DOI: 10.1002/adsc.201100898

Enantioselective Synthesis of (−)-CP-55940 *via* Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones

Li-Jie Cheng,[a] Jian-Hua Xie,[a,*] Li-Xin Wang,[a] and Qi-Lin Zhou[a,*]

[a] State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
Fax: (+86)-22-2350-6177; e-mail: jhxie@nankai.edu.cn or qlzhou@nankai.edu.cn

Received: November 18, 2011; Published online: April 13, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100898.

Abstract: A new and efficient catalytic asymmetric synthesis of the potent cannabinoid receptor agonist (−)-CP-55940 has been developed by using ruthenium-catalyzed asymmetric hydrogenation of *racemic* α-aryl ketones *via* dynamic kinetic resolution (DKR) as a key step. With $RuCl_2$-SDPs/diamine [SDPs = 7,7′-bis(diarylphophino)-1,1′-spirobiindane] catalysts the asymmetric hydrogenation of *racemic* α-arylcyclohexanones *via* DKR provided the corresponding *cis*-β-arylcyclohexanols in high yields with up to 99.3% *ee* and >99:1 *cis*-selectivities. Both ethylene ketal group at the cyclohexane ring and *ortho*-methoxy group at the phenyl ring of the substrates **6** have little effect on the selectivity and reactivity of the hydrogenations. Based on this highly efficient asymmetric ketone hydrogenation, (−)-CP-55940 was synthesized in 13 steps (the longest linear steps) in 14.6% overall yield starting from commercially available 3-methoxybenzaldehyde and 1,4-cyclohexenedione monoethylene acetal.

Keywords: asymmetric synthesis; (−)-CP-55940; dynamic kinetic resolution; hydrogenation; ruthenium

Introduction

Chiral 2,5-disubstituted 1-arylcyclohexane is an important structural motif that can be found in many natural products and biologically active molecules. Examples of bioactive natural products containing these structural units include Machaereol A and B, which are antimalarial hexahydrodibenzopyran derivatives isolated from *Machaerium multiflorum*,[1] the cannabinol-skeletal carbazole alkaloids Murrayamine O and P isolated from *Murraya euchrestifolia*,[2] and the polycyclic cannabinoid Rubranine isolated from *Aniba rosaeodora*[3] (Figure 1). Synthetic potent cannabinoid receptor agonists such as AM-2389,[4] AM-4030[5] and CP-55940[6] also possess such trisubstituted chiral cyclohexanoid cores. Several asymmetric synthetic methods have been developed for the preparation of chiral 2,5-disubstituted 1-arylcyclohexanoids and were applied to the synthesis of related natural or unnatural molecules.[7] However, the construction of this chiral core structure by catalytic asymmetric methods is scarce. In 2005, Iwabuchi et al. reported an asymmetric synthesis of (−)-CP-55940 by using organocatalyzed intramolecular aldolization reaction.[8] With 25 mol% of O-TBDPS-protected *cis*-4-D-proline as catalyst, they obtained the key chiral intermediate of (−)-CP-55940 in moderate yield (68%) with high enantioselectivity and diastereoselectivity (94% *ee* and 99% *de*).

Results and Discussion

Recently, we developed an efficient catalytic enantioselective method for the synthesis of chiral β-substituted cyclic alcohols by ruthenium-catalyzed asymmetric hydrogenation of *racemic* α-substituted cycloalkanones *via* dynamic kinetic resolution (DKR).[9] This allowed us to design a catalytic enantioselective approach to the construction of the chiral 2,5-disubstituted 1-arylcyclohexanoid unit. As a model target molecule, (−)-CP-55940, a potent non-selective cannabinoid (CB) receptor agonist with K_i values of 0.58 and 0.69 nM for human recombinant CB1 and CB2, respectively,[6] was selected to demonstrate this highly efficient catalytic method. The retro-synthetic analysis of (−)-CP-55940 is shown in Figure 2. We envisioned that the hydroxy group directly linked to the cyclo-

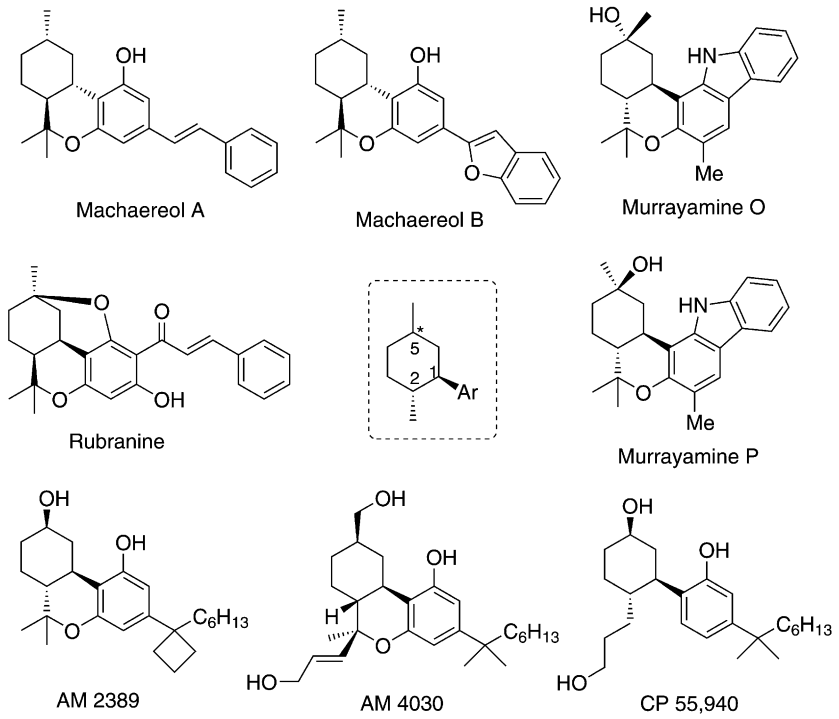


Figure 1. Selected bioactive molecules with chiral 2,5-disubstituted 1-arylcyclohexane unit.

