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Convenient total synthesis of taranabant (MK-0364), a novel cannabinoid-1 receptor inverse agonist as an anti-obesity agent

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Abstract—Being obese has various health problems that are related to type 2 diabetes mellitus, cardiovascular disease, hypertension, hyperlipidemia, and fibrinolytic abnormalities. Merck's taranabant (MK-0364), a CB1R inverse agonist, is currently in Phase 3 clinical trials, and is being actively pursued by Merck toward obesity market. Merck intends to file for FDA approval of taranabant in 2008. In order to overcome practical difficulty involved in lab-scale preparation of taranabant with a dynamic kinetic resolution procedure developed by Merck's process group, we developed a 'user-friendly' method to install stereogenic centers by adopting Evans asymmetry chemistry. This method allowed us to prepare readily sub-gram scale of the target compound in a convenient way.
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1. Introduction

In recent years, obesity has become a major health problem for many postindustrial societies. The number of deaths per year attributable to obesity is about 30,000 in UK and nearly 400,000 in United States, where obesity is set to overtake smoking as the main preventable cause of illness and premature death.[1–3] The total direct and indirect costs of obesity were estimated to be approximately €32,800 million per year in EU and $99.2 billion per year in USA.[3,4] Obesity poses a major health risk for serious diet-related chronic disease, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and some of cancers.[1] For these reasons, the World Health Organization declared obesity a global epidemic[5,6] and obesity is now considered as disease that needs pharmacological treatments.[7–9]

A lot of studies on causes of obesity have tried to identify new potential targets that could be exploited to create novel drugs. At last it was discovered that modulation of endocannabinoid system by specifically blocking the cannabinoid receptor 1 (CB1) in both the brain and periphery can provide a novel target for the treatment of obesity.[10]

Recently, among arsenal to fight obesity, rimonabant (SR141716), a selective cannabinoid-1 receptor (CB1R) inverse agonist discovered by Sanofi Aventis, was put on hold by the FDA for the approval for psychiatric safety reasons, although rimonabant has been approved in the Europe for the treatment of obesity. On the other hand, Merck's taranabant (MK-0364), another CB1R inverse agonist, is currently in Phase 3 clinical trials and Merck intends to file for FDA approval of taranabant in 2008 (Fig. 1).

With our efforts to discover and develop a new medicine for the treatment of obesity, we needed to prepare up to gram-scale of the precursors of taranabant or taranabant itself for our obesity program. Our imminent goal was to

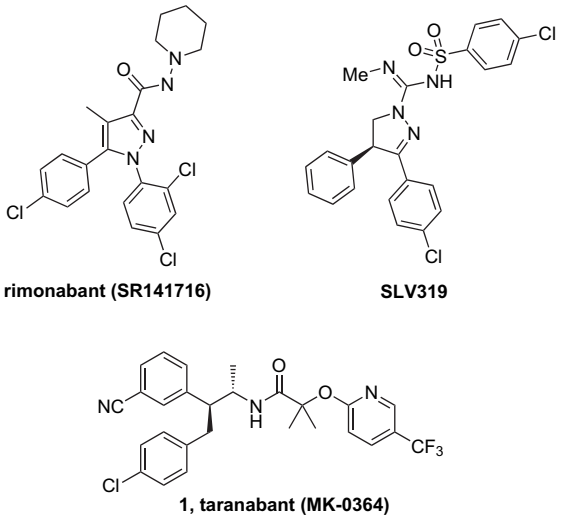

Figure 1. Structures of CB1R inverse agonists: rimonabant (SR141716), SLV319, and taranabant (MK-0364).

Keywords: Taranabant; Anti-obesity; Evans asymmetric reaction; Hydride reduction.
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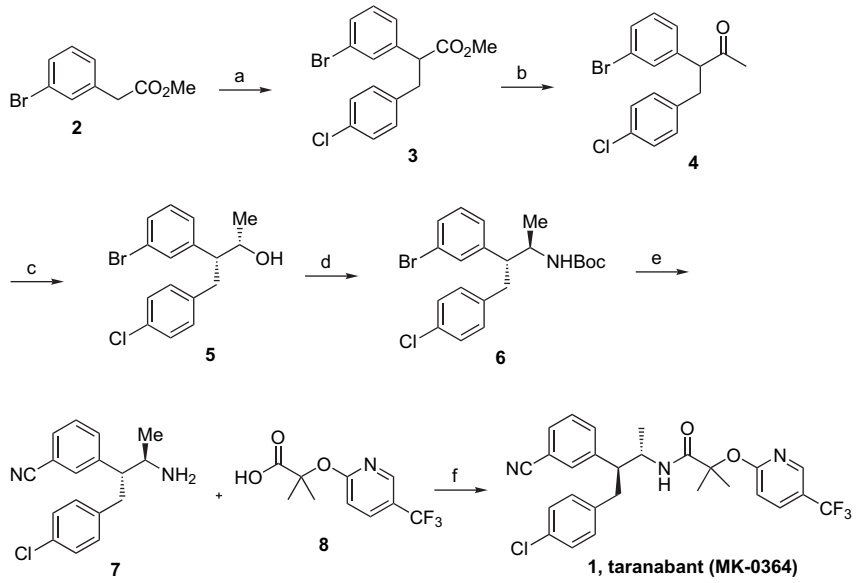
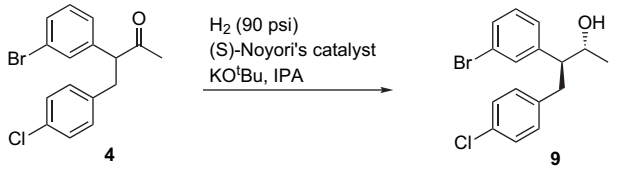


