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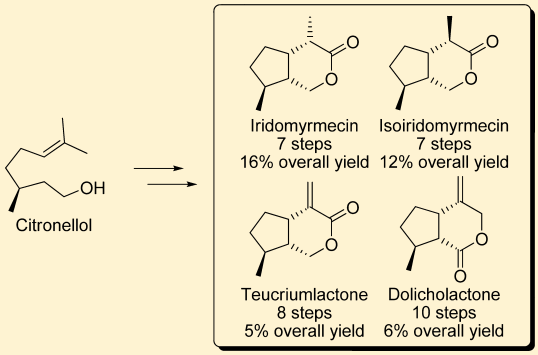
Divergent Diastereoselective Synthesis of Iridomyrmecin, Isoiridomyrmecin, Teucrimulactone, and Dolicholactone from Citronellol

Clara J. Fischman, Snow Adler, and John E. Hofferberth*

Department of Chemistry, Kenyon College, Gambier, Ohio 43022, United States

Supporting Information

ABSTRACT: The iridoid natural products iridomyrmecin, isoiridomyrmecin, teucriumlactone, and dolicholactone were prepared from citronellol using a divergent diastereoselective approach. Key steps include a highly diastereoselective enamine/enal cycloaddition and the selective reduction of masked aldehyde functionalities by ionic hydrogenation.



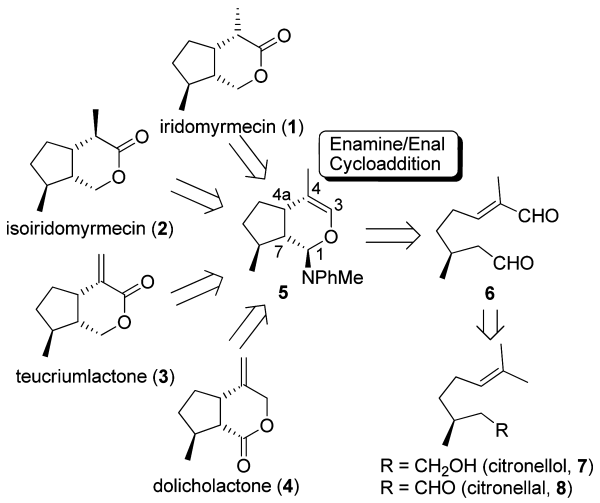
A detailed understanding of insect chemical signaling requires access to fully characterized and isomerically pure authentic standards of the involved semiochemicals. Our motivation for this synthesis project was to provide authentic standards of iridomyrmecin (**1**) and isoiridomyrmecin (**2**) to aid in elucidating their role for the parasitic wasp *Leptopilina heterotoma*. This wasp is a parasitoid of the quintessential animal research model organism *Drosophila melanogaster* and has recently drawn the attention of the research community.[1]

Although **1** and **2** have been known for some time and prepared using a diversity of synthetic approaches,[2] we took this opportunity to continue our work on the divergent diastereoselective synthesis of iridoids using citronellol or citronellal as starting materials.[3] A preliminary description of our synthetic approach to **1** and **2** was reported with a study of their role in the chemical ecology of *L. heterotoma*.[1c] We now detail an optimized version of this synthesis in addition to the total synthesis of two related natural products, teucriumlactone (**3**) and dolicholactone (**4**), using the same divergent approach.

Teucriumlactone (**3**) and dolicholactone (**4**) were first isolated from the Mediterranean plant *Teucrium marum* which is known for its cat-attracting properties and powerful lacrimatory essential oil.[4] Although **3** and **4** were first characterized over 35 years ago, few total syntheses have been reported. Teucriumlactone (**3**) was first prepared by Demuth in racemic form from a functionalized tricyclo[3.3.0.0]octan-3-one.[5] The only precedent for the enantiospecific total synthesis of **3** was reported by Wakamatsu and made use of precious geniposide as starting material.[2k] A single total synthesis of (+)-dolicholactone ((+)-**4**) was described by Lee.[6]

We envisioned the divergent synthesis of **1**-**4** from a common aminal intermediate **5** by differentiation of the resident masked aldehyde functionalities at C1 and C3 (Scheme 1). The highly diastereoselective synthesis of aminal **5**, first described by Schreiber,[7] occurs on treatment of 1,8-enedial **6** with *N*-methylaniline and represents a rapid entry into the iridoid carbon framework. Synthesis of **6** from citronellal (**8**) has been described by us[1c,3] and others,[7,8]

Scheme 1. Divergent Retrosynthetic Analysis of 1−4



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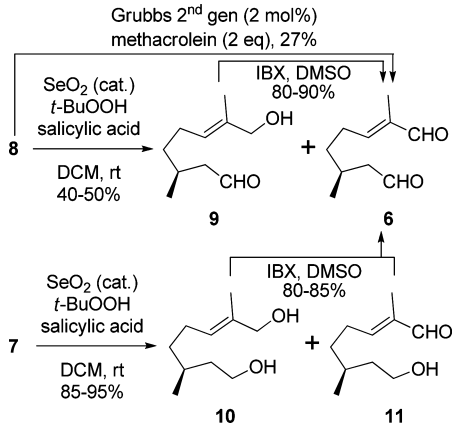
however, we now report an alternative synthesis using citronellol (**7**) as the starting material.

