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

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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.

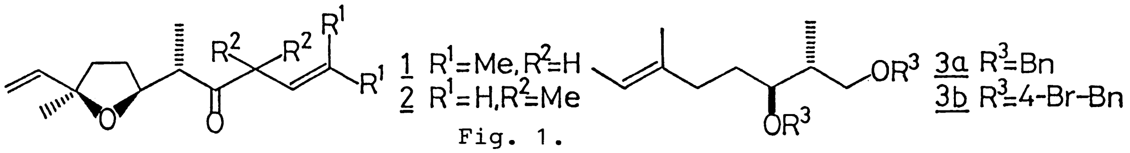

Fig. 1.

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.

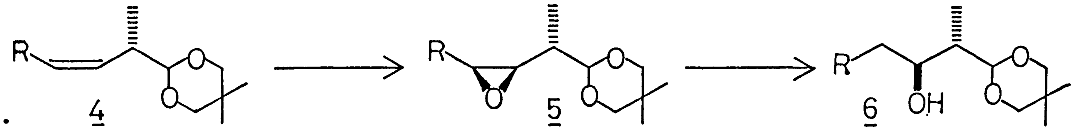

Fig. 2.

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).

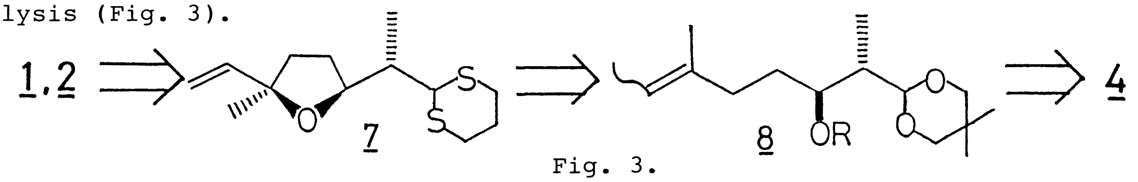

Fig. 3.

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 acetylide[10] 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-rearrangement[11] 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).

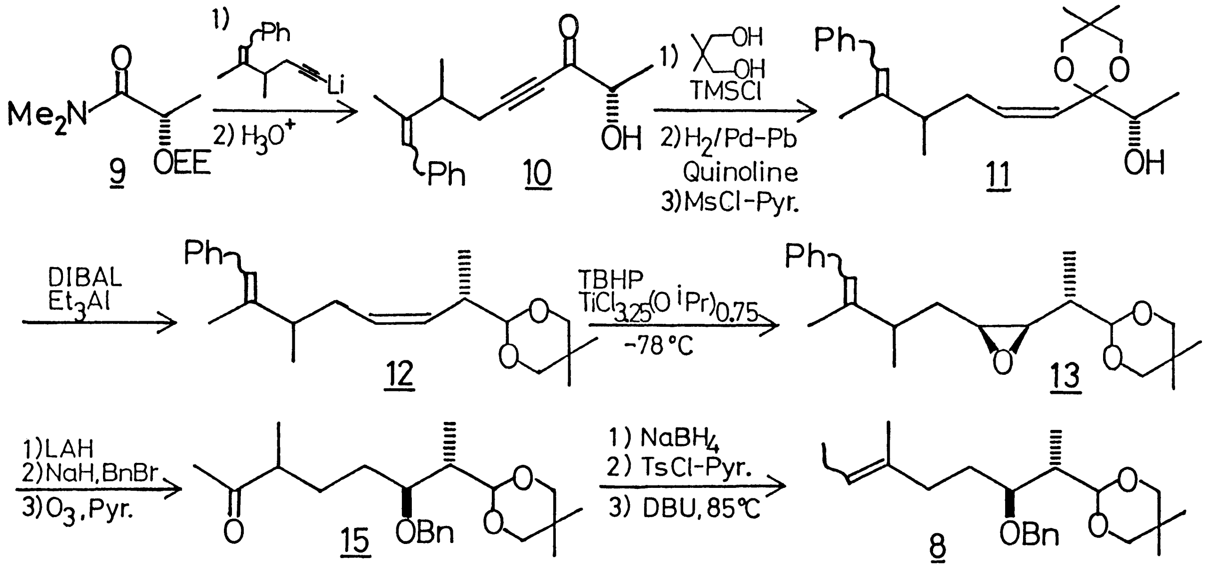

Fig. 4.

