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A NEW SYNTHESIS OF (-)-KHUSIMONE†

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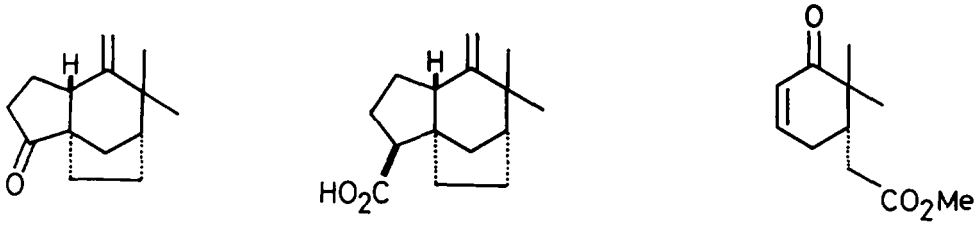
Abstract -- (-)-Khusimone **1**, the minor but essential component of vetiver oil with insect repellent activity, was synthesized starting from (S)-6,6-dimethyl-5-methoxycarbonylmethyl-2-cyclohexen-1-one **2**. Lewis acid-catalyzed Diels-Alder reaction was employed to obtain the desired carbon skeleton regio- and stereoselectively. Overall yield of **1** through 15 steps was 6.9%.

INTRODUCTION

Vetiver oil (Vetiveria zizanoides L.) is an important raw material for constituting the fragrances with high quality and contains several zizaene sesquiterpenes. It has been postulated that these sesquiterpenes play significant role to retain strong woody and amber-like notes. Among them, a norsesquiterpene, (-)-khusimone **1**, first isolated by Seshadri et al.,[1] is minor but olfactively interesting component in this essential oil.[2] Recently, Meinwald et al.[3] and Honda et al.[4] reported that **1** shows repellent activity against several pests, such as cockroaches, flies, weevils and mosquitoes. As khusimone **1** is not only useful as perfumes but has an interesting dimethylmethylenetricyclo[6,2,1,$0^{1,5}$]-undecane skeleton, much attention has been paid for its synthesis. Apart from the degradation of natural zizanoic acid to (-)-**1**,[5] two syntheses of (±)-**1** by Büchi et al.,[6] and Oppolzer et al.[7] and two chiral syntheses of **1** by Chan et al.[8] and Oppolzer et al.[9] were reported.



1 khusimone zizanoic acid **2**

Fig. I

† Synthesis of Mono- and Sesquiterpenoids, XIII. For Part XII, See K. Sakurai, K. Ikeda and K. Mori, Agric. Biol. Chem., in the press. This work was presented at the Annual Meeting of the Agricultural Chemical Society of Japan, Nagoya, April 2nd, 1988.

†† Research Fellow on leave from Takasago International Corporation(1986-1988).

We also have become interested in synthesizing (-)-khusimone **1** and related analogs to evaluate their olfactive utilities. We describe here the novel and stereoselective route to (-)-**1** using Lewis acid-catalyzed Diels-Alder strategy as a key step.

STRATEGY AND DIELS-ALDER REACTION OF 2

Our synthetic plan was based on using Diels-Alder reaction of (S)-6,6-dimethyl-5-methoxycarbonylmethyl-2-cyclohexen-1-one **2**.[8)]

If the addition of isoprene **3** proceeds only from the desired β-face of **2**, it should give a single product **C** which is convertible to (-)-**1** via exo-methylene formation, ring contraction and the formation of bridged five-membered ring.

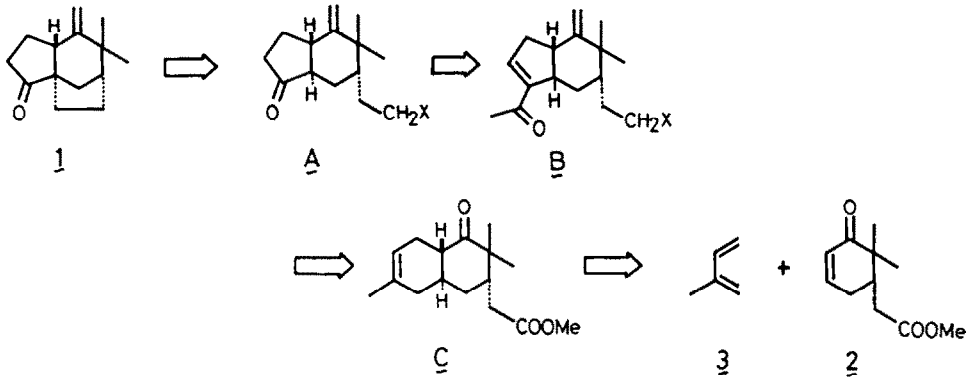


Fig. II Synthetic Plan

Although Chan used **2** for the synthesis of (-)-**1**, their photochemical route was non-stereoselective.[8)] Thus, tedious separation and isomerization of the undesired isomer to the desired isomer caused the decrease of the yield. We studied Diels-Alder route carefully, and found the optimum condition to give only the desired diastereomer (**C**; **4a**) exclusively.

There are several reports on Lewis acid-catalyzed Diels-Alder reaction of 5-substituted 2-cyclohexenone.[10)] Among them, Harayama *et al.*[10a)] reported the higher stereoselectivity and yield of the reaction between carvone and butadiene in the presence of $AlCl_3$ than in thermal reaction.[11)] Oppolzer *et al.*[10b)] and Fringnulli, Wenkert *et al.*[10c)] also reported that dienes added in the presence of Lewis acid-catalyst to simple 5-alkyl-2-cyclohexenones almost exclusively from the side opposite to alkyl substituent. It is also known that Lewis acid-catalyst markedly effects the regiochemistry of isoprene adducts.[12)]

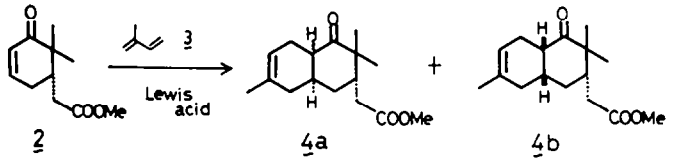
Therefore, we employed the Lewis acid-catalyzed reaction. Contrary to the results in the case of simple 5-methyl-2-cyclohexenone,[10b,c)] the enone **2** gave a mixture of diastereomers, **4a** and **4b** under general procedure previously reported.

