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Tetrahedron Letters 47 (2006) 345–348
Tetrahedron Letters

Total synthesis of racemosol and de-*O*-methylracemosol, potent cyclooxygenase (COX) inhibitors and antimalarial agents

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Received 8 September 2005; revised 25 October 2005; accepted 3 November 2005
Available online 22 November 2005

Abstract—The total synthesis of antimalarial and cyclooxygenase inhibitors, racemosol and de-*O*-methylracemosol, is described. The key steps involved the lateral lithiation reaction of *ortho*-methyl tolulate and the pyran formation via a tandem demethylation–cyclization reaction.

Racemosol (**1**) and de-*O*-methylracemosol (**2**), were isolated from the roots of *Bauhinia malabarica* Roxb, and possessed in vitro antimalarial activity.[1] Recently we have discovered that **1** and **2** are potent cyclooxygenase (COX) inhibitors, showing comparable activity to that of the standard drug, aspirin.[2] Both racemosol (**1**) and de-*O*-methylracemosol (**2**) were also isolated from *B. racemosa*[3] and *B. rufescens*.[4] A biosynthetic pathway for these tetracyclic substances (Fig. 1), involving stilbene related compounds as precursors, was proposed by Hostettmann and co-workers.[4]

The interesting biological activities of **1** and **2**, as well as the limited amounts obtained from natural sources, prompted us to investigate their total synthesis. The retro synthesis of racemosol (**1**) and de-*O*-methylracemosol (**2**) is outlined retrosynthetically in Scheme 1. On the basis of deprotection and cyclization, the tetracyclic skeleton of **1**, **2** could be obtained from intermediate **3**.

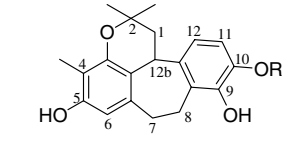
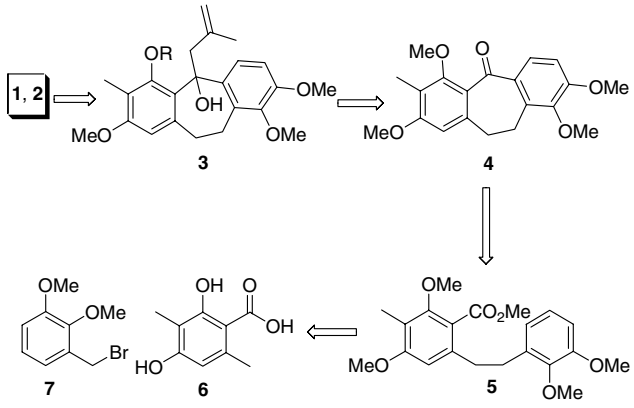


Figure 1. Structures for **1** and **2**.



Scheme 1. Retrosynthetic analysis of **1** and **2**.

The key intermediate **3** could be prepared from tricyclic ketone **4** using Grignard reaction. The required tricyclic ketone **4** can arise from the intramolecular Friedel–Crafts acylation[5] of ester **5**. The dihydrostilbene ester **5** could be constructed through C–C bond formation using the lateral lithiation reaction[6] of 2,4-dihydroxy-3,6-dimethylbenzoic acid (**6**) and 2,3-dimethoxybenzyl bromide (**7**).

The commercially available 2,4-dihydroxy-3,6-dimethylbenzoic acid (**6**) was methylated (K_2CO_3/MeI) prior to lithiation. The methoxy protected precursor **8** was treated with 1.2 equiv LDA at −78 °C and then trapped with 2,3-dimethoxybenzyl bromide (**7**)[7] to provide product **5**. The regiospecific deprotonation of the *ortho*-methyl toluate group led to the desired alkylation

