Tetrahedron Letters,Vol.25,No.24,pp 2545-2548,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

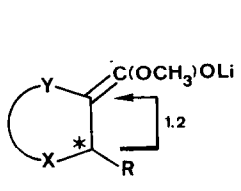
α-Alkylation of Serine with Self-Reproduction of the Center of Chirality

Dieter Seebach and Johannes D. Aebi[1)]

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule,
ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich (Switzerland)

Abstract: *The lithium enolate* 6 *of methyl (2R,4S)-2-t-butyl-3-formyl-oxazolidine-4-carboxylate* (4b) *derived from (S)-(+)-serine can be generated with LDA in THF solution at* -75^{o}C. *Alkylations* (→ 9) *and hydroxyalkylations* (→ 10, 11) *occur preferentially* (>95:5) *from the Re-face of the donor center (relative topicity lk). This stereochemical course is derived from the absolute configuration of 2-deuterio- and 2-methyl-serine* (12, 13) *obtained through the enolate* 6.

It was demonstrated previously that α-hydroxy- and α-aminoacids with additional centers of chirality, such as tartaric acid[2)], threonine, allo-threonine or β-phenylserine[3)] can be alkylated stereoselectively[2-4)] using a 1.2-asymmetric induction, see 1. It was also reported that simple α-amino-[5,6)], α-hydroxy-[5,7,8)] and α-mercapto-carboxylic[8)] acids can be



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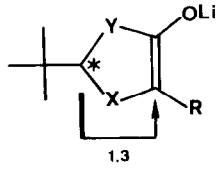

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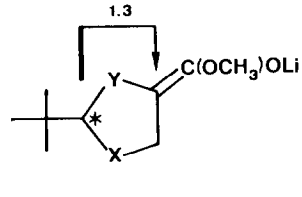

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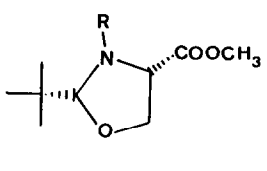
alkylated with 1.3-induction through enolates of type 2 with an endocyclic double bond. We have now realized yet another way of using a 1.3-asymmetric induction for α-alkylations of chiral, non-racemic carboxylic acids without racemization and without employing a chiral auxiliary, see the enolate 3 with an exocyclic double bond.

The commercial methyl ester hydrochloride of (S)-serine furnishes a mixture of the diastereomers 4a and 5a (ratio *ca.* 1:1)[9)] when heated with pivalaldehyde/triethylamine in pentane, with continuous removal of water. The oily crude product was formylated with the mixed anhydride of acetic and formic acid[10)] to give a 95:5-mixture of the N-formyl substituted

heterocycles 4b/5b[9]. The major diastereomer 4b was isolated by crystalization, while 5b was obtained in pure form by chromatography of the mother liquor residue. The assignment of configuration was made by NOE NMR measurements[11].



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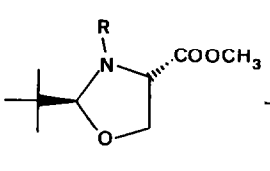
a: R=H
b: R=CHO



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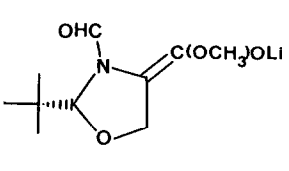

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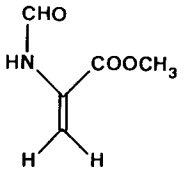

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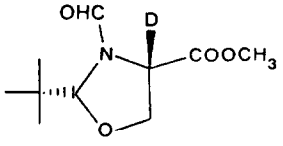
Addition of the oxazolidine 4 to a solution of lithium diisopropyl amide (LDA) in THF at dry ice temperature gave an orange solution of the enolate 6 which slowly decomposes with β-elimination. Thus, in the crude products isolated after addition of the less reactive electrophiles, the α-amino-acrylate 7 can be detected. Deuterolysis of the enolate 6 with CH_3OD leads to the recovery (71%) of a >98% diastereomerically pure (capillary GC) sample of the 4-deuterated oxazolidine 8 (78% D, by MS). Alkylations of the enolate with iodomethane, iodoethane, allylbromide and benzylbromide occur in satisfactory yields only in the presence of cosolvents such as HMPT or DMPU[12]. Addition to acetone gives a single diastereomer 10, with benzaldehyde one of the four possible diastereomers seems to be formed preferentially, see 11, and no adduct to acetophenone could be isolated. The configuration of the products as shown in the *formulae* 8 - 11 is deduced from the chemical correlation of the products 8 and



