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Studies toward the total synthesis of di- and sesterterpenes with a dicyclopenta[*a,d*]cyclooctane skeleton. Construction of a versatile A/B ring building block via a ring-closing metathesis reaction and carbocationic rearrangement

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Abstract—The cyclopentacyclooctane derivative **1**, chosen as the key building block in a synthesis of terpenoid ophiobolates and fusicoccins, has been prepared from 2-methylcyclo-pent-2-en-1-one **5**. Cyclization of the intermediate 1,9-diene of *l,u* configuration **10** under metathesis conditions (Grubbs' catalyst **15**) afforded the eight-membered ring product **13**, whereas cyclization of the *l,l* diastereomer **9** produced a seven-membered ring analog **12**. Cationic rearrangement of epoxide **26** occurred with methyl group migration to give ketone **27** as the major product.

Ophiobolin A (Fig. 1), a metabolite of the fungus *Helminthsporium oryzeo* infecting rice seedlings, was identified during the 1960s.[1] A number of related sesterterpenoids have since been isolated from terrestrial and marine microorganisms, plants, and insect secretions. Fusicoccin A[2] is the parent representative of several biogenetically related sesquiterpenes. A dicyclopenta[*a,d*]cyclooctane ring system with methyl groups, located at positions 3, 7, and 11, and a side chain at 14, constitute the distinctive structural features of ophiobolins and fusicoccins. Various oxygen-containing functional groups and double bonds further contribute to the great diversity of known structures. It has been shown recently that ophiobolin A and other ophiobolins inhibit tumor cell growth.[3] Ophiobolin M exhibits potent nematocidal activity.[4] Several fusicoccins isolated from herbaceous plants, such as serpendione,[5] show a range of biological activities.

The total synthesis of the dicyclopenta[*a,d*]cyclooctane terpenoids presents a longstanding challenge.[6,7] We were interested in exploring a synthetic approach to

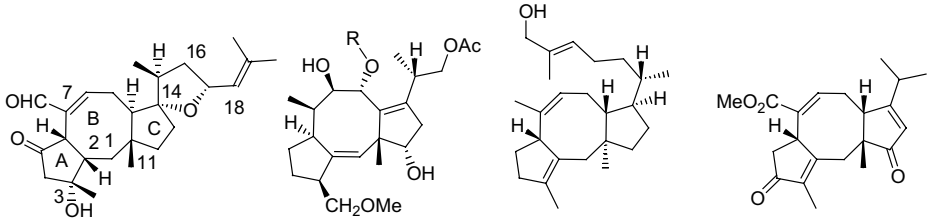

Figure 1. Representative structures of ophiobolins and fusicoccins.

Keywords: Terpenoids; Total synthesis; Mukaiyama reaction; Tsuji alkylation; Ring-closing metathesis; Carbocationic rearrangements.
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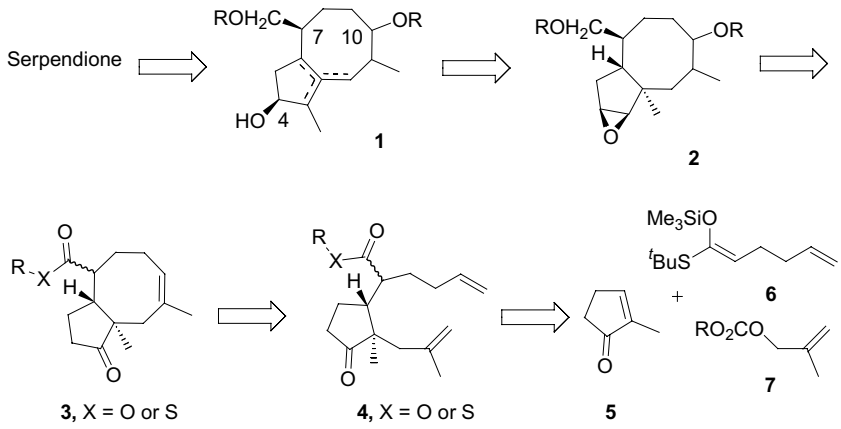


