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Stereoselective Total Synthesis of Rhoiptelol B via Prins Cyclization

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Abstract: The stereoselective total synthesis of rhoiptelol B, a diarylheptanoid isolated from *Rhoiptelea chiliantha* is described. The tetrahydropyran ring was constructed by using Prins cyclization. The key steps involved in this synthesis are Prins cyclization, Mistunobu inversion, cross metathesis, Sharpless asymmetric dihydroxylation, and hydrogenolysis.

Key words: rhoiptelol B, natural products, diarylheptanoid, Prins cyclization, Mitsunobu inversion

The plant metabolites known as diarylheptanoids, isolated from various sources,[1] contain a 1,7-diphenylheptane skeleton. Due to the special structural features of diarylheptanoids, they have different biological activities[2,3] such as antioxidant, anti-inflammatory, antitumor, neuroprotective, heptoprotective, anticancer, antialergic, cholesterol-lowering effect, and anti-HIV activities. The compound rhoiptelol B[4,5] is one of the families of diarylheptanoids containing a tetrahydropyran ring, isolated form fruits of *Rhoiptelea chiliantha* and also form bark of *Anlus hirsute* in 1996 and 2007, respectively. It has shown inhibitory activities against LPS-induced NF-KB activation, NO, and TNF-α, production, and HIF-1 in AGS cells.[5] In our ongoing program on the utilization of the highly stereoselective Prins cyclization reaction, a well-established method for constructing multisubstituted tetrahydropyrans[6] for the synthesis of polyketide motifs,[7] we have undertaken the total synthesis of rhoiptelol B (Figure 1).[8]

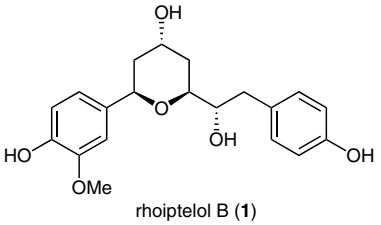
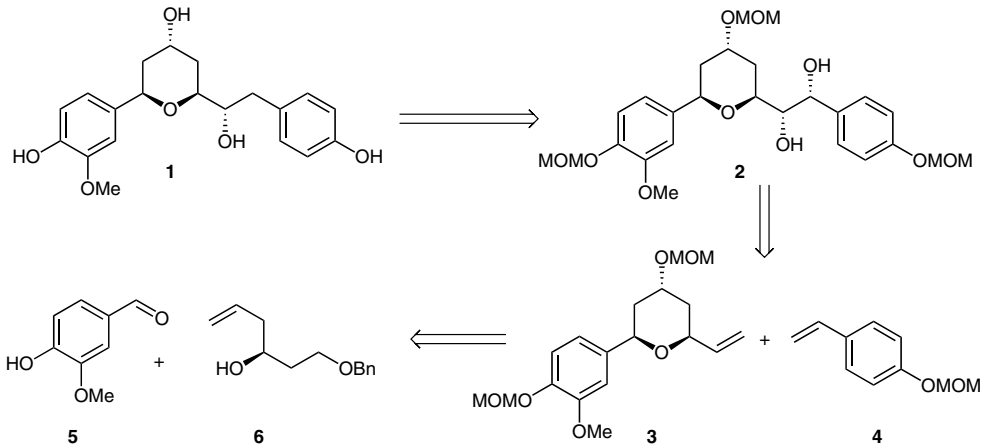


Figure 1 Structure of rhoiptelol B (**1**)

The retrosynthetic analysis of rhoiptelol B is described in Scheme 1. It could be achieved from hydrogenolysis of cyclic carbonate of diol **2**, which in turn was obtained from cross metathesis of the olefins **3** and **4** followed by Sharpless asymmetric dihydroxylation. The tetrahydropyran moiety **3** was constructed via Prins cyclization between isovalinal (**5**) and homoallylic alcohol **6**.

