211. 2,3-Disubstituted γ-Butyrolactams from the *Michael*-Additions of Doubly Deprotonated, Optically Active β-Hydroxycarboxylates to Nitroolefins

Preliminary Communication

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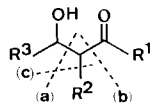
Summary

The conjugate addition of the chiral, non-racemic alkoxy-enolates **5** and **6** to nitroolefins furnishes the hydroxynitroesters **7**–**13**, which are catalytically hydrogenated to give the lactams **14**–**18**. The configuration of adduct **7** from nitroethylene was elucidated by NMR. analysis of the acetal **20** derived from **7**. The assignment establishes that the reaction follows the stereochemical rule of attack depicted in **21** and previously deduced for other electrophiles, *i.e.* formation of *erythro*-products of type **3b** and **4b**. No stereocontrol was found at the newly formed chiral centers in α- and β-position to the NO_2 group of **8**–**12**.

Stereocontrol in reactions of open-chain compounds has become one of the major current goals of synthetic organic chemistry [1]. For the construction of diastereomeric aldol- or *Reformatzky*-type products **1**, three routes have been used successfully: (a) The classical aldol reaction [2] and its modifications [3] are now well



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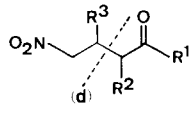

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established to be diastereoselective with (*E*/*Z*)-isomeric enolate derivatives as starting materials; method (b) is the S_N2-type ring opening with inversion of *cis*/*trans*-isomeric epoxides by lithiodithianes [4] [5] or other acyl-d[1]-reagents; recently, a third route (c) evolved, in which R^2 is introduced by diastereoselective alkylation of aldolate-enolates [6–8] or of β-lactone enolates [9], or by cuprate opening of appropriate epoxides [8] [10]. – On the other hand, diastereoselective *Michael*-

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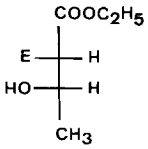
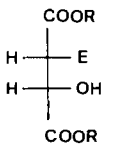
additions with formation of two new centers of chirality are hardly known. We are aware of only one case, the formation of 4-nitroketones **2** (d) from enamines [11] or enolates [12] and nitroolefins[3]).

We have now tried to combine the two selective processes indicated by **1** (c) and **2** (d), by adding nitroolefins at −78° to tetrahydrofuran solutions of the alkoxy-enolates **5** and **6** derived from enantiomerically enriched (85% e.e.) ethyl (*S*)-(+)-3-hydroxybutanoate (**3a**) [13] [14] [7] and from enantiomerically pure dimethyl (*S*)-(−)-malate (**4a**, R = CH_3) [8], respectively. The adducts **7**–**13** are isolated after the



3a E = H
b E = alkyl



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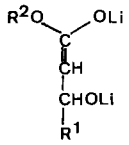
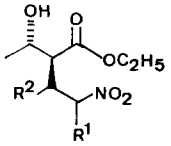
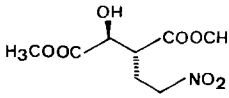


5 $R^1 = CH_3$, $R^2 = C_2H_5$ (from **3a**)
6 $R^1 = COOCH_3$, $R^2 = CH_3$ (from **4a**)

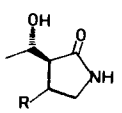


	7	8	9	10	11	12
R^1	H	H	H	H	H	CH_3
R^2	H	CH_3	CH_2Br	C_6H_5	3,4(OCH_2O)C_6H_3	H
	(56%)	(39%)	(38%)	(81%)	(54%)	(35%)

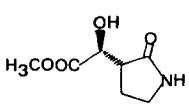


13 (31%)

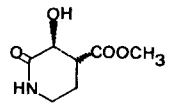
usual work-up [12] in moderate to good, non-optimized yields (chromatographed and distilled or recrystallized materials). This reaction constitutes an extension of the simple alkylations leading to **3b** [7] and **4b** [8]. – The nitroesters **7**, **8**, **10**, **11**, and **13** were catalytically hydrogenated (*Raney*-nickel) to aminoesters which spontaneously cyclized to the lactams **14**–**18**. While **18** could be a five- or a six-membered heterocycle **18a** or **18b**[4]), the other products must be γ-lactams.



