Syntheses of Several Cyclopentano-Monoterpene Lactones Using 1,3-Dioxin Vinylogous Ester

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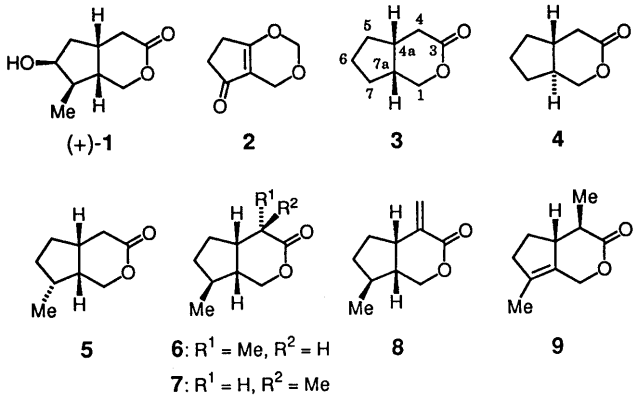
Received July 21, 1994; accepted August 24, 1994

Formal syntheses of (±)-boschnialactone (5) and three cyclopentano-monoterpene lactones [*i.e.*, (±)-iridomyrmecin (6), (±)-isoiridomyrmecin (7), and (±)-allodolicholactone (8)] have been accomplished in the form of the syntheses of 2-(methoxymethyl)-3-methyl-2-cyclopenten-1-one (11) and (±)-(4aα,7α,7aα)-hexahydro-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (19), respectively, starting from 6,7-dihydrocyclopenta-1,3-dioxin-5(4*H*)-one (2). A synthesis of (±)-isodehydroiridomyrmecin (9) has also been achieved through a route including direct substitution of the hydroxy group of 2-(*tert*-butyldimethylsilyloxymethyl)-3-methyl-2-cyclopenten-1-ol (22) with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (23) as a key step.

Keywords cyclopentano-monoterpene lactone; 1,3-dioxin vinylogous ester; carboxyolefination; isodehydroiridomyrmecin; lithium perchlorate; silyl ketene acetal

Over 30 cyclopentano-monoterpene lactones have been found as natural constituents in a large number of plant families and in various species of *Iridomyrmex*.[1] It is also well-known that some of these lactones show highly excitative activity toward cats and other *Felidae* animals, and are used by ants as agents of defense against preying insects.[2] Because of such characteristic activities as well as the presence of the contiguous stereogenic centers on their carbon skeletons, these compounds have attracted considerable attention as synthetic targets. In 1985, Murai and Tagawa reported the isolation of abelialactone, a cyclopentano-monoterpene lactone, from *Abelia grandiflora* (Caprifoliaceae)[1c] and proposed the structure (+)-**1** (absolute stereochemistry shown) for it as a result of X-ray analysis[1c] and its chemical correlation with loganin.[1i] Thereafter two other research groups reported the isolations of two lactones, named Aglykon A1 (no chiroptical data presented) and isoboonein, from *Cephaelis ipecacuanha* (Rubiaceae)[1d] and from *Rauwolfia grandiflora* (Apocynaceae),[1h] respectively. The new lactones seem to be identical and to have the same structure as (+)-**1**, but their identity has been inconclusive, awaiting an unambiguous establishment by chemical synthesis. In designing a synthetic route to **1**, the 1,3-dioxin vinylogous ester **2**[3] seemed most attractive as a starting material because of the diversity of its chemical reactivity, which includes reductive and alkylative 1,3-carbonyl transpositions and regioselective alkylations and hydroxylations at the α′-position to the carbonyl group.[3,4] In preparatory work, we have studied the stereoselective syntheses of *cis*-hexahydrocyclopenta[*c*]pyran-3(1*H*)-one (**3**), one of the parent frameworks common to cyclopentano-monoterpene lactones, and its *trans*-isomer (**4**) starting from 2-(hydroxymethyl)cyclopentanone and utilizing the "carboxyolefination/lactonization" technology.[5] In the present study, the applicability of this technology to the synthesis of **1** was tested in the syntheses of several cyclopentano-monoterpene lactones possessing a methyl group at the 7-position, such as (±)-boschnialactone (**5**),[6] (±)-iridomyrmecin (**6**),[7,8] (±)-isoiridomyrmecin (**7**),[8,9] (±)-allodolicholactone (**8**),[10] and (±)-isodehydroiridomyrmecin (**9**).[11]



Methylative 1,3-carbonyl transposition of **2** was effected by addition of methyl lithium in tetrahydrofuran (THF) at −78 °C followed by aqueous HCl treatment, giving the cyclopentenone **10** in 97% yield. The hydroxy group in **10** was then methylated[12] with methyl iodide and Ag_2O to afford the methyl ether **11**, an intermediate for the synthesis of (±)-boschnialactone (**5**)[6] described by Guilard and co-workers,[6j,k] in 94% yield.

