



Enantiopure β -methoxy carboxyl derivatives from a chiral titanium enolate and dimethyl acetals[†]

Annabel Cosp, Pedro Romea,* Fèlix Urpi* and Jaume Vilarrasa

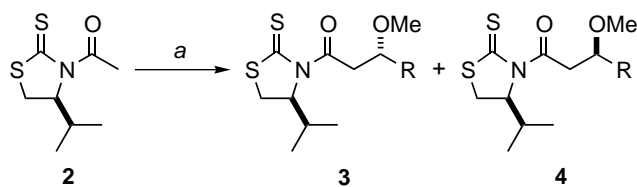
Departament de Química Orgànica, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

Received 27 April 2001; accepted 16 May 2001

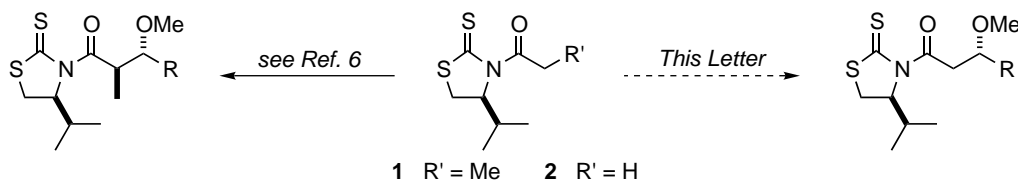
Abstract—Lewis acid-mediated reaction of the titanium enolate arising from (*S*)-*N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione with dimethyl acetals furnishes β -methoxy carboxyl adducts in good yields and stereoselectivities. The adducts can be, in turn, transformed into a wide range of enantiopure α -unsubstituted β -methoxy carboxyl derivatives in excellent yields. © 2001 Elsevier Science Ltd. All rights reserved.

The widespread presence of alkoxy groups in polyketide natural products has given rise to the development of a plethora of synthetic approaches to β -alkoxy carbonyl compounds, which usually rely on a multistep process: (i) stereoselective aldol^{1,2} or allyl transfer^{3,4} reaction, (ii) alkylation of the adduct and, if it is required, (iii) further elaboration of the carbonyl or the alkene moieties. Taking into account that the integration of a multistep sequence in a single transformation increases the efficiency of a process, we envisioned that a stereoselective addition of metal enolates to acetals might afford β -alkoxy carbonyl systems in a straightforward manner.⁵ In this context, we have recently reported⁶ that the reaction of the titanium enolate arising from **1**⁷ with dimethyl acetals gives access to enantiopure *anti* α -methyl- β -methoxy carbonyl compounds (see Scheme 1). We now report on a related case in which it is more difficult to achieve stereochemical control, that of the reaction of dimethyl acetals with the titanium enolate from (*S*)-*N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (**2**), the *N*-acetyl analogue of **1** (see Scheme 1).^{8,9}

Initial experiments showed the higher reactivity of the titanium enolate of **2** compared to the corresponding one of **1**. For instance, the titanium enolate of **2** underwent addition to benzaldehyde dimethyl acetal (**a**) at -78°C and furnished a mixture of adducts **3** and **4** (see Scheme 2) in 75% overall yield and a good diastereomeric ratio (86:14). Given that the electrophilicity of an acetal may be enhanced by coordination to a Lewis acid (LA), it was next tested the effect of several Lewis acids on the stereoselectivity and the overall yield of the process. The results are summarised in Table 1. Both $\text{BF}_3\cdot\text{OEt}_2$ and SnCl_4 afforded good



Scheme 2. (a) (i) TiCl_4 , ${}^t\text{Pr}_2\text{EtN}$; (ii) $\text{RCH}(\text{OMe})_2$, LA.



Scheme 1.

Keywords: acetals; aldol reactions; asymmetric reactions; enolates.

* Corresponding authors. Fax: +34 93 339 78 78; e-mail: promea@qo.ub.es; furpi@qo.ub.es

[†] Dedicated to Professor David A. Evans on the occasion of his 60th birthday.

Table 1. Reaction of benzaldehyde and acetaldehyde dimethyl acetal with the titanium enolate of **2**

Entry	Acetal	R	Lewis acid	Conditions (<i>T</i> , <i>t</i>) ^a	dr 3:4 ^b	Yield (%) ^c
1	a	Ph	–	–78°C, 4 h	86:14	75
2	a	Ph	BF ₃ ·OEt ₂	–78°C, 2 h	88:12	92
3	a	Ph	Et ₂ AlCl	–78°C, 2 h	55:45	45
4	a	Ph	SnCl ₄	–78°C, 2 h	85:15	92
5	a	Ph	TiCl ₄	–78°C, 2 h	69:31	95
6	b	CH ₃	–	–78°C, 4 h	64:36	30
7	b	CH ₃	BF ₃ ·OEt ₂	–78°C, 2 h	65:35	17
8	b	CH ₃	SnCl ₄	–78°C, 2 h	76:24	72
9	b	CH ₃	TiCl ₄	–78°C, 2 h	68:32	85

^a For experimental details, see Ref. 10.