As shown in entry 1 in the Table, the diastereoselectivity was high, but the yield was poor using $AlCl_3$ as the catalyst. On the other hand, the yield was fairly good (60% based on the unrecovered **2**) with less selectivity in the case of $SnCl_4$ (entry 3) and BF_3-Et_2O was in between (entry 2). Those facts revealed that reaction pathway (probably influenced by the conformation of **2**) was not so simple as that of simple 5-alkylcyclohexenone because of the presence of 4,4-dimethyl and methoxycarbonyl substituents. Thus, we decided to use catalytic amount of $SnCl_4$ because it gave better yields of adducts, and then focused our attention to improve the diastereoselectivity. Reactions were carried out under various conditions by changing solvent and reaction time. Distilled CH_2Cl_2 was the best solvent of choice (see entries 6,7 and 8). Product ratio was dramatically improved by pretreating the enone **2** with $SnCl_4$ for longer period before the addition of isoprene **3**.

Table

entry	solvent	catalyst.	eq.	2 eq.	3 eq.	temp (°C)	time-1 (h)	time-2 (h)	yield(%) 4a	4b	recovery of 2 (%)	glc yield (%)
1	CH_2Cl_2	$AlCl_3$	1	1	5	0-rt	0	56	3.3	-	86	-
2		BF_3-Et_2O	1	1	5		0	72	16.2	5.3	72	-
3		$SnCl_4$	1	1	5		0	72	15.0	12.0	55	-
4			0.1	1	15	rt	2.0	96	10.6	-	70	17 (57)
5			0.01	1	12		4.0	120	30.5	-	51	45 (92)
6			0.1	1	11		4.5	48	35.0	-	50	50(-100)
7	Toluene		0.03	1	15		1.0	48	-	-	95	-
8	CH_3CN		0.1	1	15		2.0	48	-	-	95	-

time-1; complexation period, time-2; reaction period, yield(%); isolated yield, number in parenthesis; glc yield based on the unrecovered 2.



2 4a 4b

In the best case (entry 6), **2** was complexed with $SnCl_4$ (0.1 eq) over 4.5h and then to this was added isoprene. The mixture was left to stand over ca. 2 days to give only the desired adduct **4a** in 70% yield based on the unrecovered **2** (glc yield was nearly quantitative).

It is rather difficult to rationalize this remarkable stereospecificity. Our tentative explanation is as follows; predominant conformer of **2** must be a flat half chair **2a** with equatorial methyl ester chain as judged from ^{1}H-NMR data (C5-H; Ha, δ 2.19, dddd, J=2.5, 3.1, 8.4 and 8.8Hz). Two large coupling constants prove C5-H to be axial. In this conformation, there is not much difference between both faces for steric approach. Once $SnCl_4$ was added, it formed the complex with **2** to give **2aL** and/or **2bL**. In this case, both bulkier O-Lewis acid group and methyl ester chain is present as gauche to C6-dimethyl groups in the conformer **2a**. Thus, the conformer **2aL** is not so stable as **2a** and the other conformer **2bL** exists more in equilibrium. During complexation period, $SnCl_4$ may chelate with the other carbonyl oxygen of methyl ester side chain in **2bL** to give the stabilized complex **2c**, in which endo α-face is completely blocked by bulky halogen and methoxy groups. Exo β-face possesses only quasiaxial methyl group. Consequently, isoprene added to the polarized enone only from β-face to give **4a** diastereo- and regioselectively. As the desired octalone **4a** in hand, further transformation was executed.

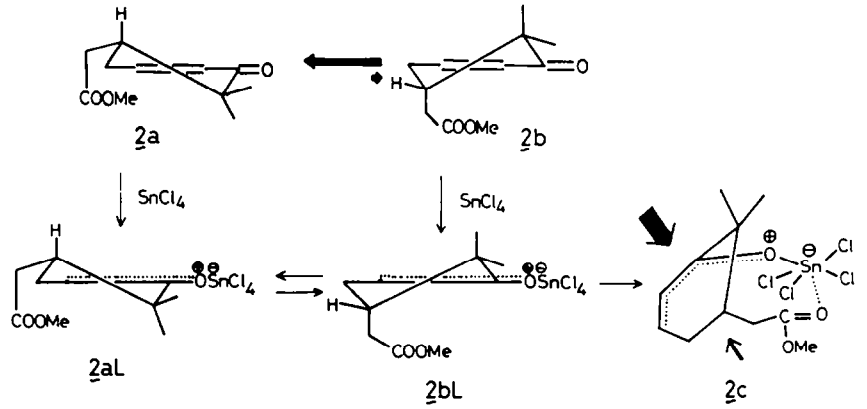


Fig. III

INTRODUCTION OF EXO-METHYLENE AND RING CONTRACTION

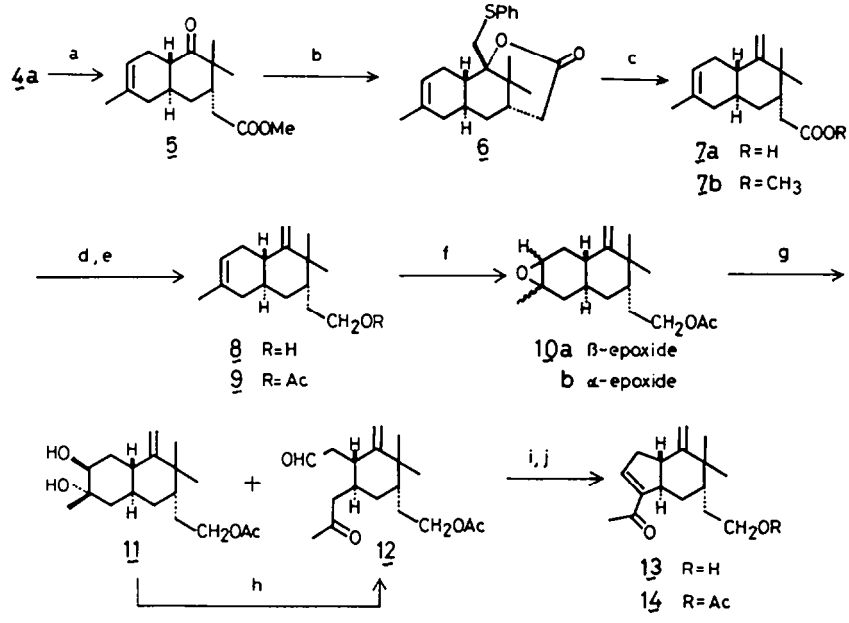
Treatment of the cis-octalone **4a** with NaOMe in MeOH gave mainly a trans-isomer **5** (**4a**/**5**=10/90-15/85). Chromatographic separation and repetition of the same process gave **5** in 95% yield. In order to introduce exo-methylene group at hindered carbonyl position, several methods were examined.

