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Catalytic Asymmetric Access to α,β Unsaturated δ-Lactones through a Vinylogous Aldol Reaction: Application to the Total Synthesis of the Prelog-Djerassi Lactone

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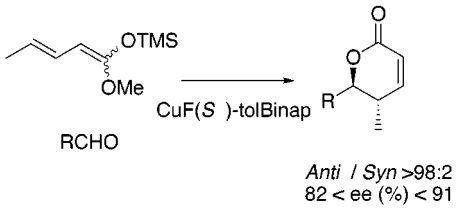
ABSTRACT



A one-step catalytic asymmetric access to α,β unsaturated δ-lactones is described, using a vinylogous Mukaiyama-aldol reaction between a γ-substituted dienolate and various aldehydes in the presence of Carreira catalyst CuF·(*S*)-tolBinap. This methodology has been further applied to a straightforward access to the Prelog-Djerassi lactone.

The α,β unsaturated and saturated δ-lactones are found in an impressive number of natural and unnatural products possessing interesting biological activities.[1−9] These compounds are also useful chiral building blocks, such as for example the Prelog-Djerassi lactone.[10,11] Efficient asymmetric syntheses of such lactones have been described but required the use of a stoichiometric amount of chiral auxiliary and/or a multiple-step sequence.[12−18]

(1) (a) Davis-Coleman, M. T.; Rivett, D. E. A. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer: New York, 1989; 55, pp 1−35. (b) Collet, L. A.; Davis-Coleman, M. T.; Rivett, D. E. A. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, E., Tamm, Ch., Eds.; Springer: New York, 1998; 75, pp 182−209.

(2) Leptomycin B and callystatin A: (a) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291. (b) Smith, A. B., III; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (c) Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57.

(3) Boronolide: Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003 and references therein.

(4) Ratjadone: Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4364.

(5) Gonodiol: Surivet, J. P.; Vatèle, J. M. *Tetrahedron* **1999**, *55*, 13011 and references therein.

(6) Pironetin: Watanabe, H.; Watanabe, H.; Bando, M.; Kido, M.; Kitahara, T. *Tetrahedron* **1999**, *55*, 9755.

(7) δ-Lactones isolated from *Cryptocarya latifolia*: Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855.

(8) Umuravumbolide: Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19.

(9) Spicigerolide: Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47.

(10) For a review, see: Martin, S. F.; Guinn, D. E. *Synthesis* **1991**, 245.

(11) For more recent approaches: (a) Oppolzer, W.; Walther, E.; Pérez Balado, C.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809. (b) Hiscock, S. D.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **1998**, *54*, 11567. (c) Chow, H.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2651. (d) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187. (e) Pilli, R. A.; Kleber, C.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811.

(12) For asymmetric reactions using vinylogous urethane chemistry, leading to *syn* unsaturated lactones, see: (a) Schlessinger, R. H.; Li, Y. J.; Von Langen, D. J. *J. Org. Chem.* **1996**, *61*, 3226. (b) Dankwardt, S. M.; Dankwardt, J. W. *Tetrahedron Lett.* **1998**, *39*, 4971.

(13) For RCM strategies, see: (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187. (c) Dirat, O.; Kouklovsky, C.; Langlois, Y.; Lesot, P.; Courtieu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3197. (d) Fuerstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

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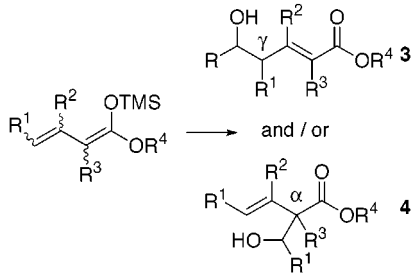
We wish to report herein an efficient catalytic asymmetric one-step protocol to access α,β unsaturated δ-lactones using a vinylogous aldol reaction.[19]

Recently, we have described the efficient formation of vinylogous aldol product using silyl dienolate **1** in good yields, excellent γ: α regioselectivity, and moderate to good enantioselectivity (Scheme 1).[20]

Scheme 1. Vinylogous Mukaiyama-Aldol Reactions



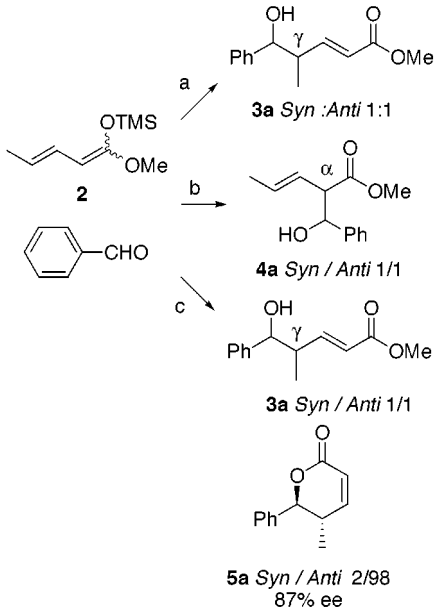
1 $R^1 = R^2 = H$; R^3 = Me; R^4 = Et
2 R^1 = Me, $R^2 = R^3$ = H; R^4 = Met

To observe the influence of a γ substituent on the course (α/γ and *syn*/*anti* ratio) of the reaction, we envisioned the reaction of γ-substituted silyl-dienolate **2**[21] with benzaldehyde. Unexpected results were observed depending on the nature of the dienolate activation (Scheme 2).

