Total Synthesis of (–)-Δ^8-*trans*-Tetrahydrocannabinol

Qinggang Huang,[a] Bin Ma,[a] Xi'an Li,[a] Xinfu Pan,[a] Xuegong She*[a,b]

[a] State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. of China

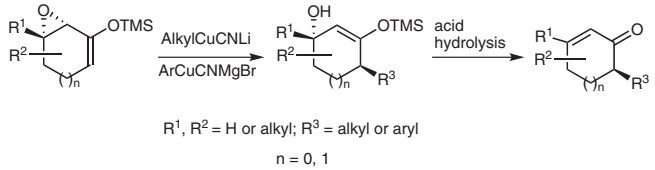
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. of China
Fax +86(931)8912582; E-mail: shexg@lzu.edu.cn

Received 21 January 2010; revised 9 March 2010

Abstract: (–)-Δ^8-*trans*-Tetrahydrocannabinol was synthesized with high regio- and stereoselectivity through S_N2' addition of an arylcyanocuprate to the optically pure enol silyl ether of α,β-epoxycyclohexanone.

Key words: addition reactions, heterocycles, tetrahydrocannabinol, deoxygenation, stereoselective synthesis

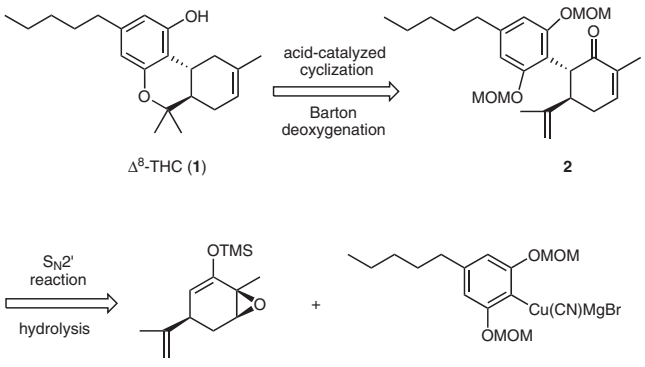
(–)-Δ^8-*trans*-Tetrahydrocannabinol (Δ^8-THC; **1**), which was isolated from the female flowering tops of *Cannabis sativa* L. for the first time in 1966,[1] is an important member of the family of cannabinoids that exhibit varying degrees of antiemetic, antiglaucoma, and analgesic activities. Recently, two cannabinoid receptors, CB1 and CB2 , have been discovered,[2] and these have attracted attention as potential therapeutic targets for the development of anti-obesity,[3] anticancer,[4] analgesic,[5] and antiglaucoma agents.[6–7] The biological activities of the cannabinoids have prompted chemists to study their synthesis. Despite many efforts to synthesize compounds of this type,[8] there are few reports of regio- and stereoselective syntheses of Δ^8-THC,[9] and this remains a significant challenge. We report a general strategy for the total synthesis of Δ^8-THC by using a highly regio- and stereoselective S_N2' reaction.[10] The S_N2' addition of aryl- or alkylcyanocuprates to enol silyl ether epoxides, which occurs with high regio- and stereoselectivities, is an important method for the formation of carbon–carbon bonds (Scheme 1).[11]



Scheme 1 Regio- and stereoselective S_N2' reactions

In our recent work on the total synthesis of (+)-machaeriol D,[12] we successfully used an S_N2'-hydrolysis reaction in the stereoselective construction of the hexahydrodibenzopyran nucleus. To explore the scope and generality of this strategy, we attempted a total synthesis of Δ^8-THC as an example of an asymmetric synthesis of a cannabinoid.

