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Asymmetric Synthesis of 2-Amino Alcohol Derivatives from (S)-α-Amino Aldehydes via Chiral Acetal Templates

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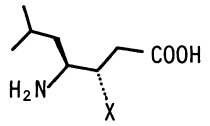
Titanium tetrachloride mediated addition of allyltrimethylsilane to chiral acetals derived from (S)-α-amino aldehydes and (+)-(2S,4S)-pentane-2,4-diol gave the anti-2-amino alcohol derivatives with considerably high diastereoselectivity. On the other hand, the same reaction by the use of acetals obtained from (-)-(2R,4R)-pentane-2,4-diol gave the products of opposite stereochemistry series as major products.

A stereoselective synthesis of 2-amino alcohols has been greatly stimulated[1] in peptidomimetic chemistry. Chiral 2-amino alcohols such as statine (1: X=OH) have been incorporated into peptides to get compounds, as exemplified by pepstatin (2), having inhibiting properties toward some class of proteolytic enzymes.[2] Although α-amino aldehydes derived from (S)-α-amino acids have a remarkable ability to yield chiral 2-amino alcohols by alkylation, the levels of the stereoselectivity are usually low,[3] and in these reactions, (1S,2S)-2-amino alcohols are formed predominantly over (1R,2S)-isomers. A new facile diastereoselective synthesis of (1R,2S)-2-amino alcohols is challenge, since they would be potentially useful for a preparation of statine analogues (e.g. 1: X=functional groups such as SH, S-alkyl) possessing the same stereochemistry as statine by conversion of hydroxy group to other functional groups by S_N2 type substitution reactions. We wish to describe an asymmetric synthesis of 2-amino alcohol derivatives through titanium tetrachloride mediated addition of allyltrimethylsilane to chiral acetals of (S)-α-amino aldehydes by an application of the effect of chiral acetal templates.[4]



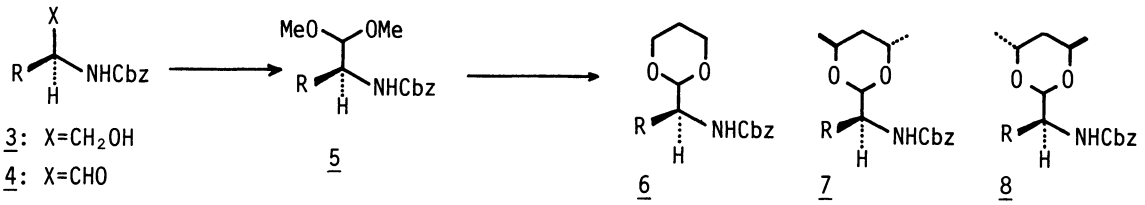
1

Iva-Val-Val-Sta-Ala-Sta
(Iva=isovaleric)

2

Acetals, used in this study, were prepared as follows. Swern oxidation[5] of (S)-2-amino alcohols (3a-c), followed by acetalization of the resulting aldehydes (4a-c) (methanol, p-toluenesulfonic acid) gave 5a-c, respectively. Transacetalization of 5a-c with 1,3-propanediol in the presence of p-toluenesulfonic acid yielded the acetals (6a-c),[6] respectively. The same reaction by the use of (+)-(2S,4S)-2,4-pentanediol and (-)-(2R,4R)-2,4-pentanediol afforded the corresponding acetals (7a-c, 8a-c), respectively.

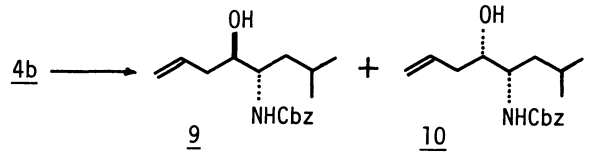
At the first stage, stereoselectivity in allylation of 4b and acetals (6a-c)



