Tetrahedron Vol. 49, No. 19, pp. 3919-3932, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Functionalization of Penicillins Via Iodine Atom Transfer Chemistry

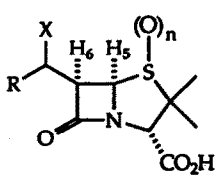
Carl B. Ziegler, Jr.* and Thomas L. Fields

Medical Research Division
American Cyanamid Company
Lederle Laboratories
Pearl River, NY 10965

(*Received in USA* 26 *January* 1993)

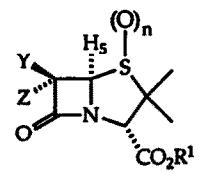
Abstract: Carbon - carbon bond formation via iodine atom transfer methodology represents a novel way to functionalize the 6-position of the penicillin nucleus. This work explores the synthetic scope and limitations to reactions of benzhydryl 6α-bromo-6β-iodopenicillanate **4a** and its sulfone **4b** with olefins.

Considerable interest has been directed towards the introduction of alkyl substituents at the penicillanic acid 6-position. Compounds of general type **1** are of interest as they comprise a part of a growing class of therapeutically useful agents, the β-lactamase inhibitors[1]. Alkyl substituted congeners **1** in this class of agents are readily prepared from the 6,6-dibromopenicillanic acid ester **2**. One of the most commonly used methods involve halogen-metal exchange followed by condensation with the appropriate electrophile[2]. Alternatively, a tributyltin hydride mediated S_H2 reaction of **2** with activated olefins (eg. acrylonitrile, acrylate esters) or an allyltributyltin mediated S_H2' scheme introduces a suitable allyl side chain[3].

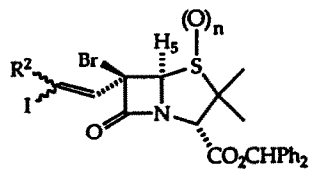


1

n = 0,2
X = OH, H



2 n=0,2; Y=Br; Z=Br
4a n=0; Y=I; Z=Br
4b n=2; Y=I; Z=Br
6 n=2; Y=H; Z=Br
7 n=2; Y=H; Z=I
8a n=0; Y=Br; Z=I
8b n=2; Y=Br; Z=I



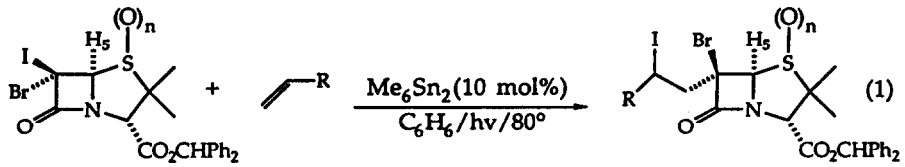
3

n = 0,2

The above described methods, though limited in scope, compliment each other in terms of available functionality tolerated on the alkyl chain. In our search for new 6-alkylpenicillanate analogues we sought another method to functionalize the penicillin 6-position. The main criterion in finding such a method would be to allow us ready access to novel 6-alkyl derivatives **1** that are amenable to further synthetic elaboration.

The introduction of iodine atom transfer chemistry by Curran as a method to vicinally functionalize

olefins and acetylenes[4] represented a potential solution to our particular problem. In practice, we found this method to be useful in the synthesis of 6-(iodoalkenyl) penicillanate esters 3[4h] from 6-bromo-6-iodopenicillanate esters 4. In this paper we present the scope and limitations of this useful method with esters 4a and 4b towards olefin vicinal substitution to form penicillanates 5. (Equation 1). It will be demonstrated that these iodine atom transfer adducts 5, in turn, are versatile intermediates for the construction of some 6-[(heterocyclyl)alkyl] penicillanate esters.



4a, n=0
4b, n=2

5

RESULTS AND DISCUSSIONS

The stereochemical assignment at the 6-position of starting materials 4a and 4b is based on X-ray crystallographic data of pivaloyl 6α-bromo-6β-iodopenicillate[5].

