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Synthesis of moenocinol and its analogs using BT-sulfone in Julia-Kocienski olefination

Hung-Jyun Huang and Wen-Bin Yang*

Genomics Research Center, Academia Sinica, No. 128, Academia Road Section 2, Nan-Kang, Taipei 11529, Taiwan

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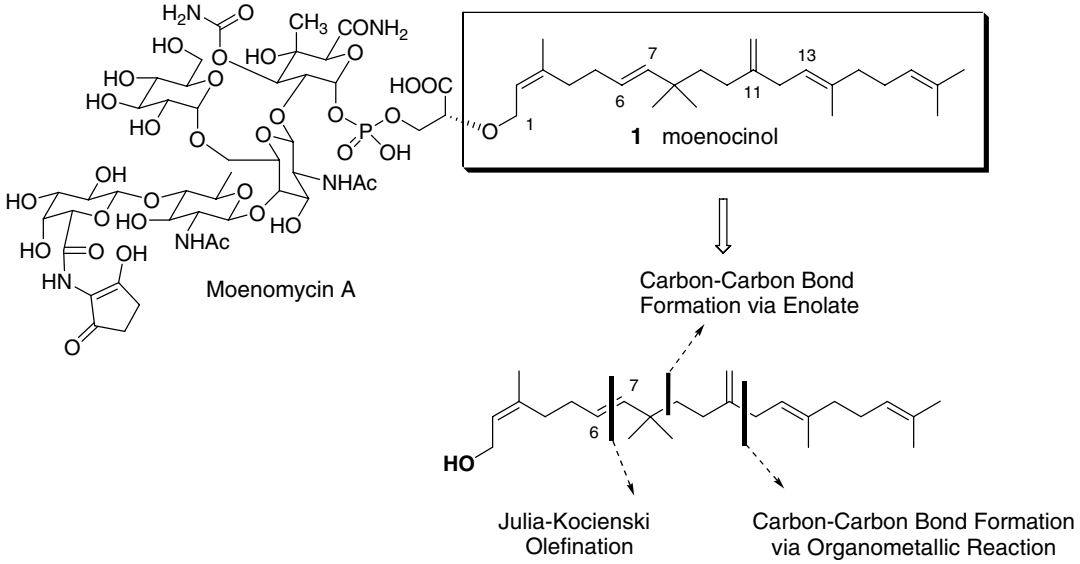
Abstract—Moenocinol ($C_{25}H_{42}O$), the acyclic terpenoid unsaturated lipid part of moenomycin antibiotics, was prepared by an expedient method, which comprised organometallic reaction, Julia-Kocienski olefination, and enolate carbon bond formation as the key steps. The starting materials, nerol and 3-butyn-1-ol, were elaborated to the benzothiazole sulfone **2** and aldehyde **3**, and the subsequent Julia-Kocienski olefination occurred in a stereospecific manner to give the desired 6*E*-configuration of moenocinol. Moenocinol (**1**) was thus synthesized by 10 linear steps in 12% overall yield, and its analogs **23**, **24**, and **28** with different chain lengths and unsaturation degrees were also realized by the similar reaction sequences.

The antibiotic moenomycin A (Scheme 1) belongs to one of the most efficient inhibitors targeting transglycosylase for the bacterial cell wall biosynthesis.[1] The structure of moenomycin consists of a pentasaccharide part linked to the phosphoglycerate moiety that is modified with the moenocinol (**1**). The moenocinol moiety is essential to the antibacterial activity of moenomycin A; lack of moenocinol or replacement of lipid chains with different lengths or saturation degrees may change the potency of such antibiotics.[2]



Scheme 1. Structure of moenocinol and its synthetic strategy.

