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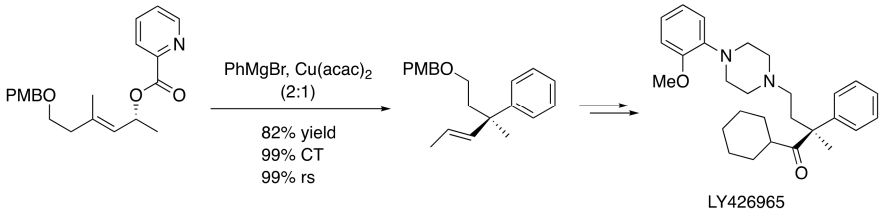

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Regio- and stereoselective S_N2' reaction of an allylic picolinate in the synthesis of LY426965

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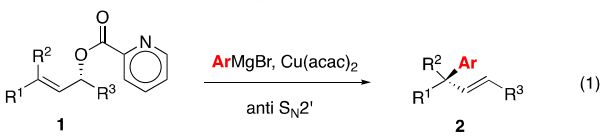
ABSTRACT

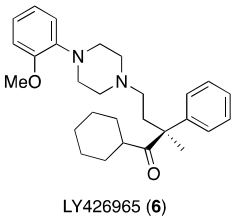
Allylic substitution of secondary γ,γ-disubstituted allylic picolinates with ArMgBr-based copper reagents was applied to the synthesis of LY426965. Reduction of (*R*)-6-(PMB-oxy)-3-hexyn-2-ol of 93% ee (PMB = *p*-MeOC$_6$H$_4$CH$_2$) using Red-Al gave (*R*,*Z*)-4-iodo-5-(PMB-oxy)hex-3-en-2-ol, which was later converted to the Me-substituted allylic picolinate by Pd-catalyzed coupling with MeZnI followed by esterification with picolinic acid. Allylic substitution with PhMgBr/Cu(acac)$_2$ proceeded with high anti S_N2' selectivity (99%). Ozonolysis, addition of *c*-Hex-MgBr to the resulting aldehyde, and reductive amination with the piperazine derivative afforded LY426965.

1. Introduction

Recently, we have reported the allylic substitution of γ,γ-disubstituted secondary allylic picolinates **1** to afford anti S_N2' products **2** possessing a quaternary C–C bond with high regio- and stereoselectivity (Scheme 1, Eq. 1).[1] The use of aryl reagents, flexibility in choosing any alkyl substituent as R^3, and attainable high enantiopurity of the products are synthetic advantages of the substitution. We also developed a stereoselective access to allylic picolinates **1** from propargylic alcohol **3** via iodoalcohols **4** (Eq. 2) because the stereochemical purity of the olefin moiety is directly transferred to enantiopurity of allylation products **2**. Feasibility of this strategy has been examined during the synthesis of mesembrine[2] and verapamil[3] successfully. To further demonstrate the synthetic potential of this strategy, LY426965 (**6**)[4] was chosen as the next target (Fig. 1), which is a serotonin 1A receptor antagonist and would clinically be useful for neuropsychiatric disorders. Up to date, **6** has been synthesized by several methods,[5]



Scheme 1. Construction of quaternary carbons via allylic substitution.



LY426965 (**6**)

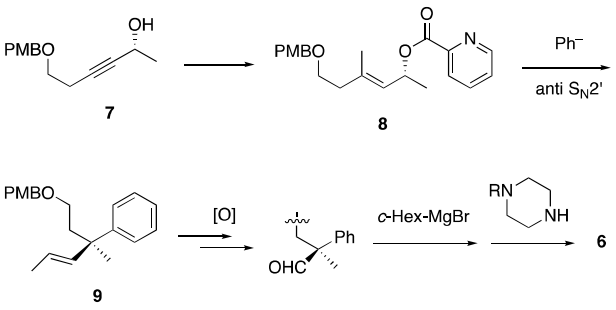
Fig. 1. The structure of LY426965.

which feature chiral phosphoramide-catalyzed addition of 3,3′-disubstituted allylsilane to the aldehyde,[5a,b] chiral sulfonamide/oxazoline/Cr complex-catalyzed addition of 3,3′-disubstituted allylic chloride to the aldehyde,[5d] and Rh-catalyzed allylic substitution of the carbonate derived from the enantioenriched tertiary allylic alcohol.[5c] These methods produce terminal alkenes, whereas our method described herein would be useful for synthesis of internal alkenes in developing a drug that is more effective than **6**.