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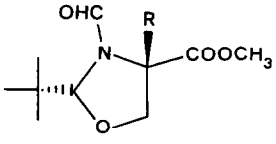
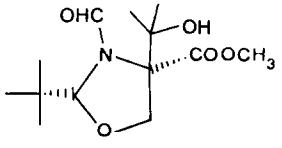


9 a: R = CH_3
b: R = C_2H_5
c: R = $CH_2CH=CH_2$
d: R = $CH_2C_6H_5$



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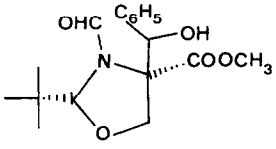

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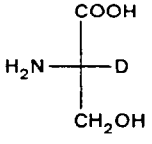
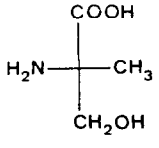


12 [(S)-(+)]



13 [(S)-(+)]

9a with α-deuterio- and α-methyl-serine 12 and 13, respectively. The hydrolysis of the oxazolidines to these aminoacids is effected by refluxing in 6 N HCl. (S)-α-Methyl-serine, a component of the antibiotic amicetine[13], has been synthesized by several methods, and its absolute configuration was established unambiguously[14].

The method of alkylation of serine described here should not only be considered as an access to branched serines, but also to products of the general structures 14 and *ent*-14 of opposite sense of chirality: suitable chemical transformations of the two enantiotopic branches on the persubstituted asymmetric carbon atom will provide either enantiomer[15].

14 ent-14

Experimental Data

If not stated otherwise, the $[\alpha]_D$ values were obtained with c=1 in chloroform. - The NMR spectra of the compounds 4b, 5b, 8-11 are not very informative due to the presence in solution of rotamers.

4b: yield 68% from serine ester hydrochloride, after crystallization from ether/pentane; m.p. 58-60°C; $[\alpha]_D = -47°$.

5b: from the mother liquor of crystallization of 4b; m.p. 44-47°C; $[\alpha]_D = -149°$.

9a: from 6 and CH_3I; yield 46% (without cosolvent), 68% (HMPT); m.p. 53-55°C; $[\alpha]_D = -28°$.

9b: from 6 and C_2H_5I, yield *ca.* 10% (without cosolvent), 62% (HMPT), 53% (DMPU); b.p. 130°C/ $6 \cdot 10^{-6}$ Torr.; $[\alpha]_D = -31°$.

9c: from 6 and 1-bromo-2-propene; yield 40% (without cosolvent), 57% (HMPT); b.p. 140°C/ $3 \cdot 10^{-5}$ Torr.; $[\alpha]_D = -8.4°$.

9d: from 6 and benzyl bromide; yield 40% (without cosolvent), 52% (DMPU); m.p. 128-130°C; $[\alpha]_D = +33°$.

10: from 6 and acetone; yield 58%; m.p. 108-110°C (from EtOEt/CH_2Cl_2; crystals contain 10% ether as solvent of crystallization); $[\alpha]_D = -66°$.

11: from 6 and benzaldehyde; yield 70% of crude product; oily mixture of several slowly equilibrating rotamers.

12: from 8; yield 89% after purification through ion exchange column; m.p. 215-225°C (dec.); $[\alpha]_D$ +12.2° (c=1, 5 N HCl) ($[\alpha]_D$ of (S)-serine +13.4°).

13: from 9a; yield 93% (from ion exchange column), colorless crystals; m.p. 250-260°C (dec.); $[\alpha]_D$ = +6.5 (c=1, H_2O) [ref. 6.3° [13a], 5.4° [14a], 6° [14b], 6.1° [14c], 4.7° [14d], 5.8° [14e]].

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(Received in Germany 26 March 1984)