Stereocontrolled synthesis of (+)- and (−)-iridomyrmecin from citronellene enantiomers

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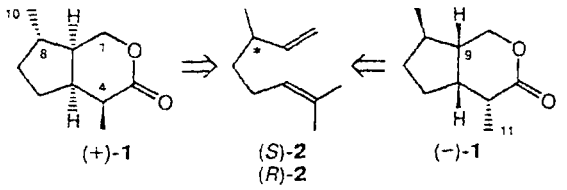
Natural (+)-iridomyrmecin and its unnatural enantiomer (−)-iridomyrmecin were synthesized by intramolecular [3+2] dipolar cycloaddition of silyl nitronates that had been generated from the nitro derivatives of (+)- and (−)-citronellenes, respectively.

Key words: iridolactone; (+)-iridomyrmecin; (−)-isoiridomyrmecin; (−)-iridomyrmecin; (+)-β-citronellene; (−)-β-citronellene; silyl nitronate, intramolecular [3+2] dipolar cycloaddition.

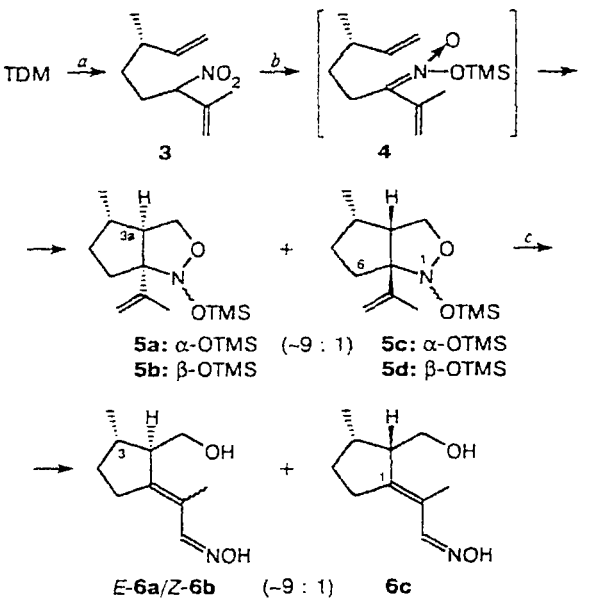
It has been shown previously[1,2] that the intramolecular [3+2] dipolar cycloaddition of silyl nitronate, generated *in situ* from the nitro derivative of (±)-linalool, opens up easy access to terpenoids incorporating an iridane carbon framework. In this communication we consider the application of this approach to the synthesis of a natural iridolactone, (+)-iridomyrmecin ((+)-**1**),[3] and its unnatural enantiomer, (−)-**1**, from (+)- and (−)-citronellenes ((*S*)-**2** and (*R*)-**2**, respectively).



In the former case, the industrially available mixture of products of the thermolysis of (+)-pinane ("technical dihydromyrcene," TDM) containing ~60% (*S*)-**2** of ~50% optical purity (*cf.* Ref. 4) was used as the source of the starting β-citronellene (*S*)-**2**. Treatment of TDM with sodium nitrite in AcOH (*cf.* Ref. 1) gave the previously unknown nitro derivative of citronellene **3** (Scheme 1) in ~90% yield (with respect to the content of compound (*S*)-**2** in TDM).

In a way similar to that previously reported for related compounds,[1,5] the transformation of nitroolefin **3** into silyl nitronate **4** after treatment with *N,O*-bis(trimethylsilyl)acetamide (BSA) is accompanied by the intramolecular cycloaddition of **4** resulting in a mixture of bicyclic adducts **5** in nearly quantitative yield. The diastereoselectivity of the process was found to be rather high: the ratio of the predominant products, (3a*R*,4*S*,6a*S*)-cyclopentanoisoxazolidines **5a/5b** (α-OTMS/β-OTMS ≈ 2 : 1), to the minor products,

Scheme 1



Reagents and conditions: *a*. $NaNO_2$/AcOH, 15—20 °C; *b*. BSA/NEt_3/MeCN/PhH, 85 °C (HMDS/NEt_3, 110 °C); *c*. KF · $2H_2O$/MeOH/THF, −40 → +20 °C.

(3a*S*,4*S*,6a*R*)-**5c/5d** (α-OTMS/β-OTMS ≈ 2 : 1), was ~9 : 1 (^{1}H NMR spectroscopy data).

