Tetrahedron Letters,Vol.27,No.29,pp 3353-3356,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

STUDIES ON THE TOTAL SYNTHESIS OF SESBANIMIDE: A HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF THE AB RING SYSTEM

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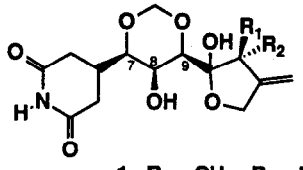
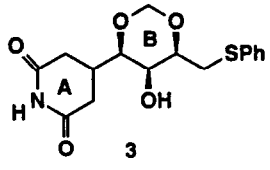
Abstract. An efficient, highly diastereoselective synthesis of the AB ring system (3) of sesbanimide is described.

Sesbanimides A (1) and B (2) are structurally novel antitumor agents isolated from several Sesbania species.[2] The very significant biological properties and low availability of these compounds from natural sources has stimulated considerable interest in their synthesis.[3] As an extension of our work on the synthesis of functionalized carbohydrates[4] we have developed and report herein a highly diastereoselective synthesis of the AB ring system 3. It is noteworthy that the three asymmetric centers of 3 have been introduced with excellent control by using stereoselective organic reactions, and that the brevity and efficiency of our synthesis of key intermediate 8 rivals approaches in which the B ring originates entirely from a readily available carbohydrate precursor.[3a-d] This work further illustrates, therefore, the power of emerging synthetic methodology for solving complex stereochemical problems.



1, $R_1 = CH_3$, $R_2 = H$

2, $R_1 = H$, $R_2 = CH_3$



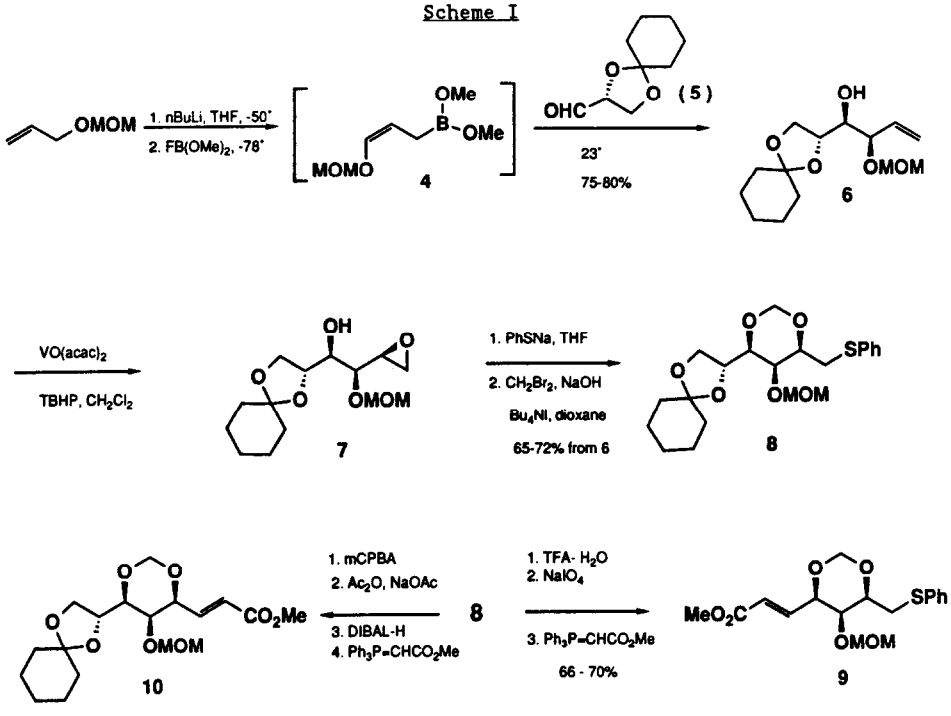
3

Based on our previous studies of the reactions of substituted allylic boronates and chiral aldehydes,[4,5] we anticipated that homoallyl alcohol 6 could be prepared by the addition of a (Z)-γ-alkoxyallylboronate to glyceraldehyde cyclohexyl ketal (5).[6] This transformation was smoothly accomplished by treating 5 with reagent 4 [generated in situ from 2.0 equiv of allyl MOM ether, 1.9 equiv of n-BuLi in THF-hexane (-50° → -30°C, 2 h), and 1.9 equiv of $FB(OMe)_2$ (-78° → 0°C, 2 h)][7,8] at 25°C for two days. After the usual workup homoallyl alcohol 6[9a,b] (m.p. 64-65°C; $[\alpha]^{23}_D$ -59.5° (c=1.0, $CHCl_3$)) was isolated in 75-80% yield by direct recrystallization and chromatography of the mother liquors. Since

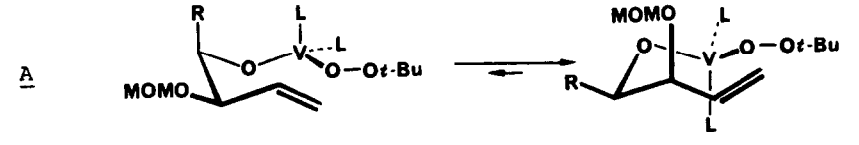
stereoisomers of 6 were not observed, the diastereoselectivity of this reaction must be >20:1.

