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Application of Cp_2TiCl-Promoted Radical Cyclization: A Unified Strategy for the Syntheses of Iridoid Monoterpenes

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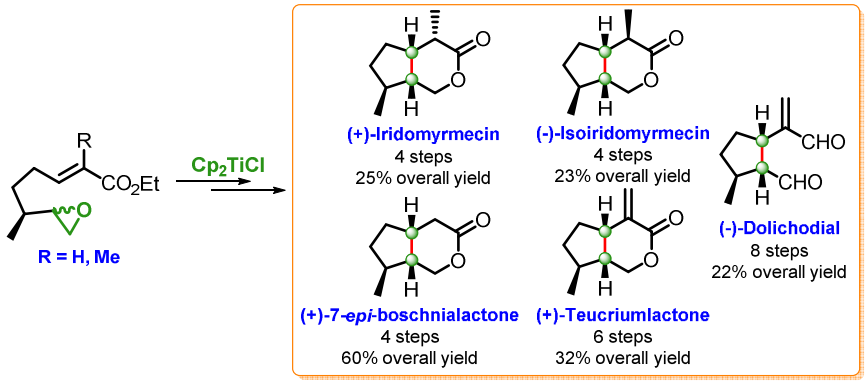


ABSTRACT:

An expedient approach toward the unified total syntheses of (+)-iridomyrmecin, (-)-isoiridomyrmecin, (+)-7-*epi*-boschnialactone, (+)-teucriumlactone and (-)-dolichodial in chirally pure forms starting from readily available (+)-*β*-citronellene is delineated combining step economy and simplicity. Highlights include a Ti(III)-mediated reductive epoxide opening-cyclization for the construction of the core cyclopenta[*c*]pyran skeleton of the iridoid lactones with complete diastereoselectivity for the newly created bridgehead stereogenic centers. Subsequent transformations facilitate a short access to (+)-teucriumlactone, (-)-dolichodial and formal access to potentially other iridoids.

INTRODUCTION

A large repertoire of structurally diverse cyclopentane monoterpenoids have been isolated from myriad plant families and various species of *Iridomyrmex*,[1] a genus of ants, in which they occur

as defensive secretions and is also known to exhibit highly excitative activity towards cats and other Felidae animals.[1a,2] In this perspective, iridoids are representative of a notable and highly recognized group of cyclopenta[*c*]pyran monoterpenoids with wide ranging biological activity profiles extensively chronicled in many traditional and folk medicine for centuries in the treatment of inflammation, anxiety, hypertension, cough and skin disorder.[3]

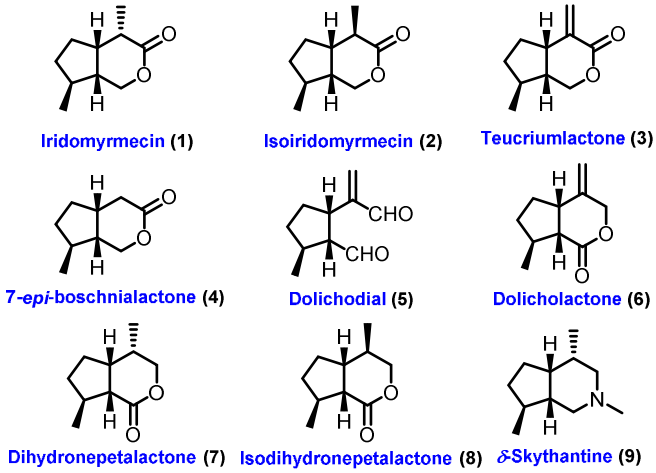


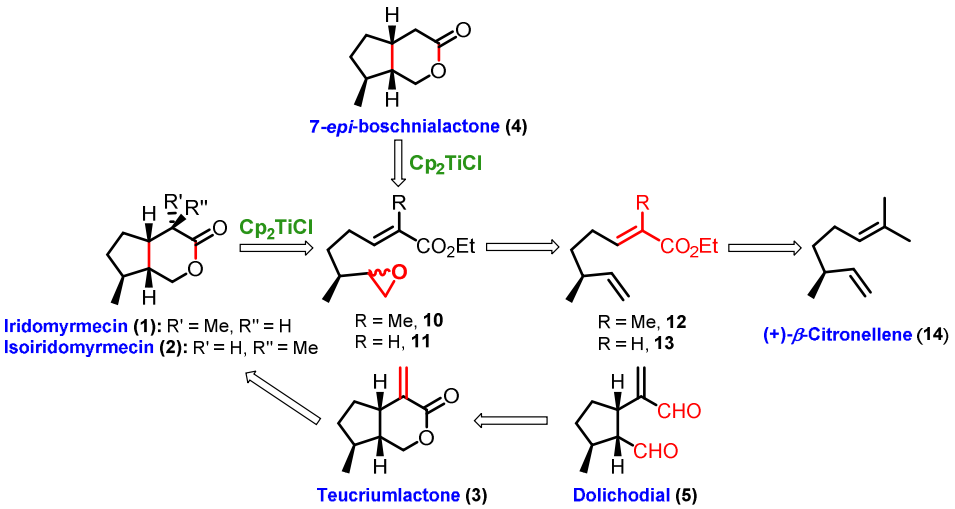
Figure 1. Structures of major naturally occurring iridoids.

