Synthesis of Several Bisabolane Type Sesquiterpenoids from Xanthorrhizol

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ABSTRACT R-(−)-Xanthorrhizol 1, the main constituent of Curcuma xanthorrhiza, has been shown to possess interesting biological activities, including antibacterial, antifungal, antitumour and antioxidant activities. Xanthorrhizol was isolated from the essential oil of C. xanthorrhiza in 39% yield by vacuum column chromatography. Curcuhydroquinone 2, an antibacterial compound isolated from the Caribbean gorgonian coral, Pseudopterogorgia rigida has been synthesised in two steps from xanthorrhizol. Xanthorrhizol has also been converted to 10R- and 10S-10,11-dihydro-10,11-dihydroxyxanthorrhizols 3 and 4, a bisabolane type sesquiterpenoid isolated from Iostephane heterophylla, using Sharpless asymmetric dihydroxylation as the key step.

ABSTRAK Kandungan utama Curcuma xanthorrhiza, R-(−)-xantorizol 1 memiliki aktiviti biologi yang menarik termasuk aktiviti antibakteria, antitumor dan antioksidan. Kromatografi turus gravi ke atas minyak pati C xanthorrhiza menghasilkan xantorizol sebanyak 39%. Kurkuhydroquinon 2, sebatian antibakteria daripada karang gorgonian Karibia, Pseudopterogorgia rigida telah disintesis daripada xantorizol dalam dua langkah. Xantorizol juga telah diubah kepada 10R- dan 10S-10,11-dihidro-10,11-dihidroksixantorizol 3 dan 4, seskuiterpenoid bisabolana yang dipisahkan daripada Iostephane heterophylla, menggunakan pendihidroksilasi asimetri Sharpless sebagai langkah utama.

(Xanthorrhizol, curcuhydroquinone, (10R/10S)-10,11-dihydro-10,11-dihydroxyxanthorrhizols, Sharpless AD)

INTRODUCTION

Xanthorrhizol 1 is a bisabolane type sesquiterpenoid obtained as the main constituent of the essential oil of temu lawak, Curcuma xanthorrhiza. It was first isolated by Rimpler et al. in 1970 [1]. John et al. have assigned R-configuration for naturally occurring (−)-xanthorrhizol [2]. With regards to its bioactivities, it has been shown that xanthorrhizol 1 exhibits antibacterial activity against Streptococcus mutans (MIC=2 μg/mL) [3]. Although nine syntheses have been reported for the synthesis of xanthorrhizol 1, the chemical modifications of this compound has not been extensively investigated. Thus, it is of great interest to explore the chemistry of 1 in order to exploit this substance as a starting material for conversion to other bisabolane type sesquiterpenoids. We found that 1 can be converted to several naturally occurring sesquiterpenoids, namely curcuhydroquinone 2 and (10R/10S)-10,11-dihydro-10,11-dihydroxyxanthorrhizols 3, 4. Curcuhydroquinone 2 was isolated by McEnroe et al. from the Caribbean gorgonian coral, Pseudopterogorgia rigida. This compound shows antibacterial activities against S. aureus and V. anguillarum [4]. (10R/10S)-10,11-Dihydro-10,11-dihydroxyxanthorrhizols 3, 4 were isolated from the Mexican medicinal plant, Iostephane heterophylla [5]. Herein we report the transformation of xanthorrhizol 1 into naturally occurring sesquiterpenoids, curcuhydroquinone 2 and (10R/10S)-10,11-dihydro-10,11-dihydroxyxanthorrhizols 3, 4.
**EXPERIMENTAL**

**General methods**

$^1$H and $^{13}$C NMR spectra (300 and 75 MHz respectively) were recorded on a Bruker Avance 300 Spectrometer using CDCl$_3$ as solvent. IR spectra were recorded on a Shimadzu 8000 spectrometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel 60 F$_{254}$. Melting points were measured with a Leica Galen III melting point apparatus and were uncorrected.

