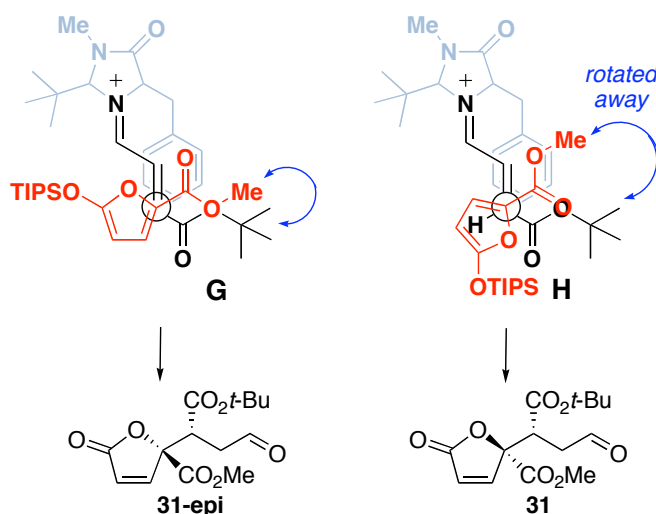
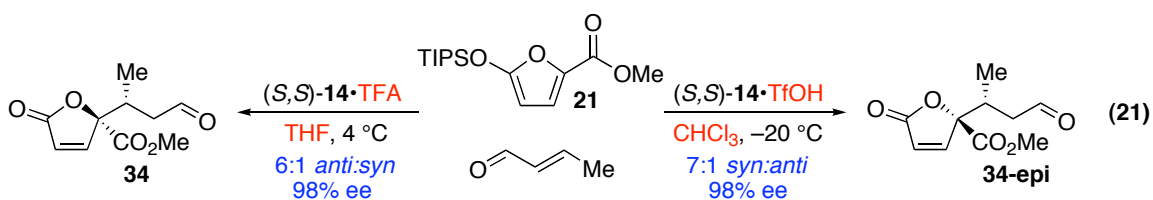


Figure 14. Transition state with *tert*-butyl-4-oxobutenoate (**30**).

While transition state **G** in figure 14 positions the furan over the empty quadrant of the iminium ion in an antiperiplanar orientation, the increased steric bulk of the *tert*-butyl group of the ester of the enal **30** may introduce an unfavorable interaction with the methyl ester of siloxyfuran **21**. This interaction could alter the nucleophile to approach via transition state **H** in order to minimize steric interaction between the methyl and *tert*-butyl ester groups.

iv. *Mukaiyama-Michael into crotonaldehyde.*

In order to test the hypothesis that the transition state for the Mukaiyama-Michael addition of this specific siloxyfuran **21** is influenced by the dipole interactions of the reaction partners, the 1,4-vinylogous Mukaiyama-Michael addition of nucleophile **21** into crotonaldehyde was performed (eq. 21).



The developed conditions provided offer access to both diastereomers of the butenolide products (**34** and **34-epi**, 6:1 and 1:7 *anti:syn*).

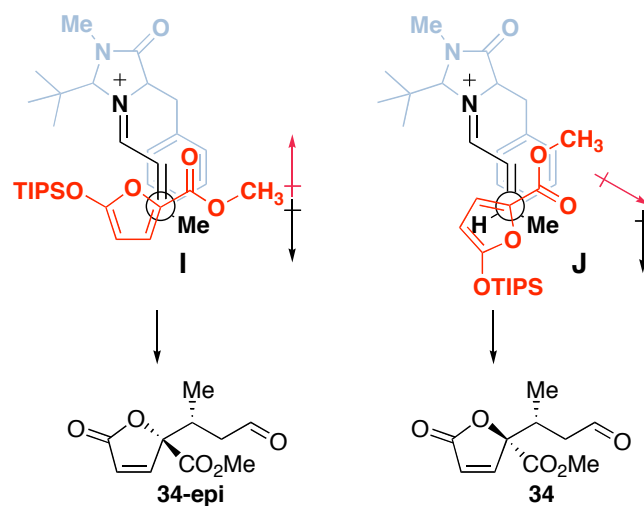


Figure 15. Electronic contributions to the transition state.

