

274. Enantioselective Generation and Diastereoselective Reactions of Chiral Enolates Derived from α -Heterosubstituted Carboxylic Acids¹⁾

Preliminary Communication

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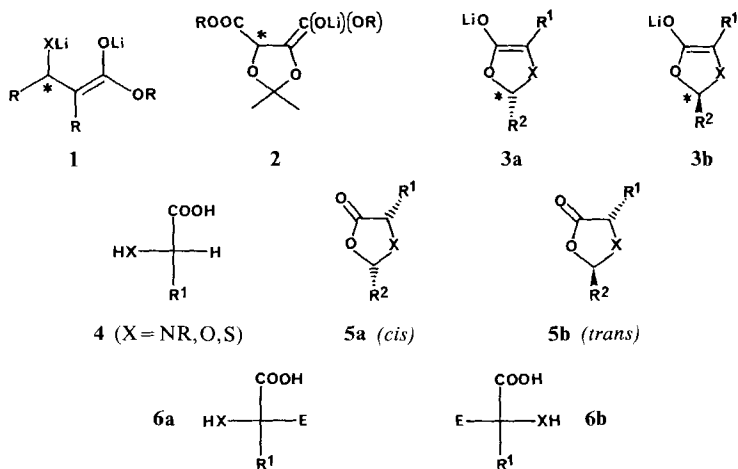
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Summary

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 (\rightarrow **8b**, **9b**, **11-13**) are highly diastereoselective. Thus, the overall enantioselective α -alkylation of chiral, non-racemic α -heterosubstituted carboxylic acids (**4** \rightarrow **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

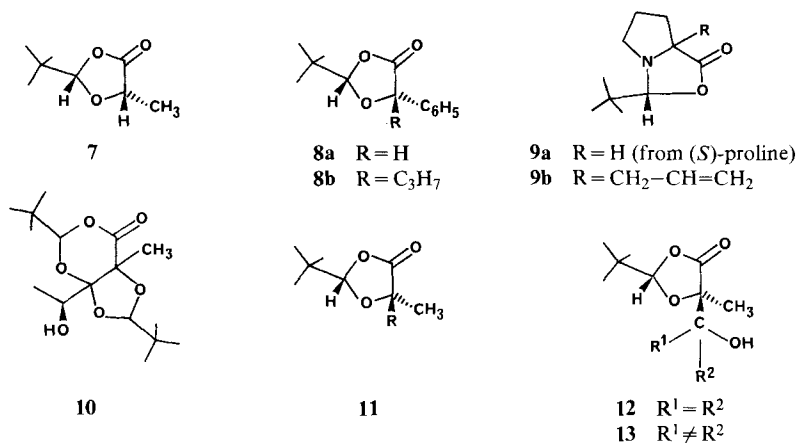


¹⁾ Part of the present results was first communicated by D.S. in lectures held in Ludwigshafen (Aug. 19, 1981) and in Oslo (Sept. 9, 1981).

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

about yet another type of chiral enolates **3**, which can be derived from α -amino-, α -hydroxy-, or α -mercapto-carboxylic acids³⁾, 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 necessary⁴⁾ in order to produce the branched⁵⁾, 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 ($R^2 = t\text{-C}_4\text{H}_9$)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 $+5^\circ$, respectively); **9a** was isolated as a single diastereomer by distillation. The



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**, $R^1 = \text{C}_6\text{H}_5$, CH_3 , $R^2 = t\text{-C}_4\text{H}_9$. 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 work¹⁾.

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° generates⁸⁾ the chiral enolate **3a**, $R^1 = \text{CH}_3$, $R^2 = t\text{-C}_4\text{H}_9$. '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 ($\pm 0.3\%$) elemental analyses were obtained of all compounds **7-13**. All spectroscopic data (IR., NMR., MS.) are in accord with the structures given here.

