A Short and Efficient Enantiospecific Synthesis of (+)-(2*R*,6*S*)-*cis*-γ-Irone *via* a Highly Diastereoselective Protonation

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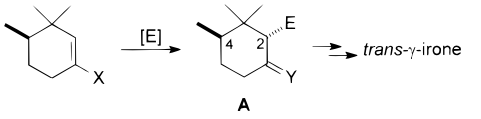
Introduction

Irones are responsible for the violet-like scent of the *Iris* essential oil and are high-priced ingredients of precious perfumes.[1] One of the main constituents of the oil is *cis*-γ-irone (**1**), which naturally occurs in both enantiomeric series, depending on the geographical origin of the *Iris* plant (Chart 1).[2]

Up to date, only one synthesis of optically active *cis*-γ-irone has been described.[3] However, this approach led to a 3:1 mixture of (−)-*trans* and (−)-*cis* diastereomers only separable by preparative GC. We report herein the first total enantiospecific synthesis of (+)-**1**.[4]

The strategy is based upon our previous observation of total (or predominant) *trans* introduction of an electrophile, starting from allylsilanes[5] (X = CH_2SiMe_3, Y = CH_2), substituted cyclohexenes[6] (X = CH_3, Y = CH_2), or enolates[4b,7] (X = OLi, Y = O), during the stereoselective synthesis of *trans*-γ-irone.



A (1)

Results and Discussion

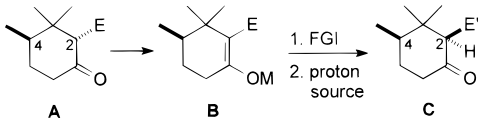
We envisioned that formation of the metal enolate **B** of **A** (Y = O), followed by a kinetic proton quench using an appropriate proton source, could result in a preferential formation of **C** containing the 4-methyl and the 2-E′ groups in the desired *cis* orientation.

In our methodology, it was necessary to control the regioselectivity of the enolate formation in order to conduct the protonation with the desired **B** enolate exclusively. Thus, since the ester group in an enolate salt of a highly enolizable β-keto ester can be selectively reduced without attack of the enolate anion,[8] E = CO_2-Me seemed to be the ideal substituent for our strategy to be achieved.

Chart 1

(+)-(2*R*,6*S*)-**1**[a] (-)-(2*S*,6*R*)-**1**[a]

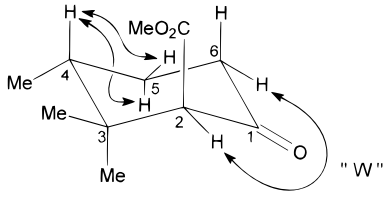
[a] Numbering follows IUPAC rules for nomenclature of carotenoids. We use it only when referring to irones.



(2)

Indeed, our originally projected synthetic plan proved fruitful, and the straightforward enantiospecific synthesis of (+)-**1** starting from (+)-(*R*)-3,4-dimethylcyclohex-2-en-1-one, (+)-**2**, is outlined in Scheme 1.

As expected, the readily available[9] enone (+)-**2** was converted into the practically single *trans*-2-carbomethoxycyclohexanone **3** in 91% yield by the 1,4-addition of lithium dimethylcuprate, followed by quenching with methyl cyanoformate[10] in hexamethylphosphoric triamide. However, subsequent purification of the product (85% yield after column chromatography) promoted partial epimerization of the highly enolizable β-keto ester, and consequently, the stereochemical assignment was performed on crude **3**. The ^{1}H NMR spectra with the help



keto-ester **3**

of double-irradiation experiments established unambigu-

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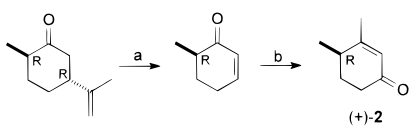
(9) Obtained in two steps from (+)−(2*R*,5*R*)-*trans*-dihydrocarvone, conveniently separated by column chromatography from its minor *cis* isomer starting from the commercial Aldrich mixture (hexane/ether 6:1). Equation 3 (a) Ozonolysis in methanol and then treatment with $Cu(OAc)_2/FeSO_4$ led to (+)−(*R*)-6-methylcyclohex-2-en-1-one (Solladié, G.; Hutt, J. *J. Org. Chem*. **1987**, *52*, 3560). (b) Treatment of this ketone with methyllithium, followed by oxidation with pyridinium chlorochromate (PCC), afforded (+)-**2** (Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun*. **1987**, 358. See also: Dauben, W. G.; Michno, D. M. *J. Org. Chem*. **1977**, *42*, 682).