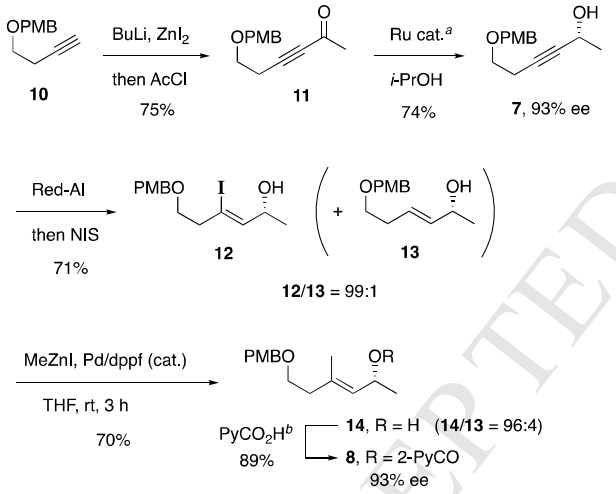
2. Results and discussion

Taking account of the method described in Scheme 1 in mind, we envisaged synthesis of **6** as delineated in Ph–. This method consists of ozonolysis of the olefin in **9** derived from **7** via allylic picolinate **8**, addition of the cyclohexyl ring (*c*-Hex) to the resulting aldehyde, and installation of the piperazine ring.

PMB ether **10** derived from commercially available 3-butyn-1-ol, PMB-OC(=NH)CCl_3, and CSA (cat.) in 81% yield was converted to ketone **11** in 75% yield according to the literature procedure[6] with a modification that less hygroscopic ZnI_2 was used instead of $ZnCl_2$ (Scheme 3). Asymmetric hydrogen transfer reaction[7] of the ketone by using RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] in *i*-PrOH gave alcohol **7** in 74% yield with 93% ee as determined by chiral HPLC analysis. The absolute configuration was tentatively determined as expected from the reagent and was proven by comparing specific rotations of the compounds (**21**, **23**, and **6**) with those reported in the literature. Subsequently, Red-Al reduction of **7** followed by iodination afforded iodoalcohol **12** in 71% yield with 99% product selectivity over protonated byproduct **13** as determined by ^{1}H NMR spectroscopy.

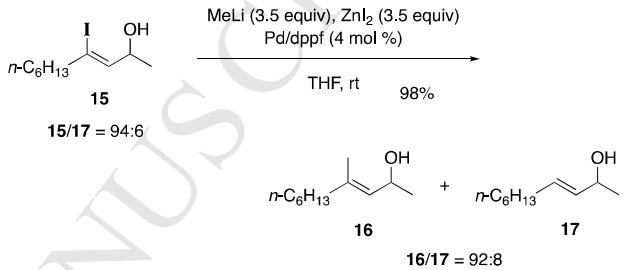


Scheme 2. Synthetic plan of LY426965 (**6**).



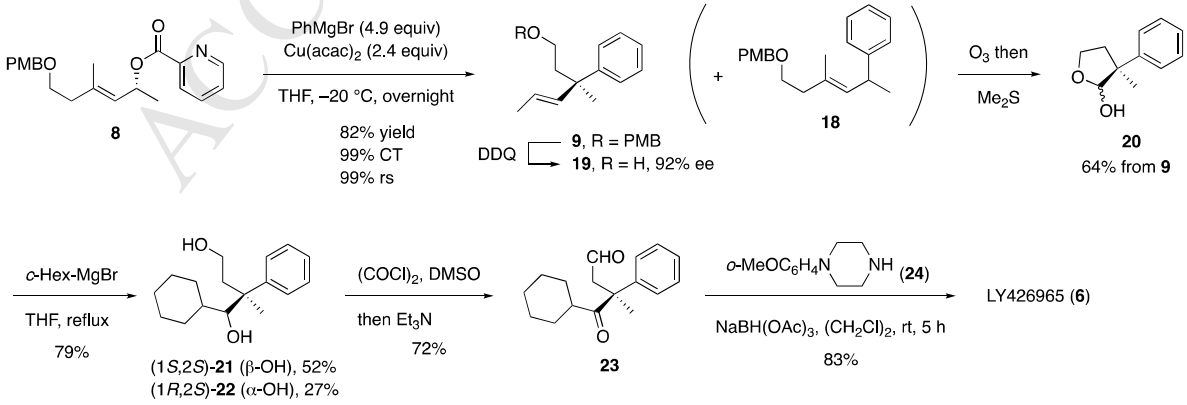
Scheme 3. Synthesis of the picolinate **7**.
[a] RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN]. [b] With [2-Cl-1-MeC$_5$H$_4$N]$^+$ I$^-$.

To find a suitable reagent for the methyl coupling of **12** without the protection of the hydroxy group, methylation of a model iodoalcohol **15** was examined first. The methylation of the corresponding bromide with Me_4CoLi_2 in the literature gave a 55:45 mixture of **16** and the *Z*-isomer.[8] Therefore, the conveniently preparable MeZnI with a Pd/dppf catalyst was selected instead, considering similar Pd-catalyzed couplings with MeZnBr[9] and with Me_2Zn.[10] The reaction proceeded cleanly to afford **16** in 98% yield with 2% drop in chemical purity over protonated byproduct **17** (Scheme 4). Methylation of **12** under the conditions established above gave allylic alcohol **14** with 96% purity over **13**. Condensation with $PyCO_2H$ using the Mukaiyama reagent followed by chromatographic purification afforded allylic picolinate **8** as a sole product in 89% yield with 93% ee as determined by chiral HPLC analysis.



