Short Asymmetric Synthesis of (+)-α-Curcumene and (+)-Xanthorrhizol

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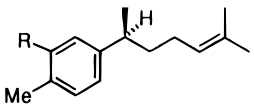
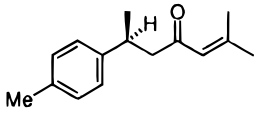
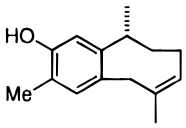
The phenolic sesquiterpenoid hydrocarbon, α-curcumene, a constituent of a large number of essential oils, was first detected in the essential oil of the rhizomes of *Curcuma aromatica* Salisb. The absolute configuration of α-curcumene ((+)-**8**) was determined[1] to be *S*, and an $[\alpha]_D$ +45.1° was observed for pure (+)-α-curcumene.[2] (−)-Xanthorrhizol (**10**), a compound structurally related to α-curcumene, was isolated from the rhizomes of *Curcuma xanthorrhiza* Roxb.[3] The *S*-configuration was assigned to (+)-xanthorrhizol through correlation with (+)-*ar*-turmerone **11** of known *S*-configuration.[4]



(+)-**8**, R = H (*S*)-α-curcumene
(+)-**10**, R = OH, (*S*)-xanthorrhizol



(+)-**11**, (*S*)-*ar*-turmerone



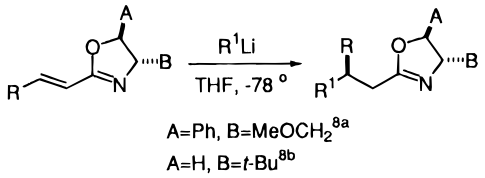
12, parvifoline

Several syntheses of nonracemic α-curcumene have been reported,[5] while only racemic syntheses[6] of xanthorrhizol have been described. To the best of our knowledge, the only synthesis leading to nonracemic material is the conversion of (+)-*ar*-turmerone (**11**) into (+)-xanthorrhizol ((+)-**10**)[4] and of (−)-parvifoline (**12**) into (−)-xanthorrhizol.[7]

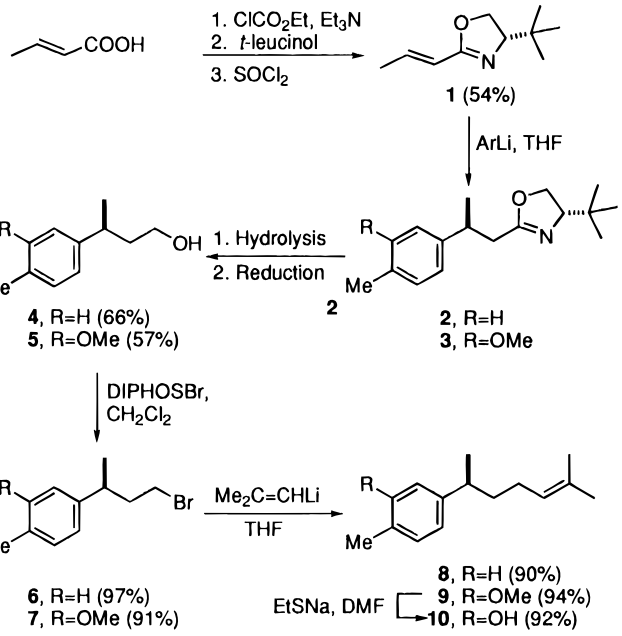
We now describe a short, efficient asymmetric synthesis of the title compounds, based upon highly stereoselective addition of organolithium reagents to chiral α,β-unsaturated oxazolines.[8] It was previously observed that addition of organolithium reagents to alkenyl oxazolines proceeded in a conjugated manner with a high degree of selectivity (Scheme 1).

