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Stereocontrol in the Addition of Nucleophiles to an Optically Active Aldehyde Derived from *L*-Serine, Leading to a Short-Step Synthesis of (2*S*,3*S*,4*R*)-Phytosphingosine

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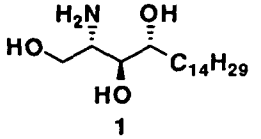
Abstract: The diastereoselective addition of dithianide to a chiral aldehyde derived from *L*-serine followed by hydrolysis of the dithiane moiety and the addition of dodecylacetylide gave a diastereomerically pure aminotriol derivative which, upon hydrogenation and deprotection, afforded (2*S*,3*S*,4*R*)-phytosphingosine in good overall yield in enantiomerically pure form.

Recent interest in the stereocontrolled construction of amino polyols coupled with increasing biological importance in the field of sphingolipids[1] involving phytosphingosine[2] has prompted the search for a short-step synthesis of amino polyols in enantiomerically pure forms. One of the most versatile syntheses of this class of compounds involves the use of chiral amino aldehydes as a convenient chiral synthon, and several approaches using the addition of organometallics to chiral amino aldehydes have appeared.[3] However, there remains an important problem of stereocontrol. In contrast to the formation of *syn*-isomers, an *anti*-selective formation of 1,2-amino alcohols or diols on an addition of organometallics to α-amino- or hydroxy-aldehydes is usually limited to a range of 80 to 90% de.[3d] In particular, in the case of amino aldehyde **2**, the stereoselectivity of the addition of an acyl anion equivalent is limited to 84% de in favor of formation of the *anti*-adduct.[3g] We have recently reported that the addition of acetylide to a chiral aldehyde derived from *L*-cysteine or *L*-serine leads to a facile synthesis of (+)-deoxybiotin in enantiomerically pure form.[4] In that study, the ability of a metal species to coordinate to heteroatoms is crucial for the *syn*-amino alcohol formation, whereas *anti*-stereocontrol using amino aldehyde **2** has met with a moderate success, producing *anti*-adduct with 72% de.[4] In the present study, the use of non-chelation intermediates to direct the newly created stereocenter has been examined in detail in order to reach a synthetically utilizable level, and we have now found that the addition of lithium dithianide **3** (Met = Li) in the presence of BF_3•Et_2O and CuI to a chiral aldehyde **2** derived from *L*-serine gave an *anti*-addition product as the sole product. The subsequent transformation into aldehyde **3** was followed by the reaction with triisopropoxytitanium acetylide **5** to afford also an *anti*-addition product in high diastereoselectivity. This paper describes an efficient approach to (2*S*,3*S*,4*R*)-phytosphingosine **1** in a diastereo- and enantioselective manner.



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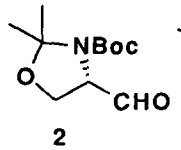

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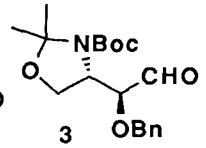

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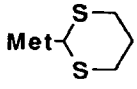

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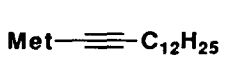

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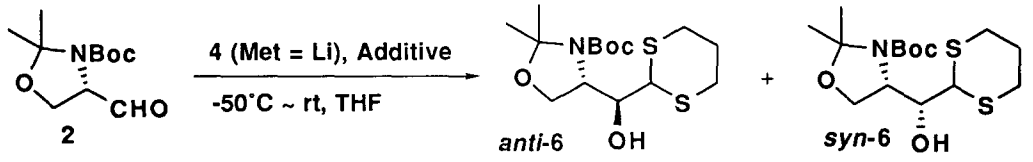


Table 1 Addition of Dithianide 4 to Amino Aldehyde 2.[a)]

