Application of the MTPA Method to Determination of Abusolute Stereochemistry. The Hydroxymethyl-substituted Chiral Carbon of Carbocycles

Yayoi SUGIMOTO, Takahiko TSUYUKI, Yoshihiko MORIYAMA,† and Takeyoshi TAKAHASHI*

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

†*Institute of Chemistry, Kyoto Prefectural University of Medicine, Taishogun, Kita-ku, Kyoto 603*

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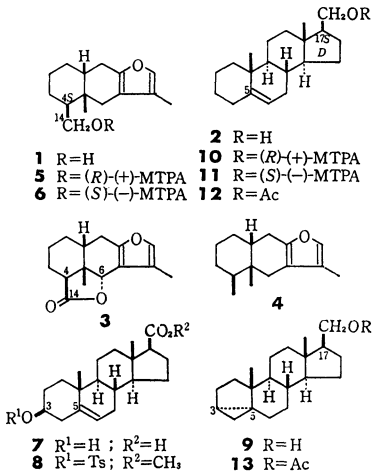
Synopsis. Application of the MTPA method is extended to determination of the absolute configuration of primary alcohols such as furanoeremophilan-14-ol and 17β-(hydroxymethyl)androst-5-ene with a hydroxymethyl group on the chiral ring carbon atom of carbocycles.

Recently Yamaguchi and Yasuhara have developed a new convenient method for determination of the absolute configurations of secondary alcohols[1] and primary alcohols with the chiral center at the 2-position.[2] An optically active alcohol was converted to the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)-MTPA; Mosher's reagent] ester (**A**) and (*S*)-(−)-MTPA ester (**B**) according to Mosher's method.[3] The magnitude of lanthanoid induced shift (LIS) by Eu(fod)$_3$-d_{27} for the methoxyl group of the (*R*)-(+)-MTPA ester (**A**) is larger than that of the (*S*)-(−)-MTPA ester (**B**) when the chiral center is in *R*-configuration. This generality is applicable to many optically active alcohols. However, successful application of this method to primary alcohols is limited to only acyclic carbinols having the chiral carbon atom at 2-position. In connection with a structural study of nigakialcohol,[4] we examined an applicability of this method for optically active primary alcohols in which a hydroxymethyl group is situated on the chiral ring carbon atom of a carbocycle. In this report, we wish to describe a successful application of this method to furanoeremophilan-14-ol (**1**) and 17β-(hydroxymethyl)androst-5-ene (**2**) with known absolute configurations.



Furanoeremophilan-14,6α-olide (**3**), isolated from *Ligularia Hodgsoni* HOOK, f., has been converted to furanoeremophilan-14-ol (**1**),[5] whose absolute stereochemistry at C-4 has been established to be *S* by conversion of **1** into a known furanoeremophilane (**4**).[5] The primary alcohol (**1**) was transformed into the corresponding (*R*)-(+)-MTPA ester (**5**) and (*S*)-(−)-MTPA ester (**6**) by Mosher's method.[3] The LIS values of the methoxyl groups of **5** and **6** were given in Table 1. The ΔLIS_{OMe} value was negative (−0.97) for the diastereomeric MTPA esters of the alcohol (**1**), indicating that the chiral center at C-4 of **1** is in an *S*-configuration, in accordance with the reported stereochemistry.[5]

A cyclopentane D-ring of 17β-(hydroxymethyl)-androst-5-ene (**2**) has an asymmetric carbon atom at C-17 position which bears a hydroxymethyl group, the absolute configuration of this carbon atom being established to be *S*. This alcohol (**2**) was prepared from 3β-hydroxyandrost-5-ene-17β-carboxylic acid (**7**).[6] Esterification and tosylation gave methyl 3β-(tosyloxy)-androst-5-ene-17β-carboxylate (**8**), which on treatment with lithium aluminium hydride afforded a mixture of 17β-(hydroxymethyl)androst-5-ene (**2**)[7] and 17β-hydroxymethyl-3α,5α-cycloandrostane (**9**) in a ratio of *ca.* 1 : 1. Reduction with lithium triethylborohydride in tetrahydrofuran (Super-Hydride) gave the same mixture (**2** and **9**) in a ratio of *ca.* 2 : 1. The ΔLIS_{OMe} value of (*R*)-(+)- and (*S*)-(−)-MTPA esters (**10** and **11**) of 17β-(hydroxymethyl)androst-5-ene (**2**) was negative (−0.36) as shown in Table 1. This indicates that the asymmetric center at C-17 is in an *S*-configuration. From these observations, it is concluded that application of the MTPA method can be extended to primary alcohols such as **1** and **2** with a hydroxymethyl group on the chiral ring carbon of carbocycles.