The above result can be explained by considering the molecular model of nitronate **4**. In fact, due to steric factors, the pre-reaction orientation **B** of dipole **4** with respect to the double bond of the same molecule, required for the formation of the minor products **5c,d**, is believed to be less favorable than configuration **A** corresponding to isoxazolidines **5a,b**.

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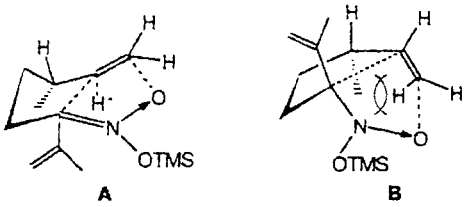


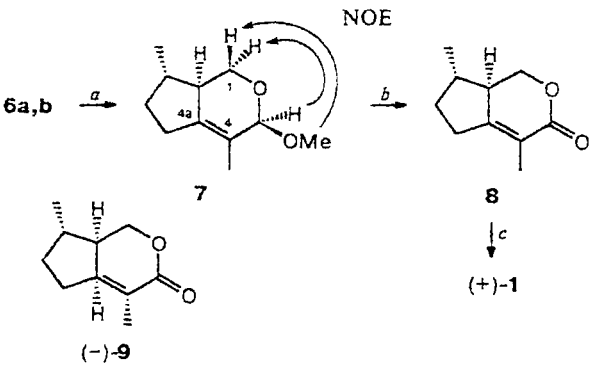
It is noteworthy that an almost identical mixture of bicyclic products **5** was obtained by heating nitro derivative **3** in the presence of hexamethyldisilazane (HMDS). This is apparently the first time this reagent has been used for the silylation of nitro compounds.

The structures of labile components of mixture **5** and its composition were determined from ^1H and ^{13}C NMR spectroscopic data and by comparing them to the spectroscopic characteristics obtained previously for related compounds.[1,5] In particular, the above ratios of compounds **5** were found by comparing the integral intensities of the signals reliably identified in the ^1H NMR spectra in the region of δ 3.2—4.2 from the protons of CH_2O groups of the main components **5a** and **5b** (see Experimental) and from those of the minor admixtures **5c** [δ: 3.90 (dd, 1 H, J = 3.2 and 8.4 Hz); 4.32 (dd, 1 H, $J_1 = J_2$ = 8.4 Hz)] and **5d** [δ: 3.24 (dd, 1 H, $J_1 = J_2$ = 8.0 Hz); 3.52 (dd, 1 H, J = 4.5 and 8.0 Hz)]. The subsequent chemical transformations of cyclopentanoisoxazolidines **5** also confirm their structure. For example, the previously discovered[1,5] transformation of type **5** isoxazolidines by treatment with $KF \cdot 2H_2O$ results in this case in a mixture of substituted cyclopentanes **6**. Their isomeric ratio, *trans*-(**6a**+**6b**)/*cis*-**6c** ≈ 9 : 1 (**6a**/**6b** ≈ 2 : 1), reflects the composition of the starting mixture **5**. The conjugated oximes **6a—c** were isolated quantitatively by means of HPLC and characterized by elemental analysis, mass spectrometric data, and ^1H NMR spectroscopy. An additional confirmation of the structure of conjugated oximes **6a** and **6b** (*cf.* Ref. 2) is that the same cyclic acetal **7** is formed when they are hydrolyzed (Scheme 2). The reagent $TiCl_3/HCl$ [6] was found to be more efficient for their hydrolysis than the previously used $Tl(NO_3)_3$.[2]

It should be noted that the preparative synthesis of acetal **7** can be performed more conveniently by directly hydrolyzing the mixture of oximes **6a—c** without separating it, followed by isolation of the target compound by flash chromatography on Al_2O_3.

Using the selected synthetic plan, acetal **7** was then oxidated with the Jones reagent to give lactone **8**, hydrogenation of which over platinum black in AcOH or in the presence of nickel boride afforded the target (+)-iridomyrmecin (+)-**1** (yield >40% with respect to the five stages described). When Pd/C was used as the catalyst, the process occurred less selectively and almost quantitatively gave a readily chromatographically separable mixture of (+)-**1** and its natural epimer (−)-isoiridomyrmecin (−)-**9** (see Ref. 7) in ~3 : 1 ratio. The conjugated reduction of lactone **8** in the presence of the

Scheme 2



Reagents and conditions: *a*. 10% solution of $TiCl_3$ in 13% HCl(aq.), MeOH, 20 °C; *b*. CrO_3, H_2SO_4(aq.), Me_2CO, 0 °C; *c*. H_2, Pt, AcOH, 20 °C, 1 bar (H_2, Ni-boride, EtOH, 100 °C, 95 bar).

