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STEREOSELECTIVE TOTAL SYNTHESIS OF (4S)-*trans*-β-ELEMENONE FROM (S)-2-CYCLOHEXEN-1-OL

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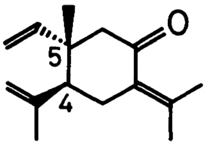
Stereoselective first total synthesis of (4*S*)-*trans*-β-elemenone was achieved from (*S*)-2-cyclohexen-1-ol, prepared easily by the asymmetric reduction of 2-cyclohexen-1-one with chiral hydride reagent.

β-Elemenone (1) is a sesquiterpenoid isopropylidene cyclohexanone isolated from the essential oils of Bulgarian Zdravets,[1a)] *Rhododendron adamsii* Rend,[1b)] *Mirica gale*,[1c)] and *Ledum palustre*.[1d)] Although total synthesis of racemic β-elemenone has been accomplished by Grieco *et al.*,[2)] the preparation of optically active one has not yet been reported. We describe herein the first stereoselective total synthesis of (4*S*)-*trans*-β-elemenone (1) from (*S*)-2-cyclohexen-1-ol (2). Construction of two chiral centers of C_4 and C_5 in 1 was achieved by 1,4-addition of organocopper reagents to the key intermediates, (3*S*,4*R*)-3,4-epoxy-1-cyclohexene (5) and (*S*)-4-isopropenyl-3-methyl-2-cyclohexen-1-one (9), respectively (*vide infra*).

The starting material, optically pure (*S*)-alcohol 2 was effectively synthesized in 95% yield from 2-cyclohexen-1-one using the chiral reducing reagent (3) of lithium aluminum hydride modified with (*S*)-4-anilino-3-methylamino-1-butanol which was prepared easily from (*S*)-aspartic acid;[3)] $[\alpha]_D^{23}$ -112.5° (c 1.06, $CHCl_3$)



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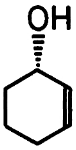

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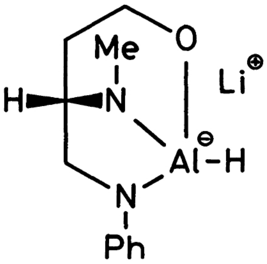

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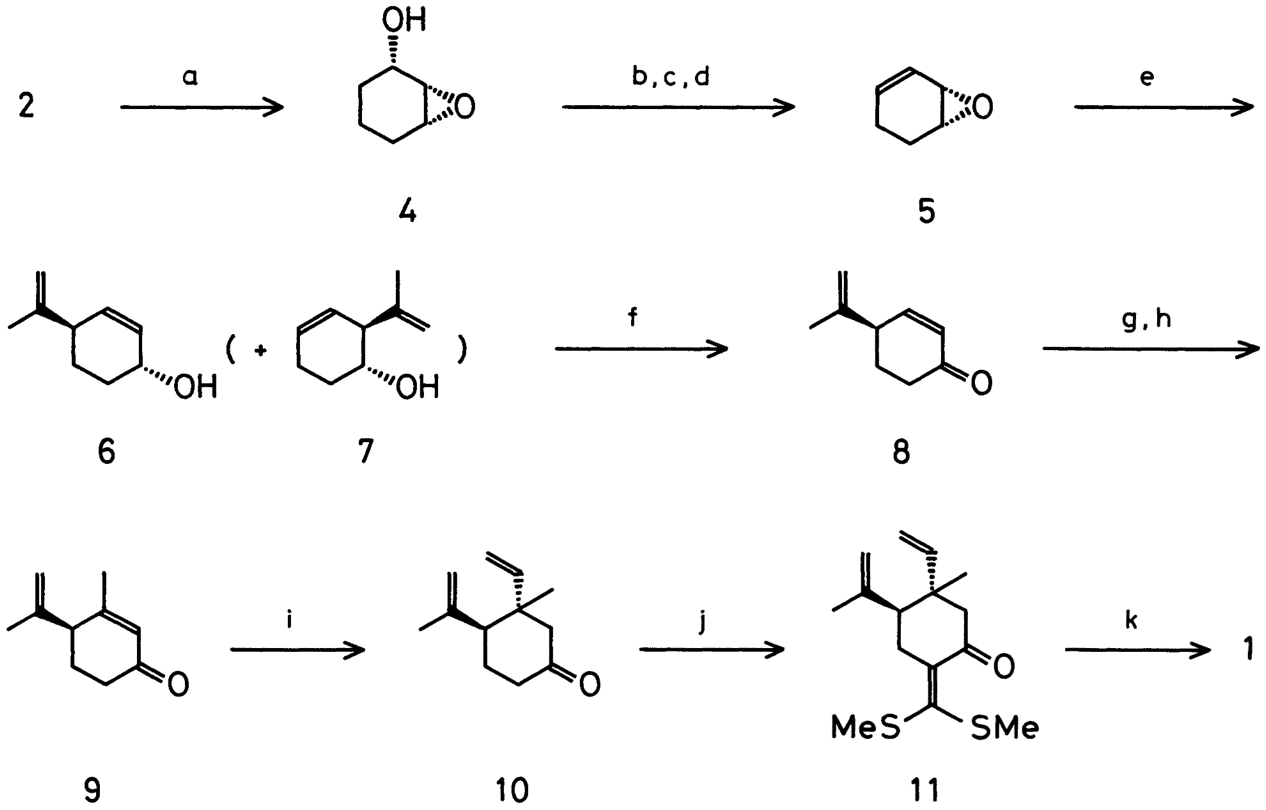
(lit.[4] $[\alpha]_D^{20}$ -112° (c 0.60, $CHCl_3$).

