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Stereoselective Generation of 1,3- and 1,4-Dioxy-Substituted Carbanions by Sparteine-Assisted Deprotonation of Chiral Precursors: Substrate or Reagent Control in the Synthesis of α,γ- and α,δ-Diols

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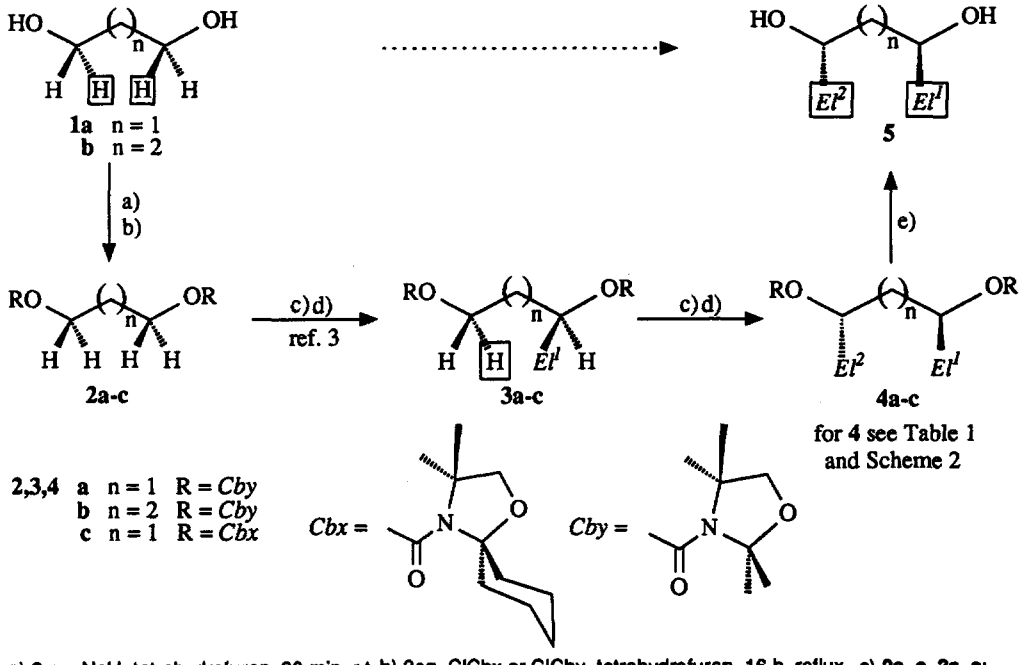
Key words: Chiral 1-oxycarbanions, enantioselective deprotonation, (-)-sparteine.

Summary: *The deprotonation of a dicarbamate, derived from (S)-butane-1,3-diol, by sec-butyllithium takes an highly diastereoselective, but opposite, direction in the presence of (-)-sparteine and of tetramethylethylenediamine (TMEDA), respectively. The (S)-pentane-1,4-diol derivative shows the same stereochemical preference under both conditions.*

As recently found by us, non-functionalized[1,2] and hetero-substituted achiral *O*-alkyl carbamates are deprotonated by *sec*-butyllithium/(-)-sparteine to form configurationally stable, homochiral lithium carbanions which yield with electrophiles *El*X the appropriate substitution products with ≥95% *ee*.[1] In all investigated cases, the chiral base system exhibits a high and reliable tendency for the abstraction of the

Scheme 1

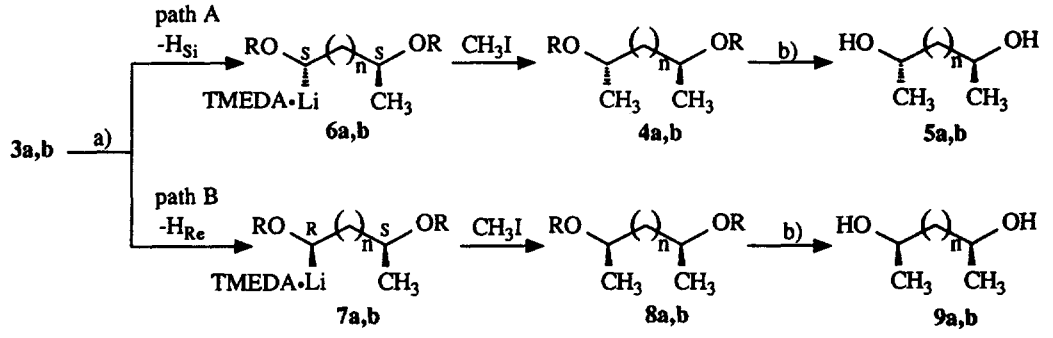


a) 3 eq. NaH, tetrahydrofuran, 30 min, r.t. b) 2eq. ClCbx or ClCby, tetrahydrofuran, 16 h, reflux. c) **2a, c, 3a, c**: 1.4 eq. *s*-BuLi/(-)-sparteine, ether, -78°C, 2-3 h. c) **2b, 3b**: 2.0 eq. *s*-BuLi/(-)-sparteine, toluene, -78°C, 4-6h. d) **2a, c, 3a, c**: 1.5 eq. CH_3I; **2b, 3b**: 2.6 eq. CH_3I. e) 0.5 eq. CH_3SO_3H, methanol, reflux, 16h; excess $Ba(OH)_2$, methanol, reflux, 4h.

