Synthesis and Absolute Configuration of the 7-Phenylhepta-4,6-diyne-1,2-diol Isolated from *Bidens pilosa*

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Received 29 March 2011; revised 24 April 2011

Abstract: The title diynediol was synthesized in enantiopure (>98.4% ee) forms, with the cross coupling of phenylacetylene with either (*R*)- or (*S*)-5-benzyloxypent-1-yn-4-ol catalyzed by nickel(II) chloride–copper(I) iodide as the key step. Comparison of the spectroscopic data (especially the optical rotations) for the synthetic and natural samples revealed that the natural diynediol is of *S*-configuration. The unexpected formation of a pyranone ring at the alkyne terminal when cleaving a benzyl protecting group with acetic anhydride and trimethylsilyl triflate is also detailed; this approach illustrates a novel and mild entry to related pyranones.

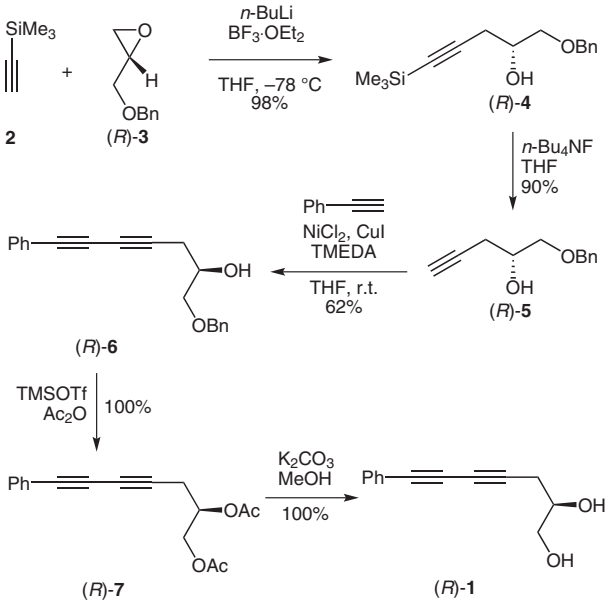
Key words: alkynes, alcohols, natural products, coupling, epoxides

The title compound (**1**) is one of the components recently isolated by Shi[1] and co-workers from *Bidens pilosa* (family Asteraceae), which has been used for a long time in traditional medicines to treat malaria, hypertension, and hyperglycerolemia.[2] Through extensive spectroscopic analyses, the planar structure of this compound was established with confidence. However, the limited amount of isolated natural sample available did not[1] allow determination of its absolute configuration. An enantioselective synthesis thus appeared to be necessary to complete the structural assignment. We therefore made the synthetic efforts presented below, which finally led to establishment of the absolute configuration of the natural product **1**.

As the target structure contains only one stereogenic center, in principle, synthesis of either enantiomer would reveal the absolute configuration of the natural product. For this reason we arbitrarily chose to begin with the *R*-isomer. The initial sequence is shown in Scheme 1. Starting from the commercially available trimethylsilyl-protected acetylene **2** and (*R*)-**3**, the expected ring-opened product (*R*)-**4** was obtained in 98% isolated yield under the conditions previously[3] reported. Removal of the trimethylsilyl protecting group was then achieved by treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran to free the terminal alkyne for the intended coupling.

The cross coupling of (*R*)-**5**[3a] with phenylacetylene was performed under the conditions developed by Lei[4] and coworkers ($NiCl_2 \cdot 6H_2O$, CuI, TMEDA). The product **6** was practically inseparable from the starting material **5** on TLC. Therefore, the progress of the reaction was monitored by ^1H NMR analysis. It was observed that in order to convert all the starting material **5** into the desired product **6**, additional amounts of phenylacetylene and catalyst must be introduced repeatedly at several hours intervals.