^b Determined by HPLC analysis of the reaction mixtures.

^c Overall yield estimated by HPLC analysis of the reaction mixtures.

results; the former was considered to be the most suitable one because of its mildness and the slightly better diastereomeric ratio it exhibits (compare entries 2 and 4 in Table 1). A similar study was carried out in the case of the acetaldehyde dimethyl acetal (**b**). As expected, this less reactive substrate required a more powerful Lewis acid in order to attain good yields (compare entries 6–9 in Table 1). The best diastereoselection was obtained with SnCl₄ (see entry 8 in Table 1).

Once established the most suitable Lewis acid for model acetals **a** and **b**, further optimisation of the experimental conditions was carried out. Addition of the titanium enolate of **2** to aromatic acetals (**a**, **c–e** in Table 2) was judged to afford >85% yield after 30 min at –78°C by HPLC analysis of the reaction mixtures and it was observed that reaction times longer than 1 h did not significantly increase the yields. On the other hand, the α,β -unsaturated acetal (**f**) proved to be highly reactive and no starting material was detected in the reaction mixture after 15 min at –78°C. In the case of aliphatic acetals (**b**, **g–i**), the rate of the process slowed down dramatically after 30 min at –78°C and higher temperatures were required to improve conversions. Thus, the above-mentioned mild conditions afforded good results for a wide range of acetals, allowing us the isolation of enantiopure diastereomers **3**¹¹ in good yields by means of chromatographic purification.^{12,13} The results are summarised in Table 2.

As it has been previously reported,^{6,7} the chiral thiazolidine-2-thione auxiliary can be easily removed by using a variety of methods, which allows the adducts to be transformed into a wide range of derivatives. As a model, **3a** was converted into the corresponding enantiopure alcohol **5**, carboxylic acid **6**, methyl ester **7**, thioester **8**, morpholine amide **9**, and Weinreb amide **10**, under very mild conditions and in excellent yields as shown in Scheme 3. In all cases, the end point of the reaction is reached when the initial yellow solution becomes almost colourless. The chiral auxiliary can be recovered by chromatography or, in most cases, by washing the reaction mixture with 1 M NaOH and acidification in $\geq 90\%$ yield.

In summary, we have described a simple and efficient methodology to obtain enantiopure α -unsubstituted β -methoxy carboxyl adducts based on the stereoselective addition of a chiral titanium enolate to a wide range of acetals. The adducts can be, in turn, easily transformed into a large number of chiral building blocks of high scope in the total synthesis of natural products.

Acknowledgements

Financial support from the Ministerio de Educación y Cultura (DGESIC, Grant PM98-1272) and the Gener-

Table 2. Reaction of dimethyl acetals with the titanium enolate of **2**

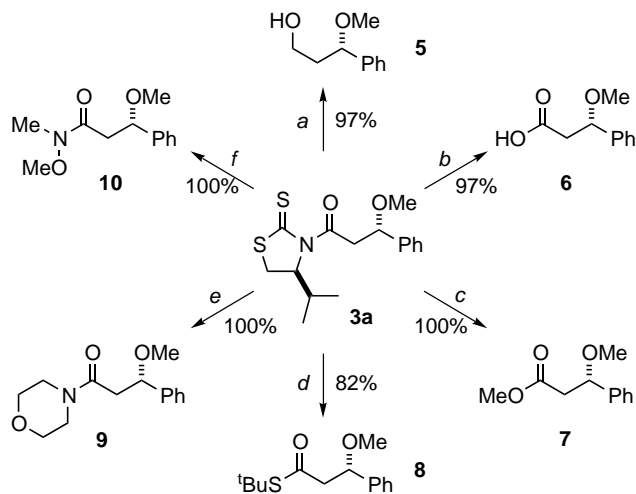
Entry	Acetal	R	Lewis acid	Conditions ^a	dr 3:4 ^b	Yield (%) ^c
1	a	Ph	BF ₃ ·OEt ₂	A	88:12	77
2	c	4-MeOPh	BF ₃ ·OEt ₂	A	93:7	87
3	d	3-MeOPh	BF ₃ ·OEt ₂	A	88:12	75
4	e	4-ClPh	BF ₃ ·OEt ₂	A	88:12	81
5	f	(<i>E</i>) PhCH=CHMe	BF ₃ ·OEt ₂	B	82:18	77
6	b	CH ₃	SnCl ₄	C	76:24	57
7	g	CH ₃ CH ₂ CH ₂	SnCl ₄	C	73:27	62
8	h	(CH ₃) ₂ CHCH ₂	SnCl ₄	C	79:21	70 ^d
9	i	(CH ₃) ₂ CH	SnCl ₄	C	71:29	60 ^d

^a A: –78°C for 1 h; B: –78°C for 15 min; C: –78°C for 30 min and –20°C for 1 h.

