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IMINO DIELS-ALDER CYCLOADDITIONS: AN APPLICATION TO THE SYNTHESIS OF (±)-ARISTEROMYCIN

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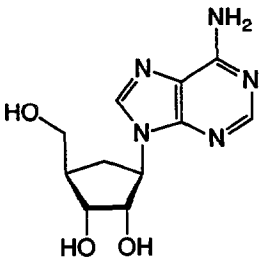
Abstract: A formal synthesis of (±)-aristeromycin starting from the imino Diels-Alder cycloadduct **3a** has been achieved with high overall yield. A novel method for the *in situ* preparation of N-sulfonylimines is reported.

Following the first synthesis[1] and isolation from natural sources,[2] the carbocyclic nucleoside aristeromycin **1** has been the subject of an exceptional body of work.[3] A great effort has been devoted to the discovery of new and efficient synthetic routes,[4] as well as of novel and more active analogues.[5] The basic strategy in most approaches involves the synthesis of the carbocyclic ribofuranosylamine **2** and its conversion to **1** through a protocol well established in nucleoside chemistry.[3]



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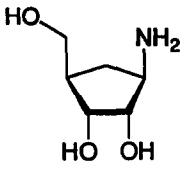


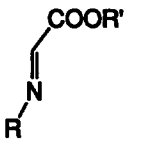
2

Among the reported works, however, only few have been concerned with the absolute stereochemistry and have culminated in enantioselective syntheses of (-)-aristeromycin.[4f-n] We reasoned that a promising starting material for a total synthesis of (-)-**1** could be the azabicyclo[2.2.1]heptene **3**.[6] In fact, the rigid skeleton of **3** allows for an excellent control of the stereochemistry in successive reactions toward **1**. Moreover, the possibility of monitoring the cycloaddition step by introducing a chiral auxiliary group (eg, **4c-e**) and the high level of stereocontrol reached in the Diels-Alder chemistry,[7] make these substrates even more attractive. In this paper we wish to communicate our preliminary results on an ongoing study on the synthesis of aristeromycin and on the diastereoselective imino Diels-Alder cycloadditions.[8]

The reaction between **4a** and cyclopentadiene was carried out under the conditions optimized by Barco et al.[6b] (benzene, 0°C). The exclusive formation of the *exo* product **3a**[9] isolated in 84% yield after chromatography, is in agreement with the reported work, where a rational explanation of the stereoselectivity of the reaction is also given.[6b] The azanorbornene **3a** was subjected to

catalytic osmylation (NMO, 1 mol eq.; OsO_4, 1%; acetone/THF 1:2, 1h, 25 °C , 94%) and the diol protected (2,2-dimethoxypropane, acetone, cat. TsOH, 15', 25°C, 98%) to afford acetonide **5**.

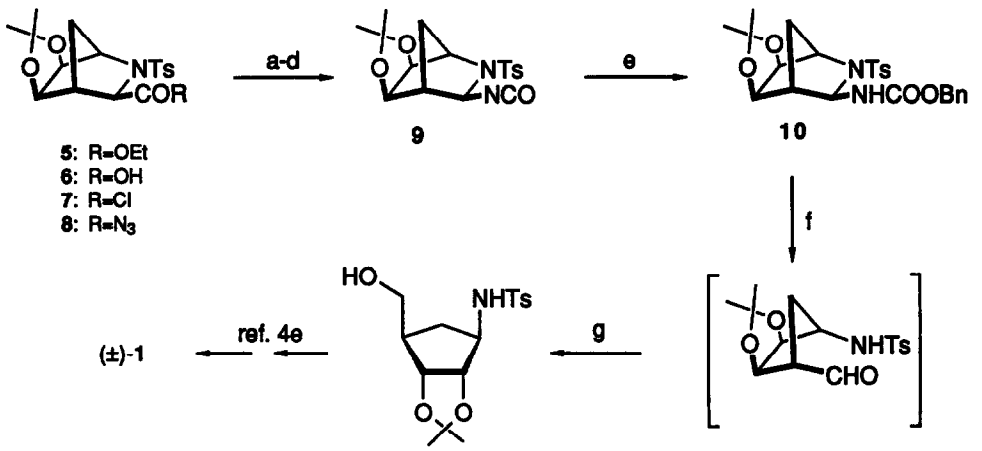
3



4

a: R=Ts, R'=Et
b: R=SO_2Ph, R'=Et
c: R=SO_2Ph, R'=(-)-menthyl
d: R=SO_2Ph, R'=(-)-bornyl
e: R=SO_2Ph, R'=(-)-8-phenylmenthyl

