

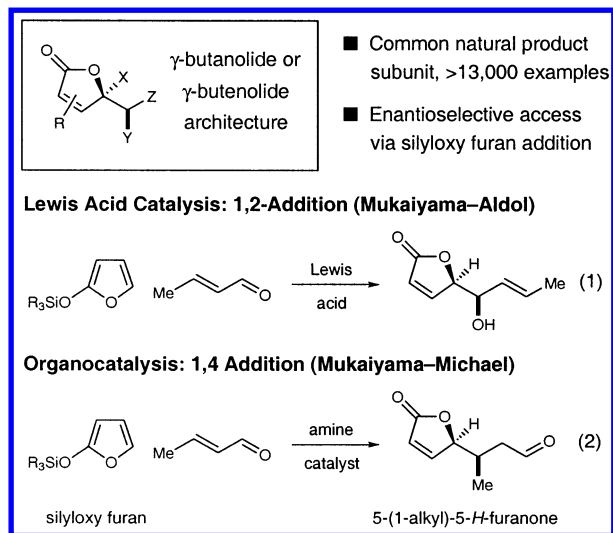
The First Enantioselective Organocatalytic Mukaiyama–Michael Reaction: A Direct Method for the Synthesis of Enantioenriched γ -Butenolide Architecture

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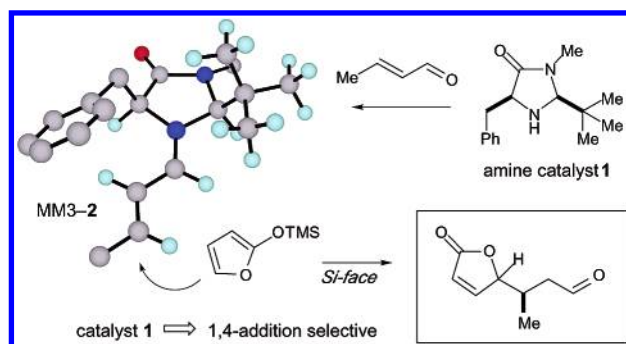
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With representation in over 13,000 natural products,¹ the γ -butenolide synthon has become a valuable architectural platform for the development of new asymmetric methodologies.^{2–5} In this context, the catalytic coupling of silyloxy furans and aldehydes using chiral Lewis acids has emerged as a preeminent strategy for butenolide synthesis (eq 1),⁶ further outlining the broad utility of the Mukaiyama–Aldol transform in asymmetric synthesis.⁷ Surprisingly, however, the analogous 1,4-addition of silyloxy furans to electron deficient olefins (eq 2) has received relatively little attention⁸ despite the numerous examples of 5-(1-alkyl)-5-*H*-furanone stereogenicity found among natural isolates⁹ (e.g., kallolide,¹⁰ pinnatin¹¹). This deficiency in Mukaiyama–Michael technology may arise, in part, from the documented selectivity of metal salts to promote 1,2-formyl activation¹² (eq 1) in preference to 1,4-olefin addition (eq 2) with ambident electrophiles such as α,β -unsaturated aldehydes.^{13,14} In this communication, we reveal that iminium organocatalysis¹⁵ using chiral imidazolidinones has overcome such limitations to provide the first enantioselective Mukaiyama–Michael reaction with simple unsaturated aldehydes. Importantly, this strategically new approach to asymmetric γ -butenolide construction further serves to highlight the complementary mechanistic function of LUMO-lowering iminium and metal catalysis and the chemical utility of enantioselective organocatalysis.¹⁶



Having established the capacity of amine catalysis to provide “nonconventional” chemoselectivity in the asymmetric conjugate addition of pyrroles to enals,^{15d} we sought to determine if this novel mechanistic paradigm might be extended to the Mukaiyama–Michael reaction. As illustrated with the calculated model MM3-2,¹⁷ we anticipated that α,β -unsaturated iminium ions arising from chiral amine **1** might be inert to silyloxy furan 1,2-addition on the basis of steric constraints imposed by the catalyst framework. As such, we assumed that catalyst **1** might partition such π -nucleophiles

toward an unprecedented 1,4-addition manifold while enforcing high levels of enantio- and diastereoselectivity in the carbon–carbon bond-forming event.



