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Efficient total synthesis of (+)-curcuphenol via asymmetric organocatalysis

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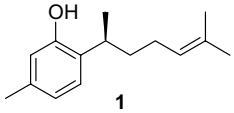
Abstract—The catalytic enantioselective synthesis of (+)-curcuphenol is described herein. This approach involves the use of an organocatalytic alkylation of *m*-anisidine, a diazotation/Sandmeyer reaction of the amine and a Negishi-type coupling with dimethylzinc. This versatile strategy allows for the rapid synthesis of other members of this class of natural products.

Curcuphenol is a bioactive sesquiterpene phenol whose different enantiomers exhibit strikingly different activities. (*S*)-(+)-Curcuphenol (**1**), isolated from the marine sponge *Didiscus flavus* and *Epipolasis* species, display antifungal activity against *Candida albicans*, antitumor activity against several human cancer cell lines and antimalarial activity against *Plasmodium falciparium*.[1] (*S*)-(+)-Curcuphenol has also been shown to inhibit proton–potassium ATPase.[2] (*R*)-(−)-Curcuphenol, isolated from the gorgonian coral *Pseudopterogorgia rigida*, exhibits antibacterial activities against *Staphylococcus aureus* and *Vibrio anguillarum*.[3] Accordingly, a versatile and efficient synthetic route to this sesquiterpene that can be utilized to explore structure–activity relationships is of significance. Though several enantioselective and racemic syntheses of curcuphenol have been reported,[4] to the best of our knowledge, the enantioselective synthesis of curcuphenol through asymmetric catalysis to introduce a stereogenic center in the benzylic position have not yet been reported. Herein we report a short, efficient asymmetric synthesis of (*S*)-(+)-curcuphenol, based on asymmetric organocatalysis.

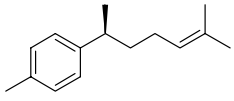
Our synthetic approach toward the target molecule was based on the organocatalytic asymmetric Friedel–Crafts alkylation of aniline which produced a stereogenic benzylic center. Recently, MacMillan and co-workers have developed catalytic enantioselective Friedel–Crafts reaction using an imidazolidinone as catalyst.[5] We employed their organocatalytic Friedel–Crafts reaction in the synthesis of curcuphenol.

The synthesis of (+)-curcuphenol **1** begins with commercially available *m*-anisidine as illustrated in Scheme 1. The amino protection of *m*-anisidine with benzyl bromide in the presence of K_2CO_3 gave **2** in 92% yield. Aldehyde **5** was obtained by the reaction of *N*,*N*-dibenzyl-3-anisidine **2** and crotonaldehyde **3** using imidazolidinone catalyst **4**. Optimal enantiocontrol was achieved with catalyst **4** (10 mol%) in CH_2Cl_2 at −40 °C to afford aldehyde (*S*)-**5** in 90% yield with an enantiomeric excess of 90%.[6] This reaction establishes the benzylic stereogenicity of curcuphenol. Catalyst **4** and crotonaldehyde **3** combine to generate α,β-unsaturated iminium ion that is anticipated to selectively populate the (*E*)-isomer to avoid nonbonding interactions between the substrate olefin and the *tert*-butyl group. Since the benzyl group on the catalyst framework effectively shields the *si*-face of the activated olefin, *N*,*N*-dibenzyl-3-anisidine **2** is predominantly added to the *re*-face exposed.[5c] Aldehyde **5** was reduced with sodium borohydride, this was followed by in situ deprotection of the benzyl groups to afford **6** in 90% yield.[7]



