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A general route to 5,6-*seco*-hexahydrodibenzopyrans and analogues: first total synthesis of (+)-Machaeridiol B and (+)-Machaeriol B

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Abstract—A general and efficient route for the synthesis of 5,6-*seco*-hexahydrodibenzopyran and *trans*-hexahydrodibenzopyran analogues was established, via a highly regio- and stereoselective S_N2' reaction of arylcyanocuprates to enol silyl ether of α,β-epoxycyclohexanone. It was applied to the first facile total synthesis of (+)-Machaeridiol B and (+)-Machaeriol B.

1. Introduction

The dibenzopyran nucleus is a structural feature found in a wide variety of products, including the tetrahydrodibenzopyran derivatives (e.g., tetrahydrocannabinol, cannabidiol) and hexahydrodibenzopyran derivatives (e.g., nonnatural hexahydrocannabinol).[1] Quite a number of hexahydrodibenzopyran derivatives have been isolated from the stem bark of *Machaerium multiflorum* Spruce (Fabaceae) (Fig. 1).[2] These natural products generally were classified into two classes according to their structural features, 5,6-*seco*-hexahydrodibenzopyrans (HHDBP's) Machaeridiols A–C

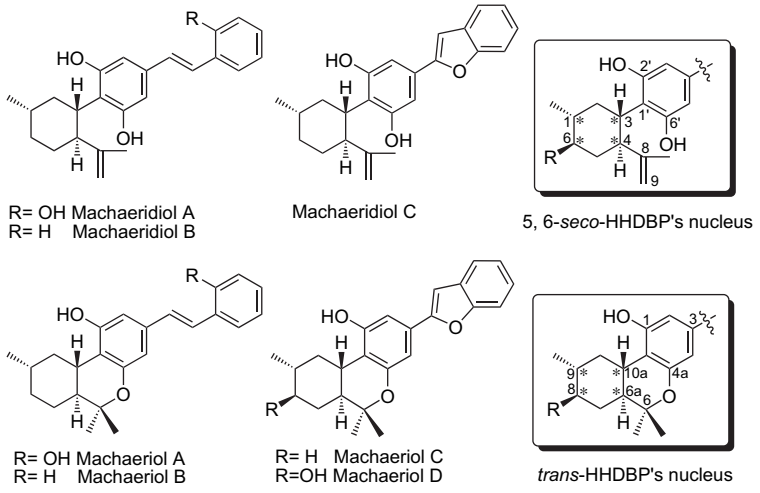

Figure 1. Representative members of 5,6-*seco*-HHDBP's and *trans*-HHDBP's.

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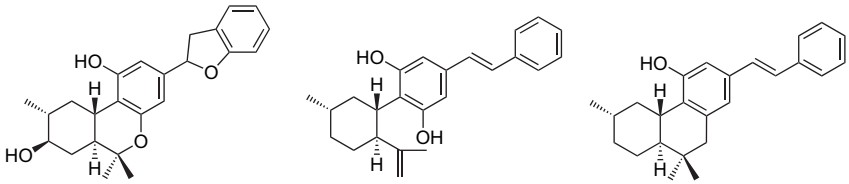


Scheme 1. The structures of (+)-Machaeriol D, (+)-Machaeridiol B, and (+)-Machaeriol B.

and *trans*-HHDBP's Machaeriols A–D. The characteristic biological activities and challenging molecular architecture of this class of natural products have stimulated synthetic efforts directed toward their total syntheses. Many different approaches[3] have been employed for the construction of the skeleton. Taking the key step of hexahydrodibenzopyrans' formation into consideration, the methods can be generally classified into two different strategies: (1) the intramolecular Diels–Alder cycloadditions and (2) the acid-catalyzed condensation of phenols with citronellal. The two strategies suffer from the general problem of formation of hexahydrodibenzopyrans derivatives that is difficult to prevent under these conditions. In our recent work of the total synthesis of (+)-Machaeriol D (Scheme 1),[4] a tandem S_N2'-hydrolysis reaction[5] sequence successfully established four stereocenters at the 5,6-*seco*-HHDBP's nucleus enantioselectively. To further explore the scope and generality of this strategy, a variety of large arylcyanocuprates were examined under the optimized conditions. In this paper, we detail our results for the S_N2'-hydrolysis reaction of substituted arylcyanocuprates. To highlight the method, the above synthetic strategy was used to assemble (+)-Machaeridiol B and (+)-Machaeriol B.

2. Results and discussion

The S_N2'-hydrolysis reaction of enol silyl ether[6] of α,β-epoxycyclohexanone **1**[4] with a variety of large arylcyanocuprates was found to be a very general route (Table 1). The unstable adducts **3a**–**3g**, which were immediately subjected to mild hydrolysis to afford **4a**–**4g** with the desired four stereocenters, have been prepared by the S_N2'-hydrolysis reaction of **2a**–**2g** in satisfactory yields in two steps (70–79%). When the *ortho*- and *para*-methoxy arylcyanocuprates (entries 2 and 3) were used, the electronic effect on the benzene ring was proved to be a tiny effect on the reaction. When sterically demanding arylcyanocuprates (entries 4 and 5) were used, the reactions also provided the desired products in good yields. To our delight, we found that the conjugative effect on the benzene ring (entries 6 and 7) was very few that the desired crucial compounds **4f** and **4g** could be obtained in 76 and 70% yields, respectively. When the arylcyanocuprate reagents were prepared, we have found that the concentration of Grignard reagents (0.5 M) is important. We have also found that the temperature of mixed arylcyanocuprate reactions should be well controlled at −40 °C and then warmed to 0 °C until CuCN disappeared absolutely.

