Synthesis of Verbenols and Related Alcohols and Their PMR Spectra with Shift Reagent*

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In connection with our investigation on the structure-activity relationships of the American cockroach sex pheromone mimic, (+)-*trans*-verbenyl acetate, a number of alcohols having 6,6-dimethylbicyclo[3.1.1]heptane skeleton were synthesized, and measured their PMR spectra in the presence of the shift reagent, Eu(dpm)₃. The induced shifts of the 6,6-*gem*-dimethyl protons and α -proton at the C-7 guided us to distinction between *cis*- and *trans*-alcohol. The configuration of secondary methyl groups was discussed from the induced shift values of the methyl protons.

The typical sexual behavior of the male American cockroach (*Periplaneta americana* L.) to the female sex pheromone was characterized as consisting of wing flutter, extension of the abdomen and attempted copulation.¹⁾ The structural elucidation of the pheromone, periplanone-B, was carried out by Persoons *et al.*²⁾ who reported the structure to be a sesquiterpenoid possessing a germacrane skeleton. On the other hand, Bowers *et al.*³⁾ discovered that (+)-bornyl acetate (bicyclic monoterpenoid) and three other plant-derived compounds excite males of the American cockroach showing the typical sexual response mentioned above. Quite recently, Nishino *et al.*⁴⁾ carefully bioassayed about twenty bicyclic monoterpenoids and found (+)-*trans*-verbenyl acetate and (–)-bornyl acetate as sex pheromone mimics of the insect.

We had a simple question why such monoterpenoids and the sesquiterpenoid sex pheromone cause the same sexual excitement. In order to solve the question, the structural key factors for the sexual activity have been investigated for the monoterpenoid mimics. We speculated from inspection of molecular model of the mimics that the distances among the acetate and geminal dimethyl groups in the active

bornyl acetates and verbenyl acetate are significant for the activity.⁵⁾ This might be extended to that some special moieties and their stereo-interaction play key roles for causing the activity. Biological assay data with many analogs are, however, required in order to give more accurate informations. Hence, verbenols and related alcohols which would be mother compounds of active mimics were synthesized as our first approach. Because the position and orientation of the acetoxyl and single methyl groups of the mimic, (+)-*trans*-verbenyl acetate, are considered to be important for the sexual activity,⁵⁾ the position of a hydroxyl group was fixed at the C-2 and a secondary methyl or methylene group was introduced to the C-3 or C-4 in our compounds as shown in Fig. 1.

Our efforts were directed to the formation of the corresponding ketones as the key compound to the alcohols. In reduction of the ketones, lithium aluminum hydride (LiAlH₄) was basically employed in giving the *cis* alcohols, whereas lithium-ammonia (Birch reduction) in the *trans* alcohols, on the basis of the fact that LiAlH₄ and Birch reduction were used to obtain isoborneol⁷⁾ and borneol⁷⁾ from camphor, respectively. When both methods were unsuccessful, Meerwein-Ponndorf reduction was performed. Synthetic routes carried out according to the above basic ideas are il-

* Studies on the Sex Pheromone Mimic of the American Cockroach, (+)-*trans*-Verbenyl Acetate. Part I.

FIG. 1.

SCHEME 1.

SCHEME 2.

lustrated in Schemes 1 and 2.

(+)-*cis*-Verbenol*¹ (**1**), mp 69~70°, $[\alpha]_D + 9.6^\circ$ [chloroform (CHCl₃)]*², (+)-*trans*-verbenol (**2**), $[\alpha]_D + 130.0^\circ$ (CHCl₃), and (+)-verbenone (**14**), $[\alpha]_D + 240.1^\circ$ (CHCl₃), were obtained from (+)- α -pinene (**13**), $[\alpha]_D + 46.9^\circ$ (neat), as per Mori *et al.*⁸⁾ Catalytic hydrogenation of **2** and **14** afforded (+)-isoverbanol (**4**), mp 61~64°, $[\alpha]_D + 43.8^\circ$, and *cis*-verbanone (**15**), PMR*³: 1.17 (3H, d, $J=7.0$, 4 β -Me), respectively. The LiAlH₄ reduction of **15** gave (+)-neoisoverbanol (**3**), mp 68~69.5°, $[\alpha]_D + 9.0^\circ$.