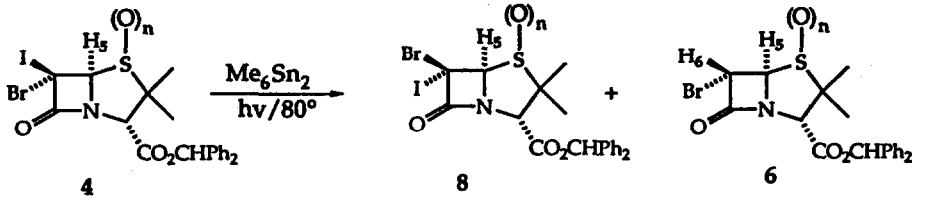
Typically, reactions with either the sulfide 4a or sulfone 4b were run under similar conditions. Thus, a benzene solution (0.3M) of 4, 1.2 equivalents of the olefin and 10 mol percent of hexamethylditin were irradiated under argon with a 300 Watt incandescent lamp at close enough range to the reaction (2-4 cm) to sustain a steady reflux. These intermolecular reactions usually required 2 to 5 hours for 90% completion. A variety of monosubstituted olefins reacted with either dihalide 4. However, reactions of 4a-b and electron poor or rich olefins (eg. acrylates or vinyl ethers) as well as di-, tri- or tetraalkyl substituted olefins were too slow. Little or no product formation is seen in these cases and decomposition of 4 is the ultimate pathway observed.

The iodine atom transfer products 5 reflected regiospecific olefin substitution consisting of diastereomeric mixtures about the newly formed carbon-iodide methine (eqn. 1). The corresponding 6,6-dibromopenicillanates 2 were unreactive under these conditions even up to reaction temperatures of 110°C.

Generally, iodine atom transfer reactions with sulfone 4b and terminal olefins produced more complex reaction mixtures than those starting with the sulfide 4a. Careful analysis of representative reaction mixtures of 4b and olefin revealed (in addition to products 5) varying amounts of reduced products 6b and, in one case, 7 (shown above) plus epimerized starting material 8b. On the other hand, only epimerized material 8a was seen in analogous reactions of 4a.

These reductions/epimerizations occur without the olefin as seen in Table 1. 6,6-Bromoiodo-penicillate esters 4a-b were irradiated as described above without olefin. The corresponding products 6 and 8

Table 1: Reduction/Epimerization of Dihalopenicillinates 4



4 8 6

4a, n=0[a]	**8a** (16%)	**6a** (0%)
4b, n=2[b]	**8b** (11%)	**6b** (18%)

a) Recovery of starting material was 32% after 6h. reaction time. The remainder was lost to decomposition.
b) Recovery of starting material was 32% after 2.5h. reaction time. The remainder was lost to decomposition.

were isolated and characterized. Under these conditions (without olefin) the sulfide **4a** incompletely epimerized to **8a** in 16% yield with substantial decomposition . The epimer **8a** is distinguished from **4a** solely by its hplc retention time and ^{1}H NMR chemical shift differences. The downfield chemical shift difference experienced by H_5 in **8a** vs. **4a** (6.0 ppm vs. 5.5 ppm respectively) is consistent with its cis orientation relative to the iodide[6]. A similar result is noted in the case of the sulfone epimer **8b**, isolated in 11% yield from **4b** (Table 1). Additionally, a new, reduced product characterized as the 6α-bromopenicillanate sulfone **6b** was isolated along with substantial (uncharacterized) decomposition material. The stereochemical assignment of **6b** is readily made by virtue of its H_5-H_6 coupling constant of 1.5 Hz, diagnostic of their trans relative orientation[3b]. The reduction of **4b** at the less favored β-face is puzzling for two reasons. Firstly, the source of the hydrogen atom is uncertain. Neither the benzene solvent nor the benzhydryl ester are likely sources[7,8]. Secondly, the selective β-facial reduction is opposite that observed in Bu_3SnH mediated reductions of dibromopenicillanates (sulfides and sulfones) where α-face selectivity is the rule[3]. However, in analogous reductions where chelation control is important (halogen-metal exchange reactions of dibromopenicillanates)[2] β-face selectivity predominates. In our case this reductive reaction course is not clear. If a planar radical species is formed, the results suggest a sulfone-assisted reduction favoring the β-face of the molecule[9]. Alternatively, the radical formed is not planar due to the strain of the system. Since there is no efficient kinetic trap (eg. Bu_3SnH) in this reaction equilibrium of this radical followed by a reductive quench would explain the production of the more thermodynamically stable **6b** and **7**. No reduction product is observed in reactions of the sulfide **4a** or the dibromide **2b** (*n*=2).