Interestingly, in spite of their confined molecular framework, they hold contiguous stereogenic centers and are characterized by a cyclopentane ring *cis*-fused to a dihydropyran or δ-lactone.[4] Many approaches have been published over the years[5-11] to obtain this privileged scaffold owing to their therapeutic potential as drug candidates and thus the furtherance in the synthesis of iridoids (Figure 1) is still on urge. To mention few notable works, Hofferberth *et al.* accessed various iridoid monoterpenes in a divergent manner from a common citronellol-derived aminal intermediate obtained by enamine/enal cycloaddition reaction.[9a,b] Mulzer *et al.* described the free radical cyclization pathway of acyclic chirally C-2-substituted 1-hexenyl radicals to construct iridoid carbon framework.[5d] Syntheses of dihydronepetalactone and dolicholactone were achieved by Jahn *et al.* in 10 steps starting from (*S*)-citronellol.[11b]

Diversifying our previous work to access cyclopentano lactone mediated by $Cp_2Ti(III)Cl$ followed by concomitant intramolecular cyclization,[12] now we are aiming to detail a variable and concise approach to gain access to a handful of iridoid monoterpene lactones in an enantiomerically divergent manner starting from (+)-*β*-citronellene.

RESULTS AND DISCUSSION

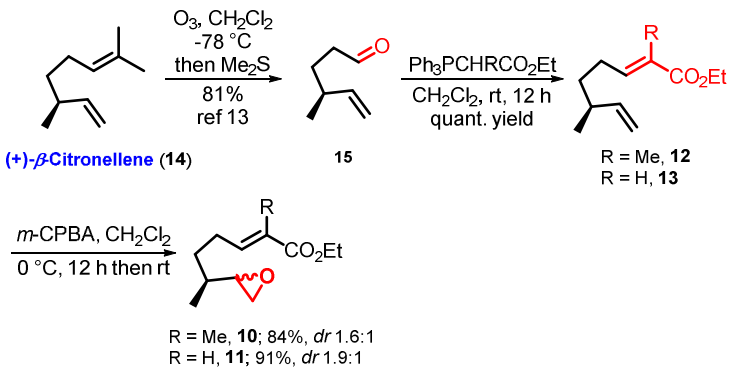
Taking advantage of the Cp_2TiCl-mediated reductive epoxide opening-cyclization, we envisioned a stereoselective divergent synthesis to assemble the core skeleton of iridoid lactones **1**-**5**. Retrosynthetically, we envisioned a direct route to iridomyrmecin (**1**), isoiridomyrmecin (**2**), 7-*epi*-boschnialactone (**4**) arising from the epoxides **10** and **11**, which have the complete carbon skeleton of the natural products, following a Ti(III)-mediated reductive epoxide cleavage-cyclization protocol (Scheme 1). Epoxides **10** and **11** in turn could be obtained from the *α,β*-unsaturated ester intermediates **12** and **13** originating from (+)-*β*-citronellene (**14**) *via* ozonolysis followed by Wittig olefination. The access to teucriumlactone (**3**) was envisaged to be derived



Scheme 1. Divergent retrosynthetic analysis.

from **1** and **2** through a selenoxide elimination (Scheme 1). Complete reduction of **1**, **2** and **3** would lead to the corresponding diols that could serve as pivotal intermediates for the synthesis of other iridoids (**5-8**) and iridoalkaloid **9** (Figure 1).

To evaluate the potentiality of the above analysis (Scheme 1), we embarked toward the synthesis of the requisite epoxides **10** and **11** bearing an *α,β*-unsaturated ester moiety. Given the background, the synthesis commenced with the conversion of (+)-*β*-citronellene (**14**) to the known aldehyde **15**[13] through ozonolysis, followed by Wittig olefination to deliver the dienyl esters **12** and **13**[14] in almost quantitative yield (Scheme 2). Selective epoxidation of the terminal alkene with *m*-CPBA at 0 °C successfully provided the desired epoxides **10** and **11**[14], a cyclization precursor for the key Ti(III)-mediated radical cyclization.

