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Synthetic Bicyclic Analogues of Quassinoids

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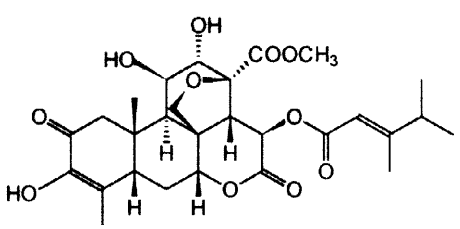
Abstract: A series of simple bicyclic analogues of quassinoids have been prepared including compounds with ring A typical of bruceolides and dehydrobruceolides. The synthesis of bicyclic compound **5** and tricyclic analogue **6** was accomplished by acid catalysed Robinson Annelation reaction. Hydroxyketone **9a** and its 2-substituted analogues were also prepared to study the structure activity relationship.

Quassinoids, the bitter degraded triterpenoids of the plant family Simaroubaceae display a wide range of biological properties including antimalarial, antileukemic, amoebicidal and antifeedant.[1] Two examples of the quassinoids are bruceantin **1** and dehydrobruceantin **2**.[2] The features considered important for biological activity in the quassinoids include the presence of a diosphenol group or an unsaturated α-ketol in ring **A**, an oxygen methylene group in ring C, as well as an ester moiety at C-15 or C-6.[3] Given the complex structure and synthesis of quassinoids, a series of structurally simple bicyclic analogues, mimicking the ring system A and B were prepared for biological evaluation.



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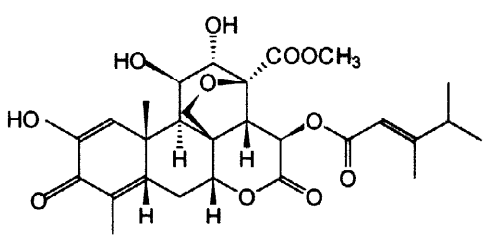

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Synthesis of bicyclic compound 5 and tricyclic analogue 6

Bicyclic enone **5** was prepared by the acid catalysed Robinson Annelation reaction[4,5] (Scheme 1). The acid catalyses the *in situ* generation of the vinyl ketone and both the Michael and Aldol steps of the reaction. A mixture of 2-methylcyclohexanone **3**, 1-chloro-3-pentanone **4** and p-toluenesulphonic acid was reacted in toluene, followed by treatment with KOH-MeOH, yielding bicyclic enone **5**. A small amount of byproduct, tricyclic ketone **6** was also formed. The ^{1}H NMR of compound **5** showed the presence of the two angular methyl groups at δ=1.76 ppm

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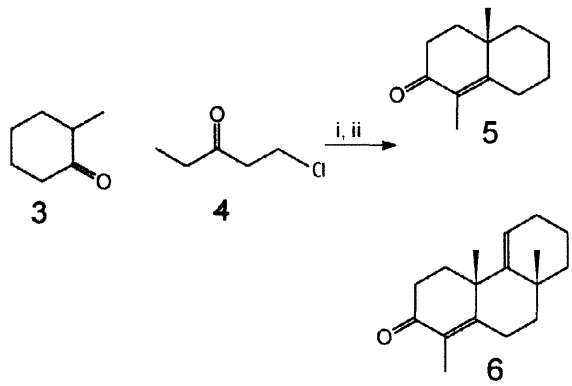
for C-4 CH_3 and 1.22 ppm for C-8 CH_3. The spectrum for tricyclic enone **6** displayed three singlets at δ=1.78 for C-4, 1.37 ppm for C-10 and 1.27 ppm for C-8 methyl groups. A triplet occurred at δ=5.51 for the C-11 vinylic proton.

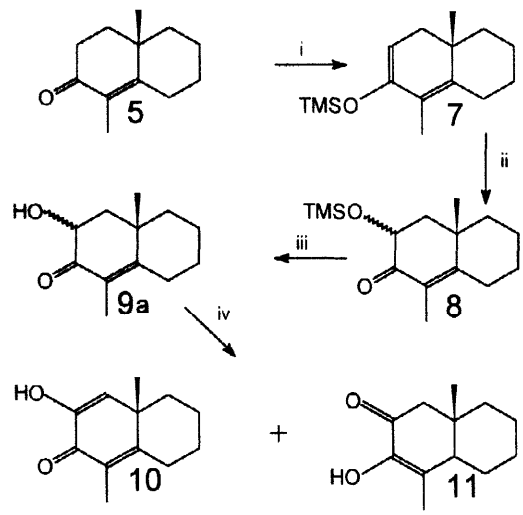
*Synthesis of hydroxyketone **9a**, diosphenols **10**, **11** and bromoketone **9b***

The synthesis employed a procedure analogous to that reported by Govindan and Fuchs[6] (Scheme 2). In



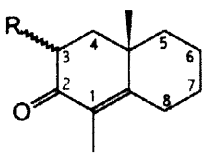
Scheme 1. Synthesis of bicyclic enone **5**. i) $NpSO_3H$, toluene, ii) 20 % KOH in MeOH

order to introduce an α-hydroxyketone into ring **A**, bicyclic ketone **5** was deprotonated[7] with lithium diisopropylamide and the resultant carbanion quenched with chlorotrimethylsilane. The formation of compound **7** was indicated by TLC examination and its structure was confirmed by its mass spectrum. The compound was further reacted without purification by oxidation with MCPBA yielding the polar (2-α,β) silyloxyenone **8**.



