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Enantioselective Total Synthesis of (+)-(2*R*,6*R*)-*trans*-γ-Irone

Honoré Monti,[*,†] Gérard Audran,[†]
Jean-Pierre Monti,[‡] and Gilbert Leandri[†]

*Laboratoire de Réactivité Organique Sélective associé
au CNRS, Faculté des Sciences de St-Jérôme,
Avenue Escadrille Normandie-Niemen,
13397 Marseille Cedex 20, France, and Laboratoire de
Biophysique, Faculté de Pharmacie, 80037 Amiens, France*

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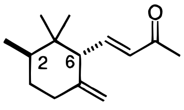
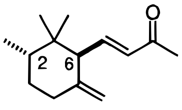
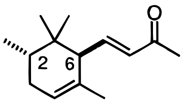
The natural occurrence of *trans*-γ-irone (**1**) has recently been demonstrated.[1] Four synthetic routes to the racemate (±)-**1** can be found in the literature,[2] but only one route for (+)-(2*R*,6*R*)-**1** and one for (−)-(2*S*,6*S*)-**1** have been reported.[3,4] These two enantioselective syntheses offer only a moderate enantiomeric excess and lack complete stereo- and/or regioselectivity. In the first synthetic approach, (+)-**1** has to be isolated from its *Z*-isomer (∼5:1) by chromatography, and, in the second, (−)-**1** is obtained as a 1:3 mixture containing a majority of (+)-*trans*-α-irone-**2**.



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



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

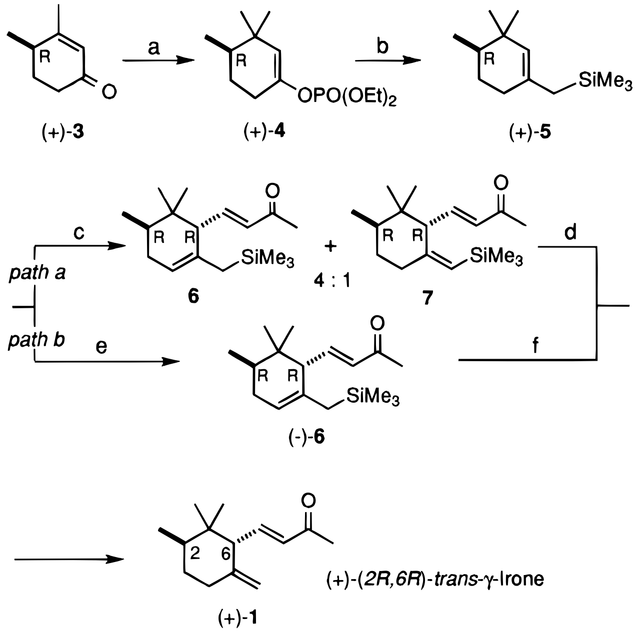


(+)-(2*S*,6*S*)-**2**[a]

[a] Numbering follows IUPAC rules for nomenclature of carotenoids.[1] We use it only when referring to irones.

We report herein a straightforward enantioselective synthesis of (+)-**1** starting from (+)-(*R*)-3,4-dimethylcyclohex-2-en-1-one, (+)-**3**, based on the H-ene reaction of butynone with a cyclohexenic allyltrimethylsilane[5−7] (Scheme 1). The readily available[8] enone (+)-**3** was converted into the cyclic diethyl enol phosphate (+)-**4** in 92% yield by the 1,4-addition of dimethylcyanocuprate Me$_2$Cu(CN)Li$_2$, followed by quenching with diethylchlorophosphate in hexamethylphosphoric triamide.[9] The nickel acetylacetonate-catalyzed reaction of (+)-**4** with (trimethylsilyl)methylmagnesium chloride gave trimethyl[(3,3,4-trimethylcyclohex-1-enyl)methyl]silane (+)-**5** in 85% yield.[9b]

Scheme 1[a]



[a] Reagents: (a) Me$_2$Cu(CN)Li$_2$, Et$_2$O, then ClPO(OEt)$_2$/HMPA (92%); (b) Me$_3$SiCH$_2$MgCl, Ni(acac)$_2$, THF (85%); (c) butynone, ZnI$_2$, 4 Å molecular sieves, CH$_2$Cl$_2$ (83%); (d) catalytic TsH, CH$_3$CN (82%); (e) butynone, Me$_2$AlCl, CH$_2$Cl$_2$ (93%); (f) TiCl$_4$, CH$_2$Cl$_2$ (93%).

