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

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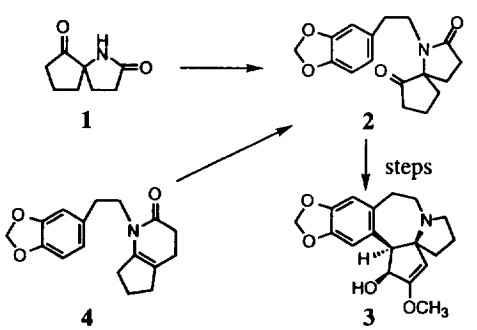
Abstract: Racemic 1-azaspiro[4.4]nonane-2,6-dione **1** was easily synthesized from cyclopentanone in five steps and resolved *via* chiral acetals into enantiomers. Cephlotaxine (−)-**3** and its enantiomer (+)-**3** were obtained from (−)-**1** and (+)-**1**, respectively, according to the literature. © 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 skeletone **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 synthesis[2] of **1** and separation of its enantiomers were carried out as shown in Scheme 2. 2-(2-Methoxycarbonylethyl)cyclopentanone **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 spirolactam **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–H_2O (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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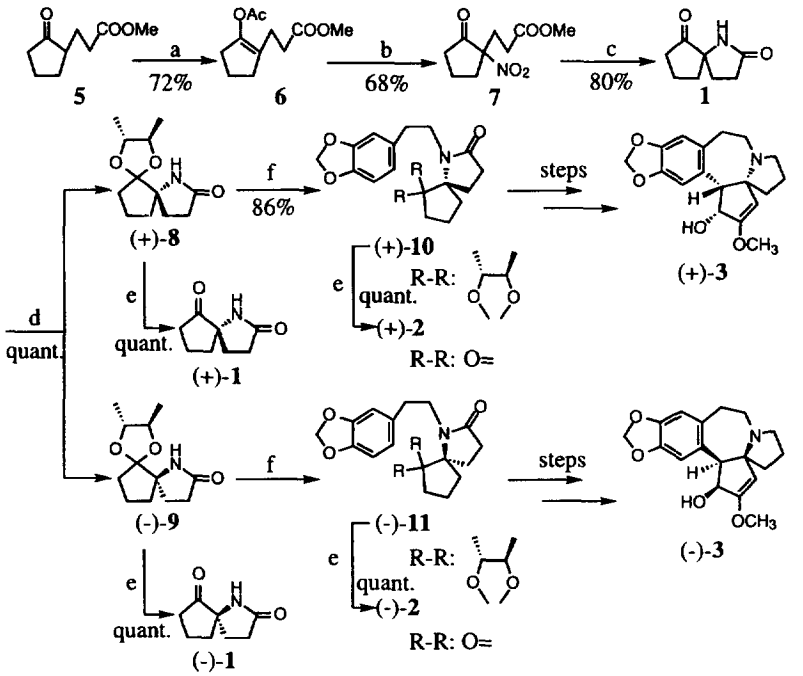


Scheme 2. Reagents and Conditions: a) isopropenyl acetate, *p*-TsOH, 110°C, 5 h; b) trifluoroacetic anhydride, ammonium nitrate, CH_2Cl_2, r.t., 30 min; c) Zn, AcOH–EtOH (2:1), reflux, 5 h; d) i) (*R,R*)-(−)-2,3-butanediol, *p*-TsOH, C_6H_6, reflux, 8 h, ii) column chromatography on silica gel by elution with $CHCl_3$; e) 5% AcOH, reflux, 2 h; f) NaH, 2-(3,4-methylenedioxyphenyl)ethanol *p*-toluenesulfonate, C_6H_6.

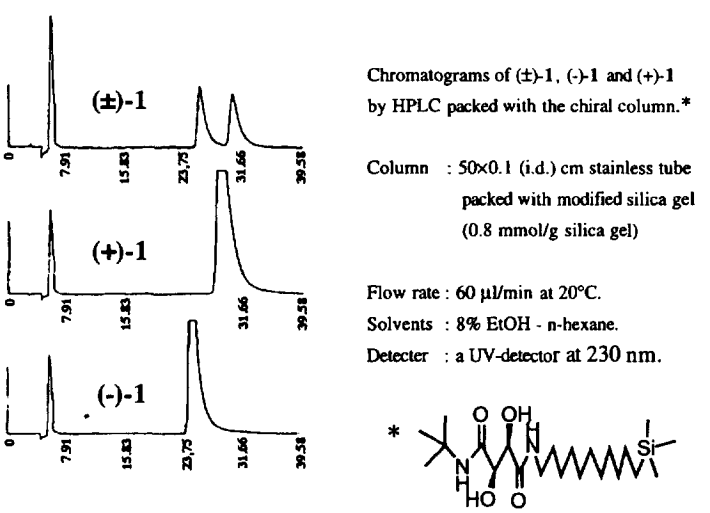


Figure 1.

