Synthesis of (*R*)-Curcumene and (*R*)-Xanthorrizol Based on 1,2-Aryl Migration *via* Phenonium Ion

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Solvolysis reaction of methyl (4*S*,5*S*)-4-(4′-methoxyphenyl)-5-tosyloxy-2(*E*)-hexenoate 5 in water-saturated $MeNO_2$ gave the 1,2-migration product, (4*S*,5*S*)-5-hydroxy-4-(4′-methoxyphenyl)-2-(*E*)-hexenoate 6 (55% yield), which was converted to methyl (*R*)-(4′-methylphenyl)hexanoate 11 in 25% overall yield (5 steps). Treatment of (*R*)-11 with MeLi gave tertiary alcohol congener 12, which was subjected to dehydration to afford (*R*)-(−)-curcumene 1. An introduction of hydroxyl group at *meta*-position of the aromatic ring in (*R*)-11 was achieved based on consecutive treatment [1) selective iodination, 2) conversion of aryl iodide to aryl boronate, 3) conversion of aryl boronate to phenol]. Thus obtained phenol (*R*)-16 was treated with MeLi to give tertiary alcohol congener 17, which was subjected to dehydration to afford (*R*)-(−)-xanthorrizol 2.

Key words (*R*)-(−)-curcumene; (*R*)-(−)-xanthorrizol; solvolysis; 1,2-aryl migration; phenonium ion

In the several important classes of natural products, bisabolane family compounds are characterized by a benzylic chiral center bearing a methyl group. (*R*)-(−)-curcumene **1** is the constituent of a large number of essential oil, and used for the syntheses of a number of other bisabolane family and other related terpene.[1)] Xanthorrizol **2** was first extracted from *Curcuma xanthorrhiza*, which is used in traditional medicine in Indonesia.[2)] Afterward, xanthorrizol **2** was also isolated from the same plant as an antitumor constituent.[3)] Moreover, xanthorrizol **2** was identified as a principle prolonging pentobarbital-induced sleeping time, of which effect was indicated to be due to inhibition of cytochrome P-450 activity.[4)] Despite their rather simple structures, the stereocenter at the benzylic position poses a significant challenge in the asymmetric synthesis of even the simplest of these molecules. Judging from the publications dealing with the synthesis of curcumene **1**, this molecule has evolved as a test target for indicating new asymmetric methodology and nine synthesis of (−)-**1** were reported.[5)] Although nine syntheses of xanthorrizol **2** have been reported, the first asymmetric synthesis of unnatural (+)-**2**[6)] and natural (−)-**2**[7)] based on chemoenzymatic transformation were reported. On the other hand, we reported construction of the stereocenter at the benzylic position based on solvolysis of (4,5-*anti*)-4-aryl-5-tosyloxy-(2*E*)-hexenoate congeners in water-saturated $MeNO_2$ affording 1,2-aryl migration products along with complete inversion in good yield.[8)] We now report that (*R*)-curcumene **1** and (*R*)-xanthorrizol **2** have been synthesized based on 1,2-aryl migration *via* phenonium ion.

We previously reported that the $BF_3 \cdot Et_2O$-assisted reaction of (4,5)-epoxy-2(*E*)-hexenoate (**3**) with benzene analog bearing electron-donating group gave (4,5-*anti*)-4-aryl-5-hydroxy-(2*E*)-hexenoate **A**.[9—11)] Moreover, solvolysis of (4,5-*anti*)-4-aryl-5-tosyloxy-(2*E*)-hexenoate **B** derived from **A** in water-saturated $MeNO_2$ gave 1,2-aryl migration product **D** along with complete inversion in good yield.[8)] In the case of this reaction, an intermolecular attack of the nucleophile (H_2O) to the σ-bridged phenonium ion **C** proceeded selectively at the C(4)-position to provide the (4,5-*anti*)-5-aryl-4-hydroxy-(2*E*)-hexenoate **D**. If this reaction were applied for the chiral synthesis of (*R*)-**1** or (*R*)-**2**, solvolysis of (4*S*,5*S*)-4-(4′-methoxyphenyl)-5-tosyloxy-(2*E*)-hexenoate **5** seems to be promising, because solvolysis of (±)-**5** gives the type **D** compound with a 7 : 1 selectivity (**D** : **A** = 7 : 1).[8)] Methoxyl group of the type **D** compound (**6**) could be convertible to methyl group. Then the $BF_3 \cdot Et_2O$-assisted reaction of (4*S*,5*S*)-4-epoxy-(2*E*)-hexenoate **3** and anisole was carried out. The synthesis of (*R*)-(−)-curcumene (**2**) from (4*S*,5*S*)-**3** is shown in Chart 2.

