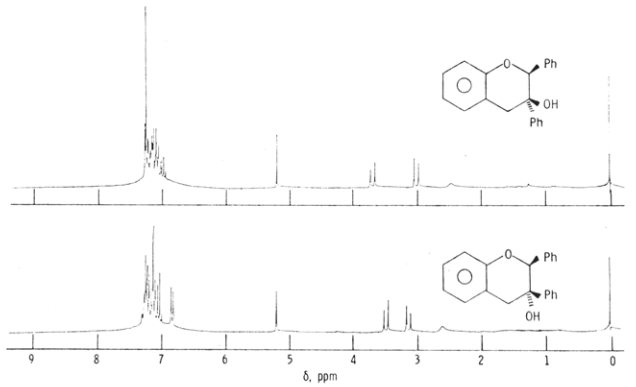


Figure 1. ^1H NMR spectra (250-MHz) of the two diphenylbenzodihydropyranol photoproducts in $CDCl_3$.

ated for 24 h with a Pyrex-filtered 450-W mercury arc. HPLC and NMR analysis of the crude photolysate indicated a ≥80% yield of two isomeric products in a ratio of 1.6/1. Flash chromatography[4] on silica gel with 9:1 hexane/ethyl acetate eluent isolated the two isomers which were identified as the isomeric 2,3-diphenyl-3-hydroxy-3,4-dihydrobenzopyrans **2** by their ^1H NMR spectra ($CDCl_3$) which are shown in Figure 1. The broad singlets at 2.5–2.7 ppm are hydroxyls. The major isomer is assumed to be *Z* (with the two phenyl rings trans), in accord with all other ketone-derived biradical cyclizations.[5,6] This assignment is supported by the doublet at 6.8 ppm assigned to (*E*)-**2**, which is due to one conformer having a 3-phenyl axial, such that its ortho protons are in the shielding cone of the benzopyran benzene ring.

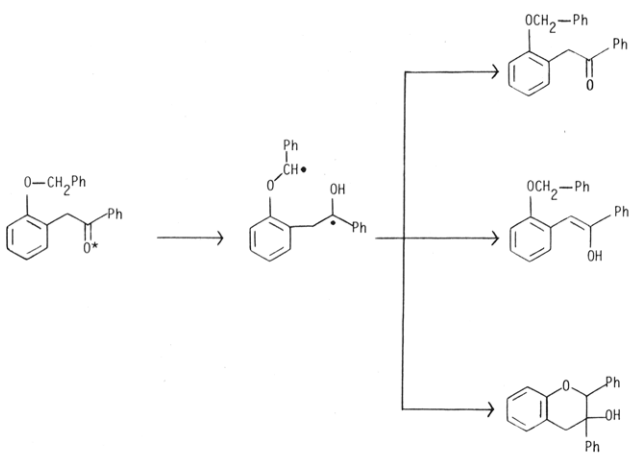
The quantum yield for the photocyclization is only 0.045 in benzene and is increased only slightly to 0.05 by the presence of 2 M pyridine. The reaction is readily quenched with conjugated dienes, $k_q\tau = 183 \pm 9$ M^{-1} in benzene. With $k_q = 6 \times 10^9$ M^{-1} s^{-1},[7] the rate of triplet decay is 3×10^7 s^{-1}. This value is much faster than radiationless decay of the triplet, so some subsequent process must be responsible for low quantum yields.

We assume that the cyclization arises by triplet state ϵ-hydrogen abstraction to generate a 1,6-biradical intermediate. The actual rate of hydrogen abstraction is comparable to that for δ-hydrogen abstraction by triplet *o*-(benzyloxy)benzophenone.[3] The insignificant rate effect caused by the extra methylene group in **1** is not surprising in light of the very large rate constants for δ-hydrogen abstraction found in the α-tolyl ketones, which have restricted conformational flexibility.[1]

The presumed 1,6-biradical intermediate has three major reactions available to it (Scheme I). Two of these paths involve internal disproportionation to the starting ketone or its enol. We have recently shown that disproportionation to enol via a 1,4-hydrogen transfer is the major reaction of several 1,5-biradicals.[6] Such a reaction involves a 1,5-H transfer in this 1,6-biradical and therefore might well dominate both cyclization and 1,7-hydrogen transfer back to ketone. We suggest that this competition causes the low cyclization quantum yield.

