Research Article

Synthetic Studies Towards the Stereoselective Construction of Bi-Cyclic Core of Cylindricine C

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ABSTRACT

The bi-cylclic core skeleton of the marine alkaloid cylindricine, has been achieved using Barbier type allylation of the quinolizidine imine and aldol reaction of the Boc-protected amino aldehyde with cyclohexanone as the key steps.

Keywords: Marine alkaloid, Cylindricine, Barbier type allylation, Aldol reaction.

1. INTRODUCTION

In 1993, Blackman et al have first isolated a family of eleven structurally related tricyclic alkaloids from the marine ascidian *Clavelina cylindrica* off the cost of Tasmania.[1-3] Among them cylindricine C (1) is a major constituent possessing an unusual [2,1-j]quinoline skeleton (Figure 1). Cylindricines have shown biological activity of brine shimp bioassay and other members shown

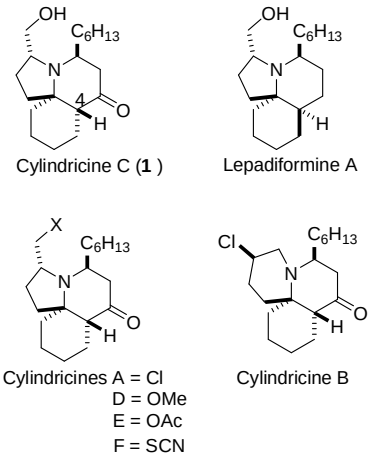


Fig. 1: Representative examples for cylindricines

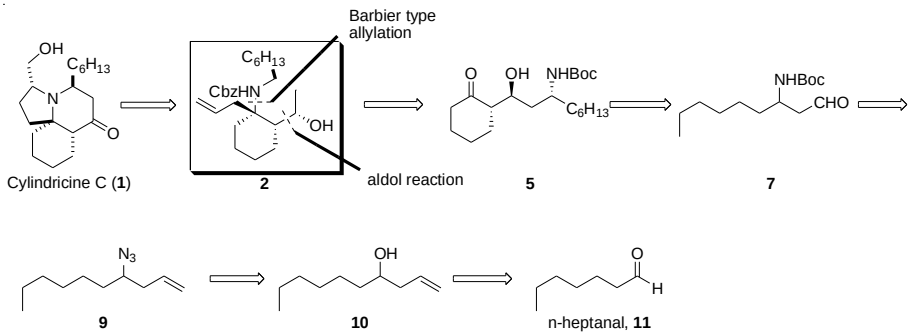
activity against a DNA repair deficient yeast strain[4] and inhibit growth of murine leukemia and human solid tumor cell lines.[5] Cylindricine C (1) is closely related in structure with the other alkaloids known as lepadiformine A,[6-11] except at the *cis*/*trans* ring juncture of the perhydroquinoline ring system and the functionality at C-4.

Given the unique structural challenging molecular framework and its biological activity makes Cylindricine is a very attractive and interesting target for the synthetic organic chemists.[12] Although certain efforts have been reported,[13-27] there is a necessity to develop more efficient and compact methods to not only construct the core skeleton of cylindricine, but for other non-natural isomers to these biologically active alkaloids. Herein we wish to report a new strategy for the bi-cyclic core skeleton for cylindricine C (1), in a stereoselective manner, based on

Barbier type zinc allylation of an intramolecular imine and aldol reaction[27] as key steps (Scheme 1).