To the bromination of (+)-nopinone (**17**), $[\alpha]_D + 12.3^\circ$, prepared from (–)- β -pinene (**16**), $[\alpha]_D - 21.0^\circ$ (neat), reaction temperature fairly affected, *i. e.*, in the case at 0°, major resultant was 3 α -bromonopinone (**18'**), whereas at room temperature (r. t.) major product was 3 β -bromonopinone (**18**). In the PMR of **18** and **18'**, the chemical shifts of the 3-H suggested the orientation of bromo moiety; 3 α -H (**18**) resonated at 4.82, while 3 β -H (**18'**) which is shielded by the C-9 methyl group at 4.39.

Dehydrobromination with 1, 8-diazabicyclo [5. 4. 0]-7-undecene (DBU) was undergone to **18**, and the resulting apoverbenone (**19**) was immediately methylated with lithium dimethylcuprate (Me₂CuLi) to give *trans*-verbanone (**20**). Protons of the introduced secondary methyl group with α configuration resonated at a higher field (1.05) than that of 4 β -methyl group of **15** (1.17). On LiAlH₄ and Meerwein-Ponndorf reduction, **20** yielded (–)-neoverbanol (**5**), mp 76.5~77°, $[\alpha]_D - 16.5^\circ$, and (+)-verbanol (**6**), mp 56~57°, $[\alpha]_D + 8.4^\circ$, respectively.

3-Methylenenopinone (**22**) which is a key

*¹ For trivial names, refer to: D.V. Banthorpe and D. Whittaker, *Chem. Rev.*, **66**, 643 (1966).

*² Specific rotations were measured in benzene at 25° (Union automatic polarimeter PM-201), unless otherwise stated.

*³ PMR spectra were taken in deuteriochloroform at 60 MHz (Hitachi R-24), unless otherwise noted. Chemical shifts are expressed in ppm tetramethylsilane, and coupling constants (J) in Hz. Singlet, doublet, triplet and multiplet are abbreviated to s, d, t, and m, respectively.

compound for introducing C_1 unit to the C-3 of the skeleton was prepared from nopinone (17) following the procedure by Bessière-Chrétien.⁹⁾ Catalytic hydrogenation of 22 afforded 3 β -methylnopinone (23) with a trace amount of its epimer (24). With lithium diisopropylamide (LDA) and methyl iodide (MeI), 3 α -methylnopinone (24) was obtained from 17. Configuration of the 3-methyl groups of 23 and 24 was established by the chemical shift of the C-9 methyl proton according to Bessière-Chrétien's data⁹⁾ [0.70 (3H, s) in 23 and 0.90 (3H, s) in 24]. 3-Methylnopinones, 23 and 24, provided (–)-3 β -methyl-*cis*-nopinol (7), $[\alpha]_D -0.8^\circ$, and (+)-3 α -methyl-*cis*-nopinol (9), mp 89~91.5°, $[\alpha]_D +45.4^\circ$, on $LiAlH_4$ reduction, respectively. Birch reduction of 23 gave (–)-3 β -methyl-*trans*-nopinol (8), mp 44~46°, $[\alpha]_D -62.6^\circ$, as a mixture with 7 (3: 1). Column chromatography with silicic acid was effective in separating them.

Meerwein-Ponndorf reduction of the methyleneketone (22) gave a mixture of *cis*- and *trans*-methylenenopinol (11 and 12). The ratio of the mixture was seemed to be depend on reaction period. (–)-3-Methylene-*trans*-nopinol (12), $[\alpha]_D -52.5^\circ$, was more abundant than (+)-3-methylene-*cis*-nopinol (11) mp 59.5~61.5°, $[\alpha]_D +76.6^\circ$, after 10 hr. The *exo* methylene group of 12 was converted to a hydroxymethyl group (25), PMR: 3.6~4.0 (2H, m), on hydroboration (BH_3)-oxidation (H_2O_2) by the procedure of Bessière-Chrétien.¹⁰⁾ The diol (25) was derived to monophenylsulfide (26),¹¹⁾ PMR: 2.91 (1H, double d, $J=6.0$ and 11.5) and 3.35 (1H, double d, $J=8.0$ and 11.5), and was finally reduced to (–)-3 α -methyl-*trans*-nopinol (10), mp 47~48.5°, $[\alpha]_D -19.2^\circ$. In order to get 10, Meerwein-Ponndorf and Birch reduction of 3 α -methylnopinone (24) were attempted. In either case, however, epimerization of the methyl group occurred, and *cis*- and *trans*-nopinol with 3 β -methyl group were obtained as the result.

The configuration of secondary methyl groups of compounds, 3–10, was assignable from reaction mechanisms in generation of the

methyls.

