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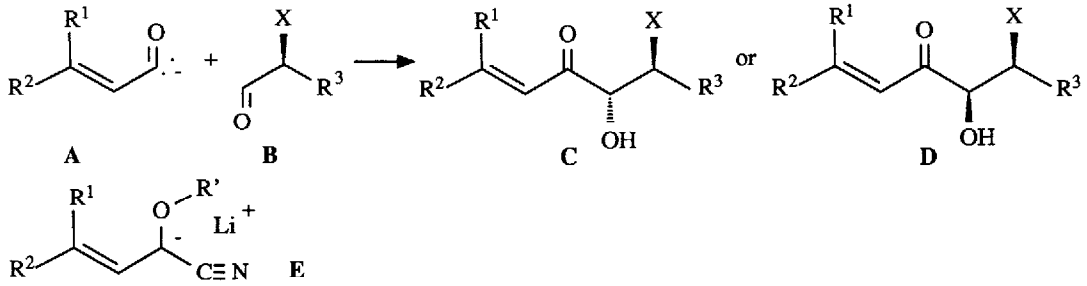
ENANTIOMERICALLY PURE α',β'-DIFUNCTIONALIZED α,β-ENONES BY HIGHLY DIASTEREOSELECTIVE NUCLEOPHILIC ALKENOYLATION OF CHIRAL ALDEHYDES

Petra Tebben, Michael Reggelin, Dieter Hoppe*

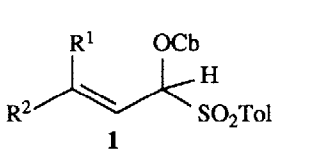
Institut für Organische Chemie, Universität Kiel, Olshausenstr. 40, D-2300 Kiel 1, FRG.

Summary: The nucleophilic alkenoylation of protected chiral α-oxy and α-amino alkanals **3** by lithiated 1-(*p*-toluenesulfonyl)-2-alkenyl carbamates **2** proceeds with virtually complete stereoselectivity to form the *syn*-diastereoisomers of the title compounds **4**.

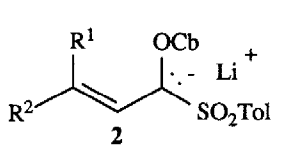
Among the reagents which accomplish the nucleophilic addition of a masked α,β-unsaturated acyl anion **A** to aldehydes or ketones (nucleophilic alkenoylation),[1] deprotonated *O*-protected cyanohydrins **E** are the best investigated ones.[2] Frequently, even here, problems of chemo- and regioselectivity are encountered.[3] Furthermore, to our best knowledge, reagents which add onto α-chiral aldehydes **B** with exclusive formation of one diastereomer **C** or **D** are not known.



As reported in the preceding Letter,[4] lithiated 1-(*p*-toluenesulfonyl)-2-alken-1-yl carbamates **2** are capable of nucleophilic acylation. On addition of various reagents **2** to enantiomerically pure (protected) (*S*)-2-oxypropanals,[5,6] **3a** or **3b**, or the (S)-α-aminoaldehyde[7] **3c** in the presence of (1.1 equiv.) tetra(isopropoxy)titanium,[8] a single diastereoisomer of the enones **4** was obtained[9,10] besides some starting materials **1** and **3** (Table).

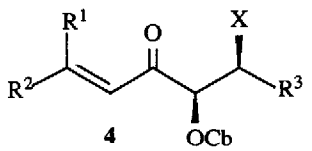


*n*BuLi, THF
-78 °C



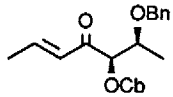
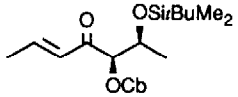
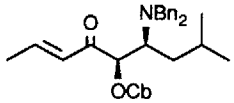
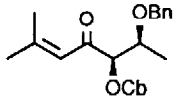
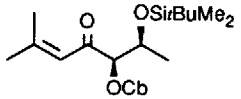
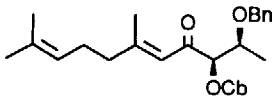
(TIPT)

1, 2	R^1	R^2	3	R^3	X
a	H	CH_3	**a**	CH_3	OBn
b	CH_3	CH_3	**b**	CH_3	OSi*t*BuMe$_2$
c	$(CH_3)_2C{=}CH{-}CH_2{-}CH_2$	CH_3	**c**	$(CH_3)_2CH{-}CH_2$	NBn_2