Since Coates reported that direct Wittig reaction of the hindered ketone gave the product in poor yield,[13] we tried Nozaki's low valent titanium-mediated methylenation[14] and Peterson type reaction with $TMSCH_2MgCl$ and successive elimination.[15] The yield of **7b**, however, was extremely poor (10-20%).

Alternatively, reductive elimination of vicinal phenylthio-carboxylate[13] was applied. Addition of phenylthiomethyllithium[16] to **5** gave δ-lactone **6** as a sole product in 78% yield. Bulky organometallic reagent approached from less hindered β-face to give an axial hydroxide ion which attacked the axial ester carbonyl to form lactone ring. The result also proved the stereochemistry of the Diels-Alder adduct **4a** to be correct. Lithium-ammonia reduction of **6** gave the desired exo-methylene acid **7a** in 75% yield. Reduction of **7a** with $LiAlH_4$ was followed by acetylation to give a diene-acetate **9** in quantitative yield.

Selective ozonization of tri-substituted olefin was unsuccessful, but treatment of **9** with m-CPBA gave a mixture of epoxides **10a** and **10b** (53:47) regioselectively in 86% yield. Periodic acid oxidation afforded a mixture of a keto-aldehyde **12** (13.4%) and trans-diaxial diol **11** (85.8%).

The latter was oxidized with $Pb(OAc)_4$ to give more **12** and the combined yield of **12** was 86.7% from **10**. Cyclization of **12** with 10% KOHaq. in refluxing benzene afforded an enone **13** in 81% yield, which on acetylation gave an enone acetate **14** (80%).



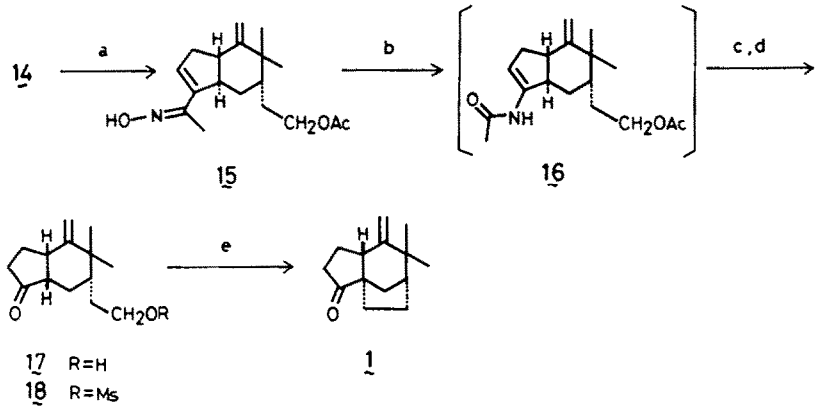
a) MeONa-MeOH b) $PhSCH_2Li$ c) $Li-NH_3$, H^+, CH_2N_2 d) LAH-Et_2O
e) Ac_2O-Pyr f) mCPBA g) HIO_4 h) $Pb(OAc)_4$ i) 10% KOHaq.
J) Ac_2O-Pyr

Fig. IV

CONVERSION TO CYCLOPENTANONE AND THE COMPLETION OF THE SYNTHESIS

Direct Baeyer-Villiger oxidation of **14** and the successive hydrolysis to give the cyclopentanone **17** was unsuccessful. Thus, Beckmann rearrangement route in Djerassi's steroid synthesis[17] was applied to our intermediate **14**. Treatment **14** with hydroxylamine hydrochloride in pyridine gave an oxime **15** in 70% yield. Beckmann rearrangement of **15** with MsCl-DMAP in pyridine and successive alkaline hydrolysis of the resulting enamide **16** afforded the desired ketol in 70% yield. Finally, mesylation of **17** (85%) and cyclization with t-BuOK in THF (98%) gave (-)-khusimone **1**, mp 78°C, $[\alpha]_D^{23}$ -109.0° (c=0.244, $CHCl_3$). Synthetic **1** was indistinguishable with authentic sample derived from natural zizanoic acid in all respects [IR, ^{1}H-NMR, ^{13}C-NMR, MS, Capillary GC (FFAP, OV-101), mp, TLC].

In conclusion, stereospecific synthesis of (-)-khusimone **1** was achieved in 6.9% overall yield through 15 steps starting from (S)-6,6-dimethyl-5-methoxycarbonylmethyl-2-cyclohexen-1-one **2**.



a) $NH_2OH \cdot HCl$-Pyr b) MsCl-Pyr, DMAP, H^+ c) 10%KOHaq.-Benzene, Δ
d) MsCl-Et_3N, CH_2Cl_2 e) t-BuOK-THF

Fig. V

EXPERIMENTAL

All bps and mps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer unless otherwise stated. ^{1}H NMR spectra were recorded with TMS as an internal standard at 400 MHz on a Bruker AM-400 spectrometer unless otherwise stated. ^{13}C NMR spectra were measured with TMS as an internal standard as $CDCl_3$ soln at 100 MHz on a Bruker AM-400 spectrometer. The multiplicities of ^{13}C-NMR were determined by a DEPT sequence. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer or a Hitachi RMU-6M spectrometer at 70 eV or Hitachi M-80 at 20 eV. Merck Kieselgel 60 Art. 7734 was used for SiO_2 column chromatography. GLC was used a HP-5840A instrument with PEG-20M and OV-101 25 m x 0.2 mm capillary column (80-220°C, 4°C/min, carrier gas He, 1 ml/min).

(S)-5-Methoxycarbonylmethyl-6,6-dimethyl-2-cyclohexen-1-one **2**. According to the method of Liu et al.,[3] **2** was obtained from ammonium salt of (-)-10-camphorsulfonic acid. **2**; bp 100°/2 torr, n_D^{24} 1.4780; $[\alpha]_D^{24}$ -60.6° (c=2.57, $CHCl_3$); νmax 2950 (s), 1740 (s), 1660 (s), 1390 (m), 1360 (m) cm^{-1}; ^{1}H-NMR δ 1.02 (3H, s), 1.19 (3H, s), 2.19 (1H, dddd, J=2.5, 3.1, 8.4, 8.8 Hz), 2.24 (1H, dd, J=3.6, 15.2 Hz), 2.42 (1H, m), 2.54 (1H, dd, J=3.6, 15.3 Hz), 2.56 (1H, m), 3.79 (3H, s), 5.97 (1H, ddd, J=1.7, 2.3, 10.1 Hz), 6.81 (1H, dddd, J=3.2, 4.9, 5.0, 10.1 Hz). ^{13}C-NMR δ 19.2 (s), 22.5 (s), 29.2 (t), 34.9 (t), 40.5 (d), 44.9 (s), 51.8 (q), 128.2 (d), 146.7 (d), 173.2 (s), 203.4 (s); MS: m/z 196 (M^+, 10 %), 123 (19), 96 (5), 68 (100, base peak), 41 (5).

