Highly stereocontrolled access to a tetrahydroxy long chain base using *anti*-selective additions

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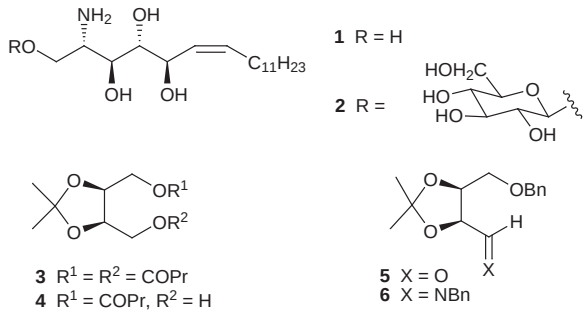
Complete diastereostereoselection was attained for the addition of acetylide and benzyloxymethyl anions to a chiral aldehyde and an imine derived from *meso*-tartaric acid, leading to a facile synthesis of (2*S*,3*S*,4*R*,5*R*,6*Z*)-2-amino-1,3,4,5-tetrahydroxyoctadecene as its pentaacetyl derivative in enantiomerically pure form.

Increasing interest in the field of cerebrosides prompted us to investigate an easy access to this class of compounds in a highly stereocontrolled fashion.[1] In conjunction with the amino polyols which recently have attracted the interest of chemists, several 2-amino-1,3,4,5-tetrahydroxyoctadecene derivatives have been found in bovine spinal cords and human brains as well as in green and red algae.[2] Among them, (2*S*,3*S*,4*R*,5*R*,6*Z*)-2-amino-1,3,4,5-tetrahydroxyoctadecene **1**, the long-chain base

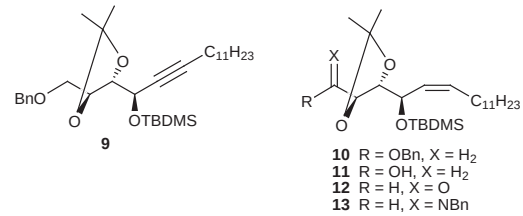


(LCB) part of a new cerebroside **2**, was isolated from the latex of *Eupohorbia characias L* and its structure has been elucidated.[3] The biological importance of such cerebrosides, especially the imparted bioactivities, makes this compound a useful target for synthesis. To the best of our knowledge, however, only two approaches to tetrahydroxy-LCB **1** have been reported; one starting from D-mannose[4a] and the other from D-glutamic acid.[4b] There still appear to be important problems of stereocontrol,[5] and we focused on the topic of stereocontrol in the addition of nucleophiles to chiral aldehydes and imines to find a solution to these problems. We have recently reported that complete *anti*-stereocontrol has been attained in an addition of nucleophiles to the chiral aldehyde derived from L-serine, leading to a short synthesis of (2*S*,3*S*,4*R*)-phytosphingosine,[6] while *syn*-selective addition of nucleophiles has also been successfully used for the synthesis of deoxybiotin.[7] In these studies, a non-chelation- or chelation-type transition state was thought to be crucial for such complete *anti*- or *syn*-stereoselection, respectively.[5–7] For the synthesis of tetrahydroxy-LCB **1**, the *anti*-stereocontrolled construction of the contiguous asymmetric carbons is likely to be difficult, as can be seen from its structure. Here we describe a new stereocontrolled approach to tetrahydroxy-LCB **1** using a tandem *anti*-selective addition of nucleophiles to the chiral aldehyde **5** and the imine **6** derived from *meso*-tartaric acid.

The chiral aldehyde **5**[8] was prepared in good overall yield in enantiomerically pure form starting from *meso*-tartaric acid using lipase-mediated desymmetrization as a crucial step. *meso*-Tartaric acid was converted into dibutyrate **3** *via* diethyl ester formation (cat. TsOH, EtOH) and acetonization (cat. TsOH, 2,2-dimethoxypropane, benzene, 94% yield for two steps) followed by reduction ($LiAlH_4$, THF, 84%) and bis-acylation (*n*-butyryl chloride, Et_3N, CH_2Cl_2, 75%). The dibutyrate **3** was treated with Lipase Amano PS in phosphate buffer–acetone at room temperature for 5 h to give the mono-ester **4** in 93% yield with > 99% ee.[9] The protection of the hydroxy functionality with an ethoxyethyl group (cat. PPTS, ethyl vinyl ether, CH_2Cl_2) was followed by hydrolysis of the ester moiety (K_2CO_3, MeOH). The benzyl etherification of the resulting ethoxyethyl ether (KHMDS, BnBr, THF) and hydrolysis of the ethoxyethyl group (cat. PPTS, PrOH) gave the alcohol, which was oxidized using the Swern oxidation to give the aldehyde **5** in enantiomerically pure form in 66% overall yield from the mono-ester **4**.†

