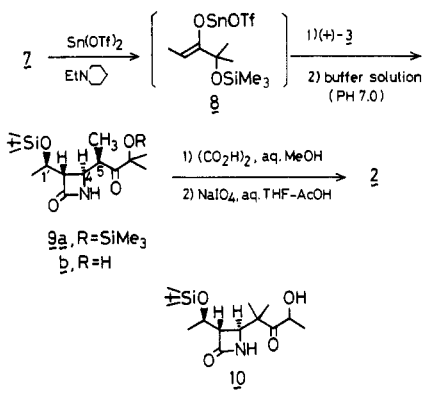
Scheme I

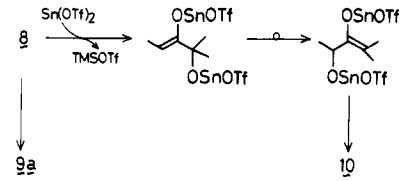


syntheses of **2** have been accomplished by highly diastereoselective aldol-type reactions which employ a boron enolate of the *chiral* oxazolidone **4** (coupled with zinc bromide)[2a] and tin(II) enolates of the *chiral* thiazolidinethione **5**[2b] and the *achiral* oxazolidinethione **6**.[2c] We now report that the utilization of the tin(II) enolate of the simple *achiral* ketone **7**[4] provides a remarkably high diastereoselectivity to afford the key precursor **2** in ≥95% diastereomeric purity.

Scheme I depicts the overall transformation we have now developed. Tin(II) enolate **8** was generated by treatment of ketone **7** (2.5 equiv based on (+)-**3** used) with tin triflate[5] (2.0 equiv) and *N*-ethylpiperidine (2.0 equiv) in dichloromethane at −70 °C, and to this solution was added a dichloromethane solution of the azetidinone (+)-**3** at that temperature. After being stirred at room temperature for 2 h, the reaction mixture was treated with a phosphate buffer solution (pH 7.0). Usual workup followed by column chromatography afforded the adduct **9a** (R = $SiMe_3$)[6] in 90% isolated yield, along with a small amount (4% yield) of the unexpected adduct **10**.[7] NMR analysis (500 MHz) of the unpurified products revealed that the diastereomeric ratio (β/α) for **9a** was 95/5.[8,9] The adduct **9a** was then subjected to desilylation followed by oxidative cleavage to afford the desired precursor **2** with ≥95% β-selectivity[10] in 72% overall yield from **9a**.

The synthetic operations described above deserve special comment. (1) Surprisingly enough, the stoichiometry of ketone to tin triflate (and amine) was found to play a key factor in determining the product composition. While the use of an excess of ketone **7** provides almost exclusively the desired adduct **9a** as described above, the use of equimolar amounts (2.5 equiv) of ketone **7**, $Sn(OTf)_2$, and the amine resulted in a considerably increased yield (40%) of the unexpected adduct **10**, together with 60% yield of **9a** (β/α = 94/6). We suggest that the enolate-to-enolate isomerization depicted below might be responsible for the formation of the unusual product **10**. (2) The specific

Enolate Isomerization



structure of ketone **7** is indispensable for the aldol-type reaction concerned.[11] Attempted reactions using 2-siloxy-3-pentanone[12] in place of ketone **7** totally failed under similar conditions, giving no adducts at all. (3) More conveniently, the tedious desilylation step in the above-mentioned procedure can be omited by treatment of the resulting reaction mixture with aqueous ammonium chloride solution instead of the buffer solution, thereby permitting direct isolation of the desilylated adduct **9b** (R = H). Thus, the synthesis of **2** from (+)-**3** can be accomplished by the two-step operation requiring no purification of the intermediate.

In summary, we have now developed a convenient new method for preparing the 1-β-methylcarbapenem key precursor. The structural simplicity of the enolate precursor, coupled with the easy availability of (+)-**3**, makes the present approach an attractive method of choice for a relatively large scale synthesis of the key precursor **2**. Further improvement of the method outlined here is in progress.

Acknowledgment. We thank Dr. T. Takaya and Mr. T. Chiba of Fujisawa Pharmaceutical Co. for their valuable discussions.

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(5) For the utilization of $Sn(OTf)_2$ for generating tin(II) enolates, see: Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, 40, 1381 and references cited therein.

(6) Mp 162 °C; IR ($CHCl_3$) 3410, 1750, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.006 (s, 3 H), 0.004 (s, 3 H), 0.125 (s, 9 H), 0.806 (s, 9 H), 1.083 (d, J = 7.02 Hz, 3 H), 1.111 (d, J = 6.4 Hz, 3 H), 1.261 (s, 3 H), 1.307 (s, 3 H), 2.834 (dd, J = 1.8 and 4.27 Hz, 1 H), 3.495 (dq, J = 5.19 and 7.02 Hz, 1 H), 3.746 (dd, J = 1.84 and 5.19 Hz, 1 H), 4.099 (dq, J = 6.41 and 4.27 Hz, 1 H), 5.817 (br s, 1 H); $[\alpha]^{17}_D$ −3.8° (*c* 1.0, $CHCl_3$) for the 94:6 mixture of **9a** and its 1α-epimer.

