CHEMCOMM Communication
www.rsc.org/chemcomm

Multi-component assembly of the bicyclic core associated with the tRNA synthetase inhibitors SB-203207 and SB-203208. Application to the synthesis of biologically active analogues†

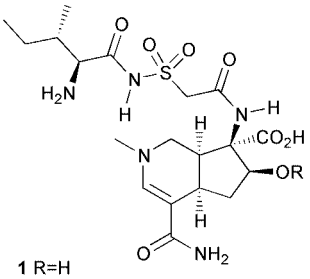
Martin G. Banwell,*[a] Curtis F. Crasto,[a] Christopher J. Easton,*[a] Tomislav Karoli,[a] Darren R. March,[a] Michael R. Nairn,[a] Peter J. O'Hanlon,[b] Mark D. Oldham,[a] Anthony C. Willis[a] and Weimin Yue[a]

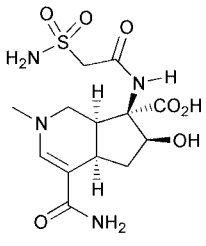
[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. E-mail: mgb@rsc.anu.edu.au*
[b] *GlaxoSmithKline, New Frontiers Science Park, Harlow, UK CM19 5AW*

Received (in Cambridge, UK) 4th June 2001, Accepted 21st June 2001
First published as an Advance Article on the web 11th October 2001

The ketone (±)-5, which embodies the bicyclic core associated with the title tRNA synthetase inhibitors 1 and 2, has been prepared *via* a three-component coupling reaction involving 2-(hydroxymethyl)cyclopent-2-enone (15), methylamine (6) and propiolamide (10); straightforward elaboration of the readily derived acetates (−)-21 and (+)-21 has provided the biologically active analogues 23 and 24, respectively, of the title compounds.

The emergence of 'superbugs' such as vancomycin-resistant *Staphylococcus aureus* has prompted extensive efforts to identify new anti-infective agents.[1] High throughput screening regimes have led to the discovery of a number of novel leads including SB-203207 (**1**) and SB-203208 (**2**) which are potent inhibitors of both bacterial and mammalian isoleucyl tRNA synthetases.[2] The structurally related natural product altemicidin (**3**),[3] a novel acaricidal and anti-tumour agent, has been the subject of an elegant total synthesis.[4] However, the methods[4,5] currently available for construction of the hexahydroazaindene core associated with such compounds are unlikely to be practical in providing a broad range of analogues of **1** and **2** for testing as anti-infective agents. On this basis we now describe a multi-component and potentially highly flexible method for construction of the azabicyclic ketones (±)-**4** and (±)-**5** as well as conversion of the latter into biologically active analogues of the title compounds.





In our initial approach to (±)-**4** and (±)-**5** we envisaged that these might be constructed in a one-pot process from methylamine (**6**), formaldehyde (**7**), cyclopent-2-enone (**8**) and the appropriate propiolic acid derivative **9** or **10** (Fig. 1). In particular, it seemed possible that in the presence of a suitable catalyst the Schiff-base (imine) derived from condensation of **6** and **7** could participate in an 'aza-Baylis–Hillman' reaction[6] with **8** to give *N*-methyl-2-(aminomethyl)cyclopent-2-enone

