Total Synthesis of (+)-Thermozymocidin (Myriocin) from D-Fructose

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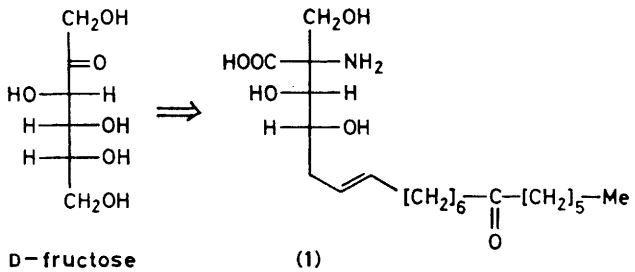
A total synthesis of thermozymocidin (**1**) has been achieved using D-fructose as the chiral synthon; the key steps of the synthesis are the transformation of D-fructose into 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid (**4**) and the stereoselective synthesis of the disubstituted (*E*)-double bond by reaction of the (*E*)-alkenylcuprate (**17**) with the tosylate (**14**).

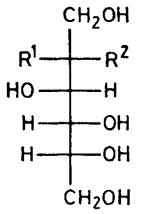
Thermozymocidin (Myriocin), an antibiotic agent, was isolated from the thermophilic fungus *Myriococcum albomyces* in 1972.[1] Structure elucidation required, in addition to a combination of chemical degradations and n.m.r., i.r., and mass spectroscopic examinations,[2] an *X*-ray analysis[3] and synthetic studies[4] to establish the relative configuration, and synthesis of the optical antipode of anhydrothermozymocidin[5] to determine the absolute configuration as (**1**).

Here we describe the first total synthesis of (+)-(**1**) using D-fructose as the source of chirality for the asymmetric centres of thermozymocidin (Scheme 1).

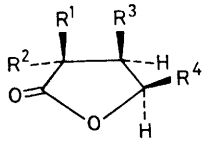
The transformation of D-fructose into 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid (**4**) was of critical importance. Initial attempts to synthesize this amino acid using Strecker, Bucherer, or Bucherer–Bergs reactions were unsuccessful. D-Fructose was then converted into fructosyl-*p*-tolylamine and treated with an excess of liquid hydrogen



Scheme 1



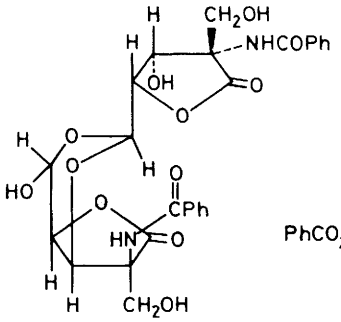
(2) R^1 = NH-*p*-MeC_6H_4, R^2 = CN
(3) R^1 = CN, R^2 = NH-*p*-MeC_6H_4
(4) R^1 = CO_2H, R^2 = NH_2



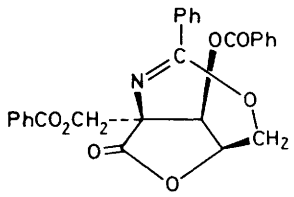
(5) R^1 = NH-*p*-MeC_6H_4, R^2 = CH_2OH, R^3 = OH, R^4 = $CHOCMe_2OCH_2$
(6) R^1 = NH-*p*-MeC_6H_4, R^2 = CH_2OH, R^3 = OH, R^4 = $CH(OH)CH_2OH$
(7) R^1 = CH_2OH, R^2 = NH-*p*-MeC_6H_4, R^3 = OH, R^4 = $CH(OH)CH_2OH$
(8) R^1, R^3 = CH_2OCMe_2O, R^2 = NH-*p*-MeC_6H_4, R^4 = $CHOCMe_2OCH_2$
(9) R^1 = NHCOPh, R^2 = CH_2OH, R^3 = OH, R^4 = $CH(OH)CH_2OH$
(11) R^1 = NHCOPh, R^2 = CH_2OCOPh, R^3 = OCOPh, R^4 = $CH(OH)CH_2OH$
(12) R^1 = NHCOPh, R^2 = CH_2OCOPh, R^3 = OCOPh, R^4 = CHO
(13) R^1 = NHCOPh, R^2 = CH_2OCOPh, R^3 = OCOPh, R^4 = CH_2OH
(14) R^1 = NHCOPh, R^2 = CH_2OCOPh, R^3 = OCOPh, R^4 = $CH_2OC_6H_4$-*p*-$MeSO_2$
(18) R^1 = NHCOPh, R^2 = CH_2OCOPh, R^3 = OCOPh, R^4 = (*E*)-$CH_2CH{=}CH[CH_2]_6$-$C([CH_2]_5Me)$-OCH_2CH_2O

cyanide in ethanol–water,† following the general Kuhn procedure.[6] Two epimeric 2-deoxy-2-hydroxymethyl-2-*p*-tolylamino-hexononitriles were obtained (80% yield): the (2*R*)-epimer (**2**) precipitated, while the desired (2*S*)-epimer (**3**) remained in the mother liquor. Unfortunately the ratio† 2*R*:2*S* was 3:1, but the (2*R*)-epimer was partially converted into the (2*S*)-epimer by equilibration in ethanol–water in the presence of an excess of liquid hydrogen cyanide. Hydrolysis of the two epimeric nitriles using concentrated HCl [40 h for the (2*R*)-and 2 h for the (2*S*)-epimer] gave two 2-deoxy-2-hydroxymethyl-2-*p*-tolylamino-hexono-1,4-lactones (90% yield). The formation of an isopropylidene acetal (**5**) established the configuration at C-2 of the (2*S*)-epimer (**6**), while the (2*R*)-epimer (**7**) afforded a bis(isopropylidene acetal) (**8**) under the same conditions (acetone, H_2SO_4).

