A FACILE SYNTHESIS OF 9-NOR-9-HYDROXYHEXAHYDROCANNABINOL *VIA* INTRAMOLECULAR REVERSE ELECTRON DEMAND DIELS-ALDER CYCLIZATION

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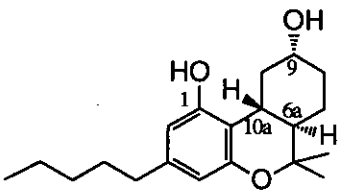
Abstract- A simple and efficient new synthesis of 9-nor-9-hydroxyhexahydrocannabinol is achieved, through the intramolecular [4+2] cycloaddition of an *o*-quinonemethide which is generated from 2-(1-hydroxy-3-methoxymethoxy-7-methyl-6-octenyl)-1,3-bis(*O*-methoxymethyl)olivetol (**12b**), which in turn is prepared by reaction of the lithiated olivetol bis(methoxymethyl)ether with 3-methoxymethoxy-7-methyl-6-octenal (**9**).

Natural and unnatural cannabinoids have been the focus of recent synthetic attention because of their therapeutic usage[1] and for application in pharmacological investigations.[2] It has been reported[3] that 9-nor-9-hydroxyhexahydrocannabinol (**1**) shows strong analgesic property similar to tetrahydrocannabinol (**3**), one of psycoactive components from marihuana. Compound (**1**) does not occur in nature and was prepared[3-5] by reduction of 9-nor-9-oxohexahydrocannabinol (**2**).[6] The analgesic properties of **1** and related unnatural cannabinoids have been thoroughly studied by Wilson *et al.*[3]



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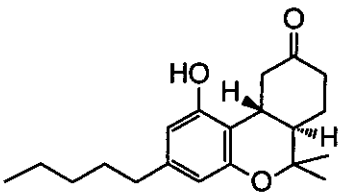

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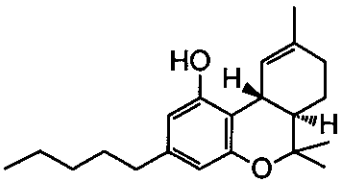

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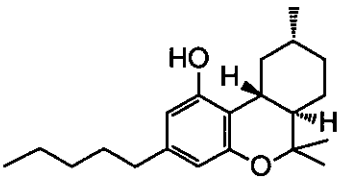
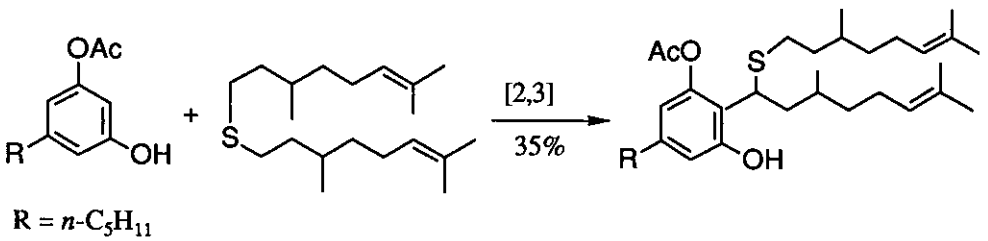
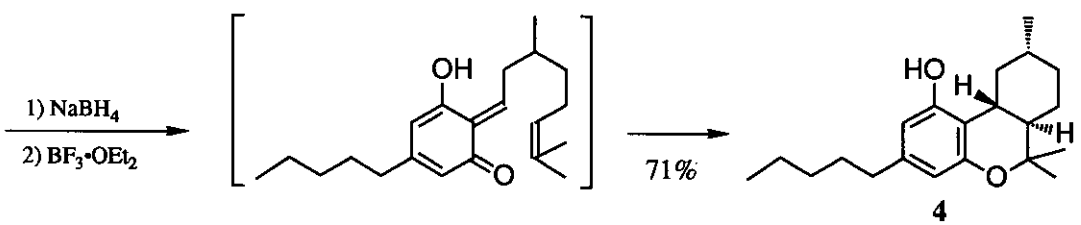


