Synthesis of Norpandamarilactonines, Pandamarilactonines, and Pandanamine

Sanjib Gogoi, Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India
E-mail: np.argade@ncl.res.in

Received 9 January 2008; revised 24 January 2008

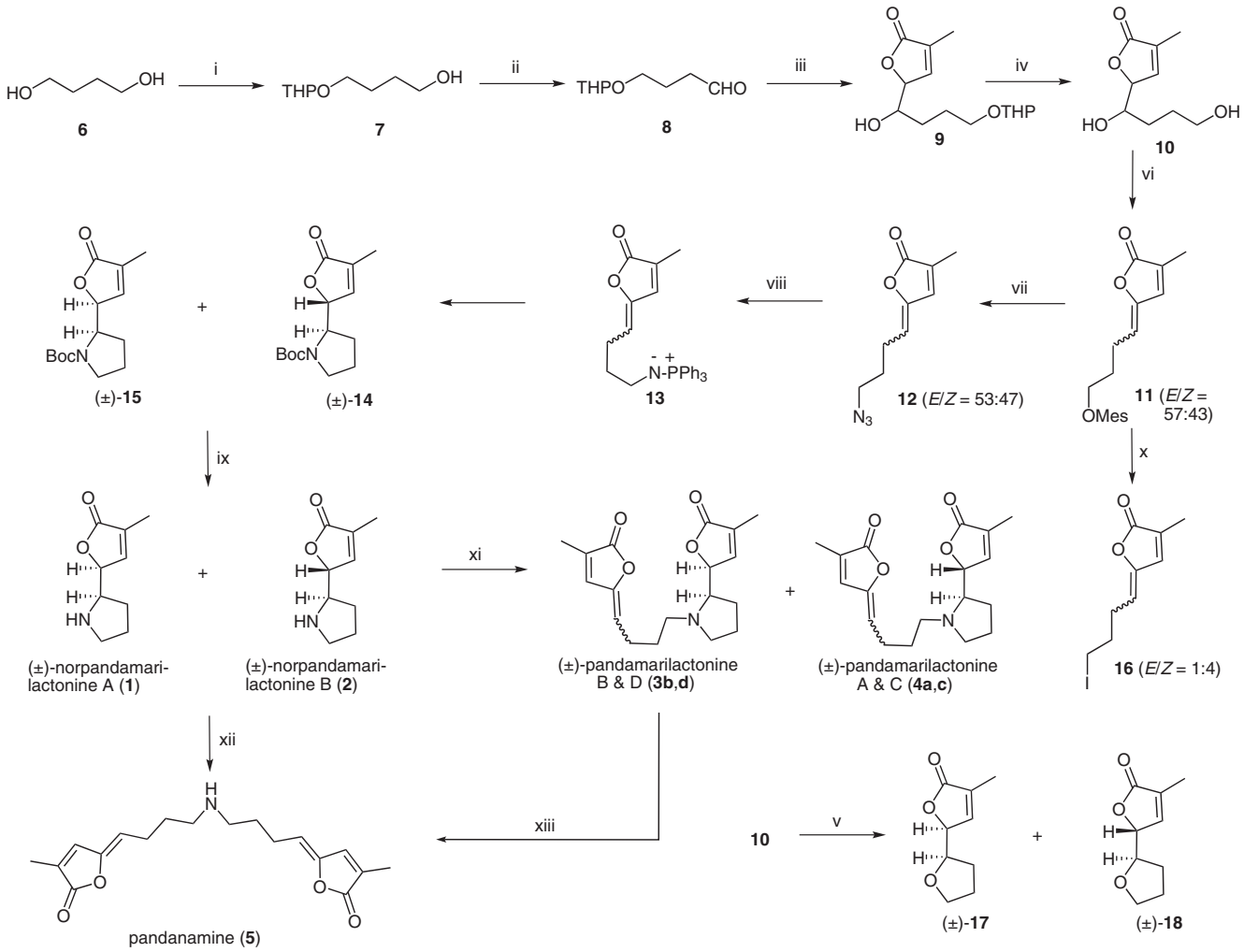
Abstract: A facile route to naturally occurring (±)-norpandamarilactonines A and B, (±)-pandamarilactonines A–D, and pandanamine has been described from 3-methylfuran-2(5*H*)-one, with a reductive intramolecular aza-Michael-type addition as the key step.