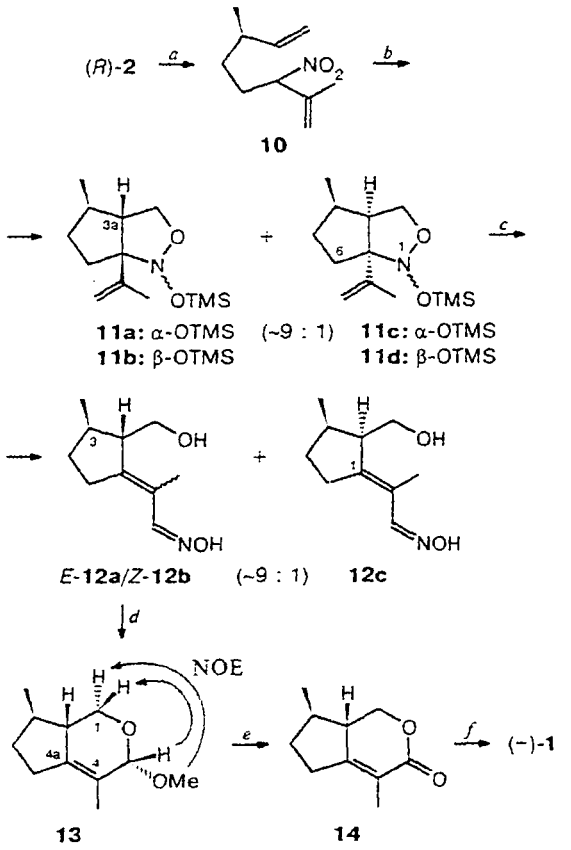
reagent $NiCl_2 \cdot 6H_2O/NaBH_4$ (*cf.* Ref. 2) for this purpose was found to be totally nonselective; this procedure resulted in the formation of nearly equal amounts of saturated lactones (+)-**1** and (−)-**9**.

The structures of the hitherto unknown compounds **7** and **8** were confirmed by the combined data from elemental analyses, ^1H NMR, IR spectroscopy, and mass spectrometry. In particular, the spatial position of the MeO group with respect to the six-membered cycle in acetal **7** was assigned on the basis of the nuclear Overhauser effects (NOE, see Scheme 2) observed in its differential spectrum. The physicochemical characteristics of iridoids (+)-**1** and (−)-**9** virtually coincided with those reported for these natural compounds.[3,7—9] The measured optical rotation angles for the former, $[\alpha]_D$ +103° (*c* 1.46, CH_2Cl_2) (data from Ref. 3: $[\alpha]_D^{17}$ +205° (*c* 0.223, CCl_4)), and for the latter, $[\alpha]_D$ −21.2° (*c* 0.24, CH_2Cl_2) (data from Ref. 7: $[\alpha]_D^{19}$ −64° (*c* 1.0, CCl_4)), correspond to an optical purity of ~50% of the compounds synthesized. Since the component (*S*)-**2** in TDM has comparable optical purity, the result obtained indicates a high degree of stereocontrol in all of the steps in the route **2** → **5** → **6** → **7** → **8** → (+)-**1**.

The synthesis of (−)-iridomyrmecin (−)-**1** (Ref. 10) from (−)-β-citronellene (Fluka, $[\alpha]_D$ −5.57°, *ee* 56%) through nitro compound **10**, cyclopentanoisoxazolidines **11**, oximes **12**, acetal **13**, and lactone **14** (Scheme 3) was carried out in exactly the same way and with a comparable overall yield.

The structures of compounds **10—14**, which were obtained for the first time, were confirmed in the same way as those described above for the related structures **3**, **5—8**. The spectroscopic characteristics of the lactone (−)-**1** synthesized by this procedure were almost identical to those published previously for it[10] and for its natural stereoisomer (+)-**1**.[9] The optical rotation angle $[\alpha]_D$ −124° (*c* 0.69, MeOH) corresponds with that of the starting diene (*R*)-**2**.

Scheme 3



Reagents and conditions: *a*. $NaNO_2$/AcOH, 15—20 °C; *b*. HMDS/NEt_3, 110 °C; *c*. $KF \cdot 2H_2O$/MeOH/THF, −40 → +20 °C; *d*. 10% solution of $TiCl_3$ in 13% HCl(aq.), MeOH, 20 °C; *e*. CrO_3, H_2SO_4(aq.), Me_2CO, 15 °C; *f*. H_2, Pt, AcOH, 20 °C, 1 bar.