Scheme 1. Synthesis of dicyclopenta[*a*,*d*]cyclooctane terpenoids. General plan.

the cyclooctapentane derivative **1** (Scheme 1), which would involve a cationic rearrangement of epoxide **2** and an annulation of dienes **4** via ring closing metathesis as the key step. It was thought that **1** would provide an advanced intermediate for the synthesis of serpendione and ceroplastols (the latter being isolated from insects' wax[8]). An oxygen function at C-10 (potentially the carbonyl group) would allow for the construction of ring C and an oxygen function at C-4 would serve for a unique ring A modification. It was assumed that dienes **4** of *like*,*like* (*l*,*l*) relative configuration would be available by tandem conjugate addition–alkylation reactions using enone **5**, ketene acetal **6**, and carbonate **7** as the starting materials.

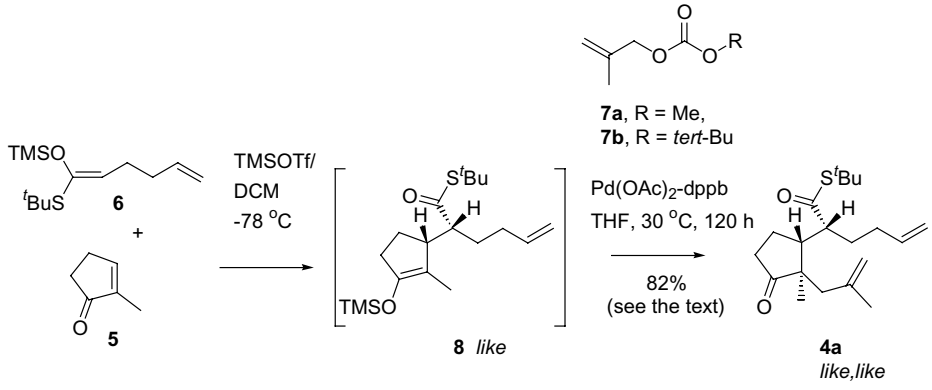
The Mukaiyama–Michael reaction of **6** with enone **5** in the presence of trimethylsilyl triflate[9] afforded the adduct **8** (Scheme 2). However, we failed to alkylate **8** with isobutenyl carbonate **7a** under the standard conditions developed[10] for the less bulky allyl methyl carbonate [$Pd(dba)_2$ THF, reflux]. After considerable experimentation, it was found that the use of carbonate **7b** and $Pd(OAc)_2$—1,4-bis(diphenylphosphino)butane (dppb) as the catalyst (3 mol %) in THF at 30 °C (5 days) formed **4a** in over 80% yield.

Diene **4a** on treatment with the second generation Grubbs' catalyst **15** (Scheme 3) in benzene at reflux temperature, gave the cyclization product in 50–65% yield. Rather unexpectedly, NMR (^1H and ^{13}C), mass and high-resolution mass spectra indicated the decahydroazulene structure **11** for this product; consequently, propene must have been the complementary metathesis product.