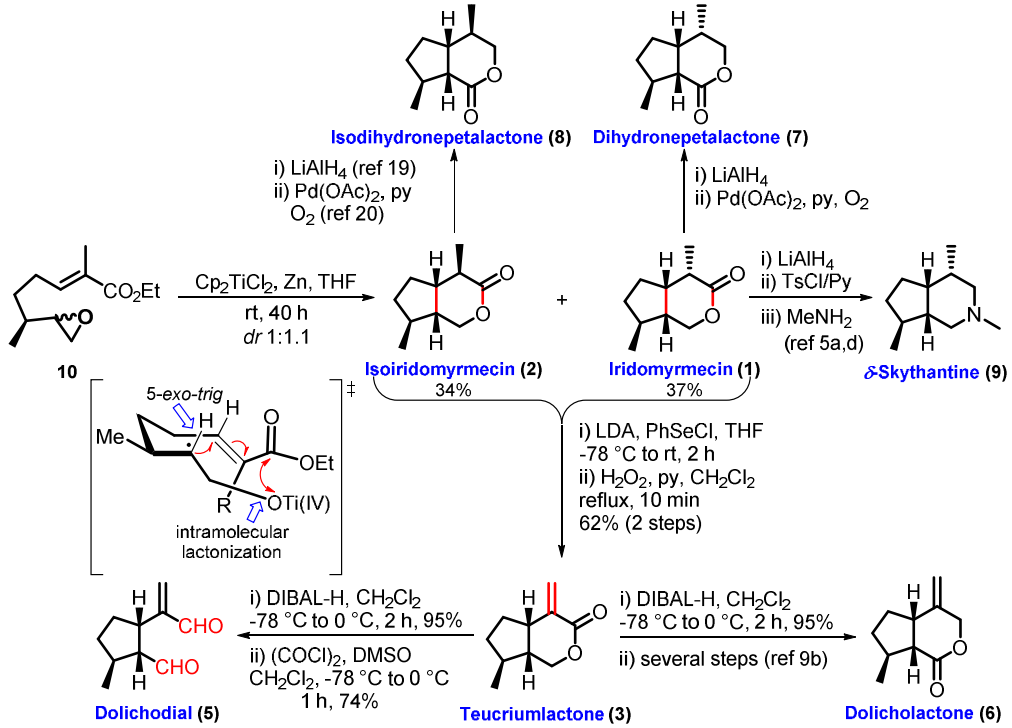


Scheme 2. Preparation of the epoxy esters **10** and **11**.

Implementation of our crucial step of reductive epoxide cleavage of epoxides **10** and **11** mediated by [Cp_2TiCl] (generated *in situ* from Cp_2TiCl_2 and activated Zn dust) followed by 5-*exo-trig* cyclization onto the *α,β*-unsaturated ester moiety successfully furnished the targeted iridolactones, iridomyrmecin (**1**) and isoiridomyrmecin (**2**) (as 1:1.1 epimeric mixture, Scheme 3) and 7-*epi*-boschnialactone (**4**) (Scheme 4) in 77% and 82% yields, respectively. The most

likely attainable transition state for the Ti(III)-mediated 5-*exo-trig* radical cyclization with subsequent intramolecular lactonization is shown in the scheme.

The epimeric mixture of **1** and **2**, in small quantity, was subjected to preparative thin layer chromatography to afford iridomyrmecin (**1**) and isoiridomyrmecin (**2**) in 37% and 34% isolated yields, respectively.[15] The data of both were identical with those in the literature.[5d-f,15a] The absolute values of the optical rotations of **1** ($[\alpha]_D^{20}$ +200.1 (c 0.28, CCl_4)) and **2** ($[\alpha]_D^{20}$ -55.48 (c 0.40, CCl_4)) were found almost identical with those of the natural compounds, $[\alpha]_D^{25.5}$ +210 (c 0.976, CCl_4) and $[\alpha]_D^{24}$ -59 (c 0.562, CCl_4), respectively, confirming their optical purity.[16] Obviously, the idea of the preparative thin layer chromatography was far from ideal to deal in large scale and thus, to address this concern, the epimeric mixture of **1** and **2** was subjected to DIBAL-H (1.0 equiv) reduction to provide the corresponding lactols, which were then resolved

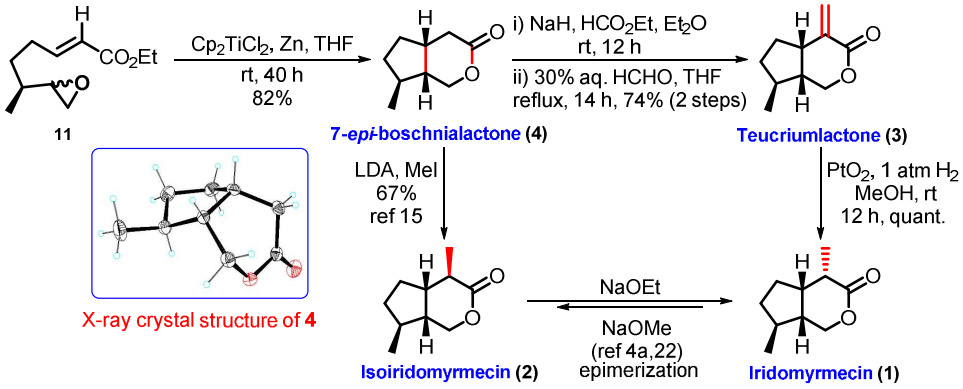


Scheme 3. Ti(III)-mediated radical cyclization and synthesis of various iridoids, **1-3** and **5-9**.

into two pairs of two diastereomers and were separated using 230-400 mesh silica gel column chromatography (3% EtOAc in hexane). The stereochemical output of the composition of the diastereomers in each pair was confirmed on oxidation with PCC separately to give iridomyrmecin (**1**) and isoiridomyrmecin (**2**) in almost quantitative yields.