1

(*S*)-(+)-Curcuphenol



(*S*)-(+)-Curcumene

Keywords: Curcuphenol; Total synthesis; Organocatalysis.
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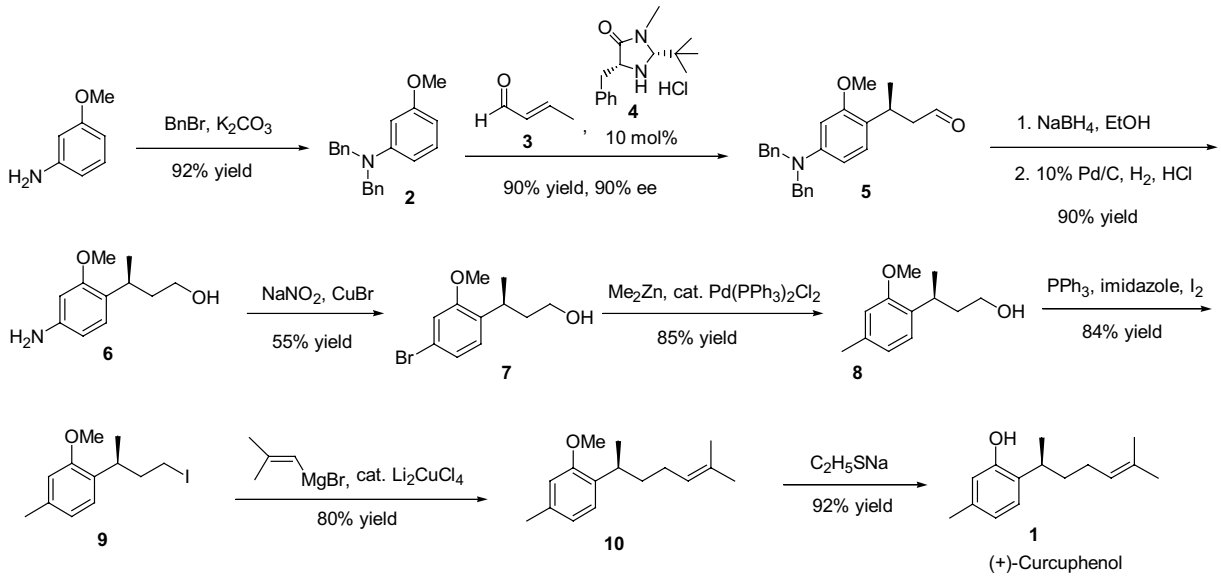

Scheme 1.

The conversion of **6** to known precursor **8** was achieved by a Sandmeyer-type bromination of aminobenzene **6**,[8] followed by a palladium-catalyzed methylation of a bromobenzene **7** under Negishi-type coupling.[9] Bromination of a aminobenzene **6** was found to be unexpectedly difficult. Experimentation with *t*-BuONO and $CuBr_2$ methods provided (*S*)-3-(4,5-dibromo-2-methoxy-phenyl)-butan-1-ol. After much experimentation, a 55% yield was obtained in the reaction of **6** with $NaNO_2$, HBr, and CuBr.[10] Compound **7** underwent methylation with dimethylzinc in the presence of $Pd(PPh_3)_2Cl_2$ (5.0 mol%) to give **8** in 85% yield ($[\alpha]_D^{23}$ +19.5 (*c* 1.0, $CHCl_3$)).[11]

Compound **8** was converted into iodide **9** via the reaction with PPh_3, imidazole, I_2 in 84% yield. The coupling of iodide **9** with 2-methyl-1-propenylmagnesium bromide catalyzed by copper(I) iodide was attempted, in accord with an early reported procedure.[4d] Unfortunately this Cu-catalyzed reaction did not provide a consistent yield of the desired product.[12] After several catalyst screening, we found that Li_2CuCl_4 was the effective catalyst for this cross-coupling reaction. Using 5 mol% of Li_2CuCl_4, good yield (80%) of cross-coupling product **10** ($[\alpha]_D^{23}$ +6.6 (*c* 1.0, $CHCl_3$))[13] was obtained after reaction at rt for 6 h. Finally, the methyl ether functionality of compound **10** was cleaved using sodium ethanethiolate in DMF to give (*S*)-(+)-curcuphenol (**1**) in 90% yield ($[\alpha]_D^{23}$ +23.8 (*c* 1.0, $CHCl_3$)).[14] The physical and spectroscopic data of **1** are in full agreement with literature data.

In conclusion, we have completed the total synthesis of (*S*)-(+)-curcuphenol, based on the organocatalytic alkylation of *m*-anisidine, and a diazotation/Sandmeyer reaction of amine followed by a Negishi-type coupling with dimethylzinc, as key steps. This versatile synthetic sequence could be employed for structure activity studies on curcuphenol to determine the biologically relevant components of the architecture. The present asymmetric route represents potential route to other members of the bisabolane family, which is now in progress and will be presented in due course.