The reaction of (4*S*,5*S*)-**3**[12)] and anisole gave (4*S*,5*S*)-**4** (72% yield), of which structure was confirmed by the direct comparison of the reported (±)-**3**.[10)] Treatment of (4*S*,5*S*)-**4**

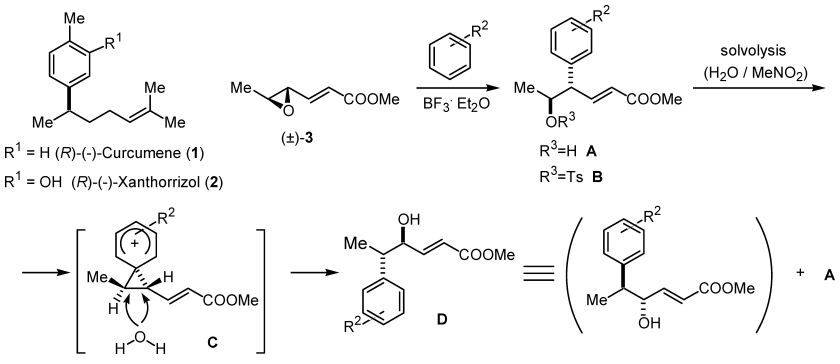

Chart 1

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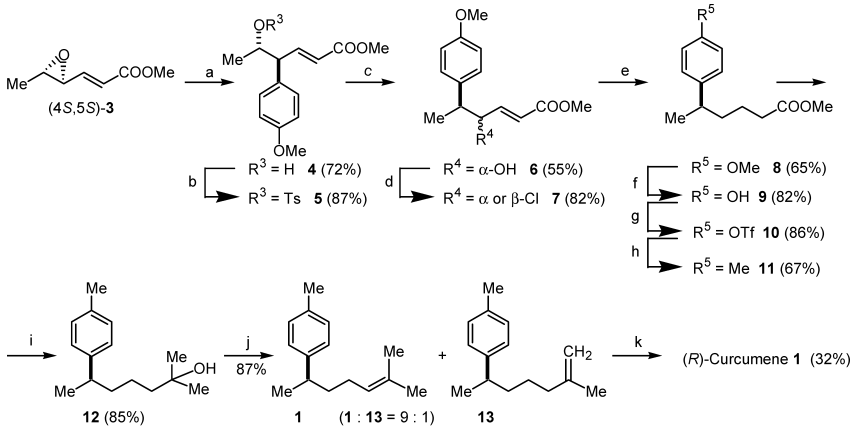
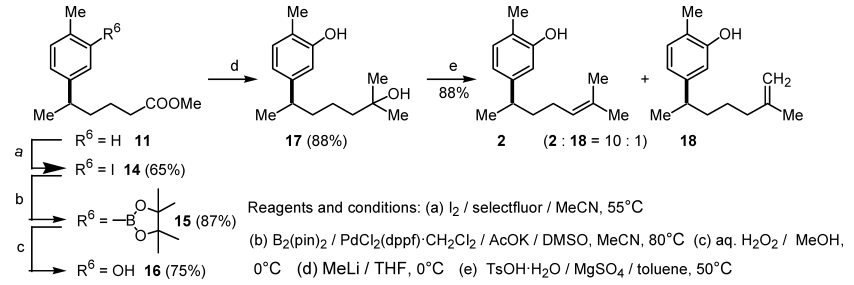


Reagents and conditions: (a) anisole / $BF_3{\cdot}Et_2O$ / CH_2Cl_2, -20°C (b) TsCl / pyridine, r.t. (c) H_2O / $MeNO_2$, 50°C (d) NCS / Ph_3P / MeCN, r.t. (e) H_2 / 20% $Pd(OH)_2$-C / MeOH (f) $C_{12}H_{25}SH$ / $AlCl_3$ / CH_2Cl_2, r.t. (g) Tf_2O / pyridine / CH_2Cl_2, r.t. (h) Me_4Sn / $Pd(PPh_3)_4$ / DMF, 80°C (i) MeLi / THF, 0°C (j) $TsOH{\cdot}H_2O$ / $MgSO_4$ / toluene, 50°C (k) Grubb's reagent (2nd generation) / $ClCH_2CH_2Cl$, 60°C