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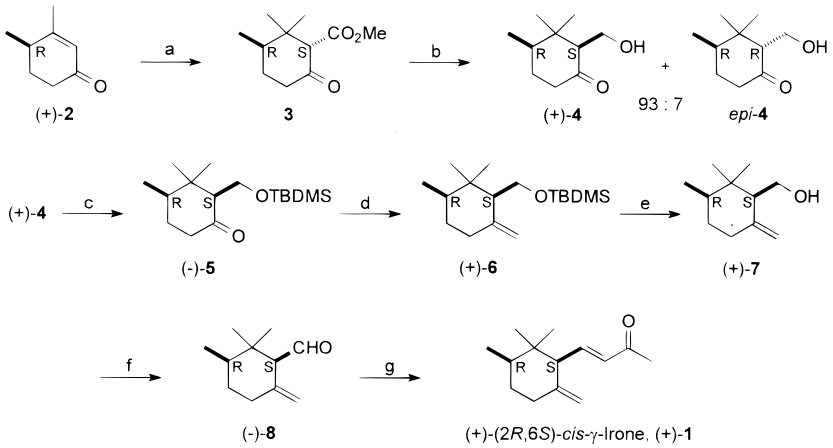
Scheme 1[a]



[a] Reagents: (a) Me_2CuLi, Et_2O then HMPA, $NCCO_2Me$ (85%); (b) (i) NaH, THF, (ii) AlH_3, THF, (iii) *t*-BuOH−Et_2O (1/3), −85 °C (74%); (c) TBDMSCl, imidazole, DMF (87%); (d) Zn−CH_2Br_2−$TiCl_4$, THF−CH_2Cl_2 (91%); (e) TBAF, THF (94%); (f) $(ClCO)_2$, DMSO, CH_2Cl_2, Et_3N, (90%); (g) $(MeO)_2POCH_2COCH_3$, $Ba(OH)_2$, THF−H_2O (40/1) (68%).

ously the *trans* relative configuration of the methyl group at C(4) and the carbomethoxy group at C(2). The value of the coupling constant between H_4 and H_{5ax} (J = 11.4 Hz) showed that H_4 is axial. In addition, the "W" coupling constant (J = 1.6 Hz) between H_{6eq} and H_{2eq} was consistent only with a conformation in which the carbomethoxy group occupies an axial position.

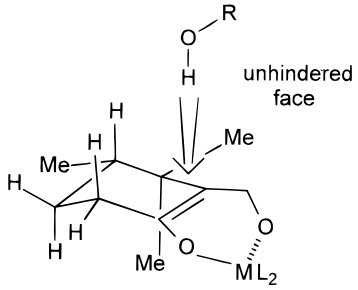
The partial epimerization of **3** was of no consequence since further metalation would generate a single sodium enolate. In the event, *β*-keto ester **3** was treated with 1.5 equiv of sodium hydride in THF from 0 °C to room temperature, *in situ* reduction of the sodium salt of the keto-ester was performed with a THF solution of AlH_3 at −10 °C,[8] and the reaction mixture was submitted to diastereoselective protonation.

Diastereoselective protonation of chiral enolates with chelating proton donors under reagent control has recently been reviewed.[11] For the stereoselective protonation of the ambident enolates, C-protonation is required. This condition is met if weak acid donors are employed as protonating agents.[12] Moreover, the highest diastereoselectivity was obtained by efficient transfer of the enolate to the proton source and not *vice versa* at low temperature. So, a low-temperature transfer apparatus consisting of two flasks connected by an insulated double-tipped stainless steel needle was used to effect the transfer of enolate to proton source at a constant temperature (both cooled at −85 °C) and at a controlled dropwise addition. Under these conditions, attempts were performed with ethyl salicylate and *tert*-butyl alcohol as the proton sources (Table 1).