3: X=CH_2OH
4: X=CHO

Cbz=$COOCH_2C_6H_5$ a: R=Me, b: $R=CH_2CHMe_2$, c: $R=CH_2C_6H_5$

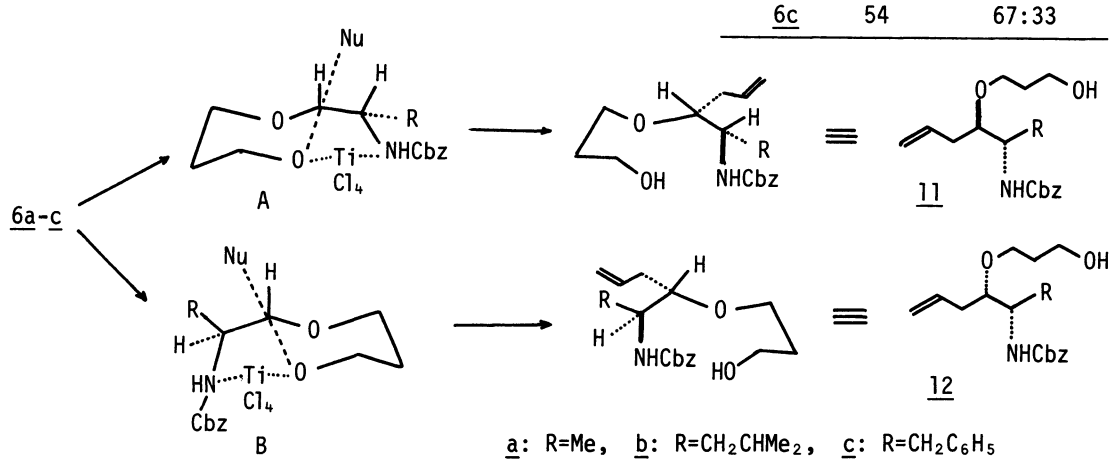
was examined. Treatment of 4b with allyltrimethylsilane (CH_2Cl_2, $TiCl_4$, -78 °C, 1 h then quenched with methanol at -78 °C) gave a 2:3 mixture[7] of 9 and 10 in a favor of syn-isomer (10). In contrast to this result, the same reaction by the use of 6a-c, the ratio of syn/anti-isomer varied in a favor of anti-isomers. Yields and the ratio of syn/anti-isomer, as shown in the Table 1, depend critically on the size of alkyl substituent at α-position. The results indicate that the reaction proceeds predominantly via the S_N2 type transition state A over the transition state B giving syn-siomer.



9 10

Table 1. Yield of 11 and 12 from 6

Acetal	Yield/%	11:12[8]
6a	90	71:29
6b	84	67:33
6c	54	67:33

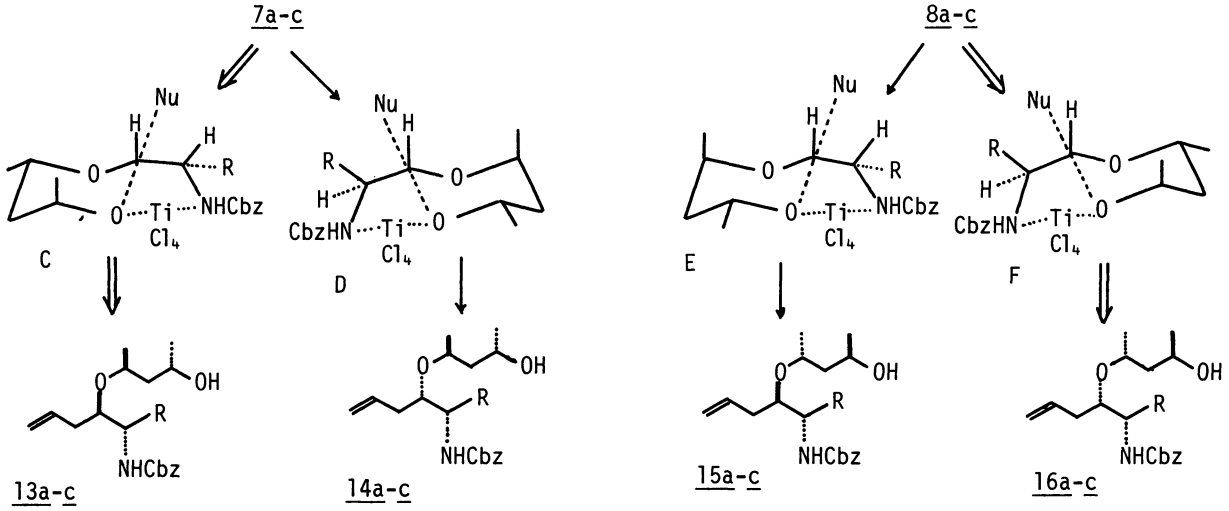


a: R=Me, b: $R=CH_2CHMe_2$, c: $R=CH_2C_6H_5$

Nu= $CH_2=CHCH_2SiMe_3$

Secondly, allylation of 7a-c and 8a-c was examined to explore the variation of syn/anti-isomer by addition of chiral auxialiary on acetals. In the cases of 7a-c, of the two transition states (C and D), C leading to anti-isomer should be sterically more favorable than D giving syn-isomers. In addition, it can be expected that template effect in C works better than in D.[9] In fact, in allylation of 7a-c, anti-isomers (13a-c) were obtained predominantly over syn-isomers (14a-c) as shown in the Table 2. Both isomers (13a-c, 14a-c) were separated by column chromatography on silica gel by elution with hexane-ethyl acetate (5:1). Allylation of 8a-c yielded syn-isomers (16a-c) as major products (Table 2). Of the two transition states (E, F), although E seems to be sterically more favorable than F, chiral template can be anticipated to work more effectively in F than E. Formation of 16a-c as major products can be accounted for mainly by this reason. But, the diaster-

eoselectivity decreased in order of 16a 16b 16c, which were consistent with the order of the size of alkyl substituesnt at α-position. The chemical behavior seen in such addition reaction correlates well with the chiral template effect as well as steric effect.



