

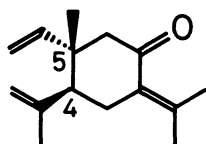
STEREOSELECTIVE TOTAL SYNTHESIS OF (4S)-*trans*- β -ELEMENONE
FROM (S)-2-CYCLOHEXEN-1-OL

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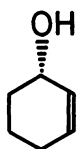
Stereoselective first total synthesis of (4S)-*trans*- β -elemenone was achieved from (S)-2-cyclohexen-1-ol, prepared easily by the asymmetric reduction of 2-cyclohexen-1-one with chiral hydride reagent.

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 (4S)-*trans*- β -elemenone (1) from (S)-2-cyclohexen-1-ol (2). Construction of two chiral centers of C₄ and C₅ in 1 was achieved by 1,4-addition of organocopper reagents to the key intermediates, (3S,4R)-3,4-epoxy-1-cyclohexene (5) and (S)-4-isopropenyl-3-methyl-2-cyclohexen-1-one (9), respectively (*vide infra*).

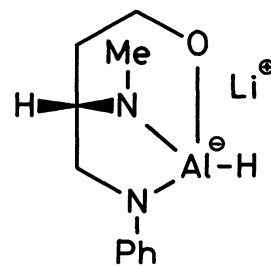
The starting material, optically pure (S)-alcohol 2 was effectively synthesized in 95% yield from 2-cyclohexen-1-one using the chiral reducing reagent (3) of lithium aluminum hydride modified with (S)-4-anilino-3-methylamino-1-butanol which was prepared easily from (S)-aspartic acid;³⁾ $[\alpha]_D^{23} -112.5^\circ$ (c 1.06, CHCl₃)



1



2



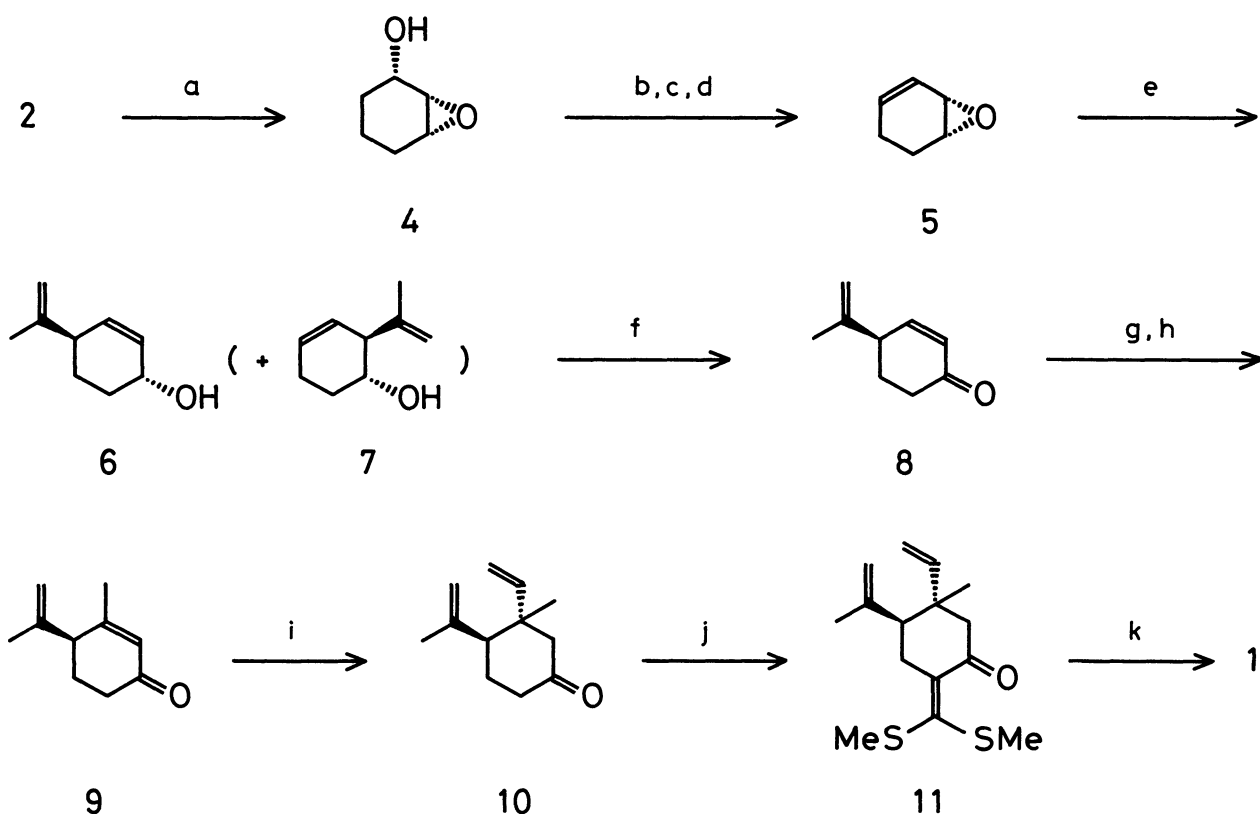
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(lit.⁴⁾ $[\alpha]_D^{20} -112^\circ$ (c 0.60, CHCl_3).

syn-Epoxidation⁵⁾ of (*S*)-alcohol 2 (cat. $\text{VO}(\text{acac})_2$, *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: $[\alpha]_D^{22} -42.1^\circ$ (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., $\text{MsCl-Et}_3\text{N}$, 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); $[\alpha]_D^{24} -56.6^\circ$ (c 0.53, CHCl_3); bp 80 °C/145 mmHg.