Transition state **I** (Fig. 15) could be favored in a non-polar solvent like CHCl_3 in order to minimize the dipole interactions of the transition state. THF may proceed through transition state **J** because it can accommodate this net charge, thus giving the *anti* product. Because these two reactions in equation 21 do not differ with respect to the steric demands of the enal, this may suggest that electronic contributions to the Mukaiyama-Michael reaction may help to control the diastereoselection of the reaction.

Interestingly, when the methyl ester group on the furan was replaced with a methyl group and subjected to the optimized $\text{TfOH}/\text{CHCl}_3$ or TFA/THF conditions, the reaction offered no sense of diastereocontrol (Fig. 16). This makes the 5-methyl ester siloxyfuran **21a** a unique substrate for the organocatalytic Mukaiyama-Michael addition

due to its ability to provide access to either the *anti* or *syn* butenolide products with excellent levels of diastereo- and enantioselectivity using a single catalyst.

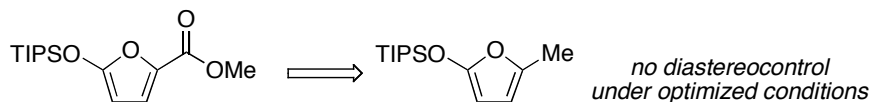


Figure 16. 5-Methyl ester versus 5-methyl siloxyfuran.

v. *Another transition state consideration.*

In a recent study, Houk and co-workers calculated the relative energies of the transition structures for the organocatalytic conjugate additions of pyrroles and indoles into an α,β -unsaturated iminium system.³² When pyrrole was employed as a π -donor, it preferably reacted through a closed Diels-Alder-like transition state with an *endo* or *exo* orientation; these two transition structures had a small energetic difference of 0.3 kcal/mol.

It is possible that a Diels-Alder-like geometry may be operative in the organocatalytic vinylogous Mukaiyama-Michael reaction. The analogous transition states for the conjugate addition of siloxyfuran **21** are illustrated in figure 17. The *endo* orientation leads to **34-epi**, which was observed when the TfOH/CHCl₃ co-catalyst/solvent combination was used, and the *exo* orientation leads to **34**, which was

³² Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Cat.* **2004**, *346*, 1175.

observed under the TFA/THF conditions. The reason for co-catalyst/solvent-mediation of either transition state structure is indeterminable.

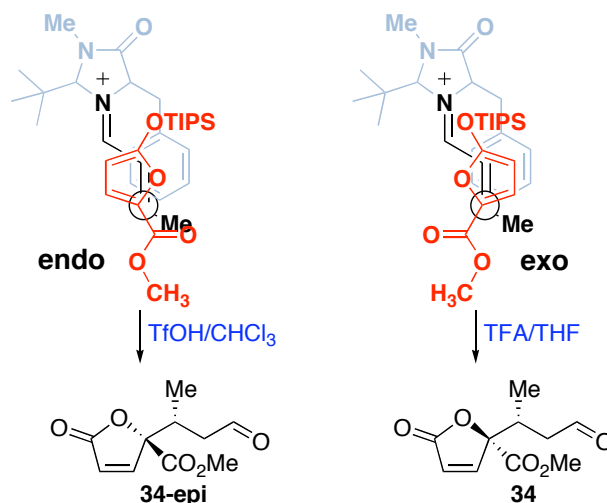


Figure 17. Possible endo and exo transition states.

Conclusion

In summary, this work further demonstrates the value of iminium catalysis in asymmetric synthesis. The first enantioselective organocatalytic vinylogous Mukaiyama-Michael addition using simple α,β -unsaturated aldehydes is presented herein. This novel methodology was highlighted with the total syntheses of spiculisporic acid (**19**) and its diastereomer *5-epi*-spiculisporic acid (**19-epi**). While the natural *anti* diastereomer **19** is abundant in nature, its epimer **19-epi** is a butanolide that is not readily available via fermentation protocols or derivatization of the naturally occurring metabolite. The use of organocatalysis to access both diastereomers of the natural product in a rapid manner makes this the most efficient enantioselective syntheses of these natural products to date.

Supporting Information.