Nu= CH_2=$CHCH_2SiMe_3$ a: R=Me, b: R=CH_2CHMe_2, c: R=$CH_2C_6H_5$

Table 2. Yield of 13/14, 15/16 and $[\alpha]_D$ of 13 and 16

Acetal	Yield/%	13:14	$[\alpha]_D^{20}$/° of 13 ($CHCl_3$)	Acetal	Yield/%	15:16	$[\alpha]_D^{20}$/° of 16 ($CHCl_3$)
7a	92	85:15	+46.20 (c, 1.06)	8a	70	20:80	-36.20 (c, 1.05)
7b	97	86:14	+27.99 (c, 1.32)	8b	75	28:72	-49.77 (c, 0.85)
7c	72	84:16	-19.90 (c, 3.71)	8c	62	33:67	-65.00 (c, 2.30)

Conversion of 13a-c to 17a-c was achieved by Jones oxidation, followed by treatment with base (7.5 M KOH, methanol, THF, 1:2:4), respectively. In a similar way, 16a-c were also converted to 18a-c, respectively, by removal of the chiral auxiliary. The stereochemistry of 17a-c was assigned as 4,5-cis and 18a-c was as 4,5-trans based on the chemical shifts for 4-H and 5-H and coupling constants for $J_{4,5}$ observed in their ^{1}H NMR ($CDCl_3$, 400 MHz) spectra.[10] Furthermore, Jones oxidation of 13b, followed by treatment with p-toluenesulfonic acid (1.5 equiv., dioxane-H_2O (2:1), reflux 36 h)[11] afforded 9 in 68.5% yield (84.5% yield based on the recovery of 13b), mp 87-91 °C, $[\alpha]_D^{20}$ -16.5° (c, 0.17, methanol). In order to prove that the chiral centers retained during these reactions, 17b was converted to 20.[3] Protection of 3-nitrogen of 17b with Boc (NaH, THF, Boc_2O, 0 °C — room temperature, 12 h), followed by oxidation with $RuCl_3 \cdot H_2O$ under Sharpless conditions[12] gave the acid (19) in 64.5% yield from 17b, mp 75-77 °C. Hydrolysis of 19 (LiOH, aqueous methanol, room temperature, 0.5 h) afforded 20, mp 135-136 °C (lit.,[3] mp 135-136 °C), $[\alpha]_D^{20}$ -26.7 ° (c, 0.27, methanol) (lit.,[3] $[\alpha]_D^{24}$ -27.6 ° (c, 0.31, methanol). Thus, the absolute configuration of these products were clearly determined and the two asymmetric centers were found to retain during these steps.

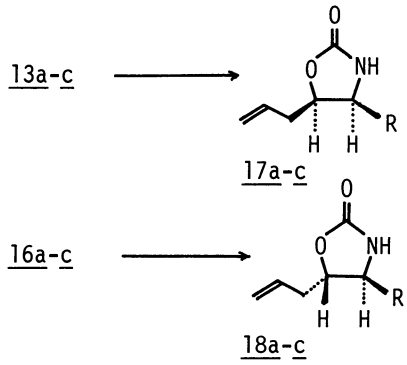
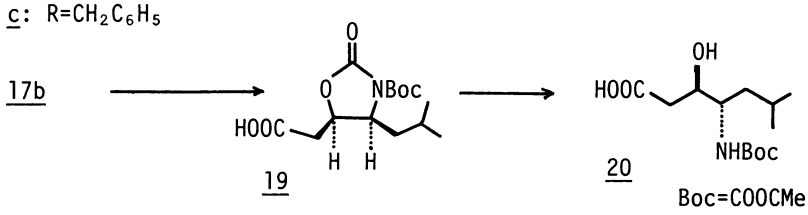


Table 3. Yield, $[\alpha]_D$, and δ ($CDCl_3$, 400 MHz) of 17, 18

Compound	Yield/%	$[\alpha]_D^{20}$/° ($CHCl_3$)	δ 4-H	δ 5-H
17a	80	+46.27 (c, 0.83)	4.63	3.93
17b	87	+13.32 (c, 1.09)	4.64	3.88
17c	81	-68.90 (c, 1.47)	4.76	3.97
18a	82	-40.80 (c, 0.87)	4.14	3.61
18b	81	-51.73 (c, 0.88)	4.17	3.57
18c	80	-67.20 (c, 0.97)	4.35	3.72



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6) All new compounds gave satisfactory microanalyses (or high MS) and spectral data (^{1}H NMR, IR, MS). All compounds were obtained as an oil otherwise noted: 5a, mp 40-41 °C; 5c, mp 75-76 °C; 7a, mp 66-67 °C; 7c, mp 92-93 °C; 8a, mp 43-44 °C; 8c, mp 90-91 °C; 13b, mp 53-55 °C; 17a, mp 73-74 °C; 17b, mp 69-70 °C; 17c, mp 78-81 °C.

7) Because of difficulty of separation, the ratio was determined after conversion to a mixture of 17b and 18b by treatment with 7.5 M KOH-methanol-THF (1:2:4).

8) The ratios were determined after conversion to a mixture of 17a-c and 18a-c by Swern oxidation followed by treatment with 7.5 M KOH-methanol-THF (1:2:4).

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