Scheme 2. Synthesis of bicyclic diphenols **10** and **11** i) LDA, -78 °C, TMSCL, RT, ii) MCPBA, CH_2Cl_2, iii) 10 % HCl, THF, iv) NaOMe, Et_2O

Desilylation of compound **8** was achieved with HCl in THF giving rise to hydroxyketone **9a** as a pair of diastereomers. The structure of compound **9a** was confirmed by its MS (M^+=194) and its ^{1}H NMR spectrum which showed the C-2 proton at δ=4.31 ppm (J=5.6 and 14 Hz). Compound **9a** was dehydrogenated with sodium methoxide in diethyl ether yielding initially (10 min) diosphenol **10**. After about 30-40 min reaction time, the presence of a mixture of diosphenols **10** and **11** was observed in the reaction mixture. Compound **10** was completely converted to the thermodynamic product, diosphenol **11** after 18 hours reaction time. Compound **10** gave an orange brown colour reaction with ferric chloride, characteristic of dehydrobruceolides isolated from *Brucea javanica*[2]. The UV spectrum of compound **10** showed a maximum at 257 nm. The ^{1}H NMR spectrum of compound **10** showed a deuterium exchangeable singlet at δ=6.42 ppm representing the hydroxyl proton at C-2 and a singlet at δ=6.03 ppm representing the vinylic proton at C-1 whilst the protons of the methyl groups at C-4 and C-10 resonated at δ=1.97 ppm and δ=1.25 ppm respectively, as expected. The NOESY spectrum of compound **10** revealed a correlation between the H-1 and the protons of the methyl group at C-10. The UV maximum (275 nm) of diosphenol **11** and the grey-black colour reaction with ferric chloride on TLC indicated that the ring A structure of compounds **10** and **11** were different. The ring structure of compound **11** was similar to that of bruceolides.[2] The ^{1}H NMR spectrum of compound **11** showed a deuterium exchangeable proton signal at δ=6.05 ppm for the OH at C-3, two doublets at δ=2.85 ppm and 2.35 ppm corresponded to the two protons at C-1 and the protons of the methyl groups at C-4 and C-10 resonated at δ=1.83 ppm and 0.97 ppm respectively.



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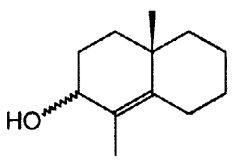

12

9	R
a	OH
b	Br
c	$OCOCH_3$
d	$OCOC_6H_5$
e	$OCOCH{=}C(CH_3)_2$
f	$OCOCH_2C(CH_3)_3$
g	$OCO(CH_2)_5CH_3$
h	$OCO(CH_2)_{16}CH_3$
i	$OCH_2O(CH_2)_2OCH_3$
j	$OCOCH_2NHOCOC(CH_3)_3$
k	$OCOCH[NHOCOC(CH_3)_3]CH(CH_3)_2$
l	$OCOCH[NHOCOC(CH_3)_3]CH_2C_6H_5$
m	$OCOCH[NHOCOC(CH_3)_3]CH(CH_3)C_2H_5$
n	$OCOCH[NHOCOC(CH_3)_3](CH_2)_7CH_3$
o	$OCOCH[NHOCOC(CH_3)_3](CH_2)_9CH_3$
p	$OCOCH[NHOCOC(CH_3)_3](CH_2)_{11}CH_3$
r	$OCOCH[NHOCOC(CH_3)_3](CH_2)_{17}CH_3$

Compound **5** was readily reduced at C-2 by sodium borohydride to yield compound **12**, as an **α/β mixture**. Compound **5** was also converted to its bromo-derivative **9b** by reacting it with phenyltrimethyl-ammonium-tribromide.

*2-Substituted analogues of compound **9a***

A series of 2-acyloxy substituted analogues of compound **9a** were prepared, so they might be evaluated biologically and structure activity relationships assessed.

Esters **9c-9h** were synthesised by reacting compound **9a** with acetic anhydride, benzoyl chloride, 3,3-dimethylacryloyl chloride, *tert*-butylacetic acid, hexanoic anhydride and stearic acid respectively. Methoxyethoxymethyl ether **9i** was prepared by reacting compound **9a** with methoxyethoxymethylchloride[8] and DMAP.

To examine the effect on the biological activity of natural amino acid substitution, compounds **9j-9m** were synthesised. Hydroxyenone **9a** was acylated with N-Boc protected glycine, valine, phenylalanine and isoleucine using an EDC/DMAP assisted coupling method,[9] resulting in compounds **9j-9m** respectively.

The α-amino acids with long alkyl side chains, the so-called lipoamino acids and their homo-oligomers, the lipopeptides, represent a class of compounds which combine structural features of lipids with those of amino acids and peptides.[10] One would expect the chimeric nature of these compounds to be reflected in their physical properties; they should be highly lipophilic due to the long alkyl side chains, yet show polar and conformational behaviour characteristic of amino acids and peptides. The appropriately protected lipidic amino acids and peptides could be covalently conjugated to, or incorporated into, poorly absorbed peptides and drugs, to enhance the passage of the pharmacologically active compounds across biological membranes. Because of their bifunctional nature, the lipoamino acids and peptides have the capacity to be chemically conjugated to drugs with a wide variety of functional groups. The linkage between drug and lipidic unit may either be biologically stable (ie. a new drug is formed) or possess biological or chemical instability (ie. the conjugate is a prodrug). In either case, the resulting conjugates would be expected to possess a high degree of membrane- like character, which maybe be sufficient to facilitate their passage across membranes.[11] The long alkyl side chains may also have the additional effect of protecting a labile parent drug from enzymatic attack.

A series of lipoamino acid conjugated **9n-9r** with increased lipophilic character was prepared by acylating hydroxyenone **9a** with the corresponding racemic lipoamino acid using the EDC/DMAP assisted coupling method. The esters were obtained as diasteromeric mixtures, which were separated by column chromatography. The absolute configuration of the diastereomeric pairs were not determined. The *in vitro* antiplasmodial and cytotoxic activities of these compounds will be reported elsewhere.

