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First Synthesis of *N*-(3-Carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone, an Unusual Quinone Isolated from *Embelia ribes*

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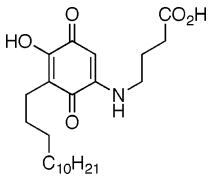

The first synthesis of the unusual nitrogen-containing 3-alkyl-1,4-benzoquinone, *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone, isolated from *Embelia ribes*, is reported. The key steps are a microwave-assisted combined Mitsunobu reaction−Claisen rearrangement to introduce the alkyl side chain into 2,5-dimethoxyphenol, followed by alkene reduction, oxidation to the quinone, and sequential displacement of the methoxy groups with hydroxide and GABA *tert*-butyl ester. Two other naturally occurring benzoquinones, *O*-methylrapanone and rapanone, were also prepared en route.

Extracts of various parts of the shrub *Embelia ribes*, known commonly as vidanga, are widely used in traditional Chinese medicine to treat a range of ailments. The extracts contain a diverse array of chemotypes, including coumarins, flavonoids, terpenes, and 1,4-benzoquinones. One of the major chemical constituents is embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) **1**, first isolated several years ago, and reported to elicit a wide range of biological effects including anthelmintic, analgesic, antifertility, antitumor, and antioxidant properties.[1] Recently a new benzoquinone derivative was isolated from the roots of *Embelia ribes* and assigned the *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone structure **2**.[2] It shares the long unbranched 3-alkyl side chain of embelin **1**, although it has two extra carbons (C-13 as opposed to C-11), and has the unusual incorporation of γ-aminobutyric acid (GABA) linked to the quinone through nitrogen. Although other quinones with 13-carbon side chains are known, e.g., rapanone **3** previously isolated from a variety of sources, better known are the sesquiterpene benzoquinones,[3−5] some of which such as the nakijiquinones **4**,[6,7] the smenospongines **5**,[8] and the metachromins **6**[9] also incorporate amino acid derived side chains at C-5 (Figure 1).

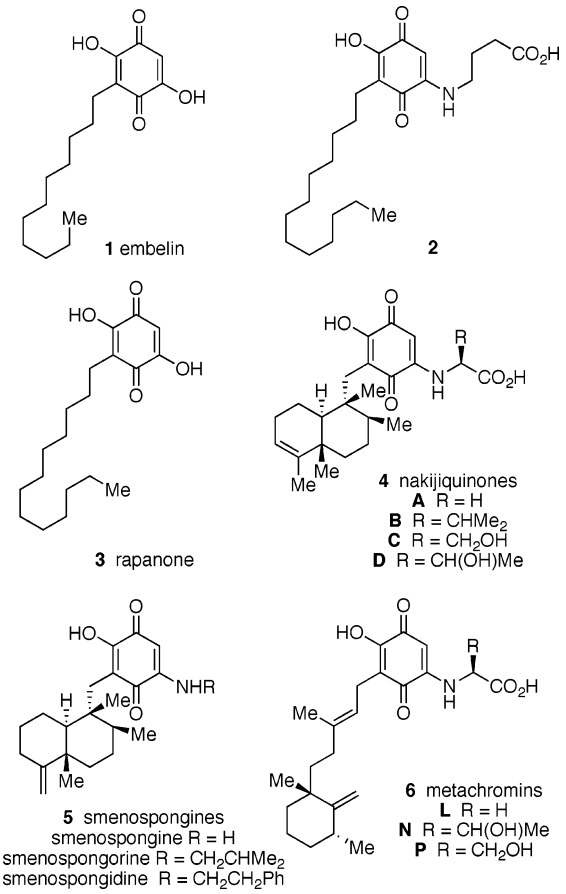

FIGURE 1. Some naturally occurring 3-alkyl-2-hydroxy-1,4-benzoquinones.

Naturally occurring quinones exhibit wide-ranging properties.[3−5] Not only do they constitute a large group of natural pigments, although surprisingly their contribution to natural coloring is relatively small, but they also participate in a range of important biological redox processes. Consequently, they have attracted the attention of synthetic chemists and there have been a number of approaches to some of the 3-alkyl-2-hydroxy-1,4-benzoquinone natural products shown in Figure 1.[10−14] Our own