Entry	Additive (equiv)	Time / h	Yield / %[b)]	*anti*-6: *syn*-6[c)]
1	none	2	96	70 : 30
2	BF_3•Et_2O (1.5)	12	88	70 : 30
3	HMPA (1.5)	16	99	77 : 23
4	BF_3•Et_2O (3.0), CuI (0.15)	36	39	93 : 7
5	BF_3•Et_2O (3.0), CuI (0.30)	36	43	>99 : <1
6	BF_3•Et_2O (3.0), CuI (0.75)	12	20	>99 : <1
7	BF_3•Et_2O (3.0), CuI (0.30)	12	70	>99 : <1

a) The reaction was carried out according to the typical experimental procedure.[7] b) Isolated yields. c) Determined by HPLC analysis (Merck Hibar Column).

The starting chiral aldehyde **2** was prepared from *L*-serine according to the published method in good overall yield.[5] First, the addition of an acyl anion equivalent was examined. Among various acyl anion equivalents examined, metal 1,3-dithianide **4** appeared to be attractive due to its ready availability and high nucleophilicity. Table 1 summarizes the results of the addition of dithianide.

As shown in Table 1, the addition of lithium dithianide **4** gave addition product **6** in good yield with a ratio of *anti* : *syn* = 70 : 30. The presence of BF_3•Et_2O did not noticeably change the product ratio, whereas HMPA improved both product ratio and yield. The desired *anti*-**6** was readily separated from *syn*-**6** by flash silica gel column chromatography. Switching the metal species to Cu (I) met with high *anti*-selectivity, in which the yield and ratio were highly influenced by the amount of CuI and reaction time. The best result was obtained by carrying out the addition in the presence of 3 eq of BF_3•Et_2O and 0.3 eq of CuI,[6] and the *anti*-adduct *anti*-**6** was obtained as the sole product in 70% yield.[7] One of the reasons for this high *anti*-selectivity may be explained in terms of the non-chelation transition state effected by the monodentate Lewis acid and the highly dissociated anion derived from the organocopper species.

Thus, with the enantiomerically pure chiral C-4 synthon *anti*-**6** in hand, we next examined the stereoselective addition of the remaining C-14 chain. For this purpose selective hydrolysis of the dithiane moiety into aldehyde was needed. Protection at the hydroxy group with a benzyl group was carried out with KHMDS and BnBr in THF in 92% yield. However, some difficulty was encountered in the subsequent hydrolysis. After several attempts the use of NBS was proved to be superior to other methods in terms of the product yield and enantiomeric purity, and the desired aldehyde **3**[8] was obtained in 67% yield without affecting its chiral centers as judged by HPLC, ^1H and ^{13}C NMR analyses. The addition of dodecylacetylide to the resulting aldehyde **3** was carried out using a titanium derivative. Table 2 summarizes the results. Several years ago the titanium acetylide was reported to be an efficient species to add to a chiral aldehyde in an *anti*-selective manner.[9] We have also reported recently that the isopropoxytitanium species are useful derivatives to effect the stereodivergent addition of enolate to imine.[10] In the present case, the addition of triisopropoxytitanium

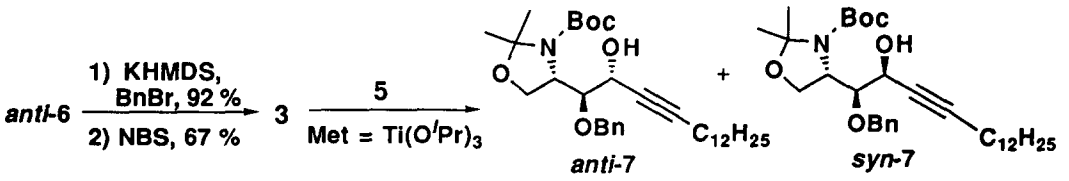


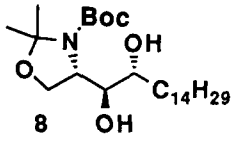
Table 2 Addition of Acetylide 5 to Aldehyde 3.[a]

