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Stereoselective synthesis of the tricyclic core ABC-rings of nakadomarin and manzamine from a common intermediate

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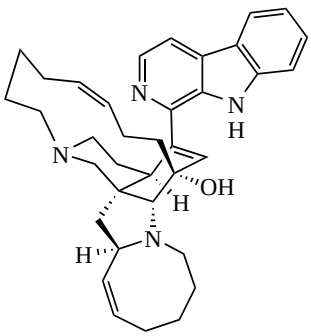
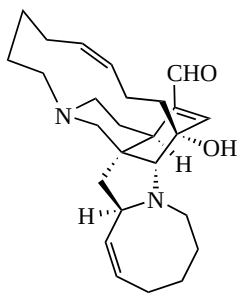
Abstract—Pauson–Khand cyclization of the enamide **9** proceeds in trifluoroethanol to give cyclopentenone **10**, which on hydrogenation gives **11**, having the core ABC-rings of nakadomarin **1**.

Manzamine A **1** was isolated in 1985 from a marine sponge (*Haliclona* sp.) and inhibits the growth of P388 mouse leukemia cells (IC_{50} 0.07 μg mL^{-1}).[1] The complex structure of manzamine disguises its simple biogenetic connection to the so-called 3-alkylpiperidine alkaloids.[2] There are many different and complex structures derived from 3-alkylpiperidines, and ircinal **2**[3] has the most obvious structural connection to **1**. There have been many reports of approaches to the synthesis of **1** and **2** and without exception they all focus on the azadecalin and attach the 5-, 8- and 13-membered ring later.[4a–p] Recently, the Winkler[5] and Martin[6] groups have completed the total synthesis of **1** and **2** (Scheme 1).

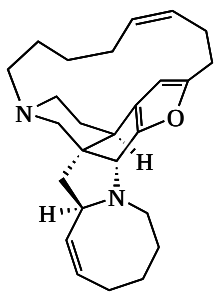
The structure of nakadomarin A **3** has recently been disclosed.[7] It was isolated from an *Amphimedon* sponge sp. (SS-264), and exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg mL^{-1}), inhibitory activity against cyclin dependent kinase **4** (IC_{50} 9.9 μg mL^{-1}), and antimicrobial activity against a fungus and a Gram-positive bacterium.



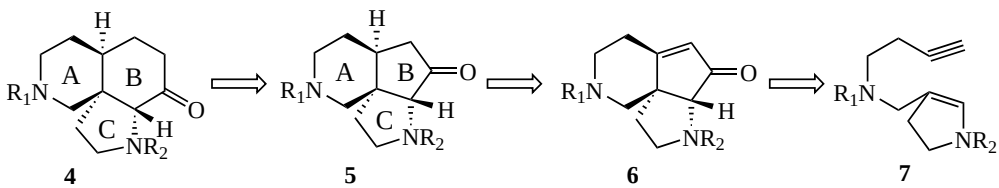
1, Manzamine A



2, Ircinal A



3, Nakadomarin



4 **5** **6** **7**

Scheme 1.

Keywords: nakadomarin; Pauson–Khand; enamide.

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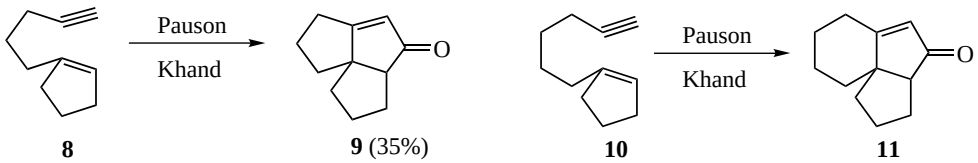
The tricyclic core structure of nakadomarin that comprises the ABC-rings **5** (manzamine lettering), in principle, can be constructed by an intramolecular Pauson–Khand reaction of **7** to give **6**, which on reduction of the cyclopentenone should give **5** (Scheme 1). Furthermore, ring expansion of the B-ring in **5** would result in the tricyclic core structure of manzamine, namely **4**. Thus, the intermediate **5** can serve as precursor to both **1** and **3**. The literature describing the many facets of Pauson–Khand reactions is substantial,[8] and while both allylamines and propargylamines have been successfully used as substrates,[9] there are no examples of enamines or enamides as substrates. The conversion of **4** into **3** also creates a quaternary carbon atom as part of the tricyclic angularly fused heterocycle.[10,11] This is a particularly demanding test of the structural latitude that the Pauson–Khand reaction can endure. It should be noted that Shore has described the conversion of **8** into **9** using standard Pauson–Khand reaction conditions,[12] but the corresponding conversion of **10** into **11** has not been reported (Eq. (1)).