Protection of **10** as the corresponding *tert*-butyldimethylsilyl ether provided **12** (98% yield), which was hydrogenated over Pd–C in EtOH to give a 54 : 46 mixture of the *cis*- and *trans*-isomers (**13** and **14**) in 97% yield. Alteration of the solvent from EtOH to cyclohexane slightly raised the ratio of the *cis*-isomer (**13**). A similar hydrogenation of **12** employing Adams catalyst instead of Pd–C furnished predominantly the *trans*-isomer (**14**). These results are listed in Table I. The structures of the *cis*- and *trans*-isomers (**13** and **14**) were assigned on the basis of the following NMR spectral and chemical evidence. (i) When the C(3)-methyl signal in **13** was irradiated, a 3% nuclear Overhauser effect (NOE) on the C(2)-methylene signal was observed due to their *cis* relationship (Chart 1). On the other hand, no NOE was observed for the corresponding signals of **14**. (ii) The C(3)-methyl carbon (δ 14.8) of **13** resonated at higher field than the corresponding carbon (δ 19.5) of **14** due to a

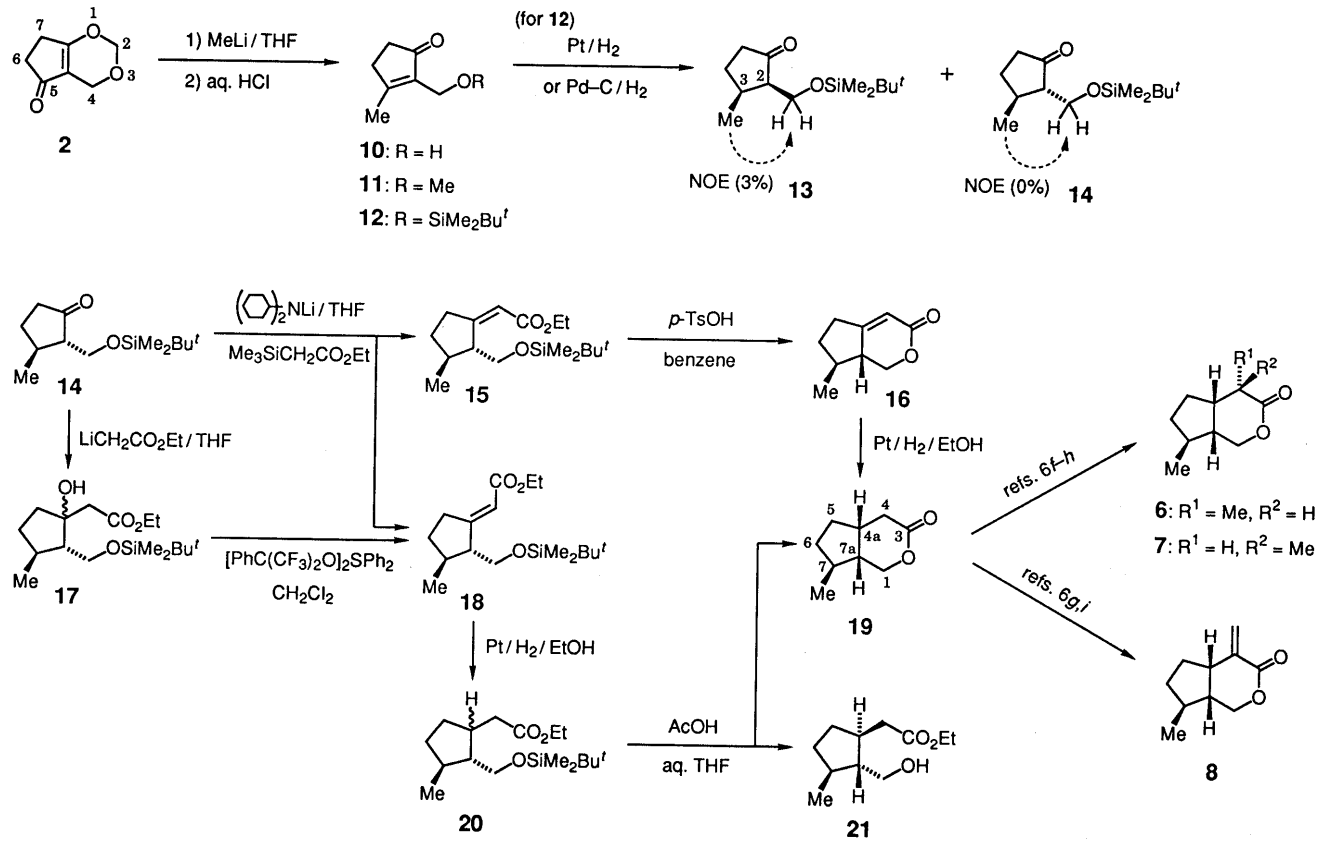


Chart 1

Table I. Catalytic Hydrogenation of the Cyclopentenone **12**

Entry	Reaction conditions[a]			Products (**13** and **14**)	
	Catalyst	Solvent	Time (h)	Yield (%)	Isomeric ratio[b] (**13**:**14**)
1	Pd–C	EtOH	1	97	54:46
2	Pd–C	Cyclohexane	1	79	62:38
3	Pt	EtOH	0.5	95	13:87
4	Pt	MeOH	1	97	9:91
5	Pt	Cyclohexane–AcOEt[c]	2	79	16:84

a) All reactions were carried out at atmospheric pressure and room temperature. *b*) Determined on the basis of ^{1}H-NMR spectral analysis. *c*) 1 : 1, v/v.

steric effect.[13] (iii) Base-catalyzed isomerization of the mixture (**13** : **14** = 54 : 46) with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene at 50 °C for 2 h provided a mixture (**13** : **14** = 7 : 93) enriched with the *trans*-isomer (**14**) in 79% yield. Thus, in the case of entry 3 in Table I, the desired *trans*-isomer (**14**) was obtained in 72% yield after separation of the mixture into its components by flash chromatography.[14]

