HETEROCYCLES, Vol. 61, 2003, pp. 125 - 131
Received, 12th February, 2003, Accepted, 8th April, 2003, Published online, 14th April, 2003

ENANTIOCONTROLLED TOTAL SYNTHESIS OF (+)-HELIANNUOL D *VIA* PALLADIUM-MEDIATED HETEROCYCLIZATION#

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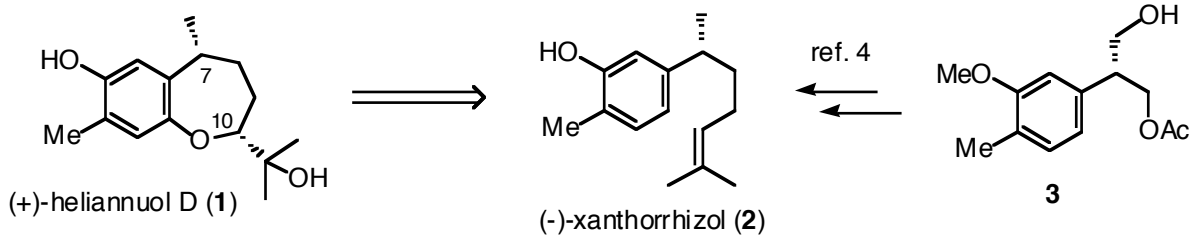
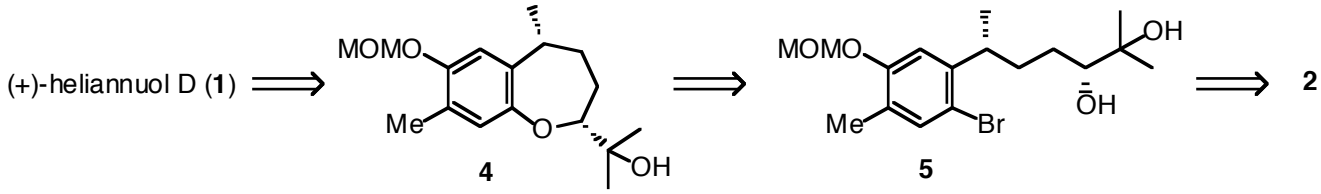
Abstract – An enantiocontrolled total synthesis of (+)-heliannuol D has been accomplished using a palladium-catalyzed cyclization of the seven-membered oxygen containing heterocycle as the key reaction.

(+)-Heliannuol D (**1**),[1] isolated by Macías and coworkers from aqueous extracts of fresh sunflower leaves (*Helianthus annuus* var. SH-222), is a naturally occurring sesquiterpenoid exhibiting allelopathic activity. This intriguing natural product has a unique carbon skeleton made up of an oxygen containing a seven-membered heterocycle fused to the aryl ring and two tertiary stereogenic centers (C-7 and 10) whose absolute configurations were determined to be *R* and *S*, respectively, by our enantioselective total synthesis of (-)-heliannuol D,[2] the unnatural enantiomer. Here we report the first enantiocontrolled total synthesis of the natural enantiomer (+)-heliannuol D (**1**) starting from (-)-xanthorrhizol (**2**).[3] In a previous paper, we reported an enantioselective total synthesis of (-)-xanthorrhizol (**2**),[4] a biologically active aromatic bisabolene sesquiterpenoid, employing lipase-catalyzed desymmetrization of the □-symmetrical prochiral 2-aryl-1,3-propanediol leading to the formation of the optically active alcohol (**3**) as the key step (Scheme 1).