In our hands, *tert*-butyl alcohol not only gave a higher diastereoselectivity in the proton transfer than ethyl salicylate but also facilitated the separation of product and proton source by simple quenching of the reaction mixture and evaporation of the solution in a rotary evaporator under reduced pressure. The keto alcohols (+)-**4** and *epi*-**4** were obtained in 74% yield as a 93:7 mixture in favor of (+)-**4**. The observed stereoselectivity might be explained in terms of the transition-state geometry. The semiempirical PM3 method[13] showed that the low-energy conformation of the intermediate presented an unhindered face.

Table 1. Kinetic Protonation

proton source	quench temp (°C)	ratio (+)-**4**/*epi*-**4**	yield (%)
ethyl salicylate	−85	90:10	46
tert-butyl alcohol	−85	93:7	74



The axial approach of the bulky proton donor by this face is clearly favored and gave *cis*-(+)-**4**. Flash chromatography afforded pure (+)-**4** (64%) as a crystalline material after solvent evaporation. The stereochemical assignments of (+)-**4** and *epi*-**4** were established by means of IR and ^{13}C studies. FT-IR dilution analyses, made in $CDCl_3$ solutions with the use of solvent subtraction technique, showed for (+)-**4** and *epi*-**4** a sole ∼3580 cm^{-1} band insensitive to dilution effects and characteristic of an intramolecular hydrogen bonded O−H vibration.[14] This consequently established the equatorial conformation of the $-CH_2OH$ chain in both enantiomers (Figure 1).

In the ^{13}C NMR spectra, (+)-**4** and *epi*-**4** were identified by the chemical shifts of the methyl groups of the *gem*-

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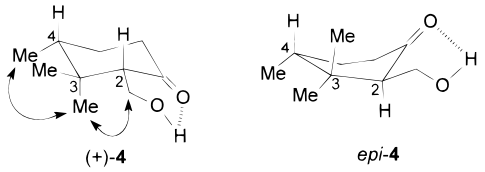

Figure 1. Favored chair conformation of cristalline (+)-**4** (heat of formation −116.3 kcal/mol) and favored twist conformation of oily *epi*-**4** (heat of formation −115.0 kcal/mol) according to the semiempirical PM3 method.

dimethyl moiety, which differed significantly. In diastereomer (+)-**4**, the signal of the Me_{3ax} (δ = 15.3 or 14.9) appeared at higher field than those of *epi*-**4** (δ = 25.6 or 25.3) because of an additive double γ steric effect.

Several Ti-based methylenation procedures[15] have been developed that avoid most of the problems encountered with Wittig-type processes.[16] In our case, the perfect sequence was realized when the hydroxyl group of (+)-**4** was first protected as the TBDMS[17] derivative (−)-**5** (87% yield). Using this condition, the keto group of (−)-**5** was methylenated, without any epimerization, by a zinc−dibromethane−titanium (IV) chloride mixed reagent[18] in THF to give (+)-**6** in 91% yield. Alcohol (+)-**7** was then produced by desilylation of (+)-**6** with Bu_4NF in 94% yield. The Swern procedure[19] oxidation of (+)-**7** afforded the aldehyde (−)-**8** in excellent yield (90%).

Numerous examples where the Horner−Wadsworth−Emmons (HWE) reaction is used for the coupling of β-keto phosphonates with aldehydes have been reported, and various modifications have also been developed.[16b,20] Among them, the barium hydroxide promoted HWE reaction is a mild and efficient method for epimerizable, base-sensitive aldehydes.[20d] This procedure, applied to aldehyde (−)-**8**, gave (+)-*cis*-γ-irone, (+)-**1**, in 68% yield as a single diastereomer, clearly indicating that the reaction occurred without loss of stereochemistry.

