274. Enantioselective Generation and Diastereoselective Reactions of Chiral Enolates Derived from α-Heterosubstituted Carboxylic Acids[1])

Preliminary Communication

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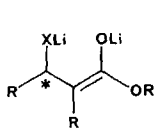
Summary

Dioxolanones **7** and **8a** and oxazolinones **9a** derived from pivalaldehyde and lactic acid, mandelic acid, and proline, respectively, furnish chiral enolates of type **3** by deprotonation with LDA. Reactions of these enolates with alkyl halides, aldehydes, and ketones (→ **8b**, **9b**, **11**–**13**) are highly diastereoselective. Thus, the overall enantioselective α-alkylation of chiral, non-racemic α-heterosubstituted carboxylic acids (**4** → **6**) is realized.

Continuing our search for chiral reagents derived from readily available enantiomerically pure starting materials ('chiral pool') [1], we recently investigated the enolates of type **1** (from β-hydroxy-butyrate [2], malate [2–4], *N*-formylaspartate [5]) and **2** (from 2,3-*O*-isopropylidentartrate [6]). We now report preliminary results



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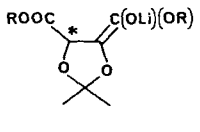

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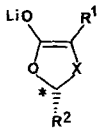
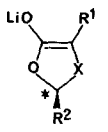
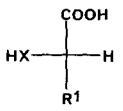


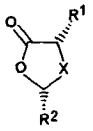
3a



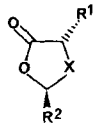
3b



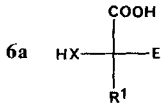
4 (X = NR, O, S)



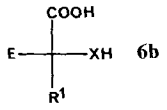
5a *(cis)*



5b *(trans)*



6a



6b

[1]) Part of the present results was first communicated by *D. S.* in lectures held in Ludwigshafen (Aug. 19, 1981) and in Oslo (Sept. 9, 1981).

[2]) Part of the projected Ph. D. thesis of *R. N.*, ETH Zürich.

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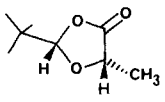
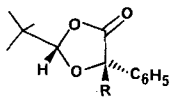
about yet another type of chiral enolates **3**, which can be derived from α-amino-, α-hydroxy-, or α-mercapto-carboxylic acids[3]), and which owe their chirality to a temporary, auxiliary asymmetric center. This center is generated by reaction of an α-heterosubstituted acid **4** with an aldehyde to give the *cis/trans*-isomeric heterocycles **5**. Separation – possibly with recycling of the undesired diastereomer – and deprotonation in the α-position to the carbonyl group can in principle furnish either one of the two enantiomeric enolates **3a** and **3b**. Diastereoselective reactions of these enolates with electrophiles and subsequent hydrolytic cleavage of the heterocycle should lead to enantiomerically enriched, α-branched α-heterosubstituted acids **6**. Note, that no 'external' chiral auxiliary compound is necessary[4]) in order to produce the branched[5]), optically active derivative **6a** or **6b** from the optically active, non-branched acid **4**.

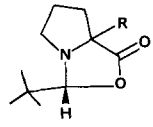
So far, we obtained best results with chiral enolates of type **3** derived from pivalaldehyde ($R^2 = t\text{-}C_4H_9$)[6]). The precursors **7**, **8a**, and **9a**[7]) were obtained by refluxing pentane solutions of this aldehyde and lactic acid, mandelic acid, and proline (the most simple *N*-alkyl-α-aminoacid), respectively, in the presence of an acid catalyst (*p*-toluenesulfonic acid, trifluoroacetic acid) for 1–3 days, with azeotropic removal of the water formed. Under these conditions **7** and **8a** were obtained in a (4:1)- and (24:1)-mixture, respectively, with the *trans*-isomers of type **5b**, which were removed by recrystallization (ether/pentane 1:1, $-78°$ and $+5°$, respectively); **9a** was isolated as a single diastereomer by distillation. The



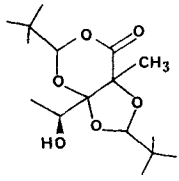
7



8a R = H
8b R = C_3H_7



9a R = H (from (*S*)-proline)
9b R = CH_2–CH=CH_2



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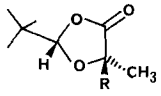

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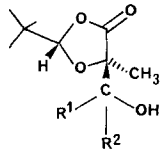

12 $R^1 = R^2$
13 $R^1 \neq R^2$

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[3]) Achiral enolates derived from amino [7] and hydroxy [8] [9] acids are well known. For 2,2-dimethyl-1,3-dioxolan- and -thioxolan-4-one enolates see [10].