A representative sampling of 6α-iodoalkyl-6β-bromopenicillanate products **5** synthesized via the iodine atom transfer method is shown in Table 2. Both sulfide **4a** and sulfone **4b** reacted with similar propensity with the four terminal olefins[10] to yield products **5** in 30 - 60% isolated yield. Product **5** formation is dependent on the presence of Me_6Sn_2 additive. In each entry the diastereomeric ratio in product **5** (about the carbon-iodine bond) ranges roughly from unity (entries d and g) to 3 (entry c). These ratios are fairly

constant throughout the course of each reaction as determined by hplc monitoring of reaction aliquots[11].

In entry d the absolute stereochemistry of the major diastereomer was determined by single crystal X-ray analysis. Its solid state structure is shown in Figure 1. As is the case with other radical - mediated S_H2 and S_H2' substitutions at the penicillin 6-position exclusive preference for the α-face is demonstrated here. This diastereomer shows the S-absolute stereochemistry about the carbon-iodide bond.

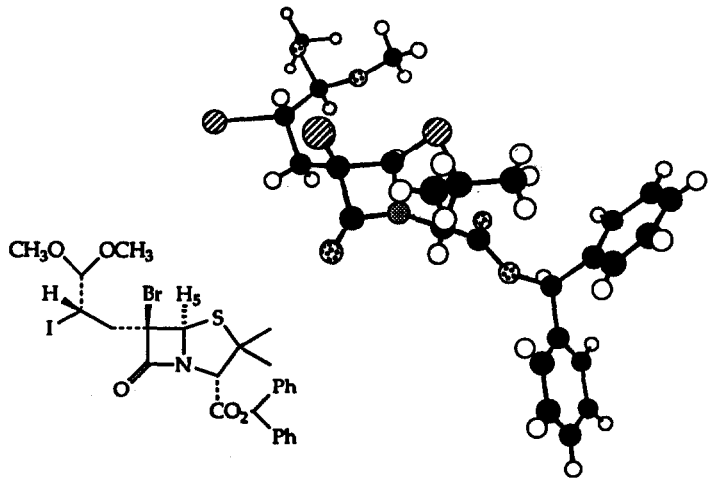
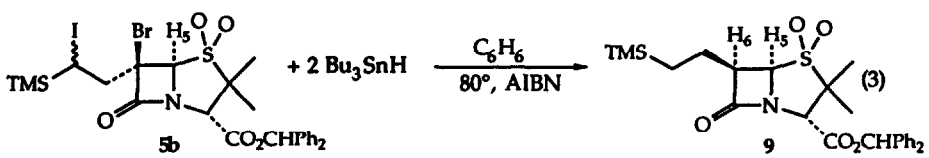


Figure 1. Solid-state structure of the major diastereomeric product component from Table 2 - Entry d.

In all the entries of Table 2, small amounts of epimerized starting materials **8a-b** and unreacted **4a-b** were seen. Additionally, in entries a-c varying amounts of reduced material were observed. The largest amounts of the reduced sulfone adducts **6b** and **7** are seen in the reaction with N-BOC-allylamine (entry c). Initially, we felt the portionwise addition of catalyst (see footnote g-Table 2) slowed the desired ditin dependent product **5** formation significantly to allow the reductive side reaction to become important. However, the same result was observed when this reaction was repeated with 10 mol % ditin initially present. Thus, it appears that the protected allyl amine is, in part, responsible for the large amount of reduced products seen here.

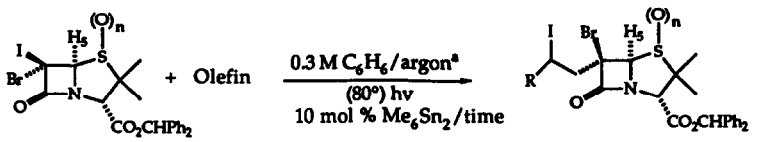
For ease in product characterization it was advantageous at times to simplify diastereomeric mixtures. Exemplary is the n-Bu_3SnH reduction of the inseparable mixture **5b** (Table 2 - entry b) shown in Eqn 3.