Scheme 4. Preliminary results of Pd-catalyzed coupling reaction.

The allylic substitution of **8** with the Ph copper reagent (2 equiv),[11,12] derived from PhMgBr and Cu(acac)$_2$ in the 2:1 ratio, proceeded smoothly and gave **9** in 82% yield with 99% regioselectivity (rs) as determined by ^{1}H NMR: δ 5.45 (dq, *J* = 15.6, 6.2 Hz, 1 H) for **9** and 5.35 (d, *J* = 8.8 Hz, 1 H) for regioisomer **18** (Scheme 5). This isomer was synthesized as a 1:1 mixture with **9** using PhMgBr/Cu(acac)$_2$ in a 3:1 ratio on the basis of the previous result.[1a] The PMB protective group in **9** was removed with DDQ to afford alcohol **19**, which was 92% ee by HPLC analysis, indicating 99% chirality transfer (CT) for the allylic substitution of picolinate **8** (93% ee).



Scheme 5. Synthesis of LY426965 (**6**).

Ozonolysis of **19** followed by Me_2S work-up afforded lactol **20** in 64% yield from **9**. Addition of *c*-Hex-MgBr to the lactol in refluxing THF produced a mixture of diastereomers **21** and **22**, which were separated by chromatography on silica gel for

determination of the structures. The major isomer obtained in 52% yield was identified as **21** by ^{1}H NMR spectroscopy and $[\alpha]_D$ analysis with the literature data[5a,b] and, thus, the minor isomer isolated in 27% yield was assigned as **22**. The isomers were mixed again and subjected to Swern oxidation to give keto aldehyde **23** in 72% yield. According to the literature procedure,[5a,b] the piperazine derivative **24** was attached to **23** in 83% yield by reductive amination. The ^{1}H and ^{13}C NMR spectra of **6** thus synthesized were consistent with those reported.[5c] The total yield was 6.1% in 11 steps from **10**. In addition, consistent specific rotations of **21**, **23**, and **6** with those reported in the literatures indicate that the allylic substitution of **8** proceeded with anti S_N2' to construct the quaternary carbon indicated in **9**.

3. Conclusion

The target compound **6** was synthesized stereoselectively by a strategy consisting of the construction of γ,γ-disubstituted secondary allylic picolinates and subsequent allylic substitution (Scheme 2). The Pd-catalyzed coupling reaction of iodoallylic alcohol **6** with MeZnI proceeded without the protection of the hydroxy group, and allylic substitution took place stereoselectively with high CT of 99%. It should be noted that the present method allows the synthesis of analogues with substituent(s) other than Ph, *c*-Hex, and/or the peperazine groups for finding a more powerful antagonist than **6**.

4. Experimental

4.1. General

The ^{1}H (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectroscopic data were recorded in $CDCl_3$ using Me_4Si (δ = 0 ppm) and the centerline of the triplet (δ = 77.1 ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (*J*) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by minus (for C and CH_2) and plus (for CH and CH_3) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer with an ionization mode of positive FAB or EI as indicated for each compound. The solvents that were distilled prior to use are THF (from Na/benzophenone) and CH_2Cl_2 (from CaH_2). After the reactions were completed, the organic extracts were concentrated by using an evaporator, and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N).

*4.2. 1-[(But-3-yn-1-yloxy)methyl]-4-methoxybenzene (**10**)*

To an ice-cold solution of $PMBOC(NH)CCl_3$ (11.85 g, 41.9 mmol) in CH_2Cl_2 (100 mL) was added but-3-yn-1-ol (1.47 g, 20.97 mmol) and CSA (731 mg, 3.15 mmol). The solution was stirred at rt overnight and diluted with hexane (200 mL). The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was diluted with hexane (100 mL) and filtered again. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **10** (3.23 g, 81%): liquid; R_f 0.62 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (t, *J* = 2.4 Hz, 1 H), 2.49 (dt, *J* = 2.8, 7.2 Hz, 2 H), 3.57 (t, *J* = 7.2 Hz, 2 H), 3.81 (s, 3 H), 4.49 (s, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (–), 55.3 (+), 67.8 (–), 69.4 (–), 72.6 (–), 81.4 (–), 113.8 (+), 129.3 (+), 130.1 (–), 159.3 (–). The ^{1}H and ^{13}C NMR spectra were consistent with those in the literature.[13]

