A Sulfolene-based Intramolecular Diels–Alder Approach to the Synthesis of Manzamine A

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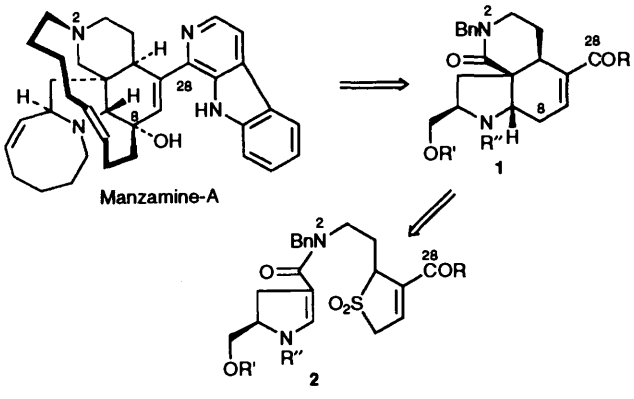
Synthetic studies towards manzamine A are described. A tandem sulfolene SO_2 extrusion intramolecular Diels–Alder cyclisation gave the C-5 epimer of the manzamine tricyclic ABC ring system *via* a C-5 to C-8 diene bearing a C-5/C-6 *Z*-alkene.

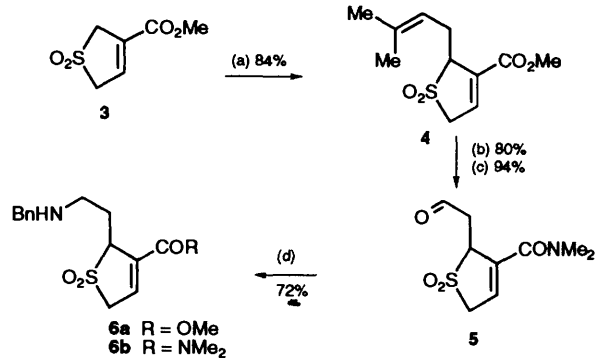
Manzamine A is a powerful antileukaemic agent, isolated from Okinawan sponge *Halicona* sp.,[1] and has an intriguing and complex structure that has stimulated the interest of synthetic chemists around the world.[2] A recent publication by Martin *et al.*,[3] outlining their progress towards the synthesis of manzamine A, prompts us to disclose the results of our synthetic studies. Our overall synthetic strategy (Scheme 1) was disclosed in a report of our early studies.[4] Our synthetic plan differs from Martin's in that the diene unit is incorporated masked as a sulfolene. Thus, our planned key intermediate was a sulfolene, such as **2**, which when heated should undergo tandem SO_2 extrusion Diels–Alder cyclisation. From the onset we were curious to identify the geometry of the dienes generated from such cheletropic extrusions and discover the stereochemical outcome of their subsequent cyclisations.



Scheme 1

We wanted to incorporate C-28 at the acid oxidation level from the start for several reasons. Molecular orbital calculations indicated that dienes with such substituents would have favourable reactivity towards a range of appropriate dienophiles. Also, we thought that an ester or amide group would survive the planned synthetic steps as well as being amenable to incorporation into the carbazole ring system at a late stage of the route. Initially we prepared the sulfolene ester **6a** as our masked diene unit but this lactamised readily, so we chose to convert the ester to a dimethylamide.

The dianion of the commercially available sulfolene **3**,†[5] formed using 2 equiv. of butyllithium in THF at −78 °C, was prenylated in the 3-position selectively, providing crystalline **4** in 80% yield.[4] The ester was efficiently converted into a dimethylamide in 80% yield by hydrolysis followed by 1,3-dicyclohexylcarbodiimide (DCC) coupling with dimethylamine. Subsequent ozonolysis was essentially quantitative and reductive amination of the aldehyde **5** with a slight excess of benzylamine gave the key sulfolene unit **6b** in 72% yield (Scheme 2).



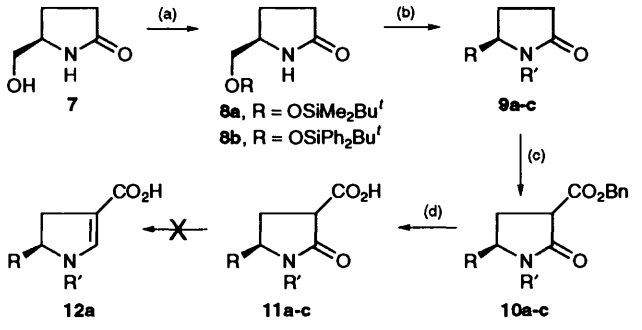
Scheme 2 (a) i, BuLi (2 equiv.)/THF; ii, prenyl bromide; (b) i, $LiOH/H_2O$/THF; ii, $DCC/Me_2NH{\cdot}HCl/Et_3N$; (c) i, O_3/CH_2Cl_2/−78 °C; ii, Me_2S; (d) $BnNH_2{\cdot}HCl/NaBH_3CN$/MeOH