With the *trans*-cyclopentanone **14** in hand, we set out to explore its carboxyolefination reaction. On the basis of the previous pilot experiment,[5] the Peterson olefination reaction[15] (lithium dicyclohexylamide, $Me_3SiCH_2CO_2Et$, THF, −78 °C, 7 h) of **14** was first tried, providing the (*Z*)-α,β-unsaturated ester **15** and its (*E*)-isomer (**18**) in 27% and 8% yields, respectively. The assignments of geometry in both isomers were based on the fact that the C(2)-proton (δ 3.00) of the (*Z*)-ester **15** resonated in $CDCl_3$ at lower field than the corresponding proton (δ 2.20) of the (*E*)-ester **18**.[5,16] There is a precedent for the *Z*-preference in a similar Peterson olefination reaction.[17] The (*Z*)-ester **15** was then subjected to the acid-promoted cyclization using *p*-toluenesulfonic acid (*p*-TsOH) in benzene at room temperature for 24 h, giving the α,β-unsaturated lactone **16** in 96% yield. Hydrogenation of **16** over Adams catalyst in EtOH for 1 h furnished the desired *cis*-lactone **19**[6f−i,18] as a sole isomer in 99% yield. This *cis* selectivity is in agreement with that[5] observed for a similar hydrogenation of the C(7)-demethyl analogue.

Another procedure for carboxyolefination reaction of **14** would be addition of the lithium enolate of ethyl acetate[6j,19] and subsequent dehydration. The former step was carried out in THF at −78 °C for 2 h, providing the tertiary alcohol **17** as an 86 : 14 mixture of the two possible diastereoisomers in 77% yield. Dehydration of **17** (*via* an *E*1 mechanism) exploiting Martin sulfurane[20] succeeded in affording the (*E*)-α,β-unsaturated ester **18** in 93% yield. Catalytic hydrogenation of **18** over Adams catalyst gave the ester **20** as a diastereoisomeric mixture, which was then deprotected with AcOH–H_2O–THF (3 : 1 : 1, v/v) at room temperature for 10 h to furnish the *cis*-lactone **19**[6f−i,18] through subsequent cyclization and the *trans*-alcohol **21** in 71% and 20% overall yields (from **18**), respectively. The ^{1}H- and ^{13}C-NMR spectral data of **19** (mp 43.5—44.5 °C) thus obtained were virtually identical with those reported for an authentic sample (mp 40.5—42 °C).[6h,18] Since the transformations of the *cis*-lactone **19** into (±)-iridomyrmecin (**6**),[7] (±)-isoiridomyrmecin (**7**),[9] and (±)-allodolicholactone (**8**)[10] have been reported (see

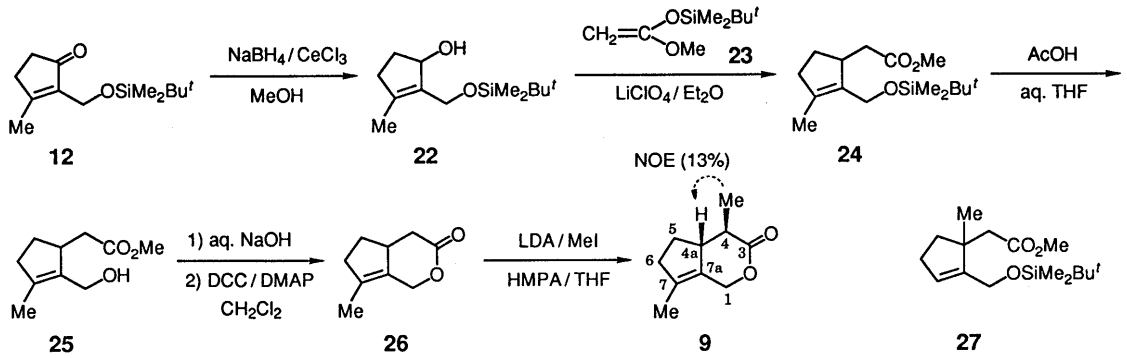


Chart 2

Chart 1), the above synthesis of **19** from **2** is tantamount to new formal racemic syntheses of these cyclopentano-monoterpene lactones.

We next turned our attention to the synthesis of (±)-isodehydroiridomyrmecin (**9**). Grieco *et al.* have recently described a direct substitution of secondary allylic alcohols with the silyl ketene acetal derived from methyl acetate in a 3.0 M solution of lithium perchlorate in diethyl ether.[21] Such a protocol appeared to be suitable for the introduction of an acetate moiety into the cyclopentane ring as an alternative to carboxyolefination reaction. Toward this end, the allylic alcohol **22**, prepared from **12** in 94% yield by 1,2-reduction with $NaBH_4$ in the presence of $CeCl_3$,[22] was treated with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (**23**)[23] in a 3.0 M solution of lithium perchlorate in diethyl ether. After 25 min at room temperature, the ester **24** was obtained in 96% yield as a mixture (93 : 7) contaminated with a by-product presumed to be the rearranged, allylic transposed isomer **27**.[21] Deprotection of **24** with AcOH–H_2O–THF (3 : 1 : 1, v/v) provided the alcohol **25** (91% yield), which was then subjected to alkaline hydrolysis and subsequent cyclization with dicyclohexylcarbodiimide (DCC) in the presence of a small amount of 4-dimethylaminopyridine (DMAP) to give the lactone **26** in 96% yield. Finally, generation of the enolate of **26** with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) in THF at −78 °C, followed by addition of methyl iodide, furnished the desired **9** as the sole isolable isomer in 57% yield. The structure of **9** was assigned on the basis of the ^{1}H-NMR spectroscopic result that a 13% NOE was observed for the C(4a)-H signal on irradiation of the C(4)-methyl signal, revealing the proximity of both protons in question. The high stereoselectivity observed in the above methylation of **26** may be explained in terms of kinetically controlled reaction from the convex side. The MS, IR (film), and ^{1}H-NMR (in $CDCl_3$) data of synthetic (±)-**9** were found to be virtually identical with those of natural (−)-isodehydroiridomyrmecin described in the literature.[11a]