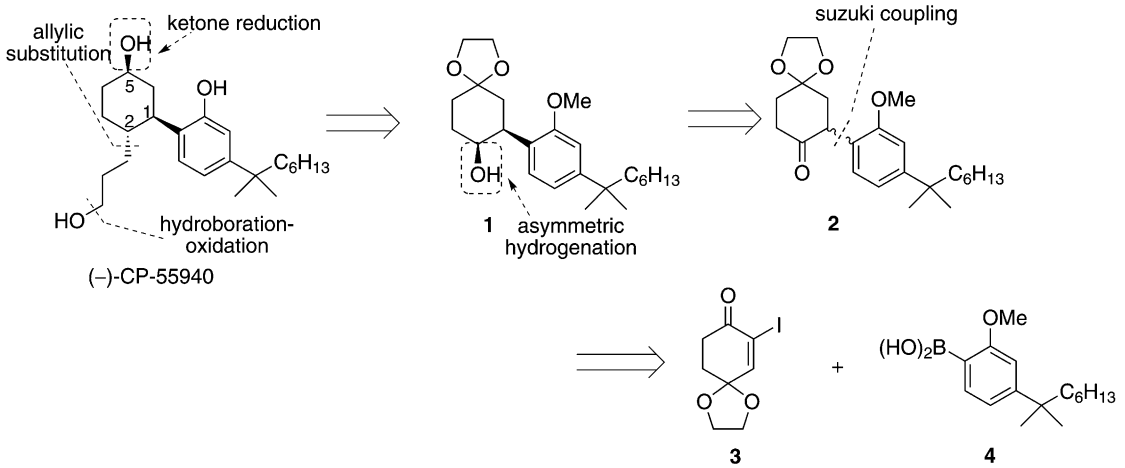
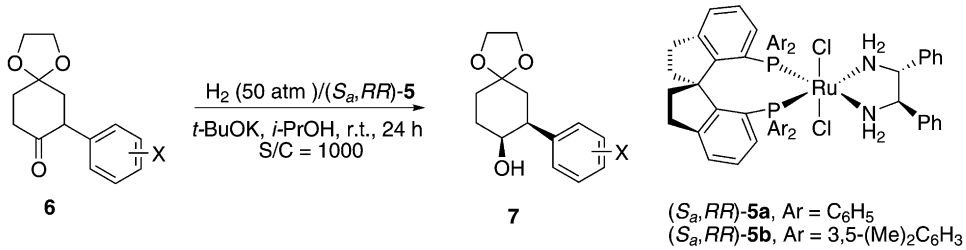


Figure 2. Strategy for the enantioselective synthesis of (−)-CP-55940.

hexane ring of (−)-CP-55940 could be formed *via* the reduction of the corresponding ketone, and the γ-hydroxypropyl group at the 2-position of the ring could be introduced *via* allylic substitution, followed by hydroboration-oxidation reaction. Thus, the chiral *cis*-3-aryl-4-hydroxycyclohexanone ethylene acetal **1**, which can be easily obtained by ruthenium-catalyzed asymmetric hydrogenation of the corresponding *racemic* 2-aryl-1,4-cyclohexanedione monoethylene acetal **2** *via* DKR, will be an ideal chiral intermediate for the enantioselective synthesis of (−)-CP-55940. And the *racemic* α-arylcyclohexanone **2** can be obtained by palladium-catalyzed Suzuki cross-coupling reaction between 2-iodo-1,4-cyclohexanedione monoethylene acetal **3** and arylboronic acid **4**.

Although the ruthenium-catalyzed asymmetric hydrogenation of *racemic* α-arylcycloalkanones *via* DKR has been demonstrated to be a highly efficient approach to chiral *cis*-2-arylcycloalkanols by Noyori[10] and us,[9f] the effects of a bulky ethylene ketal group at the 4-position of the cyclohexane ring and the *ortho*-methoxy group at the phenyl ring of the substrates on the selectivity and reactivity of the hydrogenation were unknown. We tested the asym-

Table 1. Asymmetric hydrogenation of α-aryl-1,4-cyclohexanedione monoethylene acetals **6**.[a]

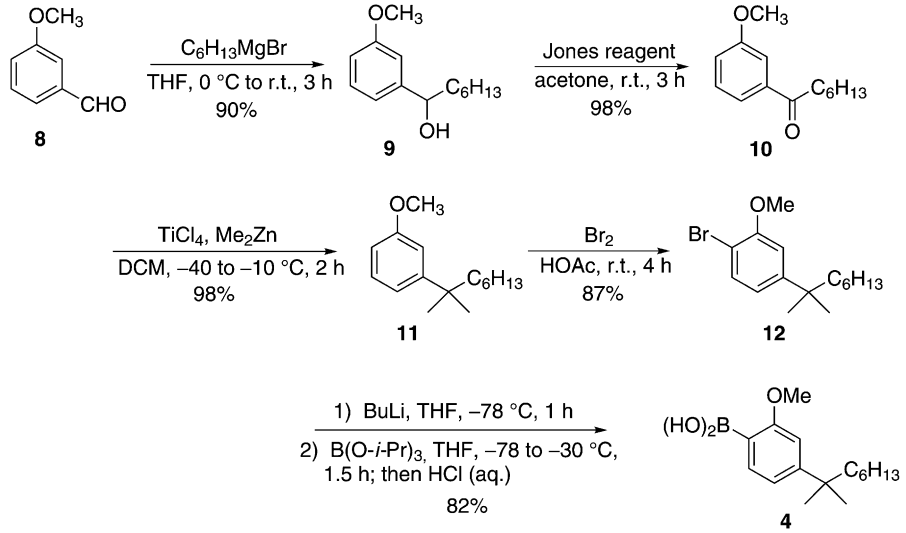


Entry	Catalyst	X	**7**	Yield [%][b]	*cis*/*trans*[c]	*ee* [%][d]
1	(S_a,*RR*)-**5a**	H	**7a**	99	>99/1	97
2	(S_a,*RR*)-**5b**	H	**7a**	99	>99/1	97
3	(S_a,*RR*)-**5a**	2-MeO	**7b**	98	>99/1	96
4	(S_a,*RR*)-**5a**	3,4-(OCH_2O)	**7c**	99	>99/1	99
5	(S_a,*RR*)-**5a**	3,5-$(MeO)_2$	**7d**	99	>99/1	99.3

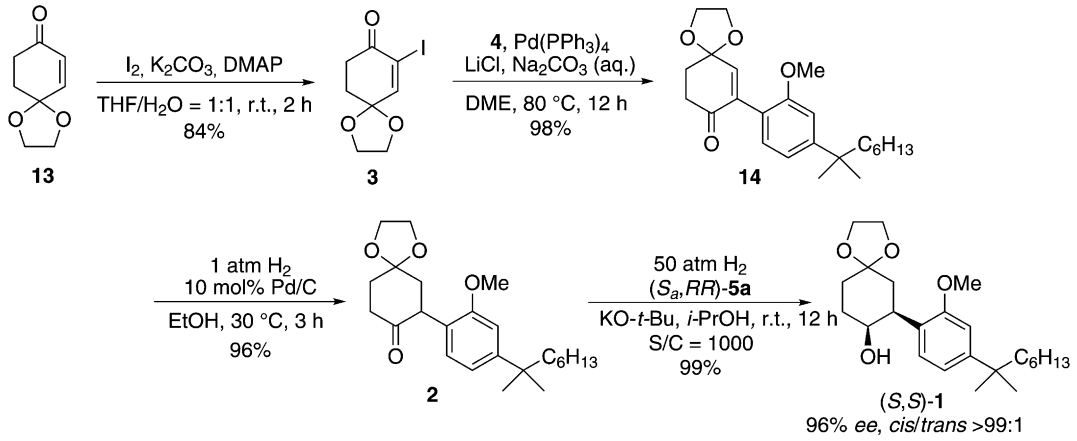
[a] The reactions were performed at 0.2 M of **6**, under 50 atm of H_2, at room temperature (25–30 °C) in *i*-PrOH containing (S_a,*RR*)-**5** (S/C = 1000) and *t*-BuOK ([*t*-BuOK] = 0.04 M) unless otherwise stated. The conversion is 100%.
[b] Isolated yield.
[c] Determined by GC.