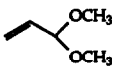
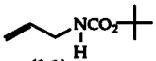
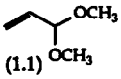
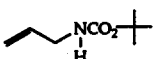
5b
3:2 mixture of diastereomers

9
72%

Table 2: Iodine Atom Transfer Products



4 5

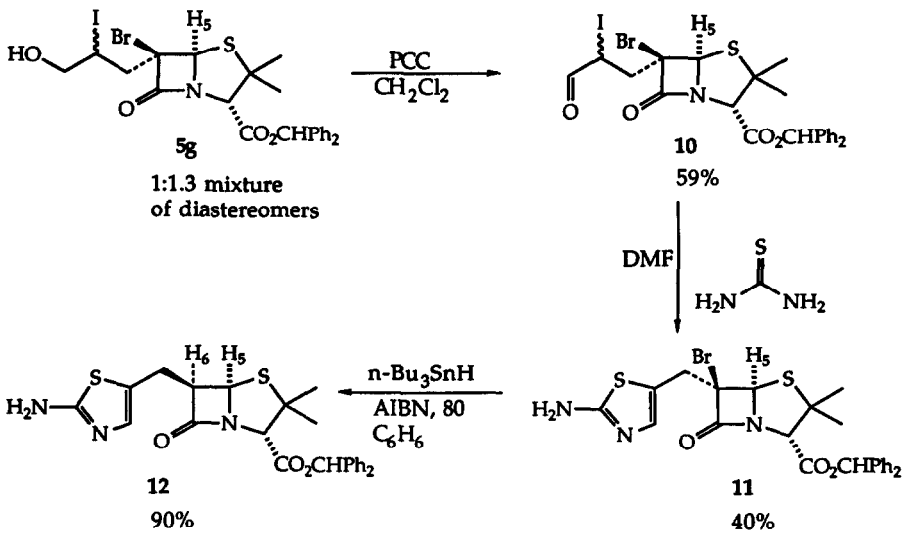
Entry	n	Olefin (equiv.)	Time	Product Diastereomeric Ratio[b,c] (isolated yield)	Other Reaction Notes/Products (isolated yield)
a	2	 (1.1)	6h	2:1[d] (32%) R= $CH(OCH_3)_2$	e
b	2	 (1.25)	2.5h	3:2[f] (46%) R= TMS	e
c	2	 (1.1)	4.5h[g]	1:3[h] (54%) R= CH_2NHCO_2t-Bu	6b (17%) 7 (18%)
d	0	 (1.1)	8h	1.3:1[d] (54%) R= $CH(OCH_3)_2$	i
e	0	 (1.2)	2.3h	1:2[f] (56%) R= TMS	
f	0	 (1.1)	5h	1:2.6[d] (31%) R= CH_2NHCO_2t-Bu	4a (10%)
g	0	 (1.1)	4.5h	1:1.3[d] (58%) R= CH_2OH	

a. The reactions were argon degassed. A 0.3 M benzene solution of **4**, olefin and ditin was irradiated for a specified time with a 300w lamp at a distance of 2.5 cm from the reaction vessel (enough to sustain a steady reflux). Reactions never went to completion as approximately 5-10% starting material **4** and 1-5% epimer **8** (both hplc determined) remained. The yields of product **5** are not adjusted to account for unreacted **4** and **8**.
b. The relative diastereomeric ratio is virtually constant throughout reaction (hplc determined).
c. Ratios indicate least polar : most polar diastereomer.
d. Ratio determined by weight of each purified diastereomer.
e. A 1-5% (hplc determined) amount of reduced product **6b** and trace amounts of **7** seen.
f. Preparatively inseparable; ratio determined by ^1H NMR of purified mixture.
g. The Me_6Sn_2 (10 mol % total) is added in 4 equal portions at 0, 0.5, 1 and 2h.
h. Preparatively inseparable; ratio determined by hplc.
i. A single crystal x-ray analysis performed on major diastereomer.

