Synthesis of Hemitectol, Tectol, and Tecomaquinone I

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Abstract: The first total syntheses of *Tectona grandis* (teak) natural products hemitectol and tectol are described. The observation of spontaneous dimerisation of hemitectol to tectol suggests the monomer is the true natural product and that the dimer is an artifact of isolation.

Key words: cyclisation, dimerisation, quinone, ring closure, total synthesis

Chan et al. recently isolated a family of pseudodimeric meroterpenes, the scabellones B–D (**1**–**3**), for example, from the New Zealand ascidian *Aplidium scabellum* (Figure 1).[1] While scabellone B (**1**) was found to exhibit antimalarial activity with an IC_{50} of 4.8 μM, biological testing was not undertaken on the other natural products in the series due to insufficient sample. Scabellones C (**2**) and D (**3**) share a 9,10-dihydropyranobenzo[*c*,*f*]chromene-1,4-dione core with only one other natural product, tecomaquinone I (**4**, Scheme 1), isolated from *Tectona grandis* (teak).[2]

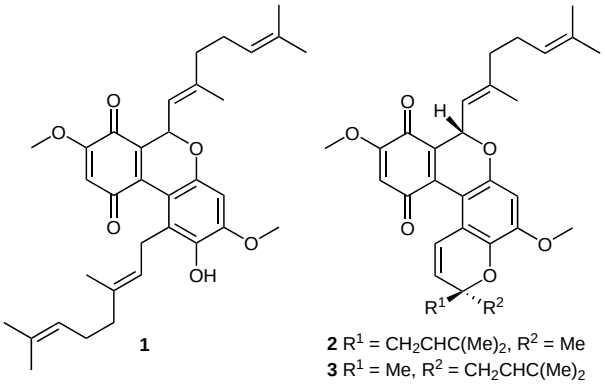
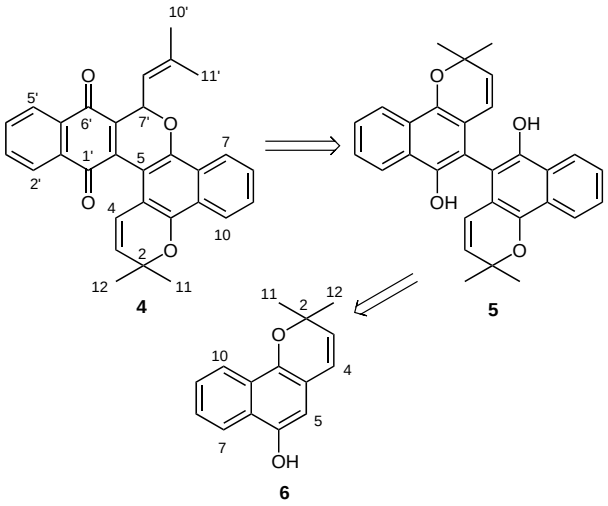


Figure 1 Structures of scabellones B–D (**1**–**3**)

The biosynthesis of tecomaquinone I has been proposed[3] to proceed via two other *T. grandis* metabolites, the mildly cytotoxic dichromenol tectol (**5**) and the recently reported antifungal hemitectol (**6**, Scheme 1).[2,4] It is pertinent to note that while there are several reports of the isolation of tectol, hemitectol has only ever been reported once, and as a mixture with tectol.[2]

While a semisynthesis of **4** (from **5**) has been reported, neither **5** nor **6** have been synthesised.[3] The finding of antimalarial activity of scabellone B (**1**)[1] provides great incentive to undertake the total synthesis of tecomaquinone I (**4**), tectol (**5**), and hemitectol (**6**) to evaluate their antimalarial bioactivities.



Scheme 1 Biosynthetic/retrosynthetic analysis of tecomaquinone I (**4**) via tectol (**5**) and hemitectol (**6**)

As a prelude to more expansive structure–antimalarial relationship investigations of scabellones B–D, we sought a scalable and flexible synthetic route to the 9,10-dihydropyranobenzo[*c*,*f*]chromene-1,4-dione scaffold. We now report a concise biomimetic synthesis of tecomaquinone I.

