DOI: 10.1002/cjoc.201201024

Expedient Synthesis of (*R*)-Curcuphenol: A Chiral Pool Strategy†

Jing Feng,[a] Guili Zhu,[a] Bo Liu,*,[a,c] and Xiangdong Zhou*,[b]

[a] *Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu, Sichuan 610064, China*

[b] *Department of Medicinal Chemistry, College of Pharmacy, The Third Military Medical University, Chongqing 400038, China*

[c] *Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China*

Curcuphenol is an interesting sesquiterpenoid with diverse bioactivities. Exploration of a concise and scalable synthetic route is still of significance in spite that many asymmetric total syntheses have been achieved. We report an expedient asymmetric synthesis of (*R*)-curcuphenol from citronellal, which features only two purification operations in the overall six-step synthesis.

Keywords sesquiterpenoid, curcuphenol, total synthesis

Introduction

Both enantiomers of curcuphenol are natural sesquiterpenoids isolated from marine and terrestrial sources.[1] While *R*-(−)-curcuphenol showed weak antimicrobial activity, *S*-(+)-curcuphenol exhibited a very wide spectra of bioactivities such as fungicidal, bactericidal, antimalarial, antiviral and antileishmanial activities. These bioactivities of these molecules have stimulated numerous total syntheses including different racemic and asymmetric versions.[2,3] These asymmetric syntheses are achieved mainly through lipase-mediated resolution,[3c,3d,3i-3k] the utilization of chiral auxiliary,[3b,3e] chiral reagent/chiral catalyst,[3a,3f,3h] or chiral starting material.[3g] The outstanding strategies among them include Pettus' four-step synthesis involving an electron-inversed demand [4+2] cycloaddition controlled by a chiral enol ether,[3b] Aggarwal's four-step synthesis involving a key lithiation-borylation cascade,[3a] and Hagiwara's seven-step synthesis with chiral pool strategy from citronellal (Scheme 1).[3g]

Herein, we would like to present our efforts on the asymmetric synthesis of curcuphenol by following a chiral pool strategy.

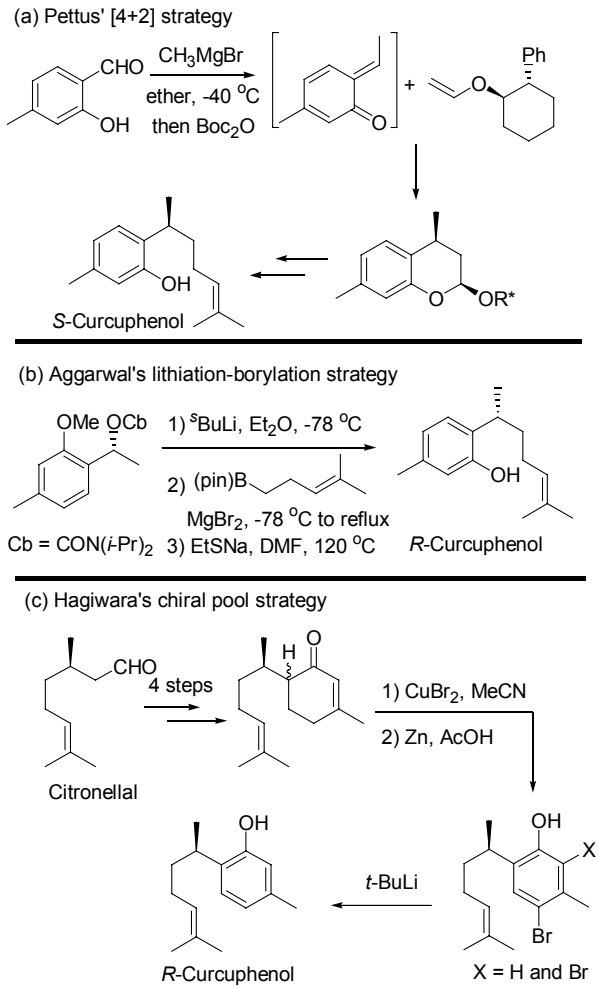
Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran was distilled from sodium-benzophenone. Dichloromethane, toluene and DMSO were distilled from calcium hydride. All the chemicals were purchased commercially and used without further purification, unless otherwise stated. Crotonaldehyde was purified by fractionation under argon atmosphere and kept at −20 ℃. TMSCl was distilled from calcium hydride. Flash chromatography was performed using silica gel (300−400 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 and 365 nm), I_2 and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid. ^{1}H and ^{13}C NMR were recorded on Bruker DRX-400 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR δ=7.26, ^{13}C NMR δ=77.16). The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Coupling constants (*J*) are reported in Hertz (Hz). High resolution Mass spectra (HRMS) were recorded by using FTMS-7 spectrometer.