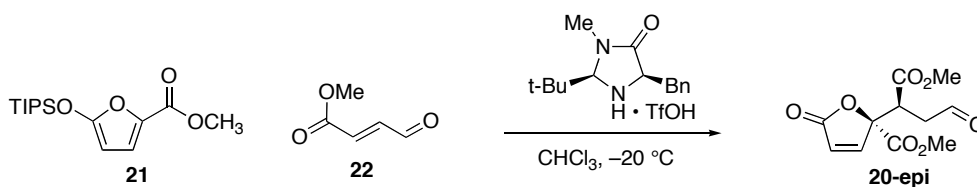
General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.³³ Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.³⁴ Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by KMnO₄ stain.

¹H and ¹³C NMR spectra were recorded on a Mercury 300 Spectrometer (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals (CDCl₃ = 7.26 ppm, C₆D₆ = 7.16 ppm, D₆-acetone = 2.05 ppm). Data for ¹H NMR are reported as follows: chemical shift (□ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ¹³C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). Mass spectra were obtained from the California Institute of Technology mass spectral facility. Gas chromatography (GC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detector using a Bodman Chiraldex □-DM

³³Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press, Oxford, 1988.

³⁴Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

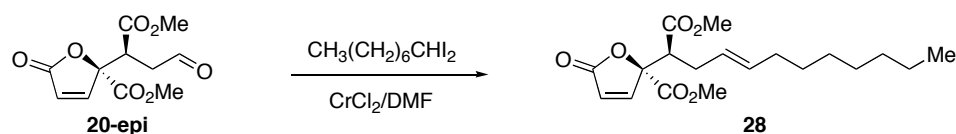
(30 m x 0.25 mm) column. High pressure liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using either a Chiralcel OD-H column (25 cm) and OD guard (5 cm) or a Chiralcel AD column (25 cm) and AD guard (5 cm) as noted. Optical rotations were recorded on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in $10^{-1} \text{ dg cm}^2 \text{ g}^{-1}$; concentration (c) is in g/100 mL.



(2*R*,1'*R*)-2-(1'-Methoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-

carboxylic acid methyl ester (20-epi). 4-Oxobut-2-enoic acid methyl ester (**22**) (574 mg, 5.03 mmol) was added to a stirring solution of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one [(*S,S*)-**14**] (82.6 mg, 0.335 mmol), trifluoromethanesulfonic acid (30 μ L, 0.335 mmol), and distilled water (60 μ L, 3.35 mmol) in CHCl_3 (16.8 mL, 0.1 M) at room temperature. The reaction mixture was cooled to -20°C . 5-Triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester (**21**) (500 mg, 1.68 mmol) was added in 1 mL CHCl_3 . The reaction mixture was stirred for 40 h, filtered over a silica plug, and concentrated. After silica gel chromatography, aldehyde **20-epi** was isolated as a pale yellow solid after reconcentration from hexanes (278 mg, 65% yield, 22:1 d.r., 97% e.e.). IR (film): 3103, 2956, 2849, 1783, 1739, 1603, 1437, 1247, 1189, 1086, 1031, 917.8, 820.2 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.72 (s, 1H, **CHO**), 7.48 (d, $J = 5.4$ Hz, 1H, **CH=CH**), 6.20 (d, $J = 5.4$ Hz, 1H, **CH=CH**), 3.94 (dd, $J = 7.2, 4.8$ Hz, 1H, **CHCO₂CH₃**), 3.80 (s, 3H, **CO₂CH₃**), 3.73 (s, 3H, **CO₂CH₃**), 3.11 (dd, $J = 19.2, 7.5$

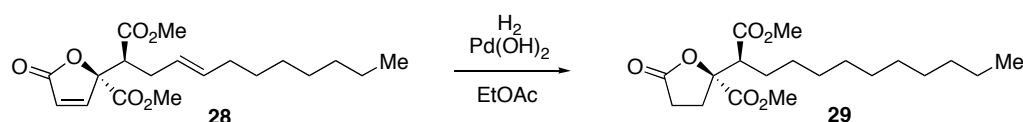
Hz, 1H, CHH-CHO), 2.55 (dd, $J = 18.6, 4.8$ Hz, 1H, CHH-CHO); ^{13}C NMR (75 MHz, CDCl_3) δ 198.1, 170.5, 169.4, 166.9, 153.8, 122.9, 88.9, 53.8, 53.3, 43.5, 39.9; HRMS (EI+) exact mass calculated for $(\text{C}_{11}\text{H}_{12}\text{O}_7)$ requires m/z 256.0583, found m/z 256.0576. $[\alpha]_D = -124.0$ ($c = 0.97$, CHCl_3). The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex β TA (155 °C, 1.0 mL/min); (2*R*,1'*R*) isomer $t_r = 62.8$ min, (2*S*,1'*S*) isomer $t_r = 58.4$ min, minor (2*S*,1'*R*) and (2*R*,1'*S*) isomers $t_r = 53.4, 55.0$ min.



