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A concise approach to the spiroiminal fragment of marineosins†

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A concise approach to the spiroiminal fragment of marineosins A and B is described. The key steps involve an acid-catalyzed *N*-acyliminium ion cyclization and a Vilsmeier–Haack type reaction with Tf_2O.

In 2008, Fencial and co-workers reported the isolation of two novel spiroiminals, marineosins A (**1**) and B (**2**) (Fig. 1), from a marine-derived *Streptomyces*-related actinomycete.[1] These two compounds are likely related to the prodigiosin class of bacterial pigments,[2] and have been shown to possess significant anticancer activities.[1] Both **1** and **2** have a *trans*-fused macrocyclic ring and a spiro-tetrahydropyran-dihydropyrrole iminal structure. Marineosins A and B differ in stereochemistry of the spiroiminal center and the MeO group in the dihydropyrrole, which leads to the significant difference in cytotoxicity toward human colon carcinoma (HCT-116) (IC_{50} = 0.5 μM for **1** and IC_{50} = 46 μM for **2**). The unique structures as well as the promising biological activities of marineosins make them attractive synthetic targets. During our studies toward these two compounds, two synthetic approaches were reported both in 2010. Lindsley and co-workers reported their studies on the proposed inverse-electron-demand hetero Diels–Alder reaction based biomimetic approach.[3] Snider and co-workers proposed an alternative biosynthesis of the marineosins and completed the synthesis of the spiroiminal moiety.[4] Herein, we wish to report our own synthetic approach to the spiroiminal fragment of marineosins A and B.

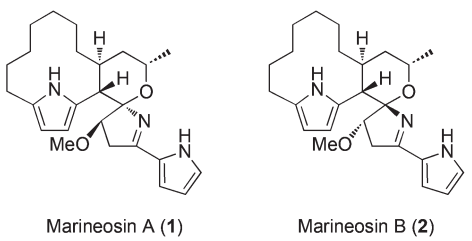
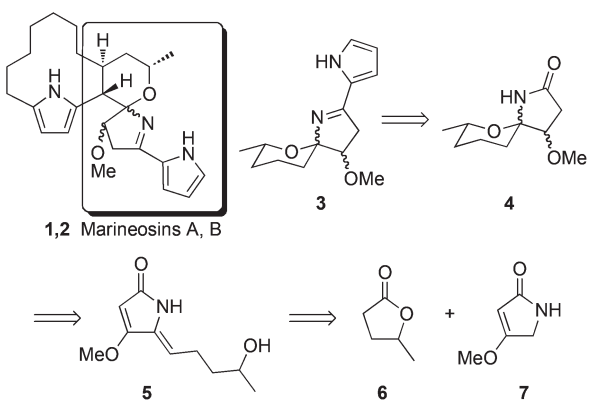


Fig. 1 Structures of marineosins A and B.

The spiroiminal core of marineosins A and B contains all the stereogenic centers and appears to be important for bioactivities. The construction of this moiety will pave the way for the synthesis of the molecules and their derivatives for biological studies. The retrosynthetic analysis is shown in Scheme 1. The sensitive pyrrole was planned to be introduced in the late stage *via* a Vilsmeier–Haack type reaction from spiroketal lactam **4**, which could be obtained from compound **5** through an acid-catalyzed *N*-acyliminium ion cyclization.[5] Compound **5** could be readily prepared from commercially available reagents **6** and **7**.

The synthesis of spiroketal lactam **4** is outlined in Scheme 2. γ-Valerolactone (**6**) was reduced with DIBAL-H at −78 °C to give hemiacetal **8** in 90% yield,[6] which was treated



Scheme 1 Retrosynthetic analysis of spiroiminal fragment **3**.

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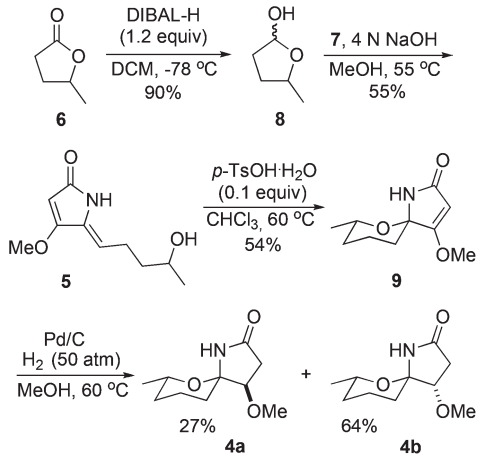
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, X-ray structure of **9**, **4a**, **4b**, **4c**, and **3b** along with NMR spectra. CCDC 919541–919545. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40208h



Scheme 2 Synthesis of compounds **4a** and **4b**.

