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Determination of absolute configuration of secondary alcohols using a new chiral agent and chemical shift simulation method

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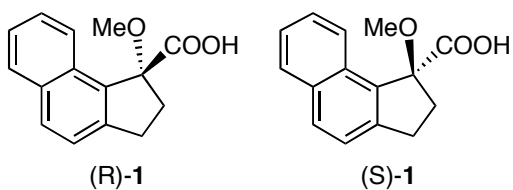
Determination of absolute configuration of secondary alcohols using new chiral auxiliary and chemical shift calculation

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Abstract—A new chiral carboxylic acid **1** was synthesized for determination of absolute configuration of secondary alcohols. Several chiral alcohols were converted to esters with **1**. Their experimental shift changes after esterification were successfully reproduced by the chemical shift simulation method combined with molecular dynamic simulation. © 2007 Elsevier Science. All rights reserved

Determination of the absolute stereochemistry of a chiral molecule in solution has received considerable attention. NMR methods have undergone significant development in recent years.[1] The method of the assignment of the absolute configuration of a chiral secondary alcohol is usually based on the derivatization of the alcohol with (R)- and (S)-chiral auxiliary followed by the comparison of the chemical shifts of the resulting diastereomers. Methoxytrifluoromethylphenyl acetic acid[2] (MTPA) and methoxyphenyl acetic acid[3] (MPA) are the typical chiral auxiliaries (Figure 1). The chemical shifts of L_1 and L_2 substituents at an asymmetric center reflect the diamagnetic ring current of the aryl ring of the chiral auxiliaries. The L_1 group should have a large aryl-induced shift influence if (S)-MPA was used. Thus the absolute configuration of a secondary alcohol can be assigned. If we correctly predict the induced chemical shift due to an introduced chiral auxiliary, we can directly determine the absolute configuration unambiguously only by one of the diastereomers. In this paper a new method for the determination of the absolute configuration of secondary alcohols using combination of chemical shift simulation[4] and a new chiral carboxylic acid is reported.
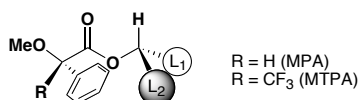

Figure 1. MPA and MTPA ester.

In the case of MPA esters, the mechanism of the assignment stems from the syn preferred conformation[5] of the diastereomeric ester in which two groups, carbonyl oxygen and methoxy groups, are in an eclipsed arrangement. Since both MTPA and MPA have rotational freedom of movement around the bond connecting the chiral center to the aryl substituent, many conformational options should be taken into account. In order to reduce the rotational freedom of movement, a condensed ring system was employed. 1-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-carboxylic acid **1** was designed for the chiral auxiliary that can be applied to assign the absolute configuration of secondary alcohols (Figure 2).
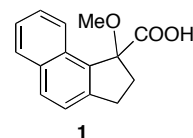

Figure 2. A new chiral auxiliary.

A new chiral carboxylic acid **1** was synthesized as shown in Scheme 1. Addition of vinyl Grignard reagent to benz[e]indan-1-one[6] (**2**), followed by protection of the resulting alcohol with a methyl group gave **3**. Oxidation with a catalytic amount of OsO_4, followed by oxidative cleavage of the resulting diol provided the aldehyde, which was oxidized to afford racemic carboxylic acid **1**.

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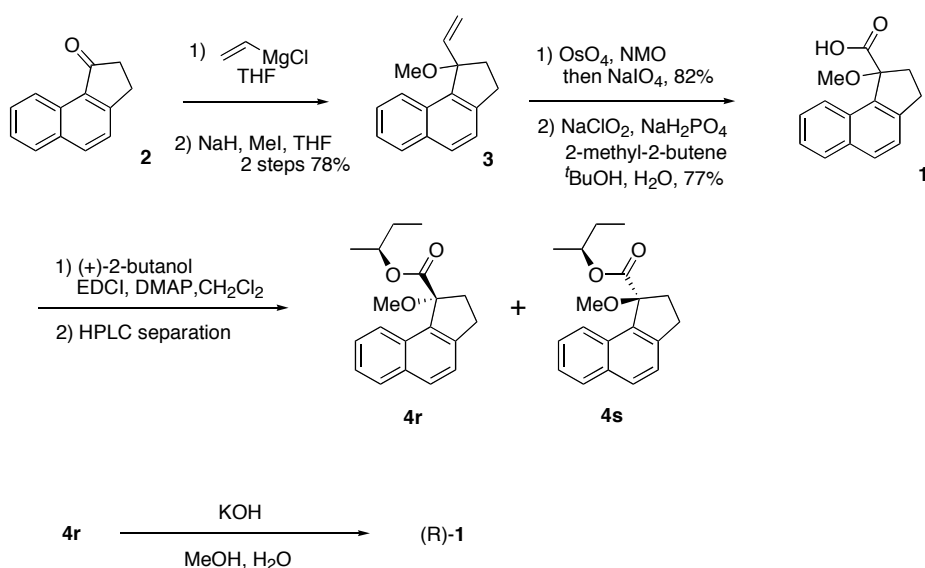
Scheme 1.

