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NMR determination of the absolute configuration of chiral 1,2- and 1,3-diols

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Abstract—Each of the chiral 1,2- and 1,3-diols examined was derivatized exclusively to a single diastereomeric acetal by the use of a new axially chiral reagent, 2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (MBC). The absolute configuration of the original 1,2- and 1,3-diols was determined by the NOE correlation between the proton signals of the reagent moiety and those of the diol moiety in the acetals.

Chiral 1,2- and 1,3-diols have increasingly become of interest to both chemists and biologists, because these compounds are frequently found in biologically active natural products.[1] The circular dichroism (CD) exciton chirality method is a reliable and physical one for determination of the absolute configuration of chiral 1,2-diols.[2] The method has also been applied to chiral acyclic 1,3-diols.[3] The modified Mosher's method has also been applied to chiral acyclic 1,3-diols for the same purpose.[4] In this paper we report a new method using an axially chiral reagent 2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (MBC, **1**) for determination of the absolute configuration of chiral 1,2- and 1,3-diols.

MBC (**1**) was prepared as shown in Scheme 1. 2-Methoxynaphthalen-1-yl(trimethyl)stannane (**2**) was prepared from 2-methoxy-1-naphthylmagnesium bromide and trimethyltin chloride.[5] Isopropyl 8-iodo-1-naphthoate (**3**) was prepared via a half-esterification of 1,8-naphthalic anhydride and subsequent iododecarboxylation.[6] Stille coupling[7] of **2** with **3** afforded isopropyl 2′-methoxy-1,1′-binaphthalene-8-carboxylate (**4**) which was alkali-hydrolyzed to yield racemic **5**. Racemic **5** was derivatized into diastereomeric esters[8] with (−)-menthol, which were separated by column chromatography. Purified diastereomers (**6a**, **6b**) were respectively reduced with diisobutyl aluminum hydride to afford enantiomers of **7**. The CD spectrum of one enantiomer of **7a** shows a negative split CD band with extrema at 224 nm ($\Delta\varepsilon$ +153.5) and 234 nm ($\Delta\varepsilon$ −152.9), amplitude A value of −306.4 in acetonitrile, whereas the other enantiomer of **7b** shows an opposite CD curve, with an A value of +322.7 and Cotton effects at 224 nm (−135.9) and 234 nm (+191.8). Based on the present Cotton effects, the absolute configuration of **7a** was confirmed to be a*S* and that of **7b** was confirmed to be a*R*, respectively. Each enantiomer of **7** was oxidized with pyridinium chlorochromate to yield (a*S*)- and (a*R*)-MBC (**1**).[9]

Figure 1. Preferred conformation of acetals from (a*R*)-MBC with 1,2-diols and 1,3-diols. Possible NOE correlations are shown by arrows.

Achiral 1,3-propanediol (**8**) and various 1,2- and 1,3-diols (**9**–**15**) possessing known absolute configurations were acetalized with (a*R*)-MBC using trimethyl orthoformate and WCl_6 as a catalyst.[10,11] In each case using chiral diols, a single diastereomeric acetal was formed exclusively. On the basis of ^{1}H NMR analyses of the respective acetals, we were able to determine the stereochemistry of every acetal and, consequently, the absolute configuration of the original diols in the following way. The preferred conformation of the acetals is depicted in Figure 1. The methine proton (H-2) in the acetal moiety, this proton is termed the acetal proton,

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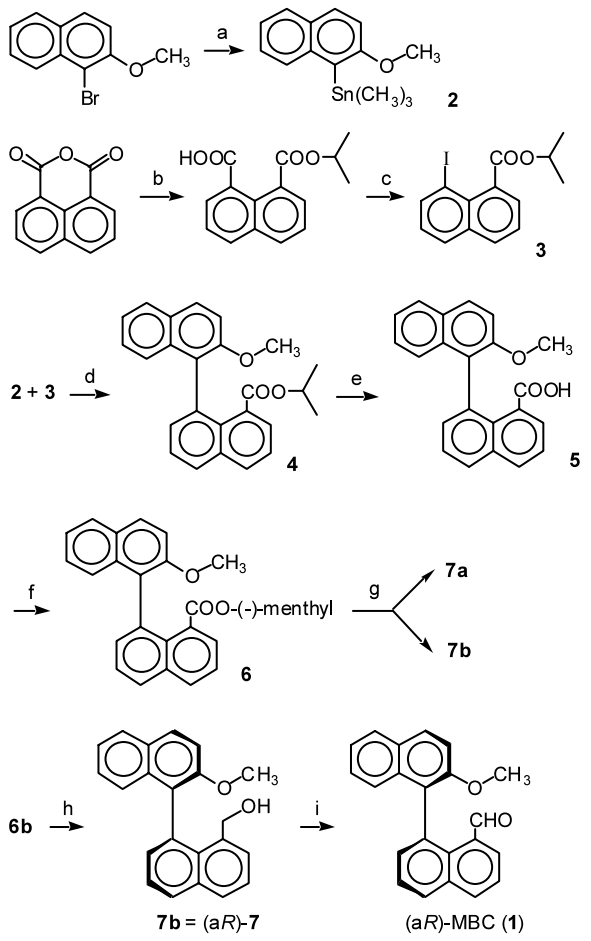
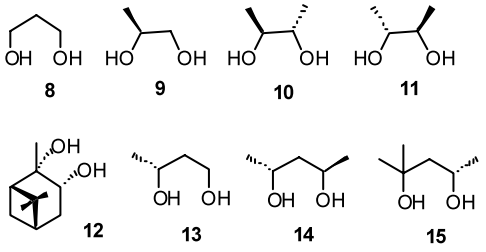