The chemical yields of the products were modest to good depending on the substituent R and R^1. A major side product of the reaction was a polymer, arising from subsequent addition of the initially formed anion to the starting oxazoline. Its amount depended on the steric bulk of R and the order of addition of the reagents with the optimal yield obtained by slow addition of the oxazoline to an excess of the organolithium reagent. This sequence was employed in a short asymmetric synthesis of (+)-*ar*-turmerone,[9] but the yield in the key asymmetric step (addition of *p*-tolyllithium to 2-propenyl-substituted oxazoline) was only 33% due to the simultaneous production of polymeric material.

Scheme 1



Scheme 2



In the present route to the title compounds, the starting chiral oxazoline **1** was prepared from crotonic acid, which was converted into the mixed anhydride[10] upon treatment with $ClCO_2Et$ (Scheme 2).

Treatment of this compound with *tert*-leucinol and cyclization of the resulting amide with $SOCl_2$ gave **1** in 54% yield. The conjugate addition was carried out by slow addition of the oxazoline **1** in THF to a solution of the corresponding aryllithium reagent in THF at −78 °C. The yields of the conjugate addition relied heavily on the method of formation of the lithium reagent. The best yield of **2** was achieved with a solution of lithium reagent, generated by treatment of *p*-bromotoluene with excess lithium (suspension in mineral oil) in Et_2O and filtered through a plug of glass wool, which was packed in the syringe (72% isolated yield of **2**). Due to the low solubility of (*o*-methoxy-*p*-tolyl)lithium in Et_2O, this reagent was prepared *in situ* by treatment of the corresponding

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(6) (a) Mane, R. B.; Krishna Rao, G. S. *Indian J. Chem.* **1974**, *12*, 938. (b) Rane, R. K.; Desai, U. V.; Mane, R. B. *Indian J. Chem.* **1987**, *26B*, 572. (c) Nagumo, S.; Irie, S.; Hayashi, K.; Akita, H. *Heterocycles* **1996**, *43*, 1175.
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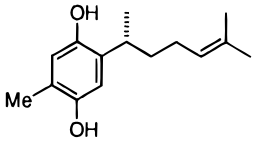
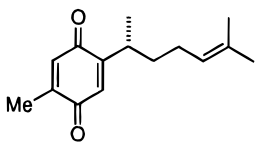
bromide with 1.0 equiv of *t*-BuLi in THF to afford the aryllithium and after addition to **1** gave a 61% isolated yield of **3**.

Analysis of the chromatographed addition products **2** and **3** (^{1}H NMR, chemical shift of the *t*-Bu group: 0.76/0.82 ppm for the major/minor isomer, respectively) revealed that the diastereomeric ratio was at least 97:3. The purification of this product was bypassed, and the crude oxazolines **2** and **3** were taken on to the alcohols **4** and **5**. Thus, hydrolysis of **2** with 1.8 M H_2SO_4[8] gave 66% yield of the known[11] (*S*)-3-(4-methylphenyl)butanoic acid, which was reduced to the alcohol **4**. Hydrolysis of **3** using TFA followed by acetylation and reduction[12] furnished the known[4,6a] (no rotation reported) alcohol **5** in 57% yield from **1**. These compounds were treated with 1,2-bis-(diphenylphoshino)ethane tetrabromide (DIPHOSBr)[13] to give the bromides **6** and **7**[14] in high yield. It should be noted that $[\alpha]_D$ for **6** was reported[1] to be +109°. On the basis of this value, the optical purity of our bromide should only be 73%, which was inconsistent with the enantiomeric purity of our products **2** and **3** (NMR, 97:1) and the observed selectivity of the addition of aryllithiums to **1**. Others have also reported discrepancies with the published optical rotation.[5e]