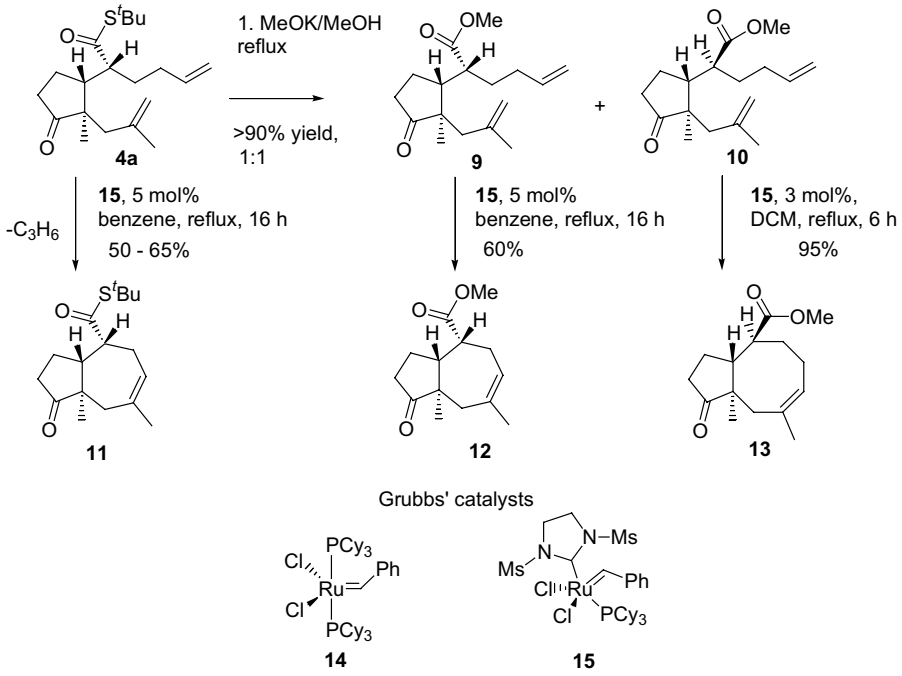
The steric strain resulting from the pseudo 1,3-diaxial interaction between the thioester group and the angular methyl group was likely to have been responsible for the abnormal course of the RCM reaction.[11] In order to replace the bulky *tert*-butylthio group with the methoxy group, thioester **4a** was treated with potassium methoxide in methanol at reflux temperature. A mixture of methyl esters **9** (*l*,*l*) and **10** (*l*,*u*) was obtained virtually quantitatively in a ratio of ca. 1:1. The epimers were isolated by flash chromatography and each was submitted to the conditions of the RCM reaction.

Diene **9** gave product **12** (7/5) in a 60% yield. Interestingly, treatment of **9** with the catalyst **14** gave the dimeric product **16** (Scheme 4). Submission of the latter to the action of **15** (5 mol %, benzene, reflux) furnished a mixture of **12** (49%) and cyclopenta[8]annulene **17** (34%).

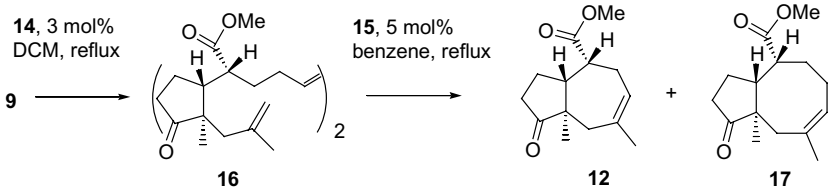
Diene **10** (*l*,*u* relative configuration) on treatment with **15** in DCM, at reflux, smoothly afforded the cyclopenta[8]annulene derivative **13**. In the most convenient procedure, thioester **4a** was subjected to methanolysis



Scheme 2. Synthesis of 1,9-diene **4a** via tandem conjugate addition and alkylation reactions.



Scheme 3. Methanolysis of **4a** and ring-closing metathesis reaction of dienes **4a**, **9**, and **10**.



Scheme 4. RCM reaction of diene **9** via dimer **16**.

and then the product was briefly chromatographed to give a mixture of **9** and **10** in a ratio of ca. 1:10. This mixture was submitted to the metathesis conditions (**15**, DCM, reflux) under which **10** formed **13**, whereas its epimer **9** was converted into the respective dimer that was easily separated by chromatography. Hence the target product **13** was obtained in three steps from enone **5** in ca. 40% overall yield.