Our synthesis of rhoiptelol B is outlined in Scheme 2. Prins cyclization[7] between known homoallylic alcohol **6**[9] and isovalinal (**5**) in the presence of TFA resulted in the trifluoroacetate salt of **7**, which on treatment with K_2CO_3 in MeOH gave tetrahydropyran diol **7** as the only isolable diastereomer in 62% yield. Inversion of the secondary hydroxyl group using Mitsunobu's protocol[10] produced in-



Scheme 1 Retrosynthetic analysis of rhoiptelol B (**1**)

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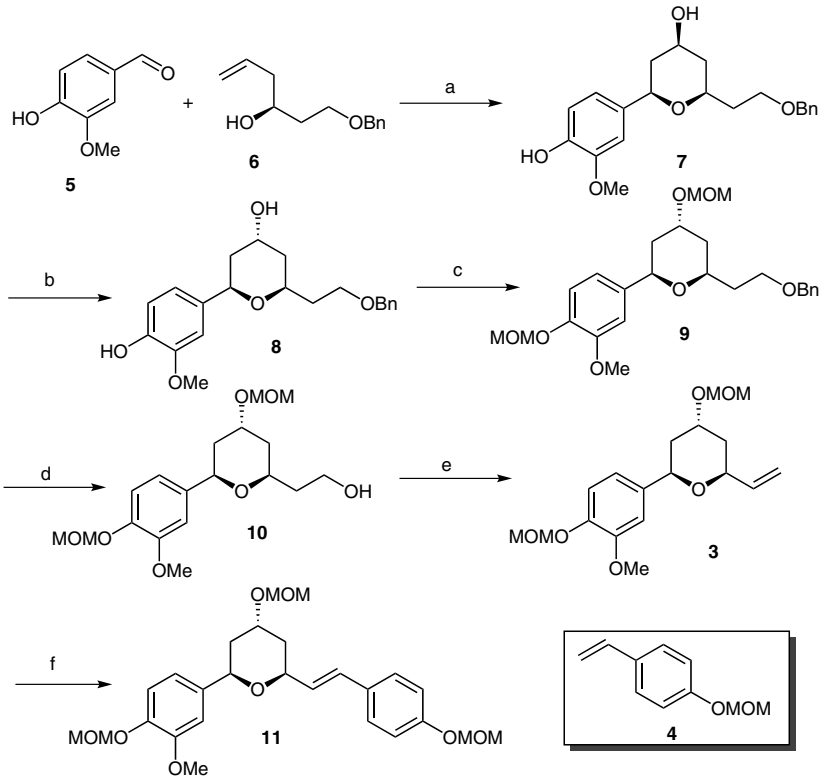

Scheme 2 *Reagents and conditions*: (a) TFA, CH_2Cl_2 then K_2CO_3, MeOH, r.t., 4 h, 62%; (b) DEAD, TPP, 4-$C_6H_4(NO_2)COOH$, THF, 30 min, 0 °C to r.t. then K_2CO_3, MeOH, r.t, 1 h, 75%; (c) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h, 87%; (d) Li/naphthalene, THF, –20 °C, 92%; (e) i) TPP, I_2, imidazole, THF, 0 °C to r.t., 4 h; ii) *t*-BuOK, THF, 0 °C to r.t., 4 h, 76% for two steps; (f) **4**, Grubbs II, CH_2Cl_2, r.t., 6 h, 72%.

versed pyranol **8** in 75% overall yield in two steps. Protection of both the aromatic and aliphatic hydroxyl functionality as its MOM ether using DIPEA and MOMCl in CH_2Cl_2 produced compound **9** in 87% yield. Removal of the benzyl group in compound **9** using Li/naphthalene[11] in THF resulted pyranyl methanol **10** in 92% yield. Iodination of primary alcohol of **10** using I_2, TPP, and imidazole in THF followed by elimination with *t*-BuOK in THF gave olefin **3** in 76% yield over two steps. The olefin **3** was subjected to cross metathesis with the olefin **4**[15] using the Grubbs second-generation catalyst in CH_2Cl_2 and afforded compound **11** in 86% yield.