A 2.5 mol/L solution of *n*-BuLi (7.4 mL, 18.5 mmol) in hexane was added to a solution of diisopropylamine (2.8 mL, 19.9 mmol) in THF (80 mL) under argon at −78 ℃. After 30 min, a solution of *tert*-butyl acetate (2.6 mL, 19.4 mmol) (pretreated by drying over $MgSO_4$) in THF (10 mL) was added dropwise. After 1 h, a solu-

* E-mail: chembliu@scu.edu.cn; Fax: 0086-28-8541-3712
Received October 20, 2012; accepted November 21, 2012; published online December 27, 2012.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201201024 or from the author.
† Dedicated to the Memory of Professor Weishan Zhou.

Scheme 1 Representative synthetic strategies towards curcuphenol



tion of *R*-(+)-citronellal (2.5 mL, 13.1 mmol) in THF (15 mL) was added and stirred for another 1.5 h. The reaction was then quenched with saturated aqueous NH_4Cl (30 mL) and diluted with H_2O (20 mL). Organic solvent was removed under reduced pressure and then EtOAc (50 mL×3) was added to extract the aqueous layer. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford crude **2** as a colourless oil.

To a solution of crude **2** in acetone (90 mL) at 0 ℃ was added dropwise an aqueous solution of Jones' reagent (1.34 mol/L, 14.7 mL, 19.7 mmol). The resultant solution was slowly warmed up to r.t. After 1 h, MeOH (6 mL) and water (60 mL) were added and the organic solvent was removed under reduced pressure. The aqueous layer was extracted with EtOAc (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL×2), H_2O (15 mL) and brine (15 mL). The acidic and basic aqueous layers were respectively extracted with EtOAc (15 mL×2). The organic layer was combined, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude **3** as a colourless oil (3.56 g). An aliquot was collected and characterized to ensure the chemical structure. R_f=0.63 (silica gel, petroleum ether∶EtOAc=19∶1, *V*/*V*), $[\alpha]_D^{21}$ +5.6 (*c* 0.47, $CHCl_3$); IR (thin film) *v*: 3142, 2963, 2922, 1738, 1715, 1403, 1371, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.07 (t, *J*=6.8 Hz, 1H), 3.31 (s, 2H), 2.51 (A of AB, dd, *J*=16.4, 5.6 Hz, 1H), 2.33 (B of AB, dd, *J*=16.4, 8.0 Hz, 1H), 2.06−1.91 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46 (s, 9H), 1.34−1.27 (m, 1H), 1.24−1.14 (m, 1H), 0.91 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.2, 166.6, 131.7, 124.3, 82.0, 51.2, 50.4, 37.0, 28.7, 28.1 (3C), 25.8, 25.6, 19.8, 17.8; HRMS (ES) *m*/*z* calcd for $C_{16}H_{28}NaO_3$ $(M+Na)^+$ 291.1936, found 291.1935.

To a solution of crude **3** (1.83 g) in CH_2Cl_2 (40 mL) was added DBU (1.9 mL, 13.7 mmol) and then crotonaldehyde (0.67 mL, 8.2 mmol) at 0 ℃. Then the solution was warmed and stirred at r.t. for 24 h, before it was quenched with saturated aqueous NH_4Cl (30 mL). The volatile organic components were removed under reduced pressure and the aqueous layer was extracted with ether (40 mL×3). The organic layer was washed with saturated aqueous NH_4Cl (20 mL×2) and brine (10 mL), dried over Na_2SO_4 and concentrated to afford crude **4** (2.04 g) as a brown oil.