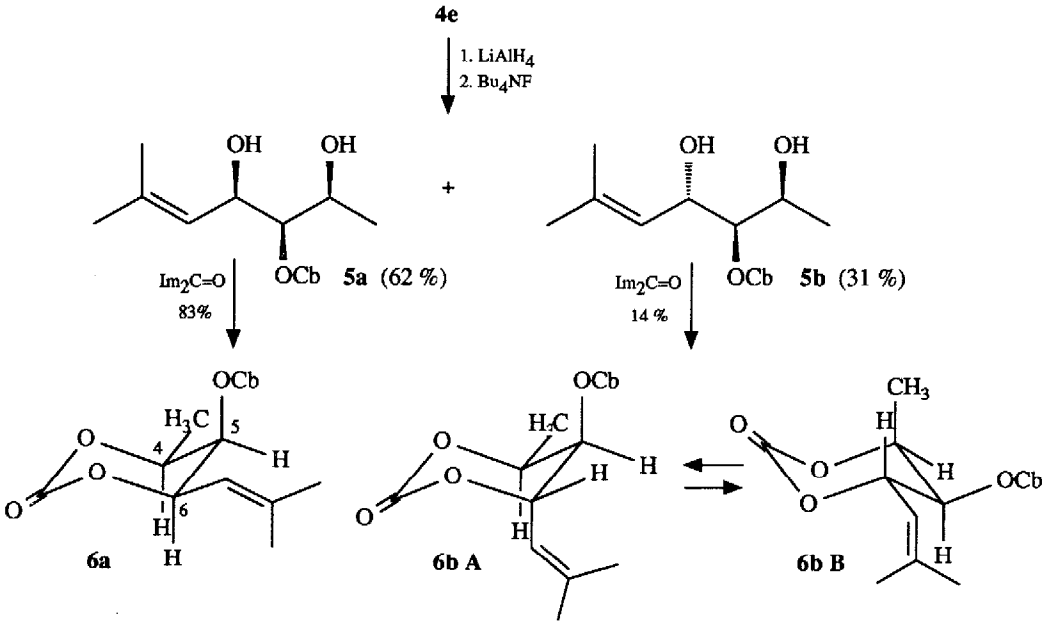
Cb = $CNiPr_2$

Table: Enones **4** Prepared

Educts	Product[a]		Yield (%)[b]	$[\alpha]_D^{20}$ [c]	Recovered **1** (%)
1a + 3a	**4a**		55	+ 19.8	33
1a + 3b	**4b**		59	+ 60.4[d]	36
1a + 3c	**4c**		83	+ 46.5	11
1b + 3a	**4d**		67	+ 53.2	30
1b + 3b	**4e**		62	+ 61.9	33
1c + 3a	**4f**		52	+ 43.8	44

[a] Satisfactory microanalyses (C ± 0.2, H ± 0.2) were obtained. [b] After LC on silica gel with ether/pentane. [c] c = 1.6 - 3.0, CH_2Cl_2, [d] c = 1.9, $CHCl_3$.

For elucidation of the stereochemistry, enone **4e** was reduced and desilylated, both diols **5a** and **5b** were converted separately to the 1,3-dioxan-2-ones[11] **6a** and **6b**.



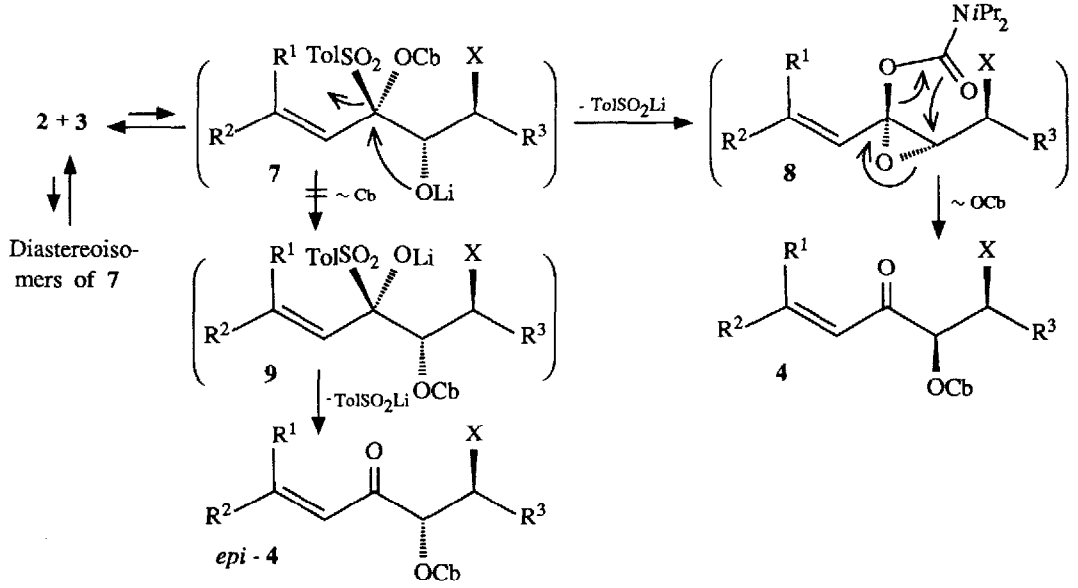
In ^{1}H-NMR, **6a** exhibits $J_{4,5} = J_{5,6} = 2.1$ Hz, which is in agreement of an all-*cis* relationship of the three protons