(3S,4aS,8aR)-3,4,4a,5,8,8a-Hexahydro-3-methoxycarbonylmethyl-2,2,6-trimethyl-1(2H)-naphthalenone **4a**. To freshly distilled CH_2Cl_2 (500 ml) and $SnCl_4$ (1.56 g, 6 mmol) under Ar was added optically pure **2** (13.4 g, 68.4 mmol) in dry CH_2Cl_2 (50 ml) at 20-25°C and the mixture was stirred for 5 h. Then isoprene (47.5 g, 0.7 mol) was added dropwise to this mixture and the mixture was stirred for 48 h at room temp. CH_2Cl_2 layer was washed with sat $NaHCO_3$ (100 ml x 3) and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2. Elution with n-hexane-EtOAc (10:1-9:1) gave **4a** (7.5 g, 2.84 mmol) and elution with n-hexane-EtOAc (9:1-5:1) gave 8.0 g of starting material **2**. **4a** was recrystallized from n-

hexane to give pure **4a** (6.32 g, 23.9 mmol, 35 %) and recovered **2** was distilled to give 7.7 g of pure **2** (50 %). **4a**; mp 83°C; $[\alpha]_D^{24}$ +13.1° (c=0.35, $CHCl_3$); vmax(KBr) 2900 (s), 1730 (s), 1700 (s), 1430 (m), 1360 (m) cm^{-1}; ^{1}H-NMR δ 1.05 (3H, s), 1.08 (3H, s), 1.60 (3H, brs), 1.68 (1H, m), 1.75 (2H, m), 1.90 (1H, m), 2.00 (1H, m), 2.22 (1H, dd, J=10.3, 14.9 Hz), 2.32 (1H, m), 2.40 (1H, m), 2.52 (1H, dd, J=3.1, 14.9 Hz), 2.54 (1H, m), 2.98 (1H, dd, J=5.9, 6.1 Hz), 3.70 (3H, s), 5.34 (1H, brs), ^{13}C-NMR δ 20.5 (q), 22.4 (q), 23.6 (q), 24.1 (t), 31.1 (t), 32.7 (t), 34.7 (d), 35.9 (t), 40.0 (d), 42.3 (d), 47.9 (s), 51.7 (q), 118.9 (d), 131.6 (s), 173.4 (s), 214.0 (s); MS: m/z 264 (M^+, 11 %), 214 (14), 173 (54), 172 (100), 121 (72), 118 (52), 105(38), 93 (67), 43 (16); Found C, 72.23; H, 9.09, Calcd for $C_{16}H_{24}O_3$, C, 72.69 ;H, 9.15 %.

(3S,4aS,8aS)-3,4,4a,5,8,8a-Hexahydro-3-methoxycarbonylmethyl-2,2,6-trimethyl-1(2H)-naphthalenone **5**. To a solution of **4a** (11.2 g, 42.3 mmol) in dry MeOH (100 ml) under Ar, was added a 1% solution of $NaOCH_3$ in dry MeOH (2 ml) at room temp. The mixture was stirred for 2-3 h at room temp and MeOH was concentrated under reduced pressure. The residue was extracted with ether. Ether layer was washed with brine, dried over $MgSO_4$ and concentrated to give a mixture of **4a** and **5** in a ratio 10:90-15:85 on GC analysis. This mixture was chromatographed over SiO_2 2 or 3 times. Elution with n-hexane-EtOAc (10:1) gave pure **5** and elution with n-hexane-EtOAc (10:1-8:1) gave a mixture of **4a** and **5** in a ratio 45:55. The latter fraction was dissolved in dry MeOH and treated with $NaOCH_3$ again as described above and reaction product was chromatographed over SiO_2 to give **5** (combined yield 10.6 g, 40.3 mmol, 95 %). **5**; mp 31°C; $[\alpha]_D^{23}$ +1.99° (c=0.30, $CHCl_3$); vmax 2950 (s), 1730 (s), 1695 (s), 1435 (m), 1380 (m), 1250 (m) cm^{-1}; ^{1}H-NMR δ 0.98 (3H, s), 1.30 (3H, s), 1.61 (1H, ddd, J=3.1, 3.9, 16.8 Hz), 1.63 (3H, brs), 1.85 (1H, m), 1.93 (3H, m), 2.05 (1H, dd, J=11.3, 16.8 Hz), 2.10 (2H, m), 2.40 (3H, m), 3.67 (3H, s), 5.40 (1H, brs), ^{13}C-NMR δ 22.1 (q), 23.2 (q), 25.2 (q), 27.1 (t), 32.1 (t), 35.1 (t), 35.7 (t), 38.7 (t), 43.7 (t), 45.6 (d), 48.1 (s), 51.7 (q), 120.3 (d), 132.6 (s), 173.5 (s), 210.0 (s). MS: m/z 264 (M^+ 1 %), 173 (34), 172 (92), 157 (base peak, 100), 118 (53), 105 (20), 93 (47), 43 (13); Found C, 72.49; H, 8.98, Calcd for $C_{16}H_{24}O$: C, 72.69; H, 9.15 %.

(1S,3S,4aS,8aS)-1-Hydroxy-1-phenylthiomethyl-2,2,6-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-3-ylacetic acid δ-lactone **6**. To a solution of **5** (4.74 g, 17.7 mmol) in dry THF (100 ml), was added $PhSCH_2Li$ (50 mmol) in THF prepared by the method of Corey et al.[16] under Ar at -78°C. The mixture was stirred for 1 h and warmed up to room temp. To this was added sat NH_4Cl and THF was evaporated. The residue was extracted with ether and the ether soln was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give pure δ-lactone **6**(4.78 g, 13.3 mmol, 75 %). **6**; $[\alpha]_D^{24.5}$ +10.5° (c=0.31, $CHCl_3$); vmax 2920 (s), 1720 (s), 1580 (s), 1225 (s), 1160 (s), 980 (s), 735 (s), 690 (s) cm^{-1}; ^{1}H-NMR δ 1.16 (3H, s), 1.36 (3H, s), 1.55 (1H, m), 1.62 (3H, brs), 1.67 (1H, m), 1.77 (2H, m), 1.88 (1H, d, J=1.91 Hz), 1.95 (1H, dd, J=4.4, 17.0 Hz), 2.15 (2H, m), 2.20 (1H, m), 2.37 (1H, d, J=19.0 Hz), 2.85 (1H, dd, J= 8.5, 19.0 Hz), 3.13 (1H, d, J=12.4 Hz), 3.51 (1H, d, J=12.4 Hz), 5.33 (1H, brs), 7.2-7.3 (5H, aromatic). ^{13}C-NMR δ 23.1 (q), 24.1 (q), 25.1 (q), 25.4 (t), 29.4 (d), 34.4 (t), 35.1 (t), 36.6 (t), 38.7 (d), 39.9 (d), 89.6 (s), 120.4 (d), 126.2 (d), 128.5 (d), 129.1 (d), 132.3 (s), 137.1 (s), 171.6 (s); MS: m/z 356 (M^+, 78 %), 233 (base peak, 100), 171 (82), 173 (49), 159 (19), 132 (21), 124 (49), 119 (32), 105 (93), 91 (23), 79 (18), 69 (21), 55 (23); Found C, 74.11; H, 7.94, Calcd for $C_{22}H_{28}O_2S$: C, 74.12; H, 7.92 %.