14 R = H (87%)
15 R = CH_3 (83%)
16 R = C_6H_5 (69%)
17 R = 3.4(OCH_2O)C_6H_3 (43%)



18a (61%)



18b

[3]) Our report [12], that lithium cyclohexenolate adds diastereoselectively to nitrostyrene, can now be substantiated: the same *RS*/*SR*- or *n*-diastereomer is formed with up to 80% preference which is produced in the enamine reaction (unpublished results from these laboratories).

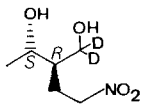
[4]) Although the IR.- and NMR.-data are not conclusive, we favour the δ-lactam structure **18b**, based on the MS. fragmentation pattern (*m/z* = 85 and $M^+ - 85 = 88$, the *McLafferty* fragmentation peaks of **18a**, appear with low intensity).

Table. *Some physical data of the products* **7**, **10–12**, **13** *of addition of doubly deprotonated β-hydroxyesters to nitroolefins, and of the lactams* **14–18**.

Compound	
7	$[\alpha]_D^{20} = -9.3°$ ($c = 1.01$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 20.99 (*qa*, CH_3CHOH); 26.16 (*t*, C(3)); 49.12(*d*, C(2));68.13 (*d*, CH_3CHOH); 73.44 (*t*, C(4))
10	Diastereomer **a**: m.p. 69–72° (CH_2Cl_2/hexane), $[\alpha]_D^{20} = -29.7°$ ($c = 1$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 1.15 (*d*, $J = 6$, CH_3CHOH); 2.68 (*d*×*d*, $J = 3$ and 11, H–C(2)) Diastereomer **b**: m.p. 78–79° (CH_2Cl_2/hexane), $[\alpha]_D^{20} = -6.3°$ ($c = 1$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 1.28 (*d*, $J = 6$, CH_3CHOH); 2.78 (*d*×*d*, $J = 3$ and 9, H–C(2))
11	Diastereomer **a**: m.p. 73–78° (CH_2Cl_2/hexane), $[\alpha]_D^{20} = -32.5°$ ($c = 1$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 22.12 (*qa*, CH_3CHOH); 78.74 (*t*, C(4)); 173.18 (*s*, C=O) Diastereomer **b**: m.p. 76–78° (CH_2Cl_2/hexane), $[\alpha]_D^{20} = -6.8°$ ($c = 1$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 21.86 (*qa*, CH_3CHOH); 77.90 (*t*, C(4)); 172.75 (*s*, C=O)
12	Diastereomer **a**: $[\alpha]_D^{20} = -14.6°$ ($c = 1.05$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 1.24 (*d*, $J = 6.6$, CH_3CHOH); 4.36–4.86 (*m*, H–C(4)) Diastereomer **b**: $[\alpha]_D^{20} = +7.4°$ ($c = 0.24$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 1.24 (*d*, $J = 7.5$, CH_3CHOH); 4.45–4.88 (*m*, H–C(4))
13	$[\alpha]_D^{20} = +11.0°$ ($c = 1.01$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 3.72 and 3.82 (2 *s*, 2 $COOCH_3$); 4.35 (*d*×*d*, $J = 3$ and 6, $CHOH$, after D_2O-exchange: *d*, $J = 3$)
14	M.p. 75–76°, $[\alpha]_D^{20} = +40.2°$ ($c = 1.01$, $CHCl_3$). – IR. ($CHCl_3$): 3430 (NH str.), 1693 (C=O str.). – ^{13}C-NMR. ($CDCl_3$): 20.55 (*qa*, CH_3CHOH); 24.05 (*t*, C(4)); 40.58 (*t*, C(5)); 46.89 (*d*, C(3)); 69.22 (*d*, CH_3CHOH); 180.74 (*s*, C=O)
15	Diastereomer **a**: m.p. 64–66°, $[\alpha]_D^{20} = -4.3°$ ($c = 1$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 14,49 (*qa*, CH_3–C(4)); 21.19 (*qa*, CH_3CHOH); 50.84 (*d*, C(4)); 65.28 (*d*, CH_3CHOH) Diastereomer **b**: $[\alpha]_D^{20} = +27.9°$ ($c = 1.02$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 19.51 and 20.76 (2 *qa*, 2 CH_3); 54.36 (*d*, C(4)); 68.91 (*d*, CH_3CHOH)
16	Diastereomer **a** (from **10a**): m.p. 135–139° ($CHCl_3$/Et_2O), $[\alpha]_D^{20} = +35.1°$ ($c = 1.01$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 49.34 (*t*, C(5)); 69.61 (*d*, CH_3CHOH) Diastereomer **b** (from **10b**): m.p. 160–163° ($CHCl_3$/Et_2O), $[\alpha]_D^{20} = -20.5°$ ($c = 1.01$, $CHCl_3$). – ^{13}C-NMR. ($CDCl_3$): 48.72 (*t*, C(5)); 65.81 (*d*, CH_3CHOH)
17	Diastereomer **a** (from **11a**): m.p. 138–142° ($CHCl_3$/Et_2O), $[\alpha]_D^{20} = +47.4°$ ($c = 1.01$, $CHCl_3$). – IR. (KBr): 3295, 1685 and 1660 Diastereomer **b** (from **11b**): m.p. 186–188° ($CHCl_3$/Et_2O), $[\alpha]_D^{20} = -38.3°$ ($c = 1.01$, $CHCl_3$). – IR. (KBr): 3403, 3210, 1665
18	M.p. 184–186° (MeOH), $[\alpha]_D^{20} = -55.8°$ ($c = 1.02$, MeOH). – IR. (KBr): 3310, 1733, 1670. – ^{1}H-NMR. (DMSO-d_6 with 10% $CDCl_3$): 1.63–2.13 (*m*, CH_2CH_2N); 2,67 (*m*, $CHCOOCH_3$); 3.07–3.30 (*m*, CH_2N); 3.63 (*s*, CH_3O); 3.98 (*d*×*d*, $J = 10$ and 4.5, after D_2O-exchange *d*, $J = 10$, $CHOH$); 5.18 (*d*, $J = 4.5$, $CHOH$); 7.57 (*s*, HN). – ^{13}C-NMR. (DMSO-d_6): 24.45, 45.80, 51.56, 68.12, 73.05, 171.29 and 173.4