Scheme 1. Synthesis of taranabant (MK-0364) by Merck's medicinal chemistry group. (a) *p*-Cl-PhCH$_2$Br, KHMDS, −78 °C to rt. (b) MeONH(Me)·HCl, Me$_2$AlCl. (c) LiBH(*sec*-Bu)$_3$, −78 °C. (d) (i) MsCl, Et$_3$N; (ii) NaN$_3$, DMF; (iii) H$_2$, Boc$_2$O, PtO$_2$. (e) (i) Zn(CN)$_2$, Pd$_2$(dba)$_3$, dppf; (ii) HCl/dioxane. (f) (i) PyBop, *N*-methylmorpholine, CH$_2$Cl$_2$; (ii) prep chiral HPLC.

design and develop a convenient, practical, and reproducible synthetic method for medicinal chemists to utilize and to provide reasonable amount of intermediates toward taranabant whenever necessity comes along for medicinal chemistry purpose. Herein we wish to report an asymmetric synthesis of taranabant (MK-0364) featuring Evans chiral auxiliary methodology to install a pivotal benzylic stereogenic center.

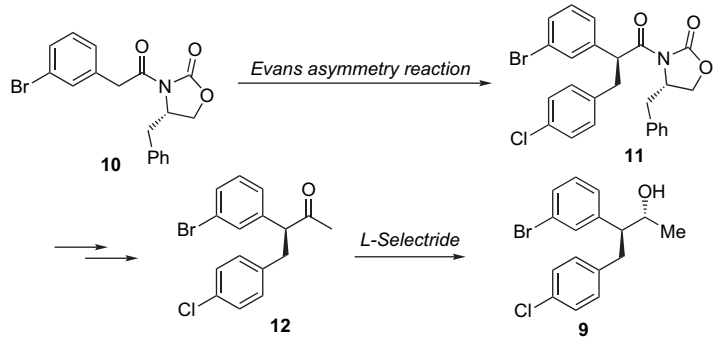
As shown in Scheme 1, the original route to taranabant employed by medicinal chemistry group at Merck has tedious column chromatography works for the isolation of intermediate alcohol **5** as well as use of preparative chiral HPLC technique to resolve taranabant (**1**) at the final stage.[11]



Scheme 2. Enantioselective reduction of ketone **4** by Merck's process chemistry group.

Although the synthetic route appears to provide small amounts of related target compounds, it is quite inefficient and time-consuming to adopt multiple column chromatography in addition to chiral HPLC for resolution for a reasonable scale-up. Then the process group at Merck developed a dynamic kinetic resolution based on a ruthenium-catalyzed enantioselective reduction to transform a racemic ketone intermediate into a single enantiomer as depicted in Scheme 2.[12]

The process provides a very elegant way to introduce chirality of taranabant and is amenable to large-scale production. However, when we actually try to perform the reaction for medicinal chemistry laboratory scale, we have found it rather inconvenient to employ super-high pressure of hydrogen gas (90–150 psi) in the presence of Noyori's catalyst (xyl-BINAP/DAIPEN) or Dow catalyst (xyl-PHANEPHOS/DPEN). It is not likely to adopt the dynamic kinetic resolution technology especially for medicinal chemists who usually deal with multi-gram scale reaction, but not up to 100-g scale for their routine laboratory projects. We envisioned that the key intermediate, the chiral bromo alcohol **9** in Scheme 3, could be derived from the corresponding chiral bromo ketone **12** upon diastereoselective reduction using L-Selectride at low temperature.[13] In turn, the requisite



Scheme 3. Synthesis of (*R*,*S*)-bromo alcohol.

(*S*)-benzyl bromo ketone **12** could be obtained by adopting Evans chiral auxiliary technology installing the first stereogenic center for taranabant.[14] We fully recognized the fact that the first stereogenic center of (*S*)-benzyl bromo ketone **12** might be vulnerable to potential epimerization along the synthesis, but we have undertaken the synthetic study considering potential benefits secured from this route if successful: user-friendly synthesis: i.e., any skilled lab personnel can synthesize requisite intermediates readily for either discovery of a new scaffold or structure–activity relationship study without being intimidated by using high-pressure hydrogen gas or chiral HPLC for resolution. Also it would provide another synthetic choice for rapid access to taranabant, an anti-obesity agent.