EXPERIMENTAL

UV Spectra were recorded on a Perkin-Elmer 402 Ultraviolet-Visible Spectrophotometer using spectroscopic grade methanol. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Bruker WM 250 spectrometer, or Bruker AMX 400, or Bruker AM 500 spectrometer. Electron Impact (EI) mass spectra were recorded on a VG Analytical LTD ZAB IF Spectrophotometer. Fast atom bombardment (FAB) spectra were recorded on a VG analytical ZAB-SE spectrometer; samples were dissolved in a 2-nitrobenzyl alcohol plus sodium iodide matrix (MNOBA + NaI) unless otherwise stated. High resolution MS (M+H or M+Na). Thin layer chromatography analysis were performed on Merck aluminium backed precoated thin layer Kiesel gel 60 F_{254} plates (0.25 mm thick). Chromatograms were visualised by spraying with p-anisaldehyde solution (135 ml of ethanol, 5 ml of concentrated H_2SO_4, 1.5 ml acetic acid, 4 ml of p-anisaldehyde) and heating at 110 °C or with ferric chloride reagent. Column chromatography was carried out by flash technique using silica gel Sorbsil C 60-H (40-60 μm) Rhone-Poulenc.

The solvents were evaporated *in vacuo*. The diastereomeric mixtures (compounds **9k-9r**) were separated, but the absolute configurations of the compounds were not determined.

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-1, 4a-dimethyl-2 (3H)-naphthalenone (5) and (±)-cis-4, 4a, 6, 7, 8, 8a, 9, 10-octahydro-1, 4a, 8a-trimethyl-2 (3H)-phenanthrenone (6). To a mixture of 2-methylcyclohexanone **3** (15 ml, 13.86 g, 0.124 mmol) and 1-chloro-3-pentanone **4** (18 ml, 18.8 g, 156 mmol) in dry toluene (80 ml) anhydrous 2-naphthalene sulphonic acid (1 g) was added and the mixture heated under reflux in nitrogen for 4 days. The mixture was concentrated to a brown syrup and and a mixture of 20 % aq. KOH (40 ml) and MeOH (40 ml) added. The mixture was heated under reflux for 7 hours, concentrated, poured into water (100 ml) and extracted with diethyl ether (3x40 ml). The combined organic extract was washed with brine (20 ml), dried ($MgSO_4$) and concentrated to a brown oil (22 ml). Distillation (b.p. 126-130°C, 4 mm Hg) of the crude product gave 11.45 g (52%) of bicyclic enone **5** as a colourless oil and 2.3 g (8 %) of tricyclic dienone **6** as a viscous yellow oil (b.p.145-150 °C, 4 mm Hg). The crude compound was purified by column chromatography (toluene:ethyl acetate 98:2 v/v). **5:** Rf=0.53, toluene:ethyl acetate 9:1 v/v, Rf=0.37, hexane:Et_2O 6:4 v/v. MS (EI) m/z (%)=178 $[M]^+$ (100), 163 (64), 150 (24), 136 (74), 121 (57), 107 (43), 93 (47), 79 (45), 67 (19), 53 (26). ^1H NMR: δ=2.75 (m, 1H, C-2 H), 2.55-2.39 (m, 2H, C-2 H_a, C-6 H_b), 2.1 (m, 1H, C-6 H_a), 2.0-1.3 (m, 7 H, C-1 Hs, C-7 Hs, C-8 Hs, C-9 Hs), 1.76 (s, 3H, C-4 CH_3), 1.22 (s, 3H, C-10 CH_3). IR: υ_{max}=2940, 2865, 1660, 1605 cm^{-1}. UV 248 nm (MeOH). **6**: The distillate with the crude compound **6** was further purified by column chromatography (toluene:ethyl acetate 99:1). MS (EI) m/z (%)= 244 $[M]^+$ (49), 229 (100), 216 (7), 201 (27), 187 (32), 173 (16), 159 (19), 145 (17), 131 (14), 115 (11), 105 (18), 91 (26), 79 (16), 67 (8), 55 (13), 41 (17), 29 (6). High resolution MS: Calculated for $C_{17}H_{25}O$ (245.1905), Found= 245.1950. ^1H NMR: δ=5.51 (t, 1H, C-11 H), 2.75-2.4 (m, 4H, C-2, C-6 H's), 2.25-2.0 (m, 2H, C-12 H's), 1.78 (s, 3H, C-4 CH_3), 1.75-1.3 (m, 6H, C-1 H, C-7 Hs, C-13 Hs, C-14 Hs), 1.37 (s, 3H, C-10 CH_3), 1.26 (s, 3H, C-8 CH_3). UV 255 nm (MeOH). IR:υ_{max}=2900, 2800, 1650, 1600 cm^{-1}.

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-1, 4a-dimethyl-2-trimethylsilyloxynaphthalene (7). A solution of bicyclic enone **5** (6 g, 33.7 mmol) in dry THF (30 ml) was added to a solution of 2M LDA (18 ml, 36 mmol) under nitrogen at -78 °C and the mixture stirred for 20 minutes. Chlorotrimethylsilane (CTMSi, 6 ml, 55.2 mmol), was added to the reaction mixture and stirred for 4 hours by which time the temperature of the bath had risen to room temperture. The mixture was poured into a solution of saturated $NaHCO_3$ (100 ml), extracted with hexane (3x30 ml), washed with brine and dried ($MgSO_4$). The solvent was removed to afford 7.9 g of compound **7** as a viscous brown oil, which was used in the next reaction without further purification. Rf=0.7 (hexane:diethyl ether 6:4 v/v). MS (EI) m/z (%)=250 $[M^+]$ (22), 235 (45), 219 (7), 207 (11), 193 (14), 105 (9), 19 (24), 73 (100), 55 (15), 28 (17).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-1, 4a-dimethyl-3-trimethylsilyloxy-2 (3H)-naphthalenone (8). A solution of crude **7** (7.8 g) in CH_2Cl_2 (50 ml) was cooled (-5 °C) and 60 % MCPBA (11.6 g, 67 mmol) in CH_2Cl_2 (15 ml) was added and the mixture stirred for 45 minutes. The mixture was washed with saturated $NaHCO_3$ (30 ml) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2x20 ml) and the combined organic extract concentrated. The residue was dissolved in hexane (50 ml), washed with saturated aqueous $NaHCO_3$ (2x30 ml), brine (30 ml) , dried (Na_2SO_4) and concentrated to give 3.82 g (46%) of compound **8** as a viscous yellow oil which was used in the next reaction without further purification. Rf=0.56 (hexane:diethyl ether 6:4 v/v). ^1H-NMR: δ=4.35 (dd, 1H J=12.7 and 6.4 Hz, 2.7 (m, 1H, C-6 H), 2.4 (m, 1H, C-2 H), 1.76 (s, C-4 CH_3), 1.37 (s, 3H, C-8 CH_3) 0.2 [s, 9H, $(CH_3)_3$].