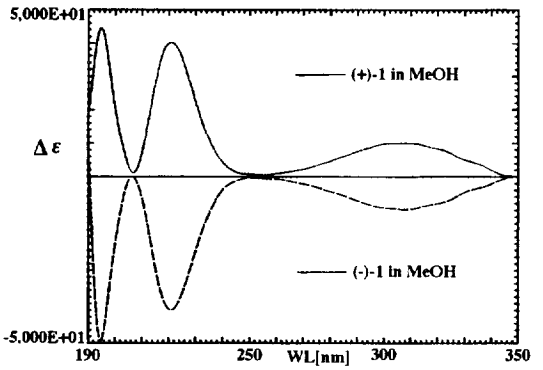


Figure 2. The CD-spectra of (+)-**1** (—) and (−)-**1** (- - -) in MeOH.

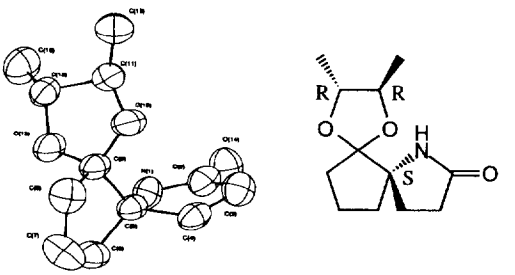


Figure 3. ORTEP diagram of (+)-**8**.

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 analysis[7] 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 (−)-**11**[8] and (+)-**10**[8], respectively, by the method reported in the literature.[1,9]

References

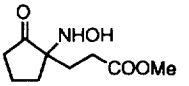
1. Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439.

2. All new compounds were fully characterized by spectrosopic data and microanalysis and/or molecular ion mass measurements. Representative data for some new compounds: **7**: ^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.98–2.84 (10H, m), 3.69 (3H, S), CIMS m/z: 216 (M^++1). **1**: ^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.85–2.54 (10H, m), 5.73 (1H, br). ^{13}C-NMR (75MHz, $CDCl_3$) 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**: $[\alpha]_D^{25.6}$ +68.2 (c=1.0, $CHCl_3$). (−)-**1**: $[\alpha]_D^{24.4}$ −68.0 (c=1.0, $CHCl_3$). (+)-**8**: ^{1}H-NMR (300MHz, $CDCl_3$) 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). ^{13}C-NMR (75MHz, $CDCl_3$) 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. $[\alpha]_D^{26.0}$ +50.2 (c=1.0, $CHCl_3$). MS m/z: 225 (M+). mp 121–122C°. (−)-**9**: ^{1}H-NMR (300MHz, $CDCl_3$) 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). ^{13}C-NMR (75MHz, $CDCl_3$) 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 96–98C°.

3. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

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.



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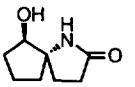

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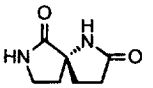
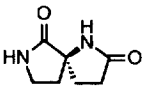
5. HPLC analysis was kindly carried out by Dr. Yasuo Dobashi, Tokyo University of Pharmacy and Life Science, using a chiral column (cited in Figure 1) prepared by himself. cf. Dobashi, Y.; Hara, S. *J. Org. Chem.* **1987**, *52*, 2490.

6. Kajtar, M.; Hollose, M.; Kinsky, K.; Majer, Z. *Coll. Czech. Chem. Commun.* **1982**, *47*, 950.



(*R*)-(+)-1,7-diazaspiro-[4.4]nonane-2,6-dione



(*S*)-(-)-1,7-diazaspiro-[4.4]nonane-2,6-dione

7. Data were obtained using a Mac Scaience MXC18, radiation CuKα (γ=1541780Å) at 298K. Data collection of 2336 data, 2128 observed (F>3.00σ(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: 0.50×0.30×0.20 mm. Crystal system: orthorhombic; space group $P2_12_12_1$; Unit Cell dimensions *a*=11.2256(27)Å, *b*=24.7065(59)Å, *c*=9.0541(23)Å; Volume 2511.10(101)$Å^3$; 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.

10. Arona, S. K.; Bates R. B.; Grady, R. A. *J. Org. Chem.* **1974**, *39*, 1269.

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