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SYNTHESIS OF IKARUGAMYCIN: STUDIES ON THE CARBOTRICYCLIC SUB-UNIT

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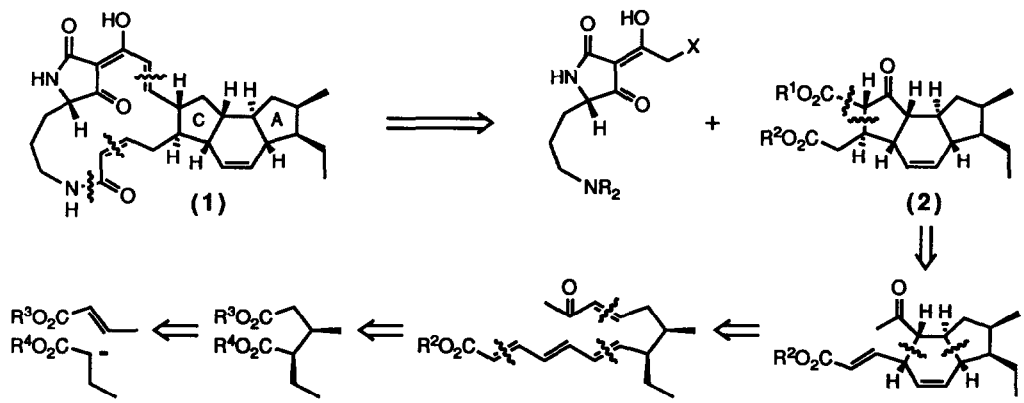
Summary: A hexahydroindane precursor to the *as*-hydrindacene portion of ikarugamycin is prepared by a stereoselective Michael reaction–Diels-Alder reaction sequence; a second Michael reaction in the desalkyl series produces an indeno[4,5-*c*]furan isomer of the *as*-hydrindacene carbotricycle.

The most structurally unusual natural products in the 3-acyltetramic acid group are ikarugamycin (1) and its congener capsimycin.[1] Both contain a 3-acyltetramic acid sub-unit embedded in a macrocyclic lactam fused to a unique non-terpenoid carbotricyclic system, an *as*-hydrindacene. Ikarugamycin has anti-protozoal properties whilst capsimycin displays antifungal activity. During our programme in the tetramic acid area,[2] we are examining a total synthesis of of ikarugamycin. The strategy, outlined in Scheme 1, envisaged connections at the tetramic acid 3-enoyl function[2b,3] and at the lactam bond as the construction for the 16-membered macrocycle; further disconnection at the *Z*-double bond and functional group interconversion leads to the key intermediate (2). Our plan entailed assembly of (2) by a Michael reaction–Diels-Alder reaction–Michael reaction approach (Scheme 1).[4] We report the realisation of the first two parts of this sequence, and the results of a second Michael reaction in a desalkyl series to produce the indeno[4,5-*c*]furan isomer of (and potential precursor to) the *as*-hydrindacene unit of (2).

