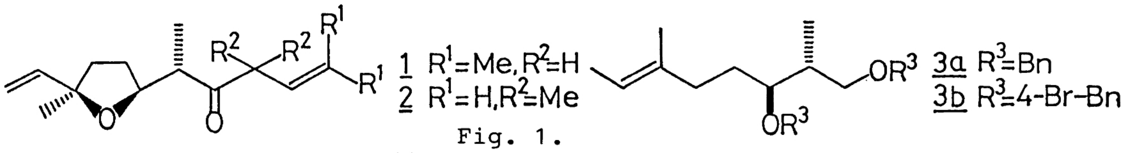
CHEMISTRY LETTERS, pp. 1259-1262, 1987.

# Stereoselective Syntheses of (+)-Davanone and (+)-Artemone via Anti-selective Epoxidation and Iodo-cyclization

Yutaka HONDA,* Aiichiro ORI, and Gen-ichi TSUCHIHASHI*
Department of Chemistry, Faculty of Science and Technology,
Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223

Chiral sesquiterpenes, (+)-Davanone and (+)-Artemone, were synthesized via anti-selective epoxidation and iodo-cyclization by the use of (S)-ethyl lactate as a chiral source.

(+)-Davanone (1) and (+)-Artemone (2) are chiral sesquiterpene ketones constituted of the cis-tetrahydrofuran having α-substituted ketone as a side chain (Fig. 1). The former was isolated from the essential oil of *Altemisia Pallens* and its gross structure was proposed by Sipma and van der Wal in 1962.[1] The relative stereochemistry was proposed by Naegeli[2] and Birch[3] by means of the synthesis of all the four diastereomers, and proven by Ohloff and Giersch in 1970.[4] The latter was isolated from the same source and the relative structure was proposed by Naegeli.[5] Recently Bartlett and Holmes reported[6] the stereoselective synthesis of racemic 1 by using iodo-cyclization of the threo-ether (Fig. 1; 3) which was prepared by using threo-selective aldol condensation,[7] followed by Jones oxidation and condensation with excess dimethallyllithium.



1 $R^1$=Me,$R^2$=H
2 $R^1$=H,$R^2$=Me
3a $R^3$=Bn
3b $R^3$=4-Br-Bn

Fig. 1.

We have already reported[8] the anti-selectivity (>99%) on the epoxidation of the (Z)-2-methyl-3,4-unsaturated aldehyde cyclic acetal (4) by the treatment with TBHP and $EtAlCl_2$ (or $TiCl_3OPr^i$). When the substrate had another double bond besides β,γ-double bond, the latter was selectively epoxidized. Furthermore, thus obtained epoxide (5) reacted with $LiAlH_4$ at sterically less hindered γ-position to afford the threo aldol equivalent (6) (Fig. 2). The acetal group was capable to be converted into the corresponding dithioacetal group, which was useful for C-C bond formation without racemization at α-position. In these reactions, roles of the acetal group were protection of the carbonyl group, activation of the 1,2-rearrangement,[11] coordination with a metal, and limitation of a nucleophile's attack by the steric hindrance.

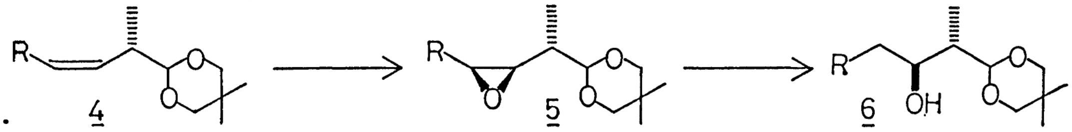


Fig. 2. 4 5 6

Thus we examined the stereoselective syntheses of the unique chiral sesquiterpenes, (+)-Davanone (1) and (+)-Artemone (2) by the application of our epoxidation and Bartlett's iodo-cyclization as the key steps with the hope of the improvement in the selectivity of the iodo-cyclization by the steric hindrance.

Retrosyntheses were as follows: 1) Allylation of 1,3-dithiane derivative (7); 2) iodo-cyclization of 8 and acetal exchange; 3) anti-epoxidation of 4 and hydrogenolysis (Fig. 3).

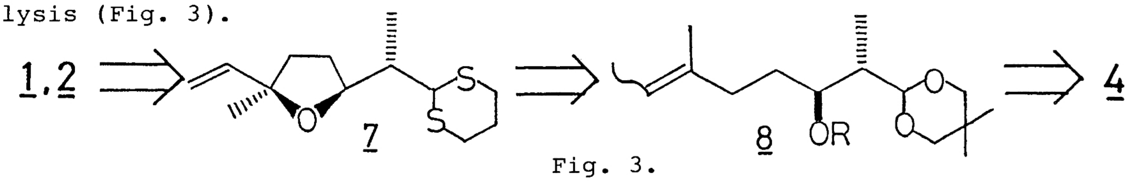


Fig. 3.