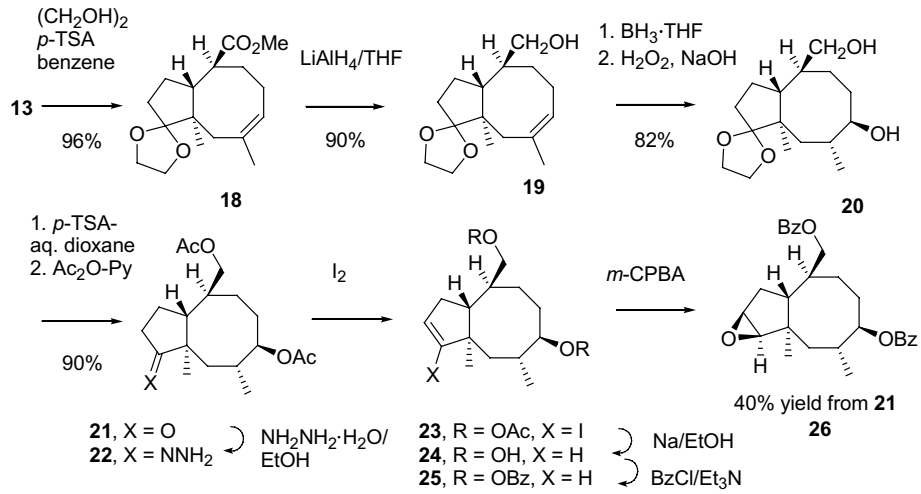
Separate cases of ruthenium-catalyzed double bond isomerization followed by RCM reaction have been reported;[12] however, until now only minor side products were formed on this route. Scrutiny of relevant RCM reactions will be published elsewhere.

Intermediate **13** was straightforwardly transformed into **21** as indicated in Scheme 5. The depicted stereochemistry for the hydroboration–oxidation product **20** was assigned on the basis of preferred reagent approach to the double bond opposite to the angular methyl group.

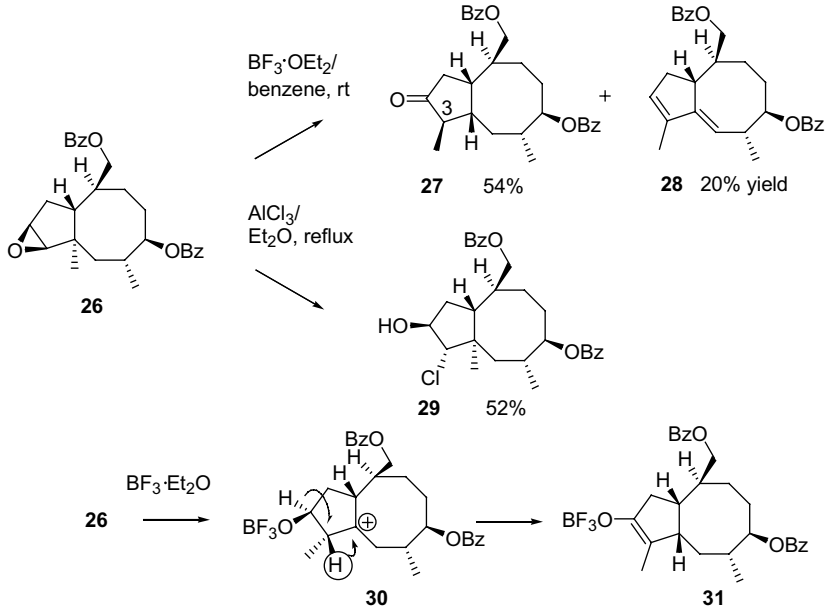
Reaction of diacetoxy ketone **21** with hydrazine turned out to be problematic. Hydrazone **22** was contaminated with another product, presumably the respective diazine.[13] Treatment of the crude product with iodine and tetramethylguanidine according to Barton et al.[14] gave iodide **23**, which was reduced with sodium in ethanol. Crude diol **24** was then benzoylated to give **25**, which was oxidized with *m*-CPBA to epoxide **26** (40% overall yield from **21**).

Treatment of **26** with $BF_3{\cdot}Et_2O$ in benzene (ambient temperature) afforded a mixture of two products that were separated by chromatography. The major product (54% yield) was assigned the gross structure **27** from its spectroscopic data (IR, ^1H and ^{13}C NMR, HR MS). It is assumed that the methyl group at C3 is oriented on the less strained, β face of the molecule, since no acid-catalyzed epimerization at this centre occurred. The minor product was identified as diene **28**.