**Extraction and purification of xanthorrhizol 1**

The fresh rhizomes of *C. xanthorrhiza* (3.35 kg) were chopped and hydrodistilled in an all glass apparatus for 8 hours. The crude oil was extracted with diethyl ether (3 x 10 mL), dried over anhydrous MgSO$_4$ and filtered. Evaporation of ether gave the essential oil (30.57 g, 0.91 %) as a light yellow oil. The essential oil was purified by vacuum column chromatography to give xanthorrhizol 1 as a pale yellow oil (11.82 g, 0.35%). $[a]_D = -49.4 (c 1.00, MeOH) [lit. [1] $[a]_D = -52.5$ (CHCl$_3$)]; IR (neat) 3412, 2963, 1728, 1658, 1585, 1427, 1254, 1119, 993, 814 cm$^{-1}$; $^1$H NMR $\delta$ 1.22 (3H, d, J=6.9 Hz, H-15), 1.55 (3H, s, H-12), 1.62 (2H, m, H-8), 1.69 (3H, s, H-13), 1.89 (2H, m, H-9), 2.24 (3H, s, H-14), 2.63 (1H, sextet, H-7), 4.69 (1H, s, OH), 5.11 (1H, br t, J=4.6 Hz, H-10), 6.63 (1H, d, J=1.8 Hz, H-2), 6.70 (1H, dd, J=7.8, 1.8 Hz, H-6), 7.05 (1H, d, J=7.8 Hz, H-5); $^{13}$C NMR $\delta$ 15.3 (C-12), 17.7 (C-14), 22.4 (C-15), 25.7 (C-13), 26.1 (C-9), 38.4 (C-8), 39.0 (C-7), 113.5 (C-2), 119.4 (C-6), 120.8 (C-4), 124.5 (C-10), 130.3 (C-5), 131.4 (C-11), 147.2 (C-1), 153.6 (C-3); EIMS m/z 218 (35) [M$^+$, C$_{15}$H$_{26}$O$_2$], 136 (100), 121 (56).

**Curcurhydroquinone 2.** Curcurquinone 5 (350 mg, 1.507 mmol) was dissolved in 10 mL of THF/H$_2$O (3:2), Na$_2$S$_2$O$_4$ (395 mg, 2.269 mmol) was added and the mixture was stirred at rt for 2 h 20 min. The THF layer was separated and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organic extracts were washed with brine and dried over anhydrous MgSO$_4$. Evaporation of the solvent yielded a pale yellow solid 2 (287 mg, 82.00%): mp 92-95°C; $[a]_D = -88.3 (c 0.89, CHCl$_3$) [lit. [9] $[a]_D = -48.0 (c 2.78, CHCl$_3$)]; IR (KBr pellet) 3358, 2926, 2856, 1514, 1420, 1188, 871, 833 cm$^{-1}$; $^1$H NMR $\delta$ 1.18 (3H, d, J=6.9 Hz, H-15), 1.52 (3H, s, H-12), 1.54-1.64 (2H, m, H-8), 1.66 (3H, s, H-13), 1.91 (2H, m, H-9), 2.15 (1H, s, H-14), 2.92 (1H, sextet, H-7), 5.10 (1H, t with further unresolved couplings, H-10), 6.54 (1H, s, H-3), 6.56 (1H, s, H-6); $^{13}$C NMR $\delta$ 15.4 (C-14), 17.7 (H-12), 21.1 (C-15), 25.7 (C-13), 26.0 (C-9), 31.4 (C-7), 37.3 (H-8), 113.4 (C-6), 117.9 (C-3), 121.7 (C-4), 123.8 (C-10), 131.8 (C-1), 132.1 (C-11), 146.7 (C-2), 147.8 (C-5); EIMS m/z 234 (54) [M$^+$, C$_{15}$H$_{26}$O$_2$], 112 (100).
Xanthorrhizyl acetate 6. To a stirred solution of xanthorrhizol 1 (1.00 g, 4.580 mmol) in diethyl ether (1 mL) was added acetic anhydride (0.935 g, 9.159 mmol) and pyridine (85 mg, 0.933 mmol). The reaction mixture was left to stir at rt for 73 hours. The organic layer was washed with 5% HCl solution (3 x 5 mL) followed by saturated NaHCO₃ solution (2 x 5 mL) and dried over anhydrous MgSO₄. The solvent was removed and purified by column chromatography (silica gel, PE/Et₂O = 9/1) to provide xanthorrhizyl acetate 6 (0.8453 g, 72.25%) as a colourless oil: IR (neat) 2962, 2925, 1767, 1677, 1508, 1451, 1369, 1219, 1119, 820 cm⁻¹; ¹H NMR δ 1.24 (3H, d, J=6.9 Hz, H-15), 1.53 (3H, s, H-12), 1.55-1.66 (2H, m, H-8), 1.69 (3H, s, H-13), 1.88-1.95 (2H, m, H-9), 2.16 (3H, s, H-14), 2.33 (3H, s, OAc), 2.69 (1H, sextet, J=6.9 Hz), 5.10 (1H, tt, J=7.2, 1.2 Hz), 6.84 (1H, d, J=1.8 Hz, H-2), 6.99 (1H, dd, J=7.8, 1.8 Hz), 7.16 (1H, d, J=7.8 Hz); ¹³C NMR δ 15.8 (C-14), 17.7 (C-12), 20.9 (C-17), 22.2 (C-5), 25.7 (C-13), 26.1 (C-9), 38.3 (C-8), 38.9 (C-7), 120.3 (C-2), 124.4 (C-6), 124.7 (C-4), 127.2 (C-10), 130.8 (C-5), 131.5 (C-11), 146.9 (C-1), 149.3 (C-3), 169.3 (C=O). EIMS m/z 260 (17) [M⁺, C₁₇H₂₄O₂], 136 (100), 121 (32).

