Assignment of Absolute Stereochemistry of Aminopolyols by the Bichromophoric Exciton Chirality Method

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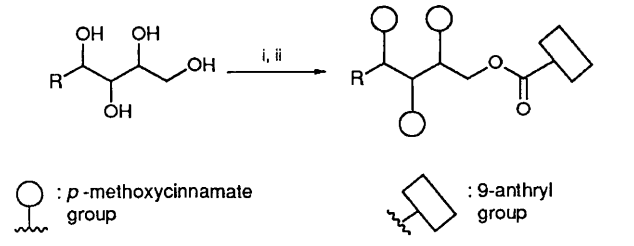
A general procedure for assigning relative and absolute configurations to multiple stereocentres in acyclic aminopolyols, and its microgram-scale application to an aminobacteriohopanetriol is presented.

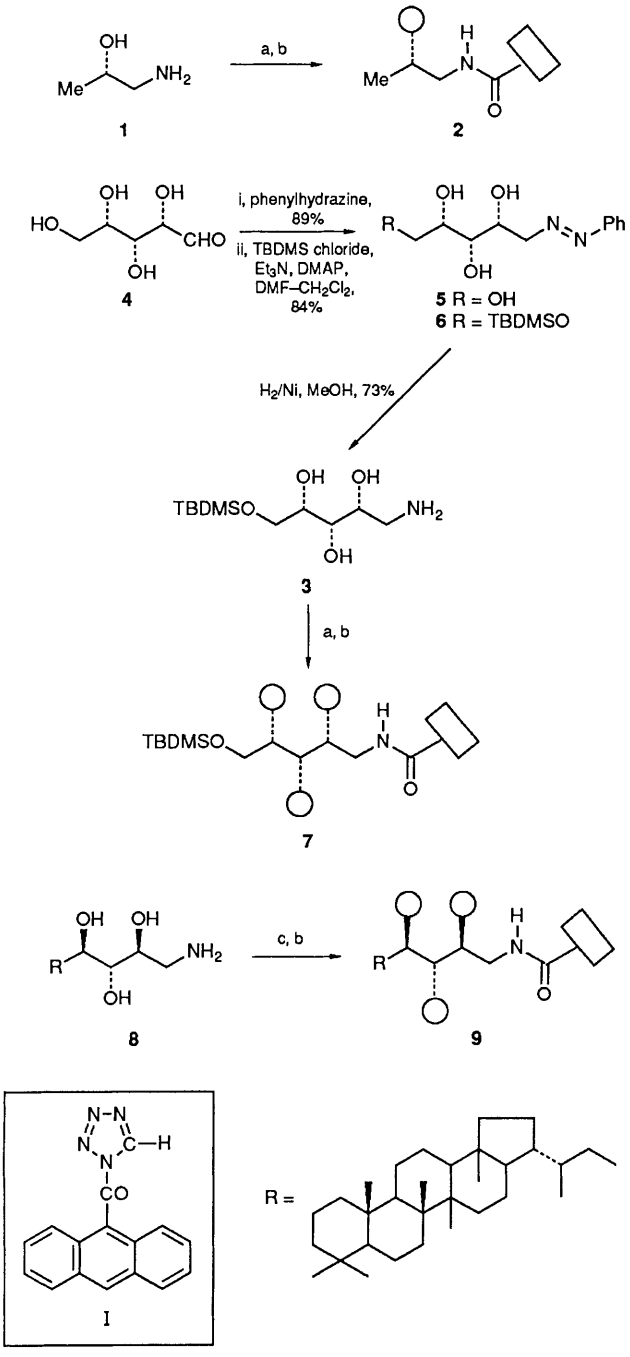
We recently reported[1] that the relative and absolute configurations of acyclic 1,2-, 1,2,3-, 1,2,3,4- and 1,2,3,4,5-polyols can be determined by the bichromophoric exciton chirality method after a two-step derivatization and comparison of circular dichroic (CD) curves with reference curves. Here we describe that this method can be extended, after modification of the derivatization procedure, to aminopolyols in a staightforward manner; the method has been applied to the side-chain aminopolyol moiety of a natural bacterial triterpenoid aminobacteriohopanetriol.

