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First asymmetric total synthesis of novel and cytotoxic 2′-*R*-hydroxylanneaquinol

V. Suresh, K. Rajesh, J. Jon Paul Selvam, Y. Venkateswarlu *

Organic Chemistry Division-I, Natural Products Laboratory, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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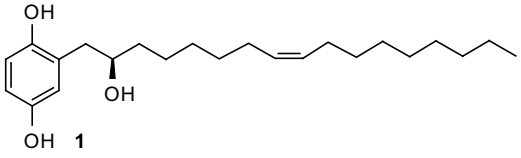
ABSTRACT

A novel cytotoxic alkylated hydroquinone 2′-*R*-hydroxylanneaquinol (**1**), isolated from the organic extract of the plant *Lannea welwitschii*, has been synthesized for the first time using commercially available 4-methoxyphenol. The key step of this process involves the kinetic resolution of epoxide **6** using Jacobsen's reaction conditions.

Hydroquinone and quinone subunits feature in a variety of natural products.[1] Alkylated hydroquinones exhibit many interesting biological properties such as cytotoxic,[2] antioxidant,[3] antitumor,[4] inhibition of HIV 1 reverse transcriptase,[5] antifungal,[6] and antimicrobial[7] activities. Two novel, cytotoxic alkylated hydroquinones, 2′-*R*-hydroxylanneaquinol **1** and lanneaquinol **2,** were isolated by Boyd and co-workers[8] from the organic extract of *Lannea welwitschii* (Hiern) Engl. (family *Anacardiaceae*). Interestingly, both compounds exhibited modest cytotoxicity against the NCI panel of 60 human tumor cells.[9,10] The bark of the medicinal plant *L. welwitschii* is used to treat abdominal pain and skin ulcers and is used to prepare ADD-199, herbal preparation[11] used by some Ghanaian patients to manage diabetes.

The biological potential of these compounds has stimulated significant interest in the synthesis of 2′-R-hydroxylanneaquinol (1). To the best of our knowledge, there is no report on the total synthesis of 2′-R-hydroxylanneaquinol. Herein, we report the first asymmetric total synthesis of 2′-R-hydroxylanneaquinol (1) by kinetic resolution of racemic epoxide 5 under Jacobsen's resolution conditions.

Our synthesis (Scheme 1) started from 2,5-dimethoxyallyl benzene **4**, which was prepared from commercially available 4-methoxyphenol **3** according to the reported procedure.[12] Epoxidation of the olefin moiety of **4** with *m*-CPBA (70%) in CH_2Cl_2 at room temperature afforded the racemic epoxide **5** in 90% yield. Compound **5** was subjected to Jacobsen's hydrolytic kinetic resolution[13] with 0.55 equiv of water using (*S*,*S*)-(salen)Co(III)(OAc) as the catalyst to give enantiomerically pure **6** (87% ee) and diol **7** each in 47% yield. Ring opening of enantiomerically pure epoxide **6** with Grignard reagent **8** using CuI in dry THF at −78 °C afforded



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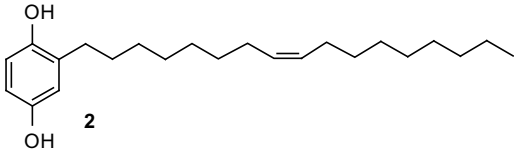

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* Corresponding author. Tel.: +91 40 27193167; fax: +91 40 27160512.
E-mail address: luchem@iict.res.in (Y. Venkateswarlu).