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-hydroxy-1, 4a-dimethyl-2 (3H)-naphthalenone (9a). A crude solution of compound **8** (3.7 g) in THF (20 ml) and 10% HCl (30 ml) was stirred at room temperature for 1 h. The mixture was

extracted with ether (3x30 ml) and the combined organic extract washed with saturated $NaHCO_3$ (25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (hexane-ether 90:10 v/v) to afford 2.05 g (76%) of **9a**. Rf=0.18 (toluene-ethyl acetate, 9:1 v/v). MS (EI) m/z (%)=194 $[M]^+$ (87), 178 (44), 165 (52), 161 (15), 152 (43), 137 (43), 123 (47), 110 (100), 105 (43), 95 (42), 91 (40), 79 (64), 67 (77). High resolution MS: Calculated for $C_{12}H_{18}O_2$ (194.1307), Found=194.1302. ^1H NMR: δ=4.31 (dd, 1H J=5.6 and 14.0 Hz, C-2 H), 3.75 (bs, 1H, OH), 2.68 (bd, 1H, C-6 H_b), 2.08 (m, 1H, C-1 H), 2.06 (m, 1H, C-6 H_a), 1.96 (m, 1H, C-7 H_b), 1.81 (s, 1H, C-4 CH_3), 1.67 (m, 1H, C-1 H_α), 1.34 (s, 3H, C-10 CH_3). UV 247 nm (MeOH). IR: υ_{max}=2450, 2940, 2860, 1660, 1606 cm^{-1}.

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-bromo-2 (3H)-naphthalenone (9b). A solution of biyclic enone (5) (120 mg, 0.674 mmol) in dry THF (6 ml) was cooled in an ice bath, PTAB (253 mg, 0.673 mmol) was added, stirred and then left to stand for 1 hour. The clear orange solution turned pale yellow and crystals of pyridine bromide precipitated. The mixture was poured into a solution (15 ml) of 0.1 N $Na_2S_2O_3$ and saturated $NaHCO_3$, extracted with ether (3x10 ml) and the combined organic extracts washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene) to yield 83 mg (48%) of bromide **9b**. MS (CI) m/z (%)=276 $[M+NH_3+2]^+$ (4), 227 (3), 216 (2), 194 (4), 176 (5), 165 (11), 150 (26), 135 (4), 121 (12), 107 (8), 91 (11), 83 (100), 55 (51). ^1H NMR: δ=5.4 (m, 1H, C-2 H), 2.65 (m, 1H, C-6 H_b), 2.5 (m, 1H, C-6 H_a), 2.35 (m, 1H, C-1 H), 1.83 (s, 3H, C-4 CH_3), 1.54 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-acetyloxy-1, 4a-dimethyl-2 (3H)-naphthalenone (9c). To a solution of **9a** (100 mg, 0.515 mmol) and DMAP (75 mg, 611 mmol) in Cl_2Cl_2 (3ml), acetic anyhdride (0.3 ml) was added and the mixture stirred for 2 hours. Further CH_2Cl_2 (15 ml) was added and the mixture washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene:ethylacetate 98:2 v/v) to obtain 89 mg (67%) of **9c**. Rf=0.45 (toluene:ethyl acetate 9:1 v/v). MS (EI) m/z (%)=236 $[M]^+$ (10), 221 (5), 94 (13), 176 (30), 161 (19), 150 (100), 135 (27), 122 (29), 107 (37), 91 (38), 79 (36), 67 (21), 55 (37). ^1H NMR: δ=5.5 (dd, 1H, J=12.6 and 7.2 Hz, C-2 H), 2.7 (bd, 1H, C-6H), 2.2 (s, 3H, $COCH_3$), 1.9 (m, 2 H, C-1 H, C-6 H), 1.8 (s, 3H, C-4 CH_3), 1.3 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-benzoyloxy-1, 4a-dimethyl-2 (3H)-naphthalenone (9d). To a cooled (0°C) solution of **9a** (55 mg, 0.283 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (2 ml) benzoyl chloride (0.2 ml) was added and the mixture stirred at room temperature for 16 hours. The mixture was diluted with CH_2Cl_2 (15 ml), washed with saturated aqueous $NaHCO_3$ (10 ml), brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (hexane-ether 90:10) to afford 42 mg (50%) of **9d**. Rf=0.49 (toluene:ethyl acetate 9:1 v/v). MS (EI) m/z (%)=299 $[M+1]^+$ (100), 245 (4), 235 (3), 193 (3), 179 (36), 78 (17), 123 (25), 105 (3). High resolution MS: Calculated for $C_{19}H_{23}O_3$ (299.1647), Found=299.1556. ^1H NMR: δ=8.11-7.43 (m, 5H, aromatic-H's), 5.75 (m, 1H, C-2 H), 2.75 (d, 1H, J=10 Hz, C-6 H_b), 2.12 (m, 2H, C-1 H, C-6 H_a), 1.85 (s, 3H, C-4 CH_3), 1.4 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [3, 3-dimethylacryloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9e). The compound was prepared according to the procedure described for **9d**. Yield: 15 mg (53%). High resolution MS: Calculated for $C_{17}H_{24}O_3$ (276.1725), Found=276.1722. MS (EI) m/z (%)=276 $[M]^+$ (87), 261 (13), 253 (22), 242 (15), 227 (43), 216 (27), 194 (84), 176 (100).
^1H NMR: δ=5.8 (s, 1H, C-2' H), 5.25 (dd, 1H J=13 and 6.4 Hz, C-2 H), 2.7 (bd, 1H, J=10 Hz, C-6H), 2.31 (m, 1H, C-6 H), 2.17 (s, 3H, C-5' CH_3), 1.91 (s, 3H, C-4' H), 1.9 (s, 3H, C-4 CH_3), 1.43 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-(*tert*-butylacetyloxy)-1, 4a-dimethyl-2 (3H)-naphthalenone (9f). To a solution of **9a** (100 mg, 0.515 mmol), DMAP (100 mg, 0.815 mm0l) and EDC (140 mg, 0.73 mmol) in CH_2Cl_2 (3 ml), *tert*-butylacetic acid (0.25 ml) was added and the mixture stirred at room temperature for 3 hours. Further CH_2Cl_2 (15 ml) was added and the mixture washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (toluene-ethyl acetate 98:2) to yield 86.3 mg (57%) of **9f**. Rf=0.73 (toluene:ethyl acetate 9:1 v/v). MS (EI)m/z (%)=292 $[M]^+$ (11), 277 (5), 236 (17), 194 (35), 176 (25), 161 (15), 150 (100), 135 (16), 121 (20), 107 (17), 99 (16), 91 (22), 79 (13), 57 (90). ^{1}H NMR: δ=5.55 (dd, 1H J=11.3 and 8.5 Hz, C-2 H), 2.67 (d, 1H, J= 10 Hz, C-6 H_b), 2.4-2.2 (m, 3H, α-CH_2, C-6 H), 1.9 (m, 1H, C-1H_a), 1.8 (s, 3H, C-4 CH_3), 1.35 (s, 3H, C-10 CH_3), 1.1 [s, 9H, $(CH_3)_3$].

