CHEMISTRY LETTERS, pp. 597-598, 1989.

The First Asymmetric 1,3-Dipolar Cycloaddition of 1-Methyl-3-oxidopyridinium and $(\underline{R})_S$-p-Tolyl Vinyl Sulfoxide. An Enantioselective Synthesis of (1S)-(-)-2α-Tropanol

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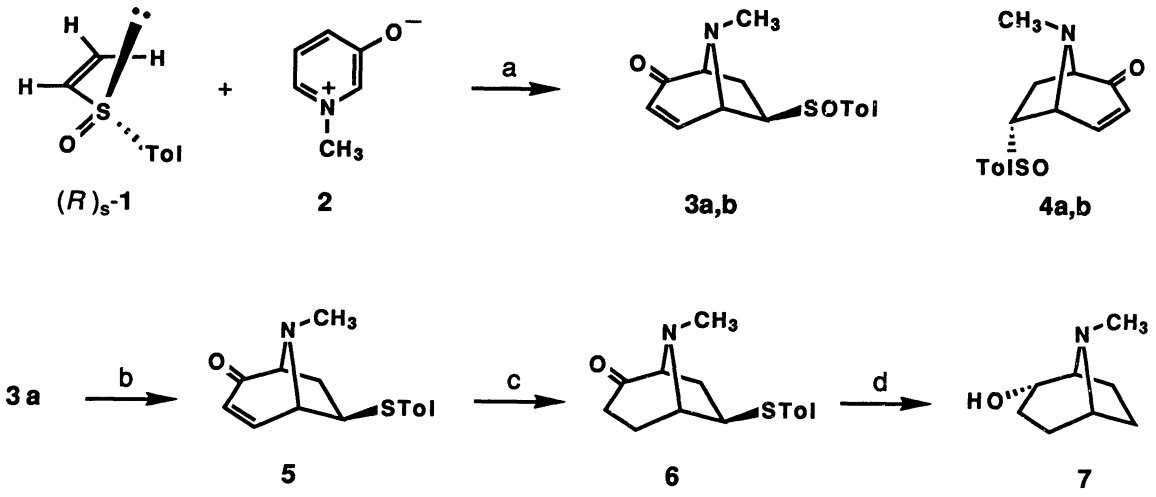
The first enantioselective synthesis of (1S)-(-)-2α-tropanol, which has the opposite absolute configuration to that of natural cocaine, was achieved by an asymmetric 1,3-dipolar cycloaddition of $(\underline{R})_S$-p-tolyl vinyl sulfoxide and 1-methyl-3-oxidopyridinium.

Having succeeded in developing a new strategy for the regio- and stereoselective construction of tropane skeleton by 1,3-dipolar cycloaddition of phenyl vinyl sulfone and further the application to the synthesis of 6α-fluoro-2β-tropanol,[1] we next attempted the first enantioselective synthesis of optically active 2-tropanol by using $(\underline{R})_S$-p-tolyl vinyl sulfoxide (1). (1R)-(+)-2α-Tropanol (+)-(7) has been prepared from natural cocaine.[2] On the other hand, (1S)-(-)-2α-tropanol (-)-(7) (unnatural absolute configuration) has been obtained by optical resolution of racemic 7 for the pharmacological studies.[3] We thought a development of a method for preparing unnatural (-)-7 by asymmetric reaction would be of great interest from both synthetic and medicinal points of view. We have already reported high asymmetric induction in a 1,3-dipolar cycloaddition of acyclic nitrones by using 1.[4] Mechanistic considerations of this type of cycloadditions[4,5] suggested that the major exo adduct (3a), which might be obtained by the reaction of 1-methyl-3-oxidopyridinium (2)[1] with 1, would have a desired absolute configuration for the synthesis of (-)-7. In the present paper, we thus describe the first chiral synthesis of (1S)-(-)-2α-tropanol (-)-7 by the asymmetric 1,3-dipolar cycloaddition of 2 with 1.

Cycloaddition reaction of 1 and the pyridinium 2 proceeded at 90 °C for 4 days to afford a mixture of three of the four possible diastereomers regioselectively. Separation of the reaction mixture on a column of silica gel gave the exo cycloadducts (3a)[6] (mp 121-122 °C, $[\alpha]_D$ -184.7°) and (3b) (mp 132-134 °C, $[\alpha]_D$ +386.9°), and the endo cycloadduct (4a) ($[\alpha]_D$ +183.5°) in 36%, 7%, and 29% yield, respectively. The configurations of 3 and 4 were assigned by their NMR spectra comparing with that of 6β-(benzenesulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one.[1] In this instance, the cycloaddition was shown to have high diastereoselectivity for the formation of exo products 3 (d.e. 68%) and endo adduct 4 (d.e. 100%). However, low level of the stereoselectivity (exo/endo, 60:40) was also observed. The major exo cycloadduct 3a, which has a desired absolute configuration for the synthesis of (-)-7, was reduced with phosphorus tribromide in DMF to afford the sulfide (5)[7]



Reagents and conditions: (a) THF, 90 °C; (b) PBr_3, DMF, 0 °C; (c) H_2/Pd-C, AcOEt, 3 atm; (d) Raney-Ni (W-4), EtOH, reflux.

(mp 59-60 °C, $[\alpha]_D$ -249.7°) in 78% yield. Catalytic hydrogenation of 5 in the presence of palladium-black gave the saturated ketone (6) (mp 114-115 °C, $[\alpha]_D$ +47.0°) in 69% yield. Moreover, the enantiomeric excess of 6 was measured after the transformation of 6 with sodium borohydride into (1S)-6β-(p-tolylsulfenyl)-8-azabicyclo-[3.2.1]octan-2β-ol (8) (mp 33-34 °C, $[\alpha]_D$ +85.7°) and shown to be no less than 96% by the 270 MHz NMR spectroscopy with a chiral shift reagent, Eu(hfc)$_3$.[8] Desulfurization of 6 with Raney-nickel (W-4) afforded (-)-7, colorless crystalline mass, mp<30 °C, $[\alpha]_D$ -15.5° (c 0.793, H_2O), lit.[3a] $[\alpha]_D$ -14.5° (H_2O), in 76% yield. The spectral data (IR and NMR) of the synthetic specimen (-)-7 were consistent with those of (+)-7.[1] The method developed in the present studies proposes a new strategy for the chiral synthesis of both enantiomers of tropane derivatives and will be useful especially for preparing the unnatural enantiomers.

This work was supported in part by grants from the Sankyo Foundation of Life Science, the Japan Research Foundation for Optically Active Compounds, and the Ministry of Education, Science and Culture of Japan (No. 63570985).

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6) All new compounds reported here gave satisfactory spectroscopic and analytical data.
7) Oxidation of 5 with MCPBA gave a mixture of 3a and 3b.
8) In the ^1H NMR spectrum, (±)-8 was resolved to a pair of singlets due to the tolyl methyl signal at 2.53 and 2.57 ppm using a chiral shift reagent, Eu(hfc)$_3$ (0.703 equiv.). By a similar treatment, the spectrum of (+)-8 showed the methyl signal at 2.53 ppm and the corresponding enantiomer was not observed with the limit of detection (<2%).

(Received January 17, 1989)