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NMR determination of the absolute configuration of β-chiral primary alcohols

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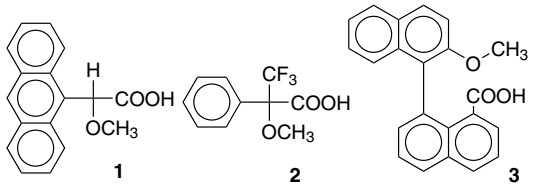
Abstract—β-Chiral primary alcohol was derivatized to an ester by the use of a new axially chiral reagent, 2′-methoxy-1,1′-binaphthalene-8-carboxylic acid (MBCA). The absolute configuration of the original β-chiral primary alcohol was determined by the NOE correlation between the proton signals of the reagent moiety and those of the β-chiral primary alcohol in the ester.

In recent years, many reagents have been developed to determine the absolute configuration of secondary chiral alcohols by NMR.[1] However, the best of our knowledge, only 9-anthryl-2-methoxyacetic acid **1**[2] is generally applicable.[3] Recently, α-methoxy-α-trifluoromethylphenylacetic acid (MTPA **2**) has also been reported in this context. However, MTPA is only applicable to the β-chiral β-methyl primary alcohols.[4] Our group has reported some methods to determine the absolute configuration of chiral secondary alcohols and chiral alkenes on the basis of NOE experiments by using axially chiral reagents.[5] But, our methods using axially chiral reagents were not applicable to determine the absolute configuration of the β-chiral primary alcohols.

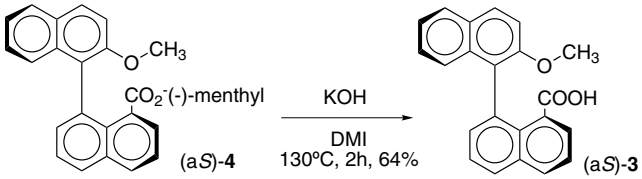


1 **2** **3**

In this letter, we report a new simple and general method to determine the absolute configuration of the β-chiral primary alcohols using an axially chiral reagent, 2′-methoxy-1,1′-binaphthalene-8-carboxylic acid (MBCA **3**), on the basis of NOE experiments.

Reagent MBCA **3**[6] was obtained from alkali-hydrolysis of **4** (Scheme 1). Synthesis of **4** has been reported previously.[7]

On the basis of ^{1}H NMR analyses of the respective esters, we were able to determine the stereochemistry of every ester and, consequently, the absolute configuration of the original β-chiral primary alcohols by using the following model (Fig. 1). The ester depicted in Figure 1a, was used to estimate the C1–C2 rotamers and C8″–C9″ rotamers. First, we predicted that the C8″–C9″ rotamers (Fig. 1b) could exist in two different conformations. Conformer **A** would be stabilized by CH–π interaction[11] between the alcohol moiety and the facing naphthalene ring. On the other hand, conformer **B** would be destabilized by steric repulsion between 2′-methoxy group and the alcohol moiety. Second, for



Scheme 1. Preparation of (a*S*)-MBCA **3**.

Keywords: Absolute configuration; β-Chiral primary alcohol; NMR; NOE.
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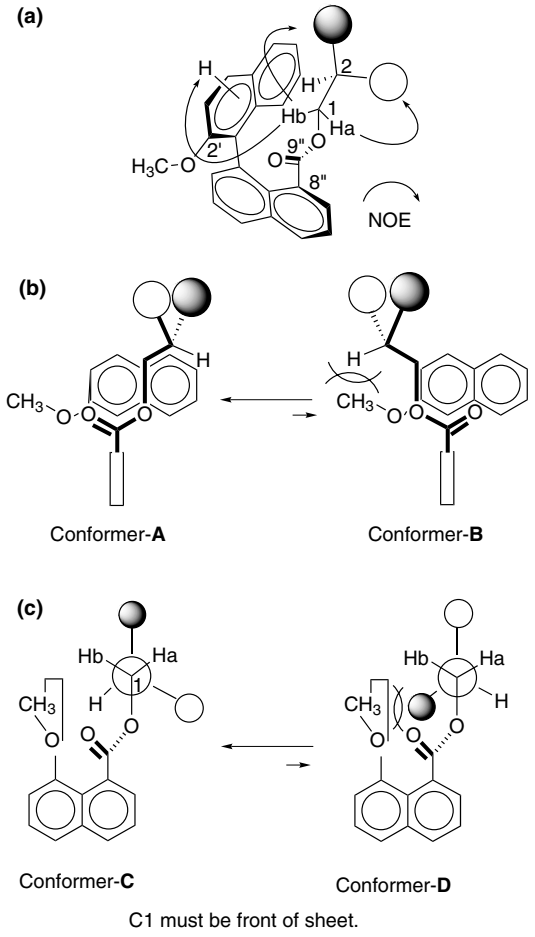


