Tetrahedron Vol. 48, No. 39, pp. 8389-8392, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

1-(*N*,*N*-Diisopropylcarbamoyloxy)-1,3-dimethylallyllithium•(-)-Sparteine: Stereochemistry of the Enantioselective Carboxylation and Methoxycarbonylation

Oliver Zschage, Dieter Hoppe*#

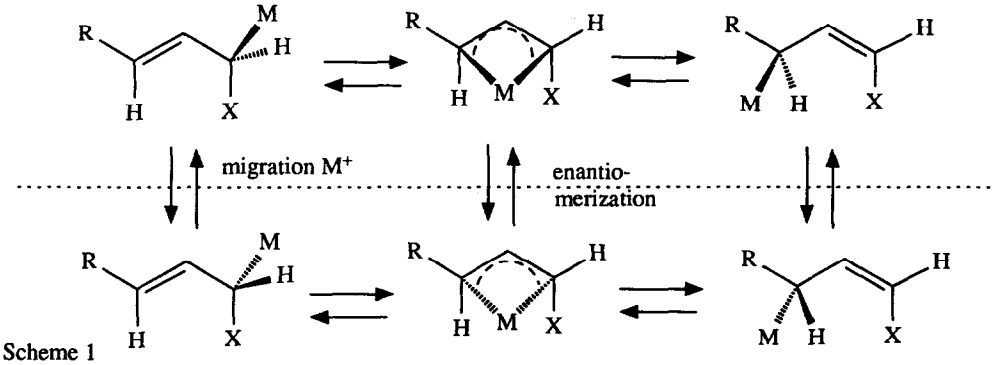
Institut für Organische Chemie der Universität Kiel
Olshausenstr. 40-60, W-2300 Kiel 1, Germany

(*Received in Germany* 25 *May* 1992)

Key words: chiral allyllithium, lithiated 2-alkenyl carbamates, asymmetric deprotonation, stereochemistry of carboxylation.

Summary. The title compound (*S*)-**3**/(-)-**2**, easily available through deprotonation of the racemic *O*-(2-alkenyl) carbamate under kinetic resolution, undergoes with carbon dioxide or methyl chloroformate predominantly α-substitution with *stereoinversion*. The absolute configuration of the formed methyl carboxylate is established by chemical correlation, thus correcting our former suggestion[3a].

Although the ion pairs formed from unsymmetrical allylic anions and alkaline-metal cations (Li^+, Na^+, or K^+) are chiral species (regardless whether the cation is bonded to the allyl moiety in η^1- or η^3-fashion), usually these racemize rapidly in solution on attempt of generating them in enantiomerically enriched form (Scheme 1). Consequently, little is known about the stereochemistry of their electrophilic substitution. So far, the only known exceptions are the lithium carbanions derived from secondary 2-alkenyl carbamates, which are configurationally stable in ether or hexane solution at -70°C. Here, the strongly chelating carbamoyl group "ties" the lithium cation to the α-carbon atom of the carbanionic part and hampers its migration from one face to the other one. The structure of a chiral 1-lithio-alkenyl carbamate, giving evidence to these important features, was uncovered recently by an X-ray crystal analysis[1].