*4.3. 6-[(4-Methoxybenzyl)oxy]hex-3-yn-2-one (**11**)*

To a solution of acetylene **10** (3.41 g, 17.9 mmol) in THF (80 mL) was added *n*-BuLi (1.55 M in hexane, 11.6 mL, 17.9 mmol) dropwise at –78 °C. The cooling bath was replaced by an ice-water bath. The solution was stirred at 0 °C for 30 min and cooled again to –78 °C. A solution of ZnI_2 (6.86 g, 21.5 mmol) in THF (15 mL) was added dropwise. After the addition, the solution was stirred at 0 °C for 20 min, cooled to –78 °C, and added AcCl (2.53 mL, 35.5 mmol) dropwise. The solution was allowed to warm to rt over 3 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford ketone **11** (3.14 g, 75%): liquid; R_f 0.48 (hexane/EtOAc 2:1); IR (neat) 2214, 1675, 1514, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.65 (t, *J* = 6.8 Hz, 2 H), 3.60 (t, *J* = 6.8 Hz, 2 H), 3.81 (s, 3 H), 4.49 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 20.4 (–), 32.7 (+), 55.3 (+), 66.8 (–), 72.8 (–), 81.9 (–), 90.6 (–), 113.9 (+), 129.4 (+), 129.8 (–), 159.3 (–), 184.7 (–); HRMS (FAB$^+$) calcd for $C_{14}H_{16}O_3$ [M$^+$]; 232.1099, found 232.1096.

*4.4. (R)-6-[(4-Methoxybenzyl)oxy]hex-3-yn-2-ol (**7**)*

A mixture of RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] (281 mg, 0.442 mmol) and crashed KOH (ca. 28 mg, 0.50 mmol) in CH_2Cl_2 (3.5 mL) was stirred at rt for 40 min. The mixture was brought to pH 7 (pH-paper) by washing with H_2O (3 mL each, 6 times). The CH_2Cl_2 solution was transferred to another flask with CH_2Cl_2. The solution was dried over CaH_2, decanted, and concentrated to afford a purple solid, to which *i*-PrOH (80 mL) and ketone **11** (1.77 g, 7.64 mmol) were added. The mixture was stirred at rt overnight and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **7** (1.33 g, 74%): liquid; R_f 0.32 (hexane/EtOAc 2:1); 93% ee determined by HPLC (Chiralcel OD-H; hexane/*i*-PrOH = 98.2:1.8, 0.5 mL/min, 35 ºC; t_R (min) = 81.3 (major), 95.1 (minor)); $[\alpha]_D^{24}$ +13 (*c* 1.05, $CHCl_3$); IR (neat) 3409, 1613, 1514, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, *J* = 6.4 Hz, 3 H), 2.49 (dt, *J* = 2.0, 7.2 Hz, 2 H), 2.57 (d, *J* = 4.0 Hz, 1 H), 3.53 (t, *J* = 7.0 Hz, 2 H), 3.79 (s, 3 H), 4.44–4.52 (m, 1 H), 4.47 (s, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 20.0 (–), 24.5 (+), 55.3 (+), 58.3 (+), 68.0 (–), 72.5 (–), 81.1 (–), 83.5 (–), 113.8 (+), 129.4 (+), 130.0 (–), 159.2 (–); HRMS (FAB$^+$) calcd for $C_{14}H_{18}O_3$ [M$^+$]; 234.1256, found 234.1261.

*4.5. (R,Z)-4-Iodo-6-[(4-methoxybenzyl)oxy]hex-3-en-2-ol (**12**)*

To an ice-cold solution of alcohol **7** (93% ee, 1.33 g, 5.69 mmol) in THF (60 mL) was added Red-Al (60 wt% in toluene, 1.036 g/mL, 2.78 mL, 8.55 mmol). The solution was heated under reflux for 2 h and cooled to rt. A solution of NIS (2.11 g, 9.38 mmol) in THF (8 mL) was added. The reaction was continued at rt for 2.5 h and quenched by carefully adding 1 N HCl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford iodoalcohol **12** (1.47 g, 71%): **12**/**13** = 99:1 by ^{1}H NMR analysis (see the ^{1}H NMR spectrum of **12**); liquid; R_f 0.38 (hexane/EtOAc 2:1); $[\alpha]_D^{23}$ +2 (*c* 1.14, $CHCl_3$); IR (neat) 3404, 1612, 1513, 1249, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.4 Hz, 3 H), 2.48 (br s, 1 H), 2.73 (t, *J* = 6.4 Hz, 2 H), 3.55 (dt, *J* = 9.6, 6.4 Hz, 1 H), 3.61 (dt, *J* = 9.6, 6.4 Hz, 1 H),