Mono-TBS protection of naphthoquinol was achieved in two steps, firstly via formation of the TBS ether of 4-methoxynaphth-1-ol (**8**, 93% yield)[5] followed by BBr_3 demethylation to afford the product (**9**)[6] as a dark red solid in 75% yield (Scheme 2).

Reaction of naphthol **9** with 3-methylbut-2-enal using ethylenediamine diacetate (EDDA) as a catalyst in chloroform[7] yielded, after chromatographic purification, protected chromenol **10**[8] as an orange solid in 81% yield. Deprotection of **10** using triethylamine trihydrogen fluoride in THF for 24 hours afforded the target product hemitectol (**6**)[9] as a dark yellow oil, as well as tectol (**5**)[10] as a white solid and bischromen **11**[11] as a yellow oil in 21%, 19% and 33% yields, respectively (Scheme 3). During the course of NMR characterisation of hemitectol in $CDCl_3$, the sample was observed to rapidly transform over hours into a mixture with tectol (**5**).

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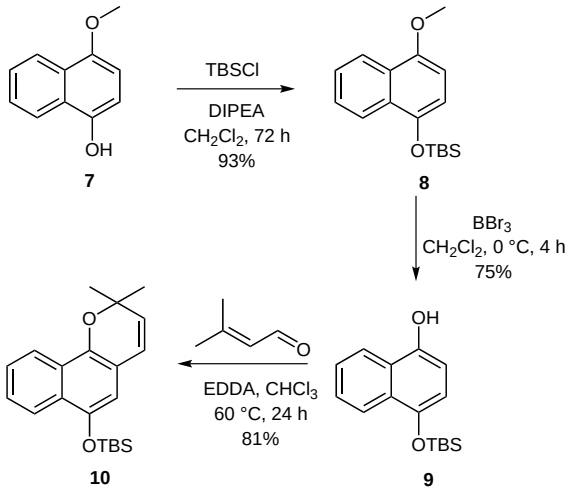
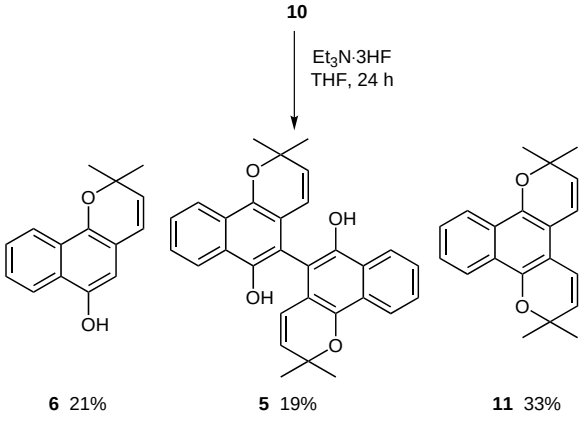


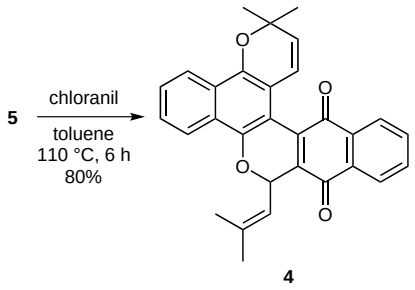
Scheme 2 Synthesis of TBS-protected hemitectol **10**



Scheme 3 Synthesis of hemitectol, tectol, and bischromen

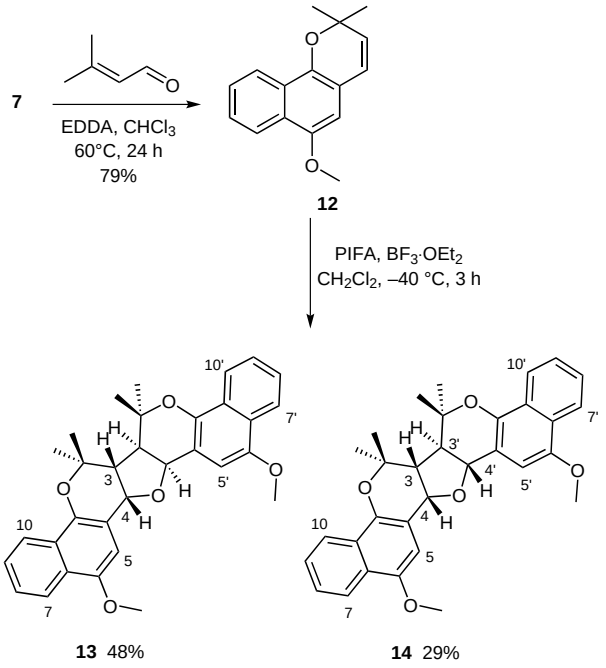
Further attempts at purification of **6**, by silica gel column chromatography using CH_2Cl_2–hexane solvent mixtures, led to complete conversion into dimer **5**.