Thus, formal racemic syntheses of several cyclopentano-monoterpene lactones and a synthesis of (±)-isodehydroiridomyrmecin (**9**) have been achieved by employing the 1,3-dioxin vinylogous ester **2** as a starting material. The above syntheses have not only exemplified the potential that the 1,3-dioxin vinylogous ester system has for natural product synthesis, but also suggest that **2** would be adaptable to the syntheses of more highly substituted cyclopentano-monoterpene lactones (*e.g.*, **1**), on the basis of its chemical reactivity.[3] Further studies directed toward the syntheses of oxygenated lactones exploiting **2** are in progress in this laboratory.

Experimental

General Notes All melting points were determined by using a Büchi model 530 capillary melting point apparatus and are corrected. TLC was run on Merck precoated silica gel 60 F_{254} plates (0.25-mm thickness). Flash chromatography[14] was performed with Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on either a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer; a Hitachi M-80 mass spectrometer; or either a JEOL JNM-GSX-500 (^{1}H 500 MHz) or a JEOL JNM-EX-270 (^{1}H 270 MHz, ^{13}C 67.8 MHz) NMR spectrometer. Chemical shifts are reported in ppm downfield from internal Me_4Si. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-dd's, dddd = doublet-of ddd's, dq = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, t = triplet.

2-(Hydroxymethyl)-3-methyl-2-cyclopenten-1-one (10) A solution of the 1,3-dioxin vinylogous ester **2**[3] (2.32 g, 16.6 mmol) in dry THF (80 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.4 M solution (23.7 ml, 33.2 mmol) of MeLi in diethyl ether was added dropwise over 15 min. After the mixture had been stirred for 30 min, 10% aqueous HCl (25 ml) was added. The reaction mixture was then warmed to room temperature and stirred for 1 h. The aqueous layer, after having been neutralized with anhydrous K_2CO_3, was separated from the organic layer and concentrated *in vacuo*. The residual slightly yellow jelly was continuously extracted with AcOEt for 3 h using a Soxhlet extractor. The AcOEt extracts and the above organic layer were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave an orange oil. Purification of the oil by flash chromatography[14] (AcOEt) gave **10** (2.03 g, 97%) as a colorless oil, MS *m/z*: 126 (M^+); IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1690 (CO), 1643 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.12 (2H, s, Me), 2.3 (1H, br, OH), 2.4—2.45 and 2.55—2.6 [2H each, m, C(4)-H's and C(5)-H's], 4.42 (2H, s, C$\underline{H}_2$OH).

2-(Methoxymethyl)-3-methyl-2-cyclopenten-1-one (11) A mixture of **10** (126 mg, 1.0 mmol), MeI (0.31 ml, 5.0 mmol), Ag_2O (255 mg, 1.1 mmol), and dry CH_2Cl_2 (1.5 ml) was stirred at room temperature in an atmosphere of N_2 for 24 h. After further additions of MeI (0.31 ml, 5.0 mmol) and Ag_2O (255 mg, 1.1 mmol), stirring was continued for an additional 24 h. An insoluble material was removed by filtration with the aid of Celite 545 and washed with CH_2Cl_2 (10 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless oil, which was purified by flash chromatography[14] [hexane–AcOEt (1 : 2, v/v)] to afford **11** (132 mg, 94%) as a colorless oil, MS *m/z*: 140 (M^+); IR ν_{max}^{film} cm^{-1}: 1701 (CO), 1649 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.18 [3H, s, C(3)-Me], 2.4—2.45 and 2.55—2.6 [2H each, m, C(4)-H's and C(5)-H's], 3.35 (3H, s, OMe), 4.08 (2H, s, C$\underline{H}_2$OMe). These spectral data were virtually identical with those reported for authentic **11**.[6j]

2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3-methyl-2-cyclopenten-1-one (12) A mixture of **10** (1.20 g, 9.5 mmol), imidazole (1.62 g, 23.8 mmol), and *N*,*N*-dimethylformamide (DMF) (5 ml) was kept stirred

under ice-cooling, and a solution of *tert*-butylchlorodimethylsilane (1.72 g, 11.4 mmol) in DMF (4 ml) was added. After having been stirred at room temperature for 1 h, the mixture was poured into cold H_2O (30 ml) and extracted with diethyl ether (4 × 20 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual pale yellow oil by flash chromatography[14] [hexane–AcOEt (5 : 1, v/v)] provided **12** (2.24 g, 98%) as a colorless oil, CIMS *m/z*: 241 (MH^+); IR ν_{max}^{film} cm^{-1}: 1700 (CO), 1650 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, *tert*-Bu), 2.20 [3H, s, C(3)-Me], 2.35—2.4 and 2.5—2.55 [2H each, m, C(4)-H's and C(5)-H's], 4.35 (2H, s, CH_2O).