Key words: 3-methylfuran-2(5*H*)-one, condensation, intramolecular aza-Michael reaction, pandamarilactonines

The genus *Pandanus* belonging to the family Pandanaceae with nearly 600 species are widely spread in tropical and subtropical regions. Several *Pandanus* species have been identified as medicinal plants and are used as a remedy for toothache, rheumatism, and hypoglycemia and as a diuretic and cardio tonic.[1] Takayama et al., in their systematic studies to isolate the bioactive natural products from plant origin, have isolated norpandamarilactonines A and B, pandamarilactonines A–D, and pandanamine from *Pandanus amaryllifolius* species.[2–6] Until now, syntheses of norpandamarilactonines have been accomplished via the coupling reactions of suitably substituted pyrroles with the appropriate furan units or their precursors and also by employing a double ring-closing metathesis and further elaboration to the pandamarilactonines and pandanamine.[3–5,7–10] We felt that the aminobutenolide and iodobutenolide would be the appropriate precursors to design all these natural products in a concise fashion. These potential precursors amino- and iodobutenolides are readily available from commercially available 3-methylfuran-2(5*H*)-one via the corresponding common intermediate mesylbutenolide **11**. Herein we report our synthetic studies towards this goal (Scheme 1).

Starting from butane-1,4-diol (**6**), the protected aldehyde **8** was obtained in two steps via a selective mono-tetrahydropyranyl protection and oxidation sequence. The base-catalyzed condensation of α-methylbutyrolactone with the aldehyde **8** followed by the tetrahydropyranyl deprotection furnished lactone-diol **10** in 69% yield (*erythro*/*threo* = 64:36).[11] The diol **10** on treatment with phosphorus pentoxide in refluxing toluene gave a diastereomeric mixture of α-methyl-γ-tetrahydrofuranylbutyrolactones **17** and **18** in ~1:1 ratio in 88% yield, which could be separated by column chromatography, via the intramolecular dehydrative cyclization pathway.[11] The diol **10** on treatment with methanesulfonyl chloride gave the desired mesylbutenolide **11**[8] [*E*/*Z* = 57:43 (^{1}H NMR)] in 77% yield, following the double mesylation and an in situ mono-elimination route. The mesylbutenolide **11** on chemoselective substitution reaction with sodium azide yielded, the azidobutenolide **12** [*E*/*Z* = 53:47 (^{1}H NMR)] in 87% yield. The azidobutenolide **12** on triphenylphosphine-induced reductive regioselective intramolecular aza-Michael-type addition to the exocyclic activated C–C double bond yielded the desired mixture of lactones **1** and **2**; the isolation of the mixture of **1/2** from the crude product using column chromatographic separation was difficult. Hence, we converted the **1/2** mixture, in situ, into their *tert*-butoxycarbonyl-protected derivatives and then isolated the mixture of **14/15** by using column chromatography on silica gel [**14/15** = 7:3 (^{1}H NMR), 77%].[10,11] The *tert*-butoxycarbonyl-deprotection of the **14/15** mixture furnished a mixture of the desired natural products **1** and **2** in 99% yield with a ratio of 1:1 (^{1}H NMR). The column chromatographic separation of diastereomeric norpandamarilactonines A and B is known in the literature.[2,7,8] At this stage, we avoided the separation of **1** and **2**, as **1** is known to epimerize to **2** probably via a β-elimination–conjugate addition mechanism.[7,8,10] The mesylbutenolide **11** (*E*/*Z* = 57:43) on reaction with lithium iodide gave the iodobutenolide **16**[4] [*E*/*Z* = 1:4 (^{1}H NMR)] in 78% yield. We surmise that the change in ratio of *E*- and *Z*- isomers could be a result of the addition of iodide to the C=C bond followed by instantaneous elimination. The reaction of the mixture of lactones **1** and **2** with iodobutenolide **16** in the presence of silver carbonate as a coupling reagent was time dependent and in 24 hours gave the desired mixture of natural products pandamarilactonines A–D in 64% yield in a 4:4:1:1 ratio, respectively, via selective N-alkylation. The same reaction in 48 hours gave exclusively pandanamine (**5**) in 66% yield via N-alkylation followed by pyrrole ring opening. The mixture of pandamarilactonines A–D also on treatment with silica gel in dichloromethane at room temperature exclusively yielded pandanamine (**5**)[5] in 63% yield via a retro-aza-Michael-type reaction. The crucial column chromatographic separation of four isomeric pandamarilactonines A–D is also well known in the literature.[3,4,7–10] The analytical and spectral data obtained for the mixture of norpandamarilactonine A and B and pandamarilactonine A–D and pandanamine were in complete agreement with the reported data.[2–5]

