



1-Azaspiro[4.4]nonane-2,6-dione and the separation and absolute configurations of its enantiomers

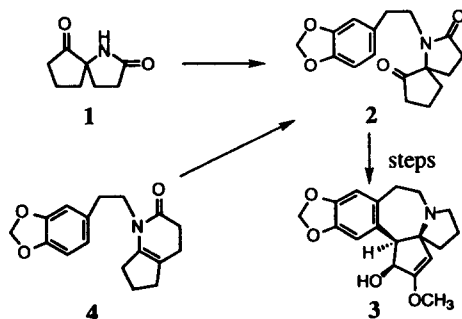
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Abstract: Racemic 1-azaspiro[4.4]nonane-2,6-dione **1** was easily synthesized from cyclopentanone in five steps and resolved *via* chiral acetals into enantiomers. Cephalotaxine (–)-**3** and its enantiomer (+)-**3** were obtained from (–)-**1** and (+)-**1**, respectively, according to the literature. © 1997 Published by Elsevier Science Ltd. All rights reserved.

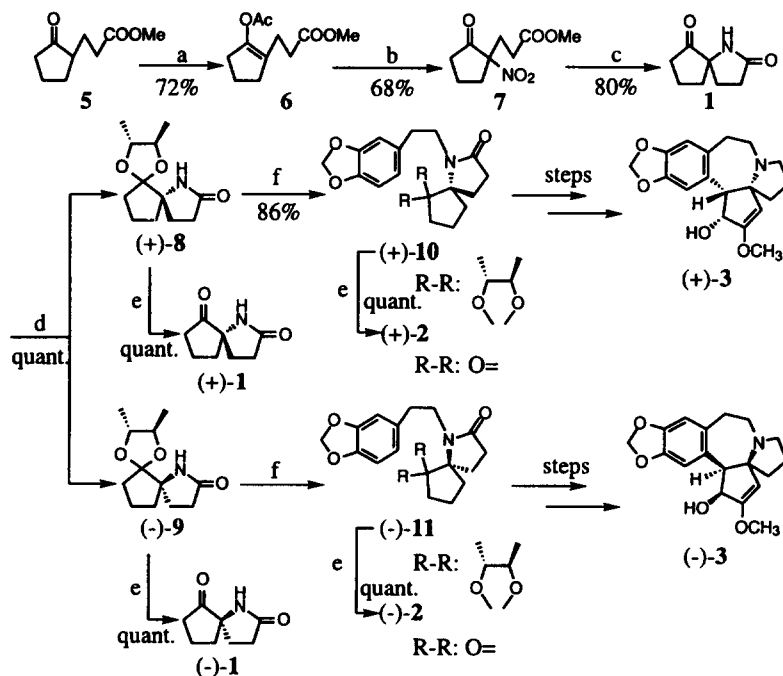
Key intermediate **2** for the total synthesis of (±)-cephalotaxine **3**, as reported by Kuehne *et al.*¹ includes the 1-azaspiro[4.4]nonane-2,6-dione skeleton **1** (Scheme 1). Compound **2** has been prepared by the oxidative rearrangement of bicyclic ene-lactam **4** with lead tetraacetate.¹ This paper presents a facile synthesis of **1** and the resolution of its enantiomers *via* chiral acetals. The absolute configuration of each enantiomer was determined based on CD spectra and X-ray analysis and were converted to the optical active cephalotaxine (–)-**3** and its enantiomer (+)-**3** by the method of Kuehne without racemization.

The synthesis² of **1** and separation of its enantiomers were carried out as shown in Scheme 2. 2-(2-Methoxycarbonyl)ethylcyclopentanone **5**, readily available by the alkylation of the pyrrolidine enamine of cyclopentanone with methyl acrylate (68%),³ was used with isopropenyl acetate to obtain enol acetate **6** in 72% yield, which was nitrated to **7** with a mixture of trifluoroacetic anhydride and ammonium nitrate in 68% yield. The desired spiro lactam **1** was obtained by reduction of **7** with zinc in acetic acid–ethanol (2:1) in good yield (80%).⁴ The acetalization of **1** with (*R,R*)-2,3-butanediol in the presence of catalytic *p*-toluenesulfonic acid gave a mixture of diastereomeric acetals (**8** and **9**) in quantitative yields. By HPLC on silica gel by elution with chloroform, **8** and **9** were easily separated in the first and second fractions, respectively. The hydrolysis of **8** and **9** with a mixture of AcOH–H₂O (5:95) gave (+)-**1** and (–)-**1** in quantitative yields, respectively. Each enantiomer was confirmed pure by HPLC using a chiral column (Figure 1).⁵

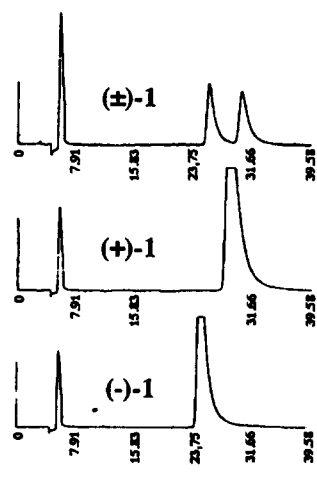


Scheme 1.