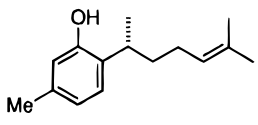
The coupling[15] of (2,2-dimethylvinyl)lithium and **6** or **7** was initially attempted with the lithium reagent generated from the corresponding vinyl bromide by treatment with 2 equiv of *t*-BuLi.[16] However, only traces of the desired coupling product were obtained. Finally, direct treatment of the vinyl bromide with excess lithium metal (suspended in mineral oil) in Et_2O produced the vinyllithium reagent, which gave α-curcumene (**8**) and xanthorrhizol methyl ether (**9**) in high yield (90, 94% respectively). Cleavage of the methyl ether in **9** using sodium ethylthiolate in DMF[4] gave xanthorrhizol **10** in 92% yield. Attempts to utilize BBr_3 to cleave the methyl ether in **9** gave a mixture of products, including some cyclized material derived from Friedel−Crafts alkylations. All the physical data for the products **8** and **10** were in satisfactory agreement with natural material except for xanthorrhizol, whose sign of rotation was (+), opposite to that of the material previously isolated.[3]



(-)-curcuhydroquinone



(-)-curcuquinone



(-)-curcuphenol

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(13) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.

(14) Crude bromide **7** was used as an intermediate in a synthesis of racemic xanthorrhizol; see ref 6a.

(15) For an example of coupling of vinyllithiums with primary halides, see: Millon, J.; Lorne, R.; Linstrumelle, G. *Synthesis* **1975**, 434.

(16) Neumann, H.; Seebach, D. *Chem. Ber.*, **1978,** 2785.

The asymmetric routes described herein represent potential routes to other members of the bisbolane family, using aryllithium reagents with different substitution patterns in the benzene ring (e.g., curcuhydroquinone, curcuquinone, curcuphenol,[17] isoperezone, and perezone).[7]

Experimental Section

(4*S*)-4-*tert*-Butyl-2-[(*E*)-1-propenyl]-2-oxazoline (1). To a stirred solution of crotonic acid (1.30 g, 15.1 mmol) in dry CH_2Cl_2 (20 mL) containing Et_3N (4.3 mL, 30.8 mmol) at −15 °C was added ethyl chloroformate (1.5 mL, 15.7 mmol) dropwise. After 45 min of stirring at −15 °C, the solution was cooled to −78 °C, and a solution of (*S*)-*tert*-leucinol (1.96 g, 16.7 mmol) in CH_2Cl_2 (50 mL) was added slowly. The mixture was allowed to warm slowly and stirred at rt for 2 h. Water and CH_2Cl_2 were added and the layers separated. The organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. The crude amide was dissolved in dry CH_2Cl_2 (30 mL), and $SOCl_2$ (1.2 mL, 16.4 mmol) was added. The mixture was stirred at rt for 10 min and quenched with water and 10% NaOH with cooling. After separation, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried and concentrated. Flash chromatography (7:3 hexane/Et_2O) gave **1** (1.35 g, 53.5%) as a pale yellow liquid: $[\alpha]_D = -138.5$ (*c* 2.0, acetone); ^{1}H NMR ($CDCl_3$) 0.85 (9 H, s), 1.83 (3 H, dd, $J = 7.0$, 1.5 Hz), 3.82−3.89 (1 H, m), 3.98−4.03 (1 H, m), 4.11−4.17 (1 H, m), 5.98 (1 H, dd, $J = 15.8$, 1.6 Hz), 6.46−6.56 (1 H, m); ^{13}C NMR ($CDCl_3$) 18.2 (q), 25.7 (q), 33.6 (s), 68.0 (t), 75.8 (d), 119.1 (d), 138.6 (d), 162.5 (s); IR (thin film) 1680, 1650, 1617. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.79; H, 10.22; N, 8.36.