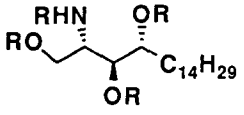
Entry	Temp / °C	Time / h	Yield / %[b]	*anti*-7: *syn*-7[c]
1	-78 ~ rt[d]	12	99	80 : 20
2	-78 ~ rt	12	94	86 : 14
3	-100 ~ rt	11	90	93 : 7
4	-105 ~ rt	10	93	95 : 5
5	-110 ~ rt	12	40	>99 : <1

a) The reaction was carried out according to the typical experimental procedure.[11] b) Isolated yields. c) Determined by GLC analysis (SE-30, 50 m Column). d) The initial Li-Ti metal exchange was conducted at -50 ~ -40 °C.

dodecylacetylide to the aldehyde **3** gave *anti*-**7** as a major product, in which separation of *anti*-**7** from *syn*-**7** was carried out readily by flash silica gel column chromatography. Lowering the reaction temperature to -105 °C improved the product ratio up to *anti* : *syn* = 95 : 5. The best diastereomer ratio was obtained when the addition was conducted at -110 °C, and the desired *anti*-**7** was obtained as the sole product.[11]

Transformation of *anti*-**7** into (2*S*,3*S*,4*R*)-phytosphingosine **1** is straightforward via hydrogenation and hydrolysis. Reduction of the triple bond and the concomitant removal of the benzyl protecting group of *anti*-**7** were carried out under an atmospheric pressure of hydrogen in the presence of 10% Pd-C in refluxing ethanol to give diol **8** in 92% yield. Subsequent hydrolysis of the Boc and acetonide groups was effected by trifluoroacetic acid and water to give (2*S*,3*S*,4*R*)-phytosphingosine **1** in 68% yield. The confirmation of the stereochemistry and enantiomeric purity was carried out by treatment of the hydrolyzed **1** with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP to give the tetraacetyl derivative **9** in 61% overall yield from **8**.[12]





1: R = H, $[\alpha]_D^{23}$ +7.0 (c 0.09, Py)

9: R = Ac, $[\alpha]_D^{23}$ +26.2 (c 0.1, $CHCl_3$)

In conclusion, we have developed a diastereospecific way for the addition of dithianide to the aldehyde **2** derived from *L*-serine. The stereospecific introduction of another chiral center was attained by the addition of triisopropoxytitanium acetylide. Thus, (2*S*,3*S*,4*R*)-phytosphingosine **1** was obtained in 6 steps starting from the aldehyde **2** in 25% overall yield.