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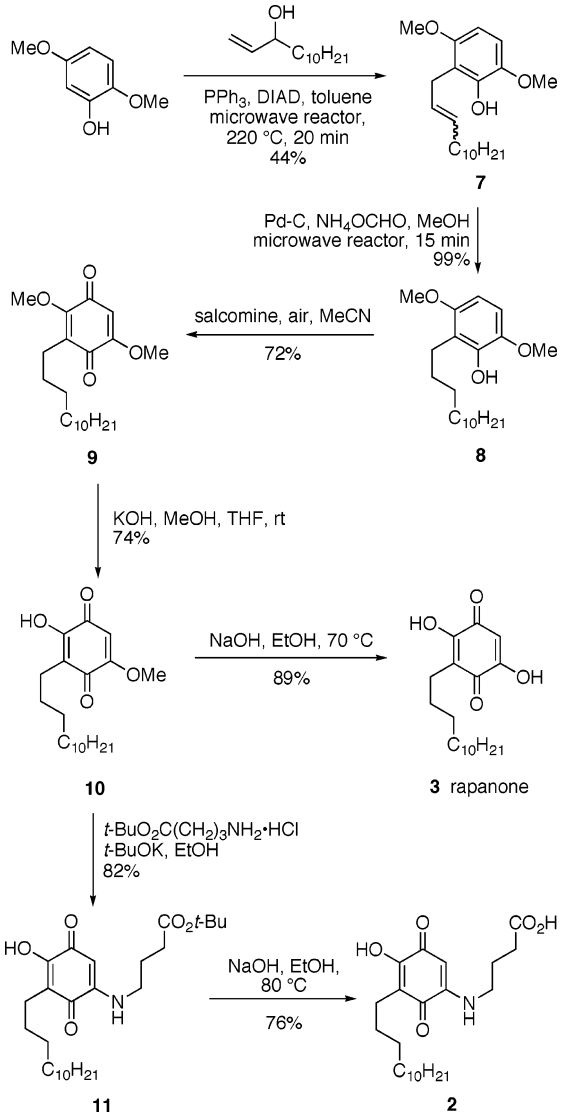
interest in quinone natural products dates back to an early synthesis of coenzyme PQQ,[15] and more recently the alkyl benzoquinones primin, pallasone-B, verapliquinones-A and -B, and panicein-A.[16] These syntheses employed the Claisen rearrangement to introduce the alkyl chain, and were rendered more concise by the use of a microwave-assisted combined Mitsunobu−Claisen rearrangement sequence. Hence primin (2-methoxy-6-pentyl-1,4-benzoquinone) was obtained from 2-methoxyphenol in four reaction steps with a total reaction time of 60 min in an overall yield of 43%.[17] We now report the use of similar methodology in the first synthesis of *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone **2**.

The synthesis started with 2,5-dimethoxyphenol that was reacted with 1-tridecen-3-ol with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in toluene at 220 °C under microwave irradiation for 20 min to give the alkylated phenol **7** as an inconsequential mixture of *E*/*Z*-isomers in moderate yield. Although both steps of this process—the Mitsunobu reaction[18,19] and Claisen rearrangement[20−23]—are known to be microwave accelerated, they had never been combined in a single pot until our original work.[17] In the present case, carrying out the conversion as two separate operations resulted in lower yield. The alkene mixture was reduced by using microwave-assisted catalytic transfer hydrogenation[24,25] to give the required tridecylphenol **8** in essentially quantitative yield. Oxidation with oxygen in the presence of salcomine[26,27] gave the 3-alkyl-2,5-dimethoxy-1,4-benzoquinone **9** (72%) (Scheme 1). Selective hydrolysis of the 2-methoxy group gave the corresponding 2-hydroxyquinone **10**, the regiochemistry in the hydrolysis of such dimethoxyquinones (vinylogous methyl esters) being rationalized by the relative stability of the enolate intermediate.[28] Quinone **10** (*O*-methylrapanone) also occurs naturally, and as an aside, was converted into rapanone **3** itself by hydrolysis of the remaining methoxy group under more forcing conditions. In both cases, the spectroscopic data matched those of the natural products. Finally, quinone **10** was converted into the new naturally occurring quinone **2**. Direct reaction with GABA gave a complex mixture, and therefore the *tert*-butyl ester of GABA was used in the addition−elimination sequence to give the desired quinone **11**, deprotection of which under basic conditions—the more normal acid mediated cleavage of the *tert*-butyl ester giving less satisfactory results—gave the natural product *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone structure **2** (Scheme 1). This short synthesis illustrates the versatility of the Mitsunobu−Claisen rearrangement protocol in routes to naturally occurring benzoquinones.