(3S,4aS,8aS)-2,2,6-Trimethyl-1-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalen-3-ylacetic acid **7a**. To a solution of metallic Li (1.08 g, 0.12 mol) in liquid NH_3 (100 ml), was added a solution of **6** (3.14 g, 8.81 mmol) in dry THF (10 ml) at -23°C, and the mixture was stirred for 1 h. Anhydrous NH_4Cl (0.5 g) was added to the reaction mixture to decompose excess of Li, then the mixture was warmed up to room temp. The resulting mixture was diluted with brine (10 ml) and was extracted with ether (50 ml). An aqueous layer was acidified with 1N-HCl to pH 3-4, and extracted with ether (50 ml x 3). The latter extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give **7a** (1.704 g, 6.87 mmol, 78 %). **7a**; n_D^{21} 1.5150; $[\alpha]_D^{21}$ +6.18° (c=0.25, $CHCl_3$); vmax 3400-3100 (brs), 1710 (s), 1630 (s), 1410 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.10 (3H, s), 1.22 (3H, s), 1.53 (1H, m), 1.58 (1H, dt, J=2.5, 9.1 Hz), 1.65 (3H, brs), 1.80 (2H, m), 1.93 (1H, dd, J=4.7, 9.1 Hz), 2.09 (4H, m), 2.12 (1H, dd, J=9.1, 14.6 Hz), 2.43 (1H, dd, J=4.7, 14.6 Hz), 4.78 (1H, brs), 4.81 (1H, brs), 5.43 (1H, brs), 10.20 (1H, br, -COOH). ^{13}C-NMR δ 23.2 (q), 26.7 (q), 28.8 (q), 29.4 (t), 33.6 (t), 34.6 (d), 34.9 (t), 38.1 (d), 39.2 (t), 40.1 (s), 42.3 (d), 106.3 (t), 120.6 (d), 132.9 (s), 155.1 (s), 180.1 (s); MS m/z 248 (M^+ ,32%), 233 (11), 205 (8), 188 (39), 173 (20), 159 (24), 145 (29), 134 (38), 119 (71), 105 (base peak, 100), 91 (69), 79 (67), 41 (60). Found C, 77.07; H, 9.84, Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74 %.

(3S,4aS,8aS)-3-Hydroxyethyl-2,2,6-trimethyl-1-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalene **8**. To a suspension of LAH (202 mg, 5.17 mmol) in dry ether (50 ml), was added dropwise **7a** (1.61 g, 6.47 mmol) in dry ether (10 ml) under Ar and the mixture was refluxed for 30 min. After be cooling, the mixture was treated with H_2O (1 ml), 15 % NaOH (1 ml), H_2O (3 ml) and ether was dried over $MgSO_4$. Ether was evaporated and the residue was chromatographed over SiO_2 to give **8** (1.392g, 5.95 mmol, 92 %). **8**; n_D^{24} 1.5204; $[\alpha]_D^{22}$ +25.1° (c=0.20, $CHCl_3$); vmax 3350 (brs), 2950 (s), 1635 (s), 1440 (m), 1380 (m), 1060 (m), 895 (s) cm^{-1}; ^{1}H-NMR δ 1.09 (3H, s), 1.19 (3H, s), 1.35 (1H, s), 1.50 (1H, m), 1.55 (2H, m), 1.65 (3H, brs), 1.70 (2H, m), 1.82 (1H, m), 1.92 (1H, dd, J=4.7, 9.1 Hz), 2.02 (2H, m), 2.10 (2H, m), 3.60 (2H, m), 4.74 (1H, brd, J=1.5 Hz), 4.78 (1H, brd, J=1.8 Hz), 5.44 (1H, brs). ^{13}C-NMR δ 23.2 (q), 26.6 (q), 29.1 (q), 29.5 (t), 31.5 (t), 32.2 (t), 34.6 (d), 38.2 (d), 39.3 (t), 40.3 (s), 42.0 (d), 62.1 (d), 105.5 (t), 120.7 (d), 132.9 (s), 156.0 (s); MS: m/z 234 (M^+, 24 %), 219 (9), 216 (8), 191 (11), 173 (14), 159 (13), 145 (31), 133 (36), 106 (54), 105 (base peak, 100), 91 (68), 79 (44), 77 (43), 67 (30), 55 (35), 41 (57). HR-MS 234.2014 Found C, 79.52; H, 10.90, Calcd for $C_{16}H_{26}O$ C, 79.99; H, 11.18 %.

(3S,4aS,8aS)-3-Acetoxyethyl-2,2,6-trimethyl-1-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalene **9**. A mixture of **8** (1.123 g, 4.80 mmol), dry pyridine (5 ml), and Ac_2O (2 ml) was stirred overnight at room temp. To the mixture, was added ice water (20 ml) and ether (50 ml). Ether layer was separated, washed with sat $CuSO_4$, sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give **9** (1.26 g, 4.56 mmol, 95 %). **9**; n_D^{24} 1.5015; $[\alpha]_D^{24}$ +14.8° (c=0.21, $CHCl_3$); vmax 2950 (s), 1740 (s), 1630 (s), 1360 (m), 1240 (m), 1030 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.09 (3H, s), 1.19 (3H, s), 1.40 (1H, m), 1.52 (3H, m), 1.63 (3H, brs), 1.73(3H, m), 1.92 (1H, dd, J=4.7, 6.2 Hz), 2.00 (1H, m), 2.03 (3H, s), 2.10 (2H, m), 4.03 (2H, m), 4.75 (1H, brs), 4.78 (1H, brs), 5.43 (1H, brs). ^{13}C-NMR δ 21.0 (q), 23.2 (q), 26.6 (q), 27.3 (t), 29.1 (q), 29.5 (t), 32.1 (t), 34.5 (d), 38.2 (d), 39.2 (t), 40.3 (s), 42.3 (d), 64.0 (t), 105.8 (t), 120.7 (d), 132.9 (s), 155.8 (s), 171.2 (s). MS: m/z 276 (M^+, 13 %), 261 (5), 201 (14), 173 (17), 145 (45), 119 (40), 105 (73), 91 (50), 79 (30), 43 (base peak, 100), 41 (40). Found C, 78.32; H, 10.12, Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21 %.