When full conversion of (*R*)-**5** into (*R*)-**6** was finally achieved as shown by ^1H NMR, we set out to cleave the benzyl protecting group to obtain the target product diol (*R*)-**1**. Because of the presence of the diyne unit, commonly employed methods such as catalytic hydrogenolysis or treatment with lithium and naphthalene[5] were not attempted. Instead, a mild, indirect procedure using acetic anhydride and trimethylsilyl triflate[6] was tried, which smoothly transformed (*R*)-**6** into the corresponding diacetate (*R*)-**7**. The acetyl groups were then hydrolyzed with potassium carbonate in methanol to deliver the desired target product diol (*R*)-**1**.

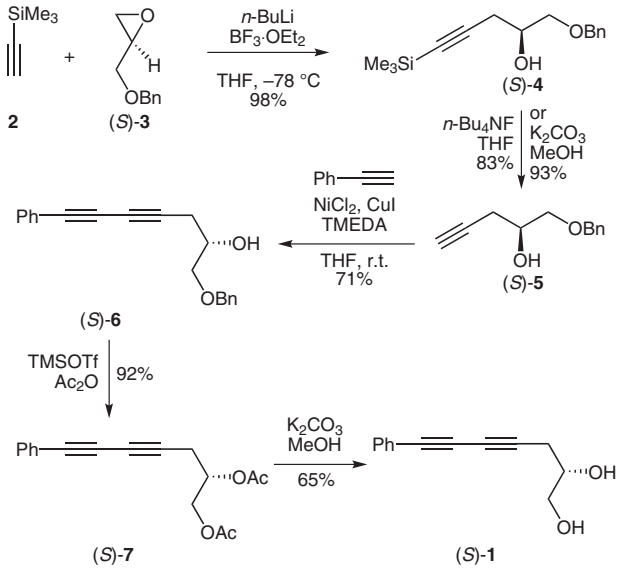


Scheme 1

The ^1H and ^{13}C NMR spectra of (*R*)-**1** were in excellent agreement with those reported for the natural sample. However, the optical rotation was of opposite sign, which revealed that (*R*)-**1** is the mirror image of the natural product.

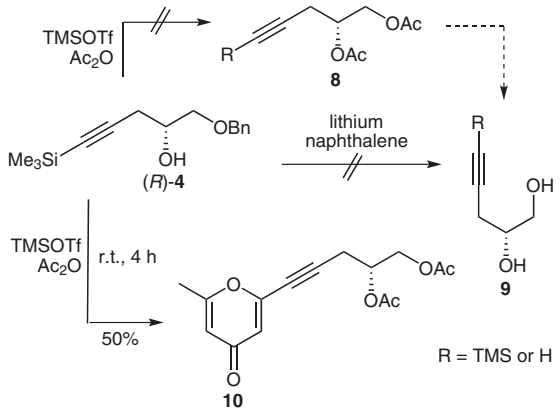
SYNTHESIS 2011, No. 13, pp 2131–2135
Advanced online publication: 26.05.2011
DOI: 10.1055/s-0030-1260604; Art ID: H34111SS

Following the sequence shown in Scheme 2, with the epoxide (*S*)-**3** as the source of the stereogenic center, the diol of the opposite configuration (*S*)-**1** was then synthesized. As expected, all spectroscopic data for (*S*)-**1** were consistent with those reported[7] for the natural product **1** in the literature.



Scheme 2

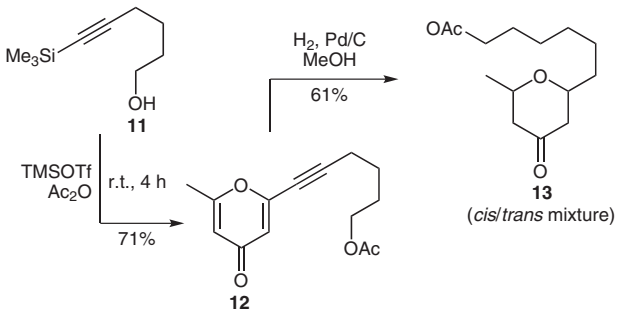
During the course of this synthesis, we also attempted to remove the benzyl protecting group before the cross coupling of the two alkynes units (Scheme 3), because the diol **9** (with R = H) was expected to be of higher polarity than **5** and consequently might be readily differentiated from the coupling product diyne **6** on silica gel. We reasoned that, under these conditions, both monitoring the progress of the cross coupling and isolation of the product **6** might be much easier.



