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Chiral α,ω-Dioxy-Carbanions from 1,3-Propanediol and 1,4-Butanediol by Sparteine-Assisted Deprotonation. Enantioselective Synthesis of 1,3- and 1,4-Diols, (*R*)-Pantolactone, and a Cyclopropane.

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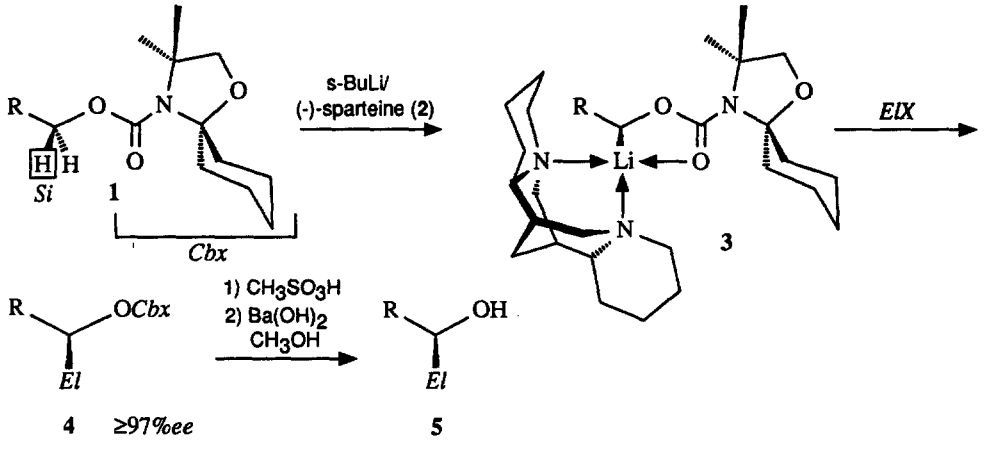
Key Words: chiral 1-oxy-carbanions, enantioselective deprotonation, (-)-sparteine.

Summary: *Prostereogenic mono- and dicarbamates of 1,3-propanediol and 1,4-butanediol are deprotonated by the sec-butyllithium/(-)-sparteine system with high enantiotopic differentiation. The electrophilic substitution of the intermediate chiral carbanions furnishes the title compounds with >95% ee.*

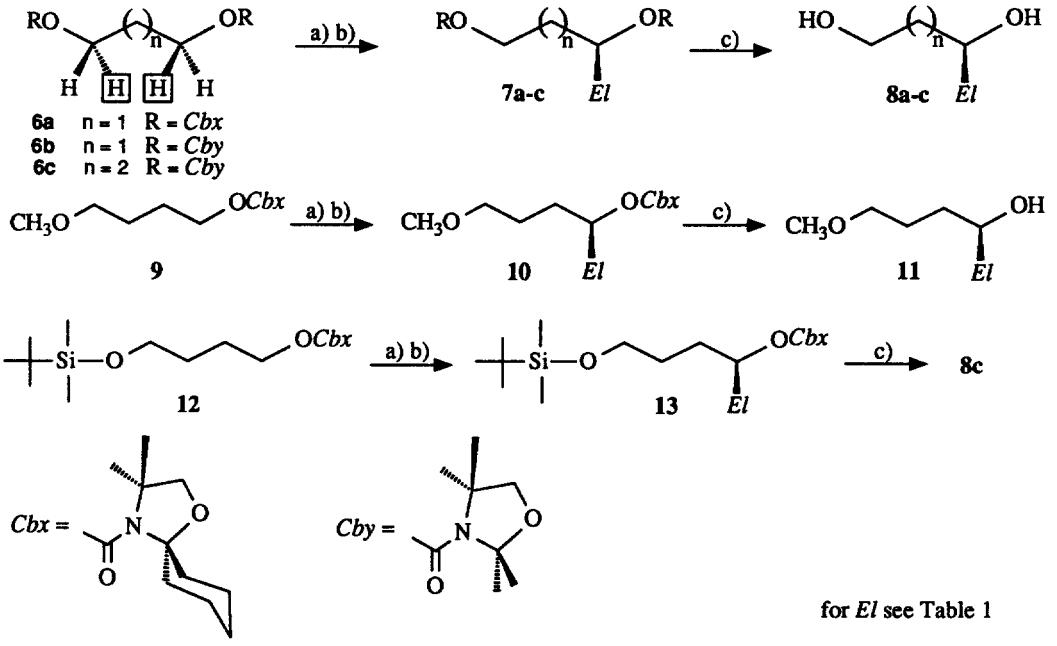
We recently reported a method for the direct generation of highly enantiomerically enriched α-oxycarbanions, derived from 1-alkanols, by simple asymmetric deprotonation.[1] The trick consists in the simultaneous protection of the hydroxy group and activation of the α-protons by a sterically demanding oxazolidine-derived carbamoyl residue followed by the application of the complex formed from *sec*-butyllithium and the readily available alkaloide (-)-sparteine (**2**). This chiral base system is capable of achieving a very efficient selection between enantiotopic protons.[2,3] The lithium carbanions **3** are configurationally stable in ethereal solution below -30°C and add electrophiles with strict stereoretention.[1] Later, the oxazolidine-carbonyl residue is removed by sequential acid and base treatment to give the alcohols **5** usually with >95% *ee* (Scheme 1).