In catalytic hydrogenation of derivatives of pinenes, verbenone and verbenols, the surface of the catalyst approaches from the less hindered α side of the molecule.¹²⁾ Therefore, all the catalytic hydrogenation products (4, 15 and 23), in our compounds should have a secondary methyl group with β configuration.

The reagent, Me_2CuLi , is known to use for Michael addition. In the reaction from apoverbenone (19) to 4-methylketone (20) using this reagent, which was established by Bessière-Chrétien,⁹⁾ a methyl anion attacks the cationic site at the C-4 of 19. Since the steric hindrance due to the dimethyl substituted bridge-ring prevents the attack of the anion from β side, the secondary methyl at C-4 of 20 is α configuration. The hindrance is also assumed to be effective to formation of the secondary methyl group of 24. In the reaction from 17 to 24, LDA makes an anionic site on the C-3 of nopinone (17) and the site must be attacked by the methyl cation (MeI) from the less hindered α side, so that 3 α -methylnopinone (24) is made.¹³⁾

For the α configuration of the secondary methyl of 10 was ascertained by the formation of 24 on Jones' oxidation of 10. This means that a hydroxymethyl group with α configuration was generated in 25, when 12 was treated with BH_3 and H_2O_2 . As shown in Fig. 2, Bessière-Chrétien¹⁰⁾ reported that compound 27 produced 28 and 28' with a ratio of 2:1 on the same treatment, in which α attack of a hydride ion was preferable to the other. The formation of the 3 α -hydroxymethyl group in 25 seems to

FIG. 2.

TABLE I. CHEMICAL SHIFTS (ppm) OF 8-CH₃, 9-CH₃, 7-H(α) AND SECONDARY CH₃ OF PAIRS OF *cis-trans* ISOMERS AND INDUCED SHIFTS (Δ ppm) OF THE PROTONS ON ADDITION OF Eu(dpm)₃ (0.08 mmol) TO CDCl₃ (0.3 ml) SOLUTION OF THE SUBSTRATES (0.2 mmol) IN THE PMR SPECTRA (100 MHz)

Compound	9-CH ₃	Δ ppm (A)	8-CH ₃	Δ ppm (B)	7-H(α) ^a	Δ ppm	sec-CH ₃ ^b	Δ ppm
(+)- <i>cis</i> -Verbenol (1)	1.08	3.34	1.35	1.35	1.28	1.98	—	—
(+)- <i>trans</i> -Verbenol (2)	0.88	1.42	1.35	1.10	1.32	5.31	—	—
(+)-Neoisoverbanol (3)	1.19	3.45	1.23	1.53	0.68	2.29	1.05	1.50
(+)-Isoverbanol (4)	1.00	1.10	1.25	0.83	1.24	3.96	1.00	0.90
(-)-Neoverbanol (5)	1.08	3.72	1.22	1.50	0.96	2.23	0.92	1.11
(+)-Verbanol (6)	0.80	1.36	1.25	1.11	1.61	4.67	0.92	1.48
(-)-3 β -Methyl- <i>cis</i> -nopinol (7)	1.02	3.16	1.21	1.14	1.30	1.91	1.08	3.93
(-)-3 β -Methyl- <i>trans</i> -nopinol (8)	0.75	1.50	1.23	0.97	1.57	4.78	1.15	3.10
(+)-3 α -Methyl- <i>cis</i> -nopinol (9)	1.09	3.20	1.23	1.20	0.73	2.23	1.17	2.16
(-)-3 α -Methyl- <i>trans</i> -nopinol (10)	0.94	1.22	1.24	0.90	1.19	4.94	1.10	4.55
(+)-3-Methylene- <i>cis</i> -nopinol (11)	1.04	3.82	1.25	1.39	0.88	2.06	—	—
(-)-3-Methylene- <i>trans</i> -nopinol (12)	0.84	1.32	1.26	0.99	1.23	5.26	—	—

^a In all compounds, this proton appeared as a sharp doublet signal with $J=8.0\sim 10.5$.

^b Coupling constants with 6.0~7.0 were observed for the doublet signal due to this methyl group.

be in conflict with the case of **28**. However, an intermediate **29** may exist in the hydroboration of **12**, since it is considered that the steric hindrance of the borane complex of the hydroxyl group at the C-2 obstructs the attach of hydride ion to the C-3 from α side.

The following reports led us to the application of a shift reagent to the PMR spectra of the alcohols to obtain more confirmable proofs for the configurational determination.