(3S,6R)-6-(3-Acetoxy-4-methylphenyl)-2-methylhentane-2,3-diol 7. A 25 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with tert-butanol (5 mL), H₂O (5 mL), AD-mix-α (1.620 g), and MeSO₂NH₂ (110 mg, 1.156 mmol). The mixture was stirred at rt until both phases were clear, and then cooled to 0°C, whereupon the inorganic salts partially precipitated. Xanthorrhizyl acetate 6 (300 mg, 1.152 mmol) was added at once, and the heterogenous slurry was stirred vigorously at 0°C for 117 hours. The reaction was quenched at 0°C by addition of Na₂SO₃ (1.73 g) and then warmed to rt and stirred for 35 minutes. The reaction mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were washed with 2N KOH solution (2 x 20 mL) and dried over anhydrous MgSO₄. Removal of the solvent and column chromatography (silica gel, hex/EtOAc = 4/6) provided 7 (169.5 mg, 86.04%) as a colourless oil: [α]D -38.2 (c 1.02, CHCl₃); IR (neat) 3418, 2928, 1746, 1508, 1369, 1219, 1119, 1015, 822 cm⁻¹; ¹H NMR δ 1.07 (3H, s, H-12), 1.13 (3H, s, H-13), 1.15 (1H, m, H-9'), 1.24 (3H, d, J=6.9 Hz, H-15), 1.40 (1H, m, H-9), 1.62 (1H, m, H-8'), 1.83 (1H, m, H-8), 2.14 (3H, s, H-14), 2.31 (3H, s, OAc), 2.70 (1H, sextet, H-7), 3.32 (1H, ddd, J=10.5, 5.1, 2.1 Hz), 6.83 (1H, d, J=1.8 Hz, H-2), 6.97 (1H, dd, J=7.8, 1.8 Hz, H-6), 7.14 (1H, d, J=7.8 Hz, H-5); ¹³C NMR δ 15.8 (C-14), 20.7 (C-17), 22.6 (C-15), 23.2 (C-12), 26.4 (C-13), 29.5 (C-9), 34.9 (C-8), 39.1 (C-7), 73.1 (C-11), 78.4 (C-10), 120.4 (C-6), 124.7 (C-2), 127.3 (C-4), 131.0 (C-5), 146.2 (C-1), 149.3 (C-3), 169.3 (C-16). EIMS m/z 276 (14) [M⁺-H₂O], 175 (100), 135 (88).

