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Trimethylaluminium-induced diastereoselective methylation onto ethyl 2-oxocyclopentane-1-carboxylate and isomerization between the dimethylaluminium-alkoxide products

Shigeki Sano, Hisashi Shimizu and Yoshimitsu Nagao*

Graduate School of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan

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Abstract—Methylation of α-disubstituted cyclopentanone **1** with Me_3Al in CH_2Cl_2 at 0 °C for 30 min gave diastereoselectively a mixture of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** in a 96:4 ratio and 83% total yield. When the same methylation was carried out at 0 °C for 1 h and then at room temperature for 120 h, a diastereomeric mixture of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** was obtained in a 12:88 ratio and in 88% total yield. The stereochemistry of the two diastereomers was determined by the results of acetalization of their diol derivatives **3** and **5**. Isomerization between the Me_2Al-alkoxides of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** and its possible mechanism were investigated by HPLC analysis of the methylation reaction process at 0 °C for 1 h and then at room temperature for 56 h and also by their mutual epimerization reactions.

We have established facile syntheses of conjugated allenyl esters by retro-Dieckmann-type ring-opening reactions of α-alkynyl-α-ethoxycarbonyl cyclopentanone and cyclohexanone derivatives using 1 N KOH or *n*-$Bu_4N^+OEt^-$.[1] Then, in order to investigate other mild syntheses (vide infra) of the conjugated allenyl esters based on the retro-aldol-type ring-opening of ethyl 2-alkyl-2-hydroxy-1-(*p*-tolylethynyl)-cyclopentane-1-carboxylates, some alkylations of ethyl 2-oxo-1-(*p*-tolylethynyl)-cyclopentane-1-carboxylate **1**[1] with organometallic reagents were attempted. Through the alkylation reactions, we observed diastereoselective methylation onto α-disubstituted cyclopentanone **1** with trimethylaluminium and an interesting isomerization between the two Me_2Al-alkoxide products, which will be described here.

The attempt to react cyclopentanone **1** with diethylzinc, methylmagnesium bromide, *n*-butyllithium, or methyllithium in THF at 0 or −78 °C resulted in recovery or decomposition of **1**. However, the nucleophilic methylation reaction of **1** with 2 mol equiv of trimethylaluminium (Me_3Al)[2,3] in CH_2Cl_2 at 0 °C for 30 min afforded diastereoselectively a mixture of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** in a 96:4 ratio (HPLC analysis)[4] and 83% total yield (entry 1), as shown in Scheme 1 and Table 1. When the same methylation with Me_3Al onto **1** was carried out at 0 °C for 1 h, the diastereomeric ratio changed to 89:11 (Table 1, entry 2), giving the diastereomeric mixture in 72% total yield. In the same methylation reaction of **1** with Me_3Al, the mixture was first stirred at 0 °C for 1 h and then at room temperature for 120 h. Surprisingly, the diastereomeric ratio between (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** was markedly changed to 12:88, giving the diastereomeric mixture in 88% total yield (Table 1, entry 3). In these reactions, no conjugated allenyl ester and methylketone formation due to ring-opening occurred. Each pure compound, (1*R**,2*S**)-**2** or (1*R**,2*R**)-**2**, was obtained by chromatographic separation of the diastereomeric mixture (entries 1 and 3) on a silica gel column with *n*-hexane–AcOEt (85:15).[5]

The stereochemistries of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** were precisely determined by their chemical conversion to methoxymethyloxymethylcyclopentanol **4** and acetal **6**,[6] respectively, as shown in Scheme 2. That is, reduction of (1*R**,2*S**)-**2** with 4.8 mol equiv of diisobutylaluminiumhydride (DIBAL) in CH_2Cl_2 at −78 °C for 1 h and then at room temperature for 2 h gave diol **3** in 83% yield. A similar reduction of (1*R**,2*R**)-**2** with

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* Corresponding author. Tel.: +81 88 633 7271; fax: +81 88 633 9503; e-mail: ynagao@ph.tokushima-u.ac.jp