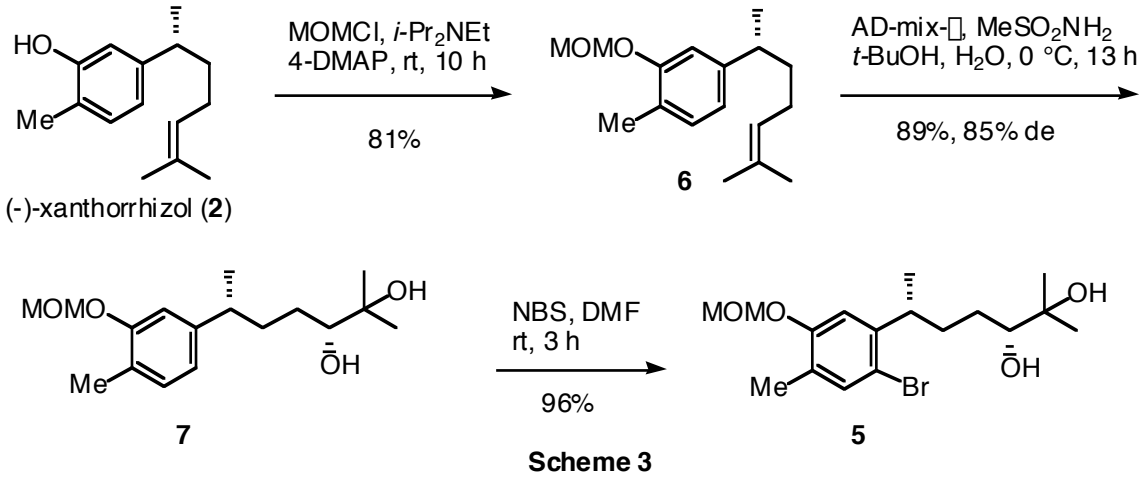
Scheme 1

In our retrosynthetic strategy, we envisioned the palladium-catalyzed heterocyclization[5] of the diol (**5**) leading to the cyclic aryl ether (**4**), a penultimate intermediate for (+)-**1**, as the key step. The substrate (**5**) for the cyclization would be derived from (-)-xanthorrhizol (**2**) (Scheme 2).



Scheme 2

After protection of the phenolic hydroxyl group in optically pure (-)-xanthorrhizol (**2**) as the methoxymethyl (MOM) ether, the resulting **6** was treated with AD-mix-β[6] in the presence of methanesulfonamide in aqueous *tert*-butanol at 0 °C to afford the diol (**7**) in 89% yield. The diastereomeric excess of **7** was determined to be 85% by the diagnostic signal of the methine proton at C-6 in the ^{1}H NMR spectrum. The stereochemistry at the newly generated stereogenic center (future C-10) of the major diastereoisomer was deduced to be *R* from literature precedents.[6] The confirmation was made by the eventual conversion of **7** to the natural heliannuol D. Reaction of **7** with *N*-bromosuccinimide in DMF provided the bromide (**5**) in 96% yield (Scheme 3).