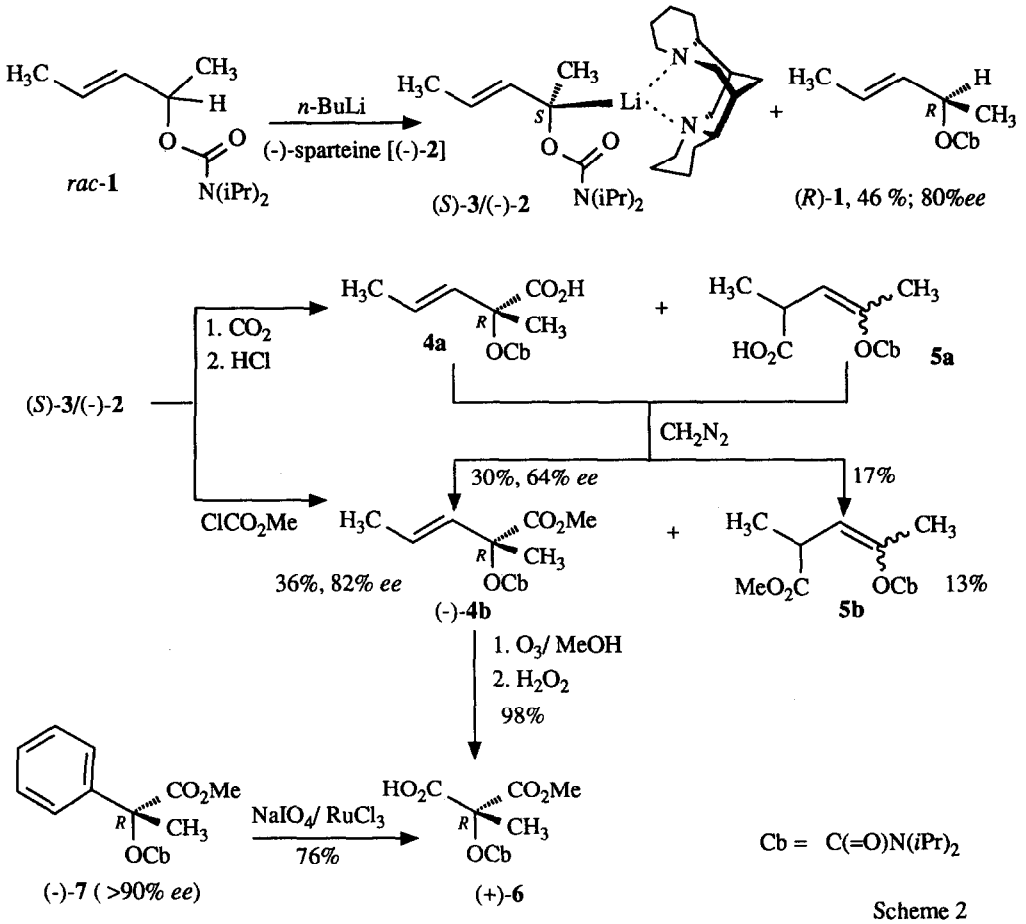
Scheme 1

A particularly facile approach to enantiomerically enriched 1-lithio-2-alkenyl carbamates consists in the deprotonation of prochiral[2] or racemic precursors[3] by means of butyllithium/(-)-sparteine complexes. We

found that electrophiles exhibit a high tendency to attack these complexes either in *anti*-S_E' processes or with stereoinversion[2b,3b] and, therefore, investigated the carboxylation of the chiral ion pair (*S*)-**3**/(-)-**2**, formed from (*E*)-1-methyl-2-butenyl *N,N*-diisopropylcarbamate (**1**) in this respect.

The racemic carbamate ester *rac*-**1** was subjected to the deprotonation by means of the complex formed from *n*-butyllithium and (-)-sparteine [(-)-**2**] to generate the lithium compound[2b] (*S*)-**3**/(-)-**2** (Scheme 2). After quench with an excess of carbon dioxide, the mixture of the crude acids **4a** and (*E*/*Z*)-**5a** was methylated by means of diazomethane to give the esters (-)-**4b** (30%; 64% *ee*) and (*E*/*Z*)-**5b** (17%)[4] besides recovered (*R*)-(-)-**1** (47%, 80% *ee*)[5]. In another experiment methyl chloroformate was added to the carbanion, affording directly the esters (-)-**4b** (36%; 82% *ee*), (*E*/*Z*)-**5b** (13%)[4] and (*R*)-(-)-**1** (46%, 80% *ee*)[5].

For the determination of the configuration, (-)-**4b** (82% *ee*) was ozonolyzed and after oxidative workup, the crystalline methyl hydrogen malonate (+)-**6** (98%) was obtained. (+)-**6** was also produced by the Lemieux oxidation[6] of the known atrolactate ester[7] (*R*)-(-)-**7** (> 90% *ee*).



Scheme 2

Thus, the compounds (-)-**4a**, (-)-**4b** and (+)-**6** have (*R*)-configuration contrarily to our former assumption[3a]; carboxylation and methoxycarbonylation of the lithium sparteine complex (*S*)-**3**/(-)-**2** proceed

with stereoinversion.

When reviewing all experimental results on the electrophilic substitution of lithium/sparteine complexes of α-carbamoyloxy-carbanions, it becomes evident, that the degree of pyramidalization has the most important influence on the stereochemical course: Carbanions with sp^3-hybridization, derived from alkyl carbamates[8] react with carbon dioxide and other electrophiles under stereoretention, whereas the sparteine complexes of the slightly pyramidal[1] allyl carbanions accept electrophiles antarafacially[2b,3b]. If sparteine is exchanged for the less sterically demanding N,N,N',N'-tetramethylethylene diamine (TMEDA), these electrophiles, which are capable of a strong bonding to the lithium, as tetra(isopropoxy)titanium or aldehydes, prefer *syn*-attack[9]. The situation is similar in the appropriate benzylic systems[7].

EXPERIMENTAL

All organometallic reactions were performed under argon at -78°C with exclusion of air and moisture. Pentane and diethyl ether were distilled over $LiAlH_4$; (-)-sparteine [(-)-**2**] was dried over CaH_2 prior to use. LC separations were carried out at 1-3 bar on "Silica Woelm 32-63" (Woelm Pharma GmbH & Co, Eschwege).

