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SYNTHESIS OF IKARUGAMYCIN: MODEL STUDIES ON A NEW STRATEGY FOR THE CLOSURE OF RING C

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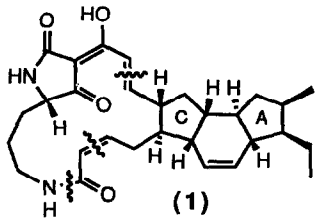
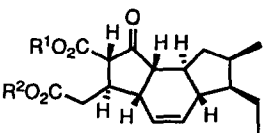
Summary: A new conjugate addition–alkylation approach suitable for the closure of ring C of ikarugamycin is demonstrated by the concise elaboration of a *trans*-disubstituted cyclopentane that has been converted into the cyclopentane analogue of the natural product.

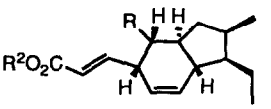
As part of our interest in the tetramic acid natural products,[1] we identified the *as*-hydrindacene (2) as an important synthetic precursor to the unusual macrocyclic lactam ikarugamycin (1), an antiprotozoal metabolite isolated from *Streptomyces phaechromogenes* .[2] Our successful construction of the ring A/B precursor (3a) is based on a stereoselective Michael reaction and Diels-Alder reaction,[3] and we envisaged a second conjugate addition to form ring C from β-ketoester (3b). In practice this reaction under kinetic control gave the alternative O-alkylation and an indeno[4,5-*c*]furan.[3] In consequence we investigated the alternative conjugate addition construction represented by (4);[4] the A/B segment (3c) should be easily available *via* (3d) by modification of our earlier sequence.[5] We report here the application of this strategy to the elaboration of a substituted cyclopentane which constitutes a concise formal synthesis of an ikarugamycin model lacking the A and B rings.[6,7]



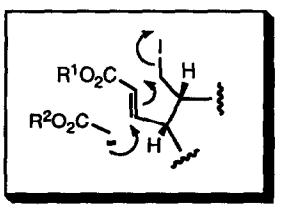
(1)



(2)



(3) a; R= COMe
b; R= $COCH_2CO_2R^1$
c; R= CH_2I
d; R= CO_2Bu^t



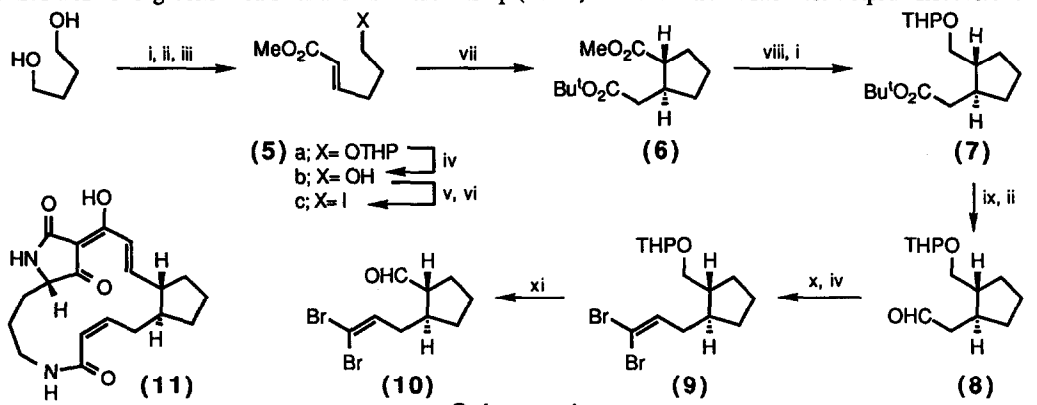
(4)

A suitable ω-iodoester (5c) for the conjugate addition–alkylation reaction was prepared (Scheme 1) from butane-1,4-diol by protection as the mono-THP ether (dihydropyran, PPTS; 48%), oxidation (PCC, NaOAc; 70%) and condensation of the resultant aldehyde with trimethyl phosphonoacetate (K_2CO_3 aq., 20°C; 85%)[8] to afford the ester (5a).[9] Removal of the THP protecting group (MeOH, Amberlite 15; 99%) and conversion of the alcohol (5b) into the tosylate (p-TsCl, pyridine; 84%) followed by treatment with NaI–Me_2CO afforded the iodide (5c) (89%).

Addition of methyl 6-iodohex-2-enoate (5c) to an excess of the lithium enolate of t-butyl acetate ($LiNPr^i_2$,

THF, -78°C) that had been treated with KOBu^t afforded the *trans*-substituted cyclopentane diester (6) as a single diastereoisomer.[4] Selective reduction of the methyl ester ($LiBH_4$, MeOH–Et_2O; 84%)[10] and protection of the alcohol formed (dihydropyran, PPTS; 97%) afforded the THP ether (7). Further reduction of the t-butyl ester ($LiAlH_4$, Et_2O; 92%) and reoxidation (PCC, NaOAc; 72%) led to the aldehyde (8) which was condensed with Ph_3P–CBr_4 at 0°C,[11] followed immediately by cleavage of the THP ether (MeOH, Amberlite 15) to afford the alcohol (9) (32% overall). Oxidation of (9) (PDC, CH_2Cl_2, molecular sieves, AcOH)[12] gave the *trans*-substituted cyclopentane-aldehyde (10),[13] which has been converted into the cyclopentane analogue (11) of ikarugamycin.[6] This constitutes a much shorter synthesis of (10), and hence of the macrocyclic tetramic acid (11), than that reported.

We have therefore demonstrated the success of the conjugate addition–alkylation approach and its convergence with proven methodology for elaboration of the macrocyclic ring of ikarugamycin. We thank SERC and ICI Agrochemicals for a CASE studentship (R.F.J.) and Dr. M.J. Bushell for helpful discussions.



Scheme 1

Reagents: i, dihydropyran, PPTS; ii, PCC, NaOAc; iii, $(MeO)_2P(O)CH_2CO_2Me$, K_2CO_3 aq.; iv, MeOH, Amberlite 15; v, p-TsCl, pyridine; vi, NaI, Me_2CO; vii, $LiCH_2CO_2Bu^t$, KOBu^t; viii, $LiBH_4$, MeOH–Et_2O; ix, $LiAlH_4$, Et_2O; x, Ph_3P, CBr_4; xi, PDC, CH_2Cl_2, 3Å molecular sieves, AcOH.

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11. E.J. Corey and P.L. Fuchs, *Tetrahedron Lett.*, 1972, **36**, 3769. The major by-product is conversion of the THP ether directly to the bromide; preliminary findings show that this may be prevented by working at -25°C.
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13. Selected data: ν_{max} 1740 and 1620 cm^{-1}; δ_H ($CDCl_3$) 2.4 (1H, dddd, C*H*CHO), 6.4 (1H, t, CH=CBr_2), and 9.6 (1H, d, *J* 3Hz, CHO); δ_C ($CDCl_3$) 202.8, 136.8, and 90.3; identical with data for material reported in ref. 6; we thank Professor R.K. Boeckman for this information. Aldehyde (10) is unstable and is best converted into its dimethyl acetal for storage.

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