Scheme 1



Since chiral 1,3- and 1,4-dioxy-substituted carbanions have gained great preparative interest,[4] we investigated whether our method is also applicable to these synthetic building blocks. The dicarbamates **6a-c**[5]

Scheme 2



for *El* see Table 1

a) **6a, 6b, 9, 12**: 1.4 eq. *s*-BuLi/(-)-sparteine, ether, -78°C, 2-6h; **6c**: 2.0 eq. *s*-BuLi/(-)-sparteine, toluene, -78°C, 4-6h. b) **6a, 6b, 9, 12**: 1.5 eq. *EIX*; **6c**: 2.6 eq. *EIX*. c) 0.5 eq.CH_3SO_3H, methanol, reflux, 16h; excess $Ba(OH)_2$; methanol, reflux, 4h.

Table 1: Enantioselective Substitution of Carbamates **6**, **9**, and **12**

Substrate	*EIX*	Product[5]				Alcohol				
		El	yield (%)[a]	%*ee*	$[\alpha]_D^{20}$		yield (%)[a]	%*ee*	$[\alpha]_D^{20}$	reference
6a	Me_3SiCl	**7aa** $SiMe_3$	78		+21.3[b]	**8aa**	85	97[c]	+15.6[d]	
6b	CH_3I	**7bb** CH_3	83		+25.5[e]	**8bb**	80	>97[c]	+23.2[f]	+25.0 [6a]
6b	Me_3SnCl	**7bc** $SnMe_3$	96	95[g]	+33.6[e]					
6c	CH_3I	**7cb** CH_3	92		+7.6[h]	**8cb**	35	97[c]	+15.1[i]	+18.2[6b]
9	CH_3I	**10 b** CH_3	79		+9.7[j]	**11 b**	58	97[c]	+12.6[k]	+12.4[6b]
9	Me_3SnCl	**10 c** $SnMe_3$	70	>99.5[l]	+35.5[m]					
12	CH_3I	**13 b** CH_3	81		+7.0[n]	**8cb**	66	97[c]	+15.2[o]	+18.2[6b]
12	CO_2, CH_2N_2	**13 d** CO_2Me	77	>95[p]	-9.6[q]					

[a] Yield after LC purification. [b] c = 1.1, acetone. [c] Determined by GC analysis of the urethane formed from (*S*)-1-phenylethyl isocyanate. [d] c = 1.0, ethanol. [e] c = 1.0, acetone. [f] c = 0.9, ethanol. [g] Determined after conversion into **7bb**. [h] c = 1.1, CH_2Cl_2. [i] c = 0.2, $CHCl_3$. [j] c = 0.9, CH_2Cl_2. [k] c = 0.2, CH_2Cl_2. [l] Determined after conversion into **10a**. [m] c = 1.0, CH_2Cl_2. [n] c = 0.6, CH_2Cl_2. [o] c = 1.1, $CHCl_3$. [p] Determined ^{1}H-NMR spectroscopically by means of $Eu(hfc)_3$. [q] c = 0.7, CH_2Cl_2.