The compound **11** on Sharpless asymmetric dihydroxylation[12] using AD-mix-α afforded diol **2** in 92% yield. The resultant diol was protected as cyclic carbonate using triphosgene and Et_3N in CH_2Cl_2, followed by hydrogenolysis which afforded compound **13** in 85% yield for two steps.[13] Finally, removal of MOM ethers using TMS-Br in CH_2Cl_2 afforded rhoiptelol B (**1**) in 72% yield (Scheme 3).[14] The synthetic sample was identical in all respects {^{1}H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$} to the naturally isolated compound.[4,8]

In summary, we described a concise stereoselective total synthesis of rhoiptelol B via Prins cyclization. Our route requires total 12 steps from known homoallylic alcohol **6** and provides 11% overall yield.

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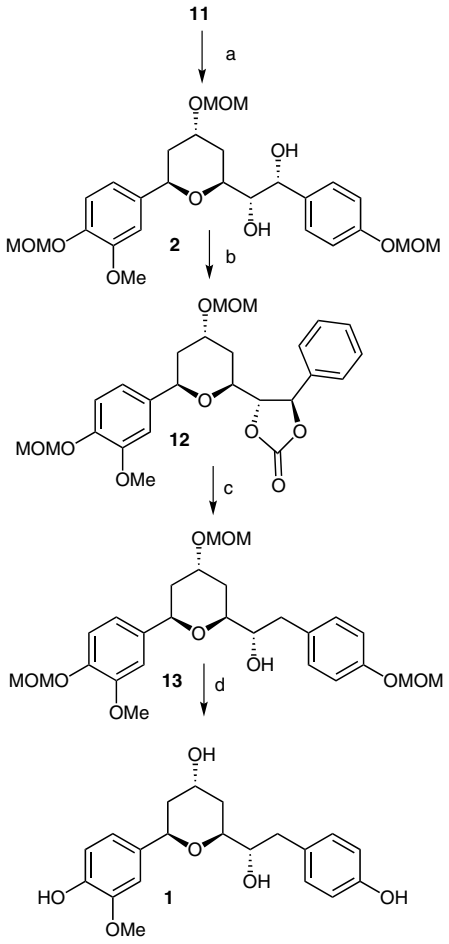

Scheme 3 *Reagents and conditions*: (a) AD-mix-α, *t*-BuOH–H_2O (1:1), $MeSONH_2$, 24 h, 0 °C, 92%; (b) triphosgene, Et_3N, CH_2Cl_2; (c) Raney-Ni, H_2, EtOH, 85% for two steps; (d) TMSBr, CH_2Cl_2, –30 °C, 4 h, 72%.

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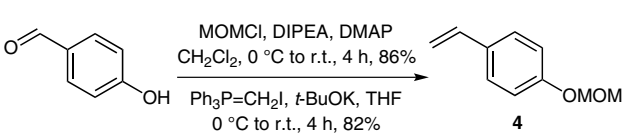
(15) Preparation of compound **4** from *p*-hydroxybenzaldehyde (Scheme 4).