si-proton at the prostereogenic methylene group. Repeated application of this procedure to a dicarbamate **2** should allow the double chain-elongation of an achiral alkanediol **1** by two electrophiles El^1X and El^2X to afford enantiomerically pure diols **5**. To our best knowledge, no other straightforward methods exist for achieving this goal (Scheme 1).

The repeated deprotonation and methylation of **2b** *in the presence of (-)-sparteine* via the monomethyl derivative **3b**[3] afforded the diastereomerically and enantiomerically pure dicarbamate **4b**[5] of (*S,S*)-2,5-hexanediol with 51% yield in a one-pot procedure. The 1,3-dicarbamate **3a**[3] gave rise to the (*S,S*)-diastereomer **4a**[5] contaminated by few of the (*R,S*)-*meso*-compound **8a** (Table 1). It is obvious, that in both cases, a high reagent-controlled stereoselection is operating in the deprotonation step.
The intrinsic diastereoselectivities were determined by carrying out the analogous experiments under the *influence of the achiral diamine TMEDA* (Scheme 2), revealing a surprisingly high chiral induction caused by the stereogenic centre in the δ- (**3b**) or γ-position (**3a**). In addition, the asymmetric induction is operating in opposite directions (Table 1). The 1,4-dicarbamate **3b**, via carbanion **6b** and path A, exhibits the same stereochemical preference as in the presence of (-)-sparteine to yield the main product (*S,S*)-**4b**. However, the 1,3-dicarbamate **3a** furnishes almost exclusively the *meso*-compound **8a**, indicating that now the diastereomeric carbanion **7a** (path B) is the precursor. The slighthly decreased stereoselectivity (16:1) in the sparteine-assisted reaction also demonstrates the competition of two antagonistic chiral inductions, in which the external one is most powerful. The origins for the high internal diastereoselection are under investigation.[6] We assume in our working hypothesis that the remote carbamoyloxy residue acts as a ligand to the lithium cation. Preliminary experiments lead to the suggestion that both the kinetic preference in the deprotonation step and the stabilities of the diastereomeric lithium·TMEDA complexes **6** and **7** lead into the direction as expressed by the product ratios[7] in Table 1.

Scheme 2



3-9: **a** n = 1, R = *Cbx*
b n = 2, R = *Cby*

a) **3a**: 1.4 eq. *s*-BuLi/TMEDA, ether, -78°C, 2-3h; **3b**: 2eq. *s*-BuLi/TMEDA, toluene, -78°C, 4-6h.
b) 0.5 eq. CH_3SO_3H, methanol, reflux, 16h; excess $Ba(OH)_2$, methanol, reflux, 4h.

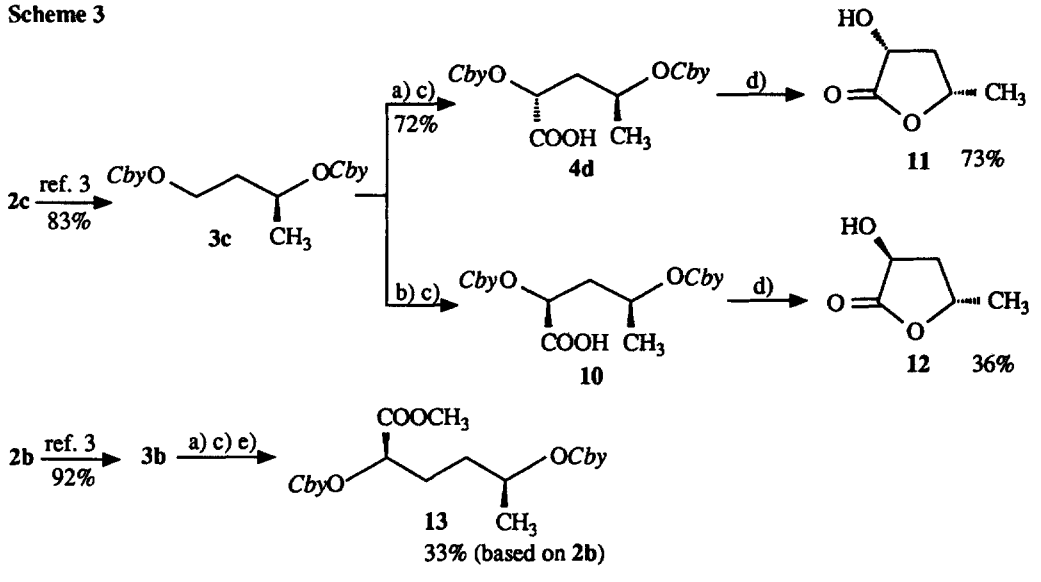
Table 1: Diastereodivergent Dimethylation