We have synthesised the acids **11a–c** for coupling with the sulfolene **6b** (Scheme 3).‡ The alcohol **7** was obtained by $NaBH_4$ reduction of methyl pyroglutamate and converted into the silyl ethers **8a** (89%) and **8b** (88%) under mild conditions. The carbamate derivatives **9b** and **9c** could not be formed directly from the sterically hindered amides **8a** and **8b**. However, the sodium anions of **8a** and **8b** reacted smoothly with ethyl chloroformate, to provide **9a** (53%) and **9b** (85%) and the lithium anion of **8b** reacted with di-*tert*-butyl carbonate to give **9c** (85%). In our hands, benzyl chloroformate reacted with the enolates from **9b** and **9c** on oxygen as well as on carbon. Although reasonable yields of **10a** (65%) and **10b** (43%) were obtained using the chloroformate reagent, **10c** was only obtained in good yield (83%) by employing benzyl cyanoformate. Hydrogenolysis of the benzyl esters provided the labile acids **11a–c**. With these acids and the sulfolene amine **6b** on hand the next target was the cycloaddition precursor **14**. The alternative strategies for this transformation are, either to couple the acid **11** with the amine unit **6b** prior to carbonyl reduction, or to convert the lactams **11** into the enamines **12** before coupling. Although Martin *et al.* have used the latter strategy we were unable to prepare **12a–c** in meaningful yields and we therefore chose to couple the acid and amine first.

The acid **11a** was coupled with the amine **6b** using carbonyldi-

† Available from the Fluka Chemical Company.

‡ Compounds **7–12** are shown as the *R*-enantiomer as required for manzamine A. Most of this work was however carried out with the *S*-series of enantiomers, derived from L-glutamic acid *via* (*S*)-pyroglutamic acid.

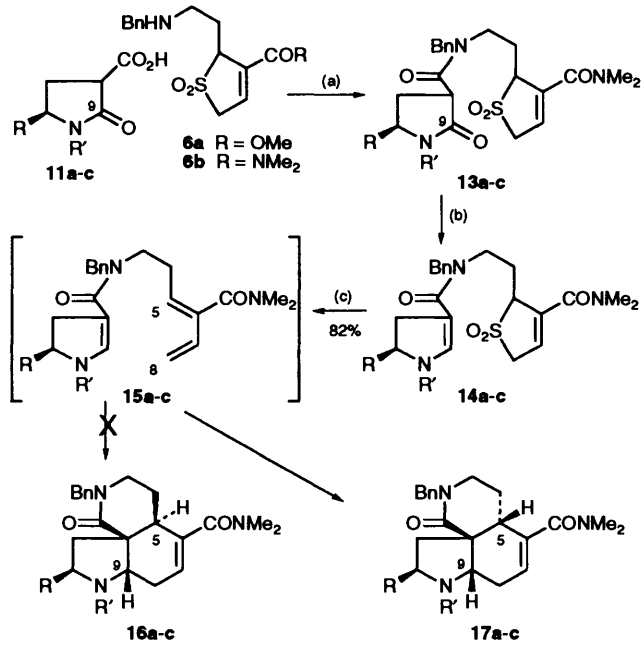


Scheme 3 (a) Bu^tMe_2Si–Cl/DMAP/Et_3N/CH_2Cl_2 (for **8a**) or Bu^tPh_2-Si–Cl/DMAP/Et_3N/CH_2Cl_2 (for **8b**); (b) i, NaH/THF; ii, EtOCOCl (for **9a**/**9b**) or i, BuLi/THF; ii, $(Bu^tO)_2CO$ (for **9c**); (c) i, $(Me_3Si)_2NLi$/THF; ii, $PhCH_2COCN$; (d) H_2/5% Pd–C/Et_2O

imidazole to provide the amide **13a** in 61% overall yield from **10a**. Next we had to reduce the C-9 carbonyl of **13a** selectively, in the presence of the three other amide carbonyls. After some experimentation we found that $LiBHEt_3$ did indeed reduce C-9 selectively and subsequent *in situ* mesylation and elimination (mesyl chloride/Et_3N) gave **14a** in 82% overall yield.