2. Results and discussion

2.1. Total synthesis of taranabant (MK-0364)

We began our synthesis with a classical Evans asymmetric reaction route as in Scheme 4.[14]

Thus, 3-bromophenyl acetic acid **13** was coupled with lithiated (*S*)-4-benzyloxazolidin-2-one via pivaloyl mixed anhydride prepared from pivaloyl chloride in the presence of a base such as triethylamine to produce *N*-acyloxazolidinone **10** in 79% yield. The mixed anhydride method usually provides the better yield of *N*-acyloxazolidinone **10** than routine acyl chloride method. Next, alkylation of **10** using NaHMDS with 1-(bromomethyl)-4-chlorobenzene at −78 °C affords the alkylated product **11** in 72% yield. LiHMDS can be also adopted as a suitable base for the conversion, but we found that use of NaHMDS gives more favorable results consistently. The ^{1}H NMR spectrum of **11** did not show any notable isomer peaks, confirming seemingly very high de value. The relative and absolute stereochemistries of the desired alkylated product **11** were further secured through single-crystal X-ray analysis as demonstrated in Figure 2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC661320.

At this juncture, we began to have confidence in the route, which could lead to taranabant without tainting potentially labile stereogenic center of acyloxazolidinone **11**. Next,

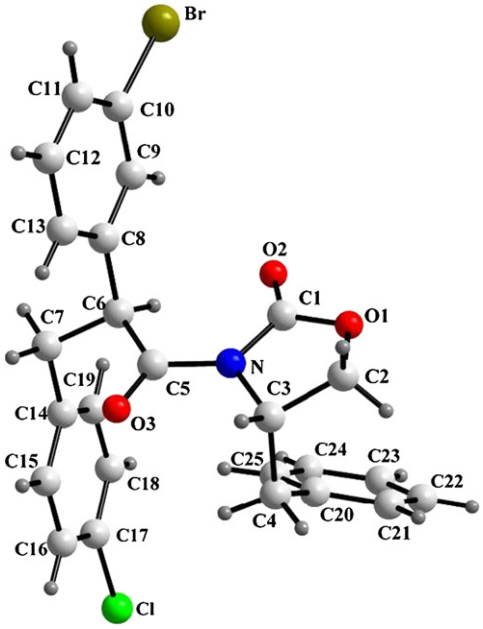
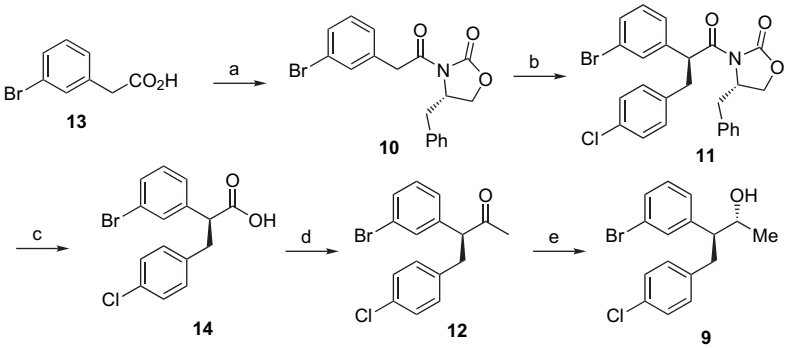


Figure 2. X-ray structure of compound **11**.

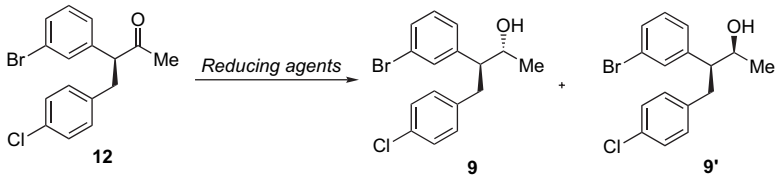
the chiral auxiliary of acyloxazolidinone **11** was cleaved by standard conditions (LiOOH, 0 °C) to produce the corresponding acid **14** uneventfully. The specific optical rotation of **14** was measured to be +10.5. Then the next three steps to prepare methyl ketone **12** proceeded in a straightforward fashion. Thus, treatment of the bromo acid **14** with oxalyl chloride provided the corresponding acyl chloride, which was directly reacted with *N*,*O*-dimethylhydroxylamine in the presence of triethylamine to give the Weinreb amide in 91% yield. The resulting Weinreb amide was treated with MeMgBr to generate the desired methyl ketone **12** in 99% yield. The transformation from bromo acid **14** to methyl ketone progressed without any purification by column chromatography. We tried to control the neighboring stereochemistry by converting the methyl ketone **12** to the alcohol with hydride reduction. We briefly screened hydride reduction conditions. The results are summarized in Table 1.

The Li^+-containing reducing agents tend to give better diastereoselectivity than Na^+- or K^+-containing counterparts (entries 1, 3, and 4). Steric factors appear to influence the stereoselectivity of reduction. Thus, use of bulky reducing



Scheme 4. Preparation of bromo alcohol **9**. (a) (i) pivaloyl chloride, Et_3N, THF, 0 °C; (ii) *n*-BuLi, (*S*)-4-benzyloxazolidin-2-one, THF, −78 °C. (b) 1-(Bromomethyl)-4-chlorobenzene, NaHMDS, THF, −78 °C. (c) LiOOH, THF, H_2O, 0 °C. (d) (i) $(COCl)_2$, CH_2Cl_2; (ii) MeONHMe, Et_3N, CH_2Cl_2; (iii) MeMgBr, THF. (e) LiBH(*sec*-Bu)$_3$, THF, −78 °C.