Using 10% of tetrabutylammonium triphenyldifluorosilicate TBAT as a racemic nonhygroscopic source of fluoride,[22] the expected vinylogous aldol product **3a** was isolated in 45% yield in a disappointing 1:1 *syn*/*anti* ratio. Changing the fluoride source to a chiral nonracemic ammonium fluoride,[20c] we were surprised to isolate only the α aldol product in 68% yield, in a 1:1 *syn*/*anti* mixture.

Moving to the Carreira catalyst CuF·(*S*)-tolBinap,[23] a 14:86 mixture of the vinylogous aldol product **3a** and the lactone **5a** was isolated in 85% yield (Table 1). The vinylogous aldol product **3a** was obtained with no *syn*/*anti* diastereoselectivity and very poor enantioselectivities (<5% ee for both *syn* and *anti* products). On the other hand, the α,β unsaturated lactone **5a** was found to be highly *anti* selective (*syn*/*anti* > 2:98) in 87% ee, suggesting that a more organized transition state had occurred.

Scheme 2[a]



[a] (a) TBAT 10%, THF, rt, 60%; (b) *N*-benzyl cinchodinium fluoride 10%, THF, rt, 60%; (c) CuF·(*S*)-tolBinap, 10%, rt, 85% (**3a**/**5a** 16/84).

Table 1. Vinylogous Mukaiyama Reactions of Dienolate **2** with Various Aldehydes in the Presence of 10% of CuF·(*S*)-tolBinap

entry	aldehyde	yield % (**4** + **5**)	ratio[a] **5**/**4**	no.	lactones **5** *anti*/*syn*[a]	ee
1	benzaldehyde	85	86/14	**5a**	>98/2	87[b], 98[c]
2	2-naphthaldehyde	95	80/20	**5b**	>98/2	85[d]
3	2,3-dimethoxy benzaldehyde	87	81/19	**5c**	>98/2	91[e], 98[c]
4	2-furaldehyde	60	50/50	**5d**	>98/2	86[f]
5	(*E*)-cinnamaldehyde	60	70/30	**5e**	>98/2	82[g]
6	isobutyraldehyde	95	64/36	**5f**	>98/2	91[h]

[a] Determined by ^{1}H NMR on the crude product. [b] HPLC DAICEL-OD, hexane/2-propanol 95/5. [c] After recrystallization (heptane). [d] HPLC DAICEL-OJ, hexane/2-propanol 82/18. [e] HPLC DAICEL-OJ, hexane/2-propanol 95/5. [f] HPLC DAICEL-OJ, hexane/2-propanol 95/5. [g] HPLC DAICEL-OJ, hexane/2-propanol 90/10. [h] HPLC ChiralPAK AD, hexanes/ethanol 99/1.

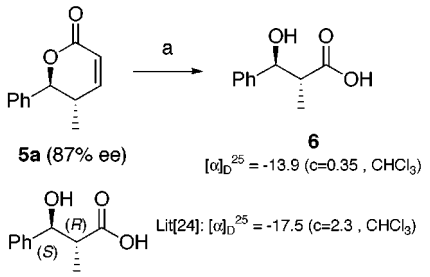
The reaction with other aromatic aldehydes (Table 1, entries 2−4) was also efficient, leading to lactones with excellent diastereoselectivities (>2:98 *syn*/*anti*) and high enantioselectivities (85−91% ee and even 98% ee for the

(14) For a palladium-catalyzed rearrangement of vinyl-oxiranes, see: Marion, F.; Le Fol, R.; Courillon, C.; Malacria, M. *Synlett* **2001**, 138.
(15) For an hydrozirconation-carbonylation strategy, see: Dupont, J.; Dupont, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 949.
(16) For (*Z*)-selective olefination strategies, see: (a) Nicoll-Griffith, D. A.; Weiler, L. *Tetrahedron* **1991**, *47*, 2733. (b) Yokokawa, F.; Fujiwara, H.; Shiori, T. *Tetrahedron Lett.* **1999**, *40*, 1915.
(17) For *cis*-alkyne reduction strategies, see: (a) Surivet, J. P.; Vatèle, J. M. *Tetrahedron* **1999**, *55*, 13011. (b) Watanabe, H.; Watanabe, H.; Bando, M.; Kido, M.; Kitahara, T. *Tetrahedron* **1999**, *55*, 9755. (c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.
(18) For an elimination strategy, see: Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855.
(19) For a general review on vinylogous Mukaiyama-aldol reaction, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.
(20) (a) Bluet, G.; Campagne, J. M. *Tetrahedron Lett.* **1999**, *40*, 5507. (b) Bluet, G.; Campagne, J. M. *Synlett* **2000**, 221. (c) Bluet, G.; Campagne, J. M. *J. Org. Chem.* **2001**, *66*, 4293.
(21) Botha, M. E.; Giles, R. G. F.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 85.
(22) (a) Pilcher, A. S.; Ammon, H. L.; Deshong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166. (b) Handy, C. J.; Lam, Y.-F.; Deshong, P. *J. Org. Chem.* **2000**, *65*, 3542.
(23) (a) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (b) Pagenkopf, B. L.; Kruger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124.

