Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 2805–2811
Tetrahedron

Synthetic studies towards furosesquiterpenoids: total synthesis of (±) desmethylpallescensin-A, (±) isopallescensin-A and (±) isopallescensin-1

Sajal Kanti Mal, Gandhi K. Kar and Jayanta K. Ray*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

Received 20 October 2003; revised 24 December 2003; accepted 22 January 2004

Abstract—A new approach for a short and efficient synthesis of common cyclohexenone intermediate towards the total synthesis of some furosesquiterpenes and their analogues are described. Regioselective alkylation of Hagemann's ester with 2/3-furyl-2-ethyl bromide followed by hydrolysis cum in situ decarboxylation and 1,4-addition with Gilman's reagent produced the cyclohexanone derivatives which have been utilized for total synthesis of (±) isopallescensin-A, (±) 10-desmethylpallescensin-A, (±) 5-desmethyl-4,5-dehydromicrocionin-1 and (±) isopallescensin-1.

1. Introduction

Furoterpenes have been found to occur abundantly in nature particularly in higher plants and marine organism. The biological activity associated with a number of drimane metabolites[1] specially furosesquiterpenes has stimulated considerable interest in their synthesis.[2] Among the broad structural variety of these natural furosesquiterpenes occupy a special place.[3] Most of these natural products have attracted much interest due to their inherent biological properties.[4] Synthesis of such furoterpenes are a challenging problem for many research laboratories even today. These includes compounds like Pallescensin A-G,[5] Pallescensin 1-3,[5] Microcionin,[5] Spiniferin[5] and several other furanosesquiterpenes. A large number of syntheses[6a–m] of several furoterpenes with complex structures have come out in last few decades and many more are still coming out. This attracted us to study the synthesis of various furoterpenes and our aim is to achieve the synthesis of such compounds via a common intermediate. One such common intermediate for the synthesis of compound **2**-**9** may be suitably substituted cyclohexenone derivatives (**1**), which in turn can easily be obtained from Hagemann's ester (Fig. 1).

The construction of a carbocyclic framework, especially one with a quaternary center, is key to the rapid and efficient synthesis of many natural products.[7] As part of our current research programme towards the synthesis of potentially bioactive furosesquiterpenes, we have developed a method for constructing a tricyclic framework using acid catalysed cyclisation reactions leading to tricyclic sesquiterpenoids and we sought to prepare a range of model compounds. These are shown in Figure 1.

In earlier synthesis of tricyclic furanosesquiterpenoids, most of the synthesis describes the linear approaches that sequentially build the tricyclic skeleton from C ring precursor or AB ring precursor to ABC tricyclic framework. In our present approach we have utilized a common AC ring precursor 2-(2-furyn-3-yl-ethyl)-3-methyl cyclohex-2-enone (**1**) (X=H) for constructing ABC tricyclic framework (Fig. 2).

2. Results and discussion

The model study in this connection was performed with 2-furyl analogue as in Scheme 1 to achieve the synthesis of (±) isopallaescensin-A and (±) isopallescensin-1.

Employing our experience[8] in the synthesis of regiospecifically substituted furan we targeted to expand our protocol towards the synthesis of furosesquiterpenes through a common intermediate (**1**). In this connection we wish to report our approach towards the synthesis of such furoterpenes and their analogues via common intermediate 2-(2-furan-3-yl-ethyl)-3-methyl-cyclohex-2-enone (**1**) (X=H) and its 2-furyl analogues (**12**) respectively. Thus the Hagemann's ester (**10**) on regioselective alkylation with 2-(2-furyl-ethyl bromide)/^{t}BuOK in ^{t}BuOH under reflux

Keywords: Hagemann's ester; Alkylation; Furoterpenes; Conjugate addition; Cyclisation; Isopallescensis-A; Desmethyl pallescensin-A.
* Corresponding author. Tel.: +913222283326; fax: +913222282252; e-mail address: jkray@chem.iitkgp.ernet.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.01.068

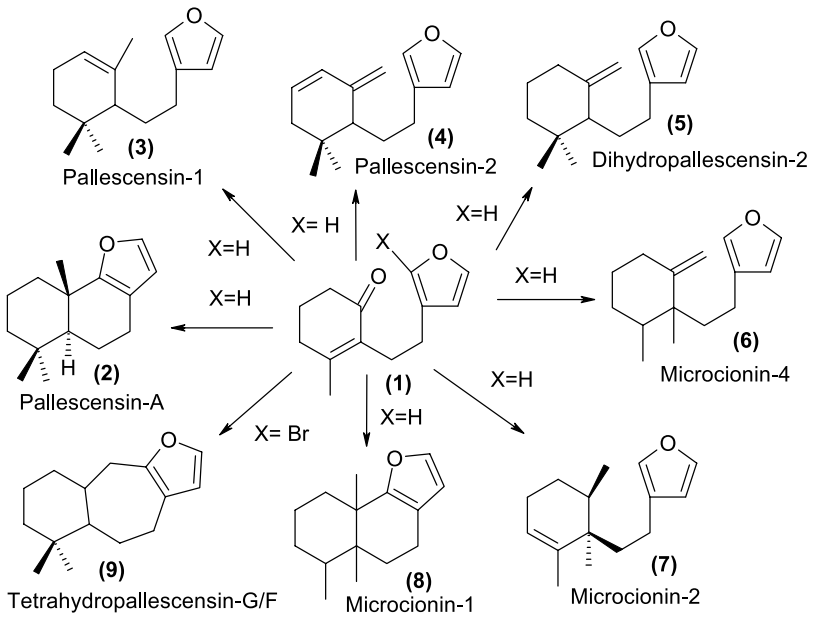


Figure 1.

