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AN EXAMINATION OF π-FACIAL SELECTIVITY IN THE DIELS-ALDER REACTION OF A CHIRAL DIENE - A SYNTHESIS OF (+)-5,6,10-TRI-(EPI)-ACTINOBOLIN.

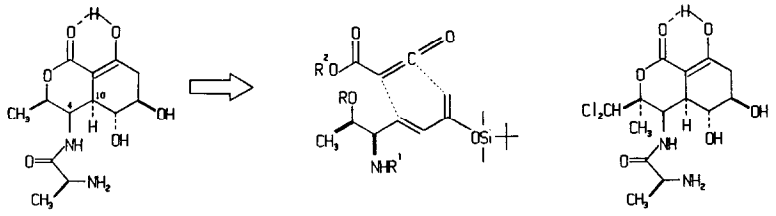
Alan P. Kozikowski* and Thaddeus R. Nieduzak
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260
James P. Springer
Merck Institute, Rahway, New Jersey 07065

Summary: The π-facial course of the Diels-Alder reaction of an L-threonine derived silyloxydiene has been examined during the course of a study aimed at the total synthesis of actinobolin/bactobolin.

Actinobolin is an antibiotic of unusually low toxicity which possesses a broad spectrum of antibiotic activity.[1a] It was first isolated as its crystalline sulfate salt by Haskell and Bartz in 1959.[1b,c] Bactobolin, a closely related chlorine containing antibiotic, has been isolated from a culture broth of Pseudomonas BMG 13-14.[2a] Bactobolin has been shown to prolong the survival period of mice implanted with mouse leukemia L-1210 cells.[2b]

In our efforts to synthesize these compounds, we were intrigued with the following dissection in which an "intermolecular" Diels-Alder reaction between a threonine-derived silyloxydiene and a

Scheme 1. A Retrosynthetic Analysis.



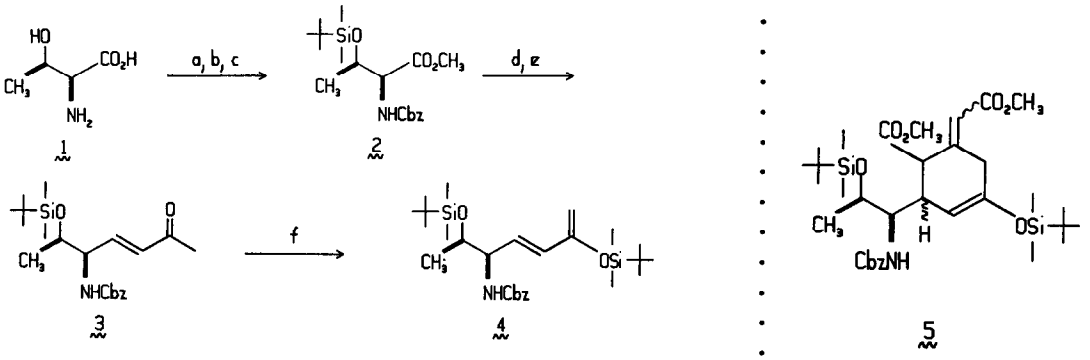
Actinobolin Bactobolin

carboalkoxyketene equivalent was envisioned to lead to the rapid assembly of these substances in the laboratory. Our intermolecular approach thus contrasts with the "intramolecular" Diels-Alder approach to actinobolin described by Ohno and co-workers.[1d]

L-Threonine (**1**) was converted via the enone **3** to the silyloxydiene **4** by the sequence shown in Scheme 2.[3] That no epimerization had occurred during any of the foregoing steps was made clear from a subsequent X-ray analysis.

The reactivity of this new diene system was surveyed with a variety of dienophiles which could potentially function as carboalkoxyketene equivalents. While 1,3-dicarboethoxyallene[4] did react to provide a cycloadduct **5** in high yield, subsequent transformations resulted unfortunately in migration of the double bond into the ring system. Methyl β-bromopropiolate,[5] also an established carboalkoxyketene equivalent, failed to react with diene **4**. In contrast, a good reaction was found when methyl propiolate was employed as the dienophile. Not unexpectedly, a mixture of diastereomers **6** resulted in which the isomer ratio varied from 3:1 (110°C, 24 h, PhH,

Scheme 2. Synthesis of the Diene Component.