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-hexyloxy-1, 4a-dimethyl-2 (3H)-naphthalenone (9g). The compound was prepared according to the procedure described for **9c**. Yield: 42 mg (44%). Rf=0.74 (toluene:ethyl acetate 9:1). MS (EI) m/z (%)=293 $[M+1]^+$ (100), 275 (5), 259 (4), 236 (6), 215 (3), 205 (4), 195 (33), 189 (7), 177 (15), 163 (7). ^{1}H NMR: δ=5.45 (dd, 1H J=13 and 6.8 Hz, C-2), 2.72 (d, 1H, J=10 Hz, C-6 H_b), 2.4 (m, 2H, α-CH_2), 2.1 (m, 1H, C-6 H_b), 1.95 (m, 2H, C-1 H_b, C-6 H_a), 1.80 (s, 3H, C-4 CH_3), 1.35 (s, 3H, C-10 CH_3), 1.35 (m, 8H, 4 CH_2), 0.85 (m, 3H, δ-CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3-steroyloxy-1, 4a-dimethyl-2 (3H)-naphthalenone (9h). The compound was prepared according to the procedure described for **9f**. Yield: 80 mg (34%). Rf=0.85 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=483 $[M+23]^+$ (67), 455 (67), 433 (15), 313 (3), 271 (6), 195 (100), 151 (43), 91 (35). High resolution MS: Calculated for $C_{30}H_{53}O_3$ (461.3995), Found= 461.4130. ^{1}H NMR: δ=5.50 (dd, 1H J=7.6 and 12 Hz, C-2 H), 2.67 (bd, 1H, J=10 Hz, C-6 H_b), 2.5-2.3 (m, 3H, α-CH_2, C-6 H), 1.92 (m, 1H, C-1 H_a), 1.78 (s, 3H, C-4 CH_3), 1.36 (s, 3H, C-4 CH_3), 1.25 (bs, 32H, 16 CH_2), 0.88 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- (methoxyethoxymethyleneoxy)-2 (3H)-naphthalenone (9i)
The compound was prepared according to the procedure described for **9d**. Yield: 32 mg (44%).
MS (FAB) m/z (%)=$[M+Na]^+$ 305 (100), 289 (7), 283 (5), 273 (5), 265 (6), 245 (7), 207 (21), 189 (4). ^{1}H NMR: δ=4.98 (d, 1H J=2.7 Hz, α-CH), 4.97 (d, 1H J=2.7 Hz, α-CH), 4.37 (dd, 1H J=5.3 and 14 Hz, C-2 H), 3.8 (m, 2H, CH_2), 3.57 (m, 2H, CH_2), 3.39 (s, 3H, CH_3), 2.7 (d, 1H, J=10 Hz, C-6 H_b), 2.1 (m, 1H, C-6 H), 1.77 (s, 3H, C-4 CH_3), 1.32 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3 (α, β)- [2- (tert-butoxycarbonylamino)-acetyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9j). The compound was prepared according to the procedure described for **9f**. Yield: 73 mg (40%). Rf=0.39 (toluene:ethyl acetate 9:1 v/v). MS (EI)m/z (%)=352 $[M+1]^+$ (27), 296 (100), 252 (45), 195 (85), 177 (38), 149 (27), 121 (14), 93 (16). High resolution MS: Calculated for $C_{19}H_{30}O_5$ N (352.2293), Found=352.2492. ^{1}H NMR: δ=5.56 (dd, 1H J=13.5 and 6.3 Hz, C-2 H), 5.51 (m, 1H, N-H), 4.02 (m, 1H, α-CH), 4.01 (m, 1H, α-CH), 2.68 (d, 1H, J=10 Hz, C-6 H_b), 1.97 (m, C-1 H), 1.78 (s, 3H, C-4 CH_3), 1.45 (s, 9H, $(CH_3)_3$), 1.36 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3 (α, β)- [2- (*tert*-butoxycarbonylamino)-3-methylbutyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9kA and 9k B). The diastereomers were prepared according to the procedure described for **9f**. **9k A**: yield 26 mg (13%). Rf=0.56 (toluene:ethyl acetate 9:1 v/v). MS (CI) m/z (%)=411 $[M+NH_3-1]^+$ (74), 392 (41), 355 (84), 294 (100), 232 (14), 179 (93), 132 (21), 72 (40). ^{1}H NMR: δ=5.5 (dd, 1H, J=7.7 Hz, 12.4 Hz, C-2 H), 5.0 (d, 1H, J=8.6 Hz, N-H), 4.35 (m, 1H, α-CH), 2.70 (d, 1H, J=10 Hz, C-6 H), 2.20 (m, 1H, CH), 1.95 (m, 2H, C-1 H_a, C-6 H), 1.8 (s, C-4 CH_3), 1.45 (s, 9H, $(CH_3)_3$), 1.40 (s, 3H, C-10 CH_3), 1.0 (d, 3H, CH_3), 0.95 (d, 3H, CH_3). IR υ_{max}=3390, 2980, 2940, 2880, 1720, 1620 cm^{-1}. **9k B**: yield: 22 mg (11%). Rf=0.46 (toluene:ethyl acetate 9:1