These results establish that ϵ-hydrogen abstraction, like δ, can occur cleanly in ketones with suitable conformational restraints. The reaction leads in this case to a high-yield

Scheme I



preparation of benzopyrans. We are now exploring the scope of this new photoreaction.

Acknowledgment. This work was supported by NSF Grant No CHE82-02404.

Registry No. **1**, 94203-48-2; (*Z*)-**2**, 94203-50-6; (*E*)-**2**, 94203-49-3.

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Enantioselective Synthesis of Swainsonine, a Trihydroxylated Indolizidine Alkaloid

Summary: A total synthesis of (−)-swainsonine in 21 steps and 6.6% overall yield starting from *trans*-1,4-dichloro-2-butene and *N*-benzyl-*p*-toluenesulfonamide is described. The synthesis employs the methodology of the Masamune/Sharpless approach to polyhydroxylated natural products.

Sir: The indolizidine alkaloid swainsonine[1] (**1**) is known to be an effective inhibitor of both lysosomal α-mannosidase[2] and mannosidase II.[3] Lysosomal α-mannosidase is involved in the cellular degradation of polysaccharides, while mannosidase II is a key enzyme in the processing of asparagine-linked glycoproteins.[4] The use of swainsonine as a biochemical tool for the study of these systems has been limited by its lack of availability. In the past year, three syntheses of swainsonine have appeared, each starting from a glucose or mannose derivative.[5]

Swainsonine is believed to be a substrate-site directed inhibitor of α-mannosidase.[2] Part of the rationale behind

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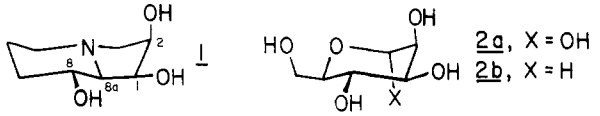
this conclusion is the structural similarity between swainsonine and α-D-mannose, **2a**, or more specifically,



N-protonated swainsonine and the mannosyl cation,[1b] the reactive intermediate involved in the hydrolysis of α-linked polysaccharides. Comparison of CPK models of swainsonine and 1,5-anhydro-D-mannitol, **2b**, indicates a close spatial relationship between the heteroatoms of the two molecules. We felt that the methodology recently developed by the Masamune/Sharpless groups for the iterative synthesis of polyhydroxylated natural products[6] was well suited for the synthesis of swainsonine or any of its stereoisomers.

In this synthesis, we demonstrate that a suitably protected nitrogen is compatible with the asymmetric epoxidation and with the other transformations in the Masamune/Sharpless iterative process. The requirements for the nitrogen protecting groups are that they render the nitrogen resistant to oxidation and that neither the nitrogen lone pair nor any part of the protecting group act as an internal nucleophile toward the epoxide function.[7] The *N*-benzyl-*p*-toluenesulfonamide moiety meets these requirements.

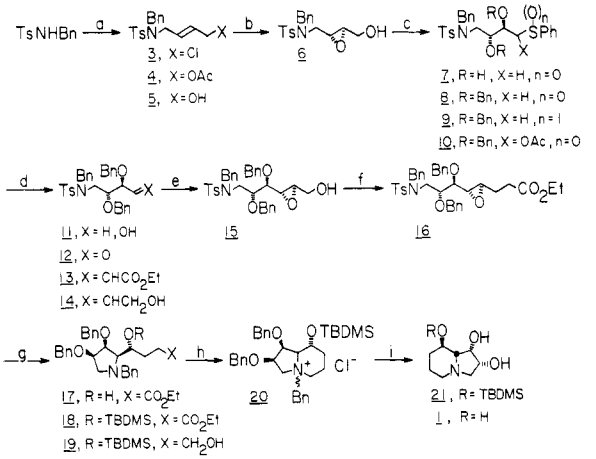
The synthesis of swainsonine is outlined in Scheme I. Alkylation of *N*-benzyl-*p*-toluenesulfonamide[8] with a threefold excess of *trans*-1,4-dichloro-2-butene (Aldrich) gives the allylic chloride **3**. This material is resistant to direct hydrolysis.[9] However, treatment of **3** with sodium acetate in DMF followed by hydrolysis affords the allylic alcohol **5** in overall 68% yield.