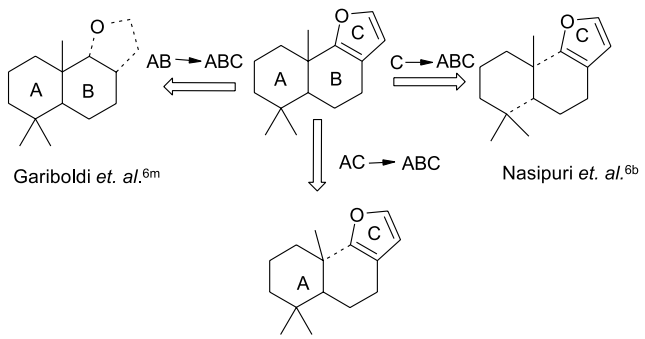
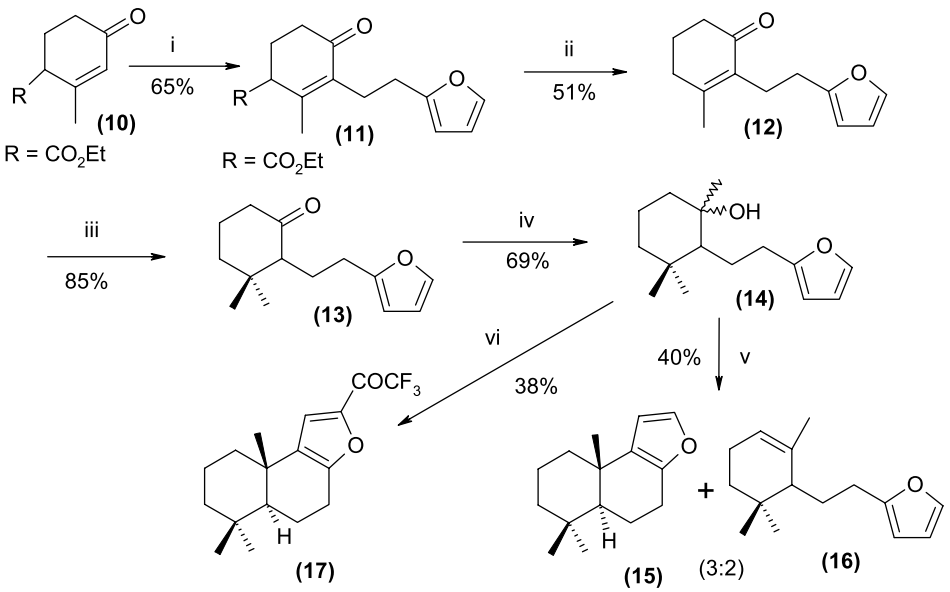
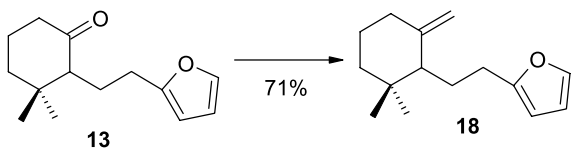


Figure 2.

afforded compound (**11**) as viscous yellow oil in 65% yield. Hydrolysis of (**11**) with KOH/EtOH–H_2O furnished 2-(2-furan-2-yl-ethyl)-3-methyl cyclohex-2-enone (**12**) in 51% yield in inert atmosphere. Conjugate addition to the α,β unsaturated ketone (**12**) with CH_3MgI/CuI met with failure. However, compound (**13**) was successfully synthesized in good yield from the cyclohexenone derivative (**12**) using Gilman's reagent (Me_2CuLi) in combination with BF_3:Et_2O.[9] The ketone (**13**) when treated with MeLi/or MeMgI in ether at −30 °C furnished the desired cyclohexanol derivative. Attempts to cyclise the cyclohexanol derivatives with BF_3:Et_2O or Poly Phosphoric Acid (PPA) met with failure. However, this compound was successfully cyclised with the help of a mixture of anhydrous HCO_2H and cyclohexane to produce a mixture of (±) isopallescensin-A



Scheme 1. Reagents and conditions: (All the reactions were carried out under argon atm) (i) ^{t}BuOK, 2-(2-furyl-ethyl bromide), reflux, 12 h (ii) KOH, EtOH–H_2O, reflux for 8 h (iii) Me_2CuLi, BF_3:Et_2O, ether, −50 °C (15 min), then −30 °C (1 h) (iv) MeLi, ether, −30 °C (1 h) (v) Anh. HCOOH, cyclohexane, rt, 30 min (vi) $(CF_3CO)_2O$, CF_3COOH, rt, 8 h.