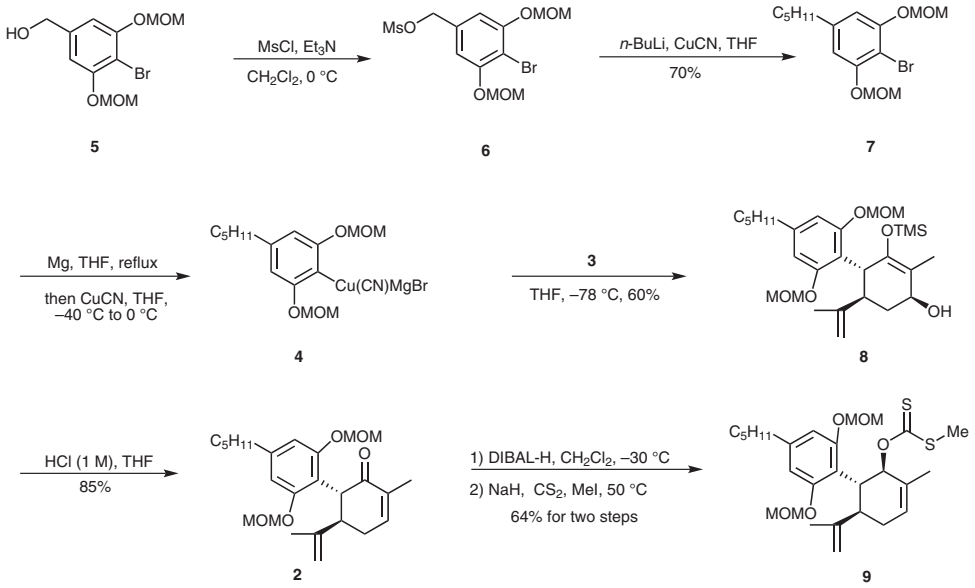
Our retrosynthetic analysis is shown in Scheme 2. Δ^8-THC (**1**) consists of a tricyclic core structure and two stereogenic centers. The problems associated with the synthesis of **1** involve the control of the *trans*-stereochemistry at the cyclohexene ring and the position of the double bond. According to our analysis, we surmised that the target molecule **1** might be available from ketone **2** by several transformations involving acid-catalyzed cyclization and Barton radical deoxygenation. In turn, the ketone **2** might be prepared by the S_N2'-hydrolysis reaction of enol silyl ether **3** with the arylcyanocuprate **4**. By this method, the problems of controlling the relative stereochemistry and the position of the double bond might be overcome.



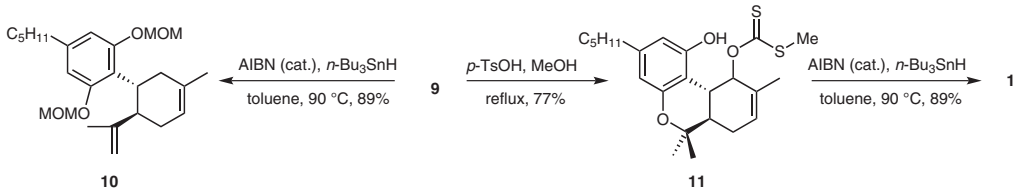
Scheme 2 Retrosynthetic analysis of Δ^8-THC

We began our synthesis by preparing the enol silyl ether **3** in an optically pure form from commercially available (–)-(*R*)-carvone through a conventional four-step sequence that has been previously reported.[12a] We then prepared the bromide **7**, another precursor for the S_N2' addition reaction (Scheme 3). The hydroxy bromide **5** was converted into the corresponding methyl sulfonate **6** in almost quantitative yield, and the desired precursor **7** was obtained in 70% yield from sulfonate **6** by means of an S_N2 reaction with butyl cyanocuprate.[13] The reaction between the freshly prepared arylmagnesium bromide of **7** and copper cyanide gave the arylcyanocuprate reagent **4**. Having the necessary components in hand, we conducted the *anti* S_N2' addition according to our previously reported procedure.[12] The unstable silyl enol ether **8** was obtained as a single diastereoisomer and immediately subjected to acid-

SYNTHESIS 2010, No. 11, pp 1766–1770
Advanced online publication: 12.04.2010
DOI: 10.1055/s-0029-1218732; Art ID: F01510SS



Scheme 3 Preparation of intermediate xanthate **9**



Scheme 4 Completion of the total synthesis of Δ8-THC (**1**)

ic hydrolysis to afford the ketone **2** in 51% yield for the two steps. Further elaboration of the enone **2** by reduction with diisobutylaluminum hydride and subsequent xanthation gave the key intermediate **9** in 63% yield for the two steps.[14]