Scheme 3

Unfortunately, all attempts to achieve the benzyl deprotection were unsuccessful. Under the Li/naphthalene[5] conditions, no desired diol **9** could be detected. Use of acetic anhydride and trimethylsilyl triflate[6] led to the formation of an entirely unexpected product that showed, among others, two alkenylic CH singlets (δ = 6.34 and 6.12 ppm) and three (rather than the expected two) uncoupled CH_3 groups (δ = 2.25, 2.10, and 2.09 ppm) in the ^1H NMR spectrum. The IR spectrum was also confusing, presenting a strong signal at 1659 cm^{-1} (accompanied by signals of moderate strength at 1622 and 1587 cm^{-1}) in addition to the expected ester carbonyl C=O stretching at 1745 cm^{-1}. These data, along with five additional carbon signals observed in the ^{13}C NMR spectrum, made it rather difficult to work out a complete structure for the unidentified product.

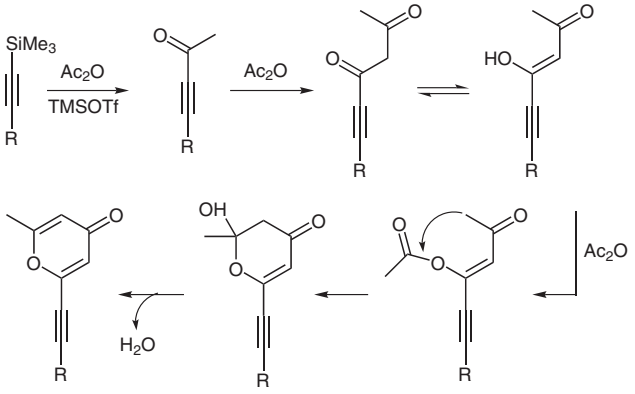
To simplify the structural assignment and also to find out whether this unexpected reaction is common to other similar alkynes, a simpler trimethylsilyl-protected alkynol **11**[8] was then examined under the same acetic anhydride and trimethylsilyl triflate[6] conditions (Scheme 4). Again, the ^1H and ^{13}C NMR spectra of the product bore a striking resemblance to those of **10** (albeit simpler). This compound was then hydrogenated over Pd/C to give a saturated ketone. The structure of the latter could be reliably assigned as **13** with the aid of the coupling information gained in the 2D NMR experiments. With this result in hand, it was then relatively straightforward to assign the structures of **12** and **10**.



Scheme 4

A rationalization for the formation of **10** and **12** is given in Scheme 5. It is known[9] that, in the presence of a Lewis acid, trimethylsilyl-protected alkynes may be readily converted into the corresponding acetylated alkynes. Therefore, in our case, an acetyl group is also very likely to be installed onto the terminal alkyne. The methyl ketone can then undergo an aldol reaction with another molecule of acetic anhydride to form an acetoacetyl group. The ketone carbonyl group at the propargylic position then enolizes to form a thermodynamically more stable conjugated system. The resulting enol hydroxy group is subsequently acetylated by a third molecule of acetic anhydride , affording an enol acetate motif. Finally, intramolecular aldol condensation (with the methyl at the terminal ketone attacking the acetate carbonyl group followed by dehydration) closes the six-membered ring and delivers the pyranone unit. It is noteworthy that, compared with the conditions[10] employed in the previous syntheses of pyranones, the present approach is remarkably mild and might

thus also be applicable to the synthesis other related pyranones.