Scheme 4

(16) **(2*R*,4*S*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-(4-hydroxy-3-methoxyphenyl)tetrahydro-2*H*-pyran-4-ol (7)**
$[\alpha]_D^{25}$ +38.3 (*c* 1.01, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.17 (m, 5 H), 6.83–6.78 (m, 2 H), 6.77–6.71 (m, 1 H), 5.45 (br s, OH, 1 H), 4.47 (s, 2 H), 4.23 (dd, *J* = 1.3, 11.3 Hz, 1 H), 3.86 (s, 3 H), 3.70–3.50 (m, 4 H), 2.18–2.08 (m, 1 H), 2.04–1.94 (m, 1 H), 1.93–1.74 (m, 2 H), 1.34–1.20 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 144.9, 144.94, 138.4, 134.0, 128.3, 127.5, 127.5, 118.9, 114.0, 108.6, 77.1, 72.9, 68.4, 66.6, 55.8, 42.5, 40.9, 36.1. IR (neat): ν_{max} = 3385, 2921, 2853, 1517, 1273, 1074, 1033, 747 cm^{-1}. ESI-MS: *m/z* = 381 $[M + Na]^+$.
(2*R*,4*R*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-(4-hydroxy-3-methoxyphenyl)tetrahydro-2*H*-pyran-4-ol (8)
$[\alpha]_D^{25}$ +32.2 (*c* 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 5 H), 6.89–6.81 (m, 3 H), 4.77 (d, *J* = 10.6 Hz, 1 H), 4.51 (s, 2 H), 4.34–4.31 (m, 1 H), 4.17–4.09 (m, 1 H), 3.86 (s, 3 H), 3.69–3.59 (m, 2 H), 1.93–1.85 (m, 2 H), 1.84–1.76 (m, 1 H), 1.75–1.69 (m, 2 H), 1.64–1.57 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 144.7, 138.5, 135.0, 128.2, 127.5, 127.4, 118.7, 114.0, 108.7, 73.2, 72.8, 69.2, 66.8, 64.9, 55.8, 40.1, 38.5, 36.2; IR (neat): ν_{max} = 3385, 2921, 2853, 1517, 1273, 1074, 1033, 747 cm^{-1}. ESI-MS: *m/z* = 381 $[M + Na]^+$.
(2*R*,4*R*,6*R*)-2-[2-(Benzyloxy)ethyl]-6-[3-methoxy-4-(methoxymethoxy)phenyl]-4-(methoxymethoxy)-tetrahydro-2*H*-pyran (9)
$[\alpha]_D^{25}$ +34.2 (*c* 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.16 (m, 5 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.86–6.75 (m, 2 H), 5.13 (s, 2 H), 4.70–4.63 (m, 3 H), 4.43 (s, 2 H), 4.08–3.96 (m, 2 H), 3.78 (s, 2 H), 3.61–3.52 (m, 2 H), 3.43 (s, 3 H), 3.33 (s, 3 H), 1.99–1.88 (m, 1 H), 1.87–1.68 (m, 3 H), 1.67–1.57 (m, 1 H), 1.51–1.39 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 145.5, 138.6, 137.5, 128.2, 127.4, 127.3, 118.1, 116.2, 109.7, 95.4, 95.0, 73.7, 72.9, 70.1, 69.9, 66.8, 56.0, 55.7, 55.3, 38.4, 36.4, 36.2. IR (neat): ν_{max} =

2927, 1513, 1267, 1153, 1037 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{25}H_{34}O_7Na$: 469.21792; found: 469.21967.

2-{(2*R*,4*R*,6*R*)-6-[3-Methoxy-4-(methoxymethoxy)-phenyl]-4-(methoxymethoxy)tetrahydro-2*H*-pyran-2-yl}ethanol (10)

$[\alpha]_D^{25}$ +34.0 (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.3 Hz, 1 H), 6.84–6.74 (m, 2 H), 5.14 (s, 2 H), 4.72 (dd, *J* = 1.1, 11.3 Hz, 1 H), 4.67 (s, 2 H), 4.17–4.02 (m, 2 H), 3.81 (s, 3 H), 3.79–3.72 (m, 2 H), 3.44 (s, 3 H), 3.35 (s, 3 H), 2.03–1.94 (m, 1 H), 1.85–1.56 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.7, 145.7, 136.9, 118.0, 109.4, 95.4, 95.1, 74.2, 73.6, 69.9, 61.6, 56.0, 55.8, 55.4, 38.3, 37.8, 36.1. IR (neat): ν_{max} = 3417, 2924, 1516, 1036 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{28}O_7Na$: 379.17191; found: 379.17272.