Chart 2



Reagents and conditions: (a) I_2 / selectfluor / MeCN, 55°C (b) $B_2(pin)_2$ / $PdCl_2(dppf){\cdot}CH_2Cl_2$ / AcOK / DMSO, MeCN, 80°C (c) aq. H_2O_2 / MeOH, 0°C (d) MeLi / THF, 0°C (e) $TsOH{\cdot}H_2O$ / $MgSO_4$ / toluene, 50°C

Chart 3

with tosyl chloride (TsCl) afforded the corresponding tosylate (4*S*,5*S*)-**5** (87% yield), which was subjected to solvolysis in water-saturated $MeNO_2$ to provide the 1,2-migration product (4*S*,5*S*)-**6** (55% yield). Treatment of (4*S*,5*S*)-**6** with *N*-chlorosuccinimide (NCS) and triphenylphosphine (Ph_3P) gave a single isomer (5*S*)-**7** (82% yield), which was subjected to hydrogenolysis to afford the saturated ester (*R*)-**8** (65% yield). Demethylation of (*R*)-**8** with a combination of $AlCl_3$ and 1-dodecanethiol ($C_{12}H_{25}SH$)[13] provided the phenol (*R*)-**9** (82% yield), which was treated with trifluoromethanesufonic anhydride (Tf_2O) to afford the corresponding trifluoromethanesufonate (*R*)-**10** (86% yield). The reaction of (*R*)-**10** with tetramethyltin (Me_4Sn) in the presence of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) gave 4-substituted toluene congener (*R*)-**11** (67% yield). Treatment of (*R*)-**11** with MeLi followed by dehydration afforded a 9 : 1 mixture (**1** : **13**=9 : 1) of dehydration products in 87% yield. For the purpose of exclusion of the undesired isomer **13**, this mixture was treated with Grubb's reagent (2nd generation) to provide (*R*)-curcumene **1** ($[\alpha]_D^{23}$ −45.0° (*c*=0.75, $CHCl_3$)) in 32% yield. Spectral data (^{1}H-, ^{13}C-NMR) were identical with those of the reported sample **1** including a specific rotation ($[\alpha]_D^{23}$ −46.2° (*c*=0.95, $CHCl_3$)).[14] Then, the synthesis of (*R*)-(−)-xanthorrizol (**2**) from (5*R*)-**11** is shown in Chart 3.

The most intriguing point in the synthesis of (*R*)-**2** from (*R*)-**11** is introduction of hydroxyl group at *meta*-position of the aromatic ring. This problem was solved by the following steps: 1) selective iodination, 2) conversion of aryl iodide to aryl boronate, 3) conversion of aryl boronate to phenol. Recently, benzene derivatives, bearing at least one bulky, alkyl group (*iso*-Pr, *tert*-Bu) were reported to give effectively the iodinated compounds using elemental iodine activated by 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor^{TM}, F-TEDA-BF_4).[15] By applying this procedure, (*R*)-**11** was treated with iodine (I_2) in the presence of Selectfluor^{TM} to give the desired iodide **14** in 65% yield. Substitution pattern of the aromatic ring of **14** was confirmed by ^{1}H-NMR analysis. The reaction of **14** with bis(pinacolato)diboron [$B_2(pin)_2$][16] in the presence of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane [$PdCl_2(dppf){\cdot}CH_2Cl_2$] afforded the corresponding aryl boronate congener **15** (87%), which was treated with 30% H_2O_2 to provide the desired phenol **16** in 75% yield. Treatment of (*R*)-**16** with MeLi gave tertiary alcohol congener **17** (88%), which was subjected to dehydration to provide a 10 : 1 mixture of **2** and **18** (**2** : **18**=10 : 1). A part of this mixture was subjected to preparative TLC to afford a synthetic (*R*)-xanthorrizol **2** ($[\alpha]_D^{24}$ −53.5° (*c*=0.75, $CHCl_3$)). Spectral data (^{1}H-, ^{13}C-NMR) of the synthetic (*R*)-xanthorrizol **2** were identical with those of the reported sample **2** including a specific rotation ($[\alpha]_D$ −54° (*c*=0.13, $CHCl_3$)).[7]