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Scheme 2. Reagents and Conditions: a) isopropenyl acetate, *p*-TsOH, 110°C, 5 h; b) trifluoroacetic anhydride, ammonium nitrate, CH₂Cl₂, r.t., 30 min; c) Zn, AcOH-EtOH (2:1), reflux, 5 h; d) i) (*R,R*)-(-)-2,3-butanediol, *p*-TsOH, C₆H₆, reflux, 8 h, ii) column chromatography on silica gel by elution with CHCl₃; e) 5% AcOH, reflux, 2 h; f) NaH, 2-(3,4-methylenedioxyphenyl)ethanol *p*-toluenesulfonate, C₆H₆.



Chromatograms of (±)-1, (-)-1 and (+)-1
by HPLC packed with the chiral column.*

Column : 50×0.1 (i.d.) cm stainless tube
packed with modified silica gel
(0.8 mmol/g silica gel)

Flow rate : 60 μl/min at 20°C.

Solvents : 8% EtOH - n-hexane.

Detector : a UV-detector at 230 nm.

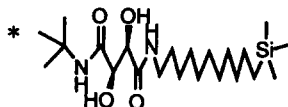


Figure 1.

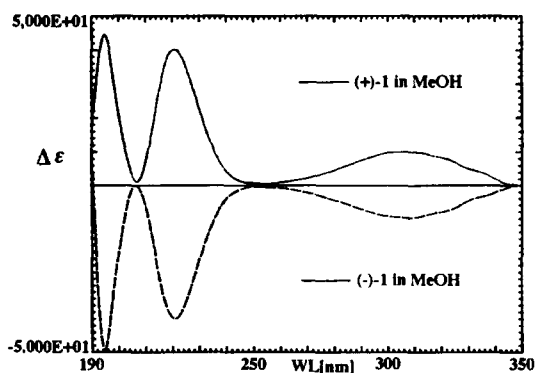


Figure 2. The CD-spectra of (+)-1 (—) and (-)-1 (---) in MeOH.

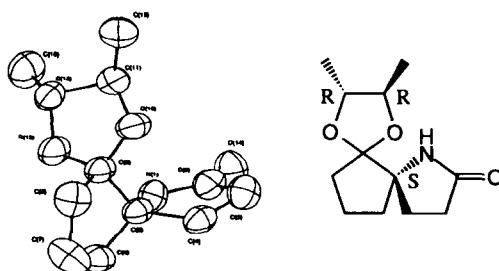


Figure 3. ORTEP diagram of (+)-8.

The CD spectra of (+)-1 and (-)-1 showed opposite absorptions as shown in Figure 2. The absolute configurations of (+)-1 and (-)-1 were suggested by comparison of the CD spectra of (+)-1 and (-)-1 with those of the known (*R*)-(+)- and (*S*)-(-)-1,7-diazaspiro[4.4]nonane-2,6-diones.⁶ X-ray analysis⁷ of (+)-8 shown in Figure 3 confirmed this consideration.

Finally, the syntheses of optical active cephalotaxine (-)-3 and its enantiomer (+)-3 were successfully carried out from (-)-11⁸ and (+)-10⁸, respectively, by the method reported in the literature.^{1,9}