v/v). MS (FAB) m/z (%)=416 $[M+23]^+$ (29), 394 $[M+1]^+$ (18), 338 (47), 294 (100), 195 (27), 177 (28), 154 (34), 136 (31), 116 (36), 91 (35). High resolution MS: Calculated for $C_{22}H_{35}O_5NNa$ (416.2413), Found= 416.1997. ^1H NMR: δ=5.51 (dd, 1H, J=7.4 Hz, 12 Hz, C-2 H), 5.04 (d, 1H J=8.6 Hz, N-H), 4.35 (m, 1H, α-CH), 2.68 (d, 1H, J=10 Hz, C-6 H), 2.20 (m, 1H, CH), 2.05 (m, 2H, C-1 H, C-6 H), 1.8 (s, 3H, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.40 (s, 3H, C-10 CH_3), 1.0 (s, 3H, CH_3), 0.95 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [2- (tert-butoxycarbonylamino)-3-benzylpropyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9l A and 9l B). The diastereomers were prepared according to the procedure described for **9f**. **9l A**: yield: 50 mg (17%). Rf=0.58 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)= 464 $[M+23)^+]$ (100), 408 (25), 364 (4), 2 (10), 316 (8), 272 (4), 215 (4), 194 (3), 176 (3), 154 (2), 120 (4). High resolution MS: Calculated for $C_{26}H_{35}O_5NNa$ (464.2413), Found=464.1895. ^1H NMR: δ=7.3 (m, 5H, aromatic H's) 5.55 (dd, 1H J=12.4 and 7.4 Hz, C-2 H), 5, 45 (d, 1H J=8.3 Hz, N-H), 4, 95 (m, 1H, α-CH), 3.35 (dd, 1H J=14 and 4.9 Hz, CH), 3.1 (dd, 1H J=14 Hz and 7 Hz, CH), 2.7 (d, 1H, J=10 Hz, C-6H_b), 2.15 (m, 1H, J=10 Hz, C-6 H_a), 1.95 (m, 2H, C-1 H), 1.8 (s, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.8 (s, 3H, C-4 CH_3), 1.25 (s, 3H, C-10 CH_3). IR data: υ_{max}=3350, 3000, 2900, 2840, 1740, 1700, 1660, 1600 cm^{-1}. **9l B**: yield: 46 mg (16%). Rf=0.50 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=464 $[M+23)^+]$ (12), 442 (22), 386 (18), 342 (100), 307 (46), 289 (30), 250 (19), 215 (4), 195 (18), 177 (27). ^1H NMR: δ=7.3 (m, 5H, aromatic H's) 5.55 (dd, 1H J=12.4 and 7.4 Hz, C-2 H), 5, 45 (d, 1H J=8.3 Hz, N-H), 4, 95 (m, 1H, α-CH), 3.35 (dd, 1H J=14 and 4.9 Hz, β-CH), 3.1 (dd, 1H J=14 Hz and 7 Hz, CH), 2.7 (d, 2H, C-6H_b), 2.15 (m, 1H, C-6 H_a), 1.95 (m, 2H, C-1 H), 1.8 (s, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.8 (s, 3H, C-4 CH_3), 1.25 (s, 3H, C-10 CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [2- (tert-butoxycarbonylamino)-3-methylpentyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9m A and 9m B). The diastereomers were prepared according to the procedure described for **9f**. **9m A**: yield: 18.9 mg (11%). Rf=0.57 (toluene:ethyl acetate 9:1 v/v). MS (CI) m/z (%)=425 $[M+NH_3]^+$ (17), 370 (42), 352 (44), 308 (57), 246 (4), 179 (100), 132 (13), 86 (22). ^1H NMR: δ=5.55 (d, 1H, J=12 Hz, C-2 H), 5.05 (m, 1H, N-H), 4.4 (m, 1H, α-CH), 2.73 (d, 1H, J=10 Hz, C-6 H_b), 2.05 (m.1H, C-6 H_a), 2-1.9 (m, C-1 H,), 1.87 (s, 3H, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.35 (s, 3H, C-10 CH_3), 1.05 (s, 3H, CH_3), 0.95 (m, 3H, CH_3). **9m B**: 23.6 mg (14%). Rf=0.49 (toluene:ethyl acetate 9:1). MS (FAB) m/z (%)=430 $[M+23]^+$ (40), 408 $[M+1]^+$ (14), 374 (10), 352 (37), 340 (30), 324 (18), 308 (100), 195 (28), 177 (38), 149 (34), 130 (82), 91 (42). High resolution MS: Calculated for $C_{23}H_{37}O_5NNa$ (430.2569), Found=430.2628. ^1H NMR: δ=5.55 (d, 1H, J=12 Hz, C-2 H), 5.1 (m, N-H), 4.4 (m, 1H, α-CH), 2.73 (d, 1H, J=10 Hz, C-6 H_b), 2.05 (m.1H, C-6 H_a), 2-1.9 (m, C-1 H,), 1.87 (s, 3H, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.35 (s, 3H, C-10 CH_3), 1.05 (s, 3H, CH_3), 0.95 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [2-tert-butoxycarbonylamino)-decanoyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9n A and 9n B). The diastereomers were prepared according to the procedure described for **9f**. **9n A**: yield: 22 mg (13%). Rf=0.62 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=486 $[M+23]^+$ (100), 430 (43), 364 (8), 330 (3), 272 (6), 215 (8), 176 (9), 142 (27). ^1H NMR: δ=5.55 (dd, 1H, J=7.4 Hz, 12.4 Hz, C-2 H), 5.0 (m, 1H, N-H), 4.35 (m, 1H, α-CH), 2.67 (d, 1H, J=10 Hz, C-6 H_a), 2.0 (m, 2H, C-1 H_a, C-6 H_b), 1.78 (s, 3H, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.37 (s, C-10 CH_3), 1.27 (m, 14 H, 7 CH_2), 0.88 (m, 3H, CH_3). **9n B**: yield: 28 mg (17%). Rf=0.54 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=486 $[M+23]^+$ (35), 430 (9), 408 (22), 364 (72), 195 (18), 178 (22), 142 (100), 91 (19). High resolution MS: Calculated for $C_{27}H_{45}O_5NNa$ (486.3195), Found=486.3151. ^1H NMR: δ=5.50 (dd, 1H J=7.4 hz, 12.4 Hz, C-2 H), 5.0 (m, 1H, N-H), 4.35 (m, 1H, α-CH), 2.70 (d, 1H, J=10 Hz, C-6 H_a), 2.10 (m, 2H, C-1 H_a, C-6 H_b), 1.78 (s, 3H, C-4 CH_3), 1.45 [s, 9H, $(CH_3)_3$], 1.37 (s, C-10 CH_3), 1.27 (m, 14 H, 7 CH_2), 0.85 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [2-tert-butoxycarbonylamino)-dodecanoyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (Compound 9o A and 9o B). The diastereomers were prepared according to the procedure described for **9f**. **9o A**: yield: 36 mg (18%). Rf=0.65 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=493 $[M+2H]^+$] (14), 436 (36), 392 (43), 368 (3), 214 (4), 178 (12). ^1H NMR : δ=5.55 (dd, 1H, J=7.4 Hz, 12.4 Hz, C-2 H), 4.95 (m, 1H, N-H), 4.35 (m, 1H, α-CH), 2.7 (d, 1H, J=10 Hz, C-6 H), 1.95 (m, 2H, C-6 H_A, C-1 H_b), 1.8 (s, C-4 CH_3), 1.4 [s, 9H, $(CH_3)_3$], 1.4 (s, 3H, C-10 CH_3), 1.25 (m, 18H, 9 CH_2), 0.85 (m, 3H, CH_3). **9o B**: yield: 31 mg (15%) Rf=0.54 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=514 $[M+23]^+$ (3), 496 $[M]^+$ (25), 474 (16), 440 (6), 418 (36), 374 (100), 2261 (18), 243 (35), 154 (57), 91 (51). High resolution MS: Calculated for $C_{29}H_{49}O_5NNa$ (514.3508), Found=514.2764. ^1H NMR: δ=5.45 (dd, 1H, J=7.4 Hz, 12.4 Hz, C-2 H), 5.05 (m, 1H, N-H), 4.35 (m, 1H, α-CH), 2.70 (d, 1H, J=10 Hz, C-6 H), 2.05 (m, 2H, C-6 H_A, C-1 H_b), 1.85 (s, C-4 CH_3), 1.4 [s, 9H, $(CH_3)_3$], 1.4 (s, 3H, C-10 CH_3), 1.25 (m, 18H, 9 CH_2), 0.85 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-hexahydro-3- [2-tert-butoxycarbonylamino)-tetradecanoyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9p A and 9p B): The diastereomers were prepared according to the procedure described for **9f**. **9p A**: yield: 25 mg (10%). Rf=0.69 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=520 $[M]^+$ (3), 465 (5), 420 (9), 385 (11), 302 (100), 258 (69), 242 (5), 198 (12), 179 (8). ^1H NMR: δ=5.5 (dd, 1H J= 13.3 and 6.5 Hz, C-2H), 4.95 (N-H), 4.3 (m, α-CH), 2.65 (d, 1H, J=10 Hz, C-6 H), 2.1 (m, 2H, C-1 H, C-6 H_a), 1.85 (s, 3H, C-4 CH_3), 1.65 (m, C-1 H), 1.5 [s, 9H, $(CH_3)_3$], 1.4 (s, C-10 CH_3), 1.3 (m, 22 H, 11 CH_2), 0.85 (m, 3H, CH_3). IR: υ_{max}=3420, 3350, 2900, 2825, 1735, 1700, 1680, 1600cm^{-1}. **9p B**: yield: 27 mg (11%). Rf=0.60 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=542 $[M+23]^+$ (4), 520 $[M+1]^+$ (2), 464 (8), 420 (56), 242 (8), (198 (100), 178 (24), 149 (21), 91 (14). High resolution MS: Calculated for $C_{31}H_{53}O_5NNa$ (542.3821), Found=542.3949. ^1H NMR: δ=5.5 (dd, 1H J= 13.3 and 6.5 Hz, C-2H), 4.95 (m, 1H, N-H), 4.3 (m, α-CH), 2.65 (d, 1H, J=10 Hz, C-6 H), 2.1 (m, 2H, C-1 H, C-6 H_a), 1.85 (s, 3H, C-4 CH_3), 1.65 (m, C-1 H), 1.5 [s, 9H, $(CH_3)_3$], 1.4 (s, C-10 CH_3), 1.3 (m, 22 H, 11CH_2), 0.85 (m, 3H, CH_3).