Rearrangement of **26** involves epoxide ring opening followed by migration of the angular methyl group to form intermediate **30** (Scheme 6). A 1,2-hydride ion shift and loss of a proton from **30** then affords enol **31**, which becomes ketone **27** after protonation. Alternatively, loss of a proton from **30** and formal dehydration leads to diene **28**. Noteworthy, treatment of **26** with $AlCl_3$ in ether (reflux temperature) under conditions used for rearrangement of similar steroid epoxides[13] affords chlorohydrin **29** as the only product.



Scheme 5. Transformation of the metathesis product **13** into epoxide **26**.



Scheme 6. Lewis acid-catalyzed rearrangement of epoxide **26**.

A study of transforming the key intermediate **27** into a dicyclopenta[*a,d*]cyclooctane ring system is in progress.

Properties of selected new compounds. **9**: R_f 0.22 (silica gel on aluminum sheets, Merck 60F 254; 10% EtOAc/hexanes). ^{1}H NMR (200 MHz): 5.90–5.66 (m, 1H, C*H*=CH$_2$), 5.10–4.92 (m, 2H, CH=C*H*$_2$), 4.83 (br s, 1H, C*H*$_2$=CCH$_3$), 4.63 (br s, 1H, C*H*$_2$=CCH$_3$), 3.70 (s, 3H, COOC*H*$_3$), 2.62–2.29 (m, 4H), 2.28–2.05 (m, 2H), 2.04–1.58 (m, 5H), 1.56 (br s, 3H, CH$_2$=CC*H*$_3$), 1.54–1.36 (m, 1H), 0.96 (s, 3H, C2′–C*H*$_3$). ^{13}C NMR (50 MHz): 222.5 (C=O), 175.6 (*C*OOCH$_3$), 141.5 (CH$_2$=*C*CH$_3$), 137.5 (*C*H=CH$_2$), 115.4, 115.4, 51.5, 51.4, 46.1, 43.8, 43.0, 37.3, 31.5, 29.8, 24.5, 23.6, 19.5. HRMS calcd for $C_{17}H_{26}O_3$: 278.1882; found: 278.1884. **10**: R_f 0.17 (10% EtOAc/hexanes). ^{1}H NMR (200 MHz): 5.90–5.66 (m, 1H, CH=C*H*$_2$), 5.10–4.92 (m, 2H, C*H*$_2$=CCH$_3$), 4.86 (br s, 1H, C*H*$_2$=CCH$_3$), 4.69 (br s, 1H, C*H*$_2$=CCH$_3$), 3.69 (s, 3H, COOC*H*$_3$), 2.74–2.39 (m, 2H), 2.38–1.56 (m, 10H), 1.52 (br s, 3H, CH$_2$=CC*H*$_3$), 0.88 (s, 3H, C2′–C*H*$_3$). ^{13}C NMR (50 MHz): 222.2 (C=O), 175.6 (*C*OOCH$_3$), 141.9 (CH$_2$=*C*CH$_3$), 137.3 (*C*H=CH$_2$), 115.9, 115.5, 51.4, 51.4, 47.0, 45.6, 43.3, 37.1, 31.8, 30.8, 23.9, 23.3, 19.1. HRMS calcd for $C_{17}H_{26}O_3$: 278.1882; found: 278.1886. **12**: mp 52–54 °C. HPLC (RP18, RI detector, MeOH/H$_2$O 60:40, 0.5 mL/min, R_t = 6.42 min, 94% purity, no contaminations of similar R_t). ^{1}H NMR (500 MHz): 5.82–5.67 (m, 1H, =C*H*), 3.66 (s, 3H, COOC*H*$_3$), 2.88–2.76 (m, 1H), 2.68–2.30 (m, 3H), 2.27–1.86 (m, 6H), 1.77 [br s, =C(C*H*$_3$), 3H], 0.76 (s, 3H, C8a–CH$_3$). ^{13}C NMR (50 MHz): 221.0 (C=O), 174.2 (*C*OOCH$_3$), 136.4 (CH=*C*), 124.2 (*C*H=C), 53.6, 51.4, 48.9, 43.1, 40.2, 35.3, 30.0, 27.6, 23.9, 14.2. Elemental analysis:

calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53; found: C, 71.27; H, 8.56.