Conclusion

Solvolysis reaction of methyl (4*S*,5*S*)-4-(4′-methoxyphenyl)-5-tosyloxy-2(*E*)-hexenoate **5** in water-saturated $MeNO_2$

gave the 1,2-migration product, (4*S*,5*S*)-5-hydroxy-4-(4′-methoxyphenyl)-2-(*E*)-hexenoate **6** (55% yield), which was converted to methyl (*R*)-(4′-methylphenyl)hexanoate **11** in 25% overall yield (5 steps). Treatment of (*R*)-**11** with MeLi followed by dehydration afforded (*R*)-(−)-**1**. An introduction of hydroxyl group at *meta*-position of the aromatic ring in (*R*)-**11** was achieved based on consecutive treatment [1) selective iodination, 2) conversion of aryl iodide to aryl boronate, 3) conversion of aryl boronate to phenol]. Thus obtained phenol (*R*)-**16** was treated with MeLi followed by dehydration to afford (*R*)-(−)-**2**.

Experimental

All melting points were measured on a Mettler FP-62 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded by a Bruker AV400M digital NMR. Spectra were taken with 5—10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. Mass spectra and the fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS-600H (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl (4*S*,5*S*)-*anti*-4-(4′-Methoxyphenyl)-5-hydroxy-2(*E*)-hexenoate 4 To a solution of (4*S*,5*S*)-**3** (3.0 g, 21.1 mmol) and anisole (4.577 g, 42.3 mmol) in CH_2Cl_2 (42 ml) was added $BF_3 \cdot Et_2O$ (3.5 ml, 28 mmol) at −20 °C, and the whole mixture was stirred for 2 h at −20 °C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to provide a residue, which was chromatographed on silica gel (700 g, *n*-hexane : AcOEt=4 : 1—2 : 1) to afford (4*S*,5*S*)-**4** (3.8 g, 72%) as a colorless oil. (4*S*,5*S*)-**4**: $[\alpha]_D^{25}$ +21.3° (*c*=2.12, $CHCl_3$). ^{1}H-NMR data of (4*S*,5*S*)-**4** was identical with those of the reported (±)-**4**.[10]

Methyl (4*S*,5*S*)-*anti*-4-(4′-Methoxyphenyl)-5-tosyloxy-2(*E*)-hexenoate 5 A mixture of (4*S*,5*S*)-**4** (3.7 g, 14 mmol), *p*-toluenesulfonyl chloride (TsCl, 5.6 g, 29 mmol), pyridine (30 ml) was stirred for 1 d at r.t. The reaction mixture was diluted with H_2O, which was extracted with AcOEt. The organic layer was washed with 1 M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was chromatographed on silica gel (200 g, *n*-hexane : AcOEt=5 : 1) to afford (4*S*,5*S*)-**5** (5.2 g, 87%). Crystallization of (4*S*,5*S*)-**5** from a mixed solvent (*n*-hexane : AcOEt=1 : 1) gave amorphous precipitate (4*S*,5*S*)-**5**. (4*S*,5*S*)-**5**: mp 105 °C, $[\alpha]_D^{22}$ +41.4° (*c*=1.00, $CHCl_3$). ^{1}H-NMR data of (4*S*,5*S*)-**5** was identical with those of the reported (±)-**5**.[8]

Solvolysis of (4*S*,5*S*)-5 A solution of (4*S*,5*S*)-**5** (10.0 g, 24.7 mmol) in water-saturated nitromethane (500 ml) was stirred for 4 d at 50 °C. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with 5% aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (700 g, *n*-hexane : AcOEt=7 : 1—4 : 1) to afford (4*S*,5*S*)-**6** (3.4 g, 55%) as a colorless oil. (4*S*,5*S*)-**6**: $[\alpha]_D^{20}$ −14.7° (*c*=1.00, $CHCl_3$). ^{1}H-NMR data of (4*S*,5*S*)-**6** was identical with those of the reported (±)-**6**.[8]