Condensation between **1** and (+)-2-butanol gave the corresponding esters **4r** and **4s** as a diastereomeric mixture. Separation of **4r** and **4s** was carried out with HPLC on silica gel. Alkaline hydrolysis of **4r** afforded (R)-**1**. Esters of other chiral secondary alcohols were prepared with (R)-**1**. The absolute configuration of (R)-**1** was confirmed with an X-ray crystallographic analysis of the ester **5** prepared from (R)-**1** and (+)-3-β-hydroxy-5-α-androstane-17-one (Figure 3).[7]
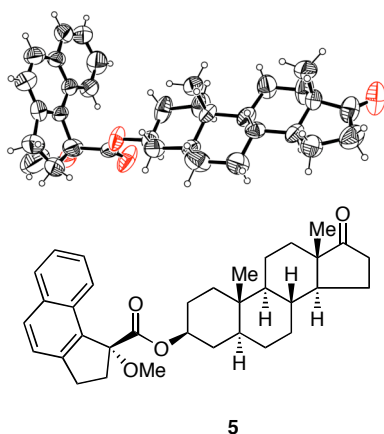

Figure 3. ORTEP drawing of **5**.

The magnitudes of the chemical shifts of the protons in the esters derivatives of chiral alcohols consist of the influence of the magnetic shielding effects of the naphthalene ring, methoxy, and carbonyl groups. In order to eliminate the carbonyl effect, the corresponding acetyl derivatives of the chiral alcohols were used as the reference compounds. In this paper, 'esterification shifts' has been called . The observed esterification shifts were thus obtained from the chemical shift differences between the ester and the corresponding reference compound.

In order to predict the esterification shifts correctly, conformational structures of conformers of the ester and their populations was necessary. Molecular mechanics or molecular orbital calculations can give many plausible structures though they correspond to motionless frozen form at 0 K. At room temperature where the nmr spectra were given, many conformers of the ester are in dynamic equilibrium. To simulate the conformational equilibrium of the ester, molecular dynamics (MD) calculation with stochastic dynamics (SD) simulation was applied. While molecular or stochastic dynamics cover all conformational space within a defined limit, energy barriers significantly greater than those at *RT* slow the exploration of conformational space substantially. Hence, the Metropolis Monte Carlo (MC) algorithm is applied so as to explore all conformational space of the compound effectively, since the ester has many rotatable bonds. The AMBER* force-field, with GB/SA chloroform solvation[8] on MacroModel V6.5[9] was applied for the MD calculation. The MD calculations of the ester with MC/SD mixed mode for 100 ps simulation were carried out. A snapshot of the structure was monitored at every 0.05 ps. A total of 2000 structures were obtained. The esterification shifts of each structure were estimated using the ring current effect of the naphthalene[10] and magnetic shielding parameters of the ether group.[11] Averaging the 2000 calculated shifts gave the predicted value of each proton of the ester.

In (-)-menthyl-(R)-**1** ester, the predicted esterification shifts are very close to the observed (Figure 4). The linear regression analysis of the observed and calculated values gave a high correlation coefficient (R^2 = 0.981, $\Delta\delta_{cal}$ = 0.937•$\Delta\delta_{obs}$, rms = 0.062; Figure 5). The highly satisfactory reproduction of the observed esterification shifts by the calculation can be explained in terms of the conformational preference of the syn form over the anti (syn/anti = 68/32, Figure 6). This analysis clearly shows that our chemical shift simulation method can be applicable to the chemical

