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# The highly diastereocontrolled addition of the lithium derivative of *tert*-butyldimethylsilyl propargyl ether to *N*-Boc-*N,O*-isopropylidene-L-serinal

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***Abstract:*** Effects of Lewis acids on diastereoselectivity of the addition of the lithium derivative of *tert*-butyldimethylsilyl propargyl ether to *N*-Boc-*N,O*-isopropylidene-L-serinal were investigated. High asymmetric induction in both directions was achieved.


α-Amino aldehydes are versatile building blocks, frequently used in the synthesis of natural products.[1–9] Adducts of α-amino aldehydes and acetylenic compounds are easily transformable to a variety of chiral natural products containing many contiguous stereogenic carbon atoms. Among these products are glycosidic antibiotics,[7] cytostatics,[3] as well as antiviral[9] and anthelmintic compounds.[8]

In this laboratory, as a part of extensive studies on the stereocontrolled synthesis of natural products, we have focused our attention on the diastereoselectivity of addition of acetylenic compounds to *N*-Boc-*N,O*-isopropylidene-L-serinal **1**. Compound **1**[10] is the most frequently used *N,N*-diprotected synthon equivalent to L-serinal itself.[11]

In 1988, Herold[12] reported the effect of additives on addition of trimethylsilylacetylene to serinal **1**. The *syn/anti* ratio for diastereoisomeric products ranged from 5:95 to 95:5, the yields were above 70%. Recently, these adducts have been transformed into β-branched α-amino acids.[13] Another acetylenic compound used by Herold was 1-pentadecynyllithium. Its addition to **1** in the presence of HMPA in THF at −78°C gave the *anti* adduct (95% diastereoselectivity). An opposite *syn* diastereoselectivity (95%) was achieved using zinc bromide in diethyl ether.[12] In 1990, Garner and Park[14] described two three-carbon elongations of the carbon backbone of aldehyde **1** using ethyl lithiopropynoate (HMPA/THF, −78°C, 78% yield, *syn/anti*=7:93) and the lithium derivative of propiolaldehyde dimethyl acetal (THF, −78°C, 87% yield, *syn/anti*=11:89).

In this laboratory, preliminary experiments concerning addition of the dilithium derivative of propargyl alcohol to variously *N,N*-diprotected serinals afforded moderate *anti* diastereoselectivity (*syn/anti*=25:75).[15] Therefore, we decided to examine another acetylenic compound, suitable for three-carbon elongation, namely the lithium derivative of *tert*-butyldimethylsilyl propargyl ether **2**, *N*-Boc-*N,O*-isopropylidene-L-serinal **1** was chosen as chiral carbonyl compound for these studies (Scheme 1).

The lithium derivative **2** (generated *in situ* from *tert*-butyldimethylsilyl propargyl ether and *n*-butyllithium) was pretreated, if necessary, with the Lewis acid, and then reacted with serinal **1** to afford a mixture of *syn*-**3** and *anti*-**4** diastereoisomeric adducts. The *syn/anti* ratio was then determined from the $^1$H NMR spectrum of the crude reaction mixture. The results are shown in Table 1.

Our results presented in Table 1 as well as the cited literature data[10,12,14,16] agree well with the predictions based on the Felkin–Anh model[17,18] of the transition state which leads to the *anti* adduct **3**, and the Cram model of the chelation-controlled transition state **B**[19] which leads to the *syn* adduct **4** (Scheme 2).

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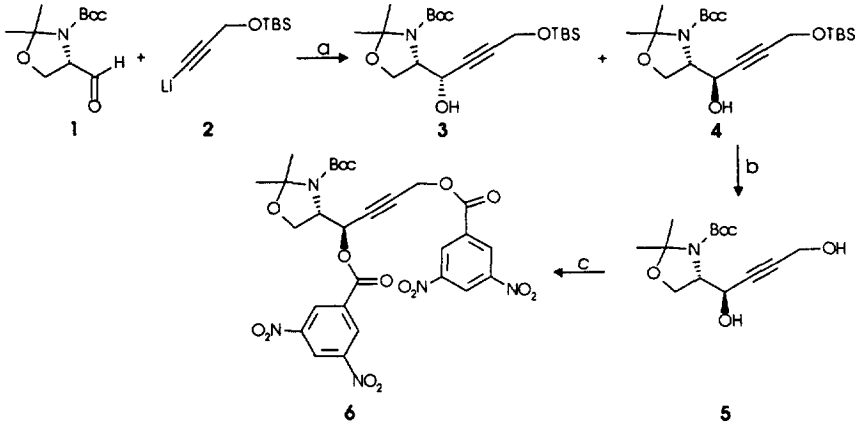
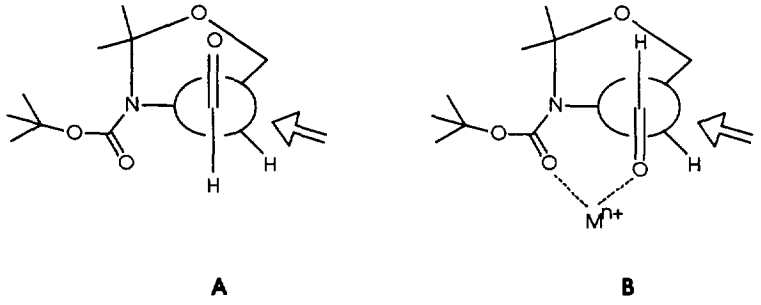


**Scheme 1.** Reaction conditions: (a) Lewis acid, toluene, −78°C→RT; (b) $Bu_4NF$, THF, RT; (c) 3.5−dinitrobenzoyl chloride, pyridine, RT.