with 4-methoxy-3-pyrrolin-2-one (**7**) and 4 N NaOH in MeOH at 55 °C to give compound **5** in 55% yield.[7] The cyclization of compound **5** was investigated with various acids. The best result was obtained by treating compound **5** with 10 mol% *p*-TsOH·H_2O in $CHCl_3$ at 60 °C for 24 h, giving compound **9** as a single isomer in 54% yield along with small amounts of **5**. It appears that an equilibrium between **9** and **5** was reached under the reaction conditions and did not change with prolonged reaction time. The structure of compound **9** was confirmed by X-ray diffraction (Fig. 2). When compound **9** was hydrogenated with Pd/C (10%) under 50 atmosphere pressure of H_2 at 60 °C, isomers **4a** and **4b** were isolated in 27% and 64% yield, respectively, with silica gel buffered with Et_3N (the X-ray structures of **4a** and **4b** are shown in Fig. 3 and 4).

With compounds **4a** and **4b** in hand, the Vilsmeier–Haack reaction was subsequently investigated. No desired product was obtained when **4a** was treated with $POCl_3$ and pyrrole.[8] To our delight, spiroiminal fragment **3a** was cleanly formed in

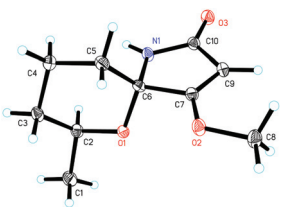


Fig. 2 The X-ray structure of compound **9**.

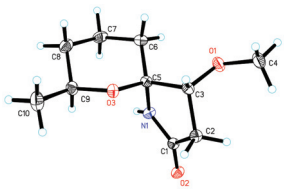


Fig. 3 The X-ray structure of compound **4a**.

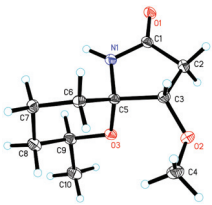
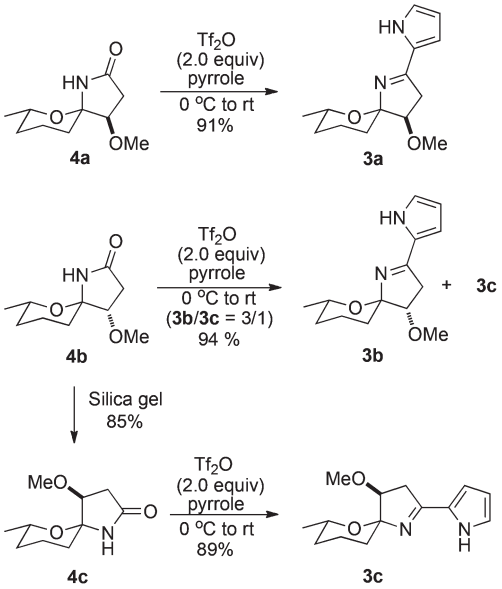


Fig. 4 The X-ray structure of compound **4b**.



Scheme 3 Synthesis of compounds **3a**, **3b**, and **3c**.

91% yield with Tf_2O (Scheme 3).[9,10] When **4b** was subjected to the reaction conditions, **3b** and **3c** (3 : 1) were obtained in 94% yield (the X-ray structure of **3b** is shown in Fig. 5). Compound **4b** can be converted to **4c** with *p*-TsOH·H_2O (0.1 equiv.) in $CDCl_3$. The ratio of **4b** to **4c** is about 1 : 0.9 at equilibrium.[11] However, compound **4c** can be isolated in 85% yield when **4b** was loaded on a silica gel column and eluted with EtOAc (**4b** was gradually converted to **4c** on the silica gel) (the X-ray structure of **4c** is shown in Fig. 6). Treating compound **4c** with Tf_2O in pyrrole gave spiroiminal **3c** in 89% yield (Scheme 3).

Fig. 7 lists four spiroiminal stereoisomers **3a–d**. Three of them were obtained. The anomeric effect[12] and the electronic repulsion between two oxygens are likely the contributing

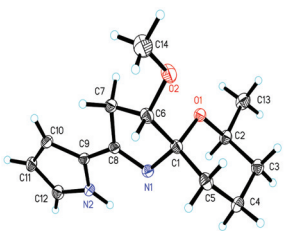


Fig. 5 The X-ray structure of compound **3b**.

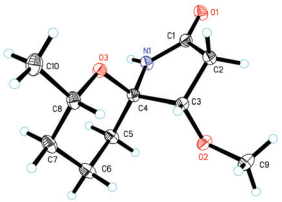


Fig. 6 The X-ray structure of compound **4c**.