| | |
|------------|--|
| 7 | (+ <i>trans</i> -Isomer, 87% from lactic acid of $[\alpha]_D^{25} = +13.6^\circ$ ($c = 2.5$, 1.5N NaOH), and 2,2-dimethylpropanal); 96% diastereomeric purity (a, b) after 2 crystallizations; m.p. <i>ca.</i> $+5^\circ$, b.p. $80^\circ/20$ Torr; $[\alpha]_D = +44.8^\circ$ (1.83) |
| 8a | (+ <i>trans</i> -Isomer, 82% from mandelic acid of $[\alpha]_D^{25} = +154.3^\circ$ ($c = 3.30$, 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. $95^\circ/10^{-3}$ Torr; $[\alpha]_D = +29.9^\circ$ (1.00) |
| 9a | From (<i>S</i>)-prolin of $[\alpha]_D^{20} = -85.0^\circ$ ($c = 5$, H_2O) (92%); >98% ds (a); b.p. $85^\circ/0.05$ Torr; $[\alpha]_D = -24.7^\circ$ (2.38) |
| 9b | From 9a and allyl bromide (55%); >98% ds; b.p. $90^\circ/10^{-3}$ Torr; $[\alpha]_D = +6.86^\circ$ (1.59) |
| 10 | From 7 (89%); >95% ds (a); m.p. 147° (ether/pentane); $[\alpha]_D = +21.5^\circ$ (0.93) |
| 11a | $R = \text{C}_2\text{H}_5$; from 7 and iodoethane (82%); 97% ds (b); b.p. $110^\circ/16$ Torr; $[\alpha]_D = +43.8^\circ$ (2.52) |
| 11b | $R = \text{CH}_2\text{-CH=CH}_2$; from 7 and 1-bromo-2-propene (77%); 98% ds (b); b.p. $130^\circ/12$ Torr; $[\alpha]_D = +52.9^\circ$ (2.23) |
| 11c | $R = \text{CH}_2\text{C}_6\text{H}_5$; from 7 and benzyl bromide (81%); 96% ds (b); b.p. $140^\circ/10^{-3}$ Torr; $[\alpha]_D = +57.6^\circ$ (2.48) |
| 12a | $R^1 = R^2 = \text{CH}_3$; from 7 and acetone (83%); >95% ds (a); m.p. 95° (ether/pentane); $[\alpha]_D = +26.3^\circ$ (0.93) |
| 12b | $R^1 - R^2 = (\text{CH}_2)_4$; from 7 and cyclopentanone (85%); >95% ds (a); m.p. 85° (ether/pentane); $[\alpha]_D = +9.3^\circ$ (1.68) |
| 12c | $R^1 = R^2 = \text{C}_6\text{H}_5$; from 7 and benzophenone (87%); >95% ds (a); m.p. 90° (ether/pentane); $[\alpha]_D = +88.7^\circ$ (0.73) |
| 13a | $R^1 = \text{CH}_3$, $R^2 = \text{H}$; from 7 and acetaldehyde (84%); 82% ds (a); b.p. $90^\circ/0.005$ Torr; $[\alpha]_D = +23.5^\circ$ (1.71) |
| 13b | $R^1 = t\text{-C}_4\text{H}_9$, $R^2 = \text{H}$; from 7 and pivalaldehyde (83%); 53% ds (a); m.p. $43\text{-}46^\circ$; $[\alpha]_D = +19.6^\circ$ (1.02) |
| 13c | $R^1 = \text{C}_6\text{H}_5$, $R^2 = \text{H}$; from 7 and benzaldehyde (85%); 84% ds (a); m.p. $88\text{-}95^\circ$; $[\alpha]_D = +34.1^\circ$ (0.82) |
| 13d | $R^1 = \text{C}_6\text{H}_5$, $R^2 = \text{CH}_3$; from 7 and acetophenone (81%); 93% ds (a); m.p. $91\text{-}98^\circ$; $[\alpha]_D = +51.2^\circ$ (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 formed⁸⁾ 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 = C₂H₅, see the *Table*) was established by hydrolysis to (–)-2-hydroxy-2-methylbutanoic acid, m.p. 72–73°; [α]_D = –6.6° (c = 1.4, 0.2 N NaOH) ([16]: m.p. 73.5°; [α]_D = –6.9°). We assume that all major diastereomers¹⁰⁾ result from attack of the electrophiles at the (*Re*)-face, i.e. *anti* to the *t*-butyl group of the enolate **3a**, R¹ = CH₃, R² = *t*-C₄H₉, 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 described⁸⁾ 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 surprising to us; aggregation [18] of these reagents might be responsible.

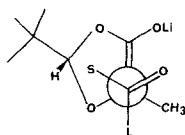
The alkylation of other enolates of type **3**, especially of those derived from amino acids is in progress and will be published shortly. Since the acids **4** with X = NR, O, and S are readily interconverted, and since many of them are inexpensive and commercially available in both enantiomeric forms, the methodology outlined here will make accessible a large variety of new chiral building blocks¹²⁾.

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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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