Table 1. Diastereoselective reduction of bromo ketone **14**



Entry	Reaction conditions	Ratio (**9**/**9′**)[a]
1	$LiBH_4$, 0 °C, MeOH	89:11
2	$LiBH_4$, −78 °C, THF	91:9
3	$NaBH_4$, 0 °C, MeOH	80:20
4	K-Selectride, −78 °C, THF	56:44
5	L-Selectride, −78 °C, THF	>99:<1

[a] All the above reaction conditions provide about the same yield (~90% yield) of alcohols **9** and **9′**, albeit in a different ratio. Selectivity was measured on Gilson™ reverse-phase preparative HPLC.

agent such as L-Selectride magnifies such steric factors to achieve even greater stereoselectivity (entry 2 and 5).[15] The specific optical rotation of bromo alcohol **9** thus obtained was +36.8.

As described in Scheme 5, the cyano group was next introduced into bromo alcohol **5** via a Pd-catalyzed cyanation following Merck's protocol.[12] Thus, we carried out the cyanation of bromide **5** to nitrile **9** under the conditions of using $Zn(CN)_2$ and in situ generated Pd [P(*o*-tol)$_3$]$_4$ as a catalyst in DMF. The yield for the conversion was approximately 70% in our hands.

Next, the cyano alcohol **15** was converted to cyano azide **16** through mesylation followed by displacement with azide. The reactions went smoothly to produce azide **16** in 94% for two steps. Transformation of the azide **16** to amine **17** was conducted successfully utilizing the Staudinger conditions (PPh_3 in mildly heated toluene/water).[16] Purification was performed efficiently by Gilson™ reverse-phase preparative HPLC using CH_3CN/water system containing 0.1% TFA. Thus, the desired amine was obtained as a TFA salt form (**17**) in 79% yield. The specific optical rotation of **17** was estimated to be +22.6.

Finally, coupling of amine TFA salt **17** with acid **8** under conditions of DMAP, EDC, and HOBt in DMF, followed by isolation by Gilson™ preparative HPLC produced taranabant without difficulty. Our synthetic taranabant obtained had identical ^{1}H NMR as well as LC–MS data reported by Merck.[11] The specific optical rotation of **1** was measured to be +35.5.[17]

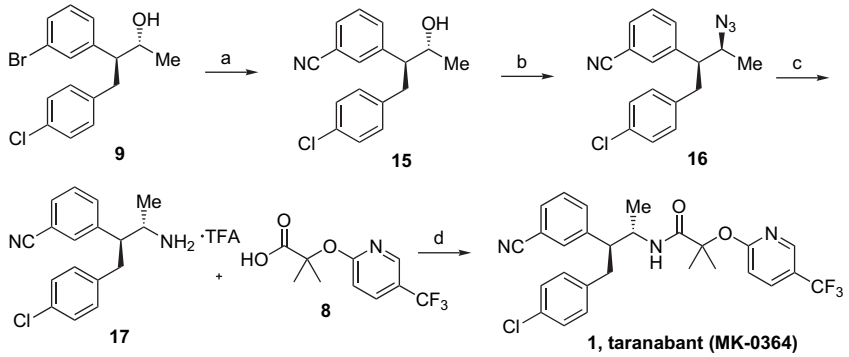
2.2. Analog of taranabant (MK-0364)

In view of the potential of taranabant or related structure as a lead compound for anti-obesity studies, we sought to prepare a few of scaffolds with similar or hopefully improved developability characteristics including biological activity. At the outset, we chose to evaluate the importance of CN group on taranabant.

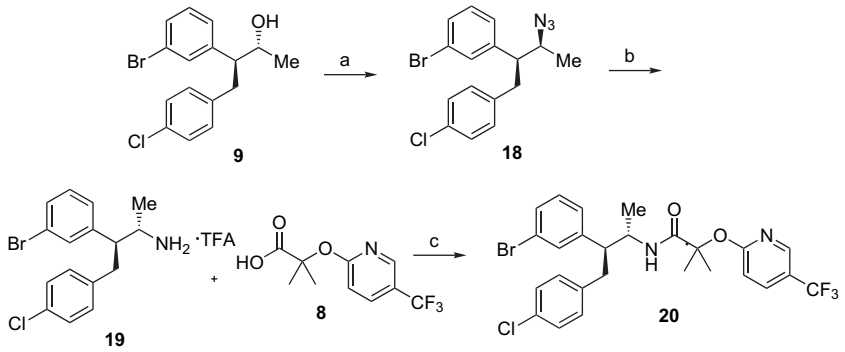
Construction of an analog **20** began with bromo alcohol **9**. The bromo alcohol **9** was converted to bromo azide **18** through mesylation followed by displacement with azide in a similar way previously described toward taranabant. The Staudinger reaction, followed by purification by Gilson™ reverse-phase preparative HPLC using CH_3CN/water containing 0.1% TFA was adopted successfully for transformation of the azide **18** to amine **19**. Finally, coupling of amine TFA salt **19** with acid **8** under conditions of DMAP, EDC, and HOBt in DMF, followed by isolation by Gilson™ preparative HPLC readily produced analog **20** (Scheme 6).