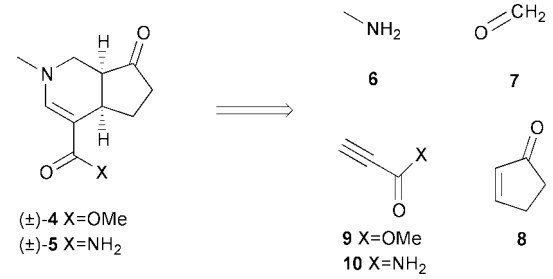
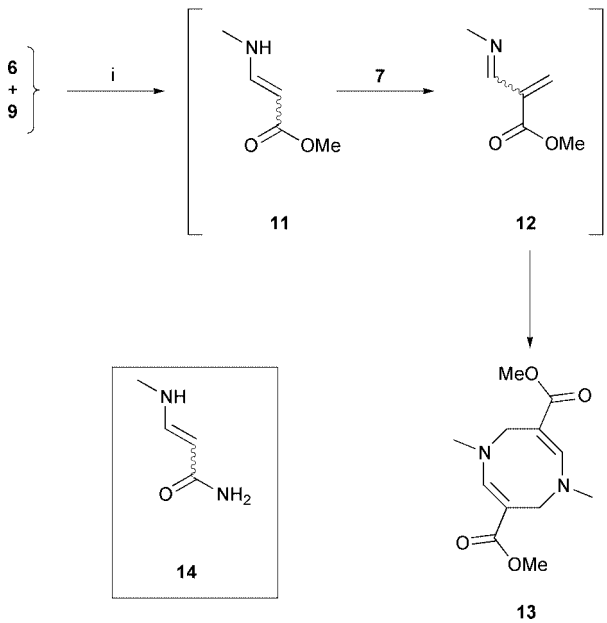


Fig. 1

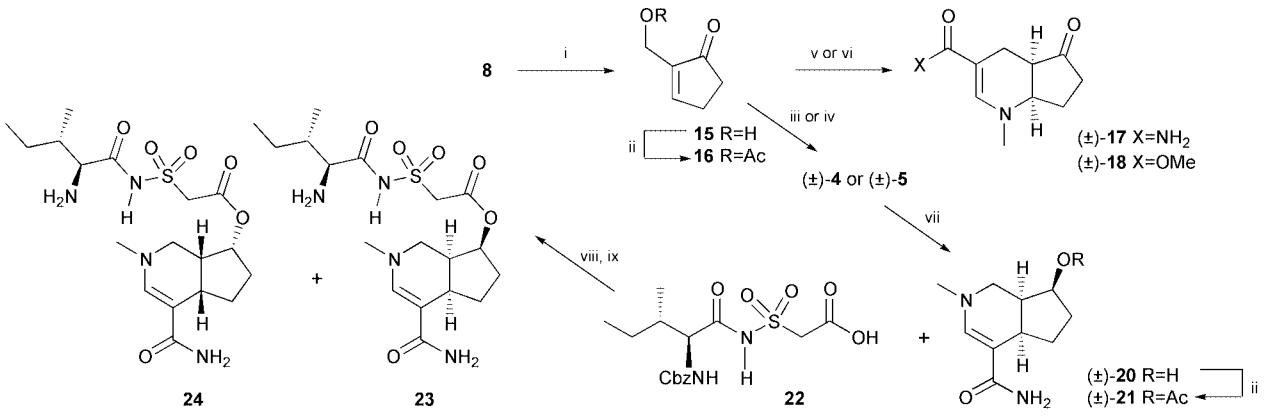
which would then react, through nitrogen in a hetero-Michael-addition reaction, with **9** or **10**. The enamine–cyclopentenone conjugate thus formed might then be expected to undergo an intra-molecular Michael-addition reaction,[7] thereby providing the target ketones (±)-**4** and (±)-**5**. In the event, mixing the four components **6**–**9** with DABCO, a proven catalyst for the Baylis–Hillman reaction, in water at room temperature (**CAUTION**—highly exothermic!) resulted in a complex mixture of products from which the 1,5-diazacycloocta-2,6-diene **13** could be isolated and the structure of which follows from spectroscopic analysis. Clearly, **6**, **7** and **9** but not **8** have been incorporated into this product and further studies revealed that simply mixing the former compounds in water (Scheme 1) provided diene **13** in 45% yield. Presumably, a key intermediate in this conversion



Scheme 1 *Conditions*: (i) H_2O, DABCO (cat.), *ca.* 18 °C, 16 h.