2. RESULTS AND DISCUSSION

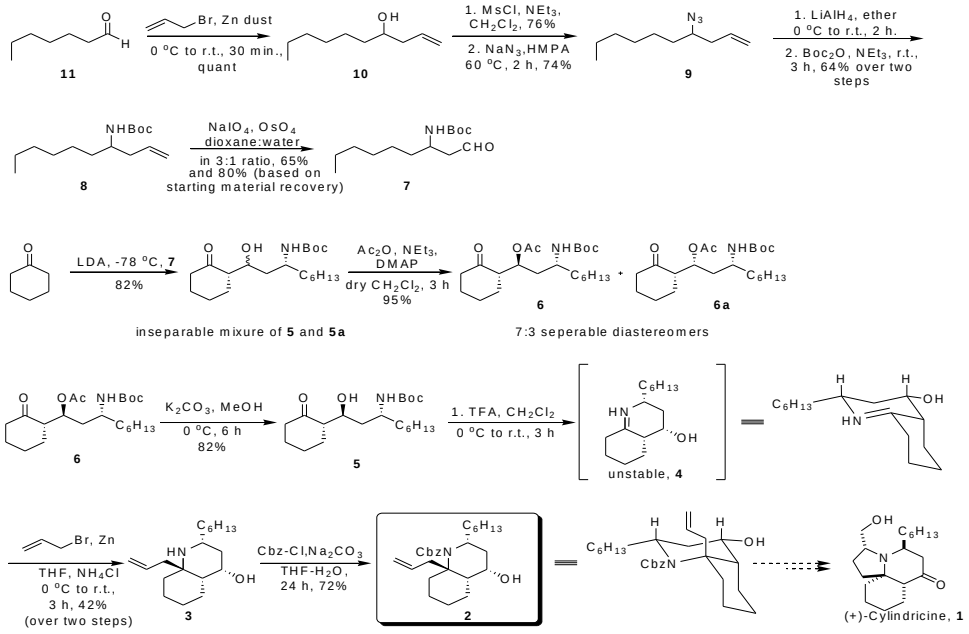
As a part of our ongoing research based on the synthesis of piperidine ring containing alkaloids,[28-29] we looked at the development of a bi-cyclic ring system of 1, which involves in the preparation of aldol addition product 5, 5 leads to the formation of intramolecular imine 4 upon Boc deprotection conditions, that undergoes Barbier type zinc allylation to afford the secondary amine 3, protected with Cbz-group to furnish bi-cyclic framework 2 containing quaternary centre of the marine alkaloid (+)-Cylindricine C (1) (Scheme 1).



Scheme 1: Retrosynthetic approach

The synthesis started with commercially available heptanal (11) which was subjected to Barbier zinc allylation to furnish homoallyl alcohol 10 in quantitative yield. The hydroxyl functionality of 10 was converted to its mesylate using MsCl/NEt_3 conditions in 76% yield. Displacement of mesyl group, following Mitsunoubu protocol achieved the azide 9 with 74% yield.

The azide group in 9 was reduced with $LiAlH_4$ to the corresponding amine, which was further treated with Boc_2O to furnish the t-butyl carbamate 8 in 64% yield over two steps. The olefinic double bond in 8 was oxidized using a one pot osmylation conditions[30] (that is, OsO_4 and $NaIO_4$ in presence of a base 2,6-lutidine) to afford β-amino aldehyde 7 in 65% yield and 80%, when the recovery of starting material is included. Subsequent aldol reaction between lithium enolate of cyclohexanone and aldehyde 7 resulted in an inseparable diastereomeric mixture of β-hydroxy ketones 5 and 5a, followed by concomitant conversion of this mixture of alcohols to their acetates generated a separable pair of diastereomers 6 and 6a (anti:syn=7:3), by column chromatography. Major diastereomer, *anti*-acetate 6 was deacetylated with K_2CO_3 in MeOH to give alcohol 5 in 82% yield with a good recovery of the starting material. It is gratifying to note that the stereochemistry of the anti-aldol product 5 was confirmed at a later stage, by NOE studies performed on its cyclized structure 2. To install the



Scheme 2: Synthesis of bi-cyclic core structure of cylindricine

quinoizidine system bearing a quaternary carbon, Boc-protected β-hydroxy ketone **5** was treated with TFA in CH_2Cl_2 as solvent at 0 ^oC to r.t. for 3h which afforded an unstable intramolecular imine **4**. Direct exposure of this crude product to Barbier type allylation conditions (i.e., allyl bromide in the presence of activated zinc dust) stereoselectively furnished the bi-cyclic amine in 42% yield over two steps. We speculated that generated allyl carbanion attacks on the quinolizidine imine in a stereoselective manner i.e., anti attack took place. Free amine **3** was protected as its carbobenzyloxy ether **2**, when treated with Cbz-Cl in presence of Na_2CO_3 in THF and water in 72% yield. The stereochemistry of **2** was assigned based on an NOE experiment. The NOE