(±)-4, 4a, 5, 6, 7, 8-Hexahydro-3- [2-tert-butoxycarbonylamino)-eicosanoyloxy]-1, 4a-dimethyl-2 (3H)-naphthalenone (9r A and 9r B). The diastereomers were prepared according to the procedure described for **9f**. **9r A**: yield: 34 mg (11%). Rf=0.73 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=604 $[M+1]^+$ (6), 549 (20), 505 (24), 326 (4), 282 (2), 195 (100), 178 (11). ^1H NMR: δ=5.5 (dd, 1H J=13 and 6.5 Hz, C-2 H), 4.95 (m, 1H, N-H), 4.35 (m, 1H, α-CH_2), 2.7 (d, 1H, C-6 H), 2.0 (m, 2H, C-1 H, C-6 H), 1.78 (s, C-4 CH_3), 1.4 [s, 9H, $(CH_3)_3$], 1.23 (s, 3H.C-10 CH_3), 1.25 (s, 34 H, 11 CH_2), 0.85 (m, 3H, CH_3). IR: υ_{max}=3380, 2940, 2860, 1760, 1720, 1680 cm^{-1}. **9r B**: yield: 32 mg (10%). Rf=0.64 (toluene:ethyl acetate 9:1 v/v). MS (FAB) m/z (%)=626 $[M+23]^+$ (10), 548 (5), 504 (48), 282 (100), 195 (22), 178 (27), 159 (24). High resolution MS: Calculated for $C_{37}H_{65}O_5NNa$ (626.4760), Found=626.4686. ^1H NMR: δ=5.50 (dd, 1H J=13 and 6.5 Hz, C-2 H), 5.05 (d, 1H, N-H), 4.35 (m, 1H, α-CH_2), 2.7 (d, 1H, J=10 Hz, C-6 H), 2.1 (m, 2H, C-1 H, C-6 H), 1.74 (s, C-4 CH_3), 1.4 [s, 9H, $(CH_3)_3$], 1.23 (s, 3H, C-10 CH_3), 1.25 (s, 34 H, 17 CH_2), 0.85 (m, 3H, CH_3).