The nitroesters and lactams isolated contain one or two more asymmetric C-atoms than the starting materials, so that up to four different diastereomers could have been formed. We analyzed the configurational composition at the nitroester and/or at the lactam stage by column or gas phase chromatographic separation or by ^{1}H- or ^{13}C-NMR. spectroscopy, or by a combination of these methods. It turns out, that the adducts from unsubstituted nitroethylene consist of mainly one

diastereomer, *i.e.* **7** with a preference of *ca.* 95:5, and **13** with an excess of *ca.* 85:15. The configuration of **7** was determined[5]) by $LiBD_4$-reduction to **19** and conversion to the acetal **20**, which clearly shows the signals of an antiperiplanar pair of



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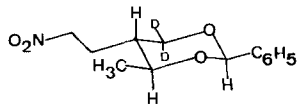

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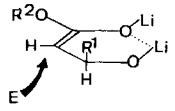

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H-atoms ($^3J(H,H) = 9$ Hz) in the ^{1}H-NMR.-spectra measured with decoupling of the appropriate neighbouring protons. This proves the configuration of **19**, and also of **7**, as well as the stereochemical course of the *Michael* addition. It follows the – strictly operational – mechanistic picture **21**, which was proposed previously [8] for reactions with other electrophiles and which leads to *erythro*-products of type **3b** and **4b**. – The adducts **8**, **10**, and **11** with two new asymmetric C-atoms at the centers of C,C-bond formation are *ca.* 1:1 diastereomeric mixtures, so is the 2-nitropropene adduct **12**. The isomers could be separated either at the nitroester (**10**–**12**) or at the lactam (**15**) stage. Although no configurational assignments have been carried out, we *tentatively assume* that the configuration of all products at the center in α-position to the carbonyl group is as shown in the *formulae* **7**–**18**, *i.e.* that the attack of the nitroolefin electrophiles occurs selectively as depicted in **21**. This would mean that the *Michael* acceptors 1-nitropropene and ω-nitrostyrenes participate in the reaction in a non-stereoselective fashion.

The new compounds – unidentified racemic isomers of **14** and **16** are known [15] [16] – were characterized by IR., ^{1}H-NMR., ^{13}C-NMR. and mass spectra and by elemental analyses, which are all compatible with the structures shown here; for some data see the accompanying *Table*. The specific rotations given for the products ought to correspond at least to enantiomeric purities of the starting materials β-hydroxybutyric and malic acid (see above); in the case of solid products from **3a**, recrystallizations might have led to enrichment of the excess enantiomer. Since *both* enantiomers of the hydroxy-acids are readily available [17], the enantiomers of the compounds **7**–**18** can also be prepared. Applications of the reaction described to other substrates and to syntheses of natural products are under investigation.

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