Three methods for the preparation of the cycloaddition substrate **6** were evaluated (Scheme 2). Theodorakis recently

Scheme 2. Alternative Approaches to the Synthesis of 6



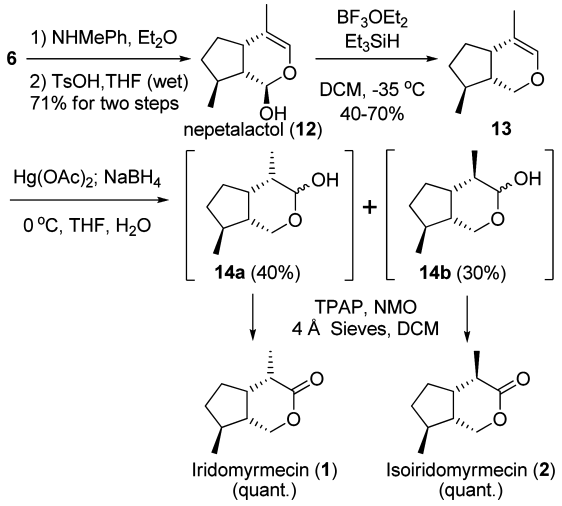
described the cross-metathesis of citronellal (**8**) with methacrolein using Grubbs second-generation catalyst (G2, 5 mol %) to provide **6** in a 75% yield (brsm) in a single operation.[8] In our hands, the same conversion with 2 mol % G2 loading gave **6** in modest isolated yield (27%). Due to the expense of both G2 and methacrolein and our desire to produce multigram quantities of **6**, other less costly methods were subsequently examined.

We previously reported the two-step oxidation of **8** to **6**, which begins with catalytic SeO_2 oxidation to provide mixtures rich in aldol **9**.[1c,3] Purification of **9** followed by IBX oxidation furnishes **6** in 30−45% yield over two steps. The formation of polar side products during the extended reaction time required for SeO_2 oxidation necessitates purification of **9** prior to oxidation. To explore the possibility that the formation of such side products was due the presence of the saturated aldehyde resident in **8**, the use of citronellol (**7**) as starting material was examined. In the event, treatment of **7** with catalytic SeO_2 (5 mol %) and *t*-BuOOH (3.6 equiv) as the stoichiometric reoxidant produced a mixture of diol **10** and aldol **11** in a 1:2 ratio and a combined yield of 95% (20 g scale). This mixture was quite pure (>90%) following aqueous workup and was directly submitted to IBX oxidation to provide **6** in 80−85% yield. Using this approach, **6** can be prepared in multigram quantities with 70−80% isolated yield from citronellol (**7**).

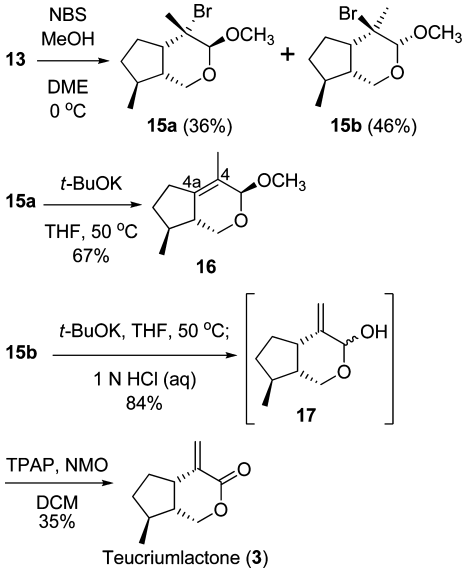
In **1**−**3**, selective reduction of C1 in **5** from the aldehyde to the alcohol oxidation state in the presence of an endocyclic enol ether is required. We envisioned an approach that involved the initial activation of C1 with a Lewis acid followed by the attack of a compatible hydridic nucleophile. Particularly attractive to us were the mild and selective ionic hydrogenation conditions (BF_3OEt_2/Et_3SiH) first described by Kraus.[9] To scrutinize this means of selective C1 reduction, nepetalactol (**12**, C1 α/β, 1:10) was prepared by treatment of **6** with *N*-methylaniline in ether followed by acid catalyzed hydrolysis of the resulting aminal (Scheme 3).[3,7] Exposure of **12** to BF_3OEt_2 (1.2 equiv) in the presence of Et_3SiH (10 equiv) at −35 °C provided the desired enol ether (**13**) in as high as 70% isolated yield.[10]

With the differentiation of the masked aldehydes complete, the potential of **13** to serve as an advanced intermediate in the synthesis of **1**−**3** was determined (Schemes 3 and 4). The enol

Scheme 3. Synthesis of Iridomyrmecin (1) and Isoiridomyrmecin (2)



Scheme 4. Synthesis of Teucriumlactone (3)



ether functionality in **13** proved resistant to hydration when exposed to *p*-TsOH in aqueous THF, and recourse was made to mercuration−reductive demercuration.[11] This process proceeded with complete regioselectivity, although it yielded all of the four potential diastereomers of acetals **14**. This mixture was partially resolved into two pairs of two diastereomers (**14a** and **14b**) using silica gel chromatography. The stereochemical composition of the diastereomers in each pair was made evident when they were separately oxidized with catalytic TPAP[12] to provide iridomyrmecin (**1**) and isoiridomyrmecin (**2**) in quantitative yield from **14a** and **14b**, respectively.

