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Highly Stereoselective Intermolecular Oxy-Michael Addition Reaction to α,β-Unsaturated Malonate Esters

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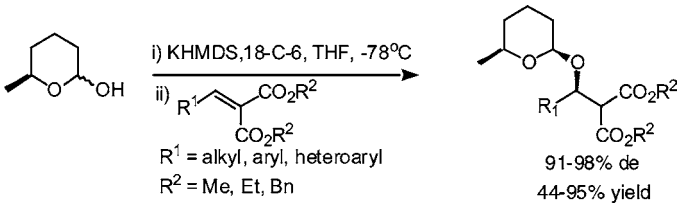
ABSTRACT



The highly diastereoselective oxy-Michael addition of the "naked" anion of (6*S*)-methyl δ lactol to alkylidiene-, arylidene-, and heteroarylidene-malonate derivatives leading to the direct formation of THP*-protected β-hydroxy ester derivatives is described. Subsequent acid-mediated deprotection affords the enantioenriched aldol products in quantitative yields.

The stereoselective addition of oxygen-centered nucleophiles to Michael acceptors has received little attention over the years despite the potential utility of the protected hydroxyl products in synthesis.[1] Our group[2] and others[3] have been involved in the development of such chiral water equivalents for addition to highly reactive nitro olefin acceptors[4] and to this end the highly diastereoselective oxy-Michael addition of the "naked" anions of enantiopure δ lactols has been described. Although useful for the asymmetric synthesis of 1,2-amino alcohols, we believed an extension of this chemistry to incorporate other Michael acceptors, while maintaining reaction efficiency and diastereoselectivity, would expand significantly the utility and scope of the reaction.

Herein, we wish to describe work leading to the first highly diastereoselective oxy-Michael reaction of a chiral water equivalent to alkylidene-, arylidene-, and hetereoarylidiene-malonate Michael acceptors.[5,6] Our initial studies focused on the attempted addition of the "naked" alkoxide of 6-methyl δ lactol **1** to α,β-unsaturated esters and lactones. However, all attempts to make an oxygen−carbon bond failed, and either starting material was returned unreacted or the alkoxide facilitated the dimerization of the Michael acceptor.[7]

It was clear that further activation of the Michael acceptor was required for successful oxygen−carbon bond formation.

(1) Reviews: (a) Misra, M.; Luthra, R.; Singh, K. L.; Sushil, K. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakunisha, K., Meth-Chon, O., Eds.; Pergamon: Oxford, UK, 1999; Vol. 4. p 25. (b) Staunton, J.; Wilkinson, B. *Top. Curr. Chem.* **1998**, *195*, 49.

(2) (a) Adderley, N. J.; Buchanan, D. J.; Dixon, D. J.; Lainé, D. I. *Angew. Chem., Int. Ed.* **2003**, *35*, 4241−4244. (b) Buchanan, D. J.; Dixon, D. J.; Scott, M. S.; Lainé, D. I. *Tetrahedron*: *Asymmetry* **2004**, *15*, 195−197.

(3) (a) Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed*. **1996**, *35*, 2388−2390. (b) Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1771−1792. (c) Enders, D.; Haertwig, A.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1793−1801.

(4) For diastereoselective/nonenantioselective additions to nitro olefin acceptors, see: (a) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem*. **2001**, 2577−2588. (b) Yakura, T.; Tsuda, T.; Matsumura, Y.; Yamada, S.; Ikeda, M. *Synlett* **1996**, 985−986.

(5) For nonenantioselective additions of oxygen-centered nucleophiles to benzylidene(or alkylidene)malonates and related Michael acceptors, see: (a) Cavicchioli, M.; Marat, X.; Monteiro, N.; Hartmann, B.; Balme, G. *Tetrahedron Lett*. **2002**, *43*, 2609−2611. (b) Marat, X.; Monteiro, N.; Balme, G. *Synlett* **1997**, 845−847. (c) Monteiro, N.; Balme, G. *J. Org. Chem*. **2000**, *65*, 3223−3226.

(6) For asymmetric diastereoselective substrate-controlled additions of achiral oxygen-centered nucleophiles, see, for example: Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 2742−2748.