(10S)-10,11-dihydroxy-xanthorrhizol 3. A solution of 7 (65.6 mg, 0.223 mmol) in 2 mL of methanol and 1 mL of water was treated with 1 mL of saturated sodium bicarbonate solution and stirred at rt for 17 hours. The solution was acidified with 10% HCl solution and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with saturated solution of NaHCO₃ (2 x 10 mL) and dried over anhydrous MgSO₄. Removal of the solvent and column chromatography (silica gel, hex/EtOAc = 3/7 to EtOAc 100%) yielded 3 (44.6 mg) as a colourless oil: [α]D -64.7 (c 0.51, MeOH); IR (neat) 3361, 2960, 2927, 1619, 1589, 1456, 1421, 1377, 1260, 1124, 814 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.08 (3H, s, H-12), 1.15 (3H, s, H-13), 1.18 (1H, m, H-9'), 1.23 (3H, d, J=6.9 Hz, H-15), 1.40 (1H, m, H-9), 1.60 (1H, m, H-8'), 1.86 (1H, m, H-8), 2.21 (3H, s, H-14), 2.64 (1H, sextet, H-7), 3.37 (1H, br d, J=10.2 Hz, H-10), 5.06 (1H, s, OH), 6.61 (1H, d, J=1.8 Hz, H-2), 6.66 (1H, dd, J=7.8, 1.8 Hz, H-6), 7.02 (1H, d, J=7.8 Hz, H-5); ¹³C NMR δ 15.4 (C-14), 23.0 (C-12), 23.2 (C-15), 26.5 (C-13), 29.6 (C-9), 35.0 (C-8), 39.3 (C-7), 73.3 (C-11), 78.6 (C-10), 113.3 (C-2), 119.4 (C-6), 121.3 (C-4), 130.9 (C-5), 146.4 (C-1), 153.9 (C-3). EIMS m/z 252 (29) [M⁺, C₁₅H₂₁O₃], 135 (100), 59 (95).

(3R,6R)-6-(3-Acetoxy-4-methylphenyl)-2-methylhentane-2,3-diol 8. Under the same conditions as described for (3S,6R)-7, xanthorrhizyl acetate 6 (300 mg, 1.152 mmol) was dihydroxylated in the presence of AD-mix-β to afford 8 (119.5 mg, 64.59%) as a colourless oil: [α]D +5.37 (c 1.08, CHCl₃); IR (neat) 3416, 2928, 1746, 1508, 1369, 1215, 1119, 820 cm⁻¹; ¹H NMR δ 1.09 (3H, s, H-12), 1.11 (3H, s, H-13), 1.23 (3H, d, J=6.9 Hz, H-15), 1.35 (2H, m, H-9 and H-9'), 1.63 (1H, m, H-8'), 1.84 (1H, m, H-8), 2.14 (3H, s, H-14), 2.31 (3H, s, OAc), 2.67 (1H, sextet, H-7), 3.21 (1H, br d, J=9.6 Hz, H-10), 6.83 (1H, d, J=1.8 Hz, H-2), 6.97 (1H, dd, J=7.8, 1.8 Hz), 7.14 (1H, d, J=7.8 Hz), ¹³C NMR δ 15.8 (C-14), 20.8 (C-17), 22.2 (C-15), 23.1 (C-12),
26.4 (C-13), 29.8 (C-9), 35.2 (C-8), 39.6 (C-7), 73.1 (C-11), 78.5 (C-10), 120.3 (C-6), 124.7 (C-2), 127.3 (C-4), 130.9 (C-5), 146.7 (C-1), 149.3 (C-3), 169.4 (C-16). EIMS m/z 276 (14) [M + H]+, 175 (100), 135 (88).