Scheme 1. Preparation of optically active MBC (**1**). [a]*Conditions and reagents*: (a) Mg, THF, rt; $ClSnMe_3$, toluene, rt, 96%. (b) *i*-PrOH, NaH, DMI, rt, 91%. (c) $PhI(OAc)_2$, I_2, CCl_4, 500 W halogen-lamp, reflux, 86%. (d) $Pd(PPh_3)_4$, Ag_2O, DMA, 150°C, 81%. (e) KOH, DMI, 130°C, 97%. (f) *o*-chloro-*N*-methylpyridinium iodide, (–)-menthol, *n*-Bu_3N, toluene, 70°C, 88%. (g) silica gel column chromatography toluene–hexane = 3:1. (h) DIBAH, CH_2Cl_2, rt, 99%. (i) PCC, CH_2Cl_2, rt, 81%.

faces the methoxynaphthalene ring because of electrical and steric repulsion between the 2′-methoxy group and two oxygen atoms of the acetal moiety. When the acetals are in the conformation shown in Figure 1, due to the diamagnetic effect of the methoxynaphthalene ring, the proton signals of the acetal moiety should appear upfield relative to those of the original diol. NOE correlations will be observed from the methoxy protons of the reagent to H-2, from H-2 to X, and from H-2 to Y, and from the methoxy protons to Y and/or Z. These NOEs can reveal the whole relative configuration of acetal. Since the absolute configuration of the reagent is known, that of the chiral diol can be determined. This methodology is based on our previous works.[12]



To obtain preliminary data for the stereochemistry of the acetal derivatives, we first acetalized an achiral diol (**8**) with MBC (**7**) and 1-naphthaldehyde to give **8a** in 95% yield and **8b**, respectively. NOE difference spectroscopy for **8a** gave NOE correlations from the 2′-methoxy protons to the acetal proton (H-2), H-4ax, and NOE correlations from the acetal proton to H-4ax and H-6ax. These NOE data enabled the whole structure of **8a** to be established (Fig. 2). The chemical shift differences of the corresponding proton signals of the acetal moieties in **8a** and **8b** ($\Delta\delta = \delta$**8a**$-\delta$**8b**) indicate that the $\Delta\delta$ values are all negative and proportional to the distance and position between the protons of the acetal moiety and the facing naphthalene ring (Fig. 2(c)). The signals for the protons of the acetal moiety in **8a** mostly appear upfield relative to the those of the original diol (**8**).

NOE difference spectroscopy for **9a** gave NOE correlations from the 2′-methoxy protons to H-2, H-4, and 6-methyl protons, and NOE correlations from H-2 to H-4 and H-5b in CD_2Cl_2. On the basis of these NOEs, the configuration of **9a** was determined as shown in Figure 3. The absolute configuration of C-4 in **9a**, therefore, was determined to be (*S*) corresponding to that of **9**. The stereochemistry of other acetals (**10a**–**15a**) was determined in a similar manner (Fig. 3). The absolute configuration of these diols determined by the present method is in complete accord with that of the known ones (**10**–**15**). Subsequently, racemic 2-methylpentane-2,4-diol was reacted with (a*R*)-MBC to give only two derivatives, **15a** and **15b** (**15a**:**15b** = 38:21)

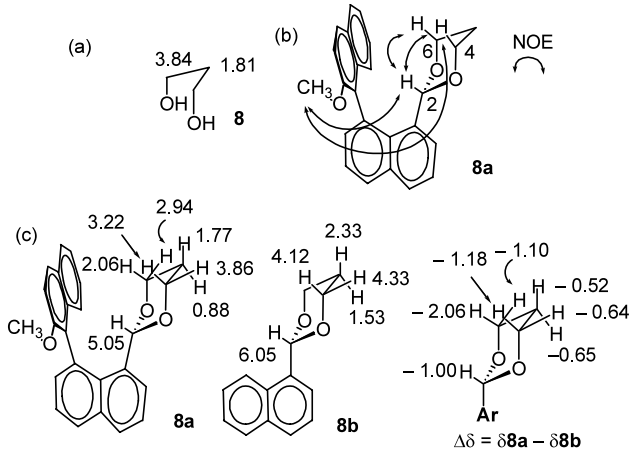


Figure 2. Configuration of the acetals (**8a** and **8b**). (a) chemical shifts in ^1H NMR ($CDCl_3$) of **8**, **8a** and **8b**. (b) Key NOE observed in **8a**. (c) Chemical shifts differences for the MNC acetals of **8** ($\Delta\delta = \delta$**8a**$-\delta$**8b**).

