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A VERSATILE SYNTHESIS OF CARBAPENEMS FROM SUBSTITUTED DIHYDROPYRANS

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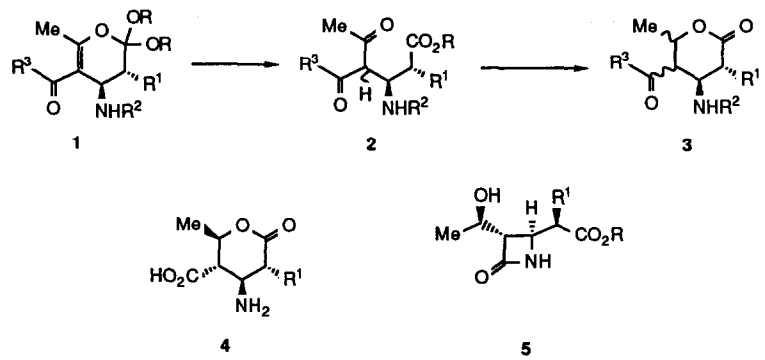
Abstract : Dihydropyrans (1) are converted by hydrolysis and reduction to δ-lactones (3), and then to azetidinones (5) which are key intermediates for the synthesis of carbapenems.

In the preceding paper[1] we described an inverse electron demand Diels-Alder reaction between 2-acylamino methylene-3-oxobutanoic acid derivatives and ketene acetals leading to dihydropyrans (1)[2]. Here we describe their conversion, via the ketoesters (2), to the δ-lactones (3) and the azetidinones (5).



Attempts to convert the dihydropyrans (1) directly to the δ-lactones (3) were not successful, the double bond proving to be remarkably inert to a variety of reducing agents[3]. However, hydrolysis of (1) in THF/dilute HCl produced derivatives of 5-oxohexanoic acid (2) in high yield (Table 1). These were mixtures of interconvertible isomers at C-4, which were easily detectable by ^{1}H-NMR, the C-4 protons giving characteristic doublets at δ 3.81 and δ 3.86 ($CDCl_3$). In CCl_4 the isomer ratio of (2a) was 7:3, but this changed to 1:1 in DMSO.

Table 1 (Ketoesters, 2)

Example	R	R^1	R^2	R^3	m.p.°C
a	Et	Me	COMe	OMe	93–6
b	Et	Me	COMe	HN–Ph–pCl	169–73
c	Et	Me	COMe	(S)–HNCH(Me)Ph	176–80*
d	Et	Me	COMe	(R)–HNCH(Me)Ph	175–8*
e	Et	Me	CO_2CH_2Ph	OMe	50–53
f	Et	Me	CO_2CH_2Ph	OCH_2Ph	N.I.+
g	Et	Me	$COCH_2Cl$	OMe	88–90
h	Me	H	COMe	OMe	N.I.+

* (2c) is the 2S,3S enantiomer and (2d) is the 2R,3R enantiomer.

+ N.I. – not isolated, reaction mixture carried through to next step.

When the reductions of the ketoesters (2) to the secondary alcohols were investigated, it was observed that spontaneous cyclisation to the δ–lactones (3) occurred under acidic conditions; when basic conditions were used, cyclisation took place following an acidic work–up. In the reduction of (2a), the four possible racemic diastereoisomers were separated by chromatography and characterised by NMR and X–ray analyses[4]. The required stereochemistry of (3) is 3,4–trans, 4,5–trans, 5,6–trans (ttt) and the other isomers are designated (ttc), (tcc) and (tct) for convenience. Many reducing agents were tried[5], but the best results were obtained by "ionic hydrogenation" using Et_3SiH/TFA which gave predominantly the (ttt) isomer (Table 2). The ratios af the isomers in the crude reaction mixtures were determined by NMR; in large scale preparations the required (ttt) isomer of (3a) could be separated by crystallisation from ethyl acetate. With example (3b) the Et_3SiH/TFA conditions gave (ttt) isomer in 70% isolated yield. In the chiral examples (3c) and (3d) the (ttt) enantiomers (3S,4S, 5R, 6S and 3R, 4R, 5S, 6R respectively) were the major products and were easily isolated in 50% yield by crystallisation.

Table 2 (δ–lactones, 3)

Example	R^1	R^2	R^3	m.p.°C
a	Me	COMe	OMe	155–6
b	Me	COMe	HN–Ph–pCl	280–d
c	Me	COMe	(S)–HNCH(Me)Ph	320–d*
d	Me	COMe	(R)–HNCH(Me)Ph	315–d*
e	Me	CO_2CH_2Ph	OMe	145–6
f	Me	CO_2CH_2Ph	OCH_2Ph	110–2
g	Me	$COCH_2Cl$	OMe	140–1
h	H	COMe	OMe	135–6+