Scheme 2. Reagents and conditions: Ph_3PCH_3I/*n*-BuLi; THF, −30 °C to rt, 3 h (N_2 atmosphere).

(**15**) and (±) isopallescensin-1 (**16**) (in the ratio 3:2) as colourless oil and the structures were confirmed from their ^1H and ^{13}C NMR spectra. The *trans*-stereochemistry of the A/B ring junction of compound (**15**) was assigned from the chemical shift value for the *gem*-dimethyl at C-4 and angular methyl group at C-10 (which appeared at δ 0.91, 0.94 and 1.14 ppm, respectively) as well as by analogy.[10] Attempt to cyclise with the help of a mixture of trifluoroacetic anhydride in trifluoroacetic acid led to the formation of the trifluoroacetyl derivatives (**17**) of isopallescensin-A (**15**) in 38% yield.

Wittig olefination of the ketone (**13**) with the ylide $Ph_3P{=}CH_2$ resulted in the formation of 1,2-dihydro isopallescensin-2 (**18**) in 71% yield Scheme 2.

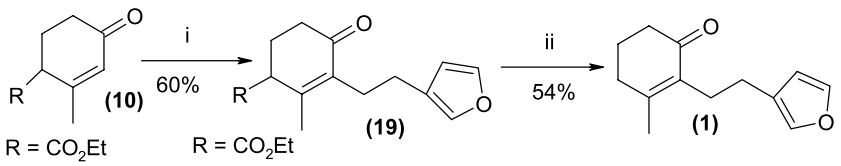
Thus the method showed the potential for the entry to the synthesis of many sesquiterpenoids via suitable furyl-ethyl cyclohexenone derivatives as common intermediates.

Being inspired with these results we then directed our efforts to apply this methodology for the synthesis of various natural pallescensins from the cyclohexenone derivative (**1**) (X=H). Compound **1** was prepared from Hagemann's ester (**10**) and 2-(3-furyl) ethyl bromide following a two steps procedure as used for the synthesis of compound **19** Scheme 3.

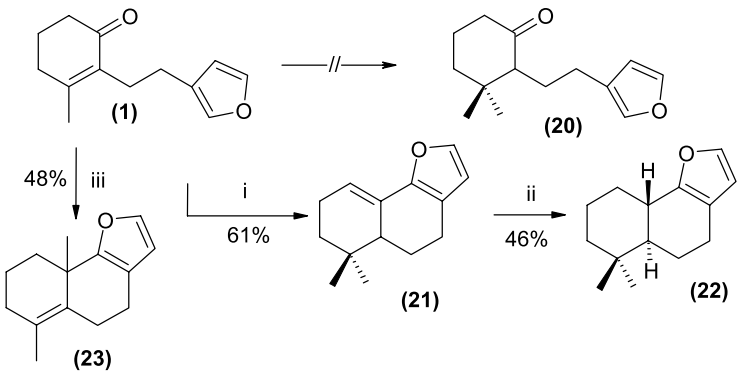
However, when this cyclohexenone derivative (**1**) (X=H) was treated with the $Me_2CuLi/BF_3{:}Et_2O$ furnished no 2-(2-furan-3-yl-ethyl)-3,3-dimethyl cyclohexanone (**20**) as expected but disappointingly it directly formed the tricyclic product (**21**) (61%), possibly through nucleophilic attack on the intermediate ketone (**20**) formed, by the activated furan moiety, followed by Lewis acid catalysed dehydration of the resulting *tert*-alcohol. We next surveyed the possibility of transforming **21** into compound **22** by hydrogenation over 5% palladium on carbon in different solvent systems. The most suitable solvent systems composed of ethyl acetate, ethanol, diethyl amine (1:1:0.2). In order to stop over reduction, the progress of the reaction was arrested before full conversion, furnished (±) 10-desmethylpallescensin-A (**22**) as a major isolable product in 46% yield. The *trans*-geometry was confirmed by 2D ^1H spectra and as well as by analogy Scheme 4.[6i]

1,2-Addition reaction of the cyclohexenone derivative (**1**) with MeLi in ether also furnished no isolable cyclohexanol derivative. In this case also the cyclohexanol derivative undergoes rapid cyclisation to produce (±) 5-desmethyl-4,5-dehydromicrocionin-1 (**23**) as the only isolable product from the reaction mixture. The crude product was identical with the product obtained after column purification. All these compounds have been characterized by the usual spectroscopic method (IR, ^1H NMR, ^{13}C NMR, Mass spectra) as well as elemental analysis.

In summary, the present study has established the feasibility of preparing the common intermediates by a very convenient method based on alkylation of Hagemann's ester with furyl-ethyl bromide to generate 2-(2/3-furan-2-yl-ethyl)-3-methylcyclohex-2-enone derivative as a common intermediate which can be exploited as a gateway to several tricyclic furoterpenes and their analogues.