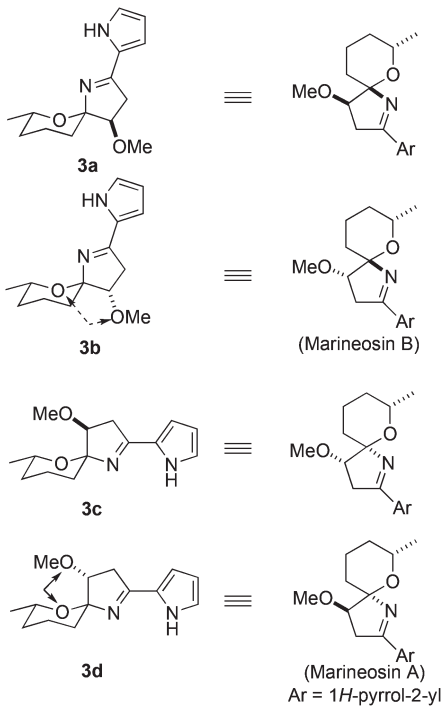


Fig. 7 Stereoisomers of spiroiminal.

factors for the stability of these isomers. In the case of marineosin A (**1**) or B (**2**), the fused macrocyclic ring in the natural product will likely make the MeO group stay away from it to ensure a more stable configuration. The stereochemistry of the MeO group will likely determine the configuration of the spiroiminal during the cyclization. Compounds **3a**, **3b**, and **3c** were previously reported by Snider and co-workers.[4] Similar discussion on the relative stability of these compounds has also been described by them.

Conclusion

In summary, we have developed a concise strategy to construct the spiroiminal fragment of marineosins A and B in five steps. The key steps involve an acid-catalyzed *N*-acyliminium ion cyclization and a Tf_2O mediated Vilsmeier–Haack type reaction to introduce the pyrrole. The application of this strategy to the synthesis of marineosins A, B and their derivatives is currently underway.

Acknowledgements

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Notes and references

1 C. Boonlarppradab, C. A. Kauffman, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 5505.
2 (*a*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*b*) N. R. Williamson, P. C. Fineran, T. Gristwood, S. R. Chawrai, F. J. Leeper and G. P. C. Salmond, *Future Microbiol.*, 2007, **2**, 605.
3 L. N. Aldrich, E. S. Dawson and C. W. Lindsley, *Org. Lett.*, 2010, **12**, 1048.
4 X.-C. Cai, X. Wu and B. B. Snider, *Org. Lett.*, 2010, **12**, 1600.
5 For leading reviews on *N*-acyliminium chemistry, see: (*a*) W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817; (*b*) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431; (*c*) J. Royer, M. Bonin and L. Micouin, *Chem. Rev.*, 2004, **104**, 2311.
6 L. A. Paquette, J. C. Lanter and H.-L. Wang, *J. Org. Chem.*, 1996, **61**, 1119.
7 (*a*) T. M. Visp, US4983743, 1991; (*b*) M. Bänziger, J. F. McGarrity and T. Meul, *J. Org. Chem.*, 1993, **58**, 4010.
8 H. Rapoport and N. Castagnoli, *J. Am. Chem. Soc.*, 1962, **84**, 2178.
9 For a leading review on the Tf_2O-promoted Vilsmeier–Haack type reaction, see: I. L. Baraznenok, V. G. Nenajdenko and E. S. Balenkova, *Tetrahedron*, 2000, **56**, 3077.
10 For leading references on the Tf_2O-promoted Vilsmeier–Haack type reaction, see: (*a*) A. G. Martínez, R. M. Alvarez, J. O. Barcina, S. M. Cerero, E. T. Vilar, A. G. Fraile, M. Hanack and L. R. Subramanian, *J. Chem. Soc., Chem. Commun.*, 1990, 1571; (*b*) D. S. C. Black, A. J. Ivory and N. Kumar, *Tetrahedron*, 1996, **52**, 4697; (*c*) D. S. C. Black, A. J. Ivory and N. Kumar, *Tetrahedron*, 1996, **52**, 7003; (*d*) V. G. Nenajdenko, I. L. Baraznenok and E. S. Balenkova, *Tetrahedron*, 1996, **52**, 12993; (*e*) V. G. Nenajdenko, I. L. Baraznenok and E. S. Balenkova, *Tetrahedron Lett.*, 1996, **37**, 4199; (*f*) I. L. Baraznenok, V. G. Nenajdenko and E. S. Balenkova, *Synthesis*, 1997, 465; (*g*) V. G. Nenajdenko, I. L. Baraznenok and E. S. Balenkova, *J. Org. Chem.*, 1998, **63**, 6132; (*h*) D. S. C. Black and R. Rezaie, *Tetrahedron Lett.*, 1999, **40**, 4251; (*i*) L. Shao, P. D. Badger, S. J. Geib and N. J. Cooper, *Organometallics*, 2004, **23**, 5939; (*j*) M. Ghandi, S. Salahi and M. Hasani, *Tetrahedron Lett.*, 2011, **52**, 270.
11 A similar ratio was obtained when **4c** was treated with *p*-TsOH·H_2O (0.1 equiv.) in $CDCl_3$.
12 For a leading review on the anomeric effect, see: R. U. Lemieux, *Pure Appl. Chem.*, 1971, **25**, 527.