Keywords: Moenocinol; Julia-Kocienski olefination; BT-sulfone; Molybdenum-catalyzed oxidation.
* Corresponding author. Tel.: +886 2 27899930x339; fax: +886 2 27899931; e-mail: wbyang@gate.sinica.edu.tw

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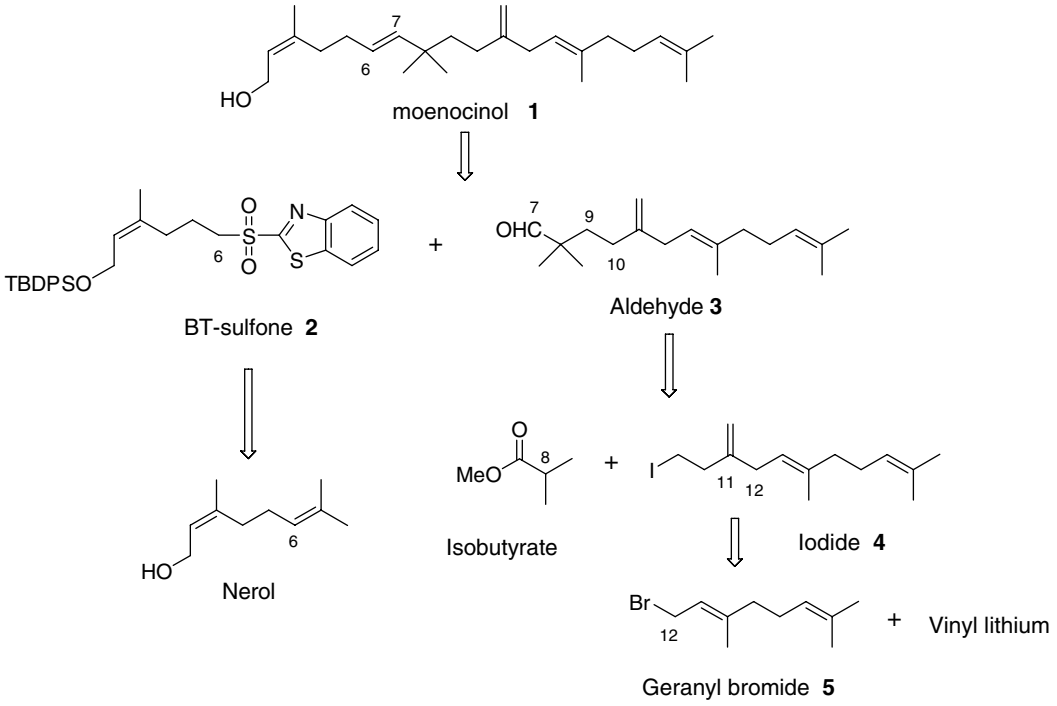
Moenocinol **1** ($C_{25}H_{42}O$, 25:5), where 25 indicates the carbon numbers and 5 indicates the degree of unsaturation, has been synthesized using different strategies.[2a,3] Herein, we demonstrate a new and straightforward synthetic approach to obtain high yields of moenocinol and its analogs. Based on the retrosynthetic analysis (Scheme 2), the strategic bonds at C_6–C_7, C_8–C_9, and C_{11}–C_{12} could be formed, respectively, by using Julia-Kocienski olefination, enolate alkylation, and organometallic reaction. The Julia-Kocienski olefination would afford the desired 6*E*-configuration in moenocinol.[4] Benzothiazole (BT) sulfone **2** could be derived from nerol. Aldehyde **3** could be prepared from methyl isobutyrate and iodide **4**, which was in turn built via substitution reaction of geranyl bromide **5** with vinyl lithium. Nerol and geranyl bromide are commercially available for this synthetic application.