With the above results in hand, the synthesis of (+)-Machaeridiol B and (+)-Machaeriol B was conducted (Scheme 2). The secondary hydroxyl of **4g** was easily protected as its TBS ether **5**. Compound **6** could be achieved through methyl xanthating of the corresponding reduced product of **5** and reduction via Barton radical deoxygenation[7] in 59% yield for three steps. After the success of deoxygenation, the TBS protecting group was removed with TBAF in refluxing THF for 12 h in 98% yield.[8] In the course of removing hydroxyl group, Barton radical deoxygenation was first tried, however, the desired product was isolated in low yield. After considerable experiment, we settled on a sequence that involved converting **7** to the corresponding methyl sulfonate in quantitative yield. Thus, treatment of this methyl sulfonate with lithium aluminum hydride in refluxing ether under argon for 8 h afforded the important compound **8** in 80% yield.[9]

Having successfully obtained the precursor **8** from **7**, we proceeded to synthesize (+)-Machaeridiol B and (+)-Machaeriol B. For deprotecting the MOM group without cyclization, $LiBF_4$,[10a] PPTS,[10b] and $NaHSO_4 \cdot SiO_2$[10c] have been attempted, but all the attempts were unsuccessful to obtain the 5,6-*seco*-HHDBP's nucleus. Finally, we found that in CH_3CN/CH_2Cl_2 (2:1) treatment of **8** with $AlCl_3$ and NaI at 0 °C could afford (+)-Machaeridiol B.[10d] As soon as the substrate **8** disappeared, the reaction was quenched with ice water. In this case, (+)-Machaeridiol B could be achieved in 50% yield. If we let the mixed reaction to react for longer time, (+)-Machaeriol B was obtained in 90% yield. The spectral properties of our synthetic products are identical with the natural products.[2]

3. Conclusion

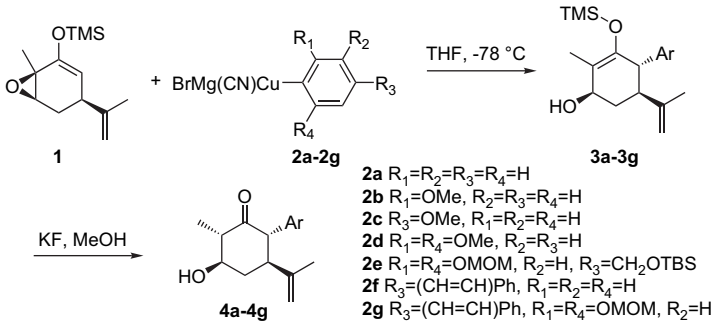
In summary, a strategy for the construction of 5,6-*seco*-HHDBP's was developed and found to be general for various arylcyanocuprates to optically active enol silyl ether of α,β-epoxycyclohexanone. Utility of this strategy, the first total synthesis of (+)-Machaeridiol B and (+)-Machaeriol B has been facilely completed. This result indicated that the S_N2'-hydrolysis reaction was useful for the construction of 5,6-*seco*-HHDBP's and *trans*-HHDBP's skeletons, important structural frameworks in a wide range of bioactive compounds. Further study to apply the present methodology for the synthesis of other natural products is in progress in our laboratory and will be reported in due course.

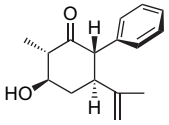
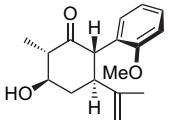
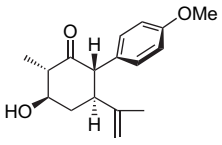
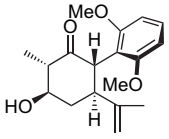
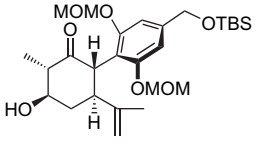
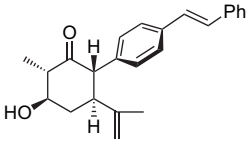
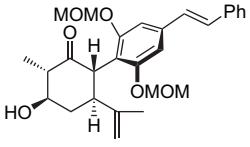
4. Experimental

4.1. General

Oxygen- and moisture-sensitive reactions were carried out under argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available