($CDCl_3$, δ = 4.67, 4-H_a; 4.89, 5-H_e; 5.31, 6-H_a).[12] The second isomer **6b** shows $J_{4,5} = J_{5,6} = 6.6$ Hz ($CDCl_3$, δ = 4.52, 4-H; 4.88, 5-H; 5.07, 6-H), indicating either two rapidly interconverting chairs **6bA** and **6bB** or the twist-boat conformer between them. For one of the 1,3-dioxan-2-ones (5-*epi*-**6a**) derived from the diastereoisomeric enone *epi*-**4e**, coupling constants *J* between 10 and 12 Hz are expected.[13] Hence, **4e** must possess the (*S*,*S*)-configuration.

A rationalization of the formation of virtually one diastereoisomer of **4** must explain at least the following facts:

1. The "*anti*-Cram" diastereoisomers **4** are obtained although the reaction conditions do not favour chelation control.[14]
2. Despite several attempts, in no case any primary α-adduct **7** (or its diastereoisomers) could be isolated.
3. The further conversion, including the migration of the carbamoyl group, proceeds rapidly at low temperatures.

Based on this evidence, we speculate that the formation of the adduct **7** from **2** and **3** might be (slightly) endergonic. Among the four diastereoisomeric adducts, present in low equilibration concentrations, only the Cram adduct **7** (which presumably is the predominant) is capable of a rapid transformation which consists in the intramolecular substitution of *p*-toluenesulfinate by the oxide to form the *trans*-1-vinyl-1-carbamoyloxy-oxirane **8**. It rearranges by migration of the OCb-group with inversion at C-2 and forms the product **4**. A similar rearrangement had been reported by us previously.[15] The alternative pathway by migration of the Cb group for which also precedents exist[16] would lead *via* intermediate **9** to *epi*-**4** with retention of the configuration of **7**.



The method affords an easy protocol for highly diastereoselective nucleophilic alkenoylations. The *N*,*N*-diisopropylcarbamoyl group (Cb) can be split off on a later stage by $LiAlH_4$ reduction under forced conditions.[17] The design of better removable Cb groups is in progress.

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6. As concluded from recovered aldehyde, **3b** does not racemize under the reaction conditions. - In contrast to the ^{1}H NMR spectrum of the racemate, **4b** in presence of 6.5 mol-% of Eu(hfc)$_3$ does not exhibit any signal doublings. Hence, the enantiomeric purity is estimated to exceed 95 % ee.
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8. General Procedure: To a solution of sulfone **1** (2 mmol) in THF (8 mL) at -78 °C in argon atmosphere, 1.6M *n*-BuLi in hexane (2.2 mmol) is added dropwise. After 0.5 h stirring, TIPT (2.2 mmol) is introduced and the aldehyde **3** (2.2 mmol) added. After 5 h stirring at -78 °C, aq. 2N HCl (4 mL) is added. The usual work-up, followed by LC on silca gel with ether/pentane (1:8 to 1:4) gives enone **4** and recovered **1**.
9. **4e**: Oil; 300 MHz ^{1}H NMR (δ, $CDCl_3$): -0.09 and -0.05 (s, $SiCH_3$); 0.84 (s, $SiCCH_3$); 1.0 -1.3 (br., $NCHCH_3$); 1.22 (d, 7-H_3); 1.87 (dd, 1-H_3); 3.84 and 4.01 (br., NCH); 4.15 (qd, 6-H); 5.49 (d, 5-H); 6.31 (dq, 3-H); 6.94 (dq, 2-H). $J_{1,2}$ = 6.9 Hz, $J_{1,3}$ = 1.7 Hz, $J_{2,3}$ = 15.6 Hz, $J_{6,7}$ = 6.2 Hz. 75 MHz ^{13}C NMR (δ, $CDCl_3$): -5.01 and -4.51 (s, $SiCH_3$), 17.91 (C-1), 18.35 ($SiCCH_3$), 20.36 (C-7), 21 (br., $NCHCH_3$), 25.69 ($SiCCH_3$), 46 (br., NCH), 68.81 (C-6), 81.18 (C-5), 129.34 (C-3), 142.10 (C-2), 154.66 (NCO), 196.56 (C-4).
10. Diastereoisomeric purity ≥ 99%, determined by GC (capillary column, CP SIL 5 CB, Chrompack Co., Müllheim, 50 m, 100 - 250 °C)
11. **6a**: mp. 75 °C (EtOAc/hexane), $[\alpha]_D^{20}$ = -16.5 (c = 1.6, CH_2Cl_2). **6b**: mp. 46 °C (EtOAc/hexane).
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