To a solution of crude **4** (1.85 g) in toluene (34 mL) was added *p*-TsOH•H_2O (347.2 mg, 1.8 mmol) at r.t. After being stirred at 80 ℃ for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL) at 0 ℃. After removal of the organic volatile under reduced pressure, the aqueous layer was extracted with ether (40 mL×3). The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated to afford crude **5** as a brown oil, which was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 80∶1, *V*/*V*) to provide **5** (747.6 mg, 55.4% over 4 steps) as a pale yellow oil. R_f=0.55 (silica gel, petroleum ether∶EtOAc=40∶1, *V*/*V*); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.60 (brs, 1H), 5.06 (t, *J*=6.8 Hz, 1H), 2.73 (tq, *J*=6.8, 6.8 Hz, 1H), 2.49−2.38 (m, 2H), 2.15−1.98 (m, 3H), 1.92−1.82 (m, 2H), 1.65 (s, 3H), 1.55 (s, 3H), 1.48−1.39 (m, 1H), 1.35−1.26 (m, 1H), 1.03 (d, *J*=5.6 Hz, 3H), 0.98 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.4, 199.3, 144.4, 142.5, 142.4, 131.4, 124.7, 47.1, 36.4, 36.2, 34.5 (2C), 31.3, 30.6, 30.5, 26.1, 25.8, 21.3 (2C), 20.3, 20.1, 17.7; IR (thin film) *v*: 3438, 3137, 2958, 2925, 1675, 1560, 1454, 1383, 1239, 823 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{15}H_{24}NaO$ $(M+Na)^+$ 243.1725, found 243.1723.

A 2.4 mol/L solution of *n*-BuLi (7.6 mL, 18.2 mmol) in hexane was added dropwise to a solution of diisopropylamine (2.8 mL, 19.9 mmol) in THF (52 mL) at 0 ℃. After 30 min, a solution of compound **5** (2.00 g, 9.1 mmol) in THF (10 mL) was added dropwise. After 1 h, a solution of TMSCl (3.5 mL, 27.5 mmol) in THF (10 mL) was added and the resultant solution was stirred for another 1.5 h. The reaction was quenched with buffer (pH=7, 40 mL) and diluted with petroleum ether (60 mL). The aqueous layer was extracted with petroleum ether (20 mL×3). The organic layer was combined,

CHINESE JOURNAL OF CHEMISTRY

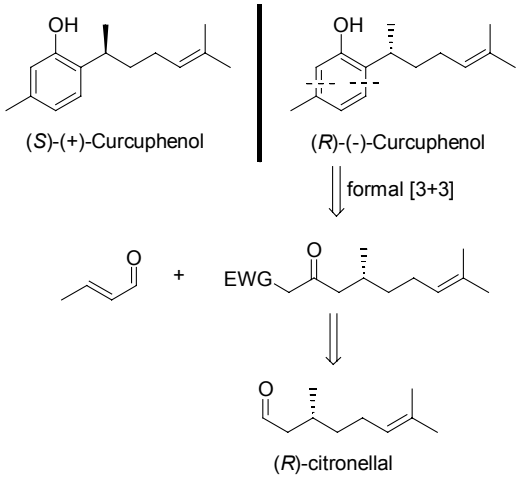
dried over Na_2SO_4 and concentrated to afford crude **6** as a brown oil.