Hydrogenation of 12 A Typical Example: Catalytic hydrogenation of **12** (537 mg, 2.23 mmol) in EtOH (10 ml) was effected over 10% Pd–C (200 mg) at atmospheric pressure and room temperature for 1 h. Removal of the catalyst by filtration and evaporation of the filtrate *in vacuo* left a mixture (524 mg, 97%) of (±)-*cis*- and (±)-*trans*-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentanone (**13** and **14**) as a colorless oil. The isomeric ratio of the mixture was determined on the basis of ^{1}H-NMR spectral analysis. The results and those from similar runs are given in Table I.

In the case of entry 3 in Table I, the mixture (705 mg) of **13** and **14** was then subjected to flash chromatography[14] [hexane–diethyl ether (6 : 1, v/v)] to give the *trans*-isomer (**14**) (535 mg, 72%) as a colorless oil, MS *m/z*: 242 (M^+); IR ν_{max}^{film} 1748 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 0.02 and 0.04 (6H, s each, $SiMe_2$), 0.86 (9H, s, *tert*-Bu), 1.17 [3H, d, J=7 Hz, C(3)-Me], 1.37 [1H, m, C(4)-H], 1.67 [1H, m, C(2)-H], 2.0—2.15 [2H, m, C(4)-H and C(5)-H], 2.25—2.35 [2H, m, C(3)-H and C(5)-H], 3.73 (1H, dd, J=10.5, 3.5 Hz) and 3.94 (1H, dd, J=10.5, 4 Hz) (CH_2O).

In the case of entry 1 in Table I, the 54 : 46 mixture (524 mg, 2.16 mmol) of **13** and **14** was dissolved in benzene (8 ml). The benzene solution, after addition of DBN (54 mg, 0.43 mmol), was heated at 50°C with stirring for 2 h. After cooling, the mixture was washed successively with 5% aqueous HCl and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil (414 mg, 79%), which was found to be a 7 : 93 mixture of the *cis*- and *trans*-isomers (**13** and **14**) on ^{1}H-NMR spectral analysis.

(±)-*trans*-(*Z*)-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentylidene]acetic Acid Ethyl Ester (15) and (±)-*trans*-(*E*)-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentylidene]acetic Acid Ethyl Ester (18) i) By the Peterson Olefination Reaction: A stirred solution of dicyclohexylamine (0.10 ml, 0.50 mmol) in dry THF (2.5 ml) was cooled to −78 °C in an atmosphere of N_2, and a 1.02 M solution (0.49 ml, 0.50 mmol) of *n*-BuLi in hexane was added dropwise. The mixture was stirred at the same temperature for 20 min, a solution of ethyl trimethylsilylacetate[24] (80 mg, 0.50 mmol) in dry THF (0.5 ml) was added dropwise, stirring was continued for 1 h, and then a solution of **14** (61 mg, 0.25 mmol) in dry THF (3 ml) was added dropwise over 10 min. The resulting mixture was further stirred at −78°C for 7 h, brought to room temperature after addition of saturated aqueous NH_4Cl (1 ml), and extracted with diethyl ether (3 × 5 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil, which was subjected to flash chromatography[14] [hexane–CH_2Cl_2 (2 : 1, v/v)]. Earlier fractions provided **15** (21 mg, 27%) as a colorless oil, MS *m/z*: 267 (M^+ −OEt), 255 (M^+ −*tert*-Bu); IR ν_{max}^{film} cm^{-1}: 1712 (ester CO), 1654 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.00 and 0.03 (6H, s each, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.00 [3H, d, J=7 Hz, C(3)-Me], 1.18 [1H, m, C(4)-H], 1.27 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.95 (1H, m) and 2.3—2.5 (3H, m) [C(3)-H, C(4)-H, and C(5)-H's], 3.00 [1H, br m, C(2)-H], 3.72 (1H, dd, J=10, 6.5 Hz) and 3.75 (1H, dd, J=10, 4 Hz) [C(2)-CH_2O], 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.80 [1H, ddd, J=2 Hz each, C(1)=$C\underline{H}CO_2Et$].

Later fractions of the above chromatography afforded **18** (6 mg, 8%) as a colorless oil, MS *m/z*: 312 (M^+), 267 (M^+ −OEt), 255 (M^+ −*tert*-Bu); IR ν_{max}^{film} cm^{-1}: 1717 (ester CO), 1654 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.04 and 0.05 (6H, s each, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.05 [3H, d, J=6.5 Hz, C(3)-Me], 1.27 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.28 [1H, m, C(4)-H], 1.85—2.0 [2H, m, C(3)-H and C(4)-H], 2.20 [1H, m, C(2)-H], 2.58 (1H, m) and 3.04 (1H, m) [C(5)-H's], 3.65 (1H, dd, J=10, 5.5 Hz) and 3.66 (1H, dd, J=10, 6.5 Hz) [C(2)-CH_2O], 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.85 [1H, ddd, J=2 Hz each, C(1)=$C\underline{H}CO_2Et$].

