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2,5 -Dimethyl-Δ^3-pyrroline: a Novel Optically Active C_2-Symmetric Secondary Amine

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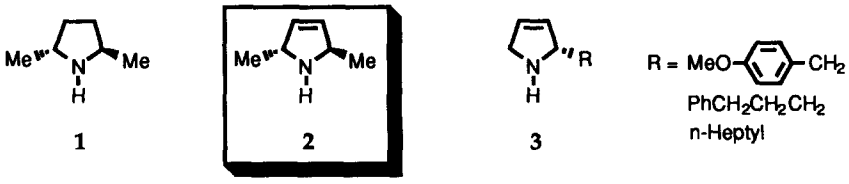
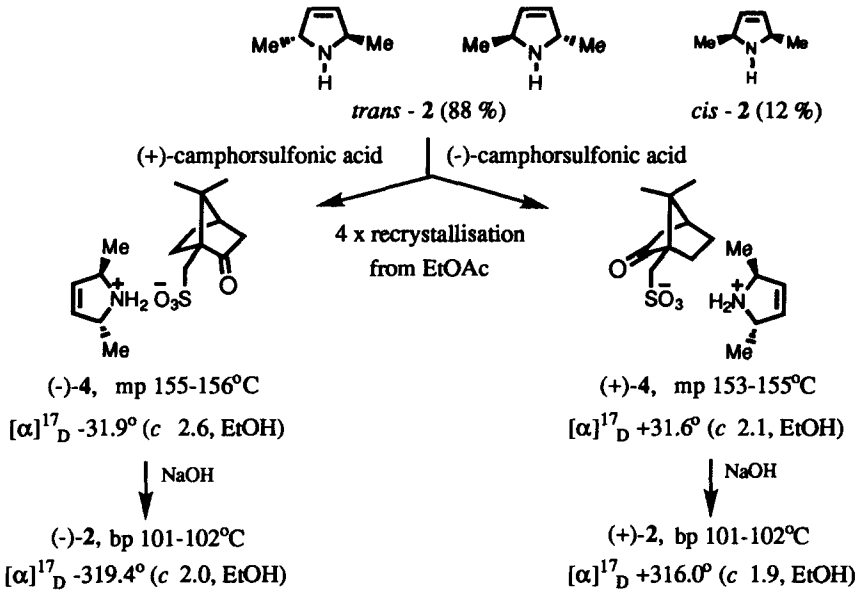
Abstract: Optical resolution of 2,5-dimethyl-Δ^3-pyrroline **2** has been carried out *via* diastereomeric salts with (+)- and (-)-10-camphorsulfonic acid. The absolute configuration of enantiomers **2** is determined and a possibility of their application in asymmetric synthesis is shown.

C_2-Symmetric compounds are important sources of chirality in asymmetric synthesis.[2] Optically active 2,5-dimethylpyrrolidine (**1**)[3] in the form of its derivatives is widely used and gives, as rule, excellent results.[2,4]



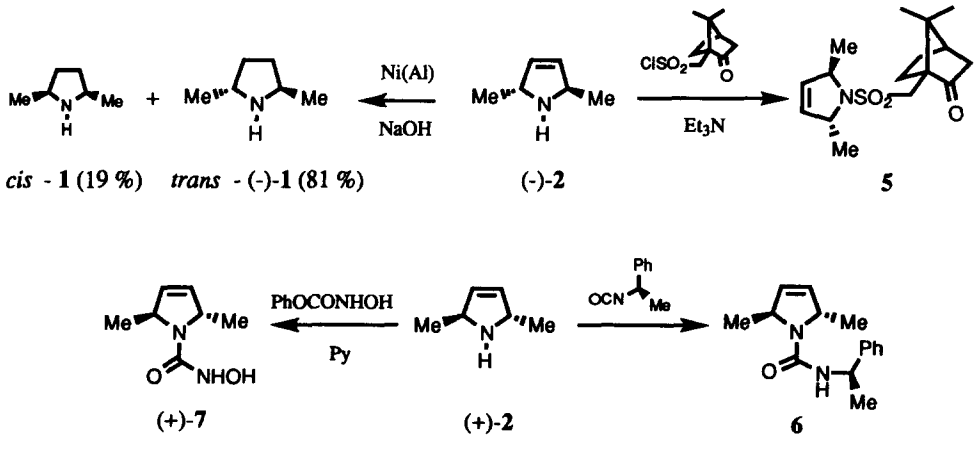
2,5-Dimethyl-Δ^3-pyrroline (**2**) is a close analog of pyrrolidine **1** and might serve as well as the latter, and additionally provide access (*via* reduction or functionalization of the double bond)[5,6] to chiral pyrrolidines with or without C_2 symmetry. Furthermore, **2** is a simple model for investigation of chiroptical properties of the Δ^3-pyrroline (allylamine) chromophore which is found in numerous alkaloids.[7] Some 2-monosubstituted Δ^3-pyrrolines **3** have been obtained in optically active form by an asymmetric α-alkylation of chiral formamidine derivatives.[6] In the present communication we wish to report a simple resolution of pyrroline **2** *via* diastereomeric salts with (+)- and (-)-10-camphorsulfonic acid (Scheme 1).

