Synthesis of Enantiomerically Pure 1-Methyl-2-alkenyl *N,N*-Diisopropylcarbamates from (*S*)- or (*R*)-Lactates

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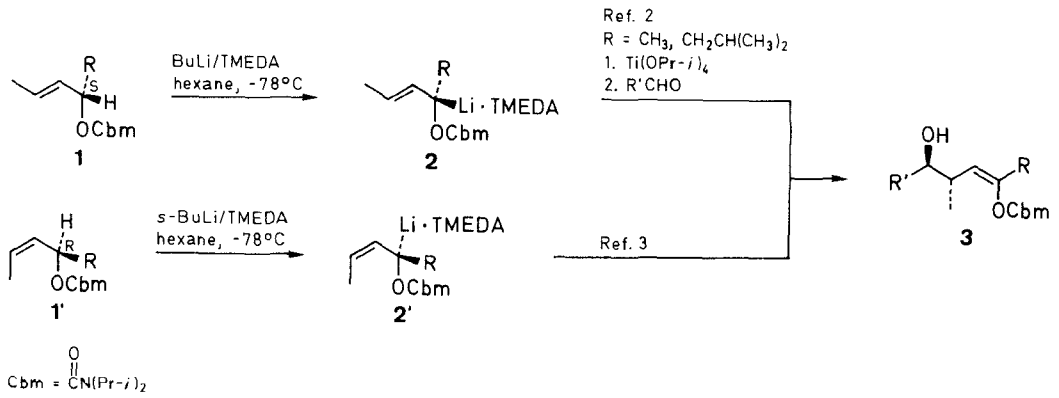
Starting from enantiomerically pure alkyl (*S*)- or (*R*)-lactates the title compounds are obtained by Wittig olefination of 2-(*N,N*-diisopropylcarbamoyloxy)propanal. The reaction sequence proceeds without racemization.

Chiral 1-methyl-2-alkenyl *N,N*-diisopropylcarbamates **1** are deprotonated by butyllithium/*N,N,N',N'*-tetramethyl ethylenediamine (TMEDA) with retention of the configuration[1] to form the α-lithio derivatives **2**. These, in contrast to all other known allyllithium derivatives exhibit at −70 °C preparatively useful configuration stability, which was utilized for enantioselective homoaldol reactions[2,3] (Scheme **A**).

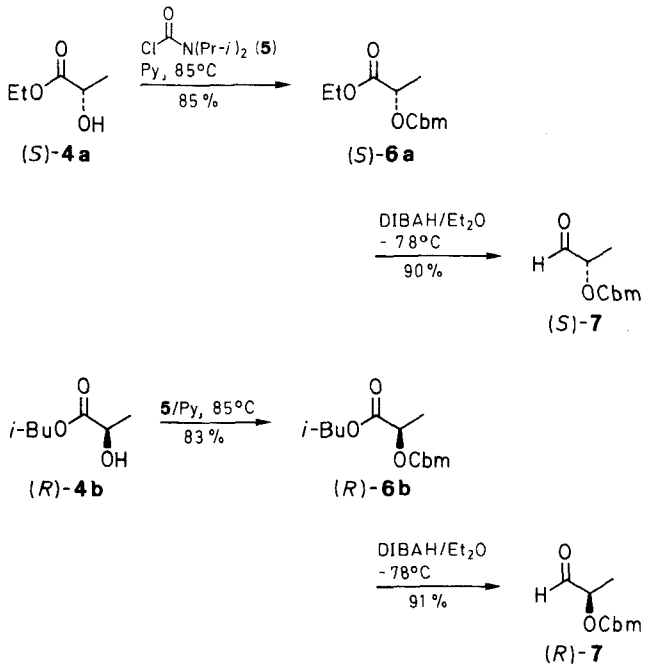
The appropriate optically active allylic alcohols were prepared by tedious classical resolution of the racemate,[4] by kinetic resolution via enzymatic ester hydrolysis,[5] or by Sharpless epoxidation.[6] Achieving optical purities higher than 90% ee by these methods is sometimes difficult.