In the bichromophoric derivatization scheme of acyclic polyols, the primary and secondary hydroxy groups were selectively labelled with 9-anthroyl chloride and *p*-methoxycinnamoyl chloride, respectively (Scheme 1). However, in the case of the aminomono-ol, (*S*)-(+)-1-aminopropan-2-ol **1** (Scheme 2), the reaction of 9-anthroyl chlorides with the terminal amino group proceeds in a poor yield of < 30%. A search of various reagents and reaction conditions has shown that 9-anthroyltetrazole **I** (Scheme 2) is an excellent reagent for the selective acylation of a terminal amino group in the presence of secondary hydroxy groups. This acylation reagent is readily prepared by reaction of 1*H*-tetrazole[2] and 9-anthroyl chloride in anhydrous tetrahydrofuran (THF) containing 1.2 equiv. of Et_3N at room temp. for 1 h; after flash chromatography, reagent **I** is isolated in > 85% yield as a yellow solid,† which can be stored at room temperature for months. Besides acylating primary amino groups selectively in high yield, the reaction with 9-anthroyltetrazole can be carried out in a variety of solvents, *e.g.* pyridine, dimethylformamide (DMF),



Scheme 1 *Reagents*: i, 9-anthroyl chloride (1.1 equiv.), DMAP, pyridine (Py), yield 40–70%; ii, *p*-methoxycinnamoyl chloride (excess), DMAP, Py, yield 90%

† *Spectroscopic data* for **I**: ^1H NMR ($CDCl_3$) δ 9.36 (s, 1H), 8.72 (s, 1H), 8.10 (m, 2H), 7.63 (m, 2H), 7.52 (m, 4H) (no exchangeable proton with D_2O which supports the absence of the –NH group in the tetrazole moiety of **I**); MS(EI 70 eV) *m/z* 274 (M^+) 17%, 205 ($M-CHN_4$) 100%.



Scheme 2 *Reagents and conditions*: a, 9-anthroyl tetrazole **I** (1.2 equiv.), Et_3N, DMF, room temp., 30 min, yield > 90%; b, *p*-methoxycinnamoyl chloride (excess), DMAP, Et_3N, CH_2Cl_2, yield > 90%; c, 9-anthroyltetrazole (1.2 equiv.), DMF, Et_3N, 60 °C, 120 min, yield 64%