In a first attempt, based on analogy with the literature,[4] the ZnI$_2$-catalyzed H-ene reaction of (+)-**5** with but-3-yn-2-one was investigated. This reaction furnished a mixture of two main products (**6** + **7**) and small amounts (9:1) of isomeric derivatives, showing that, prior to the H-ene reaction, a partial isomerization must have taken place.[10] To avoid the formation of these unwanted isomers, we ran a new experiment in the presence of 4 Å

[†] Faculté des Sciences de St-Jérôme.

[‡] Faculté de Pharmacie.

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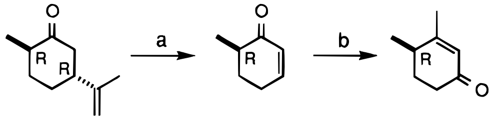
(7) Thermal ene reactions with allylsilanes. For a review, see: Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319 and references therein. See also: (a) Imazu, S.; Shimizu, N.; Tsuno, Y. *Chem. Lett.* **1990**, 1845. (b) Cai, J.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1743. Lewis acid-promoted ene reactions with allylsilanes: (a) Mikami, K.; Matsukawa, S. *Tetrahedron Lett.* **1994**, *35*, 3133. (b) Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783.

(8) 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).



(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 (+)-**3** (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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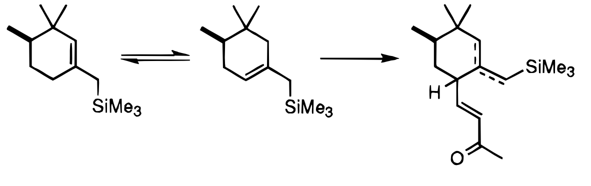
(10) In ^{1}H NMR, these rearranged products, which we did not investigate fully, were characterized by a multiplet (bis-allylic hydrogen) at 2.90 ppm.



The same isomerization has been reported using ZnCl$_2$ or ZnBr$_2$ as Lewis acid and starting from a substituted cyclohexene.[4]

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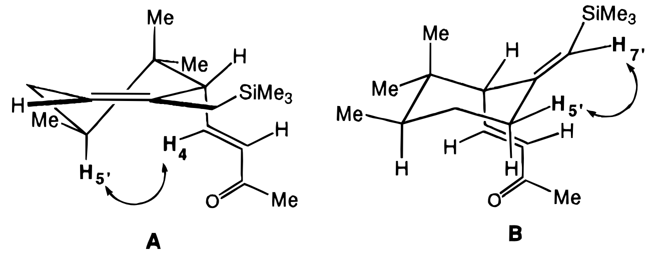
Chart 1



molecular sieves (zeolite), which can serve as cation exchangers.[11] As expected, the reaction furnished cleanly the inseparable mixture **6**/**7** (4:1) as the sole products in 83% yield. The regioselectivity of the H-ene reaction and the *trans* relationship between the substituents could be established by NMR spectroscopy. Recourse to NOESY experiments established the absolute configuration and conformation of **6** and **7**. For the major allylsilane **6**, the NOESY plots were characterized by strong cross-peaks between H_4 and $H_{5'}$ (Chart 1, **A**). Accordingly, this pair of protons must reside in close proximity; this is uniquely accommodated by **A**. The preference of molecules related to **6** (or **7**) to adopt a conformation with a pseudoaxial side chain has been reported in the literature.[2d,4,12] In the same experiment, the NOE effect for vinylic $H_{7'}$ and equatorial $H_{5'}$ (Chart 1, **B**) established the *Z* configuration of the double bond in the minor vinylsilane **7**. Further, heating the mixture (**6** + **7**) in acetonitrile with a catalytic amount of *p*-toluenesulfinic acid (TsH), according to the procedure described in the literature for protodesilylation of vinylsilanes,[13] provided (+)-*trans*-γ-irone (**1**) as the only product in 82% yield (Scheme 1, path a).