The ester function in **5** was hydrolyzed (aq. NaOH 10%, MeOH, 96%), the acid **6** transformed into chloride **7** (thionyl chloride, 15', reflux, 100%), which was treated with aqueous sodium azide under phase-transfer conditions (methylene chloride, tetramethyl ammonium bromide) to give acyl azide **8** in 89% yield. This compound underwent quantitative Curtius rearrangement (toluene, reflux, 30') to isocyanate **9**[10] which was trapped with benzyl alcohol to yield benzyl carbamate **10** (toluene, reflux, 2h, 76%). Catalytic hydrogenation and in situ reduction of the labile aldehyde **11** afforded alcohol **12** in 88% yield from **10**.[11]



5: R=OEt
6: R=OH
7: R=Cl
8: R=N_3

9

10

12

11

a. NaOH (aq.), MeOH, 25°C; b. Thionyl chloride, reflux; c. NaN_3 (aq.), CH_2Cl_2, TMAB, 25°C;
d. Toluene, reflux; e. Benzyl alcohol, toluene, reflux; f. 10% Pd/C, H_2, MeOH, 25°C;
g. $NaBH_4$, 3 eq., MeOH, 25°C.

The conversion of **6** to **12** could be performed directly without isolation of any intermediate, with high overall yield. As amido alcohol **12** was already converted to (±)-aristeromycin,[4e] the present work can be considered a formal synthesis of that carbonucleoside.

$PhSO_2NHCH_2-COOR$ $PhSO_2NHCH(Br)-COOR$

13 **14**

a: R=Et
b: R=(-)-menthyl
c: R=(-)-bornyl
d: R=(-)-8-phenylmenthyl

Once the synthetic route to **1** from **3a** was set, chiral imines **4c-e** were needed in order to test the level of diastereoselection obtainable in the Diels-Alder step. However, Albrecht and Kresze's method[6a] was not suitable for the preparation of these substrates, due to the slow reaction of N-sulfinyl p-toluenesulfonamide with hindered glyoxylates and expecially to the difficulty of purification of the resulting imines. This problem could be solved by generating in situ imines **4c-e** by dehydrobromination of the corresponding bromides. Thus, glycine ethyl ester hydrochloride, taken as an example for comparison with the known method, was reacted with benzenesulfonyl chloride (pyridine/CH_2Cl_2 1:1, 25°C 2h, 94%) to give compound **13**; this was quantitatively brominated (with the aid of UV light) to bromo derivative **14**. Treatment of **14** with triethylamine in benzene at 0°C in the presence of excess cyclopentadiene resulted in 80% isolated yield of *exo* adduct **3b**. In a similar sequence, azanorbornenes **3c-e** were obtained in excellent yields as mixture of two diastereoisomers. However, the observed diastereomeric ratios, calculated from integration of selected NMR signals, were not very encouraging: 56:44 in the case of **3c**, 53:47 in that of **3d**; 60:40 for **3e**.

To our knowledge, this is the first example of cycloaddition of chiral N-sulfonylimines. We are currently trying to understand why these substrates are so little affected by chiral induction[12] and to synthesize a more rigid chiral auxiliary to enhance the facial selectivity in these reactions.

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9. The structures assigned for all new compounds are fully consistent with their spectroscopic and analytical data. **3a**: m.p. 83-84 °C; ^{1}H-NMR ($CDCl_3$, TMS), ∂ (ppm): 1.25 (t, 3H, J=7.0 Hz), 1.46 (m, 1H), 2.04 (m, 1H), 2.42 (s, 3H), 3.31 (m, 1H), 3.48 (t, 1H, J=1.0 Hz), 4.17 (q, 2H, J=7.0 Hz), 4.58 (m, 1H), 6.17 (m, 1H), 6.25 (m, 1H), 7.27 (m, 2H), 7.76 (m, 2H).
10. **9**: m.p. 122-123°C; ^{1}H-NMR ($CDCl_3$, TMS), ∂ (ppm): 1.27 (s, 3H), 1.42 (s, 3H), 1.78 (dquint., 1H, J=11.0 Hz, J=1.5 Hz), 1.97 (bd, 1H, J=10.0 Hz), 2,45 (s, 3H), 2.58 (s, 1H), 4.00 (bs, 1H), 4.19 (bd, 1H, J=5.5 Hz), 4.54 (dt, 1H, J=5.5 Hz, J=1.5 Hz), 4.95 (s, 1H), 7.34 (d, 2h), 7.78 (d, 2H).
11. **12**: m.p. 109-110 °C; ^{1}H-NMR ($CDCl_3$, TMS), ∂ (ppm): 1.22 (s, 3H), 1.33 (d, 1H, J=14.0 Hz), 1.39 (s, 3H); 2.30 (m, 2H), 2.43 (s, 3H), 2.72 (bs, 1H), 3.69 (m, 3H), 4.37 (d, 1H, J=6.0 Hz), 4.55 (d, 1H, J=6.0 Hz), 6.53 (d, 1H, J=10.0 Hz), 7.26 (d, 2H), 7.77 (d, 2H)
12. Preliminary experiments showed that these cycloadditions are not affected by Lewis acid catalysis.

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