metric hydrogenation of several easily obtained *racemic* α-aryl-1,4-cyclohexanedione monoethylene acetals **6**, which are analogues of **2**, with $RuCl_2$-SDPs/diamine catalysts **5**[11] under the general hydrogenation conditions.[9f] Both catalysts (S_a,*RR*)-**5a** and (S_a,*RR*)-**5b** gave high yield, high enantioselectivity (97% *ee*) and excellent *cis*-selectivity (*cis*/*trans* >99:1) (Table 1, entries 1 and 2). With catalyst (S_a,*RR*)-**5a**, the substrates **6c** and **6d** with 3,4-(OCH_2O) and 3,5-$(MeO)_2$ substituents on the phenyl ring were hydrogenated to products **7c** and **7d** in 99% *ee* and 99.3% *ee*, respectively (entries 4 and 5). Furthermore, the 2-methoxy-substituted α-arylcyclohexanone **6b** also gave the corresponding *cis*-product **7b** in excellent yield with 96% *ee* and >99:1 *cis*-selectivity (entry 3). These results indicated that both ethylene ketal group at the cyclohexane ring and *ortho*-methoxy group at the phenyl ring of the substrates have no negative effect on the selectivity and reactivity of the hydrogenation.

This finding encouraged us to synthesize (−)-CP-55940 by using ruthenium-catalyzed enantioselective hydrogenation of compound **2**. The *racemic* α-arylcyclohexanone **2** was prepared from arylboronic acid **4**, which can be obtained easily from bromide **12** (Scheme 1). Although the synthesis of aryl bromide **12** has been reported,[8,12] the shortcoming of low yield of the previous methods prompted us to develop an alternative route. Starting with 3-methoxybenzaldehyde (**8**) we prepared aryl bromide **12** in 74% overall yield in 4 steps including a direct geminal dialkyla-



Scheme 1. Synthesis of arylboronic acid **4**.

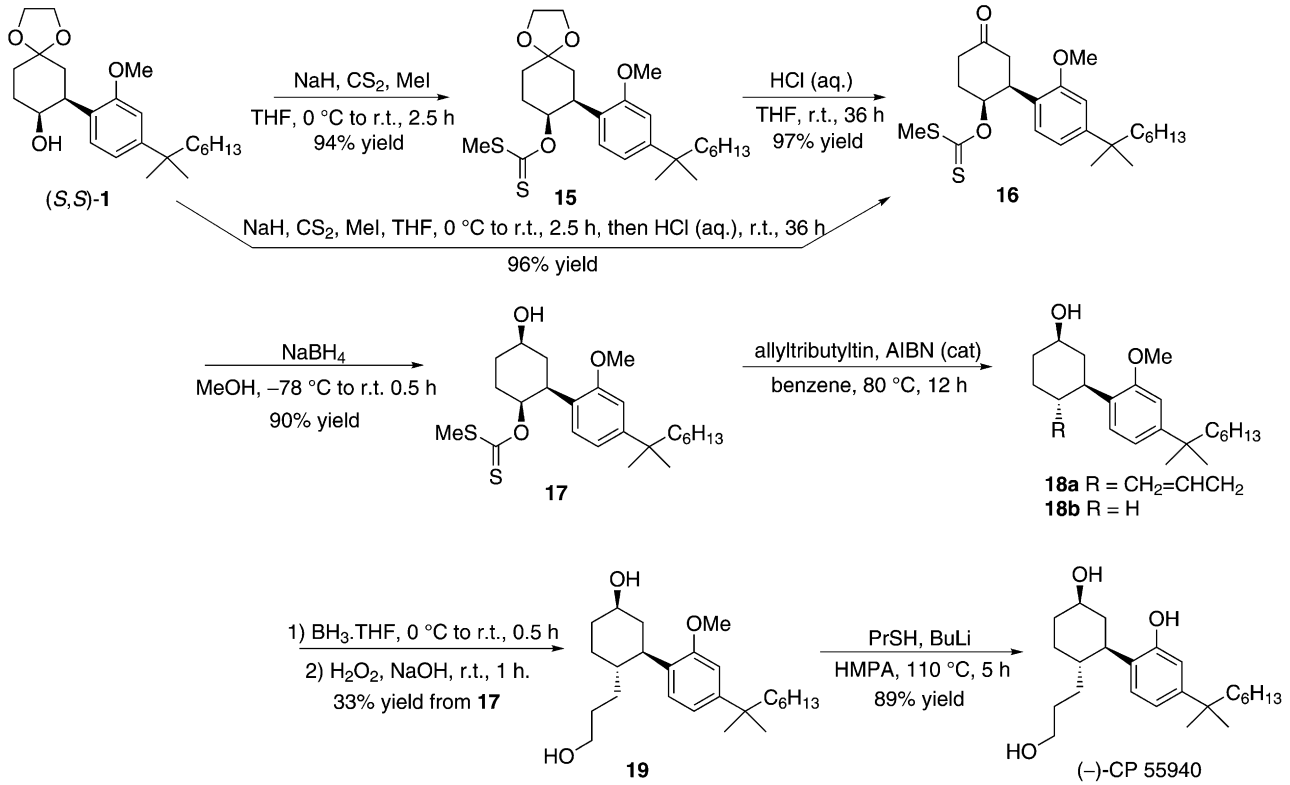


Scheme 2. Preparation and asymmetric hydrogenation of *racemic* α-arylcycloalkanone **2**.

tion reaction.[13] The aryl bromide **12** was then treated with *n*-butyllithium (1.3 equiv.) in THF at −78 °C, followed by triisopropyl borate (2.0 equiv.) and hydrochloric acid (1 N) to yield arylboronic acid **4** in 82% yield.[14]

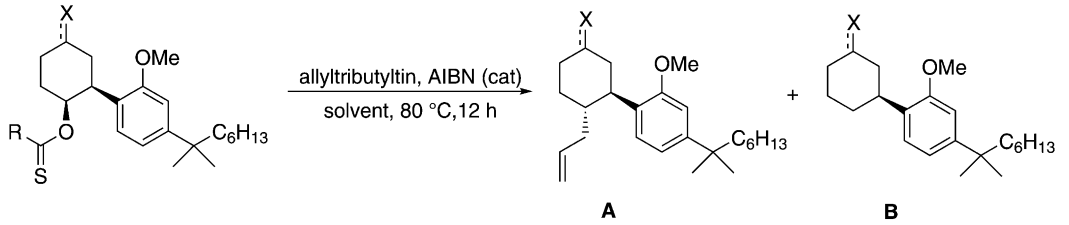
With arylboronic acid **4** at hand, we tried to prepare *racemic* α-arylcyclohexanone **2** (Scheme 2). The commercially available 1,4-cyclohexenedione monoethylene acetal **13** was treated with iodine under basic conditions to yield the corresponding iodo-substituted cyclohexenone **3** in 84% yield.[15] The Suzuki cross-coupling of iodo-substituted cyclohexenone **3** with arylboronic acid **4** catalyzed by $Pd(PPh_3)_4$[16] proceeded to afford α-arylcyclohexenone **14** in excellent yield (98%). The α-arylcyclohexenone **14** was hydrogenated over Pd-C to *racemic* α-arylcyclohexanone **2** in 96% yield. Asymmetric hydrogenation of *racemic* α-arylcyclohexanone **2** catalyzed by (S_a,*RR*)-**5a** under 50 atm H_2 produced alcohol (*S*,*S*)-**1** in 99% yield with 96% *ee* and >99:1 *cis*-selectivity.

