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ENANTIOSPECIFIC SYNTHESIS OF L-(3R AND 3S)-(β–D-RIBOFURANOSYL)-PYROGLUTAMIC ACIDS: POSSIBLE INTERMEDIATES IN C-NUCLEOSIDE BIOSYNTHESIS

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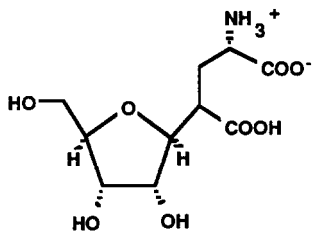
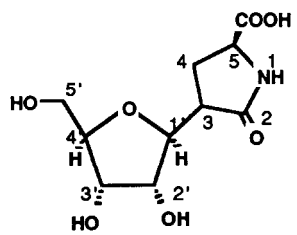
Summary: The stereospecific addition of a glycine anion equivalent to a β–ribosyl acrylate is the key step in the enantiospecific synthesis of L-3-(β-D-ribofuranosyl)-pyroglutamic acids, possible intermediates in C-nucleoside biosynthesis.

The C-nucleosides are an important class of natural product with a wide variey of interesting biological acivities which may arise from structural similarity to nucleosides.[1] However, the biosynthetic origins of the C-nucleosides[2] are markedly different from those of the nucleosides.[3] For all of the most-studied natural C-nucleosides (formycin, showdomycin, pyrazofurin, and oxazinomycin) D-ribose and either L-glutamic or pyroglutamic acid have been shown to be common precursors.[4] Furthermore, the carbon atom which becomes directly bonded to C-1' of the ribose unit has always been derived from C-4 of the glutamate precursor. Not surprisingly, it has been suggested that there might be a common intermediate (1) or (2) in the biosynthesis of all naturally-occurring C-nucleosides.[5] Such an intermediate would be an interesting and important compound, so we have developed an enantiospecific synthesis of these compounds which should be useful for further biological studies.



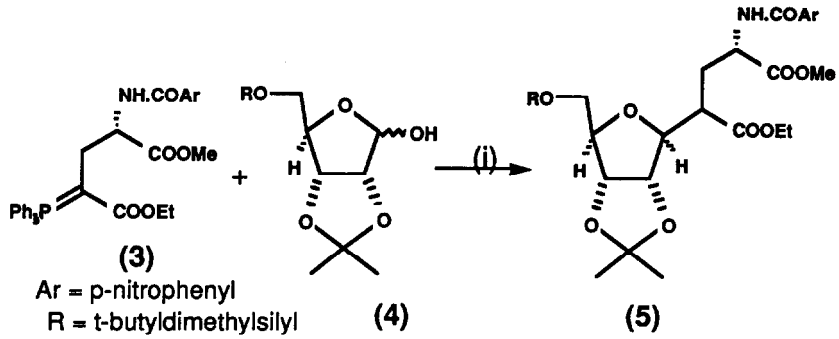
(1)



(2)

The central problem in C-nucleoside synthesis is the formation of a carbon-carbon bond from C-1' of the ribose unit with the required β–configuration (called β because of the similarity of these compounds to β-nucleosides). Many syntheses are therefore based on the elaboration of a simple C-1' functionalised ribose. It is only recently that more convergent approaches have been used.[6] Regrettably, our attempt at such an approach using reaction of our recently-described ylide 2S- N-(4-nitrobenzoyl)-4-triphenylphosphoranylidene-glutamic acid α-methyl-γ-ethyl ester (3)[7] with suitably

protected ribose, *e.g.*(**4**), gave insufficient yields of the required coupling product (**5**) (approximately 25%), (Scheme 1). Other direct approaches to (**1**) based on the known selective alkylation[8] at C-4 of N-trityl protected L-glutamic acids were also unsuccessful.