SYNTHESIS 2008, No. 9, pp 1455–1459
Advanced online publication: 27.03.2008
DOI: 10.1055/s-2008-1072534; Art ID: Z01108SS



Scheme 1 *Reagents and conditions*: (i) 3,4-dihydro-2*H*-pyran, H^+/HCl, r.t., 4 h (76%); (ii) PCC, NaOAc, CH_2Cl_2, r.t., 1 h (79%); (iii) 3-methylfuran-2(5*H*)-one, LDA, THF, –78 °C to r.t., 2 h (76%); (iv) PPTS, EtOH, 56 °C, 24 h (*erythro*/*threo* = 64:36, 91%); (v) P_2O_5, toluene, reflux, 1 h (**17**, 42%; **18**, 46%); (vi) MsCl, Et_3N, CH_2Cl_2, r.t., 24 h (77%); (vii) NaN_3, DMF, r.t., 16 h (87%); (viii) (a) Ph_3P, THF, 42 °C, 0.5 h, (b) H_2O, 42 °C, 12 h, (c) Boc_2O, CH_2Cl_2, Et_3N, 16 h (**14/15** = 7:3, 77%); (ix) TMSOTf, CH_2Cl_2, –20 °C to –5 °C, 2.5 h (**1/2** = 1:1, 99%); (x) LiI, THF, r.t., 4 h (78%); (xi) **16**, Ag_2CO_3, MeCN, r.t., 24 h (**3b/3d/4a/4c** = 4:1:4:1, 64%); (xii) **16**, Ag_2CO_3, MeCN, r.t., 48 h (66%); (xiii) silica gel, CH_2Cl_2, r.t., 1 h (63%).

In summary, we have demonstrated a simple approach to the pandamarilactonines and pandanamine by obtaining the two requisite building blocks from the corresponding common precursor in one step each and then by taking the advantage of intramolecular aza-Michael-type addition and the intermolecular coupling reactions.

^{1}H NMR spectra were recorded on either 200 MHz or 500 MHz spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on either a 200 MHz (50 MHz) or 500 MHz (125 MHz) spectrometer. FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. MS experiment was performed on a low resolution magnetic sector mass spectrometer. Column chromatographic separations were performed on silica gel (60–120 mesh), flash silica (230–400 mesh), and neutral alumina; petroleum ether = PE. Commercially available butane-1,4-diol, 3,4-dihydro-2*H*-pyran, PCC, 3-methylfuran-2(5*H*)-one, P_2O_5, NaN_3, Ph_3P, $(Boc)_2O$, TMSOTf, LiI, and Ag_2CO_3 were used.

4-(Tetrahydropyran-2-yloxy)butan-1-ol (7)

To a stirred soln of butane-1,4-diol (**6**, 10.00 g, 110.96 mmol) and concd HCl (2 drops) was added 3,4-dihydro-2*H*-pyran (9.33 g, 110.96 mmol) in a dropwise fashion at r.t. The mixture was stirred at r.t. for 3 h, diluted with EtOAc (200 mL), washed with sat. $NaHCO_3$, H_2O, and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 2:3) gave **7** (14.69 g, 76%) as a thick oil.

IR (neat): 3412, 1466, 1454, 1441 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40–1.90 (m, 10 H), 2.25 (br s, 1 H), 3.35–3.60 (m, 2 H), 3.66 (t, *J* = 6 Hz, 2 H), 3.72–3.95 (m, 2 H), 4.60 (t, *J* = 4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4, 25.2, 25.3, 26.2, 26.4, 29.7, 30.4, 30.5, 62.0, 62.2, 67.1, 67.3, 98.6, 98.7 (some of the carbons showed splitting probably because of the two different possible intramolecular hydrogen bondings).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.09; H, 10.37.