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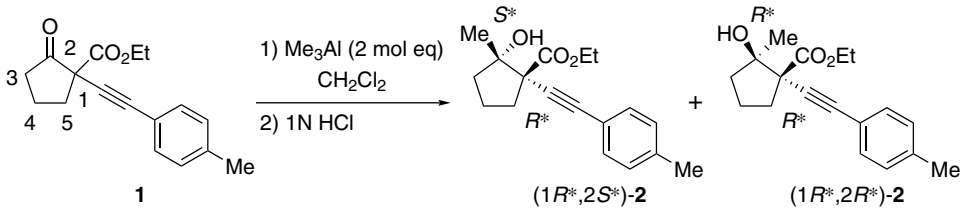


Scheme 1.

Table 1. Diastereoselective methylation of **1** with Me_3Al

Entry	Conditions	Yield[a] (%)	(1*R**,2*S**)-**2**: (1*R**,2*R**)-**2**[b]
1	0 °C, 30 min	83	96:4
2	0 °C, 1 h	72	89:11
3	0 °C, 1 h → rt, 120 h	88	12:88

[a] Total isolation yield of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2**.
[b] Determined by HPLC analysis.[4]

3 mol equiv of DIBAL gave another diol **5** in 52% yield. Diol **3** or **5** was allowed to react with dimethoxymethane as a solvent in the presence of 2 mol equiv of trimethylsilyltrifluoromethanesulfonate ($CF_3SO_3SiMe_3$) and 2 mol equiv of 2,6-lutidine at room temperature. Although the reaction of the former afforded methoxymethyloxymethylcyclopentanol **4** in 48% yield, the latter furnished acetal **6** in 83% yield. In compound **6**, ^1H–^1H NOE was observed between *ortho*-protons of the tolyl moiety and methyl protons of the cyclopentane moiety. Because no acetalization occurred, the relationship between the C1-hydoxy group and C2-hydroxymethyl group in the diol **3** should be a *trans*-configuration. On the other hand, the relationship of the corresponding both groups in the diol **5** should be a *cis*-configuration, because of its acetalization giving **6**. Based on the chemical conversions described above, determination of the stereochemistry of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2**, precursors of diols **3** and **5**, could be rationalized.

Subsequently, we monitored the methylation reaction of cyclopentanone **1** with 2 mol equiv of Me_3Al in CH_2Cl_2 at 0 °C for 1 h and then at room temperature for 56 h by utilizing the HPLC analytical method,[4] as illustrated in Figure 1. In the early stages (0–8 h) of the reaction, (1*R**,2*S**)-**2** was the major product and (1*R**,2*R**)-**2** was the minor product. It was revealed that the production of (1*R**,2*S**)-**2** gradually decreased but, in a complementary manner, the production of (1*R**,2*R**)-**2** gradually increased, with both reaching a plateau level at approximately the same time. This reaction diagram (Fig. 1) supports the outcome of Table 1 and indicates that (1*R**,2*S**)-**2** is a kinetically favourable product and (1*R**,2*R**)-**2** is a thermodynamically favourable