Using a literature protocol, reaction of tectol with chloranil in toluene[3] yielded a green solid (80% yield), the spectroscopic data for which agreed with those previously reported for tecomaquinone I (**4**)[12] (Scheme 4).



Scheme 4 Synthesis of tecomaquinone I (**4**)

The spontaneous oxidative dimerisation of hemitectol (**6**) to tectol (**5**) suggests that the latter is an artifact of natural product isolation and that the true metabolite of *Tectona grandis* is in fact hemitectol (**6**). We found no evidence for the spontaneous dimerisation of TBS-protected hemitectol **10** nor for the structurally related *O*-methyl analogue lapachenole (**12**),[13] which was prepared from **7** in 79% yield (Scheme 5).[7] In an effort to force such a dimerisation, reaction of **12** with phenyliodine(III) bis(trifluoroacetate) (PIFA) and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$),[14] yielded two products **13**[15] (48%) and **14**[16] (29%) as brown solids.



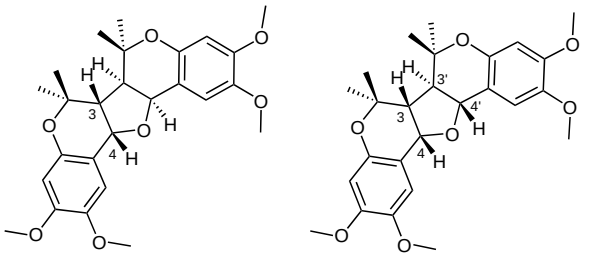
Scheme 5 Syntheses of furopyran dimers **13** and **14** via lapachenole

Analysis of the mass spectrum of **13** afforded a molecular formula of $C_{32}H_{33}O_5$ $[M + H]^+$, suggestive that lapachenole had indeed dimerised and with the incorporation of an oxygen atom. The ^1H NMR spectrum of **13** was similar to that of the starting material with the exception of the chromen ring H-3 and H-4 (δ = 5.64 and 6.39 ppm) protons being replaced by two mutually coupled doublets (δ = 2.63 and 4.94 ppm). The ^{13}C NMR spectrum of **13** contained 16 signals, further implying the presence of symmetry in the compound. Analysis of HSQC NMR data identified C-4 (δ = 73.1 ppm) as an oxymethine while interfragment HMBC correlations observed between H-3 and C-3 (δ = 49.4 ppm) and between H-4 and C-4 showed that the molecule was symmetrical through a C-4 ether linkage and the C-3,3′ bond. NOESY cross peaks observed between H-3, H-4, and one of the *gem*-dimethyl groups identified a *cis* relationship, assigning the structure of **13** as a symmetrical furopyran dimer as shown.

Two similar furopyran dimers, symmetric **15** and unsymmetric **16**, were reported by Fraga et al. from the oxidative dimerisation of precocene II using silica impregnated with silver nitrate (Figure 2).[17] X-ray crystallography was used to determine the relative configuration of both dimers.[17] Close agreement of the H-3 and H-4 chemical shifts ob-

served for **13** with those of dimer **15** confirmed the structure and *cis*,*trans*,*cis* relative configuration of **13**.