2.3. Biological evaluation

Taranabant (MK-0364, **1**) and the structurally similar analog **20** were screened via in vitro rat cannabinoid CB-1 binding assay. Both taranabant (MK-0364) and analog **20** demonstrated subnanomolar binding affinities. Taranabant turned out to be slightly less potent than the bromo analog **20** (CB1R IC_{50}=0.861 nM vs CB1R IC_{50}=0.583 nM) via in-house assay. As illustrated, bromophenyl not only retained



Scheme 5. Preparation of taranabant **1** from bromo alcohol **9**. (a) 2% cat. Pd(OAc)$_2$, P(*o*-tol)$_3$, Et_2Zn, $Zn(CN)_2$, DMF. (b) (i) MsCl, Et_3N; (ii) NaN_3, DMF, 120 °C. (c) (i) PPh_3, tol/H_2O; (ii) 0.1% TFA on Gilson™ prep HPLC. (d) DMAP, EDC, DMF.



Scheme 6. Preparation of an analog **20**. (a) (i) MsCl, Et_3N; (ii) NaN_3, DMF, 120 °C. (b) (i) PPh_3, tol/H_2O; (ii) 0.1% TFA on Gilson™ prep HPLC. (c) DMAP, EDC, DMF.

biological activity, but also even improved in vitro CB1 receptor binding affinity. This observation suggests that the cyano group on phenyl ring may be important, but not critical for activity. Presumably its function is to improve physical properties of taranabant for better developability characteristics.

3. Summary

We have achieved a convenient total synthesis of taranabant (MK-0364), a novel cannabinoid-1 receptor inverse agonist for the treatment of obesity by employing Evans asymmetry reaction. We introduced a pivotal asymmetric center via the Evans chiral auxiliary methodology and accomplished subsequent diastereoselective reduction to install adjacent essential asymmetric center for taranabant. Using this synthetic route we prepared a structurally similar analog, which retains significant cannabinoid CB-1 receptor binding affinity.

4. Experimental

4.1. General

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated. Microwave reaction was conducted with a Biotage microwave reactor. ^{1}H NMR spectra were recorded on either a Jeol ECX-400 or a Bruker DPX-300 spectrometer. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). Mass spectra were obtained with either Micromass, Quattro LC Triple Quadruple Tandem Mass Spectometer, ESI, or Agilent, 1100LC/MSD, ESI. Optical rotation data were obtained on a JASCO P-1030 automatic polarimeter. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of DMSO onto a SunFire™ Prep C18 OBD 5 μm 19×100 mm Column with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Most of the reactions were monitored by thin layer chromatography on 0.25 mm E. Merck silica gel plates (60 F_{254}), visualized with UV light using a 5% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution.

4.1.1. (*S*)-4-Benzyl-3-(2-(3-bromophenyl)acetyl)oxazolidin-2-one (10). To a stirred solution of 15.5 g (72 mmol) of 2-(3-bromophenyl)acetic acid (**13**) in 290 mL of anhydrous THF was added 11 mL (79 mmol) of triethylamine under an atmosphere of argon. The mixture was cooled to −78 °C, and trimethylacetylchloride (11.5 mL, 94 mmol) was then added using a cannula. The resulting white suspension was stirred for 10 min at −78 °C, 1 h at 0 °C, and recooled to −78 °C. Meanwhile, in a different flask, a solution of lithiated *S*-oxazolidinone was prepared by the dropwise addition of 29 mL *n*-butyllithium (2.5 M in hexane) to a −78 °C solution of 15.5 g of the auxiliary in 290 mL of anhydrous THF. The mixture was stirred for 20 min at −78 °C. The lithiated chiral auxiliary was transferred via a cannula into the reaction flask containing the preformed mixed anhydride at −78 °C. The mixture was stirred at 0 °C for 1 h and was allowed to warm to 23 °C in 16 h. The mixture was then quenched with 200 mL of saturated ammonium chloride solution. THF was evaporated in vacuo. The product was extracted with (3×200 mL) ethyl acetate. The organic layer was washed with 1 N sodium hydroxide (2×100 mL) and 1 N sodium bisulfate (1×100 mL), dried by anhydrous magnesium sulfate, filtered, and evaporated. Purification by silica gel chromatography (elution with 15–30% ethyl acetate in hexane) gave 21.4 g (79%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.50 (m, 1H), 7.45–7.42 (m, 1H), 7.33–7.20 (m, 5H), 7.15–7.12 (m, 2H), 4.72–4.66 (m, 1H), 4.33–4.17 (m, 4H), 3.27 (dd, 1H, J=13.6, 3.6 Hz), 2.78 (dd, 1H, J=9.8, 13.2 Hz); LC–MS: *m/e* 374 (M^++H).

4.1.2. (*S*)-4-Benzyl-3-((*S*)-2-(3-bromophenyl)-3-(4-chlorophenyl)propanoyl)oxazolidin-2-one (11). To a solution of oxazolidinone **10** (20.4 g, 55 mmol) and 4-chlorobenzyl bromide (17.5 g, 85 mmol) in 180 mL of anhydrous THF at −78 °C was added sodium hexamethyldisilazide (1 M in THF, 85 mL, 85 mmol). The reaction was allowed to warm to room temperature overnight. The volatile materials were removed on a rotary evaporator, and the resulting mixture was partitioned between saturated ammonium chloride (200 mL) and ethyl acetate (200 mL). The organic layer

was separated and the aqueous layer was extracted with ethyl acetate (2×200 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. Purification by silica gel chromatography (elution with 15–30% ethyl acetate in hexane) gave 19.6 g (72%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.59 (m, 1H), 7.42–7.39 (m, 1H), 7.34–7.31 (m, 1H), 7.27–7.23 (m, 5H), 7.20–7.16 (m, 3H), 6.99–6.96 (m, 2H), 5.40 (dd, 1H, J=9.6 Hz), 4.61–4.58 (m, 1H), 4.07–4.06 (m, 2H), 3.46 (dd, 1H, J=9.6, 13.6 Hz), 3.06–2.98 (m, 2H), 2.61 (dd, 1H, J=9.0, 13.6 Hz); LC–MS: *m/e* 498 (M^++H).