Figure 1. (a) Conformational correlation models for the MBCA ester. Expected NOE correlations are shown by arrows. (b) Two rotamers about C8″–C9″ bond. (c) Two rotamers about C1–C2 bond.

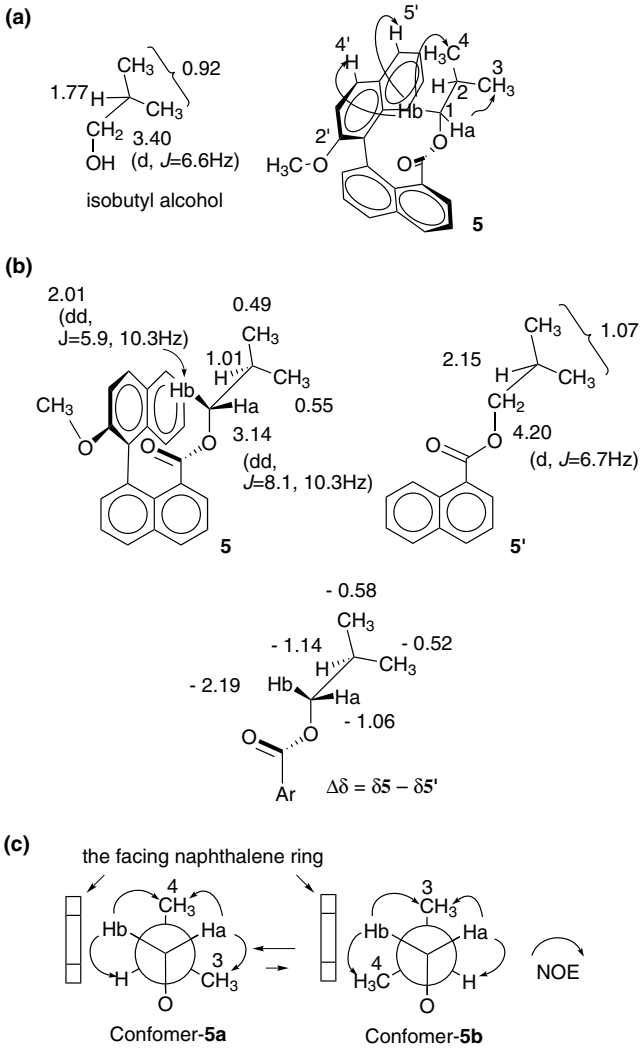
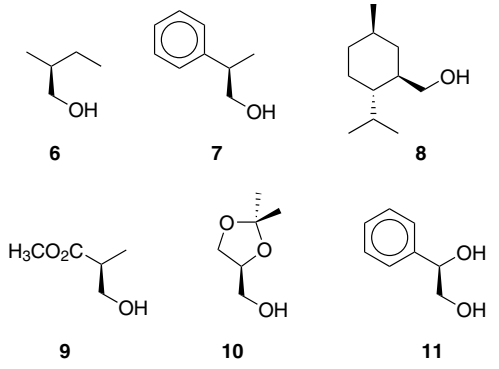


Figure 2. (a) Isobutyl alcohol and conformational correlation model for **5**. For convenience, arrows show stronger NOE correlations between each of H-1a,b and the other parts of isobutyl moiety. (b) Chemical shifts in **5** and **5**′, and the chemical shift differences of the protons of the isobutyl moieties in **5** and **5**′ [$\Delta\delta = \delta\mathbf{5} - \delta\mathbf{5}'$]. (c) Two conformers of isobutyl alcohol moiety in **5**. Chemical shifts and NOEs were measured in $CDCl_3$.