4-(Tetrahydro-2*H*-pyran-2-yloxy)butanal (8)

To a stirred suspension of PCC (17.95 g, 83.27 mmol) and NaOAc (2.04 g, 24.87 mmol) in CH_2Cl_2 (50 mL) was added rapidly a soln of alcohol **7** (14.50 g, 83.22 mmol) in CH_2Cl_2 (50 mL). The mixture immediately turned black and after 1 h of stirring, the mixture was diluted with Et_2O. The supernatant soln was filtered through basic alumina and the filtrate was concentrated in vacuo. Column chromatography of the residue (silica gel, EtOAc–PE, 1:9) gave **8** (11.32 g, 79%) as a thick oil.

IR ($CHCl_3$): 2945, 1726, 1468, 1441 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.40–1.83 (m, 6 H), 1.92 (quintet, *J* = 6 Hz, 2 H), 2.52 (t, *J* = 6 Hz, 2 H), 3.32–3.55 (m, 2 H), 3.67–3.90 (m, 2 H), 4.54 (t, *J* = 2 Hz, 1 H), 9.76 (t, *J* = 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3, 22.5, 25.3, 30.4, 41.0, 62.1, 66.3, 98.7, 202.3.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.70; H, 9.42.

5-[1-Hydroxy-4-(tetrahydro-2*H*-pyran-2-yloxy)butyl]-3-methylfuran-2(5*H*)-one (9)

To a stirred soln of 3-methylfuran-2(5*H*)-one (5.00 g, 50.97 mmol) in THF (50 mL) at –78 °C was added the soln of freshly prepared LDA (5.99 g, 55.92 mmol) in THF (15 mL) in a dropwise fashion under an argon atmosphere. The mixture was stirred at –78 °C for 30 min and a soln of aldehyde **8** (8.78 g, 50.98 mmol) in THF (10 mL) was added. Further stirring was continued for 2 h while the temperature was allowed to reach r.t. THF was removed in vacuo at r.t. The residue was then acidified with 2 M HCl and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 2:8) gave **9** (10.47 g, 76%) as a thick oil as a mixture of diastereomers.

IR ($CHCl_3$): 3439, 1759, 1655, 1456 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.40–1.90 (m, 10 H), 1.94 (br s, 3 H), 3.35–3.60 (m, 2 H), 3.60–4.00 (m, 3 H), 4.50–4.65 (br s, 1 H), 4.70–5.00 (m, 1 H), 7.00–7.25 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 19.5, 19.6, 25.1, 25.2, 25.8, 26.0, 28.6, 30.1, 30.4, 30.5, 30.8, 30.9, 62.4, 62.6, 67.3, 67.4, 67.5, 71.6, 71.9, 72.0, 83.6, 83.8, 98.8, 99.0, 99.1, 130.6, 131.0, 145.4, 146.2, 146.8, 146.9, 174.2 (only prominent carbon signals have been listed here).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.25; H, 8.34.

***erythro*- and *threo*-5-(1,4-Dihydroxybutyl)-3-methylfuran-2(5*H*)-one (10)**

To a stirred soln of lactone **9** (10.00 g, 36.99 mmol) in EtOH (30 mL) was added PPTS (900 mg, 3.58 mmol) and the mixture heated at 56 °C for 24 h. It was then concentrated in vacuo and the obtained residue was purified by column chromatography (silica gel, EtOAc–PE, 4:1) to obtain **10** (6.27 g, 91%) as a thick oil; ratio *erythro*/*threo* = 64:36.

IR ($CHCl_3$): 3390, 1751, 1655 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.50–1.88 (m, 4 H), 1.94 (br s, 3 H), 3.60–3.85 (m, 3 H), 4.70–4.90 (m, 1 H), 7.07 (quintet, *J* = 2 Hz, 0.36 H), 7.20 (quintet, *J* = 2 Hz, 0.64 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.7, 28.6, 28.7, 30.1, 30.4, 62.39, 62.42, 71.7, 71.8, 83.8, 84.2, 130.9, 131.1, 146.4, 146.7, 173.3, 174.5 (except first signal, all other carbons showed diastereomeric splitting).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.99; H, 7.63.