Synthesis of teucriumlactone (**3**) necessitated the installation of the C4 exomethylene prior to oxidation to the lactone (Scheme 4). To that end, **13** was treated with NBS in the presence of methanol to bring about a highly regioselective and stereospecific formation of bromoethers **15**. In **15a**, protons on both the pendant C4 methyl group and the bridgehead carbon C4a are capable of adopting an antiperiplanar orientation to the departing bromine during biomolecular elimination. Unfortu-

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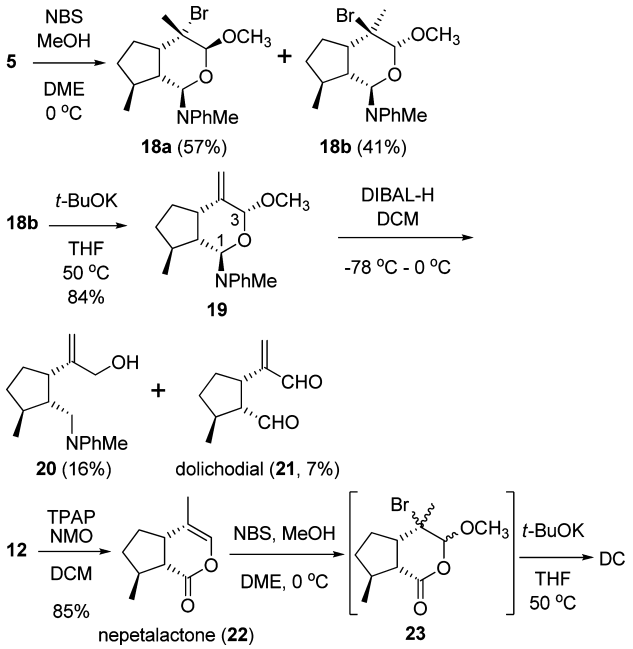
nately, exposure of **15a** to *t*-BuOK in THF at 50 °C results in the formation of a single elimination product (**16**) possessing the undesired endocyclic olefin (C4−C4a). In contrast to **15a**, the pendant C4 methyl group of **15b** uniquely possesses protons capable of adopting an antiperiplanar alignment with the departing bromine. Consistent with this observation, elimination of **15b** under the same reaction conditions occurs exclusively to form the desired exomethlyene resident in **3**. In situ hydrolysis of the elimination product and oxidation of the resulting hemiacetals (**17**) with catalytic TPAP[12] produced teucriumlactone (**3**) in modest yield (35%). Using this route, (+)-**3** was prepared from enantiomerically enriched (−)-**7** as starting material.

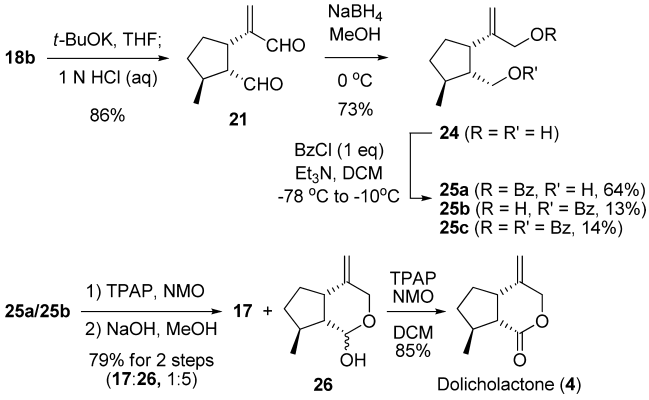
Preparation of dolicholactone (**4**) required an alternate approach to the differentiation of the masked aldehydes in intermediate **5**. One strategy considered sought to exploit the aminal resident in **5** as a protected aldehyde that could be liberated and oxidized late in the synthesis. Earlier observation that **5** was resistant to reduction by treatment with BF_3OEt_2 and Et_3SiH underpinned our conjecture that the aminal functionality could tolerate these conditions during the reduction of a C3 acetal. To examine this hypothesis, intermediate **19** was prepared (Scheme 5).

Scheme 5. Unsuccessful Approaches for the Preparation of 4



As previously described,[3] **5** undergoes a highly regioselective and stereospecific electrophilic addition when treated with NBS in the presence of methanol to generate the separable diastereomeric bromoethers **18**. When **18b** is subject to E2 conditions, elimination occurs to introduce the desired exomethylene unit resident in **19**. To our disappointment, exposure of **19** to our established ionic hydrogenation conditions (Et_3SiH, BF_3OEt_2, −35 °C) resulted only in decomposition, however, some insight was gained on DIBAL-H reduction of **19**. Following workup with aqueous Rochelle's salt, only the 3° amine **20** and dolichodial (**21**) were evident in the product mixture. The presence of **20** suggests that DIBAL-H reduction is selective for the incipient C1 iminium ion formed upon Lewis acid catalyzed ring-opening. Dolichodial (**21**), another iridoid known to be produced by *T. marum*,[4a] is the established hydrolysis product of **19**[3] and was likely formed during the workup. To avoid the possibility of reductive amination during the reduction of the C3 acetal, **5** was converted to nepetalactone (**22**)[3] by hydrolysis to nepetalactol (**12**, vide supra) and oxidation. Treatment of **22** with NBS and methanol resulted in rapid consumption of the starting material, however, the presumptive diastereomeric bromoethers (**23**) were inseparable and were submitted to E2 conditions as a mixture. Only decomposition resulted under such conditions. With these results in hand, the motivation to employ ionic hydrogenation at the C3 position as a means of masked aldehyde differentiation yielded to a more pragmatic approach to complete the synthesis of dolicholactone (**4**, Scheme 6).

Scheme 6. Synthesis of Dolicholactone (4)



Bromoether **18b** was efficiently converted to dolichodial (**21**) by treatment with *t*-BuOK in THF followed by acid-catalyzed hydrolysis.[3] Reduction of **21** with $NaBH_4$ and selective protection of the resulting diol (**24**) produced a mixture of inseparable monobenzoates **25a** and **25b** (5:1).[13] Oxidation of **25a/b** with catalytic TPAP followed by deprotection with methanolic NaOH provided readily separable hemiacetals **17** and **26** (C1 α/β, 3:20). Oxidation of **26** produced dolicholactone (**4**) in good yield (85%). This synthesis was repeated using (−)-**7** as starting material to give (+)-**4** without event.