C1–C2 rotamer, we expected conformer **C** to be the most stable among the three possible staggered rotamers because of the steric repulsion between the alcohol moiety and the facing naphthalene ring (conformer **D)** in Figure 1c. When ester exists in conformer **C**, the signals for H-1b of the alcohol moiety should appear in the upper field in comparison with H-1a, because of the diamagnetic effect of the naphthalene ring. Furthermore, NOEs will be observed between H-1b and the protons attached to the facing naphthalene ring (Fig. 1a). On the other hand, no NOEs will be observed between H-1a and protons of MBCA moiety. From chemical shifts and these NOEs, H-1a, and H-1b can be assigned (Fig. 1a). The NOE correlations between one of H-1a,b and the other parts of alcohol moiety indicates the relative configuration of the ester. Since the absolute configuration of the reagent is known, that of the β-chiral primary alcohol can be determined based on our previous works.[5b,c,7]

To obtain preliminary data, we first analyzed esters **5** and **5**′ prepared from isobutyl alcohol and MBCA (**3**) or 1-naphthalic acid. The signals for the protons of the alcohol moiety in **5** appeared at high field relative to those of original isobutyl alcohol. NOE difference spectroscopy for **5** gave no NOE correlations between the 2′-methoxy protons and H-1a,b (Fig. 2a). These results revealed that the isobutyl alcohol moiety faced the naphthalene ring. When the ester **5** is in this conformer, due to the diamagnetic effect of the naphthalene ring, the signals for H-1b of the alcohol moiety should appear upfield in comparison with H-1a. Furthermore, NOEs will be observed between H-1b and the protons of facing naphthalene ring. Actually, NOE difference spectra for **5** showed NOE correlations from H-1b (δ 2.01) to H-4′ and H-5′ of the facing naphthalene ring. On the other hand, no NOEs were observed between H-1a (δ 3.14) and the protons of MBCA moiety. From the chemical shifts and these NOEs, H-1a, and H-1b can be distinguishably assigned. In the NOE difference spectra of **5**, NOE correlations from H-1a to H-2 (3.4%), 3-Me (2.4%), and 4-Me (1.4%), and these from H-1b to H-2 (3.4%), 3-Me (1.0%), and 4-Me (2.4%)

were observed. For convenience, only stronger NOE correlations between each of H-1s and the other protons in the isobutyl moiety are shown in Figure 2a. These NOEs indicate that there were two main conformers of **5** in solution as shown in Figure 2c. The coupling constants between H-1a,b and H-2; $J_{\text{H-1a,H-2}}$ (5.9 Hz) and $J_{\text{H-1b,H-2}}$ (8.1 Hz) indicate that conformer **5a** is major in $CDCl_3$. The coupling constants of those in isobutyl alcohol and compound **5′** are 6.6 Hz and 6.7 Hz, respectively. The value 6.7 Hz for the coupling of $J_{\text{H-1,H-2}}$ may be a criterion of free rotation about the C1–C2 bond of β-chiral alcohol moiety in MBCA ester. When the ester **5** is present in solution as these conformers, all protons of the alcohol moiety can be assigned from intensities of the NOEs. Thus, the relative configuration of **5** can be determined. The chemical shift differences of the corresponding proton signals of the alcohol moieties in **5** and **5′** ($\Delta\delta = \delta\mathbf{5} - \delta\mathbf{5}'$) indicate that $\Delta\delta$ values are all negative and reflecting proportional position to the distance and position between the alcohol moiety and the facing naphthalene ring (Fig. 2b). These results indicate that the absolute configuration of β-chiral primary alcohols can be determined by the use of MBCA **3**.