We then subjected the xanthate **9** to Barton radical deoxygenation to give the compound **10** (Scheme 4).[14] We had hoped that compound **10** would cyclize under the acidic reaction conditions to give **1**, but unfortunately, a complex mixture of products was formed. Attempts to use other acidic reagents for remove the methoxymethyl protecting group gave similar results.[8m]

Given the failure of the direct synthesis from **9**, we attempted a two-step approach instead. The acidic cyclization was first performed in the presence of 4-toluenesulfonic acid for one hour in refluxing methanol and, to our delight, the desired tricyclic product **11** was isolated in 75% yield. Subsequent Barton radical deoxygenation of **11** gave the required (–)-Δ8-THC (**1**) smoothly in 90% yield; the spectral properties of this product were identical with those of the natural product.[1]

To summarize, we have completed an asymmetric synthesis Δ8-THC through the highly regio- and stereoselective S_N2' addition of an arylcyanocuprate to the enol silyl ether of an α,β-epoxycyclohexanone; this reaction gave *trans*-stereocontrol at the cyclohexene ring, and regioselective installation of the trisubstituted double bond was readily achieved. The application of this methodology to the synthesis of other cannabinoids is ongoing in our laboratory.

All chemicals were used as received. THF and toluene were refluxed with Na, whereas CH_2Cl_2 was refluxed with CaH_2 and freshly distilled prior before use. Other solvents were purified and dried by standard methods. All reactions under standard conditions were monitored by TLC on gel F254 plates. Silica gel (200–300 mesh) was used for column chromatography, and the distillation range of the PE was 60–90 °C. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 400-MHz instrument; the spectral data are reported in ppm relative to TMS as internal standard. Chemical shifts are reported as δ values relative to $CDCl_3$ (δ = 7.27 for ^1H NMR and 77.0 for ^{13}C NMR). IR spectra were recorded on a Nicolet FT-170SX spectrometer. HRMS data were determined on a Bruker Daltonics APEXII 47e FTIR spectrometer. Oxygen- and moisture-sensitive reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Optical rotations were measured on a precision automated polarimeter.

4-Bromo-3,5-bis(methoxymethoxy)benzyl Methanesulfonate (6)

MsCl (2.65 mL, 34.2 mmol) was added to a soln of the bromo compound **5** (7.0 g, 22.8 mmol) and Et_3N (6.31 mL, 45.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the mixture was stirred for 15 min. The reaction was then quenched with H_2O, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporate to dryness. The residue was purified by column chromatography [silica

gel, PE–EtOAc (3:1)] to give a white amorphous solid; yield: 8.5 g (97%).

IR (KBr): 3379, 2921, 2852, 1761, 1586, 1436, 1350, 1242, 1152, 1100, 1043, 920, 852, 804, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.87 (s, 2 H), 5.25 (s, 4 H), 5.14 (s, 2 H), 3.50 (s, 6 H), 2.96 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 133.9, 109.4, 104.7, 95.0, 70.8, 56.4, 38.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{18}BrO_7S$: 384.9956; found: 384.9956.

2-Bromo-1,3-bis(methoxymethoxy)-5-pentylbenzene (7)

BuLi (18.5 mL, 45 mmol) was added to a soln of CuCN (4.21 g, 46.8 mmol) in anhyd THF (60 mL) under argon at –50 °C. The heterogeneous mixture was allowed to warm gradually until complete dissolution occurred, and then cooled again to –78 °C. The mesylate **6** (6.91 g, 18 mmol) was added and then allowed to warm gradually to r.t. for 4 h. The resulting mixture was quenched with sat. aq NH_4Cl soln, stirred at r.t. for 30 min, and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporate to dryness. Purification of the residue by column chromatography [silica gel, PE–EtOAc (30:1)] gave a colorless oil; 4.36 g (70%).

IR (KBr): 3402, 2955, 2928, 2856, 1587, 1461, 1435, 1393, 1154, 1111, 1090, 1045, 922, 849, 726 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.68 (s, 2 H), 5.23 (s, 4 H), 3.51 (s, 6 H), 2.54 (td, *J* = 9.6, 2.4 Hz, 2 H), 1.57–1.61 (m, 2 H), 1.27–1.34 (m, 4 H), 0.90 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 143.7, 109.7, 100.6, 95.0, 56.2, 36.0, 31.3, 30.8, 22.3, 13.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{24}BrO_4$: 347.0858; found: 347.0858.