Asymmetric epoxidation of **5** under the standard conditions[10] yields the crystalline epoxy alcohol **6** in 95% ee.[11] $[[\alpha]^{20}_D$ +20.0° (*c* 1.84; $CHCl_3$)]. Conversion of **6** into the epoxy alcohol **15** is accomplished in nine steps (30% yield). The chemistry involved is similar to that used for the total synthesis of the hexoses;[6] however, we were unable to convert acetoxy sulfide **10**[12] directly into aldehyde **12** (1.8 equiv of dibal, toluene, −78 °C) without some epimerization at the α-position of **12**. Instead, complete reduction of **10** (using LAH) to alcohol **11** followed by Swern oxidation[13] to **12** proceeds with no epimerization. Treatment of aldehyde **12** with triethyl phosphonoacetate gives the desired ester **13** (*E*:*Z* 32:1). Reduction of the ester followed by asymmetric epoxidation employing (−)-Dipt results in the desired epoxy alcohol **15**, homogeneous by HPLC (≥321:1).[14]

The final two carbons required for the swainsonine backbone are added by Moffatt oxidation of **15** followed by direct addition of (carbethoxymethylene)triphenylphosphorane.[15] Diimide reduction[16] of the resultant α,β-unsaturated ester affords the epoxy ester **16** in 74% yield from **15**.

The tosyl protecting group of **16** is removed with sodium naphthalide.[17,18] None of the corresponding acyclic amine is detected, instead the pyrrolidine hydroxy ester **17** is isolated. This labile material is immediately protected using *tert*-butyldimethylsilyl triflate,[19] giving the silyl ether **18** in 68% yield from **16**. Reduction of **18** affords alcohol **19** in 79% yield. Mesylation of **19** leads directly to a mixture of cis- and trans-fused bicyclic quaternary ammonium salts **20**. Without purification, **20** is debenzylated[20] to a single amino diol **21** in quantitative yield from **19**. Desilylation of **21** was accomplished on Dowex 50W-X8 (H^+ form).[21] Washing the resin with 10% NH_4OH fol-

Scheme I[a]



[a] (a) i, NaH (1 equiv), (*E*)-$ClCH_2CH{=}CHCH_2Cl$ (3 equiv), DMF, 0 °C → room temperature, 6 h; ii, NaOAc, DMF, 120 °C, 5 h; iii, K_2CO_3, MeOH, room temperature, 2 h (68% overall). (b) (−)-Dipt (1.5 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 equiv), TBHP (3 equiv), CH_2Cl_2, −20 °C, 2.5 h (91% yield). (c) i, PhSH (1.2 equiv), *t*-BuOH, 0.5 N NaOH, 85 °C, 5 h (71% yield); ii, $PhCH_2Br$ (2.1 equiv), NaH (2 equiv), *n*-Bu_4NI, THF, room temperature, 18 h (91%); iii, MCPBA (1.5 equiv), CH_2Cl_2, −78 °C, 2 h (100%). (d) i, Ac_2O, $(CF_3CO)_2O$, 2,6-lutidine, room temperature, 3 h (71%); ii, $LiAlH_4$ (2 molar equiv), THF, 0 °C, 30 min (92%); iii, $(COCl)_2$ (1.1 equiv), Me_2SO (2.4 equiv), DBU (2 equiv), CH_2Cl_2, −60 °C, 30 min; iv, $(EtO)_2P(O)CH_2CO_2Et$, NaH, $PhCH_3$, 0 °C, room temperature (67% over two steps, 85% based on 21% recovered starting alcohol **10**); v, Dibal (3 equiv), $PhCH_3$, −78 °C, 1 h (93%). (e) (−)-Dipt (1.5 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 equiv), TBHP (3 equiv), CH_2Cl_2, −20 °C, 21 h (93%). (f) i, Dicyclohexylcarbodiimide (3 equiv), Me_2SO, C_5H_5NHOTf, 5 h, 40 °C, then Ph_3PCHCO_2Et, 24 h (89%); ii, $KO_2CN{=}NCO_2K$, pyridine, AcOH, 40 °C, 40 h (85%). (g) i, $C_{10}H_8$/Na (2 equiv), DME, −60 °C, 30 min; ii, *t*-Bu(Me)$_2$SiOTf, triethylamine, CH_2Cl_2, 0 °C, 1 h (68% over two steps); iii, Dibal (3 equiv), $PhCH_3$, 0 °C, 2 h (79%). (h) MsCl (1.1 equiv), triethylamine, CH_2Cl_2, 0 °C → room temperature, 18 h (100%). (i) i, Pd black, 10% HCO_2H/MeOH, room temperature, 18 h (100%); ii, Dowex 50W-X8, MeOH, 24 h (84%).