(3S,4aS,6RS,7RS,8aS)-3-Acetoxyethyl-6,7-epoxy-2,2,6-trimethyl-1-methylene-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene **10**. To a solution of **9** (1.205 g, 4.34 mmol) in $CHCl_3$ (50 ml), was added 80 % mCPBA (941 mg, 4.34 mmol) at 0-5 °C and the mixture was stirred overnight. $CHCl_3$ layer was washed with 5 % $Na_2S_2O_3$, sat $NaHCO_3$ and brine, dried over $MgSO_4$ and

concentrated. The residue was chromatographed over SiO_2 to give **10** (1.084 g, 3.71 mmol) as a mixture of (6S,7S)- and (6R,7R)-isomer (**10a** and **10b**) in a ratio 53 : 47 on ^{1}H-NMR spectral analysis (yield, 85 %). **10**; n_D^{24} 1.4943 ; $[\alpha]_D^{24}$ +6.55° (c=0.22, $CHCl_3$); νmax 2950 (s), 1740 (s), 1630 (s), 1360 (m), 1230 (m), 1030 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.07 (3H, s), 1.14 (3H, s), 1.33 (3H, s), 1.30-1.70 (7H, m), 1.83 (1H, m), 2.00 (1H, dd, J=2.8, 14.5 Hz), 2.03 (3H, s), 2.10 (1H, m), 2.27 (1H, dt, J=2.8, 14.5 Hz), 3.06 and 3.10 (1H, brs, brs, ratio 53:47), 4.00 (2H, m), 4.75 (2H, br); MS: m/z 292 (M^+, 85 %), 232 (82), 217 (base peak, 100), 199 (65), 189 (63), 171 (86), 150 (91), 133 (80), 119 (83), 105 (85), 91 (75), 79(51), 69 (45), 55 (43). Found C, 74.23; H, 9.44, Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65 %.

(3S,4aS,6S,7S,8aS)-3-Acetoxyethyl-6,7-dihydroxy-2,2,6-trimethyl-1-methylenedecahydronaphthalene **11** and (3S,5R,6S)-3-Acetoxy-5-(2-oxopropyl)-6-formylmethyl-2,2-dimethyl-1-methylenecyclohexane **12**. To a stirred solution of **10** (1.034 g, 3.54 mmol) in dry ether (30 ml), was added HIO_4 (110 mg, 0.482 mmol) in dry THF (10 ml) at room temp and the mixture was stirred for 30 min. To this mixture was added sat $NaHCO_3$ (20 ml) and organic layer was separated. The aqueous layer was extracted with ether (30 ml x 3). The combined organic layer was washed with sat $NaHCO_3$ several times and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2. Elution with n-hexane-EtOAc (4:1) gave **11** (147 mg, 0.474 mmol, 13.4 %) and elution with n-hexane-EtOAc (4:1-1:1) gave **12** (936 mg, 3.04 mmol, 85.5 %). Diol **11** was dissolved in dry benzene (30 ml) and to this solution under Ar were added AcONa (1.246 g, 15.2 mmol) and 90 % $Pb(OAc)_4$ (2.245 g, 4.56 mmol) at room temp. The mixture was stirred for 1-2 h and filtered. Solid was washed with dry benzene and combined benzene was washed with sat $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over SiO_2 to give **12** (817 mg, 2.63 mmol, 86.7 %) from **11**. **12** was employed for the next step without further purification. **11**; $[\alpha]_D^{25}$ -2.91° (c=0.635, $CHCl_3$); νmax 3450 (brs), 2950 (s), 1740 (s), 1630 (s), 1360 (m), 1360 (m), 1240 (m), 1120 (m), 1040 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.07 (3H, s), 1.19 (3H, s), 1.28 (3H, s), 1.42 (3H, m), 1.50-1.70 (7H, m), 1.75 (1H, dt, J=3.1, 13.8 Hz), 1.93 (1H, ddd, J=2.7, 12.0, 12.0 Hz), 2.03 (3H, s), 2.27 (1H, ddd, J=1.4, 1.5, 12.0 Hz), 3.71 (1H, t, J=2.8 Hz), 4.02 (2H, m), 4.73 (2H, dd, J=1.3, 3.6 Hz). ^{13}C-NMR δ 21.0 (q), 26.7 (q), 27.4 (d), 27.7 (q), 29.1 (q), 32.1 (t), 32.4 (t), 33.4 (d), 35.2 (d), 40.3 (s), 41.4 (t), 42.5 (d), 64.0 (t), 71.6 (s), 74.1 (d), 105.0 (t), 155.6 (s), 171.3 (s); MS: m/z 310 (M^+, 62 %), 292 (base peak, 100), 250 (22), 232 (67), 217 (77), 207 (48), 199 (43), 189 (51), 171 (37), 153 (63), 133 (46), 123 (56), 108 (55), 93 (43), 81 (33), 69 (27), 55 (41). HR-MS 310.2047 Found C, 69.36; H, 9.62, Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74 %. **12**; $[\alpha]_D^{24}$ -28.3° (c=0.25, $CHCl_3$); νmax 2950 (s), 2720 (w), 1715 (s), 1630 (s), 1360 (m), 1240 (m), 1160 (m), 1030 (m), 895 (s) cm^{-1}. ^{1}H-NMR δ 1.03 (3H, s), 1.11 (3H, s), 1.30-1.80 (7H, m), 2.00 (1H, m), 2.05 (3H, s), 2.13 (3H, s), 2.37 (1H, dd, J=7.3, 17.0 Hz), 2.62 (1H, ddd, J=2.6, 5.4, 8.4 Hz), 2.77 (1H, ddd, J=2.8, 5.4, 8.4 Hz), 4.07 (2H, m), 4.70 (1H, brs), 4.90 (1H, brs), 9.70 (1H, dd, J=1.3, 1.4 Hz). ^{13}C-NMR δ 21.1 (q), 25.2 (q), 28.1 (q), 29.4 (s), 30.8 (t), 34.2 (d), 39.9 (d), 40.1 (d), 40.7 (d), 45.9 (t), 48.4 (t), 63.9 (t), 110.0 (t), 155.1 (s), 172.1 (s), 203.5 (d), 208.9 (s); MS: m/z 308 (M^+, 56 %), 290 (58), 256 (52), 247(62), 230 (base peak, 100), 215 (51), 205 (47), 187 (98), 159 (73), 147 (87), 133 (78), 119 (86), 105 (73), 91 (70), 81 (63), 69 (67), 55 (95).