Our enantioselective organocatalytic butenolide synthesis was first examined using silyloxy furan **3**,¹⁸ imidazolidinone catalyst **1**, and crotonaldehyde (Table 1). Preliminary studies revealed that the proposed conjugate addition was indeed possible with excellent levels of syn diastereoselectivity and enantiocontrol (entry 1, 10:1 syn:anti, 85% ee); however, catalytic efficiency was poor (31% yield). On the basis of the assumption that imidazolidinone turnover was being inhibited by loss of H₂O from the catalytic cycle (presumably via formation of (TMS)₂O), we next examined the use of protic additives that might competitively scavenge the putative silyl cation intermediate. While a variety of alkyl alcohol additives were found to be productive in this context (entries 2–5), the addition of excess H₂O (2 equivs) provided optimal reaction efficiency (entries 5 and 6, $\geq$ 84% yield) and stereoselectivities at -70°C (entry 6, syn:anti 22:1, 92% ee). The superior levels of asymmetric induction and efficiency exhibited by the amine salt **1**·2,4-dinitrobenzoic acid (DBNA) in CH₂Cl₂–H₂O to afford the stereochemically enriched butenolide (*R*)-**4** in 92% ee prompted us to select these catalytic conditions for further exploration.¹⁹

Experiments that probe the scope of the α,β -unsaturated aldehyde component are summarized in Table 2. There appears to be significant latitude in the steric demands of the β -olefin substituent (entries 1–4, R = Me, Pr, *i*-Pr, Ph) to enable access to a broad variety of 5-(1-alkyl)-5-methyl-furanones (syn:anti 7:1 to 31:1, 84–99% ee). Moreover, variation in the electronic nature of the aldehyde component has apparently little influence on the relative or absolute sense of stereoreduction. For example, optimal levels of asymmetric induction are available with enals that do not readily participate in iminium formation (entry 6, R = CO₂Me, 84% yield, 99% ee), as well as aldehydes that provide stable iminium intermediates (entry 4, R = Ph, 77% yield, 99% ee). In accord with our mechanistic postulate, it is important to note that products arising from 1,2-iminium addition were not observed with all of the aldehydes examined.

Table 1. Organocatalyzed Mukaiyama–Michael Reaction of Silyloxy Furan **3** with Crotonaldehyde

entry	ROH	temp (°C)	time (h)	% yield	syn:anti	% ee ^{a,b}
1	—	−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 single-crystal X-ray analysis.

Table 2. Organocatalyzed Addition of Silyloxy Furan **3** to Representative 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	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 on the basis of nOe analysis.

Significant structural variation in the silyloxy furan system can also be realized (Table 3). Importantly, the reaction appears quite tolerant with respect to the substituent at the furanyl 5-position (entries 1–4, R = H, Me, Et, CO₂Me 90–92% ee). While high levels of *syn*-5,5'-stereogenicity are available in the construction of a wide variety of γ -butenolide systems (entries 1–4, 6), the corresponding anti isomer can also be forged with excellent levels of stereoselectivity via the appropriate selection of cocatalyst and solvent (entry 5, *syn*:anti 1:7, 98% ee, 83% yield). Moreover, the introduction of alkyl substituents at C(3) on the furan ring can also be accommodated without loss in diastereocontrol or enantioinduction (entry 6, *syn*:anti 24:1, 98% ee).

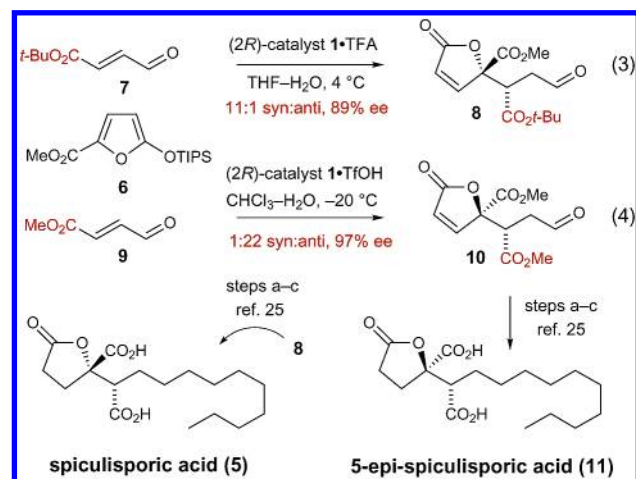
A demonstration of the utility of these enantioselective organocatalytic silyloxy furan additions and the accompanying butenolide products is presented in the four-step synthesis of spiculisporic acid (**5**),^{20,21} a *Penicillium spiculisporem* fermentation adduct²² that has found commercial application as a biosurfactant for (i) metal decontamination processes²³ and (ii) fine polymer production.²⁴ As revealed in eq 3, treatment of *tert*-butyl 4-oxobutenoate (**7**) with 2-triisopropylsilyloxy carbomethoxy furan (**6**) in the presence of 20 mol % of (2*R*,5*R*)-amine salt **1**•TFA in THF provides the stereochemical core of spiculisporic acid **8** in one step, 90% yield, 11:1 *syn*:anti selectivity and 89% ee. Elaboration of butenolide **8** to spiculisporic acid was accomplished in 54% overall yield using a three-step procedure²⁵ (see Supporting Information). Significantly, we have found that treatment of methyl 4-oxobutenoate (**9**) with furan **6** in the presence of the TFOH salt of catalyst **1** provides the opposite sense of diastereoinduction, while retaining excellent levels of enantiocontrol in the production of the *anti*-5,5'-butenolide **10** (eq 4, 22:1 *anti*:*syn*, 97% ee). Importantly, this adduct can also be efficiently converted in three steps to 5-epi-spiculisporic acid (**11**),²⁵ a butenolide that is not readily available via fermentation protocols

