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

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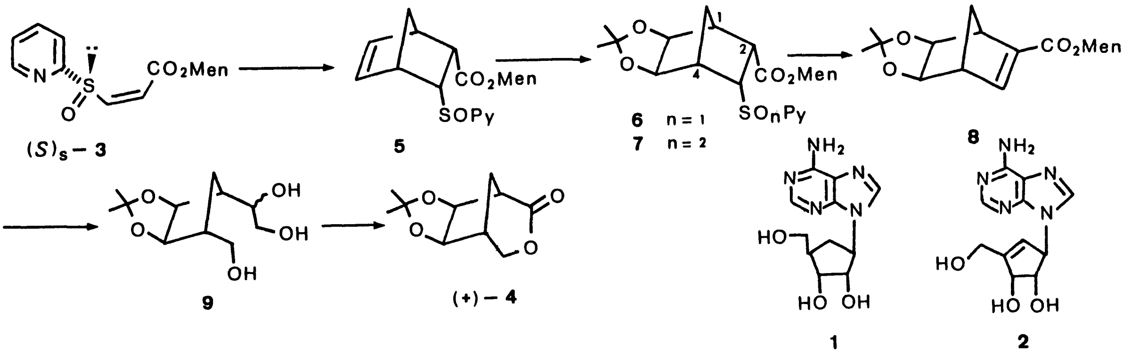
An enantioselective synthesis of a central intermediate in the synthesis of (-)-aristeromycin and (-)-neplanocin A *via* the asymmetric Diels-Alder reaction of menthyl $(\underline{S})_S$-3-(2-pyridylsulfinyl)propenoate with cyclopentadiene, is described.

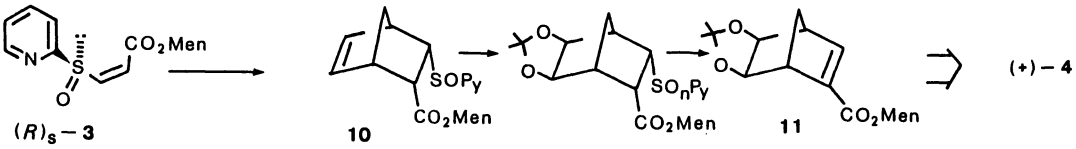
Carbocyclic nucleosides (-)-aristeromycin (**1**) and (-)-neplanocin A (**2**) were isolated from *S. citricolor* and *Actinoplanacea ampullariella*, respectively. Because of a salient antitumor activitity exhibited by the carbocyclic analogues of adenosine there have been considerable efforts directed 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 $(\underline{S})_S$- and $(\underline{R})_S$-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 $(\underline{S})_S$-**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 (*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 (*R*)$_S$- and (*S*)$_S$-3, we are currently investigating the transformation of **11** into (+)-**4.**

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References

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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, $CHCl_3$).

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