(3*S*)-3-(4-Methylphenyl)butanoic Acid. *p*-Bromotoluene (5.13 g, 30 mmol) in Et_2O (10 mL) was slowly added to a large excess of lithium (25% lithium suspension in mineral oil, containing 0.5% sodium) in Et_2O (30 mL) so as to maintain a gentle reflux. After the addition was completed, the mixture was stirred for 1 h at rt and allowed to settle before use. To a stirred solution of *p*-tolyllithium (8.0 mL 0.67 M in Et_2O, 5.36 mmol, filtered through a small plug of glass wool contained in the syringe) in dry THF (36 mL) at −78 °C was added oxazoline **1** (430 mg, 2.57 mmol) in THF (17 mL) over 1 h. After being stirred for an additional 15 min, the mixture was quenched with methanol and allowed to warm, saturated sodium chloride was added, and the mixture was extracted with ether. The combined organic layers were dried and concentrated. The resulting crude oxazoline **2** was refluxed with sulfuric acid[8] (1.8 M, 15 mL) for 36 h. On cooling, the mixture was extracted with CH_2Cl_2, dried, and concentrated. Flash chromatography (7:3 hexane/Et_2O) gave (3*S*)-3-(4-methylphenyl)butanoic acid (300 mg, 65.6%) as a waxy white solid: $[\alpha]_D = +44.8$ (*c* 2.9, acetone) (lit.[11] $[\alpha]_D = +45.0$ (*c* 6.5, $CHCl_3$)); distillation at 120 °C (0.05 mmHg) gave $[\alpha]_D = +65.0$ (*c* 4.6, benzene) as reported previously;[11] ^{1}H NMR ($CDCl_3$) 1.30 (3 H, d, $J = 7.0$ Hz), 2.33 (3 H s), 2.52−2.69 (2 H, m), 3.21−3.28 (1 H, m), 7.12 (4 H, m), 11.50−12.00 (1 H, br s); ^{13}C NMR ($CDCl_3$) 21.0 (q), 22.0 (q), 35.7 (d), 42.7 (t), 126.5 (d), 129.2 (d), 136.0 (s), 142.4 (s), 179.0 (s); IR (thin film) 3500−2500, 1710.

(3*S*)-3-(3-Methoxy-4-methylphenyl)butanol (5). To a stirred solution of 3-methoxy-4-methylbromobenzene[18] (724 mg, 3.60 mmol) in dry THF (30 mL) at −78 °C was added *t*-BuLi (2.10 mL 1.69 M solution in hexanes, 3.55 mmol). After 40 min of stirring, oxazoline **1** (300 mg, 1.80 mmol) in THF (15 mL) was added over 1 h. After being stirred for additional 15 min, the mixture was quenched with methanol and allowed to warm. Then, saturated sodium chloride was added and the mixture extracted with ether. The combined organic layers were dried and concentrated. The residue was dissolved in THF (20 mL), water (1.5 mL), and trifluoroacetic acid (2.2 mL), Na_2SO_4 (11 g) was added, and the suspension was stirred at rt for 24 h. After

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filtration, the solvent was removed, and the residue was dissolved in CH_2Cl_2 (30 mL). To this solution were added dry pyridine (2.4 mL) and acetic anhydride (3.8 mL), and the mixture was stirred at rt for 24 h, washed with 1 N HCl and water, dried, and concentrated. The residue was dissolved in THF, and $LiAlH_4$ (150 mg) was added. After 2 h, the mixture was quenched with water, Na_2SO_4 was added, and the solids were filtered off and washed with THF and Et_2O. The filtrate was dried and the solvent evaporated. Flash chromatography (7:3 hexane/Et_2O) gave **5** (198 mg, 56.7%) as a pale yellow liquid: $[\alpha]_D = +35.0$ (*c* 6.0, acetone); ^{1}H NMR ($CDCl_3$) 1.21 (1 H, br s), 1.25 (3 H, d, $J = 7.0$ Hz), 1.80−1.86 (2 H, m), 2.17 (3 H, s), 2.80−2.87 (1 H, m), 3.52−3.57 (2 H, m), 3.81 (3 H, s), 6.66 (1 H, s), 6.69 (1 H, d, $J = 7.6$ Hz), 7.04 (1 H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) 15.7 (q), 22.4 (q), 36.4 (d), 40.9 (t), 55.1 (q), 61.0 (t), 108.7 (d), 118.4 (d), 124.1 (s), 130.4 (d), 145.8 (s), 157.6 (s); IR (thin film) 3346 (br).