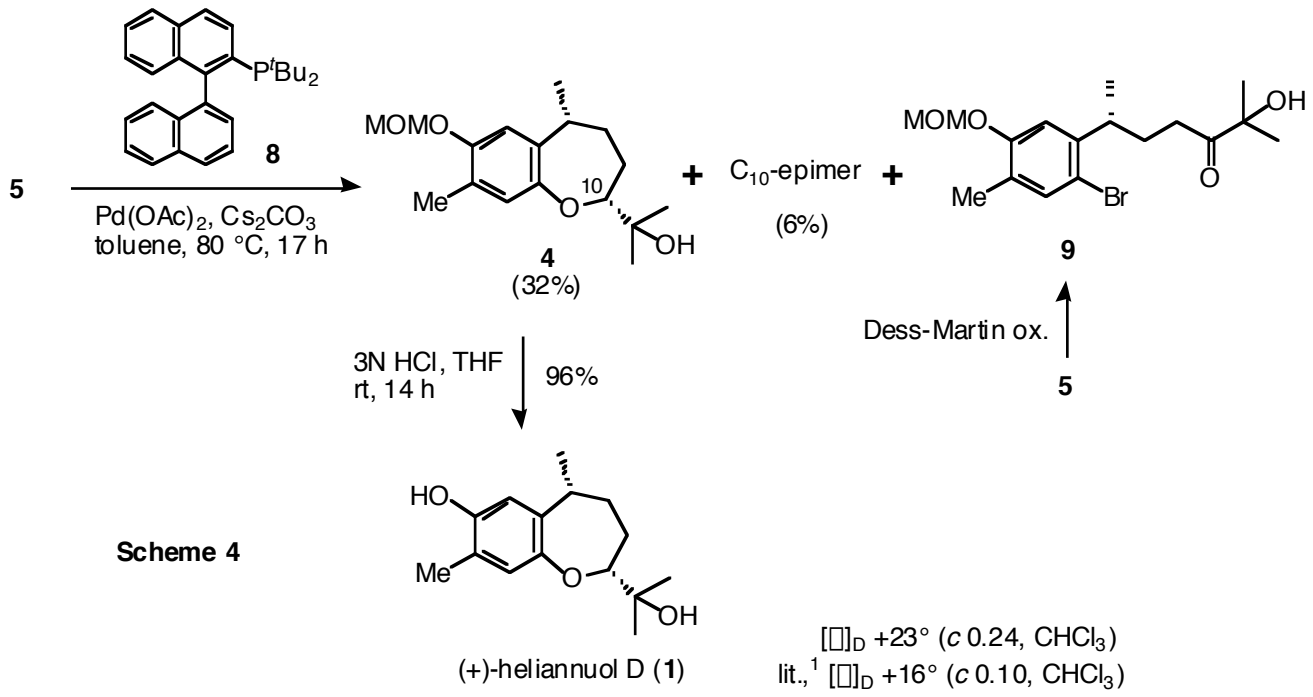


Scheme 3

With the desired substrate (**5**) in hand, we next examined the key cyclization. Treatment of **5** with a catalytic amount of palladium acetate in the presence of (*R*)-MOP[7] and cesium carbonate in toluene at 80 °C resulted in the recovery of starting material. The use of other ligands including DPPF,[5a] BINAP, etc., gave no desired cyclized product. However, when the reaction was conducted with the conditions developed by Buchwald,[5] good results were obtained. Thus, treatment of **5** with palladium acetate (3 mol %) in the presence of *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (**8**)[8] (2.5 mol %) and cesium carbonate in toluene at 80 °C produced the desired cyclic aryl ether (**4**) in 32% yield accompanied by 6% yield of the C_{10}-epimer of **4** and the ketone (**9**)[5,9] which was obtained as an inseparable mixture (*ca.* 1:1) along with an unidentified product. The structure of **9** was confirmed by comparison with an authentic

sample prepared from **5** by Dess-Martin oxidation. Hydrolysis of the *O*-MOM group in the enantiomerically pure **4** with 3N HCl in THF afforded (+)-heliannuol D (**1**) {$[\alpha]_D$ +23° (*c* 0.24, $CHCl_3$); lit.[1], $[\alpha]_D$ +16° (*c* 0.10, $CHCl_3$)} as an oil, identical in all respects to the natural product (^{1}H and ^{13}C NMR, and MS spectra) (Scheme 3).

In summary, we have completed the first enantioselective total synthesis of (+)-heliannuol D, the natural enantiomer, starting from (-)-xanthorrhizol using the palladium-catalyzed aryl ether forming cyclization reaction as the key step. This is an application of the Buchwald cyclization for the synthesis of natural products. The synthetic route developed here can also be applied to the synthesis of other helianane-type sesquiterpenoids.



Scheme 4

EXPERIMENTAL

^{1}H NMR spectra were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL AL 400 (400 MHz) spectrometer, unless otherwise noted. ^{13}C NMR spectra were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) or TMS (0.00 ppm) using JEOL AL 300 (75 MHz) and JEOL AL 400 (100 MHz) spectrometers. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. MS spectra were obtained on JEOL JMS-DX303, JMS-AX500 and JMS-SX102A. Optical rotations were determined on JASCO P-1010. Analytical thin layer chromatography (TLC) was performed on precoated plates (0.25 mm, silica gel Merck $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain.

