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STUDIES OF THE FURAN-CARBONYL PHOTOCYCLOADDITION REACTION: THE DETERMINATION OF THE ABSOLUTE STEREOSTRUCTURE OF ASTELTOXIN.

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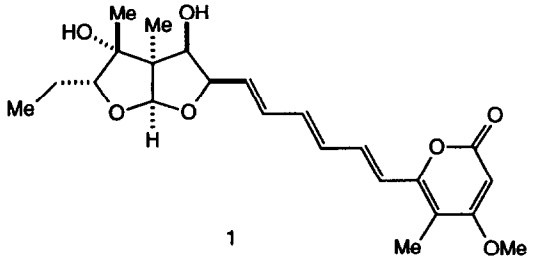
Abstract The absolute stereochemistry of (+)-asteltoxin has been determined by experiments that include the conversion of R- isopropylidene glyceraldehyde into the degradation product **2**.

Asteltoxin, 1, is one member of a growing class of microbial metabolites that have been the subject of investigations relating to their biological activity, biosynthesis, and synthesis.[1] Recently, we described a procedure that employed the furan-carbonyl photocycloaddition reaction and resulted in the synthesis of asteltoxin in racemic form.[2] In this Letter, the photocycloaddition of 3,4- dimethylfuran with R-isopropylidene glyceraldehyde and the subsequent converison of one of the photoadducts to a degradation product of asteltoxin is reported. Comparison of these materials allows the absolute stereochemistry of asteltoxin to be assigned as depicted in 1.[3]



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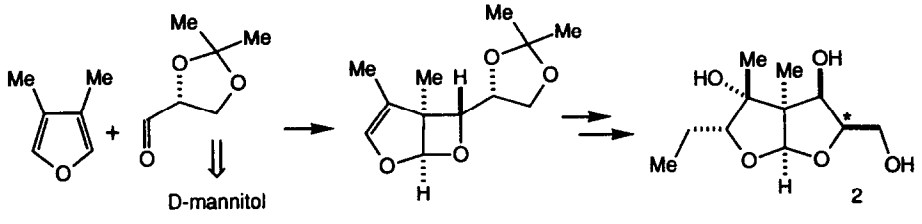
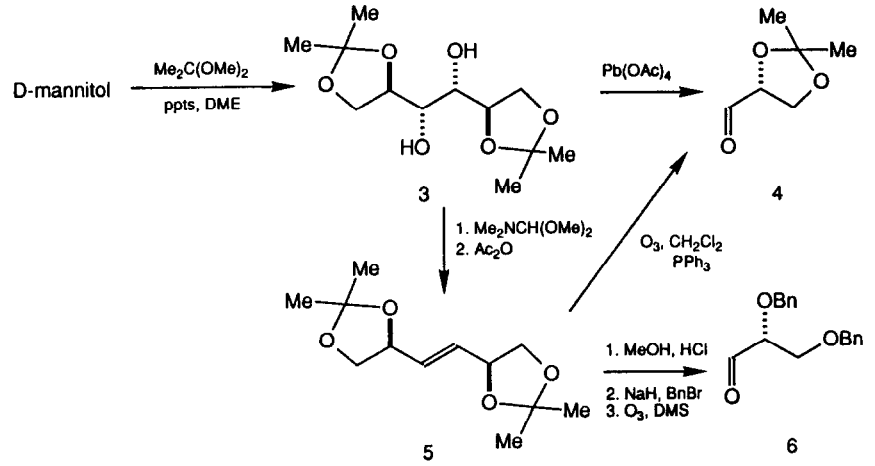


2

Our plan to establish the absolute configuration of natural (+)-asteltoxin called for the asymmetric synthesis of the indicated enantiomer of degradation product **2**. The absolute configuration of the asterisked carbon of **2** would be insured by the use of R-isopropylidene glyceraldehyde in the photocycloaddition, which in turn is readily obtainable from D-mannitol.

R-Isopropylidene glyceraldehyde has been employed as an enantiomerically pure starting material on numerous occasions.[4] The most common method for the preparation of this labile aldehyde involves the lead tetraacetate oxidation of the bisacetonide of D-mannitol.[5] Oxidative cleavage of **3** by this procedure and distillation of the reaction mixture resulted in the formation of **4** that was contaminated with acetic acid. The photocycloaddition of this material with 3,4-dimethylfuran failed, presumably due to the acetic acid promoted retro[2+2] cycloaddition. We were not able to prepare and purify a sample of **4**, by

this route, that was sufficiently free of byproducts to allow participation in a subsequent Paterno-Büchi photocycloaddition reaction.

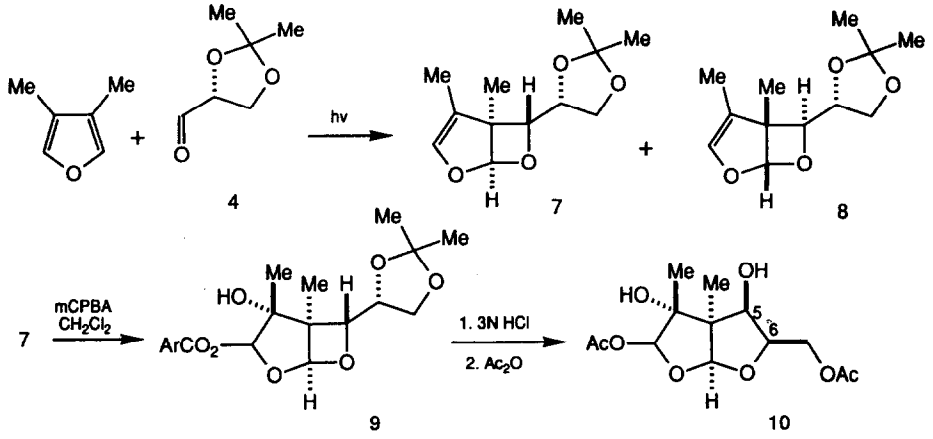


An alternative route to **4** that avoided these purification problems utilized the deoxygenation product **5**.[6] Ozonolysis of **5** in methylene chloride followed by reduction with triphenylphosphine resulted in a crude reaction mixture that was directly distilled to provide **4** in 78% yield. The olefin **5** proved to be a valuable precursor to assorted R-glyceral derivatives such as the dibenzyl ether **6**[7] and presumably could be converted to an S-glyceral synthon via a hydroxyl inversion sequence.[8]