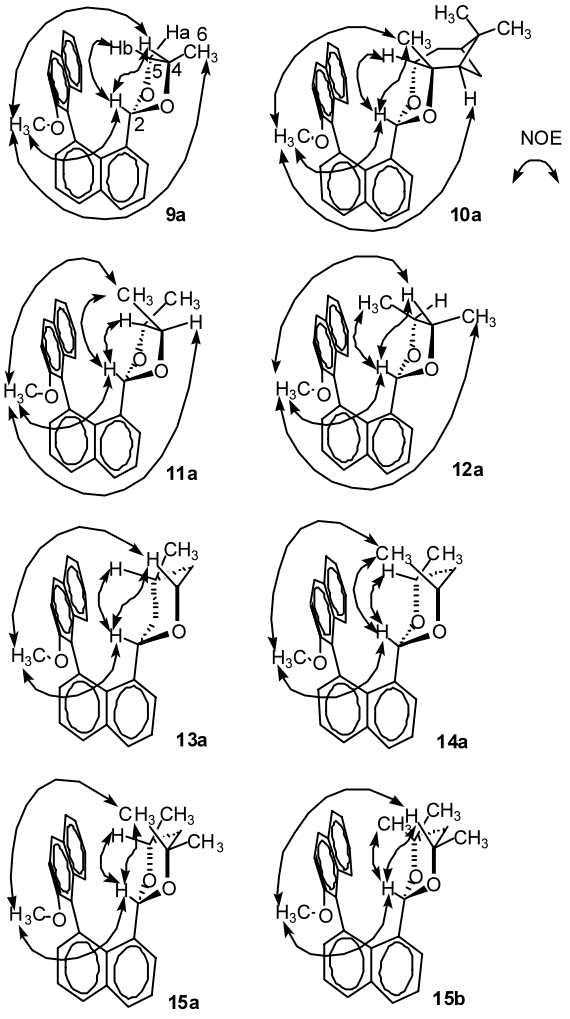


Figure 3. Configuration of the acetals (**9a**–**15a** and **15b**). NOE correlation in CD_2Cl_2 is shown by arrows.

in 59% yield. In addition, **15a** and **15b** could be well separated on silica gel PTLC plates. The stereochemistry of **15b** shown in Figure 3 was determined in the same way. Since a single diastereomeric acetal was formed exclusively with (a*R*)-MBC and each enantiomer of chiral diols, the effect of substituents, X and Y (in Fig. 1) on thermodynamic stability of the resultant acetals may be as follows; (X, Y)=(H, H)≫(H, CH_3)≫(CH_3, H)≫(CH_3, CH_3).

In summary, we have developed a new methodology to determine the absolute configuration of chiral 1,2- and 1,3-diols by using an axially chiral reagent, MBC (**1**). This method can be useful for preparation of optically active diols. Further application of this reagent to chiral *syn*-1,3-diols and polyols is under study.

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9. Spectral data: (a*R*)-2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (a*R*)-**1**. Yellow amorphous; mp 153.8–155.0°C (EtOH); $[\alpha]_D^{22}$ −131 (*c* 0.40, $CHCl_3$); IR (KBr): 2833, 1673, 1619, 1593, 1509, 1460, 1431, 1408, 1347, 1259, 1224, 1182, 1147, 1108, 1088, 1066, 1021, 929, 891, 838, 810, 788, 773, 750, 696, 627, 550, 504 cm^{-1}; EIMS *m*/*z* (rel. int. %): 313 (M^++1, 24), 312 (M^+, 100), 282 (14), 281 (56), 269 (11), 268 (13), 253 (26), 252 (38), 239 (25); HREIMS *m*/*z* (M^+): calcd for $C_{22}H_{16}O_2$: 312.1150. Found: 312.1122. NMR δ_H ppm (500 MHz, $CDCl_3$); 3.73 (3H, s), 7.30–7.38, (4H), 7.53 (dd, *J*=1.2, 6.9 Hz), 7.54 (d, *J*=7.1 Hz), 7.68 (dd, *J*=7.1, 8.1 Hz), 7.75 (dd, *J*=1.2, 7.1 Hz), 7.86 (d, *J*=7.4 Hz), 8.00 (d, *J*=7.9 Hz) 8.03 (d, *J*=7.9 Hz), 8.14 (dd, *J*=1.2, 7.1 Hz), 9.29 (1H, s).
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11. **General procedure**: To a CH_2Cl_2 (1.5 ml) solution of MBC (20.0 mg, 64.0 μmol), trimethyl orthoformate (12.8 μl, 76.8 μmol) and WCl_6 (1.3 mg, 3.2 μmol) was added diols (96.0 μmol). The reaction mixture was stirred at room temperature for 1 h. After adding one drop of Et_3N to the solution, the mixture was directly applied to preparative TLC with *n*-hexane–ethyl acetate (4:1) to afford acetals (38–82% yield).
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