Scheme 3. Reagents and conditions: (All the reactions were carried under argon atm) (i) ^{t}BuOK, 2-(3-furyl-ethyl bromide), reflux, 12 h (ii) KOH, EtOH–H_2O, reflux for 8 h.



Scheme 4. Reagents and conditions: (i) $Me_2CuLi–BF_3{:}Et_2O$, ether, −50 °C (15 min), then −30 °C (1 h) (ii) H_2/5% Pd–C (iii) MeLi, ether, −30 °C to rt.

3. Experimental

3.1. General information

The compounds described are all racemates. All reagents and solvents were reagent grade. Further purification and drying by standard methods were employed in each step. All organic solvents were evaporated under reduced pressure with a rotary evaporator. The plates used for thin-layer chromatography (TLC) were E. Merck silicagel $60F_{254}$ (0.25 mm thickness) precoated on aluminum plates, and they were visualized under short (254 nm) UV light. Column chromatography was performed using silica gel (60–120 mesh and 230–400 mesh for flash chromatography, SRL) and neutral alumina. NMR spectra were recorded on a Bruker spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C). All NMR measurements were carried out at 300 K in deuterated chloroform solution (dried with 4 Å molecular sieves) unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in δ unit in the scale relative to the resonance of $CDCl_3$ (7.26 ppm in the ^1H, 77.00 ppm for the central line of the triplet in the ^{13}C modes, respectively). Coupling constants (J) are reported in Hz. Splitting patterns are described by using the following abbreviation: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet; brd, broad doublet. ^1H NMR data are reported in this order: chemical shift; multiplicity, number of proton, coupling constant(s). IR spectra were recorded on a Parkin–Elmer 830 machine. Mass spectra were obtained from IICB, Kolkata and determined at an ionized voltage of 70 eV. Relevant data were tabulated as m/z. Elemental analyses were performed at CDRI, Lucknow.

3.1.1. 3-(2-Furan-2-yl-ethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (11). Potassium (1.07 g, 27.44 mmol) was dissolved in dry *tert*-butyl alcohol (20 mL) and then the latter was distilled off until a white solid appeared. This was cooled to room temperature (rt) and 2-methyl-4-oxocyclohex-2-ene carboxylate (Hagemann's ester) (**10**) (5 g, 27.47 mmol) was added in one portion with stirring under N_2 atmosphere. The red solution so formed turned into straw-yellow solid a few minutes after the addition. 2-Furyl ethyl bromide (4.8 g, 27.43 mmol) was then added and the resultant solution refluxed with stirring for 12 h. The cooled reaction mixture was then poured onto crushed ice, acidified with cold HCl (6 N) and extracted with ether (3×100 mL). The ether solution was washed thoroughly with water and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow liquid which was purified by reduced pressure distillation.

Faint yellow oil (4.9 g, 65%) (bp 140–142 °C/1 mm Hg); IR ($CHCl_3$): ν 1662 (–CO_2Et), 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H, J=7.1 Hz, methyl protons), 1.8 (s, 3H, methyl protons), 2.00–2.61 (m, 4H), 2.66 (brs, 4H), 3.24 (brt, 1H, J=4.8 Hz), 4.18 (q, 2H, J=7.1 Hz, methylene protons), 5.93 (d, 1H, J=2.9 Hz, furan β proton), 6.24 (dd, 1H, J=2.9, 1.9 Hz, furan β proton), 7.27 (d, 1H, J=1.9 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.01 (CH_3), 19.97 (CH_3), 24.41 (CH_2), 25.44 (CH_2), 26.74 (CH_2), 34.17 (CH_2), 47.59 (–CH), 61.13 (CH_2), 105.37 (–CH), 110.15 (–CH), 135.97, 140.74 (–CH), 151.26, 155.19, 172.13, 197.35; MS (EI, 70 eV) m/z 276 (M^+), 203, 182, 123, 67. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.74; H, 7.23.

3.1.2. 2-(2-Furan-2-yl-ethyl)-3-methyl-cyclohex-2-enone (12). A solution of KOH (3.25 g, 58.03 mmol) in 12 mL water and 12 mL ethanol was added to the ketoester (**11**) (4 g, 14.49 mmol). The reaction mixture was refluxed with stirring under N_2 atmosphere for 8 h. Excess alcohol was then removed by distillation under reduced pressure and the residue was diluted with ice water, acidified with 6 N HCl, and extracted with ether (4×50 mL). The ether extract was washed successively with brine solution, 5% $NaHCO_3$ solution, and water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether–ethyl acetate; 7:3).

Yellow oil (1.5 g, 51%); IR ($CHCl_3$): ν 1661 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (s, 3H, methyl protons), 1.86–1.96 (m, 2H), 2.25–2.39 (m, 4H), 2.58–2.63 (m, 4H), 5.90 (d, 1H, J=3.16 Hz, furan β proton), 6.23–6.25 (m, 1H, furan β proton), 7.27 (d, 1H, J=1.8 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.77 (CH_3), 22.17 (CH_2), 25.47 (CH_2), 27.73 (CH_2), 32.79 (CH_2), 38.12 (CH_2), 105.17 (–CH), 110.12 (–CH), 134.09, 140.65 (–CH), 155.62, 156.47, 198.55; MS (EI, 70 eV) m/z 204 (M^+), 136, 123, 104, 89, 67. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.32; H, 7.72.