4

Tietze[7] reported a synthesis of (+) and (-)-Hexahydrcannabinol *via* the intramolecular Diels-Alder reaction of *o*-quinonemethides prepared from 5-*n*-pentyl-1,3-cyclohexanedione and (+) and (-)-citronellal, respectively. We have established an improved method of *ortho* alkylation of phenols using an alkyl sulfide, sulfuryl chloride, and triethylamine *via* [2,3] sigmatropic rearrangement of a phenoxysulfonium ylid,[8] and applied the method to the selective synthesis of *trans*-Δ^8-tetrahydrocannabinol and *cis*-Δ^9-tetrahydro-





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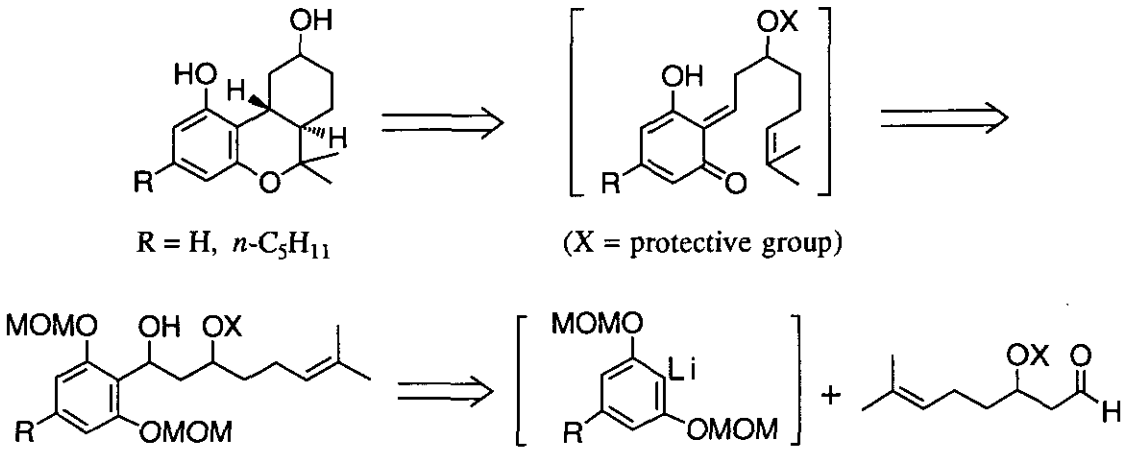
Scheme 1

cannabinol from olivetol monoacetate and isopentenyl isopropyl sulfide.[9] More recently[10,11] we explored a facile generation of *o*-quinonemethides, versatile reactive intermediates for organic synthesis, and achieved a synthesis of hexahydrocannabinol (**4**) from olivetol monoacetate and dicitronellyl sulfide in short steps as shown in Scheme 1.[11]

We here wish to report an efficient synthesis of **1** from olivetol and a readily available aliphatic couterpart based on the intramolecular [4+2] cycloaddition of *o*-quinonemethide with an olefinic moiety.

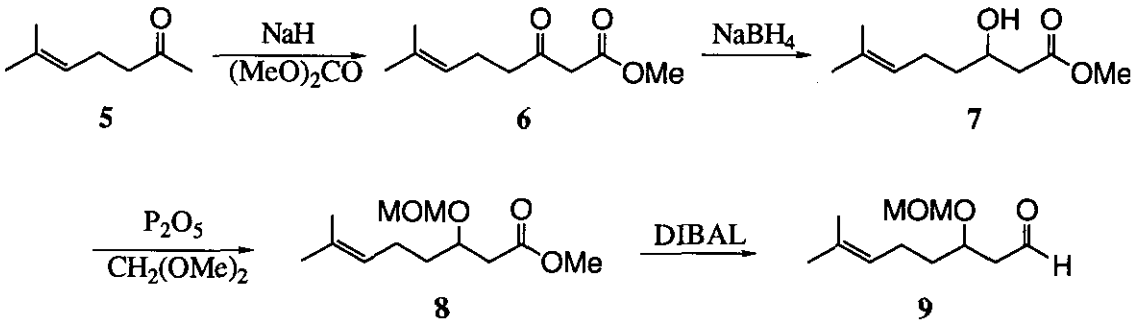
Ortho alkylation of phenols by [2,3] sigmatropic rearrangement suffers from the formation of regioisomers, i. e. 2-alkyl- and 6-alkylphenols, when unsymmetrically subsitituted phenols are used. Therefore we chose to use the reaction of regioselectively generated lithio derivatives of resorcinol and olivetol bismethoxymethyl ether with an aldehyde to yield 2-(α-hydroxyalkyl)resorcinol derivatives. Retrosynthetic analysis can be depicted as Scheme 2.