recrystallized lactones **5a** and **5c**). Reaction with 2-furaldehyde proved to be less selective, leading to the lactone with a high ee (86%) but generally in a 1:1 ratio of linear and lactone products. The reactions with unsaturated (entry 5) and aliphatic (entry 6) aldehydes were also efficient in terms of *anti*/*syn* ratio (>98/2) and ee (respectively, 82%, 91%), but the lactone/linear product ratios were somewhat lower (respectively, 70/30, 64/36) compared to aromatic aldehydes.

To determine the absolute configuration of the lactones, lactone **5a** was oxidized to the previously described enantiomerically pure compound **6**.[24] A rotation of −13.9 (for 87% ee) was found, in agreement with the reported rotation of −17.5 described for the enantiomerically pure *anti* (2*R*,3*S*) compound.

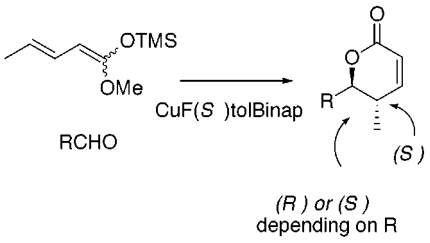
Scheme 3[a]



[a] (a) $RuCl_3$ 6%, $NaIO_4$ 4.2 equiv, $CH_3CN/CCl_4/H_2O$ (1/1/1.5), 50 °C, 24 h, 35%.

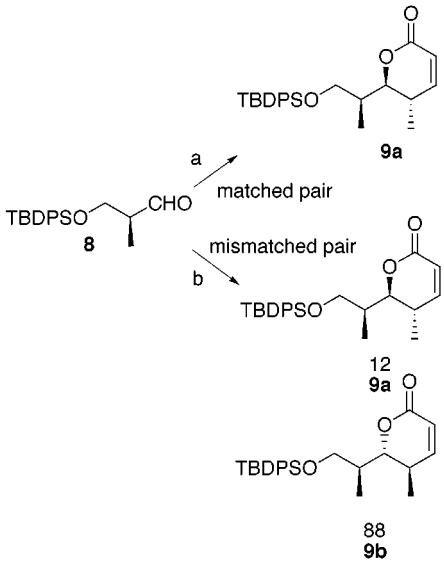
Consequently, asolute configurations of lactones **5**, obtained with CuF·(*S*)-tolBinap, were tentatively assigned as shown in Scheme 4.

Scheme 4



This methodology was then applied to chiral aldehyde **8**.[25] The reaction of chiral aldehyde **8** with the (*S*)-tolBinap ligand (matched pair) led predominantly to the *syn*/*anti* lactone **9a**.[11d,26] The other *anti*/*anti* lactone **9b**[26] could not be observed by ^{1}H NMR of the crude product, and linear products were found to be less than 10% of the mixture. After flash chromatography, lactone **9a** was isolated in a gratifying 60% yield. Using the (*R*)-tolBinap ligand with aldehyde **8** (mismatched pair), an inversion of the diastereoselectivity could be observed: a 9/1 mixture of lactones **9b**[27] and **9a** was obtained (the amount of linear products was again found to be less than 10%). After purification by flash chromatography, the mixture of lactones was isolated in 55% yield.

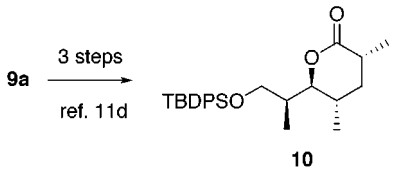
Scheme 5[a]



[a] (a) CuF·(*S*)-tolBinap, 10%, rt, 60%; (b) CuF·(*R*)-tolBinap, 10%, rt, 55%.

According to the procedures described by Cossy,[11d] the lactone **9a** was further transformed in three steps to the Prelog-Djerassi lactone **10**. This procedure constitutes a straightforward (four steps from aldehyde **8**) catalytic asymmetric access to the Prelog-Djerassi lactone (Scheme 6).

Scheme 6



In conclusion, the catalytic asymmetric vinylogous aldol of γ-substituted dienolate constitutes a valuable one-step route to α,β unsaturated lactones, as illustrated by the synthesis of the Prelog-Djerassi lactone. Further optimization

(24) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.
(25) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161.
(26) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.
(27) Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menendez, J. C.; Organ, H. M.; White, A. D. *Tetrahedron* **1992**, *48*, 7899−7938.

and applications of this reaction to the synthesis of natural products are currently under investigation.

Acknowledgment. We thank Prof. J. Cossy for kindly providing us the spectra of compounds **9a** and **10** and Dr. J. Dudash for the revision of the manuscript.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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