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STEREOSELECTIVE PREPARATION OF SYNTHETIC EQUIVALENTS OF 2-DEOXY-2-AMINO- AND 3-DEOXY-3-AMINOTETROSES FROM MALIC ACID. APPLICATION TO THE SYNTHESIS OF C_{18}-D-*RIBO*-PHYTOSPHINGOSINE

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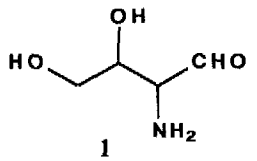
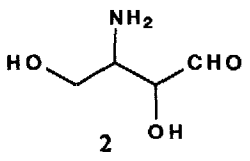
Summary: "Electrophilic amination" of β-hydroxyester **5**, derived from (S) malic acid, with di-*t*-butylazodicarboxylate allowed preparation of new synthetic equivalents of 2-deoxy-2-amino- and 3-deoxy-3-amino-tetroses. As an application, D-*ribo*-C_{18}-phytosphingosine was stereoselectively synthesized.

2-Deoxy-2-aminotetroses **1**, and 3-deoxy-3-aminotetroses **2**, are useful chiral building blocks for the synthesis of biologically active substances, including aminosugars, β-lactam antibiotics, and sphingolipids. A few syntheses of synthetic equivalents of **1** and **2** have been described in the past,[1,2] either starting from natural substances[1a,2a,2b,2d] or *via* asymmetric synthesis.[1b,2c] However, a simple general method for the preparation of equivalents of all four isomers of **1** and **2** is still lacking. In this communication we wish to describe a new entry to these valuable synthons, starting from malic acid as the chiral precursor, and based on the recently described[3] "electrophilic amination" of β-hydroxyester dianions with di-*t*-butylazodicarboxylate.[4]

Dimethyl (*S*) malate **3**,[5] was selectively reduced to the monoalcohol **4**, following the method developed by Moriwake and coworkers[6] (Scheme 1). The primary alcohol was protected with good regioselectivity as the *t*-butyldiphenylsilylether **5**. On this substrate we carried out the electrophilic amination with di-*t*-butylazodicarboxylate (Boc-N=N-Boc).[3] By performing the reaction at -50°C a moderate selectivity of 2:1 favouring the *erythro* isomer **6** was found. We did not succeed in improving this ratio on changing the temperature and/or the solvent. Although the direction of asymmetric induction remains the same, the diastereomeric ratio is lower than those usually obtained for other β-hydroxyester.[3] The two isomers **6** and **7** were easily separated and converted into the N,O-*iso*-propylidene acetal **8** and **9**, by treatment with 2-methoxypropene in CH_2Cl_2 under acid catalysis.[7,8] The more stable *trans* isomer **9** was also easily obtained from **8** through a base-mediated equilibration. In this way **9** can be prepared in a stereoconvergent way from both **6** and **7**. Reduction of **8** and **9** to the corresponding primary alcoohols **10** and **11** proceeded in high yield and without detectable epimerization, by using calcium borohydride.[10,11] Finally Swern oxidation furnished the aldehydes **12** and **13**.[12] Since the conversions of the N(Boc)-NH(Boc) group to a NH-NH_2 or a NH_2 group are well documented,[3,4] **12** and **13** can be considered as synthetic equivalents of 2-deoxy-2-amino-D-erythrose and 2-deoxy-2-amino-D-threose respectively, as well as of their hydrazino analogues. Being (R) dimethyl malate commercially available as well, also their enantiomers should be accessible. Application of these synthons to the synthesis of 4-aminohexoses is in progress. In order to preliminarily explore the stereochemical course of nucleophilic additions to **12** and **13** and at the same time to verify some interesting results obtained for the 4-deoxy-analogues,[9] we reacted these aldehydes with EtMgBr. The results, listed in Table 1 showed a behaviour similar to the 4-deoxy analogues, with the *trans* aldehyde **13** giving always preferentially the *anti*[13] adduct, and