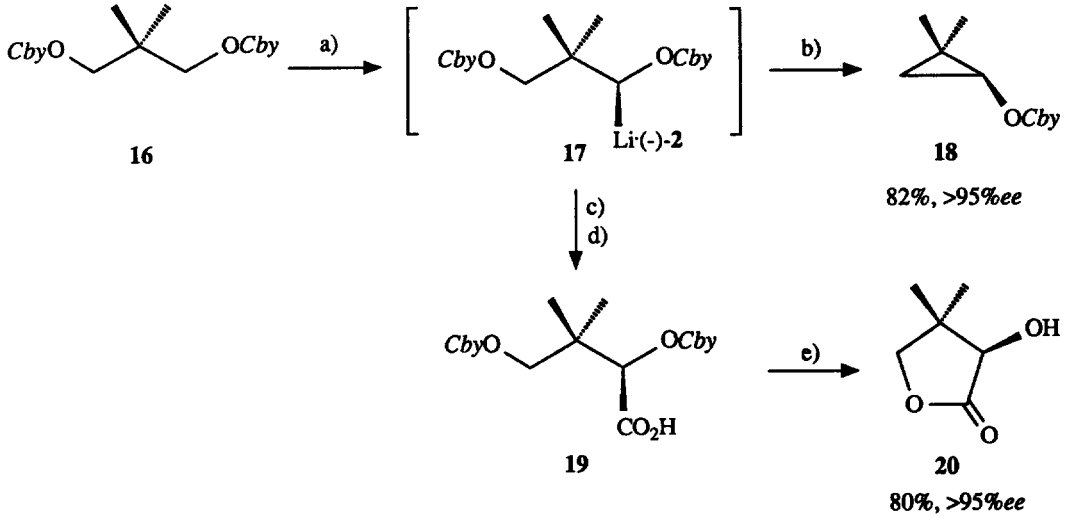
were prepared from the diols and the appropriate oxazolidine-3-carbonyl chlorides *Cbx*Cl[1] or *Cby*Cl[7] through the alkoholates. The deprotonation by *s*-BuLi/(-)-sparteine,[8] followed by the trapping with CH_3I, CO_2, Me_3SiCl or Me_3SnCl proceeded smoothly to afford the adducts **7a-c**,[5] respectively, with ≥95% *ee* in all examples (Scheme 2 and Table 1).

For establishing the absolute configurations, several products were converted into the appropriate diols **8a-c**[5] (see Table 1) and the signs of optical rotation compared with these of reported samples. Evidently, a reliable preference for the abstraction of the *si*-proton under the influence of (-)-sparteine exists also in achiral hetero-substituted alkyl carbamates. The situation becomes more complicated in chiral dicarbamates.[9]
The ω-methoxy- and ω-silyloxy-carbamates **9**[5] and **12**,[5] respectively,[8] react similarly; their substitution products **10**[5] or **13**[5] permit a selective deprotection of either the α- or the ω-hydroxyl group.

It is noteworthy, that in the lithiated 1,3-propanediyl dicarbamates, derived from **6a** and **b**, neither a carbamoyl migration nor a cycloalkylation to form a cyclopropyl carbamate[10] takes place at -70°C. The latter could be enforced in the geminally dialkylated lithio-dicarbamate **17** to form the cyclopropyl carbamate **18**[11] in the presence of Me_3SiCl, which obviously activates the leaving group (Scheme 3).

Trapping the lithium compound **17** with carbon dioxide followed by acid treatment of the substitution product **19**[5] yields (*R*)-pantolactone[12] **20** with 80% yield (based on **16**) and ≥95% *ee*; thus, one of the most efficient syntheses of this compound has been performed.[13]

Scheme 3



a) 1.5 eq. *s*-BuLi/(-)-2, -78°C, 2.5h. b) 2 eq.TMSCl, 12h, -78-25°C. c) CO_2, 12h, -78-25°C. d) 2N aq. HCl.
e) 5N HCl, 90°C, 12h.

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References and Footnotes

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5. All new products gave satisfactory elemental analysis, C ±0.27%, H ±0.19%.

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8. **General Procedure**. To a solution of (-)-sparteine **2** (703 mg, 3.0 mmol) in ether (8 ml), kept under Ar at -78°C, an aprox. 1.5 N solution of *sec*-butyllithium (2.9 mmol) in cyclohexane/isopentane is added. The carbamate **6**, **9**, **12**, or **16** (2.0 mmol), dissolved in ether (2 ml), is added dropwise and stirring is continued at -78°C for 2-6h. The appropriate electrophile *EIX* (3.0 mmol), diluted with few ether, is slowly added and stirring is continued at -78°C for 16h. After warming the reaction mixture to rt, the usual workup is performed with 2N aq. HCl/ether (10 ml each), followed by flash chromatography on silica gel with ether/pentane.
For the synthesis of **13bb** or **20**, excess gaseous CO_2 was used for *EIX*. The crude reaction product was treated with diazomethane (for **13bb**) or stirred with 5N aq. HCl (10 ml) for 12h at 90°C (for **20**).

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11. $[\alpha]_D^{25}$ = +9.2 (c=1, acetone).

12. mp = 82°C, $[\alpha]_D^{25}$ = -14.0 (c=2.8, acetone).

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