In summary, we have prepared four iridoid natural products (**1**−**4**) in a divergent manner using citronellol (**7**) as starting material. We have also demonstrated the potential of ionic hydrogenation for the selective reduction of a hemiacetal in the presence of the enol ether in readily prepared nepetalactol (**12**). Enantiomerically pure samples of **1** and **2** generated in the course of this project were instrumental in identifying (−)-**1** and (+)-**2** in the semiochemical defense repertoire of *L. heterotoma*.[1c] In contrast to the well-known natural products (+)-**1** and (−)-**2**, (−)-**1** and (+)-**2** had not been previously identified in nature.

EXPERIMENTAL SECTION

***(E)*-8-Hydroxy-3,7-dimethyloct-6-enal 6.** Racemic citronellol (**7**, 23.4 mL, 128 mmol, 1 equiv) was added to a solution of SeO_2 (0.855 g, 7.7 mmol, 0.06 equiv), salicylic acid (2.13 g, 15.4 mmol, 0.12 equiv), and *t*-BuOOH (70% in H_2O, 53 mL, 553 mmol, 4.3 equiv) in DCM (40 mL) and the resulting reaction mixture was stirred at rt for 72 h. The reaction mixture was diluted with toluene (100 mL), and the volatiles were removed by rotary evaporation. The residue was diluted with ether (400 mL) and washed with NaOH (10% w/v, 4 × 140 mL)

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and brine (1 × 120 mL). The organic layer was dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation to yield a clear-yellow oil (21.2 g, 95%). The product ratio was estimated by integration of the vinylic protons ($CDCl_3$, δ 5.42 ppm for **10**, δ 6.50 ppm for **11**) for the ^{1}H NMR spectrum of the crude mixture and was found to be 2:3 of **10**:**11**, respectively. The product mixture was dissolved in DMSO (400 mL), and IBX (47.7 g, 192 mmol, 1.5 equiv) was added. The resulting reaction mixture was stirred at rt for 2 h, diluted with ether (200 mL), stirred for an additional 5 min, and filtered over Celite. The filtrate was diluted with water (200 mL) and ether (200 mL) and shaken, and the aqueous layer was removed. The organic layer was washed with $NaHCO_3$ (aq, satd, 3 × 200 mL) and brine (1 × 200 mL), dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation to yield a pale-yellow oil (**6**, 16.4 g, 79% from **7**). The crude product was >90% pure as judged by ^{1}H NMR and was carried forward without additional purification. A tabulation of characterization data for **6** was previously reported.[3]

***rel*-((4a*S*,7*S*,7a*R*)-4,7-Dimethyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran 13.** To a solution of **12** (1.4 g, 8.3 mmol, 1 equiv) was added Et_3SiH (13.3 mL, 83 mmol, 10 equiv), and the resulting solution was cooled to −38 °C under N_2. To the cold reaction mixture was added BF_3OEt_2 (1.3 mL, 9.9 mmol, 1.2 equiv) in a single portion. The reaction mixture was stirred at −38 to −33 °C for 30 min, and water (∼5 mL) was added. The resulting biphasic mixture was allowed to warm to rt and was poured into Et_2O/H_2O (1:1, 100 mL each), and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ (anhyd). Using a rotary evaporator at moderate pressure (∼30 Torr) with an ambient temperature water bath, most (∼90%) of the solvent and volatiles were removed (**13** is very volatile, and complete removal of the solvent invariably results in product loss). The residue was purified by silica gel column chromatography (0.5% ether in pentane), and the solvent was carefully removed first by rotary evaporation with an ambient temperature water bath and second by a *brief* exposure to a stream of dry N_2 to give **13** as a mobile colorless oil (880 mg, 70%). LRMS (EI): calcd for $C_{10}H_{16}O$ ([M^+]): 152.1, found 152.1; IR (thin film): 3053, 2960, 2918, 1260, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 0.98 (d, J = 6.5 Hz, 3H), 1.05−1.12 (m, 1H), 1.13−1.29 (m, 1H), 1.48 (dd, J = 1.1, 1.1 Hz, 3H), 1.60−1.70 (m, 2H), 1.75−1.85 (m, 1H), 1.88−1.98 (m, 1H), 2.23 (dd, J = 15.3, 7.5 Hz, 1H), 3.36 (dd, J = 10.6, 7.6 Hz, 1H), 3.77 (dd, J = 10.5, 4.0 Hz, 1H), 6.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 16.8, 20.3, 31.2, 33.7, 35.4, 39.3, 66.1, 113.4, 138.3.