Having successfully realized the preparation and highly efficient asymmetric hydrogenation of *racemic*



Scheme 3. Synthesis of (−)-CP-55940.

Table 2. Free radical allylation with allyltributyltin.[a]



Entry	X	R	SM[b]	Solvent	Conversion [%][c]	Selectivity[c] **A**/**B**	Yield [%][d]
1	$(CH_2O)_2$	SMe	**15a**	toluene	100	1/1.2	60
2	$(CH_2O)_2$	OPh	**15b**	toluene	100	1/1.2	53
3	$(CH_2O)_2$	OC_6F_5	**15c**	toluene	64	1/1.2	35
4	$(CH_2O)_2$	Im[e]	**15d**	toluene	80	1/1.4	32
5	$(CH_2O)_2$	SMe	**15a**	benzene	100	1.1/1	66
6	O	SMe	**16**	benzene	100	2.4/1	20
7	H, OH	SMe	**17**	benzene	100	1.6/1	80

[a] *Reaction conditions:* substrate/allyltributyltin/AIBN = 1:5:0.5, 80 °C, 12 h.
[b] SM = starting material.
[c] Determined by ^{1}H NMR.
[d] Isolated yield.
[e] Im = imidazole.

α-arylcycloalkanone **2**, we next turned our attention to the transformation of (*S*,*S*)-**1** (96% *ee*) to (−)-CP-55940. Treatment of (*S*,*S*)-**1** with NaH, CS_2 and MeI in THF at 0 °C to room temperature[17] for 2.5 h, followed by deprotection with hydrochloric acid and reduction with sodium borohydride afforded a single isomer of *cis*,*cis*-product **17** in good yield (84% yield with three steps or 86% yield with two steps, Scheme 3). Subsequent radical substitution of **17** with allyltributyltin in benzene in the presence of azobis(isobutyronitrile) (AIBN) at 80 °C for 12 h gave a mixture of desired product **18a** and deoxygenated product **18b** in 80% yield (**18a**/**18b** = 1.6:1).[18] The separation of **18a** and **18b** was difficult. The mixture was reacted with borane (BH_3·THF) at 0 °C to room temperature for 0.5 h, followed by treatment with 2 N NaOH and H_2O_2 (30%), affording the mixture of **19** and **18b**. Compounds **19** and **18b** were easily separated by column chromatography on silica gel, providing pure **19** and **18b** in 33% and 30% yields, respectively. Finally, demethylation of **19** by PrSLi in hexamethylphosphoramide (HMPA)[19] yielded (−)-CP-55940 in 89% yield. The ^{1}H and ^{13}C NMR spectra and the optical rotation of the synthesized (−)-CP-55940 were identical to those described in the literature.[8]

Before completing the catalytic enantioselective synthesis of (−)-CP-55940, we systematically studied the allylic substitution reaction for the carbon-carbon bond formation. Direct allylic substitution of the hydroxy group of (*S*,*S*)-**1** with allylsilane catalyzed by $InCl_3$ according to Baba's method[20] yielded only a small amount of dehydroxylation product. Other methods including allylic substitution of the tosylate of compound (*S*,*S*)-**1** with allylmagnesium reagents,[21] also gave unsatisfactory results. We finally found that the free radical allylic substitution of xanthate was the method of choice for this transformation.[18] The experiment results listed in Table 2 showed that the methyl xanthate **17** gave the best result (**18a**/**18b**, 1.6:1, 80% yield, entry 7).

Conclusions

In summary, we have accomplished the efficient catalytic enantioselective synthesis of the potent cannabinoid receptor agonist (−)-CP-55940, which contains a chiral 2,5-disubsituted 1-arylcyclohexanoid unit, in 14.6% overall yield over 13 steps (the longest linear steps) from commercially available 3-methoxybenzaldehyde *via* a ruthenium-catalyzed asymmetric ketone hydrogenation as a key step.

Experimental Section

General Remarks

All reactions and manipulations which are sensitive to moisture or air were performed in an argon-filled glovebox (VAC DRI-LAB HE 493) or by using standard Schlenk techniques. Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin. Chemical reagents such as borane, dimethylzinc and allyltributyltin were purchased from Aldrich or Alfa Aesar chemical company. Anhydrous THF, Et_2O, toluene and benzene was distilled from sodium benzophenone ketyl. Anhydrous *i*-PrOH and CH_2Cl_2 were freshly dis-

tilled from calcium hydride. Melting points were measured on a RY-I apparatus and uncorrected. NMR spectra were recorded with a Bruker AV 400 spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Chemical shifts are reported in ppm downfield from internal Me_4Si. Optical rotations were determined using a Perkin–Elmer 341 MC polarimeter. High resolution mass spectra (HR-MS) were recorded on an IonSpec FT-ICR mass spectrometer with an electron spray ionization (ESI) source. HPLC analyses were determined using a Hewlett Packard Model HP 1100 Series chromatography.

Preparation of Arylboronic Acid 4

1-(3-Methoxyphenyl)heptan-1-ol (9): A solution of 3-methoxybenzaldehyde (20.0 g, 0.15 mol) in THF (80 mL) was added slowly to a solution of hexylmagnesium bromide in THF (350 mL) prepared *in situ* from 1-bromohexane (31.3 g, 0.19 mol) and magnesium turnings (4.6 g, 0.19 mol) at 0 °C. After completing the addition, the mixture was allowed to stir at room temperature for 3 h. The reaction mixture was cooled to 0 °C again and treated slowly with hydrochloride acid (1 N, 100 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3×100 mL). The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product. The crude product was purified by distillation to provide the product **9** as a colorless oil; yield: 29.4 g (90%); bp 130 °C/0.5 mm Hg. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, J = 8.1 Hz, 1 H), 6.92–6.90 (m, 2 H), 6.82–6.80 (m, 1 H) , 4.64 (t, J = 6.6 Hz, 1 H), 3.81 (s, 3 H), 1.87 (brs, 1 H), 1.83–1.64 (m, 2 H), 1.50–1.15 (m, 8 H), 0.87 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 146.7, 129.3, 118.2, 112.7, 111.3, 74.4, 55.1, 39.0, 31.7, 29.1, 25.7, 22.5, 14.0; HR-MS (ESI): m/z = 245.1516, calcd. for $C_{14}H_{22}O_2Na$ ([M + Na]$^+$): 245.1512.