At first, synthesis of 6-alkene (8) as a substrate at iodo-cyclization was examined (Fig. 4). According to the previous paper,9) the introduction of (S)-chirality at C-2 was practiced by the reaction of lithium acetylide10) with amide (9)11) followed by hydrolysis to afford α-hydroxy ketone (10) in 78% yield. In this case, the double bond at C-6 of 8 was modofied into the double bond at C-8 of 10, since migration of the double bond was easily occurred by conjugation in the step of preparation of a β,γ-unsaturated acetylene. α-Hydroxy ketone (10) was acetalized by the treatment with TMSCl and 2,2-dimethyl-1,3-propanediol, followed by hydrogenation and mesylation to give (Z)-mesylate (11) in 94% yield. Reductive 1,2-rearrangement11) of 11 by the treatment with DIBAL (1.5 equiv.) and $Et_3Al$ (1.0 equiv.) in toluene at -42 °C gave (S)-aldehyde acetal (12) in 94% yield. Acetal (12) was epoxidized by the treatment with TBHP (5 equiv.) and $TiCl_{3.25}(OPr^i)_{0.75}$8) (2.5 equiv.) in dichrolomethane at -78 °C, followed by the treatment with $K_2CO_3$ in MeOH to give anti-epoxide (13) in 80% yield. Epoxide (13) was hydrogenolyzed and protected to afford (S)-O-benzyl threo-acetal (14) in 95% yield. In the presence of pyridine, ozonolysis of 14 afforded ketone (15) in 84% yield.12) Ketone (15) was converted into 6-alkene (8, Z/E=1/1) in 67% yield by reduction with $NaBH_4$, followed by tosylation, and elimination with DBU (10 equiv.) in dimethylsulfoxide at 85 °C (Fig. 4).

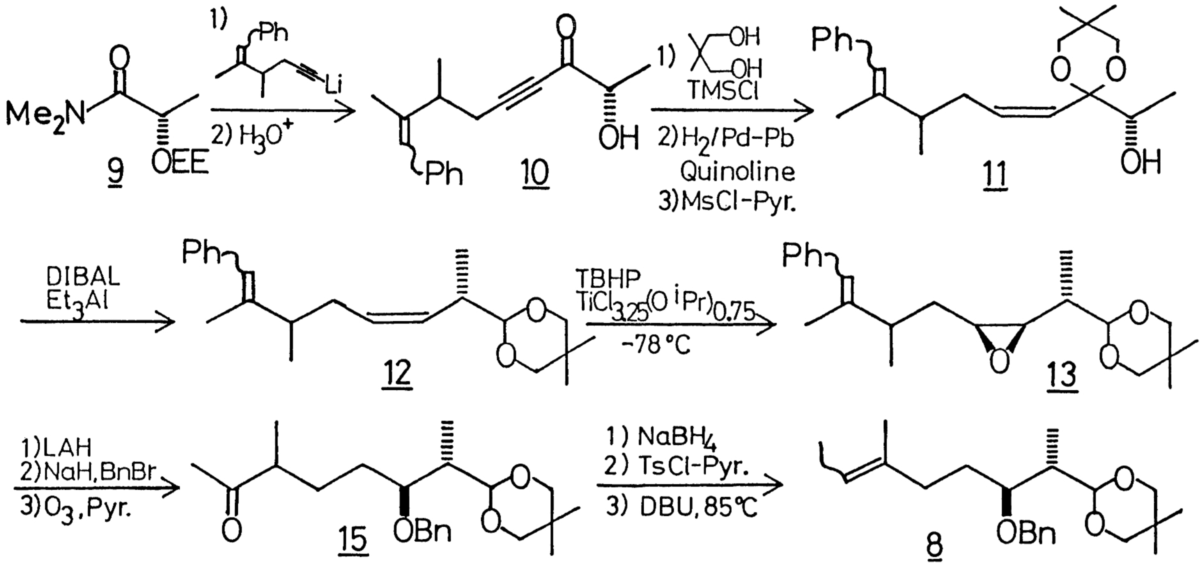


Fig. 4.