Taking advantage of the epimeric mixture of **1** and **2**, synthesis of teucriumlactone (**3**) was accomplished utilizing a selenium based two-step protocol (Scheme 3).[17] Selenylation of the epimeric mixture was followed by selenoxide elimination using 30% aq. H_2O_2-py to secure the exocyclic double bond of teucriumlactone (**3**)[9b] along with a minute quantity of the double bond isomerized product (easily separable through silica gel column chromatography). The absolute value of the optical rotation of **3**, $[\alpha]_D^{20}$ +142.25 (c 0.65, benzene), was found almost identical with that of the natural compound, $[\alpha]_D^{20}$ +145.3 (c 4.5, benzene).[9c]

Reduction of the δ-lactone moiety in teucriumlactone (**3**) with DIBAL-H furnished an intermediate diol[9] which paved the way towards the synthesis of dolichodial (**5**) and dolicholactone (**6**). Whereas swinging the diol in the other way around following the selective protection-oxidation protocol described by Hofferberth *et al.*[9b] endowed the formal synthesis of dolicholactone (**6**), it was transformed into dolichodial (**5**) under Swern oxidation[18] condition in 74% yield (Scheme 3). The spectroscopic data of dolichodial (**5**) thus obtained (Scheme 3) was identical with the literature report,[9] indicating an accomplishment of the synthesis. Optical rotation, $[\alpha]_D^{24}$ -57.48 (c 0.27, $CHCl_3$), was identical with that of the reported compound, $[\alpha]_D^{24}$ -58.1 (c 0.36, $CHCl_3$).[9]



Scheme 4. Synthesis of 7-*epi*-boschnialactone (**4**) and subsequent conversion to **1-3**.

Iridomyrmecin (**1**) and isoiridomyrmecin (**2**) after separation were independently subjected to LAH reduction[19] to give the corresponding diols[5d,19] which could be directed towards the synthesis of dihydronepetalactone (**7**) and isodihydronepetalactone (**8**) on further treatment with catalytic amount of $Pd(OAc)_2$.[20] Also, the intermediate diol obtained after reduction of iridomyrmecin (**1**) leads the way to access iridoalkaloid *δ*-skythantine (**9**) as reported earlier (Scheme 3).[5a,d]

Next, the spectroscopic data of 7-*epi*-boschnialactone (**4**) obtained by Ti(III)-mediated reaction (Scheme 4) was found to be identical with the reported values,[5c] indicating an accomplishment of the synthesis. Stereochemical outcome was ascertained by optical rotation, $[\alpha]_D^{20}$ +92.66 (c 0.98, CCl_4), comparable with that of the reported compound, $[\alpha]_D^{25}$ +82 (c 0.5, CCl_4).[5c,21] Finally, the formation of the target molecule **4** in its desired stereochemistry was unambiguously confirmed by single crystal X-ray crystallographic analysis (Scheme 4, see the supporting information for details).

Successful execution of 7-*epi*-boschnialactone (**4**) was further utilized to formally access iridomyrmecin (**1**) (44% overall yield over 7 steps; formal synthesis), isoiridomyrmecin (**2**) (40%

overall yield over 5 steps; formal synthesis) and teucriumlactone (**3**) (44% overall yield over 6 steps; formal synthesis) outlined in Scheme 4. Methylation at the *α*-position of lactone **4** in a conventional way[15] selectively furnished isoiridomyrmecin (**2**, *dr* 7:1) which on epimerization would result in the formation of iridomyrmecin (**1**).[4a,22] On the other hand, introduction of the *α*-methylene functionality present in teucriumlactone (**3**) could be achieved in two simple steps following a modified route *via* α-fomylation of lactone **4** in 74% of yield (Scheme 4).[23] Highly stereoselective hydrogenation was achieved using PtO_2/H_2 instead of Pd-C/H_2[4a,24] (under Pd-C condition, we also realized the isomerization of the double bond) to install the third stereogenic center present in iridomyrmecin (**1**) which, in turn, on epimerization reverted back to isoiridomyrmecin (**2**) (Scheme 4).[22]