syn-Epoxidation[5] of (*S*)-alcohol 2 (cat. $VO(acac)_2$, *t*-BuOOH, refluxing benzene, 5 h) gave (1*S*,2*S*,3*R*)-*cis*-2,3-epoxycyclohexan-1-ol (4) (*cis* : *trans* = 98:2)[6,7] in 74% yield: $[\alpha]_D^{22}$ -42.1° (c 1.02, $CHCl_3$); bp 100 °C/20 mmHg. Epoxy alcohol 4 was converted into the key intermediate, (3*S*,4*R*)-3,4-epoxy-1-cyclohexene (5)[8] by mesylation (quant., MsCl-Et_3N, CH_2Cl_2, -30 °C to rt, 4 h) and iodination (68%, NaI, refluxing acetone, 5 h), followed by elimination of hydrogen iodide (48%, 1,5-diazabicyclo[5.4.0]undec-5-ene, refluxing THF, 5 h); $[\alpha]_D^{24}$ -56.6° (c 0.53, $CHCl_3$); bp 80 °C/145 mmHg.

The introduction of (4*S*)-isopropenyl group was accomplished by *anti* 1,4-addition (S_N2' reaction) of organocuprates to cycloalkene epoxides.[9] Epoxide 5 was treated with several kinds of organocuprates such as bromomagnesium isopropenylcyanocuprate (THF, -78 °C to -40 °C, 2 h), isopropenylcopper-tributylphosphine complex[10a] (Et_2O, -78 °C to -40 °C, 2 h), and isopropenylcopper-boron trifluoride complex[10b] (Et_2O, -78 °C to -40 °C, 2 h) to give a mixture of the desired 1,4-adduct, (1*R*,4*R*)-4-isopropenyl-2-cyclohexen-1-ol (6) and the undesired 1,2-adduct (S_N2 product), (1*R*,2*S*)-alcohol (7) in 60% (68:32), 23% (29:71), and 26% (62:38) yields, respectively. The use of lithium isopropenylcyanocuprate (ether, -78 °C to -30 °C, 1.5 h) gave the best result to afford a 75:25 mixture of 6[11] (56%, $[\alpha]_D^{22}$ +174.3° (c 0.85, $CHCl_3$)) and 7[11] (19%, $[\alpha]_D^{22}$ -76.2° (c 0.98, $CHCl_3$)), which were easily separated on silica-gel TLC ($CHCl_3$). Alcohol 6 was confirmed to be only a single diastereomer by comparison with VPC (FFAP 50 m) and NMR spectra of a *cis* and *trans* mixture of 6, prepared by the reduction of enone 8 with lithium aluminum hydride. Oxidation of alcohol 6 with pyridinium chlorochromate[12] (CH_2Cl_2, rt, 2 h) gave (*R*)-4-isopropenyl-2-cyclohexen-1-one (8)[11] in 79% yield; $[\alpha]_D^{22}$ +157.6° (c 1.37, $CHCl_3$). β-Methylation of enone 8 was performed by the Michael addition of Grignard reagent, followed by phenylselenation of enolate formed and subsequent oxidation-elimination.[13] Thus, treatment of 8 with methylmagnesium bromide in the presence of 4 mol% copper(I) chloride (ether, -30 °C, 40 min) and then phenylselenenyl bromide (-78 °C, 1 h) afforded α-phenylseleno cyclohexanone, which was treated with sodium metaperiodate (aq dioxane, 40-50 °C, 14 h) to give one of the key intermediates, (*S*)-enone 9 in 68% yield; $[\alpha]_D^{22}$ +171.9° (c 1.01, $CHCl_3$). The (*S*)-configuration is verified by the optical rotation $[\alpha]_D$ -28.4° of (*R*)-9 reported by Lander and Mechoulans.[14]