Pyrroline **2** can be synthesized[8] or purchased[9] as a mixture of the *cis(meso)* and *trans(d,l)* isomers which are separated by recrystallisation of their N-tosyl derivatives followed by removing of the tosyl group.[10] A procedure for the direct synthesis of 2,5-*trans*-dialkyl-Δ^3-pyrrolines with 95 % stereoselectivity has also been developed.[5a] However we have found that (+)- and (-)-**2** are readily obtained by treating the mixture of *cis,trans* -isomers (*ca.* 12:88), prepared according to Evans,[8] with (+)- or (-)-10-camphorsulfonic acid (see Scheme 1).[11] The yields of (+)- and (-)-**2** were each *ca.* 20 % of the stereomeric mixture. GC-MS analyses revealed them to contain *ca.* 1 % of *cis*-**2**.



Scheme 1

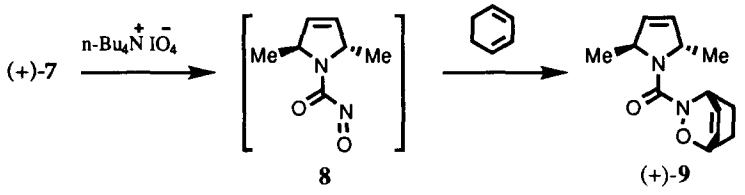
The optical purities of (-)-**2** *ca.* 95 % and (+)-**2** *ca.* 94 % were determined by ^{1}H NMR of the diastereomeric derivatives **5**,**6**[12] (Scheme 2), having previously established that the reactions of racemic *trans*-**2** with one equivalent of (1S)-(+)-10-camphorsulfonyl chloride (Et_3N, CH_2Cl_2, 5 h, RT) or (1R)-(+)-α-methylbenzyl isocyanate (CH_2Cl_2, 10 h, RT) were not accompanied by kinetic enrichment of one diastereomer. Integration of the peaks of 10-H_AH_B system of sulfonamide **5** [(2R,5R)-diastereomer: 2.80 and 3.80 ppm; (2S,2S): 3.10 and 3.52 ppm], and of the 2,5-methyl groups of urea **6** [(2S,5S)-diastereomer: 1.31 ppm; (2R,5R): 1.33 ppm] were used for determination of the ratio of the individual diastereomers.



Scheme 2

The reduction of (-)-**2** with Raney nickel (6 equiv. of Ni-Al alloy, 10 % aq. NaOH, 7 h, RT) yielded (R,R)-(-)-2,5-dimethylpyrrolidine **1** (Scheme 2). Hence, the (R,R) absolute configuration for (-)-**2** and (S,S) for (+)-**2** follows. About 19 % of *cis*-isomer **1** was formed together with *trans* -(-)-**1**[13] in this reduction.

The use of optically active pyrroline **2** as a chiral auxiliary is illustrated (Scheme 3) by a hetero-Diels-Alder reaction that was earlier studied[4e,f, 14] with N-carbamoylnitroso derivatives of other chiral amines.