Experimental

IR spectra of solutions in $CHCl_3$* were recorded on a Specord M-80 instrument. ^1H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on a Bruker AC-200 spectrometer (200.13 and 50.32 MHz, respectively). Chemical shifts in the ^1H and ^{13}C NMR spectra were measured with respect to the signals of the solvent (δ 7.27 (^1H) and 77.0 (^{13}C)). EI mass spectra were obtained on a Varian MAT 311A mass spectrometer at 70 eV. The R_f values are given for a fixed layer of Silufol grade SiO_2. The values of $[\alpha]_D$ were measured on a Jasco DIP-360 polarimeter. HPLC was performed on a column with Silasorb 600 (10 μ, 250×24 mm), using heptane—AcOEt (3 : 2, v/v) as the eluent (v = 7 mL min^{-1}) and a refractometer as the detector.

(3*RS*,6*S*)-2,6-Dimethyl-3-nitro-1,7-octadiene (3). $NaNO_2$ (110 g, 1.59 mol) was added in portions at 15 °C over a period of 3.5 h to a vigorously stirred solution of TDM (10 g) containing (*S*)-2 (6 g, 43.5 mmol) in acetic acid (330 mL). The reaction mixture was kept at 20 °C for 15 h, diluted with water (170 mL), and extracted with petroleum ether (4×50 mL). The extract was washed with water (3×20 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~11 g) was distilled *in vacuo* to collect the fraction with b.p. 62—70 °C (2 Torr). Repeated distillation gave 7.36 g (92%) of compound **3** as a viscous light yellow liquid with b.p. 71 °C (2 Torr), R_f 0.42 (heptane—ether, 95 : 5), n_D^{17} 1.4660. IR, ν/cm^{-1}: 920, 1000, 1280, 1375, 1450, 1540, 1640, 2920, 2960. MS, m/z: 137 $[M-46]^+$. ^1H NMR, δ: 1.02 (d, 3 H, MeC(6), J = 6 Hz); 1.83 (br.s, 3 H, MeC(2)); 1.20—2.30 (m, 5 H, CH_2, HC(6)); 4.85 (m, 1 H, HC—NO_2); 5.10—5.20 (m, 2 H, H_2C(1)); 5.00 (m, 2 H, H_2C(8)); 5.6 (m, 1 H, HC(7)). ^{13}C NMR, δ: 18.06 (MeC(6)); 20.15 (MeC(2)); 28.75 (C(4)); 32.37 (C(5)); 37.41 (C(6)); 92.52 (C(3)); 113.74 (C(1)); 118.56 (C(8)); 138.62 (C(2)); 142.97 (C(7)). Found (%): C, 65.37; H, 9.35; N, 7.71. $C_{10}H_{17}NO_2$. Calculated (%): C, 65.57; H, 9.29; N, 7.65.

(3*RS*,6*R*)-2,6-Dimethyl-3-nitro-1,7-octadiene (10). A procedure similar to the above, but starting with (+)-β-citronellene (*R*)-**2**, gave nitro compound **10** virtually identical (according to its R_f, b.p., and ^1H NMR spectrum) to the sample of compound **3** synthesized by us.

