



2-Anthrylmethoxyacetic Acid, a New Chiral Anisotropic Reagent for Elucidating the Absolute Configuration of Acyclic Alcohols

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Abstract: (*R*) and (*S*)-2-anthrylmethoxyacetic acids (2ATMA) have been prepared to elucidate the absolute configuration of long-chain compounds containing a secondary hydroxy group, methyl 9-hydroxystearate and 10-nonacosanol (ginnol). Copyright © 1996 Elsevier Science Ltd

We have recently demonstrated the versatility of methoxy-(2-naphthyl)acetic acid (2NMA) as a chiral anisotropic reagent for determining the absolute configuration of long-chain secondary alcohols.¹ The same reagent is also being investigated by a Spanish group.² These experiments confirmed the conformation of the 2NMA ester moiety to be the same as the one proposed for *O*-Me mandelates by Trost.³ The wider-range anisotropic effect of the 2NMA moiety than that due to MTPA, methoxy-(1-naphthyl)acetyl (1NMA), and 9-anthrylmethoxyacetyl (9ATMA) groups may be qualitatively understood by inspection of the models shown in Figure 1. The "width" of the aromatic rings of 1NMA and 9ATMA in the horizontal direction is one and a half (1.5a) times that of the phenyl ring (a) of MPA, and twice (2a) that of 2NMA. If another ring is extended horizontally, the resulting 2-anthryl ring may produce a much wider-range (3a) anisotropic effect onto the protons of the chain. This paper deals with preparation of (*R*) and (*S*)-2-anthrylmethoxyacetic acids (1: 2ATMA), and the availability of the new chiral anisotropic reagent to elucidate the absolute configuration of secondary alcohols, especially of long-chain aliphatic hydroxy compounds.

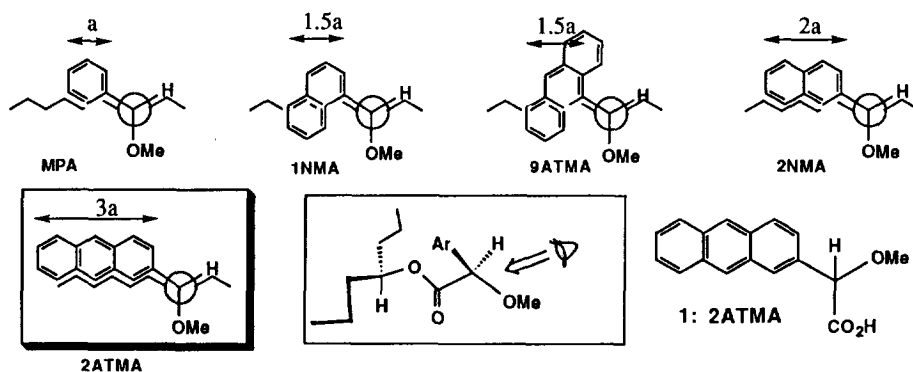


Figure 1

9,10-Anthraquinone-2-carboxylic acid, produced by oxidation ($\text{CrO}_3\text{-AcOH}$) of 2-methyl-9,10-anthraquinone, was reduced with $\text{Zn}/\text{NH}_4\text{OH}$ to give 2-anthracenecarboxylic acid.⁴ After esterification ($\text{EtOH}/\text{H}_2\text{SO}_4$), the ethyl ester was reduced with DIBAH (CH_2Cl_2), followed by oxidation (CrO_3/py), giving light-sensitive 2-anthraldehyde.⁴ The aldehyde was treated with tribromomethane and potassium hydroxide in methanol⁵ to afford (\pm)-**1** (30-80% yield). The racemic acid was esterified with (*S*)-1-phenylethanol, and the produced diastereomers were separated by prep HPLC (LiChrosorb Si60, hexane : AcOEt = 4 : 1). Each diastereomer was hydrolyzed under acidic conditions (12N HCl : dioxane = 1 : 3; 110 °C, 3 h) to give (+)-**1**, $[\alpha]_D^{25} +135^\circ$ ($c=0.20$, MeOH) and (-)-**1**, $[\alpha]_D^{25} -134^\circ$ ($c=0.20$, MeOH). Enantiomeric excess of both (*R*) and (*S*)-**1** was 100% (ChiraSpher; hexane : dioxane = 86 : 14). Absolute configuration of (+) and (-)-**1** was assigned as (*S*) and (*R*), respectively, by comparison of their CD data⁶ with those of (*S*) and (*R*)-2NMA.²