SCHEME 1



Experimental Section

Commercially available reagents and solvents were used throughout without further purification, except for tetrahydrofuran, dichloromethane, and diethyl ether, which were freshly distilled. Light petroleum refers to the fraction with bp 40−60 °C. Thin layer chromatography was carried out on aluminum foil backed plates. The plates were visualized under UV light or by vanillin stain. Flash chromatography was carried out on silica gel, with the eluent specified. IR spectra were recorded as solutions with chloroform as solvent. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 500 MHz (^{13}C frequencies 100 and 125 MHz, respectively); chemical shifts are quoted in ppm. In the ^{13}C spectra, signals corresponding to C, CH, CH_2, or CH_3 groups, as assigned from DEPT, are noted.

3,6-Dimethoxy-2-(tridec-2-enyl)phenol 7. A 35 mL sealable microwave reactor vessel was charged with a solution of tridec-1-en-3-ol (400 mg, 2.02 mmol) in toluene (10 mL). To that

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solution was added 2,5-dimethoxyphenol (560 mg, 3.63 mmol), triphenylphosphine (952 mg, 3.63 mmol) and DIAD (715 μL, 3.63 mmol). The reaction mixture was irradiated in a CEM Discover microwave reactor to 220 °C for 20 min. After cooling to room temperature the solvent was removed and the residue was subjected to flash chromatography, eluting with 10% ether in light petroleum, to give the title compound (300 mg, 44%) as a mixture of geometric isomers and as a clear oil; R_f 0.69 (25% ether in light petroleum); IR ($CHCl_3$) ν_{max}/cm^{-1} 3536, 2920, 2854, 1462, 1097, 1080; ^1H NMR (400 MHz; $CDCl_3$) δ *Major isomer* 6.66 (1 H, d, J = 8.8 Hz), 6.35 (1 H, d, J = 8.8 Hz), 5.71 (1 H, s), 5.60−5.44 (2 H, m), 3.85 (3 H, s), 3.77 (3 H, s), 3.37 (2 H, d, J = 6.0 Hz), 1.96 (2 H, q, J = 6.8 Hz), 1.39−1.25 (16 H, m), 0.89 (3 H, app t, J = 6.8 Hz); *Minor isomer* 6.79 (1 H, d, J = 8.8 Hz), 6.54 (1 H, s), 6.14 (1 H, d, J = 8.8 Hz), 5.86−5.73 (2 H, m), 4.53 (2 H, d, J = 6.0 Hz), 3.84 (3 H, s), 3.76 (3 H, s), 2.07 (2 H, ddd, J = 7.2, 7.2, 6.8 Hz), 1.39−1.25 (16 H, m), 0.89 (3 H, app t, J = 6.8 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ *Major isomer* 152.5 (C), 144.2 (C), 141.2 (C), 130.8 (CH), 127.3 (CH), 116.1 (C), 107.9 (CH), 101.1 (CH), 69.7 (CH_2), 56.3 (CH_3), 56.0 (CH_3), 31.9 (CH_2), 29.6 (CH_2), 29.54 (CH_2), 29.51 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 26.5 (CH_2) 22.7 (CH_2), 14.1 (CH_3); the following signals were observed for the *Minor isomer* 136.0 (CH), 124.6 (CH), 112.2 (CH), 103.3 (CH), 56.5 (CH_3), 55.6 (CH_3), 32.6 (CH_2); HRMS (ESI^+) found (MH^+) 335.2581, $C_{21}H_{35}O_3$ requires 335.2586.

3,6-Dimethoxy-2-tridecylphenol 8. To a solution of 3,6-dimethoxy-2-(tridec-2-enyl)phenol **7** (20.0 mg, 0.06 mmol) in methanol (3 mL) was added ammonium formate (20.0 mg, 0.30 mmol) and Pd/C (10 mg). The mixture was irradiated in a CEM Discover microwave reactor with a reflux condenser attached at 15 W and 65 °C for 15 min. The reaction mixture was filtered through a plug of Celite and the solvent was removed. The residue was subjected to flash chromatography, eluting with 10% ether in light petroleum, to give the title compound (20 mg, 99%) as a clear oil; R_f 0.69 (25% ether in light petroleum); IR ($CHCl_3$) ν_{max}/cm^{-1} 3539, 2926, 2854, 1489, 1123, 1092; ^1H NMR (500 MHz; $CDCl_3$) δ 6.64 (1 H, d, J = 8.7 Hz), 6.34 (1 H, d, J = 8.7 Hz), 5.70 (1 H, s), 3.85 (3 H, s), 3.78 (3 H, s), 2.66 (2 H, dd, J = 8.0, 7.5 Hz), 1.58−1.22 (22 H, m), 0.90 (3 H, app t, J = 7.0 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ 152.8 (C), 144.3 (C), 141.1 (C), 118.2 (C), 107.5 (CH), 100.9 (CH), 56.4 (CH_3), 55.9 (CH_3), 32.0 (CH_2), 29.97 (CH_2), 29.92 (CH_2), 29.82 (CH_2), 29.81 (CH_2), 29.78 (CH_2), 29.76 (CH_2), 29.70 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS (ESI^+) found (MH^+) 337.2718, $C_{21}H_{37}O_3$ requires 337.2742.