3.79 (s, 3 H), 4.44 (s, 2 H), 4.39–4.48 (m, 1 H), 5.70 (d, *J* = 7.2 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 21.9 (+), 45.1 (–), 55.3 (+), 68.3 (–), 72.68 (–), 72.74 (+), 103.6 (–), 113.8 (+), 129.4 (+), 130.1 (–), 140.5 (+), 159.2 (–); HRMS (FAB^+) calcd for $C_{14}H_{19}O_3I$ [M^+]; 362.0379, found 362.0372. The ^{1}H spectrum of **13**, obtained from this experiment and several attempts of the iodinations, was identical with that reported[14] and that prepared by Red-Al reduction of *rac*-**7** independently. Thus, Red-Al (3.6 M in toluene, 0.41 mL, 1.48 mmol) was added to a solution of *rac*-**7** (57 mg, 0.24 mmol) in toluene (5 mL). The solution was heated to 100 °C for 20 min, cooled to 0 °C, and added saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford *rac*-**13** (32 mg, 55%): liquid; R_f 0.34 (toluene/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.4 Hz, 3 H), 1.70–1.89 (br s, 1 H), 2.32 (q, *J* = 6.4 Hz, 2 H), 3.47 (t, *J* = 6.4 Hz, 2 H), 3.80 (s, 3 H), 4.25 (quint., *J* = 6.4 Hz, 1 H), 4.44 (s, 2 H), 5.59 (dt, *J* = 15.4, 6.0 Hz, 1 H), 5.64 (dt, *J* = 15.4, 6.0 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 32.5, 55.2, 68.8, 69.3, 72.5, 113.8, 127.1, 129.3, 130.4, 136.1, 159.2.

*4.6. (R,E)-6-[(4-Methoxybenzyl)oxy]-4-methylhex-3-en-2-ol (**14**)*

To an ice-cold solution of ZnI_2 (4.59 g, 14.4 mmol) in THF (35 mL) was added MeLi (1.16 M in Et_2O, 12.2 mL, 14.2 mmol). The mixture was stirred at rt for 1 h and added a solution of iodoalcohol **12** (**12**/**13** = 99:1, 1.46 g, 4.03 mmol) in THF (5 mL). The mixture was stirred at rt for 15 min and added a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (208 mg, 0.201 mmol) and dppf (109 mg, 0.200 mmol) in THF (15 mL). The mixture was stirred at rt for 3 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford allylic alcohol **14** (710 mg, 70%): **14**/**13** = 96:4 by ^{1}H NMR analysis (see the ^{1}H NMR spectrum of **14**); liquid; R_f 0.22 (hexane/EtOAc 2:1); $[\alpha]_D^{24}$ +12 (*c* 1.00, $CHCl_3$); IR (neat) 3406, 1613, 1514,1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.2 Hz, 3 H), 1.50 (br s, 1 H), 1.69 (d, *J* = 1.2 Hz, 3 H), 2.30 (t, *J* = 6.8 Hz, 2 H), 3.53 (t, *J* = 6.8 Hz, 2 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 4.57 (dq, *J* = 8.4, 6.2 Hz, 1 H), 5.26 (dq, *J* = 8.4, 1.2 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 16.7 (+), 23.5 (+), 39.3 (–), 55.3 (+), 64.6 (+), 68.4 (–), 72.5 (–) 113.8 (+), 129.3 (+), 130.5 (–), 130.6 (+), 134.6 (–), 159.1 (–); HRMS (FAB^+) calcd for $C_{15}H_{22}O_3$ [M^+]; 250.1569, found 250.1569.

*4.7. (R,E)-6-[(4-Methoxybenzyl)oxy]-4-methylhex-3-en-2-yl picolinate (**8**)*

To an ice-cold solution of alcohol **14** (710 mg, 2.84 mmol) in CH_2Cl_2 (50 mL) were added picolinic acid (1.04 g, 8.45 mmol), Et_3N (2.37 mL, 17.0 mmol), DMAP (351 mg, 2.87 mmol), and 2-chloro-1-methylpyridinium iodide (2.19 g, 8.57 mmol). The mixture was heated under reflux for 2 h, cooled to 0 °C, and diluted with saturated NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **8** (898 mg, 89%): liquid; R_f 0.59 (three-development with hexane/EtOAc 2:1; *cf.* **14**, R_f 0.65); $[\alpha]_D^{20}$ –19 (*c* 1.01, $CHCl_3$); 93% ee by HPLC analysis (Chiralcel OD-H; hexane/*i*-PrOH = 94:6, 30 ºC; t_R (min) = 15.9 (major), 18.2 (minor)); IR (neat) 1713, 1513, 1247, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.4 Hz, 3 H), 1.79 (d, *J* = 1.2 Hz, 3 H), 2.27–2.40 (m, 2 H), 3.54 (t, *J* = 6.8 Hz, 2 H), 3.79 (s, 3 H), 4.43 (s, 2 H), 5.42 (dq, *J* = 9.0, 1.2 Hz, 1 H), 5.95 (dq, *J* = 9.0, 6.4 Hz, 1 H), 6.85 (dm, *J* = 8.8 Hz, 2 H), 7.24 (dm, *J* = 8.8 Hz, 2 H), 7.46 (ddd, *J* = 7.6, 4.6, 1.2 Hz, 1 H), 7.82 (dt, *J* = 1.8, 7.6 Hz, 1 H), 8.11 (dm, *J* = 7.6 Hz, 1 H), 8.77 (dm, *J* = 4.6 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 17.0 (+), 20.9 (+), 39.4 (–), 55.3 (+), 68.3 (–), 69.8 (+), 72.5 (–), 113.7 (+), 125.1 (+), 125.8 (+), 126.6 (+), 129.2 (+), 130.5 (–), 136.9 (+), 137.4 (–), 148.6 (–), 149.9 (+), 159.1 (–), 164.6 (–); HRMS (FAB^+) calcd for $C_{21}H_{26}NO_4$ [$(M+H)^+$] 356.1862, found 356.1863.