(7) IR ($CHCl_3$) 3500, 3400, 1760, 1700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.77 (s, 9 H), 1.08 (s, 3 H), 1.13 (d, J = 6.0 Hz, 3 H), 1.19 (s, 3 H), 1.25 (d, J = 7.5 Hz, 3 H), 2.77 (dd, J = 2.0 and 6.0 Hz, 1 H), 3.82 (d, J = 2.0 Hz, 1 H), 4.10 (dq, J = 6.0 and 6.0 Hz, 1 H), 4.50 (q, J = 7.5 Hz, 1 H), 6.80 (br s, 1 H).

(8) The two stereoisomers, **9a** and its 1α-epimer, are clearly distinguishable by 500-MHz NMR. Selected δ values for **9a**/its 1α-epimer are as follows: 1.083/1.130 (d, 5-CH_3), 1.111/1.190 (d, 1'-CH_3), 2.834/2.706 (dd, 3-H), 3.746/3.695 (dd, 4-H).

(9) This high β-diastereoselectivity can be rationalized by essentially the same cyclic transition state as advanced for explaining the comparably high β-selectivity observed with the boron[2a] and tin(II) enolates.[2b]

(10) Determined by the ^1H NMR spectrum which is in accord with the reported values.[1]

(11) It is noteworthy that a similar reaction employing the tin enolate of 2,2-dimethyl-3-pentanone was found to afford only a low yield (≤10%) of the corresponding adduct, although the diastereoselectivity was quite high (≥95% β). Another notable finding is that an attempted reaction of the silyl enol ether of ketone **7** with (+)-**3** in the presence of zinc iodide did not afford any adducts at all.

(12) This ketone is of special interest because both the tin enolates generated directly from this ketone and via the enolate-to-enolate isomerization could give rise to the identical adduct.

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Chelate Selectivity in Chelation-Controlled Allylations. A New Synthesis of Castanospermine and Other Bioactive Indolizidine Alkaloids

Summary: An efficient synthesis of polyhydroxylated indolizidine alkaloids relies on new heteroatom-selective Sakurai reactions with $TiCl_4$.

Sir: Synthetic carbohydrate chemistry has, in the past decade, enjoyed a renaissance as a critical testing ground for evaluating new methods of relative and absolute ste-

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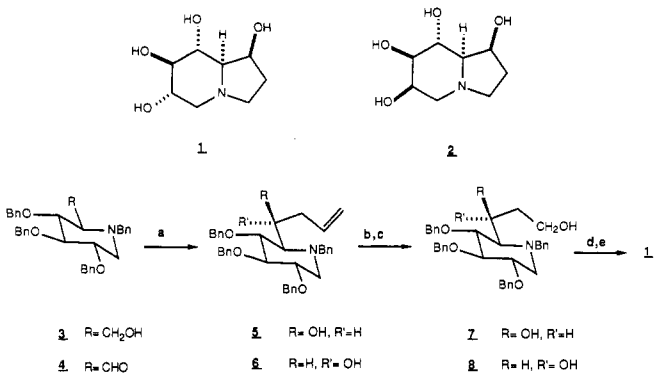
Scheme I[a]



[a] (a) allyltrimethylsilane (3.6 equiv), $TiCl_4$ (2.4 equiv), CH_2Cl_2, −85 °C; 15 h; (b) O_3, CH_2Cl_2, −78 °C; (c) $NaBH_4$, ethanol; (d) MsCl, Et_3N, CH_2Cl_2; (e) H_2, Pd/C.

reochemical control. This is particularly appropriate, since carbohydrates and glycoconjugates are being implicated ever more frequently as potent physiologic and metabolic mediators. Recently interest has intensified in the synthesis of castanospermine (1) (CS, Scheme I), 6-epi-CS (2), swainsonine, and other naturally occurring indolizidine alkaloids that inhibit enzymatic glycoside hydrolysis.[3] As structural analogues of monosaccharides, these alkaloids exert powerful effects on the biosynthesis of glycoproteins in numerous tumor cell lines and hold promise as anticancer agents.[4] Additionally 1 blocks the processing and cell-surface expression of oncogene products in acute-transforming retroviruses.[5] By its effect on the HIV envelope protein, 1 also inhibits the fusion of T-helper cells, a viral-induced process that weakens the immune system.[6] We now describe a new synthesis of 1, the most efficient to date,[7] which relies on a general method for heteroatom-selective chelation during Sakurai allylation of aza-gluco, aza-manno, or aza-galacto aldehydes. We also report the first synthesis of naturally occurring 6-epicastanospermine (2) from D-mannose resulting in a surprising revision of its absolute configuration.

