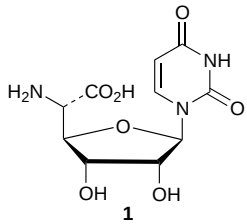
Total synthesis of carbocyclic nikkomycin C

Simon E. Ward,[a] Andrew B. Holmes[a]* and Ray McCague[b]

[a] *University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE*

The carbocyclic analogue 11 of nikkomycin C 1 is prepared by a sequence involving allylic rearrangement of the imino ester adduct 3, palladium-mediated substitution of the allylic lactone 4c with uracil bis(trimethylsilyl)ether 6, and osmylation of the double bond.

The imino Diels–Alder reaction is a versatile tool for the preparation of a variety of natural products.[1–4] As part of a programme to investigate the synthesis of amino acid derivatives, we were interested in elaboration of the azabicyclo-[2.2.1]heptene skeleton *via* acid catalysed rearrangement.[5] We have investigated the scope of these rearrangements, and the palladium catalysed allylic substitutions of the resulting lactones, to prepare cyclopentene amino acid derivatives. The methodology has been exemplified in the synthesis of a carbocyclic nikkomycin analogue.[6,7]



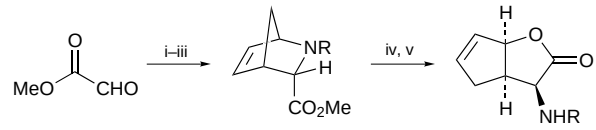
1

The nikkomycins and polyoxins are a family of nucleoside-type antibiotics which exhibit a broad spectrum of biological activity.[8–12] Carbocyclic nucleosides display comparable biological activity to the natural furanose materials, whilst maintaining an inherent stability towards β-glycosidase hydrolysis *in vivo*.[13–15] Our synthesis of a carbocyclic nikkomycin analogue **11** using bicyclic lactones illustrates a general approach to carbocyclic nucleosides.

The required lactone **4** was synthesised from the imino Diels–Alder adduct **3**. The stereochemistry of the amino acid side chain of nikkomycin necessitated use of the *endo* cycloadduct. The *endo* adducts are inherently more difficult to prepare than their *exo* diastereoisomers, since the imines required for the Diels–Alder reactions with unactivated dienes need to be activated by the presence of electron withdrawing groups on the nitrogen terminus. These electron withdrawing groups then appear to exert a greater requirement to adopt the *endo* conformation in the transition state and so give rise to the *exo* adducts. The solution to this problem is to use iminium salts as dienophiles[5] and to effect a resolution to produce enantiomerically pure material.

Cycloaddition of the iminium ion derived from methyl glyoxylate[16] to cyclopentadiene gave the azabicyclo-[2.2.1]heptene **3** (R = H) (Scheme 1). Derivatisation of the nitrogen with an electron withdrawing group [*e.g.* Ts, Bz, BnOCO (Z)] enables the acid-catalysed allylic rearrangement to occur. This is effected in good yield by treatment of the derived carboxylic acids with trifluoroacetic acid to give the lactones **4a**–**c**.

Treatment of the lactones with a variety of palladium(0) reagents effected efficient conversion into the π-allyl palladium complexes. Initial attempts to couple uracil as its sodium salt

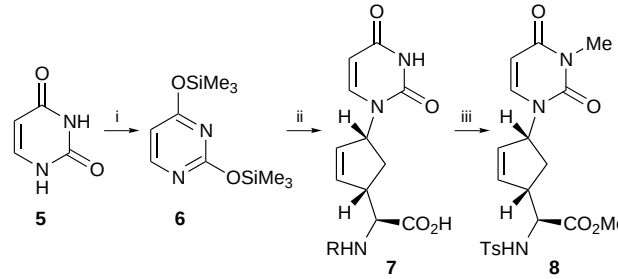


2 **3** **4a** R = Ts **b** R = Bz **c** R = Z

Scheme 1 i, NH_4Cl (aq.); ii, cyclopentadiene; iii, *N*-derivatisation (see text) (70–82% overall); iv, LiOH, H_2O–THF; v, trifluoroacetic acid, CH_2Cl_2 (80–85% overall)

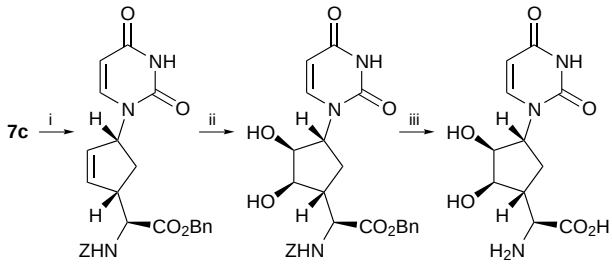
using a palladium-catalysed π-allyl substitution reaction proved fruitless.[17] More positive results were achieved using uracil bis(trimethylsilyl)ether† following the report of Benneche and co-workers for the preparation of a thymidine-substituted cyclopentene (Scheme 2).[18] Treatment of the *N*-tosyl lactone **4a** with tetrakis(triphenylphosphine)palladium(0) in the presence of DIPHOS at 25 °C in acetonitrile gave rise to a moderate yield (31%) of the required substitution product **7** (R = Ts). Somewhat unexpectedly, treatment of this product with (trimethylsilyl) diazomethane[21] gave the dimethylated derivative **8**, where the uracil nitrogen had also been methylated.[22] The uracil substitution reactions can be considerably improved by the use of chlorotrimethylsilane to promote formation of the π-allyl palladium intermediate.[7] It is thought that the function of the chlorotrimethylsilane is to trap the carboxylate species produced during formation of the π-allyl complex, and thus favour this in the equilibrium with the starting lactone. Repetition of the uracil substitution reaction under these conditions with the *N*-benzyloxycarbonyl derivative **4c** afforded the analogous cyclopentene **7c**. Benzylation of **7c** gave the ester **9** from which the protecting groups were later cleaved by hydrogenolysis (Scheme **3**). Dihydroxylation of the alkene **9** afforded an approximately 2 : 1 mixture of the diol **10** and its all-*cis* diastereoisomer. The poor selectivity of cyclopentene dihydroxylations can be rationalised on steric[23] or electronic[24] grounds.[7] Finally, hydrogenolysis of the benzyl protecting groups gave the required target molecule **11** in good yield.‡

In summary, this route has therefore demonstrated a rapid assembly of the nikkomycin skeleton and has further demonstrated the synthetic versatility of cycloadducts of imino Diels–Alder reactions.