In the PMR of isborneol and borneol, the protons of geminal dimethyl groups (C-8*⁴ and C-9) are influenced showing down-field shifts by addition of Eu(fod)₃¹⁴⁾ and Eu(dpm)₃.¹⁵⁾ In comparison of such spectra between isborneol and borneol,^{14,15)} the C-8 methyl protons more largely shift to a lower field than the C-9 methyl ones in isborneol, while both methyl protons show small down-field shifts with nearly same intensity in borneol. Thus, comparative analysis of the induced shifts of the protons of geminal dimethyl groups may be distinguishable between epimeric bicyclic

monoterpene alcohols in the PMR with a shift reagent.

According to this conception, we took the spectra in the CDCl₃ (0.3 ml) solution of a mixture of the alcohol and the shift reagent [Eu(dpm)₃] at 100 MHz (JEOL PS-100). The ratio of the mixture was changed from 1:0 to 1:0.2, 1:0.4 and 1:0.6. Among the ratios, 1:0.4 [actually 0.2 mmole of the alcohol: 0.08 mmole of Eu(dpm)₃] was the best in the resolution and the separation of different protons. The PMR results are listed in table I.

As assumed, in the *cis* alcohols the C-9 methyl protons showed larger down-field shifts (3.16~3.82 ppm, *A* in the table) than the C-8 methyl protons (1.14~1.53 ppm, *B* in the table). On the other hand, in the *trans* alcohols, both *A* and *B* values were rather small with a range of 1.0~1.5 ppm, although the *A* value is slightly larger than the *B* value. When man considers the situation of the C-8 and C-9 methyl groups against the hydroxyl groups of a pair of *cis-trans* alcohols, the C-9 methyl group locates most closely to the β -hydroxyl group in *cis*-alcohol. This may cause the largest induced shift of the C-9 methyl protons in *cis*-alcohol, as compared with the other cases.

A distinct sharp doublet ($J=8.7\sim 8.9$)

*4 The numbering of bornane is as follows:

ascribed to the 7-H(α) has been observed in the PMR spectra of verbenols and verbenone¹⁶⁾, and was evidence in our spectra of all compounds reported here ($J=8\sim 10.5$). In our compounds, the proton situates below the plane made up of C-1-2-4-5, and is close to α -substituent of the C-2, C-3 and C-4. Accordingly, the 7-H(α) doublet must be more affected by 2 α -hydroxyl group (*trans*-alcohol) than 2 β -hydroxyl group (*cis*-alcohol) in our PMR experiment. In fact, the induced shifts of the doublet signal of 7-H(α) were larger in the *trans* alcohols (4~5 ppm) than in the *cis*-alcohols (about 2 ppm) as shown in the table. This PMR behavior of the 7-H(α) signal after addition of a shift reagent is useful in determining configuration of the hydroxyl group of 6, 6-dimethylbicyclo [3. 1. 1] heptanols.

Configuration of the secondary methyl group seems to be confirmed from its induced shift value in the PMR of 3~10 by addition of Eu(dpm)₃. Sen *et al.*¹⁷⁾ applied Eu(dpm)₃ to the PMR of four isomeric 3-aminopinane for their configurational and conformational analyses. In the isomers, secondary methyl groups of 3 β -amino-2 α H-pinane and 3 α -amino-2 β H-pinane showed larger down-field shift than those of the two other isomers on addition of the shift reagent. Furthermore, Paasivirta *et al.*¹⁸⁾ reported that in *endo*-campheniol (see the footnote in *4), the 3 α -methyl protons more greatly shifted to a lower field than the 3 β -methyl protons when Eu(dpm)₃ was used for the PMR spectra. Hence, it is assumable that the methyl group with the same configuration to the vicinally positioned hydroxyl group (α - α or β - β) is more influenced by shift reagents than the group with the opposite relationships (α - β , β - α).

In our alcohols possessing a vicinal secondary methyl-hydroxyl group (7~10), larger induced shifts of the secondary methyl protons were observed for the compounds having α - α (10, 4.55) and β - β (7, 3.93 ppm) relationships in comparison with the compounds having α - β (9, 2.16) and β - α (8, 3.10) relationships. Moreover, the similar trend was observable in the alcohols with a 1, 3 relation be-

tween the two groups (3~6). The secondary methyl protons shifted to a lower field in 6 (4 α -Me, 2 α -OH; 1.48) and 3 (4 β -Me, 2 β -OH; 1.50) with larger induced shifts than those in 5 (4 α -Me, 2 β -OH; 1.11) and 4 (4 β -Me, 2 α -OH; 0.90 ppm).