(2*R*,1'*R*)-2-(1'-Methoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-

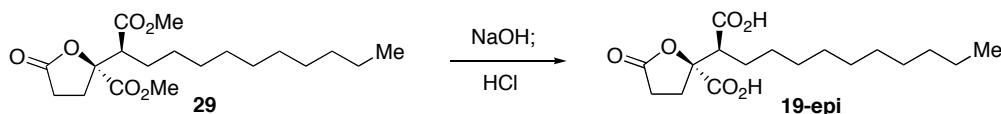
carboxylic acid methyl ester (28). Chromous chloride (383 mg, 3.12 mmol) and *N,N*-dimethyl formamide (243 μL , 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $\text{CrCl}_2:\text{DMF}$ complex. 1,1-Diiodooctane (287 mg, 0.780 mmol) and aldehyde **20-epi** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF. TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. Undecenyl methyl ester **28** was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2922, 2852, 1777, 1742, 1724, 1439, 1260, 1186, 1101, 968.8, 916.5, 833.0 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.25 (d, $J = 5.4$ Hz, 1H, CH=CH), 6.00 (d, $J = 5.4$ Hz, 1H, CH=CH), 5.22 (dt, $J = 15.3, 6.6$ Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 5.09 (dt, $J = 15.3, 6.6$ Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 3.58 (s, 3H,

CO₂CH₃), 3.50 (s, 3H, CO₂CH₃), 3.12 (dd, $J = 8.1, 4.8$ Hz, 1H, CHCO₂CH₃), 2.18 (m, 1H, CHHCH=CH), 2.03 (m, 1H, CHHCH=CH), 1.73 (dt, $J = 6.9, 6.0$ Hz, 2H, CH=CHCH₂), 1.03 (m, 10H, (CH₂)₅), 0.66 (t, 3H, $J = 6.6$ Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 170.2, 167.4, 153.3, 134.5, 125.3, 122.8, 89.6, 53.7, 52.5, 50.1, 32.7, 32.0, 29.5, 29.4, 29.3, 29.3, 22.9, 14.3; HRMS (EI/CH₄) exact mass calculated for (C₁₉H₂₈O₆) requires m/z 352.1886, found m/z 352.1881. $[\alpha]_D = -70.0$ ($c = 1.0$, CHCl₃).

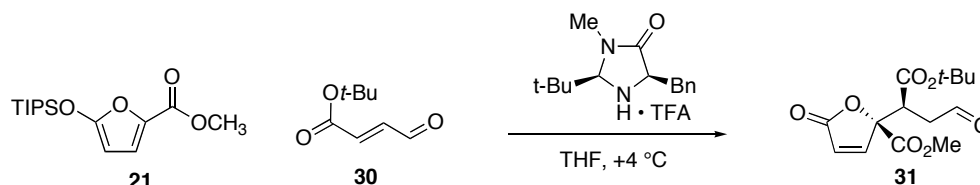


(2*R*,1'*R*)-2-(1'-Methoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (29). A 25 mL round bottom flask equipped with a magnetic stir bar and containing undecenyl methyl ester **28** (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with EtOAc (2.8 mL, 0.1 M). The system was evacuated and purged with H₂ gas three times. The reaction was stirred at ambient temperature under a hydrogen atmosphere until TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford (–)-epi-spiculisporic acid methyl ester **29** as a clear oil after concentration (101 mg, quantitative yield). IR (film): 2955, 2926, 2855, 1796, 1740, 1456, 1436, 1269, 1230, 1165, 1060, 985.5, 896.9 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.79 (s, 3H, CO₂CH₃), 3.70 (s, 3H, CO₂CH₃), 3.11 (dd, $J = 10.8, 3.3$ Hz, 1H, CHCO₂CH₃), 2.60 (m, 4H, CH₂CH₂CO₂), 1.77 (m, 1H, CHCHH(CH₂)₈), 1.56 (m, 1H, CHCHH(CH₂)₈), 1.25 (m, 16H, (CH₂)₈), 0.87 (t, 3H, $J = 6.6$ Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 172.2, 170.6, 86.5, 60.7, 53.5, 52.3, 50.4, 32.1, 29.8, 29.8, 29.6,