*4.8. (R,E)-1-Methoxy-4-[{(3-methyl-3-phenylhex-4-en-1-yl)oxy}methyl]benzene (**9**)*

To an ice-cold suspension of $Cu(acac)_2$ (881 mg, 3.37 mmol) in THF (14 mL) was added a solution of PhMgBr (0.98 M in THF, 7.0 mL, 6.86 mmol) dropwise. The mixture was stirred at 0 °C for 1 h, cooled to –40 °C, and added a solution of picolinate **8** (93% ee, 497 mg, 1.40 mmol) in THF (2 mL). The resulting mixture was allowed to warm to –20 °C over 2 h, stirred at –20 ºC overnight, and diluted with saturated NH_4Cl and ammonium hydroxide solution. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford **9** (355 mg, 82%): **9**/**18** = 99:1 by ^{1}H NMR analysis (see the ^{1}H NMR spectrum of **9**); liquid; R_f 0.63 (hexane/EtOAc 2:1); $[\alpha]_D^{19}$ +1.9 (*c* 1.02, $CHCl_3$); IR (neat) 1613, 1513, 1248, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.71 (dd, *J* = 6.2, 1.4 Hz, 3 H), 2.07 (ddd, *J* = 13.6, 9.2, 5.8 Hz, 1 H), 2.15 (ddd, *J* = 13.6, 9.2, 5.8 Hz, 1 H), 3.35 (dt, *J* = 5.8, 9.2 Hz, 1 H), 3.39 (dt, *J* = 5.6, 9.2 Hz, 1 H), 5.45 (dq, *J* = 15.6, 6.2 Hz, 1 H), 5.62 (dq, *J* = 15.6, 1.4 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.14–7.24 (m, 3 H), 7.25–7.33 (m, 4 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 18.2 (+), 26.1 (+), 40.7 (–), 42.5 (–), 55.3 (+), 67.5 (–), 72.6 (–), 113.8 (+), 122.2 (+), 125.8 (+), 126.5 (+), 128.1 (+), 129.2 (+), 130.7 (–), 139.6 (+), 147.9 (–), 159.1 (–); HRMS (EI^+) calcd for $C_{21}H_{26}O_2$ [M^+] 310.1933, found 310.1935.

Synthesis of a mixture of **9** and **18**: To an ice-cold suspension of $Cu(acac)_2$ (22 mg, 0.084 mmol) in THF (1 mL) was added a solution of PhMgBr (0.94 M in THF, 0.28 mL, 0.263 mmol) dropwise. The mixture was stirred at 0 °C for 1 h, cooled to –40 °C, and added a solution of picolinate **8** (93% ee, 20 mg, 0.056 mmol) in THF (0.5 mL). The resulting mixture was stirred overnight, and diluted with saturated NH_4Cl. The product was extracted with hexane and purified as described above to afford a mixture of **9** and **18** in a 1:1 ratio as determined by ^{1}H NMR spectroscopy: liquid; R_f 0.63 (hexane/EtOAc 2:1); selected signals of ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.9 Hz, 3 H), 1.70 (d, *J* = 1.6 Hz, 3 H), 5.38 (d, *J* = 9.0 Hz, 1 H).

*4.9. (R,E)-3-Methyl-3-phenylhex-4-en-1-ol (**19**)*

To a solution of the PMB ether **9** (273 mg, 0.879 mmol) in CH_2Cl_2 (8 mL) and H_2O (0.8 mL) was added DDQ (212 mg, 0.934 mmol). The mixture was stirred at rt overnight and filtered through a pad of Celite with CH_2Cl_2 to afford a mixture of alcohol **19** and 4-(MeO)C_6H_4CHO. The mixture was separated by chromatography on silica gel for the next reaction. Characterization of **19**: liquid; R_f 0.30 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ –11 (*c* 1.05, $CHCl_3$); 92% ee (99% CT) by HPLC analysis (Chiralcel OD-H; hexane/*i*-PrOH = 98:2, 1.0 mL/min, 35 ºC; t_R (min) = 15.5 (the product), 19.4 (the enantiomer)); IR (neat) 3334, 1599, 1445, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (br s, 1 H), 1.38 (s, 3 H), 1.73 (dd, *J* = 6.4, 1.6 Hz, 3 H), 2.02