(*R*) and (*S*)-**1** were condensed with (*S*)-10-nonacosanol (ginnol),⁷ and the ¹H-NMR spectra (Figure 2) of the diastereomers were recorded. As can be seen in spectrum (b), the 1-CH₃ signal, 9 bonds distant from C-10, of (*R*)-2ATMA ester is dramatically shielded by the anthryl ring and appears at δ 0.822; thus, the spectrum shows two completely separated methyl signals.⁸ Other methylene protons are also shielded by the aromatic ring, many of them appearing as isolated signals. The signals of the shielded protons were easily assigned by routine 2D NMR techniques. The calculated $\Delta\delta$ values ($\Delta\delta = \delta_R - \delta_S$) are indicated in structure **2a**. The distribution of + and - $\Delta\delta$ values are compatible with *S*-configuration of the 10-hydroxy group, thus substantiating that 2ATMA ester exists in the same conformation (Figure 1) as that of *O*-Me mandelate, 2NMA, and their analogs. The $\Delta\delta$ values of the protons that are more than 5 bonds distant from C-10 are remarkably greater than those of the 2NMA ester of ginnol (**2b**).

As another example to show the versatility of 2ATMA, this reagent was applied to methyl (*S*)-9-hydroxystearate. The results are shown in **3a**. The systematic arrangement of + and - $\Delta\delta$ values, which led to correct *S*-configuration of the 9-OH group, also supports the general utility of this reagent. The $\Delta\delta$ values of **2a** and **3a** suggest the zigzag conformation of these acyclic compounds, which is also confirmed by values obtained for 2NMA esters **2b** and **3b**.

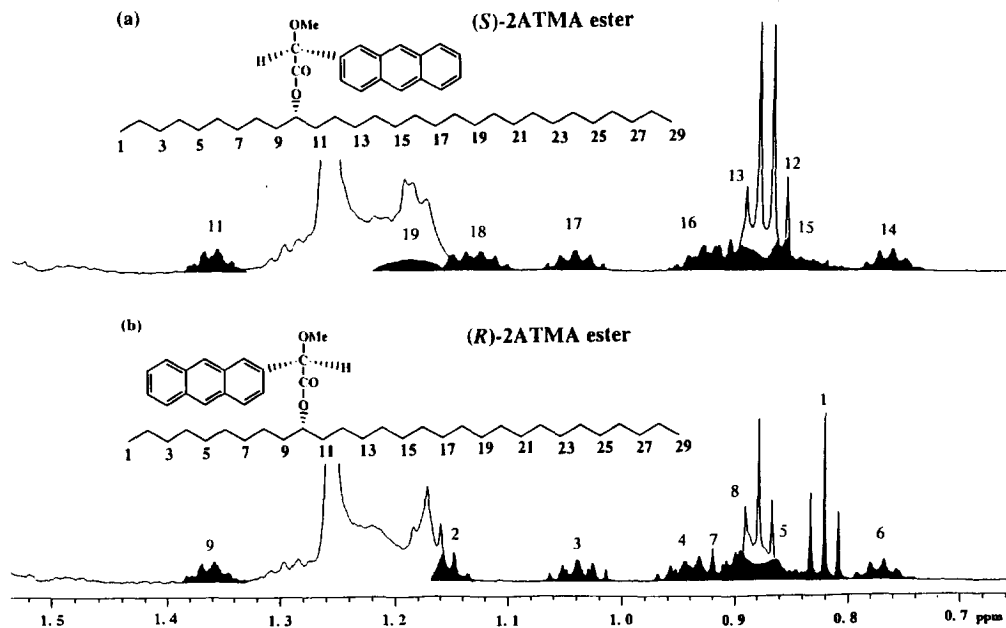
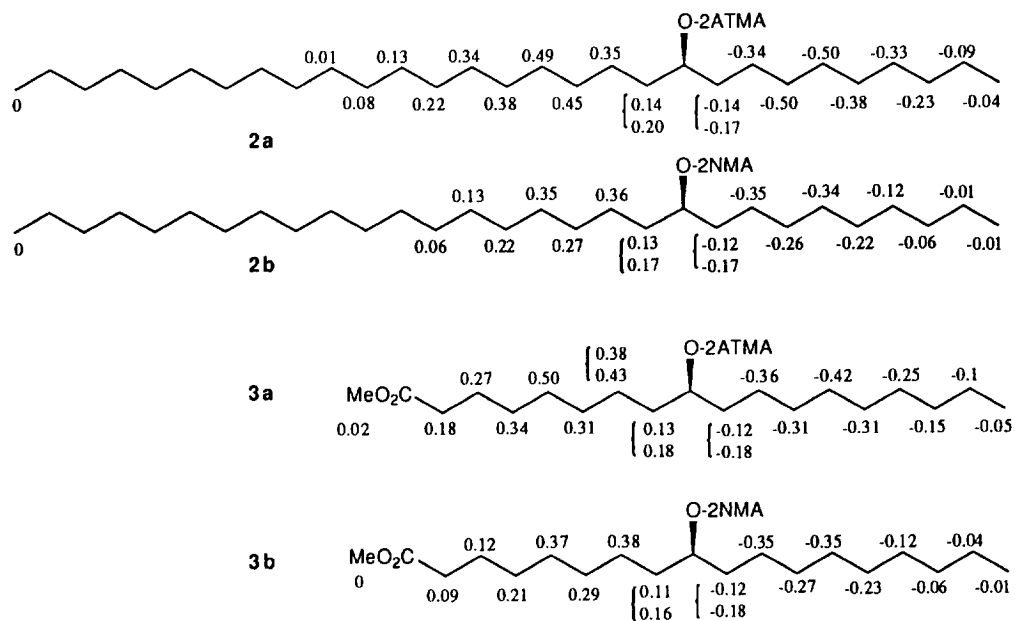