Scheme 5

In summary, through chiral building block based syntheses, it has been shown that the 7-phenylhepta-4,6-diyne-1,2-diol isolated from *Bidens pilosa* (family *Asteraceae*) is of (*S*)-configuration.[11] The cross coupling between the phenylacetylene and alkyne **5** was found to be much slower than self-coupling of the former. It was hence necessary to use a rather large excess of phenylacetylene to drive the desired cross coupling to completion. In the debenzylation with acetic anhydride and trimethylsilyl triflate an unexpected condensation of additional acetyl groups onto the alkyne terminal leading to formation of a pyranone was observed. The mild conditions also appear to be applicable to the synthesis of other related pyranones.

All chemicals were reagent grade and used as purchased. Flash column chromatography was carried out on silica gel (300–400 mesh). Petroleum ether (PE), where used, had a boiling range of 60–90 °C. NMR spectra were recorded on a Varian Mercury 300 (300 MHz for ^{1}H) or a Bruker Avance NMR 400 (400 MHz for ^{1}H) spectrometer. IR spectra were measured on a Nicolet 380 infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer, and HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter.

(*S*)-1-(Benzyloxy)-7-phenylhepta-4,6-diyn-2-ol [(*S*)-6]

TMEDA (28 μL, 0.189 mmol) was added to a mixture of $NiCl_2·6H_2O$ (14 mg, 0.047 mmol) and CuI (9 mg, 0.047 mmol) in THF (1 mL) and stirred at ambient temperature. After 5 min at the same temperature, a solution of alkyne (*S*)-**5** (45 mg, 0.237 mmol) in THF (1.0 mL) was added, followed by phenylacetylene (neat, 130 μL, 1.183 mmol). The mixture was stirred at ambient temperature for 12 h. Then, to the reaction mixture were added $NiCl_2·6H_2O$ (14 mg, 0.047 mmol), CuI (9 mg, 0.047 mmol), TMEDA (28 μL, 0.189 mmol) and phenylacetylene (130 μL, 1.183 mmol). After completion of the addition, stirring was continued for another 5 h before an additional portion of phenylacetylene (130 μL, 1.183 mmol) was added. The mixture was stirred at ambient temperature for 12 h (starting material **5** was still present in significant amounts as shown by ^{1}H NMR analysis). To the mixture were added $NiCl_2·6H_2O$ (14 mg, 0.047 mmol), CuI (9 mg, 0.047 mmol), TMEDA (28 μL, 0.189 mmol) and phenylacetylene (130 μL, 1.183 mmol). Stirring was continued for 5 h then a final portion of phenylacetylene (130 μL, 1.183 mmol) was added. The mixture was stirred for 12 h and concentrated on a rotary evaporator. The residue, which did not contain any starting material **5** as shown by ^{1}H NMR analysis, was purified by chromatography on silica gel (EtOAc–PE, 1:4) to give (*S*)-**6**.

Yield: 49 mg (0.169 mmol, 71% from **5**); yellowish oil; $[\alpha]_D^{23}$ +23.4 (*c* 1.2, $CHCl_3$).

FTIR (film): 3429, 3063, 3033, 2911, 2861, 2245, 2168, 1593, 1490, 1453, 1442, 1361, 1203, 1103, 1027, 755, 890 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (br d, *J* = 8.1 Hz, 2 H), 7.41–7.30 (m, 8 H), 4.60 (s, 2 H), 4.09–3.98 (m, 1 H), 3.65 (A of an ABX, dd, *J* = 9.5, 3.5 Hz, 1 H), 3.56 (B of an ABX, dd, *J* = 9.3, 6.3 Hz, 1 H), 2.65 (d, *J* = 6.5 Hz, 2 H), 2.61 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 132.5, 129.0, 128.4, 128.3, 127.8, 127.7, 121.7, 80.1, 75.3, 74.0, 73.4, 72.7, 68.8, 67.1, 24.6.

MS (ESI): *m*/*z* = 313.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{18}O_2Na$: 313.1199; found: 313.1204.