(ddd, *J* = 13.2, 8.4, 6.4 Hz, 1 H), 2.09 (ddd, *J* = 13.2, 8.4, 6.0 Hz, 1 H), 3.49–3.67 (m, 1 H), 5.45 (dq, *J* = 15.6, 6.4 Hz, 1 H), 5.66 (dq, *J* = 15.6, 1.6 Hz, 1 H), 7.15–7.21 (m, 1 H), 7.27–7.34 (m, 4 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 18.2 (+), 26.0 (+), 42.4 (–), 44.0 (–), 60.1 (–), 122.5 (+), 126.0 (+), 126.4 (+), 128.2 (+), 139.6 (+), 147.8 (–); HRMS (EI^+) calcd for $C_{13}H_{18}O$ [M^+] 190.1358, found 190.1358.

*4.10. (1S,2S)- and (1R,2S)-1-Cyclohexyl-2-methyl-2-phenylbutane-1,4-diols (**21** and **22**)*

Ozonolysis of **19**. To a solution of the above alcohol **19** in CH_2Cl_2 (8 mL) was gently bubbled a stream of O_3/O_2 at –78 °C for 15 min. Argon gas was bubbled to remove excess O_3 in the solution (ca. 10 min) and then Me_2S (2 mL, 27 mmol) was added. The solution was left overnight and concentrated. The residue was purified by chromatography on silica gel to afford hemiacetal **20** (101 mg, 64% from the PMB ether **9**) as a 6:4 mixture of the diastereomers: liquid; R_f 0.22 (hexane/EtOAc 2:1); IR ($CHCl_3$) 3363, 1445, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 and 1.42 (2s, 1.8 H and 1.2 H), 2.04 (ddd, *J* = 11.4, 7.2, 2.0 Hz, 0.6 H), 2.22 (ddd, *J* = 12.8, 7.8, 6.4 Hz, 0.4 H), 2.36 (ddd, *J* = 12.8, 7.8, 6.2 Hz, 0.4 H), 2.64 (dt, *J* = 11.4, 9.8 Hz, 0.6 H), 2.69–2.86 (m, 1 H), 3.29–3.54 (m, 1 H), 3.88 (dt, *J* = 6.4, 7.8 Hz, 0.4 H), 4.07–4.20 (m, 1 H), 4.27 (ddd, *J* = 9.8, 8.4, 2.0 Hz, 0.6 H), 7.19–7.42 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 27.3, 33.1, 37.0, 49.7, 52.0, 65.7, 66.7, 103.2, 103.4, 126.0, 126.38, 126.42, 127.1, 128.5, 144.8, 145.8.

Reaction with *c*-Hex-MgBr. To a solution of hemiacetal **20** (99 mg, 0.555 mmol) in THF (2 mL) was added a solution of *c*-Hex-MgBr (0.72 M, 6.24 mL, 4.50 mmol). The mixture was heated under reflux overnight and cooled to 0 °C. The reaction was quenched by adding 1 N HCl and the resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a diastereomeric mixture of alcohols **21** and **22** (116 mg, 79%), which were separated by chromatography on silica gel (hexane/EtOAc) to afford **21** (76 mg, 52%) and **22** (40 mg, 27%). Major isomer **21**: solids; mp 46–47; R_f 0.12 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ –22 (*c* 1.15, MeOH); lit.[5a,b] $[\alpha]_D^{24}$ –21.8 (*c* 1.05, MeOH) for 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–1.34 (m, 7 H), 1.39 (s, 3 H), 1.47–1.57 (m, 2 H), 1.62–1.70 (m, 2 H), 1.7–2.3 (br s, 2 H), 1.98 (dt, *J* = 13.6, 6.6 Hz, 1 H), 2.04–2.14 (m, 1 H), 3.49 (dt, *J* = 11.0, 6.6 Hz, 1 H), 3.60 (dt, *J* = 11.0, 6.6 Hz, 1 H), 3.70 (d, *J* = 3.6 Hz, 1 H), 7.18–7.23 (m, 1 H), 7.29–7.36 (m, 4 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 18.8 (+), 26.3 (–), 26.8 (–), 28.5 (–), 33.5 (–), 39.9 (+), 43.8 (–), 45.8 (–), 59.7 (–), 82.2 (+), 126.1 (+), 126.6 (+), 128.4 (+), 145.8 (–). Minor isomer **22**: solids; mp 50–51; R_f 0.20 (hexane/EtOAc 2:1); $[\alpha]_D^{21}$ +14 (*c* 0.98, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–1.88 (m, 13 H), 1.38 (s, 3 H), 2.08 (dt, *J* = 14.0, 7.6 Hz, 1 H), 2.17 (ddd, *J* = 14.0, 7.6, 5.6 Hz, 1 H), 3.42 (d, *J* = 2.0 Hz, 1 H), 3.48 (ddd, *J* = 10.4, 7.6, 5.6 Hz, 1 H), 3.66 (dt, *J* = 10.4, 7.6 Hz, 1 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 20.8 (+), 26.36 (–), 26.41 (–), 27.0 (–), 27.4 (–), 34.2 (–), 39.1 (+), 41.4 (–), 45.5 (–), 59.7 (–), 83.6 (+), 126.4 (+), 127.1 (+), 128.3 (+), 145.0 (–); HRMS (FAB^+) calcd for $C_{17}H_{27}O_2$ [$(M+H)^+$] 263.2011, found 263.2009.