(±)-5, 6, 7, 8-Tetrahydro-3-hydroxy-1, 4a-dimethyl-2 (4aH)-naphthalenone (10). To a solution of **9a** (20 mg, 0.103 mmol) in dry diethyl ether (2 ml) 100 µl of 30% NaOMe in methanol was added and the mixture stirred at room temperature for 10 min, diluted with ether (10 ml), washed with brine, dried ($NaSO_4$) and concentrated to yield 14.4 mg (72%) of dehydro diosphenol **10**. Rf 0.36 (toluene-ethyl acetate 9:1 v/v). MS (FAB, MNOBA) m/z (%)=193 $[M+1]^+$ (100), 175 (68), 160 (20), 149 (88), 136 (63), 121 (44), 95 (34), 91 (53). High resolution MS: Calculated for $C_{12}H_{17}O_2$ (193.1229), Found=193.1224. ^1H NMR: δ=6.43 (s, 1H, OH, exchangeable with D_2O), 6.03 (s, 1H, C-1 H), 2.85 (bd, 1H J=13.8 Hz, C-6 H), 2.15 (d, 1H, J=10 Hz, C-6 H), 1.97 (s, 3H, C-4 CH_3), 2.1-1.2 (m, 6H, C-7, C-8, C-9 Hs), 1.25 (s, 3H, C-10 CH_3). ^{13}C NMR δ=182 (C-3), 164 (C-5), 144 (C-2), 126.37 (C-4), 126.16

(C-1), 40.38 (C-10), 40.11 (C-9), 28.1 (C-6), 27.64 (C-7), 24.51 (C-10 CH_3), 21.08 (C-8), 10.71 (C-4 CH_3).

(±)-4a, 5, 6, 7, 8, 8a-Hexahydro-2-hydroxy-1, 4a-dimethyl-3 (4H)-naphthalenone (11). To a solution of **9a** (100 mg, 0.515 mmol) in dry THF (4ml), 30% w/w NaOMe in MeOH (0.5 ml) was added and the mixture stirred at room temperature for 17 h, diluted with ether (15 ml), washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to yield 62 mg (62%) of diosphenol **11**. Rf 0.38 (toluene-ethyl acetate 9:1 v/v). MS (EI) m/z (%)=194 $[M]^+$ (39), 177 (26), 163 (40), 149 (27), 123 (66), 109 (62), 95 (86), 91 (54), 81 (64), 77 (53). High resolution MS: Calculated for $C_{12}H_{18}O_2$ (194.1307), Found=194.1302. ^1H NMR: δ=6.05 (s, 1H, OH, exchangeable with D_2O, C-3 H), 2.35 (d, 1H, J=10 Hz, C-1 H_a), 1.8 (s, 3H, C-4 CH_3), 0.95 (s, 3H, C-10 CH_3). UV 275 nm (MeOH).

(±)-2, 3, 4, 4a, 5, 6, 7, 8-Octahydro-1, 4a-dimethyl-2-naphthol (12). To a solution of bicyclic enone **5** (94 mg, 0.528 mmol) in absolute ethanol (20 ml), excess $NaBH_4$ (150 mg, 3.69 mmol) was added and mixture stirred for 45 min at room temperature. A few drops of acetic acid was added to the mixture, poured into a saturated solution of $NaHCO_3$ and extracted with ether (3x15 ml). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (toluene: ethyl acetate 95:5) to obtain 80 mg (84%) of compound **12**. MS (EI) m/z (%)=180 $[M]^+$ (11), 179 (20), 163 (100), 147 (24), 133 (8), 121 (18), 105 (18), 95 (53), 81 (37), 67 (22), 55 (57). High resolution MS: Calculated for $C_{12}H_{19}O$ (179.1436), Found=179.1453. ^1H NMR: δ=4.05 (m, 1H, C-3 H), 2.48 (bd, 2H, J=10 Hz, C-6 H), 1.91 (m, 1H, C-6 H_a) 1.8-1.15 (m, 10H, C-2 Hs, C-1 Hs, C-7 Hs, C-8Hs. C-9 Hs), 1.71 (s, 3H, C-4 CH_3), 1.1 (s, 3H, C-10 CH_3).

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