ESI-HRMS analysis of **14** established a molecular formula of $C_{32}H_{33}O_5$ $[M + H]^+$, being isomeric with **13**, while close analysis of COSY, HSQC, and HMBC data identified **14** to have the same planar skeleton as **13** (Scheme 5). However, unlike the symmetrical analogue **13**, the ^1H NMR and ^{13}C NMR spectra of **14** were more complex, suggesting an unsymmetrical structure. NOESY correlations were observed between the tetrahydrofuran protons H-3 (δ = 2.74 ppm), H-4′ (δ = 4.88 ppm), H-4 (δ = 5.13 ppm), and two of the *gem*-dimethyl groups (δ = 1.64, 1.60 ppm) indicating these protons to be *cis*-related. Further NOESY correlations were observed between H-3′ (δ = 2.10 ppm) and the remaining two methyl groups (δ = 1.17, 1.70 ppm) indicating these protons to be on the opposite face of the molecule (Scheme 5). The structure and relative configuration of **14** agreed with the configuration reported by Fraga et al.[17] for their second furopyran dimer **16**.



15 **16**

Figure 2 Furopyran dimers **15** and **16**

In summary, we have successfully accomplished the first syntheses of the natural products hemitectol (**6**) and tectol (**5**) with the use of a silyl-protected naphthol in combination with a S_EAr–cycloaddition reaction. Hemitectol (**6**) was discovered to spontaneously dimerise to the natural product tectol (**5**) in the presence of silica or triethylamine. Future work will focus on applying this strategy to access other related analogues.