CONCLUSION

In conclusion, an efficient unified approach to a plethora of iridoid monoterpenes was developed in a divergent manner starting from (+)-*β*-citronellene. Cp_2TiCl-mediated reductive epoxide cleavage and radical cyclization demonstrate a well-amenable method to assemble the core skeleton of iridolactones *en route* to diverse iridoid monoterpenes in highly stereoselective manner. Synthesis of (+)-iridomyrmecin (**1**), (-)-isoiridomyrmecin (**2**), (+)-7-*epi*-boschnialactone (**4**) were achieved in 4 steps with 25%, 23% and 60% overall yields, respectively. Moreover, the potential utility of the route was nicely articulated by the total synthesis of (+)-teucriumlactone (**3**, in 6 steps) and (-)-dolichodial (**5**, in 8 steps) 32% and 22% overall yields, respectively. Even though not executed, the designed approach is also amenable for the synthesis of other iridoid natural products, such as **6-8** and the related monoterpene alkaloid **9**. Further exploration of this

strategy for the synthesis of highly functionalized iridoids/cyclopentanoid natural products are under investigation and will be reported in due course.

General Experimental Details:

All the reactions were carried out under inert atmosphere in oven-dried glassware using dry solvents, unless otherwise stated. All chemicals purchased from commercial suppliers were used as received unless otherwise stated. Reactions and chromatography fractions were monitored by Merck silica gel 60 F-254 glass TLC plates and visualized using UV light, 7% ethanolic phosphomolybdic acid-heat or 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Flash column chromatography was performed with 100-200 mesh silica gel and yields refer to chromatographically and spectroscopically pure compounds.

Instrumentation:

All NMR spectra were recorded in $CDCl_3$ on a 400 MHz instruments at 300 K and are calibrated to residual solvent peaks ($CHCl_3$ 7.26 ppm and 77.0 ppm). For ^{1}H-NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double of doublet, ddd = doublet of doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, dq = doublet of quartet, quint = quintet, sext = sextet, m = multiplet), coupling constants (Hz) and integration. Infrared (FT-IR) spectra were recorded on PerkinElmer Spectrum BX spectrophotometer and reported in ν_{max} in cm^{-1}. High resolution mass spectrometry (HRMS) was performed on Micromass Q-TOF Micro instrument. Optical rotations were measured on JASCO P-2000 polarimeter. Melting point is uncorrected and was determined in capillary tube on Buchi melting point M-560 apparatus. X-Ray crystallographic structure was collected on a Bruker Apex-II CCD diffractometer.

Experimental Procedures and Characterization Data:

Preparation of the aldehyde 15:

The required aldehyde **15** was synthesized by ozonolysis following the literature procedure[13] and the spectroscopic data were in full accord with those reported.

General procedure for HWE olefination:

To a solution of the aldehyde **15** (1.50 g, 13.38 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added phosphorane reagent (1.1 equiv) at 0 °C. The solution was stirred overnight at room temperature and then concentrated in *vacuo* to an oily, white residue. Flash column chromatography (silica

gel, 8% EtOAc in hexane) afforded the required *α,β*-unsaturated ester (quantitative yield) as a clear oil.

Data for 12: Yield 2.42 g, quantitative as colorless oil.

***R*$_f$ =** 0.7 (silica gel, 20% EtOAc in hexane); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.74 (td, J = 7.5, 1.0 Hz, 1H), 5.72-5.62 (m, 1H), 5.01-4.93 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.19-2.09 (m, 3H), 1.82 (br s, 3H), 1.46-1.39 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 168.3, 143.9, 142.2, 127.7, 113.2, 60.4, 37.5, 35.3, 26.4, 20.2, 14.3, 12.3; **IR ν_{max} (neat, cm^{-1})** 3149, 1708, 1487, 1367, 1240, 1147, 1049, 1002, 970, 914; **HRMS (ESI)** calcd for $C_{12}H_{20}O_2Na$ 219.1361 ($[M + Na]^+$), found 219.1360.

Data for 13: Prepared following the literature procedure[14] and the spectroscopic data were in full accord with those reported. Yield 2.61 g, quantitative as colorless oil.

General procedure for the preparation of the epoxides 10 and 11:

To a solution of the dienyl ester **12** or **13** (1.0 equiv) in CH_2Cl_2 (3.0 mL/mmol) was added *m*-CPBA (77%, 1.1 equiv) portion-wise at 0 °C. The reaction mixture was stirred overnight and warmed to room temperature. The reaction was then quenched with saturated aqueous Na_2SO_3 and extracted with ethyl acetate. After washing with saturated aqueous $NaHCO_3$ solution, water and brine, the solvent was dried over anhydrous Na_2SO_4. After concentration, purification by column chromatography (silica gel, 10% EtOAc in hexane) afforded the epoxides as colorless oils.

Data for 10: Scale of reaction 2.0 g, 10.19 mmol; yield 1.81 g, 84% (*dr* 1.6:1, *syn*:*anti*) as colorless oil.