^b Determined by HPLC analysis of the reaction mixtures.

^c Isolated yield of **3**.

^d Isolated yield of the corresponding Weinreb amide.



Scheme 3. (a) NaBH₄ (4 equiv.), THF-H₂O, rt, 4 h; (b) LiOH (5 equiv.), CH₃CN-H₂O, 0°C, 4 h; (c) CH₃OH, K₂CO₃ (5 equiv.), rt, 4 h; (d) ^tBuSH (1.5 equiv.), K₂CO₃ (3.5 equiv.), CH₃CN, rt, 24 h; (e) morpholine (2 equiv.), THF, rt, 4 h; (f) NH(OMe)Me·HCl (1.5 equiv.), Et₃N (1.1 equiv.), DMAP cat., CH₂Cl₂, rt, 24 h.

alitat de Catalunya (1998SGR00040 and 2000SGR00021) and a doctorate studentship (Generalitat de Catalunya) to A.C. are acknowledged.

References

- For a review on stereoselective aldol reactions, see: Cowden, C. J.; Paterson, I. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp. 1–200.
- For recent developments on stereoselective catalytic aldol reactions, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Heidelberg: Springer, 1999; Vol. 3, pp. 997–1065.
- For reviews on allylmetal additions, see: (a) Hoppe, D.; Roush, W. R.; Thomas, E. J. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21b, pp. 1357–1602; (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
- For recent developments on stereoselective catalytic allyl transfer reactions, see: Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 2, pp. 965–979.
- For a nice example just published, see: Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covell, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 231–234.
- Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615–617.
- N*-Acylated 4-alkyl-1,3-thiazolidine-2-thiones have been introduced in asymmetric synthesis by Nagao, Fujita et al.: (a) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga,

- H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243–4249; (b) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393. For recent examples of titanium-mediated aldol reactions based on these auxiliaries, see: (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902; (d) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949–8952.
- Enantioselectivity on acetate metal enolate aldol reactions still continues to be a challenge. For recent examples, see: (a) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193–8200 and references cited therein; (b) Le Sann, C.; Simpson, T. J.; Smith, D. I.; Watts, P.; Willis, C. L. *Tetrahedron Lett.* **1999**, *40*, 4093–4096.
 - To the best of our knowledge, stereoselective acetate-type aldol addition to non-cyclic acetals has not been reported before. On the other hand, non stereoselective acetate-type Mukaiyama aldol additions to acetals have attracted more attention. For example, see: (a) Matsuda, I.; Hasegawa, Y.; Makino, T.; Itoh, K. *Tetrahedron Lett.* **2000**, *41*, 1405–1408; (b) Chen, J.; Otera, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 91–93; (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915–7916; (d) Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* **1993**, 371–373; (e) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259–4275; (f) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043–1054.
 - Neat TiCl₄ (0.12 mL, 1.1 mmol) was added dropwise to a solution of **2** (203 mg, 1 mmol) in CH₂Cl₂ (8 mL), at 0°C under N₂. The yellow solution was stirred for 5 min at 0°C and cooled at –78°C, and a solution of ^tPr₂EtN (0.19 mL, 1.1 mmol) in CH₂Cl₂ (1 mL) was added. The dark red enolate solution was stirred for 30 min at –78°C and 2 h at –50°C, and 1 equiv. each of Lewis acid and dimethyl acetal was successively added dropwise. The resulting mixture was stirred at the temperature and time showed in Tables 1 and 2. The reaction was quenched by the addition of saturated aqueous NH₄Cl (6 mL) and the layers were separated. The aqueous layer was re-extracted with CH₂Cl₂ and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated. Purification by MPLC (hexanes/EtOAc) afforded the pure major diastereomer **3**.
 - All new compounds have spectroscopic and analytical data consistent with the assigned structure. The absolute configurations of adducts **3a** and **3g** have been established by chemical correlation.
 - Chromatographic removal of non-reacted starting material **2** proved to be difficult in the case of adducts **3h** and **3i**; it became more appropriate to isolate them as the corresponding Weinreb amides.
 - Commercial or deactivated (2.5% Et₃N) flash silica gel causes loss of material; thus, it is strongly recommended to use MPLC quality silica gel (silica gel 60 Å, 20–45 μm, SDS) to obtain good and reproducible results. It is also worth mentioning that chromatographic purification can be visually monitored because all of the adducts prepared to date are bright yellow.