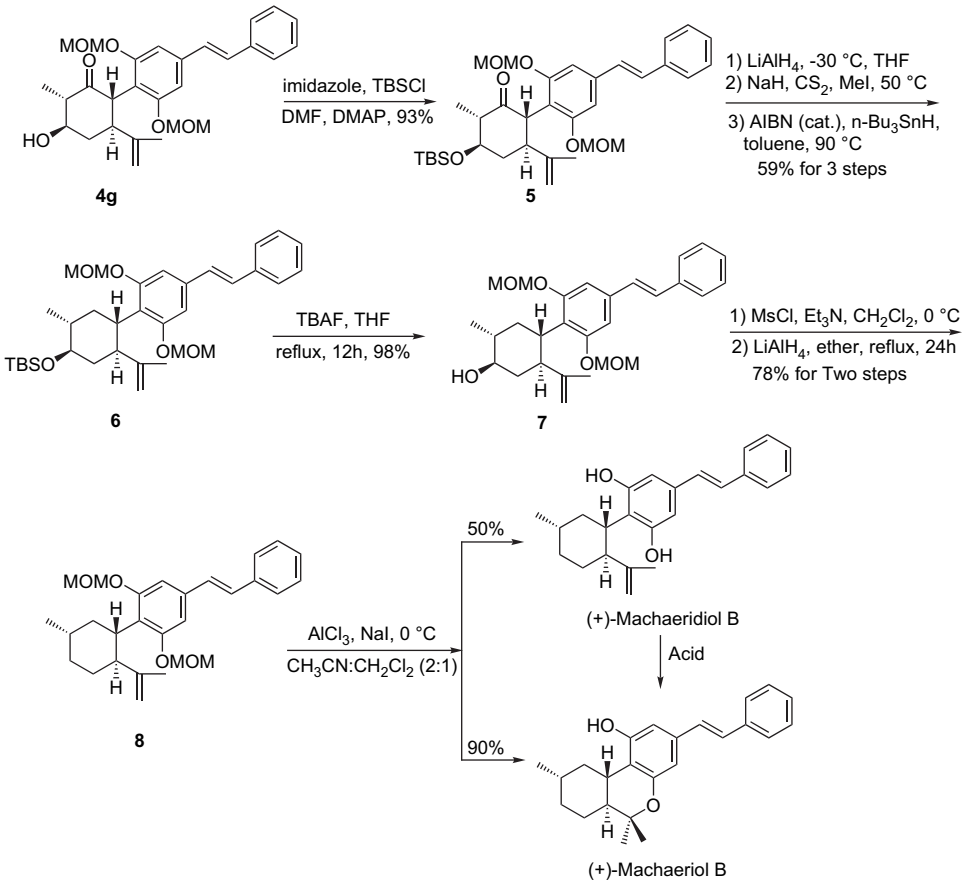
Table 1. The S_N2'-hydrolysis reaction of **1** with various large arylcyanocuprates



Entry	ArCu(CN)MgBr	Products[a]	Yield[b] (two steps) (%)
1	**2a**	 **4a**	79
2	**2b**	 **4b**	76
3	**2c**	 **4c**	71
4	**2d**	 **4d**	75
5	**2e**	 **4e**	74
6	**2f**	 **4f**	76
7	**2g**	 **4g**	70

[a] All reactions were carried out with 2 equiv of the freshly-prepared arylcyanocuprates reagents in the presence of **1** (1 equiv) at −78 °C, warming the reaction mixture to −10 °C over 45 min, stirring for an additional 3 h at −10 °C to 0 °C, leading to the silyl enol ethers, which were immediately subjected to mild hydrolysis to afford α-aryl ketones.

[b] Isolated yields.



Scheme 2. Total synthesis of (+)-Machaeridiol B and (+)-Machaeriol B.

reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200–300 mesh). Optical rotations were measured on a precision automated polarimeter. Infrared spectra were recorded on a FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^{1}H and 77.0 for ^{13}C).

4.1.1. Formation of ArMgBr. The system with a magnetic stir bar, reflux condenser, a stopcock, and a 25-mL addition funnel was charged with magnesium dust (2.2 mmol), evacuated, and placed under argon. 1,2-Dibromoethane (0.01 mL) was added via syringe to the magnesium suspension in dry THF (1 ml) to initiate Grignard formation, and then a solution of substrates of ArBr (2 mmol) in dry THF (3 ml) was added dropwise via addition funnel to the refluxing mixture. After addition the solution was refluxed for 45 min, at that time Mg had been dissolved.

4.1.2. Formation of the Cuprate. The aryl magnesium bromide solution was added to a stirred and cooled (−40 °C) mixture of CuCN (2 mmol) in dry THF (2 ml) under argon. The reaction mixture was gradually warmed to homogeneity (0 °C).

4.2. Synthesis of silyl enol ether 3a–3g

To a solution of arylcyanocuprates reagents **2a**–**2g** (2 mmol) at −78 °C was added a solution of enol silyl ether epoxides **1** (1 mmol) in dry THF (2 mL) by cannula under argon. The reaction mixture was allowed to warm to −10 °C to 0 °C for 3 h. Ether was added, and the organic phase was washed with saturated aqueous NH_4Cl, dried ($NaSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using first 30:1 petroleum ether/EtOAc and then 10:1 petroleum ether/EtOAc, gave **3a**–**3g** as a colorless oil.

4.3. Synthesis of β-hydroxy ketone 4a–4g

To a solution of silyl enol ethers **3a**–**3g** in MeOH was added KF, and the mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and water was added. The resulting mixture was extracted with EtOAc (3×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (petroleum/EtOAc, 5:1) afforded **4a**–**4g** as a colorless oil.

4.3.1. (2*S*,3*R*,5*S*,6*S*)-3-Hydroxy-2-methyl-6-phenyl-5-(prop-1-en-2-yl)cyclohexanone 4a (Table 1, entry 1). $[\alpha]_D^{25}$ −35 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.31 (m, 3H), 7.00 (d, *J*=7.8 Hz, 2H), 4.61 (s, 2H), 3.50–3.59 (m, 2H), 2.53–2.69 (m, 2H), 2.51 (m, 1H), 2.17–2.24 (m, 1H), 2.01 (q, *J*=12.0 Hz, 1H), 1.57 (s, 3H), 1.17 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 144.4, 136.3, 129.3, 127.9, 126.8, 113.4, 74.6, 60.1, 53.7, 46.9, 40.6, 18.4, 10.7. HRMS calcd for $C_{16}H_{21}O_2$ $[M+H]^+$: 245.1542; found: 245.1545.