1-(3-Methoxyphenyl)heptan-1-one (10): A solution of CrO_3 (16.0 g, 0.16 mol) and sulfuric acid (8.8 mL) in water (32.4 mL) was added dropwise to a solution of 1-(3-methoxyphenyl)heptan-1-ol (**9**) (28.0 g, 0.13 mmol) in acetone (300 mL) at below 5 °C. After completion of the addition, the reaction mixture was allowed to stir at room temperature for 3.0 h. The mixture was then filtered through a pad of Florisil and the filtrate was concentrated under reduced pressure. The residue was treated with 100 mL of ice-cooled water and extracted with diethyl ether (3×200 mL). The combined organic layer was washed with saturated sodium bicarbonate solution and brine successively, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to provide the product **10** as a pale yellow oil; yield: 27.7 g (98%). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.53 (d, J = 7.6 Hz, 1 H), 7.50 (s, 1 H), 7.35 (t, J = 7.9 Hz, 1 H), 7.08 (dd, J = 8.2, 2.0 Hz, 1 H), 3.84 (s, 3 H), 2.94 (t, J = 7.6 Hz, 2 H), 1.72 (m, 2 H), 1.39–1.31 (m, 6 H), 0.89 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 159.7, 138.4, 129.4, 120.6, 119.1, 112.2, 55.2, 38.6, 31.6, 28.9, 24.3, 22.4, 13.9; HR-MS (ESI): m/z = 243.1353, calcd. for $C_{14}H_{20}O_2Na$ ([M + Na]$^+$): 243.1356.

1-(1,1-Dimethylheptyl)-3-methoxybenzene (11):[13b] To a solution of $TiCl_4$ (1.1 mL, 9.5 mmol) in CH_2Cl_2 (18 mL) was added dropwise a solution of dimethylzinc (1.2 M in toluene, 8 mL, 9.5 mmol) at −40 to −50 °C, and the obtained orange solution was stirred at the same temperature for 45 min. A solution of 1-(3-methoxyphenyl)heptan-1-one (**10**) (1.0 g, 4.5 mmol) in CH_2Cl_2 (18 mL) was slowly added at −40 to −50 °C. After completion of the addition, the mixture was allowed to slowly warm to −10 °C over a period of 2 h. The reaction mixture was quenched by slowly pouring into an ice-cooled aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×20 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to afford the product **11** as a colorless oil; yield: 1.1 g (98%). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.23 (t, J = 8.0 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 6.89 (s ,1 H), 6.72 (dd, J = 8.0, 2.0 Hz, 1 H), 3.82 (s, 3 H), 1.60–1.56 (m, 2 H), 1.28–1.20 (m, 12 H), 1.05 (brs, 2 H), 0.84 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 151.6, 128.8, 118.4, 112.6, 109.7, 55.0, 44.6, 37.7, 31.8, 30.0, 29.0, 24.7, 22.7, 14.1; HR-MS (ESI): m/z = 257.1878, calcd. for $C_{16}H_{26}ONa$ ([M + Na]$^+$): 257.1876.

1-Bromo-4-(1,1-dimethylheptyl)-2-methoxybenzene (12):[8,12] To a stirred solution of 1-(1,1-dimethylheptyl)-3-methoxybenzene (**11**) (4.5 g, 19.2 mmol) in AcOH (50 mL) was slowly added bromine (3.1 g, 19.2 mmol) in AcOH (10 mL) at room temperature and the reaction mixture was stirred at the same temperature for 4 h. The reaction mixture was quenched with H_2O and extracted with Et_2O (3× 150 mL). The combined organic extract was washed with 2 N NaOH (50 mL) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to afford 5.7 g products containing **12** (91%, determined by ^{1}H NMR) and 1-bromo-2-(1,1-dimethylheptyl)-4-methoxybenzene (9%), which are inseparable.

12; ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.43 (d, J = 8.0 Hz, 1 H), 6.86 (s, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 3.90 (s, 3 H), 1.59–1.55 (m, 2 H), 1.28–1.03 (m, 14 H), 0.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 151.0, 132.5, 119.6, 110.0, 108.2, 56.0, 44.5, 37.9, 31.7, 29.9, 28.9, 24.6, 22.6, 14.1; HR-MS (ESI): m/z = 335.0975, calcd. for $C_{16}H_{26}ONa$ ([M + Na]$^+$): 257.1876.

2-Methoxy-4-(2-methyloctan-2-yl)phenylboronic acid (4): BuLi (2.4 M in THF, 0.87 mL, 2.1 mmol) was added dropwise to a solution of aryl bromide **12** (550 mg, 91% pure, 1.6 mmol) in THF (20 mL) at −78 °C. The mixture was stirred at the same temperature for 1 h and triisopropyl borate (0.74 mL, 3.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 30 min and at −30 °C for 1 h. The mixture was acidified with hydrochloric acid (1 N, 15 mL) and extracted with ether (3×50 mL). The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to give **4** as a white solid; yield: 364 mg (82%); mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.7 Hz, 1 H), 7.01 (d, J = 7.8 Hz, 1 H), 6.87 (s, 1 H), 5.86–5.77 (m, 2 H), 3.92 (s, 3 H), 1.62–1.58 (m, 2 H), 1.30–1.20 (m, 12 H), 1.05 (brs, 2 H), 0.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 155. 6, 136.3, 119.0, 107.7, 55.3, 44.4, 38.2, 31.7, 29.9, 28.8, 24.6, 22.6, 14.0;

^{11}B NMR (128 MHz, $CDCl_3$): $\delta = 29.48$; HR-MS (ESI): $m/z = 277.1980$, calcd. for $C_{16}H_{26}BO_3$ ($[M-H]^-$): 277.1981.

Preparation of α-Arylcyclohexanone 2

7-Iodo-1,4-dioxaspiro[4.5]dec-6-en-8-one (3): To a solution of enone **13** (2.0 g, 13 mmol) in THF/H_2O (60 mL, v/v = 1/1) was added K_2CO_3 (2.2 g, 16 mmol), I_2 (5.0 g, 20 mmol,) and DMAP (0.32 g, 2.6 mmol) successively. After stirring at room temperature for 2 h, the mixture was diluted with EtOAc (50 mL) and saturated $Na_2S_2O_3$ solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to afford the product **3** as a white solid; yield: 3.1 g (84%); mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.40 (s, 1H), 4.08–4.00 (m, 4H), 2.82 (t, $J = 6.5$ Hz, 2H), 2.24 (t, $J = 6.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.3$, 155.1, 107.2, 105.0, 65.0, 33.2, 33.0; HR-MS (ESI): $m/z =$ 302.9487, calcd. for $C_8H_9IO_3Na$ ($[M+Na]^+$): 302.9489.