(*R*)-1-(Benzyloxy)-7-phenylhepta-4,6-diyn-2-ol [(*R*)-6]

Obtained through cross coupling of phenylacetylene with (*R*)-**5** using the procedure for the conversion of (*S*)-**5** into (*S*)-**6** described above.

$[\alpha]_D^{27}$ –22.0 (*c* 1.0, $CHCl_3$). Other data were as those for (*S*)-**6**.

(*S*)-7-Phenylhepta-1,2-diacetyloxy-4,6-diyne [(*S*)-7]

A solution of Me_3SiOTf (46 μL, 0.255 mmol) in Ac_2O (1.0 mL) was added to a solution of (*S*)-**6** (37 mg, 0.127 mmol) in Ac_2O (1.0 mL) and stirred at –40 °C. The mixture was stirred at the same temperature for 30 min (TLC showed completion of the reaction), then sat. aq $NaHCO_3$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Removal of solvent by rotary evaporation left an oil, which was purified by chromatography on silica gel (EtOAc–PE, 1:4) to give diacetate (*S*)-**7**.

Yield: 33 mg (0.116 mmol, 92%); yellowish oil; $[\alpha]_D^{25}$ +64.0 (*c* 0.31, $CHCl_3$).

FTIR (film): 2968, 2250 (very weak), 2170 (very weak), 1747, 1495, 1444, 1372, 1222, 1046, 758, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.47 (br d, *J* = 6.8 Hz, 2 H), 7.36–7.29 (m, 3 H), 5.20–5.09 (m, 1 H), 4.37 (A of an ABX, dd, *J* = 12.1, 3.8 Hz, 1 H), 4.23 (B of an ABX, *J* = 12.0, 5.9 Hz, 1 H), 2.77 (A of an ABX, dd, *J* = 17.5, 6.6 Hz, 1 H), 2.72 (B of an ABX, dd, *J* = 17.5, 6.6 Hz, 1 H), 2.11 (s, 3 H), 2.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.1, 132.6, 129.1, 128.4, 121.6, 77.9, 75.7, 73.8, 69.0, 67.6, 63.7, 22.1, 20.9, 20.7.

MS (ESI): *m*/*z* = 307.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{16}NaO_4$: 307.0941; found: 307.0947.

(*R*)-7-Phenylhepta-1,2-diacetyloxy-4,6-diyne [(*R*)-7]

Obtained from (*R*)-**6** using the same procedure for conversion of (*S*)-**6** into (*S*)-**7** described above.

$[\alpha]_D^{24}$ –61.9 (*c* 0.35, $CHCl_3$). Other data were as those for (*S*)-**7**.

(*S*)-7-Phenylhepta-4,6-diyne-1,2-diol [(*S*)-1]

A solution of (*S*)-**7** (24 mg, 0.084 mmol) and K_2CO_3 (0.035 g, 0.253 mmol) in MeOH (1 mL) was stirred at ambient temperature for 30 min (TLC showed disappearance of **7**), then sat. aq NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Removal of solvent by rotary evaporation

left an oil, which was purified by chromatography on silica gel (EtOAc–PE, 1:2) to give the known diacetate (*S*)-**1**.

Yield: 11 mg (0.055 mmol, 65%); yellowish oil; $[\alpha]_D^{24}$ –7.1 (*c* 0.4, acetone) {Lit.[1] $[\alpha]_D^{20}$ –7.0 (*c* 0.4, acetone)}; 98.4% ee measured by HPLC (CHIRALPAK IC column; 0.46 × 25 cm; particle size 5 μm; *n*-hexane–*i*-PrOH, 90:10; flow rate 0.7 mL/min; 214 nm).