(1*S*,3a*R*,4*S*,6a*S*)-6a-Isopropenyl-4-methyl-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (5a) and (1*R*,3a*R*,4*S*,6a*S*)-6a-isopropenyl-4-methyl-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (5b). *A*. A solution of nitro compound **3** (0.62 g, 3.38 mol), BSA (1.38 g, 6.8 mmol), and Et_3N (0.17 g, 1.7 mmol) in benzene (4 mL) and MeCN (0.4 mL) was heated at 85 °C for 8 h (Ar) and then worked up with petroleum ether and water. The aqueous layer was separated and extracted with petroleum ether. Usual work up of the combined organic layer gave 0.74 g of a product, whose distillation *in vacuo* gave 0.5 g (68%) of a mixture **5a**/**5b** (~2 : 1) containing ~10% isomers **5c** and **5d** (^1H NMR spectroscopy data) as a colorless liquid with b.p. 43—44 °C (2 Torr), n_D^{20} 1.4674. ^1H NMR, δ: 0.17 (**5a**) and 0.20 (**5b**) (s, 9 H, Me—Si); 1.00 (**5b**) (d, 3 H, MeC(4), J = 6.2 Hz); 1.04 (**5a**) (d, 3 H, MeC(4), J = 6.4 Hz); 1.20—2.70 (**5a**,**b**) (m, 6 H, CH_2); 1.83 (br.s, 3 H, Me); 2.62 (**5a**,**b**) (m, 1 H, HC(3a)); 3.61 (**5a**) (dd, 1 H, β-HC(3), J = 7.9 and 2.9 Hz); 3.96 (**5b**) (dd, 1 H, β-HC(3), J_1 = J_2 = 7.9 Hz); 4.19 (**5b**) (dd, 1 H, α-HC(3), J = 9.1 and 7.9 Hz); 4.49 (**5a**) (dd, 1 H, α-HC(3), J = 8.7 and 7.9 Hz); 4.74, 4.83 (**5a**) (both br.s, 2 H, H_2C=C); 4.80, 5.02 (**5b**) (both br.s, 2 H, H_2C=C). ^{13}C NMR, δ: −0.42 (**5b**), −0.22 (**5a**) (Me—Si); 20.32 (**5a**), 20.59 (**5b**) (Me); 23.58, 27.58, 30.65, 32.93, 34.87, 38.01 (**5a**,**b**) (CH_2); 45.02 (**5a**), 48.96 (**5b**) (C(3a)); 73.82 (**5b**), 75.20 (**5a**) (C(3)); 91.85 (**5b**), 92.38 (**5a**) (C(6a)); 109.69 (**5a**), 110.18 (**5b**) (H_2C=C); 145.62 (**5a**), 147.02 (**5b**) (H_2C=C). High resolution MS, m/z: 255.16597 $[M]^+$; calculated for $C_{13}H_{25}NO_2Si$, m/z: 255.16531.

B. A solution of nitro compound **3** (1.0 g, 5.46 mmol) and Et_3N (1.1 g, 11 mmol) in HMDS (5 mL) was heated at 110 °C for 20 h (Ar). The reaction mixture was worked up as in the previous experiment to give 0.7 g (50%) of a mixture of isomers **5** almost identical to the sample described above (according to the ^1H NMR spectrum).

(1*R*,3a*S*,4*R*,6a*R*)-6a-Isopropenyl-4-methyl-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (11a) and (1*S*,3a*S*,4*R*,6a*R*)-6a-isopropenyl-4-methyl-1-trimethylsilyloxyperhydrocyclopenta[*c*]isoxazole (11b). Using a procedure similar to that described above, nitro compound **10** was transformed into a mixture of isoxazolidines **11**, whose spectral characteristics coincide with those given for the isomer mixture **5**.

* Unless specified otherwise.

2-[(2*R*,3*S*)-2-Hydroxymethyl-3-methyl-*E*-cyclopentylidene]propanaldoxime (6a), 2-[(2*R*,3*S*)-2-hydroxymethyl-3-methyl-*Z*-cyclopentylidene]propanaldoxime (6b), and 2-[(2*S*,3*S*)-2-hydroxymethyl-3-methyl-*E*-cyclopentylidene]propanaldoxime (6c). A solution of isomer mixture 5 (0.34 g, 1.3 mmol) in THF (2 mL) was added in one portion to a suspension of $KF \cdot 2H_2O$ (0.3 g, 3.19 mmol) in MeOH (2 mL) and THF (2 mL) vigorously stirred at −40 °C. The reaction mixture was warmed to 20 °C over a period of 40 min, stirred for 2 h at this temperature, and diluted with 40 mL of ether. The precipitate was filtered off and washed with ether on the filter, and the filtrate was concentrated *in vacuo*. The residue (~0.3 g) was chromatographed on SiO_2 (30 g). Gradient elution from petroleum ether to ethyl acetate (up to 40% of the latter) gave 0.18 g (76%) of a mixture of isomers **6** as a viscous light yellow oil, R_f 0.54 (petroleum ether—AcOEt, 1 : 1). Found (%): C, 65.85; H, 9.34. $C_{10}H_{17}NO_2$. Calculated (%): C, 65.54; H, 9.35. MS, *m/z*: 183 $[M]^+$, 146, 145, 144, 152. Individual components of the mixture were quantitatively isolated by means of HPLC.

^1H NMR, δ for oxime **6a**: 0.95 (d, 3 H, MeC(3), J = 6.9 Hz); 1.34 (m, 1 H, β-HC(4)); 1.82 (br.s, 3 H, MeC(2)); 1.92 (m, 1 H, α-HC(4)); 2.21 (m, 1 H, HC(3)); 2.56 (m, 2 H, $H_2C(5)$); 3.48 (dd, 1 H, HCO, J = 10.8 and 8.7 Hz); 3.59 (dd, 1 H, HCO, J = 10.8 and 4.7 Hz); 8.1 (s, 1 H, HCN). $[\alpha]_D^{25}$ +54.9° (*c* 0.71, CH_2Cl_2).