Hydrogenolysis (Pd–C, 1M HCl) of 2-deoxy-2-hydroxymethyl-2-*p*-tolylamino-mannono-1,4-lactone (**6**) gave (**4**) in 80% yield.‡ Attempts to effect selective *N*-benzoylation of (**4**) with the conventional Schotten–Baumann reaction[7] or its modifications[8] failed, as did attempts to use reagents for the selective *N*-acylation[8] of aminoalcohols. The best synthesis of 2-benzoylamino-2-deoxy-2-hydroxymethylmannono-1,4-lactone (**9**) (60% yield) was by the perbenzoylation of the amino acid (**4**) using an excess of benzoyl chloride in pyridine followed by methanolysis in the presence of a catalytic amount of triethylamine.‡ Sodium periodate oxidation of the lactone (**9**) gave the hemiacetal dimer (**10**) (100% yield), characterized by the lack of aldehyde carbonyl group (i.r.) and aldehyde proton (n.m.r.), and the presence of a $2M - 3H_2O$ peak in the mass spectrum.§ Therefore it was necessary to transform compound (**9**) into the tribenzoylated vicinal diol (**11**) according to the following sequence: treatment with acetone and sulphuric acid to afford the cyclic isopropylidene acetal¶ (90% yield), esterification with benzoyl chloride in pyridine (90% yield), and hydrolysis of the isopropylidene acetal with acetic acid in tetrahydrofuran (THF)–H_2O (90% yield).



(10)



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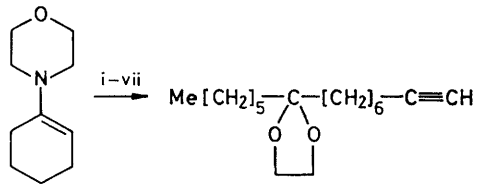

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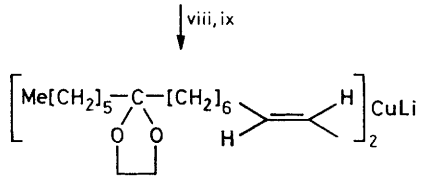

(17)

Scheme 2. *Reagents:* i, $C_6H_{13}COCl$, $CHCl_3$, Et_3N; HCl, H_2O; NaOH, H_2O, EtOH; ii, MeOH, H_2SO_4; iii, ethylene glycol, *p*-$MeC_6H_4SO_3H$, toluene; iv, $LiAlH_4$; v, $MeSO_2Cl$, pyridine; vi, KBr, n-$C_{16}H_{33}Bu^n_3P^+Br^-$, H_2O, benzene; vii, HC≡C–Li, THF–HMPT; viii, Bu^i_2AlH, I_2, THF; ix, Bu^tLi (2 equiv.), CuBr·Me_2S.

† Fructosyl-*p*-tolylamine proved to be better than fructosyl-phenylamine for the hydrocyanation reaction. Extensive experimentation involving changes in solvents and other reaction conditions did not improve the yields or the epimer ratio.

‡ This reaction was also performed on the corresponding (2*R*)-compound (the glucono-1,4-lactone) to give the (2*R*)-product.

§ This structure (**10**) was assigned in analogy with the work of Hecht on the structure of the species resulting from the oxidation of 2-acetamido-2-deoxy-D-mannono-1,4-lactone. (S. M. Hecht, K. M. Rupprecht, and P. M. Jacobs, *J. Am. Chem. Soc.*, 1979, **101**, 3982, and references therein).

¶ A bis(isopropylidene acetal) resulted when the (2*R*)-epimer was treated under the same conditions.

Sodium periodate oxidation of the diol (**11**) gave the perbenzoylated aldehyde (**12**) in 100% yield. Reduction of the aldehyde (**12**) with $NaBH_3CN$ in THF (100% yield) and subsequent treatment of the alcohol (**13**) with toluene-*p*-sulphonyl chloride, 4-(dimethylamino)-pyridine,[9] and triethylamine in CH_2Cl_2 at −20 °C gave the toluene-*p*-sulphonate (**14**) in 95% yield.

The synthesis of the side chain was accomplished starting from 1-morpholinocyclohexene by standard reactions (Scheme 2). The terminal alkyne (**15**) was treated with di-isobutylaluminium hydride and then with methyl- or butyl-lithium under the appropriate conditions[10] to give a vinylalanate. Reaction of this vinylalanate derivative with the toluene-*p*-sulphonate (**14**) in hexamethylphosphoric triamide (HMPT) gave one main product, the structure of which was tentatively assigned as (**16**). This behaviour is probably due to the presence of some unreacted vinylalane which, like a Lewis acid, induces the formation of the carbocation, and therefore favours the intramolecular substitution of the toluene-*p*-sulphonate.

The vinylalane was therefore transformed into the lithium divinylcuprate (**17**), which was allowed to couple, under the normal conditions[11] modified by the use of HMPT as co-solvent, with (**14**). Protected anhydrothermozymocidin (**18**) was obtained, after silica gel chromatography, in 26% yield. Final hydrolysis of the protecting groups gave (**1**), indistinguishable chromatographically and spectroscopically from naturally obtained thermozymocidin.

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