***R*$_f$ =** 0.6 (silica gel, 20% EtOAc in hexane); **^{1}H NMR (400 MHz, CDCl$_3$)** (major isomer) δ 6.78-6.69 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.79-2.75 (m, 1H), 2.74-2.69 (m, 1H), 2.54 (dd, J = 4.9, 2.8, 1H), 2.32-2.18 (m, 3H), 1.85-1.81 (m, 3H), 1.74-1.32 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 168.1, 141.5, 128.1, 60.5, 56.6, 46.7, 35.7, 32.2, 26.2, 16.8, 14.3, 12.4; **IR ν_{max} (neat, cm^{-1})** 2964, 1708, 1543, 1390, 1265, 1178, 1126, 1026, 975, 956, 837; **HRMS (ESI)** calcd for $C_{12}H_{20}O_3Na$ 235.1310 ($[M + Na]^+$), found 235.1313.

Data for 11: Prepared following the literature procedure[14] and the spectroscopic data were in full accord with those reported in the literature. Scale of reaction 2.0 g, 10.98 mmol; yield 1.98 g,

91% (*dr* 1.9:1, *syn*:*anti*) as colorless oil. For ^{1}H NMR and ^{13}C NMR spectra, see supporting information.

General procedure for Cp_2TiCl-mediated radical cyclization

In a flame dried round bottom flask containing dry THF (30 mL/mmol) were added activated Zn (9.0 equiv) and Cp_2TiCl_2 (3.0 equiv) under inert atmosphere and stirred for 1 h at room temperature (color changed from deep red to green). Into this solution, the epoxide (1.0 equiv) in THF (15 mL/mmol) was cannulated at room temperature under N_2 atmosphere and continuously stirred for 40 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and stirred for an additional 15 min. The solvent was evaporated in *vacuo* and extracted with diethyl ether, washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* afforded the crude compounds of interest.

Preparation of iridomyrmecin (1) and isoiridomyrmecin (2):

General procedure outlined above for Cp_2TiCl-mediated radical cyclization was followed. Scale of reaction 1.0 g, 4.71 mmol; yield 610 mg (77%, epimeric mixture of **1** and **2**); (purification by flash column chromatography, 15% EtOAc in hexane) as viscous colorless oil.

Data for iridomyrmecin (1): Yield 14.5 mg (37%, white solid); (purification by preparative thin layer chromatography on 30 mg scale)[5d].

R_f = 0.61 (silica gel, 30% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.26 (dd, J = 11.7 and 3.0 Hz, 1H), 4.18 (d, J = 11.7 Hz, 1H), 2.78-2.54 (m, 2H), 1.91-1.74 (m, 4H), 1.15 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.11-0.95 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.2, 67.9, 45.5, 41.2, 37.9, 37.3, 34.1, 29.8, 18.3, 12.7; **IR ν_{max} (neat, cm^{-1})** 3300, 2926, 1746, 1643, 1455, 1380, 1280, 1158, 1109, 1021; **HRMS (ESI)** calcd for $C_{10}H_{16}O_2Na$ 191.1048 ($[M + Na]^+$), found 191.1049; optical rotation $[\alpha]_D^{20}$ +200.1 (c 0.28, CCl_4).

Data for isoiridomyrmecin (2): Yield 13.4 mg (34%, white solid); (purification by preparative thin layer chromatography on 30 mg scale)[5d,15].

R_f = 0.6 (silica gel, 30% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.34 (dd, J = 11.2, 6.1 Hz, 1H), 3.94 (t, J = 11.2 Hz, 1H), 2.35-2.24 (m, 1H), 2.15-2.08 (m, 1H), 2.06-1.99 (m, 2H), 1.91-1.85 (m, 1H), 1.69-1.60 (m, 1H), 1.31-1.24 (m, 2H), 1.18 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.4, 69.4, 45.2, 43.1, 39.0, 38.2, 35.6, 33.0, 19.1, 13.9; **IR ν_{max} (neat, cm^{-1})** 3301, 2926, 2361, 1746, 1647, 1455, 1380, 1248, 1169, 1018; **HRMS**

(ESI) calcd for $C_{10}H_{16}O_2Na$ 191.1048 ($[M + Na]^+$), found 191.1047; optical rotation $[\alpha]_D^{20}$ -55.48 (c 0.40, CCl_4).

Preparation of teucriumlactone (3):

A solution of the epimeric mixture of **1** and **2** (60 mg, 0.36 mmol, 1.0 equiv) in dry THF (1.5 mL) was slowly added over a 10-min period to a cooled (-78 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (0.12 mL, 0.82 mmol) and *n*-butyllithium (0.42 mL of 1.80 M, 0.76 mmol) in hexane] in dry tetrahydrofuran (1.5 mL). After 30 min, a solution of PhSeCl (75 mg, 0.39 mmol, 1.1 equiv) in dry tetrahydrofuran (1.0 mL) was added at -78 °C. After addition was complete the reaction mixture was warmed to room temperature over 2 h. The reaction was then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. After washing with water and brine, the solvent was dried over anhydrous Na_2SO_4. After concentration, the crude product was subjected to the next reaction without further purification.