7-(2-Methoxy-4-(2-methyloctan-2-yl)phenyl)-1,4-dioxaspiro[4.5]dec-6-en-8-one (14): 2-Iodoenone **3** (67 mg, 0.24 mmol) was added to a mixture of arylboronic acid **4** (100 mg, 0.36 mmol), LiCl (30 mg, 0.72 mmol) and Na_2CO_3 (2 M in water, 0.34 mL, 0.67 mmol) in 1,2-dimethoxyethane (3 mL). The mixture was degassed three times and charged with N_2, and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) was added. The reaction mixture was heated to 80 °C with vigorous stirring for 12 h. The resulting reaction mixture was cooled to room temperature and added to water (20 mL). The product was extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford the product **14** as a white solid; yield: 92 mg (98%); mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.00$ (d, $J = 7.8$ Hz, 1H), 6.89 (d, $J = 7.9$ Hz, 1H), 6.84 (s, 1H), 6.53 (s, 1H), 4.05 (s, 4H), 3.74 (s, 3H), 2.78 (t, $J =$ 6.6 Hz, 2H), 2.31 (t, $J = 6.6$ Hz, 2H), 1.62–1.54 (m, 2H), 1.32–1.14 (m, 12H), 1.08 (brs, 2H), 0.85 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz,): $\delta = 196.9$, 156.7, 152.0, 142.9, 139.8, 129.7, 122.01, 118.1, 109.0, 104.7, 65.0, 55.6, 44.5, 37.9, 36.1, 33.4, 31.7, 30.0, 28.9, 24.6, 22.6, 14.0; HR-MS (ESI): $m/z =$ 409.2346, calcd. for $C_{24}H_{34}O_4Na$ ($[M+Na]^+$): 409.2349.

3-(2-Methoxy-4-(1,1-dimethylheptyl)phenyl)cyclohex-2-enone (2): To a solution of compound **14** (50 mg, 0.13 mmol) of in ethanol (3 mL) was added 5% palladium on activated carbon (27 mg, 0.013 mmol). The mixture was stirred under atmospheric pressure of H_2 for 3 h and was then filtered through a pad of Florisil. The filtrate was concentrated under reduced pressure and purified by chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford product **2** as a white solid; yield: 48 mg (96%); mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, $J = 8$ Hz, 1H), 6.88 (d, $J = 8$ Hz, 1H), 6.82 (s, 1H), 4.16–4.40 (m, 5H), 3.77 (s, 3H), 2.81 (td, $J = 14.0$, 7.1 Hz, 1H), 2.54–2.43 (m, 2H), 2.19–2.11 (m, 3H), 1.60–1.54 (m, 2H), 1.27–1.07 (m, 14H), 0.84 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.6$, 156.7, 150.3, 128.2, 123.6, 118.0, 108.5, 107.7, 64.7, 64.6, 55.3, 47.7, 44.6, 39.5, 38.3, 37.7, 34.3, 31.7, 30.0, 28.9, 28.9, 24.6, 22.6, 14.1; HR-MS (ESI): $m/z = 411.2501$, calcd. for $C_{24}H_{36}O_3Na$ ($[M+Na]^+$): 411.2506.

Asymmetric Synthesis of (−)-CP-55940

(7*S*,8*S*)-7-(2-Methoxy-4-(2-methyloctan-2-yl)phenyl)-1,4-dioxaspiro[4.5]decan-8-ol [(*S*,*S*)-1]: The catalyst {$RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN]} (9.7 mg, 0.01 mmol) was placed in a hydrogenation vessel in a glove box under argon atmosphere. Anhydrous *i*-PrOH (24.0 mL) was introduced with a syringe, and the vessel was purged with hydrogen and pressurized to 20 atm for 5 min. After releasing the pressure, compound **2** (10 mmol in 12.0 mL *i*-PrOH) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol/mL, 10.0 mL, 2 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirring at room temperature for 12 h, the reaction was stopped. The reaction mixture was concentrated and purified through a short silica gel column (petroleum ether/ethyl acetate = 2:1) to furnish alcohol (*S*,*S*)-**1** as a colorless oil; yield: 3.7 g (99%); $[\alpha]_D^{18}$: +40.9 (*c* 1.06, $CHCl_3$); 96% *ee*. SFC (Chiralpak AD-H column, 25 cm × 0.46 cm ID; 2-propanol/CO_2 = 10:90; 40 °C; 100 bar; 2.0 mL min^{-1}; 220 nm): t_R(major) = 9.86 min; t_R (minor) = 11.82 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J = 8$ Hz, 1H), 6.90 (dd, $J =$ 8.0, 1.6 Hz, 1H), 6.82 (d, $J = 1.6$ Hz, 1H), 4.10–3.88 (m, 5H), 3.81 (s, 3H), 3.50 (d, $J = 13.2$ Hz, 1H), 2.37 (t, $J = 13.2$ Hz, 1H), 2.10–1.91 (m, 3H), 1.61–1.55 (m, 4H), 1.45 (s, 1H), 1.27–1.20 (m, 12H), 1.06 (brs, 2H), 0.84 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7$, 149.9, 127.2, 126.7, 117.9, 109.6, 108.2, 67.0, 64.3, 64.2, 55.1, 44.5, 38.9, 37.7, 32.7, 31.7, 30.0, 29.7, 29.0, 28.9, 28.7, 24.6, 22.6, 14.1; HR-MS (ESI): $m/z = 413.2666$, calcd. $C_{24}H_{38}O_4Na$ ($[M+Na]^+$): 413.2662.

***O*-(7*S*,8*S*)-7-[2-Methoxy-4-(2-methyloctan-2-yl)phenyl]-1,4-dioxaspiro[4.5]decan-8-yl *S*-methyl carbonodithioate (15):** To a suspension of NaH (1.3 g, 53.3 mmol) in THF (100 mL) was added a solution of (*S*,*S*)-**1** (4.2 g, 10.7 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, CS_2 (0.96 mL, 16 mmol) was added in one portion. The reaction mixture was continued to stir at room temperature for 45 min. MeI (0.81 mL, 16 mmol) was added to the mixture with stirring. After stirring for 45 min, the reaction was quenched with aqueous NH_4Cl until no hydrogen gas was evolved the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL), the organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford the product **15** as a pale yellow oil; yield: 4.8 g (94%); $[\alpha]_D^{20}$: +70.7 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.02$ (d, $J = 7.8$ Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 6.76 (s, 1H), 6.02 (s, 1H), 4.00 (m, 4H), 3.83 (s, 3H), 3.70 (d, $J = 13.2$ Hz, 1H), 2.42 (s, 3H), 2.40–2.32 (m, 3H), 2.04–1.71 (m, 4H), 1.57–1.53(m, 2H), 1.27–1.02(m, 12H), 1.02 (brs, 2H), 0.84 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.7$, 156.5, 149.6, 126.8, 125.4, 117.6, 108.9, 107.9, 80.4, 64.4, 64.3, 55.2, 44.6, 37.6, 36.8, 34.4, 31.7, 29.9, 29.7, 28.9, 28.9, 27.3, 24.5, 22.6, 18.4, 14.0; HR-MS (ESI): $m/z = 503.2258$, calcd. $C_{26}H_{40}O_4S_2Na$ ($[M + Na]^+$): 503.2260.

