Total Synthesis of (±)-Cephalotaxine

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A total synthesis of (±)-cephalotaxine has been achieved in a stereoselective manner by a synthetic sequence involving an acid-catalysed cyclisation of the α-sulphinylacetamide **12** as a key step.

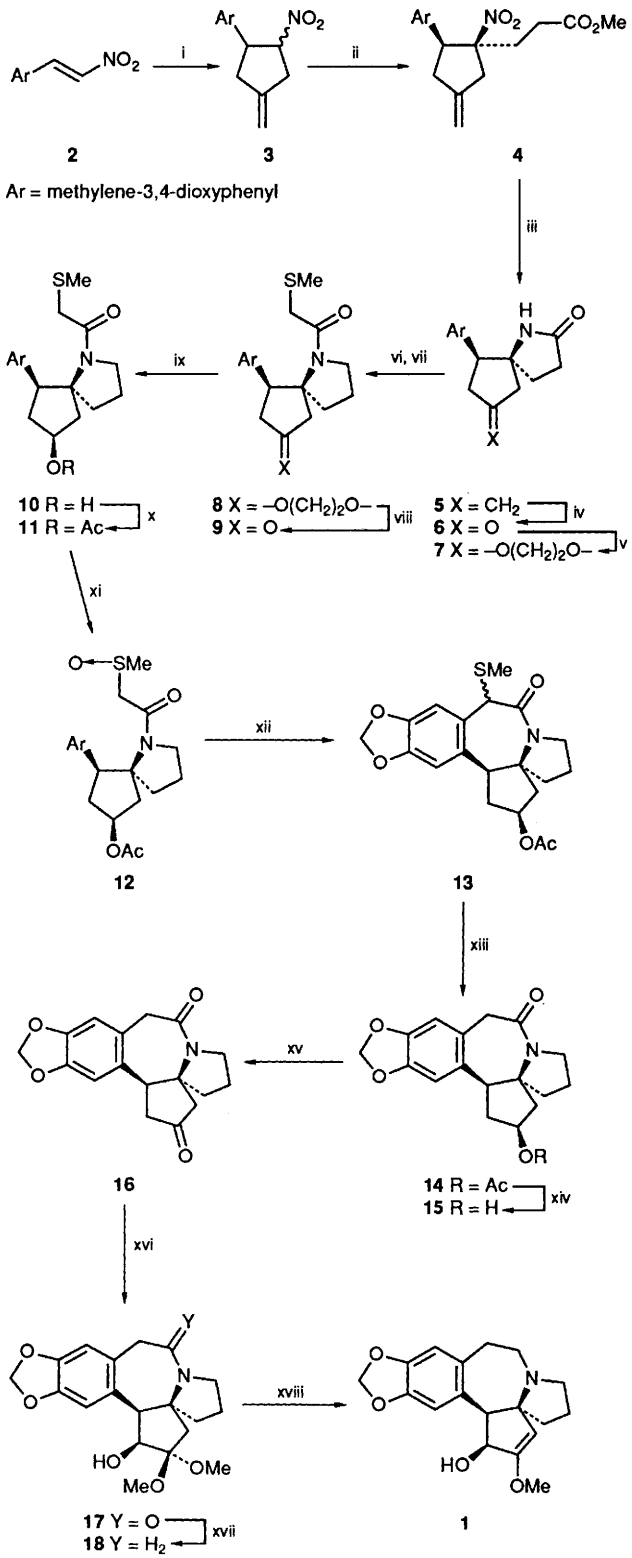
Cephalotaxine **1**, the predominant alkaloid of the *Cephalotaxus* species,[1] has attracted much attention from synthetic chemists due to its unique structural features and the antileukaemic activity of its ester derivatives. So far, five total syntheses of (±)-**1** have been reported.[2] We now describe a stereoselective synthesis of (±)-**1** *via* an acid-catalysed cyclisation of the α-sulphinylacetamide **12**[3] as a key step.