When heated in toluene at reflux for 72 h compound **14a** underwent a tandem SO_2 cheletropic extrusion/Diels–Alder cyclisation to give a single stereoisomeric product in 82% isolated yield. Careful monitoring of the reaction indicated that SO_2 extrusion was complete in *ca.* 12 h, but the cyclisation was much slower. The gross structure of the cyclisation product was confirmed by ^1H NMR decoupling and COSY experiments. We attempted to distinguish between the stereoisomers **16a** and **17a** using NOE and NOSY experiments but there was some ambiguity in the results because of conformational mobility. There was, however, a clear NOE between 5-H and 9-H and this appears to rule out isomer **16a** and support isomer **17a**. Since, when heated, **13a** gave a diene having a C-5/C-6 alkene of *Z* configuration, we presume that the cyclisation precursor has the same geometry. From our molecular modelling studies * and from the precedent of Martin's earlier model studies with unsubstituted dienes, we had expected that **16a** would be the major cyclisation product from either alkene isomer and we were surprised to obtain **17a** as the only isolated stereoisomer. For some time we have been trying to obtain a crystalline derivative of the Diels–Alder product to clear any doubts about its stereochemistry, but numerous derivatization strategies were thwarted because of its lack of reactivity and no crystalline derivative yet produced has provided a crystal suitable for X-ray analysis. If the stereochemical analysis of our Diels–Alder product is correct then it is clear that the substituent on the diene, as well as the diene geometry has a significant effect on the stereochemical outcome of Diels–Alder reactions of this type. In our present studies we are investigating the effects of substituents on the dienophile unit (cyclisations of **14b** and **14c**) as well as considering various different diene substituents. A broad study of this area will be useful so that we can begin to understand the subtle factors which are responsible for stereochemical control in this unusual class of intramolecular Diels–Alder cyclisations. We shall report the full details of these studies in due course.

* Molecular orbital calculations carried out using MOPAC V (QCPE 455); J. J. P. Stewart, *J. Comp. Chem.*, 1990, **10**, 209 and 221.



Scheme 4 (a) $(Imidazole)_2CO/CH_2Cl_2$; (b) i, $LiBHEt_3$/THF; ii, $MsCl/Et_3N$; (c) toluene/reflux/72 h

Experimental

Melting point determinations were carried out on an electrothermal apparatus and were recorded uncorrected. IR absorption spectra were run either neat (for liquids) or as Nujol mulls (for solids) on a Perkin-Elmer 1710 FT-IR instrument. ^1H NMR spectra were recorded at 300 MHz on a Bruker AC-300 instrument, as solutions in deuteriochloroform. Chemical shifts are referenced to tetramethylsilane and *J* values are rounded to the nearest 0.5 Hz. Mass spectra were recorded at low resolution on a Finnigan 4500 instrument and at high resolution on a Kratos Concept 1-S instrument. After aqueous work-up of reaction mixtures, organic solutions were routinely dried with anhydrous magnesium sulfate and 'evaporated' refers to removal of solvent on a rotary evaporator. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} glass-backed plates. The plates were visualised by the use of a UV lamp, or by dipping in a solution of vanillin in ethanolic sulfuric acid, followed by heating. Silica gel 60 (particle sizes 40–63 μm) was employed for flash chromatography. All compounds were characterized by a full range of spectroscopic data, including detailed 300 MHz ^1H NMR studies and high resolution mass spectrometry.

Amide **13a**.—A suspension of the benzyl ester **10a** (146 mg, 0.50 mmol) and 5% palladium-on-carbon (15 mg) in dry diethyl ether (10 cm^3) was stirred vigorously under an atmosphere of hydrogen. After 4 h the mixture was filtered through Celite and carefully evaporated at room temperature, to provide the unstable acid **11a**. This acid was dissolved in dichloromethane (5 cm^3) under argon and carbonyldiimidazole (82 mg, 0.50 mmol) was added to the solution. After the mixture had been stirred for 2 h, a solution of the amine **6b** (147 mg, 0.46 mmol) in dichloromethane (5 cm^3) was added to it and this was followed after a further 19 h by saturated aqueous ammonium chloride (15 cm^3). The mixture was then extracted with dichloromethane (4 × 25 cm^3). The combined organic fractions were dried, filtered and evaporated and purification of the residue by flash chromatography [EtOAc–MeOH (19:1)] provided **13a** (152

mg, 65%), ν_{max}/cm^{-1} 1783, 1720, 1640 and 1302; δ_H(300 MHz, $CDCl_3$) (complicated amide rotamers) 1.32 (3 H, t, *J* 7, OCH_2CH_3), 1.95–2.3 (1 H, m, CH_2 and 4-H), 1.90–2.40 (3 H, m), 2.60 (1 H, m), 2.94 (3 H, br s, NMe_2), 3.00 (3 H, br s, NMe_2), 3.2–3.7 (2 H, m, NCH_2), 3.7–4.05 (6 H, m, $COCHCH$, EtO_2CNCH_2, O_2SCH_2, O_2SCH), 4.27 (2 H, 2 × overlapping q, *J* 7, OCH_2CH_3), 4.32–5.20 (2 H, series of overlapping d, CH_2Ph), 6.03 (1 H, m, $=CHCH_2$) and 7.3 (5 H, m, Ph); *m/z* (+ve FAB) 506 $[M + H]^+$ 89% (Found: $[M + H]^+$, 506.1976. $C_{24}H_{32}N_3O_7S$ requires 506.1961).