Educt	Diamine	Products[a)]	yield(%)[b)]	Ratio(*S,S*):(*R,S*)[c)]	$[\alpha]_D^{20}$ [d)]
3a	(-)-sparteine	**4a+8a**	56	94:6	+31.3[e)]
3a	TMEDA	**4a+8a**	44	2:98	+ 0.3[e)]
3b	(-)-sparteine	**4b+8b**	51[f)]	>98:2	+13.4[g)]
3b	TMEDA	**4b+8b**	60	88:12	+11.5[h)]

a) Satisfactory elemental analyses obtained from all products. b) Combined yield after LC purification.
c) Values from ^{13}C-NMR or GC analysis. d) Optical rotation of the mixture **4** and **8** (optically inactive).
e) c = 1, acetone. f) Based on **2b**. g) c = 1, CH_2Cl_2. h) c = 0.9, CH_2Cl_2.

The removal of the carbamoyl groups[1,2] in **4a** and **4b** yields practically enantiopure (*S,S*)-diols **5a**[8] (85% yield) and **5b**[9](87% yield), respectively. From **9a**[10], *meso*-2,4-pentanediol[11] was obtained by the same deprotection procedure (82% yield). The diastereodivergency observed in the deprotonation of **3a** (or related compounds) can be advantageously utilized when different electrophiles *El*^{1}X and *El*^{2}X are used, as is demonstrated by the synthesis of the diastereomeric α-hydroxy-γ-lactones **11**[12] and **12**[12]. In addition, the reagent-controlled double substitution permits an easy access to (2*R*, 5*S*)-2,5-dihydroxyalkanoic acids and their esters from achiral α,ω-dicarbamates, disclosed for **13**[13] in Scheme 3.

Scheme 3



a) **3b**: 4.5 eq. *s*-BuLi/(-)-sparteine, toluene, -78°C, 4-6h; **3c**: 1.4 eq. *s*-BuLi/(-)-sparteine, ether, -78°C, 2-3h.
b) 1.4 eq. *s*-BuLi/TMEDA, ether, -78°C, 2-3h. c) **3b**: CO_2, toluene, -78°C, 16h; **3c**: CO_2, ether, -78°C, 16h.
d) 5N HCl, reflux, 16h. e) CH_2N_2, CH_3OH, ether, r.t., 2h

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References and Footnotes

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2 Hintze, F.; Hoppe, D. *Synthesis* **1992**, in press.

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5 The compounds gave satisfactory elemental analysis.

6 For diastereotopically directed reductive lithiations of 1,1-dibromides under the influence of 3-oxy groups see:a) Hoffmann, R.W.; Bewersdorf, M.; Krüger, M.; Mikolaiski, W.; Stürmer, R. *Chem. Ber.* **1991**, *124*, 1243-1252; b) Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* **1991**, *124*, 1259-1264.

7 Since the product ratio increases further and the yields drop with prolonged stirring, a diastereoselective decomposition of the lithium compounds **6a** and **7b**, respectively, can not be excluded.

8 **5a**: $[\alpha]_D^{25}$= +39.6 (c=1.5, $CHCl_3$). For *ent*-**5a**: $[\alpha]_D^{25}$= -41.3 (c not reported, $CHCl_3$); Fry, A. J.; Britton, W. E. *J. Org. Chem.* **1973**, *38*, 4016-4021.

9 **5b**: $[\alpha]_D^{20}$= +38.6 (c=0.7, $CHCl_3$) ref.: $[\alpha]_D^{25}$= +35.1 (c=9.49, $CHCl_3$); Serk-Hanssen, K.; Stallberg-Stenhagen, S.; Stenhagen, E. *Arkiv. Kemi.* **1953**, *5*, 203-221.

10 More conveniently, **9a** is prepared from *rac*-**3a** by the same procedure.

11 R_F = 0.09 (ethyl acetate/hexane 1:1), Dale, J. *J. Chem. Soc.* **1961**, 910-922.

12 **11**: $[\alpha]_D^{20}$= +3.6 (c=0.8, methanol) **12**: $[\alpha]_D^{20}$= -59.8 (c=1, methanol). The ^{1}H-NMR data are identical with those reported for the racemates[12a,b] a) Plusquellec, D.; Venien, F. *C. R. Acad. Sc. Paris*, **1973**, *Série C*, 715. b) Daremon, C.; Rambaud, R.; Verniette, M. *C. R. Acad. Sc. Paris*, **1971**, *Série C*, 1273.

13 **13**: $[\alpha]_D^{20}$= -8.5 (c=0.8, CH_2Cl_2), ≥ 95% *ds* (^{13}C-NMR),

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