(1*S*)-1-(4-Methylphenyl)-3-bromobutane (6). DIPHOSBr[13] was prepared from $Ph_2PCH_2CH_2PPh_2$ (400 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and Br_2 (0.10 mL, 1.94 mmol) in CH_2Cl_2 (1 mL) at 0 °C. 3-(4-Methylphenyl)butanoic acid (160 mg, 0.90 mmol) was reduced with $LiAlH_4$ (220 mg) in THF at rt to give alcohol **4** in quantitative yield. Crude **4** was dissolved in CH_2Cl_2, and a solution of DIPHOSBr (5 mL, 0.83 mmol) was added at 0 °C. The mixture was allowed to warm to rt and stirred for 30 min. Hexane and Et_2O were added, the mixture was filtered through a pad of silica gel, the solids were washed with Et_2O, and the filtrate was concentrated. Flash chromatography (hexane) gave **6** (198 mg, 96.9%) as a pale yellow liquid: $[\alpha]_D = +80.0$ (*c* 2.0, acetone) (lit.[1] $[\alpha]_D = +109.0°$ (*c* 2.27, $CHCl_3$)); ^{1}H NMR ($CDCl_3$) 1.24 (3 H, d, $J = 6.7$ Hz), 2.03−2.10 (2 H, m), 2.30 (3H, s), 2.86−2.93 (1 H, m), 3.12−3.20 (1 H, m), 3.25−3.33 (1 H, m), 7.05−7.12 (4 H, m); ^{13}C NMR ($CDCl_3$) 20.9 (q), 21.9 (q), 32.1 (t), 37.8 (d), 41.0 (t), 126.8 (d), 129.2 (d), 135.8 (s), 142.3 (s).

(1*S*)-1-(3-Methoxy-4-methylphenyl)-3-bromobutane (7). Alcohol **5** (310 mg, 1.50 mmol) was converted into bromide **7** as described for **4**. Flash chromatography (98:2 hexane/Et_2O) gave **7** (373 mg, 90.7%) as a pale yellow liquid: $[\alpha]_D = +90.0$ (*c* 2.5, acetone); ^{1}H NMR ($CDCl_3$) 1.30 (3 H, d, $J = 7.0$ Hz), 2.07−2.14 (2 H, m), 2.20 (3 H, s), 2.90−2.97 (1 H, m), 3.19−3.25 (1 H, m), 3.30−3.36 (1 H, m), 3.84 (3 H, s), 6.69−6.73 (2 H, m), 7.07 (1 H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) 15.7 (q), 21.8 (q), 32.3 (t), 38.1 (d), 41.0 (t), 55.1 (q), 108.8 (d), 118.3 (d), 124.4 (s), 130.5 (d), 144.2 (s), 157.6 (s).

(*S*)-(+)-α-Curcumene (8). 1-Bromo-2-methylpropene (0.5 mL, 4.9 mmol) in Et_2O (1 mL) was slowly added to a large excess of lithium (25% lithium suspension in mineral oil, containing 0.5% sodium) in Et_2O (3 mL) so as to maintain gentle reflux. After the addition was completed, the mixture was stirred for 1 h at rt, diluted with 15 mL of THF at −40 °C, and allowed to settle before use. To a stirred solution of the bromide **6** (100 mg, 0.44 mmol) in THF (3 mL) was added a solution of (2-methylpropenyl)lithium (3.4 mL 0.23 M solution, 0.78 mmol, filtered through glass wool contained in the syringe) at −78 °C. The mixture was allowed to warm slowly and stirred overnight at rt, saturated ammonium chloride was added, and the mixture was extracted with Et_2O. The combined organic layers were dried and concentrated. Flash chromatography (hexane) gave **8** (80 mg, 90.0%) as a pale yellow liquid: $[\alpha]_D = +50.2$ (*c* 4.7, acetone) (lit.[2] $[\alpha]_D = +45.1$); ^{1}H NMR ($CDCl_3$) 1.19 (3 H, d, $J = 7.0$ Hz), 1.50 (3 H, s), 1.50−1.65 (2 H, m), 1.65 (3 H, s), 1.81−1.89 (2 H, m), 2.30 (3 H, s), 2.60−2.67 (1 H, m), 5.04−5.10 (1 H, m), 7.04 (4H, s); ^{13}C NMR ($CDCl_3$) 17.6 (q), 20.9 (q), 22.4 (q), 25.7 (q), 26.1 (t), 38.4 (t), 39.0 (d), 124.5 (d), 126.8 (d), 128.9 (d), 131.3 (s), 135.1 (s), 144.6 (s).