Next key step of introduction of *trans* vinyl group to C_5 of β-elemenone was



a, *t*-BuOOH-cat. $VO(acac)_2$; b, MsCl-Et_3N; c, NaI; d, DBU; e, CH_2=CH(CH_3)CuCNLi; f, PCC; g, MeMgBr-cat. CuCl and then PhSeBr; h, $NaIO_4$; i, (CH_2=CH)$_2$CuCNLi$_2$; j, LHDS, CS_2, and then LHDS, MeI; k, Me_2CuLi

achieved by the stereocontrolled addition of organocuprate to 3,4-disubstituted 2-cyclohexen-1-one.$^{15)}$ The Michael addition of dilithium divinylcyanocuprate$^{16)}$ to enone 9 (ether, -70 °C to -50 °C, 2 h) furnished the desired cyclohexanone 10$^{2a)}$ in 78% yield, which was homogeneous in VPC and TLC and had spectral attributes of a single isomer; $[\alpha]_D^{20}$ -26.2° (c 1.05, $CHCl_3$). The last step, introduction of isopropylidene group *via* α-dithiomethylene derivative (11) was successfully performed according to Dieter's method.$^{17)}$ Cyclohexanone 10 was converted (i. lithium hexamethyldisilazide (LHDS), CS_2, ii. LHDS, CH_3I) to 11 in 70% yield without any formation of α'-dithiomethylene isomer,$^{2a)}$ $[\alpha]_D^{21}$ +27.3° (c 0.96, $CHCl_3$). Methylation of 11 with lithium dimethylcuprate gave (4*S*)-*trans*-β-elemenone (1)$^{2a)}$ in 85% yield; $[\alpha]_D^{23}$ +39.3° (c 1.02, $CHCl_3$).

As mentioned above, first total synthesis of natural (4*S*)-β-elemenone with high optical purity was achieved in a stereoselective manner from pure (*S*)-2-cyclohexen-1-ol obtained easily by the asymmetric reduction of 2-cyclohexen-1-one with chiral hydride reagent 3.

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6) ^{1}H NMR and/or IR spectra of chiral compounds obtained were identical with those of racemic ones, **4**,[7] **5**,[8] **9**,[14] **10**,[2a] **11**,[2a] and **1**.[2a]

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11) **6**: ^{1}H NMR (CCl_4) δ 1.10-2.25 (m, 4H), 1.70 (s, 3H), 2.45-2.90 (m, 1H), 3.33 (broad s, 1H), 3.90-4.25 (m, 1H), 4.70 (m, 2H), and 5.67 (dd, J = 11 and 12 Hz, 2H); IR (neat) 3400-3000, 2800, and 1600 cm^{-1}. **7**: ^{1}H NMR (CCl_4) δ 1.10-2.30 (m, 5H), 1.70 (s, 3H), 2.40-2.80 (m, 1H), 3.20-3.75 (m, 1H), 4.80 (m, 2H), and 5.12-5.83 (m, 2H); IR (neat) 3500-3100, 2800, and 1620 cm^{-1}. **8**: ^{1}H NMR (CCl_4) δ 1.55-2.55 (m, 4H), 1.80 (s, 3H), 2.75-3.23 (m, 1H), 4.70-5.00 (m, 2H), 5.85 (dd, J = 5 and 2 Hz, 1H), and 6.72 (dd, J = 5 and 3 Hz); IR (neat) 2900 and 1660 cm^{-1}.

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