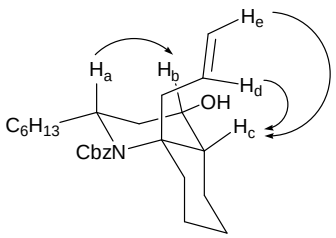


Fig. 2: NOE enhancements

enhancements observed between the protons H_a and H_b, H_c and H_d, and H_c and H_e as shown in figure 2. This supported the stereochemical outcome with structure 2 in figure 2, with the protons H_a and H_b, and H_c with both the protons H_d and H_e were situated in the same face of the piperidine ring.

3. CONCLUSION

In conclusion, we have achieved the bi-cylclic core skeleton comprising of a quaternary centre of cylindricine 2, with a linear sequence of 12 steps from the aldehyde, heptanal 11 (with an overall yield of 3.9%). Our synthetic route requires commercially less expensive materials than previous reports. The bi-cyclic skeleton with a quaternary carbon was assembled through the Barbier type allylation of the quinolizidine imine 4 and aldol reaction of the Boc-protected amino aldehyde 7 with cyclohexanone. Our strategy also provides potential access to cylindricine C (1) and its structurally related analogues. Further synthetic work towards the total synthesis of cylindricine C (1) is currently actively pursued in our laboratory.

4. ACKNOWLEDGMENTS

R.V.N.S.M. thanks the UGC, New Delhi for research fellowship and S.C. is thankful to the DST New Delhi for funding a research grant.

7. EXPERIMENTAL

Spectral data for selected compounds(R)-tert-Butyl dec-1-en-4-ylcarbamate (8)

A 50-mL, oven dried, two necked round-bottomed flask was charged with a solution of $LiAlH_4$ (0.65 g, 17.7 mmol) in dry ether (10 mL) cooled to -5 ^oC using ice-salt bath. To it was added homoallyl azide 9 (1.6 g, 8.8 mmol) in dry ether (10 mL) dropwise under a flow of nitrogen. The resultant mixture was stirred at 0 ^oC for 30 min., and for 1 h at r.t. The reaction was then quenched with 5 mL 10% of NaOH solution at 0 ^oC. The solution was allowed to stir for 2 h at r.t. After the precipitate formed was filtered, the organic layer was dried over Na_2SO_4, filtered and concentrated to give its corresponding amine as a colorless oil (1.5 g, 82%).

Crude amine (1.2 g) was dissolved in THF (20 mL) and to it were added distilled Et_3N (2.93 mL, 21 mmol) and followed by Boc_2O (di-tert-butyl dicarbonate) (3.2 mL, 14 mmol) at 0 ^oC under nitrogen atmosphere. The mixture was stirred at r.t. for 6 h and diluted with 10 mL of ethyl acetate. The organic layer was washed with 10 mL of water and brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification of residue by column chromatography on 100-200 mesh of silica gel (elution with hexane/ethyl acetate = 10:1) provided 9 as a colourless liquid (1.39 g, 79%).

IR (KBr): ν_{max} 3345, 2930, 1694, 1521, 1366, 1248, 1175, 913 and 649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.84-5.64 (m, 1H), 5.11-5.00 (m, 2H), 4.23 (d, J = 9.1 Hz, 1H), 3.69-3.50 (m, 1H), 2.29-2.06 (m, 2H), 1.52-1.36 (m, 10H), 1.36-1.18 (m, 9H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 134.5, 117.4, 78.8, 50.0, 39.5, 34.7, 32.7, 29.0, 28.3, 25.8, 22.5 and 14.0; ESIMS: m/z 256 $(M+H)^+$.

(R)-tert-Butyl 1-oxononan-3-ylcarbamate (7)

To a solution of 8 (1.3 g, 5.1 mmol) dissolved in a 3:1 ratio of dioxane and H_2O (20 mL) at 0 ^oC was added 2,6-lutidine (1.18 mL, 10.2 mmol), OsO_4 (0.020 g, 0.08 mmol) followed by $NaIO_4$ (4.36 g, 20.4 mmol.) in one portion. The temperature slowly raised to room temperature for 2 h. The reaction was stirred at this temperature for further 8 h and monitored by TLC, which indicates the reaction was almost completed. Then water (10 mL) and CH_2Cl_2 (16 mL) were added to it. The organic layer was separated and aqueous layer was

extracted with CH_2Cl_2 (2 x 10 mL). Combined organic layers were washed with brine (16 mL) and dried over Na_2SO_4. The solvent was evaporated and residue was purified by column chromatography to afford aldehyde 7 as a colorless oil (0.85 g) with 65% yield and 80% when the recovery of the starting material is included.