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6. See for a review, Lipshutz, B. H. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 107-138, and the references therein.
7. A typical procedure for *anti*-**6**: To a solution of 1,3-dithiane (36 mg, 0.3 mmol) in THF (3 mL) was added *n*-BuLi (1.69 M in *n*-hexane, 0.18 mL, 0.3 mmol) at -50 °C, and the mixture was stirred at that temperature for 15 min. CuI (5.7 mg, 0.03 mmol) was added to the mixture, which was stirred for 15 min at -50 °C. The resulting deep orange mixture was added to a mixture of the aldehyde **2** (23.0 mg, 0.1 mmol) and BF_3•Et_2O (85.2 mg, 0.6 mmol) in THF (2.0 mL) at -50 °C, and the mixture was gradually warmed to room temperature during 12 h. Usual work-up and purification on TLC gave *anti*-**6** (25.0 mg, 70%) as the sole product: ^{1}H NMR (270MHz, $CDCl_3$) 1.50 (s, 12H), 1.62 (s, 3H), 1.98-2.05 (m, 2H), 2.65-2.80 (m, 2H), 2.09-3.10 (m, 3H), 3.88-4.45 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) 25.34, 27.62, 27.89, 28.41, 48.63, 59.46, 63.31, 71.93, 80.45, 94.05, 153.93 ppm; $[\alpha]_D^{23}$ -35.7 (c 4.6, $CHCl_3$).
8. The ^{1}H NMR data was in good agreement with that reported:[3e] ^{1}H NMR (270 MHz, $CDCl_3$) 1.45 (s, 9H), 1.56 (s, 3H), 1.62 (s, 3H), 3.75-3.81 (m, 1H), 3.89-3.94 (m, 2H), 4.10-4.25 (m, 1H), 4.53 (d, 1H, *J* = 11.70 Hz), 4.63 (d, 1H, *J* = 11.70 Hz), 7.35 (brs, 5H). 9.62 (d, 1H, *J* = 5.90 Hz) ppm; ^{13}C NMR (68 MHz, $CDCl_3$) 26.76, 27.21, 28.27, 57.32, 57.49, 64.49, 73.42, 80.37, 84.12, 128.27, 128.41, 128.59, 148.01, 153.83, 200.75 ppm; $[\alpha]_D^{23}$ -54.0 (c 2.2, $CHCl_3$).
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10. Shimizu, M.; Kume, K.; Fujisawa, T. *Chem. Lett.* **1996**, 545-546.
11. A typical procedure for *anti*-**7**: To a solution of 1-tetradecyne (17.5 mg, 0.09 mmol) in THF (2.5 mL) was added *n*-BuLi (1.69 M in *n*-hexane, 0.06 mL, 0.1 mmol) was added at -78 °C, and stirred at that temperature for 30 min. A solution of chlorotitanium triisopropoxide (1.0 M in *n*-hexane, 0.1 mL, 0.1 mmol) was added at -78°C, and the mixture was allowed to stand at 0 °C for 2 h. A solution of the aldehyde **3** (11 mg, 0.03 mmol) in THF (1.5 mL) was added at -110 °C, and the whole mixture was gradually warmed to room temperature. Usual work-up and purification on TLC gave *anti*-**7** (6.2 mg, 40%) as the sole product: ^{1}H NMR (270 MHz, $CDCl_3$) 0.88 (t, 3H, *J* = 6.60 Hz), 1.23-1.30 (m, 18H), 1.49-1.58 (m, 18H, including singlets at 1.49, 1.51, and, 1.53 ppm), 2.15 (t, 2H, *J* = 8.24 Hz), 3.68-3.73 (m, 1H), 3.85-3.96 (m, 1H), 4.01-4.22 (m, 2H), 4.52 (d, 1H, *J* = 11.55 Hz), 4.91 (d, 1H *J* = 11.55 Hz), 4.65-4.78 (m, 1H), 7.25-7.43 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) 14.09, 14.16, 22.66, 24.73, 26.85, 28.36, 28.45,28.56, 29.00, 29.15, 29.33, 29.49, 29.62, 31.88, 56.84, 60.36, 61.12, 65.32, 72.72, 81.46, 85.36, 94.05, 127.84, 127.98, 128.41, 137.70, 153.93 ppm; $[\alpha]_D^{23}$ -38.2 (c 2.2, $CHCl_3$).
12. **9**: ^{1}H NMR (270 MHz, $CDCl_3$) 0.88 (t, 3H, *J* = 6.60 Hz), 1.20-1.45 (m, 24H), 1.56-1.72 (m, 2H), 2.02 (s, 3H), 2.05 (s, 6H), 2.08 (s, 3H), 3.97 (dd, 1H, *J* = 11.72 and 2.97 Hz), 4.26 (dd, 1H, J = 11.72 and 4.62 Hz), 4.40-4.51 (m, 1H), 4.85-4.96 (m, 1H), 5.10 (dd, 1H, *J* = 8.57 and 2.97 Hz), 5.95 (d, 1H, *J* = 9.24 Hz) ppm; $[\alpha]_D^{23}$ +26.2 (c 0.1, $CHCl_3$). Spectral properties were identical with the reported data.[3g]

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