Asymmetric Synthesis of α-Substituted β-Formyl δ-Lactones via a Michael Addition/α-Alkylation Protocol

D. Enders*, J. Vázquez

Institut für Organische Chemie, Professor-Pirlet-Str. 1, 52074 Aachen, Germany
Fax: +49 (241) 8888127; E-mail: enders@RWTH-Aachen.de

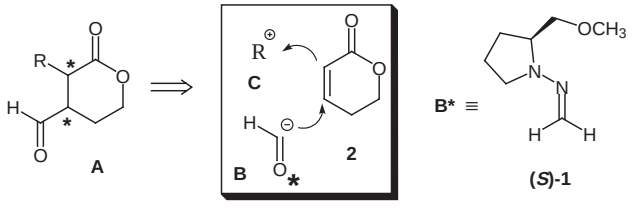
Received 28 January 1998

Abstract: An efficient *trans*-diastereo- and enantioselective synthesis of α-substituted β-formyl δ-lactones **5** (de ≥98%, ee = 80 - 95%) is described, employing formaldehyde-SAMP-hydrazone (**1**) as a neutral formyl anion equivalent. The new procedure involves the Michael addition of **1** to 5,6-dihydro-2H-pyran-2-one (**2**) followed by *trans*-selective α-alkylation and subsequent oxidative cleavage of the auxiliary.

Key words: SAMP-hydrazone, formyl anion equivalent, alkylation of lactones, Michael addition, asymmetric synthesis

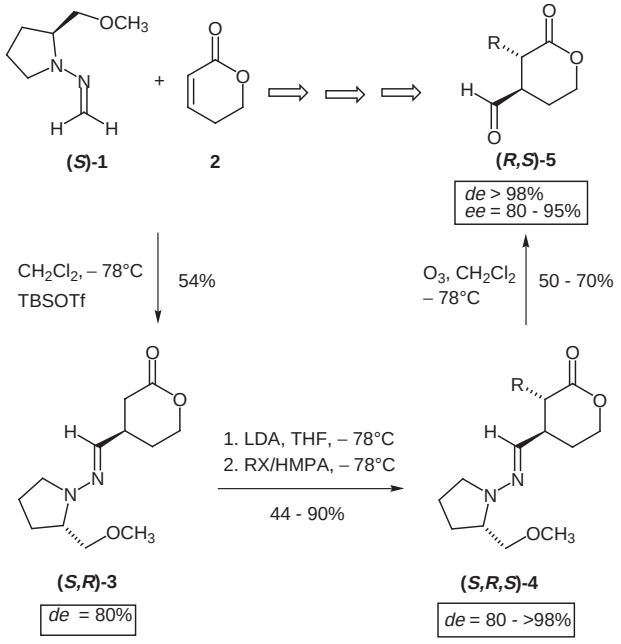
Lactones[1] and their derivatives feature as important subunits in many natural products, such as sesquiterpenes,[2] α-methylene lactones[3] and macrolides.[4] In addition, they show various biological properties, such as in semiochemicals, flavours and fragances, antibiotics or cytostatics. Therefore the efficient and flexible asymmetric synthesis of lactone building blocks is of great interest.[5]

The previously demonstrated utility of formaldehyde SAMP-hydrazone *(S)*-**1** as a neutral chiral formyl anion and cyanide equivalent[6] for nucleophilic additions to nitroalkenes,[7] sugar aldehydes,[8] α,β-unsaturated ketones[9] and trifluoromethylketones[10] should allow the introduction of the formyl group at the β-position of lactones via 1,4-addition. To the best of our knowledge, asymmetric nucleophilic formylation of α,β-unsaturated lactones has not been reported yet**.** Additionally, a subsequent alkylation should introduce further complexity at the α-centre. Thus, the retrosynthetic analysis of the δ-lactones **A** leads to the synthons **B** and **C** and 2-pentenolide **2** as the Michael acceptor (Figure).