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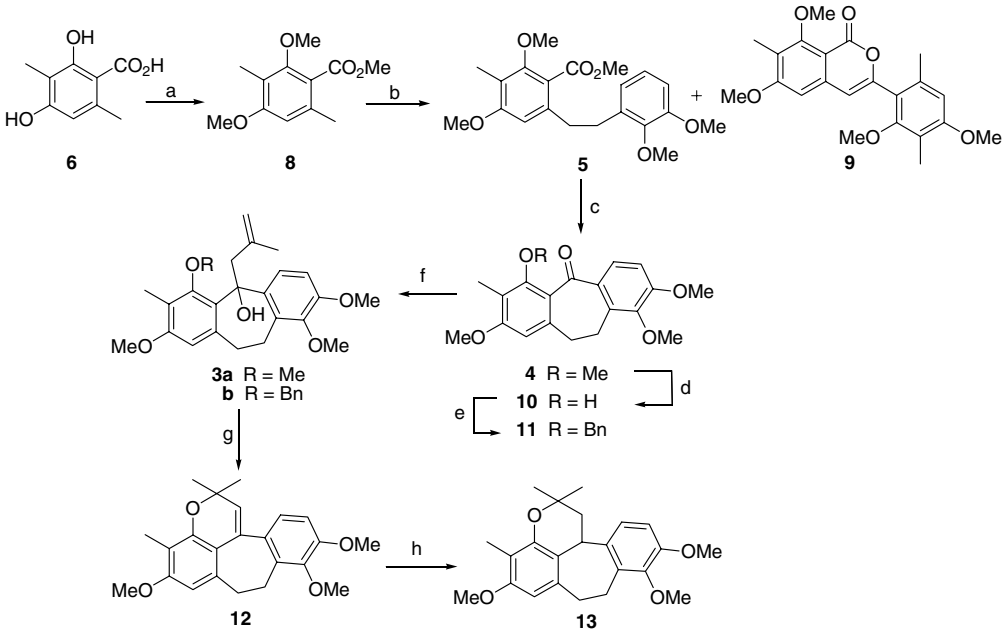
doi:10.1016/j.tetlet.2005.11.016

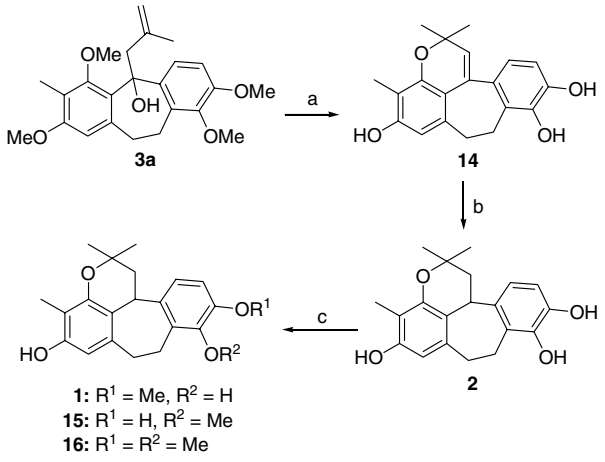


Scheme 2. Reagents and conditions: (a) K_2CO_3, DMF, MeI (96%); (b) 1.2 equiv LDA, 2,3-dimethoxybenzyl bromide (**7**), THF, −78 °C (67%); (c) PPA (92%); (d) 1.0 M BBr_3, CH_2Cl_2, −78 °C (92%); (e) BnBr, K_2CO_3, reflux acetone (95%); (f) β-methallyl magnesium chloride, THF, −20 °C to rt (93%); (g) concd HCl/EtOH, reflux 24 h (74%); (h) H_2/Pd–C (98%).

product **5**[8] (67%) and the self-coupled isocoumarin **9**[9] (30%). The formation of the isocoumarin from *ortho*-toluate coupling has previously been reported[10] and in this case it was suppressed by slow addition of benzyl bromide **7** to the anion intermediate of **8**. Attempts were made to protect the C–O bond with bulky benzyloxy and isopropoxy group to decrease the self-coupled product, however a poor yield of the desired product was obtained. Intramolecular Friedel–Crafts acylation[5] of ester **5** was performed directly in polyphosphoric acid to provide the seven-membered tricyclic ketone **4**[11] (92%). The conversion of the ester to the carboxylic acid in this case is no longer required. Grignard reaction of **4** with β-methallyl magnesium chloride in toluene:THF (10:1) at −20 °C gave the corresponding alcohol **3a**[12] (93%). Unfortunately, demethylation of **3a** with BBr_3 prior to cyclization met with failure. An alternative route using a benzyloxy protecting group was carried out. Selective demethylation of **4** with 1.0 M BBr_3 at −78 °C in CH_2Cl_2 and reprotection of the hydroxy group of **10**[13] with benzylbromide provided the benzyloxy product **11**[14] in good yield. Grignard reaction of **11** gave the corresponding alcohol **3b**[15] (75%). Debenzylation, cyclization and dehydration of compound **3b** with concd HCl in refluxing ethanol provided the desired tetracycle **12**[16] (74%). Hydrogenation of compound **12** using H_2/Pd–C afforded compound **13**[17] in excellent yield. This route should enable us to construct racemosol (**1**) and de-*O*-methylracemosol (**2**) as well as several analogues (Scheme 2).