ii) *Via* Addition–Dehydration Route: A stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in dry THF (6 ml) was cooled to −78°C under N_2, and a 1.35 M solution (1.1 ml, 1.5 mmol) of *n*-BuLi in hexane was added dropwise. After the mixture had been stirred at that temperature for 30 min, AcOEt (0.15 ml, 1.5 mmol) was added, and stirring was continued for 20 min. A solution of **14** (242 mg, 1.0 mmol) in dry THF (2 ml) was then added dropwise over 3 min, and the mixture was stirred at −78°C for an additional 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl (2 ml), and the mixture was allowed to warm to room temperature. The aqueous layer was separated from the organic layer and extracted with diethyl ether (3 × 10 ml). The ethereal extracts and the above organic layer were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[14] [hexane–AcOEt (15 : 1, v/v)] furnished (±)-(2α,3β)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-hydroxy-3-methylcyclopentaneacetic acid ethyl ester (**17**) (254 mg, 77%) as a colorless oil, MS *m/z*: 313 (M^+ −OH); IR ν_{max}^{film} cm^{-1}: 3550 (OH), 1719 (ester CO); ^{1}H-NMR ($CDCl_3$) major isomer δ: 0.077 and 0.083 (s each, $SiMe_2$), 0.90 (s, *tert*-Bu), 1.00 [d, J=6.5 Hz, C(3)-Me], 1.1—1.2 [m, C(4)-H], 1.27 (t, J=7 Hz, $OCH_2\underline{Me}$), 1.3—1.4 [m, C(2)-H], 1.75—1.9 [m, C(5)-H's], 1.95—2.1 [m, C(3)-H and C(4)-H], 2.48 and 2.85 (d each, J=14.5 Hz, $C\underline{H}_2CO_2Et$), 3.85 (dd, J=10.5, 5.5 Hz) and 3.86 (dd, J=10.5, 4 Hz) [C(2)-CH_2O], 3.97 (s, OH), 4.15 (q, J=7 Hz, $OC\underline{H}_2Me$); minor isomer δ: 0.05 (s, $SiMe_2$), 0.89 (s, *tert*-Bu), 1.06 [d, J=6.5 Hz, C(3)-Me], 1.27 (t, J=7 Hz, $OCH_2\underline{Me}$), 1.5—1.85 (m, ring protons), 2.57 and 2.72 (d each, J=16 Hz, $C\underline{H}_2CO_2Et$), 3.57 (dd, J=10.5, 6 Hz) and 3.66 (dd, J=10.5, 4 Hz) [C(2)-CH_2O], 3.73 (s, OH), 4.17 (q, J=7 Hz, $OC\underline{H}_2Me$). The ^{1}H-NMR spectrum of this oil indicated that it was an 86 : 14 mixture of the two diastereoisomers.

A solution of **17** (217 mg, 0.66 mmol) in dry CH_2Cl_2 (5 ml) was stirred in an atmosphere of N_2, and a 0.15 M solution (4.9 ml, 0.74 mmol) of bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy] diphenyl sulfurane[20b] in dry CH_2Cl_2 was added dropwise. After having been stirred at room temperature for 2 h, the reaction mixture was poured into H_2O (5 ml). The CH_2Cl_2 layer was separated from the aqueous layer, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a colorless oil. Purification of the oil by flash chromatography[14] [hexane–AcOEt (25 : 1, v/v)] provided **18** (190 mg, 93%) as a colorless oil, which was identical [by comparison of the IR and ^{1}H-NMR spectra and TLC behavior] with the one prepared by method (i).

(±)-*cis*-5,6,7,7a-Tetrahydro-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (16) A mixture of **15** (162 mg, 0.52 mmol), *p*-TsOH · H_2O (15 mg, 0.08 mmol), and benzene (2 ml) was stirred at room temperature for 24 h. The reaction mixture was then washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[14] [hexane–AcOEt (2 : 1, v/v)] gave **16** (76 mg, 96%) as a colorless oil, MS *m/z*: 152 (M^+); IR ν_{max}^{film} cm^{-1}: 1722 (CO), 1658 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.13 [3H, d, J=7 Hz, C(7)-Me], 1.47, 1.67, 2.08, 2.45, 2.51, and 2.66 [1H each, m, C(5)-H's, C(6)-H's, C(7)-H, and C(7a)-H], 3.98 (1H, dd, J=12.5, 10.5 Hz) and 4.55 (1H, dd, J=10.5, 6 Hz) [C(1)-H's], 5.77 [1H, ddd, J=2 Hz each, C(4)-H].

(±)-(4aα,7α,7aα)-Hexahydro-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (19) i) From **16**: A solution of **16** (73 mg, 0.48 mmol) in EtOH (2 ml) was hydrogenated over Adams catalyst (7 mg) at atmospheric pressure and room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **19** (73 mg, 99%) as a colorless solid, mp 40—42 °C. Recrystallization of the solid from hexane afforded an analytical sample as colorless needles, mp 43.5—44.5 °C; IR ν_{max}^{Nujol} 1759 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.06 [3H, d, J=6.5 Hz, C(7)-Me], 1.1—1.3 [2H, m, C(5)-H and C(6)-H], 1.75—1.9 [3H, m, C(6)-H, C(7)-H, and C(7a)-H], 2.01 [1H, m, C(5)-H], 2.35 [1H, m, C(4)-H], 2.55–2.65 [2H, m, C(4)-H and C(4a)-H], 4.11 (1H, dd, J=11.5, 4.5 Hz) and 4.27 (1H, dd, J=11.5, 4.5 Hz) [C(1)-H's]; ^{13}C-NMR ($CDCl_3$) δ: 18.7 (Me), 33.4 [C(5)], 34.7 [C(6)], 34.8 [C(4)], 34.8 [C(4a)], 37.5 [C(7)], 44.6 [C(7a)], 69.0 [C(1)], 173.7 [C(3)]; high-resolution MS calcd for $C_9H_{14}O_2$: 154.0994, found: 154.0996. *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.82; H, 9.19. The ^{1}H- and ^{13}C-NMR spectra of this sample were virtually identical with those reported for authentic **19** (mp 40.5—42 °C).[6h,18]

ii) From **18**: A solution of **18** (108 mg, 0.35 mmol) in EtOH (7 ml) was hydrogenated over Adams catalyst (14 mg) at atmospheric pressure and room temperature for 4 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure provided (±)-*trans*-