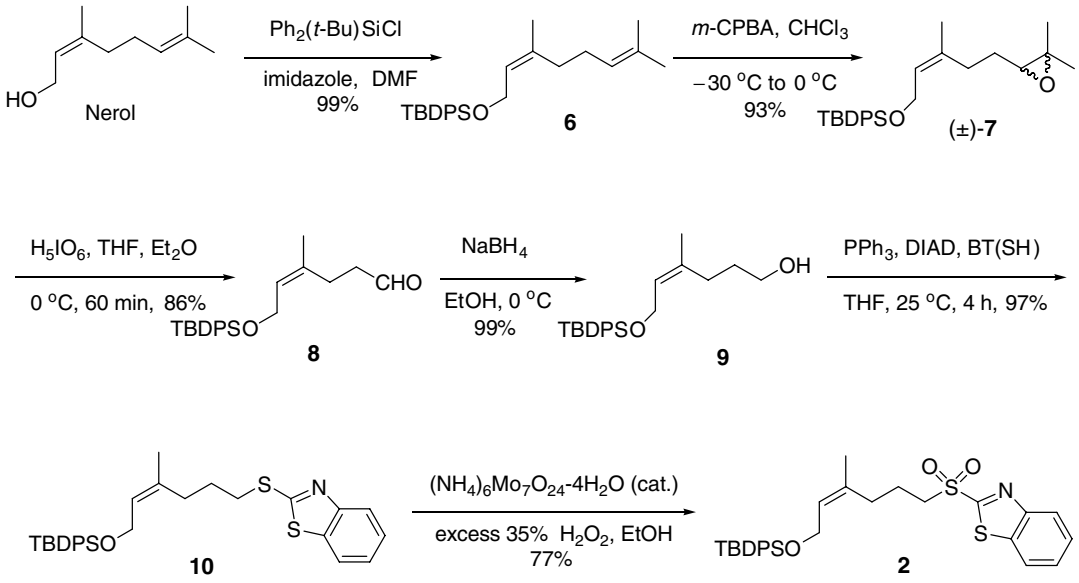
The benzothiazole (BT) **2** was prepared from nerol in 59% overall yield (Scheme 3). The OH group of nerol was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether, giving **6**, and epoxidation with *m*-CPBA afforded a racemic mixture of (±)**7**,[5] which was cleaved by periodic acid to give aldehyde **8**. When the TBDPS protecting group in **6** was replaced by *tert*-butyldimethylsilyl (TBDMS) group, the yield of the periodic acid cleavage reaction dropped drastically due to the undesired acid-catalyzed deprotection of the TBDMS group. Reduction of compound **8** by $NaBH_4$/EtOH, at 0 °C gave 99% of the alcohol **9**. The Mitsunobu reaction[6] with BT(SH), PPh_3, and DIAD (THF, 25 °C, 4 h) gave **10** in 97% yield. The molybdenum-catalyzed oxidation[7] of sulfide **10** gave BT-sulfone **2** in 77% yield.[8] The double bond was not affected under such mild oxidation conditions. The 1-phenyltetrazole-2-sulfone analog of **2** was also prepared; albeit in a lower yield. BT-sulfone **2** was stable on standing at room temperature for a prolonged period.

On the other hand, 3-butyn-1-ol was treated with NaI and Me_3SiCl in acetonitrile to give 3-iodobut-3-en-1-ol,[9,10] which was converted to the TBDPS ether **11** in 72% overall yield (Scheme 4). Metalation of **11** by *n*-BuLi (1.5 equiv) at −110 °C gave the corresponding vinyllithium, which reacted with geranyl bromide in THF at −78 °C, followed by removal of the TBDPS group with 1 M TBAF to give alcohol **12** in 65% yield.[11] Alcohol **12** was activated as the corresponding iodide **4** (PPh_3, imidazole, I_2, Garegg-Samuelsson reaction) for the coupling reaction with the lithium enolate of methyl isobutyrate. The coupling product was then reduced by DIBAL-H (2.2 equiv) to afford alcohol **13** in 59% overall yield. Alcohol **13** was oxidized to aldehyde **3** (cat. TPAP, NMO in CH_2Cl_2 at room temperature), which underwent Julia-Kocienski olefination with BT-sulfone **2** to give **14** exclusively in the 6*E* form. The product showed a large coupling constant (15.6 Hz) between the olefinic protons on the newly formed C_6=C_7 double bond. No 6*Z* isomer was observed in the ^{1}H NMR spectrum of the reaction mixture. After removal of the TBDPS group, moenocinol **1**[12] was obtained in 12% overall yield from 3-butyn-1-ol by 10 linear steps. The spectral properties of this synthetic sample was in agreement with the published data for moenocinol.[3d,f,13]