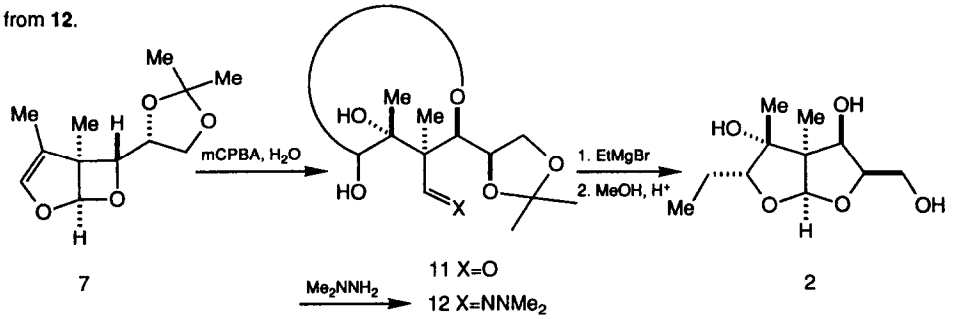
The photocycloaddition of **4** (1.50g, 11.5mmol; prepared from **5**) and 3,4-dimethylfuran (23mmol) in Et_2O (3ml) with a 450W Hanovia lamp fitted with a Vycor filter afforded a 1.2:1.0 mixture of **7** and **8**, respectively, in 35% combined yield. In addition, substantial racemization occurred in this reaction. The chiral shift reagent $Eu(hfc)_3$ indicated **7** and **8** were obtained in ca. 54% ee. Since **4** was shown to exist in 96% ee by analysis of the derived soketal ($NaBH_4$, MeOH) and prolonged irradiation of **7** and **8** did not result in a lowering of their enantiomeric excess, this result is presumed to reflect the photolability of **4** towards racemization under the conditions of the reaction. We did not examine the effect of an increase in the furan/aldehyde ratio on the ee of this reaction. The high exo- selectivity (relative face selectivity) in combination with the poor diastereotopic face selectivity with regard to the chiral aldehyde was expected on the basis of results from previous studies.[9] A mechanistic interpretation of these results has been presented elsewhere.[10]

At this point, the identity of **7** and **8** was unknown. The two diastereomers were separated by SiO_2 chromatography and treated separately with mCPBA in methylene chloride. The less mobile (SiO_2) and major photoproduct **7** gave rise to **9** which was hydrolyzed and acetylated to provide the bis tetrahydrofuran **10**. The cis disposition of the hydroxyl and acetoxymethyl substituents at C_5 and C_6 was indicated by the comparison of the coupling constant ($J_{5,6}$ = 2.2Hz) in **10** with those of related compounds (cis and trans isomers) prepared in previous studies.[2]

Confident now of the identity of **7**, the synthesis of **2** from **7** was carried out in four additional steps. The oxidation of **7** with mCPBA in aqueous THF produced a material which has spectral data consistent with the structure **11**. Without isolation, **11** was directly converted to the hydrazone **12** in 62%



yield from **7** upon treatment with N,N-dimethylhydrazine. The reaction of **12** with excess ethylmagnesium bromide proceeded with the same sense of face selectivity observed in our previous studies but to a lesser degree (3:1).[2a] Treatment of the crude reaction mixture with methanol and Amberlyst 15 effected the removal of the acetonide and cyclization to the bistetrahydrofuran **2** which was isolated in 40% yield from **12**.



The optical rotation of **2** obtained by this five step synthetic sequence was $[\alpha]_D^{25} = +30.2 \pm 0.4$ (c = 0.72, MeOH). Compound **2**, obtained from (+)-**1** by ozonolysis and reduction as previously described,[2a] exhibited a rotation of the same sign ($[\alpha]_D^{25} = +53 \pm 2$ (c = 0.31, MeOH)) which is in close correspondence to the synthetic substance of 54% ee (corrected rotation of synthetic **2** = +55.9). On the basis of these experiments, we conclude that the absolute configuration of (+)-asteltoxin is as depicted in **1**.

The proposal for the biosynthesis of asteltoxin by Vleggaar and Steyn that is consistent with ^{13}C and ^{18}O labeling studies involves the polyepoxidation of a straight chain polyene precursor.[11] A subsequent epoxide ring opening is followed by a 1,2-bond migration in the form of an epoxide (or pinacol) rearrangement that provides a branched aldehyde that is utilized in the formation of the bistetrahydrofuran moiety. The latter rearrangement is related to the conversion of averufin to versiconal acetate on the way to aflatoxin B_1.[12] It is interesting to note that aurovertin B is structurally related to asteltoxin by the same 1,2-bond migration[11c] that is characteristic of the averufin to versiconal acetate interconversion. The determination of the absolute stereostructure of asteltoxin allows by inference the assignment of stereochemistry of the epoxidation reactions mediated by the putative monooxygenase(s) in the *in vivo* synthesis of asteltoxin. Comparison of the absolute stereochemistry of related congeners such as citreoviridin[1f] and aurovertin B[1d] provides insight into the stereochemical relations of biosynthetic transformations leading to these compounds.[13]

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