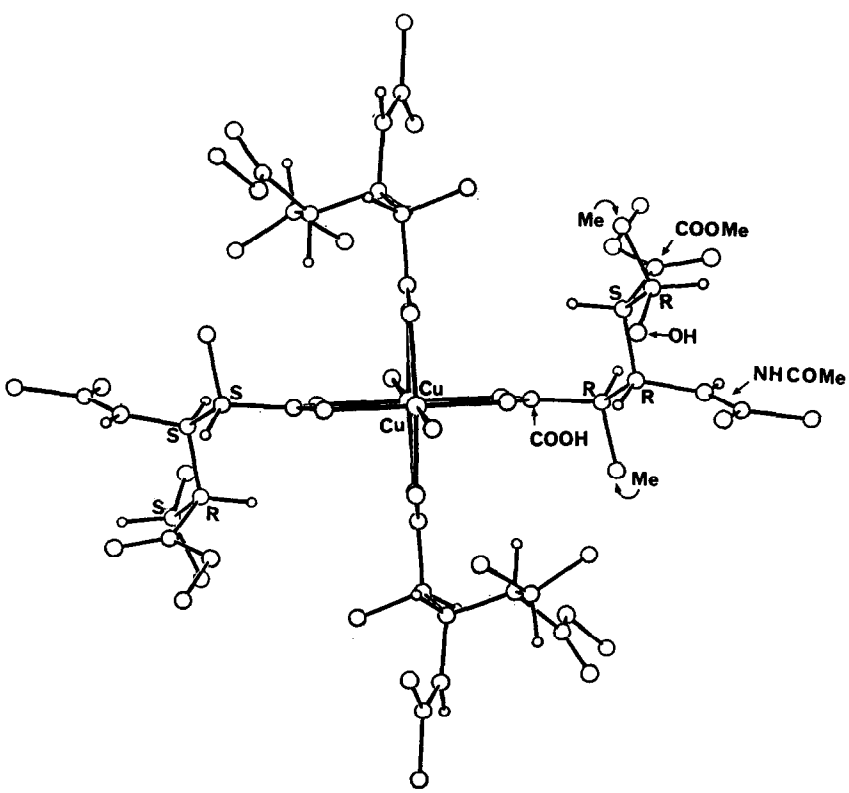
* (3c) is the 3S,4S, 5R, 6S enantiomer and (3d) is the 3R,4R, 5S, 6R enantiomer.

+ (3h) is the 4,5–trans, 5,6–trans isomer.

The protecting groups of compounds (3) in Table 2 were removed under different conditions giving the amino-acids (4, R^1=Me or H). Refluxing 6N HCl was required to deprotect (3a) and, although some epimerisation occurred at the C-3 methyl group, the required amino-acid lactone (4, R^1=Me), crystallised from the cooled reaction in 40% yield as the hydrochloride salt[6]. For the deprotection of the bisamides (examples 3b, 3c, 3d) refluxing 10N HCl was required; some epimerisation at C-3 again took place and the product was isolated in 20-30% yield. However, examples (3e) and (3f) were easily deprotected in almost quantitative yield, (3e) with 6N HCl at room temperature[7] and (3f) by hydrogenation Example (3h), an intermediate for thienamycin and its congeners, lacks the C-3 methyl group, so that epimerisation was not a problem during the deprotection step in refluxing 6N HCl (71% yield)

The amino-acid (4, R^1=Me), was converted to the azetidinone esters (5, R^1=Me), by standard procedures of alcoholysis followed by teatment with Et_3N/DCCI[7]. These azetidinones, building blocks for 1-methyl thienamycin analogues, can thus be obtained in a convenient five step process from readily available intermediates. The methodology used has the obvious potential to produce a wide variety of chiral carbapenems carrying substituents in the 1 and 6 positions.

Acknowledgements: We thank Brian Wright and Howard Beeley for NMR spectra and for help with interpretation, and Dr Mary McPartlin of North London Polytechnic for all X-ray data.



REFERENCES AND NOTES:

1. Previous communication
2. European Patent, EP 230771
3. Hydrogenation over palladium or platinum catalysts was very slow, and the starting material was recovered from reactions using:
   i) DIBAL, ii) Mg/MeOH, iii) $NaBH_4$/Te, iv) BH_3/THF, v) $NaBH_4/Ce^{4+}$

4. NMR data: ($CDCl_3$)

(ttt) mp 155–6°C
δ 1.38 (d,3H), 1.39 (d,3H), 1.98 (s,3H), 2.64 (dq,1H) 2.79 (dd,1H), 3.73 (s,3H), 4.26 (ddd,1H), 4.58 (d,1H), 6.00 (d.1H) chair conformation (NOE)
(ttt) mp 109–10°C
δ 1.30 (d,3H), 1.39 (d,3H), 2.01 (s,3H), 3.07 (dd,1H), 3.08 (dq, 1H), 3.76 (s,3H), 3.80 (ddd,1H), 4.98 (dq,1H), 6.10 (d,1H) boat conformation (NOE)
(tcc) mp 214–5°C
δ 1.36 (d,3H), 1.41 (d,3H), 2.00 (s,3H), 2.97 (dq,1H) 3.22 (dd,1H), 3.75 (s,3H), 4.19 (ddd,1H), 4.62 (dq,1H) 6.40 (d,1H) chair conformation (NOE)
(tct) mp 128–9°C
δ 1.18 (d,3H), 1.42 (d,3H), 2.00 (s,3H), 2.62 (dd,1H) 2.99 (dq,1H), 3.77 (s,3H), 4.53 (dq,1H), 4.81 (ddd,1H) 6.54 (d,1H) chair conformation (NOE)

The thin crystals of (ttt) isomer were not suitable for X-ray analysis, but hydrolysis of the lactone with copper acetate gave turquoise rhombs whose crystal structure is shown on the previous page. It is a dimeric copper (II) salt containing two pairs of enantiomeric 5-hydroxy hexanoic acid derivatives, whose stereo-chemistry can be related back to the (ttt) isomers.

5. For example i) $NaBH_4$, ii) $NaBH_4$/HOAC, iii) $NaBH_4$/tartaric acid, iv) $Zn(BH_4)_2$, v) $NaBH_3CN$, vi) $BH_3.HNPr_2$/$Mg(CO_2CF_3)_2$

6. NMR (d_6-DMSO)
   1.35 (d,3H), 1.39 (d,3H), 2.88 (dd,1H), 2.93 (dq,1H) 3.66 (dd,1H), 4.56 (dq,1H), 8.7 (broad, 1H).

7. Hatanaka made (3e) by a different route and performed the deprotection in high yield · M.Hatanaka, Tetrahedron Lett. 28, 83 (1987)

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