Scheme 2

We chose 6-methyl-5-hepten-2-one (**5**) as a starting meterial for the preparation of β-methoxymethoxyaldehyde (**9**). Treating of **5** with sodium hydride and dimethyl carbonate gave methyl 7-methyl-3-oxo-6-octenoate (**6**) in

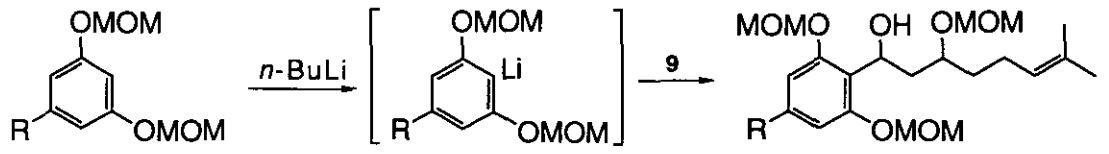
91% yield.[12] Reduction of **6** with sodium borohydride in dry methanol at -5°C produced β-hydroxy ester (**7**) in 89% yield, which, after protection of the β-hydroxyl group as methoxymethyl ether by the published method[13] in 70% yield, was converted to the corresponding aldehyde (**9**) in 87% yield by the DIBAL reduction in dry hexane (Scheme 3).



5 **6** **7** **8** **9**

Scheme 3

As a preliminary experiment, resorcinol was used as a dihydric phenol for the alkylation and subsequent cyclization. Regiospecific *ortho*-metalation of 1,3-bis(*o*-methoxymethyl)resorcinol (**10a**) with *n*-butyllithium followed by condensation with aldehyde (**9**) gave **12a** in 45% yield after chromatography on silica gel (scheme 4).



10 **11** **12**

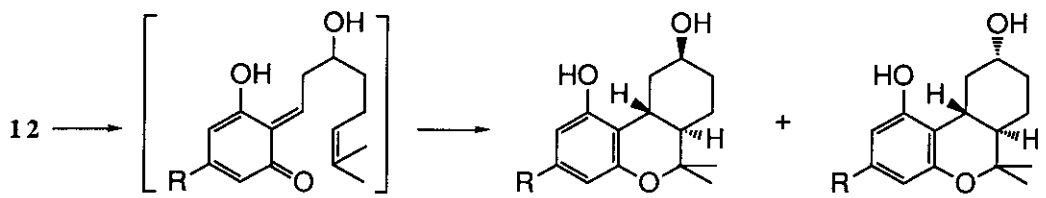
a; R = H, **b**; R = *n*-C_5H_{11}

Scheme 4

The structure of **12a** was based on the 270-MHz proton nmr analysis; the allylic methyls were observed at δ 1.60 (s) and 1.68 (s), and the methoxymethoxyl groups of the benzene ring showed singlets at δ 3.49 (6H)

and 5.22 (4H). The methoxymethoxyl group in the aliphatic chain showed signals at δ 3.40 (3H) and 4.17 (2H). The benzyl proton was observed as a doublet at δ 5.39 (1H, J = 6.3 Hz). The vinyl proton was observed at δ 5.14 (1H, J = 9.7 Hz) as a triplet.