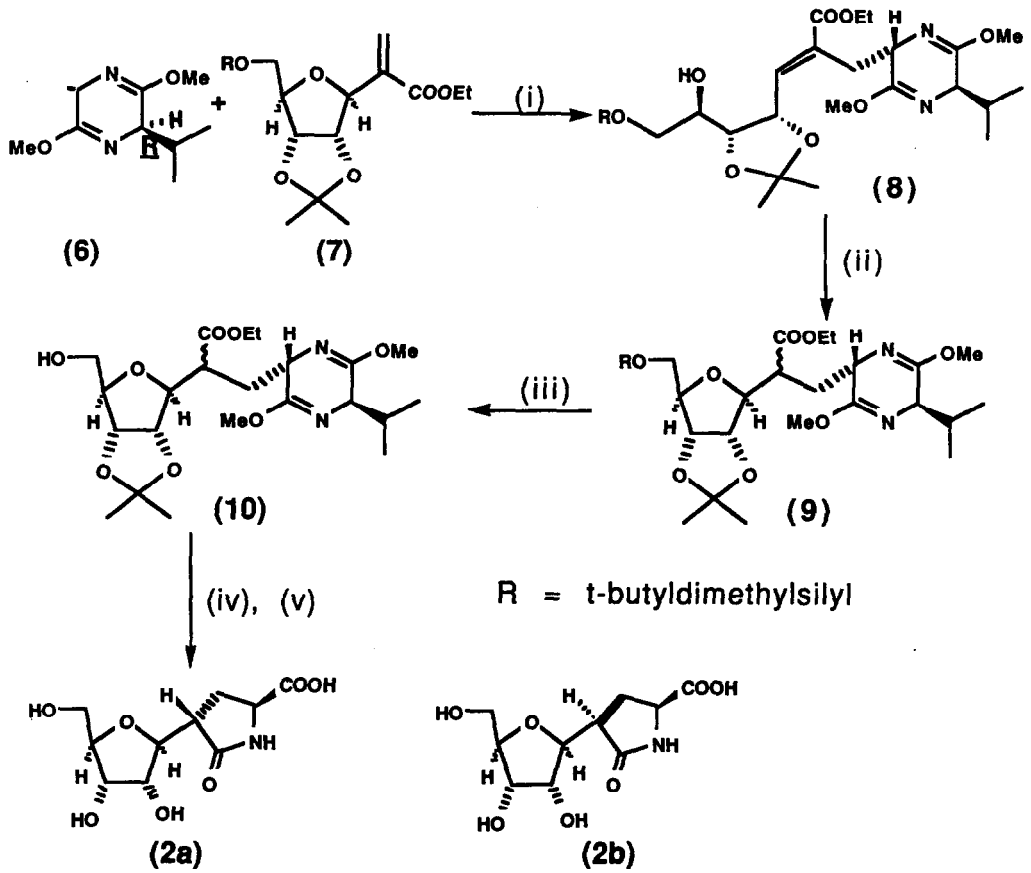


Scheme 1 (i) Toluene, reflux, 24h.

Successful synthesis of the target molecules was achieved via addition of Schollkopf's glycine anion equivalent (**6**)[9] to the known ribosyl acrylate (**7**)[10] (53%), (Scheme 2). The product of this reaction was the sole coupling product detected by ^{1}H n.m.r. (500 MHz) and was obtained (to the limits of our detection) as a single geometric and stereoisomer (**8**). This stereoselectivity thus matches that recently described for the same reaction performed on methyl acrylate.[11] Base catalysed ring-closure of this intermediate to a 1:1 mixture of furanose compounds (**9**) was highly stereoselective (greater than 20:1 β to α).[12] The products were both assigned as the required β-isomers on the basis of the ^{13}C n.m.r. spectrum, which contained resonances for the isopropylidene methyl groups at 25.57, 25.60, 27.43, and 27.50 p.p.m., well within the ranges typical for compounds possessing the β-configuration.[13] The remaining deprotection steps were routine, and gave the target molecule (**2**) as a 1:1 mixture of isomers at the C-3 position. Final purification and separation of the isomers was achieved by h.p.l.c. (reverse phase ODS column, 0.1% HCOOH in water), which gave (**2a**) and (**2b**) in a 23% combined yield from precursor (**6**).

Both isomers of (**2**) were identified as being in the pyroglutamate form by positive argon fast atom bombardment mass spectroscopy, which showed strong molecular ions at *m/z* 262 (*M*H$^+$, 15% relative to 118), and full structural assignment was performed by ^{1}H n.m.r. spectroscopy. Individual resonances were readily assigned (Table 1), and the stereochemistries were determined by nOe difference spectroscopy. For both compounds the H-2' resonances were enhanced on irradiation at H-3 (approximately 5% in each case), while for (**2b**) a similar enhancement of H-3' was also observed. These results strongly support the assignment of the β configuration to both products. For compound (**2b**), irradiation of the H-5 resonance enhanced the low field H-4 resonance (δ 2.78)(7%) and the H-3 resonance (3%), but not the high field H-4 resonance (δ 2.10). Irradiation of the high field H-4 resonance enhanced only the low field H-4 resonance (19%). However, irradiation of the low field H-4 resonance enhanced the high field H-4 resonance (25%) and the H-5 resonance (13%). These results clearly indicated a *cis* arrangement of the carboxyl and ribofuranosyl substituents about the pyrrolidinone ring. Similar experiments for (**2a**) indicated a *trans*

arrangement. Assuming that the configurations at C-5 were not changed from those in (**9**), the absolute configurations were assigned as (3S,5S) for (**2a**) and (3R,5S) for (**2b**).