IR (KBr): ν_{max} 2926, 2855, 1713, 1220, 1169 and 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.74 (t, J = 2.3 Hz, 1H), 4.62 (d, J = 9.0 Hz, 1H), 4.05-3.87 (m, 1H), 2.68-2.47 (m, 2H), 1.57-1.38 (m, 10H), 1.38-1.19 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.3, 155.4, 79.6, 49.2, 46.5, 35.1, 31.7, 28.9, 28.3, 26.0, 22.5 and 14.0; ESIMS: m/z 258 $(M+H)^+$.

(1R,3S)-3-(tert-Butoxycarbonylamino)-1-((S)-2-oxocyclohexyl)nonyl acetate (6)

To a solution of diisopropylamine (0.51 mL, 3.73 mmol) in THF (5 mL) was added at 0 ºC n-butyllithium (2.5 M in hexanes, 1.5 mL, 3.73 mmol). The mixture was stirred at this temperature for 0.5 h, and afterward cooled to -78 ºC. Cyclohexanone (0.4 mL, 3.73 mmol) was then added, and the reaction mixture was further stirred at -78 ˚C for 1 h. The aldehyde 7 (0.8 g, 3.11 mmol) in THF (5 mL) was injected slowly in the solution, and after stirring for 5 minute at -78 ºC an NH_4Cl aqueous solution (10 mL) and Et_2O (20 mL) were poured into the reaction mixture. The phases were then separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried on Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of residue on silica gel (petrolium ether/EtOAc in 5:1) afforded 5 and 5a as a mixture of inseperable diastereomers (0.906 g, 82%) as a colorless oil.

To a stirred solution of the epimeric mixture of alcohol (650 mg, 1.8 mmol) in CH_2Cl_2 (9 mL) at 0 ^oC under nitrogen atmosphere were added pyridine (0.44 mL, 5.49 mmol) dimethyl amino pyridine (18.9 mg, 0.18 mmol) followed by acetic anhydride (0.519 mL, 5.49 mmol). After being stirred for 12 h at room temperature, the reaction was diluted with water (2 mL), aqueous layer was extracted with CH_2Cl_2 (3 x 16 mL). Combined organic layers were washed with water, brine (10 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure, crude was purified by column chromatography to furnish 6 (483 mg) and 6a (207 mg) in 7:3 ratio as separable diastereomers with total yield of 95%.

6: IR (KBr): ν_{max} 3360, 2926, 2856, 1710, 1514, 1457, 1367, 1242, 1172 and 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) : δ 5.32 (d, J = 8.3 Hz, 1H), 4.61-4.40 (m, 1H), 3.72-3.46 (br.s, 1H), 2.87-2.62 (m, 1H), 2.60-2.18 (m, 2H), 2.18-1.97 (m, 5H) 1.96-1.85 (br.s, 1H), 1.81-1.13 (m, 24H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.6, 170.7, 155.6, 78.8, 69.6, 52.8, 47.3, 42.1, 36.2, 34.8, 31.7, 29.1, 28.3, 27.3, 25.7, 24.5, 22.5, 21.2 and 13.9; ESIMS: m/z 420.1 $(M+Na)^+$.

tert-Butyl (1R,3S)-1-hydroxy-1-((S)-2-oxocyclohexyl)nonan-3-ylcarbamate (5)

To a solution of 6 (400 mg, 1.01 mmol) in methanol (8 mL) at 0 ^oC was added K_2CO_3 (278.5 mg, 2.01 mmol). After 3 h stirring at this temperature, solvent was completely removed by evaporation, the mixture was extracted with EtOAc (3 x 10 mL). The extract was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (5:1) to give 5 (293 mg, 82%) as a colourless oil.