Table 3. Organocatalyzed Addition of Representative Silyloxy Furans with Crotonaldehyde

entry	silyloxy furan	product	% yield	syn:anti	% ee ^{a,b}
1	TMSO-2-furan-H		87	8:1	90
2	TMSO-2-methylfuran-Me		80	22:1	92
3	TMSO-2-ethylfuran-Et		83	16:1	90
4	TIPSO-2-methylfuran-CO2Me		86	6:1	98 ^c
5	TIPSO-2-methylfuran-CO2Me		83	1:7	98 ^d
6	2-methyl-5-methyl-2-TMSO-furan-Me		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 **1**•TFA in THF. ^d With 20 mol % catalyst **1**•TFOH in CHCl₃.

or derivatization of the naturally occurring metabolite. Studies to characterize the physical and material properties of 5-epi-spiculisporic acid are now underway.



With regard to the synthetic and operational advantages of the organocatalytic Mukaiyama–Michael, it is important to note that (i) the sense of asymmetric induction observed in all cases was readily anticipated by the previously described computational model MM3-2 and (ii) all of the conjugate additions described herein were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst.

In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of the first enantioselective catalytic Mukaiyama–Michael addition using simple α,β -unsaturated aldehydes. A full account of this survey will be forthcoming.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) This number is based on a survey of the Beilstein database.
- (2) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.
- (3) (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–629. (b) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. In *Advances in Asymmetric Synthesis*; Haassner, A., Ed.; JAI Press: Stamford, 1998; Vol. 3, pp 113–189. (c) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333–1350.
- (4) (a) Larchevêque, M.; Valette, G.; Cuvigny, T.; Normant, H. *Synthesis* **1975**, 256. (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028. (c) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242. (d) Grieco, P. A.; Ohfuné, Y.; Majetich, G. *J. Org. Chem.* **1979**, *44*, 3092. (e) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. (f) Sturm, T.-J.; Marolewski, A. E.; Rezenka, D. S.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039. (g) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583. (h) Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1993**, *126*, 1905. (i) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428. (j) Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic R. N. *Tetrahedron* **2001**, *57*, 583.
- (5) For an elegant approach to the construction of enantioenriched γ -butenolides from epoxides, see: Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456–2457.
- (6) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894. (c) Szlosek, M.; Franck, X.; Figadere, B.; Cave, A. *J. Org. Chem.* **1998**, *63*, 5169–5172. (d) Szlosek, M.; Figadere, B. *Angew. Chem., Int.* **2000**, *39*, 1799.
- (7) For excellent reviews that incorporate this topic, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 29.1. (c) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8. (d) Carreira, E. M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8B2.
- (8) To our knowledge there have only been two reports of enantioselective catalytic Mukaiyama–Michael reactions with silyloxy furans. In both cases, electrophiles were employed that could not participate in 1,2-addition: (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028. (b) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568–570. (c) Desimoni, G.; Fata, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203–10212.
- (9) The Beilstein database reports >200 natural isolates that incorporate the 5-(1-alkyl)-5-*H*-furanone or 5-(1-alkyl)-5-alkyl-furanone structural motif.
- (10) Look, S. A.; Burch, M. T.; Fenical, W.; Zheng, Q. T.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741–5746.
- (11) Rodriguez, A. D.; Shi, J. G.; Huang, S. P. D. *J. Org. Chem.* **1998**, *63*, 4425–4432.
- (12) Metal-mediated silyloxy furan additions to α,β -unsaturated aldehydes are typically highly selective for carbonyl addition, see: (a) von der Ohe, F.; Bruckner, R. *Tetrahedron Lett.* **1998**, *39*, 1909–1910. (b) von der Ohe, F.; Bruckner, R. *New J. Chem.* **2000**, *24*, 659–669.
- (13) To our knowledge there has been only one example of a metal-mediated 1,4-addition of enolsilanes to ambident electrophiles: Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131–4132.