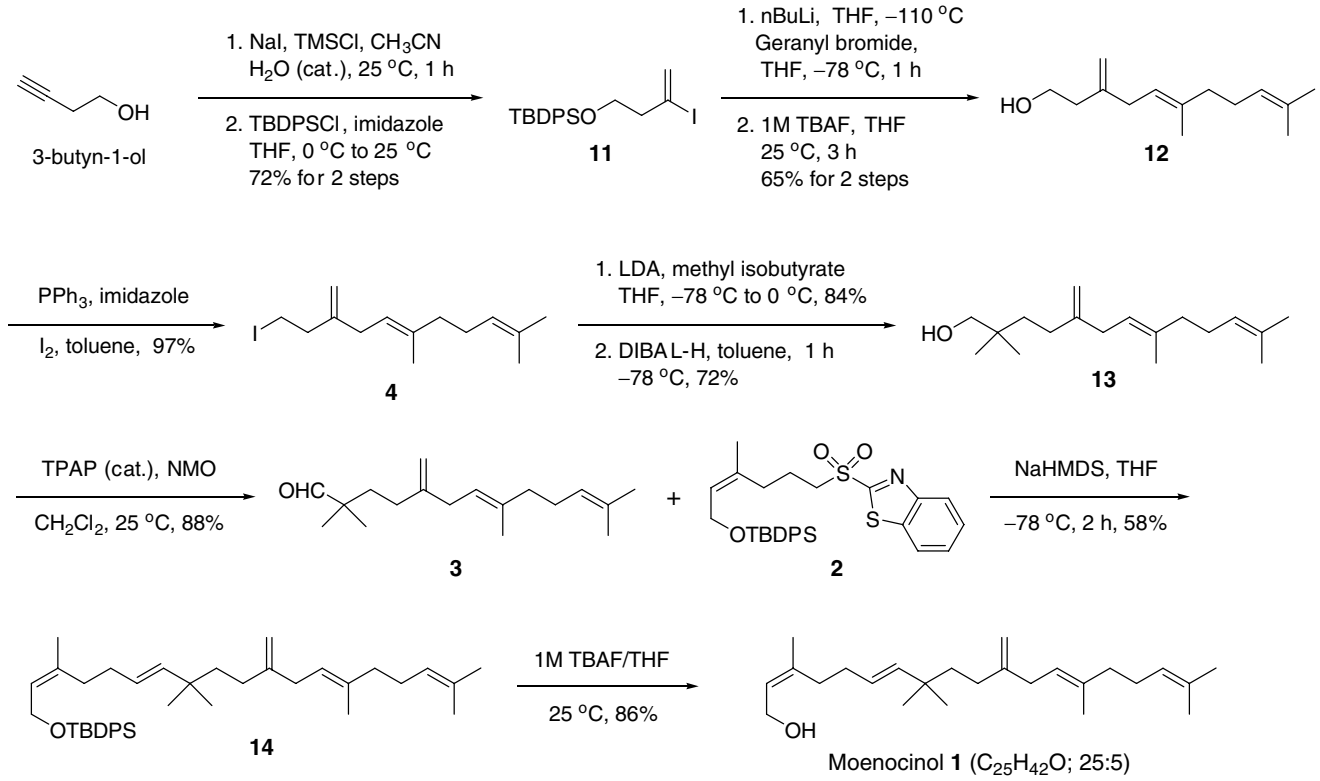
BT-sulfone **2** is a common precursor for the synthesis of unsaturated analogs of moenocinol, for example, **23** (21:4) and **24** (26:5) as shown in Scheme 5. The lithium enolate of methyl isobutyrate was reacted with geranyl bromide or farnesyl bromide to give **15** ($n = 1$, 90%); **16** ($n = 2$, 93%), respectively. The reduction of esters