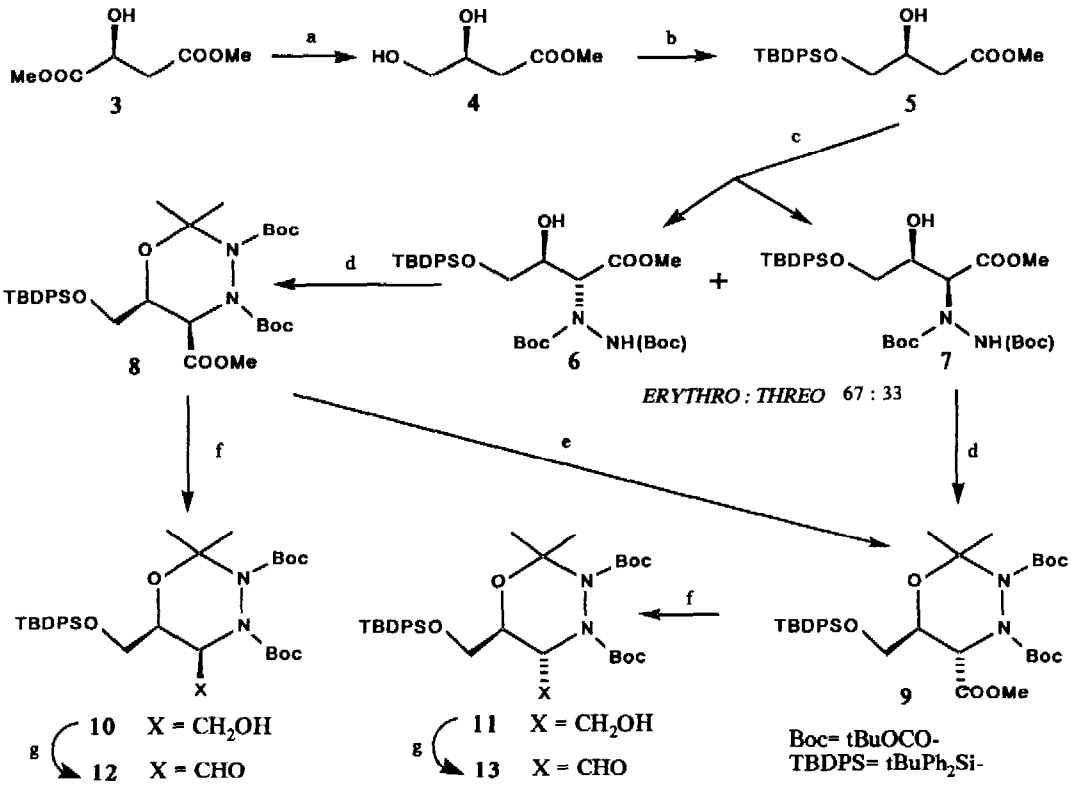


1



2

SCHEME 1



a) BH_3, cat. $NaBH_4$, 88% (ref. 5). b) *t*-$BuPh_2SiCl$, imidazole, DMF, r.t., 48 h, 71%. c) 1) LDA, THF; 2) *t*-BuOOC-N=N-COO*t*-Bu , 62% (overall); d) MeO-$C(CH_3)$=CH_2, *p*-TSA, CH_2Cl_2, 71% for **8**, 57% for **9**; e) *t*-BuOK, THF, -78°C→25°C, 75%; f) $CaCl_2$, $NaBH_4$, THF, EtOH, 90% for **10**, 81% for **11**. g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→ -30°C.

the *cis* aldehyde affording the *syn* or *anti* adducts depending on the presence of HMPA as cosolvent.[14]

10 and **11** can also be employed for the preparation of synthetic equivalents of 3-deoxy-3-amino-tetroses as esemplified by the preparation of **16** and **17**, which have the L-*erythro* configuration. Actually protection of the free hydroxyl in **10** as methoxyethoxymethyl (MEM) or benzyloxymethyl (BOM) ether, followed by hydrolysis of the silyl ether with *n*-Bu_4NF afforded in high yields the alcohols **14** and **15**, which were then converted into the corresponding 3-deoxy-3-amino-L-*erythrose* equivalents by Swern oxidation.[12]