IR (KBr): ν_{max} 3354, 2927, 2856, 1700, 1511, 1366 and 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.63 (d, J = 8.3 Hz,1H), 3.71 (dd, J = 5.1, 6.2 Hz, 1H), 3.66-3.54 (m, 1H), 3.53-3.40 (br.s, 1H), 2.55-2.20 (m, 3H), 2.19-2.00 (m, 2H), 1.99-1.81 (m, 1H), 1.81-1.16 (m, 21H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.1, 156.5, 79.2, 67.4, 56.0, 47.9, 42.5, 38.4, 35.3, 31.7, 29.6, 29.1, 28.3, 27.7, 26.2, 24.7, 22.6 and 14.0; ESIMS: m/z 378 $(M+Na)^+$.

(2S)-Benzyl 8a-allyl-2-hexyl-4-hydroxyoctahydroquinoline-1(2H)-carboxylate (2)

To a stirred solution of Boc-protected amine 5 (267 mg, 0.75 mmol) dissolved in 2 mL dry CH_2Cl_2 under a nitrogen inlet needle, cooled to -10 ^oC was added 25% trifluoroacetic acid in CH_2Cl_2 (0.692 mL, 2.26 mmol). The temperature slowly raised to 0 ^oC and TLC checked after 4 hours, indicated complete consumption of the starting material. The rection was cooled to 0 ^oC, CH_2Cl_2 (5 mL) was added, ice water followed by $NaHCO_3$ (solid) were added in excess in order to bring pH 8-9. The mixture was extracted in CH_2Cl_2 (3 x 10 mL). The organic layer washed with brine solution (5 mL), concentrated in vacuo to yield 4 (135 mg, 75%) and this unstable imine was taken for the next step without any further purification.

A stirred solution of imine 4 (60 mg, 0.24 mmol) dissolved in dry THF (2 mL) under nitrogen atmosphere, was cooled to -10 ^oC were added allylbromide (0.04 mL, 0.47 mmol)

and activated zinc dust (31 mg, 0.47 mmol). The reaction was allowed to stir for 30 min. at same temperature. Then a saturated solution of NH_4Cl (1 mL) was added and mixture was further stirred for 45 min. at -10 ^oC. The reaction was quinched by adding 5 mL of EtOAc. The mixture was filtered, layers separated, aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were given brine wash (5 mL), dried over Na_2SO_4 and concentrated in vacuo to give reddish oily residue and pure compound was obtained by column chromatography using 2% MeOH in CH_2Cl_2 as eluents to furnish 3 (39 mg, 56%).

To a stirred solution of compound 3 (24 mg, 0.086 mmol) in $CHCl_3$ (1 mL) and H_2O (1 mL) was added solid Na_2CO_3 (30 mg, 0.2581 mmol) at 0 ^oC under nitrogen atmosphere. After 10 min. Cbz-Cl (0.04 mL, 0.2581 mmol) was added. The reaction was allowed to stir for 2 days at r.t. then TLC checked. The reaction was quinched by adding water followed by CH_2Cl_2. The aqueous layer were separated and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were given brine wash (2 mL), dried over Na_2SO_4, concentrated IR (KBr) : ν_{max} 3414, 2925, 1711, 1604, 1513, 1461, 1286, 1254, 1168, 1032, 829 and 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) : δ 7.46-7.27 (m, 5H), 5.87-5.68 (m, 1H), 5.20-5.01 (m, 4H), 4.21-4.07 (dt, J = 6.4, 2.1 Hz, 2H), 3.68-3.57 (m, 1H), 2.33-2.20 (m, 1H), 2.18-2.04 (m, 2H), 1.94-1.65 (m, 4H), 1.65-1.09 (m, 16H), 0.88 (distorted t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 136.3, 129.7, 128.5, 128.0, 114.3, 67.0, 64.4, 50.2, 48.5, 42.7, 38.8, 31.0, 29.7, 29.5, 29.4, 26.1, 22.7 and 14.1; ESIMS: m/z 414.3 $(M+H)^+$; HRMS: Calcd for $C_{26}H_{40}NO_3$ $(M+H)^+$: 414.3003 and found: 414.2981.

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