Trienic Precursor **14a**.—To a stirred solution of the amide **13a** (110 mg, 0.22 mmol) in dry tetrahydrofuran (5 cm^3) at −78 °C under argon, was added a solution of lithium triethylborohydride in tetrahydrofuran (1.0 mol dm^{-3}; 240 mm^3, 0.24 mmol)*. After 90 min; 1 mol dm^{-3} HCl (10 cm^3) was added to the mixture which was allowed to warm to room temperature, when it was extracted with ether (10 cm^3) and dichloromethane (4 × 10 cm^3). The combined organic extracts were dried and evaporated and the residue was dissolved in dichloromethane (5 cm^3) under argon. To this solution was added mesyl chloride (19 mm^3, 0.24 mmol) and triethylamine (34 mm^3, 0.24 mmol) and stirring was continued. After 40 min, more triethylamine (68 mm^3, 0.48 mmol) was added to the mixture which was then stirred for a further 22 h. Saturated aqueous $NaHCO_3$ (20 cm^3) was added to the mixture which was then extracted with dichloromethane (5 × 20 cm^3). The combined organic fractions were dried and evaporated and the residue purified by flash chromatography [gradient elution, EtOAc to EtOAc–MeOH (19:1) provided **14a** (88 mg, 82%)], ν_{max}/cm^{-1} 1704, 1638, 1409 and 1308; δ_H(300 MHz, $CDCl_3$) (complicated by amide rotamers) 1.2 (3 H, m, OCH_2CH_3), 2.00–2.30 (2 H, m, CH_2), 2.92 (2 H, m, $CH_2C=$), 2.96 (3 H, br s, NMe_2) 3.02 (3 H, br s, NMe_2), 3.54 (2 H, ~t, *J* 7, CH_2N), 3.75 (2 H, m, EtO_2CNCH_2), 3.82 (2 H, br s, O_2SCH_2), 3.97 (1 H, m, O_2SCH), 4.09 (2 H, m, OCH_2CH_3), 4.64 (1 H, d, *J* 17, NCH_2Ph), 4.70 (1 H, d, *J* 17, NCH_2Ph), 6.02 (1 H, d, *J* 2, $=CHCH_2SO_2$), 6.82 (1/2 H, br s, NCH=C), 6.92 (1/2 H, br s, NCH=C) and 7.1–7.5 (5 H, m, Ph); *m/z* (+ve FAB) 490 $[M + H]^+$ 63% (Found: $[M + H]^+$, 490.2008. $C_{24}H_{32}N_3O_6S$ requires 490.2011).

Diels–Alder Cycloadduct **17a**.—A stirred solution of the trienic precursor **14a** (104 mg, 0.21 mmol) in degassed, dry toluene (10 cm^3) under argon, was heated at reflux for 5 days, after which it was evaporated. The residue was purified by flash chromatography [EtOAc–MeOH (19:1)] to provide the tricyclic product **17a** (72 mg, 80%), ν_{max}/cm^{-1} 1694, 1639, 1341 and 1104; δ_H(300 MHz, $CDCl_3$) 1.20–1.30 (3 H, 2 × overlapping t, *J* 7, CH_2CH_3), 1.78 (1 H, m, 4-H), 1.91 (1 H, dd, *J* 12.5, 6.5, 27-H), 2.01 (1 H, m, 4-H), 2.19 (1 H, br d, *J* 17, 8-H), 2.27 (1 H, m, 4-H), 2.33 (1 H, m, 27-H), 2.57 (1 H, m, 5-H), 2.84 (1 H, dd, *J* 17, 7, 8-H), 2.96 (3 H, s, NMe), 2.99 (1 H, 2 × overlapping s, NMe), 3.24–3.27 (2 H, m, 3-H_2), 3.34–3.47 (2 H, m, 26-H_2), 4.06–4.16 (2 H, m, CH_2CH_3), 4.36 [0.3 H, d, *J* 14.5, CH_2Ph (minor rotamer)], 4.44 (0.7 H, d, *J* 14.5, CH_2Ph (major rotamer)], 4.59 (1 H, m, 9-H), 4.65 [0.7 H, d, *J* 14.5, CH_2Ph [(major rotamer)], 4.73 [0.3 H, d, *J* 14.5, CH_2Ph (minor rotamer)], 5.91 (1 H, m, 7-H) and 7.19–7.32 (5 H, m, Ph); *m/z* (+ve FAB) 426 $[M + H]^+$ 22% (Found: $[M + H]^+$, 426.2390. $C_{23}H_{32}N_3O_4$ requires 426.2393).

* 1 mm^3 = 1 μl.

Acknowledgements

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