5 **6** **7** **8**

Scheme 2 i, HMDS, $(NH_4)_2SO_4$, reflux, 3 h; ii, $Pd(PPh_3)_4$, DIPHOS, **4**, Me_3SiCl, MeCN, (20–55% overall); iii, Me_3SiCHN_2, MeOH, 91% (R = Ts)



Scheme 3 i, BnBr, $NaHCO_3$, DMF, 90%; ii, OsO_4, NMO·H_2O, Bu^{t}OH, THF, 18 h, 52%; iii, H_2 Pd/C, EtOH, 2 h, 95%

We thank the EPSRC and the LINK Asymmetric Synthesis Initiative (Chiroscience Ltd and the Department of Trade and Industry) for financial support, the EPSRC Swansea Mass Spectrometry Service for mass spectrometry data, Dr V. K. Aggarwal for helpful advice and pre-prints of refs. 7*b*,*c* and Professor J. M. Williams and Dr B. Adger for their interest in this work.

Footnotes and References

* E-mail: abh1@cus.cam.ac.uk

† Preparation of the bis(trimethylsilyl)uracil **6** using Vorbrüggen[19] or Cossy[20] methodology was, in our hands, difficult to reproduce consistently. Development of the Benneche protocol using refluxing hexamethyldisilazane with a catalytic quantity of ammonium sulfate gave reproducibly good results, provided the reflux time was prolonged to 3–4 h.

‡ All new compounds exhibited spectroscopic and combustion analysis (or high resolution mass spectrometry) properties in accordance with the assigned structures.

1 S. M. Weinreb, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, ed. L. A. Paquette, p. 401.
2 S. M. Weinreb and P. M. Scola, *Chem. Rev.*, 1989, **89**, 1525.
3 A. B. Holmes, A. Kee, T. Ladduwahetty and D. F. Smith, *J. Chem. Soc., Chem. Commun.*, 1990, 1412.
4 D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press Inc., London, 1987.
5 T. Kobayashi, K. Ono and H. Kato, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 61.
6 H. Baumgartner, C. Marschner, R. Pucher, M. Singer and H. Griengl, *Tetrahedron Lett.*, 1992, **33**, 6443.
7 (*a*) V. K. Aggarwal, N. Monteiro, G. J. Tarver and S. D. Lindell, *J. Org. Chem.*, 1996, **61**, 1192; (*b*) V. K. Aggarwal, N. Monteiro, G. J. Tarver and R. McCague, *J. Org. Chem.*, 1997, **62**, 4665; (*c*) V. K. Aggarwal and N. Monteiro, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2531.
8 H. Hagenmaier, A. Keckeisen, H. Zähner and W. A. König, *Liebigs Ann. Chem.*, 1979, 1494.
9 H. Hagenmaier, A. Keckeisen, W. Dehler, H. P. Fiedler, H. Zähner and W. A. König, *Liebigs Ann. Chem.*, 1981, 1018.
10 W. A. König, W. Hass, W. Dehler, H. P. Fiedler and H. Zähner, *Liebigs Ann. Chem.*, 1980, 622.
11 M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, T. Miyazawa, E. E. Jenkins and J. A. McCloskey, *Tetrahedron*, 1982, **38**, 1599.
12 K. Kobinata, M. Uramoto, M. Nishii, H. Kusakabe, G. Nakamura and K. Isono, *Agric. Biol. Chem.*, 1980, **44**, 1709.
13 A. D. Borthwick and K. Biggadike, *Tetrahedron*, 1992, **48**, 571.
14 L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10 611.
15 V. E. Marquez and M.-I. Lim, *Med. Res. Rev.*, 1986, **6**, 1 (*Chem. Abstr.*, 1986, **104**, 144 017z).
16 J. M. Hook, *Synth. Commun.*, 1984, **14**, 83.
17 F. Liotta, C. R. Unelius, J. Kozak and T. Norin, *Acta Chem. Scand.*, 1992, **46**, 686.
18 L. L. Gundersen, T. Benneche, F. Rise, A. Gogoll and K. Undheim, *Acta Chem. Scand.*, 1992, **46**, 761.
19 H. Vorbrüggen, K. Krolikiewicz and B. Bennau, *Chem. Ber.*, 1981, **114**, 1234.
20 J. Cossy and P. Pale, *Tetrahedron Lett.*, 1987, **28**, 6039.
21 T. Aoyama and T. Shioiri, *Chem. Pharm. Bull.*, 1981, **29**, 3249.
22 M. Jokic and V. J. Skaric, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2225.
23 G. Poli, *Tetrahedron Lett.*, 1989, **30**, 7385.
24 N. Katagiri, Y. Ito, K. Kitano, A. Toyota and C. Kaneko, *Chem. Pharm. Bull.*, 1994, **42**, 2653.

Received in Cambridge, UK, 11th August 1997; 7/05825J