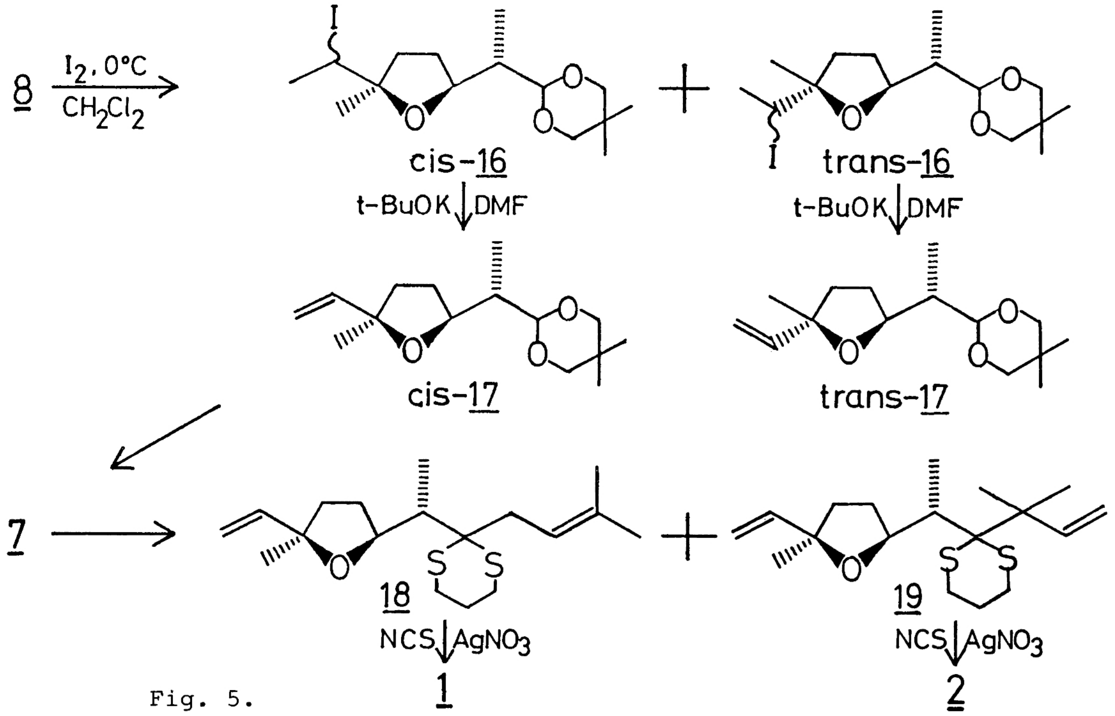


Fig. 5.

6-Alkene (8) was stepwisely treated with iodine[13] in the presence of CaCO$_3$ at 0 °C to give the crude 7-iodo acetal (16) in 96% yield. The ratio of cis/trans of 16 was determined by HPLC analysis [14] to be 21/1 when the reaction was run in dichloromethane, and reduced into 7/1 in acetonitrile. The selectivity of E-8 was found to be better than that of Z-8 (E-8=32/1, Z-8=15/1).[15] The selectivity was better than the Bartlett's results (3a=6/1, 3b=16/1)[6,16] obtained by using some benzyl groups as a protecting group. It was concluded that the higher selectivity was caused by the bulk of the acetal group. The crude 16 was separated by the silica-gel column chromatography (benzene, hexane-ethyl acetate) to yield cis-16 (88%) and trans-16 (4%) respectively. They were treated with t-BuOK in N,N-dimethylformamide[6] to yield cis-7-alkene (cis-17, 94%) and trans-7-alkene (trans-17, 73%) respectively. Their structure were concluded by the δ-value of H-7 at $^1$H NMR mesurement.[17] cis-17 was converted into the dithioacetal (7) by the treatment with 1,3-propanedithiol and trifluoroborane diethyl etherate[11] in 84% yield.

Since the generation of an anion of 7 was disturbed by the steric hindrance of the tetrahydrofuran ring, lithiation was carried out by the treatment with BuLi (2.0 equiv.) for 30 min at 0 °C. The anion was treated with prenylbromide at -78 °C to give a normal product (18, 41%) and an abnormal product (19, 19%) and recovered 7 (39%). The abnormal product (19) was probably formed via 2,3-sigmatropic rearrangement of the intermediary S-ylide as depicted in Fig. 6.[18] The protected Davanone (18) was treated with NCS (4 equiv.) and AgNO$_3$ (4.5 equiv.) in the presence of buffer in aqueous acetonitrile and acetone at 0 °C,[19] followed by evaporation at 0 °C and purification by silica-gel column chromatography (hexane-ethyl acetate) to afford (+)-Davanone (1) in 72% yield. Abnormal product (19) was also converted to afford (+)-Artemone (2) in 70% yield in the same manner (Fig. 5).