***O*-(1*S*,2*S*)-2-[2-Methoxy-4-(2-methyloctan-2-yl)phenyl]-4-oxocyclohexyl *S*-methyl carbonodithioate (16):** To a solution

of ketal **15** (7.4 g, 15.5 mmol) in THF (200 mL) was added aqueous HCl (10%, 200 mL) at room temperature. After the reaction mixture had been stirred for 36 h, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 ×100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to afford the product **16** as a pale yellow oil; yield: 6.5 g (97%). The product **16** also could be obtained directly from the treatment of the reaction mixture of the synthesis of compound **15** with aqueous HCl for 36 h; yield: 96% yield. $[\alpha]_D^{18}$: +87.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.1 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78 (d, *J* = 1.5 Hz, 1H), 6.15 (d, *J* = 2.0 Hz, 1H), 3.86–3.79 (m, 4H), 3.14 (t, *J* = 14.0 Hz, 1H), 2.67–2.58 (m, 2H), 2.55–2.39 (m, 5H), 2.16–2.04 (m, 1H), 1.57–1.53 (m, 2H), 1.27–0.97 (m, 14H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.1, 210.0, 156.3, 150.3, 126.6, 124.1, 117.9, 108.1, 79.4, 55.2, 44.6, 41.6, 39.1, 37.7, 36.3, 31.7, 29.9, 29.0, 28.9, 24.5, 22.6, 18.8, 14.1; HR-MS (ESI): *m/z* = 459.2002, calcd. $C_{24}H_{36}O_3S_2Na$ ($[M+Na]^+$): 459.1998.

***O*-(1*S*,2*S*,4*R*)-4-Hydroxy-2-[2-methoxy-4-(2-methyloctan-2-yl)phenyl]cyclohexyl *S*-methyl carbonodithioate (17):** $NaBH_4$ (1.7 g, 44.7 mmol) was added to a solution of compound **16** (6.5 g, 14.9 mmol) in CH_3OH (120 mL) at −78 °C. The mixture was stirred at −78 °C for 0.5 h and was warmed to room temperature. After quenching with H_2O the reaction mixture was stirred at room temperature for 30 min and extracted with Et_2O (3 ×100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford the product **17** as a colorless oil; yield: 5.9 g (90%); $[\alpha]_D^{18}$: +75.6 (*c* 1.0, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 5.96 (d, *J* = 1.9 Hz, 1H), 3.95–3.86 (m, 1H), 3.82 (s, 3H), 3.38 (dt, *J* = 12.8, 2.4 Hz, 1H), 2.43 (s, 3H), 2.37–1.94 (m, 5H), 1.78–1.70 (m, 1H), 1.63–1.53 (m, 3H), 1.27–1.00(m, 14H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.7, 156.3, 149.6, 127.0, 125.5, 117.7, 107.8, 79.8, 70.2, 55.2, 44.6, 37.6, 37.4, 34.9, 31.7, 29.9, 28.9, 28.8, 27.9, 24.5, 22.6, 18.4, 14.01; HR-MS (ESI): *m/z* = 461.2156, calcd. $C_{24}H_{38}O_3S_2Na$ ($[M+Na]^+$): 461.2155.

(1*R*,3*R*,4*R*)-4-(3-Hydroxypropyl)-3-(2-methoxy-4-(2-methyloctan-2-yl)phenyl)cyclohexanol (19): A mixture of thionocarbonate **17** (2.3 g, 5.3 mmol), allyltributyltin (7.8 mL, 26.5 mmol), and AIBN (431 mg, 2.6 mmol) in benzene (80 mL) was refluxed under nitrogen for 12 h. The solution was concentrated and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to afford an inseparable mixture of **18a** and **18b** as a colorless oil; yield: 1.5 g (80%, **18a**/**18b** = 1.6:1).

The mixture of **18a** and **18b** was dissolved in dry THF (80 mL) and cooled to 0 °C with ice bath. A solution of borane in THF (1.0 M, 4.7 mL, 4.7 mmol) was slowly added over a period of 30 min, and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was cooled with ice again, and treated with aqueous NaOH solution (2 N, 1.4 mL, 2.8 mmol,) and 30% aqueous hydrogen peroxide solution (0.5 mL, 5.8 mmol,). The resulting reaction mixture was stirred at room temperature for 1 h, diluted with water and ether, and extracted with ether (3 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 3:1–1:1) to offer the product **19** as a colorless oil; yield: 676 mg (33% yield from **17**); $[\alpha]_D^{17}$: −31.0 (*c* 0.50, $CHCl_3$) [lit[8] $[\alpha]_D^{30}$: −33.6 (*c* 0.42, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.79 (s, 1H), 3.78 (s, 3H), 3.73–3.68 (m, 1H), 3.44–3.39 (m, 2H), 2.84 (brs, 1H), 2.07–1.95 (m, 3H), 1.81–1.04 (m, 25H) ,0.97–0.88 (m, 1H), 0.83 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 148.8, 129.8, 126.2, 118.3, 108.7, 70.9, 63.1, 55.5, 44.6, 43.5, 40.5, 37.6, 35.5, 31.7, 30.0, 29.9, 29.9, 29.0, 28.9, 24.6, 22.6, 14.0; HR-MS (ESI): *m/z* = 413.3028, calcd. $C_{25}H_{42}O_3Na$ ($[M+Na]^+$): 413.3026.

(−)-CP 55,940: To a solution of *n*-PrSH (3.5 mL, 38.4 mmol) in hexamethylphosphoric triamide (30.0 mL) was added *n*-BuLi (2.4 M in hexane, 10.7 mL, 25.6 mmol) at 0 °C. After stirring at 0 °C for 10 min and at room temperature for 10 min, the mixture was added to another flask containing compound **19** (1.0 g, 2.6 mmol). The resulting mixture was heated to 100–120 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1:1) to afford (−)-CP 55,940 as a white solid; yield: 850 mg (89%); mp 50–52 °C; $[\alpha]_D^{33}$: −27.0 (*c* 0.2, $CHCl_3$) [lit[8] $[\alpha]_D^{29}$: −28.2 (*c* 0.15, $CHCl_3$); $[\alpha]_D^{33}$: −27.7 (*c* 0.2, $CHCl_3$)]. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.93 (brs, 1H), 6.68 (brs, 2H), 3.55 (m, 1H), 3.29–3.23 (m, 2H), 2.81 (brs, 1H), 1.96–1.90 (m, 3H), 1.50–1.46 (m, 3H), 1.29–0.85 (m, 21H), 0.77 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 155.5, 149.4, 129.5, 127.4, 118.5, 114.0, 71.7, 63.6, 45.8, 44.6, 42.5, 39.8, 38.2, 36.5, 33.0, 31.4, 31.2, 31.0, 30.6, 29.6, 25.8, 23.7, 14.5; HR-MS (ESI): *m/z* = 399.2878, calcd. $C_{24}H_{40}O_3Na$ ($[M+Na]^+$): 399.2870.

Acknowledgements

We thank the National Natural Science Foundation of China, the National Basic Research Program of China (973 Program, No.2010CB833300, 2011CB808600), "111" Project of the Ministry of Education of China (Grant No. B06005), and Program for New Century Excellent Talents in University (NCET-08-0292) for financial support.