References

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2. All new compounds were fully characterized by spectroscopic data and microanalysis and/or molecular ion mass measurements. Representative data for some new compounds: 7: ¹H-NMR (300MHz, CDCl₃) δ: 1.98–2.84 (10H, m), 3.69 (3H, s), CIMS m/z: 216 (M⁺+1). 1: ¹H-NMR (300MHz, CDCl₃) δ: 1.85–2.54 (10H, m), 5.73 (1H, br). ¹³C-NMR (75MHz, CDCl₃) δ: 17.33, 29.58, 30.18, 34.70, 35.81, 66.99, 178.80, 217.17. MS m/z: 153 (M⁺). mp 133–134°C. (+)-1: [α]_D^{25.6} +68.2 (c=1.0, CHCl₃). (-)-1: [α]_D^{24.4} -68.0 (c=1.0, CHCl₃). (+)-8: ¹H-NMR (300MHz, CDCl₃) δ: 1.20 (3H, d, J=5.6Mz), 1.22 (3H, d, J=5.6Mz), 1.65–1.75 (3H, m), 1.76–1.82 (2H, m), 1.86–1.91 (2H, m), 2.35–2.40 (2H, m), 2.45–2.50 (1H, m), 3.56–3.63 (2H, m), 5.55 (1H, br). ¹³C-NMR (75MHz, CDCl₃) δ: 15.53, 15.98, 16.53, 29.26, 30.31, 32.24, 34.63, 67.37, 77.89, 79.29, 115.02, 177.51. [α]_D^{26.0} +50.2 (c=1.0, CHCl₃). MS m/z: 225 (M⁺). mp 121–122°C. (-)-9: ¹H-NMR (300MHz, CDCl₃) δ: 1.20 (3H, d, J=2.5MHz), 1.21 (3H, d, J=2.5MHz), 1.63–1.80 (4H, m), 1.67–1.94 (3H, m), 2.28–2.40 (2H, m), 2.47–2.52 (1H, m), 3.58–3.62 (2H, m), 5.54 (1H, br). ¹³C-NMR (75MHz, CDCl₃) δ: 16.19,

16.36, 16.83, 29.26, 30.66, 33.41, 35.29, 68.17, 78.78, 79.22, 115.46, 178.39. $[\alpha]_D^{25.6} -60.6$ ($c=1.0$, CHCl_3). MS m/z : 225 (M^+). mp 96–98°C.

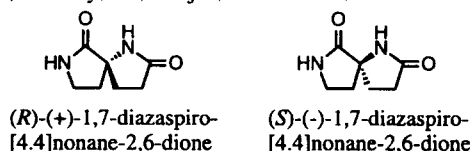
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4. Catalytic hydrogenation (5% Pd–C, MeOH–AcOH 5:1, H_2 2 atm, 5 h) of nitroester **7** afforded the desired amide **1** in low yield (35%). Various products were obtained in catalytic hydrogenations (5% Pd–C, H_2 2.5 atm) using other solvents, such as hydroxyamine **12** in 21% yield in EtOH (24 h) and alcohol **13** in 22% and 46% yield in EtOH–AcOH (30:1) (9 h) and in EtOH–AcOH– H_2O (10:0.1:1) (12 h), respectively.



5. HPLC analysis was kindly carried out by Dr. Yasuo Dobashi, Tokyo University of Pharmacy and Life Science, using a chiral column (cited in Figure 1) prepared by himself. cf. Dobashi, Y.; Hara, S. *J. Org. Chem.* **1987**, *52*, 2490.

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7. Data were obtained using a Mac Science MXC18, radiation $\text{CuK}\alpha$ ($\gamma=1541780\text{\AA}$) at 298K. Data collection of 2336 data, 2128 observed ($F>3.00\sigma(F)$). All diagrams and calculation results were obtained using a Crystan 6.3.1 (Mac Science, Japan). Structural refinement was made to $R=0.0537$ and $wR=0.0560$. Crystal dimensions: $0.50\times0.30\times0.20$ mm. Crystal system: orthorhombic; space group $P2_12_12_1$; Unit Cell dimensions $a=11.2256(27)\text{\AA}$, $b=24.7065(59)\text{\AA}$, $c=9.0541(23)\text{\AA}$; Volume $2511.10(101)\text{\AA}^3$; $Z=8$, density (calc): 1.351Mg m^{-3} , Absorption Coefficient: none.: Authors thank Mr. Tadashi Hata, Sankyo Co. Ltd., for the X-ray analysis of (+)-**8**.

8. The direct alkylation of amides {(+)-**1** and (–)-**1**} with alkyl halides in the presence of bases and phase transfer catalysts was not conducted successfully. For the alkylation of (+)-**8** and (–)-**9** to (+)-**10** and (–)-**10**, respectively, tosylate (in Scheme 2) was better than any corresponding alkyl halide.

9. (–)-**3**, mp 118–120°C (lit.¹⁰ mp 122–124°C): $[\alpha]_D^{24.0} -184.6$ ($c=0.5$, CHCl_3) {lit.¹⁰ $[\alpha]_D -188$ (CHCl_3)}. (+)-**3**, mp 118–120°C: $[\alpha]_D^{27.6} +188.9$ ($c=1.1$, CHCl_3). Synthesis of (–)-cephalotaxine has recently been reported: Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115.

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