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# α-Alkylation of (*S*)-Glyceric Acid through the *tert*-Butylthioester of (2*R*,4*S*)-2-*tert*-Butyl-1,3-dioxolane-4-carboxylic Acid

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*Abstract:* The thioester (**9**) mentioned in the title is prepared in three steps from (*S*)-serine. Deprotonation with $LiN(CHMe_2)_2$ generates a chiral enolate (**10**) which is alkylated preferentially from the *Re*-face (*cis* to the *tert*-butyl group), to give products of type **11**. Possible reasons for the steric course of the reaction of the thioester enolate (relative topicity *lk*, see **13**) and the value of the products thus available as synthetic building blocks with a persubstituted, OH-functionalized asymmetric carbon atom (see **4**, **5**, **6**) are discussed.

Enantiomerically pure starting materials with enantiotopic branches on an asymmetric carbon atom, especially a functionalized one, are of particular value[1]. Thus, α-hydroxymethylated carboxylates **1**[2], glycerates **2**[3], and the amino-glutarate **3**[4] have been used as versatile building blocks for syntheses. Only recently, similar, readily available starting materials[5] with a persubstituted center, such as the α-alkylated serines **4**[6] have become available. We now describe a simple synthetic access to certain α-alkylated glyceric acids **5**, which, like the amino analogues **4**, may be useful for the elaboration of target molecules containing persubstituted centers of either sense of chirality as indicated by the formulae **6a** and **6b**.

(*S*)-Serine was converted to (*S*)-glyceric acid by diazotation, following a literature procedure[7]. Acetalization and esterification to the methyl 1,3-dioxolane carboxylate (**7**) was effected by treatment with excess pivalaldehyde dimethylacetal. The *tert*-butyl ester **8** and the *tert*-butyl thioester **9** of the same heterocyclic carboxylic acid were prepared in *ca.* 50% yield, from the methyl ester **7** by known methods[8]. Of both *tert*-butyl esters **8** and **9**, the pure, crystalline *trans*-isomer of (2*R*,4*S*)-configuration was isolated; they prevailed in the crude products to the extend of 3:1 to 5:1[9], the *trans*-configuration follows from NOE and other NMR measurements. For conditions of the conversions leading to **8** and **9**, as well as to the other products described here, and for characteristic data see table 1.

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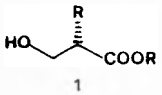
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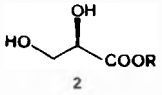
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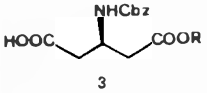
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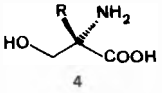
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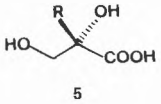
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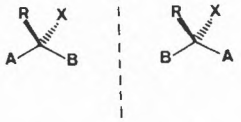
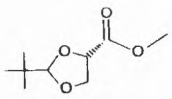

6a 6b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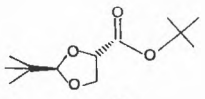
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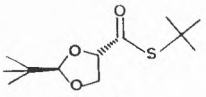
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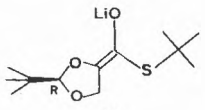
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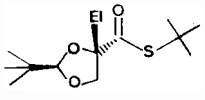

11a: El = D
11b: El = $CH_2CH=CH_2$
11c: El = $CH_2Ph$
11d: El = $C(OH)(Me)_2$
11e: El = CH(OH)Me
11f: El = CH(OH)Ph
11g: El = CH(OH)CH=CHPh
11h: El = C(OH)(Me)Ph

The enolate of the methyl ester **7** could not be alkylated under any set of conditions which we tried: we obtained at most 5% of product with benzaldehyde at very low temperature, the main course of reaction is the decomposition of the enolate. The *tert*-butyl ester **8** could be deprotonated to an enolate, but products of alkylation were formed in poor yield and/or with unsatisfactory stereoselectivity. In contrast, the enolate **10** of the thioester **9** could be generated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −75°C, it was stable up to −20°C, and it reacted with electrophiles in good yields and with acceptable, although electrophile-dependant diastereoselectivities to give the compounds **11** (simple iodoalkanes did not react with **10**). In two cases (**11b**, **11d**) the product configuration was proved by NOE $^1$H-NMR measurements to be as shown in the formula **11**, and we assume, that the reaction takes place in all cases with a 1,3-induction of relative topicity *lk*[10]. For yields, diastereoselectivities and characteristic data of the compounds **11** see table 1. Hydrolysis experiments are underway, they should produce α-substituted glyceric acids **5**.

Table 1. Reaction conditions, yields, selectivities and some physical data of the compounds **7**–**9** and **11**. The yields are those of chromatographed ($SiO_2$) materials. – The fraction of the main diastereomer (% *ds*) was determined by $^{13}$C NMR of the crude products. – Correct elemental analyses (±0.3%) of all compounds. – $[\alpha]_D^{25}$ in $CHCl_3$, $c \approx 1$. – If not stated otherwise, the electrophiles were added to the solution of the enolate **10** at dry-ice temperature, the reaction times varied from 5 min ($C_6H_5CHO$) to 14 h ($RCH_2Br$, with warming to +10°C). – **10** was generated at −75°C from **9** and LDA in 1 h.