We have now found a very efficient route for the preparation of both enantiomers of 1-methyl-2-alkenyl carbamates **9a–e**, starting from commercially available ethyl (*S*)-lactate or isobutyl (*R*)-lactate, respectively. The ester **4** is acylated by *N,N*-diisopropylcarbamoyl chloride[7,8] **5** and the carbamate **6** partially reduced[9] to yield the aldehyde **7** (Scheme **B**).

Aldehydes (*R*)- and (*S*)-**7** thus obtained have enantiomerical purities of ≥ 95% ee; this was proven by ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent, Eu(hfc)$_3$. Compound **7** shows only low base sensitivity. After refluxing a sample with triethylamine (7 equiv) in diethyl ether for 14 h, (*S*)-**7** was recovered with 74% yield and ≥ 95% ee.

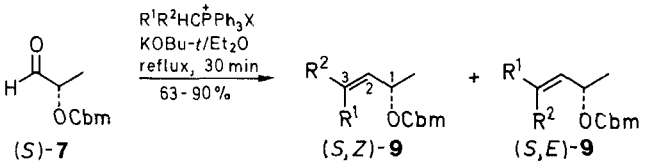


Scheme **A**



Scheme **B**

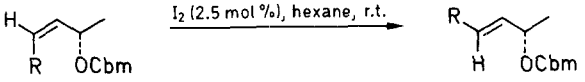
The Wittig olefination of **7** by the variant of Fitjer,[10] using the triphenylphosphonium salt[11] **8** in slight excess over potassium *tert*-butoxide in diethyl ether as solvent, gave the alkenyl carbamates **9a–e** in high yield with a *Z*/*E* ratio from 89:11 to 47:53 (Scheme **C**, Table 2). The olefination proceeds without racemization; (*S*)-**9a**, on ozonolysis followed by reductive workup, furnished enantiomerically pure aldehyde (*S*)-**7**.



8, 9	R^1	R^2	8, 9	R^1	R^2
a	H	H	**d**	Ph	H
b	CH_3	H	**e**	$CH=C(CH_3)_2$	H
c	CH_3	CH_3			

Scheme **C**

Compounds (*Z*)- and (*E*)-**9b,d,e** are easily separated by chromatography on silica gel. In the mixtures of (*Z*/*E*)-**9d,e** the *E*-isomer can be enriched without racemization by treatment with 2.5 mole% iodine[12] in hexane at room temperature (Scheme **D**).



Starting Material	R	*E*/*Z*	Reaction Time	Product	Yield (%)	*E*/*Z*
(*S*,*Z*)-**9d**	Ph	2:98	48 h	(*S*,*E*)-**9d**	–[a]	99:1
(*S*,*Z*)-**9e**	$CH=C(CH_3)_2$	3:97	1 h	(*S*,*E*)-**9e**	78	90:10

[a] Not determined.