Methyl (5*S*)-4-Chloro-5-(4′-Methoxyphenyl)-2(*E*)-hexenoate 7 To a solution of (4*S*,5*S*)-**6** (3.3 g, 13.2 mmol) and Ph_3P (5.19 g, 19.8 mmol) in CH_2Cl_2 (160 ml) was added a solution of NCS (2.64 g, 19.8 mmol) in CH_2Cl_2 (100 ml) at −20 °C, and the whole mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (500 g, *n*-hexane : AcOEt=20 : 1) to afford (5*R*)-**7** (2.90 g, 82%) as amorphous precipitate (*R*)-**7**: mp 55 °C, $[\alpha]_D^{23}$ −57.4° (*c*=1.09, $CHCl_3$). IR (neat): 1725 cm^{-1}. ^{1}H-NMR: δ 1.42 (3H, d, *J*=7 Hz), 3.10 (1H, dq, *J*=6.8, 7.1 Hz), 3.71 (3H, s), 3.79 (3H, s), 4.52 (1H, dt, *J*=1.3, 8.0 Hz), 5.89 (1H, dd, *J*=1.3, 15.4 Hz), 6.82 (1H, dd, *J*=8.0, 15.4 Hz), 6.84 (2H, d, *J*=8.6 Hz), 7.11 (2H, d, *J*=8.6 Hz). ^{13}C-NMR: δ 18.0, 45.6, 51.9, 55.4, 65.9, 114.1 (2C), 122.9, 129.0 (2C), 133.9, 145.5, 158.9, 166.3. HR-MS (EI) Calcd for $C_{14}H_{17}Cl^{35}O_3$: 268.0866. Found: 268.0864. Calcd for $C_{14}H_{17}Cl^{37}O_3$: 270.0837. Found: 270.0841.

Methyl (*R*)-(4′-Methoxyphenyl)hexanoate 8 A solution of (*R*)-**7** (2.84 g, 10.6 mmol) in MeOH (50 ml) was hydrogenated over 20% $Pd(OH)_2$–C (0.28 g) at room temperature under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to give a crude oil which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt=9 : 1) to afford (*R*)-**8** (1.62 g, 65%) as a colorless oil. (*R*)-**8**: $[\alpha]_D^{23}$ −11.0° (*c*=2.50, $CHCl_3$); IR (neat): 1738 cm^{-1}. NMR: δ 1.21 (3H, d, *J*=6.8 Hz), 1.45—1.61 (4H, m), 2.26 (2H, t, *J*=7 Hz), 2.65 (1H, sixtet, *J*=6.8 Hz), 3.64 (3H, s), 3.79 (3H, s), 6.83 (2H, d, *J*=8.7 Hz), 7.09 (2H, d, *J*=8.7 Hz). ^{13}C-NMR: δ 22.6, 23.3, 34.2, 38.1, 39.0, 51.6, 55.4, 113.9 (2C), 127.9 (2C), 139.4, 158.0, 174.2. HR-MS (EI) Calcd for $C_{14}H_{20}O_3$: 236.1413. Found: 236.1415.

Methyl (*R*)-(4′-Hydroxyphenyl)hexanoate 9 To a suspension of (*R*)-**8** (1.57 g, 6.6 mmol) and $AlCl_3$ (2.66 g, 20 mmol) in CH_2Cl_2 (33 ml) was added 1-dodecanethiol ($C_{12}H_{25}SH$, 4.1 g, 20 mmol) at 0 °C and the whole mixture was stirred for 12 h at r.t. The reaction mixture was poured into ice and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (60 g, *n*-hexane : AcOEt=6 : 1) to afford (5*R*)-**9** (1.21 g, 82%) as a colorless oil. (*R*)-**9**: $[\alpha]_D^{25}$ −17.8° (*c*=1.0, $CHCl_3$); IR (neat): 3404, 1713 cm^{-1}. NMR: δ 1.21 (3H, d, *J*=7.1 Hz), 1.43—1.59 (4H, m), 2.26 (2H, t, *J*=7.2 Hz), 2.63 (1H, sixtet, *J*=7.1 Hz), 3.64 (3H, s), 4.75 (1H, s), 6.76 (2H, d, *J*=8.5 Hz), 7.04 (2H, d, *J*=8.5 Hz). ^{13}C-NMR: δ 22.6, 23.3, 34.2, 38.1, 39.0, 51.6, 115.3 (2C), 128.1 (2C), 139.6, 153.8, 174.4. HR-MS (EI) Calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1265.

Methyl (*R*)-(4′-Trifluoromethanesufonyloxyphenyl)hexanoate 10 To a solution of (*R*)-**9** (1.18 g, 5.3 mmol) and pyridine (1.64 g, 21 mmol) in CH_2Cl_2 (27 ml) was added trifluoromethanesufonic anhydride (Tf_2O, 1.95 g, 6.9 mmol) at 0 °C and the whole mixture was stirred for 2 h at r.t. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (40 g, *n*-hexane : AcOEt=20 : 1) to afford (*R*)-**10** (1.61 g, 86%) as a colorless oil. (*R*)-**10**: $[\alpha]_D^{23}$ −10.2° (*c*=1.57, $CHCl_3$); IR (neat): 1739, 1422, 1141 cm^{-1}. NMR: δ 1.24 (3H, d, *J*=7.1 Hz), 1.41—1.64 (4H, m), 2.28 (2H, t, *J*=6.8 Hz), 2.74 (1H, sixtet, *J*=7.1 Hz), 3.65 (3H, s), 7.19 (2H, d, *J*=8.8 Hz), 7.24 (2H, d, *J*=8.8 Hz). ^{13}C-NMR: δ 22.3, 23.1, 34.1, 37.7, 39.5, 51.6, 117.3, 120.5, 121.3 (2C), 128.8 (2C), 147.9, 174.0. HR-MS (EI) Calcd for $C_{14}F_3H_{17}O_5S$: 354.0749. Found: 354.0744.