Thus, informations from the PMR spectra added a shift reagent are very valuable for the stereochemical elucidation of the 6, 6-dimethylbicyclo[3. 1. 1] heptanols.

EXPERIMENTAL

All boiling and melting points were uncorrected. IR spectra were recorded on a JASCO IRA-1. Gas chromatography was done with a Shimadzu 4BM-PF using a 2 m $\times$ 3 mm column packed with 3% OV-225 at 120° flowing nitrogen, unless otherwise stated. Mass spectra were taken on a Shimadzu GCMS-7000 with the same column in the GC measurement. Column chromatography was performed with silicic acid. Solutions were dried over MgSO₄, and evaporations were carried out at 35° *in vacuo*. *n*-Hexane, ethyl acetate, tetrahydrofuran are abbreviated as H, EtOAc, and THF in this section. The PMR data of the compounds in the table are omitted. For the specific rotations and PMR spectra, refer to the footnotes.

(+)-*cis*-Verbenol (1), (+)-*trans*-verbenol (2) and (+)-verbenone (14). These compounds were synthesized from (+)- α -pinene, $[\alpha]_D +46.9^\circ$ (neat), according to Mori *et al.*⁹⁾ The physical data agreed with the reported values, except for the specific rotations. (+)-*cis*-Verbenol (1), mp 69~70°; $[\alpha]_D +9.6^\circ$ ($c=0.94$, CHCl₃), -4.0° ($c=0.87$). (+)-*trans*-Verbenol (2), 103°/18 mm Hg; $[\alpha]_D +130.0^\circ$ ($c=1.0$, CHCl₃), $+120.2^\circ$ ($c=1.2$); [*cf.* its acetate, $[\alpha]_D +153.0^\circ$ ($c=0.97$, CHCl₃), $+147.0^\circ$ ($c=2.0$)]. (+)-Verbenone (14), $[\alpha]_D +240.1^\circ$ ($c=1.2$, CHCl₃), $+236.8^\circ$ ($c=1.1$).

(+)-*cis*-Verbanone (15). (+)-Verbenone (14) (1.8 g) in methanol (50 ml) was hydrogenated in the presence of 5% palladium-carbon at r.t. for 1 hr. After chromatography (H: EtOAc=10:1), pure (+)-*cis*-verbanone (15) was given, $[\alpha]_D +48.5^\circ$ ($c=1.2$); IR (film): 1705 cm⁻¹; PMR: 1.01 (3H, s), 1.17 (3H, d, $J=7.0$), 1.36 (3H, s); GC: t_R 6.6 min; MS: m/e 152 (M⁺, C₁₀H₁₆O), 137 (M⁺ - 15), 85 (Base peak).

(+)-*Neoisoverbanol* (3). Lithium aluminum hydride was added in excess to a solution of 15 in ether, and stirred the mixture at r.t. overnight. The ether was removed after usual treatment. The resulting residue was recrystallized from H to give (+)-*neoisoverbanol* (3), mp 68~69.5°; $[\alpha]_D +9.0^\circ$ ($c=0.48$); IR

(KBr): 3320 cm^{-1} ; GC: t_R 4.8 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 85 (Base peak).

(+)-*Isoverbanol* (4). Hydrogen gas was passed through a cyclohexane (20 ml) solution of (+)-*trans*-verbanol (2) (300 mg) in the presence of platinum oxide (40 mg) at r.t. for 30 min. A residue of the reaction mixture was recrystallized from H to give (+)-*isoverbanol* (4), mp $61 \sim 64^\circ$, $[\alpha]_D + 43.8^\circ$ ($c=0.5$); IR (KBr): 3280 cm^{-1} ; GC: t_R 5.5 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 85 (Base peak).

