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Stereoselective synthesis of β-homothreonine and 3-amino substituted carbohydrates

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Abstract

Both diastereomers of β-homothreonine derivatives and other precursors of 3-amino substituted carbohydrates together with stereoselectively in position 2 deuterated analogues have been synthesized by 1,4-addition of homochiral nitrogen nucleophiles to γ-alkoxy enoates. The product distribution of the 1,4-addition of lithium amides strongly depends on the nature of the substrate. The configuration can in one case be controlled by the reagent irrespective of the substrate stereochemistry, in other cases the topicity of the addition is complementary to published results. © 1998 Elsevier Science Ltd. All rights reserved.

Key words: Michael reaction, chelation controlled delivery, β-amino acids, γ-lactones, amino sugars

We investigated the influence of the chiral centre in γ-alkoxy substituted enoates **2** on the stereoselectivity of the addition of chiral nitrogen nucleophiles [1]. The diastereomeric ratio of the products strongly depends on the solvent, with ether being by far superior to THF. The topicity of the addition of **1a** to **2a** is predetermined by the reagent configuration: *anti*-**3a** is formed from **(S)-1a** + **(S)-2a** (Table, #1), while the β-homothreonine derivative *syn*-**3b** dominates for **(R)-1a/(S)-2a** (#2). In contrast, the addition of the achiral nitrogen nucleophile **1b** to **2a** is only slightly *syn* selective (#3).

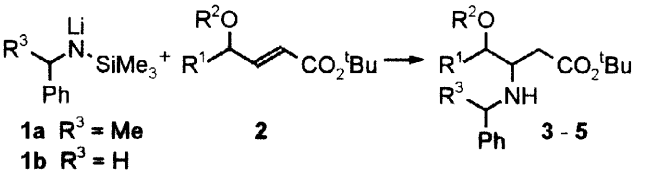
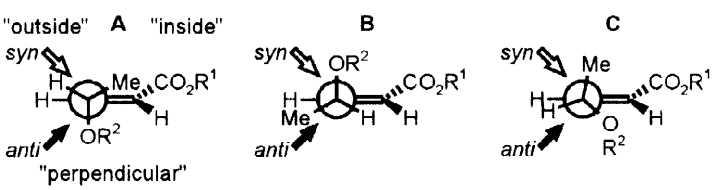


Table:
anti/syn Selectivity of the reactions under investigation (solvent: ether) [2]

#			R^1	R^2	Main product	$[\alpha]_D^{20}$ (c=1, $CHCl_3$)	Yield [%]	*anti* [%]	*syn* [%]
1	**(S)-1a**	**(S)-2a**	Me	MOM	(α*S*,3*R*,4*S*)-**3a**	-36	95	96	4
2	**(R)-1a**	**(S)-2a**	Me	MOM	(α*R*,3*S*,4*S*)-**3b**	+47	74	14	86
3	**1b**	**(S)-2a**	Me	MOM	(3*S*,4*S*)-**3c**	+8	89	32	68
4	**(S)-1a**	**(R)-2b**	Ph	MOM	(α*S*,3*S*,4*S*)-**4a**	+46	27	1	99
5	**(R)-1a**	**(R)-2b**	Ph	MOM	(α*R*,3*S*,4*S*)-**4b**	+36	39	12	88
6	**(S)-1a**	**(S)-2c**	$CH_2OC(CH_3)_2$		(α*S*,3*R*,4*S*)-**5a**	-32	75	5	95
7	**(R)-1a**	**(S)-2c**	$CH_2OC(CH_3)_2$		(α*R*,3*R*,4*S*)-**5b**	+24	82	10	90

Very similar reactions of **1b** have been reported only recently by Yamamoto et al. to be highly *syn* selective [3]. Upon addition of **1b** to O-silyl or O-trityl analogues of **2a**, *syn*:*anti* selectivities up to 100:0 for R^2 = OTrt have been observed in THF as solvent. This is explained by close analogy to the Felkin-Anh [4a] model **A**, where the C=O moiety has been replaced by the E-configured $C{=}CHCO_2R^1$ group [4b]. This model explains *syn* selectivity in non-chelated reactions, but can not account for the reagent control observed by us. A modified Felkin-Anh model **B** has been suggested [4b]. Divergent results for organocuprate 1,4-additions led to the development of



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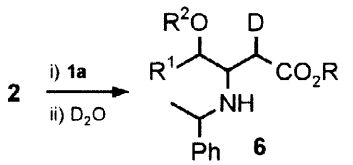
model **C** [4b,c]. The pronounced solvent dependence of the selectivity [except for **(S)-1a** + **(S)-2a**] found by us suggests that lithium amide delivery in ether is controlled by lithium „chelation" between reagent and substrate. Consequently, the reagent control observed leads to the assumption that the reaction proceeds through different transition state geometries depending on the configuration of the reagent used, e.g. **A** for the *anti* selective reaction (S)-**1a** + (S)-**2a** (#1), **B** for the *syn* selective reaction (R)-**1a** + (S)-**2a** (#2).