4.3.2. (2*S*,3*R*,5*S*,6*S*)-3-Hydroxy-6-(2-methoxyphenyl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4b (Table 1, entry 2). $[\alpha]_D^{25}$ −40 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (td, *J*=6.9, 2.4 Hz, 1H), 6.83–6.97 (m, 3H), 4.60 (t, *J*=1.8 Hz, 2H), 4.00 (d, *J*=11.7 Hz, 1H), 3.75 (s, 3H), 3.60 (t, *J*=10.5 Hz, 1H), 2.79 (td, *J*=12.3, 3.3 Hz, 1H), 2.50–2.60 (m, 1H), 2.17–2.26 (m, 2H), 2.00 (q, *J*=12.0 Hz, 1H), 1.59 (s, 3H), 1.20 (d, *J*=6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.9, 157.0, 145.1, 130.1, 127.9, 125.3, 120.2, 112.6, 110.4, 74.5, 55.3, 53.6, 45.3, 40.7, 18.4, 10.8. HRMS calcd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1648; found: 275.1646.

4.3.3. (2*S*,3*R*,5*S*,6*S*)-3-Hydroxy-6-(4-methoxyphenyl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4c (Table 1, entry 3). $[\alpha]_D^{25}$ −32 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, *J*=9.0 Hz, 2H), 6.83 (d, *J*=9.0 Hz, 2H), 4.62 (s, 2H), 3.77 (s, 3H), 3.53 (d, *J*=12.9 Hz, 2H), 2.51–2.64 (m, 3H), 2.17–2.23 (m, 1H), 2.03 (q, *J*=12.0 Hz, 1H), 1.57 (s, 3H), 1.17 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 158.3, 144.6, 130.2, 128.4, 113.4, 74.6, 59.3, 55.0, 53.7, 47.1, 40.6, 18.4, 10.7. HRMS calcd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1648; found: 275.1651.

4.3.4. (2*S*,3*R*,5*S*,6*S*)-3-Hydroxy-6-(2,6-dimethoxyphenyl)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4d (Table 1, entry 4). $[\alpha]_D^{25}$ −28 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (t, *J*=6.4 Hz, 1H), 6.51 (d, *J*=7.5 Hz, 2H), 4.45 (d, *J*=11.1 Hz, 2H), 4.09 (d, *J*=12.3 Hz, 1H), 3.72 (s, 6H), 3.10 (td, *J*=12.6, 3.3 Hz, 1H), 2.31–2.38 (m, 1H), 2.25 (d, *J*=4.2 Hz, 1H), 2.15 (dt, *J*=12.9, 3.6 Hz, 1H), 2.03 (q, *J*=12.0 Hz, 1H), 1.88 (s, 1H), 1.63 (s, 3H), 1.24 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 158.1, 146.0, 128.0, 115.3, 111.5, 104.5, 103.7, 73.9, 55.6, 53.2, 49.2, 43.9, 40.2, 17.9, 11.2. HRMS calcd for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1754; found: 305.1753.

4.3.5. (2*S*,3*R*,5*S*,6*S*)-3-Hydroxy-2-methyl-5-(prop-1-en-2-yl)-6-(4-styrylphenyl)cyclohexanone 4f (Table 1, entry 6). $[\alpha]_D^{25}$ −26 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J*=8.0 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 7.36 (t, *J*=8.0 Hz, 2H), 7.25 (td, *J*=8.4, 0.8 Hz 1H), 7.08 (s, 2H), 7.00 (d, *J*=8.4 Hz, 2H), 4.63 (q, *J*=1.6 Hz, 2H), 3.57–3.61 (m, 2H), 2.57–2.66 (m, 2H), 2.22–2.26 (m, 2H), 2.03 (q, *J*=12.0 Hz, 1H), 1.59 (s, 3H), 1.20 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 144.3, 137.4, 135.9, 135.9, 129.7, 128.6, 128.5, 128.3, 127.5, 126.4, 126.2, 113.6, 74.7, 59.9, 53.8, 47.0, 40.6, 18.5, 10.7. HRMS calcd for $C_{24}H_{27}O_2$ $[M+H]^+$: 347.2012; found: 347.2010.

4.3.6. (2*S*,3*S*,5*R*,6*S*)-2-(2,6-Bis(methoxymethoxy)-4-styrylphenyl)-5-hydroxy-6-methyl-3-(prop-1-en-2-yl)cyclohexanone 4g (Table 1, entry 7). $[\alpha]_D^{25}$ −24 (*c* 1.0, $CHCl_3$); IR (KBr) 3463 (–OH), 2932, 1707, 1603, 1576, 1450, 1037, 922, 823, 753, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J*=7.2 Hz, 2H), 7.35 (t, *J*=7.6 Hz, 2H), 7.25 (t, *J*=7.6 Hz, 1H), 7.08 (s, 2H), 6.97 (s, 2H), 5.08–5.19 (m, 4H), 4.54 (d, *J*=12.0 Hz, 2H), 4.09 (d, *J*=12.0 Hz, 1H), 3.72 (td, *J*=10.8, 4.0 Hz, 1H), 3.46 (s, 6H), 3.13 (td, *J*=12.4, 3.6 Hz, 1H), 2.38–2.42 (m, 1H), 2.20 (dt, *J*=12.4, 3.6 Hz, 1H), 2.06 (d, *J*=4.8 Hz, 1H), 1.99 (q, *J*=12.0 Hz, 1H), 1.69 (s, 3H), 1.26 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 156.5, 155.9, 145.5, 137.6, 137.2, 128.7, 128.6, 127.5, 126.4, 116.4, 112.1, 106.2, 95.2, 94.6, 73.8, 56.0, 53.2, 49.7, 44.0, 40.1, 18.4, 11.2. HRMS calcd for $C_{28}H_{38}NO_6$ $[M+NH_4]^+$: 484.2699; found: 484.2694.