The acid-catalyzed reaction of **12a** was attempted using 0.1 - 0.4 equiv. of *p*-toluenesulfonic acid (1.4 - 5.6 × 10^{-3} M) in refluxing dry methanol for 3 h. Although the starting material had run out after 1 h, the desired cycloaddition products (**14a**) and/or (**15a**) were not obtained. The product was a mixture of several components which exhibited presence of hydroxy groups but absence of methoxymethyl ether groups, indicating that the reaction stopped at the deprotection step under the reaction conditions. Finally, we succeeded in preparing the cycloaddition products (**14a** and **15a**) by treating **12a** with 0.5 - 0.8 equiv. of *p*-toluenesulfonic acid (0.7 - 1.1 × 10^{-2} M) in methanol at reflux for 3 h. Gas chromatographic and nmr analysis of the products indicated the ratio of axial hydroxy compound (**14a**) to equatorial hydroxy compound (**15a**) was about 65:35 (Scheme 5).



13 **14** **15**

a; R = H, **b**; R = n-C_5H_{11}

Scheme 5

The stereochemistry of the hydroxyl group and C-10a was assigned on the basis of the C-9 and C-10a proton signals in the 270 MHz spectra. The C-9 proton (δ 4.29) of **14a** appeared as a broader signal, but the C-9 proton (δ 3.89 ppm) of **15a** appeared as a septet signal, indicative of an axial proton in **15a**. The peaks of C-10a proton of **14a** and **15a** appeared at δ 2.98 and 2.51, respectively, as triplets, indicative of the *trans*-6a,10a structure of the both compounds.

Next the same reaction sequence was applied to make cannabinoids (**1**) (**14b** and **15b**) starting from olivetol bis(methoxymethyl) ether (**10b**). The acid treatment of **12b** in methanol at reflux resulted in the formation of **14b** and **15b** in a ratio of 65:35 in 76% yield, which were separated by column chromatography and recrystallized to give pure crystalline compounds. The structures were confirmed by the comparison of the nmr spectra with the reported ones.[3]

The predominant formation of the axial hydroxy compounds (**14a**) and (**14b**) needs some comments. The previous synthesis of hexahydrocannabinol *via* intramolecular cycloaddition reaction by us[11] and others[7,14,15] produced equatorial 9-methyl compounds exclusively irrespective of structures of the precursors of *o*-quinonemethides and reaction conditions. These selectivity may be accounted for in terms of the preferred conformation in the 6-membered transition state, i.e. equatorial methyl conformation in preference to equatorial one. In contrast, axial hydroxy conformation may be a preferred one in case of **14**. It is very likely that intramolecular hydrogen bonding plays an important role in determining the conformation in the transition state.

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and uncorrected. Ir spectra were measured on a Hitachi 260-10 spectrometer. ^{1}H-Nmr and ^{13}C spectra were recorded on JEOL-EX 270 (270 MHz) spectrometer with tetramethylsilane as an internal standard. Gas chromatographic determination was performed on a Shimadzu GC-14A. Column chromatography was carried out with Fujidavison silica gel BW-127 ZH (Fuji Davison Chemical Industries). Elemental analyses were carried out by Perkin-Elmer 2400.

Methyl 3-oxo-7-methyl-6-octenoate (**6**). A mixture of dimethyl carbonate (13.5 g, 150 mmol) and sodium hydride (10.5 g, 240 mmol, 55% dispersion in mineral oil) in dry dioxane (100 ml) was stirred and heated under reflux in N_2 atmosphere. And to this suspension was added dropwise a solution of 6-

methyl-5-hepten-2-one (**5**) (7 g, 55 mmol) in dry dioxane (24 ml) over 1.5 h. The mixture was refluxed for additional 1 h. The reaction mixture was quenched and neutralized with aq. 4N HCl while in cooling in an ice-bath, and extracted with ether for several times. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel developing with a mixture of hexane-ethyl acetate (90:10) to gave 9.3 g (91%) of **6** as a colorless liquid. Ir (neat)ν_{max}: 2930, 1740 and 1710 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.61 (3H, s), 1.67 (3H, s), 2.28 (2H, dd, J = 5.7 and 7.3 Hz), 2.57 (2H, t, J = 7.3 Hz), 3.45 (2H, s), 3.74 (3H, s), 5.07 (1H, t, J = 5.7 Hz).