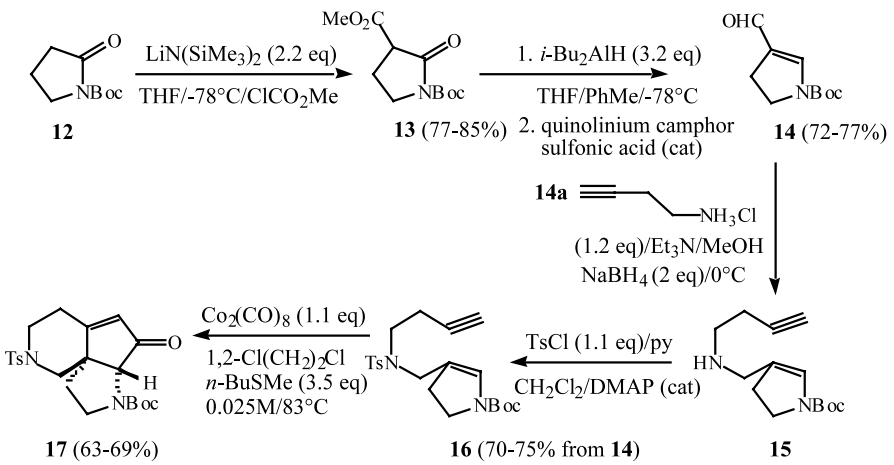
8 **9** (35%) **10** **11** (1)

Treatment of **12**[13] with $LiN(SiMe_3)_2$/THF at −78°C followed by methyl chloroformate gave **13** (Scheme 2). Reduction of **13** with diisobutylaluminum hydride in THF at −78°C, followed by dehydration using quinolinium camphor sulfonic acid (cat.) gave **14**.[14] Reductive amination of **14** with 1-amino-3-butyne hydrochloride **14a**[15]/Et_3N/MeOH/$NaBH_4$ at −5°C gave the *sec*-amine **15**. Attempted complexation of **15** with $Co_2(CO)_8$ gave a complex intractable mixture, therefore we masked the *sec*-amino group as its *p*-toluenesulfonamide derivative **16**. Exposure of **16** to a wide variety of conditions that have been used for Pauson–Khand reactions gave either no reaction or decomposition to complex mixtures that contained no detectable amounts of the tricyclic adduct **17**. However, using the Living-house–Pagenkopf et al.[16] conditions, where β,β,β-trifluoroethanol is used as solvent, we were able to isolate **17** in 25% yield. This could be improved to 50–55% yield if the reaction mixture was washed with aqueous ethylenediaminetetraacetic acid (EDTA) in the work-up.[17,18] The yield of **17** was further increased by employing the Sugihara procedure.[19] Treatment of **16** with $Co_2(CO)_8$ (1.1 equiv.)/*n*-BuSMe (3.5 equiv.) in 1,2-dichloroethane at 83°C gave **17** in 63–69% yield.

While the IR, ^1H and ^{13}C NMR spectral data[20] were in agreement with the proposed structure for **17**, confirmation of the structure was sort by X-ray crystallography. Hydrogenation of **17** gave **18** (65%) and **19** (30%) (Scheme 3). The assignment of stereochemistry for **18** was confirmed by removal of the Boc protecting group and formation of the *p*-nitrophenylcarbamate derivative **20**, which gave crystals suitable for X-ray crystallography. Fig. 1 shows an ORTEP representation of **20** that indicates the correct relative stereochemistry of the ABC-ring fusions (see **1**). The stereoisomer **19** was characterized in the same way. Use of $Pd/BaSO_4/H_2$ or Raney nickel did not change the ratio of **18** and **19** to any significant extent.[21]

A variety of methods to ring expand the cyclopentanone **18** into a cyclohexanone derivative were attempted without success, except the classical diazoalkane technology. Treatment of the acid stable derivative **21** with ethyl diazoacetate/$BF_3{\cdot}OEt_2$ resulted in the formation of **22** (53%), which exists in the enol form (δ 12.2s for the hydrogen bonded -OH) (Scheme 4).