3 β -*Bromonopinone* (18). Bromine (3 ml) was added to a solution of (+)-*nopinone* (17) (6.2 g), $[\alpha]_D + 12.3^\circ$ ($c=0.95$), in ether (120 ml), and the mixture was stirred at r.t. for 30 min. After the reaction was completed by refluxing for 30 min, the ether solution was washed with NaHSO_3 and NaHCO_3 solutions. Removal of the solvent gave a crude crystal which included a trace amount of 3 α -*bromonopinone* (18'). Recrystallization of the crude crystal from ether afforded 3 β -*bromonopinone* (18), mp $111 \sim 112^\circ$; $[\alpha]_D - 9.8^\circ$ ($c=0.92$); IR (KBr): 1710 cm^{-1} ; PMR: 0.88 (3H, s), 1.37 (3H, s), 1.72 (1H, d, $J=10.0$), 2.0~3.2 (5H, m), 4.82 (1H, double quartet, $J=1.0, 8.0, 10.5$); 3 α -*Bromonopinone* (18'), mp $68 \sim 69^\circ$; $[\alpha]_D + 125^\circ$ ($c=0.94$); IR (KBr): 1700 cm^{-1} ; PMR: 0.85 (3H, s), 1.38 (3H, s), 4.39 (1H, double d, $J=3.5, 7.5$).

(+)-*trans*-*Verbanone* (20). A mixture of the *bromonopinone* (18) (2.7 g), DBU (2.7 g) and dimethylformamide (30 ml) was stirred at 160° for 3 hr in argon atmosphere. The reaction mixture was poured into water, and extracted with ether. Evaporation of the ether gave a residue. Column chromatography (H: EtOAc=10:1) of the residue afforded crude *apoverbanone* (19). To an ether solution of Me_2CuLi [prepared from cuprous iodide (4.2 g) in ether (20 ml) and 5% methyl lithium in ether (28 ml)], the crude 19 (2.8 g) was added. The mixture was stirred at r.t. for 2 hr in argon gas, and the reaction mixture was washed with water and evaporated to give a crude 20 which afforded pure (+)-*trans*-*verbanone* (20) (1.6 g) by column chromatography (H: EtOAc=10:1), $[\alpha]_D + 28.3^\circ$ ($c=0.99$); IR (film): 1710 cm^{-1} ; PMR: 0.84 (3H, s), 1.05 (3H, m), 1.32 (3H, s); GC: t_R 6.2 min; MS: m/e 152 (M^+ , $C_{10}H_{18}O$), 137 ($M^+ - 15$), 83 (Base peak).

(-)-*Neoverbanol* (5). The *verbanone* (20) (215 mg) in ether (20 ml) was reduced with LiAlH_4 at r.t. for 2 hr. Excess LiAlH_4 was decomposed with water and 15% NaOH solution. A crude crystal (200 mg) after removal of the ether was refined by recrystallization from H to obtain pure (-)-*neoverbanol* (5), mp $76.5 \sim 77^\circ$; $[\alpha]_D - 16.5^\circ$ ($c=1.1$); IR (KBr): 3300 cm^{-1} ; GC: t_R 5.0 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 85 (Base peak).

(+)-*Verbanol* (6). A solution of 20 (497 mg) in isopropanol (1 ml) was mixed to aluminum isopropoxide which was prepared from aluminum foil (178mg) and isopropanol (5 ml) in the presence of HgCl_2 (10 mg) (refluxing for 2 hr). The reaction continued for 18 hr distilling the acetone. Termination of the reaction was determined by TLC, i.e., two spots due to 5 and 6 were gradually converted to almost one spot corresponding to 6 after 18 hr. The solution was treated with 1 N-HCl and extracted with ether. Concentration of the ether gave a residue. The residue was column-chromatographed (H: EtOAc=7:1) to give (+)-*verbanol* (6), mp $56 \sim 57^\circ$ (from H); $[\alpha]_D + 8.4^\circ$ ($c=0.48$); IR (KBr): 3240 cm^{-1} ; GC: t_R 5.8 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 85 (Base peak).

3-Methylenepinone (22). Ethanol (1.1 ml) and sodium metal (1.2 g) were added successively to a solution of *nopinone* (17) (7.5 g) and ethyl formate (6.1 g) in ether (110 ml), and stirred for 2 hr. At this time, the sodium was perfectly consumed, and a brown precipitation was formed. By addition of water, the ether and water layers were separated. The water layer was acidified with 1 N-HCl, and extracted with ether. This ether solution produced a yellow crystal of hydroxymethylenepinone (21), PMR: 7.17 (1H, broad s), after evaporation. The crude crystal was immediately used to the next reaction. To a solution of 21 (10.8 g) in ether (200 ml), K_2CO_3 (42.4 g) and 37% formaldehyde solution (43 ml) were added. The reaction at r.t. was terminated after 2 hr. Evaporation of the ether gave a residue, and the residue was column-chromatographed (H: EtOAc=5:1) to give 3-methylenepinone (22), (7.8 g), $[\alpha]_D + 23.5^\circ$ ($c=1.1$); IR (film): $1705, 1610\text{ cm}^{-1}$, PMR: 0.89 (3H, s), 1.35 (3H, s), 5.37 (1H, m), 6.31 (1H, m); GC: t_R 5.1 min; MS: m/e 150 (M^+ , $C_{10}H_{14}O$), 135 ($M^+ - 15$), 107, 83 (Base peak).

