Pergamon

Tetrahedron Letters 43 (2002) 8463–8466

TETRAHEDRON LETTERS

Highly diastereoselective Michael reaction of (*S*)-mandelic acid enolate. Chiral benzoyl carbanion equivalent through an oxidative decarboxylation of α-hydroxyacids

Gonzalo Blay, Isabel Fernández, Belén Monje, José R. Pedro* and Rafael Ruiz

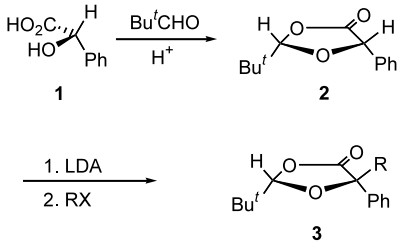
Departament de Química Orgànica, Facultat de Química, Universitat de València, E-46100 Burjassot (València), Spain

Received 21 June 2002; revised 23 September 2002; accepted 24 September 2002

Abstract—The reaction of the lithium enolate of the 1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with α,β-unsaturated carbonyl compounds proceeds readily to give the corresponding Michael adducts in good yields and high diastereoselectivity. Subsequent basic hydrolysis of the acetal and oxidative decarboxylation of the α-hydroxyacid moiety provides chiral 2-substituted 1,4-dicarbonyl compounds with very high enantiomeric excesses.

The Michael reaction[1] is a convenient and useful reaction for carbon–carbon bond formation that affords two potential contiguous stereogenic centers in the resulting molecule. However, despite the recent advances in this area there is still a great need to develop new methodologies to construct those stereogenic centers in a diastereo- and enantioselective fashion.[2] In this context, the strategies employed to exert stereocontrol in the newly created stereogenic centers involve the introduction of chiral information at the Michael acceptor or at the enolate as well as the use of chiral catalysts.[3]

We have recently reported the use of methyl mandelate as an umpoled masked synthon for nucleophilic benzoylation of alkyl halides.[4] In this letter we wish to report the highly stereoselective Michael addition of (*S*)-mandelic acid enolate to α,β-unsaturated carbonyl compounds and the transformation of the resulting adducts into enantioenriched 1,4-dicarbonyl compounds, in an overall sequence where mandelic acid is used as a chiral benzoyl carbanion equivalent.



Scheme 1.

Mandelic acid is readily available in both enantiomerically pure forms, although deprotonation at the α-carbon to give the corresponding enolate results in loss of the stereochemical information. Yet, it is possible to carry out the alkylation of enolates derived from optically active (*S*)-mandelic acid (**1**) without racemization,[5] through its previous conversion into a (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with pivalaldehyde (Seebach principle of self-regeneration of stereocenters) (Scheme 1).[6]

The enolate derived from **2** also reacted with saturated and α,β-unsaturated carbonyl compounds, such as 2-cyclohexenone, to give the 1,2-adducts with good yields and diastereoselectivities, while the 1,4-addition product was not observed at all.[5] On the other hand, the Michael addition of **2** to ethyl crotonate, with low yield and diastereoselectivity,[7] and a highly diastereoselective 1,4-addition of the enolate of (*R*,*R*)-*cis*-1,3-dioxolan-4-one (*ent*-**2**) to cyclopentenone, in a synthesis of a muscarinic receptor antagonist,[8] have been reported.

Herein we report our results on the highly diastereoselective Michael reaction of the lithium enolate of the (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with some α,β-unsaturated carbonyl compounds **4** to give the corresponding

* Corresponding author. Tel.: +34-963864329; fax: +34-963864328; e-mail: jose.r.pedro@uv.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02099-3

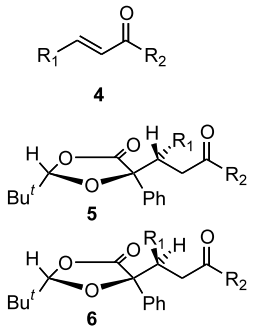


Figure 1.

Michael adducts **5** and **6** with good yields and high diastereoselectivities. These adducts upon basic hydrolysis of the acetal furnish compounds **7** and **8** which by subsequent oxidative decarboxylation of the α-hydroxyacid moiety provide access to chiral 2-substituted 1,4-dicarbonyl compounds **9** and **10** with high enantiomeric excesses (Fig. 1).

Initially, we performed the reaction of the lithium enolate of **2** with enone **4a** (Table 1) using a direct addition protocol, that is to say, compound **2** was deprotonated by addition to a freshly prepared solution of LDA (1.25 equiv.) in THF at −78°C, and then enone **3a** (1 equiv.) was added to the resulting enolate solution. This process provided a fair yield (49%) of a separable diastereoisomer mixture of **5a** and **6a**; however, only moderate diastereoselectivity (**5a**–**6a** ratio 35:65) was obtained (entry 1).[9] The reaction was also performed using an inverse addition protocol[10] as it is known that similar enolates suffer some decomposition even at low temperatures. So a mixture of the (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** and enone **4a** was treated in THF at −78°C with LDA. In this way, both the yield as well as the diastereoselectivity increased slightly to 60% and to **5a**–**6a** ratio 30:70, respectively (entry 2).

