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NON-RACEMIPING SYNTHESIS AND STEREOSELECTIVE REDUCTION OF CHIRAL a-AMINO KETONES

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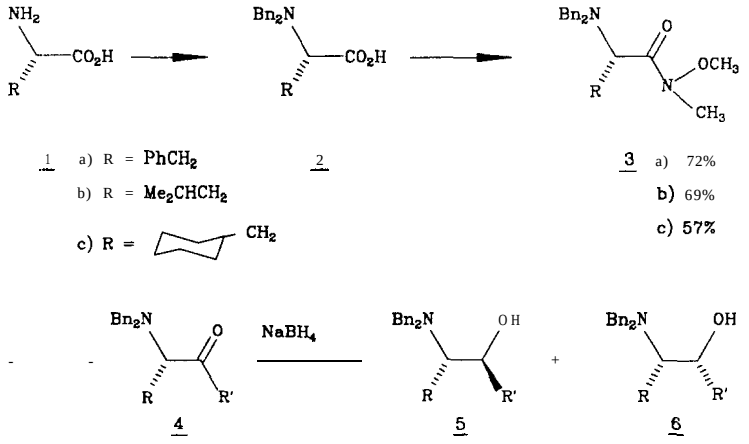
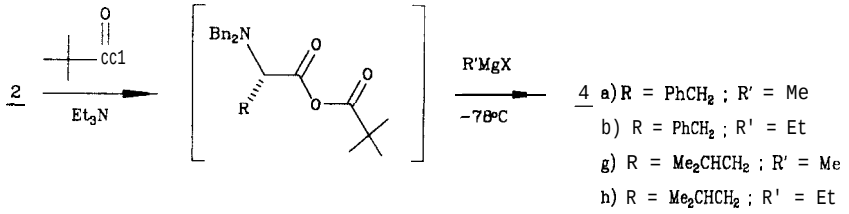
Abstract: a-Amino acids can be doubly benzylated at nitrogen, forming N,N-dibenzyl amino acids which can be converted into a-amino ketones 4 without appreciable racemization. The latter undergo stereoselective reduction with $NaBH_4$ under non-chelation control to form amino alkohols 5.

We have previously shown that α-N,N-dibenzylamino aldehydes, prepared in optically active form from the corresponding amino acids 1, undergo Grignard reactions and other nucleophilic additions with a high degree of non-chelation control to form adducts of the type 6 which can be deprotected using Pd-black/H_2[1]. The source of this surprising stereoselectivity was traced to the presence of two protective groups at nitrogen (protective group tuning)[2]. In order to reverse the sense of diastereoselectivity, Lewis acidic reagent systems such as $TiCl_4/(CH_3)_2Zn$ and $SnCl_4$/allylsilanes were applied[1,3], but the degree of chelation control was not consistently > 90%. An alternative strategy for the synthesis of diastereomers 5 would be the stereoselective reduction of the corresponding ketones 4, provided hydride delivery occurs with non-chelation control and no racemization sets in along the sequence[4]. In this communication we report that this is indeed possible.



The protected acids 2 were prepared in 70-72% yield by treatment of amino acids 1 with benzyl bromide and K_2CO_3 to form the benzyl esters of 2[1]

followed by hydrolysis of the crude products with KOH in CH_3OH/dioxane or by chemoselective 0-debenzylation using Pd/H_2. The amides 3 were then prepared according to the Weinreb method[5] and reacted with alkyllithium or Grignard reagents to form ketones 4 (Table 1). In the case of 2a (R = benzyl) a one-step conversion to the ketone 4a was tested using the Gilman ketone synthesis[6]: Treatment of 2a with 2.2 equivalents of methyllithium at 0°C/2h in THF afforded ketone 4a in 75% yield. Alternatively, the Mukaiyama one-vot ketone synthesis[7] from acids was also successful (4a: 76%: 4b: 77%; 4g: 79%; 4h: 79%)[8]:



The crucial reduction was performed with $NaBH_4/CH_3OH$[8]. Indeed, the desired diastereomers 5 were obtained with a high degree of non-chelation control') (Table 1). In order to check whether any racemization occurs along the sequence, several of the products 4 were 0-acylated using the Mosher-Chloride"): As in the case of the Grignard additions to the corresponding aldehydes[1], the ee-values turned out to be 98.5-100%, showing that essentially no racemization occurs, provided the conversion of the amides 3 to the ketones 4 is performed in the temperature range of -3ooc to -40°C (at -1ooc to ooc 5% - 10% racemization may occur). Reduction using $LiAlH_4$/THF at -78°C is generally more diastereoselective (5 : 6 = 98 : 2), but racemization may occur (2-15%) and is therefore not generally recommended.