3 β -*Methylnopinone* (23). Hydrogen gas was bubbled into a mixture of 22 (1.5 g), platinum oxide (100mg) and methanol at r.t. for 30 min. Column chromatography (H: EtOAc=7:1) of the concentrate gave 3 β -*methylnopinone* (23) (1.3 g) with a trace amount of 3 α -*methylnopinone* (24). 3 β -*Methylnopinone* (23), IR (film): 1720 cm^{-1} ; PMR: 0.70 (3H, s), 1.12 (3H, d, $J=6.0$), 1.29 (3H, s), 1.68 (1H, d, $J=9.0$); GC: t_R 6.3 min; MS: m/e 152 (M^+ , $C_{10}H_{18}O$), 137 ($M^+ - 15$), 109, 95, 83 (Base peak).

(-)-3 β -*Methyl-cis-nopinol* (7). The usual LiAlH_4 reduction of 23 (520 mg) afforded a crude alcohol. Column chromatography of the crude alcohol separately afforded 3 β -*methyl-cis-nopinol* (7) (497 mg) and 3 α -*methyl* isomer (10) (29 mg) whose origin was the contaminated 3 α -*methylnopinone* (24). 3 β -*Methyl-cis-nopinol* (7), $[\alpha]_D - 0.8^\circ$ ($c=1.0$); IR (film): 3400 cm^{-1} ;

GC (PEG 20M, 120°); t_R 8.0 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 121, 85 (Base peak).

(-)-3 β -Methyl-trans-nopinol (8). To a mixture of THF (3 ml) and liquid ammonia (9 ml), 3 β -methyl-nopinone (23) (402 mg) was added at -78°, and stirred. Furthermore, ammonium chloride (700 mg) and lithium metal (20 mg) were added to the solution. The cooling bath was removed and allowed to stand to r.t. to release the ammonia. After water and ether were added to the solution, the ether was dried and removed to give a residue which showed two main spots and several minor spots in a TLC analysis. Components corresponding to the two spots were separated by column chromatography (H: EtOAc = 7: 1). One of them was (-)-3 β -methyl-trans-nopinol (8) (296 mg), mp 44~46°; $[\alpha]_D - 62.6^\circ$ ($c = 0.48$); IR (KBr): 3240 cm^{-1} ; GC (PEG 20M, 120°): t_R 9.2 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 85 (Base peak). Another component was 7.

3 α -Methylnopinone (24). To a solution of nopinone (17) (2.0 g) in THF (5 ml), LDA [prepared from 15% *n*-butyllithium in hexan (8.8 ml), diisopropylamine (2.0 ml) and THF (5 ml)] was added in argon atmosphere under ice-cooling. The temperature was raised to r.t., and methyl iodide (0.94 ml) was added to the reaction mixture. After 30 min the mixture was poured into a saturated NH_4Cl solution, and extracted with ether. The residue of the extract was chromatographed (H: EtOAc = 10: 1) to afford 3 α -methylnopinone (24) (1.4 g), $[\alpha]_D + 29.0^\circ$ ($c = 1.0$); IR (film): 1710 cm^{-1} ; PMR: 0.90 (3H, s), 1.31 (3H, d, $J = 7.0$), 1.33 (3H, s); GC: t_R 6.0 min; MS: m/e 152 (M^+ , $C_{10}H_{16}O$), 137 ($M^+ - 15$), 109, 83 (Base peak). This chromatography also afforded the unchanged nopinone (17) (555 mg) and 3,3-dimethylnopinone (23 mg), PMR: 0.84 (3H, s), 1.25 (3H, s), 1.30 (3H, s), 1.32 (3H, s).

(+)-3 α -Methyl-cis-nopinol (9). 3 α -Methylnopinone (24) gave (+)-3 α -methyl-cis-nopinol (9) by the usual reduction with $LiAlH_4$, mp 89~91.5° (from H); $[\alpha]_D + 45.4^\circ$ ($c = 0.46$); IR (KBr): 3280 cm^{-1} ; GC: t_R 3.5 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 136 ($M^+ - 18$), 121, 97, 85 (Base peak).