Scheme 2 (i) THF, -78°C, 4h, then AcOH (1 equivalent), quench. (ii) cat. DBU, CH_3CN, reflux, 20h. (iii) $^nBu_4N^+F^-$, THF, RT, 1h. (iv) aq. HCl (0.25 N), RT, 2d. (v) aq. LiOH (2 equivalents), RT, 4h.

In an attempt to prevent formation of the lactam (**2**), alkaline hydrolysis of the ethyl ester (**10**) was carried out prior to the final deprotection steps (iv) and (v) (Scheme 2). Although ^1H n.m.r. spectroscopy of the crude products showed that this was successful, cyclisation occurred when purification was attempted by h.p.l.c. (pH 6). Hence the original target molecules (**1**) were never obtained in pure form. This behaviour has been noted previously for substituted glutamic acids.[14]

In summary we have developed a high-yielding synthesis of ribosyl lactams (2) which are possible intermediates in C-nucleoside bosynthesis. This synthesis should prove useful when further biological studies are performed.

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Table 1. ^{1}H n.m.r. assignments (500 MHz, D_2O, pH *ca.* 7, $Me_3SiCD_2CD_2COONa$ 0.00 p.p.m.) for (2a,b)(δ p.p.m./Hz)

	(2a)	(2b)
1'-H	4.17 (dd, 3.0, 7.0)	3.98 (dd, 5.0, 5.5)
2'-H	3.97 (dd, 4.0, 7.0)	4.26 (dd, 5.5, 5.5)
3'-H	4.04 (dd, 4.0, 5.5)	4.03 (dd, 5.5, 5.5)
4'-H	3.91 (ddd, 3.0, 5.0, 5.5)	3.85 (ddd, 3.0, 5.0, 5.5)
5'-H	3.65 (ABX, 5.0, 12.5)	3.59 (ABX, 5.0, 12.5)
	3.73 (ABX, 3.5, 12.5)	3.73 (ABX, 3.0, 12.5)
3-H	2.93 (ddd, 3.0, 9.0, 9.0)	2.92 (ddd, 5.0, 6.5, 10.0)
4-H	2.30 (ddd, 3.5, 9.0, 13.5)	2.10 (ddd, 6.0, 6.5, 13.5)
	2.54 (ddd, 9.0, 10.0, 13.5)	2.78 (ddd, 9.5, 19.0, 13.5)
5-H	4.35 (dd, 3.5, 10.0)	4.34 (dd, 6.0, 9.5)

References

1. J.G.Buchanan, *Prog.Chem.Org.Nat.Prod.*, 1983, 44, 243.
2. J.G.Buchanan and R.H.Wightman in 'Topics in Antibiotic Chemistry', ed. P.G.Sammes, Wiley, Chichester, 1982, vol 6, p. 229.
3. S.C.Hartman in 'Metabolic Pathways', 3rd edn., ed. D.M.Greenberg, Academic Press, New York, 1970, vol. 4, p. 1.
4. R.J.Suhadolnik and N.L.Reichenbach, *Biochemistry*, 1981, 20, 7042.
5. J.G.Buchanan, M.R.Hamblin, G.R.Sood, and R.H.Wightman, *J.Chem.Soc., Chem.Commun.*, 1980, 917.
6. A.G.M.Barrett, H.B.Broughton, S.V.Attwood, and A.A.L.Gunatilaka, *J.Org.Chem.*, 1986, 51, 495.
7. J.E.Baldwin, R.M.Adlington, and N.G.Robinson, *J.Chem.Soc., Chem.Commun.*, 1987, 153.
8. R.K.-Y.Zee Chang and R.E.Olson, *Biochem.Biophys.Res.Commun.*, 1980, 94, 1128.
9. U.Schollkopf, *Pure Appl.Chem.*, 1983, 55, 1799.
10. P.D.Kane and J.Mann, *J.Chem.Soc.,Perkin Trans.I*, 1984, 657.
11. U.Schollkopf, D.Pettig, U.Busse, E.Egert, and M.Dyrbusch, *Synthesis*, 1986, 737.
12. M.C.Clingerman and J.A.Secrist III, *J.Org.Chem.*, 1983, 48, 3141.
13. H.Ohrui, G.H.Jones, J.G.Moffatt, M.L.Maddox, A.T.Christensen, and S.K.Byram, *J.Am.Chem.Chem.Soc.*, 1975, 97, 4602.
14. L.Fowden, *Biochem.J.*, 1966, 98, 57.

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