Table 1. Michael reaction of 1,3-dioxolan-4-one **2** with enone **4a**

Entry	Addition	HMPA (equiv.)	Yield[a] (%)	**5a**:**6a**[b]
1	Direct	0	49	35:65
2	Inverse	0	60	30:70
3	Direct	3	64	97:3
4	Inverse	3	85	100:0
5	Direct	6	53	98:2
6	Inverse	6	82	99:1

[a] Yields refer to isolated products.
[b] Ratios determined by ^{1}H NMR.

The effect of the enolate aggregation state was also examined. In most cases, the use of HMPA as an additive appreciably increases the reactivity as well as substantially modifies the selectivity.[11] In our case, when 3 equiv. of HMPA were used (entries 3 and 4) in the Michael addition of the lithium enolate of **2** to enone **4a** an improvement of the reaction yield, specially with the inverse addition protocol (85%, entry 4), together with an increase and a full reversion of the diastereoselectivity were observed. Thus, only compound **5a** was obtained (de >99%). Addition of more HMPA (6 equiv.) (entries 5 and 6) did not further enhance the yield nor modified the diastereoselectivity.

Table 2 shows the results observed for the reaction of the lithium enolate of **2** with some representative α,β-unsaturated carbonyl compounds **4a**–**c** using the inverse addition protocol. In all the three cases the reaction proceeded with high diastereoselectivity (entries 2, 4 and 6) and the resulting Michael adducts were obtained as only one diastereoisomer out of the four possible ones, attending to the configuration of the two newly created stereogenic centers.

With the Michael adducts **5** and **6** in our hands, we carried out the basic hydrolysis of the acetal moiety to obtain the corresponding α-hydroxy-δ-oxocarboxylic acids **7** and **8**, respectively. Compound **7b** was obtained as an open α-hydroxyacid while the rest of the products were obtained as cyclic hemiacetal-acids, **7a**, **8a**, and **8b**, or as lactone-acids **7c** and **8c** in almost quantitative yield (Fig. 2). This fact strongly facilitated the stereochemical assignments.[12]

The oxidative decarboxylation of the open α-hydroxyacid **7b** and the cyclic hemiacetal-acids **7a**, **8a**, and **8b** was carried out using a catalytic procedure developed recently in our laboratory for α-hydroxyacids which employs oxygen as terminal oxidant in the presence of pivalaldehyde and of a catalytic amount of the Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex

Table 2. Michael reaction of 1,3-dioxolan-4-one **2** with α,β-unsaturated carbonyl compounds **4** using the inverse addition protocol

Entry	R_1	R_2	HMPA (equiv.)	Product	Yield[a] (%)	**5**:**6**[b]
1	Me	Et	0	**5a**–**6a**	60	30:70
2	Me	Et	3	**5a**–**6a**	85	100:0
3	Ph	Me	0	**5b**–**6b**	34	65:35
4	Ph	Me	3	**5b**–**6b**	83	2:98
5	Me	OMe	0	**5c**–**6c**	40	40:60
6	Me	OMe	3	**5c**–**6c**	74	0:100

[a] Yields refer to isolated products.
[b] Ratios determined by ^{1}H NMR.

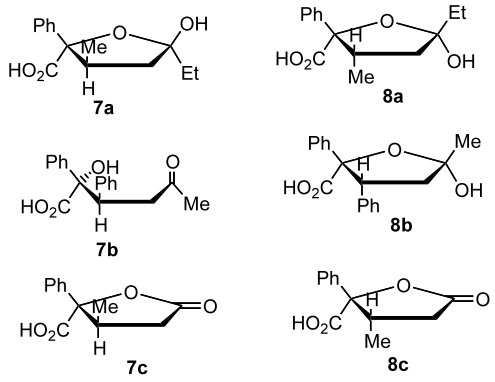


Figure 2.

(Fig. 3).[13] Under these conditions the 1,4-dicarbonyl compounds **9b**, **9a**, **10a** and **10b** were obtained, respectively, with fair to good yields (Fig. 4, Table 3).[14] Much more important these products were obtained enantiomerically enriched (ee >99%) as proven by ^{1}H NMR experiments using the chiral lanthanide shift reagent Eu(hfc)$_3$ under conditions previously optimized for a racemic mixture.[15]

In summary, we have developed a strategy for the asymmetric Michael reaction of a masked benzoyl anion equivalent with α,β-unsaturated carbonyl compounds that formally involves the use of (*S*)-mandelic acid as the source of benzoyl anion and as source of chiral information. This strategy appears as a convenient method for the synthesis of highly enantioenriched 2-substituted 1,4-dicarbonyl compounds.

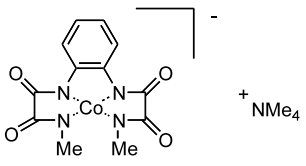


Figure 3.