The crude residue of the selenenylated lactone was dissolved in CH_2Cl_2 (6 mL) and pyridine (1 mL) followed by H_2O_2 (1 mL, 30% w/w) were added. The mixture was then heated under reflux for 10 min, diluted with Et_2O-water and extracted with Et_2O. After washing with 1 N HCl, water and brine, the solvent was dried over anhydrous Na_2SO_4. After filtration and concentration in *vacuo*, the resulting residue was purified by flash column chromatography (silica gel, 12% EtOAc in hexane) to afford **3** (37 mg, 62% yield) as colorless liquid.

$\boldsymbol{R_f}$ = 0.5 (silica gel, 30% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.06-6.00 (m, 1H), 5.49-5.43 (m, 1H), 4.17 (dd, J = 11.3, 4.0 Hz, 1H), 4.04 (dd, J = 11.4, 5.0 Hz, 1H), 3.18-3.09 (m, 1H), 2.15-2.06 (m, 1H), 1.98-1.78 (m, 3H), 1.48-1.36 (m, 1H), 1.29-1.15 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.4, 140.4, 124.6, 68.2, 45.3, 41.8, 36.8, 34.9, 33.9, 18.9; **IR ν_{max} (neat, cm^{-1})** 3300, 2952, 2923, 1737, 1596, 1459, 1371, 1307, 1260, 1218, 1153, 1118, 1020, 910; **HRMS (ESI)** calcd for $C_{10}H_{14}O_2Na$ 189.0891 ($[M + Na]^+$), found 189.0895; optical rotation $[\alpha]_D^{20}$ +142.25 (c 0.65, benzene).

DIBAL-H reduction of 3 to its corresponding diol compound:

To a solution of **3** (30 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was slowly added DIBAL-H (1.0 M solution in toluene, 0.6 mL) at -78 ºC. After being stirred for 2 h at 0 ºC, the reaction mixture was quenched with slow addition of methanol and saturated aqueous Rochelle salt at 0 ºC. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulfate, filtered,

and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (silica gel, 40% EtOAc in hexane) to furnish the corresponding diol (29 mg, 95%).

***R*$_f$ =** 0.52 (silica gel, 80% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.18-5.15 (m, 1H), 4.92 (s, 1H), 4.10 (s, 2H), 3.52-3.45 (m, 1H), 3.45-2.85 (m, 3H), 2.75-2.66 (m, 1H), 1.92-1.71 (m, 3H), 1.68-1.52 (m, 2H), 1.16-1.08 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.3, 111.2, 68.1, 63.1, 51.6, 44.0, 37.2, 33.7, 30.9, 20.8; **IR ν_{max} (neat, cm^{-1})** 3321, 2948, 2866, 1647, 1456, 1027, 897; **HRMS (ESI)** calcd for $C_{10}H_{18}O_2Na$ 193.1204 ($[M + Na]^+$), found 193.1210; optical rotation $[\alpha]_D^{24.5}$ -5.43 (c 0.6, CCl_4).

Preparation of Dolochodial (5):

To a solution of oxalyl chloride (38 µL, 0.44 mmol, 3.0 equiv) in dry CH_2Cl_2 (2 mL) at –78 °C, DMSO (68 µL, 0.95 mmol, 6.5 equiv) was added slowly, in drop wise manner, with stirring under nitrogen atmosphere. After 15 min stirring, previously prepared diol (25 mg, 0.147 mmol, 1.0 equiv) dissolved in dry CH_2Cl_2 (1 mL) was cannulated into the reaction mixture. After 15 min of stirring at –78 °C, Et_3N (0.2 mL, 1.47 mmol, 10.0 equiv) was added and stirred for another 30 min at –78 °C. Then the reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to furnish dolichodial **5** (18 mg, 74%).

***R*$_f$ =** 0.7 (silica gel, 20% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.54 (s, 1H), 9.42 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 1.1 Hz, 1H), 6.13 (s, 1H), 3.35-3.26 (m, 1H), 2.82-2.74 (m, 1H), 2.51-2.38 (m, 1H), 2.11-2.01 (m, 1H), 1.94-1.85 (m, 1H), 1.78-1.66 (m, 1H), 1.32-1.23 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.4, 194.6, 149.8, 134.9, 60.1, 39.9, 34.4, 33.5, 30.1, 20.5; **IR ν_{max} (neat, cm^{-1})** 2925, 2854, 1741, 1647, 1514, 1117, 1023; **HRMS (ESI)** calcd for $C_{10}H_{14}O_2Na$: 189.0891 ($[M + Na]^+$), found 189.0892; optical rotation $[\alpha]_D^{24}$ -57.48 (c 0.27, $CHCl_3$).