4.4. Compound 5

To a solution of **4g** (1.23 g, 2.64 mmol) and imidazole (360 mg, 5.28 mmol) in dry DMF (2 mL) at room temperature were added TBSCl (480 mg, 3.17 mmol) and DMAP (cat.), and stirred for 3 h. The reaction mixture was then diluted with ether, washed with water and brine. The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 15:1) afforded **5** (1.43 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ −27 (*c* 1.0, $CHCl_3$); IR (KBr) 3399, 2931, 2856, 1713, 1603, 1467, 1450, 1253, 1038, 837, 775, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J*=8.0 Hz, 2H), 7.35 (t, *J*=8.0 Hz, 2H), 7.23–7.27 (m, 1H), 7.05 (d, *J*=1.6 Hz, 2H), 6.97 (d, *J*=3.2 Hz, 2H), 5.10–5.19 (m, 4H), 4.54 (d, *J*=4.0 Hz, 2H), 4.11 (d, *J*=11.6 Hz, 1H), 3.68 (td, *J*=10.4, 4 Hz, 1H), 3.49 (s, 3H), 3.46 (s, 3H), 3.11 (td, *J*=12.4, 3.6 Hz, 1H), 2.43–2.47 (m, 1H), 1.99–2.12 (m, 2H), 1.70 (s, 3H), 1.19 (d, *J*=6.8 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 156.5, 156.1, 145.9, 137.6, 137.3, 128.8, 128.6, 127.5, 126.5, 116.7, 111.9, 106.5, 106.3, 95.2, 94.8, 74.6, 56.1, 56.0, 53.9, 49.9, 44.0, 40.9, 25.8, 18.4, 18.0, 11.8, −4.4, −4.7. HRMS calcd for $C_{34}H_{52}NO_6Si$ $[M+NH_4]^+$: 598.3606; found: 598.3602.

4.5. Compound 6

(1) To a slurry solution of compound **5** (0.72 g, 1.24 mmol) in dry THF (5 mL) at −30 °C was added slowly a solution of $LiAlH_4$ (51.8 mg, 1.36 mmol) in THF. The reaction mixture was then stirred at this point for 1 h, judged by TLC. H_2O (1 mL) was added carefully. The resulting slurry was filtered off and washed with EtOAc (100 mL). The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 10:1) afforded the alcohol (0.51 g, 70%) as a white amorphous solid. $[\alpha]_D^{25}$ −6 (*c* 1.0, $CHCl_3$); IR (KBr) 3506, 2903, 1602, 1571, 1466, 1451, 1251, 1039, 922, 840, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J*=8.4 Hz, 2H), 7.36 (t, *J*=8.0 Hz, 2H), 7.24–7.28 (m, 1H), 7.07 (d, *J*=16.4 Hz, 1H), 7.02 (d, *J*=16.4 Hz, 1H), 6.98 (d, *J*=8.0 Hz, 2H), 5.18–5.28 (m, 4H), 4.58 (s, 1H), 4.48 (d, *J*=1.2 Hz, 1H), 3.76 (t, *J*=9.6 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 3.42 (t, *J*=10.8 Hz, 2H), 3.03 (td, *J*=12.0, 2.8 Hz, 1H), 1.87 (dt, *J*=12.0, 4.0 Hz, 1H), 1.51–1.67(m, 6H), 1.18 (d, *J*=6.4 Hz, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 157.2, 147.3, 137.5, 137.2, 128.8, 128.6, 128.5, 127.6, 126.5, 117.9, 110.6, 107.1, 106.6, 95.7, 94.6, 74.6, 74.4, 56.3, 56.2, 48.2, 46.0, 42.8, 41.7, 25.9, 18.7, 18.1, 15.2, −4.0, −4.6. HRMS calcd for $C_{34}H_{54}NO_6Si$ $[M+NH_4]^+$: 576.3763; found: 576.3760.

