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Highly Diastereoselective Michael Addition of α-Hydroxy Acid Derivatives and Enantioselective Synthesis of (+)-Crobarbatic Acid

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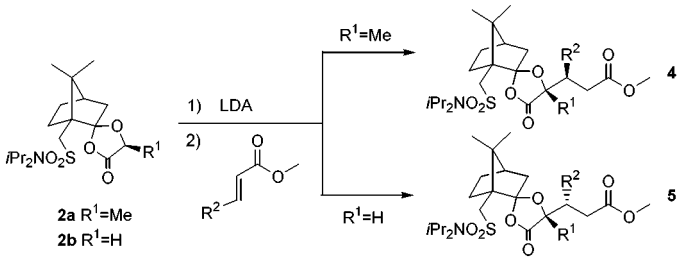
ABSTRACT



Michael addition of enolates of 2a and 2b to α,β-unsaturated esters took place selectively on different faces (*Si* and *Re*, respectively) of the double bond to give the corresponding products 4 and 5, respectively, with >98% de. Subsequent hydrolysis of these Micheal adducts gives 3,4-disubstituted γ-lactones with high enantiomeric excesses.

The Michael addition reaction is one of the most important processes for C−C bond formation in organic synthesis.[1] A number of methods for asymmetric Michael addition were developed in the 1980s.[2] In previous reports, diastereoselective Michael addition reactions using α-amino acid derivatives as Michael donors have been examined as a method for introducing an α-substituent.[3] Stereoselective synthesis of an α-substituted α-hydroxy acid has been explored.[4] However, application of the Michael addition reaction with respect to the newly formed bond on the α-hydroxy acid derivative is quite rare[5] and has not been probed thoroughly. Recently, we have shown that chiral dioxolanones **2a** and **2b**, derived from **1**, could be used for the preparation of enantiopure α-substituted α-hydroxy acids.[6] As a result, we decided to explore the diastereo-

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(2) (a) Viteva, L. Z.; Gospodovva, T. S.; Stefanovsky, Y. N. *Tetrahedron* **1994**, *50*, 7193. (b) Yamamoto, H.; Kanemasa, S.; Wada, E. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2739. (c) Enders, D.; Papadopoulos, K.; Rendenbach, B. E. M.; Appel, R.; Knoch, F. *Tetrahedron Lett*. **1986**, *27*, 3491. (d) Schollkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1194. (e) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem*. **2000**, *65*, 1758.

(3) (a) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem*. **1992**, 51. (b) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem*. **1990**, *55*, 4411. (c) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem*. **1991**, *56*, 2875. (d) Achqar, A. E.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319.

(4) (a) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4. (b) Seeback, D. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1980. (c) Coppola, G. M.; Schuster, H. F. In *α-Hydroxy Acids In Enantioselective Synthesis*; Academic Press: Weinheim, 1997.

(5) (a) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592. (b) Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102. (c) Hattori, K.; Yamamoto, H. *J. Org. Chem*. **1993**, *58*, 5301.

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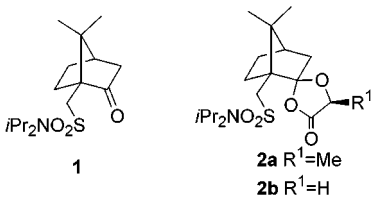
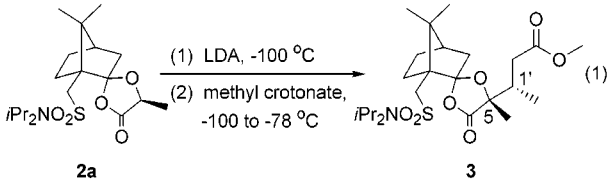
selective Michael addition of enolates derived from **2a** and **2b** to α,β-unsaturated esters. The results are reported herein. A concise and highly enantioselective synthesis of (+)-crobarbatic acid employing this methodology is also described.



At the outset, we investigated the diastereoselectivity of the addition of enolate derived from **2a** to methyl crotonate (eq 1). Treatment of **2a** with lithium diisopropylamide (LDA)



in tetrahydrofuran (THF) at −100 °C followed by addition of methyl crotonate in 3 h at −78 °C gave compound **3** in 92% yield as the sole product, as judged by 400 MHz ^{1}H NMR measurement of the crude mixture (Table 1, entry 1).