We reasoned that aldehyde 4 (Scheme I), available enantiomerically pure from D-glucose by oxidation of protected (+)-aminoalditol 3,[8] might undergo a highly selective chelation-controlled Sakurai reaction of the sort Keck,[9] Danishefsky,[10] and others[11] have observed with α- and β-alkoxy aldehydes. In the case of 4, whose carbonyl group may form either α-amino or β-alkoxy chelates, chelation control will depend critically on the choice of metal.[11a,12] Addition of allylmagnesium chloride to 4 afforded a 32:68 ratio of 5 and 6. However, the Sakurai condensation of 4 with allyltrimethylsilane (2.4 equiv)/$TiCl_4$ (3.6 equiv)/CH_2Cl_2 (−85 °C, 15 h) produced only 5 (75% yield; >95:<5 diastereomer ratio by NMR).[13] Use of BF_3 etherate or Bu_4NF led only to recovered starting material. The structure of 5 was established by ozonolysis (CH_2Cl_2, −78 °C, 20 min) and then reduction ($NaBH_4$, EtOH) to diol 7. Selective monomesylation of 7 followed by exhaustive hydrogenolysis (Pd/C) afforded pure (+)-castanospermine in 55% yield from 5 and 19% overall yield from methyl α-D-glucopyranoside. Similarly 6 was converted via 8 to 1-epicastanospermine.

Table I

run	aldehyde	conditions	products (ratio)	yield, %
1	4	allyl-MgCl, THF	5:6 (32:68)	69
2	4	allyl-TMS, $TiCl_4$, CH_2Cl_2	5:6 (>95:<5)	75
3	4	allyl-TMS, BF_3·OEt_2, CH_2Cl_2	4	63
4	4	allyl-TMS, Bu_4NF, CH_2Cl_2	4	65
5	9	allyl-MgCl, THF	10:11 (56:44)	95
6	9	allyl-TMS, $TiCl_4$, CH_2Cl_2	10:11 (>95:<5)	66
7	12	allyl-MgCl, THF	13:14 (70:30)	90
8	12	allyl-TMS, $TiCl_4$, CH_2Cl_2	13:14 (83:17)	47
9	12	allyl-$SnBu_3$, $TiCl_4$, CH_2Cl_2	13:14 (>95:<5)	82

Formation of 5 may best be rationalized by selective cyclic chelate formation between $TiCl_4$ and the α-aminocarbonyl group of 4, with approach of the nucleophile from the less hindered (α) face. This remarkable preference for N-chelation was again evident in equally stereoselective Sakurai reactions of 9[8] and 12,[14] which gave 10 and 13, respectively (see Scheme II and Table I). In the case of 12, selectivity was enhanced by using allyltri-*n*-butylstannane as the nucleophile. As with 4 and other related aldehydes, addition of allylmagnesium chloride to 9 and 12 exhibited poor selectivities.[11,15]

The stereochemistry of adducts 10 and 13 was secured in two ways. First, both 10 and 13 were carried on to 6-epi-CS (2) and 8-epi-CS (14) in 42% and 67% yields, respectively, by a series of steps paralleling the conversion of 5 to 1 (Scheme II). The ^1H NMR J values and coupling patterns for several diagnostic protons in 1, 2, and 14 were strikingly similar.[16] Furthermore, both 10 and its C1 epimer 11 (from allylmagnesium chloride addition) were converted to the corresponding quinolizidine alkaloids 15

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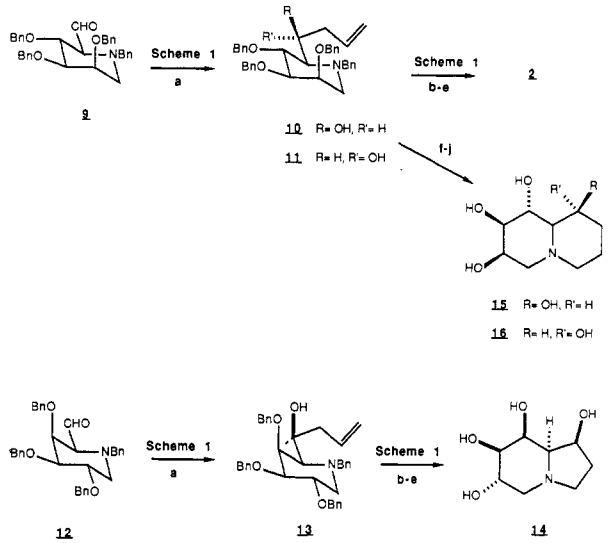
(16) A summary of relevant coupling constants (Hz) is tabulated below