29.6, 28.2, 28.1, 27.5, 27.3, 23.0, 14.4; HRMS (EI/CH₄) exact mass calculated for (C₁₉H₃₃O₆)⁺ requires m/z 357.2277, found m/z 357.2273. $[\alpha]_D = +10.3$ (c = 1.0, CHCl₃).



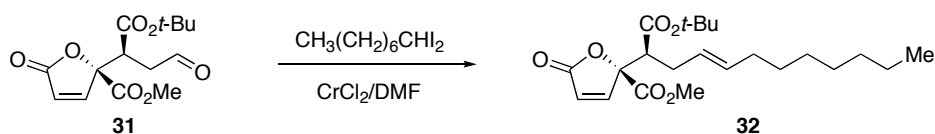
(-)-Epi-spiculisporic acid (19-epi). Dimethyl ester **29** (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 °C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 °C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na₂SO₄) and recrystallized from hot water to yield (-)-epi-spiculisporic acid **19-epi** as a white solid (20 mg, 76% yield). IR (film): 2917, 2850, 1801, 1709, 1466, 1420, 1182, 1133, 1055, 953.8 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 3.03 (dd, J = 9.3, 4.2 Hz, 1H, CHCO₂H), 2.57 (m, 4H, CH₂CH₂CO₂C), 1.66 (m, 2H, CHCH₂(CH₂)₈), 1.30 (m, 16H, (CH₂)₈), 0.90 (t, J = 6.6 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CD₃OD) δ 178.4, 175.4, 173.8, 88.0, 51.9, 33.3, 30.9, 30.9, 30.7, 30.7, 30.7, 29.5, 29.1, 29.0, 28.3, 24.0, 14.7; HRMS (FAB+) exact mass calculated for (C₁₇H₂₉O₆)⁺ requires m/z 329.1964, found m/z 329.1962. $[\alpha]_D = -6.3$ (c = 0.75, EtOH).



(2*S*,1'*R*)-2-(1'-*tert*-Butoxycarbonyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-

carboxylic acid methyl ester (31). 4-Oxobut-2-enoic acid *tert*-butyl ester (**30**) (469 mg, 3.00 mmol) was added to a stirring solution of the (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one TFA salt [(*S,S*)-**14**] (72.3 mg, 0.200 mmol), and distilled water (36 μ L, 2.00 mmol) in THF (8 mL) at room temperature. The reaction mixture was cooled to 4 °C. 5-Triisopropylsilyloxy-furan-2-carboxylic acid methyl ester (**21**) (300 mg, 1.01 mmol) was added in 2 mL of THF. The reaction mixture was stirred at 4 °C for 43 h, filtered over a pad of silica gel, and concentrated. After silica gel chromatography, aldehyde **31** was isolated as a yellow solid after reconcentration from hexanes (268 mg, 90% yield, 11:1 d.r., 89% e.e.). IR (film): 2918, 2852, 1775, 1733, 1720, 1458, 1366, 1239, 1145, 1108, 1021, 828.8 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.69 (s, 1H, **CHO**), 7.60 (d, J = 5.7 Hz, 1H, **CH=CH**), 6.17 (d, J = 6.3 Hz, 1H, **CH=CH**), 3.81 (dd, J = 9.9, 4.5 Hz, 1H, **CHCO₂C(CH₃)₃**), 3.79 (s, 3H, **CO₂CH₃**), 2.92 (dd, J = 18.0, 9.3 Hz, 1H, **CHH-CHO**), 2.58 (dd, J = 18.6, 3.9 Hz, 1H, **CHH-CHO**), 1.39 (s, 9H, **C(CH₃)₃**); ^{13}C NMR (75 MHz, CDCl_3) δ 198.0, 170.5, 168.0, 166.8, 153.9, 122.3, 88.6, 83.4, 54.0, 45.0, 40.8, 28.0 (3); HRMS (CI) exact mass calculated for ($\text{C}_{14}\text{H}_{19}\text{O}_7$) requires m/z 299.1131, found m/z 299.1121. $[\alpha]_{\text{D}} = +9.9$ (c = 0.95, CHCl_3). The diastereomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex β -TA (170 °C,