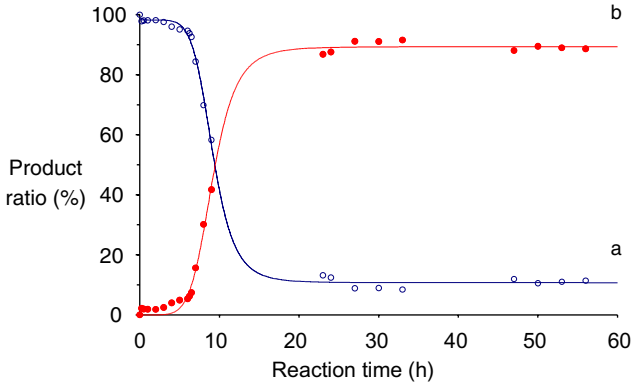
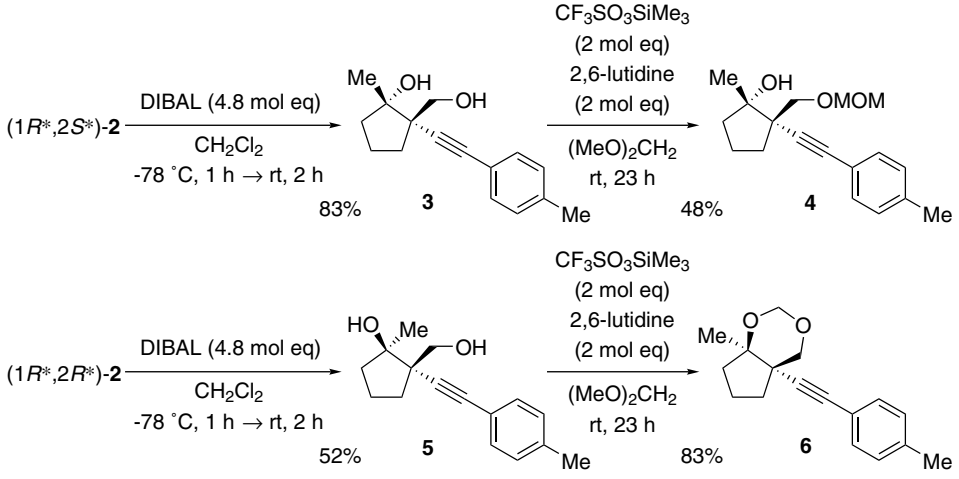


Figure 1. Reaction diagram of methylation onto **1** using Me_3Al (reaction conditions: Me_3Al (2 mol equiv), CH_2Cl_2, 0 °C (1 h) → rt (56 h)). (a) (1*R**,2*S**)-**2**; (b) (1*R**,2*R**)-**2**; HPLC-analytical conditions: see Ref. 4.



Scheme 2.

product. We also envisaged isomerization of Me_2Al-alkoxide of (1*R**,2*S**)-**2** into Me_2Al-alkoxide of (1*R**,2*R**)-**2** via an epimerization reaction of the Me_2Al-alkoxy group involving retro-aldol-type ring-opening followed by aldol-type cyclization through the methylation reaction of **1** with Me_3Al for longer reaction times. Of the two possible equilibrium conformers "**1A**" and "**1B**" of the cyclopentanone **1** possessing both ethoxycarbonyl and *p*-tolylethynyl groups at the geminal position, more preferential conformer would seem to be "**1A**", since "**1B**" is characterized by the steric repulsion between the axial-ethoxycarbonyl group and protons on the cyclopentanone ring (Fig. 2). The conformer "**1A**" may be fixed by weak chelation among the equatorial-CO_2Et group, Me_3Al and the C=O group of cyclopentanone.[7] Thus, the kinetically preferential formation of Me_2Al-alkoxide of (1*R**,2*S**)-**2** can be rationalized in terms of the favourable sterically controlled approach of dimeric or monomeric Me_3Al from the less hindered β face onto the ketone carbonyl group of "**1A**" and/or "Fixed **1A**", as shown in Figure 2.[2,3,7] Formation of Me_2Al-alkoxide of (1*R**,2*R**)-**2** via a sterically controlled approach of dimeric or monomeric Me_3Al from the less hindered α face onto the ketone carbonyl group of "**1B**" may be almost negligible during the early stages in the reaction diagram (Fig. 1).

Finally, in order to understand the isomerization between the Me_2Al-alkoxides of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** in the methylation reaction of **1** with Me_3Al, the following reactions were examined. Treatment of a diastereomeric mixture of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** (95:5)[4] with 1 mol equiv of Me_3Al in CH_2Cl_2 at 0 °C for 1 h and then at room temperature for 120 h followed by quenching with 1 N HCl gave a 7:93 ratio[4] of the same diastereomeric mixture with 78% total recovery (Scheme 3 and Table 2, entry 1), as we anticipated. When pure (1*R**,2*R**)-**2** was subjected to the same treatment, the diastereomeric mixture of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** was obtained in 90% recovery and in a 7:93 ratio[4] (Table 2, entry 2). Treatment of pure (1*R**,2*S**)-**2** or (1*R**,2*R**)-**2** with