In conclusion, the first complete enantiospecific total synthesis of (+)-(2*R*,6*S*)-*cis*-γ-irone, (+)-**1**, has been achieved by a short and efficient seven-step procedure, giving an overall yield of 25% starting from (+)-**2** (Scheme 1). In addition, starting from (−)-**2**,[21] this synthetic pathway formally constituted synthesis of (−)-(2*S*,6*R*)-*cis*-γ-irone.

Experimental Section

General Methods. For analytical thin-layer chromatographies, Merck silica gel F-254 on aluminum plates was used. Column chromatographies were performed with Merck silica gel 60 (70−230 mesh) and Merck silica gel (230−400 mesh) for flash chromatography, using mixtures of diethyl ether and petroleum ether as eluent. GC analyses were carried out using a WCOT fused silica column (25 m × 0.32 mm i.d.; CP−Wax-52 CB stationary phase; N_2 carrier gas: 50 KPa). Enantiomeric excess determinations were carried out using a MEGADEX DETTBSβ fused silica column (30 m × 0.25 mm i.d.; N_2 carrier gas: 75 KPa). Microanalyses were performed at our University. FT-IR spectra were recorded (2 cm^{-1} resolution, 128 scans) using dilution technique and subtraction of solvent bands (200 μm KBr cell, $CDCl_3$). ^1H NMR and ^{13}C NMR spectra in solution were recorded in $CDCl_3$ at 200 and 50 MHz respectively, unless otherwise cited. MO calculations were performed using HyperChem release 5 package (Hypercube, Waterloo, Ontario, Canada) without any modification and running on a 450 MHz PC. Structures were minimized with the following parameters: restricted Hartree−Fock (RHF) level, minimization algorithm, until the root-mean-square energy gradient was less than 0.001 kcal/mol Å, accelerated convergence. Melting points are uncorrected. Unless otherwise stated, solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduce pressure.

Methyl (1*S*,3*R*)-2,2,3-Trimethyl-6-oxo-cyclohexanecarboxylate (3). To a stirred suspension of copper(I) iodide (4.61 g, 24.2 mmol) in dry ether (70 mL) at −5 °C was added dropwise MeLi (1.5 M in ether, 30.3 mL, 48.4 mmol) under an argon atmosphere. The mixture was stirred for 1 h at −5 °C, and a solution of (+)-**2** (1.50 g, 12.1 mmol) in ether (10 mL) was added dropwise. The reaction mixture was stirred for a further 1 h at 0 °C, HMPA (15 mL, 88.0 mmol) was added dropwise under vigorous stirring, the mixture was slowly cooled to −70 °C, and methyl cyanoformate (6.20 g, 72.6 mmol) in ether (20 mL) was added dropwise. The solution was allowed to rise to room temperature, poured into a saturated aqueous NH_4Cl/NH_4OH solution, and extracted with ether. The organic layers were combined, washed with brine, dried, and evaporated. ^1H and ^{13}C NMR spectra of the crude residue (2.17 g, 91%) established unambiguously the *trans* relative configuration for **3**. IR (neat): ν 1730, 1710, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H), 1.01 (s, 3H), 1.53 (dddd, J = 13.6, 12.0, 11.4, 5.1 Hz, 1H), 1.89 (dddd, J = 13.6, 7.2, 4.1, 3.4 Hz, 1H), 2.27 (dqd, J = 11.4, 6.9, 4.1 Hz, 1H), 2.32 (dddd, J = 14.4, 5.1, 3.4, 1.6 Hz, 1H), 2.88 (ddd, J = 14.4, 12.0, 7.2 Hz, 1H), 3.09 (d, J = 1.6 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 21.0, 26.1, 30.1, 34.2, 38.7, 40.6, 51.7, 67.8, 169.2, 207.0. Subsequent column chromatography of the residue yielded a 2:3 mixture of *cis*/*trans*-**3** (2.04 g, 85%). Anal. Calcd for $C_{11}H_{18}O_3$ (*cis*:*trans* mixture): C, 66.64; H, 9.15. Found: C, 66.82; H, 9.18.