Scheme **D**

Table 1. Compounds **6–7** Prepared

Product	Yield (%)	bp (°C/Torr)	$[\alpha]_D^{20}$ (*c*, solvent)	R_F[a]	Molecular Formula	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{13}C-NMR (75 MHz, $CDCl_3$) δ
(*S*)-**6a**	85	91/0.05	+25.4° (neat)	0.54	$C_{12}H_{23}NO_4$[b] (245.3)	1755, 1700	1.21 (d, $NCH(CH_3)_2$, J = 7.0), 1.27 (t, CH_2CH_3, J = 7.0), 1.48 (d, H-3, J = 7.0), 3.94 (m, NCH), 4.18 (q, CH_2CH_3, J = 7.0), 5.09 (q, H-2, J = 7.0)	14.15 (CH_2CH_3), 17.28 (C-3), 20.91 ($NCH(CH_3)_2$), 46.18 (NCH), 60.98 (CH_2CH_3), 68.87 (C-2), 154.62 (C=O), 171.66 (C-1)
(*R*)-**6b**	83	77/0.1	−19.2° (neat)	0.61	$C_{14}H_{27}NO_4$[b] (273.4)	1755, 1700	0.93 (d, $CH(CH_3)_2$, J = 6.8), 1.23 (d, $NCH(CH_3)_2$, J = 7.0), 1.50 (d, H-3, J = 7.1), 1.94 (tqq, $CH(CH_3)_2$, J = 6.8), 3.87 (m, NCH), 3.93 (AB, CH_2), 5.11 (q, H-2, J = 7.0)	17.98 (C-3), 19.00 and 19.03 ($CH(CH_3)_2$), 20.94 ($NCH(CH_3)_2$), 27.83 ($CH(CH_3)_2$), 46.11 (NCH), 68.87 (C-2), 70.93 (CH_2), 154.54 (C=O), 171.63 (C-1)
(*S*)-**7**	90	79/0.05	−22.3° (1.2, CH_2Cl_2)	0.32	$C_{10}H_{19}NO_3$[c] (201.3)	2810, 2720, 1740, 1690	1.24 (d, $NCH(CH_3)_2$, J = 6.3), 1.40 (d, H-3, J = 7.2), 3.95 (m, NCH), 4.97 (qd, H-2), 9.59 (d, H-1, J = 1.1)	14.19 (C-3), 20.68 ($NCH(CH_3)_2$), 46.01 (NCH), 74.68 (C-2), 154.37 (C=O), 199.11 (C-1)
(*R*)-**7**	91		+23.6° (1.3, CH_2Cl_2)				–	

[a] Eluent: Et_2O/pentane (1:1).
[b] Satisfactory microanalyses obtained: C ±0.12%, H ±0.04%.
[c] MS (70 eV) m/z (%): 201 (M^+, 8), 186 ($M - CH_3$, 100), 144 ($OCON(i\text{-}Pr)_2$, 59).

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 283b spectrophotometer, optical rotations on Perkin-Elmer polarimeter 241. GC analysis were performed on a Shimadzu GC-14A FID apparatus with a capillary column (50m, CP SIL 5CB). Et_2O used for metal-organic reactions was dried by distillation from $LiAlH_4$ under Ar atmosphere.

Ethyl (*S*)-2-(*N*,*N*-Diisopropylcarbamoyloxy)propanoate [(*S*)-6a]: A solution of ethyl (*S*)-lactate (**4a**; 12.4 g, 105 mmol) and *N*,*N*-diisopropylcarbamoyl chloride[7,8] (**5**; 16.3 g, 100 mmol) in pyridine (16.4 mL, 210 mmol) is stirred for 12 h at 85 °C. The mixture is quenched at r.t. with ice (50 g) and conc. HCl (20 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers are washed with sat. aq $NaHCO_3$ solution (50 mL), dried (Na_2SO_4)

Table 2. Compounds **9a–e** Prepared

Product	Yield (%)	*Z*/*E*-Ratio[a]	$[\alpha]_D^{20}$ (solvent, *c*)	R_f (TLC)[b]	mp (°C) (solvent)	Molecular Formula[c]	IR (neat) ν(cm^{-1})
(*S*)-**9a**	81	–	+23.4° (MeOH, 3.1)	0.58	oil	$C_{11}H_{21}NO_2$ (199.3)	1695, 1650
(*R*,*E*)-**9b** + (*R*,*Z*)-**9b**	90	89 : 11	−9.1° (CH_2Cl_2, 1.1) −59.8° (CH_2Cl_2, 1.1)	0.78 0.79	oil oil	$C_{12}H_{23}NO_2$ (213.3) $C_{12}H_{23}NO_2$ (213.3)	1700, 1670 1695, 1670
(*S*)-**9c**	63	–	+35.3° (MeOH, 1.8)	0.79	oil	$C_{13}H_{25}NO_2$ (227.3)	1690, 1650
(*S*,*E*)-**9d** + (*S*,*Z*)-**9d**	79	47 : 53	−23.6° (MeOH, 1.1) +151.4° (MeOH, 1.5)	0.78 0.82	oil 34 (Et_2O)	$C_{17}H_{25}NO_2$ (275.4) $C_{17}H_{25}NO_2$ (275.4)	1695, 1650 1690, 1650
(*S*,*E*)-**9e** + (*S*,*Z*)-**9e**	80	52 : 48	+47.0° (MeOH, 2.0) +170.2° (MeOH, 1.9)	0.51 0.56	oil oil	$C_{15}H_{27}NO_2$ (253.4) $C_{15}H_{27}NO_2$ (253.4)	1690, 1650 1690, 1650