In addition, a more efficient method that led to pyran formation via a tandem demethylation–cyclization[18] was applied to our system. Indeed, in the presence of $AlCl_3$/EtSH in CH_2Cl_2, compound **3a** was smoothly demethylated and cyclized to deliver a tetracyclic product **14**[19] (84%). To our delight, this method had the advantage of three reactions namely demethylation, cyclization and dehydration in one pot. The natural product de-*O*-methylracemosol (**2**)[20] could be obtained from hydrogenation (H_2/Pd–C) of **14**. Racemosol (**1**)[21] was obtained as the major product from methylation of **2**, together with other methylated products, c–9 methoxy (**15**) and dimethoxy (**16**),[2] as shown in Scheme 3. The synthetic racemosol (**1**) and de-*O*-methylracemosol (**2**) were characterized by spectroscopic techniques and they were identical in all respects to natural products **1** and **2**.[1,3,4]

In conclusion, the bioactive natural products de-*O*-methylracemosol (**2**) and racemosol (**1**) were successfully synthesized in 44% and 22% overall yields from the com-



Scheme 3. Reagents and conditions: (a) $AlCl_3$/EtSH, CH_2Cl_2, 0 °C to rt (84%); (b) H_2/Pd–C (95%); (c) K_2CO_3, DMF, MeI (50%).

mercially available 2,4-dihydroxy-3,6-dimethyl benzoic acid (**6**). Structure modification as well as the asymmetric synthesis of racemosol and related compounds are under investigation.

Acknowledgements

Financial support originated from the Postgraduate Education and Research Program in Chemistry (PERCH) and the Biodiversity Research and Training Program (BRT). We are grateful to the Department of Chemistry, Faculty of Science, Mahidol University, and The Medicinal Chemistry and Natural Product Laboratory at Chulabhorn Research Institute (CRI), for research facilities.