This new methodology was applied to six β-chiral primary alcohols (**6**–**11**). Alcohol **8** was stereoselectively prepared from (*S*)-menthone.[8] β-Chiral primary alcohols (**6**–**11**) possessing known absolute configurations. The chiral alcohols were reacted with (a*S*)- and (a*R*)-**3** to yield esters (**12**–**17**).[9,10] The primary alcohol of **11** was selectively esterified with both enantiomer. No NOE was observed between H-1a,b and 2′-methoxy protons in all derivatives; **12**–**17**, indicating that all alcohol moieties in the derivatives were facing the naphthalene ring. In the NOE difference spectra of (a*S*)-**12**, NOE correlations from H-1a (δ 3.16) to H-2, 3-Me (0.5%), 5-Me (2.4%), and those from H-1b (δ 2.09) to H-4′ (0.4%), H-5′ (0.5%), H-2, 3-CH_2 (2.2%), 4-Me, 5-Me (1.2%) were observed. The intensities of NOE correlations between H-1b and H-2 and between H-1b and 4-Me could not be determined because the signals of H-2 and 4-Me overlapped with each other. In the spectra, no NOE was observed between H-1a and 4-Me. On the other hand, in the NOE difference spectra of (a*R*)-**12**, NOE correlations from H-1a (δ 3.23) to H-2 (3.2%), 3-CH_2 (1.5%), 4-Me (0.9%), 5-Me (1.7%), and from H-1b (δ 2.08) to H-4′ (0.4%), H-5′ (0.4%), H-2 2.2% 3-CH_2 (1.2%), 5-Me (2.4%) were observed. In the spectra, no NOE was also observed between H-1b and 4-Me. These results revealed that the absolute configuration of the alcohol moiety of both diastereomers **12** was 2*S*, and it corresponded to that of original alcohol **6**.

The configurations of other esters except (a*S*)-**16** were determined in a similar manner (Fig. 3). In Figure 3, for convenience, only stronger NOE correlations between each of H-1a,b and the other parts of alcohol moiety are shown as in Figure 2a. The absolute configurations of other alcohols (**6**–**11**) were determined by this method, and they were in complete accord with those reported. All conformers of **12**–**17** were similar to the conformer **C** shown in Figure 1 except (a*S*)-**14**. Because of steric repulsion between the isopropyl group and the ester oxygen atom (Fig. 4, (a*S*)-**14a**), the conformation of (a*S*)-**14** is actually (a*S*)-**14b** in solution. This result was supported by the coupling constants between H-11a,b and H-3; $J_{\text{H-11a,H-3}}$ (4.7 Hz), $J_{\text{H-11b,H-3}}$ (6.2 Hz). In (a*S*)-**16**, intensities of NOE between H-1 and H-3α,β could not be observed, because signals of H-2 and H-3α,β almost completely overlapped each other. These results could not reveal the absolute configuration of (a*S*)-**16**. On the other hand, signals of H-2 and H-3α, β are separated, and the absolute configuration of (a*R*)-**16** could be determined.

As a result, the strategy to determine the absolute configuration of β-chiral primary alcohol is depicted as follows: (i) β-chiral primary alcohol is derived to the corresponding ester with one enantiomer of MBCA; (ii) the H-1a,b of the alcohol moiety can be determined by their chemical shifts and NOE correlations with protons of MBCA moiety; (iii) whole configuration of the ester can be determined by considering the intensities of NOE correlations between the H-1a,b and other protons of the alcohol moiety; (iv) the coupling constants of between α-*gem*-protons and β-methine proton are available to elucidate the major conformer in solution; (v) owing to the known the absolute configuration of MBCA, the absolute configuration of the β-chiral primary alcohol can be determined; and (vi) if the absolute configuration of the β-chiral primary alcohol is not determined clearly such as the case of (a*S*)-**16**, the other diastereomer synthesized from the another enantiomer of MBCA should be analyzed.

In summary, we have developed a new method to determine the absolute configuration of β-chiral primary alcohols by the use of an axially chiral reagent, MBCA (**3**) following NMR analysis. A method for elucidating the relative configuration of acyclic organic compounds was reported on the basis of carbon–proton spin-coupling constants ($^{2,3}J_{\text{CH}}$) and interproton spin-coupling constants ($^{3}J_{\text{HH}}$).[12] Now we are under studying the determination of γ-chiral primary alcohols by combination this our method and the method for elucidating the relative configuration of acyclic organic compounds.