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



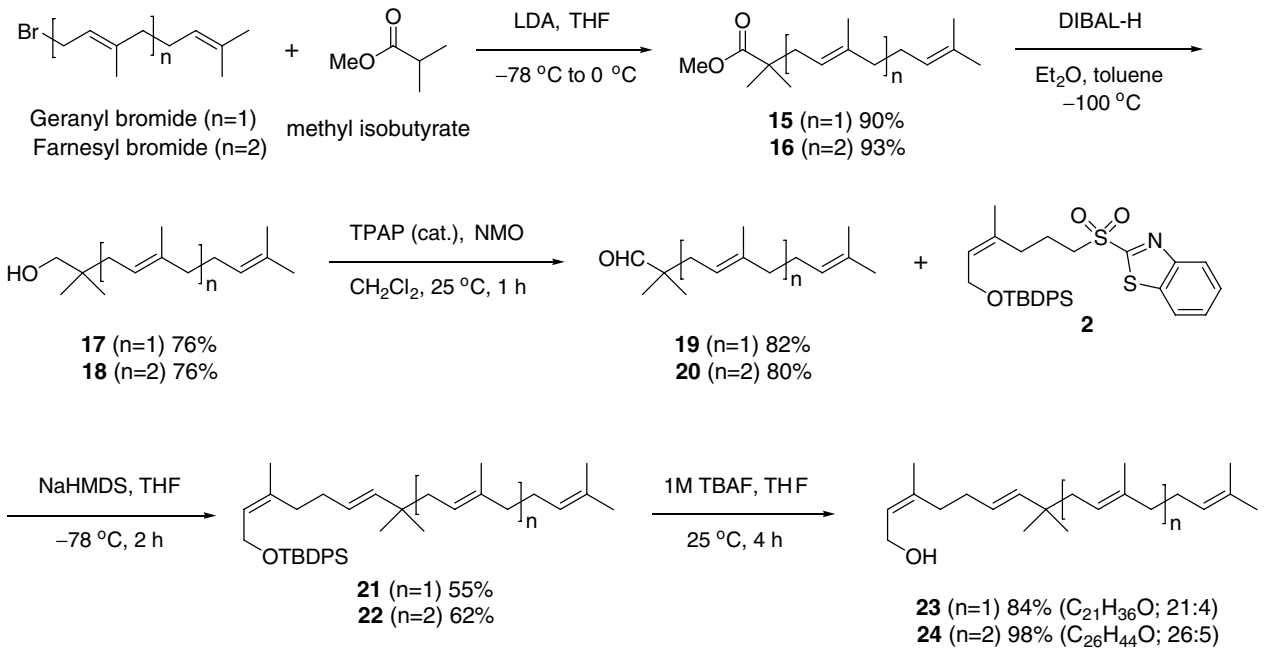
Scheme 3. Synthesis of the common precursor **2**, a BT-sulfone for Julia-Kocienski olefination.



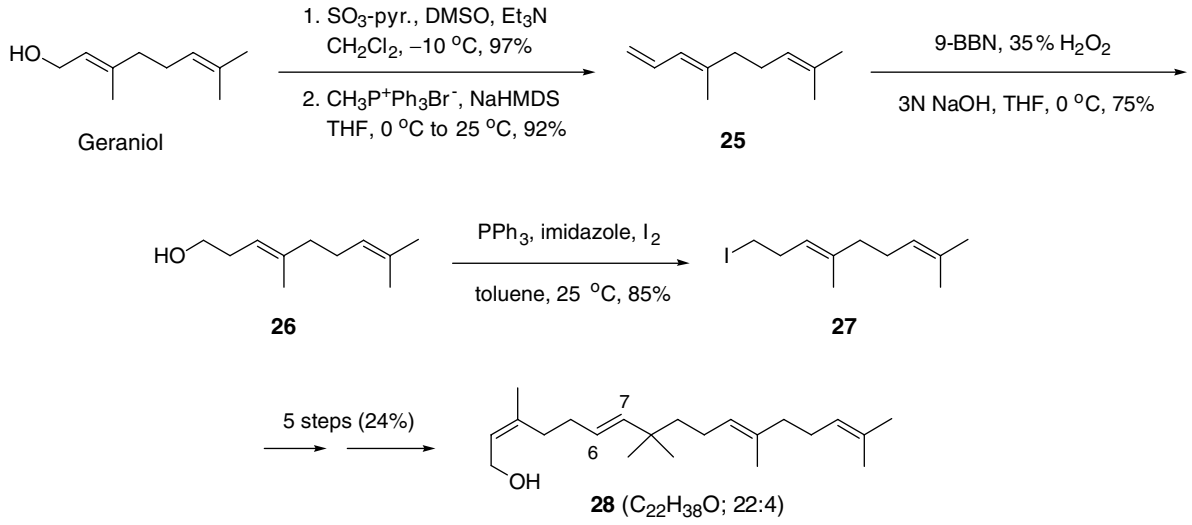
Scheme 4. Stereoselective synthesis of moenocinol **1**.