(2) To a solution of this alcohol (0.51 g, 0.87 mmol) in dry THF (6 mL) at room temperature was added NaH (57% suspension in mineral oil, 109 mg, 2.18 mmol) under an argon atmosphere. The reaction mixture was stirred for 30 min before CS_2 (1.5 mL) was introduced into the flask and was

heated to 50 °C for 2 h. Then, MeI (0.54 mL, 8.7 mmol) was added and stirred for another 5 h. After cooling to ambient temperature, the reaction mixture was filtered and concentrated. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 50:1) afforded the xanthate ester (0.54 g, 93%) as a yellow oil. $[\alpha]_D^{25}$ +23 (*c* 1.0, $CHCl_3$); IR (KBr) 3388, 2953, 2930, 1602, 1574, 1466, 1220, 1044, 839, 774, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=8.0 Hz, 2H), 7.34 (t, *J*=8.0 Hz, 2H), 7.22–7.27 (m, 1H), 7.04 (d, *J*=16.0 Hz, 1H), 6.98 (d, *J*=16.0 Hz, 1H), 6.90 (s, 2H), 6.26 (t, *J*=10.4 Hz, 1H), 5.17–5.28 (m, 4H), 4.66 (s, 1H), 4.53 (d, *J*=1.2 Hz, 1H), 3.71 (t, *J*=10.8 Hz, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.51 (m, 1H), 3.18 (td, *J*=13.0, 2.8 Hz, 1H), 2.35 (s, 3H), 1.91 (m, 2H), 1.62–1.70 (m, 4H), 1.06 (d, *J*=6.4 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.7, 157.9, 156.9, 146.6, 137.4, 137.2, 128.8, 128.6, 128.3, 127.4, 126.4, 116.0, 111.2, 106.3, 106.1, 95.5, 95.3, 86.0, 73.9, 56.3, 56.2, 47.1, 42.7, 42.5, 41.4, 25.8, 18.7, 18.5, 18.0, 15.1, −4.0, −4.7. HRMS for $C_{36}H_{53}O_6S_2Si$ $[M+H]^+$: 673.3054; found: 673.3051.

(3) To a solution of the xanthate ester (0.45 g, 0.67 mmol) in dry toluene (2 mL) at room temperature were sequentially added AIBN (cat.) and *n*-Bu_3SnH (neat, 0.45 mL, 2.68 mmol) under an argon atmosphere. The mixture was carefully deoxygenated by bubbling argon through it for 30 min. The reaction flask was then immersed into a preheated oil bath (90 °C) and the mixture was stirred at this temperature for 30 min. After cooling to ambient temperature, the solvent was evaporated. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 30:1) afforded **6** (342 mg, 90%) as a white amorphous solid. $[\alpha]_D^{25}$ −3 (*c* 1.0, $CHCl_3$); IR (KBr) 3363, 2952, 2928, 1602, 1571, 1452, 1253, 1043, 924, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.54 (m, 2H), 7.31–7.39 (m, 2H), 7.22–7.27 (m, 1H), 7.06 (s, 2H), 6.94 (d, *J*=10.8 Hz, 2H), 5.17–5.27 (m, 4H), 4.58 (s, 1H), 4.46 (s, 1H), 3.57 (s, 3H), 3.54 (s, 3H), 3.30–3.53 (m, 2H), 3.07 (t, *J*=11.2 Hz, 1H), 1.50–1.89 (m, 1H), 1.74–11.77 (m, 1H), 1.51–1.64 (m, 6H), 0.97 (d, *J*=6.4 Hz, 3H), 0.90 (m, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 155.8, 148.5, 137.3, 136.4, 128.7, 128.6, 128.3, 127.4, 126.4, 122.1, 110.0, 106.6, 95.3, 94.6, 77.0, 56.1, 46.4, 42.3, 40.9, 38.0, 37.4, 25.9, 19.1, 18.9, 18.1, −3.9, −4.6. HRMS calcd for $C_{34}H_{51}O_5Si$ $[M+H]^+$: 567.3507; found: 567.3500.

4.6. Compound 7

To a solution of protected **6** (1.39 g, 1.25 mmol) in dry THF (10 mL) was added TBAF (1.16 g). The reaction mixture was stirred at ambient temperature for 12 h. The organic solution was concentrated in vacuo and purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 5:2) afforded the alcohol **7** (1.25 g, 98%) as a white amorphous solid. $[\alpha]_D^{25}$ +10 (*c* 1.0, $CHCl_3$); IR (KBr) 3396, 2950, 2926, 1601, 1571, 1449, 1152, 1040, 921, 824, 732, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J*=8.0 Hz, 2H), 7.34 (t, *J*=8.0 Hz, 2H), 7.24 (t, *J*=6.8 Hz, 1H), 7.06 (d, *J*=2.8 Hz, 2H), 6.94 (s, 2H), 5.17–5.28 (m, 4H), 4.57 (s, 1H), 4.46 (s, 1H), 3.55 (s, 3H), 3.48 (s, 3H), 3.35–3.40 (m, 2H), 3.13 (t, *J*=12.0 Hz, 1H), 1.99 (dt, *J*=12.0, 3.2 Hz, 1H), 1.78 (q, *J*=12.0 Hz, 1H), 1.46–1.69 (m, 7H), 1.05 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.8, 148.1, 137.3, 136.5, 128.6, 128.3, 127.5, 126.4, 121.7, 110.2, 106.6, 106.5, 95.2, 94.6, 76.3, 56.1, 56.1, 46.2, 41.8, 40.6, 37.9, 37.3, 18.9, 18.3. HRMS calcd for $C_{28}H_{40}NO_5$ $[M+NH_4]^+$: 470.2949; found: 470.2943.