13: ^{1}H NMR (200 MHz): 5.55–5.39 (m, 1H, =C*H*), 3.67 (s, 3H, COOCH_3), 2.78–2.60 (m, 1H), 2.52–1.98 (m, 7H), 1.98–1.70 (m, 3H) overlapping 1.72 [br s, 3H, =C(CH_3)], 1.68–1.40 (m, 1H), 0.92 (s, 3H, C9a–CH_3). ^{13}C NMR (50 MHz): 221.0 (C=O), 175.8 (*C*OOCH$_3$), 135.2 (CH=*C*), 126.0 (*C*H=C), 52.4, 51.6, 45.6, 42.2, 37.4, 35.8, 30.6, 27.2, 25.0, 22.8, 16.4. HRMS calcd for $C_{15}H_{22}O_3$: 250.1569; found: 250.1574. **20**: ^{1}H NMR (400 MHz, $CDCl_3$+D_2O): 4.02–3.80 (m, 4H, OCH_2-CH_2O), 3.62 (dd, J = 10.6, 3.7 Hz, 1H, CH_2OH), 3.41 (dd, J = 10.6, 1.0 Hz, 1H, CH_2OH), 3.05 (dt, J = 10.5, 3.6 Hz, 1H, C*H*OH), 2.15–2.02 (m, 1H), 2.00–1.34 (m, 12H), 1.30–1.14 (m, 1H), 1.09–0.87 (m, 1H) overlapping 0.97 (d, J = 6.4 Hz, 3H, C8–CH_3), 0.84 (s, 3H, C9a–CH_3).^{13}C NMR (100 MHz, $CDCl_3$): 120.7 (OCO), 79.3 (C7), 65.1 (*C*H_2OH), 63.5 (O*C*$H_2$$CH_2$O), 63.2 (O*C*$H_2$-$CH_2$O), 47.2, 42.0, 40.6, 38.5, 36.6, 31.9, 30.8, 24.4, 21.8, 20.6, 19.2. HRMS (ESI) calcd for $C_{16}H_{28}O_4$ Na: 307.1880; found: 307.1891. **26**: ^{1}H NMR (400 MHz, $CDCl_3$): 8.05–7.98 (m, 4H), 7.58–7.51 (m, 2H), 7.46–7.40 (m, 4H), 4.65 (dt, J = 10.6, 4.1 Hz, 1H, C*H*OBz), 4.33 (dd, J = 11.0, 4.1 Hz, 1H, CH_2OBz), 4.09 (dd, J = 11.0, 8.8 Hz, 1H, CH_2OBz), 3.33 (d, J = 2.9 Hz, 1H, epoxide H_a), 3.06 (d, J = 2.9Hz, 1H, epoxide H_b), 2.38–2.14 (m, 2H), 2.08–1.86 (m, 5H), 1.82–1.50 (m, 4H), 1.04 (d, J = 6.7 Hz, 3H, CHCH_3), 0.85 (s, 3H, C1b–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 166.4 (C=O), 165.9 (C=O), 133.0, 132.8, 130.6, 130.1, 129.5, 129.5, 128.4, 128.3, 81.6, 66.6 (*C*HOBz), 66.1 (*C*H_2OBz), 52.0, 43.2, 41.5, 35.6, 33.2, 33.1, 30.7, 26.8, 22.2, 21.7, 19.5. HRMS (ESI) calcd for $C_{28}H_{32}O_5$Na: 471.2142; found 471.2170. **27**: IR (film): 1739 cm^{-1} (m, C=O), 1715 cm^{-1} (s, COOBz). ^{1}H NMR (400 MHz, $CDCl_3$): 8.08–7.99 (m, 4H), 7.60–7.54 (m, 2H), 7.49–7.42 (m, 4H), 4.81 (br t, J = 8.9 Hz, 1H, C*H*OBz), 4.32 (dd, J = 11.1, 3.7 Hz, 1H, CH_2OBz), 4.25 (dd, J = 11.1, 5.3 Hz, 1H, CH_2OBz), 2.60–2.34 (m, 4H), 2.30–1.92 (m, 7H), 1.84–1.71 (m, 2H), 1.17 (d, J = 7.5Hz, 3H, C1–CH_3), 1.05 (d, J = 6.6 Hz, 3H, C8–CH_3).