(*S*)-(+)-Xanthorrhizol Methyl Ether (9). Bromide **7** (90 mg, 0.35 mmol) in THF (3 mL) was treated with solution of (2-methylpropenyl)lithium (2.8 mL 0.23 M solution, 0.64 mmol) as described for **6**. Flash chromatography (98:2 hexane/Et_2O) gave **9** (76 mg, 93.6%) as a pale yellow liquid: $[\alpha]_D = +49.6$ (*c* 5.0, acetone)(lit.[4] $[\alpha]_D = +51.6$); ^{1}H NMR ($CDCl_3$) 1.21 (3 H, d, $J = 7.0$ Hz), 1.51 (3 H, s), 1.51−1.65 (2 H, m), 1.65 (3 H, s), 1.83−1.89 (2 H, m), 2.16 (3H, s), 2.59−2.66 (1 H, m), 3.8 (3 H, s), 5.05−5.10 (1 H, m), 6.63 (1 H, s), 6.67 (1 H, d, $J = 7.6$ Hz), 7.02 (1 H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$) 15.8 (q), 17.7 (q), 22.5 (q), 25.7 (q), 26.2 (t), 38.4 (t), 39.5 (d), 55.2 (q), 108.9 (d), 118.7 (d), 123.8 (s), 124.6 (d), 130.3 (d), 131.4 (s), 146.7 (s), 157.6 (s).

(*S*)-(+)-Xanthorrhizol (10). To a suspension of NaH (105 mg, 60% in mineral oil, 2.6 mmol) in dry DMF (5 mL) was added dropwise ethanethiol (0.18 mL, 2.44 mmol) at 0 °C (ice bath). After the addition was completed, the cooling bath was removed and the mixture stirred at rt for 15 min. Xanthorrhizol methyl ether (**9**) (92 mg, 0.4 mmol) in DMF (1.5 mL) was added and the mixture heated to reflux for 3.5 h, cooled, diluted with water, neutralized with concentrated HCl, and extracted with Et_2O. The combined organic layers were dried and concentrated. Flash chromatography (9:1 hexane/Et_2O) gave **10** (80 mg, 91.7%) as a pale yellow liquid: $[\alpha]_D = +52.8$ (*c* 3.6, acetone) (lit.[3] $[\alpha]_D = -52.5$); ^{1}H NMR ($CDCl_3$) 1.18 (3 H, d, $J = 7.0$ Hz), 1.51 (3 H, s), 1.51−1.65 (2 H, m), 1.66 (3 H, s), 1.82−1.90 (2 H, m), 2.20 (3 H, s), 2.56−2.63 (1 H, m), 4.58 (1 H, br s), 5.07 (1 H, br t, $J = 7.0$ Hz), 6.59 (1 H, s), 6.66 (1 H, d, $J = 7.6$ Hz), 7.01 (1 H, d, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$) 15.3 (q), 17.6 (q), 22.3 (q), 25.7 (q), 26.1 (t), 38.3 (t), 39.0 (d), 113.5 (d), 119.4 (d), 120.9 (s), 124.5 (d), 130.8 (d), 131.4 (s), 146.2 (s), 153.5 (s).

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