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7. To a solution of 2,3-dimethoxybenzylalcohol (0.25 g, 1.48 mmol) in 10 mL of dry CH_2Cl_2 at 0 °C was added PBr_3 (1.5 mL, 1.5 mmol). After stirring for 2 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3×20 mL). The combined organic solution was washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes) gave **7** as a colourless oil (0.24 g, 71%).
8. Compound **5**: viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, ArCH_3), 2.89 (m, 4H, $2 \times$ CH_2), 3.78, 3.81, 3.84, 3.89, 3.96 (5s, 15H, $5 \times$ OCH_3), 6.46 (s, 1H, H-5), 6.78 (m, 2H, Ar*H*), 7.00 (t, 1H, $J = 7.9$ Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 32.1, 35.1, 52.1, 55.5, 55.6, 60.6, 61.8, 107.1, 110.3, 117.5, 120.7, 122.0, 123.8, 135.3, 138.6, 147.1, 152.7, 156.3, 159.3, 168.9; IR (neat): ν_{max} 2998, 2942, 2835, 1727, 1602, 1583, 1481, 1268, 1224, 1152, 1010 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 375 ([M+H]$^+$, 15), 374 (M$^+$, 53), 343 (52), 342 (66), 327 (44), 324 (18), 136 (100). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00%. Found: C, 67.74; H, 6.89%.
9. Compound **9**: white solid; mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13, 2.23, 2.33 (3s, 9H, $3 \times$ ArCH_3), 3.67, 3.72, 3.82, 3.92 (4s, 12H, $4 \times$ OCH_3), 6.40 (s, 1H, Ar*H*), 6.52 (s, 1H, Ar*H*), 6.60 (s, 1H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 20.2, 55.5, 55.8, 61.4, 61.7, 101.7, 107.7, 107.8, 116.9, 119.8, 121.7, 136.7, 139.2, 152.0, 157.7, 159.2, 159.6, 160.7, 163.59; IR (KBr): ν_{max} 3422, 2933, 2845, 1717, 1656, 1595, 1467, 1131, 988 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 385 ([M+H]$^+$, 21), 384 (M$^+$, 100), 341 (70), 325 (47). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29%. Found: C, 68.93; H, 6.47%.
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11. Compound **4**: colourless solid; mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H, ArCH_3), 3.12 (2dt, 4H, $J = 4.9$, 5.5 Hz, $2 \times$ CH_2), 3.73, 3.82, 3.90, 3.95 (4s, 12H, $4 \times$ OCH_3), 6.48 (s, 1H, H-9), 6.80 (d, 1H, $J = 8.8$ Hz, H-3), 7.81 (d, 1H, $J = 8.8$ Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 28.9, 32.8, 55.6, 55.7, 59.8, 62.1, 104.7, 109.8, 118.2, 126.8, 127.8, 133.1, 135.9, 138.5, 146.2, 155.2, 157.1, 159.9, 195.5; IR (KBr): ν_{max} 3448, 2934, 1650, 1595, 1587, 1446, 1349, 1284, 1129, 1085 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 343 ([M+H]$^+$, 20), 342 (M$^+$, 2), 327 (5), 326 (30), 325 (100). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%. Found: C, 70.34; H, 6.12%.