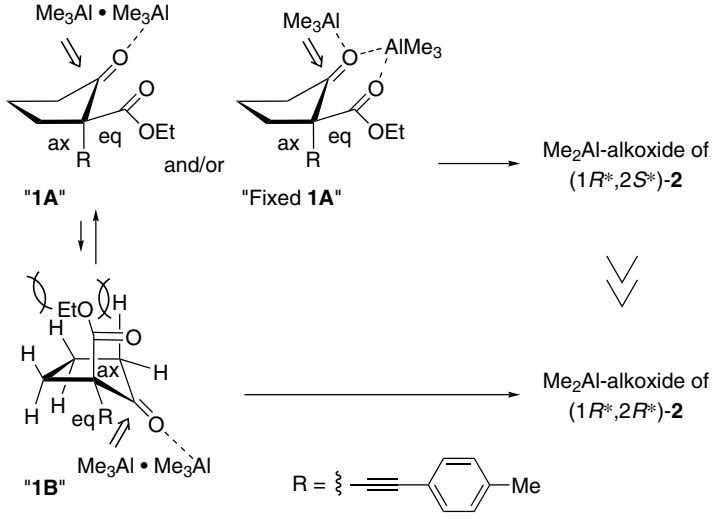
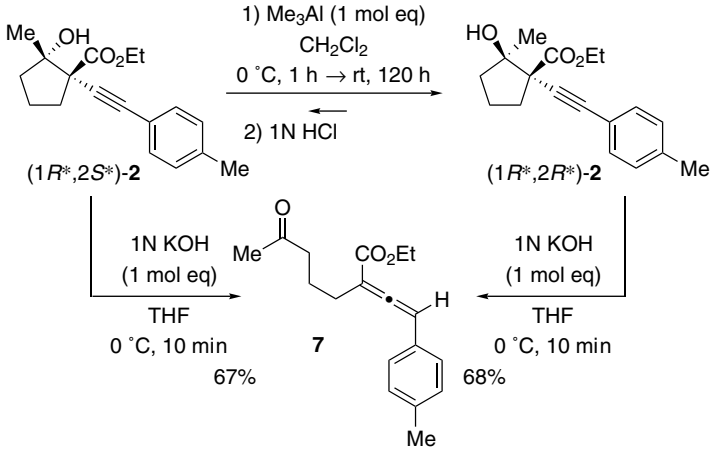


Figure 2. Possible mechanism for kinetically controlled methylation onto **1** using Me_3Al.



Scheme 3.

Table 2. Epimerization reaction between the Me_2Al-alkoxides of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2**[a]

Entry	Ratio[b] before reaction (1*R**,2*S**)-**2**:(1*R**,2*R**)-**2**	Ratio[b] after reaction (1*R**,2*S**)-**2**:(1*R**,2*R**)-**2**	Recovery[c] (%)
1	95:5	7:93	78
2	0:100	7:93	90

[a] Reaction conditions: see Scheme 3.
[b] Determined by HPLC analysis: see Ref. 4.
[c] Total recovery of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2**.