Table 1. Diastereoselective Michael Addition of **2a** with Methyl Crotonate

entry	additive	*T* (h)	yield (%)	de (%)[a]
1		3	92	>98
2	HMPA (2 equiv)	3	86	>98
3	HMPA (6 equiv)[b]	3	84	>98
4	12-crown-4 ether (2 equiv)	2.5	88	>98
5	$ZnCl_2$ (1.5 equiv)	2.5	89	>98
6	$SnCl_2$ (1.5 equiv)	2.5	86	>98

[a] No second isomer has been detected by 400 MHz ^{1}H NMR spectroscopy on the crude mixture. [b] See ref 8.

The stereochemistry of Michael adduct **3** was confirmed by X-ray crystallographic analysis. The excellent facial selectivity of the enolate of **2** is exemplified again.[6] To expand the scope of this diastereoselective Michael addition, we investigated the possibility of stereoselective variants at C_1' of Michael adduct **3**. When the reaction was conducted in a similar manner with the addition of additive prior to enolate formation[7] (Table 1, entries 2−6), Michael adduct **3** was obtained as the sole product in a slightly lower yield. Thus, it is reasonable to assume that the Michael addition of the enolate of **2a** to methyl crotonate did not proceed through a chelated transition structure in all cases.[9]

On the basis of the above preliminary survey, several (*E*)-monosubstituted α,β-unsaturated esters were treated with the lithium enolates derived from **2a** or **2b** in THF at −100 °C without additives (eq 2). After 3 h at −78 °C, the corresponding products were obtained with very high diastereoselectivities and yields (Table 2). The stereochemistry of

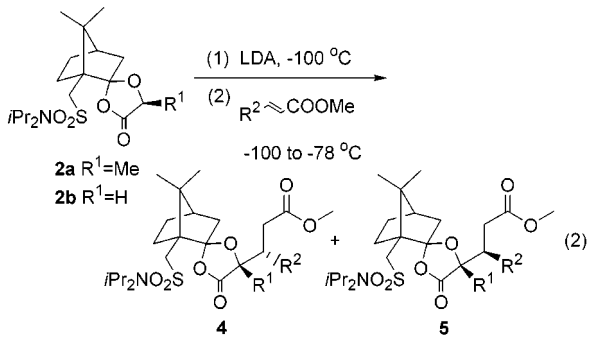


Table 2. Diastereoselective Michael Addition of **2a** and **2b** with α,β-Unsaturated Esters

entry	R^1	R^2	product	yield (%)	**4**:**5**[a]
1	Me	H	**a**	88	
2	Me	Ph	**b**	78	>99:1
3	Me	Pr	**c**	88	>99:1
4	Me	*i*Pr	**d**	84	>99:1
5	H	H	**e**	76	
6	H	Me	**f**	82	<1:99
7	H	Ph	**g**	77	<1:99

[a] No second isomer has been detected by 400 MHz ^{1}H NMR spectroscopy on the crude mixture.

Michael adducts was confirmed by X-ray crystallographic analysis for **3** and **5g**[10] and nuclear Overhauser effect experiments.[11] Interestingly, the enolate of **2a** gave Michael adduct **4**, whereas the enolate of **2b** gave Michael adduct **5**. It is not clear if Michael addition of the enolates of **2a** and **2b** to the α,β-unsaturated esters took place on different faces (*Si* and *Re*, respectively) of the double bond. The reason is currently under investigation.

(6) Chang, J.-W.; Jang, D.-P.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *Org. Lett.* **1999**, *1*, 2061.

(7) It has been found that the *E* lithium enolate of ethyl propionate reacted with ethyl (*E*)-crotonate gave *anti* and *syn* 1,4-adducts in a ratio of 71:29. The stereoselectivity was increased to 10:1 if HMPA was added after enolate formation and further increased to >20:1 if HMPA was added prior to enolate formation. See: Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661.

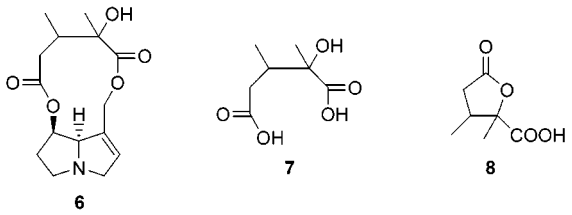
(8) Yen, K.-F.; Uang, B.-J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 697.