shift prediction of a highly flexible compound such as (-)-menthyl-(R)-**1** ester. A similar analysis for the antipode of the chiral alcohol using the observed shifts of (-)-menthyl-(R)-**1** ester gave a poor correlation (R^2 = 0.218, $\Delta\delta_{cal}$ = – 0.265•$\Delta\delta_{obs}$ + 0.326, rms = 0.543; Figure 5). Thus, the absolute configuration of (-)-menthol was confirmed unambiguously with this calculation. This analysis clearly shows that our method can be applied for the determination of the absolute configuration of the secondary alcohol.
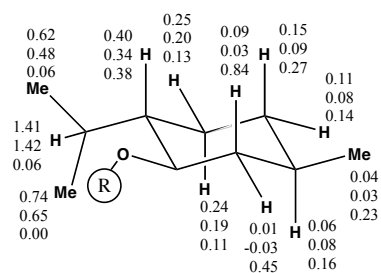
Figure 4. Observed (upper) and calculated esterification shifts of (R)-1 ester (middle), and calculated esterification shifts of (R)-**1** ester of antipode alcohol (lower). Positive denotes up-field shift.
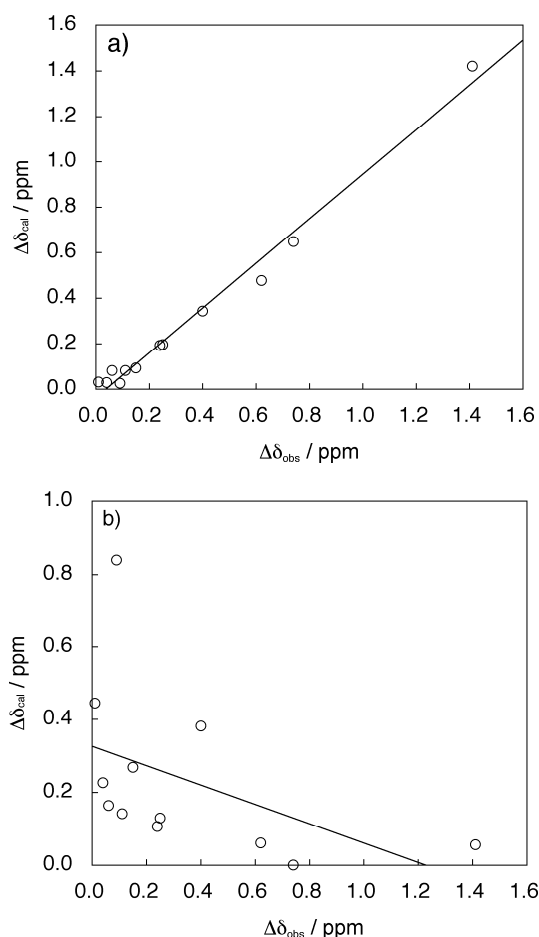

Figure 5. Plot of the regression between the observed and calculated esterification shifts a) in (-)-menthyl-(R)-**1** and b) in the corresponding ester of the antipode of the chiral alcohol.
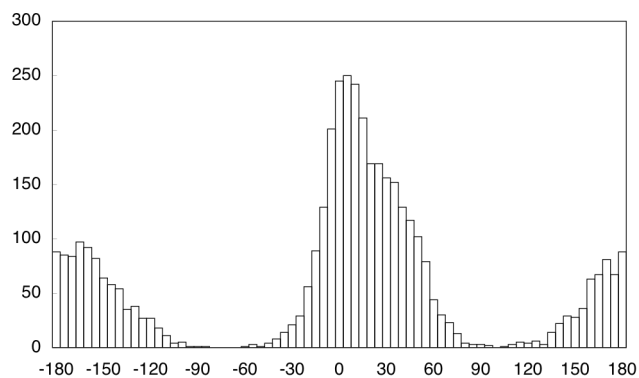
Figure 6. Histogram of torsion angle, O=C–C–O of (-)-menthyl-(R)-**1**.