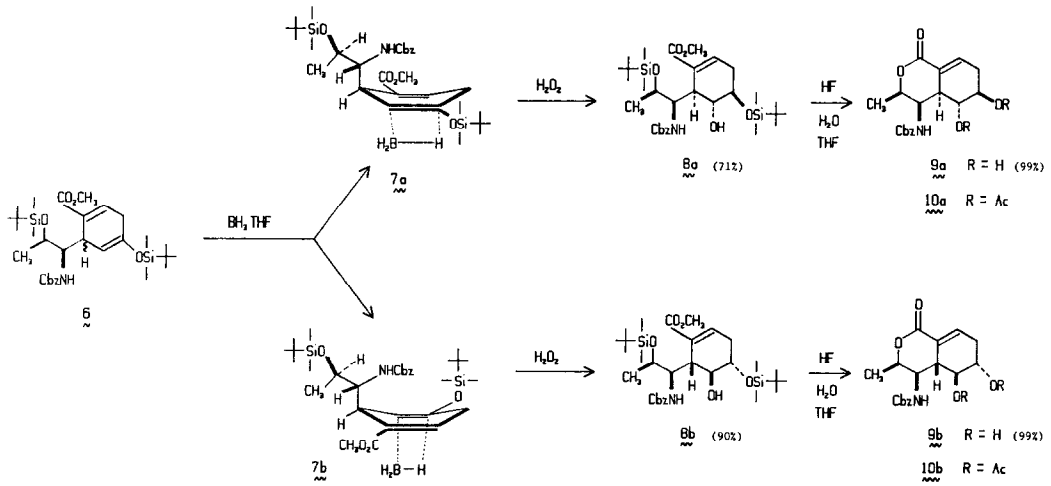


a) CbzCl, H_2O, NaOH (97%); b) CH_3OH, H^+ (99%); c) t-Bu$(CH_3)_2$SiCl, DMF, imid (99%); d) Dibal, $C_6H_5CH_3$, -78°C (85%); e) $(C_6H_5)_3P$=CHCOCH$_3$, THF, reflux (95%); f) t-Bu$(CH_3)_2$SiOTf, C_6H_6, Et_3N, 50°C (96%).

85%) to 1.7:1 (220°C, 3 h, neat, 87%).

Each pure isomer from the first set of reaction conditions was further transformed to its corresponding lactone (**9a** or **9b**) in order that an analysis of coupling constants could be made in these more rigid bicyclic systems. A facial specific hydroboration reaction was first carried out on the silyl enol ether group of **6a** and **6b**.[6] This reaction was predicted to occur opposite the amine bearing appendage through that conformation which minimizes $A^{(1,2)}$-strain (Scheme 3).[7] Oxidative workup then leads to the diol system having the trans-diequatorial arrangement of hydroxyl groups required for the construction of actinobolin. Lastly, HF/H_2O treatment provided the desired δ-lactone systems which were further derivatized as their diacetates **10a** and **10b**. Unfortunately, while a discernable difference in the coupling constants between H-4 and H-10 of **9a**

Scheme 3. Further Transformations of the Cycloadduct 6.



