AN APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE (1)

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Abstract - 2-Azabicyclo[2.2.1]hept-5-en-3-one (1) was obtained with a 13% enantiomeric excess by hydrolysis of the adduct formed by Diels-Alder addition of cyclopentadiene to the new chiral dienophile (+)-10-camphorsulphonyl cyanide (6) which was prepared in three steps from (+)-10-camphorsulphonic acid (3) in 44% overall yield.

The synthesis of the optically active lactam 1 for subsequent ready transformation in (1R,2R,3S,4R)-4-amino-2,3-dihydroxy-1-cyclopentylmethanol (carbocyclic ribofuranosylamine) (2) or its 2-deoxy and 3-deoxy derivatives, is a key step in the preparation of carbocyclic nucleoside analogs, some of which have already been synthesized and have proved to exhibit, even in racemic form, very interesting antineoplastic and antiviral properties. Only recently research has begun on the enantiomerically pure forms of these compounds, which have been prepared by resolution of the racemic mixture, enzymatic synthesis, chemical synthesis from the optically active substituted cyclopentane or enantioselective chemical synthesis. The aim of the work described in this article was to obtain 1 by an asymmetric Diels-Alder reaction between the cyclopentadiene and a chiral dienophile, for which we chose a chiral sulphonyl cyanide (R*-SO₂CN); this compound generally reacts with cyclopentadiene in good yield under mild conditions and provide the most direct route to the lactam 1, which can be easily transformed into 2.

![Scheme 1](image1)

a) PCl₅; b) Na₂SO₃, NaHCO₃; c) ClCN; d) cyclopentadiene; e) AcOH/H₂O
(+)-10-Camphorsulphonyl cyanide (6) was synthesized (Scheme 1) from commercial (+)-10-camphorsulphonic acid (3) (if necessary, it would also be possible to use the (-) enantiomer). 3 was first transformed into its chloride 4 and then, by treatment with a mixture of sodium sulphite and sodium bicarbonate, into its sodium salt 5, which was reacted with cyanogen chloride 6, 8 (direct reaction of sulphonyl chlorides with alkaline cyanides is ineffective 9). The overall yield was 44% and the synthetic route was checked spectroscopically (ir, nmr, ms) and by elementary analysis. The Diels-Alder reaction between the sulphonyl cyanide 6 and cyclopentadiene was carried out at 0°C, and the adduct 7 was readily hydrolysed by aqueous acetic acid in the same reaction medium (yield 82% for the two steps). The 1H nmr spectrum obtained in the presence of chiral europium reagent revealed a 13% excess of one enantiomer over the other. In view of the slight enantioselectivity, total elucidation of the configuration of the major enantiomer was not carried out. We are currently testing various derivatives of 6 in an attempt to improve enantioselectivity.

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage instrument and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer (KBr discs, v max in cm⁻¹). The nmr spectra were obtained in CDCl₃ with Varian FT 80A (80 MHz) and Bruker WM (250 MHz) spectrometers using TMS as the internal standard (chemical shifts in δ values, J in Hz). Mass spectra were obtained with a Varian MAT-711 mass spectrometer at 70 eV. Microanalyses were determined with a Perkin-Elmer 240B instrument (C,H,N). For column chromatography, Merck silica gel 60 (70-230 mesh) was used and analytical thin-layer chromatography was performed on precoated Merck silica gel 60 F254 (0.25 mm).

(+)-10-Camphorsulphonyl chloride (4). (+)-10-Camphorsulphonic acid (3) (5.0 g, 21.6 mmol) was slowly added at 0°C to stirring PCl₅ (13.47 g, 54 mmol). Stirring was continued for 4 h at RT before the mixture was poured onto ice to give solid 4, which was filtered out and recrystallized from heptane, mp 67-68°C, yield 4.46 g (89%); ir: 1740 (CO), 1370 and 1170 (SO₂); ¹H nmr: 0.92 (s, 3H, -CH₃); 1.14 (s, 3H, -CH₃); 1.60-2.50 (m, 7H); 3.72 (d, 1H, J=14.60, -HCH-SO₂); 4.30 (d, 1H, J=14.60, -HCH-SO₂); mm m/z (relative intensity): 252 (M+2, 33%), 250 (M, 2), 215 (M-CI, 2) 151 (M-SO₂Cl, 32), 123 (151-Cl, 53), 109 (123-CH₂, 93), 81 (100).

(+)-10-Camphorsulphonyl cyanide (6). The chloride 4 (14.00 g, 55.8 mmol) was added to a solution of Na₂SO₃·7H₂O (14.08 g, 55.8 mmol) and NaHCO₃ (9.37 g, 111.6 mmol) in water (56 ml). The mixture was stirred for 4 h at RT before cooling to -5°C and addition of CCL₄ (9.00 g, 147 mmol) in one lot. ¹H nmr was recorded. Stirring was continued for 30 min and the reaction mixture was then extracted with methylene chloride. The organic phase was dried (Na₂SO₄) and the solvent was evaporated under vacuum to afford solid 6, mp 111°C, yield 6.50 g (49%); ir: 2200 (CN), 1730 (CO), 1370 and 1180 (SO₂); ¹H nmr: 0.93 (s, 3H, -CH₃); 1.10 (s, 3H, -CH₃); 1.55 (m, 1H); 2.25-3.50 (m, 6H); 3.30 (d, 1H, J=15.25, -HCH-SO₂); 3.88 (d, 1H, J=15.25, -HCH-SO₂); mm m/z (relative intensity): 215 (M-CN, 20), 199 (M-CN-O, 5), 183 (M-CN-O₂, 24), 151 (M-SO₂Cl, 39), 123 (151-Cl, 58), 109 (123-CH₂, 100), 81 (80). Anal. Calcld for C₃₁H₅₁NO₅S: C, 54.77; H, 6.22; N, 5.81. Found: C, 55.06; H, 6.12; N, 5.10.

2-Azabicyclo[2.2.1]hept-5-en-3-one (1). The sulphonyl cyanide 6 (300 mg, 1.24 mmol) was dissolved at 0°C in freshly distilled cyclopentadiene (1.5 ml) and stirred for 3 h before addition of 1:4 AOH/H₂O (8 ml). The reaction mixture was then brought to pH 8 by slow addition of 12N NaOH and extracted with methylene chloride. The organic phase was dried (Na₂SO₄) and the solvent was evapo
rated under vacuum to leave a residue that was purified on a column of silica gel (4 g) with 3:7 heptane/AcOEt as eluent, yield 110 mg (82%); 1H nmr: 2.17 (d of t, 1H, \text{-CH-}, J=1.90, 7.90); 2.34 (d of t, 1H, \text{-CH-}, J=1.80, 7.90); 3.16 (m, 1H, \text{:CH-N}); 4.29 (m, 1H, \text{:CH-CO}); 6.10 (hr, 1H, NH); 6.70 (m, 2H, CH=CH).

In the presence of chiral europium reagent\(^{11}\) (mole ratio 1/3), the 250 MHz \(^1\)H nmr signal at \(\delta = 2.34\) ppm corresponding to one of the diastereotopic protons of the methylene bridge split in two; the excess of one enantiomer over the other was estimated as 13%.

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REFERENCES


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