The second stereochemically critical step in this synthesis involved the epoxidation of 6. Whereas a mixture of diastereomers (~1:1) was obtained when MCPBA was employed, application of the $VO(acac)_2$-TBHP system[10] provided 7[9a] as the sole product in excellent yield. This is one of the most highly stereoselectivity epoxidations yet reported for a homoallylic alcohol lacking a (Z)-olefinic substituent.[10a] The stereochemistry of 7 was assigned by the hydrolytic conversion to glucitol hexacetate [(i) NaOH, dioxane-H_2O;

Scheme I



(ii) BCl_3, CH_2Cl_2; (iii) Ac_2O, NaOAc] and is consistent with epoxidation having occurred via conformation B.

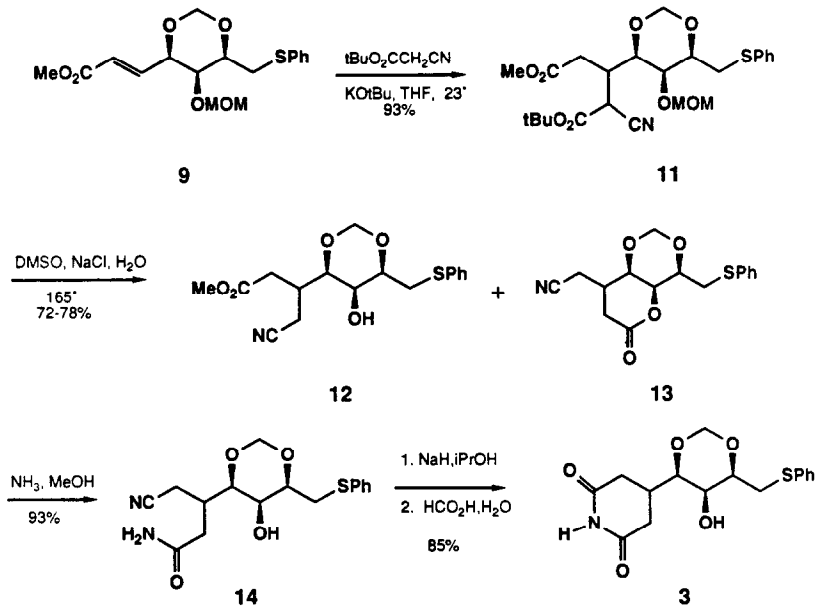


With the three stereocenters of the B ring now in place, epoxide 7 was treated with PhSNa in THF. The resulting 1,3-diol[9a,b] $([\alpha]^{23}_D$ + 15.5° (c=1.0, $CHCl_3$) was subjected to the methylenation conditions described by Fleet,[3a] providing 8[9a,b] in 65-72% overall yield

from 6. Hydrolysis of 8 with 2% aqueous trifluoroacetic acid (0°C, 5 min), periodate cleavage of the 1,2-diol[9a,b] and standard Wittig olefination then gave unsaturated ester 9[9a] as a 2:1 mixture of olefin isomers in 66-70% yield. Alternatively, the opposite end of 8 could be unmasked and elaborated selectively by using the Pummerer-Wittig sequence described by Masamune and Sharpless.[11] Intermediates 9 and 10 are heterochirally related and are ideally functionalized for use in syntheses of either enantiomer of sesbanimide.

An efficient method for elaboration of the glutarimide ring system is summarized in Scheme II. The Michael reaction of 9 with tert-butyl cyanoacetate proceeded smoothly to

Scheme II



give 11[9a] as a mixture of diastereomers. Subjection of 11 to the Krapcho decarboxylation procedure (NaCl, H_2O, DMSO, 165°C)[12] effected cleavage of the $-CO_2C(Me)_3$ unit as well as deprotection of the MOM ether. The resulting mixture (~1:1) of cyanoester 12 and cyanolactone 13 underwent smoot ammonolysis in MeOH, providing amide 14 in excellent yield. Finally, the succinimide synthesis was completed by treatment of 14 with NaO^iPr in i-PrOH followed by a mild formic acid hydrolysis;[13] the yield of succinimide 3[9a,b] ($[\alpha]^{22}_D$ + 55° (c=0.6, $CHCl_3$)) was 53% from 9, and 17-21% overall from ketal 5.

In summary, we have developed an efficient, highly stereoselective synthesis of the sesbanimide AB fragment 3 by a route featuring the reactions of allylic boronic ester 4 and aldehyde 5, and the epoxidation of homoallylic alcohol 6 as the stereochemically critical steps. This sequence promises to find application in the synthesis of other carbohydrate-

based systems. Such investigations, along with efforts to develop a stereoselective solution to the C ring of sesbanimide, are in progress and will be reported in due course.

Acknowledgement. This research was generously supported by grants from the National Institutes of Health (CA-29847 and AI-20779).

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(Received in USA 7 May 1986)