3.1.3. 2-(2-Furan-2-yl-ethyl)-3,3-dimethyl-cyclohexanone (13). To a stirred suspension of CuI (1.40 g, 7.35 mmol) in dry ether (5 mL) under N_2 at −25 °C (bath temperature) was added MeLi in ether (1.3 M) (11.2 mL, 14.55 mmol). The resulting yellow suspension was cooled to −50 °C and BF_3:Et_2O (0.93 mL, 7.33 mmol) was added. After 20 min the cyclohexanone (0.5 g, 2.45 mmol) in Et_2O (5 mL) was added dropwise (15 min) and the mixture was stirred at −30 °C for 15 min. An additional lot of BF_3:Et_2O (0.93 mL, 7.33 mmol) was added and stirring was continued at −30 °C for 1 h and then allowed to 0 °C. Quench it with aqueous NH_4Cl and extracted with ether (3×50 mL). The ether extract was washed successively with ice water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether–ethyl acetate 8:2).

Sweet smelling yellow oil (0.46 g, 85%); IR ($CHCl_3$): ν 1708 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75 (s, 3H), 1.01 (s, 3H), 1.59–2.5 (m, 8H), 2.6–2.65 (m, 3H), 5.95 (d, 1H, J=3.04 Hz), 6.25 (brs, 1H), 7.28 (d, 1H, J=1.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.44 (CH_3), 22.11 (CH_2), 22.89 (CH_2), 25.27, 26.70 (CH_2), 29.20 (CH_3), 39.22 (CH_2), 41.19 (CH_2), 59.48 (–CH), 104.78 (–CH), 109.77 (–CH), 140.54 (–CH), 155.64, 212.97; MS (EI, 70 eV) m/z 220 (M^+), 126, 106, 88, 67. Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.21; H, 8.95.

3.1.4. 2-(2-Furan-2-yl-ethyl)-1,3,3-trimethyl-cyclohexanol (14). To a stirred solution of ketone (**13**) (0.3 g, 1.36 mmol) at −30 °C in dry ether (5 mL), an ethereal solution of MeMgI [prepared from Mg turnings (0.035 g, 1.46 mmol), MeI (0.1 mL) in dry ether (5 mL)] or MeLi

(1.3 M, 1.1 mL, 1.36 mmol) was added dropwise for 30 min. The mixture was stirred for an additional 1 h at 0–5 °C. After workup with ether, the cyclohexanol (**14**) was obtained as yellow oil, which was purified by column chromatography (silica gel, pet ether–ethyl acetate 1:1).

Yellow oil (0.22 g, 69%); IR ($CHCl_3$): ν 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 0.96 (s, 3H), 1.16 (s, 3H), 1.44–1.69 (m, 8H), 2.62–2.75 (m, 4H), 5.99 (d, 1H, J=2.9 Hz), 6.27 (brs, 1H), 7.29 (d, 1H, J=1.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.23, 21.36, 24.37, 29.67, 30.25, 31.84, 34.70, 41.16, 41.73, 53.34, 65.80, 104.63, 110.01, 140.68, 156.20. MS (EI, 70 eV) m/z 236 (M^+), 221, 219, 81, 67. Anal. calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.34; H, 10.11.

3.1.5. 6,6,9a-Trimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[2,1-*b*]furan (15). Alcohol (**14**) (0.1 g, 0.42 mmol) was dissolved in cyclohexane (1.5 mL), and formic acid (100%) (0.1 mL) was added. The mixture was stirred vigorously for 1 h at rt under inert atmosphere. The upper layer of the two phase system was yellow to brown in colour, the bottom layer was dark purple. Ice water (5 mL) was added, the aqueous layer was extracted with ether (2×25 mL). The combined extracts were washed with 5% $NaHCO_3$ solution and brine. Solvent removed and the crude products were purified by flash chromatography (200–400 mesh, pet ether).

Colourless oil (36 mg, 40% [this is mixture of two isomers which was separated using preparative thin-layer chromatographic technique, elution with hexane]); IR ($CHCl_3$): 2928, 1496, 1435, 1295, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.94 (s, 3H), 1.14 (s, 3H), 1.38–1.90 (m, 8H), 2.54–2.69 (m, 3H), 6.15 (d, 1H, J=1.9 Hz), 7.17 (d, 1H, J=1.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.89, 21.16, 22.63, 23.26, 24.33, 27.39, 34.19, 38.22, 41.97, 48.49, 53.43, 109.92, 120.25, 140.56, 156.61. Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.76; H, 9.96.

3.1.6. 2-[2-(2,6,6-Trimethyl-cyclohex-2-enyl)-ethyl]-furan (16). Colourless oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H), 1.02 (s, 3H), 1.47 (s, 3H), 1.6–1.7 (m, 4H), 1.93–1.97 (m, 2H), 2.36–2.7 (m, 4H), 5.96 (brs, 1H, vinylic proton), 6.26 (brs, 1H), 7.28 (brs, 1H). Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.84; H, 9.98.