Methyl (*R*)-(4′-Methylphenyl)hexanoate 11 To a solution of (*R*)-**10** (1.58 g, 4.5 mmol) and tetramethyltin (Me_4Sn, 1.20 g, 6.7 mmol) in DMF (18 ml) was added tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 0.12 g, 0.1 mmol) under nitrogen atmosphere at 0 °C and the whole mixture was stirred for 13 h at 80 °C. The reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (90 g, *n*-hexane : AcOEt=20 : 1) to afford (*R*)-**11** (0.655 g, 67%) as a colorless oil. (*R*)-**11**: $[\alpha]_D^{22}$ −22.9° (*c*=1.35, $CHCl_3$); IR (neat): 1740 cm^{-1}. NMR: δ 1.22 (3H, d, *J*=7.1 Hz), 1.46—1.61 (4H, m), 2.23—2.28 (2H, m), 2.31 (3H, s), 2.66 (1H, sixtet, *J*=7.1 Hz), 3.64 (3H, s), 7.07 (2H, d, *J*=8.2 Hz), 7.09 (2H, d, *J*=8.2 Hz). ^{13}C-NMR: δ 21.1, 22.5, 23.3, 34.3, 37.9, 39.5, 51.6, 127.0 (2C), 129.2 (2C), 135.5, 144.3, 174.3. HR-MS (EI) Calcd for $C_{14}H_{20}O_2$: 220.1463. Found: 220.1479.

(6*R*)-2-Hydroxy-2-methyl-6-(4′-methylphenyl)heptane 12 To a solution of (5*R*)-**11** (0.185 g, 0.84 mmol) in THF (1.5 ml) was added 1 M MeLi solution in Et_2O (2.52 ml, 2.52 mmol) at 0 °C and the whole mixture was stirred for 2 h at 0 °C. Under ice-cooling, to the reaction mixture was added 5% aqueous $KHSO_4$ and it was extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (4 g, *n*-hexane : AcOEt=20 : 1—9 : 1) to afford (6*R*)-**12** (0.157 g, 85%) as a colorless oil. (6*R*)-**12**: $[\alpha]_D^{23}$ −29.8° (*c*=1.13, $CHCl_3$). IR (neat): 3366 cm^{-1}. NMR: δ1.16 (6H, s), 1.22 (3H, d, *J*=6.8 Hz), 1.25—1.63 (6H, m), 2.32 (3H, s), 2.66 (1H, sixtet, *J*=6.8 Hz), 7.08 (2H, d, *J*=8.3 Hz), 7.09 (2H, d, *J*=8.3 Hz). ^{13}C-NMR: δ 21.1, 22.5, 22.6, 29.4 (2C), 39.1, 39.6, 44.1, 71.2, 127.0 (2C), 129.2 (2C), 135.4, 144.8. MS (EI) *m/z*: 219 (M^+-1).

(*R*)-(−)-Curcumene 1 A mixture of (6*R*)-**12** (0.135 g, 6 mmol), $TsOH \cdot H_2O$ (0.058 g, 0.3 mmol) and $MgSO_4$ (0.148 g, 1.2 mmol) in toluene (2 ml) was stirred for 12 h at 60 °C. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (2 g, *n*-hexane) to a 9 : 1 mixture (**1** : **13**=9 : 1) of dehydration products (0.108 g, 87%) as a colorless oil. A mixture of this mixture (0.09 g, 0.45 mmol) and Grubb's reagent (2nd generation, 0.038 g, 0.31 mmol) in $ClCH_2CH_2Cl$ (0.5 ml) was stirred for 12 h at 60 °C. The reaction mixture was evaporated to give a residue, which was subjected to the preparative TLC (silicagel, *n*-hexane) to afford (*R*)-**1** (0.029 g, 32%) as a colorless oil. (*R*)-**1**: $[\alpha]_D^{23}$ −45.0° (*c*=0.75, $CHCl_3$). ^{1}H-NMR:δ1.21 (3H, d, *J*=6.8 Hz), 1.52 (3H, s), 1.52—1.64 (2H, m), 1.67 (3H, s), 1.82—1.93 (2H, m), 2.32 (3H, s), 2.61—2.70 (1H, m), 5.06—5.11 (1H, m), 7.07 (2H, d, *J*=8.2 Hz), 7.09 (2H, d, *J*=8.2 Hz). ^{13}C-NMR: δ 17.8, 21.1, 22.6, 25.9, 26.3, 38.6, 39.2, 124.7, 127.0 (2C), 129.1 (2C), 131.5, 135.3,