† Electronic supplementary information (ESI) available: spectral data for **5**, crystal data for (±)-**21** (CCDC 165269), HPLC for (+)- and (−)-**21**. See http://www.rsc.org/suppdata/cc/b1/b104890m/

 DOI: 10.1039/b104890m



Scheme 2 *Reagents and conditions*: (i) DABCO (*ca*. 0.25 mol% wrt **8**), aq. HCHO (1.5 mole equiv.), THF, 18 °C, 23 h; (ii) Ac_2O (2 mole equiv.), Et_3N (1.65 mole equiv.), DMAP (cat.), CH_2Cl_2; (iii) **6** (1.5 mole equiv.), **9** (1.5 mole equiv.), DABCO (1.25 mole equiv.), H_2O, 18 °C, 5–7 days; (iv) **14** (1.6 mole equiv.), DABCO (1 mole equiv.), EtOH, 18 °C, 15 h; (v) **14** (1.7 mole equiv.), EtOH, 18 °C, 15 h; (vi) **11** (1 mole equiv.), $Pd(PPh_3)_4$ (10 mol%), THF, 18 °C, 10–14 days; (vii) L-Selectride® (1.0 mole equiv. of a 1 M solution in THF), THF, −17 °C, 0.5 h; (viii) **22** (2 mole equiv,), Et_3N (2 mole equiv.), ClCOCOCl (2 mole equiv.), 0 °C, 0.5 h then (+)- or (−)- **20**, Et_3N (1 mole equiv.), DMAP (cat.), DMF, 0 to 18 °C, 1.5 h; (ix) H_2 (1 atm), 10% Pd on C (cat.), MeOH, 18 °C, 4 h.

is the enamine **11**[8,9] (resulting from Michael addition of methylamine to methyl propiolate) which condenses with **7** to give the 1-aza-3-methoxycarbonylbuta-1,3-diene **12** that, in turn, undergoes cyclodimerisation to the observed product. An analogous sequence starting with amide **10**, and which would have been presumed to involve intermediate **14**,[8] failed to deliver the bis(carboxamide) analogue of compound **13**.

The above-mentioned and ready condensation of **7** with **11**, rather than its participation in an initial Baylis–Hillman reaction with **8**, clearly thwarted attempts to implement the proposed four-component coupling approach to targets (±)-**4** and (±)-**5**. To circumvent such problems, **7** and **8** were subject to a dedicated Baylis–Hillman reaction then an aqueous solution of the resulting 2-(hydroxymethyl)cyclopent-2-enone (**15**)[10] (Scheme 2) was treated with **6** and **9** in the presence of stoichiometric amounts of DABCO. In this manner the unstable ketone (±)-**4** was eventually obtained (*ca*. 20% after *ca*. 5 days). An analogous reaction using propiolamide **10** afforded the more stable congener (±)-**5** (*ca*. 20%). A superior method (40% yield after *ca*. 15 h) for producing (±)-**5** involved treating an ethanolic solution of the acetate **16**, derived from alcohol **15**, with **14**[8] (resulting from Michael addition of methylamine to propiolamide) in the presence of DABCO. Surprisingly, the same reaction when carried out in the absence of DABCO afforded the isomeric hexahydroazaindene (±)-**17** (40%) as the major product of reaction. Similarly, when a THF solution of **16** was treated with **11** in the presence of $(Ph_3P)_4Pd$ the structurally related ester (±)-**18** (*ca*. 20%) was obtained.