2,5-Dimethoxy-3-tridecyl-1,4-benzoquinone 9. To a solution of 3,6-dimethoxy-2-tridecylphenol **8** (20.0 mg, 0.06 mmol) in acetonitrile (2 mL) was added salcomine (5.8 mg, 0.018 mmol) and the mixture was stirred overnight open to the air. The solvent was evaporated and the residue was subjected to flash chromatography, eluting with 25% ether in light petroleum, to give the title compound (14.9 mg, 72%) as a yellow solid; mp 56−57 °C (lit.[11] mp 54−55 °C); R_f 0.25 (25% ether in light petroleum); UV (MeOH) λ_{max}/nm 209 (log ϵ 3.86), 286 (3.92), 369 (2.72); IR ($CHCl_3$) ν_{max}/cm^{-1} 2927, 2854, 1652, 1596, 1458, 1325, 1048; ^1H NMR (500 MHz; $CDCl_3$) δ 5.73 (1 H, s), 4.05 (3 H, s), 3.80 (3 H, s), 2.43 (2 H, dd, J = 7.5, 7.5 Hz), 1.43−1.17 (22 H, m), 0.88 (3 H, app t, J = 7.0 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ 183.6 (C), 182.4 (C), 158.8 (C), 155.9 (C), 130.8 (C), 105.4 (CH), 61.3 (CH_3), 56.4 (CH_3), 31.9 (CH_2), 29.7−28.7 (9 × CH_2), 23.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI^+) found (MH^+) 351.2524, $C_{21}H_{35}O_4$ requires 351.2535.

2-Hydroxy-5-methoxy-3-tridecyl-1,4-benzoquinone (5-*O*-methylrapanone) 10. To a solution of 2,5-dimethoxy-3-tridecyl-1,4-benzoquinone **9** (40.0 mg, 0.114 mmol) in a mixture of methanol: THF (1:1; 2 mL) was added water (1 mL) and potassium hydroxide (19 mg, 0.34 mmol). The mixture was stirred at room temperature for 1 h and was then diluted with hydrochloric acid (2 M; 10 mL). The mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, the solvent was evaporated, and the residue was subjected to flash chromatography, eluting with 25% ether in light petroleum, to give the title compound (28.3 mg, 74%) as a yellow/orange solid; mp 74−76 °C (lit.[11] mp 87−88 °C); R_f 0.33 (50% ether in light petroleum); UV (EtOH) λ_{max}/nm 207 (log ϵ 3.78), 286 (4.00), 416 (2.58); IR ($CHCl_3$) ν_{max}/cm^{-1} 3352, 2926, 2854, 1644, 1609, 1390, 1355, 1319; ^1H NMR (500 MHz; $CDCl_3$) δ 7.22 (1 H, s), 5.84 (1 H, s), 3.86 (3 H, s), 2.44 (2 H, dd, J = 7.5, 7.5 Hz), 1.47−1.25 (22 H), 0.88 (3 H, app t, J = 7.0 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ 182.9 (C), 181.8 (C), 161.2 (C), 151.6 (C), 119.3 (C), 102.2 (CH), 56.8 (CH_3), 32.0 (CH_2), 29.7−28.1 (9 × CH_2), 22.78 (CH_2), 22.72 (CH_2), 14.2 (CH_3); HRMS (ESI^+) found (MH^+) 337.2361, $C_{20}H_{33}O_4$ requires 337.2379.

2,5-Dihydroxy-3-tridecyl-1,4-benzoquinone (rapanone) 3. Aqueous sodium hydroxide (2 M; 1 mL) was added to a solution of 5-*O*-methylrapanone **10** (15.0 mg, 0.045 mmol) in ethanol (2 mL). The mixture was heated to 70 °C for a period of 2 h and allowed to cool to room temperature. The reaction mixture was diluted with hydrochloric acid (2 M; 5 mL) then extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated to give the title compound (12.8 mg, 89%) as an orange solid; mp 139−140 °C (methanol) (lit.[29] mp 141−142 °C); R_f 0.0 (50% ether in light petroleum); UV (EtOH) λ_{max}/nm 206 (log ϵ 4.09), 290 (4.11); IR ($CHCl_3$) ν_{max}/cm^{-1} 3357, 2926, 2854, 1640, 1364; ^1H NMR (500 MHz; $CDCl_3$) δ 7.68 (2 H, br s), 6.01 (1H, s), 2.45 (2 H, dd, J = 8.0, 7.5 Hz), 1.49−1.26 (22 H, m), 0.89 (3 H, app t, J = 7.0 Hz); HRMS (ESI^-) found ($M - H^{+\bullet}$) 321.2071, $C_{19}H_{29}O_4$ requires 321.2066.