(*E*,*Z*)-3-Methyl-5-[4-(4-methylsulfonyloxy)butylidene]furan-2(5*H*)-one (11)

To a stirred soln of diol **10** (4.00 g, 21.48 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (14.99 mL, 107.52 mmol) and MsCl (3.49 mL, 45.13 mmol) at 0 °C. The mixture was further stirred at r.t. for 24 h and then diluted with CH_2Cl_2 (50 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 2:3) gave **11** (4.07 g, 77%) as a thick oil; ratio *E*/*Z* = 57:43).

IR ($CHCl_3$): 1757 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.80–2.10 (m, 5 H), 2.30–2.60 (m, 2 H), 3.02 (s, 1.71 H), 3.03 (s, 1.29 H), 4.15–4.30 (m, 2 H), 5.14 (t, *J* = 8 Hz, 0.43 H), 5.57 (t, *J* = 8 Hz, 0.57 H), 7.01 (d, *J* = 2 Hz, 0.43 H), 7.32 (d, *J* = 2 Hz, 0.57 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.5, 10.8, 22.1, 22.3, 28.4, 29.1, 37.4, 68.6, 68.8, 110.8, 111.5, 129.7, 131.0, 133.5, 137.5, 149.2, 149.5, 170.7, 170.8 (except one, all other carbons showed *E*/*Z* splitting).

Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02. Found: C, 48.61; H, 5.69; S, 13.12.

(*E*,*Z*)-5-(4-Azidobutylidene)-3-methylfuran-2(5*H*)-one (12)

To a stirred soln of mesylate **11** (3.50 g, 14.21 mmol) in DMF (15 mL) was added NaN_3 (4.67 g, 71.84 mmol) and the mixture was stirred at r.t. for 16 h. The mixture was then diluted with EtOAc (50 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 1:9) gave **12** (2.39 g, 87%) as a thick oil; ratio *E*/*Z* = 53:47.

IR ($CHCl_3$): 2097, 1769, 1763 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.60–1.85 (m, 2 H), 2.00 (s, 1.41 H), 2.03 (s, 1.59 H), 2.35 (q, *J* = 8 Hz, 1.06 H), 2.46 (q, *J* = 8 Hz, 0.94 H), 3.25–3.40 (m, 2 H), 5.13 (t, *J* = 8 Hz, 0.47 H), 5.57 (t, *J* = 8 Hz, 0.53 H), 7.00 (br s, 0.47 H), 7.30 (br s, 0.53 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.5, 10.8, 23.3, 23.4, 28.3, 28.6, 50.2, 50.8, 111.4, 112.2, 129.5, 130.8, 133.4, 137.5, 149.0, 149.4, 170.8, 170.9.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.80; H, 5.70; N, 21.85.

***threo*- and *erythro*-1-(*tert*-Butoxycarbonyl)-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidines (14 and 15)**

To a stirred soln of azide **12** (1.00 g, 5.18 mmol) in THF (5 mL) at 42 °C was added Ph_3P (1.36 g, 5.18 mmol). The mixture was stirred for 30 min and then H_2O (0.47 mL, 25.89 mmol) was added and it was stirred at 42 °C for 12 h. The mixture was concentrated in vacuo, CH_2Cl_2 (10 mL) was added followed by $(Boc)_2O$ (1.36 g, 6.23 mmol) and Et_3N (2.16 mL, 15.52 mmol). The mixture was stirred at r.t. for 16 h and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with H_2O and brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 1:9) gave a mixture of **14** and **15** (1.07 g, 77%) as a thick oil; ratio **14**/**15** = 7:3.

IR ($CHCl_3$): 1755, 1682 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (s, 2.70 H), 1.47 (s, 6.30 H), 1.60–2.10 (m, 7 H), 3.20–3.50 (m, 2 H), 3.90–4.30 (m, 1 H), 5.00–5.40 (m, 1 H), 7.03 (br s, 0.70 H), 7.16 (br s, 0.30 H).

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.96; H, 8.01; N, 5.18.