	$J_{1,2\beta}$	$J_{1,2\alpha}$	$J_{2\alpha,2\beta}$	$J_{2\beta,3\alpha}$	$J_{2\beta,3\beta}$
1	1.8	6.7	14.0	8.6	8.5
2	1.8	7.0	13.8	8.9	8.9
14	2.6	7.2	13.8	8.9	8.9

Scheme II[a]



[a] (f) acetic anhydride, pyridine; (g) borane–dimethyl sulfide, THF; (h) MsCl, Na_2CO_3, CH_2Cl_2; (i) H_2, Pd/C, 3:1 EtOH/CH_3OH; (j) K_2CO_3, 3:1 CH_3OH/H_2O.

and **16** as shown in Scheme II. The ^1H NMR spectrum of **15** showed a 1.8-Hz coupling of the C-1 proton to the adjacent cis hydrogen at the ring fusion, trans coupling in isomer **16** resulting in a coupling constant of 8.9 Hz.

6-Epicastanospermine, recently isolated from seeds of the Australian tree *Castanospermum australe*, had been assigned the absolute configuration shown in **2** by analogy with **1**.[3b] Although spectra and chromatographic properties of natural and synthetic **2** were identical, chiroptical measurements revealed them to be enantiomeric structures. Thus the natural (dextrorotatory) form of **2** must correspond to L-mannose in its hydroxyl group configuration, which helps to explain why (+)-**2** was a weak inhibitor of α-mannosidase.[1b] Unfortunately (−)-**2** was an even poorer inhibitor when tested against jackbean α-mannosidase. We conclude that structure–activity relationships in castanospermine and its congeners are far more subtle than has been suggested in the biochemical literature.

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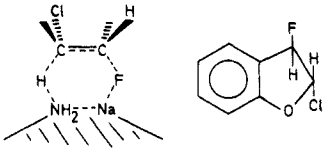
Unusual Regiospecificity in Syn Elimination from *trans*-2-Chloro-3-fluoro-2,3-dihydrobenzofuran Promoted by Complex Base[1]

Summary: Elimination from *trans*-2-chloro-3-fluoro-2,3-dihydrobenzofuran induced by $NaNH_2$–NaO-*t*-Bu in THF results in syn dehydrofluorination to the exclusion of β-aryl-activated syn dehydrochlorination.

Sir: In 1979, we reported[2] a most unusual regiospecificity in syn eliminations from *trans*-1-fluoro-2-halocyclohexanes induced by a mixture of $NaNH_2$–NaO-*t*-Bu in THF ("complex base"[3]). Thus, both *trans*-1-bromo-2-fluorocyclohexane and *trans*-1-chloro-2-fluorocyclohexane gave dehydrofluorination products exclusively.[2] Such reversal of the normal leaving group element effect ordering of I > Br > Cl ≫ F[4] was ascribed to special interactions between the fluoro leaving group and the base counterion in the syn-elimination transition-state **1**. Subsequently, it was demonstrated that preferential loss of the "normally poorer" halogen leaving group in such syn eliminations disappears in the presence of 15-crown-5.[5] Complexation of Na^+ by the crown ether prohibits the special leaving group–Na^+ interactions shown in **1**.



1 **2**

To further probe the propensities for competitive syn dehydrochlorination and syn dehydrofluorination in elimination reactions induced by complex base, we prepared a sample of *trans*-2-chloro-3-fluoro-2,3-dihydrobenzofuran[6] (**2**). Baciocchi and co-workers[7] observed only 3-fluorobenzofuran, the product of β-aryl-activated syn dehydrochlorination, in reactions of **2** with EtOK–EtOH, *t*-BuOK–*t*-BuOH, and *t*-BuOK–*t*-BuOH in the presence of 18-crown-6.

Compound **2** (2.9 mmol) was added to a magnetically stirred heterogeneous mixture of $NaNH_2$ (4.3 mmol) and in situ generated NaO-*t*-Bu (4.3 mmol) in 10 mL of THF at room temperature under nitrogen.[5] After 1 min, a sample was removed and quenched by injection into a solution of THF–H_2O (9:1) which contained *o*-xylene as an internal standard. Analysis by GC and GC/MS showed complete conversioin of **2** into 2-chlorobenzofuran (>97% yield), the product of syn dehydrofluroination. With complex base, there is a striking reversal of the elimination regiospecificity from that reported for more ordinary base–solvent combinations. Thus the special transition-state interactions depicted in **1** are shown to produce exclusive syn dehydrofluorination even when a competitive syn dehydrochlorination process would have been facilitated by a β-aryl-activating group.

(1) Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Graduate School of Texas Tech University for support of this research.
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