3.1.7. 2,2,2-Trifluoro-1-(6,6,9a-trimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[2,1-*b*] furan-2-yl)-ethanone (17). A mixture of cyclohexanol (**14**) (50 mg, 0.21 mmol), trifluoroacetic anhydride (2 mL), and trifluoroacetic acid (0.5 mL) was stirred for 8 h at rt under argon atmosphere. The brown mixture was then poured onto crushed ice and extracted with ether (3×25 mL). The ether extract was then washed successively with ice-cold 5% $NaHCO_3$ solution and brine and then dried (Na_2SO_4) and concentrated. The crude compound thus obtained was purified by column chromatography (Silica gel/benzene–pet ether, 1:9)

Colourless oil (25 mg, 38%); IR ($CHCl_3$): ν 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 3H, *gem*-dimethyl protons), 0.92 (s, 3H, *gem*-dimethyl protons), 1.17 (s, 3H, angular methyl protons), 1.22–2.15 (m, 9H), 2.69–2.85 (m, 2H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.39, 18.74, 21.28, 23.64, 25.02, 27.10, 33.18, 33.38, 34.66, 38.10, 41.78, 51.79, 113.81, 129.4, 152.5, 160.56, 192.5; MS (EI, 70 eV) m/z 314 (M^+), 299 ($M-15$, B^+), 271, 257, 245, 243, 231, 217, 178, 137, 121, 103, 89, 67. Anal. calcd for $C_{17}H_{21}F_3O_2$: C, 64.96; H, 6.73. Found: C, 65.14; H, 6.65.

3.1.8. 2-[2-(2,2-Dimethyl-6-methylene-cyclohexyl)-ethyl]furan (18). A 1.6 M solution of *n*-butyllithium (1.0 mL, 1.6 mmol) was injected slowly to a cold (−30 °C) stirred suspension of methyltriphenylphosphonium iodide (0.65 g, 1.60 mmol) in dry THF (2.5 mL), under argon atmosphere. After 2.5 h a THF solution of (0.5 mL) of the cyclohexanone (**13**) (0.1 g, 0.46 mmol) was injected dropwise. The stirring was continued at −30 °C for about 30 min and then allowed to attain rt. It was further stirred at rt (3–3.5 h) before quenching with ice water. The THF was removed in rotary evaporator under reduced pressure. Extraction with ether (3×25 mL) followed by the usual work up afforded the crude product which was purified by column chromatography (Neutral alumina/benzene–pet ether, 1:5).

Colourless oil (70 mg, 71%); IR ($CHCl_3$): ν 1635, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.94 (s, 3H), 1.4–2.2 (m, 8H), 2.41–2.65 (m, 3H), 4.56 (brs, 1H), 4.8 (brs, 1H), 5.95 (d, 1H, J=3.0 Hz), 6.28 (dd, 1H, J=3.0, 1.8 Hz), 7.27 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.56, 24.76, 26.28, 26.57, 28.29, 32.22, 36.01, 39.20, 53.43, 104.41, 107.61, 109.30, 140.57, 155.32, 156.14; MS (EI, 70 eV) m/z 218 (M^+), 203, 121, 67. Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.62; H, 10.10.

3.1.9. 3-(2-Furan-3-yl-ethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (19). Potassium (0.64 g, 16.41 mmol) was dissolved in dry *tert* butyl alcohol (12 mL) and then the latter was distilled off until a white solid appeared. This was cooled to rt and 2-methyl-4-oxocyclohex-2-ene carboxylate (Hagemann's ester) (**10**) (3 g, 16.48 mmol) was added in one portion with stirring under N_2 atmosphere. The red solution so formed turned into straw-yellow solid a few minutes after the addition. 3-furyl ethyl bromide (2.9 g, 16.57 mmol) was then added and the resultant solution refluxed with stirring for 12 h. The cooled reaction mixture was then poured onto crushed ice, acidified with cold HCl (6 N) and extracted with ether (3×100 mL). The ether solution was washed thoroughly with water and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow liquid which was purified by reduced pressure distillation.

Yellow oil (2.7 g, 60%); (bp 148–150 °C/1 mm Hg); IR ($CHCl_3$): ν 1666, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, 3H, J=7.0 Hz, methyl protons), 1.86 (s, 3H, methyl protons), 2.20–2.57 (m, 8H), 3.24 (brt, 1H, J=4.7 Hz), 4.24 (q, 2H, J=7.0 Hz, methylene protons), 6.27 (d, 1H, J=1.1 Hz, furan β proton), 7.21(brs, 1H, furan α proton), 7.33 (brs, 1H, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.27, 18.14, 23.35, 25.49, 25.98, 34.25, 47.60, 61.27, 111.13, 124.38, 137.60, 139.20, 142.47, 150.67, 172.06, 197.25; MS (EI, 70 eV) m/z 276 (M^+), 261($M-15$), 203 ($M-CO_2Et$), 135, 95, 81. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.78; H, 7.18.