(3aR,5S,7aS)-3-Acetyl-5-hydroxyethyl-6,6-dimethyl-7-methylene-3a,4,5,6,7,7a-hexahydroindene **13**. A mixture of **12** (780 mg, 2.53 mmol) in benzene (50 ml) and 10 % KOH solution (30 ml) was refluxed for 1 h. After being cooled, benzene layer was separated, washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give pure **13** (508 mg, 2.05 mmol, 81 %). **13**; $[\alpha]_D^{24}$ -82.8° (c=0.385, $CHCl_3$); νmax 2960 (s), 2900 (s), 1665 (s), 1640 (s), 1360 (m), 1240 (m), 1040 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.10 (3H, s), 1.19 (3H, s), 1.45 (1H ,m), 1.70 (4H, m), 2.28 (3H, s), 2.38 (4H, m), 2.62 (1H, dddt, J=1.2, 1.5, 6.5, 11.6 Hz), 3.71 (2H, m), 4.68 (1H, brs), 4.74 (1H, brs), 6.78 (1H, dd, J=2.3, 5.1 Hz), ^{13}C-NMR δ 25.8 (q), 26.8 (q), 28.0 (t), 29.9 (q), 31.7 (t), 33.4 (t), 40.1 (s), 43.6 (d), 45.9 (d), 49.5 (d), 61.9 (t), 104.0 (t), 144.7 (d), 148.8 (s), 155.1 (s), 197.1 (s); MS: m/z 248 (M^+, 58%), 233 (29), 203 (53), 187 (31), 161 (40), 148 (86), 133 (43), 119 (32), 105 (42), 91 (50), 84 (50), 58 (base peak, 100), HR-MS 248.3299, Found C, 76.96; H, 9.73, Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74 %.

(3aS,5S,7aS)-3-Acetyl-5-acetoxyethyl-6,6-dimethyl-7-methylene-3a,4,5,6,7,7a-hexahydroindene **14**. A mixture of **13** (462 mg, 1.86 mmol), dry pyridine (4 ml), and Ac_2O (2 ml) was stirred for 5-6 h at room temp. The mixture was diluted with ice-water (10 ml) and extracted with ether. Ether layer was washed with sat $CuSO_4$, sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give **14** (431 mg, 1.48 mmol, 80 %). **14**; $[\alpha]_D^{22.5}$ -78.1° (c=0.28, $CHCl_3$); νmax 2960 (s), 2900 (m), 1740 (s), 1665 (s), 1640 (s), 1360 (m), 1240 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.10 (3H, s), 1.20 (3H, s), 1.50 (1H, m), 1.65 (1H, m), 1.77 (2H, m), 2.03 (3H, s), 2.28 (3H, s), 2.37 (4H, m), 2.61 (1H, m), 4.12 (2H, m), 4.70 (1H, brs), 4.77 (1H, brs), 6.78 (1H, brs), ^{13}C-NMR δ 21.0 (q), 25.8 (q), 26.6 (q), 28.0 (t), 28.4 (t), 29.8 (q), 33.3 (t), 40.1 (s), 43.8 (d), 46.0 (d), 49.6 (d), 64.0 (t), 104.2 (d), 144.7 (d), 148.7 (s), 154.9 (s), 171.1 (s), 196.8 (s), MS: m/z 290 (M^+, 100%), 275 (21), 247 (21), 230 (68), 215 (44), 203 (41), 187 (96), 173 (24), 159 (27), 149 (96), 133 (53), 119 (40), 105 (49), 91 (54), 81 (37), 67 (38), 61 (83), 55 (44); Found C, 74.13; H, 8.95, Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02 %.

(3aS,5S,7aS)-5-Acetoxyethyl-6,6-dimethyl-7-methylene-3-(1-oximinoethyl)-3a,4,5,6,7,7a-hexahydroindene **15**. A mixture of **14** (400 mg, 1.38 mmol), pyridine (50 ml), 95 % EtOH and NH_2OH-HCl (400 mg) was refluxed for 1 h. EtOH was evaporated and the residue was diluted with ice-water and extracted with ether. The ether layer was washed with brine 3 times, dried over SiO_2 to give **15** (294 mg, 0.965 mmol, 70 %). **15**; n_D^{21} 1.5233; $[\alpha]_D^{23}$ -49.5°(c=0.15, $CHCl_3$); νmax 3350 (s), 2950 (s), 1735 (s), 1640 (s), 1360 (m), 1240 (m), 1040 (m), 1040 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.10 (3H, s), 1.20 (3H, s), 1.50 (1H, m), 1.62 (3H, m), 1.80 (1H, m), 2.03 (3H, s), 2.07 (3H, s), 2.32 (2H, m), 2.40 (2H, m), 2.62 (1H, dt, J=7.2, 11.2 Hz), 4.13 (2H, ddd, J=1.2, 2.0, 7.8 Hz), 4.70 (1H, brs), 4.75 (1H, brs), 6.25 (1H, brs), ^{13}C-NMR δ 11.8 (q), 21.1 (q), 25.8 (q), 27.4 (t), 28.8 (t), 30.0 (q), 32.8 (t), 40.0 (s), 43.6 (d), 46.5 (d), 49.8 (d), 64.0 (t), 103.8 (t), 133.0 (d), 144.4 (s), 154.3 (s), 155.6 (s), 171.6 (s); MS: m/z 305 (M^+, 100 %), 288 (87), 272 (32), 228 (84), 218 (40), 212 (28), 200 (66), 186 (30), 172 (19), 158 (31), 149 (38), 131 (25), 117 (21), 105 (28), 91 (37), 79 (21), 69 (18), 55 (25); Found C, 70.49; H, 8.87; N, 4.69, Calcd for $C_{18}H_{27}NO_3$ C, 70.79; H, 8.91; N, 4.59 %.