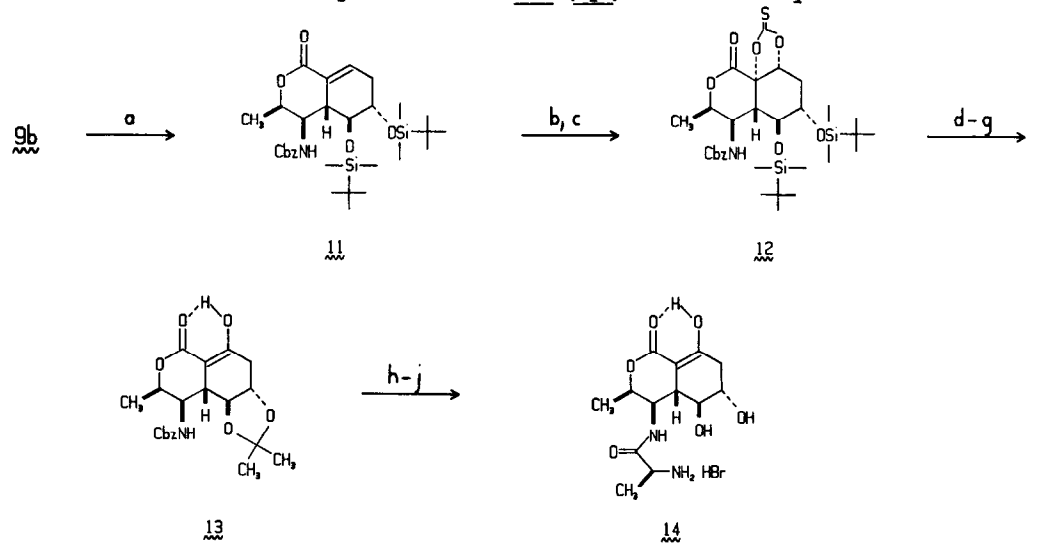
and **9b** was anticipated, these couplings were in fact found to be identical (2.5 Hz) for the two lactones. Consequently, an X-ray structural analysis was carried out on the diacetate **10b** prepared from the major lactone isomer.[8] From this X-ray analysis, we discovered that our original notions about the stereochemistry of the hydroboration process were well founded.[9] However, the stereochemistry at C-10 (and consequently that at C-5 and C-6) was opposite that

required to assemble actinobolin in stereochemically correct form. It is, in fact, the minor isomer from the Diels-Alder reaction which must be used to procure the target structure.

While methods are presently being sought to better control the stereochemical outcome of the intermolecular Diels-Alder reaction, the chemistry required to use the remaining double bond of the cycloadduct to introduce the C-8 carbonyl group (present in its enol form) and the precise techniques needed to perform the peptide coupling reaction have been studied using **9b**.

After innumerable studies, a hydroxyl group was finally introduced into the disilyl lactone **11** at C-8 by a sequence of reactions involving: (a) vicinal hydroxylation with osmium tetroxide and N-methylmorpholine N-oxide[10] (b) thionocarbonate formation with N,N'-thiocarbonyldiimidazole[11] and (c) tri-n-butyltin hydride reduction.[12] In order to maximize the yield obtained in the oxidation of the C-8 alcohol to ketone, the silyl groups of **12** were removed and the vicinal diol reprotected as its acetonide. A PCC/NaOAc oxidation then afforded the desired enolized β-keto ester **13** in 81% yield.[13] Lastly, the Cbz group was removed by hydrogenolysis, and the free amine immediately subjected to a peptide coupling reaction employing a mixed anhydride of Z-alanine.[14] Acidolysis of the intermediate with anhydrous hydrogen bromide in dichloromethane at 0°C removed both the amine and oxygen protecting groups to afford (+)-5,6,10-tri-(epi)-actinobolin as its crystalline hydrogen bromide salt **14** (Scheme 4).

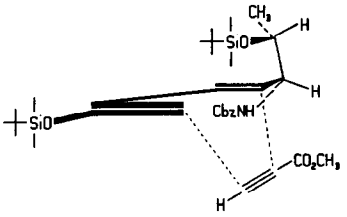
Scheme 4. Completion of the Tri-(epi)-actinobolin Synthesis.



a) t-Bu$(CH_3)_2$SiCl, imd, DMF (100%); b) OsO_4, NMO, acetone/H_2O (94%); c) $(imd)_2C=S$, THF (100%); d) n-Bu_3SnH, C_6H_6 (85%); e) $BF_3 \cdot OEt_2$, CH_3CN; f) 2-methoxypropene, H^+, THF; g) PCC, NaOAc, CH_2Cl_2 (73% overall from 12); h) H_2, Pd/C, CH_2Cl_2; i) Z-Ala-OCO_2i-Bu, CH_2Cl_2; j) HBr, CH_2Cl_2 (78% overall from 13).

The present effort does delineate a useful way of converting an amino acid into a reactive Diels-Alder diene. Based upon a consideration of steric and electronic factors as well as the now assignable isomer ratios, we suggest the following transition state picture to rationalize the production of **7b** as the major diastereomer of the Diels-Alder reaction. This transition state minimizes electron withdrawal from the diene system (by the "inside" nitrogen substituent) and favors approach of the dienophile from the bottom face anti to the bulky silyloxy bearing appendage. Further studies of such diastereoselective Diels-Alder reactions are being

conducted.[15,16]



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