4.1.3. (*S*)-2-(3-Bromophenyl)-3-(4-chlorophenyl)propanoic acid (14). A 0.05 M solution of oxazolidinone **11** (19 g, 38 mmol) in a 3:1 mixture of THF and H_2O was treated with 30% H_2O (35 mL, 306 mmol), followed by LiOH (3.2 g, 76 mmol) at 0 °C. The resulting mixture was stirred and allowed to warm to room temperature overnight. THF was then removed under vacuum. The residue was washed with dichloromethane (500 mL×2) to remove (*S*)-4-benzyloxazolidin-2-one. The desired product was isolated by ethyl acetate extraction of the acidified (pH 1–2) aqueous phase. No further purification was required. Standing under high vacuum yielded 13 g (98%) of the title compound. $[\alpha]^{24.7}$ +10.5 (*c* 0.815, $CHCl_3$).

4.1.4. (*S*)-3-(3-Bromophenyl)-4-(4-chlorophenyl)butan-2-one (12). To a solution of acid **14** (2.85 g, 8.39 mmol) in dichloromethane (25 mL) at 0 °C were added dimethylformamide (one drop) and oxalyl chloride (1.5 mL, 16 mol) dropwise. The reaction was allowed to warm to room temperature for 2 h and concentrated to dryness to give the crude acyl chloride, which was used without further purification. To a solution of the acyl chloride in dichloromethane (40 mL) were added *N*-methoxy-*N*-methylamine hydrochloride (2.5 g, 25 mmol) and triethylamine (5.8 mL, 42 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was diluted with ether (100 mL) and successively washed with water, dilute aqueous sodium hydrogen sulfate, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness to afford (*S*)-2-(3-bromophenyl)-3-(4-chlorophenyl)-*N*-methoxy-*N*-methylpropanamide (91%), which was used without further purification. LC–MS: *m/e* 382 (M^++H).

To a solution of (*S*)-2-(3-bromophenyl)-3-(4-chlorophenyl)-*N*-methoxy-*N*-methylpropanamide (10.2 g, 27 mmol) in anhydrous tetrahydrofuran (95 mL) at 0 °C was added methylmagnesium bromide (3 M in ether, 18 mL, 53 mmol). After stirring at 0 °C for 2 h, the reaction was quenched with methanol (4 mL) and 2 M hydrochloric acid (40 mL). The volatile materials were removed by concentrating on a rotary evaporator and the residue was partitioned between saturated ammonium chloride (150 mL) and ether (150 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2×150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness to afford (*S*)-3-(3-bromophenyl)-4-(4-chlorophenyl)butan-2-one (99%), which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.39 (m, 1H), 7.33–7.32 (m, 1H), 7.21–7.16 (m, 3H), 7.09–7.06 (m, 1H), 7.00–6.95 (m, 2H), 3.82 (t, J=7.4 Hz), 3.35 (dd, J=13.9, 7.5 Hz), 2.84 (dd, 1H, J=13.9, 7.3 Hz), 2.04 (s, 3H).

4.1.5. (2*R*,3*S*)-3-(3-Bromophenyl)-4-(4-chlorophenyl)butan-2-ol (9). L-Selectride® (1 M solution in THF, 9.5 mL) was added to a solution of ketone (**12**, 2.13 g, 6.31 mmol) in anhydrous THF (32 mL) under N_2 at −78 °C. The mixture was stirred at −78 °C for 1.5 h and warmed to −40 °C. The aqueous NaOH (3 N, 9.6 mL) and 30% H_2O_2 (4.9 mL) were added slowly and stirred vigorously for 2 h at 0 °C. The reaction mixture was diluted with ethyl acetate and the organic phase was separated. The organic phase was washed with water, saturated $Na_2S_2O_3$, and brine, and dried over $MgSO_4$. After evaporation, the residue was purified using column chromatography on silica gel (hexane/ethyl acetate=6:1) to give desired products (1.98 g, 92%) as colorless oil. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.39 (m, 1H), 7.30–7.28 (m, 1H), 7.20–7.09 (m, 6H), 4.67 (br, 1H), 3.83–3.76 (m, 1H), 3.02 (dd, 1H, J=6.0, 13.5 Hz), 2.90–2.78 (m, 2H), 0.88 (d, 3H, J=6.5 Hz). ^{13}C NMR (DMSO-d_6, 300 MHz): δ 144.8, 140.0, 132.3, 131.3, 130.7, 130.1, 129.3, 129.0, 128.4, 121.5, 68.2, 53.7, 37.2, 21.9. Reduction of ketone (**12**) with $NaBH_4$ provided the mixture of diastereomers. Major diastereomer was identified as **9**. Minor diastereomer (**9′**): ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.30–7.29 (m, 2H), 7.19–7.13 (m, 3H), 7.10–7.08 (m, 1H), 6.99 (d, 2H, J=8.0 Hz), 4.84 (br, 1H), 3.79–3.73 (m, 1H), 3.32–3.28 (m, 1H), 2.83–2.75 (m, 2H), 0.89 (d, 3H, J=6.0 Hz); $[\alpha]^{24.3}$ +36.8 (*c* 0.585, $CHCl_3$).