Scheme 3

The hydroxamic acid (+)-**7**[15] was prepared by reaction of (+)-**2** with phenoxycarbonyl hydroxylamine according to the procedure[4e] developed for the derivative of pyrrolidine **1**. Oxidation of (+)-**7** with $(Bu_4N)IO_4$ (CH_2Cl_2, 1.5 h, RT) in the presence of a twofold excess of cyclohexadiene leads to the adduct (+)-**9**.[16] The ^1H and ^{13}C NMR spectra of the crude reaction mixture showed only one set of signals. We think that only one diastereomer **9** is the product of the reaction of dienophile **8** with cyclohexadiene because the coincidence of chemical shifts of all protons and ^{13}C nuclei of two possible diastereomers is very unlikely. Known hetero-Diels-Alder reactions[4e,f, 14b] of other carbamoylnitroso compounds possessing the amine moiety with local C_2 symmetry are characterized by very high diastereoselectivity and the diastereomers of the adducts obtained independently always have different ^1H and ^{13}C chemical shifts. According to a stereochemical model of the transition state of such kind of reactions which was offered earlier,[4e, 14] one can suppose the absolute configuration for the bicyclic moiety of adduct (+)-**9** to be (1'S,4'R).

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References and Notes

1. On leave from the Institute of Chemical Physics, Russian Academy of Sciences, Moscow, Russia. Present address: Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4.
2. Whitesell, J. K. *Chem.. Rev.* **1989**, *89*, 1581.
3. (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663. (b) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. (c) Yamazaki, T.; Gimi, R.; Welch, J. T. *Synlett* **1991**, *8*, 573. (d) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.*. **1989**, *54*, 1755. (e) Zwaagstra, M. E.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1993**, *4*, 2163. (f) Kim, M. J.; Lee, I.S. *Synlett* **1993**, 767.
4. (a) Hart, D. J.; Huang, H. C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507. (b) Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002. (c) Yamazaki, T.; Welch, J. T.; Plummer, J. S.; Gimi, R. H. *Tetrahedron Lett.* **1991**, *32*, 4267. (d) Chen, L.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1181. (e) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 103. (f) Defoin, A.; Pires, J.; Tissot, I.; Tschamber, T.; Bur, D.; Zehnder, M.; Streith, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1209.

5. (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A. K. *J. Org. Chem.* **1986**, *51*, 4296.

6. (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (b) Meyers, A. I.; Dupre, B. *Heterocycles*, **1987**, *25*, 113.

7. Hartmann, T.; Witte, L. In *Alkaloids, Chemical and Biological Perspectives* ; Pelletier, S. W. Ed.; Pergamon: Oxford, Vol. 9, 1995; pp. 155-233 and references therein.

8. Evans, G. G. *J. Am. Chem. Soc.* **1951**, *73*, 5230.

9. Aldrich Chemical Co., Milwaukee, WI.

10. Lemal, D. M.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 1335.

11. A solution of **2** (20.0 g, 0.206 mol, *cis/trans* = *ca.* 12:88, prepared from its picrate[8] mp 106-109°C) in MeOH (50 mL) was added to a solution of (+)-10-camphorsulfonic acid[9] (46.5 g, 0.200 mol) in MeOH (250 mL) with stirring and cooling (15°C) and the solvent was evaporated in *vacuo*. Four recrystallizations of the residue (65.8 g, mp 98-139°C) from EtOAc (500, 1000, 2 x 900 mL) afforded salt (-)-**4** (14.8 g) (Scheme 1). The salt was dissolved in a minimum amount of water and the solution was added dropwise to NaOH pellets, simultaneously distilling off the crude amine (bp 100-105°C) which was then twice distilled over KOH pellets, providing (-)-**2** (3.80 g, 19 % yield based on the stereomeric mixture) (Scheme 1). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (6H, d, J = 6.5 Hz, 2,5-Me), 1.69 (1H, br.s, NH), 4.10 (2H, m, 2,5-H), 5.71 (2H, 3,4-H). Pyrroline (+)-**2** was similarly obtained using (-)-10-camphorsulfonic acid.