(+)-(2*S*,4*R*)-2-Hydroxymethyl-3,3,4-trimethyl-cyclohexan-1-one (*cis*-(+)-4) and (2*R*,4*R*)-2-Hydroxymethyl-3,3,4-trimethyl-cyclohexan-1-one (*epi*-4). Preparation of Alane. To a cooled (0 °C) quantity of anhydrous $AlCl_3$ (254 mg, 1.90 mmol) was added dry THF (10 mL) under an argon atmosphere. The resulting solution was stirred at 0 °C for 5 min, and a solution of lithium aluminum hydride (1.0 M in THF, 5.7 mL, 5.7 mmol; 3 equiv) was added dropwise. The resulting colorless solution was allowed to warm to room temperature and stirred for 20 min to give a solution of alane ($C \approx$ 0.48 M in THF).

To a suspension of NaH (50% dispersion, 218 mg, 4.54 mmol) in THF (10 mL), cooled to 0 °C, was added dropwise a THF solution (5 mL) of partially epimerized **3** (600 mg, 3.03 mmol). After being stirred for 20 min, the reaction mixture was cooled to −10 °C, and the alane solution (10 mL, 4.8 mmol) was added via syringe under an argon atmosphere. After being stirred for a further 1 h, the enolate solution was cooled to −85 °C and transferred, with a controlled dropwise addition, via an insulated double-tipped stainless steel needle, to the cooled (−85 °C) proton source (400 mL solution of ether/*tert*-butyl alcohol: 3/1). The stirred solution was allowed to warm to −20 °C over a period of 3 h, Celite (15 g) and $Na_2SO_4 \cdot 10H_2O$ (15 g) were added, and the mixture was allowed to rise rt. After 30 min, the mixture was filtered through a pad of $MgSO_4$ and concentrated to give 380

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(21) Prepared like (+)-**2** starting from (−)-(2*S*,5*S*)-*trans*-dihydrocarvone (Hua, D. H.; Venkataraman, S. *J. Org. Chem*. **1988**, *53*, 1095).

(22) This value is quite different with those reported in the literature in which discrepancies in the magnitude of the specific rotation already occurs: (−)-*cis*-γ-irone[3] (ee 76%), $\alpha^{20}_D = -5.4$ (*c* 1.66, $CHCl_3$); (+)-*cis*-γ-irone (*cis*-γ/*cis*-α irone mixture: 9/1), $\alpha^{20}_D = +2.0$ (*c* 0.443, CH_2Cl_2), Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1984**, *67*, 325.

mg (74% yield) of (+)-**4** and *epi*-**4** as a 93:7 mixture in favor of (+)-**4**. Flash chromatography of the crude mixture afforded 330 mg (64%) of pure (+)-**4** as crystalline material and 20 mg (4%) of *epi*-**4**.

(+)-4. Mp: 57−59 °C. $[\alpha]^{25}_D$: +6.1 (*c* 1.0, $CHCl_3$). IR ($CDCl_3$): ν 3584, 1699, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.62 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.06 (s, 3H), 1.50−1.63 (m, 1H), 1.75−1.90 (m, 2H), 2.38 (m, 3H), 2.48 (dd, J = 10.3, 4.2 Hz, OH), 3.67 (ddd, J = 11.5, 10.3, 3.2 Hz, 1H), 3.99 (ddd, J = 11.5, 9.1, 4.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 15.3, 26.4, 31.1, 40.9, 41.3, 41.9, 58.5, 62.3, 214.9. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.38; H, 10.64.

***epi*-4.** IR ($CDCl_3$): ν 3583, 1697, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 3H), 0.99 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.57−1.67 (m, 1H), 1.66 (partially overlaped ddt, J = 13.6, 6.5, 4.4 Hz, 1H), 2.05 (m, 1H), 2.28 (br. dt, J = 14.6, 4.9 Hz, 1H), 2.42 (dddd, J = 14.5, 11.4, 6.1, 1.1 Hz, 1H), 2.52 (ddd, J = 9.4, 3.6, 0.8 Hz, OH), 3.63 (m, 1H), 3.99 (t, J = 10.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5, 25.3, 25.6, 29.3, 37.4, 39.1, 40.6, 58.2, 59.2, 214.3. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.61.