144.8. HR-MS (EI) Calcd for $C_{15}H_{22}$: 202.1722. Found: 202.1722.

Methyl (*R*)-(3′-Iodo-4′-methylphenyl)hexanoate 14 To a solution of (*R*)-**11** (0.408 g, 1.85 mmol) in MeCN (20 ml) were added iodine (I_2, 0.258 g, 1.02 mmol) and F-TEDA-BF_4 (0.361 g, 1.02 mmol) at r.t. and the whole mixture was stirred for 2 h at 55 °C. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (70 g, *n*-hexane : AcOEt=20 : 1) to afford (*R*)-**14** (0.415 g, 65%) as a colorless oil. (*R*)-**14**: $[\alpha]_D^{20}$ −10.7° (*c*=0.45, $CHCl_3$); IR (neat): 1738 cm^{-1}. NMR: δ 1.20 (3H, d, *J*=6.8 Hz), 1.43—1.61 (4H, m), 2.24—2.29 (2H, m), 2.39 (3H, s), 2.56—2.65 (1H, m), 3.65 (3H, s), 7.05 (1H, dd, *J*=1.9, 7.6 Hz), 7.14 (1H, d, *J*=7.6 Hz), 7.61 (1H, d, *J*=1.9 Hz). ^{13}C-NMR: δ 17.8, 21.1, 22.6, 25.9, 26.3, 38.6, 39.2, 124.7, 127.0, 129.1, 131.5, 135.3, 144.8, 174.1. MS (EI) *m/z*: 346 (M^+).

Methyl (*R*)-(3′-4,4,5,5-Tetramethyl-1,3,2-dioxoborolanyl-4′-methylphenyl)hexanoate 15 A flask charged with $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.045 g, 0.06 mmol), AcOK (0.324 g, 3.3 mmol) and Bis(pinacolato)diboron [$B_2(pin)_2$, 0.363 g, 1.4 mmol] was flushed with nitrogen. A solution of (*R*)-**14** (0.38 g, 1.1 mmol) in DMSO (10 ml) was added to the above flask and the whole mixture was stirred for 4 h at 80 °C. The reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (30 g, *n*-hexane : AcOEt=20 : 1) to afford (*R*)-**15** (0.331 g, 87%) as a colorless oil. (*R*)-**15**: $[\alpha]_D^{20}$ −7.9° (*c*=1.35, $CHCl_3$); IR (neat): 1740 cm^{-1}. NMR: δ 1.22 (3H, d, *J*=7.1 Hz), 1.34 (12H, s), 1.44—1.65 (4H, m), 2.25—2.28 (2H, m), 2.50 (3H, s), 2.65—2.70 (1H, m), 3.64 (3H, s), 7.09 (1H, d, *J*=7.8 Hz), 7.13 (1H, dd, *J*=1.9, 7.8 Hz), 7.54 (1H, d, *J*=1.9 Hz). ^{13}C-NMR: δ 21.9, 22.5, 23.4, 25.0 (2C or 4C), 25.1 (4C or 2C), 34.3, 37.9, 39.4, 51.6, 83.5, 129.2, 130.1, 134.7, 142.6, 143.5, 174.3. HR-MS (EI) Calcd for $C_{20}BH_{31}O_2$: 346.2315. Found: 346.2312.