12. Compounds **5,6** were identified on the ^{1}H NMR (400 MHz) spectra. **(2R,5R)-1-[(1'S)-10'-Camphorsulfonyl]-2,5-dimethyl-Δ^3-pyrroline 5** in C_6D_6: δ 0.64 (3H, 7'-Me), 0.87 (1H, m, 6'-H_{exo}), 1.10 (3H, 7'-Me), 1.32 (6H, d, J = 6.5 Hz, 2,5-Me), 1.48 (1H, t, J = 4.5 Hz, 4'-H), 1.51 (1H, d, J = 18.0 Hz, 3'-H_{endo}), 1.63 (2H, m, 5'-H_{exo}, 6'-H_{endo}), 2.00 (1H, m, 3'-H_{exo}), 2.60 (1H, m, 5'-H_{endo}), 2.80 (1H, d, J = 14.6 Hz, 10'-H_A), 3.80 (1H, d, J = 14.6 Hz, 10'-H_B), 4.41 (2H, m, 2,5-H), 5.00 (2H, 3,4-H). **(2S,5S)-1-[(αR)-N-α-Methylbenzylcarbamoyl]-2,5-dimethyl-Δ^3-pyrroline 6** in $CDCl_3$: δ 1.31 (6H, d, J = 6.1 Hz, 2,5-Me), 1.52 (3H, d, J = 7.0 Hz, α-Me), 4.38 (1H, br.d, J = 7.0 Hz, NH), 4.59 (2H, br.m, 2,5-H), 5.07 (1H, m, α-H), 5.63 (2H, 3,4-H), 7.22-7.36 (5H, m, Ph).

13. The optical rotation angle $[\alpha]^{17}_D$ -8.5° (*c* 3, EtOH) was measured for the mixture of isomers **1** (*ca.* 19:81 *cis:trans*); lit.[3a]: $[\alpha]^{20}_D$ -11.5° (*c* 1.5, EtOH) for pure (R,R)-**1**.

14. (a) Brouillard-Poichet, A.; Defoin, A.; Streith, J. *Tetrahedron Lett.* **1989**, *30*, 7061. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron: Asymmetry* **1990**, *1*, 363. (c) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 5349. (d) Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1173. (e) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**,*75*, 109.

15. **(2S,5S)-2,5-Dimethyl-Δ^3-pyrroline-1-carbohydroxamic acid 7** was purified by flash chromatography (EtOAc), yield 78 %. Colourless crystals, mp 48-51°C, $[\alpha]^{20}_D$ +241.6° (*c* 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (6H, d, J = 6.2 Hz, 2,5-Me), 4.63 (2H, m, 2,5-H), 5.65 (2H, 3,4-H), 6.95 (1H, OH), 7.70 (1H, br.s, NH); ^{13}C (50 MHz, $CDCl_3$): δ 19.95 (2,5-Me), 60.20 (C_2,C_5), 130.12 (C_3,C_4), 159.53 (CO).

16. **3-[(2S,5S)-2,5-Dimethyl-Δ^3-pyrroline-1-carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 9** was purified by flash chromatography (EtOAc-hexane 70:30), yield 86 %. Colourless crystals, mp 82-83°C, $[\alpha]^{20}_D$ +299.8° (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (6H, d, J = 6.1 Hz, 2,5-Me), 1.41 (2H, m, 7'-H_{endo}, 8'-H_{endo}), 2.16 (1H, m, 8'-H_{exo}), 2.33 (1H, m, 7'-H_{exo}), 4.68 (1H, m, J = 5.5, 3.5, 1.8 Hz, 4'-H), 4.72 (1H, m, J = 5.4, 3.6, 2.0 Hz, 1'-H), 4.81 (2H, m, 2,5-H), 5.60 (2H, 3,4-H), 6.58 (2H, m, J = 8.1, 5.5, 5.4, 1.8 Hz, 5',6'-H); ^{13}C (50 MHz, $CDCl_3$): δ 20.19 (2,5-Me), 20.68 ($C_{8'}$), 23.38 ($C_{7'}$), 50.23 ($C_{4'}$), 61.21 (C_2,C_5), 70.52 ($C_{1'}$), 129.96 (C_3,C_4), 131.62 ($C_{5'}$), 132.43 ($C_{6'}$), 159.76 (CO).

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