^1H NMR, δ for oxime **6b**: 0.92 (d, 3 H, MeC(3), J = 7.0 Hz); 1.40, 1.92 (both m, 2 H, HC(4)); 1.83 (br.s, 3 H, MeC=); 2.22 (m, 1 H, HC(3)); 2.45, 2.52 (both m, 2 H, HC(5)); 2.68 (m, 1 H, HC(2)); 3.48, 3.52 (both br.s, 2 H, HCO); 8.1 (br.s, 1 H, HCN). $[\alpha]_D^{25}$ +17.0° (*c* 0.82, CH_2Cl_2).

^1H NMR, δ for oxime **6c**: 1.12 (d, 3 H, MeC(3), J = 6.9 Hz); 1.52, 1.85 (both m, 2 H, HC(4)); 1.90 (br.s, 3 H, MeC=); 2.11 (m, 1 H, HC(3)); 2.45, 2.58 (both m, 2 H, HC(5)); 2.90 (m, 1 H, HC(2)); 3.57 (dd, 1 H, HCO, J = 11.2 and 5.6 Hz); 3.78 (dd, 1 H, HCO, J = 11.2 and 6.4 Hz); 8.2 (br.s, 1 H, CHN). $[\alpha]_D^{25}$ −78.4° (*c* 0.69, CH_2Cl_2).

2-[(2*S*,3*R*)-2-Hydroxymethyl-3-methyl-*E*-cyclopentylidene]propanaldoxime (12a), 2-[(2*S*,3*R*)-2-hydroxymethyl-3-methyl-*Z*-cyclopentylidene]propanaldoxime (12b), and 2-[(2*R*,3*R*)-2-hydroxymethyl-3-methyl-*E*-cyclopentylidene]propanaldoxime (12c). Similarly to the above procedure, the mixture of isoxazolidines **11** was transformed into oximes **12a** with $[\alpha]_D^{25}$ −55.2° (*c* 0.92, CH_2Cl_2), **12b** with $[\alpha]_D^{25}$ −20.3° (*c* 0.71, CH_2Cl_2), and **12c** with $[\alpha]_D^{25}$ +77.0° (*c* 1.32, CH_2Cl_2).

(3*R*,7*S*,7a*R*)-3-Methoxy-4,7-dimethyl-1,3,5,6,7,7a-hexahydrocyclopenta[*c*]pyran (7). A 10% solution of $TiCl_3$ in 13% HCl (11 mL) was added dropwise over a period of 5 min to a solution of isomer mixture **6** (1 g, 5.5 mmol) in MeOH (20 mL) and petroleum ether (20 mL) stirred at 20 °C (Ar). The reaction mixture was allowed to stand for 10 h and worked up with petroleum ether and water. The aqueous layer was separated, and the organic layer was washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue (~1 g) was chromatographed on Al_2O_3 (30 g). Elution with an AcOEt—petroleum ether mixture (1 : 5) gave ~0.9 g of a compound with R_f 0.82 (AcOEt—petroleum ether, 1 : 4), whose distillation afforded 0.85 g (84%) of compound 7 as a colorless liquid with b.p. 48 °C (2 Torr). IR (thin layer), ν/cm^{-1}: 950, 1050, 1080, 1090, 1190, 1250, 1350, 1380, 1392, 1464, 2800—3000. ^1H NMR, δ: 1.05 (d, 3 H, MeC(7), J = 6.2 Hz); 1.23, 1.40 (both m, 2 H, HC(6)); 1.61 (br.s, 3 H, MeC(4)); 1.85—2.0 (m, 2 H, HC(5)); 2.25—2.37 (m, 2 H, HC(7), HC(7a)); 3.32 (dd, 1 H, β-HCO, J = 10.7 and 0.5 Hz); 3.43 (s, 3 H, MeO); 3.83 (dd, 1 H, α-HCO, J = 10.7 and 5.5 Hz); 4.56 (br.s, 1 H, HC(3)). ^{13}C NMR, δ: 14.73 (MeC(7)); 18.50 (MeC(4)); 27.25 (C(6)); 33.34 (C(5)); 38.19 (C(7)); 47.19 (C(7a)); 55.31 (MeO); 62.43 (C(1)); 98.02 (C(3)); 122.58 (C(4)); 141.03 (C(4a)). MS, *m/z*: 152 $[M-30]^+$. Found (%): C, 72.53; H, 10.18. $C_{11}H_{18}O_2$. Calculated (%): C, 72.53; H, 9.89. $[\alpha]_D^{25}$ −14.7° (*c* 0.33, CH_2Cl_2).