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(5) ***tert*-Butyl(4-methoxynaphthalen-1-yloxy)dimethylsilane (8)**
IR (ATR): 2929, 2857, 1625, 1596, 1461, 1384, 1273, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 2 H, H-5, H-8), 7.60–7.56 (m, 2 H, H-6, H-7), 6.86 (d, *J* = 8.5 Hz, 1 H, H-3), 6.73 (d, *J* = 8.5 Hz, 1 H, H-2), 4.03 (s, 3 H, OCH_3), 1.20 (s, 9 H, H-4′, H-5′, H-6′), 0.36 (s, 6 H, H-1′, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C-1), 145.2 (C-4), 128.6 (ArC), 126.6 (ArC), 125.8 (ArCH), 125.5 (ArCH), 122.5 (ArCH), 122.0 (ArCH), 111.9 (C-3), 103.5 (C-2), 55.7 (OCH_3), 26.0 (C-4′, C-5′, C-6′), 18.5 (C-3′), –4.2 (C-1′, C-2′). ESI-HRMS: *m/z* calcd for $C_{17}H_{25}O_2Si$ $[MH^+]$: 289.1618; found: 289.1624.
(6) **4-(*tert*-Butyldimethylsiloxy)naphthalene-1-ol (9)**
IR (ATR): 3255, 2929, 1595, 1471, 1347, 1266, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.09 (m, 2 H, H-5, H-8), 7.50–7.47 (m, 2 H, H-6, H-7), 6.68 (s, 2 H, H-2, H-3), 1.09 (s, 9 H, H-4′, H-5′, H-6′), 0.24 (s, 6 H, H-1′, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4 (C-1), 138.7 (C-4), 126.4 (2 × Ar-C), 125.7 (ArCH), 125.5 (ArCH), 122.7 (ArCH), 121.5 (ArCH), 112.0 (C-2), 108.3 (C-3), 25.9 (C-4′, C-5′, C-6′), 18.4 (C-3′), –4.3 (C-1′, C-2′). ESI-HRMS: *m/z* calcd for $C_{16}H_{23}O_2Si$ $[MH^+]$: 275.1462; found: 275.1462.
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(8) ***tert*-Butyl(2,2-dimethyl-2*H*-benzo[*h*]chromen-6-yloxy)dimethylsilane (10)**
IR (ATR): 2930, 1595, 1457, 1409, 1370, 1274, 1084 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.03 (m, 2 H, H-7, H-10), 7.43–7.40 (m, 2 H, H-8, H-9), 6.54 (s, 1 H, H-5), 6.35 (d, *J* = 9.7 Hz, 1 H, H-4), 5.63 (d, *J* = 9.7 Hz, 1 H, H-3), 1.49 (s, 6 H, H-11, H-12), 1.08 (s, 9 H, H-4′, H-5′, H-6′), 0.24 (s, 6 H, H-1′, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8 (C-6), 142.4 (C-10b), 129.9 (C-3), 128.3 (ArC), 126.0 (ArC), 125.5 (ArCH), 125.3 (ArCH), 122.9 (C-4), 122.5 (ArCH), 121.8 (ArCH), 115.0 (C-4a), 110.9 (C-5), 76.2 (C-2), 27.6 (C-11, C-12), 25.9 (C-4′, C-5′, C-6′), 18.4 (C-3′), –4.2 (C-1′, C-2′). ESI-HRMS: *m/z* calcd for $C_{21}H_{29}O_2Si$ $[MH^+]$: 341.1931; found: 341.1919.
(9) **Hemitectol (6)**
Dark yellow oil. IR (ATR): 3419, 2973, 1586, 1451, 1402, 1369, 1360, 1257, 1070 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.03–7.96 (m, 2 H, H-7, H-10), 7.46–7.37 (m, 2 H, H-8, H-9), 6.60 (s, 1 H, H-5), 6.43 (d, *J* = 9.5 Hz, 1 H, H-4), 5.75 (d, *J* = 9.5 Hz, 1 H, H-3), 1.42 (s, 6 H, H-11, H-12). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.4 (C-6), 143.7 (C-10b), 130.4 (C-3), 125.6 (ArCH), 125.1 (ArC), 124.9 (ArC), 124.7 (ArCH), 122.6 (C-4), 122.1 (ArCH), 121.1 (ArCH), 115.2 (C-4a), 105.9 (C-5), 75.7 (C-2), 27.1 (C-11, C-12). ESI-HRMS: *m/z* calcd for $C_{15}H_{15}O_2$ $[MH^+]$: 227.1067; found: 227.1063.
(10) **Tectol (5)**
White solid; 206–209 °C (lit.[2] 207–208 °C). IR (ATR): 3420, 2973, 1586, 1451, 1402, 1369, 1361, 1221, 1071 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.17–8.08 (m, 4 H, H-7, H-7′, H-10, H-10′), 7.52–7.44 (m, 4 H, H-8, H-8′, H-9, H-9′), 5.78 (d, *J* = 9.9 Hz, 2 H, H-4, H-4′), 5.59 (d, *J* = 9.9 Hz, 2 H, H-3, H-3′), 1.45 (s, 6 H, H-11, H-11′), 1.43 (s, 6 H, H-12, H-12′). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.1 (C-6, C-6′), 140.6 (C-10b, C-10b′), 130.0 (C-3, C-3′), 125.5 (2 × ArC), 125.4 (2 × ArCH), 125.1 (2 × ArC), 125.0 (2 × ArCH), 122.5 (2 × ArCH), 121.2 (2 × ArCH), 120.9 (C-4, C-4′), 115.9 (C-4a, C-4a′), 113.2 (C-5, C-5′), 75.2 (C-2, C-2′), 27.0 (C-11, C-11′, C-12, C-12′). ESI-HRMS: *m/z* calcd for $C_{30}H_{26}O_4Na$ $[MNa^+]$: 473.1723; found: 473.1714.

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(12) **Tecomaquinone I (4)**
Green solid; mp 187–189 °C (lit.[2] 188–189 °C). IR (ATR): 3360, 2978, 1690, 1568, 1277, 1237, 1197, 1109 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.14–8.09 (m, 2 H, H-7, H-10), 8.07–8.05 (m, 1 H, H-2′), 8.04–8.01 (m, 1 H, H-5′), 7.95–7.86 (m, 2 H, H-3′, H-4′), 7.65–7.60 (m, 1 H, H-9), 7.57–7.53 (td, *J* = 7.0, 1.5 Hz, 1 H, H-8), 6.36 (d, *J* = 9.9 Hz, 1 H, H-4), 6.34 (d, *J* = 9.1 Hz, 1 H, H-7′), 5.62 (d, *J* = 9.9 Hz, 1 H, H-3), 5.44 (td, *J* = 9.0, 1.5 Hz, 1 H, H-8′), 2.03 (br s, 3 H, H-11′), 1.60 (s, 3 H, H-12), 1.59 (s, 3 H, H-10′), 1.55 (s, 3 H, H-11). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.8 (C-6′), 181.6 (C-1′), 146.5 (C-6), 142.4 (C-10b), 141.7 (C-9′), 135.9 (ArC), 135.4 (ArC), 134.0 (ArC), 133.8 (2 × ArCH), 132.9 (ArC), 131.3 (ArC), 128.2 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 125.3 (ArCH), 125.3 (C-3), 124.7 (ArC), 123.8 (C-4), 122.5 (ArCH), 121.8 (ArCH), 117.6 (C-8′), 113.0 (C-4a), 111.2 (C-5), 75.5 (C-2), 67.3 (C-7′), 28.2 (C-12), 25.5 (C-10′), 25.2 (C-11), 18.7 (C-11′). ESI-HRMS: *m/z* calcd for $C_{30}H_{25}O_4$ [MH^+]: 449.1747; found: 449.1726.

