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STUDIES ON THE SYNTHESIS OF NARGENICIN A_1. AN EXAMPLE OF AN INTRAMOLECULAR DIELS-ALDER REACTION THAT PROCEEDS WITH A BOAT-LIKE CONFORMATION OF THE CONNECTING CHAIN

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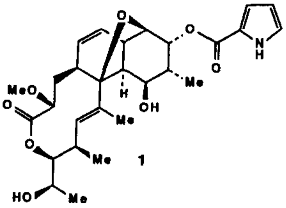
Abstract: The intramolecular Diels-Alder reaction of triene 2 proceeds with excellent stereoselectivity via boat transition state B and provides cycloadduct 4 in 78% yield.

In connection with recent studies directed towards the synthesis of nargenicin A_1 (1)[3] we had occasion to explore the intramolecular Diels-Alder reaction of triene 2.[3c,4] Based on literature precedent[5] and prior experience[6] we expected that this cyclization would provide selective access to the cis-fused octalin nucleus of 1. Although two diastereomeric cis-fused cycloadducts could be produced, we were optimistic that 3, suitably functionalized for further elaboration to 1, would predominate since the Diels-Alder reaction would proceed via chair-like transition state A. On the other hand, for cis fused diastereomer 4 to be obtained, the Diels-Alder reaction would be constrained by the acetonide blocking group to proceed via B with a boat-like conformation of the connecting



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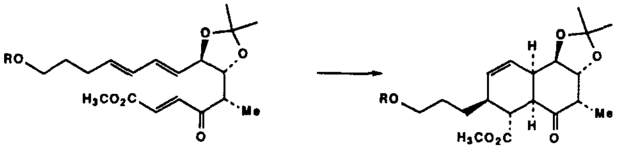
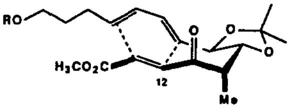
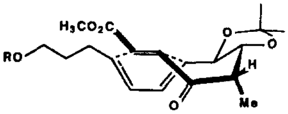


2
3



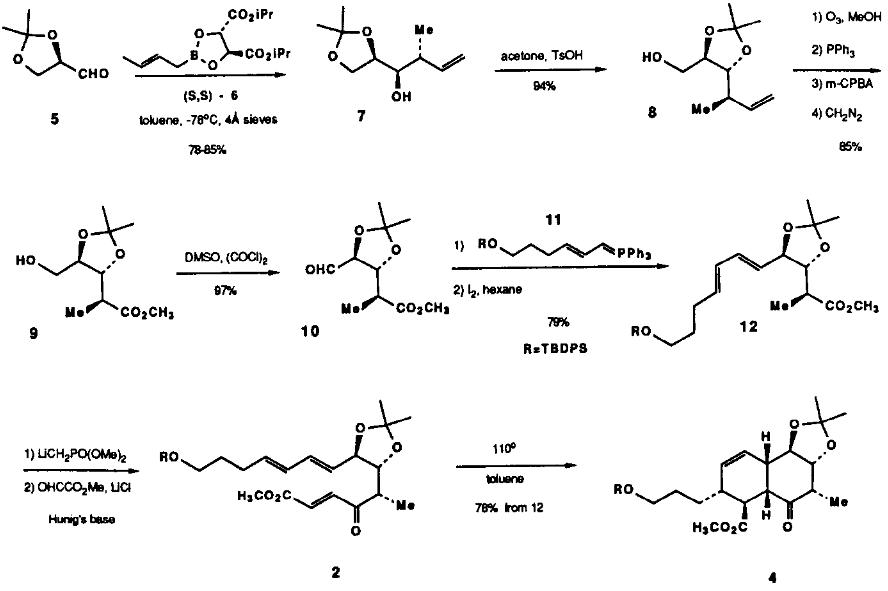
A (chair)



B (boat)

blocking group to proceed via B with a boat-like conformation of the connecting chain. Although several reports have appeared suggesting that intramolecular Diels-Alder reactions may proceed via boat-like conformations as in B, experimental evidence in those cases has been lacking.[5,7] Moreover, computational studies have suggested that the chair conformations, at least in simple systems, should be favored.[8] It was with great suprise, therefore, that we discovered that the cyclization of 2 proceeds with exceptional selectivity via B, providing the undesired diastereomer 4 as the only observed cycloadduct! Details of this investigation follow.