Figure

We now describe the *trans*-diastereo- and enantioselective synthesis of the title α-substituted β-formyl δ-lactones via Michael addition of formaldehyde SAMP-hydrazone *(S)*-**1** to 2-pentenolide **2** as the key step. As is depicted in the Scheme, it was necessary to use a Lewis acid in order to activate the α,β-unsaturated lactone **2**. Various Lewis acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, $TiCl_4$, $ZnCl_2$, etc) were tested, but as was previously observed with enones,[9] only trialkylsilyl (TBS or TMS) triflates as promoters gave rise to the formation of the desired Michael adduct (*S,R*)-**3** in acceptable yield (54%) and good diastereomeric excess (de = 80%). It should be mentioned that attempts to isolate the corresponding silylketene acetal were not successful. The reaction was therefore quenched with pH 7 buffer or Et_3N to neutralize the triflic acid generated.[11] It was also observed that tetrahydrofuran instead of dichloromethane as solvent gave rise to undesired byproducts. In addition, it was necessary to use dilute conditions to avoid the byproducts resulting from both the electrophilic and the nucleophilic nature of *(S)*-**1**. Initially, the reaction is quite fast, but an optimum time is about 30 h after which no improvement of the yield was observed. Related 1,4-additions of **1** to 2-butenolide gave poor yields but excellent diastereoselectivities.



Scheme

Unfortunately, the mixture of β-epimers **3** was only separable by HPLC on chiral stationary phases and therefore this mixture was directly used in the subsequent deproto-

Downloaded by: East Carolina University. Copyrighted material.

nation / α-alkylation step. After metalation of the lactone **3** with lithium diisopropylamide (LDA) at – 78 °C in THF, HMPA (2.5 - 5 equivalents) and the requisite alkylating agents were added stepwise to afford the α-substituted lactone hydrazones **4** in medium to excellent yields (44 - 90%) and diastereomeric excesses of de = 80 – ≥98% (Table 1).[12] The optimum alkylating temperature concerning yield and stereoselectivity turned out to be – 78 °C for more reactive electrophiles and – 35 °C in the case of less reactive halides.

Table 1. Stepwise Michael addition/α-alkylation of (*S*)-**1** to 2-pentenolide **2** and subsequent hydrazone cleavage to lactones **5**

4 , 5	RX	yield **4** [a] (%)	$[\alpha]_D^{RT}$ (c, $CHCl_3$)	de[b] (%)	yield **5** (%)	$[\alpha]_D^{RT}$ (c, $CHCl_3$)	ee (%)
a	AllylBr	90	– 158.5 (1.20)	>98 (98)	c	–	–
b	MeI	89	– 126.4 (2.88)	80[d,e] (78)	70	+ 36.4 (1.11)	82[f]
c	BnBr	77	– 155.7 (0.97)	80[e] (>98)	59	– 9.0 (0.89)	80[g]
d	*n*-PrI	67	– 132.6 (1.44)	88 (74)	68	+ 21.5 (0.78)	89[h]
e	$TBSO(CH_2)_2I$	44	– 99.7 (1.30)	94 (59)	50	– 1.3 (0.77)	95[i]

[a] Yield after flash chromatography. [b] Determined by HPLC on chiral stationary phases [chiralpak AD (4.6 x 250 mm), (*S,S*)-Whelk-O 1 (4 x 250 mm), chiralcel OJ (4.6 x 250 mm)] after HPLC separation. Figures in brackets refer to the de values of the alkylation reactions. [c] **5a** decomposes during ozonolysis. [d] After flash chromatography. [e] Diastereoisomers were not separable by HPLC. [f] Determined as de of the corresponding acetal derived from (*R,R*)-2,3-butanediol by GC on chiral stationary phases (Lipodex E 25m). [g] Determined as de of the corresponding acetal by HPLC on chiral stationary phases [(*S,S*)-whelk-O 1 (4 x 250 mm)] [h] Determined by shift experiments using *(R)*-1-(9-anthryl)-2,2,2-trifluoroethanol as co-solvent. [i] Determined as de of the corresponding hydrazone **4.**