Methyl 3-hydroxy-7-methyl-6-octenoate (**7**) . To a solution of **6** (8.37 g, 45.4 mmol) in 80 ml of anhydrous methanol was added sodium borohydride (2.06 g, 54.5 mmol) at −60°C. The mixture was allowed to warm to −5°C, and stirred for an additional 10 min at −5°C. And then 40 ml of water were added, and the solution was saturated with sodium chloride. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chlomatography using hexane-ethyl acetate (75:25) as eluent to give 7.52 g (89%) of **7** as a colorless liquid. Ir (neat)ν_{max}: 3550, 2950, 1740 and 1440 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.30 – 1.90 (2H, m), 1.62 (3H, s), 1.69 (3H, s), 2.11 (2H, q, J = 7.3 Hz), 2.20 (1H, br s), 2.48 (2H, m), 3.71 (3H, s), 4.01 (1H, m), 5.11 (1H, t, J = 6.6 Hz); ^{13}C nmr ($CDCl_3$)δ: 17.4, 23.9, 25.4, 36.4, 41.9, 51.4, 67.4, 123.5, 132.0, 173.1.

Methyl 3-methoxymethoxy-7-methyl-6-octenoate (**8**). To a stirred solution of **7** (2 g, 10.7 mmol) in chloroform (20 ml, dried over phosphorus pentoxide) were added methylal (65 ml, 730 mmol) and phosphorus pentoxide (15.2 g, 100 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature over a 30 min period and was further stirred for 30 min. The mixture was poured into an ice-cooled saturated sodium carbonate aqueous solution. The remaining oil in the reaction flask was washed with ether for several times and the combined mixture was extracted with ether. The

organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on developing with a mixture of hexane-ethyl acetate (80:20) to give 1.6 g (70%) of **8** as a colorless liquid. Ir (neat)ν_{max}: 2910 and 1740 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.30 – 1.90 (2H, m), 1.60 (3H, s), 1.69 (3H, s), 2.05 (2H, m), 2.53 (2H, m), 3.36 (3H, s), 3.69 (3H, s), 3.98 (1H, m), 4.67 (2H, s), 5.10 (1H, t, J = 6.6 Hz).

3-Methoxymethoxy-7-methyl-6-octenal (9). To a solution of 1.48 g (6.9 mmol) of ester (**8**) in a mixture of 29 ml of dry glyme and 29 ml of dry hexane were added dropwise 5.6 ml (8.3 mmol) of DIBAL (diisobutylaluminium hydride)(25% in toluene, 1.5 M) with syringe over 15 min under N_2 at −65°C. After stirring for 15 min at −65°C, 10 ml of methanol were added. The mixture was poured into a mixture of ether and water, the precipitate of aluminium salt was separated by filtration through celite. The aqueous layer was extracted with ether, and the combined organic layer was washed with water, and dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column using hexane-ethyl acetate (85:15) as an eluent to give 1.11 g (87%) of **9**. Ir (neat)ν_{max}: 2910, and 1730 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.50 – 1.90 (2H, m), 1.61 (3H, s), 1.69 (3H, s), 2.05 (2H, q, J = 7.5 Hz), 2.61 (2H, m), 3.36 (3H, s), 4.08 (1H, quint, J = 5.6 Hz), 4.67 (2H, s), 5.09 (1H, t, J = 7.5 Hz), 9.80 (1H, t, J = 2.2 Hz); ^{13}C nmr ($CDCl_3$)δ: 17.6, 23.7, 25.6, 34.9, 48.7, 55.5, 72.9, 95.9, 13.3, 132.2, 201.3.