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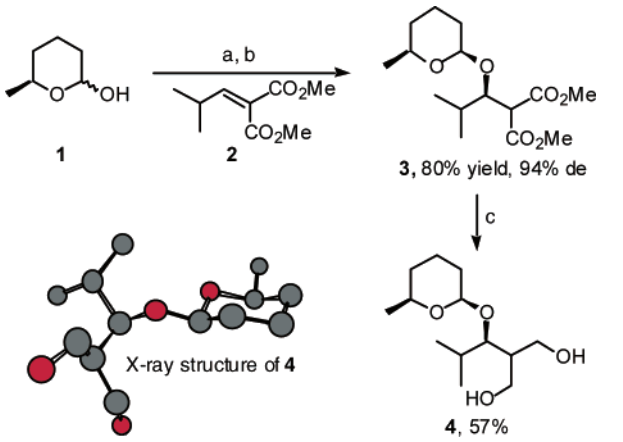
Accordingly, alkylidenemalonate acceptor[8] **2** was chosen as a test substrate. The initial conditions adopted were identical to those previously established for the additions to β-substituted nitro olefin acceptors. Thus, deprotonation of the epimeric mixture of (6*S*)-methyl δ lactol **1** with KHMDS in THF at −78 °C and addition of 18-crown-6 (1.0 equiv) generated the "naked" chiral lactol alkoxide nucleophile. Addition of **2** (0.67 equiv) to this mixture for 1 h and quenching with acetic acid (2.0 equiv) at −78 °C afforded, after aqueous workup, the crude oxy-Michael adduct **3** in a pleasing >94% diastereomeric excess (de). Purification by flash column chromatography afforded **3** in an excellent 80% yield. The relative stereochemistry of the major diastereomeric product was unambiguously determined by single-crystal X-ray diffraction on the bis hydroxymethyl product **4**, obtained by lithium aluminum hydride reduction of **3** (Scheme 1).

Scheme 1. Stereoselective Oxy-Michael Addition of the "Naked" Anion of **1** to Dimethyl Malonate Derived Acceptor **2**[a]

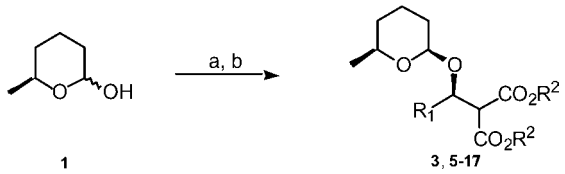


[a] Key: (a) KHMDS (1.0 equiv), 18-crown-6 (1.0 equiv), −78 °C, THF then **2** (0.67 equiv) for 1 h; (b) AcOH (2.0 equiv); (c) $LiAlH_4$, Et_2O, 0 °C.

Having identified alkylidene malonate **2** as a suitably reactive substrate, the scope of the oxy-Michael addition to a range of alkylidene-, arylidene-, and heteroarylidene-malonate derivatives was probed. Malonate acceptors were chosen in which the ester substituent was varied from methyl to ethyl and benzyl and the β-substituent varied between alkyl, branched alkyl, aromatic, and heteroaromatic groups. The conditions for the oxy-Michael reaction were as described above for the test substrate, and the results are detailed below (Scheme 2, Table 1).

With aromatic and heteroaromatic β-substituents, the reaction diastereoselectivities were uniformly excellent (≥96% de in all cases), and the yields were good for all malonate

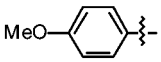
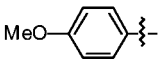
Scheme 2. Stereoselective Oxy-Michael Addition of the "Naked" Anion of **1** to a Range of Malonate-Derived Acceptors[a]



[a] Key: (a) KHMDS (1.0 equiv), 18-crown-6 (1.0 equiv), −78 °C, THF then $R^1CHC(CO_2R^2)_2$ (0.67 equiv); (b) AcOH (2.0 equiv).

ester types. While diastereoselectivities remained high, some erosion in yield (entries 5 and 14) was witnessed with a linear hexyl group at the β-position. This was due to a competing γ-deprotonation pathway, as deconjugated products were clearly visible in the crude reaction mixtures. When the β-substituent was an isopropyl group, slightly lowered reaction diastereoselectivities were noted and the selectivity