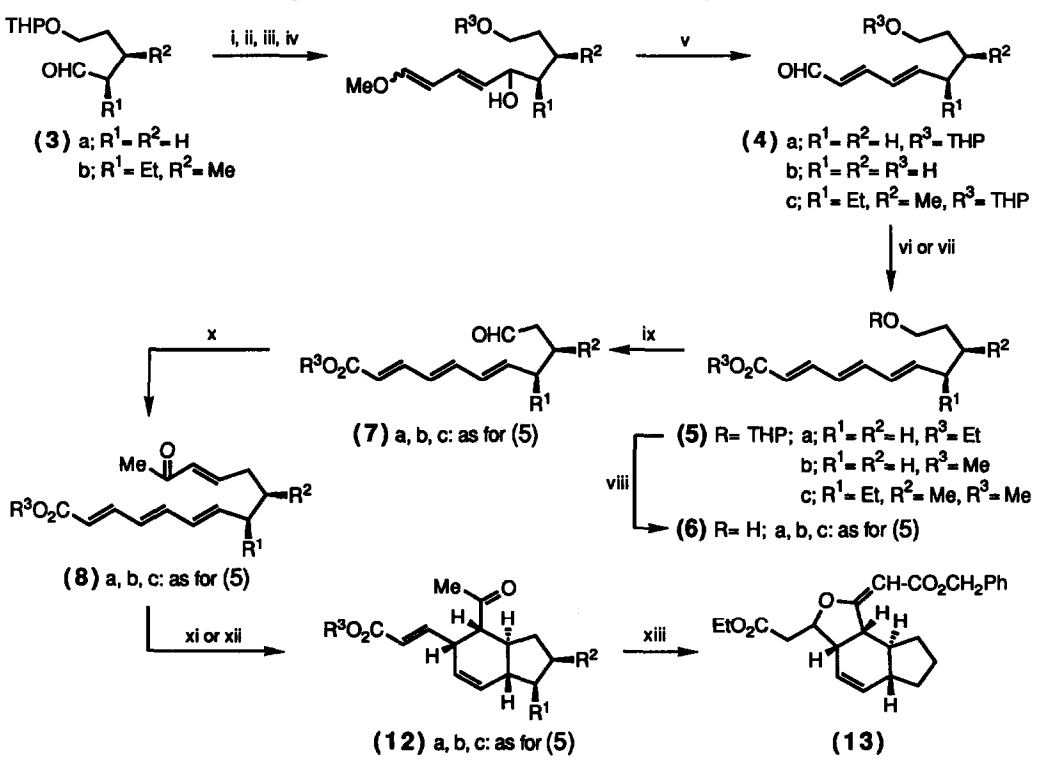


Scheme 1

We first investigated the construction sequence in the ring A-unsubstituted series. Thus pentane-1,5-diol was protected as the mono-THP ether and oxidised to aldehyde (3a) [i, dihydropyran, PPTS (0.1 mol equiv.); 60%: ii, PCC, NaOAc; 78%]. The diene portion was elaborated (Scheme 2) by addition of the lithio-derivative of (*Z*)-1-methoxybut-1-en-3-yne (BuLi, THF, -78°C) to aldehyde (3a) followed by sequential addition of ethanol, $LiAlH_4$, and 1M hydrochloric acid;[5] treatment of the intermediate methoxydienol under mild acidic conditions [THF: H_2O (95:5), p-TsOH (0.04 mol equiv.)] led to the dienal (4a) [43% from (3a)].[6,7] The triene

esters (5a,b) were formed by condensation of (4a) with carboethoxy- and carbomethoxy-methylenetriphenylphosphoranes (toluene, reflux), or with trimethyl phosphonoacetate (K_2CO_3 aq., 20°C)[8] (73, 73, and 80%, respectively). The THP ether was efficiently removed (Amberlite 15, MeOH) to afford alcohols (6a,b) (90, 81%) which were oxidised (PCC, NaOAc) to the aldehydes (7a,b) (61, 82%). Alcohol (6b) was also prepared from 2,3-dihydropyran by hydration to 2-hydroxytetrahydropyran[9] and chain extension with (*Z*)-1-methoxy-but-1-en-3-yne as above to give the hydroxydienal (4b) (51%). Condensation of (4b) with carbomethoxy-methylenetriphenylphosphorane (toluene, reflux) gave (6b) in a less efficient reaction (44%) than from (4a). The triene-ester aldehydes (7a,b) were condensed with dimethyl (2-oxopropyl)phosphonate under mild conditions (K_2CO_3 aq., 20°C) to assemble the dienophile unit and complete construction of the cycloaddition substrates (8a,b) (81, 79%), isolated as the all-*E* isomers.

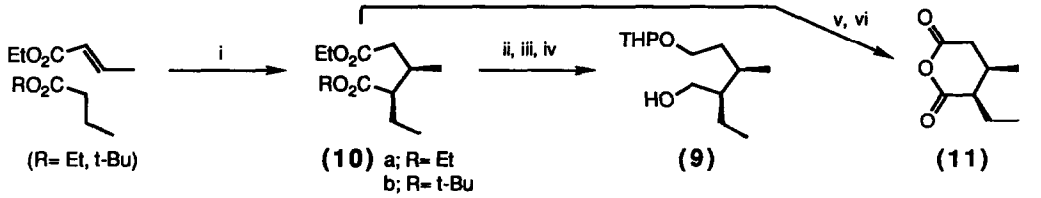
Extension of this methodology to the series substituted in ring A required a route to the *erythro*-2-ethyl-3-methylpentane-1,5-diol derivative (9) based on the diastereoselective Michael addition of a butyrate enolate to a but-2-enoate ester (Scheme 3).[10] Thus ethyl and t-butyl butyrates as their *Z*-enolates[11] [LDA, THF-HMPA (4:1), -78°C] were treated with ethyl but-2-enoate at -78°C to give predominantly the *erythro*-2-ethyl-3-methylglutarates (10a) (65%, >20;1 *erythro: threo* by ^{13}C n.m.r. spectroscopy) and (10b) (97%, 5:1 *erythro: threo*). The stereochemical assignments for (10a,b)[10a,12] were confirmed by conversion of the diesters to the