(5*R*,6*R*)-6-[2,6-Bis(methoxymethoxy)-4-pentylphenyl]-5-isopropenyl-2-methylcyclohex-2-en-1-one (2)

1 M HCl (1 mL) was added to a soln of bromide **8** (0.70 g, 1.38 mmol) in THF (2 mL), and the mixture was stirred for 1 h. The reaction quenched with H_2O, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporate to dryness. Purification of the residue by column chromatography [silica gel, PE–EtOAc (5:1)] gave a colorless oil; yield: 0.49 g (85%); $[\alpha]_D^{25}$ +52.6 (*c* 1.0, $CHCl_3$).

IR (KBr): 3331, 2954, 2927, 2856, 1675, 1611, 1585, 1435, 1397, 1238, 1153, 1109, 1083, 1043, 968, 925, 893 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 6.0 Hz, 1 H), 6.59 (s, 2 H), 5.06 (s, 4 H), 4.56 (s, 1 H), 4.53 (s, 1 H), 4.14 (d, *J* = 12.4 Hz, 1 H), 3.47 (td, *J* = 12.4, 4.4 Hz, 1 H), 3.43 (s, 6 H), 2.50–2.59 (m, 3 H), 2.32 (dt, *J* = 18.0, 4.8 Hz, 1 H), 1.82 (s, 3 H), 1.64 (s, 3 H), 1.59 (t, *J* = 7.2 Hz, 2 H), 1.29–1.33 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.0, 146.1, 143.3, 142.9, 135.2, 114.9, 112.0, 108.2, 94.5, 56.0, 48.6, 47.2, 36.3, 31.6, 31.5, 30.8, 22.5, 18.9, 16.2, 14.0.

HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd for $C_{25}H_{40}NO_5$: 434.2949; found: 434.2948.

***O*-{(1*R*,5*R*,6*R*)-6-[2,6-Bis(methoxymethoxy)-4-pentylphenyl]-5-isopropenyl-2-methylcyclohex-2-en-1-yl} *S*-Methyl Dithiocarbonate (9)**

DIBAL-H (1.42 mL, 1.42 mmol) was added to a soln of ketone **2** (0.49 g, 1.18 mmol) in CH_2Cl_2 (5 mL) at –78 °C under argon, and the mixture was stirred for 3 h. The reaction was quenched with sat. aq NH_4Cl and the mixture was stirred at r.t. for 30 min. The resulting slurry was filtered and the residue was washed with EtOAc (8 × 5 mL). The combined organic phase was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, petroleum–EtOAc (10:1)] to give the intermediate alcohol as a colorless oil; yield: 0.35 g (70%); $[\alpha]_D^{25}$ +38.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3400, 2955, 2926, 2856, 1710, 1643, 1610, 1579, 1437, 1398, 1376, 1153, 1108, 1038, 923, 896 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.70 (s, 1 H), 6.65 (s, 1 H), 5.60 (s, 1 H), 5.07–5.21 (m, 4 H), 4.61 (s, 1 H), 4.54 (s, 1 H), 3.94 (s, 1 H), 3.70 (td, *J* = 12.8, 4.0 Hz, 1 H), 3.49 (s, 3 H), 3.47 (s, 3 H), 3.30–3.35 (m, 1 H), 2.52 (t, *J* = 8.0 Hz, 2 H), 2.11–2.18 (m, 2 H), 1.85 (s, 3 H), 1.58–1.61 (m, 2 H), 1.46 (s, 3 H), 1.26–1.32 (m, 4 H), 0.88–0.90 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 155.6, 146.4, 143.6, 136.3, 123.1, 115.4, 111.1, 108.7, 108.4, 95.6, 94.7, 72.3, 56.2, 56.1, 40.7, 39.5, 36.2, 33.3, 31.7, 30.9, 22.5, 21.2, 18.1, 14.1.

HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd $C_{25}H_{42}NO_5$: 436.3105; found: 436.3110.

To a soln of the alcohol intermediate (0.33 g, 0.80 mmol) in anhyd THF (2 mL) at r.t. was added NaH (60% suspension in mineral oil, 64 mg, 1.6 mmol) under argon. The mixture was stirred for 30 min then CS_2 (0.5 mL) was added and the mixture was heated to 50 °C for 2 h. MeI (0.54 mL, 8.7 mmol) was added and the mixture was stirred for another 5 h at 50 °C, then cooled to r.t. The cooled mixture was filtered and concentrated to give a residue that was purified by column chromatography [silica gel, PE–EtOAc (10:1)] to give the xanthate ester **9** as a yellow oil; yield: 0.37 g (91%); $[\alpha]_D^{25}$ –128.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 3393, 2955, 2926, 2854, 1710, 1642, 1609, 1582, 1436, 1397, 1378, 1238, 1152, 1110, 1082, 1046, 972, 924, 867 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.57 (s, 2 H), 5.45 (s, 1 H), 5.09–5.18 (m, 4 H), 4.53 (s, 1 H), 4.47 (s, 1 H), 4.39 (s, 1 H), 3.99 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.52 (s, 6 H), 3.09 (t, *J* = 10.8 Hz, 1 H), 2.51 (t, *J* = 7.8 Hz, 2 H), 2.44 (s, 3 H), 2.18–2.28 (m, 1 H), 1.97–2.05 (m, 1 H), 1.75 (s, 3 H), 1.62 (s, 3 H), 1.56–1.58 (m, 2 H), 1.23–1.32 (m, 4 H), 0.87–0.91 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.3, 156.3, 147.3, 142.8, 132.1, 128.0, 117.9, 111.1, 107.9, 95.2, 77.0, 55.9, 47.1, 40.8, 36.4, 36.2, 31.6, 30.9, 22.5, 21.3, 19.5, 14.0, 12.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{41}O_5S_2$: 509.2395; found: 509.2388.

2-[(1*R*,6*R*)-6-Isopropenyl-3-methylcyclohex-3-en-1-yl]-1,3-bis(methoxymethoxy)-5-pentylbenzene (10)

AIBN (cat.) and Bu_3SnH (neat, 0.23 mL, 1.34 mmol) were added sequentially to a soln of the xanthate **9** (0.02 g, 0.039 mmol) in anhyd toluene (0.5 mL) at r.t. under argon. The mixture was carefully deoxygenated by bubbling argon through it for 10 min. The flask was then immersed in a preheated oil bath (110 °C), and the mixture was stirred at this temperature for 1 h then cooled to r.t. The solvent was evaporated and the residue was purified by column chromatography [silica gel, PE–EtOAc (30:1)] to give a colorless oil; yield: 0.014 mg (89%); $[\alpha]_D^{25}$ –68.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3428, 2956, 2927, 2856, 1643, 1609, 1581, 1435, 1397, 1237, 1153, 1110, 1044, 971, 925, 886 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.55 (s, 2 H), 5.24 (s, 1 H), 5.07–5.13 (m, 4 H), 4.47 (s, 1 H), 4.45 (s, 1 H), 4.00 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.42–3.48 (m, 6 H), 2.91 (td, *J* = 10.5, 4.8 Hz, 1 H), 2.50 (t, *J* = 8.0 Hz, 2 H), 2.14–2.16 (m, 1 H), 1.96–2.02 (m, 1 H), 1.70–1.79 (m, 2 H), 1.52–1.66 (m, 8 H), 1.31–1.32 (m, 4 H), 0.89 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, CDCl3): δ = 149.1, 142.3, 131.3, 125.9, 120.1, 110.0, 108.4, 95.1, 55.9, 45.1, 36.6, 36.2, 31.7, 31.0, 30.7, 29.5, 23.4, 22.5, 19.3, 14.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{39}O_4$: 403.2848; found: 403.2850.