FTIR (film): 3360, 2926, 2248, 2163, 1490, 1442, 1092, 1026, 754, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.47 (br d, *J* = 7.5 Hz, 2 H), 7.35–7.28 (m, 3 H), 4.00–3.90 (m, 1 H), 3.80 (A of an ABX, dd, *J* = 11.2, 2.8 Hz, 1 H), 3.64 (B of an ABX, dd, *J* = 11.2, 6.4 Hz, 1 H), 2.65 (A of an ABX, dd, *J* = 17, 6.5 Hz, 1 H), 2.60 (B of an ABX, dd, *J* = 17, 6.5 Hz, 1 H), 3.07–2.06 (v. br, 2 H, 2 × OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5, 129.1, 128.4, 121.6, 79.8, 75.6, 73.8, 70.2, 67.4, 65.4, 24.6.

MS (ESI): *m*/*z* = 223.0 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{12}O_2Na$: 223.0730; found: 223.0737.

(*R*)-7-Phenylhepta-4,6-diyne-1,2-diol [(*R*)-1]

(*R*)-**1** was obtained from (*R*)-**7** using the same procedure for conversion of (*S*)-**7** into (*S*)-**1** described above.

$[\alpha]_D^{26}$ +7.0 (*c* 0.4, acetone); 98.9% ee as measured by HPLC (CHIRALPAK IC column; 0.46 × 25 cm; particle size 5 μm; *n*-hexane–*i*-PrOH, 90:10; flow rate 0.7 mL/min; 214 nm). Other data were as those for (*S*)-**1**.

(*R*)- 1,2-Diacetyloxy-5-(6-methyl-4-oxo-4*H*-pyran-2-yl)pent-4-yne (10)

A solution of Me_3SiOTf (110 μL, 0.61 mmol) in Ac_2O (1.0 mL) was added to a solution of (*R*)-**4** (50 mg, 0.19 mmol) in Ac_2O (2.0 mL) and stirred at –40 °C. The mixture was stirred at the same temperature for 4 h (TLC showed completion of the reaction), then sat. aq $NaHCO_3$ (2 mL) was added. The mixture was extracted with Et_2O (3 × 5 mL) and the combined organic layer was washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation left an oil, which was purified by chromatography on silica gel (EtOAc–PE, 2:1) to give diacetate **10**.

Yield: 28 mg (0.096 mmol, 50%); yellowish oil; $[\alpha]_D^{22}$ –43.8 (*c* 0.25, $CHCl_3$).

FTIR (film): 2245, 1746, 1659, 1622, 1587, 1435, 1392, 1374, 1223, 1047, 918, 867 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 1.9 Hz, 1 H), 6.12 (s, 1 H), 5.27–5.16 (m, 1 H), 4.35 (A of an ABX, dd, *J* = 12.1, 3.7 Hz, 1 H), 4.20 (B of an ABX, dd, *J* = 12.1, 4.4 Hz, 1 H), 2.82 (d, *J* = 6.0, 1 H), 2.11 (s, 1 H), 2.10 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 170.4, 170.0, 166.3, 147.7, 119.3, 115.0, 92.2, 75.0, 68.6, 63.6, 21.9, 20.8, 20.7, 19.9.

MS (ESI): *m*/*z* = 315.2 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{16}O_6Na$: 315.0839; found: 315.0848.

6-(6-Methyl-4-oxo-4*H*-pyran-2-yl)hex-5-ynyl Acetate (12)

Me_3SiOTf (650 μL, 2.82 mmol) was added to a solution of **11** (120 mg, 0.71 mmol) in Ac_2O (4.0 mL) stirred at –40 °C under argon. After completion of the addition, the bath was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 2 h (TLC showed completion of the reaction), then sat. aq $NaHCO_3$ (5 mL) was added to the blood-red mixture. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL) before being dried over anhydrous $MgSO_4$. Removal of solvent by rotary evaporation left an oil, which was purified by chromatography on silica gel (EtOAc–PE, 3:2) to give acetate **12**.

Yield: 125 mg (0.50 mmol, 71%); unstable yellow oil.