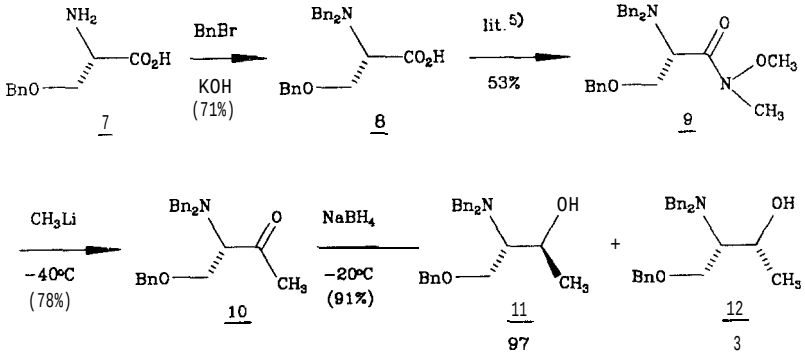
In the case of ketone 4a obtained directly from the acid 2 (R = benzyl) by the Gilman-Reaction, the reduction product 5a is also essentially enantiomerically pure (ee = 99%). The same applies to the reduction of 4a prepared by the Mukaiyama one-pot ketone synthesis. The adducts can be deprotected at nitrogen using Pd-black/H_2[1], $Pd(OH)_2/H_2$[11] or $Pd/C/H_2$; the yields range from 75-95%, depending upon the substrate and catalyst used.

Table 1. Weinreb-Synthesis and stereoselective reduction of ketones **4**

Amide	R'-metal[a)]	Ketone (% yield)	Yield of **5/6** (%)	Ratio **5** : **6**
3a	Me-Li	**4a** (94)	88	a) 94 : 6
3a	Me-MgI	**4a** (92)	88	a) 94 : 6
3a	Et-Li	**4b** (89)	93	b) 95 : 5
3a	n-Bu-Li	**4c** (72)	94	c) 95 : 5
3a	Ph-Li	**4d** (89)	86	d) 95 : 5
3a	2-Thienyl-Li	**4e** (74)	90	e) 95 : 5
3a	Undecyl-MgBr	**4f** (52)	87	f) 95 : 5
3b	Me-Li	**4g** (96)	90	g) 90 : 10
3b	Et-Li	**4h** (89)	92	h) 92 : 8
3b	n-Bu-Li	**4i** (57)	98	i) 94 : 6
3b	Ph-Li	**4j** (87)	95	j) 95 : 5
3b	2-Thienyl-Li	**4k** (75)	84	k) 95 : 5
3c	Me-Li	**4l** (83)	81	1) 94 : 6
3c	Et-Li	**4m** (66)	93	m) 92 : 8
3c	n-Bu-Li	**4n** (67)	90	n) 91 : 9
3c	Ph-Li	**4o** (96)	86	0) 95 : 5
3d	2-Thienyl-Li	**4p** (78)	92	p) 95 : 5

a) Me = methyl: Et = ethyl: Ph = phenyl; n-Bu = n-butyl

Additional functionality in the R-substituent of ketones **4** does not interfere with non-chelation control, e.g., in the case of the **serine**[12)] derived ketone **10** prepared from commercially available **7** (ee of **11** is > 99%):



In summary, this is the first systematic study of a non-racemizina synthesis of chiral α-amino ketones from amino acids and their non-chelation controlled reduction to amino alcohols.

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References and Notes

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4) The reduction of a-amino ketones has been described many times previously with varying degrees of success, depending upon the protective group. Most often racemic materials were used, so that little information is available regarding possible racemization during their synthesis and reactions (review: M. Tramontini, Synthesis 1982, 605). Bulky N,N-dialkylamino ketones are generally reduced with non-chelation control. BOC-protected a-amino ketones can be reduced under chelation-control with $Et_3SiH/TiCl_4$: S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, Tetrahedron Lett. 28 (1987) 6331.

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6) M.J. Jorgenson, Org. React. 18 (1970) 1.

7) M. Araki, T. Mukaiyama, Chem.Lett. 1974, 663.

8) General procedures: At -30°C the stirred soln of 3 mmol of a protected amino acid 2 in 20 ml of dry THF is treated with 0.42 ml (3 mmol) of NEt_3 and 0.47 ml (3 mmol) of 2,2-dimethyl propionic acid chloride[7]. After 20 min the soln is cooled to -78°C and slowly (10 min) treated with 3.2 mmol of a Grignard reagent. After an additional 20 min at -78°C, 10 ml of sat. NH_4Cl soln is added. The org. phase is separated, the aqueous phase is extracted several times with ether, the combined org. phases are washed with NaCl soln and dried over $MgSO_4$. Following chromatography, the ketones 4 (0.54 mmol) are dissolved in 10 ml of dry CH_3OH (some THF is added if the ketone is not soluble enough), cooled to -20°C and treated with $NaBH_4$ (42 mg, 1.1 mmol). After 3-4 h the mixture is quenched with H_2O and extracted several times with ether. After washing with NaCl soln and drying over $MgSO_4$, the solvents are removed and the residue is chromatographed over SiO_2: pet ether/ether (9:1) or pet ether/ethyl acetate (14:1).

9) In a statine synthesis we have previously used $NaBH_4/CH_3OH$ to reduce N,N-dibenzylamino ketoesters: M.T. Reetz, M.W. Drewes, B.R. Matthews, K. Lennick, J. Chem. Soc., Chem. Commun. 1989, 1474.

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12) Ketones derived from N-sulfonyl serine react with L-selectride or $LiBH_4$ to form 9:1 or 1:6 mixtures of non-chelation/chelation controlled adducts, respectively, but this has not been generalized to include other amino acids: R.C. Roemmele, H. Rapoport, J. Org. Chem. 54 (1989) 1866.