2-(1-Hydroxy-3-methoxymethoxy-7-methyl-6-octenyl)-1,3-bis(*O*-methoxymethyl)resorcinol (12a). To to stirred solution of *n*-buthyllithium in hexane (1.4 ml, 2.5 M, 3.35 mmol) and 0.7 ml of TMEDA (4.52 mmol) in 10 ml of anhydrous ether was added 1,3-bis(*O*-methoxymethyl)resorcinol (0.45 g, 2.26 mmol) at −10°C. After reaction mixture was allowed to warm to room temperature and stirred for additional 6 h, a solution of **9** (0.5 g, 2.7 mmol) in 1 ml of hexane was added, and the mixture was stirred for 2 h under N_2. The solution was quenched by the addition of suturated ammonium chloride, separated, and the ethereal phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude

oil was purified by column chromatography using hexane – ethyl acetate (65:35) as eluent to give 0.39 g (45%) of oil **12a**. Ir (neat)ν_{max}: 3550, 2940, 1600, 1470 and 1040 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.60 (3H, s), 1,68 (3H, s), 1.40 – 1.95 (4H, m), 2.05 (2H, m), 3.39 (3H, s), 3.44 (1H, s), 3.49 (6H, s), 3.85 (1H, m), 4.72 (2H, m), 5.14 (1H, t, J = 7.3 Hz), 5.22 (4H, s), 5.39 (1H, d, J = 6.3 Hz), 6.80 (2H, d, J = 8.6 Hz), 7.13 (1H, t, J = 8.6 Hz); ^{13}C nmr ($CDCl_3$)δ: 17.6, 23.8, 25.6, 35.4, 42.4, 55.5, 56.2, 64.5, 75.5, 94.6, 96.2, 108,3. 121.2, 124.2, 128.4, 131.5, 155.5.

2-(1-Hydroxy-3-methoxymethoxy-7-methyl-6-octenyl)-5-pentyl-1,3-bis(*O*-methoxymethyl)olivetol (**12b**). The desired (**12b**) was synthesized in 40% yield according to the above mentioned ptocedure for the preparation of **12a**, from 0.3 g (1.11 mmol) of 1,3-bis(*O*-methoxymethyl)olivetol and aldehyde **9** of 0.25 g (1.33 mmol) instead of 1,3-bis(*O*-methoxymethyl)-resorcinol. Ir (neat)ν_{max}: 3550, 2950, 1590, 1620 and 1040 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 0.89 (3H, t, J = 6.6 Hz), 1.31 (6H, m), 1.40 – 1.80 (4H, m), 1.59 (3H, s), 1.68 (3H, s), 2.05 (2H, m), 2.53 (2H, t, J = 7.8 Hz), 3.39 (3H, s), 3.43 (1H, s), 3.49 (6H, s), 3.79 (1H, m), 4.71 (2H, m), 5.14 (1H, t, J = 7.3 Hz), 5.20 (4H, s), 5.26 (1H, dd, J = 3.6 and 9.9 Hz), 6.62 (2H, s).

1,9-Dihydroxy-6,6-dimethyl-6a,7,8,9,10,10a-hexahydro-6H-dibenzo-[b,d]pyran (**14a**) and (**15a**). A solution of 82 mg (0.21 mmol) of **12a** and 32 mg (0.17 mmol) of p-toluenesulfonic acid in 15 ml of anhydrous methanol was refluxed for 3 h under N_2. The reaction mixture was concentrated by a rotary evaporator. The residue was poured into a mixture of ether and water, and the aqueous layer was extracted with ether. The combined organic layers were washed successively with saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on a silica gel column using acetone-petroleum (30:70) as an eluent to give initially 18.5 mg of **14a**, followed by a mixture of 3.6 mg **14a** and **15a**, and then 14.8 mg of **15a** in 71% combined yield. Crystallization from acetone-pentroleum ether gave **14a** and **15a** as a white crystals, respectively. Gas chromatographic analysis of the products (**14a** and **15a**) indicate that axial and equatorial hydroxy compounds were obtained in a ratio of about 65:35.

