

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

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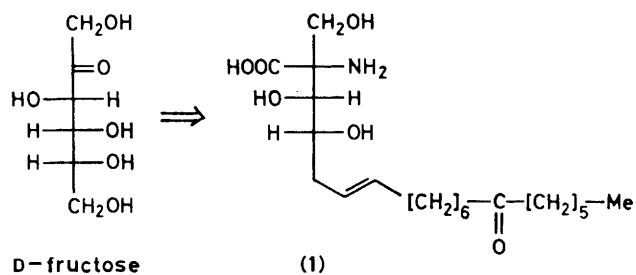
A total synthesis of thermozymocidin (**1**) has been achieved using D-fructose as the chiral synthon; the key steps of the synthesis are the transformation of D-fructose into 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid (**4**) and the stereoselective synthesis of the disubstituted (*E*)-double bond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

Thermozymocidin (Myriocin), an antibiotic agent, was isolated from the thermophilic fungus *Myriococcum albotomyces* 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 analysis³ and synthetic studies⁴ to establish the relative configuration, and synthesis of the optical antipode of anhydrothermozymocidin⁵ to determine the absolute configuration as (**1**).

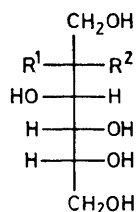
Here we describe the first total synthesis of (+)-(**1**) using D-fructose as the source of chirality for the asymmetric centres of thermozymocidin (Scheme 1).

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 un-

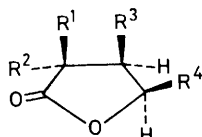
successful. D-Fructose was then converted into fructosyl-*p*-tolylamine and treated with an excess of liquid hydrogen



Scheme 1



- (2) $R^1 = \text{NH-}p\text{-MeC}_6\text{H}_4$, $R^2 = \text{CN}$
 (3) $R^1 = \text{CN}$, $R^2 = \text{NH-}p\text{-MeC}_6\text{H}_4$
 (4) $R^1 = \text{CO}_2\text{H}$, $R^2 = \text{NH}_2$



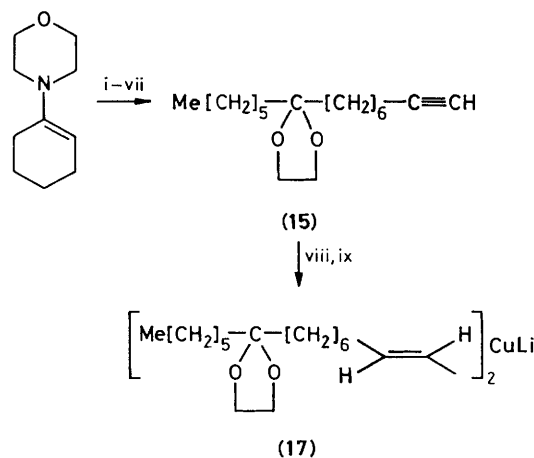
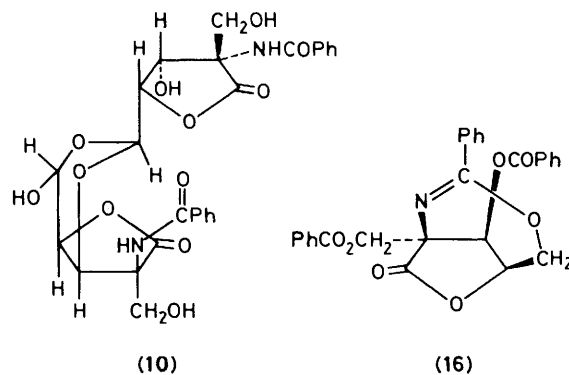
- (5) $R^1 = \text{NH-}p\text{-MeC}_6\text{H}_4$, $R^2 = \text{CH}_2\text{OH}$, $R^3 = \text{OH}$,
 $R^4 = \text{CHOCMe}_2\text{OCH}_2$
 (6) $R^1 = \text{NH-}p\text{-MeC}_6\text{H}_4$, $R^2 = \text{CH}_2\text{OH}$, $R^3 = \text{OH}$,
 $R^4 = \text{CH(OH)CH}_2\text{OH}$
 (7) $R^1 = \text{CH}_2\text{OH}$, $R^2 = \text{NH-}p\text{-MeC}_6\text{H}_4$, $R^3 = \text{OH}$,
 $R^4 = \text{CH(OH)CH}_2\text{OH}$
 (8) $R^1, R^3 = \text{CH}_2\text{OCMe}_2\text{O}$, $R^2 = \text{NH-}p\text{-MeC}_6\text{H}_4$,
 $R^4 = \text{CHOCMe}_2\text{OCH}_2$
 (9) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OH}$, $R^3 = \text{OH}$,
 $R^4 = \text{CH(OH)CH}_2\text{OH}$
 (11) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OCOPh}$, $R^3 = \text{OCOPh}$,
 $R^4 = \text{CH(OH)CH}_2\text{OH}$
 (12) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OCOPh}$, $R^3 = \text{OCOPh}$,
 $R^4 = \text{CHO}$
 (13) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OCOPh}$, $R^3 = \text{OCOPh}$,
 $R^4 = \text{CH}_2\text{OH}$
 (14) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OCOPh}$, $R^3 = \text{OCOPh}$,
 $R^4 = \text{CH}_2\text{OC}_6\text{H}_4\text{-}p\text{-MeSO}_2$
 (18) $R^1 = \text{NHCOPh}$, $R^2 = \text{CH}_2\text{OCOPh}$, $R^3 = \text{OCOPh}$,
 $R^4 = (E)\text{-CH}_2\text{CH}=\text{CH}[\text{CH}_2]_6\text{-}$
 $\text{C}([\text{CH}_2]_5\text{Me})\text{-OCH}_2\text{CH}_2\text{O}$

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, H₂SO₄).

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*-benzylation of (4)

[†] 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.



Scheme 2. Reagents: i, C₆H₁₃COCl, CHCl₃, Et₃N; HCl, H₂O; NaOH, H₂O, EtOH; ii, MeOH, H₂SO₄; iii, ethylene glycol, *p*-MeC₆H₄SO₃H, toluene; iv, LiAlH₄; v, MeSO₂Cl, pyridine; vi, KBr, *n*-C₁₀H₁₈Bu⁺P⁺Br⁻, H₂O, benzene; vii, HC≡C-Li, THF-HMPT; viii, Bu₂AlH, I₂, THF; ix, Bu⁺Li (2 equiv.), CuBr·Me₂S.

with the conventional Schotten-Baumann reaction⁷ or its modifications⁸ failed, as did attempts to use reagents for the selective *N*-acylation⁸ of aminoalcohols. The best synthesis of 2-benzoylamino-2-deoxy-2-hydroxymethylmannono-1,4-lactone (9) (60% yield) was by the perbenzylation 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 2*M* - 3H₂O 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)-H₂O (90% yield).

[§] 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 diisobutylaluminium hydride and then with methyl- or butyllithium under the appropriate conditions¹⁰ to give a vinylalane. Reaction of this vinylalane 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 conditions¹¹ 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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