12. Compound **3a**: viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 3H, CH_3), 2.17 (s, 3H, ArCH_3), 2.90–3.50 (m, 4H, $2 \times$ CH_2), 2.98, 3.15 (2d, 2H, $J = 14.3$ Hz, $2 \times$ CH_2), 3.80, 3.80, 3.85, 3.88 (4s, 12H, $4 \times$ OCH_3), 4.56, 4.68 (2s, 2H, $2 \times$ C*H*), 6.45 (s, 1H, H-9), 6.80 (d, 1H, $J = 9.0$ Hz, H-3), 7.83 (d, 1H, $J = 9.0$ Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): 9.5, 23.9, 25.1, 35.5, 53.0, 55.3, 55.4, 60.2, 61.9, 79.4, 79.4, 108.7, 108.7, 114.1, 117.8, 122.8, 128.8, 132.9, 137.6, 138.2, 142.6, 145.4, 150.9, 157.7; IR (neat): ν_{max} 3446, 2935, 2834, 1735, 1598, 1486, 1282, 1220, 1128, 1090 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 398 (M$^+$, 1), 380 (47), 374 (53), 349 (64), 343 (47), 342 (72), 136 (100). Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59%. Found: C, 72.79; H, 7.84%.
13. Compound **10**: yellow solid; mp 167–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, ArCH_3), 3.02 (d, 2H, $J = 10.1$ Hz, CH_2), 3.12 (d, 2H, $J = 10.1$ Hz, CH_2), 3.70, 3.75, 3.78 (3s, 9H, $3 \times$ OCH_3), 6.20 (s, 1H, H-9), 6.82 (d, 1H, $J = 8.8$ Hz, Ar*H*), 7.90 (d, 1H, $J = 8.8$ Hz, Ar*H*), 14.55 (s, 1H, ArO*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.7, 25.2, 37.4, 55.4, 55.7, 60.9, 103.4, 109.7, 111.5, 114.1, 128.9, 132.8, 137.2, 143.8, 144.9, 155.8, 162.1, 165.4, 195.9; IR (KBr): ν_{max} 3448, 3089, 2919, 1607, 1582, 1488, 1413, 1144, 1090 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 329 ([M+H]$^+$, 28), 328 (M$^+$, 100), 313 (13), 310 (26), 297 (14). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%. Found: C, 69.41; H, 6.20%.
14. Compound **11**: white solid; mp 145–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, ArCH_3), 2.94–3.14 (m, 4H, $2 \times$ CH_2), 3.70, 3.80, 3.83 (3s, 9H, $3 \times$ OCH_3), 4.75 (s, 2H, OCH_2), 6.40 (s, 1H, H-9), 6.78 (d, 1H, $J = 8.8$ Hz, Ar*H*), 7.19–7.35 (m, 5H, $4 \times$ Ar*H*), 7.70 (d, 1H, $J = 8.8$ Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 28.9, 32.8, 55.6, 55.7, 59.8, 76.3, 104.8, 109.9, 118.6, 126.8, 126.9, 127.6, 127.8, 128.0, 128.3, 128.5, 133.1, 135.9, 137.5, 138.5, 146.2, 155.2, 155.6, 159.9, 195.5; IR (KBr): ν_{max} 3447, 2941, 1649, 1597, 1454, 1292, 1223, 1131, 1085 cm^{-1}; MS (EI): *m*/*z* (relative intensity) 418 (M$^+$, 19), 417 (17), 402 (25), 401 (100), 400 (21), 135 (41). Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26%. Found: C, 74.95; H, 5.93%.
15. Compound **3b**: viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 3H, CH_3), 2.25 (s, 3H, ArCH_3), 2.92–3.25 (m, 4H, $2 \times$ CH_2), 3.25, 3.65 (2d, 2H, $J = 11.0$ Hz, $2 \times$ CH_2), 3.78, 3.84, 3.87 (3s, 9H, $3 \times$ OCH_3), 4.52, 4.67 (2s, 2H, $2 \times$ C*H*), 4.76 (d, 1H, $J = 10.8$ Hz, OCH_2), 4.89 (d, 1H, $J = 10.8$ Hz,