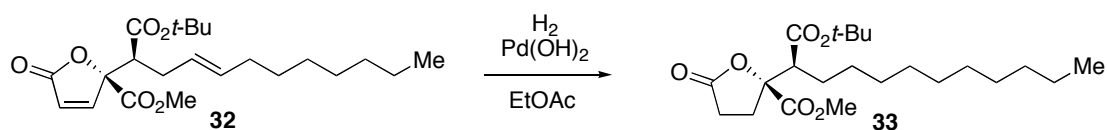
1.0 mL/min); (2*S*,1'*R*)/(2*R*,1'*S*) isomers t_r = 28.2 min, (2*S*,1'*S*)/(2*R*,1'*R*) isomers t_r = 30.3 min. The enantiomeric ratio was determined by HPLC analysis of the 2,2-dimethylpropane acetal, obtained by acetal formation of the aldehyde with 2,2-dimethylpropane diol and paratoluenesulfonic acid, using a Chiralcel OD-H and OD-H guard column (1.5% ethanol/hexanes, 214 nm, 1.0 mL/min); (2*S*,1'*R*) isomer t_r = 19.6 min, (2*R*,1'*S*) isomer t_r = 16.6 min.



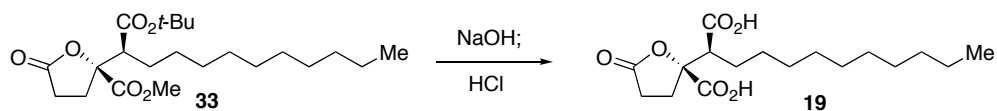
(2*S*,1'*R*)-2-(1'-*tert*-Butoxycarbonyl-undec-3'-enyl)-5-oxo-2,5-dihydrofuran-2-

carboxylic acid methyl ester (32). Chromous chloride (383 mg, 3.12 mmol) and *N,N*-dimethyl formamide (243 μ L, 3.12 mmol) were stirred in anhydrous THF (7.8 mL) under an N_2 atmosphere at room temperature for 1 h to generate the $CrCl_2$:DMF complex. 1,1-Diiodooctane (287 mg, 0.780 mmol) and aldehyde **31** (100 mg, 0.390 mmol) were added in 1.3 mL of anhydrous THF. TLC analysis showed consumption of the aldehyde after 3.5 h. The reaction was quenched with H_2O and the aqueous layer was extracted three times with pentanes. The pentane layers were dried (Na_2SO_4) and concentrated. Undecenyl methyl ester **32** was afforded as a white solid after silica gel chromatography (77 mg, 65% yield). IR (film): 2956, 2928, 2856, 1783, 1740, 1723, 1457, 1437, 1369, 1256, 1156, 1099 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 5.4 Hz, 1H, **CH=CH**), 6.18 (d, J = 5.4 Hz, 1H, **CH=CH**), 5.46 (dt, J = 15.3, 6.6 Hz, 1H, **CH₂CH=CHCH₂**), 5.25 (dt, J = 15.6, 6.6 Hz, 1H, **CH₂CH=CHCH₂**), 3.77 (s, 3H, **CO₂CH₃**), 3.21 (dd, J = 9.6, 4.8 Hz, 1H, **CHCO₂C(CH₃)₃**), 2.20 (m, 2H, **CHCH₂CH=CH**), 1.94 (dt, J = 6.6, 6.0 Hz, 2H,

CH=CHCH₂), 1.41 (s, 9H, CO₂C(CH₃)₃), 1.24 (m, 10H, (CH₂)₅), 0.87 (t, $J = 6.6$ Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 169.7, 167.2, 153.7, 134.5, 124.9, 122.7, 89.4, 82.3, 53.7, 51.2, 32.8, 32.1, 30.7, 29.5, 29.4, 28.2 (3), 23.0, 14.4; HRMS (CI) exact mass calculated for (C₂₂H₃₅O₆)⁺ requires m/z 395.2433, found m/z 395.2428. $[\alpha]_D = -3.9$ ($c = 0.98$, CHCl₃).