[a] Determined by GC.
[b] Solvent System for TLC: Et_2O/pentane (1 : 1 for **9a–d**; 1 : 4 for **9e**).
[c] Satisfactory microanalyses obtained: C ±0.18, H ±0.24.

Table 3. ^{1}H-NMR Data of Compounds **9a–e**[a]

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	1-C$\underline{H}_3$ ($J_{1',1}$)	NC$\underline{H}$	CH(C$\underline{H}_3$)$_2$	R-3
9a	4.95–5.50 (m) 5.5	5.91 (ddd) 17.0, 10.5	4.95–5.50 (m)	1.31 (d) 6.5	3.91 (sept) 6.5	1.20 (d) 7.0	4.95–5.50 (m, H-3')
(*Z*)-**9b**	5.35–5.70 (m) –[b]	5.35–5.70 (m) –[b]	5.35–5.70 (m) 6.7	1.30 (d) 6.4	4.1 (m)	1.20 (d) 6.9	1.72 (d, H-4)
(*E*)-**9b**	5.26 (dq) 6.4	5.52 (dd) 15.4	5.69 (dq) 6.4	1.30 (d) 6.5	3.9 (m)	1.20 (d) 6.9	1.69 (d, H-4)
9c	*5.53 (dq)* 8.0	*5.17 (m)*	–	*1.25 (d)* 7.0	*3.98 (m)*	*1.18 (d)* 7.0	*1.68 (s, H-4)* 1.71 (s, 3-C$\underline{H}_3$)
(*Z*)-**9d**	5.52–6.03 (m) –[b]	5.52–6.03 (m) 10.5	6.47 (d)	1.38 (d) 6.5	3.90 (m)	1.19 (d) 6.5	7.21–7.52 (m, C$_6\underline{H}_5$)
(*E*)-**9d**	5.50 (dq) 6.0	6.22 (dd) 16.5	6.61 (d)	1.43 (d) 6.5	3.94 (m)	1.23 (d) 6.5	7.15–7.50 (m, C$_6\underline{H}_5$)
(*Z*)-**9e**	5.74 (dq) 8.5	6.13–6.26 (m) 9.2	5.32 (dd) 8.5	1.33 (d) 6.5	3.91 (m)	1.20 (d) 6.9	6.13–6.26 (m, H-4), 1.75 (s, H-6), 1.81 (s, 5-C$\underline{H}_3$)
(*E*)-**9e**	5.37 (dq) 6.5	5.58 (dd) 15.1	6.43 (dd) 10.9	1.34 (d) 6.5	3.91 (m)	1.21 (d) 6.9	5.81 (d, H-4), 1.75 (s, H-5), 1.77 (s, 6-C$\underline{H}_3$)

[a] 300 MHz, $CDCl_3$; δ, J(Hz).
[b] Not determined.