4.7. Compound 8

(1) To a solution of **7** (210 mg, 0.46 mmol) and triethylamine (0.13 mL, 0.93 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added MsCl (0.06 mL, 0.70 mmol) and stirred for 5 min. The reaction was then quenched with water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and evaporate to dryness. Purification of the residue through column chromatography on silica gel (petroleum/EtOAc, 5:2) afforded methyl sulfonated compound (238 mg, 97%) as a white amorphous solid. $[\alpha]_D^{25}$ −7 (*c* 1.0, $CHCl_3$); IR (KBr) 3372, 2925, 1733, 1602, 1450, 1354, 1172, 1039, 920, 823, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J*=7.6 Hz, 2H), 7.34 (t, *J*=7.6 Hz, 2H), 7.22–7.27 (m, 1H), 7.04 (d, *J*=16.0 Hz, 1H), 6.98 (d, *J*=16.0 Hz, 1H), 6.95 (d, *J*=12.0 Hz, 2H), 5.20–5.26 (m, 4H), 4.59 (s, 1H), 4.50 (s, 1H), 4.46 (s, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 3.39 (t, *J*=8.4 Hz, 1H), 3.17 (t, *J*=12.0 Hz, 1H), 3.05 (s, 3H), 2.26 (d, *J*=12.0 Hz, 1H), 1.71–1.91 (m, 4H), 1.53 (s, 3H), 1.04 (d, *J*=5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 155.8, 146.8, 137.2, 136.8, 128.6, 128.5, 127.5, 126.5, 120.5, 111.1, 106.5, 95.2, 94.6, 87.4, 56.2, 56.1, 45.8, 39.3, 38.9, 38.1, 37.4, 36.9, 18.8, 18.5. HRMS calcd for $C_{29}H_{42}NO_7S$ $[M+NH_4]^+$: 548.2682; found: 548.2724.

(2) To a solution of this methyl sulfonated compound (0.753 mg, 1.42 mmol) in dry ether (3 mL) was added lithium aluminum hydride (0.267 mg, 5.68 mmol) under argon. This mixture was stirred at the reflux temperature for 8 h, cooled, and treated with saturated ammonium chloride solution. The inorganic solids were separated by filtration and washed with ether (5×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc, 50:1) afforded **8** (495 mg, 80%) as a white amorphous solid. $[\alpha]_D^{25}$ +13 (*c* 1.0, $CHCl_3$); IR (KBr) 3386, 2948, 2920, 1901, 1571, 1449, 1152, 1041, 923, 823, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J*=8.0 Hz, 2H), 7.33 (t, *J*=8.0 Hz, 2H), 7.25 (m, 1H), 7.05 (s, 2H), 6.96 (d, *J*=4.4 Hz, 2H), 5.20–5.28 (m, 4H), 4.59 (d, *J*=2.4 Hz, 1H), 4.46 (d, *J*=1.2 Hz, 1H), 3.57 (s, 3H), 3.52 (s, 3H), 3.37 (td, *J*=11.2, 4.0 Hz, 1H), 2.96 (td, *J*=12.0, 3.6 Hz, 1H), 1.62–1.82 (m, 5H), 1.59 (s, 3H), 1.46 (qd, *J*=13.2, 3.2 Hz, 1H), 1.12 (qd, *J*=9.2, 3.6 Hz, 1H), 0.94 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 155.7, 149.7, 137.4, 136.2, 128.8, 128.6, 128.1, 127.4, 126.4, 123.1, 109.5, 106.6, 95.2, 94.6, 56.1, 56.0, 47.6, 39.4, 38.4, 35.4, 33.3, 33.2, 22.6, 19.2. HRMS calcd for $C_{28}H_{40}NO_4$ $[M+NH_4]^+$: 454.3000; found: 454.2996.

4.8. (+)-Machaeridiol B

To a solution of compound **8** (55 mg, 0.126 mmol) in CH_3CN/CH_2Cl_2 (2:1) at 0 °C was added NaI (299 mg, 1.89 mmol) and $AlCl_3$ (253 mg, 1.89 mmol). As soon as compound **8** disappeared, the reaction was quenched with

ice water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification of the residue through column chromatography on silica gel (petroleum/EtOAc, 4:1) afforded (+)-Machaeridiol B (22 mg, 50%) as a yellow amorphous solid. $[\alpha]_D^{25}$ +14.5 (*c* 0.53, MeOH) {lit.[2] $[\alpha]_D^{25}$ +17.8 (*c* 0.53, MeOH)}; IR (KBr) 3386, 2919, 2851, 1612, 1578, 1449, 1424, 1370, 1254, 1117, 1020, 960, 749 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 8.10 (s, 2H), 7.50–7.51 (m, 2H), 7.31–7.35 (m, 2H), 7.21–7.25 (m, 1H), 6.96 (m, 2H), 6.58 (d, *J*=1.6 Hz, 1H), 6.53 (d, *J*=1.6 Hz, 1H), 4.65 (d, *J*=2.0 Hz, 1H), 4.37 (m, 1H), 3.34 (m, 1H), 3.14 (m, 1H), 1.78–1.86 (m, 1H), 1.74–1.78 (m, 1H), 1.67–1.72 (m, 1H), 1.61(s, 3H), 1.58 (m, 1H), 1.41–1.54 (m, 2H), 1.05–1.45 (m, 1H), 0.91 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 158.2, 156.6, 150.7, 138.6, 136.5, 129.9, 129.5, 128.1, 128.1, 127.2, 119.6, 109.9, 107.1, 106.2, 48.0, 40.0, 38.9, 36.2, 34.2, 34.0, 23.03, 19.5. HRMS calcd for $C_{24}H_{27}O_2$ $[M-H]^+$: 347.2011; found: 347.2017.