(2*S*,1'*R*)-2-(1'-*tert*-Butoxycarbonyl-undecyl)-5-oxo-tetrahydrofuran-2-carboxylic acid methyl ester (33). A 25 mL round bottom flask equipped with a magnetic stir bar and containing undecenyl *tert*-butyl ester **32** (100 mg, 0.284 mmol) and activated palladium on carbon (10 mg) was charged with EtOAc (2.8 mL, 0.1M). The system was evacuated and purged with H₂ gas three times. TLC analysis showed the reaction complete after 4.5 h, at which point the reaction mixture was filtered over a pad of Celite and a pad of silica gel with EtOAc to afford (–)-*epi*-spiculisporic acid methyl ester **33** as a clear oil after concentration (94.0 mg, 92% yield). IR (film): 2957, 2927, 2855, 1797, 1744, 1731, 1460, 1369, 1249, 1169, 1132, 1055 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 3.78 (s, 3H, CO₂CH₃), 2.94 (dd, $J = 10.8, 3.0$ Hz, 1H, CHCO₂C(CH₃)₃), 2.50 (m, 4H, CH₂CH₂CO₂C), 1.73 (m, 1H, CHCHH(CH₂)₈), 1.47 (m, 1H, CHCHH(CH₂)₈), 1.43 (s, 9H, CO₂C(CH₃)₃), 1.23 (m, 16H, (CH₂)₈), 0.85 (t, $J = 6.6$ Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 171.1, 170.8, 86.7, 81.9, 53.2, 51.9, 32.1, 29.8, 29.8, 29.6, 29.6, 29.5, 28.4, 28.3, 28.2 (3), 22.9, 14.4; HRMS (CI) exact mass calculated for (C₂₂H₃₉O₆)⁺ requires m/z 399.2746, found m/z 399.2736. $[\alpha]_D = -21.4$ ($c = 1.1$, CHCl₃).



(-)-Spiculisporic acid (19). *tert*-Butyl ester **33** (28.7 mg, 0.0805 mmol) was taken up in 0.5 mL THF and 1 mL of 4N aqueous NaOH. The biphasic mixture was refluxed at 100 °C for 5.5 h and then cooled to room temperature. The reaction mixture was acidified with 1N aqueous HCl to pH=1. The aqueous layer was extracted four times with EtOAc. The organic layers were concentrated to a white solid. The hydrolyzed intermediate was dissolved in a small amount of THF and 2 mL of 1N aqueous HCl was added. The reaction mixture was refluxed at 100 °C for 3.5 h, after which it was cooled to room temperature and extracted four times with EtOAc. The organic layers were dried (Na_2SO_4) and recrystallized from hot water to yield the title compound **19** as white crystals (20 mg, 76% yield). IR (film): 2919, 2850, 1793, 1778, 1716, 1654, 1559, 1540, 1510, 1458, 1419, 1290, 1182, 927.3 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 3.01 (dd, $J = 10.8, 2.7$ Hz, 1H, CHCO_2H), 2.53 (m, 4H, $\text{CH}_2\text{CH}_2\text{CO}_2\text{C}$), 1.85 (m, 1H, $\text{CHCHH}(\text{CH}_2)_8$), 1.52 (m, 1H, $\text{CHCHH}(\text{CH}_2)_8$), 1.29 (m, 16H, $(\text{CH}_2)_8$), 0.90 (t, $J = 6.6$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, CD_3OD_3) δ 178.3, 175.3, 173.9, 88.1, 52.5, 33.3, 30.9, 30.8, 30.8, 30.7, 30.6, 30.5, 29.2, 29.0, 29.0, 23.9, 14.7; HRMS (FAB+) exact mass calculated for $(\text{C}_{17}\text{H}_{29}\text{O}_6)^+$ requires m/z 329.1964, found m/z 329.1965. $[\alpha]_D = -10.9$ ($c = 0.43$, EtOH). Commercial (-)-spiculisporic acid: $[\alpha]_D = -10.2$ ($c = 1.0$, EtOH). ^1H , ^{13}C , and IR spectra of synthetic **19** were identical to the natural spiculisporic acid.