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lowed by lyophilization gives swainsonine (1) in 84% yield from **21**, mp 140–142 °C (after sublimation), mmp 138–142 °C,[22] $[\alpha]^{25}_D$ −73.8° (*c* 0.21, EtOH)[23] [lit.[1d] mp 144–145 °C, $[\alpha]^{24}_D$ −83.4° (*c* 0.32 EtOH)].

The ^1H and ^{13}C NMR, IR, and TLC behavior[1a,b,d] of our swainsonine matches that published for material from natural sources. When hepatoma HG-2 cells were cultured in the presence of synthetic swainsonine and natural swainsonine, identical effects on the secreted proteins, antitrypsin and antichymotrypsin, were observed.[24]

This synthesis of swainsonine is highly stereoselective in both a relative and an absolute sense and appears to be the first reported noncarbohydrate route to this natural product. Although the synthesis is linear, it is unambiguous. This route also provides for controlled stereochemical variations throughout, allowing selective access to all 16 epimers and/or enantiomers of swainsonine. We are presently working on the synthesis of swainsonine isomers that are epimeric at C-2 and at both C-2 and C-8.[25] By analogy to the proposed mechanism of enzyme inhibition by swainsonine, these isomers might act as inhibitors of glucose and galactose processing enzymes, respectively.

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Supplementary Material Available: Experimental details and physical and spectral data for each isolated compound (20 pages). Ordering information is given on any current masthead page.

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(24) We thank Professor H. F. Lodish and N. H. Kong of the M.I.T. Biology Department for performing this biological assay.

(25) **Note Added in Proof**: We have recently completed the syntheses of these two ("gluco" and "galacto") swainsonine isomers.

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Metal Ion Controlled Addition to α,β-Dialkoxy Carbonyl Compounds

Summary: Complementary stereoselection in the addition of carbon and hydride nucleophiles to α,β-dialkoxy carbonyl systems can be obtained with Mg^{2+}-based (syn addition) and Li^+- and Ti^{4+}-based (anti addition) reagents.

Sir: Asymmetric addition to acyclic chiral carbonyl compounds is a valuable synthetic transformation for which several theoretical models have been proposed.[1-6] The chelate model, which requires a suitably positioned internal ligand, can produce highly selective, predictable addition processes, due to the conformationally biased, cyclic nature of the complexed carbonyl.[5,6] The critical role played by the metal counterion in promoting chelate formation in alkoxy carbonyl systems and thus enabling control of the direction of nucleophilic addition was established by Still in 1980[6] and has been more fully defined recently by Reetz,[7] Mulzer,[8] and others.[9] However, in carbonyl compounds with multiple functional groups, several chelate structures are a priori feasible and the relative contributions of the possible chelate structures, as well as of relevant nonchelate models, will presumably influence the stereochemical outcome of addition. We have been attempting to elucidate the critical parameters responsible for directed chelate control in carbonyl compounds with multiple functional groups and present here studies on the nucleophilic addition of organometallic and metal hydride reagents to four closely related α,β-dialkoxy carbonyl systems, 2,3-*O*,*O*-dibenzylglyceraldehyde (1)[10] and 2,3-*O*-

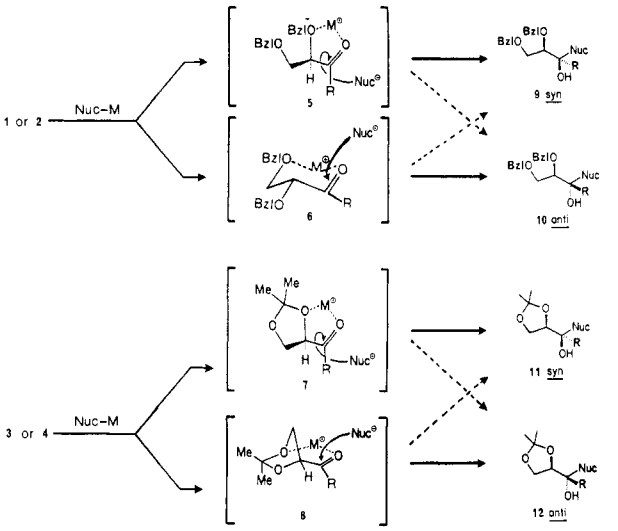

Figure 1. Anticipated stereochemical course of nucleophilic addition via chelated structures. Nucleophilic addition governed by the non-chelate, Felkin model would produce anti products in all cases.

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