**7**: The crude (*S*)-glyceric acid from diazotation of (*S*)-(−)-serine [7] was treated in MeOH with $Me_3CCH(OMe)_2$ and a trace of HCl. Evaporation of the solvent and treatment with the same acetal ($CH_2Cl_2$/TosOH) gives **7** [73%, *b.p.* 90°C/0.1 Torr (Kugelrohr), mixture of diastereomers].

**8**: From **7** by saponification (KOH/MeOH/$H_2O$) and esterification (DMF/$(COCl)_2$, *t*BuOH) [8a], *cis*/*trans*-ratio 1:3. Pure *trans*-isomer: *m.p.* 40.0–41.5°C, $[\alpha] = -20$; *cis*-ester: oil, $[\alpha] = -18$.

**9**: From **7** by treatment with $(Me)_2AlSC(Me)_3$ [8b], *cis*/*trans*-ratio 1:3 to 1:5, depending on reaction time. *cis*-Ester: oil, $[\alpha] = -66$; *trans*-ester (**9**): *m.p.* 27.5–29.5°C, $[\alpha] = -62$.

**11a**: By sequential treatment of the solution containing **10** and diisopropylamine with one equivalent *t*BuLi and MeOD, 90% D-incorporation, 80% yield, > 95% *ds* of *trans* (by NMR), *m.p.* 28–30°C, $[\alpha] = -66$.

**11b**: By addition of LDA to a 1:1.5 mixture of **9** and allyl bromide in THF/20% HMPT, 63% yield, 94% *ds* of (2*R*,4*S*)-isomer (by NOE NMR), viscous oil, $[\alpha] = -11$.

**11c**: From **9** and benzyl bromide (as described for **11b**), 75% yield, 60% *ds*, white powder.

**11d**: By addition of acetone to **10** at −100°C, 77% yield, > 95% *ds* of (2*S*,4*R*)-isomer (by NOE NMR), *m.p.* 35.0–37.5°C, $[\alpha] = +57$.

**11e**: From **10** and acetaldehyde, 25% yield, 60% *ds*.

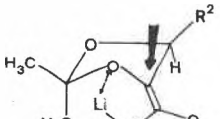
**11f**: From **10** and benzaldehyde, 69% yield, 92% *ds*, *m.p.* 134.0–136.0°C, $[\alpha] = -39.5$.

**11g**: From **10** and cinnamaldehyde, 60% yield, 66% *ds*; separation furnished diastereomer A: 46% yield, *m.p.* 81.5–83.5°C, $[\alpha] = -42$; diastereomer B: 14% yield, *m.p.* 97.0–99.0°C, $[\alpha] = +34$.

**11h**: By addition of acetophenone to **10** at −100°C, 63% yield, 89% *ds*, *m.p.* 100.0–102.0°C, $[\alpha] = -87$.

The results described here constitute yet another example of α-alkylation of α-heterosubstituted carboxylic acids with «self reproduction of the center of chirality»[11], resting upon a 1,3-asymmetric induction on the reaction of an exocyclic enolate[6, 12]. The products thus accessible have the general structure **5** and are potential starting materials for target molecules containing the enantiomeric stereogenic units indicated by **6a** and **6b**.

The stereochemical course of the present reaction warrants a comment. Obviously, the electrophiles attack the enolate **10** from the face *cis* to the *tert*-butyl group (see **11**). So far, this at first sight «surprizing»[13] type of induction was only observed[12, 13] with «exocyclic» enolates derived from 1,3-dioxolanes[14], i.e. heterocycles containing just one $sp^2$-carbon atom, while exocyclic[6, 15] and «endocyclic»[16] enolates containing two or more trigonal centers in a five-membered ring exhibit the «expected» preferred attack from the face opposite to a substituent on the ring. The stereochemical course observed here may not only be caused by puckering of the five-membered ring, as suggested previously[12, 13, 17], but also by the fact that chelation between the enolate lithium atom and the neighbouring oxygen atom renders the nucleophilic enolate carbon atom a bridgehead center which is attacked from the *exo*- rather than from the *endo*-face (see **12** and **13**). Our continuing attempts to crystallize one of the heterocyclic enolates of this type and to determine the structure by X-ray diffraction have thus far not been successful[18].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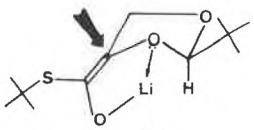
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Finally, the difference between the enolates of the *tert*-butyl ester (**8**) and the *tert*-butyl thioester (**9**) is noteworthy. It is known that thioesters are more acidic than the oxygen analogues (ca. 2 $pK_a$ units[19]). So far, *tert*-butyl thioesters have been used as acylating reagents, due to their selective activation by certain metal ions or by oxidation[20]. Also, *tert*-butyl thioester enolates have been shown to be better nucleophiles in Michael additions[21]; furthermore, the cyclopropane carboxylate of *tert*-butyl thiol can be deprotonated to give a synthetically useful enolate, in contrast to *O*-esters[22]. While, in the present case, the methyl ester enolate (from **7**) was extremely labile[23], the thermal stability of the *tert*-butyl substituted enolates from **8** and **9** was comparable (up to −20°C), but the *S*-derivative **10** gave better yields and, more importantly, reacted with higher diastereoselectivity, an effect which was observed before[24], and which should be exploited more often.

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