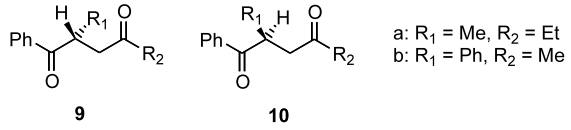


Figure 4.

Table 3. Oxidative decarboxylation of cyclic hemiacetal-acids **7** and **8**

Entry	S.m.	R_1	R_2	Product	Yield [a] (%)
1	**7a**	Me	Et	**9a**	75
2	**8a**	Me	Et	**10a**	78
3	**7b**	Ph	Me	**9b**	58
4	**8b**	Ph	Me	**10b**	60[a]

[a] Reaction time 24 h.

Typical experimental procedures

Michael reaction (inverse addition): A solution of freshly prepared LDA (1.25 mmol) in dry THF (1.3 mL) was slowly added to a solution of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** (220 mg, 1 mmol) and the α,β-unsaturated carbonyl compound **4** (1.25 mmol) in dry THF–HMPA (5 mL:0.53 mL) at −78°C. The reaction was allowed to reach −40°C and it was quenched with a saturated aqueous solution of NH_4Cl at this temperature, and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (silica gel, hexane–diethyl ether or hexane–dichloromethane) to afford Michael adducts **5** and **6**. Yields are included in Table 2.

Basic hydrolysis of the Michael adducts: The Michael adduct **5** or **6** (0.28 mmol) was treated with 5% ethanolic KOH (0.63 mL, 0.56 mmol) at room temperature until complete reaction of the starting material (TLC). The solution was poured into ice and acidified with 1 M HCl until pH ≈ 2. The aqueous mixture was extracted with EtOAc (3×30 mL), the organic layers were washed with brine until neutrality was reached, dried, filtered and concentrated under reduced pressure to give compounds **7** or **8** in almost quantitative yield.

Oxidative decarboxylation of compounds **7** and **8**: See Ref. 4.

Acknowledgements

This work was financially supported by the Spanish Government (MCYT, projects PB97-1411 and BQU 2001-3017) and in part by Generalitat Valenciana. R.R. (Ramón y Cajal program) and B.M. (FPI program) thank MCYT for a grant.

References

1. (a) Jung, H. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, p. 1; (b) Perlmuter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Baldwin, J. E.; Magnus, P. D., Eds.; Pergamon Press: Oxford, 1992.
2. (a) d'Angelo, I.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771; (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336; (e) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171; (f) Enders, D.; Berner, O. M.; Vignola, N.; Bats, J. W. *Chem. Commun.* **2001**, 2498; (g) Hupe, E.; Knoechel, P. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3022; (h) Vázquez, I.; Prieto, A.; Fernández, R.; Enders, D.; Lassaletta, J. M. *Chem. Commun.* **2002**, 498.
3. (a) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579; (b) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 916.

4. Blay, G.; Fernández, I.; Formentin, P.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron* **2001**, *57*, 1075.
5. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.
6. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
7. Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102.
8. Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775.
9. The stereochemical structures of the Michael adducts **5** and **6** were elucidated by NOEs. These experiments showed that in all of the cases the electrophile **4** entered *anti* to the *t*-Bu group. The absolute stereochemistry of the newly formed quaternary carbon was then assigned to be *S* upon the consideration that the absolute configuration of the acetal carbon bearing the *t*-Bu group in **2** is *S* (see Refs. 5 and 6) and it keeps unaltered from **2** to **5** or **6**. For the assignment of the stereochemistry at the tertiary stereocenter see Ref. 12.
10. Kraus, G.; Dneprovskaia, E. *Tetrahedron Lett.* **2000**, *41*, 21.
11. *Handbook of Reagents for Organic Synthesis. Acidic and Basic Reagents*; Reich, J. H., Rigby, J. H., Eds.; John Wiley and Sons: Chichester, 1999; p. 160.
12. The stereochemical structures of the cyclic hemiacetal acids **7a**, **8a**, and **8b**, and lactone acids **7c** and **8c** was established by NOEs. The absolute stereochemistry of the tertiary carbon was assigned upon the consideration that the absolute configuration of the quaternary carbon bearing the carboxy group was *S* in all the cases as explained in Ref. 9. These experiments also allowed the complete stereochemistry of compounds **5** and **6** to be established. For example, the new tertiary stereocenter was found to be *R* in compound **7a**, and consequently the same configuration was assigned to this carbon in its precursor **5a**.
13. Estrada, J.; Fernández, I.; Pedro, J. R.; Ottenwaelder, X.; Ruiz, R.; Journaux, Y. *Tetrahedron Lett.* **1997**, *38*, 2377.
14. However, the cyclic compounds **7c** and **8c**, which have a lactone instead of a hemiacetal moiety, did not react under these conditions.
15. Racemic mixtures of 1,4-dicarbonyl compounds were prepared starting from racemic mandelic acid.