Scheme 2

Reagents: i, (*Z*)-MeOCH=CHC≡CLi, THF, -78°C; ii, EtOH; iii, $LiAlH_4$; iv, 1M HCl aq.; v, p-TsOH, THF aq.; vi, Ph_3PCHCO_2Et or Ph_3PCHCO_2Me, toluene, reflux; vii, $(MeO)_2P(O)CH_2CO_2Me$, K_2CO_3 aq., 20°C; viii, Amberlite 15, MeOH; ix, PCC, NaOAc; x, $(MeO)_2P(O)CH_2COMe$, K_2CO_3 aq., 20°C; xi, toluene, reflux; xii, Et_2AlCl, CH_2Cl_2, 20°C; xiii, LDA, THF-HMPA, -78°C, $PhCH_2OCOCN$, 10 min.

corresponding glutaric anhydride, i.e. predominantly *cis*-isomer (11) [i, from (10a): KOH, MeOH aq.; 56%; from (10b): p-TsOH, C_6H_6, reflux; 79%; then KOH, MeOH aq.; 62%; ii, Ac_2O, reflux; 81% in each series]. The diastereoisomer mixture containing (10b) was carried forward without separation. The less hindered ethyl ester was reduced chemoselectively[13] [$LiBH_4$, MeOH (1 mol equiv.), Et_2O; 83%], the alcohol protected [dihydropyran, PPTS (0.25 mol equiv.); 93%] and the t-butyl ester reduced ($LiAlH_4$, Et_2O, reflux; 93%) to afford THP-alcohol (9). The sequence developed for protected pentanediol was now applied (Scheme 2). Oxidation to the aldehyde (3b) (89%), four-carbon chain extension with the methoxybutenyne to produce the dienal (4c) (58%) and condensation with carbomethoxymethylenetriphenylphosphorane (toluene, reflux; 73%) or trimethyl phosphonoacetate (K_2CO_3 aq., 20°C; 82%) afforded the triene ester (5c). Removal of the THP group to give (6c) (Amberlite 15, MeOH; 98%) followed by oxidation (PCC, NaOAc; 93%) gave the aldehyde (7c) from which the cycloaddition substrate (8c) was assembled [dimethyl (2-oxopropyl)phosphonate, K_2CO_3 aq., 20°C; 82%]. The ratio of diastereoisomers (5:1 *erythro: threo*) was unchanged throughout this sequence.



Scheme 3

Reagents: i, LDA, THF-HMPA, -78°C; ii, $LiBH_4$, MeOH-Et_2O; iii, dihydropyran, PPTS; iv, $LiAlH_4$, Et_2O; v, from (10a): KOH, MeOH aq.; from (10b): p-TsOH, C_6H_6, reflux; then KOH, MeOH aq.; vi, Ac_2O, reflux.

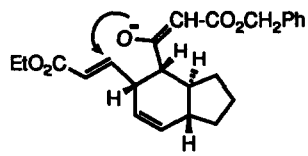
The tetraenes (8a-c) underwent cycloaddition either thermally (0.05M in toluene, reflux 20-24h) or with Lewis-acid catalysis (Et_2AlCl, CH_2Cl_2, 20°C, 18h)[14] to produce the hexahydroindanes (12a-c) as single pure diastereoisomers after one crystallisation in acceptable yields: (12a) 67% thermally, 63% with Et_2AlCl; (12b) 70 and 61%; (12c) 51 and 43%. The Lewis-acid procedure, although milder, was less efficient, producing some tetraene polymerisation; the reduced yields of (12c) relative to (12a,b) are attributed to a separation at this stage of the 5:1 mixture of *erythro-* and *threo*-arrangements of ring A substituents (see above).

The endo-diastereoselectivity of these cycloadditions is well precedented[14,15] and supported by our spectral data,[7] e.g. δ_H for C*H*COMe: (12a) 2.87 (1H, dd, *J* 11.3 and 6.2 Hz); (12b) 2.88 (1H, dd, *J* 11 and 6.2 Hz); (12c) 2.85 (1H, dd, *J* 11.2 and 6.3 Hz), representing one 'axial-axial' and one 'axial-equatorial' coupling, not available from any other cycloaddition geometry. The stereochemistry of the ring A substituents relative to the bridgehead hydrogens has been rationalised and is observed in related cycloadditions.[4a,b,15]

The final part of our strategy towards the intermediate (2) called for elaboration of bicycles (12) from a ketone to a β-ketoester and an intramolecular Michael addition to form ring C. C-Acylation of the ketone (12a) was envisaged with a cyanoformate;[16] in the event, treatment of the enolate of (12a) [$LiNPr^i_2$, THF, HMPA (1 mol equiv.), -78°C, 10 min] with benzyl cyanoformate led to the isolation of a single tricyclic compound (76%) characterised as the octahydroindeno[4,5-*c*]furan (13).[7] The β-ketoester from C-acylation is thus undergoing *in situ* ring closure of its enolate *via* conjugate addition of the keto oxygen atom in a 5-exo-trig manner (14). This is isomeric with the desired ring closure through carbon, which may be regarded as a 5-(enol-exo)-exo-trig (15) or a 5-(enol-endo)-exo-trig (16) process,[17] and must be kinetically less favourable.