4.9. (+)-Machaeriol B

To a solution of compound **8** (55 mg, 0126 mmol) in CH_3CN/CH_2Cl_2 (2:1) at 0 °C were added NaI (299 mg, 1.89 mmol) and $AlCl_3$ (253 mg, 1.89 mmol), and the resulting mixture was stirred for another 5 min. The reaction was quenched with ice water and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification of the residue through column chromatography on silica gel (petroleum/EtOAc 5:1) afforded (+)-Machaeriol B (40 mg, 90%) as a yellow amorphous solid. $[\alpha]_D^{25}$ +116 (*c* 0.36, MeOH) {lit.[2] $[\alpha]_D^{25}$ +115.4 (*c* 0.39, MeOH)}; IR (KBr) 3381, 2865–2976, 1614, 1509, 1451, 1420, 1355, 1323, 1267, 1138, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.0 Hz, 2H), 7.33 (t, *J*=8 Hz, 2H), 7.24 (t, *J*=7.2 Hz, 1H), 6.98 (d, *J*=16.0 Hz, 1H), 6.89 (d, *J*=16.0 Hz, 1H), 6.62 (d, *J*=1.2 Hz, 1H), 6.40 (d, *J*=1.2 Hz, 1H), 5.15 (s, 1H), 3.08 (d, *J*=13.6 Hz, 1H), 2.51 (td, *J*=9.8, 2.4 Hz, 1H), 1.84–1.87 (m, 2H), 1.64–1.66 (m, 1H), 1.50 (t, *J*=9.6 Hz, 1H), 1.41 (s, 3H), 1.12 (s, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 0.80 (q, *J*=12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 155.1, 137.3, 136.7, 128.6, 128.5, 128.1, 127.5, 126.5, 113.0, 108.5, 105.6, 77.2, 49.0, 38.8, 35.6, 35.4, 32.8, 28.0, 27.7, 22.6, 19.0. HRMS calcd for $C_{24}H_{27}O_2$ $[M-H]^+$: 347.2017; found: 347.2017.

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References and notes

1. For natural tetrahydrocannabinol (THC), see: (a) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646; (b) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1971**, *93*, 217; For natural cannabidiol (CBD), see: (c) Mechoulam, R.; Shvo, Y. *Tetrahedron* **1963**, *19*, 2073; (d) Mechoulam, R.; Gaoni, Y. *Tetrahedron Lett.* **1967**, 1109; For nonnatural hexahydrocannabinol (HHC), see: (e) Edery, H.; Grunfeld, Y.; Ben-Zvi, Z.; Mechoulam, R. *Ann. N.Y. Acad. Sci.* **1971**, *191*, 40; (f) Mechoulam, R.; Lander, N.; Varkony, T. H.; Kimmel, I.; Becker, O.; Ben-Zvi, Z. *J. Med. Chem.* **1980**, *23*, 1068.
2. Muhammad, I.; Li, X. C.; Jacob, M. R.; Tekwani, B. L.; Dunbar, D. C.; Ferreira, D. *J. Nat. Prod.* **2003**, *66*, 804.
3. For total syntheses of THC and CBD, see: (a) Razdan, R. K. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, NY, 1981; Vol. 4, pp 185–262; (b) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 1; (c) Childers, W. E.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276; (d) Crombie, L.; Crombie, W. M. L.; Jamieson, S. V.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1243; (e) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193; (f) Crombie, L.; Crombie, W. M. L.; Palmer, C. J.; Jamieson, S. V. *Tetrahedron Lett.* **1983**, *24*, 3129; (g) Rickards, R. W.; Ronnenberg, H. *J. Org. Chem.* **1984**, *49*, 572; (h) Baek, S.-H.; Srebnik, M.; Mechoulam, R. *Tetrahedron Lett.* **1985**, *26*, 1083; (i) Vaillancourt, V.; Albizati, K. F. *J. Org. Chem.* **1992**, *57*, 3627; For total syntheses of HHC, see: (j) Tietze, L.-F.; Kiedrowski, G. v.; Berger, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 221; (k) Lu, Z.; Sato, N.; Inoue, S.; Sato, K. *Chem. Lett.* **1992**, 1237; (l) Casiraghi, G.; Cornia, M.; Casnati, G.; Fava, G. G.; Belicchi, M. F. *J. Chem. Soc., Chem. Commun.* **1986**, 271; (m) Cornia, M.; Casiraghi, G.; Casnati, G.; Zetta, L. *Gazz. Chim. Ital.* **1989**, *119*, 329; (n) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671; (o) Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695; (p) Wang, T.; Burgess, J. P.; Reggio, P. H.; Seltzman, H. H. *Synth. Commun.* **2000**, *30*, 1431.
4. 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.
5. For a review on S_N2' reaction, see: (a) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503; For recent references on 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.; Lafrenière, 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.
6. (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.
7. (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 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.

8. (a) Corey, E. J.; Venkateswalu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190; (b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429; (c) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095.
9. Paquette, L. A.; Fischer, J. W.; Browne, A. R.; Doecke, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 686.
10. (a) Ireland, R. E.; Vaarney, M. D. *J. Org. Chem.* **1986**, *51*, 6350; (b) Monti, H.; Léandri, G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021; (c) Ramesh, C.; Ravindranath, N.; Das, B. *J. Org. Chem.* **2003**, *68*, 8146; (d) Mother, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789.