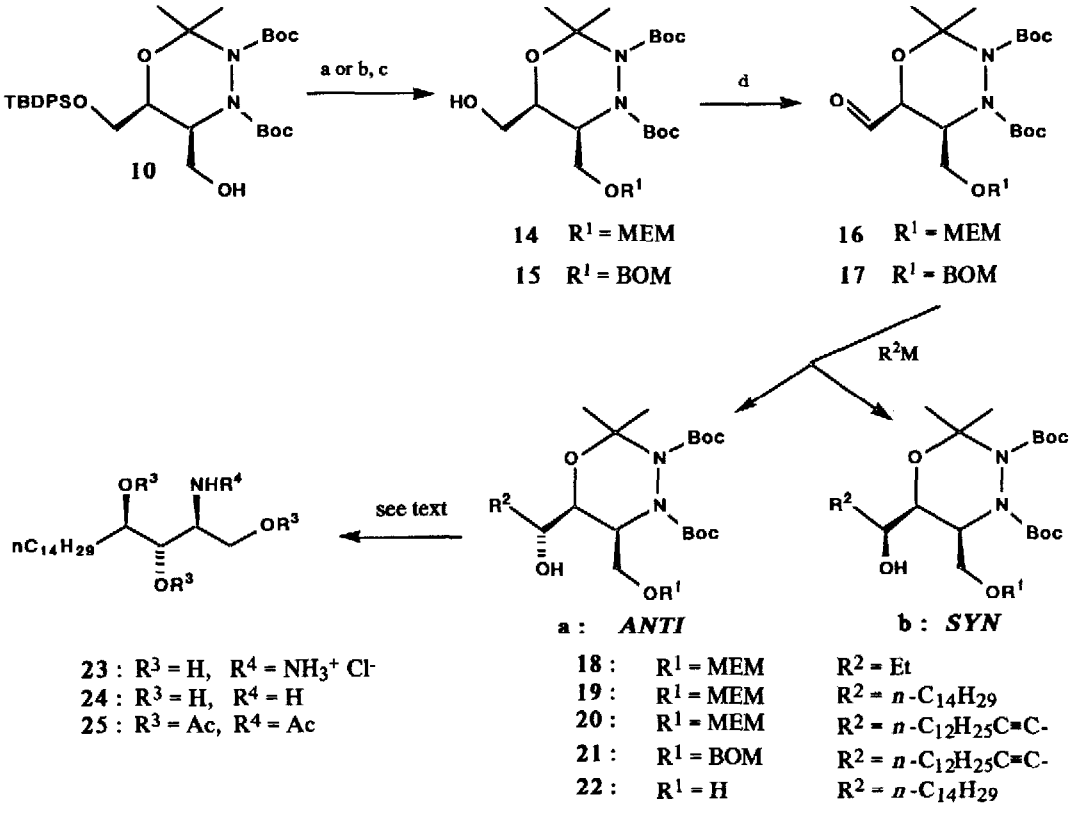
As a first application of these synthons we report here the synthesis of C_{18}-D-*ribo*-phytosphingosine **24**[15] and of its hydrazino analogue **23** (Scheme 2). This important aminotriol is widely distributes, as well as its C-16 and C-20 analogues, as amides of α-hydroxy long chain acids in plant sphingolipids, and was also detected in human brain and kidney lipids.[15d] A few preparation of **24** or of C-16 and C-20 analogues, starting from sugars,[15b,15c] C_{18}-D-*erythro*-sphingosine,[15a] *iso*-propylidene glyceraldehyde,[15d] or *via* asymmetric synthesis[15e] have

TABLE 1
Diastereoselection in addition of EtMgBr to **12** and **13**[a]

Aldehyde	Solvent	*Anti*:*Syn* ratio	Yield
12	THF	25 : 75	70%
12	THF/ HMPA	64 : 36	71%
13	THF	87 : 13	63%
13	THF/HMPA	87 : 13	67%

a) All reactions carried out at -78°C→ 0°C; *Anti*:*Syn* ratios determined by spectrodensitometry.

SCHEME 2



a) MEM-Cl, Et_3N, CH_3CN, reflux, 30h, 91%. b) BOM-Cl, Et_3N, CH_3CN, reflux, 24 h, 95%. c) *n*-Bu_4NF, THF, r.t., 20h, 91% for **14**, 95% for **15**. d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→ -30°C.

been reported. In order to synthesize stereoselectively the required *ribo* isomer, we studied the condensation of some organometallic reagents with **16** and **17** under various conditions.

The results, shown in Table 2, indicate that *anti* adducts are generally preferred, but that the diastereoselectivity is enhanced by using lithium tetradecyne[16] instead of *n*-$C_{14}H_{29}MgBr$, and performing the reaction in the presence of HMPA. The type of protecting group had little influence. For comparison we examined also the condensation of EtMgBr with **16**, which turned out to be stereorandom. The alkynes **20a,b** were easily transformed in 80-90% yield into the saturated compounds **19a,b** by hydrogenation (10% Pd-C, EtOH, r.t.). In the same way **21a,b** were converted into **22a,b** in

TABLE 2
Condensation of various C-nucleophiles to aldehydes **16** and **17**[a]

