CHEMISTRY LETTERS, pp. 185-186, 1987.

A New Route to (-)-Aristeromycin and (-)-Neplanocin A *via* the Asymmetric Diels-Alder Cycloaddition

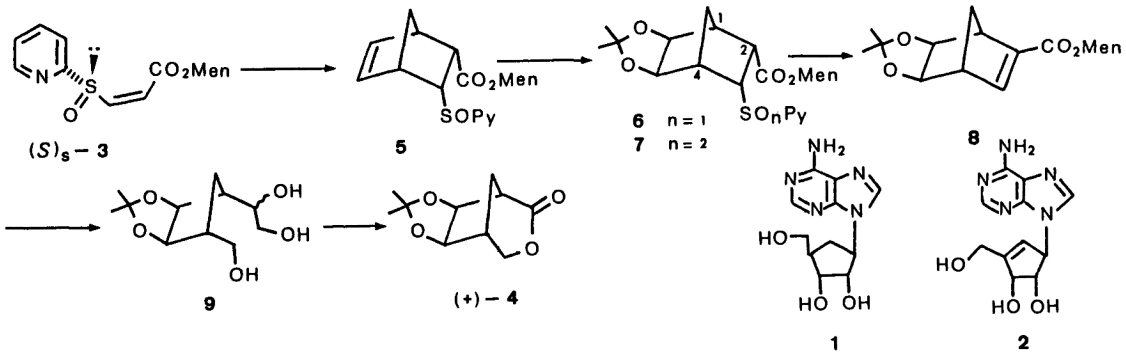
Yoshitsugu ARAI, Yoshikazu HAYASHI, Masatoshi YAMAMOTO, Hiromitsu TAKAYAMA, and Toru KOIZUMI*

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01

An enantioselective synthesis of a central intermediate in the synthesis of (-)-aristeromycin and (-)-neplanocin A *via* the asymmetric Diels-Alder reaction of menthyl $(S)_S$-3-(2-pyridylsulfinyl)propenoate with cyclopentadiene, is described.

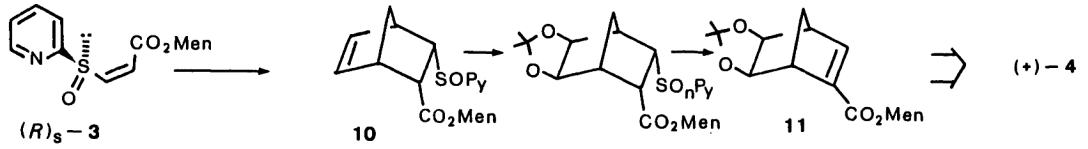
Carbocyclic nucleosides (-)-aristeromycin (**1**) and (-)-neplanocin A (**2**) were isolated from *S. citricolor* and *Actinoplanacea ampullariella*, respectively. Because of a salient antitumor activitity exhibited by the carbocyclic analogues of adenosine there have been considerable efforts directed toward their total synthesis.[1] These efforts have been culminated in the first enantioselective synthesis of **1** and **2** by Ohno and his collaborators.[2] The strategy for the synthesis was based on an enzymatic approach. Recently, we reported that the Diels-Alder cycloaddition of $(S)_S$- and $(R)_S$-3-(2-pyridylsulfinyl)propenoates (**3**) with furan proceeded smoothly to give the corresponding cycloadducts with high diastereoselectivity.[3] In this letter we wish to report an enantioselective synthesis of a central intermediate **4** in the Ohno's synthesis based upon an asymmetric Diels-Alder approach by the use of **3**.

The Diels-Alder reaction of $(S)_S$-**3** and cyclopentadiene in the presence of a Lewis acid (Et_2AlCl, -78 °C, 3 h) gave the cycloadduct **5** as almost single diastereomer in 96% yield.[4] The *endo* configuration of both the sulfinyl and ester groups in **5** was assigned on the basis of ^{1}H-NMR spectroscopy. The diastereomeric excess (d.e.) was proved to be no less than 96% as checked by NMR and HPLC analysis. Hydroxylation (osmium(VIII) tetroxide, trimethylamine *N*-oxide, rt, 12 h) of **5** and subsequent acetonide formation (2,2-dimethoxypropane, acetone, *p*-toluenesulfonic acid, reflux, 3 h) led to **6** and **7** in a ratio of *ca.* 3:1, in quantitative yield. Treatment of the former with *m*-chloroperbenzoic acid gave quantitatively the sulfone **7**. Treatment of **7** with diazabicyclo-[5.4.0]undec-7-ene (DBU) caused elimination to give the α,β-unsaturated ester **8** in 61% yield accompanied with the epimerized sulfone (C-2 epimer of **7**, 26%). Ozonolysis (O_3, CH_2Cl_2; Me_2S , -70 °C; $LiAlH_4$, 0 °C→rt) of **8** gave the triol **9** as a diastereomeric mixture. Oxidative cleavage of **9** with sodium metaperiodate



which followed by Collins oxidation of the resulting anomeric hemiacetal, finally afforded the Ohno's lactone **4** ($[\alpha]_D^{25}$ +46.7°(c 0.48, chloroform) in 48% yield from **8**. The IR spectrum of **4** was superimposable with that of an authentic sample.[2)]

Since Ohno et al. have converted the lactone **4** into (-)-aristeromycin and (-)-neplanocin A, our approach involving the asymmetric Diels-Alder reaction constitutes a formal total synthesis of these antibiotics.



In addition, the Diels-Alder reaction of $(\underline{R})_S$-**3** and cyclopentadiene proceeded to give the endo-diastereomer **10** in 92% yield (d.e. >96%). The cycloadduct **10** was converted into the unsaturated ester **11** as described above. In order to disclose an enantioconvergent route to (+)-**4** starting from each of $(\underline{R})_S$- and $(\underline{S})_S$-**3**, we are currently investigating the transformation of **11** into (+)-**4**.

We are grateful to Professor M. Ohno (The University of Tokyo) for providing spectral data and for valuable discussion. This work was supported by a grant from the Japan Research Foundation for Optically Active Compounds.

References

1) For recent syntheses, see: R.C. Cermak and R. Vince, Tetrahedron Lett., 22, 2331 (1981); C.K.H. Tseng and V.E. Marquez, ibid., 26, 3669 (1985); W.C. Faith, C.A. Booth, B.M. Foxman, and B.B. Snider, J. Org. Chem., 50, 1983 (1985).

2) M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, J. Am. Chem. Soc., 105, 4049 (1983).

3) H. Takayama, A. Iyobe, and T. Koizumi, J. Chem. Soc., Chem. Commun., 1986, 771.

4) All new compounds gave satisfactory 270 MHz NMR, IR, and high resolution mass and/or elemental data. **5**: mp 141-142 °C, $[\alpha]_D^{25}$ +41.9°(c 1.0, $CHCl_3$); **8**: colorless oil, $[\alpha]_D^{25}$ -18.1°(c 2.9, $CHCl_3$); **10**: mp 82-84 °C, $[\alpha]_D^{27}$ -134.5° (c 1.3, $CHCl_3$); **11**: colorless oil, $[\alpha]_D^{26}$ -92.6°(c 4.15, $CHCl_3$).

(Received October 20, 1986)