Acknowledgements

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6. Synthesis of (*S*)-3-(4-dibenzylamino-2-methoxy-phenyl)-butyraldehyde (**5**): To a solution of compound **2** (4.56 g, 15.0 mmol), catalyst **4** (370 mg, 1.50 mmol), and HCl (as a 4 N solution in 1,4-dioxane, 380 μL, 1.50 mmol) in CH_2Cl_2 (15 mL) at −40 °C was added crotonaldehyde **3** (597 mg, 5.22 mmol). After stirring for 48 h at this temperature, the reaction mixture was purified by column chromatography (silica, 5% EtOAc in hexanes) to afford product **5** (5.05 g, 90%) as a colorless, viscous oil; 90% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.70 (t, J = 2.4 Hz, 1H), 7.21–7.40 (m, 10H), 6.96 (d, J = 8.6 Hz, 1H), 6.34 (dd, J = 8.6, 2.0 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H), 4.67 (s, 4H), 3.64 (s, 3H), 3.52–3.68 (m, 1H), 2.48–2.75 (m, 2H), 1.28 (d, J = 6.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.7, 155.9, 147.5, 137.2, 127.0, 125.7, 125.3, 125.1, 119.9, 103.1, 94.8, 53.4, 53.1, 49.3, 25.6, 18.9; HRMS calcd for $C_{25}H_{27}NO_2^+$: 373.2042, found: 373.2051; $[\alpha]_D^{23}$ +5.5 (*c* 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiralcel OD and OD guard column (2.0% isopropanol/hexanes, 1 mL/min); *S*-isomer t_r = 21.9 min, *R* isomer t_r = 24.5 min.
7. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.92 (d, J = 8.2 Hz, 1H), 6.26 (dd, J = 8.2, 2.0 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 3.74 (s, 3H), 3.37–3.55 (m, 3H), 3.06–3.35 (m, 3H), 1.56–1.87 (m, 2H), 1.19 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.9, 143.9, 125.8, 122.9, 106.1, 97.0, 59.5, 53.7, 39.2, 25.6, 19.7; HRMS calcd for $C_{11}H_{17}NO_2^+$: 195.1259, found: 195.1264; $[\alpha]_D^{23}$ +23.7 (*c* 1.0, $CHCl_3$).
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10. Compound **7**: ^{1}H NMR (200 MHz, $CDCl_3$) 7.08 (s, 1H), 7.07 (d, J = 1.4 Hz, 1H), 7.01 (d, J = 1.4 Hz, 1H), 3.84 (s, 3H), 3.24–3.62 (m, 3H), 1.65–1.96 (m, 3H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 157.6, 133.9, 128.3, 124.1, 120.0, 114.2, 61.1, 55.9, 40.4, 27.9, 20.9; HRMS calcd for $C_{11}H_{15}BrO_2^+$: 259.0255, found: 259.0247; $[\alpha]_D^{23}$ +15.2 (*c* 1.0, $CHCl_3$).
11. Reported rotation values for **8**: $[\alpha]_D^{25}$ +22.4 (*c* 1.25, $CHCl_3$); Ref. 4a: $[\alpha]_D^{20}$ +22.8 (*c* 4, $CHCl_3$); Ref. 4d: $[\alpha]_D^{20}$ +17.8 (*c* 4.5, $CHCl_3$); Ref. 4f.
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13. Reported rotation values for **10**: $[\alpha]_D^{25}$ +7.8 (*c* 1.0, $CHCl_3$); Ref. 4d: $[\alpha]_D^{20}$ +1.5 (*c* 4.5, $CHCl_3$); Ref. 4f.
14. Reported rotation values for **1**: $[\alpha]_D$ = +24.6 (natural curcuphenol); Ref. 1a: $[\alpha]_D^{25}$ +26.6 (*c* 0.35, $CHCl_3$), (natural curcuphenol); Ref. 2b: $[\alpha]_D^{20}$ +24.8 (*c* 1, $CHCl_3$); Ref. 4d: $[\alpha]_D^{27}$ +26.0 (*c* 0.3, $CHCl_3$); Ref. 4e: $[\alpha]_D^{20}$ +23.1 (*c* 4.5, $CHCl_3$); Ref. 4f.