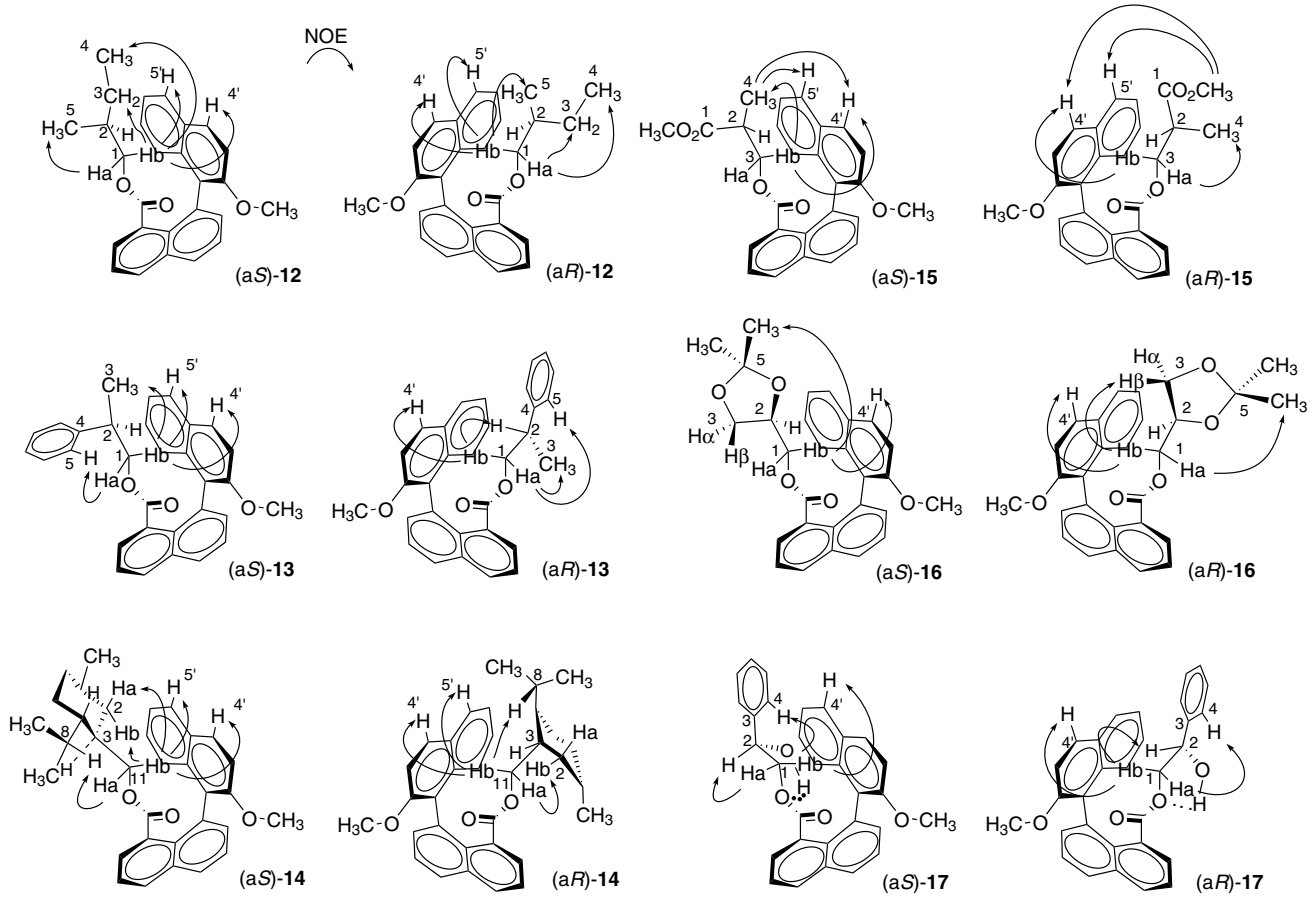


Figure 3. In conformational correlation models for esters (**12**–**17**), for convenience, stronger NOE correlations between each of α-geminal protons and the other parts of alcohol moiety are shown by arrows. The chemical shifts and coupling constants of the H-1a,b in compounds **12**–**17** are following: (a*S*)-**12**: H-1a; 3.16 (dd, *J* = 8.3, 10.3), H-1b; 2.09 (dd, *J* = 4.8, 10.3), (a*R*)-**12**: H-1a; 3.23 (dd, *J* = 7.3, 10.4), H-1b; 2.08 (dd, *J* = 5.7, 10.4), (a*S*)-**13**: H-1a; 3.55 (dd, *J* = 8.5, 10.6), H-1b; 2.28 (dd, *J* = 6.5, 10.6), (a*R*)-**13**: H-1a; 3.55 (dd, *J* = 9.6, 10.1), H-1b; 2.41 (dd, *J* = 5.4, 10.1), (a*S*)-**14**: H-11a; 3.40 (dd, *J* = 4.7, 10.8), H-11b; 2.20 (dd, *J* = 6.2, 10.8), (a*R*)-**14**: H-11a; 3.45 (dd, *J* = 7.6, 10.6), H-11b; 2.14 (dd, *J* = 3.6, 10.6), (a*S*)-**15**: H-3a; 3.66 (dd, *J* = 9.3, 10.9), H-1b; 2.09 (dd, *J* = 4.9, 10.9), (a*R*)-**15**: H-1a; 3.34 (dd, *J* = 7.9, 11.1), H-3b; 2.49 (dd, *J* = 5.9, 11.1), (a*S*)-**16**: H-1a; 3.39 (dd, *J* = 4.4, 10.8), H-1b; 2.29 (dd, *J* = 4.3, 10.8), (a*R*)-**16**: H-1a; 3.43 (dd, *J* = 7.7, 11.4), H-1b; 16 (dd, *J* = 3.6, 11.4), (a*S*)-**17**: H-11a; 3.55 (dd, *J* = 3.6, 11.4), H-11b; 2.38 (dd, *J* = 8.5, 11.4), (a*R*)-**17**: H-1a; 3.45 (dd, *J* = 10.1, 11.3), H-1b; 2.45 (dd, *J* = 2.5, 11.3).

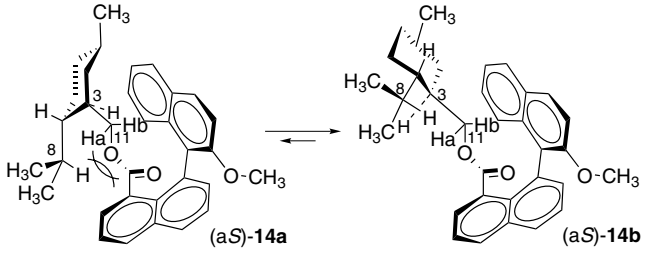


Figure 4. Two preferable conformers of (a*S*)-**14**.