To ascertain the wide applicability of our method, a similar analysis was carried out for other chiral alcohols. The observed and calculated esterification shifts of the chiral alcohols are shown in Figure 7 together with the calculated values for the ester of the corresponding antipode of the alcohols by using (R) chiral acid. Structurally similar (-)-isopulegol gave a high correlation coefficient (R^2 = 0.988, $\Delta\delta_{cal}$ = 0.933•$\Delta\delta_{obs}$, rms = 0.043, syn/anti = 66/34) and a low value (R^2 = 0.330, $\Delta\delta_{cal}$ = – 0.392•$\Delta\delta_{obs}$ + 0.340, rms = 0.491) for its antipode. A similar high correlation coefficient was obtained for a bicyclic alcohol, (-)-borneol (R^2 = 0.962, $\Delta\delta_{cal}$ = 1.143•$\Delta\delta_{obs}$, rms = 0.065, syn/anti = 71/29) which allows us to determine the absolute stereochemistry unambiguously when we consider a low correlation coefficient (R^2 = 0.015, $\Delta\delta_{cal}$ = 0.208•$\Delta\delta_{obs}$ + 0.372, rms = 0.393) for its antipode. As an open chain chiral alcohol, (+)-2-butanol was selected. Again, a high correlation coefficient (R^2 = 0.896, $\Delta\delta_{cal}$ = 1.589•$\Delta\delta_{obs}$, rms = 0.112, syn/anti = 70/30) was obtained. The calculated values in this case are significantly larger than the observed as shown in a rather large coefficient (1.589) of the linear least-squares equation. This is the result of over estimation of the proportion of the syn conformer in the calculated structure compared with the real case. By contrast, a low value (R^2 = 0.736, $\Delta\delta_{cal}$ = – 2.273•$\Delta\delta_{obs}$ + 0.720, rms = 0.335) for its antipode was obtained. The difference of the two correlation coefficients is not large enough, but the completely opposite sign of the two coefficients of the linear least-squares equations were sufficient to assign unambiguously the correct absolute configuration of the alcohol.
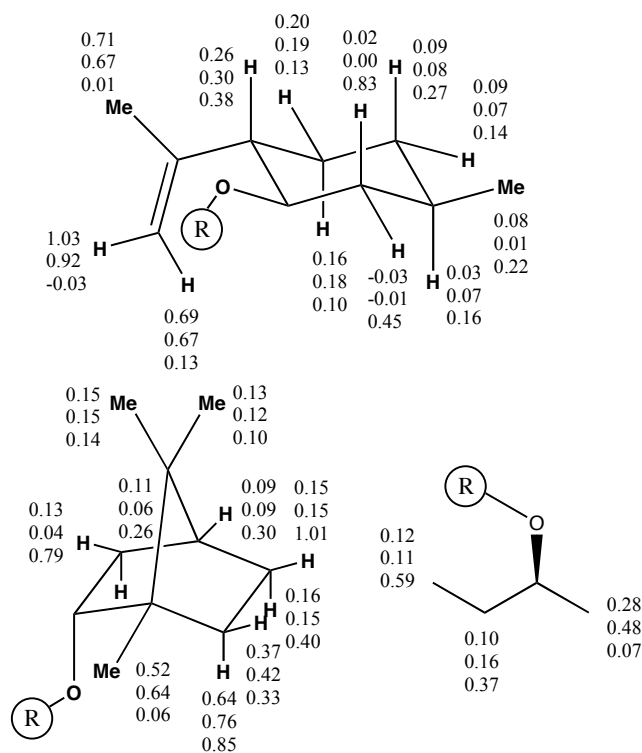
Figure 7. Observed (upper) and calculated esterification shifts of (R)-**1** ester (middle), and calculated esterification shifts (R)-**1** ester of antipode alcohol (lower). Positive denotes up-field shift.

In conclusion, a new chiral carboxylic acid **1** was synthesized for the development of a new method of the determination of the absolute configuration of secondary alcohols. Esters derived from chiral secondary alcohols and **1** showed large shift values due to the naphthalene ring of **1**. The values were larger than those obtained from MTPA. The absolute configuration can be easily assigned by comparing the experimental and calculated esterification shift values. This analysis clearly shows that our chemical shift simulation method can be applied for the chemical shift prediction of the highly flexible compounds such as the esters of the several chiral alcohols.

Acknowledgments

Supplementary Material

Experimental details and spectral data of products, Histograms of esters, and plots of regression analysis are available.

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7. The crystal data for **5** is as follows: **5**: $C_{34}H_{42}O_4$, FW = 514.68, orthorhombic, space group $P2_12_12_1$ with $a = 7.1365(9)$, $b = 14.8112(19)$, $c = 27.426(4)$ Å, $V = 2898.9(6)$ Å^3, and $Z = 4$. The measurement was performed with a Bruker SMART-APEX three-circle diffractometer, equipped with a CCD area detector; graphite-monochromated MoK radiation (= 0.71073 Å); unique reflections 4069, observed 1584 with $|F_o| > 4.0$ $|F_o|$. The structures were solved by the direct method and refined by full-matrix least squares refinements on F^2 of all data using SHELXL-97 software(Sheldrick, G. M. Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed using AFIX instructions. The structure converged with $R = 0.0847$, $wR = 0.2501$. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 287157.
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