***N*-(3-*tert*-Butoxycarbonylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone 11.** To a solution of 5-*O*-methylrapanone **10** (7.0 mg, 0.0208 mmol) in ethanol (1 mL) was added a solution of *tert*-butyl 4-aminobutyrate hydrochloride (12.2 mg, 0.063 mmol) and potassium *tert*-butoxide (7.0 mg, 0.063 mmol) in ethanol (1 mL). The mixture was stirred at room temperature for 20 h, diluted with hydrochloric acid (2 M; 10 mL), and extracted with dichloromehane (4 × 10 mL). The combined organic phases were dried over $MgSO_4$, the solvent was evaporated, and the residue was subjected to flash chromatography, eluting with 25% ether in light petroleum, to give the title compound (7.9 mg, 82%) as a purple solid; mp 82−85 °C; R_f 0.62 (50% ether in light petroleum); UV (EtOH) λ_{max}/nm 210 (log ϵ 4.39), 317 (4.35), 499 (3.33); IR ($CHCl_3$) ν_{max}/cm^{-1} 3696, 3358, 2927, 2854, 1721, 1649, 1597, 1394; ^1H NMR (500 MHz; $CDCl_3$) δ 8.05 (1 H, br s), 6.55 (1 H, br s), 5.37 (1 H, s), 3.21 (2 H, dd, J = 13.0, 7.0 Hz), 2.39 (2 H, dd, J = 7.0, 7.0 Hz), 2.33 (2 H, t, J = 7.0 Hz), 1.95 (2 H, pent, J = 7.0 Hz), 1.46 (9 H, s), 1.30−1.25 (22 H, m), 0.88 (3 H, app t, J = 7.0 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ 182.5 (C), 178.9 (C), 172.0 (C), 155.0 (C), 149.8 (C), 115.8 (C), 91.8 (CH), 81.1 (C), 42.3 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 29.77−29.45 (9 × CH_2), 28.2 (CH_3), 23.4 (CH_2), 22.78 (CH_2), 22.73 (CH_2), 14.2 (CH_3); HRMS (ESI^+) found (MH^+) 464.3394, $C_{27}H_{46}NO_5$ requires 464.3376.

***N*-(3-Carboxypropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone 2.** To a solution of *N*-(3-*tert*-butoxycarbonylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone **11** (9.0 mg, 0.019 mmol) in ethanol (3 mL) was added aqueous sodium hydroxide (2 M; 1 mL). The mixture was stirred at 80 °C for 2 h, cooled to room temperature, and acidified with hydrochloric acid (2 M; 2 mL). The ethanol was evaporated and the aqueous residue was extracted with ethyl acetate (4 × 5 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. Preparative TLC, eluting with 10% MeOH in dichloromethane, gave the title compound (6.0 mg, 76%) as a red solid; mp 177−180 °C (lit.[2] mp not given); UV (MeOH) λ_{max}/nm 326 (log ϵ 3.92), 500

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(2.74); IR ($CHCl_3$) ν_{max}/cm^{-1} 3620, 3409, 2926, 2854, 1682, 1573, 1455, 1370, 1139; ^1H NMR (500 MHz; DMSO-*d*) δ 7.80 (1 H, br s), 5.31 (1 H, s), 3.24−3.17 (2 H, m), 2.31−2.21 (4 H, m), 1.79−1.75 (2 H, m), 1.37−1.26 (22 H, m), 0.88 (3 H, app t, J = 7.0 Hz); ^{13}C NMR (125 MHz; DMSO-*d*) δ 182.5 (C), 178.4 (C), 174.1 (C), 156.7 (C), 149.3 (C), 115.7 (C), 91.7 (CH), 31.3 (CH_2), 30.9 (CH_2), 29.0−28.7 (9 × CH_2), 27.6 (CH_2), 22.7 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 14.0 (CH_3); HRMS (ESI^+) found (MH^+) 408.2737, $C_{23}H_{38}NO_5$ requires 408.2750.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of compounds **7**−**11**, **3**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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