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Diastereoselective Reactions of Grignard Reagents with Chiral Amino Lactols Derived from L-Aspartic Acid

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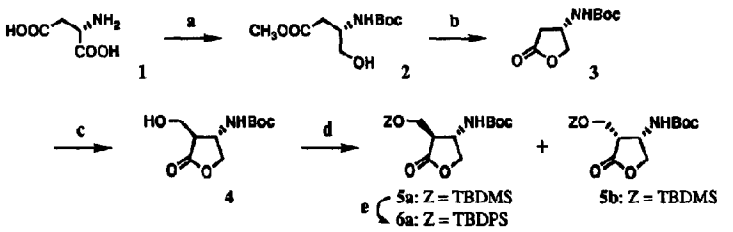
Abstract: Nucleophilic additions to chiral amino lactols obtained from L-aspartic acid containing a chiral α-silyloxymethyl function by simple Grignard reagents exhibited high stereoselectivity to provide the corresponding optically active amino alcohols containing three contiguous stereogenic centers. The mechanistic origin of the asymmetric induction is rationalized based on chelation controlled models.

Due to their well documented and useful structural features for the synthesis of biologically active compounds, there has been increasing interest in the utilization of α-amino acids as homochiral starting materials. Thus, a number of efficient techniques to utilize such compounds have been accomplished and numerous excellent reviews have appeared.[1] Because of its versatility and commercial availability, chiral synthetic units elaborated from L-aspartic acid are particularly well known and of great interest with respect to obtaining pharmacologically potent substances.[2] In a recent continuation of our work designed to extend the employment of α-amino acids, several types of stereoselective conjugate addition employing chiral synthons derived from L-glutamic acid[3] and the application to the total synthesis of antileukemic lignan-lactone, (-)-hinokinin,[4] have been developed in this laboratory.

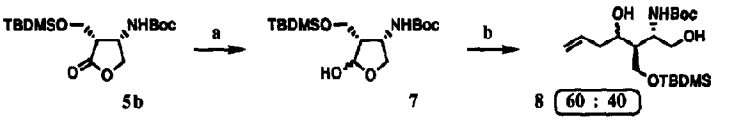
The purpose of the present communication is to demonstrate that highly diastereofacial differentiating reactions of chiral L-aspartic acid-derived amino lactols with a chiral α-silyloxymethyl group, occur with simple Grignard reagents,[5] leading to the corresponding optically active amino alcohols bearing three stereogenic centers. The mechanistic aspects of the asymmetric induction are also investigated.

As shown in Scheme 1, chiral γ-lactone 3 was prepared from L-aspartic acid (**1**) through successive esterification, Boc-protection, and regioselective reduction of the resulting diester, followed by cyclization in high yield. 3 thus obtained was submitted to hydroxymethylation in the presence of HMPA, leading to the diastereomer mixture of **4** (maximally 9 : 1), which was easily separated after protection with TBDMSCl to yield enantiomerically and diastereomerically pure lactones **5a**, $[\alpha]_D^{19}$-48.5 (c 1.00, $CHCl_3$), and **5b**, $[\alpha]_D^{19}$-16.8 (c 0.93, $CHCl_3$), respectively.[6] Compound **6a** with a larger protecting group was generated by the repetition of deprotection and protection of **5a**, since it was impossible to remove the minor diastereomer from **6a** in the case of direct TBDPS-protection of **4**.



Scheme 1. Reagents and conditions: (a) 1, MeOH-benzene, *p*-TsOH, reflux; 2, $(Boc)_2O$, Na_2CO_3, dioxane; 94% (2 steps); 3, $NaBH_4$, MeOH, -10 °C; 75%; (b) CSA, benzene, reflux; 97%; (c) LDA, HMPA, HCHO, -78 °C; 73%; (d) TBDMSCl, imidazole, DMF; 90% (**5a**); 10% (**5b**); (e) 1, concd. HCl, MeOH; 2, TBDPSCl, imidazole, DMF; 76% (2 steps).

Initially, nucleophilic attack was carried out by treatment of allylmagnesium bromide with *cis*-amino lactol **7** obtained from the DIBALH reduction of **5b** (Scheme 2), which resulted in the almost non-stereoselective formation of **8** (60 : 40 diastereomer mixture; the ratio was determined after chromatographic separation).



Scheme 2. Reagents and conditions: (a) DIBALH, toluene, -78°C; 43%; (b) allylmagnesium bromide, THF, -78 °C - r.t.; 60%.

Next, we investigated the utilization of the *trans*-amino lactols **9a** and **9b** (**9a**: Z=TBDMS; 100%; **9b**: Z=TBDPS; 91%) similarly prepared from **5a**. When **9a** was treated with allylmagnesium bromide at -78 to -20 °C, it afforded moderately diastereodifferentiated products (**10a** and **11a**) containing contiguous stereogenic centers in the ratio of 86 : 14 (determined by HPLC). With these results in hand, we further examined the reaction with several types of Grignard reagents under various conditions in order to enhance the selectivity. The details are summarized in Table 1. Finally, it became apparent that lowering the reaction temperature (Entries 3:4, 5:6, and 8:9) as well as increasing the steric bulkiness of the silyl-protecting group (Entries 1:2 and 3:5) clearly led to an increase of the diastereoselectivity of **10**,[7] however, the yield of the products generally decreased inversely.