14a mp: 194.7 – 195.3°C. **15a** mp: 209.7 – 213.7°C. **14a** Ir (KBr)ν_{max}: 3500, 3400, 3170, 2950, 1620, 1580, and 1460 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.06 (3H, s), 1.38 (3H, s), 1.15 - 1.80 (6H, m), 1.96 (1H, d, J = 12.5 Hz), 2.98 (1H, t, J = 9.2 Hz), 3.25 (1H, dd, J = 3.0 and 13.9 Hz), 4.29 (1H, br s), 6.31 (1H, d, J = 7.9 Hz), 6.39 (1H, d, J = 7.9 Hz), 6.45 (1H, br s), 6.93 (1H, t, J = 7.9 Hz); ^{13}C nmr ($CDCl_3$): 18.7, 22.6, 27.3, 29.0, 29.1, 32.9, 36.1, 49.2, 67.0, 107.8, 109.9, 112.5, 127.3, 155.0, 155.2. *Anal.* Calcd for $C_{15}H_{20}O_3$, C, 72.55, H, 8.12; Found, C, 71.72, H, 8.06. **15a** Ir (KBr)ν_{max}: 3500, 3200, 2950, 1620, 1590 and 1460 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 1.06 (3H, s), 1.39 (3H, s), 1.10 – 2.35 (7H, m), 2.51 (1H, t, J = 10.4 Hz), 3.53 (1H, d, J = 12.4 Hz), 3.89 (1H, sep, J = 4.3 Hz), 6.10 – 6.50 (1H, m), 6.23 (1H, d, J = 8.1 Hz), 6.37 (1H, d, J = 8.1 Hz), 6.9 (1H, t, J = 8.1 Hz), *Anal.* Calcd for $C_{15}H_{20}O_3$, C, 72.55, H, 8.12. Found, C, 72.13, H, 8.17.

9-nor-9-Hydroxyhexahydrocannabinol (14b) and (15b). The desired compounds (**14b** and **15b**) were synthesized in 76% combined yield according to the above mentioned method for the preparation of **14a** and **15a**, from 150 mg of **12b** instead of **12a**. Gas chromatographic analysis of the products indicate that ratio axial (**14b**) and equatorial hydroxy compound (**15b**) were obtained in a ratio of about 65:35. Crystallization from acetone-petroleum ether gave **14b** and **15b** as white crystalline, respectively. (**14b**) mp: 135.6 – 136.7°C (lit.,[3] mp 138 – 140°C). Ir (KBr)ν_{max}: 3300, 2950, 1630, 1590 and 1450 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 0.88 (3H, t, J = 6.1 Hz), 1.06 (3H, s), 1.37 (3H, s), 1.15 – 1.85 (11H, m), 1.96 (1H, d, J = 12.9 Hz), 2.43 (3H, t, J = 7.8 Hz), 2.95 (1H, t, J = 9.4 Hz), 3.21 (1H, d, J = 15.2 Hz), 4.28 (1H, br s), 6.09 (1H, br s), 6.15 (1H, s), 6.25 (1H, s); ^{13}C nmr ($CDCl_3$)δ: 14.0, 18.8, 22.5, 22.6, 27.4 28.8, 30.6, 30.9, 31.5, 33.0, 35.4, 36.2, 49.3, 67.1, 108.3, 109.7, 109.8, 142.7, 154.5, 154.9. *Anal.* Calcd for $C_{20}H_{30}O_3$, C, 75.42, H, 9.51. Found, C, 75.00, H, 9.65. **15b** mp: 182.4 – 184.0°C (lit.,[3] 178 – 179°C). Ir (KBr)νmax: 3440, 3150, 2950, 1630, 1590 and 1430 cm^{-1}; ^1H nmr ($CDCl_3$)δ: 0.88 (3H, t, J = 5.9 Hz), 1.05 (3H, s), 1.37 (3H, s), 1.10 – 2.20 (13H, m), 2.41 (3H, m), 3.52 (1H, d, J = 12.2 Hz), 3.89 (1H, quint, J = 4.3 Hz), 6.08 (1H, s), 6.23 (1H, s), 6.29 (1H, br s).

ACKNOWLEDGEMENT

We are thankful to Dr. Masatoshi Asami and Dr. Kiyoshi Honda for helpful discussions.

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Received, 6th January, 1992