(2*S*,4*R*,6*R*)-2-(2-Iodoethyl)-6-[3-methoxy-4-(methoxymethoxy)phenyl]-4-(methoxymethoxy)-tetrahydro-2*H*-pyran (11)

$[\alpha]_D^{25}$ +28.4 (*c* 0.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.2 Hz, 1 H), 6.97 (d, *J* = 1.9 Hz, 1 H), 6.88 (dd, *J* = 1.6, 8.2 Hz, 1 H), 6.86–5.89 (m, 1 H), 5.31 (m, 1 H), 5.12 (m, 1 H), 5.20 (s, 2 H), 4.81 (dd, *J* = 1.8, 11.7 Hz, 1 H), 4.76 (d, *J* = 0.9 Hz, 2 H), 4.47–4.42 (m, 1 H), 4.16–4.13 (m, 2 H), 3.89 (s, 3 H), 3.50 (s, 3 H), 3.43 (s, 3 H), 2.04–1.98 (m, 1 H), 1.94–1.90 (m, 1 H), 1.75–1.69 (dtd, *J* = 2.7, 11.9, 14.3 Hz, 1 H), 1.64–1.58 (dtd, *J* = 2.7, 11.7, 14.3, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 145.6, 139.0, 137.2, 118.2, 116.2, 4.8, 109.8, 95.5, 95.1, 73.9, 73.3, 70.0, 56.0, 55.8, 55.4, 38.2, 35.9. IR (neat): ν_{max} = 2923, 2851, 1513, 1266, 1153, 1075, 1037 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{26}O_6Na$: 361.16163; found: 361.16216.

(2*R*,4*R*,6*S*)-2-[3-Methoxy-4-(methoxymethoxy)phenyl]-4-(methoxymethoxy)-6-[(*E*)-4-(methoxymethoxy)styryl]-tetrahydro-2*H*-pyran (2)

$[\alpha]_D^{25}$ +6.4 (*c* 0.74, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.11 (d, *J* = 8.8 Hz, 1 H), 7.01–6.89 (m, 4 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 6.15 (d, *J* = 6.2, 16.0 Hz, 1 H), 5.21 (s, 2 H), 5.16 (s, 2 H), 4.89–4.82 (m, 1 H), 4.78 (s, 2 H), 4.65–4.55 (m, 1 H), 4.22–4.15 (m, 1 H), 3.90 (s, 3 H), 3.50 (s, 3 H), 3.47 (s, 3 H), 3.45 (s, 3 H), 2.06–1.94 (m, 2 H), 1.83–1.65 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 149.6, 145.7, 137.1, 130.8, 129.6, 128.7, 127.5, 118.4, 116.3, 116.1, 109.9, 95.5, 95.1, 94.3, 74.1, 73.4, 70.1, 56.0, 55.9, 55.8, 55.4, 38.1, 36.3. IR (neat): ν_{max} = 2925, 2852, 1511, 1266, 1235, 1152, 1077, 1037, 999 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{26}H_{34}O_8Na$: 497.21229; found: 497.21459.

(1*S*,2*R*)-1-{(2*S*,4*S*,6*R*)-6-[3-Methoxy-4-(methoxymethoxy)-phenyl]-4-(methoxymethoxy)tetrahydro-2*H*-pyran-2-yl}-2-[4-(methoxymethoxy)phenyl]ethane-1,2-diol (12)