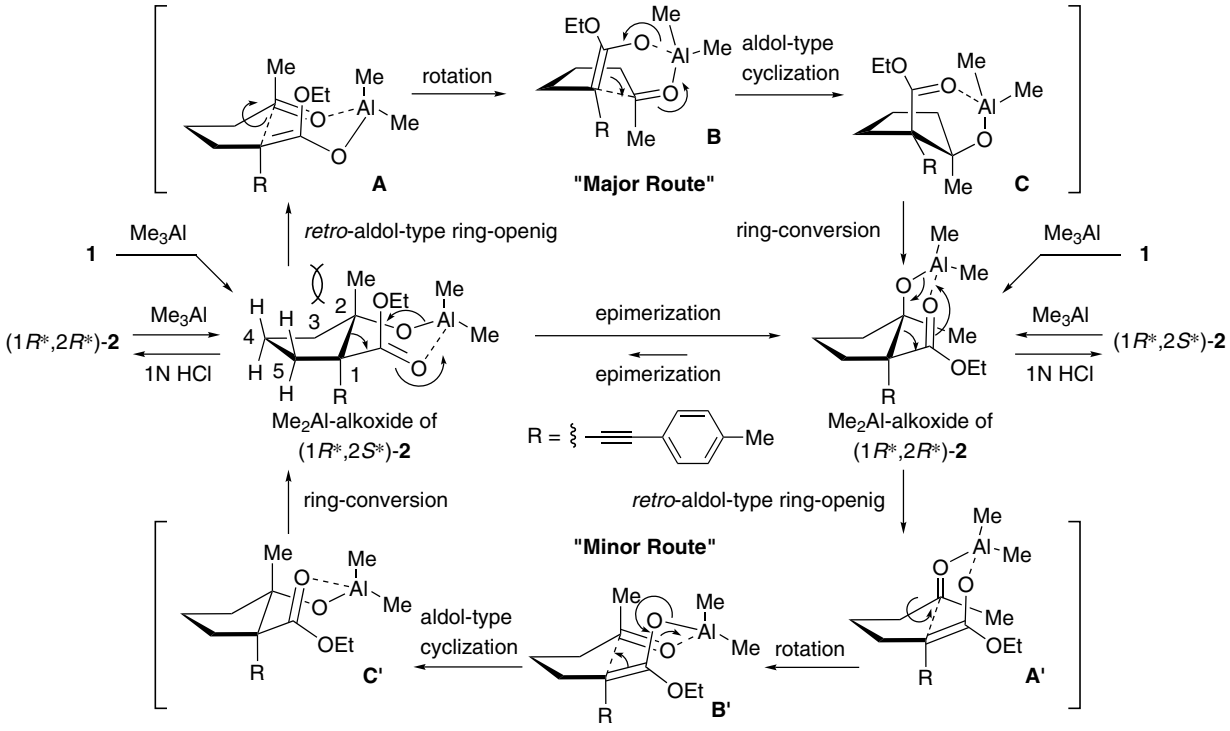


Figure 3. Possible epimerization mechanism between the Me_2Al-alkoxides of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2**.

1 mol equiv of 1 N KOH in THF at 0 °C for 10 min furnished the same conjugated allenyl ester **7** in 67% or 68% yield,[8] respectively (Scheme 3).[1,9,10] Thus, we realized a new type of epimerization reaction between the Me_2Al-alkoxides of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** via retro-aldol-type ring-opening followed by aldol-type cyclization and ring-conversion after rotation of the methylketone moiety around the σ-bond between C2 and C3 under equilibrium conditions, as depicted in Figure 3 [see 'Major (**A** → **B** → **C**) and Minor (**A**′ → **B**′ → **C**′) routes']. This remarkable epimerization reaction must be governed by the following factors. (1) A stereoelectronic requirement for maximum overlap of the C1–C2 σ-bond with the π-bond of the ester carbonyl group is satisfied for easy cleavage of the C1–C2 σ-bond. (2) Two types of six-membered Al···O chelations in the Me_2Al-alkoxides of both (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** and both Me_2Al-enolates promote readily retro-aldol-type ring-opening followed by aldol-type cyclization. Due to these Al···O chelations, generation of the ring-opened compound **7** may be effectively retarded. (3) The Me_2Al-alkoxide of (1*R**,2*R**)-**2** is more stable than the Me_2Al-alkoxide of (1*R**,2*S**)-**2**, since the latter is characterized by steric repulsion between the axial-C2-methyl group and protons on the cyclopentanone ring. Although weak alkaline-induced epimerization reactions of diterpene β-alkoxyester and β-alkoxylactone bicyclic moieties via generation of formyl were reported by Fujita and Nagao and other groups,[11–17] to our knowledge this is the first example of an Al-promoted epimerization reaction of the β-aluminiumalkoxyester monocyclic moiety via transient generation of ketone.