Deprotonation with kinetic resolution of the rac-(E)-1-methyl-2-butenyl N,N-diisopropylcarbamate (*rac*-**1**); *solution of (S)-***3**/(-)-**2**. To a solution of carbamate *rac*-**1** (4.0 mmol, dissolved in 10 ml pentane) and (-)-sparteine [(-)-**2**] (2.0 mmol) at -78°C was added slowly a solution of *n*-BuLi (2.2 mmol; 1.6N in hexane) and stirred vigorously for 9 h below -70°C before the appropriate electrophile was added.

Carboxylation and esterification; methyl (3E,2R)-2-methyl-2-(N,N-diisopropylcarbamoyloxy)pent-3-enoate [(-)-**4b**] *and methyl (3E/Z)-4-methyl-4-(N,N-diisopropylcarbamoyloxy-2-methyl)but-3-enoate* [(3*E*/*Z*)-**5b**]. Into the solution of (*S*)-**3**/(-)-**2** (produced from 4 mmol of *rac*-**1**), a stream of excess dry gaseous carbon dioxide was passed for 30 min. After stirring for 1 h at -78°C, the reaction mixture was poured on 2N aq. HCl (20 ml). The mixture was extracted three times with each 20 ml of ether. The solvent was evaporated in vacuum from the combined extracts, the crude product was diluted with ether (10 ml) and was treated with an excess of ethereal diazomethane solution at room temperature. The reaction mixture was stirred for 45 min and then poured onto a mixture of 2N aq. HCl (10 ml) and ether (20 ml). The aq. solution was extracted three times with ether (each 20 ml), the combined ethereal solutions were washed with aq. sat. $NaHCO_3$ (20 ml) and dried over Na_2SO_4. After evaporation of the solvent in vacuum, the residue was purified by LC (silica gel; diethyl ether/pentane 1:8), affording 163 mg (30%) of **4b** with $[\alpha]_D^{20}$ = -1.8 (c= 2.0, MeOH). The enantiomeric excess of 64% *ee* was determined ^{1}H-NMR spectroscopically with tris[(3-heptafluoropropylhydroxymethylene)-d-camphorato]europium(III), [Eu(hfc)$_3$]. A stronger shift to lower field of the 2-CH_3 in the enantiomer (-)-**4b** was observed. In addition 87 mg (17%) of γ-adduct **5b** (*E*/*Z*-mixture) and 203 mg (47%) of the educt (-)-(*R*)-**1** {$[\alpha]_D^{20}$ = -8.6 (c = 1.8, $CHCl_3$; 80% *o.p.*} were isolated.

4b: R_F= 0.45 (E/P, 1:1); 300-MHz ^{1}H-NMR ($CDCl_3$): δ = 1.242 (d,iPr-H_3); 1.671 (s,2-CH_3); 1.740 (d,5-H_3); 3.725 (s,OCH_3); 3.26 und 4.05 (two m,NCH); 5.766 (dq,4-H); 5.841 (d,3-H); J_{iPr}= 6.8 Hz; $J_{4,5}$= 5.0 Hz; $J_{3,4}$= 15.6 Hz; 75.5-MHz ^{13}C-NMR ($CDCl_3$): δ = 17.87 (C-5); 21.21 (C-iPr); 23.37 (2-CH_3); 46.08 (NCH); 52.11 (OCH_3); 79.32 (C-2); 126.53 (C-4); 130.98 (C-3); 153.99 (NCO); 172.50 (C=O).

$C_{14}H_{25}NO_4$; calc. C 61.97 H 9.29; found C 62.01 H 9.24.

(*E*/*Z*)-**5b:** R_F= 0.35 (E/P, 1:1); 300-MHz ^{1}H-NMR ($CDCl_3$): δ = 1.242 (d,5-H_3); 1.251 (d,iPr-CH_3); 1.910 and 1.923 (two d,4-CH_3); 3.351 (dq,2-H); 3.664 and 3.707 (two s,OCH_3); 3.20 and 4.05 (two m,NCH); 5.076 (dq,3-H); J_{iPr}= 6.4 Hz; $J_{2,5}$= 7.3 Hz; $J_{3,2}$= 9.1 Hz; $J_{3,4\text{-}Me}$= 1.1 Hz; 75.5-MHz ^{13}C-NMR ($CDCl_3$): δ = 17.93 (C-5); 19.84 and 21.13 (4-CH_3); 20.53 (iPr-C); 36.78 (C-2), 46.21 (NCH); 51.73 and 52.62 (OCH_3); 114.22 and 115.33 (C-3); 146.50 and 147.56 (C-4); 152.57 (NCO); 175.15 (C=O).

