



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

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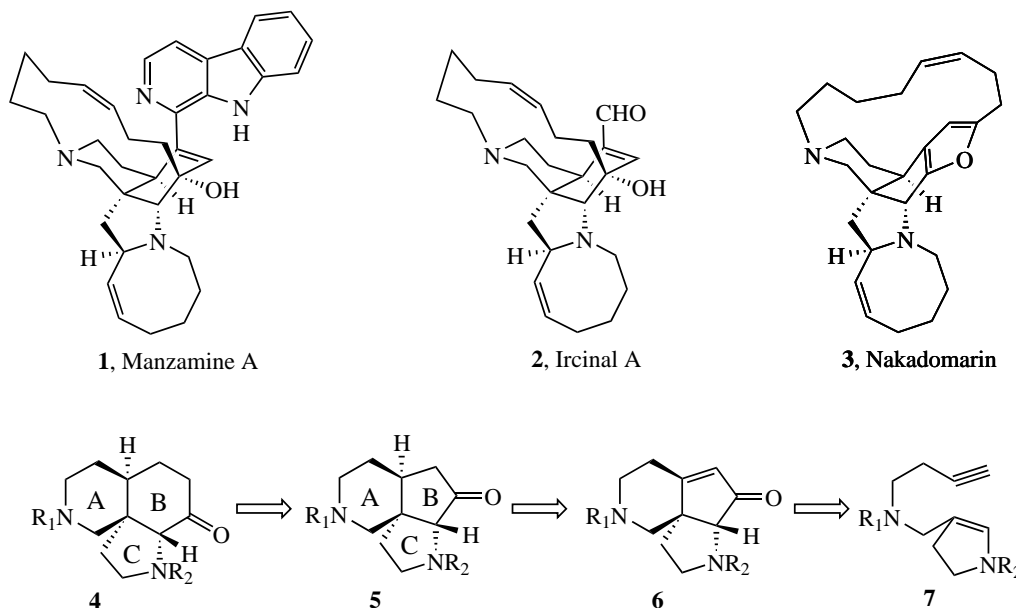
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Abstract—Pauson–Khand cyclization of the enamide **9** proceeds in trifluoroethanol to give cyclopentenone **10**, which on hydrogenation gives **11**, having the core ABC-rings of nakadomarin **1**. © 2002 Elsevier Science Ltd. All rights reserved.

Manzamine A **1** was isolated in 1985 from a marine sponge (*Haliclona* sp.) and inhibits the growth of P388 mouse leukemia cells (IC_{50} $0.07 \mu\text{g mL}^{-1}$).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 Winkler⁵ and Martin⁶ 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} $1.3 \mu\text{g mL}^{-1}$), inhibitory activity against cyclin dependent kinase 4 (IC_{50} $9.9 \mu\text{g mL}^{-1}$), and antimicrobial activity against a fungus and a Gram-positive bacterium.



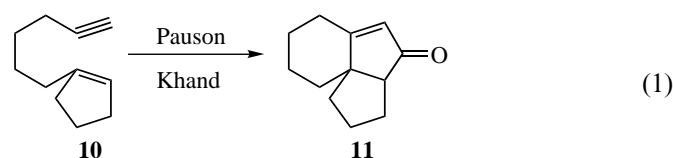
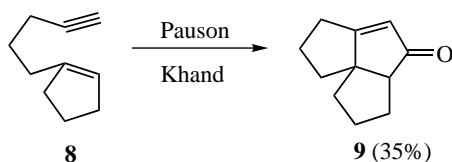
Scheme 1.

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)).



Treatment of **12**¹³ with $\text{LiN}(\text{SiMe}_3)_2/\text{THF}$ 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/ $\text{Et}_3\text{N}/\text{MeOH}/\text{NaBH}_4$ at -5°C gave the *sec*-amine **15**. Attempted complexation of **15** with $\text{Co}_2(\text{CO})_8$ 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-