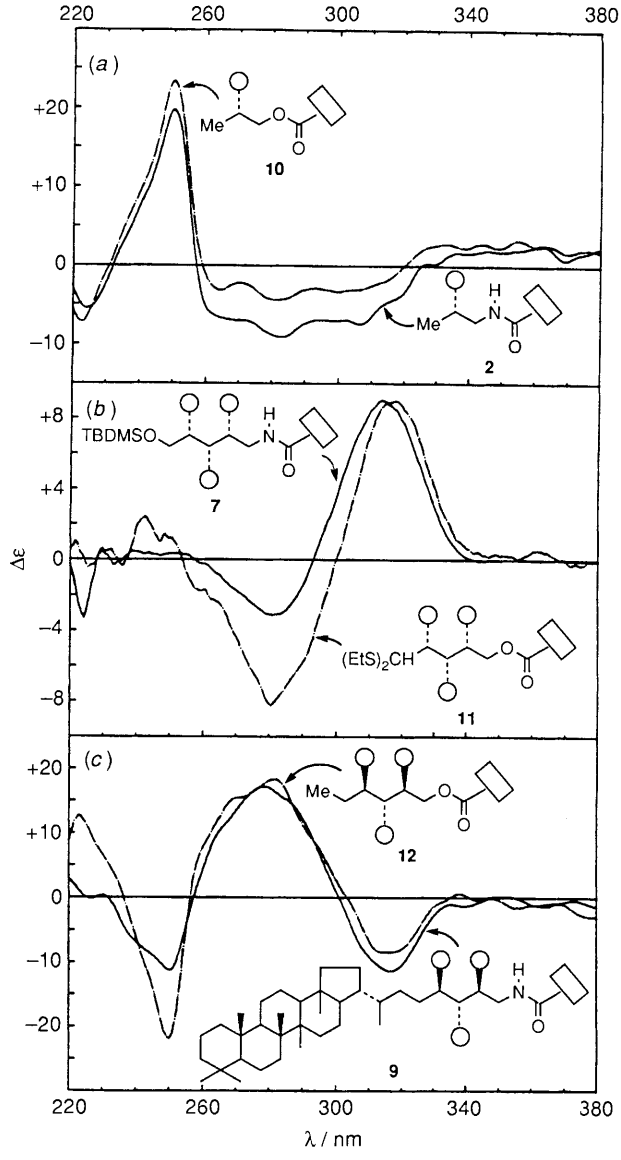


Fig. 1 CD spectra of derivatized amino alcohols and polyols in methylcyclohexane. (*a*) Aminomono-ol **2** and 1,2-diol **10**. (*b*) D-Xylo series; 1-amino-2,3,4-triol **7** and 1,2,3,4-tetrol **11**. (*c*) L-Ribo series; aminohopanetriol **9** and 1,2,3,4-tetrol **12**.

THF, CH_2Cl_2, MeCN, 50% THF–MeOH, thus facilitating the acylation of various substrates.

The procedure for bichromophoric derivatization of an amino alcohol is as follows. To the aminomono-ol **1** (4.3 mg) in DMF (2 ml) was added 9-anthroyltetrazole (1.2 equiv.) and excess Et_3N, the solution was stirred at room temp. for 30 min, and the crude product was purified directly by TLC (MeOH–CH_2Cl_2, 7:93) to give the anthramide in 94% yield. Subsequent treatment of the anthramide with excess *p*-methoxycinnamoyl chloride and Et_3N in CH_2Cl_2 in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) afforded the derivatized aminomono-ol **2** in 93% yield after TLC (EtOAc–hexane, 30:70) purification. The *tert*-butyldimethylsilyl (TBDMS) aminotriol **3** was prepared from D-(−)-xylose **4** by conversion to its phenylhydrazone,[3] silylation of the primary hydroxy group and reduction (Scheme 2); **3** was then derivatized by the standard procedure described above to yield **7**. Derivatization of the natural aminotriol hopanoid **8**[4] (200 μg, 366 nmol) was performed at 60 °C for 2 h in DMF because it was practically insoluble in this solvent (and other solvents).

Fig. 1 shows the CD spectra of derivatized amino alcohols **2, 7** and **9** and the corresponding polyol derivatives **10, 11** and **12** in methylcyclohexane; good agreement is seen in the spectra of the derivatives of polyols and corresponding aminopolyols in this solvent. In applications of the exciton chirality method,[1,5] CD spectra are measured in acetonitrile to avoid ester exchange that may occur in solvents such as MeOH; however, in the present acyclic series, the agreement was not as satisfactory in the more polar acetonitrile, presumably owing to subtle conformational differences between the aminopolyols and polyols in this solvent.‡

The strong positive Cotton effect (CE) at 251 nm, seen in the CD spectra of derivatized aminomono-ol **2** and diol **10** (Fig. 1*a*) containing only one centre of chirality, indicates the stereochemistry at this centre. In derivatives **7/11** and **9/12**

‡ The effect of solvent polarity is under study.

with three centres of chirality, the CD curves are more complex. Here the CE around 250 nm, the shorter branch of the exciton-split anthroate ^1B_b transition, is most strongly influenced by the interaction between the 1-anthroate and 2-cinnamate chromophores,[1] while the characteristic shape of the remainder of the CD curves results from all possible pairwise interactions involving the chromophores attached to all three chiral centres.[1] However, the strongly positive 250 nm CE, $\Delta\varepsilon$ +20~30, observed for the D-xylo configuration[1] in acetonitrile is absent in **7**/**11** taken in methylcyclohexane (Fig. 1*c*). This is probably due to different conformer distributions in these solvents, as supported by the observation of pronounced positive CEs in acetonitrile, $\Delta\varepsilon_{253}$ +17.6 and +22.4 for **7** and **11**, respectively.

The similarity between the CD curves of derivatized hopanoid **9** and L-ribose derivative **12** is in agreement with the known side-chain stereochemistry of the aminobacteriohopanetriol,[6] which was determined by multistep chemical reactions and NMR spectroscopy. The present work describes a micro-scale method for assigning relative and absolute configurations to ω-aminopolyols containing up to four additional contiguous hydroxy or amino groups. Furthermore, because the CD data of *O*-acylates and *N*-acylates are similar,[5,7,8] the amino group does not necessarily have to be at the terminal position.

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