OCH_2), 6.50 (s, 1H, H-9), 6.80 (d, 1H, $J = 9.0$ Hz, H-3), 7.38–7.56 (m, 5H, PhH), 7.86 (d, 1H, $J = 9.0$ Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): 9.7, 23.8, 25.5, 35.1, 53.2, 55.4, 55.5, 60.0, 76.3, 79.5, 108.8, 109.0, 114.1, 118.0, 122.3, 127.5, 128.0, 128.2, 128.4, 128.7, 128.8, 132.2, 136.0, 138.1, 138.5, 142.7, 145.8, 150.9, 155.9, 156.8; IR (neat): ν_{max} 3387, 2935, 2832, 1597, 1480, 1274, 1124 cm^{-1}; MS (EI): m/z (relative intensity) 419 (59), 365 (48), 327 (95), 91 (100). Anal. Calcd for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22%. Found: C, 75.89; H, 6.90%.

16. Compound **12**: viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 6H, 2 × *gem*-CH_3), 2.00 (s, 3H, ArCH_3), 3.00 (m, 4H, 2 × CH_2) 3.70, 3.74, 3.80 (3s, 9H, 3 × OCH_3), 5.52 (s, 1H, H-1), 6.11 (s, 1H, H-6), 6.62 (d, 1H, $J = 8.0$ Hz, ArH), 7.00 (d, 1H, $J = 8.4$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.3, 24.8, 26.8, 36.2, 55.6, 61.0, 74.9, 104.9, 109.5, 112.0, 114.6, 124.2, 129.8, 134.2, 135.1, 135.6, 136.3, 144.3, 152.2, 152.3, 157.1; IR (neat): ν_{max} 3008, 2961, 2929, 2855, 1597, 1492, 1465, 1359, 1283, 1270, 1135, 1088, 908 cm^{-1}; MS (EI): m/z (relative intensity) 366 (M$^+$, 5), 365 (12), 352 (26), 351 (100), 321 (10). Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15%. Found: C, 75.64; H, 7.11%.
17. Compound **13**: white solid; mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H, *gem*-CH_3), 1.60 (s, 3H, *gem*-CH_3), 2.02 (dd, 1H, $J = 12.8$, 6.0 Hz, H-1), 2.02 (s, 3H, ArCH_3), 2.43 (t, 1H, $J = 12.8$ Hz, H-1), 2.93–3.47 (m, 4H, 2 × CH_2), 3.74, 3.85, 3.86 (3s, 9H, 3 × OCH_3), 4.58 (dd, 1H, $J = 12.6$, 5.9 Hz, H-12b), 6.14 (s, 1H, H-6), 6.72 (d, 1H, $J = 8.7$ Hz, ArH), 7.04 (d, 1H, $J = 8.7$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.3, 22.7, 23.2, 30.5, 32.2, 35.2, 38.4, 55.3, 55.6, 61.1, 73.1, 105.1, 109.2, 111.7, 114.8, 120.3, 135.6, 136.2, 136.8, 145.5, 151.3, 152.3, 156.2; IR (KBr): ν_{max} 3448, 2970, 2936, 2836, 1601, 1578, 1490, 1466, 1273, 1129, 1078, 810 cm^{-1}; 369 ([M+H]$^+$, 17), 368 (M$^+$, 65), 353 (24), 351 (20), 313 (32), 312 (100), 283 (79). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66%. Found: C, 74.69; H, 7.43%.
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19. Compound **14**: yellowish solid; mp 224–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.36 (s, 6H, 2 × *gem*-CH_3), 1.91 (s, 3H, ArCH_3), 2.84 (m, 4H, 2 × CH_2), 5.50 (s, 1H, H-1), 6.14 (s, 1H, H-6), 6.56 (m, 2H, ArH), 8.20, 9.22, 9.30, (3s, 3H, 3 × ArOH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.6, 23.8, 26.6, 35.2, 74.6, 109.2, 109.3, 112.5, 113.0, 118.9, 127.9, 128.5, 132.2, 135.1, 136.1, 140.4, 144.8, 152.1, 154.8; IR (KBr): ν_{max} 3505, 3354, 3254, 2924, 1616, 1592, 1499, 1363, 1274, 1098, 810 cm^{-1}; MS (EI): m/z (relative intensity) 324 (M$^+$, 9), 310 (22), 309 (100). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21%. Found: C, 73.82; H, 6.41%.
20. Compound **2**: yellowish solid; mp 230–233 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + acetone-d_6): δ 1.25 (s, 3H, *gem*-CH_3), 1.45 (s, 3H, *gem*-CH_3), 1.88 (dd, 1H, $J = 13.0$, 6.0 Hz, H-1), 1.93 (s, 3H, ArCH_3), 2.30 (t, 1H, $J = 12.9$, 12.6 Hz, H-1), 2.82–3.25 (m, 4H, 2 × CH_2), 4.45 (dd, 1H, $J = 12.1$, 5.9 Hz, H-12b), 5.22 (s, 1H, ArOH), 6.02 (s, 1H, H-6), 6.55 (d, 1H, $J = 8.5$ Hz, ArH), 6.65 (d, 1H, $J = 8.5$ Hz, ArH); ^{13} C NMR (75 MHz, DMSO-d_6): δ 8.7, 22.9, 23.4, 30.6, 32.7, 34.8, 38.9, 73.7, 110.0, 110.2, 112.4, 114.8, 116.2, 130.2, 135.8, 137.4, 142.3, 143.8, 153.3, 154.4; IR (KBr): ν_{max} 3404, 2972, 2927, 1596, 1578, 1501, 1451, 1411, 1365, 1283, 1164, 1131, 1104, 1084, 1009, 908 cm^{-1}; MS (EI): m/z (relative intensity) 327 ([M+H]$^+$, 9), 326 (M$^+$, 38), 311 (11), 309 (16), 271 (31), 270 (100). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79%. Found: C, 73.44; H, 7.00%.
21. Compound **1**: yellowish solid; mp 129–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H, *gem*-CH_3), 1.45 (s, 3H, *gem*-CH_3), 1.89 (dd, 1H, $J = 13.0$, 6.0 Hz, H-1), 1.93 (s, 3H, ArCH_3), 2.33 (t, 1H, $J = 12.9$ Hz, H-1), 2.80–3.30 (m, 4H, 2 × CH_2), 3.79 (s, 3H, OCH_3), 4.47 (dd, 1H, $J = 12.1$, 5.9 Hz, H-12b), 4.43 and 5.63 (2s, 2H, 2 × ArOH), 6.01 (s, 1H, H-6), 6.58 (d, 1H, $J = 8.6$ Hz, ArH), 6.75 (d, 1H, $J = 8.5$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.2, 22.1, 23.3, 30.3, 32.1, 34.0, 38.1, 55.9, 73.3, 107.4, 109.1, 109.3, 114.6, 115.6, 128.4, 135.9, 137.0, 141.7, 145.0, 152.1, 152.4; IR (KBr): ν_{max} 3423, 2973, 2928, 1594, 1492, 1459, 1442, 1273, 1107, 1089 cm^{-1}; 341 ([M+H]$^+$, 12), 340 (M$^+$, 53), 323 (16), 285 (28), 284 (100). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.11; H, 7.40.