- (14) For examples of enantioselective catalytic Mukaiyama–Michael reactions with electrophiles that cannot readily participate in 1,2-addition, see: (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994–1995. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865–868. (c) Evans, D. A.; Johnston, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649. (d) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142. (e) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (f) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97–100. (g) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921–8924. (h) Bernardi, A.; Karamfilova, K.; Sanguinetti, S.; Scolastico, C. *Tetrahedron* **1997**, *53*, 13009–13026. (i) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028. (j) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165–1170.
- (15) Diels–Alder: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. Nitron cycloaddition: (c) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. Pyrrole substitution: (d) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. Indole substitution: (e) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. Aniline substitution: (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.
- (16) For notable examples of enantioselective organocatalytic reactions, see: Aldol reaction: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Agami, C.; Meyneir, F.; Puchot, C. *Tetrahedron* **1984**, *40*, 1031. (d) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (e) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (f) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. Phase-transfer catalysis: (g) O'Donnell, M. J.; Bennett, W. D.; Wu, S. D. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (h) Corey, E. J.; Bo, Y. X.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (i) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. Epoxidation: (j) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (k) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (l) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (m) Tian, H. Q.; She, X. G.; Shu, L. H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (n) Denmark, S. E.; Wu, Z. C. Baylis–Hillman Reaction (o) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (p) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287. Asymmetric Strecker synthesis: (q) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (r) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (s) Corey, E. J.; Grogan, G. *J. Org. Lett.* **1999**, *1*, 157. Acyl transfer: (t) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. Intramolecular Stetter: (u) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. For an excellent review on enantioselective organocatalysis, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
- (17) A Monte Carlo simulation using the MM3 force-field; Macromodel V6.5.
- (18) Asaoka, M.; Miyake, K.; Takei, H. *Chem. Lett.* **1977**, 167.
- (19) To a 2-dram vial equipped with a magnetic stir bar and charged with (2S,5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one was added solvent, 2,4-dinitrobenzoic acid and aldehyde, and then it was placed in a bath at appropriate temperature. The solution was stirred for 10 min before the addition of silyloxy furan substrate in one portion. The resulting solution was stirred at a constant temperature until the reaction was determined to be complete by a GLC conversion assay using dibenzyl ether as an internal standard. The reaction mixture was then transferred cold through a silica gel plug with ethyl acetate into a flask and carefully concentrated in vacuo. The resulting residue was purified by silica gel chromatography (solvents noted) and fractions carefully concentrated in vacuo to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.
- (20) Inoue, K. *Fureguransu Janaru* **1983**, *11*, 53–55.
- (21) Total syntheses of spiculisporic acid: Brandaenge, S.; Dahlman, O.; Lindqvist, B.; Maahlen, A.; Moersch, L. *Acta Chem. Scand., Ser. B* **1984**, *10*, 837–844.
- (22) (a) Birkinshaw, J. H.; Raistrick, H. *Biochem. J.* **1934**, *228*, 828–836. (b) Asano, M.; Kameda, Y. *J. Pharm. Soc. Jpn.* **1941**, *61*, 80–86.
- (23) Pekdemir, T.; Tokunaga, S.; Ishigami, Y.; Hong, H.-J. *J. Surfactants Detergents* **2000**, *3*, 43–46.
- (24) Yamazaki, S.; Suzuki, H.; Ishigami, Y. *Kagaku Gijutsu Hokoku* **1988**, *83*, 125–133.
- (25) (a) $\text{CH}_3(\text{CH}_2)_6\text{CHI}_2$, $\text{CrCl}_2\cdot\text{DMF}$, THF. (b) Pd/C, H_2 , EtOAc. (c) 4 N NaOH, 100 °C then adjusted to pH = 1 with 1 N HCl, 100 °C.

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