2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-methylcyclopentaneacetic acid ethyl ester (**20**) (106 mg) as a colorless oil, which was dissolved in AcOH–H_2O–THF (3:1:1, v/v) (6 ml). After having been stirred at room temperature for 10 h, the solution was concentrated *in vacuo*. The residue was co-evaporated *in vacuo* with two 3-ml portions of benzene to leave a colorless oil, which was then subjected to flash chromatography[14] [CH_2Cl_2–AcOEt (15:1, v/v)]. Earlier fractions afforded **19** (38 mg, 71% from **18**) as a colorless solid, which was identical [by comparison of IR and ^{1}H-NMR spectra and TLC mobility] with the one obtained by method (i).

Later fractions of the above chromatography gave (±)-(1α,2β,3α)-2-(hydroxymethyl)-3-methylcyclopentaneacetic acid ethyl ester (**21**) (14 mg, 20% from **18**) as a colorless oil, MS *m/z*: 200 (M^+); IR ν_{max}^{film} cm^{-1}: 3420 (OH), 1736 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.02 [3H, d, J=7 Hz, C(3)-Me], 1.20 [1H, m, C(2)-H], 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.38 [1H, m, C(5)-H], 1.65—1.85 [4H, m, C(3)-H, C(4)-H's, and C(5)-H], 2.20 [1H, m, C(1)-H], 2.30 (1H, br, OH), 2.35 (1H, dd, J=15.5, 6.5 Hz) and 2.46 (1H, dd, J=15.5, 8 Hz) ($C\underline{H}_2CO_2Et$), 3.54 (1H, dd, J=11, 6.5 Hz) and 3.63 (1H, dd, J=11, 4.5 Hz) ($C\underline{H}_2OH$), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2Me$).

(±)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3-methyl-2-cyclopenten-1-ol (22) A mixture of **12** (721 mg, 3.0 mmol) and a 0.4 M solution (7.5 ml, 3.0 mmol) of $CeCl_3$ in MeOH was stirred at room temperature, and $NaBH_4$ (113 mg, 3.0 mmol) was added in portions over 5 min. The resulting mixture was then stirred at room temperature for 30 min. After addition of H_2O (6 ml) under ice-cooling, the mixture was extracted with diethyl ether (3 × 20 ml). The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography[14] [hexane–AcOEt (5:1, v/v)] provided **22** (685 mg, 94%) as a colorless oil, MS *m/z*: 241 (M^+-1); IR ν_{max}^{film} 3400 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ: 0.10 and 0.11 (6H, s each, $SiMe_2$), 0.91 (9H, s, *tert*-Bu), 1.70 [3H, s, C(3)-Me], 1.7—1.75 (1H), 2.1–2.25 (2H), and 2.50 (1H) [m each, C(4)-H's and C(5)-H's], 2.89 (1H, br, OH), 4.28 and 4.44 (2H, d each, J=12 Hz, CH_2O), 4.90 [1H, br m, C(1)-H].

(±)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-3-methyl-2-cyclopenteneacetic Acid Methyl Ester (24) A mixture of **22** (776 mg, 3.2 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (**23**)[23] (1.21 g, 6.4 mmol), and a 3.0 M solution (16 ml, 48 mmol) of lithium perchlorate in dry diethyl ether was stirred at room temperature in an atmosphere of Ar for 25 min. After addition of diethyl ether (40 ml), the reaction mixture was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual oil was purified by flash chromatography[14] [hexane–CH_2Cl_2 (2:1, v/v)] to afford crude **24** (913 mg, 96%) as a colorless oil, MS *m/z*: 298 (M^+); IR ν_{max}^{film} 1742 cm^{-1} (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.05 and 0.06 (6H, s each, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.51 [1H, m, C(5)-H], 1.66 [3H, s, C(3)-Me], 2.05 [1H, m, C(5)-H], 2.13 (1H, dd, J=15, 10.5 Hz) and 2.73 (1H, dd, J=15, 4 Hz) ($C\underline{H}_2CO_2Me$), 2.15—2.35 [2H, m, C(4)-H's], 3.17 [1H, br, C(1)-H], 3.66 (3H, s, OMe), 4.14 (1H, d, J=12 Hz) and 4.23 (1H, d, J=12 Hz) [C(2)-CH_2O]. On the basis of the ^{1}H-NMR spectrum, this oil is presumed to be a 93:7 mixture of **24** and (±)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-methyl-2-cyclopenteneacetic acid methyl ester (**27**) [^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, $SiMe_2$), 0.91 (s, *tert*-Bu), 1.16 [s, C(1)-Me], 2.36 (d, J=14 Hz) and 2.46 (d, J=14 Hz) ($C\underline{H}_2CO_2Me$), 3.64 (s, OMe), 4.20 [m, C(2)-CH_2O], 5.59 [dddd, J=2 Hz each, C(3)-H]].