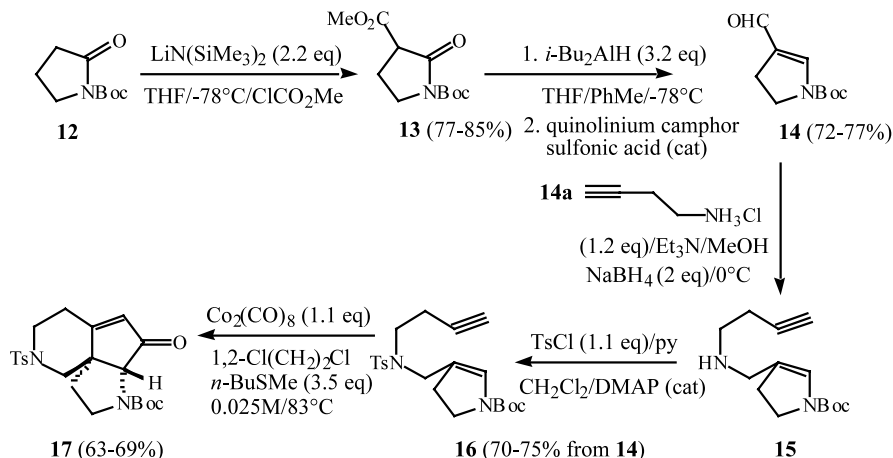
house–Pagenkopf et al.¹⁶ conditions, where β,β,β -trifluoroethanol is used as solvent, we were able to isolate **17** in 25% yield. This could be improved to 50–55% yield if the reaction mixture was washed with aqueous ethylenediaminetetraacetic acid (EDTA) in the work-up.^{17,18} The yield of **17** was further increased by employing the Sugihara procedure.¹⁹ Treatment of **16** with $\text{Co}_2(\text{CO})_8$ (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 data²⁰ 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

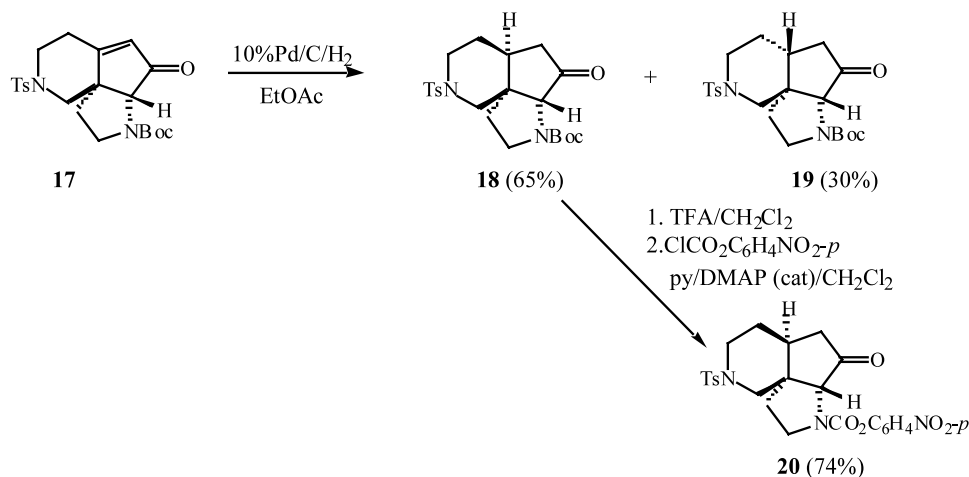
characterized in the same way. Use of $\text{Pd}/\text{BaSO}_4/\text{H}_2$ or Raney nickel did not change the ratio of **18** and **19** to any significant extent.²¹

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/ $\text{BF}_3 \cdot \text{OEt}_2$ resulted in the formation of **22** (53%), which exists in the enol form (δ 12.2s for the hydrogen bonded -OH) (Scheme 4).

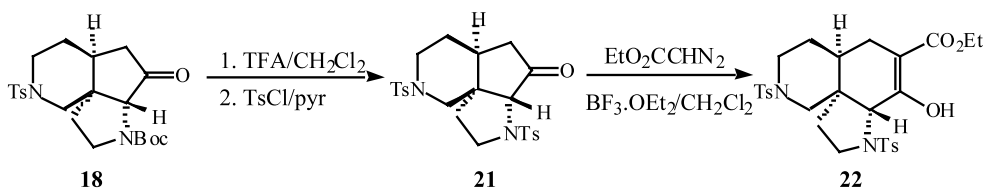
In summary, the Pauson–Khand reaction provides a reasonably concise route to the nakadomarin and manz-



Scheme 2.



Scheme 3.



Scheme 4.

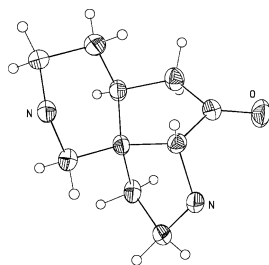


Figure 1. View of **20** with heteroatoms labelled. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale. The Ts and $\text{CO}_2\text{-C}_6\text{H}_4\text{NO}_2\text{-}p$ groups have been removed for clarity.

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

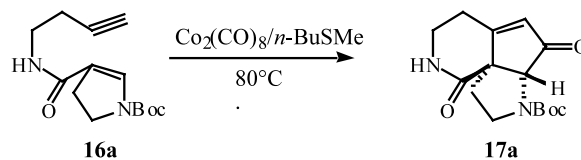
Acknowledgements

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 - 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**.
 - 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.



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- 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 $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_5\text{S}$ (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).
- Reduction of **17** with $\text{Li}/\text{NH}_3/\text{THF}$ has given inconclusive results.