Iridomyrmecin, *rel*-(4*S*,4a*R*,7*S*,7a*R*)-4,7-Dimethylhexahydrocyclopenta[*c*]pyran-3(1*H*)-one, 1, and Isoiridomyrmecin, *rel*-(4*R*,4a*R*,7*S*,7a*R*)-4,7-Dimethylhexahydrocyclopenta[*c*]pyran-3(1*H*)-one, 2. To a solution of **13** (130 mg, 0.85 mmol, 1 equiv) in THF (8 mL) was added diH_2O (2 mL), and the reaction mixture was cooled to 0 °C in an ice bath. $Hg(OAc)_2$ (408 mg, 1.2 mmol, 1.5 equiv) was added in a single portion affecting an immediate color change of the reaction mixture from colorless to bright yellow. The reaction mixture was stirred for 30 min at 0 °C and ambient temperature diH_2O (30 mL) was added. The reaction mixture was again cooled to 0 °C, and $NaBH_4$ (199 mg, 5.1 mmol, 6 equiv) was added portionwise over 90 s. The resulting mixture was stirred for an additional 5 min prior to the addition of dry ice (∼3 g). When the reaction mixture ceased bubbling, its pH was found to be ∼7 (by pH paper), and it was poured into a separatory funnel containing water (50 mL) and EtOAc (50 mL). The liquid mercury was removed, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the solvent was removed by rotary evaporation. The residue was purified by silica gel column chromatography (8% ether in hexanes) to give **14a** (58 mg, 40%) and **14b** (43 mg, 30%). To a solution of **14a** (13 mg, 0.08 mmol, 1 equiv) in DCM (5 mL) under N_2 were added powdered molecular sieves (4 Å, spatula tip) and NMO (anhyd, 9 mg, 0.08 mmol, 1 equiv). The resulting slurry was stirred for 5 min. To the reaction mixture was added TPAP (1.3 mg, 0.004 mmol, 5 mol %), and the resulting green slurry was stirred for 3 h and filtered over Celite, and the volatiles were removed by rotary evaporation. The residue was purified by silica gel column chromatography (0−80% ether in pentane) to give **1** as white needles (13 mg, quant, mp 57−58 °C (lit. 59.5−60.5 °C)[2p]). The identical oxidation protocol was employed for **14b** to provide **2** as white needles (quant, mp 59−61 °C (lit. 57.5−58.0 °C)[2r]). A tabulation of characterization data for **1** and **2** was previously reported.[2r,3]

***rel*-(3*S*,4*S*,4a*R*,7*S*,7a*R*)-4-Bromo-3-methoxy-4,7-dimethyloctahydrocyclopenta[*c*]pyran, 15a, and *rel*-(3*R*,4*R*,4a*R*,7*S*,7a*R*)-4-Bromo-3-methoxy-4,7-dimethyloctahydrocyclopenta[*c*]pyran, 15b.** To a solution of **13** (0.316 g, 2.08 mmol, 1 equiv) in 3:1 DME/MeOH (v/v, 12 mL) under N_2 at 0 °C was added a solution of NBS (0.313 g, 2.08 mmol, 1 equiv) in 3:1 DME/MeOH (v/v, 4 mL) over 40 min in the dark. The resulting solution was stirred for 1 h, diluted with Et_2O (20 mL) and H_2O (20 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ (anhyd), filtered, and concentrated by rotary evaporation. The components of the residue were isolated by silica gel column chromatography (1% Et_2O in hexanes) to give **15a** (0.280 g, 46%) and **15b** (0.195 g, 36%) as light-brown viscous oils. For **15a**: HRMS (ESI, TOF): calcd for $C_{11}H_{19}BrO_2$ ([M + Na]$^+$): 285.0466, found 285.0478; IR (thin film): 2948, 2923, 2865, 1454, 1383, 1257, 1098, 1073 cm^{-1}, ^{1}H NMR (C_6D_6, 300 MHz, ppm): 0.80 (d, J = 6.8 Hz, 3H), 0.95−1.10 (m, 1H), 1.60−1.77 (m, 2H). 1.79−1.95 (m, 2H), 2.03 (s, 3H), 2.00−2.15 (m, 1H), 2.44 (dd, J = 13.9, 8.7 Hz, 1H), 3.18 (dd, J = 11.3, 11.3 Hz, 1H), 3.43 (s, 3H), 3.65 (dd, J = 11.7, 5.85 Hz, 1H), 4.70 (s, 1H); ^{13}C NMR (C_6D_6, 75 MHz, ppm): 21.4, 27.3, 29.6, 31.8, 35.2, 45.8, 50.8, 56.4, 64.9, 68.3, 103.7. For **15b**: HRMS (ESI, TOF): calcd for $C_{11}H_{19}BrO_2$ ([M + Na]$^+$): 285.0466, found 285.0454; IR (thin film): 2945, 2918, 1448, 1403, 1380, 1258, 1100, 1055 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz, ppm): 0.58 (d, J = 7.0 Hz, 3H), 0.72−0.90 (m, 1H), 1.12−1.30 (m, 1H), 1.37−1.50 (m, 1H), 1.60−1.73 (m, 1H), 1.70 (s, 3H), 1.74−1.93 (m, 1H), 2.10−2.20 (m, 1H), 2.42−2.53 (m, 1H), 2.94 (s, 3H), 3.17−3.32 (m, 2H), 4.69 (s, 1H); ^{13}C NMR (C_6D_6, 75 MHz, ppm): 20.6, 26.4, 27.2, 31.9, 32.9, 42.3, 49.3, 54.0, 58.3, 66.6, 103.1.

***rel*-(3*S*,7*S*,7a*R*)-3-Methoxy-4,7-dimethyl-1,3,5,6,7,7a-hexahydrocyclopenta[*c*]pyran, 16.** To a solution of **15a** (64 mg, 0.24 mmol, 1 equiv) in THF (5 mL) under N_2 was added *t*-BuOK (138 mg, 1.2 mmol, 5 equiv). The reaction mixture was warmed to 50 °C and was stirred for 1 h. Analysis of the reaction mixture by TLC (SiO_2, 10% EtOAc in hexanes) revealed that some starting material remained, an additional aliquot of *t*-BuOK (20 mg, 0.18 mmol, 0.8 equiv) was added and the reaction mixture was stirred for an additional 100 min. The reaction mixture was diluted with ether and water (30 mL each), and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation. The residue was purified by silica gel column chromatography (0−100% ether in pentane) to give **16** as a pale-brown oil (29 mg, 67%). HRMS (ESI, TOF): calcd for $C_{11}H_{18}O_2$ ([M + Na]$^+$): 205.1204, found 205.1202; IR (ATR): 2953, 2926, 2868, 1457, 1376, 1356, 1259, 1197, 1155, 1078, 1043, 1012, 957, 869, 795, 684, 668, 643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 1.02 (d, J = 6.2 Hz, 3H), 1.22−1.45 (m, 2H), 1.55−1.59 (m, 3H), 1.84−1.93 (m, 1H), 2.00−2.13 (m, 1H), 2.15−2.41 (m, 2H), 3.29 (dd, J = 10.5, 9.9 Hz, 1H), 3.39 (s, 3H), 4.15 (dd, J = 10.5, 5.5 Hz, 1H), 4.87−4.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 13.8, 18.1, 27.5, 33.0, 38.3, 46.7, 53.9, 67.6, 100.6, 122.4, 143.0.

