

Total synthesis of carbocyclic nikkomycin C

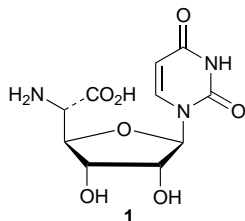
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The carbocyclic analogue **11** of nikkomycin C **1** is prepared by a sequence involving allylic rearrangement of the imino ester adduct **3**, palladium-mediated substitution of the allylic lactone **4c** with uracil bis(trimethylsilyl)ether **6**,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

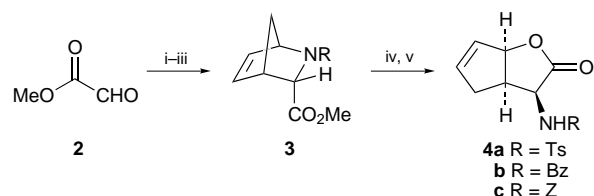


The nikkomycins and polyoxins are a family of nucleoside-type antibiotics which exhibit a broad spectrum of biological activity.^{8–12} Carbocyclic nucleosides display comparable biological activity to the natural furanose materials, whilst maintaining an inherent stability towards β -glycosidase hydrolysis *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 dienophiles⁵ and to effect a resolution to produce enantiomerically pure material.

Cycloaddition of the iminium ion derived from methyl glyoxylate¹⁶ 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**.

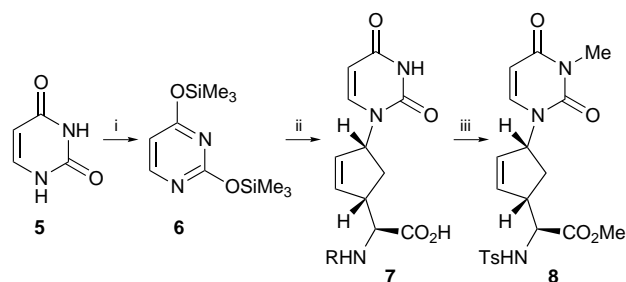
Treatment of the lactones with a variety of palladium(0) reagents effected efficient conversion into the π -allyl palladium complexes. Initial attempts to couple uracil as its sodium salt



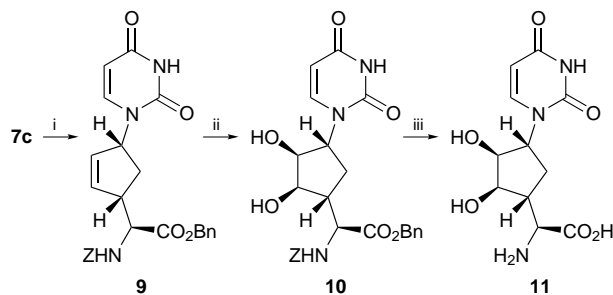
Scheme 1 i, NH_4Cl (aq.); ii, cyclopentadiene; iii, *N*-derivatisation (see text) (70–82% overall); iv, LiOH , H_2O –THF; v, trifluoroacetic acid, CH_2Cl_2 (80–85% overall)

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) diazomethane²¹ 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**. Benzoylation 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 steric²³ or electronic²⁴ 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.



Scheme 2 i, HMDS, $(\text{NH}_4)_2\text{SO}_4$, reflux, 3 h; ii, $\text{Pd}(\text{PPh}_3)_4$, DIPHOS, **4**, Me_3SiCl , MeCN , (20–55% overall); iii, $\text{Me}_3\text{SiCHN}_2$, MeOH , 91% (R = Ts)



Scheme 3 i, BnBr, NaHCO₃, DMF, 90%; ii, OsO₄, NMO·H₂O, Bu^tOH, THF, 18 h, 52%; iii, H₂ Pd/C, EtOH, 2 h, 95%

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Footnotes and References

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† Preparation of the bis(trimethylsilyl)uracil **6** using Vorbrüggen¹⁹ or Cossy²⁰ 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.

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