(3*S*,7*R*,7a*S*)-3-Methoxy-4,7-dimethyl-1,3,5,6,7,7a-hexahydrocyclopenta[*c*]pyran (13). Similarly to the above procedure, the mixture of oximes **12** was transformed into acetal **13** with b.p. 48 °C (2 Torr) and $[\alpha]_D^{25}$ −26.9° (*c* 0.33, CH_2Cl_2). Its ^1H and ^{13}C NMR spectra virtually coincide with those reported for compound 7.

(7*S*,7a*R*)-4,7-Dimethyl-5,6,7,7a-tetrahydrocyclopenta[*c*]-pyran-3(1*H*)-one (8). A solution of acetal 7 (0.85 g, 4.57 mmol) in acetone (30 mL) vigorously stirred at 0 °C was titrated with the Jones reagent prepared from CrO_3 (1.32 g, 15.7 mmol), concentrated H_2SO_4 (1.15 mL), and H_2O (4 mL) until stable yellow coloring was obtained (~2.4 mL). The reaction mixture was diluted with water (50 mL) and extracted with ether (3×25 mL). The combined extracts were washed with saturated $NaHCO_3$ and water (10 mL of each), dried with $MgSO_4$, and concentrated *in vacuo*. The residue (0.73 g) was chromatographed on SiO_2. Gradient elution from up to 20% of AcOEt in petroleum ether gave 0.68 g (80%) of compound **8** as a colorless liquid with b.p. 120 °C (1 Torr), R_f 0.43 (petroleum ether—AcOEt, 1 : 1). IR (thin layer), ν/cm^{-1}: 770, 1030, 1081, 1125, 1145, 1170, 1310, 1400, 1460, 1720, 2800, 3000. ^1H NMR, δ: 1.03 (d, 3 H, MeC(7), J = 9.3 Hz); 1.36, 1.52 (both m, 2 H, HC(6)); 1.69 (br.s, 3 H, MeC(4)); 2.02 (m, 1 H, HC(7)); 2.2—2.5 (m, 3 H, HC(5), HC(7a)); 3.81 (dd, 1 H, β-HCO, J = 12.6 and 10.2 Hz); 4.35 (dd, 1 H, α-HCO, J = 10.2 and 5.9 Hz). ^{13}C NMR, δ: 12.5 (MeC(7)); 17.8 (MeC(4)); 28.7 (C(6)); 33.6 (C(5)); 38.2 (C(7)); 46.5 (C(7a)); 70.1 (C(1)); 118.7 (C(4)); 161.3 (C(4a)); 165.2 (C(3)). MS, *m/z*: 166 $[M]^+$. Found (%): C, 72.38; H, 8.59. $C_{10}H_{14}O_2$. Calculated (%): C, 72.29; H, 8.43. $[\alpha]_D^{25}$ +58.2° (*c* 0.33, CH_2Cl_2).

(7*R*,7a*S*)-4,7-Dimethyl-5,6,7,7a-tetrahydrocyclopenta[*c*]-pyran-3(1*H*)-one (14). Similarly to the above procedure, acetal **13** was transformed into lactone **14** with b.p. 120—121 °C (1 Torr) and $[\alpha]_D^{25}$ −93.4° (*c* 0.33, CH_2Cl_2). Its ^1H and ^{13}C NMR spectra virtually coincide with those reported for compound **8**.