Acknowledgments

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6. Spectral data: (a*S*)-2′-methoxy-1,1′-binaphthalene-8-carboxylic acid (a*S*)-**2**; colorless amorphous; mp: 263.0–264.0 °C (hexane/CH_2Cl_2)[‡]; $[\alpha]_D^{22}$ +63 (*c* 0.31, $CHCl_3$); IR (KBr): 2839, 1686, 1620, 1593, 1509, 1460, 1421, 1363, 1331, 1294, 1260, 1210, 1147, 1094, 1065, 1019, 910, 836, 813, 781, 751, 692, 665, 639, 624 cm^{-1}; EIMS *m*/*z* (rel. int.%): 329 (M^++1, 24), 328 (M^+, 100), 295 (23), 268 (21), 267 (10), 252 (28), 239 (24); HREIMS *m*/*z* (M^+): calcd for $C_{22}H_{16}O_3$: 328.1099. Found: 328.1007; NMR δ_H ppm (500 MHz, $CDCl_3$); 3.72 (3H, s), 7.16 (2H), 7.20–7.25, (2H), 7.50 (2H), 7.54 (dd, *J* = 7.1, 7.8Hz), 7.67 (dd, *J* = 7.4, 7.6 Hz), 7.73 (d, *J* = 8.1 Hz), 7.85 (d, *J* = 8.9 Hz), 7.97 (d, *J* = 8.1 Hz), 8.07 (d, *J* = 7,4 Hz).
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9. General procedure: to a $CH_3CN/CHCl_3$ (1:1 = 1.5 ml) solution of MBCA (10.0 mg, 30.5 μmol), *o*-chloro-*N*-methyl pyridinium iodide (11.7 mg, 45.8 μmol), K_2CO_3 (8.4 mg, 60.9 μmol), 18-crown-6-ether (0.8 mg, 3.05 μmol) was added β-chiral primary alcohol (27.5 μmol). The reaction mixture was stirred at room temperature for 8–24 h. The mixture was directly applied to preparative TLC with to afford corresponding esters.
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[‡]The crystal shape change at 190 °C.