(+)-3-Methylene-cis-nopinol (11) and (-)-3-methylene-trans-nopinol (12). To a solution of aluminum isopropoxide in isopropanol [prepared from aluminum foil (107 mg), $HgCl_2$ (6 mg) and isopropanol (3 ml)], 3-methylenopinone (22) (550 mg) in isopropanol (1 ml) was added, and refluxed for 15 hr, distilling the resulting acetone. The reaction mixture was poured into 1 N-HCl, and extracted with ether. An oily residue of the ether layer was column-chromatographed (H: EtOAc = 10: 1) to provide 11 (87 mg) and 12 (322 mg). (+)-3-Methylene-cis-nopinol (11), mp 59.5

~61.5°, $[\alpha]_D + 76.6^\circ$ ($c = 1.1$); IR (KBr): 3370, 1640, 900 cm^{-1} ; GC: t_R 3.9 min; MS: m/e 152 (M^+ , $C_{10}H_{16}O$) 137 ($M^+ - 15$), 119, 91 (Base peak). (-)-3-Methylene-trans-nopinol (12), $[\alpha]_D - 52.5^\circ$ ($c = 1.0$); IR (film): 3380, 1630, 895 cm^{-1} ; GC: t_R 4.7 min; MS: m/e 152 (M^+ , $C_{10}H_{16}O$), 137 ($M^+ - 15$), 134, 119, 109, 91, 85 (Base peak).

3 α -Hydroxymethyl-trans-nopinol (25). A solution of 12 (900 mg) in THF (2 ml) was added to a solution of borane in THF [prepared by addition of BF_3 -etherate (2.5 ml) of $NaBH_4$ (475 mg) suspension in THF (10 ml)] under ice-cooling, and stirred at r. t. for 1 hr. After addition of 3 N-NaOH (2.3 ml) and 30% $-H_2O_2$ (2.3 ml) the mixture was refluxed for 1 hr. Water and enough ether were added. The ether layer was dried and concentrated. The resulting residue was chromatographed (H: EtOAc = 2: 1 after 3: 1) to give 3 α -hydroxymethyl-trans-nopinol (25) (593 mg), mp 37~38.5° (from H); $[\alpha]_D - 9.0^\circ$ ($c = 0.98$); IR (nujol): 3410, 3160 cm^{-1} ; PMR 0.90 (3H, s), 1.26 (3H, s), 3.6~4.0 (2H, broad m), 4.50 (1H, broad d, $J = 8.0$); GC and MS were taken using diacetate of 25, t_R 9.5 min; m/e 239 ($M^+ - 15$), 213 ($M^+ - 40$), 211, 194 ($M^+ - 60$), 152, 134, 85, 43 (Base peak).

Monophenylsulfide of 25 (26). Tributylphosphine (2.7 ml) was added to a solution of 25 (478 mg) in pyridine (2 ml) and diphenyl disulfide (2.2 g) in argon atmosphere, and stirred at r.t. overnight. The pyridine was removed at r. t. with a vacuum pump and the resulting residue was subjected to column chromatography (H: EtOAc = 3: 1 after 7: 1) to obtain 26, mp 63~65° (from H); $[\alpha]_D - 51.8^\circ$ ($c = 0.54$); PMR: 0.86 (3H, s), 1.21 (3H, s), 2.91 (1H, double d, $J = 6.0, 11.5$), 3.35 (1H, double d, $J = 8.0, 11.5$), 4.38 (1H, broad d, $J = 7.0$), 7.1~7.6 (5H, m); MS: m/e 262 (M^+ , $C_{16}H_{22}OS$), 244 ($M^+ - 18$), 177, 153, 110 (Base peak).

(-)-3 α -Methyl-trans-nopinol (10). The monophenylsulfide (26) (324 mg) was subjected to Birch reduction by the same procedure performed to get compound 8 [THF (4 ml), liquid ammonia (8 ml), lithium metal (20 mg), at -78° for 2 hr]. The resulting crude crystal was column-chromatographed (H: EtOAc = 7: 1) to afford pure (-)-3 α -methyl-trans-nopinol (10), mp 47~48.5° (from H); $[\alpha]_D - 19.2^\circ$ ($c = 1.54$); IR (KBr): 3280 cm^{-1} ; GC: t_R 5.5 min; MS: m/e 154 (M^+ , $C_{10}H_{18}O$), 139 ($M^+ - 15$), 121, 111, 93, 85 (Base peak).

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