3.1.10. 2-(2-Furan-3-yl-ethyl)-3-methyl-cyclohex-2-enone (1). A solution of KOH (1.62 g, 28.92 mmol) in 8 mL water and 8 mL ethanol was added to the ketoester (**11**) (2 g, 7.25 mmol). The reaction mixture was refluxed with stirring under N_2 atmosphere for 8 h. Excess alcohol was then removed by distillation under reduced pressure and the residue was diluted with ice water, acidified with 6 N HCl, and extracted with ether (4×50 mL). The ether extract was washed successively with brine solution, 5% $NaHCO_3$ solution, and water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography.

Light orange oil (0.79 g, 54%); IR ($CHCl_3$): ν 1662 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz) δ 1.84 (s, 3H), 1.88–2.03 (m, 2H), 2.29–2.54 (m, 8H), 6.28 (brs, 1H), 7.18 (brs, 1H), 7.32 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.19, 22.22, 23.98, 26.05, 32.82, 37.83, 111.18, 126.29, 134.77, 138.85, 142.49, 156.04, 198.63; MS (EI, 70 eV) *m/z* 204 (M^+), 161, 110, 108, 95, 81. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.79; H, 7.75.

3.1.11. 6,6-Dimethyl-4,5,5a,6,7,8-hexahydro-naphtho[1,2-*b*]furan (21). To a stirred suspension of CuI (1.12 g, 5.87 mmol) in dry ether (5 mL) under N_2 at −25 °C (bath temperature) was added MeLi in ether (1.3 M) (8.95 mL, 11.81 mmol). The resulting yellow suspension was cooled to −50 °C and BF_3:Et_2O (0.74 mL, 5.86 mmol) was added. After 20 min the cyclohexanone (0.4 g, 1.96 mmol) in Et_2O (2 mL) was added dropwise (15 min) and the mixture was stirred at −30 °C for 15 min. An additional lot of BF_3:Et_2O (0.74 mL, 5.86 mmol) was added and stirring was continued at −30 °C for 1 h and then allowed to 0 °C. Quench it with aqueous NH_4Cl and extracted with ether (4×50 mL). The ether extract was washed successively with ice water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether).

Sweet smelling yellow oil (0.24 g, 61%); IR ($CHCl_3$): 1475, 1380, 1372, 1273, 1135, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 1.03 (s, 3H), 1.38–1.45 (m, 2H), 1.97–2.17 (m, 3H), 2.53–2.56 (m, 4H), 5.97 (brs, 1H vinylic proton, not exchangeable with D_2O), 6.22 (d, 1H, *J*=1.7 Hz) 7.23 (d, 1H, *J*=1.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.23, 22.37, 22.42, 24.53, 28.00, 29.68, 31.26, 37.65, 45.27, 110.82, 115.17, 127.58, 140.35, 140.85; MS (EI, 70 eV) *m/z* 202 (M^+), 187, 172, 131, 119, 105, 91, 81. Anal. calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.42; H, 8.76.

3.1.12. 6,6-Dimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[1,2-*b*]furan (22). To a solution of **21** (30 mg, 0.15 mmol) in ethyl acetate (1 mL), ethanol (1 mL), and diethyl amine (0.2 mL) was added 20 mg 5% Palladium on carbon. This stirred mixture was blanked with hydrogen. After 12 h stirring at rt the catalyst was removed by filtration through celite, and the filtrate concentrated. The residue was chromatographed on silica gel (elution with hexane).

Colourless oil (14 mg, 46%); IR ($CHCl_3$): 2925, 1598, 1453, 1220, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H), 1.04 (s, 3H), 1.15–1.41 (m, 4H), 1.45–2.12 (m, 6H), 2.41–2.44 (m, 2H), 6.14 (brs,1H), 7.22 (brs, 1H); MS (EI, 70 eV) *m/z* 204 (M^+). Anal. calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.56; H, 10.13.

3.1.13. 6,9a-Dimethyl-4,5,7,8,9,9a-hexahydro-naphtho[1,2-*b*]furan (23). To a stirred solution of **1** (0.1 g, 0.49 mmol) in ether at −30 °C in N_2 atmosphere add MeLi in ether (1.3 M) (0.35 mL, 0.45 mmol) solution into the reaction mixture. Stirring was continued for 2 h at that temperature, and then allowed reaching the rt. Quench with ice cold NH_4Cl solution and extracting with ether (3×25 mL), washed with ice water and dried (Na_2SO_4). Solvent was removed and chromatographed on silica gel (elution with pet ether).