Table 1. Scope of the Stereoselective Oxy-Michael Addition of **1** to Malonate-Derived Acceptors

entry	R^1	R^2	product	yield/%	de/%[a]
1		Me	**5**	95	>98
2		Me	**6**	82	>98
3		Me	**7**	81	>98
4		Me	**3**	80	94
5		Me	**8**	44	96
6		Bn	**9**	90	>98
7		Bn	**10**	88	>98
8		Bn	**11**	93	93
9		Et	**12**	88	>98
10		Et	**13**	77	96
11		Et	**14**	60	>98
12		Et	**15**	76	>98
13		Et	**16**	72	91
14		Et	**17**	52	96

[a] Measured by analysis of the 400, 500, or 600 MHz ^1H NMR spectra of the crude reaction product.

(7) For an interesting (nonenantioselective) synthesis of tetrahydrofurans using an oxy-Michael/Michael cyclization strategy, see: Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2003**, *68*, 4239−4246.

(8) Readily synthesized by condensation, see: Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094−10105.

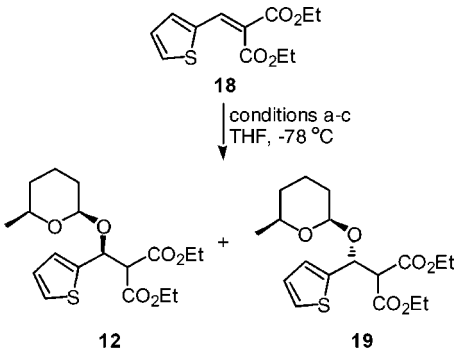
was somewhat dependent on the ester group. Thus, for the dimethyl ester case (entry 4), a reaction de of 94% was observed; with the dibenzyl ester a de of 93% was recorded (entry 8) and with the diethyl ester (entry 13) the de was 91%. In all three cases, however, the reaction yields were good to excellent.

The relative stereochemistry of the major oxy-Michael adduct **13** from addition to the acceptor derived from 2-furaldehyde and diethyl malonate was unambiguously determined by single-crystal X-ray diffraction. In view of the known stereochemistry of **4**, and the correlation with the stereochemical outcomes found in the additions to β-substituted nitro olefin acceptors, we have assigned the stereochemistries of all of the other major adducts in Table 1 by analogy.

The presence of the crown ether in all of the above reactions was critical for high stereoselectivity and the short reaction times. When the reactions were performed without this sequestering agent, the observed selectivities dropped to between 1:1 and 3:1, and the reaction rates were dramatically reduced.[9]

For example, subjecting the Michael acceptor **18**, derived from thiophene 2-carboxaldehyde and diethyl malonate, to 1.5 equiv of the potassium salt of 6-methyl δ lactol (in the absence of 18-crown-6) in THF at −78 °C for 20 min gave the oxy-Michael adducts **12** and **19** in a ratio of 1.6:1 at 6% conversion. A repeat of the same reaction but allowing for an extended reaction time of 4 h provided **12** and **19** in a ratio of 2.6:1 at 61% conversion. However, when the same reaction was repeated, but with 18-crown-6 (1 equiv relative to the alkoxide) added after 4 h, and the reaction continued for a further 60 min before quenching, **12** and **19** were produced in the improved ratio of 4.7:1 at 99% conversion (Scheme 3).

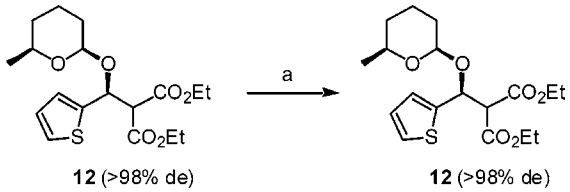
Scheme 3. Probing the Dependence of Reaction Diastereoselectivity and Conversion on Time and 18-Crown-6 Additive[a]



[a] Key: (a) **1**, KHMDS (1.0 equiv), 30 min, then **18** (0.67 equiv), 20 min, then AcOH (2.0 equiv); (b) **1**, KHMDS (1.0 equiv), 30 min, then **18** (0.67 equiv), 4 h, then AcOH (2.0 equiv); (c) **1**, KHMDS (1.0 equiv), 30 min, then **18** (0.67 equiv), 4 h, then 18-crown-6 (1.0 equiv), 1 h, then AcOH (2.0 equiv).