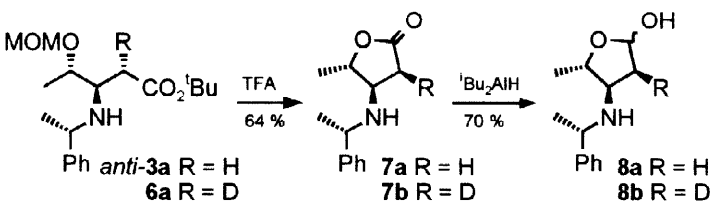
Substrate configuration governs the topicity of the addition to **2b**. Compounds *syn*-**4a** (#4) or *syn*-**4b** (#5) are obtained stereoselectively from **2b** irrespective of the reagent configuration (**1a**), if ether is used as solvent. Presumably, this addition is also controlled by intermolecular „chelation", as the corresponding *anti*-products have exclusively been observed by Yamamoto et al. on addition of **1b** to the γ-(trialkylsilyloxy) analogues of **2b** („non-chelation") [3]. Rotamer **B** (with Ph instead of Me) should be a good transition state model. The 1,3-dioxolan-4-yl residue in **2c** has been reported to favour *syn* attack of achiral nucleophiles [5]. This result also holds both for additions of **(S)-1a** and **(R)-1a**, resp., where *syn* adducts are formed (#6,7).



	R^1	R^2	Configuration
6a	Me	MOM	α*S*,2*S*,3*R*,4*S*
6b	Me	MOM	α*R*,2*R*,3*S*,4*S*
6c	Me	$CH_2OC(CH_3)_2$	α*S*,2*S*,3*R*,4*S*

Trapping of the intermediate ester enolate with D_2O affords α-deuterated derivatives with high 2,3-*anti* selectivity [6] (dr > 95:5) and high deuterium incorporation (**6a,b**: 90-95 %, **6c**: >80 %).

The relative configuration of the γ-lactones **7** obtained from **3** or **6**, resp., has been established by NOE difference spectra. Lactols **8** are obtained after reduction of the corresponding lactones **7** with DIBALH [7].



Acknowledgments. This project was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie which is gratefully acknowledged.

References and Notes

[1] Davies, S.G.; Hedgecock, C.J.R.; McKenna, J.M. *Tetrahedron: Asymmetry* **1995**, *6*, 827.

[2] **General procedure for the tandem addition / deuteration**: 1.0 mmol Amine (193 mg **1a** or 178 mg **1b**) in 25 ml ether, is deprotonated with 1 equiv. n-BuLi at -20°C (15 min) under Ar. 0.5 mmol Ester (108 mg **2a**, 139 mg **2b**, 114 mg **2c**) is added slowly at -78°C and stirring is continued at low temperature for further 4-8 h. The reaction is quenched with 5 mmol (100 µl) D_2O (99.9% D) at -78°C and warmed up (4 h) to room temperature. Satd. NH_4Cl solution is added and the mixture is extracted with ethyl acetate (2x50 ml). The organic layers are washed until neutral, dried over $MgSO_4$, and evaporated in vacuo. The residual oil is purified by flash chromatography (ethyl acetate / pet. ether). The *anti*/*syn* ratio was determined by GC-MS using a HP5-MS capillary column (30 m).

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[6] Sewald, N.; Hiller, K.D.; Helmreich, B. *Liebigs Ann. Chem.* **1995**, 925. The relative configuration at C-2 and C-3 was established by NOE difference spectra and vicinal coupling constants of the corresponding β-lactam.

[7] Analytical data of **8b**: ^{1}H NMR (DMSO-D_6): [α anomer] δ = 7.38-7.15 (m, 5H), 6.00 (br, 1H), 5.21 (br d, *J* 5.8, 1H), 3.79 (dq, *J* 6.3, 6.1, 1H), 3.75 (q, *J* 6.6, 1H), 2.35 (dd, *J* 7.7, 6.3, 1H), 2.13 (dd, *J* 7.7, 5.8, 1H), 1.23 (d, *J* 6.6, 3H), 1.01 (d, *J* 6.1, 3H); [β anomer] δ = 7.38-7.15 (m, 5H), 5.89 (d, *J* 4.9, 1H), 5.22 (dd, *J* 4.9, 1.5, 1H), 3.73 (q, *J* 6.5, 1H), 3.53 (dq, *J* 7.3, 6.2, 1H), 2.66 (dd, *J* 7.3, 6.8, 1H), 1.90 (dd, *J* 6.8, 1.5, 1H), 1.22 (d, *J* 6.5, 3H), 1.11 (d, *J* 6.2, 3H); ^{13}C NMR (DMSO-D_6): [α anomer] δ = 146.2, 128.5, 126.8, 126.7, 97.0, 77.4, 61.6, 56.0, 25.4, 19.2; [β anomer] δ = 146.5, 128.5, 126.8, 126.7, 97.1, 79.2, 60.5, 56.3, 25.6, 21.0; (CHD signal hidden by the DMSO-D_6-signal).