15 and **16** using 2.2 equiv of DIBAL-H gave alcohols **17** and **18**, which were readily transformed into aldehydes **19** (82%) and **20** (80%) by NMO in the presence of a catalytic amount of TPAP. Julia-Kocienski olefination of **19** and **20** with BT-sulfone **2** afforded **21** and **22** having exclusively the 6*E*-configuration as shown by the large coupling constant (15.6 Hz) in the ^{1}H NMR spectra. The TBDPS group was removed by 1 M TBAF to give the moenocinol analogs **23** ($C_{21}H_{36}O$, 21:4)[14] and **24** ($C_{26}H_{44}O$, 26:5)[15] in 5 linear steps from geranyl bromide and farnesyl bromide with 26% and 34% overall yields.

We also synthesized **28** ($C_{22}H_{38}O$, 22:4)[16] bearing an extra sp^3 carbon (C_9) by extension of geraniol (Scheme 6). Geraniol was oxidized to an aldehyde (SO_3·pyridine, DMSO), and reacted with Wittig reagent ($CH_3P^+Ph_3Br^-$, NaHMDS) to give triene **25**. The



Scheme 5. Synthesis of (21:4) and (26:5) moenocinol analogs **23** ($C_{21}H_{36}O$) and **24** ($C_{26}H_{44}O$).



Scheme 6. Synthesis of (22:4) moenocinol analog **28** ($C_{22}H_{38}O$) with sp^3 carbon between isoprene units.

terminal double bond in **25** reacted selectively with 9-BBN, and the subsequent oxidation with H_2O_2 in the presence of 3 N NaOH gave alcohol **26**. By the procedures similar to that delineated in Scheme 4, alcohol **26** was activated as iodide **27** to culminate in the synthesis of **28** with 14% overall yield in 9 linear steps from geraniol. The C_6=C_7 double bond in **28** formed by the Julia-Kocienski olefination also existed exclusively in the *E*-configuration ($J = 15.6$ Hz).

In conclusion, we have devised an efficient and high-yielding method for the synthesis of moenocinol **1** and its analogs **23**, **24**, and **28**. A BT-sulfone **2** served as the common precursor for Julia-Kocienski olefination to build the desired *E*-configuration at the C_6=C_7 double bonds of these unsaturated lipids. In comparison with the lengthy procedures (>10 steps) and low yields (<10%) in the previous syntheses of moenocinol,[3] our current synthetic method has the advantages of shorter route (10 steps), higher yield (12%) and exclusive formation of the desired *E*-isomer. Further chemical modifications and linkage of the unsaturated lipids to phosphoglycerate and sugars are under investigation in order to establish the structure and activity relationship of moenomycin antibiotics.