TABLE 1. LANTHANOID INDUCED SHIFT (LIS) VALUES OF THE METHOXYL GROUP IN THE ACID MOIETY FOR (*R*)-(+)- AND (*S*)-(−)-MTPA ESTERS OF **1** AND **2**

Original alcohol	Furanoeremophilan-14-ol (**1**)		17β-(Hydroxymethyl)androst-5-ene (**2**)	
MTPA esters in CCl_4 (mmol/ml)	(*R*)-(+)- (**5**) 0.12	(*S*)-(−)- (**6**) 0.14	(*R*)-(+)- (**10**) 0.18	(*S*)-(−)- (**11**) 0.17
LIS_{OMe} value[a]	6.81	7.78	5.30	5.66
ΔLIS_{OMe} value	−0.97		−0.36	
Absolute configuration	(4*S*)		(17*S*)	

a) Determined at the molar ratio of Eu(fod)$_3$-d_{27}/each MTPA ester (1 : 1) at 60 MHz.

Experimental

Melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and were uncorrected. IR spectra were measured using a Hitachi 260-30 spectrometer. Mass spectra (MS) were taken on a Hitachi RMU-6-Tokugata mass spectrometer at 70 eV with a direct inlet system and high resolution mass spectra on a JMS-D300 (JEOL) mass spectrometer. Relative intensities are expressed in % in parentheses. ^{1}H NMR spectra were measured on a Hitachi R-20B (60 MHz) or a Varian EM-390 (90 MHz) spectrometer with TMS as an internal standard. Thin layer chromatography (TLC) was carried out on Kieselgel GF_{254} (E. Merck). Wakogel C-200 (Wako) was used for silica gel column chromatography.

(R)-(+)- and (S)-(−)-MTPA Esters (5 and 6) of Furanoeremophilan-14-ol (1). Furanoeremophilan-14-ol[5] (**1**; 21.6 mg and 18.7 mg) was converted into (*R*)-(+)-MTPA ester (**5**; 17.3 mg, 42% yield) and (*S*)-(−)-MTPA ester (**6**; 27.1 mg, 75% yield) by the usual method.[3] (*R*)-(+)-MTPA ester (**5**): an oil, IR (liq) 1742, 1640, and 1562 cm^{-1}; ^{1}H NMR (60 MHz) δ (CCl_4) 1.00 (3H, s), 1.87 (3H, d, J=2 Hz), 3.53 (3H, $-OCH_3$), *ca.* 4.2—4.6 (2H, m), 6.95 (1H, m), and *ca.* 7.3—7.7 (5H, m); MS *m/e* 450 (M^+) and 189 (100). (*S*)-(−)-MTPA ester (**6**): an oil, IR (liq) 1742, 1642, and 1562 cm^{-1}; ^{1}H NMR (60 MHz) δ (CCl_4) 1.01 (3H, s), 1.88 (3H, d, J= 2 Hz), 3.53 (3H, $-OCH_3$), *ca.* 4.0—4.8 (2H, m), 6.95 (1H, m), and *ca.* 7.3—7.7 (5H, m); MS *m/e* 450 (M^+) and 189 (100).

Methyl 3β-(Tosyloxy)androst-5-ene-17β-carboxylate (8). Methyl 3β-hydroxyandrost-5-ene-17β-carboxylate (30.4 mg), prepared from pregnenolone *via* 3β-hydroxyandrost-5-ene-17β-carboxylic acid (**7**),[6] was treated with tosyl chloride (45.4 mg) in pyridine (8 ml) at room temperature overnight. To the reaction mixtrure, dichloromethane was added and the solution was washed with dilute hydrochloric acid. The organic layer was worked up as usual and the residue was subjected to separation by preparative TLC (developed with diethyl ether–hexane, 1 : 1) to give a tosylate (**8**; 40.5 mg), mp 143.5—144.5 °C (from diethyl ether); IR (Nujol) 1707, 1198, and 1172 cm^{-1}; ^{1}H NMR (90 MHz) δ ($CDCl_3$) 0.67, 0.98, 2.44, 3.67 (each 3H, s), 4.30 (1H, m), 5.28 (1H, m), and 7.30 (2H, d, J=8.5 Hz); MS *m/e* 314 (M−TsOH)$^+$ and 299. No molecular ion peak was observed.