Light yellow oil (48 mg, 48%); IR ($CHCl_3$): 1540, 1497, 1367, 1263, 1110, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H, methyl protons), 1.72 (s, 3H, methyl protons), 1.98–2.12 (m, 4H), 2.25–2.45 (m, 4H), 2.70–2.73 (m, 2H), 6.14 (d, 1H, *J*=1.7 Hz, furan β proton), 7.22 (d, 1H, *J*=1.7 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.32 (CH_2), 19.18 (CH_3), 22.96 (CH_2), 23.91 (CH_2), 25.71 (CH_3), 32.13 (CH_2), 34.08 (CH_2), 36.71, 109.87, 114.77, 126.60, 132.83, 140.45, 158.27; MS (EI, 70 eV) *m/z* 202 (M^+), 187, 172, 159, 131, 119, 105, 91, 81. Anal. calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.13; H, 8.82.

Acknowledgements

Financial support from DST (New Delhi) and CSIR (New Delhi) (for fellowship to S.M.) is gratefully acknowledged.

References and notes

1. (a) For review: Fraga, B. M. *J. Nat. Prod. Rep.* **1990**, *7*, 515–537, and **1988**, *5*, 497–521. (b) Honan, P.; Inman, W.; Crew, P. *J. Nat. Prod.* **1990**, *53*, 143. (c) Fontana, A.; Muniain, C.; Cimino, G. *J. Nat. Prod.* **1998**, *61*, 1027–1029. (d) Fraga, B. M. *Nat. Prod. Rep.* **1994**, *11*, 533–554. (e) Fraga, B. M. *Nat. Prod. Rep.* **1995**, *12*, 303–320. (f) Cimino, G.; Rosa, S. D.; Stefano, S. D.; Morrone, R.; Sodano, G. *Tetrahedron* **1985**, *41*, 1093–1100.
2. (a) Yick, C. Y.; Tsang, T. K.; Wong, H. N. C. *Tetrahedron* **2003**, *59*, 325–333. (b) Yim, H. K.; Liao, Y.; Wong, H. N. C. *Tetrahedron* **2003**, *59*, 1877–1884.
3. *Chem. Rev.* **1993**, *93* (5), (special issue on marine natural products).
4. (a) Fontana, A.; Tramice, A.; Cutignano, A.; d'Ippolito, G.; Gavagnin, M.; Cimino, G. *J. Org. Chem.* **2003**, *68*, 2405–2409. (b) Fontana, A.; Giminez, F.; Marin, A.; Mollo, E.; Cimino, G. *Experientia* **1994**, *50*, 510–516. (c) Faulkner, D. J.; Molinsky, T. F.; Andersen, R. J.; Dumdei, E. J.; Dilip, De. S. E. *Pharmacol Toxicol Endocrinol* **1990**, *97C*(2), 233–240. (d) Fontana, A.; Avila, C.; Martinez, E.; Ortea, J.; Trivellone, E.; Cimino, G. *J. Chem. Ecol.* **1993**, *19*, 339–356.
5. (a) Cimino, G.; De Stefano, S.; Guerrieo, A.; Minale, L. *Tetrahedron Lett.* **1975**, *16*, 1417–1420, see also 1421–1425 and 1425–1428. (b) Cimino, G.; De Stefano, S.; Guerrieo, A.; Minale, L. *Tetrahedron Lett.* **1975**, *16*, 3723–3726.

(c) Cimino, G.; De. Stefano, S.; Minale, L.; Trivellone, E. *Tetrahedron Lett.* **1975**, *16*, 3727–3730.

6. (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572–4580. (b) Nasipuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, *11*, 2776–2778. (c) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685–3689. (d) Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1580–1587. (e) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 105–108. (f) Snider, B. B.; O'Hare, S. M. *Synth. Commun.* **2001**, *31*, 3753–3758. (g) Moiseenkov, A. M.; Surkova, A. A.; Lozanova, A. V.; Veselovsky, V. V. *Russ. Chem. Bull.* **1997**, *46*, 1956–1960. (h) Lange, U.; Blechert, S. *Synthesis* **1995**, *9*, 1142–1146. (i) Shishido, K.; Umimoto, K.; Ouchi, M.; Irie, O.; Omodani, T.; Takata, T.; Shibuya, M. *J. Chem. Res., Synopses* **1993**, *2*, 58–59. (j) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.* **1992**, *57*, 7118–7122. (k) Shishido, K.; Umimoto, K.; Omodani, T.; Takata, T.; Ouchi, M.; Irie, O.; Ozaki, M.; Shibuya, M. *Tennen. Yuki Kagobutsu Toronkai Koen Yushishu* **1991**, *33*, 220–227. (l) Shishido, K.; Umimoto, K.; Shibuya, M. *Heterocycles* **1990**, *31*, 597–598. (m) Liotta, D.; Ott, W. *Synth. Commun.* **1987**, *17*, 1655–1665. (n) Gariboldi, P.; Jommi, G.; Sisti, M. *J. Org. Chem.* **1982**, *47*, 1961–1962.
7. (a) Corey, E. J.; Guzmann-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.
8. Chakraborty, A.; Kar, G. K.; Ray, K. J. *Tetrahedron* **1997**, *53*, 2989–2996.
9. Lipshutz, H. B.; Elsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351–1358.
10. Brieskorn, C. H.; Fuchs, A.; Bredenberg, J. B.; McChesney, J. D.; Wenkert, E. *J. Org. Chem.* **1964**, *29*, 2293–2298.