Acknowledgments

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References and notes

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8. *Data for compound* **2**: IR (neat) cm^{-1} = 2930, 2856, 1715, 1326, 1148, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H, *t*-Bu), 1.64 (s, 3H, 3-CH_3), 1.86–1.91 (m, 2H), 1.97–2.00 (m, 2H), 3.32 (m, 2H), 4.11 (d, J = 6.0 Hz, 2H, O–CH_2), 5.45 (t, J = 6.0 Hz, 1H, 2-H), 7.33–8.15 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 152.6, 136.7, 135.5, 135.4, 135.0, 133.7, 129.6, 128.0, 127.6, 126.8, 125.4, 122.3, 60.2, 53.9, 30.0, 26.7, 22.7, 20.2, 19.0; HRMS (ESI) *m*/*z* $(M+Na)^+$ 572.1712; calcd for $C_{30}H_{35}NO_3S_2SiNa$: 572.1725.
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12. *Data for compound* **1** *(moenocinol)*: IR (neat) cm^{-1} = 3318, 2901, 2924, 2855, 2361, 1446, 1377, 999, 973; ^1H NMR (600 MHz, $CDCl_3$) δ 0.94 (s, 6H, $CH_3 \times 2$), 1.37–1.34 (m, 2H), 1.58 (s, 3H), 1.59 (s, 3H), 1.66 (s, 3H), 1.72 (s, 3H), 1.88–1.86 (m, 2H), 2.01–1.99 (m, 2H), 2.13–2.05 (m, 6H), 2.67 (d, J = 7.2 Hz, 2H, 12-H), 4.09 (d, J = 7.2 Hz, 2H, *exo*-C=CH_2), 4.66 (d, J = 4.2 Hz, 2H, 1-H), 5.08 (t, J = 6.6 Hz, 1H, 17-H), 5.15 (t, J = 7.2 Hz, 1H, 13-H), 5.23 (dt, J = 15.6, 6.6 Hz, 1H, 6-H), 5.34 (d, J = 15.6 Hz, 1H, 7-H), 5.42 (t, J = 7.2 Hz, 1H, 2-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1, 140.7, 139.8, 136.4, 131.4, 125.2, 124.4, 124.3, 121.9, 108.3, 59.1, 41.4, 39.8, 35.5, 35.0, 32.2, 31.4, 31.3, 27.3, 26.7, 25.7, 23.5, 17.7, 15.9; HRMS (ESI) *m*/*z* 359.3372 $(M+H)^+$; calcd for $C_{25}H_{42}OH$: 359.3314.
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14. *Data for compound* **23**: IR (neat) cm^{-1} = 3339, 2960, 2925, 2864, 2360, 1445, 1377, 971; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 6H, $CH_3 \times 2$), 1.11 (br, 1H, OH), 1.55 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.91 (d, J = 7.6 Hz, 2H, 9-H), 1.97–2.14 (m, 8H), 4.08 (d, J = 7.2 Hz, 2H, 1-H), 5.05–5.12 (m, 2H, 10-H and 14-H), 5.23 (dt, J = 15.6, 6.4 Hz, 1H, 6-H), 5.38–5.44 (m, 2H, 2-H and 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.8, 136.2, 131.2, 124.7, 124.5, 124.4, 121.4, 59.1, 41.0, 40.0, 36.6, 32.3, 31.4, 29.4, 27.0, 26.7, 25.7, 23.5, 17.7, 16.1; HRMS (ESI) *m*/*z* 327.2691 $(M+Na)^+$; calcd for $C_{21}H_{36}ONa$: 327.2664.
15. *Data for compound* **24**: IR (neat) cm^{-1} = 3358, 2959, 2925, 2855, 2360, 1446, 1379, 972; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 6H, $CH_3 \times 2$), 1.07 (br, 1H, OH), 1.56 (s, 3H, CH_3), 1.58 (s, 6H, $CH_3 \times 2$), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.90–2.11 (m, 14H), 4.09 (m, 2H), 5.06–5.13 (m, 3H), 5.23 (dt, J = 15.6, 8.4 Hz, 1H, 7-H), 5.40 (d, J = 15.6 Hz, 1H, 6-H), 5.42 (t, J = 6.0 Hz, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.9, 136.3, 134.9, 131.3, 124.7, 124.4, 124.3, 124.2, 121.3, 59.1, 41.0, 40.0, 39.8, 36.6, 32.3, 31.4, 29.4, 27.0, 26.8, 26.6, 25.7, 23.5, 17.7, 16.2, 16.0; HRMS (ESI) *m*/*z* 395.3245 $(M+Na)^+$; calcd for $C_{26}H_{44}ONa$: 395.3290.
16. *Data for compound* **28**: IR (neat) cm^{-1} = 3341, 2959, 2924, 2856, 2361, 1446, 1377, 972; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 6H, $CH_3 \times 2$), 1.25–1.20 (m, 2H), 1.36 (br s, 1H, OH), 1.56 (s, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 1.71 (s, 3H), 1.88–1.82 (m, 2H), 1.96–1.92 (m, 2H), 2.13–2.01 (m, 6H), 4.09 (dd, J = 7.2, 0.8 Hz, 2H), 5.09–5.06 (m, 2H), 5.23 (dt, J = 15.6, 6.0 Hz, 1H), 5.36 (d, J = 15.6 Hz, 1H), 5.42 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 139.8, 134.6, 313.3, 125.1, 125.0, 124.4 ($2 \times C$), 59.1, 43.2, 39.7, 35.7, 32.3, 31.4, 27.3 ($2 \times C$), 26.8, 25.7, 23.4, 23.3, 17.7, 15.9; HRMS (ESI) *m*/*z* 319.2980 $(M+H)^+$; calcd for $C_{22}H_{38}OH$: 319.3001.