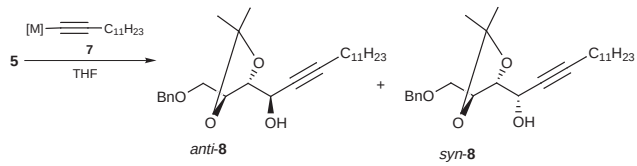
As shown in Table 1, the *anti*-selective addition of acetylide to aldehyde **5** was conducted with triisopropoxytitanium acetylide **7** as described earlier[7,10] to give the desired adduct *anti*-**8** in 98% yield as single diastereomer (entry 1),‡ whereas modest *syn*-selectivity was observed with halomagnesium, lithium, or dichlorocerium acetylide (entries 2–5).

The *anti*-propargyl alcohol *anti*-**8** was then transformed into the imine **13** possessing the functionalities necessary for the synthesis of tetrahydroxy-LCB **1** *via* the following sequences: protection of the hydroxy group with TBDMS (TBDMSCl, imidazole, DMF, **9**: 95%); partial reduction of the triple bond



under the Lindlar conditions [H_2, Pd/$BaSO_4$, quinoline, MeOH, **10**: 99%, ($Z : E$ = > 99 : < 1)]; removal of the benzyl protecting group (Ca, liq. NH_3, **11**, 86%); Swern oxidation of the hydroxy group (oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, **12**: 93%); benzylimination ($BnNH_2$, Et_2O, **13**: 100%).

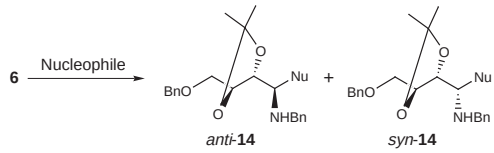
Table 1 Addition of dodecylacetylide to aldehyde **5**



Entry	[M]	*T*/°C	Yield (%)[a]	*anti* : *syn*[b]
1	$Ti(OPr^i)_3$	−78–0	98	> 99 : < 1
2	MgBr	−78–0	43	40 : 60
3	MgCl	−50–0	66	24 : 76
4	Li	−78–0	43	27 : 73
5	$CeCl_2$	−78–rt	48	23 : 77

[a] Isolated yields. [b] Determined by ^1H and ^{13}C NMR analyses.

Table 2 Addition of nucleophiles to imine **6**



anti-**14** *syn*-**14**

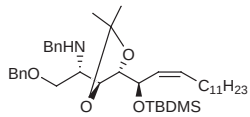
Entry	Nucleophile	Solvent	*T*/°C	Additive (equiv)	Yield (%)[a]	*anti*:*syn*[b]
1	Li-dithianide	THF	−50–rt	none	33	< 1 : > 99
2	Li-dithianide	THF	−50–0	BF_3•Et_2O (4.0)	78	> 99 : < 1
3	LiC≡CTMS	THF	−78–rt	none	17	< 1 : > 99
4	LiC≡CTMS	THF	−78–0	BF_3•Et_2O (4.0)	55	> 99 : < 1
5	2-FurylLi	THF	−78–rt	none	16	< 1 : > 99
6	2-FurylLi	THF	−78–rt	BF_3•Et_2O (4.0)	34	> 99 : < 1
7	TMSCN	CH_2Cl_2	−78–rt	BF_3•Et_2O (4.0)	48	88 : 12
8	$LiCH_2OBn$[c]	THF	−78–0	BF_3•Et_2O (4.0)	78	> 99 : < 1

[a] Isolated yields. [b] Determined by HPLC analysis (Merck Hibar Column). [c] Preparation of this anion, see ref. 12.