[4]) This clearly distinguishes the present, economic method from that used by *Schöllkopf et al.* [11] for the preparation of optically active α-amino acids through diketopiperazines.

[5]) There is a great need for synthetic methods of stereoselective generation of persubstituted (quaternary) C-centers [12].

[6]) Recently, *Fráter et al.* [13] have also described the generation and reactions of the enolates **3**, $R^1 = C_6H_5$, CH_3, $R^2 = t\text{-}C_4H_9$. The conditions (HMPT as cosolvent), the types of substrates (only alkyl halides) and – in some cases – the chemical yields and the optical rotations of the starting materials and products reported differ, however, from those in our work[1]).

[7]) This compound was previously prepared by a different route [14].

configuration of **7** was deduced from NOE-NMR. measurements; by analogy, the *cis*-configuration was assumed also for **8a**, while the *t*-butyl group of the bicyclic proline derivative **9a** is expected to be in an *exo*-position. For data about **7**, **8a**, and **9a** and about the products obtained from them see the *Table*.

Addition of lithium diisopropyl amide (LDA) to a dilute tetrahydrofuran (THF) solution of the lactic acid derivative **7** at $-78°$ generates[8]) the chiral enolate **3a**, $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$. 'Selfcondensation', leading to the dimer **10**, takes place at higher concentrations, or when only 0.5 mol-equiv. of the base are

Table. *Yields, purities, and some physical data of the products* **7**–**13**

All yields are those of distilled or recrystallized and/or chromatographed materials. The diastereomeric compositions were either determined by ^1H- or ^{13}C-NMR. (a) or by capillary GC. (b). The specific rotations $[\alpha]_D^{24-26}$ (conc.) were all measured in chloroform solutions of mixtures of the given ratio of diastereomers. B.p. are air bath temperatures during bulb-to-bulb distillations. Correct (±0.3%) elemental analyses were obtained of all compounds **7**–**13**. All spectroscopic data (IR., NMR., MS.) are in accord with the structures given here.

7	(+*trans*-Isomer, 87% from lactic acid of $[\alpha]_D^{25} = +13.6°$ ($c = 2{,}5$, 1.5N NaOH), and 2,2-dimethylpropanal); 96% diastereomeric purity (a,b) after 2 crystallizations; m.p. *ca.* +5°, b.p. 80°/20 Torr; $[\alpha]_D = +44.8°$ (1.83)
8a	(+*trans*-Isomer, 82% from mandelic acid of $[\alpha]_D^{25} = +154.3°$ ($c = 3.30$, H_2O)); >99% diaster. purity (a) after 1 recrystallization; m.p. 140°; $[\alpha]_D = +88.7$ (1.17)
8b	From **8a** and iodopropane (84%); 95% ds (a); b.p. 95°/10^{-3} Torr; $[\alpha]_D = +29.9°$ (1.00)
9a	From (*S*)-prolin of $[\alpha]_D^{20} = -85.0°$ ($c = 5$, H_2O) (92%); >98% ds (a); b.p. 85°/0.05 Torr; $[\alpha]_D = -24.7°$ (2.38)
9b	From **9a** and allyl bromide (55%); >98% ds; b.p. 90°/10^{-3} Torr; $[\alpha]_D = +6.86°$ (1.59)
10	From **7** (89%); >95% ds (a); m.p. 147° (ether/pentane); $[\alpha]_D = +21.5°$ (0.93)
11a	$R = C_2H_5$; from **7** and iodoethane (82%); 97% ds (b); b.p. 110°/16 Torr; $[\alpha]_D = +43.8°$ (2.52)
11b	$R = CH_2{-}CH{=}CH_2$; from **7** and 1-bromo-2-propene (77%); 98% ds (b); b.p. 130°/12 Torr; $[\alpha]_D = +52.9°$ (2.23)
11c	$R = CH_2C_6H_5$; from **7** and benzyl bromide (81%); 96% ds (b); b.p. 140°/10^{-3} Torr; $[\alpha]_D = +57.6°$ (2.48)
12a	$R^1 = R^2 = CH_3$; from **7** and acetone (83%); >95% ds (a); m.p. 95° (ether/pentane); $[\alpha]_D = +26.3°$ (0.93)
12b	$R^1 - R^2 = (CH_2)_4$; from **7** and cyclopentanone (85%); >95% ds (a); m.p. 85° (ether/pentane); $[\alpha]_D = +9.3°$ (1.68)
12c	$R^1 = R^2 = C_6H_5$; from **7** and benzophenone (87%); >95% ds (a); m.p. 90° (ether/pentane); $[\alpha]_D = +88.7°$ (0.73)
13a	$R^1 = CH_3$, $R^2 = H$; from **7** and acetaldehyde (84%); 82% ds (a); b.p. 90°/0.005 Torr; $[\alpha]_D = +23.5°$ (1.71)
13b	$R^1 = t\text{-}C_4H_9$, $R^2 = H$; from **7** and pivalaldehyde (83%); 53% ds (a); m.p. 43–46°; $[\alpha]_D = +19.6°$ (1.02)
13c	$R^1 = C_6H_5$, $R^2 = H$; from **7** and benzaldehyde (85%); 84% ds (a); m.p. 88–95°; $[\alpha]_D = +34.1°$ (0.82)
13d	$R^1 = C_6H_5$, $R^2 = CH_3$; from **7** and acetophenone (81%); 93% ds (a); m.p. 91–98°; $[\alpha]_D = +51.2°$ (1.18)