Aldehyde	Reagent	Solvent	*Anti*:*Syn* ratio	Yield
16	EtMgBr	THF	50 : 50[b]	70%
16	*n*-$C_{14}H_{29}MgBr$	THF	65 : 35[c]	68%
16	*n*-$C_{12}H_{25}C{\equiv}C$-Li	THF	74 : 26[d]	69%
16	*n*-$C_{12}H_{25}C{\equiv}C$-Li	THF/HMPA	85 : 15[d]	71%
17	*n*-$C_{12}H_{25}C{\equiv}C$-Li	THF	77 : 23[c]	75%
17	*n*-$C_{12}H_{25}C{\equiv}C$-Li	THF/HMPA	85 : 15[c]	71%

a) All reactions carried out at -78°C → 0°C. b) Determined by n.m.r.. c) Determined by HPLC (refractometer). d) Determined by HPLC after hydrogenation to **19a,b**.

78% yield, with simultaneous cleavage of BOM ether. With the desired stereochemistry secured, we finally studied the conversion of **19a** and **22a** into our targets. By using a sequence usually employed satisfactorily by us on similar substrates[17] (1. AcOH: 1N HCl 2:1, 70°C, 6 h; 2. H_2, PtO_2, EtOH/H_2O, 1 day; 3. Ac_2O, pyridine, r.t.), **19a** was converted, *via* **23** and **24** into tetraacetyl D-*ribo*-C_{18}-phytosphingosine **25** in only moderate (28%) overall yield. In a similar way, **19b** gave the tetracetyl L-*lyxo*-C_{18}-phytosphingosine in 32% yield.[18] **25** showed very close $[\alpha]_D$ (+ 24.7°, c 0.5, $CHCl_3$; lit.[15c]: +26.3°, c 2, $CHCl_3$) and identical ^1H and ^{13}C n.m.r. to the previously reported data.[15c,15d,19]

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6) Saito S., Hasegawa T., Inaba M., Nishida R., Fujii T., Nomizu S., and Moriwake T., *Chem. Lett.*, **1984**, 1389.
7) The relative configuration of **8** and **9** was determined by ^1H n.m.r. which showed, for **9** a J between H-2 and H-3 = 8.0 Hz., typical of a *trans* substitution and identical to the one determined for the 4-deoxy analogue (see ref. 9), the configuration of which was unambigously established (ref. 3). It was not possible to determine the same J for **8**. Configuration of **8** was later proved also by conversion into C_{18}-D-*ribo*-phytosphingosine **24**.
8) The ^1H n.m.r. spectra of all compounds containing the N(Boc)-N(Boc) moiety were unresolved at 29°C, due to restricted rotation of the Boc groups. Nicely resolved spectra were obtained in most cases performing the ^1H n.m.r. measurement in d-6 DMSO at 90-100°C.
9) Guanti G., Banfi L., and Narisano E., accompanying communication.
10) Luly J.R., Dellaria J.F., Plattner J.J., Soderquist J.L., Yi N., *J. Org. Chem.*, **1987**, *52*, 1487.
11) In order to avoid epimerization it is important to use a slight excess of $CaCl_2$ relative to $NaBH_4$ (ref. 10).
12) In order to avoid epimerization problems, aldehydes **12**, **13**, **16**, and **17** were synthesized just before the next condensation reaction, and used as such without purification. Yields in the tables are overall yields of 2 steps starting from the primary alcohols.
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14) A possible interpretation of these results is reported in ref. 9.
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16) *n*-Tetradecyne was prepared from sodium acetylide and *n*-dodecyl bromide according to Garner P., Park J.M., and Malecki E., *J. Org. Chem.*, **1988**, *53*, 4395, and was lithiated with *n*-BuLi at 0°C.
17) For example L-*ribo* and L-*lyxo* 3,4-*bis*-(*t*-butossicarbonyl)-5-(1-hydroxypropyl)-2,2,6-trimethyl-perhydro-1,3,4-oxadiazine were converted in > 50% yields into the corresponding 2,4-diacetoxy-3-acetylamino-hexanes by a similar procedure: Guanti G., Banfi L., Narisano E., unpublished results.
18) Conversion of **22a** to **25** under the same conditions proceeded in lower yields.
19) We measured a δ of 4.93 ppm for H-4 in the ^1H n.m.r. This value fits pefectly with that reported in ref. 15d, but is different from the value of 4.69 ppm reported in ref. 15c. Since all the other n.m.r. data correspond, we believe that the 4.69 value derives from a typing error.

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