The ^{1}H NMR spectrum of the major isomer **21** was consistent with that in the literature,[5a,b] while the ^{13}C NMR spectrum was corrected. In addition, ^{13}C–APT NMR spectrum supported the structure.

*4.11. (S)-4-Cyclohexyl-3-methyl-4-oxo-3-phenylbutanal (**23**)*

To a solution of oxalyl chloride (0.136 mL, 1.59 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.225 mL, 3.17 mmol) at –70 °C. The solution was stirred at –70 °C for 40 min and the diastereomeric mixture of alcohols **21** and **22** (104 mg, 0.396 mmol) in CH_2Cl_2 (3 mL) was added to the solution, which was then stirred at the same temperature for 1.5 h before addition of Et_3N (0.88 mL, 6.31 mmol). The mixture was warmed to –30 °C over 2 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **23** (73 mg, 72%): liquid; R_f 0.60 (hexane/EtOAc 2:1); $[\alpha]_D^{19}$ +139 (*c* 1.16, $CHCl_3$); lit.[5c] $[\alpha]_D^{20}$ +120.7 (*c* 1.0, $CHCl_3$) for **23** of 92% ee; lit.[5a,b] $[\alpha]_D^{24}$ +158.58 (*c* 1.0, $CHCl_3$) for **23** of 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–1.00 (m, 1 H), 1.05–1.22 (m, 3 H), 1.30–1.44 (m, 2 H), 1.50–1.61 (m, 2 H), 1.62–1.73 (m, 2 H), 1.75 (s, 3 H), 2.40 (tt, *J* = 11.6, 3.2 Hz, 1 H), 2.77 (dd, *J* = 16.0, 2.2 Hz, 1 H), 2.96 (dd, *J* = 16.0, 2.2 Hz, 1 H), 7.25–7.33 (m, 3 H), 7.34–7.41 (m, 2 H), 9.59 (t, *J* = 2.2 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 20.3 (+), 25.47 (–), 25.57 (–), 25.61 (–), 30.6 (–), 30.8 (–), 46.1 (+), 52.1 (–), 54.5 (–), 126.6 (+), 127.7 (+), 129.0 (+), 139.9 (–), 201.7 (+), 213.9 (–). The ^{1}H and ^{13}C NMR spectra were consistent with those in the literature.[5c]

*4.12. LY426965 (**6**)*

To a solution of aldehyde **23** (56 mg, 0.217 mmol) and amine **24** (42 mg, 0.218 mmol) in $(CH_2Cl)_2$ (3 mL) was added $NaBH(OAc)_3$ (93 mg, 0.439 mmol). The solution was stirred at rt for 5 h and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc three times, and the combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give the LY426965 (**6**) (79 mg, 83%): liquid; R_f 0.12 (hexane/EtOAc 2:1); $[\alpha]_D^{19}$ +32 (*c* 1.11, $CHCl_3$); lit.[5c] $[\alpha]_D^{20}$ +34.3 (*c* 0.95, $CHCl_3$) for **6** of 92% ee; lit.[5a,b] $[\alpha]_D^{24}$ +34.28 (*c* 0.95, $CHCl_3$) for **6** of 93% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–1.68 (m, 10 H), 1.57 (s, 3 H), 2.10–2.43 (m, 5 H), 2.65 (br s, 4 H), 3.09 (br s, 4 H), 3.84 (s, 3 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.87–6.96 (m, 2 H), 6.96–7.02 (m, 1 H), 7.22–7.29 (m, 3 H), 7.31–7.38 (m, 2 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ 20.3 (+), 25.59 (–), 25.65 (–), 25.70 (–), 30.6 (–), 31.0 (–), 33.9 (–), 46.1 (+), 50.4 (–), 53.5 (+), 54.2 (+), 55.0 (+), 55.4 (–), 111.2 (+), 118.3 (+), 121.0 (+), 123.0 (+), 126.9 (+), 127.1 (+), 128.6 (+), 141.15 (–), 141.21 (–), 152.3 (–), 215.3 (–). The ^{1}H and ^{13}C NMR spectra were consistent with those in the literature.[5c]

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Appendix A. Supplementary data

Supplementary data (HPLC chromatograms and NMR spectra) related to this article can be found at https://xxxxx.

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