Diastereofacially selective reduction of ketone (±)-**5** with L-Selectride® yielded the alcohol (±)-**20** (96%), the readily available acetate derivative, (±)-**21** (63%), of which proved suitable for single-crystal X-ray analysis. Alcohol (±)-**20** was readily coupled with the acid chloride derived from **22** and the resulting diastereomeric mixture of esters was subjected to hydrogenolytic deprotection to produce an inseparable and *ca*. 1 : 1 mixture of **23** and **24**. In an effort to obtain diastereomerically pure samples of these materials several methods for preparing the monochiral forms of ketone **5** were examined but none of the several chiral catalysts that have been used to effect asymmetric Baylis–Hillman reactions[11] proved effective in promoting the enantioselective coupling of **14** and **15**. While various chiral ester derivatives of **15** participated in reaction with **14** to produce ketone **5** in acceptable chemical yield, the observed diastereomeric excesses were disappointing (< 17%). As a consequence, the racemic acetate (±)-**21** was resolved using chiral HPLC techniques (see ESI†). Coupling of each of the enantiopure alcohols with the acid chloride derivative of **22** gave, after hydrogenolytic deprotection, the target molecules **23** [from (−)-**21**] and **24** [from (+)-**21**]. Independent testing of **23** and **24** as inhibitors of *S. aureus*-derived IRS[12] revealed that the former compound shows an IC_{50} of 3.7 μM while the analogous value for the 'unnatural' diastereoisomer **24** is 12.4 μM. Interestingly, this difference in activity is even more pronounced with *S. aureus*-derived LRS (0.42 μM *vs*. no inhibition at 100 μM), *S. aureus*-derived VRS (6.35 μM *vs*. no inhibition at 100 μM) and rat liver IRS (0.57 μM *vs*. 13.5 μM).

We thank GlaxoSmithKline (Australia) Pty Ltd for financial support and Dr Brian Metcalf (formerly of SmithKline Beecham US) for his encouragement and advice. Lucy M. Mensah (GSK, Harlow) is thanked for carrying out the reported enzyme inhibition assays.

Notes and references

1 T. F. Gale, J. Görlitzer, S. W. O'Brien and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2267. For an up-to-date overview of antibiotic resistance see: C. M. Henry, *Chem. Eng. News*, 2000, **78**, 41.

2 A. L. Stefanska, R. Cassels, S. J. Ready and S. R. Warr, *J. Antibiot.*, 2000, **53**, 357; C. S. V. Houge-Frydrych, M. L. Gilpin, P. W. Skett and J. W. Tyler, *J. Antibiot.*, 2000, **53**, 364. For the production and biological evaluation of semi-synthetic analogues of **1** and **2** see: M. G. Banwell, C. F. Crasto, C. J. Easton, A. K. Forrest, T. Karoli, D. R. March, L. Mensah, M. R. Nairn, P. J. O'Hanlon, M. D. Oldham and W. Yue, *Biorg. Med. Chem. Lett.*, 2000, **10**, 2263.

3 A. Takahashi, H. Naganawa, D. Ikeda and Y. Okami, *Tetrahedron*, 1991, **47**, 3621 and references cited therein.

4 A. S. Kende, *Pure Appl. Chem.*, 1997, **69**, 407 and references cited therein.

5 T. Sano, Y. Horiguchi, K. Imafuku and Y. Tsuda, *Chem. Pharm. Bull.*, 1990, **38**, 366; E. W. Baxter, D. Labaree, S. Chao and P. S. Mariano, *J. Org. Chem.*, 1989, **54**, 2893.

6 A. Kamimura, Y. Gunjigake, H. Mitsudera and S. Yokoyama, *Tetrahedron Lett.*, 1998, **39**, 7323 and references cited therein.

7 For examples of related cyclisations see: Y. Özlü, D. E. Cladingboel and P. J. Parsons, *Tetrahedron*, 1994, **50**, 2183.

8 Yu. I. El'natanov and R. G. Kostyanovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 382 (*Chem. Abtsr.*, 1989, **110**, 23303).

9 N. L. Zaichenko, I. I. Chervin, V. N. Voznesenskii, Yu. I. El'natanov and R. G. Kostyanovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 779 (*Chem. Abtsr.*, 1989, **110**, 22952).

10 A. B. Smith III, S. J. Branca, M. A. Guaciaro, P. M. Wovkulich and A. Korn, *Org. Synth.*, 1983, **61**, 65.

11 Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219 and references cited therein.

12 A. J. Pope, M. McVey, K. Fantom and K. J. Moore, *J. Biol. Chem.*, 1998, **273**, 31702 and references cited therein.