^{13}C NMR (100 MHz, $CDCl_3$): 219.9 (C=O), 166.5 (*C*OBz), 165.9 (*C*OBz), 133.1, 132.9, 130.6, 130.0, 129.6, 129.5, 128.5, 128.4, 79.4, 69.0, 53.4, 45.9, 41.7, 39.4, 38.5, 37.6, 36.9, 31.8, 28.7, 20.9, 16.3. HRMS (ESI) calcd for $C_{28}H_{32}O_5$Na: 471.2142; found: 471.2172. **28**: ^{1}H NMR (400 MHz, $CDCl_3$): 8.08–8.01 (m, 4H), 7.58–7.53 (m, 2H), 7.47–7.41 (m, 4H), 5.76 (br s, 1H, =C2–H), 5.14 (br d, J = 8.9 Hz, 1H, =C4–H), 4.95–4.89 (m, 1H), 4.48 (dd, J = 11.1, 2.9 Hz, 1H, CH_2OBz), 4.27 (dd, J = 11.1, 8.2 Hz, 1H, CH_2OBz), 2.92–2.77 (m, 2H), 2.73–2.63 (m, 1H), 2.43–2.33 (m, 1H), 2.06–1.60 (m, 5H) overlapping 1.77 (br s, 3H, C3–CH_3), 1.14 (d, J = 6.4 Hz, 3H, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 166.6 (*C*OBz), 166.2 (*C*OBz), 150.5, 139.5, 132.9, 132.8, 131.6, 130.8, 130.3, 129.5, 128.4, 128.3, 120.2, 79.0, 44.2, 41.9, 37.3, 29.7, 29.2, 18.4, 12.9. HRMS (ESI) calcd for $C_{28}H_{30}O_4$Na: 453.2036; found: 453.2052. **29**: ^{1}H NMR (400 MHz, $CDCl_3$): 8.05–7.99 (m, 4H), 7.60–7.51 (m, 2H), 7.48–7.39 (m, 4H), 4.67 (dt, J =10.4, 3.9 Hz, 1H, C*H*OBz), 4.33 (dd, J = 11.0, 4.4 Hz, 1H, CH_2OBz), 4.17 (dd, J = 11.0, 9.1 Hz, 1H, CH_2OBz), 4.02 (dt, J = 8.0, 1.5 Hz, 1H, C*H*OH), 3.82 (d, J = 1.5 Hz, 1H, C*H*Cl), 2.77–2.66 (m, 1H), 2.42–2.24 (m, 2H), 2.18–1.88 (m, 5H), 1.86–1.66 (m, 3H), 1.63–1.51 (m, 1H), 1.05 (s, 3H, C9a–CH_3), 1.01 (d, J = 6.4 Hz, 3H, CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 166.4 (*C*OBz), 165.9 (*C*OBz), 133.0, 132.8, 130.7, 130.1, 129.5, 129.5, 128.4, 128.3, 92.2, 81.2, 66.6 (*C*H_2OBz), 63.0, 46.9, 43.0, 39.7, 39.7, 37.7, 34.6, 27.3, 22.1, 21.4, 21.2. HRMS (ESI) calcd for $C_{28}H_{33}ClO_5$Na: 507.2017; found 507.2031.

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