**Table 1.** Diastereoselectivity of the addition of acetylene **2** to serinal **1**

| Entry | Additive | Solvent | Temperature [°C] | Yield [%] | Diastereoisomeric Ratio *syn*-**3**:*anti*-**4** |
|---|---|---|---|---|---|
| 1 | HMPA | toluene | -78→0 | 85 | 5:>95 |
| 2 | $Et_2AlCl$ | toluene | -78→RT | 56 | 21:79 |
| 3 | $EtAlCl_2$ | toluene | -78→RT | 45 | 23:77 |
| 4 | none | toluene | -78→RT | 80 | 26:74 |
| 5 | none | toluene | RT | 75 | 40:60 |
| 6 | $MgBr_2{\cdot}Et_2O$ | toluene/$Et_2O$ | -78→RT | 49 | 80:20 |
| 7 | $BF_3{\cdot}Et_2O$ | toluene | -78→RT | 60 | 85:15 |
| 8 | $ZnCl_2$ | toluene/$Et_2O$ | -78→RT | 65 | 91:9 |
| 9 | $SnCl_4$ | toluene | -78→RT | 46 | >95:5 |



**Scheme 2.**

The experimental procedure makes it possible to form the transmetallated derivative from the original lithioacetylene. The transmetallated nucleophile is less reactive than the lithioacetylene itself, so that better stereoselectivity can be obtained. The *syn* selectivity appears to result from α-chelation which involves the Boc oxygen atoms and the aldehyde carbonyl group. Therefore, the carbamate

functionality of the *N*-protecting group does not exclude the *syn* selectivity if the α-chelation is strong enough.

Consequently, the *anti* selectivity predominates if the α-chelation is negligible, as in the case of organoaluminum compounds. The greater steric hindrance is expected for the diethylaluminum derivative than for compound **2** itself. On the other hand, the reaction is carried out in toluene, which excludes the formation of well separated ion pairs, so the attacking nucleophile is probably the complete metallated acetylene molecule.

The above results offer the possibility of control of the stereoselective synthesis of the desired diastereoisomeric intermediates **3** and **4**. Studies on other acetylenic synthons are now in progress in this laboratory.

## Experimental

### *General*

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. $^1$H NMR spectra were recorded using a Bruker AM 500 (500 MHz) spectrometer, and $^{13}$C NMR spectra were recorded using a Bruker AM 500 (125 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer in KBr pellets. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Flash-column chromatography was performed according to Still *et al.*[20] on silica gel (Kieselgel-60, Merck, 200–400 mesh). *tert*-Butyldimethysilyl propargyl ether was obtained according to the literature procedure.[21]

### *Addition of lithium derivative of* tert-*butyldimethylsilyl propargyl ether* **2** *to aldehyde* **1** *— typical procedure*

A 25 mL flask containing *tert*-butyldimethylsilyl propargyl ether (0.34 g, 1.98 mmol) and toluene (6 mL) was cooled under argon −78°C, and then *n*-butyllithium (1.6 M in hexane, 1.2 mL, 1.92 mmol) was added, followed by diethylaluminium chloride (1.8 M in toluene, 1.1 mL, 1.93 mmol) after 0.5 h. Stirring was continued for 2 h, then the solution of the protected serinal (**1**, 0.23 g, 0.99 mmol) in toluene (3 mL) was added dropwise. After 3.5 h, the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into 1 M aqueous $NaH_2PO_4$ (20 mL). It was then extracted with ethyl acetate (3×50 mL), and the organic layer was worked up in the usual manner, to yield 0.45 g of the crude mixture of diastereoisomers. The column chromatography (hexane–ethyl acetate, 95:5→8:2) afforded 0.05 g (12%) of *syn*-adduct **3**, and 0.18 (44%) of *anti*-adduct **4**.

### *Analytical and spectral data for* syn-**3**

Oil; $[\alpha]_D^{20} = -35.8$ (*c* 1.1, $CHCl_3$); $\nu_{max}$ (film/cm$^{-1}$) 3442, 2934, 1693, 1473, 1393, 1258, 1172, 1088, 838; $\delta_H$ (200 MHz, $C_6H_6$, 60°C) 4.77 (dt, $J_1$=7.5, $J_2$=1.7, 1H), 4.21 (d, J=2.0, 2H), 4.10 (dd, $J_1$=9.7, $J_2$=2.1, 2H), 3.78 (dd, $J_1$=9.7, $J_2$=6.5, 1H), 1.65 (s, 3H), 1.42 (s, 3H), 1.36 (s, 9H), 0.95 (s, 9H), 0.10 (s, 6H); $\delta_C$ (50 MHz, $CHCl_3$) 154.4, 95.0, 82.0, 81.5, 74.0, 65.0, 64.1, 62.5, 51.6, 28.3, 25.8, 25/4, 25.2, 14.0–5.2; m/z (LSIMS, NBA) 422 $(M+Na)^+$, 400 $(M+H)^+$, 344, 326, 300,286, 200, 101; m/z (HRLSIMS) calculated for $C_{20}H_{38}NO_5Si$ $(M+H)^+$ 400.2519, found 400.2511.