Methyl (*R*)-(3′-Hydroxy-4′-methylphenyl)hexanoate 16 To a solution of (*R*)-**15** (0.29 g, 0.84 mmol) in MeOH (1 ml) was added 30% H_2O_2 (1 ml) at 0 °C and the whole mixture was stirred for 2 h at 0 °C. The reaction mixture was poured into a suspension of Et_2O and 5% aqueous $Na_2S_2O_3$ and stirred for 30 min at 0 °C. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (20 g, *n*-hexane : AcOEt=4 : 1) to afford (*R*)-**16** (0.148 g, 75%) as a colorless oil. (*R*)-**16**: $[\alpha]_D^{20}$ −25.1° (*c*=0.25, $CHCl_3$); IR (neat): 3417, 1714 cm^{-1}. NMR: δ 1.21 (3H, d, *J*=7.1 Hz), 1.46—1.58 (4H, m), 2.21 (3H, s), 2.25—2.28 (2H, m), 2.61 (1H, sixtet, *J*=7.1 Hz), 3.64 (3H, s), 4.68 (1H, s), 6.60 (1H, d, *J*=1.6 Hz), 6.66 (1H, dd, *J*=1.6, 7.6 Hz), 7.02 (1H, d, *J*=7.6 Hz). ^{13}C-NMR: δ 15.4, 22.5, 23.3, 34.2, 37.8, 39.5, 51.6, 113.6, 119.5, 121.2, 131.0, 146.8, 153.9, 174.3. HR-MS (EI) Calcd for $C_{14}H_{20}O_3$: 236.1413. Found: 236.1410.

(6*R*)-2-Hydroxy-2-methyl-6-(3′-hydroxy-4′-methylphenyl)heptane 17 To a solution of (*R*)-**16** (0.119 g, 0.5 mmol) in THF (2 ml) was added 1 M MeLi solution in Et_2O (2.02 ml, 2.02 mmol) at 0 °C and the whole mixture was stirred for 2 h at 0 °C. Under ice-cooling, to the reaction mixture was added 5% aqueous $KHSO_4$ and it was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (2 g, *n*-hexane : AcOEt=4 : 1) to afford (6*R*)-**17** (0.105 g, 88%) as a colorless oil. (6*R*)-**17**: $[\alpha]_D^{25}$ −30.2° (*c*=1.50, $CHCl_3$). IR (neat): 3366 cm^{-1}. NMR: δ 1.16 (6H, s), 1.21 (3H, d, *J*=6.8 Hz), 1.37—1.62 (6H, m), 2.21 (3H, s), 2.62 (1H, sixtet, *J*=6.8 Hz), 4.65 (1H, s), 6.61 (1H, d, *J*=1.5 Hz), 6.67 (1H, dd, *J*=1.5, 7.7 Hz), 7.02 (2H, d, *J*=7.7 Hz). ^{13}C-NMR: δ 15.6, 22.5 (2C), 29.3 (2C), 38.9, 39.5, 43.9, 71.6, 113.7, 119.2, 121.3, 130.9, 147.1, 154.0. HR-MS (EI) Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1775.

(*R*)-(−)-Xanthorrizol 2 A mixture of (6*R*)-**17** (0.079 g, 0.33 mmol), $TsOH\cdot H_2O$ (0.032 g, 0.17 mmol) and $MgSO_4$ (0.079 g, 0.66 mmol) in toluene (1 ml) was stirred for 6 h at 60 °C. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (2 g, *n*-hexane : AcOEt=9 : 1) to a 10 : 1 mixture (**2** : **18**=10 : 1) of dehydration products (0.064 g, 88%) as a colorless oil. A part of this mixture was subjected to the preparative TLC (silicagel, *n*-hexane : AcOEt=6 : 1) to afford (*R*)-**2** (0.016 g) as a colorless oil. (*R*)-**2**: $[\alpha]_D^{24}$ −53.5° (*c*=0.75, $CHCl_3$). IR (neat): 3387 cm^{-1}. ^{1}H-NMR: δ 1.20 (3H, d, *J*=7.1 Hz), 1.53 (3H, s), 1.49—1.64 (2H, m), 1.67 (3H, s), 1.82—1.93 (2H, m), 2.21 (3H, s), 2.61 (1H, sixtet, *J*=7.1 Hz), 4.54 (1H, s), 5.06—5.10 (1H, m), 6.61 (1H, d, *J*=1.5 Hz), 6.67 (1H, dd, *J*=1.5, 7.8 Hz), 7.02 (1H, d, *J*=7.8 Hz). ^{13}C-NMR: δ 15.5, 17.8, 22.5, 25.8, 26.3, 38.5, 39.2, 113.7, 119.6, 120.9, 124.7, 130.9, 131.6, 147.4, 153.8. HR-MS (EI) Calcd for $C_{15}H_{22}O$: 218.1671. Found: 218.1687.

References and Notes

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