Column chromatography was performed on a silica gel, KANTO Silica Gel 60 N (63-210 mesh). All reactions were performed in oven-dried glassware under positive pressure of argon or nitrogen, unless otherwise noted.

(6*R*)-6-(3-Methoxymethoxy-4-methyl)phenyl-2-methyl-2-heptene (6): To a solution of (-)-xanthorrhizol (**2**)[4] (40.1 mg, 0.184 mmol) in *i*-Pr_2NEt (1.0 mL) was added 4-DMAP (2.2 mg, 0.018 mmol) at 0 ˚C. After stirring for 10 min, methoxymethyl chloride (0.04 mL, 0.551 mmol) was added and the mixture was stirred for 10 h at rt. After evaporation of the solvent, the residual oil was extracted with CH_2Cl_2 and the extracts were washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hex/AcOEt = 95/5) gave **6** (38.9 mg, 81%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 6.8 Hz, 3H), 1.54 (s, 3H), 1.57 (s, 3H), 1.90 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 2H), 2.22 (s, 3H), 2.65 (ddq, *J* = 6.0, 6.8, 6.8 Hz, 1H), 3.50 (s, 3H), 5.10 (t, *J* = 6.4 Hz, 1H), 5.19 (d, *J* = 7.2 Hz, 1H), 5.21 (d, *J* = 7.2 Hz, 1H), 6.76 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 17.8, 22.6, 25.8, 26.3, 38.4, 39.4, 55.9, 94.5, 112.8, 119.9, 124.4, 130.3, 131.1, 146.6, 155.2; IR (neat) 2924, 1613, 1246 cm^{-1}; MS (EI) *m/z*: 262 (M^+), 45 (base peak); HRMS (EI) Calcd for $C_{17}H_{26}O_2$ 262.1922, found 262.1911; $[\alpha]_D$ -22.9° (*c* 1.29, $CHCl_3$).

(3*R*,6*R*)-6-(3-Methoxymethoxy-4-methyl)phenyl-2-methylheptane-2,3-diol (7): To a solution of **6** (0.37 g, 1.41 mmol) and $MeSO_2NH_2$ (0.33 g, 3.52 mmol) in *t*-BuOH/H_2O (18.5 mL, 1/1) was added AD-mix-β (5.5 g) at 0 ˚C and the mixture was stirred for 13 h at the same temperature. Na_2SO_3 (1.07 g, 8.46 mmol) was added to the solution at 0 ˚C and the mixture was stirred for 10 min, then allowed to warm to rt and stirred for 30 min. The mixture was extracted with $CHCl_3$, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, hex/AcOEt = 70/30) gave an inseparable mixture of **7** and the C_3-epimer (0.38 g, 90%, 85% de) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 (s, 3H), 1.13 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.26-1.49 (m, 2H), 1.57-1.66 (m, 1H), 1.80-1.90 (m, 1H), 2.21 (s, 3H), 2.65 (m, 1H), 3.27 (dd, *J* = 2.0, 10.0 Hz, 1H), 3.51 (s, 3H), 5.18 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H) 6.76 (d, *J* = 7.6 Hz, 1H), 6.87 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 22.4, 23.1, 26.4, 29.9, 35.4, 39.9, 55.9, 78.6, 94.4, 112.7, 119.9, 124.5, 130.4, 146.3, 155.0; IR (neat) 3425, 2957, 1247 cm^{-1}; MS (EI) *m/z*: 296 (M^+), 45 (base peak); HRMS (EI) Calcd for $C_{17}H_{28}O_4$ 296.1988, found 296.1993; $[\alpha]_D$ +7.54° (*c* 0.96, $CHCl_3$).