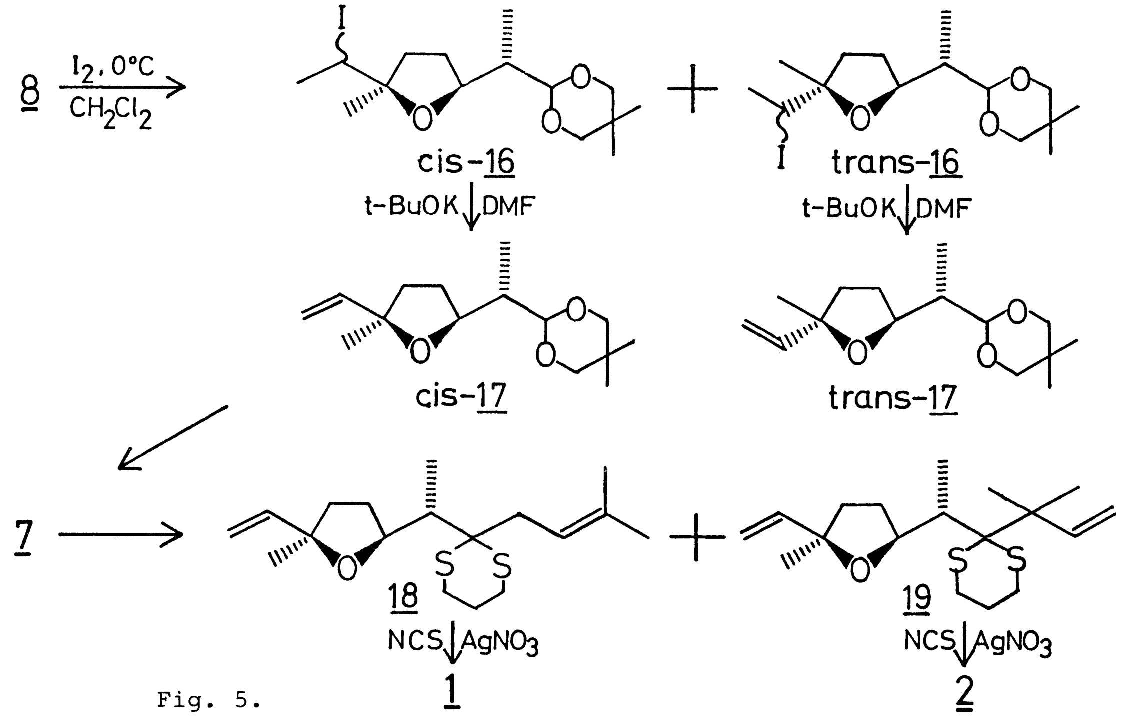

Fig. 5.

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).

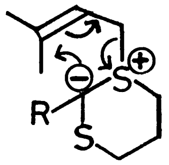

Fig. 6.

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

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

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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, $k'_{trans\text{-}7S}=4.14$, $\alpha_1=k'_{trans\text{-}7R}/k'_{trans\text{-}7S}=1.05$, $\alpha_2=k'_{cis\text{-}7R}/k'_{trans\text{-}7S}=1.50$, $\alpha_3=k'_{cis\text{-}7S}=k'_{trans\text{-}7S}=1.59$.

15) Determined by ^{1}H NMR measurement of 16. The chemical shifts (δ-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.

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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 δ-value was described. cis-17 has the double doublet (δ 5.80 ppm) for which the vinyl hydrogen (H-7) is responsible at lower field than trans-17 (δ 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.

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

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