Table 4. Selected ^{13}C-NMR Data of Compounds **9a–e**[a]

Compound	C-1	C-2	C-3	1-C$\underline{H}_3$	NC$\underline{H}$	CH(C$\underline{H}_3$)$_2$	C=O	R-3
9a	72.34	140.33	116.07	21.68	47.15	22.47	156.16	–
(*Z*)-**9b**	66.94	131.37	125.83	20.93	45.56	21.01	155.18	13.12 (C-4)
(*E*)-**9b**	70.93	126.40	131.92	20.77	45.88	21.12	154.81	17.66 (C-4)
9c	68.34	126.07	134.52	23.01	45.65	21.15, 21.37	155.41	25.60 (C-4), 18.24 (3-CH$_3$)
(*Z*)-**9d**	67.82	129.78	132.41	21.15	45.58	20.97	154.85	–
(*E*)-**9d**	70.97	130.12	130.53	20.75	45.80	21.12	155.00	–
(*Z*)-**9e**	67.54	128.70	125.54	18.07	45.68	21.15, 21.41	155.31	120.07 (C-4), 137.40 (C-5), 15.28 (5-C$\underline{H}_3$), 20.36 (C-6)
(*E*)-**9e**	71.14	130.75	127.20	20.93	45.75	21.16	155.11	124.46 (C-4), 135.83 (C-5), 18.28 (5-C$\underline{H}_3$), 25.95 (C-6)

[a] 75 MHz, $CDCl_3$; δ.

and the solvent is removed. The residue is distilled to give (*S*)-**6a**; yield: 20.9 g (85%); bp 91 °C/0.05 Torr.

Compound (*R*)-**6b** is prepared analogously from isobutyl (*R*)-lactate.

(*S*)-2-(*N,N*-Diisopropylcarbamoyloxy)propanal [(*S*)-7]: Typical Procedure:

To the solution of (*S*)-**6a** (12.3 g, 50 mmol) in dry Et_2O (100 mL), kept below −70 °C, a 1 M DIBAH solution in hexane (60 mL, 60 mmol) is slowly added and the mixture stirred for 2 h. Then water (16 mL) is added dropwise, and the reaction mixture is allowed to warm up to 0 °C. In a separation funnel, the mixture is diluted with Et_2O (250 mL), and the phases mixed by gentle shaking for approximatly 15 min. The aluminum oxides are filtered and after drying (Na_2SO_4) the solvent is removed. The residue is distilled to afford (*S*)-**7**; yield: 9.1 g (90%); bp 79 °C/0.05 Torr.

(1*S*,2*Z*)-1-Methyl-2-butenyl *N,N*-Diisopropylcarbamate [(*S*)-9b]: Typical Procedure:

To a stirred suspension of KOBu-*t* (1.12 g, 10 mmol) in Et_2O (50 mL) ethyltriphenylphosphonium iodide[12] (4.60 g, 11 mmol) is added and the solution is refluxed for 30 min. Then (*S*)-**7** (2.01 g, 10 mmol) is dropwise introduced at r.t. After 30 min reflux, the solution is quenched with H_2O (50 mL), the aqueous layer is extracted with pentane (3 × 50 mL) and the combined organic layers are dried (Na_2SO_4) and concentrated. The residue is separated by column chromatography on silica gel (500 g) with Et_2O/pentane (1:10) as eluent to afford (*S,Z*)-**9b**; yield: 1.70 g (80%) and (*S,E*)-**9b**; yield: 0.209 g (10%) (Tables 2–4).

(1*S*,2*E*)-1,5-Dimethyl-2,4-hexadienyl *N,N*-Diisopropylcarbamate [(*S*)-9e] by *Z/E*-Isomerization of 9e; Typical Procedure:

A solution of (*S,Z*)-**9e** (505 mg, 2 mmol) and iodine (13 mg, 0.05 mmol) in hexane (5 mL) is stirred for 1 h at r.t. Then a 0.5 M aq solution of $Na_2S_2O_3$ (1 mL, 0.5 mmol) is added and the colorless mixture is extracted with Et_2O (3 × 10 mL). The combined organic layers are dried (Na_2SO_4), the solvent is reduced and the residue is chromatographed on silica gel (100 g) with Et_2O/pentane (1:10) as eluent to give (*S,E*)-**9e**; yield: 392 mg (78%) and (*S,Z*)-**9e**; yield: 47 mg (9%) (Tables 2–4).

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