4.1.6. 3-((2*S*,3*R*)-1-(4-Chlorophenyl)-3-hydroxybutan-2-yl)benzonitrile (15). $Zn(CN)_2$ (212 mg, 1.80 mol) was added to a solution of bromo alcohol (**9**, 1.02 g, 3.00 mmol) and DMF (4 mL). The atmosphere of the mixture was then exchanged to nitrogen gas for 20 min, and the batch was heated to 56 °C. In a separate flask, DMF (3 mL) was charged and exchanged to nitrogen gas. $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) and P(*o*-tol)$_3$ (75.3 mg, 0.24 mmol) were charged to this flask, and solution was heated to 56 °C over 40 min and held for an additional 15 min. $ZnEt_2$ (0.082 mL, 0.09 mmol) was then added to the catalyst solution over 15 min, and the resulting slurry was aged at 56 °C for 1 h. The $Zn(CN)_2$ mixture was transferred to the catalyst slurry over 1 h at 56 °C, and the mixture was aged an additional 2 h. The reaction was cooled with an ice bath to 5–10 °C. Concentrated NH_4OH (5 mL) was added, keeping the batch temperature at <30 °C, and the batch was aged for 1 h. The slurry was then filtered over a pad of silica gel that was wetted with toluene. The cake was washed with 20 L of toluene. To the filtrate were added 3 mL of 20% aqueous NH_4OH and toluene (3 mL). After mixing well, the layers were separated, and the organic layer was washed with 10 mL each of 15% aqueous NaCl solution and water. This solution of alcohol **15** (71% yield) was carried forward to the mesylation reaction. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.65 (s, 1H), 7.59 (d, 1H, J=7.6 Hz), 7.50 (d, 1H, J=7.6 Hz), 7.38 (t, 1H, J=7.6 Hz), 7.19 (d, 2H, J=8.0 Hz), 7.09 (d, 2H, J=8.0 Hz), 4.70 (d, 1H, J=4.4 Hz), 3.85–3.83 (m, 1H), 3.06–3.01 (m, 1H), 2.95–2.87 (m, 2H), 0.90 (d, 3H, J=6.4 Hz).

4.1.7. 3-((2*S*,3*S*)-3-Azido-1-(4-chlorophenyl)butan-2-yl)benzonitrile (16). To a solution of alcohol **15** (1.7 g,

5.9 mmol) in ethyl acetate (16 mL) at 0 °C were added triethylamine (1.1 mL, 7.6 mmol) and methanesulfonyl chloride (0.6 mL, 7.6 mmol). After stirring at 0 °C for 1.5 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (15 mL). After stirring at room temperature for 1 h, the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to afford (2*R*,3*S*)-4-(4-chlorophenyl)-3-(3-cyanophenyl)butan-2-yl methanesulfonate, which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.52 (m, 1H), 7.45 (m, 1H), 7.43–7.39 (m, 2H), 7.18–7.14 (m, 2H), 6.99–6.94 (m, 2H), 5.08–5.03 (m, 1H), 3.2–3.0 (m, 3H), 2.89 (s, 3H), 1.33 (d, 3H, *J*=6.4 Hz).

To a solution of (2*R*,3*S*)-4-(4-chlorophenyl)-3-(3-cyanophenyl)butan-2-yl methanesulfonate in dimethylformamide (5 mL) was added sodium azide (1.9 g, 29 mmol). After stirring at 120 °C for 2 h, the reaction mixture was poured into water (20 mL), and the product was extracted with ether (2×25 mL). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The residue was purified on a silica gel column to yield azide **16** (94% for two steps), which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, *J*=10.4 Hz), 7.40–7.33 (m, 2H), 7.26–7.22 (m, 1H), 7.14–7.11 (d, *J*=8.4 Hz), 6.82 (d, 2H, *J*=8.4 Hz), 3.72–3.65 (m, 1H), 3.29 (dd, 1H, *J*=2.4, 12 Hz), 2.86–2.76 (m, 2H), 1.15 (d, 3H, *J*=6.4 Hz); LC–MS: *m/e* 285 (M^++H).

4.1.8. 3-((2*S*,3*S*)-3-Amino-1-(4-chlorophenyl)butan-2-yl)benzonitrile trifluoroacetic acid (17). To the toluene (2 mL) solution of azide **16** (430 mg, 1.38 mmol) from the previous step was added water (1 mL), and the batch was heated to 70 °C. A solution of PPh_3 (543 mg, 2.08 mol) in toluene (1 mL) was added to the batch for over 1 h (slowly in order to control nitrogen evolution). The batch was aged for an additional 7 h and then cooled to ambient temperature. Purification by Gilson™ HPLC system (elution with 0.1% TFA of H_2O and acetonitrile) gave 438 mg (79%) of the TFA salt form. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.58 (m, 1H), 7.54 (m, 1H), 7.45 (m, 2H), 7.14 (d, 2H, *J*=8.4 Hz), 6.96 (d, 2H, *J*=8.4 Hz), 3.67–3.64 (m, 1H), 3.22–3.15 (m, 1H), 2.98–2.92 (m, 1H), 1.16 (d, 3H, *J*=6.8 Hz); LC–MS: *m/e* 285 (M^++H), $[\alpha]^{24.4}$ +22.6 (*c* 0.790, $CHCl_3$).