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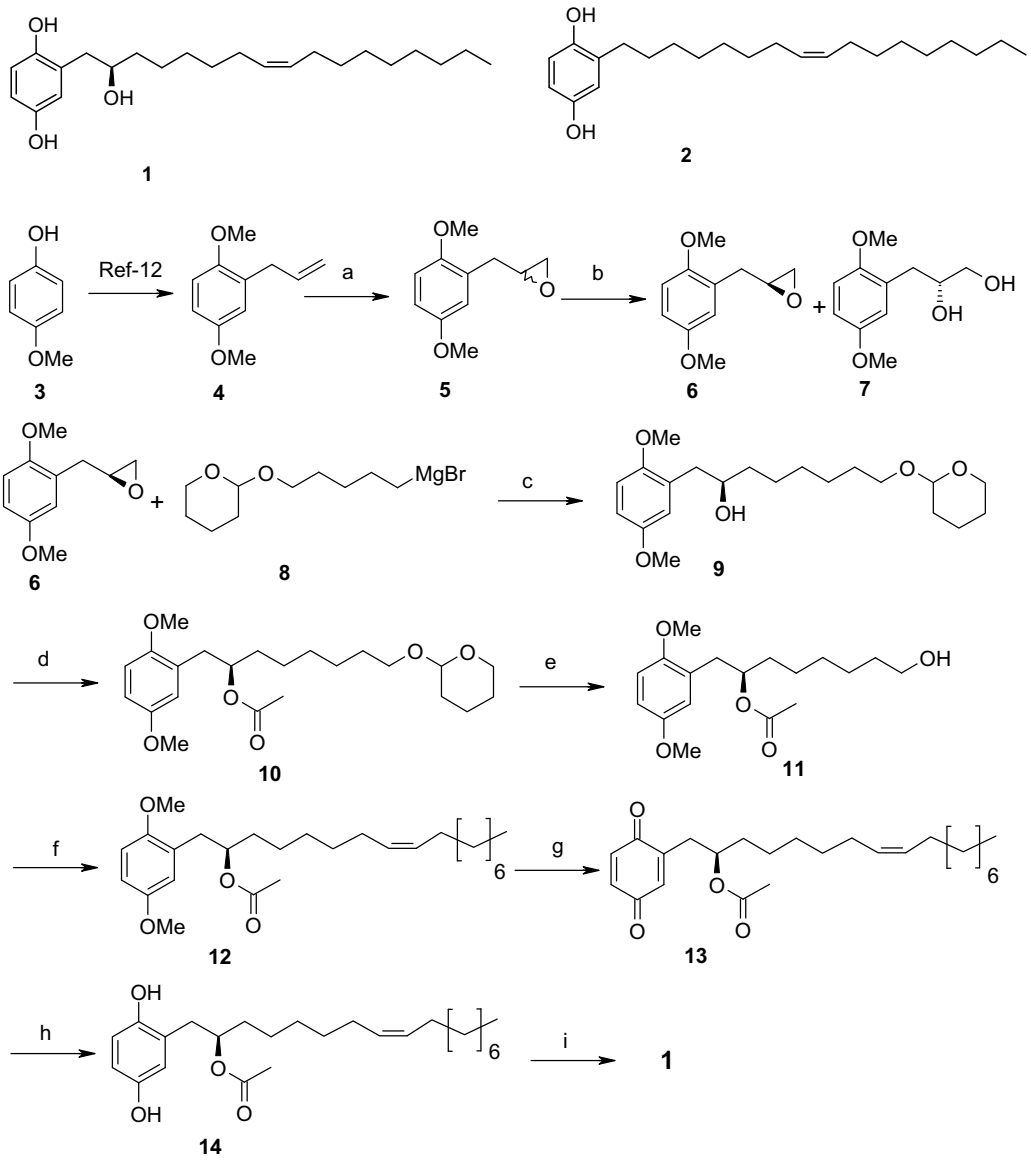

Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 90%; (b) (*S*,*S*)-(salen)Co(III)(OAc), 0.55 equiv H_2O, 47%; (c) CuI, THF, −78 °C, 5 h, 70%; (d) Ac_2O, pyridine, DMAP (10 mol %), CH_2Cl_2, rt, 95%; (e) *p*-TSA (10 mol %), MeOH, rt, 2 h, 98%; (f) (i) IBX, DMSO, DCM, rt, 4 h, 95%; (ii) $CH_3(CH_2)_7CH_2PPh_3^+Br^-$, *n*-BuLi, THF–HMPA, −78 °C, 2 h, 75%; (g) CAN, 1:1 CH_3CN/H_2O, rt, 15 min, 85%; (h) $Na_2S_2O_4$, Et_2O, H_2O, rt, 5 min, (80%); (i) $NaOCH_3$, MeOH, 0 °C, 2 h, (90%).

secondary alcohol **9** in 70% yield.[14] Grignard reagent **8** was prepared by reaction of the THP ether of 5-bromo-1-pentanol and Mg in dry THF. The THP ether of 5-bromo-1-pentanol was itself prepared from 1,5-pentanediol. The secondary hydroxyl group in compound **9** was acetylated using Ac_2O, pyridine, and DMAP in CH_2Cl_2 to afford **10** in 95% yield. Deprotection of the THP ether **10** with *p*-TSA in methanol afforded primary alcohol **11** in 98% yield. The alcohol **11** was oxidized using iodoxybenzoic acid (IBX) in dry DMSO and dry CH_2Cl_2 to afford the corresponding aldehyde in 95% yield (not isolated), which was subjected to a Wittig olefination[15] with nonyl tri phenyl phosphonium bromide in tetrahydrofuran–hexamethyl phosphoric acid triamide (THF–HMPA) and *n*-butyllithium at −78 °C to afford *Z*-olefin **12** in 75% yield. Deprotection of the two aromatic methoxy groups in **12** was attempted using MeMgI,[16] TMSI,[17] NaSEt,[18] BBr_3,[19] and PhSH/K_2CO_3,[20] which all gave mixtures of products. However, the demethoxylation was achieved using CAN in 1:1 CH_3CN–H_2O medium to afford 1,4-quinone **13** in 85% yield.[21] Reduction of the quinone **13** with $Na_2S_2O_4$ in Et_2O–H_2O afforded hydroquinone **14** in 80% yield. Finally, the acetate in **14** was cleaved with NaOMe in methanol to give the desired 2′-*R*-hydroxylanneaquinol (**1**) in 90% yield. The physical and spectroscopic data[22] (MS, ^1H and ^{13}C NMR, IR, and optical rotation) of **1** were found to be identical with those reported in the literature.[8]

In conclusion, we have achieved the first asymmetric total synthesis of 2′-R-hydroxylanneaquinol (**1**) from the readily available starting material 4-methoxyphenol (**3**) by 10 distinct steps with an overall yield of 13%. The synthesis involves utilization of Jacobsen's hydrolytic kinetic resolution and a Wittig reaction as key steps.