$[\alpha]_D^{25}$ +24.6 (*c* 0.44, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.13 (d, *J* = 3.2 Hz, 1 H), 7.03–7.00 (m, 2 H), 6.91–6.86 (m, 2 H), 5.23 (s, 3 H), 5.16 (s, 3 H), 4.84 (d, *J* = 5.0 Hz, 1 H), 4.77 (dd, *J* = 1.6, 11.7 Hz, 1 H), 4.69 (s, 3 H), 4.17–3.69 (m, 1 H), 3.90 (s, 3 H), 3.52 (s, 3 H), 3.47 (s, 3 H), 3.32 (s, 3 H), 2.50–2.48 (m, 1 H), 2.02–1.94 (m, 1 H), 1.77–1.67 (m, 1 H), 1.63 (br s, OH, 1 H), 1.37–1.23 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 149.7, 16.4, 134.2, 127.7, 118.2, 116.1, 109.7, 95.4, 95.1, 94.4, 74.7, 74.3, 73.6, 70.0, 56.1, 55.9, 55.4, 43.3, 37.9, 32.1, 29.6, 25.6. IR (neat): ν_{max} = 3449, 2925, 2852, 1512, 1266, 1153, 1076, 1036, 1000 cm^{-1}. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{26}H_{36}O_{10}Na$: 531.21809; found: 531.22007.

(*S*)-1-{(2*S*,4*S*,6*R*)-6-[3-Methoxy-4-(methoxymethoxy)-phenyl]-4-(methoxymethoxy)tetrahydro-2*H*-pyran-2-yl}-2-[4-(methoxymethoxy)phenyl]ethanol (13)

$[\alpha]_D^{25}$ +11.20 (*c* 0.87, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.09 (m, 3 H), 7.02–6.82 (m, 4 H), 5.23 (s, 2 H), 5.16 (s, 3 H), 4.81–4.64 (m, 3 H), 4.36–4.24 (m, 1 H), 4.25–4.19 (m, 1 H), 3.89 (s, 3 H), 3.78–3.60 (m, 1 H), 3.51 (s, 3 H), 3.46 (s, 3 H), 3.37 (s, 3 H), 2.90–2.70 (m, 2 H), 2.51 (br s, OH, 1 H), 2.08–1.87 (m, 2 H), 1.79–1.64 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 149.6, 137.0, 131.8, 130.7, 130.3, 128.7, 118.2, 116.2, 114.1, 109.7, 95.5, 95.1, 94.5, 77.0, 74.4, 74.0, 70.1, 56.1, 55.8, 55.4, 38.6, 38.3, 31.9. IR (neat): ν_{max} = 3450, 2925, 2854, 1636 cm^{-1}. ESI-MS: *m/z* = 515 [M + Na]$^+$.

Rhoiptelol B (1):

Mp 65–67 °C; $[\alpha]_D^{25}$ +87.4 (*c* 0.3, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 7.05 (br s, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 4.67 (dd, *J* = 10.7, 3.2 Hz, 1 H), 4.26 (t, *J* = 3.2 Hz, 1 H), 3.85 (s, 3 H), 3.80 (dt, *J* = 12.7, 2.9 Hz, 1 H), 3.59 (dt, *J* = 7.4, 3.2 Hz, 1 H), 2.84 (dd, *J* = 13.0, 6.6 Hz, 1 H), 2.67 (dd, *J* = 13.0, 7.4 Hz, 1 H), 1.91 (dd, *J* = 13.3, 3.0 Hz, 1 H), 1.82 (dd, *J* = 14.3, 2.9 Hz, 1 H), 1.73 (ddd, *J* = 13.6, 10.9, 2.8 Hz, 1 H), 1.57 (dd, *J* = 13.6, 2.0 Hz, 1 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 156.7, 148.8, 146.8, 136.2, 131.4, 131.3, 131.1, 119.8, 116.0, 115.8, 115.7, 111.1, 76.4, 75.2, 74.3, 65.7, 56.4, 41.2, 39.7, 35.0; IR (neat): ν_{max} = 3392, 2953, 2928, 1595, 1502, 1365, 1174, 1083, 854, 716 cm^{-1}. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{24}O_6Na$: 383.1470; found: 383.1461.