4.1.9. *N*-((2*S*,3*S*)-4-(4-Chlorophenyl)-3-(3-cyanophenyl)-butan-2-yl)-2-methyl-2-(5-(trifluoromethyl)pyridin-2-yloxy)propanamide (taranabant, MK-0364, 1). To a solution of 2-methyl-2-(5-(trifluoromethyl)pyridin-2-yloxy)-propanoic acid[11] (**8**, 410 mg, 1.65 mmol) in dichloromethane (5 mL) were added amine salt (**17**, 438 mg, 1.10 mmol), DMAP (268 mg, 2.20 mmol), and then EDC (253 mg, 1.32 mmol). The mixture was stirred at room temperature overnight. The product was extracted with dichloromethane (2×10 mL). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The residue was purified on Gilson™ HPLC system to yield taranabant (MK-0364: 560 mg, 0.77 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H), 7.83 (dd, 1H, *J*=2.4, 8.8 Hz), 7.45 (d, 1H, *J*=7.6 Hz), 7.31 (t, 1H, *J*=8.0 Hz), 7.25–7.21 (m, 2H), 7.08 (d, 2H, *J*=8.4 Hz), 6.86 (d, 1H, *J*=8.8 Hz), 6.72 (d, 2H, *J*=8.4 Hz), 5.83 (d, 1H, *J*=8.8 Hz), 4.38–4.28 (m, 1H), 3.11 (dd, 1H, *J*=3.2, 12.8 Hz), 2.87–2.74 (m, 2H), 1.75 (s, 3H), 1.71 (s, 3H), 0.87 (d, 3H, *J*=6.8 Hz); LC–MS: *m/e* 516 (M^++H); $[\alpha]^{25.0}$ +35.5 (*c* 0.455, $CHCl_3$).

4.1.10. *N*-((2*S*,3*S*)-4-(4-Chlorophenyl)-3-(3-bromophenyl)butan-2-yl)-2-methyl-2-(5-(trifluoromethyl) pyridin-2-yloxy)propanamide (20). The title compound was prepared according to the similar procedures described above. Purification by preparative HPLC yielded the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H), 7.81 (dd, 1H, *J*=2.0, 8.4 Hz), 7.30 (d, 1H, *J*=7.6 Hz), 7.16 (t, 1H, *J*=2.0 Hz), 7.10–7.03 (m, 3H), 6.89 (d, 1H, *J*=7.6 Hz), 6.84 (d, 1H, *J*=8.0 Hz), 6.77 (d, 2H, *J*=8.8 Hz), 5.81 (d, 1H, *J*=9.2 Hz), 4.32–4.26 (m, 1H), 3.03 (d, 1H, *J*=12 Hz), 2.84–2.75 (m, 2H), 1.73 (s, 3H), 1.71 (s, 3H), 0.88 (d, 3H, *J*=6.8 Hz); LC–MS: *m/e* 569 (M^++H).

4.2. Pharmacological test: in vitro activity analysis

The compounds of the present invention were analyzed for their binding characteristics for CB_1 and CB_2 and the pharmacological activity thereof in accordance with the method disclosed in Ref. 18. The analysis was performed using [^{3}H]CP-55940, which is a selectively radioactivity-labeled 5-(1,1-dimethyheptyl)-2[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol, purchased from Perkin–Elmer Life Sciences, Inc. (Boston, Massachusetts, USA), through a rat CB-1 receptor binding protocol as follows.

The tissue obtained from the brain of SD rats was homogenized with a Dounce homogenate system in TME (50 mM Tris, 3 mM $MgCl_2$ and 1 mM EDTA, pH 7.4) at 4 °C, and the homogenate was centrifuged at 48,000*g* for 30 min at 4 °C. The pellet was re-suspended in 5 mL of TME and the suspension was divided into aliquots and stored at −70 °C until its use in the following assay.

Test compound (2 μl) was diluted in dimethylsulfoxide and added to a deep well of a polypropylene plate, to which 50 μl of [^{3}H]CP-55940 diluted in a ligand buffer solution (0.1% bovine serum albumin (BAS)+TME) was added. The tissue concentrations were determined by Bradford protein analysis, and 148 μl of brain tissue of the required concentration was added to the plate. The plate was covered and placed in a 30 °C incubator for 60 min, and then transformed on GF/B filtermat pretreated in polyethylenimine (PEI) using a cell harvester. Each filter was washed five times and dried at 60 °C for 1 h. Then, the degree of radioactivity retained by the filter was measured using Wallac Microbeta™ (Perkin–Elmer Life Sciences, Inc., Massachusetts, USA) and the activity of the compound for inhibiting CB_1 receptor was determined therefrom.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.056.

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