For the introduction of a hydroxymethyl moiety into the imine **13**, three types of nucleophiles were investigated for the addition reaction in terms of diastereoselectivity, in which the imine **6** was used as a model substrate, and Table 2 summarizes the results.

As shown in Table 2, lithium dithianide in THF added to the imine **6** to give *syn*-**14** (Nu = 1,3-dithiane) as the sole product, whereas reversal of the diastereoselectivity was observed in the same reaction conducted in the presence of an excess BF_3•Et_2O, giving *anti*-**14** stereospecifically (entries 1 and 2).[7] Similar trends of reversal of the diastereoselectivity were observed in the cases with the lithium acetylide and 2-furyllithium (entries 3–6). TMSCN in the presence of BF_3•Et_2O[11] also effected the predominant formation of the *anti*-adduct *anti*-**14** (Nu = CN) (entry 7). For the preparation of tetrahydroxy-LCB, the use of a hydroxymethyl anion equivalent was more preferable in terms of functional group manipulation and, therefore, benzyloxymethyllithium[12] was used for the addition in the presence of BF_3•Et_2O to give *anti*-**14** (Nu = $BnOCH_2$) as the sole product in good yield (entry 8). This high selectivity is most probably explained in terms of non-chelation (for *anti*-adduct) and chelation transition states (for *syn*-adduct).

Thus, addition of benzyloxymethyllithium to the imine **13** was conducted as in the case with **6** in the presence of BF_3•Et_2O to give, as expected, the desired *anti*-adduct **15** exclusively in



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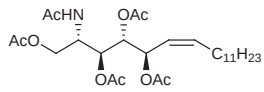

16

32% yield.§ Deprotection of the benzyl group was carried out with Na-NH_3, and subsequent hydrolysis with TFA followed by acetylation gave the pentaacetyl derivative **16** of tetrahydroxy-LCB **1** in 11% overall yield from **15**.¶

In conclusion, the present synthesis using a tandem *anti*-addition reaction to the chiral aldehyde and the imine realizes a rapid access to biologically important molecules in a highly stereocontrolled fashion. Since the level of the diastereoselectivity attained on the addition of nucleophiles to α-hydroxy aldehyde and imine was extremely high, this procedure may be applied to the syntheses of a variety of amino polyols of biological importance in a stereocontrolled manner.

Notes and references

† The enantiomeric purity was determined by HPLC using a chiral stationary column (Daicel OJ).

‡ To a solution of tridecyne (1.63 g, 647 mmol) in 70 ml of THF was added BuLi (1.68 M in n-hexane, 4.62 ml, 7.76 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min. A solution of $ClTi(OPr^i)_3$ (1.0 M in n-hexane, 7.8 ml, 7.76 mmol) was added to the mixture at −78 °C and it was allowed to stand at −60 °C for 1 h. A solution of **5** (647 mg, 2.58 mmol) in THF (35 ml) was added to the resulting mixture at −78 °C, and the mixture was stirred at that temperature for 2 h. After usual work-up, the crude oil was purified by flash silica gel chromatography to give the propargyl alcohol *anti*-**8** (1.09 g, 98%) as a colorless oil.

§ To a solution of $SnCl_2$ (214 mg, 1.15 mmol) in THF (2 ml) was added a solution of LiBr (100 mg, 1.15 mmol) in THF (2 ml) and the mixture was stirred at room temperature for 30 min. A solution of $BnOCH_2Cl$ (180 mg, 1.15 mmol) in THF (2 ml) was added to the resulting mixture, to which was added BuLi (1.68 M in n-hexane, 2.74 ml, 4.61 mmol) at −78 °C, and stirred for 1 h at that temperature. BF_3•Et_2O (164 mg, 1.152 mmol) was added to the mixture and after 10 min a solution of **13** prepared *in situ* from **12** (131 mg, 0.288 mmol) and $BnNH_2$ (32.4 mg, 0.302 mmol) in THF (2 ml) was added at −78 °C, and the whole mixture was gradually warmed to 0 °C. After usual work-up, the crude oil was purified on preoperative TLC to give **15** (60.7 mg, 32%) as a colorless oil.

¶ The spectral properties are identical with the reported data (ref. 4).

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