Methoxycarbonylation of (*S*)-**3**/(-)-**2** *with methyl chloroformate;* (-)-**4b** *and* (*E*/*Z*)-**5b**. Addition of 1.4 g (15 mmol) of methyl chloroformate to the above described solution of (*S*)-**3**/(-)-**2** and stirring of the reaction mixture at -78°C for 5 min yielded, after described workup and separation, 388 mg (36%) of **4b** with 82% *ee* ($[\alpha]_D^{20}$ = -2.5, c = 1.5, MeOH), besides 144 mg (13%) **5b** and 388 mg (46%) (*R*)-**1** (80% *ee*).

Ozonolysis of **4b**; *methyl hydrogen* (*S*)-*2-methyl-2-(N,N-diisopropylcarbamoyloxy)malonate* [(+)-**6**]. Ozonolysis of **4b** (1.0 mmol; 82% *ee*) in MeOH (10 ml) at -78°C and oxidative workup [10 ml H_2O_2 (30proc.)/ 20 ml HCOOH] afforded, after LC purification with ether/pentane (1:1) 269 mg (98%) of (+)-**6** with $[\alpha]_D^{20}$ = +38.6 (c = 1.0, CH_2Cl_2) colourless crystals, mp. 86°C (pentane); R_F= 0.2 (E/P 1:1); 200-MHz ^{1}H-NMR ($CDCl_3$): δ = 1.212 and 1.307 (two d,iPr-H_3); 1.788 (s,2-CH_3); 3.843 (s,OCH_3); 4.043 (m,NCH); 8.042 (s,OH); J_{iPr}= 6.8 Hz; 50-MHz ^{13}C-NMR ($CDCl_3$): δ = 20.28 and 21.26 (2x,C-iPr); 22.08 (2-CH_3); 46.36 and 47.37 (2x,NCH); 53.52 (OCH_3); 79.16 (C-2); 154.71 (NCO); 170.21 and 170.95 (COOH and COOMe). $C_{12}H_{21}NO_6$; calc. C 52.39 H 7.63 N 5.01; found C 52.12 H 7.73 N 5.05.
Lemieux oxidation[6] *of atrolactate ester (R)*-(-)-**7**[7]; (+)-**6**. 270 mg (0.88 mmol) (*R*)-(-)-**7** (> 90% *ee*; $[\alpha]_D^{20}$ = -8.0, CH_2Cl_2) were dissolved in a mixture of tetrachloromethane (5 ml), acetonitrile (5 ml) and water (8 ml). 3.42 g (16 mmol) $NaIO_4$ and 4 mg (2.2 mol%) $RuCl_3$ were added and the reaction mixture was stirred for 7 days at room temperature. It was diluted with dichloromethane (20 ml) and extracted three times with dichloromethane (10 ml) each. The combined solutions were washed with satd. $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by flash chromatography afforded 183 mg (76%) of compound (+)-**6** with $[\alpha]_D^{20}$ = +41.0 (c=1.0, CH_2Cl_2).

Acknowledgement. - Generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

NOTES AND REFERENCES

New address: Institut für Organische Chemie der Westfälischen Wilhelms-Universität zu Münster, Corrensstr. 40, W-4400 Münster.

1. Marsch, M.; Harms, K; Zschage, O; Hoppe, D.; Boche, G. *Angew. Chem.* **1991**, *103*, 338-339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 321-322.
2. a) Hoppe, D.; Zschage, O. *Angew. Chem.* **1989**, *101*, 67-69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69-71; b) Zschage O.; Hoppe, D. *Tetrahedron*, in press; c) Paulsen, H.; Hoppe, D. *Tetrahedron*, in press; d) Férézou, J.P.; Julia, M.; Khourzom, R.; Pancrazi, A.; Robert, P. *Synlett* **1991**, 611-614.
3. Preliminary communications: a) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Angew. Chem.* **1990**, *102*, 336-337, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 296-297; b) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron*, preceding paper; c) A ratio *rac*-**1** : base of 1 : 0.55 and a prolonged reaction time (9 h) were used in these experiments. A ratio of 1 : 1 after 3 h does not cause a decrease in the enantiomeric purities[3b].
4. No attempts were made to separate the stereoisomers and to assign their configurations.
5. Schwark, J.-R.; Hoppe, D. *Synthesis* **1990**, 291-294.
6. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
7. Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem.* **1990**, *102*, 1455-57, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1424-26.
8. a) Hoppe, D; Hintze, F.; Tebben, P. *Angew. Chem.* **1990**, *102*, 1457-1459; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422-1424; b) Hoppe, D; Hintze, F. *Synthesis* **1992**, in press.
9. Krämer, T.; Hoppe, D. *Angew. Chem.* **1986**, *98*, 171-173; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 160-162.