References

[1] a) I. Muhammad, X.-C. Li, C. Dunbar, M. A. Elsohly, I. A. Khan, *J. Nat. Prod.* **2001**, *64*, 1322–1325; b) I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani, C. Dunbar, D. Ferreira, *J. Nat. Prod.* **2003**, *66*, 804–809.

[2] T.-S. Wu, M.-L. Wang, P.-L. Wu, *Tetrahedron Lett.* **1995**, *36*, 5385–5388.

[3] I. B. De Alleluia, R. Brez Fo, O. R. Gottlien, E. G. Magalhäes, R. Marques, *Phytochemistry* **1978**, *17*, 517–521.
[4] S. P. Nikas, S. O. Alapafuja, I. Papanastasiou, C. A. Paronis, V. G. Shukla, D. P. Papahatjis, A. L. Bowman, A. Halikhedkar, X. Han, A. Makriyannis, *J. Med. Chem.* **2010**, *53*, 6996–7010.
[5] a) P. E. Harrington, I. A. Stergiades, A. Makriyannis, M. A. Tius, *J. Org. Chem.* **2000**, *65*, 6576–6582; b) G. A. Thakur, S. L. Palmer, P. E. Harrington, I. A. Stergiades, M. A. Tius, A. Makriyannis, *J. Biochem. Biophys. Methods* **2002**, *54*, 415–422.
[6] a) M. R. Johnson, L. S. Melvin Jr, U.S. Patent 4,371,720, **1981**; b) L. A. Matsuda, S. J. Lolait, M. J. Brownstein, A. C. Young, T. I. Bonner, *Nature* **1990**, *346*, 561–564.
[7] For review, see: a) G. A. Thakur, S. P. Nikas, R. I. Duclos Jr, A. Makriyannis, in: *Marijunan and cannabinoid research: methods and protocols*, (Ed.: E. S. Onaivi), Totowa, Humana Press Inc., **2006**, pp 113–148; for selected papers, see: b) J. P. Marino, S. L. Dax, *J. Org. Chem.* **1984**, *49*, 3671–3672; c) J. W. Huffman, H. H. Joyner, M. D. Lee, R. D. Jordan, W. T. Pennington, *J. Org. Chem.* **1991**, *56*, 2081–2086; d) J. M. Wiebe, A. S. Caillé, L. Trimble, C. K. Lau, *Tetrahedron* **1996**, *52*, 11705–11724; e) A. G. Chittiboyina, C. R. Reddy, E. B. Watkins, M. A. Avery, *Tetrahedron Lett.* **2004**, *45*, 1689–1691; f) D. L. Goanvic, M. A. Tius, *J. Org. Chem.* **2006**, *71*, 7800–7804; g) Y. R. Lee, L. Xia, *Tetrahedron Lett.* **2008**, *49*, 3283–3287; h) D. D. Dixon, D. Sethumadhavan, T. Benneche, A. R. Banaag, M. A. Tius, G. A. Thakur, A. Bowman, J. T. Wood, A. Makriyannis, *J. Med. Chem.* **2010**, *53*, 5656–5666.
[8] N. Itagaki, T. Sugahara, Y. Iwabuchi, *Org. Lett.* **2005**, *7*, 4181–4183.
[9] a) W.-J. Bai, J.-H. Xie, Y.-L. Li, S. Liu, Q.-L. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 81–84; b) S. Liu, J.-H. Xie, W. Li, W.-L. Kong, L.-X. Wang, Q.-L. Zhou, *Org. Lett.* **2009**, *11*, 4994–4997; c) J.-H. Xie, S. Liu, W.-L. Kong, X.-C. Wang, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 4222–4223; d) J.-H. Xie, W.-L. Kong, L.-X. Wang, W.-J. Bai, L.-X. Wang, Q.-L. Zhou, *Front. Chem. China* **2009**, *4*, 299–306; e) S. Liu, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 7650–7652; *Angew. Chem. Int. Ed.* **2007**, *46*, 7506–7508; f) J.-H. Xie, S. Liu, X.-H. Huo, X. Cheng, H.-F. Duan, B.-M. Fan, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem.* **2005**, *70*, 2967–2973.
[10] T. Ohkuma, J. Li, R. Noyori, *Synlett* **2004**, 1383–1386.
[11] J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404–4405.
[12] J. W. Huffman, S. Yu, V. Showalter, M. E. Abood, J. L. Wiley, D. R. Compton, E. A. Martin, R. D. Bramblett, P. H. Reggio, *J. Med. Chem.* **1996**, *39*, 3875–3877.
[13] a) M. T. Reetz, J. Westermann, *J. Org. Chem.* **1983**, *48*, 254–255; b) C. Bourne, S. Roy, J. L. Wiley, B. R. Martin, B. F. Thomas, A. Mahadevan, R. J. Razdan, *Bioorg. Med. Chem.* **2007**, *15*, 7850–7864.
[14] M. Veguillas, M. Ribagorda, M. C. Carreño, *Org. Lett.* **2011**, *13*, 656–659.
[15] M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263–1266.
[16] D. J. Wustrow, L. D. Wise, *Synthesis* **1991**, 993–995.
[17] D. P. Sutherlin, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 5267–5283.
[18] For examples of carbon-carbon bond formation *via* the reaction of free radical allylic substitution reaction, see: a) G. Keck, J. B. Yates, *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831; b) F. O. Andersson, B. Classon, *J. Org. Chem.* **1990**, *55*, 4699–4704; c) J. Flandor, S. Y. Tam, *Tetrahedron Lett.* **1990**, *31*, 597–660; d) J. E. Golden, J. Aubé, *Angew. Chem.* **2002**, *114*, 4492–4494; *Angew. Chem. Int. Ed.* **2002**, *41*, 4316–4318; e) L. M. Mikkelsen, T. Skrydstrup, *J. Org. Chem.* **2003**, *68*, 2123–2128; f) M. H. D. Postema, J. L. Piper, V. Komanduri, L. Liu, *Angew. Chem.* **2004**, *116*, 2975–2978; *Angew. Chem. Int. Ed.* **2004**, *43*, 2915–2918; g) N. Albæk, M. Petersen, P. Nielsen, *J. Org. Chem.* **2006**, *71*, 7731–7740; h) D. Horton, K. Chen, Z. No, H. C. Lee, *Carbohydr. Res.* **2007**, *342*, 259–267.
[19] For examples of demethylation using lithium alkanethiolate in HMPA, see: a) M. Nakatani, Nakamura, M. A. Suzuki, M. Inoue, T. Katoh, *Org. Lett.* **2002**, *4*, 4483–4486; b) B. M. Trost, H. C. Shen, L. Dong, J.-P. Surivet, C. Sylvain, *J. Am. Chem. Soc.* **2004**, *126*, 11966–11983, and ref.[8]
[20] M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem.* **2004**, *116*, 1438–1440; *Angew. Chem. Int. Ed.* **2004**, *43*, 1414–1416.
[21] G. W. Kabalka, Z. Wu, M.-L. Yao, *Appl. Organomet. Chem.* **2008**, *22*, 516–522.