[8]) An equivalent amount of a 1M LDA solution in THF/hexane 1:3 is added to a 0.17M solution of **7** in THF at such a rate, that the temperature of the reaction mixture does not exceed $-70°$. – After 30–40 min, the electrophile is added, and the temperature is allowed to rise to between -40 and $-20°$ before aqueous work-up.

employed. With alkyl halides, symmetrical ketones, and aldehydes or unsymmetrical ketones the products **11**, **12**, and **13**, respectively, are formed[8]) with chemical yields of 80–90% and – in most cases – with diastereoselectivities (% ds)[9]) well above 90%, see the *Table*.

The (*R*)-chirality at the newly formed asymmetric center of **11a** ($R = C_2H_5$, see the *Table*) was established by hydrolysis to (–)-2-hydroxy-2-methylbutanoic acid, m.p. 72–73°; $[\alpha]_D = -6.6°$ ($c = 1.4$, 0.2 N NaOH) ([16]: m.p. 73.5°; $[\alpha]_D = -6.9°$). We assume that all major diastereomers[10]) result from attack of the electrophiles at the (*Re*)-face, *i.e. anti* to the *t*-butyl group of the enolate **3a**, $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$, see the *trans*-configurations drawn in the *formulae* **11–13**.

The enolates generated from the other two precursors, **8a** and **9a**, in the same way as described[8]) above for **7**, were propylated and allylated (see the *Table*) to **8b** (95% ds)[9])[11]) and **9b** (> 98% ds)[9])[11]), respectively.

The high degree of diastereoselectivity of reactions of the enolates **3** is surprizing to us; aggregation [18] of these reagents might be responsible.

The alkylation of other enolates of type **3**, especially of those derived from amino acids is in progress and will be published shortly. Since the acids **4** with X = NR, O, and S are readily interconverted, and since many of them are inexpensive and commercially available in both enantiomeric forms, the methodology outlined here will make accessible a large variety of new chiral building blocks[12]).

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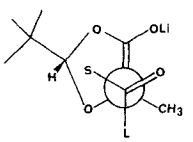
[9]) In contrast to *enantiomeric excess* (% e.e.), the *diastereomeric excess* (% d.e.) is – for obvious reasons – not a useful number to give! [15]. We propose as an abbreviation in discussions of diastereoselective reactions % ds *(diastereoselectivity)*. The coincidence of d.e. and ds with the initials of authors ([15] and [this paper]) is strictly accidental!

[10]) As in other cases [6], the stereochemical course of such reactions can revert, when changing the electrophile from alkyl halide to carbonyl compounds. The products **13** contain 3 centers of chirality. Only 2 of the possible 4 diastereomers are observed (see *Table 1*); the major one might be formed following the topology **A** (*cf.* [9] [17]).



A (S = small, L = large)

[11]) The *cis*-configuration of **8b** drawn in the *formula* has not been proved by us, see however [13]. We expect the substitution **9a** → **9b** to take place with retention of configuration.

[12]) For instance gem. disubstituted oxirans, *cf.* [19].

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