Teucriumlactone, *rel*-(4a*S*,7*S*,7a*R*)-7-Methyl-4-methyleneoctahydrocyclopenta[*c*]pyran-3-ol, 3. A solution of **15b** (136 mg, 0.52 mmol, 1 equiv) in THF (12 mL) was warmed to 50 °C in an oil bath under N_2 and *t*-BuOK (291 mg, 2.6 mmol, 5 equiv) was added. The resulting mixture was stirred at 50 °C for 2 h, allowed to cool to rt, and HCl (1 N, aq, 5 mL) was added. The resulting biphasic mixture was stirred at rt for 30 min, poured into 1 N NaOH (aq, 10 mL), and diluted with diH_2O (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the solvent was removed by rotary evaporation. The resulting

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residue (**17**, 73 mg, 84%) was dissolved in DCM (5 mL); 4 Å molecular sieves (powdered, spatula tip) and NMO (anhyd, 52 mg, 0.44 mmol, 1 equiv) were added, and the resulting slurry was stirred for 5 min before TPAP (8 mg, 0.022 mmol, 0.05 equiv) was added. The reaction mixture was stirred for 2 h, and TLC analysis (SiO_2, 25% EtOAc in hexanes) indicated that the reaction was not complete. Additional NMO (10 mg, 0.085 mmol, 0.16 equiv) and TPAP (1.6 mg, 0.005 mmol, 0.01 equiv) were added. The reaction mixture was stirred for an additional 45 min and filtered through a plug of Celite. The volatiles in the filtrate were removed by rotary evaporation and the resulting residue was purified by silica gel column chromatography (SiO_2, 0−100% ether in pentane) to give **3** as a viscous oil (25 mg, 32%). HRMS (ESI, TOF): calcd for $C_{10}H_{14}O_2$ ($[M + Na]^+$): 189.0891, found 189.0891; IR (thin film): 2957, 2865, 1734, 1625, 1466, 1403, 1378, 1303, 1261, 1153, 1111, 1081, 1027, 948, 805, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, ppm): 1.05 (d, J = 6.1 Hz, 3H), 1.10−1.30 (m, 1H), 1.34−1.49 (m, 1H), 1.78−1.98 (m, 3H), 2.05−2.17 (m, 1H), 3.12 (ddd, J = 9.3, 9.3, 9.3 Hz, 1H), 4.02 (dd, J = 11.4, 4.9 Hz, 1H), 4.16 (dd, J = 11.3, 3.9 Hz, 1H), 5.44 (s, 1H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 18.0, 32.9, 34.0, 36.0, 41.2, 44.8, 123.5, 139.7, 167.9. This synthetic route was repeated using (−)-citronellol as starting material to give (+)-teucrimulactone with $[\alpha]^{22}_D$ = +122 ($CHCl_3$, c = 0.35).