(*E*,*Z*)-5-(4-Iodobutylidene)-3-methylfuran-2(5*H*)-one (16)

To a stirred soln of mesylate **11** (280 mg, 1.14 mmol) in THF (10 mL) was added LiI (380 mg, 2.84 mmol) and the mixture was stirred

at r.t. for 4 h. THF was removed in vacuo at r.t. and the residue was stirred with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O and brine and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, EtOAc–PE, 1:9) gave **16** (247 mg, 78%) as a thick oil; ratio *E*/*Z* = 1:4.

IR ($CHCl_3$): 1767, 1676, 1620, 1443 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.90–2.10 (m, 5 H), 2.25–2.55 (m, 2 H), 3.10–3.25 (m, 2 H), 5.12 (t, *J* = 8 Hz, 0.80 H), 5.54 (t, *J* = 8 Hz, 0.20 H), 6.99 (br s, 0.80 H), 7.38 (br s, 0.20 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (*Z*-isomer): 5.3, 10.2, 26.8, 32.4, 111.4, 129.0, 137.4, 148.8, 170.5; δ (*E*-isomer): 5.9, 10.5, 26.5, 32.3, 110.8, 130.3, 133.7, 149.2, 170.4.

Anal. Calcd for $C_9H_{11}IO_2$: C, 38.87; H, 3.99. Found: C, 38.71; H, 4.03.

erythro- and *threo*-3-Methyl-5-(tetrahydro-2*H*-furan-2-yl)furan-2(5*H*)-one (17 and 18)

To a stirred soln of diol **10** (200 mg, 1.07 mmol) in toluene (8 mL) was added P_2O_5 (305 mg, 2.15 mmol) and the mixture was heated to reflux for 1 h. Toluene was removed in vacuo and the obtained residue was purified by flash column chromatography (EtOAc–PE, 1:1) to obtain **17** (76 mg, 42%) and **18** (83 mg, 46%) as thick oils.

erythro-3-Methyl-5-(tetrahydro-2*H*-furan-2-yl)furan-2(5*H*)-one (17)

IR ($CHCl_3$): 1763, 1640, 1202 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.75–2.10 (m, 7 H), 3.70–4.00 (m, 3 H), 4.65–4.80 (m, 1 H), 7.17 (quintet, *J* = 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.7, 25.5, 28.0, 68.9, 79.4, 82.6, 130.8, 147.2, 174.1.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.09.

threo-3-Methyl-5-(tetrahydro-2*H*-furan-2-yl)furan-2(5*H*)-one (18)

IR ($CHCl_3$): 1784, 1757, 1653 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.80–2.10 (m, 7 H), 3.70–3.90 (m, 2 H), 4.05–4.20 (m, 1 H), 4.85–4.95 (m, 1 H), 7.01 (quintet, *J* = 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.8, 25.8, 27.4, 69.3, 77.6, 82.4, 131.4, 145.6, 174.1.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.40; H, 7.13.

Norpandamarilactonine A (1) and B (2)

To a stirred soln of carbamates **14** and **15** (800 mg, 2.99 mmol) in CH_2Cl_2 (10 mL) at –20 °C was added dropwise TMSOTf (0.54 mL, 2.99 mmol) under an argon atmosphere. The mixture was stirred for 2.5 h allowing the temperature of the mixture to rise to –5 °C, then 25% liquid NH_3 soln (6 mL) was added. The mixture was then extracted with CH_2Cl_2 (3 × 30 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo directly gave a mixture of pure norpandamarilactonine A and B (495 mg, 99%) as a thick oil; ratio **1/2** = 1:1.

IR ($CHCl_3$): 3402, 1759, 1655 cm^{-1}.

^1H NMR (500 MHz; $CDCl_3$): δ = 1.50–1.90 (m, 4 H), 1.93 (s, 3 H), 2.10 (br s, 1 H), 2.85–3.00 (m, 2 H), 3.15–3.25 (m, 1 H), 4.70–4.85 (m, 1 H), 7.02 (s, 0.5 H), 7.14 (s, 0.5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.7, 25.1, 25.6, 26.9, 27.8, 46.5, 47.0, 60.2, 60.3, 83.7, 84.2, 130.7, 131.2, 146.6, 147.7, 174.2, 174.3 (except first signal, all other carbons showed diastereomeric splitting).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.38. Found: C, 64.71; H, 7.74; N, 8.31.