The introduction of (4*S*)-isopropenyl group was accomplished by *anti* 1,4-addition ($\text{S}_{\text{N}}2'$ 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 ($\text{S}_{\text{N}}2$ 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 6¹¹⁾ (56%, $[\alpha]_D^{22} +174.3^\circ$ (c 0.85, CHCl_3)) and 7¹¹⁾ (19%, $[\alpha]_D^{22} -76.2^\circ$ (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 chlorochromate¹²⁾ (CH_2Cl_2 , rt, 2 h) gave (*R*)-4-isopropenyl-2-cyclohexen-1-one (8)¹¹⁾ in 79% yield; $[\alpha]_D^{22} +157.6^\circ$ (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; $[\alpha]_D^{22} +171.9^\circ$ (c 1.01, CHCl_3). The (*S*)-configuration is verified by the optical rotation $[\alpha]_D -28.4^\circ$ of (*R*)-9 reported by Lander and Mechoulans.¹⁴⁾

Next key step of introduction of *trans* vinyl group to C₅ of β -elemenone was



a, *t*-BuOOH-cat. VO(acac)₂; b, MsCl-Et₃N; c, NaI; d, DBU; e, CH₂=CH(CH₃)CuCNLi; f, PCC; g, MeMgBr-cat. CuCl and then PhSeBr; h, NaIO₄; i, (CH₂=CH)₂CuCNLi₂; j, LHDS, CS₂, and then LHDS, MeI; k, Me₂CuLi

achieved by the stereocontrolled addition of organocuprate to 3,4-disubstituted 2-cyclohexen-1-one.¹⁵⁾ The Michael addition of dilithium divinylcyanocuprate¹⁶⁾ 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; $[\alpha]_D^{20} -26.2^\circ$ (c 1.05, CHCl₃). 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), CS₂, ii. LHDS, CH₃I) to 11 in 70% yield without any formation of α' -dithiomethylene isomer,^{2a)} $[\alpha]_D^{21} +27.3^\circ$ (c 0.96, CHCl₃). Methylation of 11 with lithium dimethylcuprate gave (4*S*)-*trans*- β -elemenone (1)^{2a)} in 85% yield; $[\alpha]_D^{23} +39.3^\circ$ (c 1.02, CHCl₃).

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.

References

- 1) a) I. Ognjanov, V. Herout, M. Horak, and F. Sorm, *Collect. Czech. Chem. Commun.*, **24**, 2371 (1959); b) G. V. Pizulerskii and N. V. Belova, *Zh. Obshch. Khim.*, **34**, 1345 (1964); c) D. H. E. Tattje and R. Bos, *Pharm. Weekbl.*, **109**, 1189 (1974) [*Chem. Abstr.*, **83**, 103117m (1975)]; d) Y. Naya, Y. Nagahama, and M. Kotake, *Heterocycles*, **10**, 29 (1978).
- 2) a) G. Majetich, P. A. Grieco, and M. Nishizawa, *J. Org. Chem.*, **42**, 2327 (1977); b) T.-L. Ho and T. W. Hall, *Synth. Commun.*, **12**, 97 (1982); c) O. Soria and L. A. Maldonado, *ibid.*, **12**, 1093 (1982).
- 3) T. Sato, Y. Gotoh, and T. Fujisawa, *Tetrahedron Lett.*, **23**, 4111 (1982); T. Sato, Y. Gotoh, Y. Wakabayashi, and T. Fujisawa, *ibid.*, in press.
- 4) S. Yamada, N. Takamura, and T. Mizoguchi, *Chem. Pharm. Bull.*, **23**, 2539 (1975).
- 5) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
- 6) ¹H 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)}
- 7) A. Bongini, G. Cardills, M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, **47**, 4626 (1982).
- 8) J. K. Crandall, D. B. Banks, P. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).
- 9) a) D. M. Wieland and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 3047 (1971); b) J. Staroscik and B. Rickborn, *ibid.*, **93**, 3046 (1971); c) J. P. Marino and N. Hatanaka, *J. Org. Chem.*, **44**, 4467 (1979); d) J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, **1979**, 675.
- 10) a) M. Suzuki, T. Suzuki, T. Kawagichi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980); b) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, and K. Maruyama, *J. Org. Chem.*, **47**, 119 (1982).
- 11) 6: ¹H NMR (CCl₄) 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: ¹H NMR (CCl₄) 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: ¹H NMR (CCl₄) 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.
- 12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.
- 13) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
- 14) N. Lander and R. Mechoulam, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 484.
- 15) F. E. Ziegler, G. R. Reid, W. L. Studt, and P. A. Wender, *J. Org. Chem.*, **42**, 1991 (1977); P. M. Wege, R. D. Clark, and C. H. Heathcock, *ibid.*, **41**, 3144 (1976); S. Danishefsky, M. Kahn, and M. Silvestri, *Tetrahedron Lett.*, **23**, 703 (1982).
- 16) B. H. Lipshutz, R. S. Wilhelm, and J. Kozlowski, *Tetrahedron Lett.*, **23**, 3755 (1982).
- 17) R. K. Dieter, *J. Org. Chem.*, **46**, 5031 (1981).

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