(3*R*,6*R*)-6-(2-Bromo-5-methoxymethoxy-4-methyl)phenyl-2-methylheptane-2,3-diol (5): To a

solution of **7** (18 mg, 0.061 mmol) in DMF (1.5 mL) was added dropwise a solution of NBS (16.2 mg, 0.091 mmol) in DMF (0.5 mL) at rt. After stirring for 3 h, the solvent was evaporated to give an oil, which was taken up with CH_2Cl_2 then washed with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, hex/AcOEt = 70/30) gave **5** (21.5 mg, 94%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.15 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.31-1.46 (m, 2H), 1.77-1.86 (m, 2H), 2.18 (s, 3H), 3.17 (ddq, *J* = 6.8, 6.8, 6.8 Hz, 1H), 3.27 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.47 (s, 3H), 5.14 (d, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 6.8 Hz), 6.92 (s, 1H), 7.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.6, 21.2, 23.1, 26.4, 29.7, 34.3, 38.2, 55.9, 73.0, 78.5, 94.4, 112.7, 115.7, 126.9, 134.0, 144.1, 154.7; IR (neat) 3419, 1487, 1147 cm^{-1}; MS (EI) *m/z*: 374 (M^+), 376 (M^++2), 45 (base peak); HRMS (EI) Calcd for $C_{17}H_{27}O_4Br$ 374.1093, found 374.1127; $[\alpha]_D$ +6.48° (*c* 0.94, $CHCl_3$).

5-Methoxymethyl ether of heliannuol D (4), the C_{10}-epimer, and (6*R*)-6-(2-bromo-5-methoxymethoxy-4-methyl)phenyl-3-oxo-2-methylheptan-2-ol (9): To a mixture of $Pd(OAc)_2$ (0.27 mg, 1.2 μmol), Cs_2CO_3 (24.8 mg, 7.6 μmol) and *rac*-di-*tert*-butylphosphinobinaphthyl (1.82 mg, 4.6 μmol) was added a solution of **5** (14.3 mg, 38.0 μmol) in degassed toluene (1 mL) at rt. After stirring at 80 °C for 17 h, the mixture was cooled to rt and diluted with AcOEt. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Preparative TLC (hex/AcOEt = 70/30) gave a mixture of **4** and the C_{10}-epimer (4.2 mg, 38%), a mixture of **9** and an unidentified compound (3.6 mg), and recovered **5** (3.2 mg, 23%). Separation of the diastereomeric mixture of **4** by HPLC [Mightysil Si60 250-20 (5 μmL) column, flow rate 10 ml/min, hex/AcOEt = 95/5] provided **4** (3.6 mg, 32%) (T=158 min) and the C_{10}-epimer (0.6 mg, 6%) (T=159 min).

4: a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 6H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.72 (br s, 1H), 1.78 (br s, 1H), 2.05 (br s, 1H), 2.17 (s, 3H), 2.95 (s, 1H), 3.30 (dd, *J* = 1.3, 11.2 Hz, 1H), 3.50 (s, 3H), 5.14 (s, 2H), 6.75 (s, 1H), 6.80 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 18.8, 24.6, 25.7, 26.2, 31.9, 39.0, 56.1, 72.5, 90.4, 95.1, 115.4, 123.4, 126.0, 137.6, 151.2, 152.4; IR (neat) 3467, 1152, 1069 cm^{-1}; MS (EI) *m/z*: 294 (M^+), 83 (base peak); HRMS (EI) Calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1826; $[\alpha]_D$ +24.4° (*c* 0.89, $CHCl_3$).