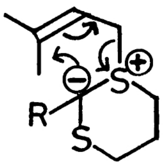


Fig. 6.

The physical properties ($\alpha_D$, IR, $^1$H NMR, $^{13}$C NMR) of 1 and 2 agreed with the natural ones well.$^{20)}$

References

1) G. Sipma and B. van der Wal, *Rec. Trav. Chim. Pays-Bay*, 87, 715 (1968).

2) P. Naegeli and G. Weber, *Tetrahedron Lett.*, 1970, 959.

3) A. J. Birch, J. E. T. Corrie, and G. S. R. Subba Rao, *Aust. J. Chem.*, 23, 1811 (1970).

4) G. Ohloff and W. Giersch, *Helv. Chim. Acta.*, 53, 841 (1970).

5) P. Naegeli, J. Klimes, and G. Weber, *Tetrahedron Lett.*, 1970, 5021.

6) P. A. Bartlett and C. P. Holmes, *Tetrahedron Lett.*, 24, 1365 (1983).

7) C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, 37, 4087 (1981).

8) Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1986, 1417.

9) Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1986, 13.

10) This acetylene was prepared from ethyl 3-oxobutyrate by dialkylation at C-2, decarboxylation, followed by Wittig reaction with $PhCH=PPh_3$.

11) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1985, 1153.

12) In the absence of pyridine, the benzyl group was partially oxidized to give the benzoyl group.

13) Since the reaction rate of E-8 was extremely larger than one of Z-8, 0.5 equivalent of iodine was added and stirred for 1 h until E-8 disappeared. And then Z-8 was treated with 0.8 equivalent of iodine by stepwise addition.

14) By using Develosil (Nomura Chemical Co., LTD.); hexane / ethyl acetate = 40/1 (v/v), flow rate 0.5 ml/min, $k'_{\text{trans-7S}}=4.14$, $\alpha_1=k'_{\text{trans-7R}}/k'_{\text{trans-7S}}=1.05$, $\alpha_2=k'_{\text{cis-7R}}\ /\ k'_{\text{trans-7S}}=1.50$, $\alpha_3=k'_{\text{cis-7S}}=k'_{\text{trans-7S}}=1.59$.

15) Determined by $^1$H NMR measurement of 16. The chemical shifts ($\delta$-value) based on H-1 of cis-7S, cis-7R, trans-7R, and trans-7S were 4.64, 4.61, 4.58, and 4.54 ppm respectively.

16) S. D. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.*, 103, 3963 (1981).

17) A. F. Thomas, W.F. Thommen, B. Willhalm, E. Hagamann, and E. Wenkert, *Helv. Chim. Acta.*, 57, 2055 (1974); Determination of the stereochemistry of linalyl oxide by the use of $\delta$-value was described. cis-17 has the double doublet ($\delta$ 5.80 ppm) for which the vinyl hydrogen (H-7) is responsible at lower field than trans-17 ($\delta$ 5.58 ppm).

18) E. Hunt and B. Lythgoe, *J. Chem. Soc., Chem. Commun.*, 1972, 757. Dithiane (7) was treated with prenylbromide (1.05 equiv.) and $AgBF_4$ (1.00 equiv.) to afford sulfonium salt (94%). According to this paper, obtained salt was treated with BuLi (1.50 equiv.) in THF at -78 °C to give 19 in 26% yield without 18.

19) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 36, 3553 (1971).

20) (+)-Davanone (1); $[\alpha]_D^{28}$ +84.2° ($c$ 0.43, $CHCl_3$) {lit.$^{15)}$ $[\alpha]_D^{20}$ +81.3° ($c$ 7.4, $CHCl_3$)}; IR (film) $\nu$ 1710, 1635 cm$^{-1}$; HRMS Found: m/z 236.1777. Calcd for $C_{15}H_{24}O_2$: M$^+$, m/z 236.1774. (+)-Artemone (2); $[\alpha]_D^{31}$ +73.3° ($c$ 0.36, $CHCl_3$) {lit.$^{5)}$ $[\alpha]_D$ +41.4° ($c$ 1.90, $CHCl_3$), purity 95%}; IR (film) $\nu$ 1710, 1630 cm$^{-1}$; HRMS Found: m/z 236.1757. Calcd for $C_{15}H_{24}O_2$: M$^+$, m/z 236.1774.

( Received March 13, 1987 )