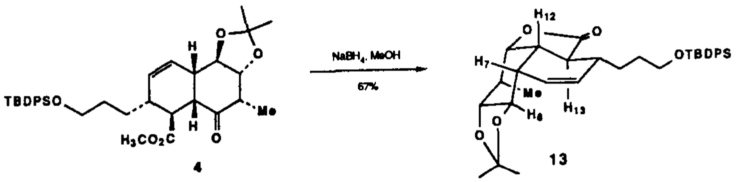
The synthesis of 2 commenced with the reaction of D-glyceraldehyde acetonide 5 and diisopropyl tartrate modified (E)-crotylboronate (S,S)-6.[9] This reaction, described in detail elsewhere,[9] provides 7 with 96% diastereoselectivity. Exposure of 7 to catalytic pTsOH in acetone provides an easily separated 10:1 equilibrium mixture of 8 and 7; after one recycle of recovered 7, diastereomerically pure 8[10] ($[\alpha]^{23}_{D}$ + 29.6° (c 1.2, CH_2Cl_2)) was obtained in 94% yield. Ozonolysis of 8 (MeOH, -78°C), reduction of the intermediate α-methoxy-



hydroperoxide with Ph_3P, oxidation of the resulting aldehyde with mCPBA and finally treatment with CH_2N_2 provided hydroxy ester 9 ($[\alpha]^{25}_{D}$ + 24.8° (c 1.4,

CH_2Cl_2)) in 85% yield. Oxidation of 9 by using a standard Swern procedure[11] provided crude 10 which, without purification, was immediately treated with 1.05 equiv. of ylid 11[12] in THF (-78°C). The resulting mixture of dienes was then isomerized to E,E-12 (>10:1; $[\alpha]^{25}_D$ + 14.4° (c 2.9, CH_2Cl_2)) by exposure to catalytic I_2 in hexane (76% yield from 9). Treatment of 12 with 2 equiv. of $LiCH_2PO(OMe)_2$ in THF at -78°C set the stage for introduction of the dienophile via a modified Horner-Wadsworth-Emmons reaction (MeO_2CCHO, diisopropylethylamine, LiCl, CH_3CN, 23°C, 5 min).[13] Triene 2 thus prepared cyclized smoothly at 110°C in toluene (22 h), providing cycloadduct 4 ($[\alpha]^{25}_D$ - 10.7° (c 1.1, CH_2Cl_2)) as the only detected product in 78% overall yield from 12.

The stereochemistry of 4 was assigned following conversion to lactone 13 ($[\alpha]^{25}_D$ + 18.0° (c 2.5, CH_2Cl_2)). Homonuclear decoupling experiments established the ring fusion to be cis ($J_{7,12}$ = 5 Hz) while difference NOE studies showed strong interactions between H(13), H(8) and the C(10)-methyl group. Similarly, H(9), H(11) and H(12) were shown to be cis by the NOE technique (irradiation of H(11)). These data are uniquely consistent with the stereostructure depicted here for 13, requiring in turn that the Diels-Alder reaction of 2 proceeded via B rather than A.



Studies designed to probe the generality of this result are in progress. Hand in hand with these efforts we hope to uncover a selective pathway to nargenicin precursors such as 3.

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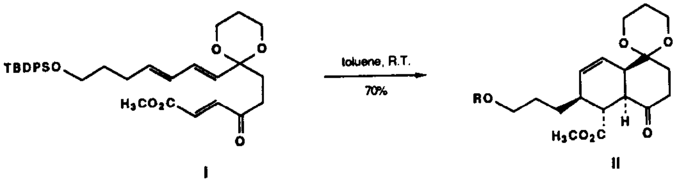
6. The intramolecular Diels-Alder reaction of i provides cis-fused ii with 10:1 selectivity (Roush, W.R.; Coe, J.W., unpublished research).



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10. (a) Spectroscopic properties of all new compounds are fully consistent with the assigned structures. (b) A satisfactory combustion analysis (±0.3% for C, H) was obtained for compounds 2, 4, 7, 8, 12, and 13.

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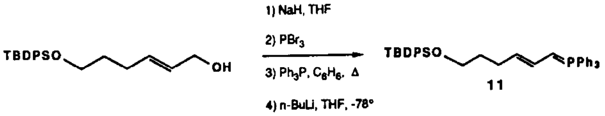
12. Ylid 11 was prepared as summarized below.



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