_O_-[(6a_R_,10a_R_)-1-Hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6_H_-benzo[_c_]chromen-10-yl] _S_-Methyl Dithiocarbonate (11)

TsOH (0.20 g, 1.16 mmol) was added to a soln of the xanthate **9** (0.30 g, 0.59 mmol) in MeOH (3 mL), and the mixture was refluxed for 1 h. The MeOH was removed in vacuo, H_2O (2 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporate to dryness. The residue was purified by column chromatography [silica gel, PE–EtOAc (10:1)] to give a yellow oil; yield: 0.19 g (77%); $[\alpha]_D^{25}$ –96.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3428, 2956, 2928, 2856, 1706, 1642, 1623, 1578, 1427, 1380, 1362, 1262, 1182, 1131, 1114, 1046, 973, 869, 785 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (s, 1 H), 6.28 (s, 1 H), 6.11 (d, *J* = 0.8 Hz, 1 H), 4.84 (s, 1 H), 4.42 (d, *J* = 3.2 Hz, 1 H), 3.27 (dd, *J* = 11.2, 1.6 Hz, 1 H), 2.44 (s, 3 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 1.93 (td, *J* = 12.6, 4.8 Hz, 1 H), 1.81–1.85 (m, 1 H), 1.79 (s, 3 H), 1.56 (t, *J* = 7.2 Hz, 2 H), 1.41 (s, 3 H), 1.22–1.37 (m, 4 H), 1.10 (s, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2, 154.9, 154.1, 143.2, 130.6, 129.9, 110.3, 107.6, 77.0, 76.6, 47.9, 42.0, 35.4, 34.3, 31.5, 30.6, 27.4, 22.5, 21.8, 19.8, 14.0, 13.1.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{33}O_3S_2$: 421.1871; found: 421.1879.

Δ^8-THC (1)

AIBN (cat.) and Bu_3SnH (neat, 1 mL, 5.96 mmol) were added sequentially to a soln of the xanthate ester **11** (0.042 g, 0.10 mmol) in anhyd toluene (2 mL) at r.t. under argon. The mixture was carefully deoxygenated by bubbling argon through it for 10 min. The flask was then immersed into a preheated oil bath (110 °C), and the mixture was stirred at this temperature for 1 h then cooled to r.t. The solvent was evaporated, and the residue was purified by column chromatography [silica gel, PE–EtOAc (10:1)] to give a yellow oil; yield: 0.028 g (89%); $[\alpha]_D^{25}$ –185 (*c* 0.6, $CHCl_3$).

IR (KBr): 3410, 2957, 2928, 2856, 1625, 1580, 1428, 1376, 1259, 1184, 1130, 1083, 1031, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (d, *J* = 1.2 Hz, 1 H), 6.12 (d, *J* = 1.2 Hz, 1 H), 5.44 (d, *J* = 4.4 Hz, 1 H), 4.68 (s, 1 H), 3.20 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.71 (td, *J* = 10.8, 4.8 Hz, 1 H), 2.43–2.47 (m, 2 H), 2.14–2.19 (m, 1 H), 1.80–1.84 (m, 3 H), 1.67 (s, 3 H), 1.55–1.58 (m, 2 H), 1.39 (s, 3 H), 1.27–1.33 (m, 4 H), 1.12 (s, 3 H), 0.87–0.91 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 154.7, 142.7, 134.7, 119.3, 110.8, 110.1, 107.6, 76.6, 44.9, 36.0, 35.4, 31.6, 30.6, 27.9, 27.6, 23.5, 22.5, 18.5, 14.0.

HRMS (ESI): *m/z* [M – H]$^+$ calcd for $C_{21}H_{29}O_2$: 313.2168; found: 313.2169.

Acknowledgment

We are grateful for the generous financial support by the MOST (No. 2010CB833200) and the NSFC (QT program, 20872054, 20732002).

References

(1) (a) Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, *88*, 367. (b) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934. (c) Binder, M.; Franke, I.; Schmidt, B.; Dietrich, W. *Helv. Chim. Acta* **1982**, *65*, 807.

(2) (a) Gernard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. *Biochem. J.* **1991**, *279*, 129. (b) Skaper, S. D.; Buriani, A.; Dal Toso, R.; Petrelli, L.; Romamello, S.; Faca, L.; Leon, A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 3984. (c) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature (London, U.K.)* **1990**, *346*, 61. (d) Munro, S.; Thomas, K. L.; Abu-shaar, M. *Nature (London, U.K.)* **1993**, *365*, 61.