Acknowledgments

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22. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. Spectral data of selected compounds: Compound **6**: pale yellow oil; $[\alpha]_D^{25}$ +1.7 (*c* 2.6, $CHCl_3$). IR (film): 2996, 2943, 2834, 1500, 1226, 1046, 806, 707 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.63–6.76 (m, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.10 (m, 1H), 2.88 (dd, 1H, *J* = 14.0, 8.5), 2.76 (dd, 1H, *J* = 10.9, 5.4), 2.70 (dd, 1H, *J* = 5.4, 3.9), 2.49 (dd, 1H, *J* = 5.4, 2.3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 151.8, 126.8, 116.9, 111.9, 111.2, 55.9, 55.6, 51.6, 47.1, 33.4; ESIMS *m/z* (rel int.) 195 [M+1]. Compound **11**: colour less liquid, $[\alpha]_D^{25}$ −5.71 (*c* 0.36, $CHCl_3$). IR (film): 3442, 2930, 2857, 1733, 1500, 1226, 1048, 1024, 803, 709 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.56 (m, 3H), 5.08 (q, 1H, *J* = 6.6), 3.77 (s, 3H) 3.72 (s, 3H), 3.58 (t, 2H, *J* = 6.6), 2.86 (dd, 1H, *J* = 13.9, 5.87), 2.67 (dd, 1H, *J* = 13.2, 7.3), 1.94 (s, 3H), 1.08–1.61 (br m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 153.1, 152.0, 127.3, 117.4, 111.7, 111.1, 73.7, 62.8, 55.8, 55.6, 34.9, 33.7, 32.6, 29.1, 25.5, 25.2, 21.0; EIMS *m/z* (rel int.) 324 [M$^+$], 264 (M–CH_3COOH), 177, 151, 121. Compound **12**: colour less liquid, $[\alpha]_D^{25}$ −6.2 (*c* 0.36, $CHCl_3$). IR (film): 2927, 2858, 1736, 1502, 1458, 1234, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66–6.75 (m, 3H), 5.27–5.37 (m, 2H), 5.11 (q, 1H, *J* = 6.0), 3.77(s, 3H), 3.74 (s, 3H), 2.90 (dd, 1H, *J* = 13.5, 5.2), 2.69 (dd, 1H, *J* = 13.5, 7.5), 1.96–2.04 (br m, 4H), 1.95 (s, 3H), 1.52 (2H), 1.27–1.40 (18H), 0.88 (t, 3H, *J* = 6.7); ^{13}C NMR (75MHz, $CDCl_3$): δ 170.5, 153.1, 152.0, 130.0, 129.6, 127.3, 117.3, 111.7, 111.1, 73.8, 55.8, 55.6, 34.9, 33.8, 31.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 27.2, 27.1, 25.2, 22.6, 21.1, 14.0; ESIMS *m/z* (rel int.) 455 [M+Na], 373, 268. Compound **1**: white solid, $[\alpha]_D^{25}$ +0.65 (*c*, 1.0, $CHCl_3$). IR (film): 3346, 3164, 2921, 2851, 1462, 1204, 1021, 811, 722, 614 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (br–OH, 1H), 6.73 (d, 1H, *J* = 9.0), 6.57 (dd, 1H, *J* = 8.3, 3.0), 6.49 (d, 1H, *J* = 3.0), 5.33 (m, 2H), 4.96 (br–OH, 1H), 3.93 (dddd,1H, *J* = 12.0, 9.8, 5.2, 3.0), 2.75 (dd, 1H, *J* = 14.3, 3.0), 2.70 (dd, 1H, *J* = 14.3, 7.5), 1.92–2.04 (m, 4H), 1.70 (br s, 1H), 1.50 (m, 2H), 1.26 (br s, 17H), 0.88 (t, 3H, *J* = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.2, 148.9, 130.2, 129.4, 126.5, 118.0, 117.8, 114.7, 74.4, 38.8, 36.9, 31.9, 29.7, 29.5, 29.4, 29.3, 29.1, 29.0, 27.2, 27.0, 25.5, 22.6, 14.0; HREIMS *m/z*: found 385.27 [M+Na] $C_{23}H_{38}O_3$.