(+)-Iridomyrmecin ((+)-1). *A.* PtO_2 (20 mg) was added to a solution of lactone **8** (0.4 g, 2.4 mmol) in ethyl acetate (5 mL) and acetic acid (0.5 mL). The reaction mixture was stirred at 20 °C for 12 h under hydrogen, then the catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residue was dissolved in ether (10 mL). The ethereal extract was washed with saturated $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated *in vacuo* to give 0.37 g (92%) of enantiomer (+)-**1** as a viscous colorless oil, R_f 0.47 (petroleum ether—AcOEt, 1 : 1), which crystallizes from pentane when cooled (−15 to −10 °C) as colorless prisms with m.p. 59.5—60.5 °C (Ref. 3: m.p. 61—62 °C), $[\alpha]_D^{25}$ +103° (*c* 1.46, CH_2Cl_2). ^1H NMR, δ: 1.05 (d, 3 H, Me(10), J = 5.6 Hz); 1.13 (d, 3 H, Me(11), J = 6.6 Hz); 1.0—1.2, 1.7—1.9 (both m, 6 H, CH, CH_2); 2.5—2.75 (m, 2 H, HC(5), HC(9)); 4.16 (d, 1 H, α-HC(1), J = 11.7 Hz); 4.27 (dd, 1 H, β-HC(1), J = 11.7 and 3.0 Hz). ^{13}C NMR, δ: 16.16 (Me(10)); 17.29 (Me(11)); 32.13 (C(6)); 36.19 (C(7)); 39.11 (C(8)); 39.70 (C(4)); 42.71 (C(9)); 46.74 (C(5)); 67.78 (C(1)); 170.3 (C(3)).

B. A solution of $NaBH_4$ (68.4 mg, 1.8 mmol) in water (2 mL) was added in two portions to a solution of $NiCl_2 \cdot 6H_2O$ (143 mg, 0.6 mmol) in water (4 mL). The resulting suspension was stirred for 5 min and then decanted, and a solution of

lactone **8** (0.1 g, 0.6 mmol) in ethanol (2 mL) was added to the precipitate. The reaction mixture was stirred for 4 h at 90—95 °C under hydrogen (95 bar) and then filtered. The filtrate was concentrated *in vacuo* to give 110 mg (77%) of a mixture of compounds (+)-**1** and **9** (95 : 5, ^{1}H NMR spectroscopy data).

(−)-Iridomyrmecin ((−)-1). Similarly to the above procedure (method *A*), compound **14** was transformed into lactone (−)-**1** with m.p. 59.5—60.5 °C (Ref. 10: m.p. 59—60 °C) and $[\alpha]_D^{25}$ −124.4° (*c* 0.69, MeOH). Its ^{1}H and ^{13}C NMR spectra virtually coincide with those listed above for stereomer (+)-**1**.

(−)-Isoiridomyrmecin (9). *A.* $NiCl_2 \cdot 6H_2O$ (238 mg, 1 mmol) was added at 0 °C (Ar) to a vigorously stirred solution of lactone **8** (0.34 g, 2.1 mmol) in MeOH (25 mL), and then $NaBH_4$ (0.55 g, 14.5 mmol) was added in portions over a period of 10 min. The reaction mixture was stirred at 0 °C for 1 h and at 20 °C for 3 h, treated with water (50 mL), neutralized with 50% H_2SO_4, and extracted with ether (50 mL). The extract was washed with water (3×20 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give 0.21 g (62%) of a mixture of compounds (+)-**1** and **9** (~1 : 1, ^{1}H NMR spectroscopy data) as a colorless oil, which was chromatographed on 100 g of SiO_2. Elution with a petroleum ether—AcOEt mixture (3 : 1) gave 90 mg (26%) of enantiomer (+)-**1** and 105 mg (31%) of compound **9**.

Lactone **9** was obtained as colorless crystals with m.p. 56—57 °C (pentane) (Ref. 7: m.p. 58—59 °C), R_f 0.43 (petroleum ether—AcOEt, 1 : 1) $[\alpha]_D^{25}$ −21.2° (*c* 0.24, CH_2Cl_2). ^{1}H NMR, δ: 0.92 (d, 3 H, Me(10), J = 5.6 Hz); 1.22 (d, 3 H, Me(11), J = 6.6 Hz); 1.0—1.4, 1.7—2.2 (both m, 7 H, CH, CH_2); 2.25—2.40 (m, 1 H, HC(9)); 3.85 (dd, 1 H, α-HC(1), J = 12.0 and 10.5 Hz); 4.40 (dd, 1 H, β-HC(1), J = 10.5 and 7 Hz). ^{13}C NMR, δ: 13.82 (Me(10)); 19.03 (Me(11)); 32.97 (C(6)); 35.56 (C(7)); 38.13 (C(8)); 38.93 (C(4)); 43.02 (C(9)); 45.15 (C(5)); 69.31 (C(1)); 177.23 (C(3)).

B. 5% Pd/C (15 mg) was added to a solution of lactone **8** (0.2 g, 1.2 mmol) in ethyl acetate (10 mL). The reaction mixture was stirred at 20 °C for 2 h under hydrogen. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give 0.18 g (90%) of a mixture of compounds (+)-**1** and **9** (~3 : 1, ^{1}H NMR spectroscopy data).

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