Next, we envisaged that dimethylaluminum chloride (Me_2AlCl), which is a mild Lewis acid and a proton scavenger,[14] would be an ideal catalyst for the H-ene reaction. In agreement with our expectation, (+)-**5** reacted cleanly at low temperature (−30 °C) with but-3-yn-2-one, furnishing the desired H-ene adduct as the single regioisomer (−)-**6** in 93% yield. Isocyclic core allylsilanes suffer ready protodesilylation with a Lewis acid like $TiCl_4$ before all further reactions.[15] Indeed, this generally unwanted parasite reaction, applied to allylsilane (−)-**6**, provided (+)-**1** in 93% yield (Scheme 1, path b). Remarkably, this protodesilylation proceeded without any further isomerization of the exocyclic double bond, and a single diastereomer was detected by capillary GC. The high optical purity of (+)-(2*R*,6*R*)-**1** was verified by HPLC (column, Chiralcel OD-H, 25 cm × 0.46 cm, i.d.), and the $[\alpha]^{25}_{D}$ +59.4 ($c = 1.2$, CH_2Cl_2) is in good agreement with the literature value,[4] which is $[\alpha]^{25}_{D}$ −43.3 ($c = 0.8$, CH_2Cl_2) for (−)-**1** with a reported 70% ee.

In conclusion, the first complete enantioselective total synthesis of (+)-(2*R*,6*R*)-*trans*-γ-irone ((+)-**1**) has been achieved by a short four-step procedure, giving an overall yield of 68% starting from (+)-**3** (Scheme 1, path b). In addition, starting from (−)-**3**,[16] this synthetic pathway formally constituted synthesis of (−)-(2*S*,6*S*)-*trans*-γ-irone.

Experimental Section

For analytical thin-layer chromatography, Merck silica gel F-254 on aluminum plates was used. Column chromatography was performed with Silica gel 60 (70−230 mesh) using mixtures of diethyl ether and pentane as eluant. Chiral HPLC analyses were performed on Analprep EC 93 (column, Chiralcel OD-H 25 cm × 0.46 cm i.d.). GC analyses were carried out on a Chrompack 9001 using a WCOT fused silica column (25 m × 0.32 mm i.d.; CP-Wax-52 CB stationary phase). Microanalyses were performed on a Technicon CHN analyzer at our University. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. NMR spectra were recorded at 200 or 300 MHz for ^1H and 50 or 75.5 MHz for ^{13}C on a Bruker AM-200 or Bruker AC-300 spectrometer with $CDCl_3$ as solvent (Bruker AM-400 for NOESY experiments). Chemical shifts (δ) are relative to tetramethylsilane as internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Unless otherwise stated, solutions were dried with magnesium sulfate and evaporated in a rotary evaporator under reduced pressure.

Diethyl (+)-(4*R*)-(3,3,4-Trimethylcyclohex-1-en-1-yl)phosphoric Triester ((+)-4). To a stirred suspension of copper(I) cyanide (3.76 g, 42.0 mmol) in dry ether (100 mL) at −30 °C was added dropwise MeLi (1.5 M in ether, 56.0 mL, 84.0 mmol) under Ar atmosphere. The mixture was stirred for 1 h at −20 °C and cooled to −78 °C, and then (+)-**3** (1.74 g, 14.0 mmol) in ether (10 mL) was added dropwise. The reaction mixture was slowly warmed to −30 °C and stirred at this temperature for 1 h, and then a mixture of $ClPO(OEt)_2$ (6.1 mL, 42.0 mmol) and HMPA (7.3 mL, 42.0 mmol) in THF (10 mL) was added dropwise. The solution was allowed to rise to rt, stirred for 12 h and then poured into a saturated aqueous NH_4Cl/NH_4OH solution (100 mL) and extracted with ether (3 × 60 mL). The organic layers were combined, washed with 50 mL of brine, dried, and evaporated. The oily residue was subjected to column chromatography on silica gel (pentane/ether 2:1) to afford 3.56 g (92%) of (+)-**4**. $[\alpha]^{25}_{D}$ +33.4 ($c = 1.8$, $CHCl_3$). IR (neat): ν 3060, 1690, 1280, 1040, 980, 810 cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$): δ 0.84 (s, 3H), 0.87 (d, $J = 6.4$ Hz, 3H), 0.99 (s, 3H), 1.30 (td, $J = 7.1$, 1.0 Hz, 6H), 1.37−1.69 (m, 3H), 2.02−2.33 (m, 2H), 4.10 (dq, $J = 7.9$, 7.1 Hz, 4H), 5.20 (br s, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.8, 15.5 (d, $J = 6.1$ Hz), 22.5, 27.0, 28.7, 34.1, 37.1, 63.5 (d, $J = -5.8$ Hz), 121.3 (d, $J = 4.9$ Hz), 145.9 (d, $J = -9.1$ Hz). Anal. Calcd for $C_{13}H_{25}O_4P$: C, 56.51; H, 9.12. Found: C, 56.62; H, 9.15.