17β-(Hydroxymethyl)androst-5-ene (2). Super-Hydride (0.5 ml; 1 M lithium triethylborohydride solution in tetrahydrofuran, Aldrich) was added to a solution of the tosylate (**8**; 30.0 mg) in tetrahydrofuran (2 ml) and the solution was refluxed for 3 h under nitrogen. Usual work-up afforded a mixture (17.0 mg) of 17β-(hydroxymethyl)androst-5-ene (**2**) and 17β-hydroxymethyl-3α,5α-cycloandrostane (**9**) in a ratio of *ca.* 2 : 1. To the mixture acetic anhydride (3 ml) and pyridine (10 drops) were added and the reaction mixture was stirred overnight at room temperature. After the usual work-up, the reaction product was purified by preparative TLC (developed with hexane–diethyl ether, 4 : 1) to give a mixture (20.3 mg) of acetates (**12** and **13**). This procedure was repeated and two crops of the acetate mixture (**12** and **13**) were combined. The combined mixture (39.7 mg) was subjected to separation by column chromatography on silica gel (15 g) impregnated with 20% silver nitrate. Elution with a mixture of hexane–diethyl ether (19 : 1) gave 5-ene acetate (**12**; 21.3 mg), 3α,5α-cyclo acetate (**13**; 10.2 mg), and a mixture (10.0 mg) of **12** and **13**. **12**: mp 78—79.5 °C (from hexane); IR (Nujol) 1742 cm^{-1}; ^{1}H NMR (90 MHz) δ ($CDCl_3$) 0.67, 1.00, 2.01 (each 3H, s), 4.03 (2H, d-like, J=7 Hz), and 5.23 (1H, m); MS *m/e* 330 (M^+; 92), 270 (26), and 255 (100); Found: *m/e* 330.2568. Calcd for $C_{22}H_{34}O_2$: M, 330.2558. **13**: mp 60—64 °C (from hexane); IR (Nujol) 1742 cm^{-1}; ^{1}H NMR (90 MHz) δ ($CDCl_3$) 0.20—0.55 (3H, m), 0.67, 0.91, 2.02 (each 3H, s), and 4.12 (2H, dd, J=15 and 6 Hz); MS *m/e* 330 (M^+; 77), 270 (32), and 255 (100); Found: *m/e* 330.2555. Calcd for $C_{22}H_{34}O_2$: M, 330.2558.

17β-(Acetoxymethyl)androst-5-ene (**12**; 90 mg) was heated with an excess of lithium aluminium hydride in tetrahydrofuran (5 ml) under reflux for 30 min. The reaction mixture was worked up as usual to give 17β-(hydroxymethyl)androst-5-ene (**2**; 78.4 mg) quantitatively, mp 136—137.5 °C (from diethyl ether–hexane); IR (Nujol) 3380 cm^{-1}; ^{1}H NMR (90 MHz) δ ($CDCl_3$) 0.67, 1.01 (each 3H, s), 3.60 (2H, m), and 5.25 (1H, m); MS *m/e* 288 (M^+; 100), 273 (96), and 255 (38); Found: C, 83.47; H, 11.19%. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18%.

(R)-(+)- and (S)-(−)-MTPA Esters (10 and 11) of 2. (*R*)-(+)-MTPA ester (**10**; 36.9 mg, 96% yield) and (*S*)-(−)-MTPA ester (**11**; 30.4 mg, 87% yield) were prepared from 17β-(hydroxymethyl)androst-5-ene (**2**; 22 mg and 20 mg, respectively).[3] **10**: IR (liq) 1751 cm^{-1}; ^{1}H NMR (60 MHz) δ (CCl_4) 0.68, 0.97 (each 3H, s), 3.49 (3H, $-OCH_3$), 4.20 (2H, m), 5.15 (1H, m), and *ca.* 7.2—7.6 (5H, m); MS *m/e* 504 (M^+; 100) and 255 (63). **11**: IR (liq) 1751 cm^{-1}; ^{1}H NMR (60 MHz) δ (CCl_4) 0.62, 0.97 (each 3H, s), 3.51 (3H, $-OCH_3$), 4.18 (2H, m), 5.16 (1H, m), and *ca.* 7.1—7.6 (5H, m); MS *m/e* 504 (M^+; 87) and 255 (100).

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