C_{10}-epimer of **4**: a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 6H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.70-1.81 (m, 2H), 1.87-1.94 (m, 1H), 2.00-2.12 (m, 1H), 2.66 (br s, 1H, D_2O exchangeable), 2.91-2.99 (m, 1H), 3.30 (dd, *J* = 1.2, 11.2 Hz, 1H), 3.50 (s, 3H), 5.11 (d, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 6.76 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 18.6, 24.4, 25.5, 26.1, 31.7, 38.8, 56.1, 72.5, 90.5, 95.1, 115.4, 123.5, 126.1, 137.7, 151.4, 152.5; IR (neat) 3438, 1500, 1021 cm^{-1}; MS (EI) *m/z*: 294 (M^+), 83 (base peak); HRMS (EI) Calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1825; $[\alpha]_D$ +20.9° (*c* 0.89,

$CHCl_3$).

Oxidation of the Diol (5): To a solution of **5** (7.1 mg, 0.019 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (10.6 mg, 0.025 mmol) at 0 °C. After stirring for 12 h at rt, the mixture was quenched by addition of saturated aq. $NaHCO_3$ (0.5 mL) and saturated aq. $Na_2S_2O_3$ (0.5 mL) at 0 °C. After being stirred for a further 30 min at rt, the resulting mixture was extracted with AcOEt. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Preparative TLC (hex/AcOEt = 50/50) gave **9** (0.8 mg, 11%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.89-1.95 (m, 2H), 2.19 (s, 3H), 2.37-2.53 (m, 2H), 3.18-3.24 (m, 1H), 3.47 (s, 3H), 5.16 (d, *J* = 6.8 Hz, 1H), 5.18 (d, *J* = 6.8 Hz, 1H), 6.89 (s, 1H), 7.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 21.7, 26.4, 26.5, 30.9, 33.4, 37.6, 56.1, 76.1, 94.6, 112.5, 116.0, 127.5, 134.3, 143.0, 155., 214.3; IR (neat) 3391, 1716, 1147, 1082, 1036 cm^{-1}; MS (EI) *m/z*: 372 (M^+), 374 (M^++2), 83 (base peak); HRMS (EI) Calcd for $C_{17}H_{25}O_4Br$ 372.0936, found 372.0954. This was identical with one of the compounds prepared in the mixture above.

(+)-Heliannuol D (1): To a solution of **4** (5.4 mg, 0.018 mmol) in THF (1 mL) was added 3N hydrochloric acid (0.11 mL, 0.33 mmol) at 0 °C. After the mixture was stirred for 14 h at rt, an additional 3N hydrochloric acid (0.08 mL, 0.24 mmol) was added at 0 °C and stirring was continued for 14 h at rt. The resulting mixture was extracted with $CHCl_3$, the organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, hex/AcOEt = 70/30) gave **1** (4.4 mg, 96%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 6H), 1.29 (d, *J* = 6.9, 3.0 Hz, 3H), 1.71 (br s, 1H), 1.76 (br s, 1H), 1.88 (br s, 1H), 2,04 (br s, 1H), 2.16 (s, 3H), 2.90 (s, 1H), 3.29 (dd, *J* = 1.3, 11.2 Hz, 1H), 4.78 (br s, 1H, D_2O exchangeable), 6.54 (s, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.4, 18.8, 24.6, 25.7, 26.2, 31.9, 38.6, 72.6, 90.5, 115.6, 121.9, 123.4, 138.0, 149.3, 151.5; IR (neat) 3369, 1064 cm^{-1}; MS (EI) *m/z*: 250 (M^+), 151 (base peak); HRMS (EI) Calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1531; $[\alpha]_D$ +22.9° (*c* 0.24, $CHCl_3$).

ACKNOWLEDGEMENTS

We thank Professor Macías, University of Cádiz, for providing us with spectral data of the natural heliannuol D. We are grateful to Professor Stephen L. Buchwald and Ms Karen Torraca, Massachusetts Institute of Technology, for providing us with *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl and for helpful discussions. We also thank Professor Tamio Hayashi, Kyoto University, for giving us the MOP ligand.

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[#] Dedicated to The Japan Institute of Heterocyclic Chemistry on the occasion of its 30th Anniversary.

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