Our approach started with Trost's palladium-mediated methylenecyclopentane annelation[4] to the nitroalkene **2**, which gave the methylenecyclopentane derivative **3**† as an oily diastereoisomeric mixture (*ca.* 8:2) in 90% yield. Michael addition of the isomeric mixture of **3** to methyl acrylate[5] gave the nitroester **4** (m.p. 107–108 °C) as a single stereoisomer. Reduction of the nitro group with zinc in ethanolic HCl followed by treatment with alkali and oxidative cleavage of the resulting lactam **5** with OsO_4–$NaIO_4$ gave the ketolactam **6** (m.p. 195–196 °C). The ketolactam **6** was then transformed into the sulphoxide **12** (m.p. 172–174 °C) in a straightforward manner as shown in Scheme 1.

Cyclisation of the sulphoxide **12**‡ was effected by treating

† Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds.

‡ Attempts to cyclise either the sulphoxides **12** (=CH_2 or =O instead of OAc) were unsuccessful.



Scheme 1 *Reagents, conditions and % yields*: i, CH_2=C(CH_2TMS)CH_2OAc, $Pd(OAc)_2$, $(Pr^iO)_3P$, THF, reflux, 90%; ii, CH_2=$CHCO_2Me$, Triton B, THF, Bu^tOH, room temp., quantitative; iii, Zn, conc. HCl, EtOH, reflux, then NaOH, 81%; iv, OsO_4, $NaIO_4$, THF, H_2O, 0 °C → room temp., quantitative; v, $HOCH_2$-CH_2OH, *p*-TsOH, $(CH_2Cl)_2$, reflux, quantitative; vi, Red-Al, benzene, reflux, 90%; vii, $MeSCH_2CO_2H$, DCC, CH_2Cl_2, room temp., 98%; viii, AcOH, H_2O, reflux, 92%; ix, $NaBH_4$, EtOH, room temp., quantitative; x, Ac_2O, pyridine, 0 °C → room temp., 92%; xi, $NaIO_4$, MeOH, H_2O, 0 °C → room temp., quantitative; xii, $(CF_3CO)_2O$, CH_2Cl_2, 0 °C → room temp., 85%; xiii, Raney-Ni, acetone, reflux, quantitative; xiv, K_2CO_3, MeOH, room temp.; xv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C → room temp., 83% from **14**; xvi, $PhI(OAc)_2$, KOH, MeOH, 0 °C, 78%; xvii, Red-Al, benzene, reflux, 83%; xviii, p-TsOH, THF, reflux, 85%. TMS = trimethylsilyl, DCC = 1,3-dicyclohexylcarbodiimide, DMSO = dimethyl sulphoxide.

with either trifluoroacetic anhydride (1 equiv.) in dichloromethane at room temperature[3] or anhydrous toluene-*p*-sulphonic acid (*p*-TsOH; 5 equiv.) in boiling 1,2-dichloroethane for 10 min[3] to give the benzazepinone derivative **13** as a single stereoisomer in 85 and 77% yields, respectively. Desulphurisation of **13** with Raney-nickel gave the acetate **14** (m.p. 188–189 °C),§ which was hydrolysed with K_2CO_3 in methanol followed by Swern oxidation of the alcohol **15** to give the ketolactam **16** (m.p. 189–190 °C). The IR, NMR and mass spectra of **16** were identical with those of an authentic sample (lit. m.p.[2c] 188–189 °C) kindly provided by Professor Hanaoka. The conversion of the ketolactam **16** into (±)-cephalotaxine **1** was carried out by using essentially the procedure of Hanaoka.[2c] Oxidation of **16** with $PhI(OAc)_2$,[6] followed by Red-Al [sodium bis(2-methoxyethoxy)aluminium; Aldrich] reduction and then treatment of the hydroxyacetal **18** with toluene-*p*-sulphonic acid in tetrahydrofuran (THF) gave (±)-**1** (m.p. 122–124 °C) (lit.[2e] 122–124 °C). Thus, we achieved the synthesis of (±)-**1** in 18 steps and in 21% overall yield from the nitrostyrene **2**.

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§ The stereochemical assignment of the hydroxy and acetoxy groups of **10**–**15** was based on the fact that $NaBH_4$ reduction of **16** gave exclusively the alcohol **15**, which is assumed to be formed as a result of hydride attack from the convex face of **16**.