***rel*-(1*R*,3*R*,4a*S*,7*S*,7a*S*)-3-Methoxy-*N*,7-dimethyl-4-methylene-*N*-phenyloctahydrocyclopenta[*c*]pyran-1-amine, 19, *rel*-2-((1*S*,2*R*,3*S*)-3-Methyl-2-((methyl(phenyl)amino)methyl)cyclopentyl)prop-2-en-1-ol, 20, and *rel*-(1*R*,2*S*,5*S*)-2-Methyl-5-(3-oxoprop-1-en-2-yl)cyclopentanecarbaldehyde 21.** To a solution of **18b** (405 mg, 1.1 mmol, 1 equiv) in THF (50 mL) was added *t*-BuOK (740 mg, 6.6 mmol, 6 equiv) in one portion, and the reaction mixture was warmed to 50 °C and stirred under N_2 for 1 h. The reaction mixture was poured into ether (50 mL) and diH_2O (50 mL), shaken, and separated. The aqueous layer was extracted with ether (1 × 50 mL), and the combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the solvent was removed by rotary evaporation to give **19** as a viscous, pale-yellow oil (250 mg, 79%). Because of its instability on silica gel, **19** was not purified to homogeneity. However, the formation of **19** from **18b** is clean and efficient. To establish its identity, characterization of crude **19** is presented below in tabular form and in graphical form in the Supporting Information. A sample of the crude product (**19**, 50 mg, 0.17 mmol, 1 equiv) was dissolved in DCM (1 mL) and was cooled to −78 °C in a dry ice/isopropanol bath. To the cold solution was added DIBAL-H (0.5 M in toluene, 110 μL, 5.2 mmol, 3 equiv), and the reaction mixture was allowed to warm to 0 °C and stirred at this temperature for 2 h. Little evidence of reaction was apparent by TLC (SiO_2, 10% EtOAc in hexane), and additional DIBAL-H (0.5 M in toluene, 100 μL, 5.0 mmol, 2.9 equiv) was added. The reaction mixture was stirred for 1 h and allowed warm to rt. The reaction was quenched by the addition of EtOAc (1.2 mL) and Rochelle's salt (aqueous, satd, 130 mL). The resulting biphasic mixture was shaken, the organic layer was separated and dried over $MgSO_4$ (anhyd), and the volatiles were removed by rotary evaporation. The residue was purified by silica gel column chromatography (0−100% ether in hexanes) to give **20** (7 mg, 16%) and dolichodial (**21**, 2 mg, 7%). For **19**: HRMS (ESI, TOF): calcd for $C_{18}H_{25}NO_2$ ($[M + Na]^+$): 310.1783, found 310.1783; IR (thin film): 2952, 1599, 1500, 1447, 1342, 1309, 1253, 1092, 1056, 949, 907, 752 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz, ppm): 0.98 (d, J = 6.6 Hz, 3H), 1.08−1.2 (m, 1H), 1.83−2.00 (m, 3H), 2.10−2.28 (m, 2H), 2.78−2.89 (m, 1H), 2.91 (s, 3H), 3.28 (s, 3H), 5.05 (ddd, J = 1.4, 1.4, 1.4 Hz, 1H), 5.13 (d, J = 0.5 Hz, 1H), 5.24 (ddd, J = 0.96, 0.96, 0.96 Hz, 1H), 5.48 (d, J = 10.5 Hz, 1H), 6.90−7.00 (m, 1H), 7.10−7.40 (m, 3H); ^{13}C NMR (C_6D_6, 75 MHz, ppm): 21.1, 31.7, 32.7, 34.4, 36.4, 43.3, 49.7, 55.0, 83.7, 103.1, 112.9, 117.1 (2C), 119.7, 129.3 (2C), 145.3, 151.5. For **20**: HRMS (ESI, TOF): calcd for $C_{17}H_{25}NO$ ($[M + Na]^+$): 282.1834, found 282.1846; IR (thin film): 3310, 3094, 2952, 2867, 1600, 1505, 1034, 898, 748, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, ppm): 1.03 (d, J = 6.7 Hz, 3H), 1.10−1.22 (m, 1H), 1.63−2.14 (m, 5H), 2.67−2.78 (m, 2H), 2.82 (s, 3H), 2.89 (dd, J = 13.9, 6.6 Hz, 1H), 3.07 (dd, J = 13.9, 7.9 Hz, 1 H), 4.06 (s, 1H), 4.93 (s, 1H), 5.16 (d, J = 1.3 Hz, 1H), 6.72−6.86 (m, 3H), 7.26 (dd, J = 9.1, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 21.6, 30.1, 33.1 38.3, 40.3, 44.0, 46.9, 55.0, 67.6, 110.4, 115.0 (2C), 118.3, 129.0 (2C), 150.2, 150.7. Tabulation of characterization data for **21** was previously reported.[3]

***rel*-2-((1*S*,2*R*,3*S*)-2-(Hydroxymethyl)-3-methylcyclopentyl)-prop-2-en-1-ol, 24.** To a solution of **21** (290 mg, 1.7 mmol, 1 equiv) in methanol (30 mL) at 0 °C was added $NaBH_4$ (133 mg, 3.5 mmol, 2 equiv) in one portion. The reaction mixture was stirred at 0 °C for 40 min, and NH_4Cl (aq, satd, 10 mL) was added. The reaction mixture was allowed to warm to rt and was poured into ether (50 mL) and diH_2O (50 mL). The biphasic mixture was shaken and separated. The aqueous layer was extracted with ether (4 × 40 mL). The combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation. The residue was purified by column chromatography (SiO_2, 3% methanol in DCM) to give **24** (216 mg, 73%) as a thick colorless oil. A tabulation of characterization data for **24** was previously reported.[3]