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(15) **Furan Dimer A (13)**
Brown solid; mp 112.1–115.1 °C. IR (ATR): 2938, 1637, 1598, 1457, 1382, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.17 (m, 4 H, H-8, H-8′, H-9, H-9′), 7.52–7.46 (m, 4 H, H-7, H-10, H-7′, H-10′), 6.77 (s, 2 H, H-5, H-5′), 4.94 (d, *J* = 6.5 Hz, 2 H, H-4, H-4′), 3.97 (s, 6 H, OCH_3, OCH_3′), 2.63 (d, *J* = 6.5 Hz, 2 H, H-3, H-3′), 1.57 (s, 6 H, H-11, H-11′), 1.46 (s, 6 H, H-12, H-12′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7 (C-6, C-6′), 142.8 (C-10b, C-10b′), 126.3 (2 × ArC), 126.3 (2 × ArC), 126.0 (2 × ArCH), 126.0 (2 × ArCH), 122.0 (2 × ArCH), 121.8 (2 × ArCH), 115.4 (C-4a, C-4a′), 77.3 (C-2, C-2′), 73.1 (C-4, C-4′), 55.8 (OCH_3, OCH_3′), 49.4 (C-3, C-3′), 27.9 (C-12, C-12′), 26.9 (C-11, C-11′). ESI-HRMS: *m/z* calcd for $C_{32}H_{33}O_5$ [MH^+]: 497.2323; found: 497.2307.

(16) **Furan Dimer B (14)**
Brown solid; mp 216.0–218.6 °C. IR (ATR): 2938, 1637, 1598, 1457, 1382, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.15 (m, 4 H, H-7, H-7′, H-10, H-10′), 7.52–7.42 (m, 4 H, H-8, H-8′, H-9, H-9′), 7.06 (s, 1 H, H-5), 6.96 (s, 1 H, H-5′), 5.13 (d, *J* = 8.3 Hz, 1 H, H-4), 4.88 (d, *J* = 10.5 Hz, 1 H, H-4′), 4.07 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3′), 2.74 (t, *J* = 8.3 Hz, 1 H, H-3), 2.10 (dd, *J* = 10.5, 8.3 Hz, 1 H, H-3′), 1.70 (s, 3 H, H-12′), 1.64 (s, 3 H, H-11), 1.60 (s, 3 H, H-11′), 1.17 (s, 3 H, H-12). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0 (C-6′), 149.1 (C-6), 141.5 (C-10b), 141.0 (C-10b′), 126.6 (2 × ArCH), 126.1 (2 × ArCH), 125.9 (ArC), 125.9 (ArC), 125.5 (ArC), 125.1 (ArC), 122.0 (ArCH), 121.9 (2 × ArCH), 121.6 (ArCH), 119.8 (C-4a′), 116.6 (C-4a), 102.8 (C-5), 99.4 (C-5′), 80.6 (C-2′), 77.8 (C-4), 76.6 (C-2′), 76.2 (C-4′), 56.0 (OCH_3), 55.8 (OCH_3′), 55.6 (C-3′), 49.6 (C-3), 31.7 (C-12′), 29.9 (C-11), 24.0 (C-11′), 22.6 (C-12). ESI-HRMS: *m/z* calcd for $C_{32}H_{33}O_5$ [MH^+]: 497.2323; found: 497.2305.

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