(+)-(4*R*)-Trimethyl[(3,3,4-trimethylcyclohex-1-en-1-yl)methyl]silane ((+)-5). To a stirred mixture of enol phosphate (+)-**4** (2.76 g, 10 mmol) and $Ni(acac)_2$ (257 mg, 1.0 mmol) in THF (50 mL) was added 0.25 equiv of a 1 M ethereal solution of (trimethylsilyl)methylmagnesium chloride (2.5 mL, 2.5 mmol) at rt. This addition process was repeated every 1 h for a total of 11 h of reaction time and 2.5 equiv of Grignard reagent (25 mL, 25 mmol). The reaction was quenched with 50 mL of a 20% aqueous NH_4Cl solution and stirred for 45 min. After extractive workup with ether (3 × 50 mL), the organic layers were combined, washed with 50 mL of brine, dried, and evaporated. Purification by chromatography on silica gel (pentane) afforded 1.79 g (85%) of (+)-**5**. $[\alpha]^{25}_{D}$ +52.3 ($c = 2.0$, $CHCl_3$). IR (neat): ν 3030, 1660, 1255, 850 cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.83 (s, 3H), 0.91 (d, $J = 6.1$ Hz, 3H), 0.99 (s, 3H), 1.41 (s, 2H), 1.37−1.59 (m, 3H), 1.75−2.05 (m, 2H), 4.95 (br s, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ −1.4, 15.9, 23.2, 27.3, 28.2, 29.6, 31.1, 34.7, 38.1, 131.4, 132.2. Anal. Calcd for $C_{13}H_{26}Si$: C, 74.20; H, 12.45. Found: C, 74.32; H, 12.41.

(1′*R*,5′*R*,3*E*)-4-(5′,6′,6′-Trimethyl-2′-[(trimethylsilyl)methyl]cyclohex-2′-en-1′-yl)but-3-en-2-one and (1′*R*,3′*R*,3*E*)-4-(2′,2′,3′-Trimethyl-(*Z*)-6′-[(trimethylsilyl)methylidene]cyclohex-1′-yl)but-3-en-2-one (6 + 7). A suspension of allylsilane (+)-**5** (421 mg, 2.0 mmol), anhydrous ZnI_2 (958 mg, 3.0 mmol),

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(16) Prepared like (+)-**3** starting from (−)-(2*S*,5*S*)-*trans*-dihydrocarvone (Hua, D. H.; Venkataraman, S. *J. Org. Chem.* **1988**, *53*, 1095).

powdered 4 Å molecular sieves (0.6 g), and butynone (204 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at rt for 12 h under Ar atmosphere. After filtration and removal of the solvent, the residue was chromatographed on silica gel (pentane/ether 20:1) to afford 462 mg (83%) of a ~4:1 inseparable mixture of **6** and **7** (based on capillary GC and integration of ^{1}H NMR peaks). Anal. Calcd for $C_{17}H_{30}OSi$ (**6** + **7**): C, 73.31; H, 10.86. Found: C, 73.46; H, 10.90.