To a solution of crude **6** in DMSO (60 mL) was added $Pd(OAc)_2$ (244.9 mg, 1.09 mmol) at r.t. and the resulting solution was stirred at 40 ℃ for 8 h under oxygen atmosphere. The reaction mixture was then diluted with EtOAc (160 mL) and water (100 mL). After filtration, the organic layer was washed with water (60 mL×2) and brine (30 mL). The aqueous layer was extracted with EtOAc (50 mL×3), which was washed as above. The organic layer was combined, dried over Na_2SO_4 and concentrated to afford brown oil, which was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 40∶1, *V*/*V*) to afford (*R*)-curcuphenol (1.67 g, 84% over two steps) as a pale yellow oil. R_f = 0.47 (silica gel, petroleum ether∶EtOAc = 17∶1, *V*/*V*), $[\alpha]_D^{25}$ –23.1 (*c* 1.0, $CHCl_3$), {lit.[3a] $[\alpha]_D^{21.3}$ –18.4 (*c* 0.4, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (d, *J*=7.6 Hz, 1H), 6.74 (d, *J*=7.6 Hz, 1H), 6.60 (s, 1H), 5.14 (t, *J*=6.8 Hz, 1H), 4.71 (s, 1H), 2.98 (tq, *J*=6.8, 6.8 Hz, 1H), 2.28 (s, 3H), 2.00−1.90 (m, 2H), 1.70 (s, 3H), 1.73−1.58 (m, 2H), 1.55 (s, 3H), 1.24 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.0, 136.7, 132.2, 130.1, 127.0, 124.7, 121.9, 116.3, 37.4, 31.5, 26.2, 25.9, 21.2, 21.0, 17.8; IR (thin film) *v*: 3443, 2962, 2922, 1512, 1451, 1119, 810 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{15}H_{22}NaO$ $(M+Na)^+$ 241.1568, found 241.1570.

Results and Discussion

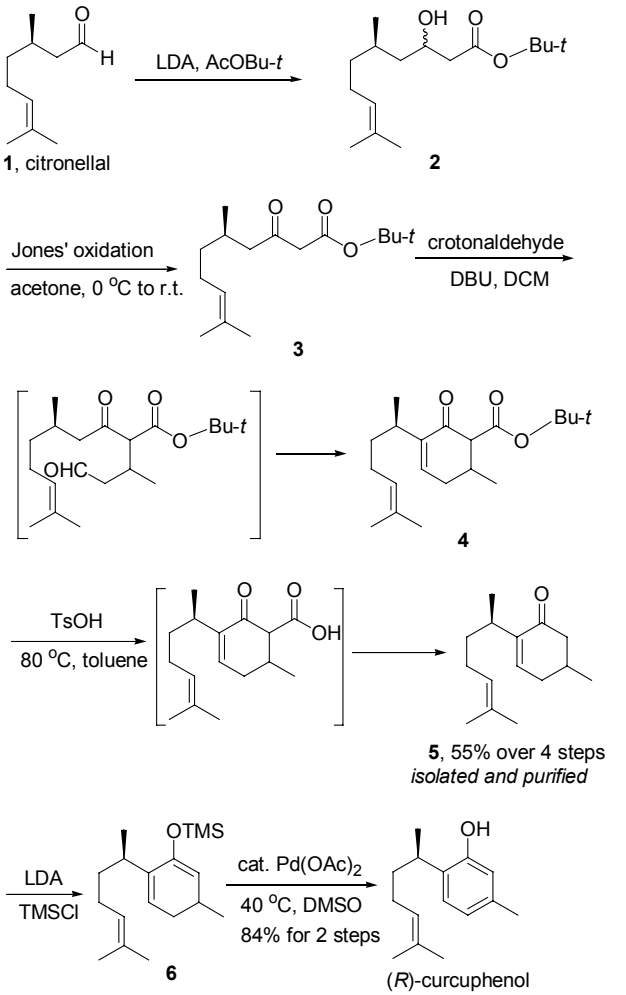
In view of biosynthesis, curcuphenol is very likely derived from the structurally related citronellal. Accordingly, to construct the benzene ring in the target molecule, we preferred a formal [3+3] annulation with crotonaldehyde and the activated β-keto ester derived from citronellal, as depicted in Scheme 2.