When a single diastereoisomeric product of the oxy-Michael reaction was subjected to the "unselective" reaction conditions, no change in the diastereomeric ratio was observed. Thus, by adding 1.5 equiv of KHMDS to **12** (>98 de) in the presence of 0.5 equiv of lactol in THF at −78 °C and quenching after 1 h, the starting material **12** was returned unchanged (Scheme 4).

Scheme 4. Proof of the Irreversibility of the "Unselective" Oxy-Michael Addition of the Potassium Salt of **1**[a]

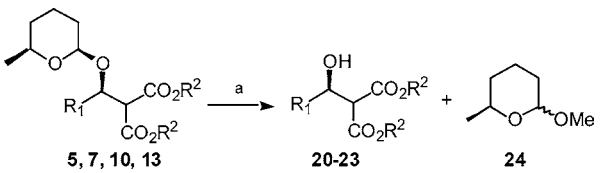


[a] Key: (a) **1** (0.5 equiv), THF, −78 °C, KHMDS (1.5 equiv), 30 min, then AcOH (3.0 equiv).

These experiments indicate that either with or without 18-crown-6, the oxy-Michael reactions of the potassium salt of 6-methyl δ lactol to malonate derived Michael acceptors are irreversible at −78 °C. The sequestering of the potassium counterion with 18-crown-6 leads to a substantial rate enhancement and improved diastereoselectivity at the β-center.

As well as inducing excellent levels of stereocontrol in its addition to the electron poor alkenes, the naked lactol anion allows access to enantiomerically enriched products not previously accessible by other methods. Thus, treatment of Michael adducts **5**, **7**, **10**, and **13** with polymer-supported sulfonic acid resin in methanol at room temperature leads to quantitative THP* removal. The epimeric THP* methyl ether side products (**24**) are volatile, and thus, after simple filtration and evaporation, essentially pure, enantiomerically enriched β-hydroxy malonate ester products **20**−**23** are afforded in quantitative yield. The enantiomeric excess of the thiophene derivative was measured as >98% ee by chiral HPLC and confirmed that no racemization was occurring in the deprotection step. Interestingly, any attempt at purification of these product materials by chromatographic methods led to extensive decomposition, thus highlighting the uniqueness of our approach (Scheme 5, Table 2).

Scheme 5. Acid-Mediated Deprotection of Oxy-Michael Adducts[a]



[a] Key: (a) MP-TsOH II, MeOH, rt.

Table 2. Results of Acid-Mediated Methanolysis Reactions

entry	R^1	R^2	product	yield/%	ee/%
1		Me	**20**	100	>98[a]
2		Me	**21**	100	>98[b]
3		Bn	**22**	97	>98[b]
4		Et	**23**	100	96[b]

[a] ee determined by chiral HPLC using a Chiralcel AD column. [b] ee assigned by analogy to that of **20** (entry 1) and with the de of the starting material.

The deprotected products **20**−**23**, the esters **3**, **5**−**17**, and the diol **4** (or derivatives thereof) should find a number of uses in natural product synthesis and in the study of asymmetric reaction pathways utilizing malonic acid derived nucleophiles.

In summary, the naked anion of enantiopure 6-methyl δ lactol undergoes highly diastereoselective oxy-Michael additions to a range of alkylidiene-, arylidene-, and heteroarylidenemalonate esters. The reactions occur under kinetic control in THF at −78 °C and provide a complementary but direct asymmetric route to protected β-hydroxy ester products. The synthetic utility of these products as well as the origins of the high stereocontrol observed in the reactions will be reported in due course.

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Supporting Information Available: Experimental procedures and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The "unselective" reaction is routinely carried out to identify the ^{1}H NMR resonances of the minor diastereoisomer originating from the β-stereocenter of the *cis*-THP* adducts in the "selective" reaction.