The *trans*-configuration of the α,β-disubstituted δ-lactones **4** was determined by ^{1}H NMR spectroscopy through the trans-diaxial coupling constants (9.5 - 10.7 Hz) of the methine hydrogens at the two new stereogenic centres. NOE experiments on compound **4b** (R = Me) confirmed this relative configuration. The absolute configuration of the minor diastereomer (*R,R*)-**4b** was determined by X-ray structure analysis, the configuration of the major isomer therefore being (3*S*,4*R*). In addition, we have recently obtained the crystal structure of the major *trans*-diastereomer of (*R,S*)-**4c**.[13] Assuming a uniform reaction pathway for all cases, the relative topicity for the nucleophilic attack of **1** to the α,β-unsaturated δ-lactone **2** is the same as previously reported for 1,4-additions to enones.[9]

In some cases the diastereomers of the δ-lactones **4** were separable by flash chromatography (**4b**) or by HPLC (**4c**,**d**) and thus it was possible to use the diastereomerically enriched lactone hydrazones **4** in the following oxidation step. This hydrazone cleavage to remove the auxiliary was carried out by ozonolysis[14] at –78 °C in dichloromethane affording the title aldehyde δ-lactones (*R,S*)-**5** in acceptable yields (50 - 70%) and high diastereo- and enantiomeric excesses (de ≥98%, ee = 80 - 95%, Table 1).

The α-substituted β-formyl δ-lactones **5** are not very stable and their purification required special silica gel (particle size 0.063 - 0.10 mm) to avoid partial decomposition. Upon prolonged standing they tend to decompose and should therefore be stored as their corresponding acetals[15] or should be prepared directly before use in further reactions.

In summary, our Michael addition / α-alkylation protocol employing formaldehyde SAMP-hydrazone as a neutral chiral formyl anion equivalent in the 1,4-addition to 2-pentenolide opens a stereoselective entry to 3-substituted 2-oxo-tetrahydro-2*H*-4-pyrancarbaldehydes, which are useful building blocks for the asymmetric synthesis of bioactive compounds.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz prize, Sonderforschungsbereich 380) and the Fonds der Chemischen Industrie. We thank the Ministerio de Educación y Cultura for a postdoctoral fellowship to J.V. We also thank Degussa AG, BASF AG, Bayer AG and former Hoechst AG for the donation of chemicals.

References and Notes

(1) For general reviews on lactones see: a) Pielartzik, H.; Irmisch-Pielartzik, B.; Eicher, T. *In Houben-Weyl*, 4th ed., Vol. E5, part 1; Falbe, J., Ed.; Thieme: Stuttgart **1985**; p 715. b) Boyd, G.V. *In The Chemistry of Acid Derivatives, The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: Chichester **1979**; p 492; **1992**; p 548. c) Mulzer, J. *In Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I.; Winterfeldt, E.; Eds.; Pergamon: Oxford **1991**; p 323. d) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869-1888 and references cited therein.

(2) Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo **1973**.

(3) For reviews see: a) Grieco, P. A. *Synthesis* **1975**, 67. b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem.* **1985**, *97*, 96; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94. c) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157. d) Sarma, J. C.; Sharma, R. P. *Heterocycles* **1986**, 441. e) Ito, M. *Pure Appl. Chem.* **1991**, *63*, 13.

(4) For reviews see: a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem.* **1977**, *89*, 602; *Angew. Chem. Int. Ed. Engl* **1977**, *16*, 587. c) Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1. d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. e) Boeckmann Jr., R. K.; Goldstein, S. W. In *The Total Synthesis of Natural Products*, Vol. 7; ApSimon, J., Ed.; Wiley: New York **1988**; p1.