Pandamarilactonines A–D (3b, 3d, 4a, and 4c)

To a stirred soln of the 1:1 mixture of **1** and **2** (100 mg, 0.60 mmol) in MeCN (10 mL) was added freshly prepared iodolactone **16** (166 mg, 0.60 mmol) and Ag_2CO_3 (181 mg, 0.66 mmol). The mixture was stirred at r.t. for 24 h. Solvent was removed in vacuo and the crude product was dissolved in CH_2Cl_2 (20 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (neutral alumina, EtOAc–PE, 2:3) gave a mixture of four pandamarilactonines (121 mg, 64%) as a thick oil; ratio **3b/3d/4a/4c** = 4:1:4:1.

Pandanamine (5)

Method A: To a stirred soln of the 1:1 mixture of **1** and **2** (30 mg, 0.18 mmol) in MeCN (5 mL) was added freshly prepared iodolactone **16** (50 mg, 0.18 mmol) and Ag_2CO_3 (54 mg, 0.20 mmol). The mixture was stirred at r.t. for 48 h. Solvent was removed in vacuo and the crude product was dissolved in CH_2Cl_2 (20 mL), washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (neutral alumina EtOAc–PE, 1:1) gave **5** (38 mg, 66%) as a thick oil.

Method B: To a stirred soln of mixtures of **3b**, **3d**, **4a**, and **4c** (30 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) and MeOH (2 mL) was added silica gel (1.00 g). The mixture was stirred for 2 h. Solvent was removed in vacuo and the residue obtained was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1) to furnish **5** (19 mg, 63%) as a thick oil.

IR ($CHCl_3$): 3422, 1761, 1663 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.92–2.05 (m, 4 H), 1.97 (br s, 6 H), 2.30–2.55 (m, 4 H), 2.96 (dd, *J* = 8, 8 Hz, 4 H), 5.17 (t, *J* = 8 Hz, 2 H), 7.03 (br s, 2 H).

MS (*m*/*z*) 318, 264, 226, 148, 125, 116, 107.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.98; H, 7.42; N, 4.53.

Acknowledgment

S.G. thanks CSIR, New Delhi, for the award of a research fellowship.

References

(1) (a) Peungvicha, P.; Temsiririrkul, R.; Prasain, J. K.; Tezuka, Y.; Kadota, S.; Thirawarapan, S. S.; Watanabe, H. *J. Ethnopharmacol.* **1998**, *62*, 79. (b) Tan, M. *Philippine Medicinal Plants in Common Use: Their Phytochemistry and Pharmacology*; AKAP: Quezon City, **1980**. (c) Many websites describe the occurrence and properties of *P. amaryllifolius* leaves.
(2) Takayama, H.; Ichikawa, T.; Kitajima, M.; Nonato, M. G.; Aimi, N. *J. Nat. Prod.* **2001**, *64*, 1224.
(3) Takayama, H.; Ichikawa, T.; Kuwajima, T.; Kitajima, M.; Seki, H.; Aimi, N.; Nonato, M. G. *J. Am. Chem. Soc.* **2000**, *122*, 8635.
(4) Takayama, H.; Ichikawa, T.; Kitajima, M.; Nonato, M. G.; Aimi, N. *Chem. Pharm. Bull.* **2002**, *50*, 1303.
(5) Takayama, H.; Ichikawa, T.; Kitajima, M.; Aimi, N.; Lopez, D.; Nonato, M. G. *Tetrahedron Lett.* **2001**, *42*, 2995.
(6) Salim, A. A.; Garson, M. J.; Craik, D. J. *J. Nat. Prod.* **2004**, *67*, 54.

(7) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E. *Tetrahedron Lett.* **2002**, *43*, 5583.
(8) Blanco, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Sanfeliu, E. *Eur. J. Org. Chem.* **2004**, 48.
(9) Takayama, H.; Sudo, R.; Kitajima, M. *Tetrahedron Lett.* **2005**, *46*, 5795.
(10) Honda, T.; Ushiwata, M.; Mizutani, H. *Tetrahedron Lett.* **2006**, *47*, 6251.
(11) The stereochemical assignments of compounds **10**, **14**, **15**, **17**, and **18** are based on NMR parameters.[8]