Preparation of 7-*epi*-boschnialactone (4):

General procedure outlined above for Cp_2TiCl-mediated radical cyclization was followed to prepare **4**. Scale of reaction 500 mg, 2.52 mmol; yield 318 mg as a white solid, 82% after purification by flash column chromatography (15% EtOAc in hexane). Crude solid was

crystallized in crystals suitable for X-ray crystallographic analysis from 5% EtOAc/hexane [m.p. = 57.6–58.9 ºC (lit.[15a] 57-58 ºC), see ORTEP presentation, **Figure S1**].

R_f **=** 0.4 (silica gel, 30% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.27 (dd, J = 11.5, 4.3 Hz, 1H), 4.10 (dd, J = 11.5, 4.7 Hz, 1H), 2.66-2.54 (m, 2H), 2.38-2.30 (m, 1H), 2.05-1.97 (m, 1H), 1.91-1.75 (m, 3H), 1.30-1.09 (m, 2H), 1.05 (d, J = 6.0 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.7, 68.9, 44.5, 37.4, 34.7 (2C), 34.5, 33.3, 18.6; **IR ν_{max} (neat, cm^{-1})** 2952, 1747, 1456, 1383, 1246, 1167, 1076, 1045, 971; **HRMS (ESI)** calcd for $C_9H_{14}O_2Na$: 177.0891 ([M + Na]$^+$), found 177.0892; optical rotation $[\alpha]_D^{20}$ +92.66 (c 0.98, CCl_4).

Formal synthesis of teucriumlactone (3) from 7-*epi*-boschnialactone (4):

NaH dispersion in mineral oil (60%, 260 mg, 6.5 mmol, 10 equiv), contained in a dry three-necked flask to which an addition funnel, condenser, and mechanical stirrer were attached, was washed three times with dry hexane and suspended in dry Et_2O (9 mL) under N_2 atmosphere. A mixture of **4** (100 mg, 0.65 mmol) and ethyl formate (5 mL, dried over K_2CO_3 and distilled from P_2O_5) was slowly added to the stirred suspension, immediately following the addition of absolute ethanol (2.4 mL), at a rate that maintained a gentle reflux of the reaction solvent. After stirring overnight, the reaction mixture was cooled to room temperature and the precipitated solids were rapidly filtered by suction and the resulting solid material was washed well with dry Et_2O and dried in *vacuo* to give the sodium salt of α-formyl lactone as a light tan powder.

To a solution of the sodium salt of α-formyl lactone in dry THF (10 mL) was added a solution of 30% aq. HCHO (5.2 mL) and the resulting solution was refluxed for 18 h. After cooling, the reaction mixture was quenched with 4 N HCl and extracted with Et_2O. The combined organic layers were washed with water, brine and dried over sodium sulfate, filtered, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (silica gel, 12% EtOAc in hexane) to furnish **3** (80 mg, 74%). The spectroscopic data were in full accord with the previous one as well as with the literature report.

Formal synthesis of iridomyrmecin (1) from teucriumlactone (3):

To a solution of **3** (20 mg, 0.12 mmol, 1.0 equiv) in MeOH (3 mL) was added PtO_2 (27 mg). The reaction vessel was then evacuated and refilled with H_2 (1 atmospheric pressure). The reaction mixture was stirred overnight under hydrogen atmosphere and then filtered through a short pad of Celite and further washed with MeOH. The combined organic extracts were concentrated in *vacuo* to give the crude product, which was purified by flash column chromatography (silica gel,

15% EtOAc in hexane) to furnish **3** (19 mg, quant.). The spectroscopic data were in full accord with the previous one as well as with the literature report.

Formal synthesis of isoiridomyrmecin (2) from 7-*epi*-boschnialactone (4):

A solution of **4** (30 mg, 0.19 mmol, 1.0 equiv) in dry THF (1.5 mL) was added dropwise using a syringe at -78 °C under argon to a solution of LDA [prepared from diisopropylamine (44 µL, 0.31 mmol) and *n*-butyllithium in hexane (0.17 mL of 1.7 M, 0.29 mmol)] in THF (1.5 mL) at -78 °C and the mixture was stirred at the same temperature for 30 min. Methyl iodide (35 µL, 0.57 mmol, 3.0 equiv) was added and then stirred for 30 min at -78 °C, then allowed to warm to room temperature over 2 h. The reaction was quenched by aqueous ammonium chloride and extracted with Et_2O. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to leave an oil, which was submitted to preparative thin layer chromatography to give **2** (21 mg, 67%)[15]. The spectroscopic data were in full accord with the previous one as well as with the literature report.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Copies of ^{1}H and ^{13}C NMR spectra of products and X-ray crystallographic data (ORTEP) of **4** (PDF).

CIF data for **4** (CIF).

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Notes

The authors declare no competing financial interest.

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