(±)-2-(Hydroxymethyl)-3-methyl-2-cyclopenteneacetic Acid Methyl Ester (25) A solution of the above crude **24** (87 mg, 0.29 mmol) in AcOH–H_2O–THF (3:1:1, v/v) (2 ml) was stirred at room temperature for 2.5 h. The reaction mixture was then concentrated *in vacuo* to leave a colorless oil, which was dissolved in diethyl ether (20 ml). The ethereal solution was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residual oil by flash chromatography[14] [CH_2Cl_2–AcOEt (5:1, v/v)] gave **25** (49 mg, 91%) as a colorless oil, MS *m/z*: 184 (M^+); IR ν_{max}^{film} cm^{-1}: 3420 (OH), 1736 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.50 [1H, m, C(5)-H], 1.71 [3H, s, C(3)-Me], 1.85 (1H, br, OH), 2.11 [1H, m, C(5)-H], 2.2—2.4 [2H, m, C(4)-H's], 2.35 (1H, dd, J=15.5, 7.5 Hz) and 2.59 (1H, dd, J=15.5, 6 Hz) ($C\underline{H}_2CO_2Me$), 3.20 [1H, br, C(1)-H], 3.69 (3H, s, OMe), 4.08 (1H, d, J=12.5 Hz) and 4.18 (1H, d, J=12.5 Hz) ($C\underline{H}_2OH$).

(±)-4,4a,5,6-Tetrahydro-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (26) A solution of **25** (424 mg, 2.3 mmol) in MeOH (7 ml) was stirred under ice-cooling, and 1 N aqueous NaOH (7 ml) was added dropwise. After having been stirred at room temperature for 40 min, the reaction mixture was concentrated *in vacuo* to half the initial volume, acidified with 10% aqueous HCl, and extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residual colorless oil (390 mg) was dissolved in dry CH_2Cl_2 (200 ml), and DCC (570 mg, 2.76 mmol) and DMAP (40 mg) were added. The mixture was then stirred at room temperature for 1 h and concentrated *in vacuo*. After addition of hexane (50 ml) to the residual semisolid, the insoluble material that resulted was removed by filtration and washed with hexane. The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography[14] [hexane–AcOEt (2:1, v/v)] provided **26** (336 mg, 96%) as a colorless oil, MS *m/z*: 152 (M^+); IR ν_{max}^{film} 1736 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.44 [1H, m, C(5)-H], 1.70 [3H, s, C(7)-Me], 2.20 [1H, dd, J=17, 11.5 Hz, C(4)-H], 2.22 [1H, m, C(5)-H], 2.35—2.5 [2H, m, C(6)-H's], 2.90 [1H, dd, J=17, 6 Hz, C(4)-H], 3.04 [1H, br, C(4a)-H], 4.86 (1H, m) and 5.02 (1H, d, J=13.5 Hz) [C(1)-H's].

(±)-*cis*-4,4a,5,6-Tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-3(1*H*)-one [(±)-Isodehydroiridomyrmecin] (9) A stirred solution of diisopropylamine (0.09 ml, 0.64 mmol) in dry THF (2 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.24 M solution (0.5 ml, 0.62 mmol) of *n*-BuLi in hexane was added dropwise. After the mixture had been stirred for 30 min, a solution of **26** (76 mg, 0.5 mmol) in THF (1 ml) containing HMPA (0.1 ml, 0.57 mmol) was added dropwise over 5 min. Stirring was then continued for 2 h, and MeI (0.15 ml, 2.4 mmol) was added. The resulting mixture was further stirred at −78 °C for 2 h, brought to room temperature after addition of saturated aqueous NH_4Cl (1 ml), and extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a pale yellow oil. Purification of the oil by flash chromatography[14] [hexane–AcOEt (5:1, v/v)] gave **9** (47 mg, 57%) as a colorless oil, MS *m/z* (relative intensity): 166 (M^+) (14), 151 (5), 138 (4), 121 (26), 109 (16), 107 (19), 93 (58), 91 (28), 81 (33), 79 (30), 77 (29), 67 (17), 55 (24), 53 (28), 51 (20), 45 (26), 43 (73), 41 (100); IR ν_{max}^{film} 1736 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.26 [3H, d, J=7 Hz, C(4)-Me], 1.47 [1H, dddd, J=13, 10, 8.5, 7 Hz, C(5)-H], 1.67 [3H, s, C(7)-Me], 2.15—2.25 [1H, m, C(5)-H], 2.17 [1H, dq, J=11.5, 7 Hz, C(4)-H], 2.3—2.5 [2H, m, C(6)-H's], 2.73 [1H, br, C(4a)-H], 4.90 (1H, m) and 5.02 (1H, d, J=14 Hz) [C(1)-H's]; ^{13}C-NMR ($CDCl_3$) δ: 13.7 [C(7)-Me], 14.1 [C(4)-Me], 29.0 [C(5)], 37.8 [C(6)], 44.8 [C(4)], 48.5 [C(4a)], 67.4 [C(1)], 127.9 [C(7) or C(7a)], 133.9 [C(7a) or C(7)], 174.5 [C(3)]; high-resolution MS calcd for $C_{10}H_{14}O_2$: 166.0993, found: 166.0999. The MS, IR, and ^{1}H-NMR spectra of this sample were virtually identical with those of natural (−)-isodehydroiridomyrmecin reported in the literature.[11a]

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