Scheme 2 Retrosynthetic analysis



Initiated from (*R*)-citronellal, we extended the carbon chain by reacting it with lithium enolate derived from *tert*-butyl acetate and LDA, to achieve compound **2** (Scheme 3). Due to the self-condensation, application of ethyl acetate afforded inferior yield in this step. While Swern oxidation led to a complex mixture, Jones' oxidation smoothly oxidized compound **2** to the β-keto ester **3**. Subsequently, to construct the six-membered ring, a Michael-aldol cascade was attempted with different bases such as potassium carbonate, *N*,*N*,*N*′,*N*′-tetramethylpiperidine, tetrahydropyrrole and proline. DBU was finally selected as the optimum to prompt the formation of compound **4**. Then, in the presence of *para*-toluenesulfonic acid (TsOH) , *tert*-butyl group in **4** was removed by releasing one molecule of isobutene to *in situ* generate the unstable β-keto acid intermediate, which immediately decomposed to compound **5**.

Scheme 3 Synthesis of (*R*)-curcuphenol from citronellal



The aromatization of **5** proved to be not as straightforward as we imagined. In fact, Moriuchi and Hirao's oxidative aromatization with $VO(acac)_2$/Bu_4NBr,[4] Sharpless' organoselenium chemistry[5] and Stahl's Pd-catalyzed aerobic dehydrogenation[6] in the presence of 2-dimethylamino pyridine and TsOH failed to accomplish this aromatization to achieve curcuphenol. While IBX oxidation did furnish the desired natural product, it was contaminated by inseparable impurities.[7] Eventually, we completed the synthesis by con-

verting compound **5** to silyl enol ether **6** followed by palladium-catalyzed aromatization.[8] All the characterization data including optical rotation, IR, NMR and HRMS are in good accordance with the reported data.[3a,3b]

Conclusions

In general, we have accomplished an asymmetric synthesis of (*R*)-curcuphenol from the cheap starting material, (*R*)-citronellal, in 46% overall yield after six steps or only two purification operations. The current synthetic strategy is obviously applicable to the synthesis of (*S*)-curcuphenol and can serve as an efficient source to scalable synthesis of both enantiomers.

Acknowledgement

We are grateful for financial support from the the National Natural Science Foundation of China (Nos. 21172154, J1103315).

References

[1] (a) Armas, H. T. D.; Mootoo, B. S.; Reynolds, W. F. *J. Nat. Prod.* **2000**, *63*, 1593; (b) Freyer, A. J.; Patil, A. D.; Killmer, L.; Zuber, G.; Myers, C.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 309; (c) McEnroe, F.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661; (d) Bohlman, F.; Lonitz, M. *Chem. Ber.* **1978**, *111*, 843.

[2] For racemic synthesis of curcuphenol, see: (a) Montiel, L. E.; Zepeda, L. G.; Tamariz, J. *Helv. Chim. Acta* **2010**, *93*, 1261; (b) Ghosh, S.; Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Tetrahedron* **2007**, *63*, 644; (c) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461; (d) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553.

[3] For asymmetric synthesis of curcuphenol, see: (a) Aggarwal, V. K.; Ball, L. T.; Carobene, S.; Connelly, R. L.; Hesse, M. J.; Partridge, B. M.; Roth, P.; Thomas, S. P.; Webster, M. P. *Chem. Commun.* **2012**, *48*, 9230; (b) Green, J. C.; Jimenez-Alonso, S.; Brown, E. R.; Pettus, T. R. *Org. Lett.* **2011**, *13*, 5500; (c) Serra, S. *Tetrahedron*: *Asymmetry* **2011**, *22*, 619; (d) Kamal, A.; Malik, M. S.; Shaik, A. A.; Azeeza, S. *Tetrahedron*: *Asymmetry* **2007**, *18*, 2547; (e) Lu, J.; Xie, X.; Chen, B.; She, X.; Pan, X. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1435; (f) Kim, S.-G.; Kim, J.; Jung, H. *Tetrahedron Lett.* **2005**, *46*, 2437; (g) Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895; (h) Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 2700; (i) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Chem. Pharm. Bull.* **2001**, *49*, 1581; (j) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758; (k) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1829.

[4] Moriuchi, T.; Kikushima, K.; Kajikawa, T.; Hirao, T. *Tetrahedron Lett.* **2009**, *50*, 7385.

[5] Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

[6] Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209.

[7] Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

[8] Ihara, M.; Makita, K.; Takasu, K. *J. Org. Chem.* **1999**, *64*, 1259.

(Zhao, X.)