(3) Di Marzo, V.; Goparaju, S. K.; Wang, L.; Liu, J.; Batkai, S.; Jarai, Z.; Fezza, F.; Miura, G. I.; Palmiter, R. D.; Sugiuram, T.; Kunos, G. *Nature (London, U.K.)* **2001**, *410*, 822.

(4) Parolaro, D.; Massi, P.; Rubino, T.; Monti, E. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2002**, *66*, 319.

(5) Palmer, S. L.; Thakur, G. A.; Makriyannis, A. *Chem. Phys. Lipids* **2002**, *121*, 3.

(6) Porcella, A.; Maxia, C.; Gessa, G. L.; Pani, L. *Eur. J. Neurosci.* **2001**, *13*, 409.

(7) Chien, F. Y.; Wang, R. F.; Mittag, T. W.; Podos, S. M. *Arch. Ophthalmol.* **2003**, *121*, 87.

(8) For selected examples, see: (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273. (b) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1967**, *89*, 4552. (c) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6159. (d) Fahrenholtz, K. E.; Lurk, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 2079. (e) Fahrenholtz, K. E.; Lurk, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934. (f) Chan, T. H.; Chaly, T. *Tetrahedron* **1982**, *23*, 2935. (g) Rickards, R. W.; Ronneberg, H. *J. Org. Chem.* **1984**, *49*, 572. (h) Childers, W. E. Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276. (i) Malkov, A. V.; Koovsky, P. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1257. (j) William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771. (k) William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017. (l) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P. V.; Millier, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (m) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861. (n) Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269. (o) Ballerini, E.; Minuti, L.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **2009**, *74*, 4311.

(9) (a) Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, 88; 367. (b) Petrzika, T.; Sikemeier, C. *Helv. Chim. Acta.* **1967**, *50*, 1416. (c) Handrick, G. R.; Razdan, R. K.; Uliss, D. B.; Dalzell, H. C.; Boger, E. *J. Org. Chem.* **1997**, *42*, 2563. (d) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (e) Qi, L.; Yamamoto, N.; Meijler, M. M.; Altobell, L. J. III; Koob, G. F.; Wirsching, P.; Janda, K. D. *J. Med. Chem.* **2005**, *48*, 7389.

(10) For a review of the S_N2' reaction, see: (a) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. For recent references on the S_N2' reaction, see: (b) Li, L.; Rayabarapu, D. K.; Nandi, M.; Cheng, C. *Org. Lett.* **2003**, *5*, 1621. (c) Smith, A. B. III; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *; 124*, 14516. (d) Spino, C.; Beaulieu, C.; Lafreniére, J. *J. Org. Chem.* **2000**, *65*, 7091. (e) Wang, X.; Wu, Y.; Jiang, S.; Singh, G. *J. Org. Chem.* **2000**, *65*, 8146. (f) Xie, C.; Nowak, P.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4427. (g) Iura, Y.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 291. (h) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. (i) Soorukram,

D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409. (j) Calaza, M. I.; Yang, X.; Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 529.

(11) (a) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. (b) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114. (c) Marino, J. P.; Jaén, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. (d) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389. (e) Marino, J. P.; Pradilla, F.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898. (f) Clive, D. L. J.; Wickens, P. L.; Silva, G. V. J. *J. Org. Chem.* **1995**, *; 60*, 5532.

(12) (a) Wang, Q. L.; Huang, Q. G.; Chen, B.; Lu, J. P.; Wang, H.; She, X. G.; Pan, X. F. *Angew. Chem. Int. Ed.* **2006**, *22*, 3651. (b) Huang, Q. G.; Wang, Q. L.; Zheng, J. Y.; Zhang, J. Y.; Pan, X. F.; She, X. G. *Tetrahedron* **2007**, *63*, 1014.

(13) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. J. *J. Org. Chem.* **1984**, *49*, 3928.

(14) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574. (b) Barton, D. H. R.; Lobberding, D. C. A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329. (c) For a review see: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.