(−)-(2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)methyl-3,3,4-trimethylcyclohexan-1-one ((−)-5). The keto alcohol (+)-**4** (600 mg, 3.54 mmol) was dissolved in DMF (20 mL), imidazole (843 mg, 12.4 mmol) and *tert*-butyldimethylsilyl chloride (723 mg, 4.80 mmol) were added, and the mixture was stirred for 3 h at room temperature. The reaction was poured into water and extracted with ether. The combined organic extracts were washed with small portions of water and brine, dried, filtered, and concentrated. Column chromatography gave 881 mg (87%) of (−)-**5**. $[\alpha]^{25}_D$: −24.9 (*c* 1.0, $CHCl_3$). IR (neat): ν 1720, 1256, 1087, 838 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.05 (s, 3H), 0.55 (s, 3H), 0.85 (s, 9H), 0.88 (d, J = 6.7 Hz, 3H), 1.10 (s, 3H), 1.40−1.65 (m, 1H), 1.69−1.92 (m, 2H), 2.21−2.50 (m, 3H), 3.62 and 4.07 (ABX, J = 10.2, 6.3, 4.1 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.5, −5.4, 14.9, 15.1, 18.2, 25.9, 27.0, 32.0, 41.7, 41.8, 42.3, 57.9, 63.3, 211.2. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.85; H, 11.29.

(+)-[(1*S*,3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]-methyl-*tert*-butyldimethylsilyl Oxide (+)-6. Preparation of Lombardo's Reagent. To a suspension of Zn dust (2.87 g, 44 mmol) and CH_2Br_2 (1.01 mL, 14.4 mmol) in THF (25 mL), stirred under an argon atmosphere at −40 °C was added dropwise neat $TiCl_4$ (1.13 mL, 10.3 mmol). The mixture was then allowed to warm to 5 °C and was stirred for 3 days at this temperature to produce a thick gray slurry of the active reagent.

To a CH_2Cl_2 (6 mL) solution of ketone (−)-**5** (300 mg, 1.05 mmol), stirred at 5 °C under an argon atmosphere, was added the Zn−CH_2Br_2−$TiCl_4$ mixed methylenation reagent (2.5 equiv). After being stirred for 4 h at this temperature, the reaction mixture was diluted with CH_2Cl_2 and then poured into a cold saturated $NaHCO_3$ aqueous solution. The mixture was extracted with ether. The combined extracts were washed with brine, dried, filtered, and concentrated. The residue was subjected to column chromatography to afford 270 mg (91%) of pure (+)-**6** as an oil. $[\alpha]^{25}_D$: +30.8 (*c* 1.0, $CHCl_3$). IR (neat): ν 3088, 1648, 1256, 1089, 836 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.57 (s, 3H), 0.79 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 1.02 (s, 3H), 1.24 (m, 1H), 1.38 (m, 1H), 1.50 (m, 1H), 1.87 (br. t, J = 4 Hz, 1H), 2.02 (br. td, J = 13.0, 5.4 Hz, 1H), 2.25 (ddd, J = 12.6, 4.0, 2.0 Hz, 1H), 3.78 and 3.87 (ABX, J = 10.5, 7.3, 4.1 Hz, 2H), 4.62 (br. s, 1H), 4.80 (br. s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, 14.8, 15.8, 18.2, 25.9, 26.7, 32.8, 37.3, 38.2, 42.4, 55.5, 60.8, 107.2, 148.0. Anal. Calcd for $C_{17}H_{34}OSi$: C, 72.27; H, 12.13. Found: C, 72.46; H, 12.16.