(9) It has been suggested that HMPA (in THF, a polar aprotic solvent) does not disrupt enolate tetramers. See: (a) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (b) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(10) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149424 for **3**, CCDC-149423 for **5g**, and CCDC-149425 for (+)-**8**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

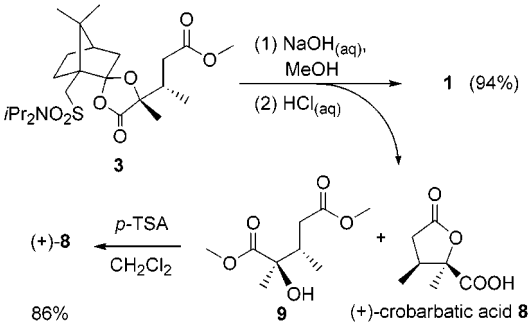
(11) Further evidence for other Michael adducts without X-ray crystallographic analysis were confirmed by NOE experiments of the corresponding products after hydrolysis and lactonization [eqs 3 and 4]. For details, see Supporting Information.

To extend this methodology further, the synthesis of *trans*-crobarbatic acid **8**[12] is explored. *trans*-Crobarbatic acid **8** is the hydrolysis product of crobarbatine **6** and represents the cyclic form of necic acid **7**. Crobarbatic acid has been shown

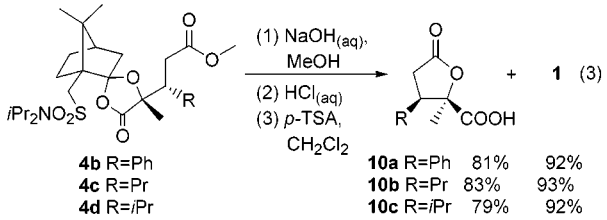


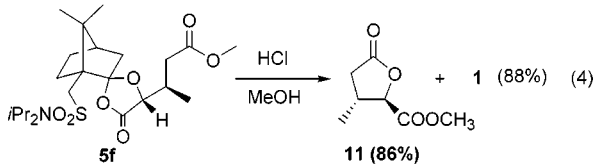
to bear two *trans* methyl groups. However, its absolute configuration is still unknown.[13] Our synthesis commenced with the removal of chiral auxiliary by heating **3** with 2 N sodium hydroxide in methanol (Scheme 1). The resulting

Scheme 1



solution was acidified to give a mixture of α-hydroxy glutaric acid **9** and γ-lactone **8**, (+)-crobarbatic acid,[14] and chiral auxiliary was recovered in 94% yield. The mixture was completely converted to (+)-**8** in CH_2Cl_2 utilizing *p*-toluenesulfonic acid as catalyst[12a,15] in 86% yield from **3**. The structure of (+)-**8** was unambiguously determined by X-ray crystallographic analysis.[10] Similarly, *trans*-3,4-disubstituted γ-lactones **10a**−**c** were synthesized in high yield and enantiopurity (eq 3). To avoid epimerization of the tertiary





α-carbon, hydrolysis and lactonization of **5f** were achieved by heating with anhydrous hydrochloride in methanol to give lactone **11** (eq 4).[16]

In conclusion, the lithium enolates of α-hydroxy acid derivatives **2a** and **2b** underwent diastereospecific Michael addition. It also provided a concise synthetic route to (+)-crobarbatic acid **8** and enantiopure *trans*-3,4-disubstituted γ-lactones.

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Note Added after ASAP: A spelling error in the title of this Letter and two symbol errors in ref 1a were present in the version posted ASAP on 3/7/01. These errors were corrected in the version posted 3/29/01.

Supporting Information Available: The detailed experimental procedures and characterization data for new compounds; NOE spectral data for **10a**−**c** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For previous syntheses, see: (a) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861. (b) Donohoe, T. J.; Stevenson, C. A.; Helliwell, M.; Irshad, R.; Ladduwahetty, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1315. (c) Chen, M.-Y.; Fang, J.-M. *J. Org. Chem.* **1992**, *57*, 2937. (d) Honda, T.; Ishikawa, F.; Yamane, S.-I. *J. Chem. Soc., Perkin Trans. I* **1996**, 1125.

(13) Puri, S. C.; Sawhney, R. S.; Atal, C. K. *Experientia* **1973**, *29*, 390.

(14) (+)-**8**: $[\alpha]^{25}_D$ +3.56 (*c* 1.4, H_2O). Lit.[12b] (−)-**8**, $[\alpha]_D$ −3.7 (*c* 1.4, H_2O) and $[\alpha]^{18}_D$ −8.0 (*c* 0.2, H_2O).

(15) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239.

(16) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1991**, *56*, 3083.