(5) For alternative asymmetric syntheses of δ-lactones developed in our group see: a) Enders, D.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1223. b) Enders, D.; Gröbner, R.; Runsink, J.

Downloaded by: East Carolina University. Copyrighted material.

Synthesis **1995**, 947. c) Enders, D.; Kaiser, A. *Heterocycles* **1997**, *46*, 631. d) Enders, D.; Teschner, P.; Gröbner, R.; Raabe, G. *Synthesis* **1999**, 237.
(6) Enders, D.; Bolkenius, M.; Vázquez, J.; Lassaletta, J. M.; Fernández, R. *J. Prakt. Chem.* **1998**, *340*, 281.
(7) a) Lassaletta, J. M.; Fernández, R. *Tetrahedron Lett.* **1992**, *33*, 3691-3694. b) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Tetrahedron Lett.* **1994**, *35*, 471. c) Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 48. d) Lassaletta, J. M.; Fernández, R.; Gasch, C.; Vázquez, J. *Tetrahedron* **1996**, *52*, 9143.
(8) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Pareja, C. *Tetrahedron Lett*. **1996**, *37*, 5787.
(9) a) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Díez, E. *J. Am. Chem. Soc.* **1996**, *118*, 7002. b) Díez, E.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E.; Vázquez, J. *J. Org. Chem.* **1997**, *62*, 5144.
(10) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Vázquez, J.; Díez, E.; Monge, A.; Lassaletta, J. M. *Angew. Chem*. **1998**, *110*, 3598; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3428.
(11) **General procedure for the Michael addition:** To a cooled (– 78 °C) solution of 2-pentenolide **2** (10 mmol) and *(S)*-**1** (20 mmol) in CH_2Cl_2 (80 ml) was added dropwise TBS triflate (12 mmol) pre-cooled at – 30 °C. The mixture was stirred for 30 h, neutralized with Et_3N at – 78 °C and allowed to warm to 0 °C. The mixture was washed with water, dried ($MgSO_4$) and purified by flash chromatography (SiO_2, Et_2O/pentane 3:1→Et_2O).
(12) a) Posner, G. H.; Loomis, G. L. *J. Chem. Soc., Chem. Commun.* **1972**, 892. b) Herrmann, J. L.; Schlessinger, R. H. *J Chem. Soc., Chem. Commun*. **1973**, 711.
c) **General procedure for the α-alkylation**: A solution of the 1,4-adduct **3** (2 mmol) in THF (4 ml) cooled at – 78 °C was treated with a solution of LDA (2.2 mmol) in THF (4 ml) at – 78 °C. After stirring for 3h, HMPA (0.87 ml or 1.74 ml) was added dropwise. The mixture was then treated with the alkyl halide (2.6 mmol) and kept at – 78 °C or warmed up to – 35 °C until consumption of the starting material was detected by TLC. After hydrolysis with saturated NH_4Cl solution the aqueous phase was extracted with Et_2O and the combined organic phase was extracted with water and dried ($MgSO_4$). The crude material was purified by flash chromatography (SiO_2, Et_2O/pentane).
(13) Complete crystallographic details for compounds (*R,R*)-**4b** and (*R,S*)-**4c** will be published in a full paper in due course.
(14) **Typical procedure for ozonolysis:** Ozone was bubbled through a solution of **4** (1 mmol) in dry CH_2Cl_2 (25 ml) at –78 °C until the mixture retained its initial colour (TLC control). Me_2S (1.1 mmol) was added and the mixture was allowed to warm to room temperature, concentrated in vacuo, and the residue purified by flash chromatography (SiO_2, 0.063-0.100 mm, Et_2O/pentane).
(15) a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. b) Enders, D.; Whitehouse, D.L. *Synthesis* **1996**, 621.

Article Identifier:
1437-2096,E;1999,0,05,0629,0631,ftx,en;G04099ST.pdf

Downloaded by: East Carolina University. Copyrighted material.