***rel*-(4a*S*,7*S*,7a*R*)-7-Methyl-4-methyleneoctahydrocyclopenta[*c*]pyran-1-ol, 17.** To a solution of **24** (182 mg, 1.1 mmol, 1 equiv) in DCM (5 mL) was added Et_3N (376 μL, 2.8 mmol, 2.5 equiv), and the resulting solution was cooled to −78 °C under N_2. A stock solution of BzCl (100 μL/mL v/v) was prepared in DCM, and an aliquot of this stock solution (1.24 mL, 1.1 mmol, 1 equiv) was added to the cold reaction mixture dropwise over 2 min. The reaction mixture was stirred for 15 min at −78 °C and allowed to warm to −10 °C over 40 min. Analysis of the reaction mixture by TLC (SiO_2, 25% EtOAc in hexanes) suggested the presence of **25a−c** and sm. The reaction was quenched by the addition of NH_4Cl (aq, satd, 2 mL), and the resulting biphasic mixture was poured into NH_4Cl (30 mL) and EtOAc (30 mL) and shaken, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation. The residue was purified by column chromatography (SiO_2, 15−40% EtOAc in hexanes) to give the monobenzoate products, **25a** and **25b**, as an inseparable mixture (140 mg, 77% br s m), **25c** (36 mg, 13% br s m), and **24** (69 mg, recovered). The identity of **25a**/**25b** was corroborated by HRMS ((ESI, TOF): calcd for $C_{17}H_{22}O_2$ ($[M + Na]^+$): 297.1467, found 297.1476), and the relative proportion of **25a** to **25b** was determined by NMR. Although a number of well-resolved ^1H NMR signals are present (in $CDCl_3$) that reveal the ratio of the constitutional isomers in the mixture, the carbinol (RC**H**$_2$OR) protons were selected. For **25a** the signals for the two alcohol carbinol protons (RC**H**$_2$OH) resonate at 3.36 ppm and 3.52 ppm. For **25b** the signals for all four carbinol protons (RC**H**$_2$OH and RC**H**$_2$OBz) appear in the spectrum as a multiplet between 3.9 and 4.2 ppm (m, 4H). Using the integration values of these signals, **25a**:**25b** was determined to be 5:1. To a solution of **25a**/**25b** (**25a**/**25b** (1:5), 109 mg, 0.4 mmol, 1 equiv) in DCM (10 mL) under N_2 were added molecular sieves (4 Å, powdered, spatula tip), NMO (anhyd, 67 mg, 0.6 mmol, 1.5 equiv), and TPAP (6.6 mg, 0.02 mmol, 5 mol %). The reaction mixture was stirred for 5 h and filtered through Celite, and the volatiles were removed from the filtrate by rotary evaporation. The residue was dissolved in methanol (15 mL), and NaOH (30 mg, 0.75 mmol, 1.9 equiv) was added. The resulting solution was stirred for 50 min, and the volatiles were removed by rotary evaporation. The residue was dissolved in ether (30 mL) and poured into $NaHCO_3$ (aq, satd, 30 mL). The resulting biphasic mixture was shaken and separated. The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ (anhyd) and filtered, and the volatiles were removed by rotary evaporation. The residue was purified by silica gel column chromatography to give **17** (8.2 mg, 12%) and **26** (45 mg, 67%, C1 α/β, 3:20). For **25c**: HRMS (ESI, TOF): calcd for $C_{24}H_{26}O_4$ ($[M + Na]^+$): 401.1729, found 401.1749; IR (thin film): 3068, 2952, 2868, 1789, 1720, 1451, 1272, 1212, 1111, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, ppm): 1.05 (d, J = 6.5 Hz, 3H), 1.10−1.23 (m, 1H), 1.67−1.72 (m, 2H), 1.87−2.03 (m, 2H), 2.06−2.17 (m, 1H), 2.73 (dd, J = 17.2, 8.6 Hz, 1H), 4.04 (dd, J = 11.2, 7.2 Hz, 1H), 4.20 (dd, J = 11.2, 6.8 Hz, 1H), 4.77 (dd, J = 19.0, 13.6 Hz,

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2H), 5.00 (s, 1H), 5.19 (s, 1H), 7.28−7.67 (m, 6H), 7.90−8.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 21.9, 29.7, 33.2, 37.3, 44.2, 47.2, 66.2, 67.8, 112.7, 128.4 (2C), 128.9 (2C), 129.5 (2C), 130.3 (2C), 132.7, 132.8, 133.0, 134.5, 143.6, 166.2, 166.7. For **26**: HRMS (ESI, TOF): calcd for $C_{10}H_{16}O_2$ ([M + Na]$^+$): 191.1048, found 191.1047; IR (thin film): 3393, 3079, 2953, 2870, 1651, 1454, 1109, 1028, 898 cm^{-1}; ^{1}H NMR (major anomer, C_6D_6, 300 MHz, ppm): 1.04 (d, J = 6.8 Hz, 3H), 1.05−1.18 (m, 1H), 1.54−1.68 (m, 1H), 1.70−1.85 (m, 2H), 1.87−2.01 (m, 1H), 2.03−2.20 (m, 1H), 2.96 (dd, J = 13.7, 7.1 Hz, 1H), 3.43 (bs, 1H, O**H**), 4.05 (d, J = 12.7 Hz, 1H), 4.50 (d, J = 12.6 Hz, 1H), 4.83−4.89 (m, 2H), 4.94 (d, J = 4.0 Hz, 1H); ^{13}C NMR (major anomer, C_6D_6, 75 MHz, ppm): 20.5, 29.0, 32.5, 34.9, 41.8, 53.9, 65.2, 95.2, 108.9, 145.0.

Dolicholactone, *rel*-(4a*S*,7*S*,7a*R*)-7-Methyl-4-methylenehexahydrocyclopenta[*c*]pyran-1(3*H*)-one, 4. To a solution of **26** (20 mg, 0.12 mmol, 1 equiv) in DCM (10 mL) under N_2 were added molecular sieves (4 Å, powdered, spatula tip), NMO (anhyd, 15 mg, 0.12 mmol, 1 equiv), and TPAP (2.6 mg, 0.006 mmol, 5 mol %). The reaction mixture was stirred for 2 h and filtered through Celite. The volatiles of the filtrate were removed by rotary evaporation, and the residue was purified by silica gel column chromatography (0−100% ether in pentane) to give **4** (17 mg, 85%) as a clear, colorless oil. HRMS (ESI, TOF): calcd for $C_{10}H_{14}O_2$ ([M + Na]$^+$): 189.0891, found 189.0898; IR (thin film): 3084, 2957, 2870, 1733, 1376, 1155, 1047, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 1.13 (d, J = 6.6 Hz, 3H), 1.16−1.27 (m, 1H), 1.38−1.52 (m, 1H), 1.83−1.95 (m, 1H), 1.99−2.12 (m, 1H), 2.19−2.39 (m, 1H), 2.45 (dd, J = 10.6, 8.4 Hz, 1H), 2.98−3.12 (m, 1H), 4.53 (dd, J = 12.0, 0.8 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 1.1 Hz, 1H), 5.03 (d, J = 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): 19.9, 32.4, 34.6, 39.2, 42.0, 51.1, 70.9, 113.3, 142.2, 173.9. This synthetic route was repeated using (−)-citronellol as starting material to give (+)-dolicholactone with $[\alpha]^{22}_D$ = +44.5 ($CHCl_3$, c = 0.36).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all novel compounds and reference spectra for those previously reported. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*hofferberthj@kenyon.edu

Notes

The authors declare no competing financial interest.

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