(1RS,5S,8S)-8-Hydroxyethyl-7,7-dimethyl-6-methylene-2-indanone **17**. A stirred solution of the mixture of **15** (167 mg, 0.38 mmol), DMAP (40 mg), and dry pyridine (50 ml), was added MsCl (43 mg, 0.38 mmol) at 0-5°C under Ar and the mixture was stirred for 1-2 h. Ice-water (25 ml) and 1N-HCl (10 ml) were added to this mixture and the mixture was stirred overnight at 0-5°C. The mixture was extracted with ether and ether layer was washed with sat $CuSO_4$, sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to afford enamide **16**, νmax 3400 (brs), 3350 (m), 2950 (s), 1735 (s), 1700 (m), 1640 (s), 1525 (m), 1360 (m), 1240 (m), 890 (s) cm^{-1}, ^{1}H-NMR (100 MHz) 1.09 (3H, s), 1.22 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.40 (5H, m), 3.30 (1H, br), 4.00 (2H, m), 4.75 (2H, dd, J=1.2, 1.4 Hz), 4.90 (1H,

br), 7.00 (1H,br), **16** was employed for the next step without purification. The mixture of **16** in benzene (10 ml) and 10 % KOH (10 ml) was refluxed for 1 h. Benzene layer was washed with brine 2 times, dried over $MgSO_4$ and concentrated. The residue was chromatographed over SiO_2 to give **17** (50 mg, 0.228 mmol) as a mixture of (1S)-**17** and (1R)-**17** in a ratio 1:3 to 1:2 on ^{1}H-NMR spectral analysis. Yield was 70 % from **15**. **17** was employed for the next step without further purification. **17**; $[\alpha]_D^{23}$ +8.0° (c=0.40, $CHCl_3$); vmax 3450 (s), 2900 (s), 1735 (s), 1650 (m), 1460 (m), 1360 (m), 1050 (m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.05 (3H, s), 1.17 (3H,s), 3.18 (1H, m), 3.63 (2H, m), 3.73 (2H, m), 4.78 (1H, brs), 4.92 (1H, brs); MS: m/z 222 (M^+, 87 %), 207 (base peak, 100), 189 (47), 177 (26), 161 (62), 149 (43), 133 (64), 119 (69), 105(87), 91 (83), 79 (65), 67 (50), 55 (60).

(3aS,6S,7aRS)-6-Mesyloxyethyl-5,5-dimethyl-4-methylene-3a,4,5,6,7,7a-hexahydro-1-indanone **18**. To a mixture of (1RS)-**17**, Et_3N (0.5 ml) and dry CH_2Cl_2, was added MsCl (15 mg) at -10-0°C under Ar and the mixture was stirred for 30 min. CH_2Cl_2 layer was washed with sat $NaHCO_3$ and brine and dried over $MgSO_4$. CH_2Cl_2 layer was evaporated to give a mixture of (1R)-**18** and (1S)-**18** (30 mg, 0.10 mmol, 87.7 %), in a ratio 1:3 to 1:2 on ^{1}H-NMR analysis. **18** was chromatographed over SiO_2 and employed for the next step. **18**; $[\alpha]_D^{24.5}$ -1.14° (c=0.85, $CHCl_3$); vmax 2950 (s), 1735 (s), 1630 (s), 1350 (m), 1170 (m), 910 (s) cm^{-1}; ^{1}H-NMR δ 1.07 and 1.13 (3H, s), 1.19 and 1.20 (3H, s), 1.70-2.00 (4H, m), 2.20- 2.50 (4H, m), 3.00 and 3.10 (3H, s), 3.23 (1H, br), 4.28 (2H, m), 4.83 (1H, brs), 4.97 (1H, brs).

(-)-Khusimone **1**. To a soln of **18** (30 mg, 0.10 mmol) in dry THF (15 ml), was added t-BuOK (15 mg, 0.13 mmol) at room temp under Ar and the mixture was stirred for 1 h at room temp. To this was added sat NH_4Cl soln and THF was evaporated. The residue was extracted with ether and ether was washed with brine, dried over $MgSO_4$ and concentrated to give crude (-)-**1**. This was chromatographed over SiO_2 and recrystallized from distilled n-hexane to afford pure (-)-**1** (20 mg, 0.098 mmol, 98 %). It has the following spectral data which was identical with those of one prepared from natural (+)-vetivenoic acid. (-)-**1**; mp 78°C; $[\alpha]_D^{23}$ -109.0° (c=0.244, $CHCl_3$); vmax(KBr) 3100 (s), 1730 (s), 1640 (s), 1380 (m), 910(m), 890 (s) cm^{-1}; ^{1}H-NMR δ 1.09 (3H, s), 1.10 (3H, s), 1.19 (1H, ddd, J=1.1, 5.9, 10.3 Hz), 1.50 (1H, m), 1.57 (2H, m), 1.74 (1H, ddd, J=3.0, 4.2, 11.6 Hz), 1.82 (1H, dd, J=4.4, 6.8 Hz), 1.87 (1H, dt, J=1.8, 11.0 Hz), 1.92 (1H, dd, 4.9, 5.1 Hz), 2.03 (1H, dddd, J=1.2, 5.5, 11.0, 12.5 Hz), 2.25 (1H, ddd, J=9.6, 11.0, 19.3 Hz), 2.37 (1H, ddd, J=1.2, 8.7, 19.3 Hz), 2.69 (1H, dddd, J=1.0, 2.2, 5.5, 11.6 Hz), 4.71 (1H, dd, J=0.85, 1.1 Hz), 4.88 (1H, dd, J=0.85, 1.1 Hz), ^{13}C-NMR δ 21.6 (t), 25.6 (t), 25.7 (q), 28.1 (q), 28.4 (t), 35.9 (t), 38.0 (t), 40.6 (s), 47.8 (d), 50.0 (d), 57.7 (s), 106.2 (t), 154.8 (s), 222.0 (s); MS: m/z 204 (M^+, 82 %), 189 (53), 161 (45), 147 (30), 133 (56), 119 (65), 108 (base peak, 100), 105 (42), 96 (48), 91 (30), 79 (20), 67 (22), 55 (17), 41 (15), HR-MS 204.1514 Found C, 82.09; H, 9.65, Calcd for $C_{14}H_{20}O$=204.1527 C, 82.36; H, 9.87 %.

According to the method of Maurer,[2] authentic (-)-khusimone **1** was prepared from (+)-vetivenoic acid isolated from vetiver oil produced in Indonesia. (-)-**1**; mp 78°C; $[\alpha]_D^{24.5}$ -110.5° (c=0.31, $CHCl_3$); Found C, 82.09; H, 9.84, Calcd for $C_{14}H_{20}O$: C, 82.37; H, 9.87 %.

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