Figure 2. Parts (δ 1.54 - 0.66) of ¹H-NMR spectra (600 MHz, CDCl_3) of (*S*) (a) and (*R*)-2ATMA (b) esters of ginnol.



It will be important to examine the potency of 2ATMA for cyclic compounds. Figure 3 shows the $\Delta\delta$ values obtained for 2ATMA ester (4) of *l*-menthol together with 9ATMA (5), 2NMA (6), and MPA (methoxyphenylacetic acid) (7) esters. The

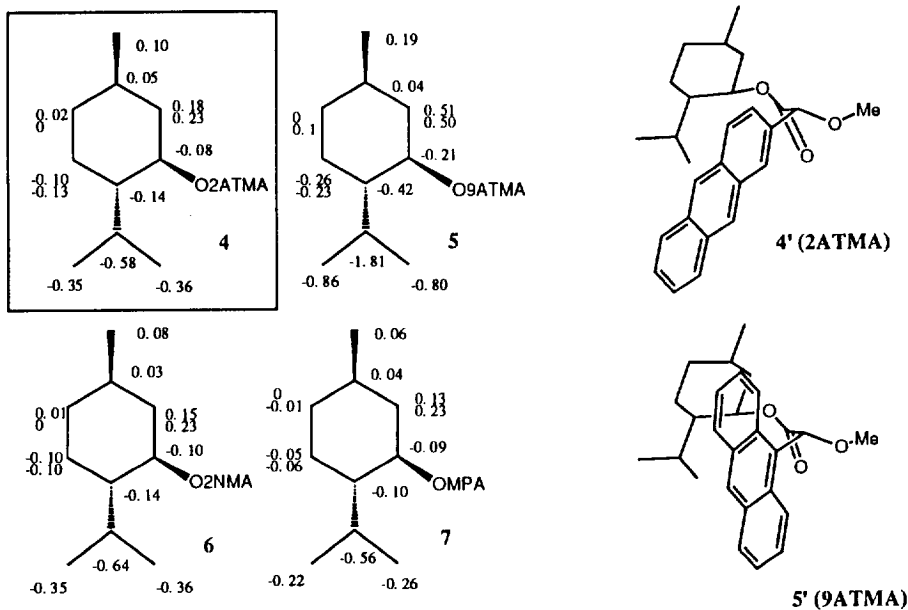


Figure 3

values of **4** are in the same magnitude as those of **6** and **7**, while 9ATMA ester (**5**) shows extraordinarily large values. This can be understood by molecular models **4'** and **5'**: The anisotropy of the "three" benzene rings of anthracene is effectively given onto the protons of the menthyl moiety in 9ATMA ester **5'**. On the contrary, anisotropy of only "one" benzene ring is effective in 2ATMA ester **4'**.

In conclusion, 2ATMA has proved to be an extremely efficient chiral anisotropic reagent to determine the absolute configuration of long-chain secondary alcohols. It should be pointed out that the upfield shift of the protons on the same side of the anthryl ring of 2ATMA is so great that only one diastereomer is necessary [cf. spectra (a) and (b) in Figure 1] to deduce the absolute configuration, and study along this line is now in progress.

References and Notes

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6. (*S*)-2ATMA: CD (MeOH) λ_{ext} 254.8 nm ($\Delta\epsilon$ +13.2). (*R*)-2ATMA: CD (MeOH) λ_{ext} 253.8 nm ($\Delta\epsilon$ -11.5).
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8. Spectrum (a) of (*S*)-2ATMA ester of ginnol also exhibits two methyl signals at δ 0.869 and 0.881. We at first thought that the anisotropic effect of 2ATMA reached 29-Me. However, the distance from the 2ATMA moiety, 19-bonds apart, is so long that we now believe that the difference in chemical shift of the two methyl groups is due to the small upfield shift of 1-Me, intrinsically caused by the 2ATMA group, even though the anthryl moiety is directed toward the opposite side.

(Received in Japan 8 April 1996; revised 7 May 1996; accepted 9 May 1996)