**(10R)-10,11-dihydro-10,11-dihydroxyxanthorrhizol 4.** Following the same procedure as described for (10S)-3, diol-8 (30 mg, 0.102 mmol) gave 4 (18.7 mg, 70.57%) as a colourless oil: [α]D0 +3.33 (c 0.30, MeOH); IR (neat) 3382, 2962, 2927, 1619, 1589, 1503, 1456, 1421, 1256, 1124, 993 cm ⁻¹; 1H NMR δ 11.11 (3H, s, H-12), 1.14 (3H, s, H-13), 1.22 (3H, d, J=6.9Hz, H-15), 1.34 (2H, m, H-9 and H-9'), 1.58 (1H, m, H-8'), 1.85 (1H, m, H-8), 2.21 (3H, s, H-14), 2.61 (1H, sextet, H-7), 3.30 (1H, dd, J=9.9, 2.1 Hz, H-10), 6.62 (1H, d, J=1.8 Hz, H-2), 6.67 (1H, dd, J=7.8, 1.8 Hz, H-6), 7.02 (1H, d, J=7.6 Hz); 13C NMR δ 15.3 (C-14), 23.1 (C-12), 23.4 (C-15), 26.5 (C-13), 29.9 (C-9), 35.5 (C-8), 39.7 (C-7), 73.1 (C-11), 78.8 (C-10), 113.4 (C-2), 119.1 (C-6), 121.1 (C-4), 130.8 (C-5), 146.7 (C-1), 153.8 (C-3). EIMS m/z 252 (29) [M⁺, C₁₅H₂₀O₄], 135 (100), 59 (95).

**RESULTS AND DISCUSSION**

Hydrodistillation of the chopped fresh rhizomes of *C. xanthorrhiza* yielded essential oil in 0.91 % yield. Xanthorrhizol 1 was isolated from the essential oil by vacuum column chromatography in 39% yield based on the crude essential oil or 0.35% based on the fresh rhizomes. Xanthorrhizol 1 obtained by this method was slightly contaminated by germacrane type sesquiterpenoids. However 1 was used for the reaction without further purification.

In the synthesis of curcuhydroquinone 2, xanthorrhizol 1 was first converted to curcuquinone) using Frenyi’s salt oxidation (Teuber oxidation) [6] (Scheme 1). Reduction of the resulting quinone 5 furnished curcuhydroquinone 2 in quantitative yield. Curcuhydroquinone 2 has been synthesised in 30% overall yield from 1. Attempts to prepare this compound by Elbs persulphate hydroxylation of 1 gave very poor overall isolated yield of only 5.7%. In addition, this method involved tedious worked up. Thus, Frenyi’s salt oxidation route was more promising method in the synthesis of curcuhydroquinone 2. Spectral properties of 2 were identical with those of natural products except our synthetic product solidified on standing at room temperature (mp 92-95°C).

In the route to the compound 3, xanthorrhizol 1 was protected as its acetate derivative 6 (Scheme 2). The protected compound 6 was subjected to Sharpless AD using AD-mix-α [7] to produce diol derivative 7. The diastereomeric excess was >95% as determined by 1H NMR analysis of its (S)-MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid) ester derivative. The absolute configuration of the newly formed stereogenic center was confirmed to be S by means of the modified Mosher's method [8]. Saponification of 7 under mild condition with aqueous sodium bicarbonate in methanol afforded targeted molecule 3. The stereoisomer of 3, i.e. triol 4 was prepared using the same route as in the synthesis of 3 except AD-mix-β was used in this preparation. The 1H NMR spectra of compounds 3 and 4 were almost identical, suggesting that these two compounds were isomers. The difference of configuration at H-10 of compounds 3 and 4 was shown by the difference in 1H chemical shifts. The signal of H-10 of compound 3 (δ 3.37, 1H, br d, J=10.2 Hz) was downfield relative to compound 4 (δ 3.30, 1H, dd, J=9.9, 2.1 Hz) (Δδ=0.07 Hz). The spectroscopic properties of synthetic 3 and 4 were identical with those of the natural products [5].
CONCLUSION

Xanthorrhizol has been isolated from the essential oil of C. xanthorrhiza in 39% yield. This compound has been converted to curcuhydroquinone using Fremy’s salt oxidation as the key step. Both enantiomeric forms of 10, 11-dihydro-10,11- dihydroxyxanthorrhizols have also been prepared from xanthorrhizol by the Sharpless AD route. These findings have opened ways of using this sesquiterpenoid as chiral building block for the synthesis of useful bioactive bisabolane type sesquiterpenoids.

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