### *Analytical and spectral data for* anti-**4**

Oil; $[\alpha]_D^{20} = -40.7$ (*c* 1.2, $CHCl_3$); $\nu_{max}$ (film/cm$^{-1}$) 3441, 2932, 1691, 1473, 1393, 1257, 1173, 1086, 838; $\delta_H$ (200 MHz, $C_6D_6$, 60°C) 4.64 (bs, 1H), 4.21 (d, J=2.0, 2H), 4.00 (m, 2H), 3.72 (dd, $J_1$=8.5, $J_2$=7.2, 1H), 1.69 (s, 3H), 1.46 (s, 3H), 1.39 (s, 9H), 0.94 (s, 9H), 0.09 (s, 6H); $\delta_C$ (50 MHz, $CDCl_3$) 154.0, 94.9, 84.4, 82.5, 81.2, 72.5, 64.9, 63.9, 62.4, 51.6, 28.3, 25.2, 22.2, 18.2, 13.9–5.3;

m/z (EIMS) 400 $(M+H)^+$, 384, 343 $(M-C_4H_8)^+$, 326, 310, 286, 228, 200, 144, 100; m/z (HR EIMS) calculated for $C_{16}H_{29}NO_5Si$ $(M-C_4H_8)^+$ 343.1815, found 343.1813.

*Desilylation of adduct* anti-***4*** *leading to diol* anti-***5***

To a solution of adduct *anti*-**4** (220 mg, 0.55 mmol) in THF (10 mL) solid $Bu_4NF$ (15 mg) was added and a mixture was stirred at room temperature for 16 h; then a saturated aqueous solution of $NH_4Cl$ (15 mL) was added and a mixture extracted with $Et_2O$ (2×15 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–ethyl acetate 1:1) which afforded diol *anti*-**5** (123 mg, 78%).

*Analytical and spectral data for* anti-***5***

Oil; $[\alpha]_D^{20} = -55.5$ (*c* 1.2, $CHCl_3$); $\nu_{max}$ (film/$cm^{-1}$) 3284, 2988, 1692, 1383, 1025, 847; $\delta_H$ (200 MHz, $CDCl_3$) 4.97, (bs, 1H), 4.59 (bs, 1H), 4.27 (s, 2H), 4.15 (m, 1H), 4.0 (m, 2H), 3.04 (bs, 1H), 1.60 (s, 3H), 1.51 (s, 3H), 1.50 (s, 9H); $\delta_C$ (50 MHz, $CDCl_3$) 154.1, 94.9, 84.3, 83.8, 81.5, 64.9, 63.9, 62.2, 50.76, 28.3, 26.0, 24.9; m/z (LSIMS, NBA) 308 $(M+Na)^+$, 286 $(M+H)^+$, 230, 212, 200, 172, 100; m/z (HR LSIMS) calculated for $C_{14}H_{24}NO_5$ $(M+H)^+$ 286.1654, found 286.1650.

*Preparation of compound* anti-***6***

Esterification of diol *anti*-**5** with 3,5-dinitrobenzoyl chloride was carried out under standard conditions to afford the desired yellow crystalline compound *anti*-**6** in a 86% yield.

*Analytical and spectral data for* anti-***6***

mp 75–79°C (from hexanes–ethyl acetate 1:1); $[\alpha]_D^{20} = -67.0$ (*c* 1.2, $CHCl_3$); $\nu_{max}$ (KBr/$cm^{-1}$) 3101, 2978, 1742, 1701, 1547, 1366, 1345, 1267, 1157, 721; $\delta_H$ (200 MH, $CDCl_3$) 9.25–9.15 (m, 6H), 6.15 (s, 1H), 5.10 (s, 2H), 4.5–4.1 (m, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.46 (s, 9H); $\delta_C$ (50 MHz, $CDCl_3$) 161.7, 161.5, 152.6, 151.3, 148.7, 133.3, 132.8, 129.8, 129.6, 122.8, 122.7, 94.7, 82.2, 81.3, 80.8, 66.0, 63.8, 59.8, 53.9, 28.2, 27.0, 23.8; m/z (LSIMS, NBA) 696 $(M+Na)^+$, 674 $(M+H)^+$, 618, 574, 560, 482, 406, 362, 195; m/z (HR LSIMS) calculated for $C_{28}H_{27}N_5O_{15}Na$ $(M+Na)^+$ 696.1405, found 696.1401.

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