Acknowledgements

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4. HPLC-analytical conditions. Column: ULTRON Vx-octyl 250 mm × Φ4.6 mm, detection: UV 254 nm, mobile phase: 0.01 M SDS–50% MeCN, flow rate: 1.0 mL/min.
5. The spectroscopic data of (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** are as follows. (1*R**,2*S**)-**2**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, s), 1.32 (3H, t, J = 6.8 Hz), 1.82–2.02 (4H, m), 2.22–2.29 (1H, m), 2.35 (3H, s), 2.43–2.50 (1H, m), 2.54 (1H, s), 4.23 (2H, q, J = 6.8 Hz), 7.12 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14, 20.65, 21.47, 23.67, 35.79, 37.87, 58.94, 61.52, 83.10, 85.97, 86.83, 119.64, 129.02, 131.69, 138.48, 171.82; IR (neat) 3545, 2980, 2230, 1729, 1511 cm^{-1}; EI-MS calcd for $C_{18}H_{22}O_3$: MW 286.1569, found *m/e*: 286.1581 (M^+). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.34; H, 7.32. (1*R**,2*R**)-**2**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.3 Hz), 1.62 (3H, s), 1.80–1.94 (3H, m), 2.02–2.07 (1H, m), 2.19–2.25 (1H, m), 2.34 (3H, s), 2.49–2.57 (1H, m), 3.24 (1H, s), 4.26 (2H, q, J = 7.3 Hz), 7.10 (2H, d, J = 8.3 Hz), 7.29 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 20.23, 21.45, 24.21, 36.49, 38.59, 56.07, 61.61, 83.96, 84.29, 88.33, 120.08, 128.99, 131.45, 138.22, 172.68; IR (neat) 3501, 2981, 2228, 1733, 1510 cm^{-1}; EI-MS calcd for $C_{18}H_{22}O_3$: MW 286.1569, found *m/e*: 286.1590 (M^+). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.14; H, 7.87.
6. The spectroscopic data of **3** and **5** are as follows. Compound **3**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, s), 1.67–1.78 (2H, m), 1.90–2.02 (2H, m), 2.08–2.13 (1H, m), 2.18–2.22 (1H, m), 2.34 (3H, s), 3.41 (3H, s), 3.47 (2H, d, J = 9.3 Hz), 3.62 (2H, d, J = 9.3 Hz), 4.69 (2H, d, J = 6.6 Hz), 4.72 (2H, d, J = 6.6 Hz), 7.10 (2H, d, J = 8.3 Hz), 7.32 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.19, 21.43, 22.68, 33.85, 37.89, 52.62, 55.41, 70.72, 81.49, 84.67, 90.03, 96.65, 119.93, 128.99, 131.69, 138.17; IR (neat) 3551, 2952, 2879, 2226, 1511 cm^{-1}; FAB-MS calcd for $C_{18}H_{24}O_3Na$: 311.1623, found *m/e*: 311.1614 (M^++Na). Compound **5**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (3H, s), 1.84–1.93 (3H, m), 1.95–2.03 (2H, m), 2.34 (3H, s), 2.59–2.67 (1H, m), 3.83 (1H, d, J = 11.7 Hz), 3.83 (1H, d, J = 11.7 Hz), 4.84 (1H, d, J = 7.3 Hz), 4.88 (1H, d, J = 7.3 Hz), 7.09 (2H, d, J = 7.8 Hz), 7.26 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.14, 20.17, 21.43, 34.24, 39.94, 44.66, 67.87, 84.14, 84.20, 87.91, 90.43, 120.12, 128.99, 131.42, 138.07; IR (neat) 2972, 2856, 2222, 1511 cm^{-1}; EI-MS calcd for $C_{17}H_{20}O_2$: MW 256.1463, found *m/e*: 256.1448 (M^+). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.84. Found: C, 79.43; H, 8.00.
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8. The spectroscopic data of **7**: pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (3H, t, J = 7.1 Hz), 1.75–1.86 (2H, m), 2.08 (3H, s), 2.35 (3H, s), 2.34–2.51 (4H, m), 4.21 (2H, q, J = 7.1 Hz), 6.54 (1H, t, J = 2.9 Hz), 7.15 (2H, d, J = 8.3 Hz), 7.18 (2H, d, J = 8.3 Hz); IR (neat) 2981, 1943, 1713, 1514 cm^{-1}; EI-MS calcd for $C_{18}H_{22}O_3$: MW 286.1569, found *m/e*: 256.1578 (M^+). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.04; H, 7.85.
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