We have therefore realised the first two parts (conjugate addition–cycloaddition) of our strategy and

demonstrated that the final conjugate addition takes an alternative kinetic pathway to provide a heterocyclic isomer of the desired carbotricycle. We are pursuing the use of the indenofuran as a precursor to the required framework.[18] We thank SERC and ICI Agrochemicals for a CASE studentship (R.F.J.) and Dr. M.J. Bushell for helpful discussions.



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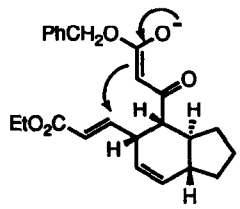

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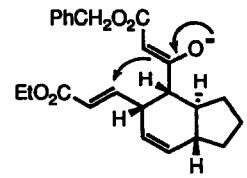

(16)

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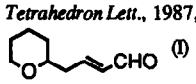

(I)

7. All new compounds gave spectral data (i.r., u.v., n.m.r., m.s.) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. Selected data: (**12a**) m.p. 112°C; δ_H ($CDCl_3$) 1.05 and 1.2 (each 1H, m, $CH_2CH_2CH_2$), 1.25 (3H, t, *J* 7Hz, CO_2CH_2Me), 1.65-1.9 (5H, m, 2xCH_2CH, CH), 2.05 (1H, m, CH), 2.1 (3H, s, COMe), 2.87 (1H, dd, *J* 11.3 and 6.2 Hz, CHCOMe), 3.42 (1H, m, CHCHCHCO$_2$Et), 4.15 (2H, q, *J* 7 Hz, CO_2CH_2Me), 5.37 (1H, ddd, *J* 9.7, 4.2, and 2.7 Hz, CH=CH), 5.79 (1H, dd, *J* 15.5 and 0.9 Hz, CHCO$_2$Et), 6.02 (1H, d, *J* 9.7 Hz, CH=CH), and 6.7 (1H, dd, *J* 15.5 and 9.1 Hz, CHCHCO$_2$Et); (**12b**) m.p. 90-92°C; (**12c**) m.p. 141-143°C; (**13**) (isolated as a single diastereoisomer; the C=C geometry is not yet known) m.p. 112-114°C; δ_H ($CDCl_3$) 1.2 (2H, m, CH_2), 1.25 (3H, t, *J* 7.1 Hz, CO_2CH_2Me), 1.45 (1H, m, CH), 1.72 (2H, m, CH_2), 1.92 (3H, m, CH, CH_2), 2.68 (1H, m, CH), 2.76 (1H, dd, *J* 15.1 and 5.5 Hz, CHHCO$_2$Et), 2.83 (1H, dd, *J* 11.6 and 7.5 Hz, CH), 2.89 (1H, dd, *J* 15.1 and 6.7 Hz, CHHCO$_2$Et), 4.15 (2H, q, *J* 7.1 Hz, CO_2CH_2Me), 4.63 (1H, ddd, *J* 10, 5.5, and 6.7 Hz, CH=CO), 4.9 (1H, s, CHCO$_2$CH$_2$Ph), 5.13 (2H, s, CH_2Ph), 5.52 (1H, dt, *J* 9.8 and 3 Hz, CH=CH), 6.04 (1H, d, *J* 9.8 Hz, CH=CH), and 7.35 (5H, m, Ar).
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12. The ^1H and ^{13}C n.m.r. data were compared with a sample prepared from ethyl cyanoacetate and ethyl but-2-enoate (cf. H.R. Snyder and R.E. Putnam, *J. Am. Chem. Soc.*, 1954, **76**, 33) as a 1:2 mixture of *cis*-(11) and *trans*-anhydride isomers separable by h.p.l.c.; crystallisation of diacid from this route gave a pure sample of the *threo*-acid and hence of the *trans*-anhydride. Our data for the diacid and anhydride isomers agree with that reported [Snyder and Putnam (see above); S. Ito and Y. Hirata, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 672]; additionally n.O.e. enhancements between H-2 and H-3 were observed in *cis*-(11) that were absent in the *trans*-anhydride.
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18. Preliminary experiments indicate that under thermodynamic control (-30°C, 3h) the formation of furan (13) is reversible and material tentatively identified as a ring A unsubstituted analogue of (2) is obtained.

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