The observed stereochemical outcome of these reactions can be rationalized by consideration using the 6- and 7-membered chelation controlled models **A**, **B**, **C**, and **D** (Fig. 1)[5a,b] of the corresponding tautomeric open chain aldehydes of the *cis*-7 and *trans*-**9** rather than non chelation (Felkin-Anh or Conforth) ones, since

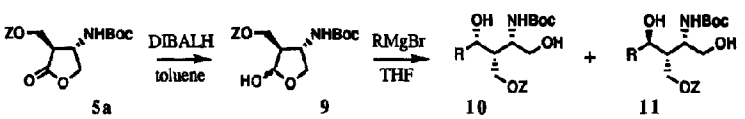


Table 1. Nucleophilic Addition to Chiral Amino Lactols (9) with Grignard Reagents.

Entry	Z	RMgBr [a]	Temp. (°C)	Yield [b] (%)	Ratio of [c] 10 : 11
1	TBDMS	CH_2=$CHCH_2$	-78 - -20	55	86 : 14
2	TBDPS	CH_2=$CHCH_2$	-78 - 0	100	89 : 11 [d]
3	TBDMS	C_4H_9	-78 - r.t.	53	85 : 15
4	TBDMS	C_4H_9	-78 - -20	38	92 : 8
5	TBDPS	C_4H_9	-78 - r.t.	22	90 : 10
6	TBDPS	C_4H_9	-78 - -20	19	91 : 9
7	TBDMS	$C_6H_5CH_2$	-78 - r.t.	67	84 : 16
8	TBDMS	C_6H_5	-20 - r.t.	36	93 : 7
9	TBDMS	C_6H_5	-78 - r.t.	85	96 : 4

a) 8 equiv. of Grignard reagents were used. (b) Isolated yield. (c) Determined by HPLC. (Cosmosil or Chiralpak AD). (d) Ratio after chromatographic separation.

the diastereofacial preference was not obtained in the reaction with *cis*-**7**. Although nucleophiles are unable to differentiate the diastereofaces via intermediate **C** or **D** in the *cis*-form, under the *trans*-model **A** or **B** the reaction could proceed through the attack to the carbonyl function from the top face of the chelation structures due to the shielding effect of the large silyl group which occupies the equatorial conformation, leading to the formation of the corresponding 3,4-*syn* products.

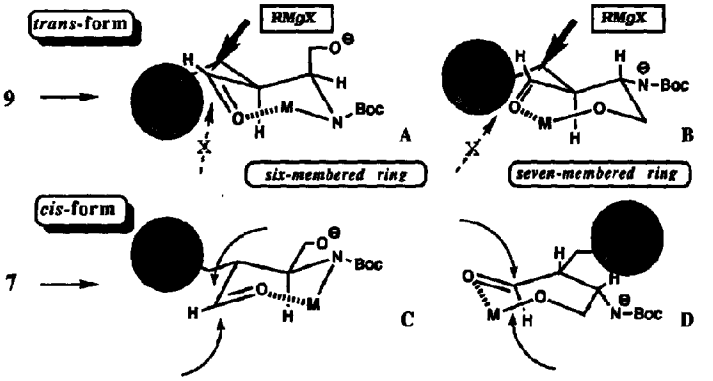


Fig. 1 Structure models of the reaction intermediate.

In summary, an efficient and general method to construct three contiguous stereogenic centers including a chiral hydroxymethyl function has been established. This strategy could provide a new method for the

synthesis of naturally occurring β-lactone antibiotics such as F-(244)[8] with the same chiral functional groups employing our reported process.[4]

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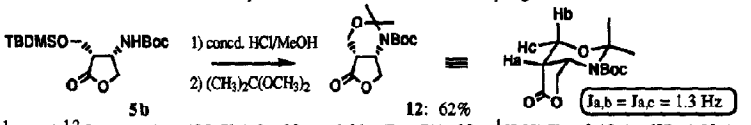
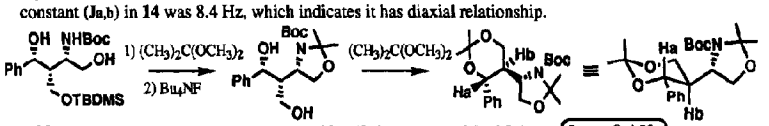
6. In order to assign the relative configurations within **5b** it was converted to the bicyclic **12**, which was ascertained to have a *cis* relationship based on the observed vicinal coupling constants.



5b **12**: 62%

7. ^{1}H and ^{13}C NMR data ($CDCl_3$) for **10a** and **11a** (R = Ph). **10a**: ^{1}H NMR δ 0.13 (s, 6H), 1.00 (s, 9H), 1.54 (s, 9H), 4.55-3.25 (m, 8H), 5.04 (d, 1H, J = 5.2 Hz), 6.05-5.53 (br, 1H), 7.34 (s, 5H). ^{13}C NMR δ -6.15, 17.8, 25.7, 28.2, 47.2, 52.7, 60.0, 64.0, 72.9, 79.2, 125.8, 128.1, 128.2, 143.0, 156.2. **11a**: ^{1}H NMR δ 0.08 (s, 6H), 0.95 (s, 9H), 1.49 (s, 9H), 4.55-3.25 (m, 8H), 5.17 (d, 1H, J = 4.1 Hz), 6.05-5.53 (br, 1H), 7.27 (s, 5H). ^{13}C NMR δ -3.76, 17.7, 25.5, 28.2, 50.2, 50.5, 60.6, 64.5, 72.1, 79.8, 126.8, 127.1, 128.7, 142.4, 157.4. Observed chemical sifts (^{1}H and ^{13}C NMR) of the other diastereomers were almost identical with those of **10a** or **11a**. And the stereochemistry of the newly created stereogenic center of **10a** was proved to be ***R*** by transformation into the acetonide **14** after separation from **11a** using silica-gel column chromatography, since the observed vicinal coupling constant (Ja,b) in **14** was 8.4 Hz, which indicates it has diaxial relationship.



10a **13**: 50% **14**: 95%

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