FTIR (film): 2956, 2236, 1738, 1658, 1391, 1240, 935 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (s, 1 H), 6.12 (s, 1 H), 4.11 (t, *J* = 6.0 Hz, 2 H), 2.51 (t, *J* = 6.7 Hz, 2 H), 2.27 (s, 3 H), 2.06 (s, 3 H), 1.81–1.75 (m, 2 H), 1.75–1.69 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (^1H-coupling established by 2D HSQC) = 179.3 (q), 171.0 (q), 166.3 (q), 148.3 (q), 118.6 (coupled to ^1H at δ = 6.33 ppm), 114.7 (coupled to ^1H at δ = 6.12 ppm), 98.0 (q), 73.3 (q), 63.6 (coupled to ^1H at δ = 4.11 ppm), 27.7 (coupled to ^1H at δ = 1.81–1.75 ppm), 24.3 (coupled to ^1H at δ = 1.75–1.69 ppm), 20.9 (coupled to ^1H at δ = 2.06 ppm), 19.9 (coupled to ^1H at δ = 2.27 ppm), 19.0 (coupled to ^1H at δ = 2.51 ppm).

MS (ESI): *m*/*z* = 271.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{16}O_4Na$: 271.0941; found: 271.0948.

6-(6-Methyl-4-oxo-tetrahydro-2*H*-pyran-2-yl)hexyl Acetate (13)

A mixture of **12** (40 mg, 0.16 mmol) and 10% Pd/C (40 mg) in MeOH (2.5 mL) was stirred at ambient temperature under H_2 (1 atm) for 6 h. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator to dryness. The residue was purified by chromatography on silica gel (EtOAc–PE, 1:6) to give **13**.

Yield: 25 mg (0.10 mmol, 61%); yellowish oil.

FTIR (film): 2934, 2859, 1738, 1239, 1038 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (coupling established by 2D COSY) = 4.05 (t, *J* = 6.6 Hz, 2 H, coupled to ^1H at δ = 1.72–1.61 ppm), 3.77–3.67 (m, 1 H, coupled to the methyl at δ = 1.33 ppm), 3.60–3.54 (m, 1 H, coupled to ^1H at δ = 1.72–1.61 and 1.55–1.46 ppm), 2.32 (br d, *J* = 14 Hz, 2 H), 2.23 (br t, *J* = 11.4 Hz, 1 H), 2.22 (br t, *J* = 11.1 Hz, 2 H), 2.06 (s, 3 H), 1.72–1.61 (m, 3 H), 1.55–1.46 (m, 2 H), 1.36–1.32 (m, 6 H), 1.33 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (^1H-coupling established by 2D HSQC) = 207.7 (q), 171.2 (q), 76.9 (coupled to ^1H at δ = 3.57 ppm), 73.2 (coupled to ^1H at δ = 3.71 ppm), 64.5 (coupled to ^1H at δ = 4.05 ppm), 49.4 (coupled to ^1H at δ = 2.34 (d, 1 H) and 2.23 (t, 1 H) ppm), 47.6 (coupled to ^1H at δ = 2.32 (d, 1 H) and 2.22 (t, 1 H) ppm), 36.3 (coupled to ^1H at δ = 1.70 and 1.54 ppm), 29.1 (coupled to ^1H at δ = 1.34 ppm), 28.5 (coupled to ^1H at δ = 1.65 ppm), 25.8 (coupled to ^1H at δ = 1.66 ppm), 25.2 (coupled to ^1H at δ = 1.36 ppm), 22.1 (coupled to ^1H at δ = 1.47 and 1.34 ppm), 21.0 (coupled to the doublet at δ = 1.33 ppm).

MS (ESI): *m*/*z* = 279.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{24}O_4Na$: 279.1567; found: 279.1574.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by the National Basic Research Program of China (the 973 Program, 2010CB833200), the National Natural Science Foundation of China (21032002, 20921091, 20672129, 20621062, 20772143), and the Chinese Academy of Sciences (KJCX2.YW.H08).

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