6. ^{1}H-NMR (300 MHz, $CDCl_3$): δ −0.08 (s, 9H), 0.72 (d, J = 6.5 Hz, 3H), 0.76 (s, 3H), 0.77 (s, 3H), 1.15 and 1.37 (AB, J = −17.0 Hz, 2H), 1.52−1.72 (m, 2H), 1.91−2.15 (m, 1H), 2.18 (s, 3H), 2.19 (d, J = 9.3 Hz, 1H), 5.20−5.25 (m, 1H), 5.92 (d, J = 15.8 Hz, 1H), 6.58 (dd, J = 15.8, 9.3 Hz, 1H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ −1.1, 14.9, 20.9, 25.6 , 26.5, 26.6, 31.6, 32.3, 35.4, 56.5, 120.9, 132.5, 133.4, 148.9, 198.2.

7. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 9H), 0.70 (d, J = 6.6 Hz, 3H), 0.71 (s, 3H), 0.85 (s, 3H), 2.07−2.15 (m, 1H), 2.17 (s, 3H), 2.38 (tdd, J = 12.4, 5.0, 2.0 Hz, 1H), 2.84 (d, J = 7.6 Hz, 1H), 5.23−5.28 (m, 1H), 6.01 (dd, J = 15.8, 1.1 Hz, 1H), 7.00 (dd, J = 15.8, 7.6 Hz, 1H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 0.5, 15.5, 20.6, 27.1, 27.6, 31.9, 35.9, 36.5, 38.2, 58.0, 125.9, 132.0, 147.0, 156.2, 197.9.

(−)-(1′*R*,5′*R*,3*E*)-4-(5′,6′,6′-Trimethyl-2′-[(trimethylsilyl)methyl]cyclohex-2′-en-1′-yl)but-3-en-2-one ((−)-6). To a stirred, cooled (−30 °C) solution of allylsilane (+)-**5** (421 mg, 2.0 mmol) and butynone (150 mg, 2.2 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise Me_2AlCl (1 M solution in CH_2Cl_2, 2.4 mL, 2.4 mmol) under Ar atmosphere. After 20 min at this temperature, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried, and evaporated. The residue was purified by chromatography (pentane/ether 20:1), which gave 518 mg (93%) of pure (−)-**6**. $[\alpha]^{25}_D$ −170.3 (c = 1.9, $CHCl_3$). IR (neat): ν 3040, 1690, 1680, 1630, 1250, 850 cm^{-1}. Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.86. Found: C, 73.43; H, 10.89. (For ^{1}H- and ^{13}C-NMR, see above).

(+)-(1′*R*,3′*R*,3*E*)-4-(2′,2′,3′-Trimethyl-6′-methylidenecyclohex-1′-yl)but-3-en-2-one [(+)-(2*R*,6*R*)-*trans*-γ-Irone, (+)-1]. (i) Using *p*-Toluenesulfinic Acid. To a solution of **6** + **7** (278 mg, 1.0 mmol) and *p*-toluenesulfinic acid (31 mg, 0.2 mmol) in 10 mL of CH_2Cl_2 was added one drop of water, and the mixture was refluxed for 3 h. After cooling to rt, the reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried, and evaporated. The residue was chromatographed (pentane/ether 15:1) to afford 170 mg (82%) of pure (+)-**1**.

(ii) Protodesilylation with $TiCl_4$. To a stirred, cooled (−70 °C) solution of (−)-**6** (278 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise $TiCl_4$ (1 M solution in CH_2Cl_2, 3.0 mL, 3.0 mmol). TLC monitoring showed the total disappearance of (−)-**6** after 1 h. The reaction mixture was then poured into a saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried, and evaporated to afford a residue, from which (+)-**1** (192 mg, 93%) was obtained pure after chromatography (pentane/ether 15:1). $[\alpha]^{25}_D$ +59.4 (c = 1.2, CH_2Cl_2). IR (neat): ν 3060, 1680, 1650, 1620, 990, 895 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.80 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.88 (s, 3H), 1.20−1.40 (m, 1H), 1.50−1.75 (m, 2H), 2.15−2.25 (m, 2H), 2.24 (s, 3H), 2.61 (d, J = 8.9 Hz, 1H), 4.66 (br s, 1H), 4.71 (br s, 1H), 6.06 (d, J = 15.8 Hz, 1H), 7.05 (dd, J = 15.8, 8.9 Hz, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.4, 21.3, 26.9, 27.2, 31.3, 36.2, 37.6, 59.4, 110.3, 131.8, 147.3, 147.8, 198.3. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.55; H, 10.72.

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