(+)-(1*S*,3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexane-1-methanol ((+)-7). A solution of (+)-**6** (200 mg, 0.71 mmol) in THF (8 mL) was cooled to 0 °C, and tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 4 h. Cold water was added, and the resultant mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and concentrated. The residual oil was chromatographed to afford 112 mg (94%) of the alcohol (+)-**7**. Mp: 38−39 °C. $[\alpha]^{25}_D$: +38.7 (*c* 1.0, $CHCl_3$). IR (neat): ν 3650, 3020, 1640, 1040, 900 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.54 (s, 3H), 0.80 (d, 3H, J = 6.7 Hz), 1.00 (s, 3H), 1.26 (m, 1H), 1.35−1.63 (m, 3H), 2.00 (m, 2H), 2.30 (ddd, J = 12.7, 4.4, 2.9 Hz, 1H), 3.80 (m, 2H), 4.63 (br. s, 1H), 4.92 (br. s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 15.7, 26.5, 32.9, 37.0, 38.1, 42.0, 56.4, 59.5, 106.5, 148.0. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.13; H, 12.01.

(−)-(1*S*,3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexane-1-carbaldehyde ((−)-8). A solution of oxalyl chloride (159 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) was cooled to −70 °C, and a solution of dry DMSO (195 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at −70 °C for 15 min, and a solution of alcohol (+)-**7** (140 mg, 0.83 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 30 min at −70 °C, Et_3N (0.70 mL, 5 mmol) was added, and the reaction mixture was allowed to warm to room temperature over a period of 3 h. Water was added, and the resultant mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water until neutral, dried, filtered, and concentrated. A column chromatography of the residue yielded 125 mg (90%) of aldehyde (−)-**8** as a colorless oil. $[\alpha]^{25}_D$: −62.2 (*c* 1.0, CCl_4). IR (neat): ν 3100, 1735, 1650, 900 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.83 (d, J = 5.7 Hz, 3H), 0.95 (s, 3H), 0.97 (s, 3H), 1.17−1.60 (m, 3H), 2.07 (br.t, J = 12.7 Hz, 1H), 2.29 (br. dt, J = 12.7, 3.3 Hz, 1H), 2.51 (br. d, J = 4.8 Hz, 1H), 4.49 (br. s, 1H), 4.91 (br. s, 1H), 9.89 (d, J = 4.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 15.2, 27.0, 31.4, 35.9, 37.9, 41.6, 65.1, 109.3, 145.1, 205.2. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.34; H, 10.95.

(+)-(1′*S*,3′*R*,3*E*)-4-(2′,2′,3′-Trimethyl-6′-methylidenecyclohex-1′-yl)but-3-en-2-one ((+)-(2*R*,6*S*)-*cis*-γ-Irone, (+)-1). A mixture of diethyl (2-oxopropyl)phosphonate (352 mg, 1.81 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (62 mg, 0.36 mmol, heated to 100−140 °C for 2 h under a flux of argon before use) in THF (4 mL) was stirred at room temperature for 30 min under an argon atmosphere. A solution of aldehyde (−)-**8** (100 mg, 0.60 mmol) in wet THF (4 mL, 40:1 THF/H_2O) was then added. After being stirred for 18 h, the reaction mixture was diluted with CH_2Cl_2 and washed with a saturated $NaHCO_3$ aqueous solution and then brine. The organic extracts were dried, filtered, and concentrated. Purification by column chromatography yielded 84 mg (68%) of (+)-(2*R*,6*S*)-*cis*-γ-irone, (+)-**1**, as a colorless violet-like scented oil, with diastereomeric excess (de) and enantiomeric excess (ee) > 99% as determined by GC analyses. $[\alpha]^{25}_D$: +0.4 (*c* 3.0, $CHCl_3$).[22] IR (neat): ν 3055, 1675, 1650, 1635, 890 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.69 (s, 3H), 0.83 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H), 1.31 (m, 1H), 1.41 (m, 1H), 1.53 (m, 1H), 2.07 (br. td, J = 13.4, 5.0 Hz, 1H), 2.26 (s, 3H), 2.31 (ddd, J = 13.4, 4.4, 2.4 Hz, 1H), 2.52 (br. d, J = 10.3 Hz, 1H), 4.40 (br. d, J = 1.3 Hz, 1H), 4.76 (br. d, J = 1.3 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 6.90 (dd, J = 15.9, 10.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.42, 15.92, 27.31, 27.76, 31.95, 36.33, 38.86, 42.03, 57.88, 108.76, 133.67, 147.18, 148.89, 198.18. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.37; H, 10.74.

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