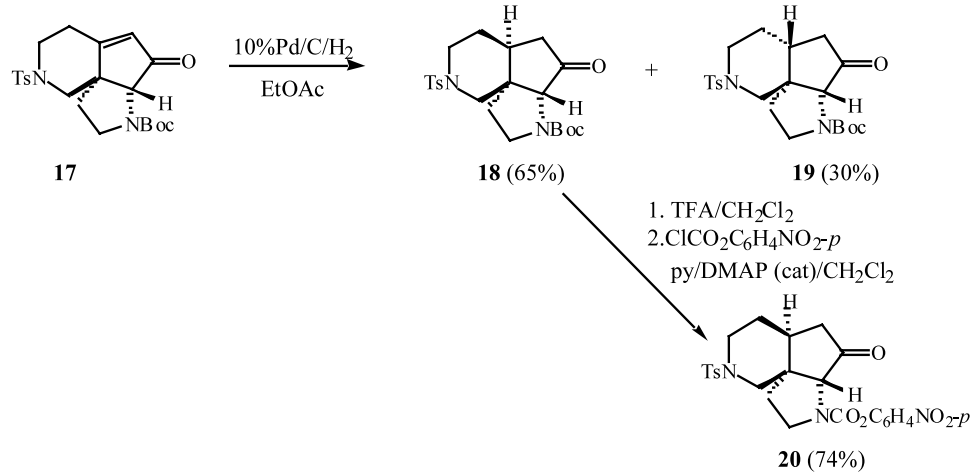
In summary, the Pauson–Khand reaction provides a reasonably concise route to the nakadomarin and manz-



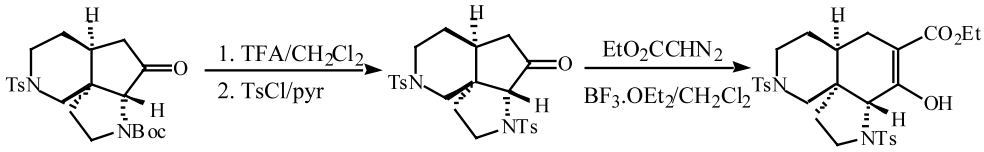
12 **13** (77-85%) **14** (72-77%)

17 (63-69%) **16** (70-75% from **14**) **15**

Scheme 2.



Scheme 3.



Scheme 4.

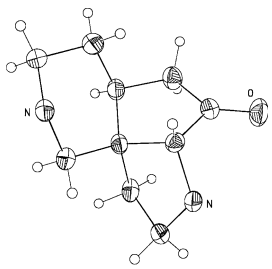


Figure 1. View of **20** with heteroatoms labelled. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms shown are drawn to an arbitary scale. The Ts and CO_2-$C_6H_4NO_2$-*p* groups have been removed for clarity.

amine core structures. It is planned to investigate if the stereoselectivity of the reduction of **17** can be improved.

Acknowledgements

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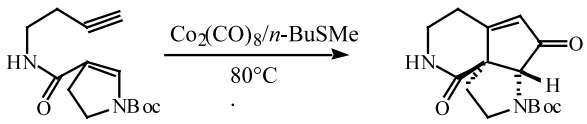
17. It appears as though the product **10** is complexed to cobalt residues, and purification of the product leads to extensive decomposition. Removal of the cobalt residues by washing with aqueous EDTA doubles the yield of **10**.
18. Treatment of the amide analog **16a** with the *n*-BuSMe accelerated Pauson–Khand reaction conditions did not produce any of the tricyclic amide **17a**. It seems that the added conformational rigidity of the amide linking chain is sufficient to prevent cyclization.



16a **17a**

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20. **17**. IR (film) 2976, 1718, 1701, 1688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (2H, d, $J=8$ Hz), 7.30 (2H, d, $J=8$ Hz), 5.82 (1H, s), 4.05 (1H, m), 3.93 (1H, d, $J=12.1$ Hz), 3.78 (1H, m), 3.12 (1H, br q), 2.74 (1H, m), 2.39 (3H s), 2.37–2.28 (2H, m), 2.16 (1H, m), 1.95 (1H, m), 1.45 (9H, s), 1.42 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 175.4, 144.0, 133.0, 129.9, 127.3, 80.3, 66.1, 55.7, 46.3, 28.3, 28.1, 21.4, 40.9, 38.1, 25.6, 22.0, 20.6. HRMS calcd for $C_{22}H_{29}N_2O_5S$ (MH^+) 433.1786. Found 433.1786. **20**. IR (film) 2923, 1754, 1726, 1711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (2H, d, $J=8$ Hz), 7.68 (2H, d, $J=8$ Hz), 7.44 (2H, d, $J=8$ Hz), 7.37 (2H, d, $J=8$ Hz), 4.63 (1H, s), 3.70 (4H, m), 2.69 (1H, dd, $J=12.7$ Hz, $J=53.3$ Hz), 2.46 (3H, s), 2.45–2.38 (2H, m), 2.17 (1H, d, $J=20$ Hz), 2.07 (1H m), 1.95 (1H, m), 1.67 (1H, m), 1.52 (2H, m).
21. Reduction of **17** with Li/NH_3/THF has given inconclusive results.