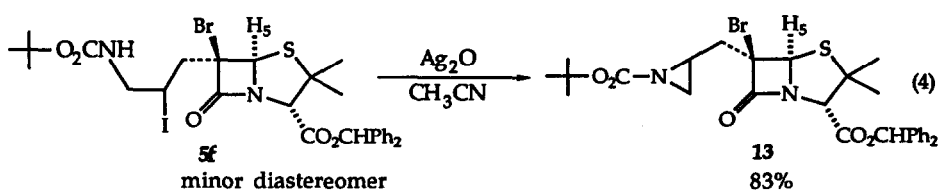
Two equivalents of n-Bu_3SnH cleanly reduced this 3:2 mixture to **9** in 72% yield. The stereochemical assignment about the 6-position was confirmed by the ^1H NMR coupling constant $J_{H_5\text{-}H_6}$ = 5Hz which is consistent with the cis relative orientation between H_5-H_6.

Some of the vicinally functionalized iodide products of Table 2 proved to be useful intermediates in the preparation of 6-[(heterocyclyl)methyl]penicillins[12]. In the event, the diastereomeric mixture of vicinal iodoalcohols **5g** (Table 2-entry g) was oxidized to the corresponding α-iodoaldehydes **10** as shown in Scheme 1. The diastereomeric mixture **10** is unstable[13] and is best utilized with minimal purification. Condensation of the mixture **10** with thiourea resulted in a 40% yield of the aminothiazole **11**. Tributyltin hydride reduction of **11** cleanly formed the β-[(aminothiazolyl)methyl]penicillanate **12** in 90% yield.

Scheme I



The minor component **5f** from the diastereomeric pair (Table 2 - entry f) formed the N-BOC-aziridine **13** in 83% yield[14] (Eqn. 4) on treatment with Ag_2O in refluxing acetonitrile. This silver-assisted nucleophilic substitution produces a pure component **13** whose absolute stereochemistry was not determined.



In conclusion, carbon-carbon bond formation via iodine atom transfer methodology represents a novel way to functionalize the 6-position of the penam nucleus. The 6α-bromo-6β-iodopenicillates **4a** and **4b** used in this study react with a variety of terminal olefins. The vicinal substitution products of the iodine atom

transfer process are useful intermediates for further synthetic transformations.

EXPERIMENTAL SECTION

Melting points are uncorrected. Elemental analyses were obtained for all new compounds reported when possible. Chromatographic separations were done using either thin layer plates (Analtech silica gel GF), flash column-silica gel or high pressure liquid chromatography-hplc, analytical or preparative on a Waters Delta Prep 3000 (using silica gel columns). Hplc operational parameters were the following: UV detection set at 270 mm, flow rate 3 ml/min (analytical separations), EtOAc-hexane eluent system. Hplc relative product ratios were determined via comparison of peak areas; no internal standards were used. ^{1}H NMR spectra were recorded using a NT-300 WB or a GE-300 Spectrometer. Mass spectra were recorded on a Finnigan Mat 90 (for chemical ionization spectra-CI and desorption chemical ionization - DCI) or a VG ZAB-SE spectrometer (for fast atom bombardment spectra-FAB). The following matrix components or mixture were used for the FAB mass spectra: mNBA-m-nitrobenzyl alcohol, MB + Na - a 4:1 mixture of dithiothreitol to dithioerythitol (magic bullet) and sodium chloride (Na) or trifluoroacetic acid (TFA). In some cases ammonia (NH_3) was used in the chemical ionization experiments. IR spectra were recorded on Perkin-Elmer Model 21 infrared spectrometer. Abbreviations used: AIBN-azobisisobutyronitrile. The single crystal X-ray analysis was performed by Molecular Structure Corporation, 3200 Research Forest Dr., The Woodlands, TX.

Benzhydryl 6α-bromo-6β-iodopenicillanate 4a. A modified procedure of Volkman[5b] was followed. To CH_2Cl_2 (30 ml) cooled to 0°C was sequentially added IBr (8.5 gm - 41 mmol), 2.5N H_2SO_4 (11ml) and $NaNO_2$ (1.9 gm - 2.7 mmol) (caution-foaming!!). To this was added benzhydryl 6-aminopenicillanate p-toluenesulfonic acid salt[15] (7.6 gm - 13.7 mmol) portionwise via spatula over 0.5 h while the reaction temperature was maintained between 0-5°C. The resultant reaction was stirred another 0.5 h. Then, 1M sodium bisulfite (3.5 ml) was added dropwise over 20 min. The organic layer was separated and the aqueous portion was extracted once with CH_2Cl_2 (50 ml). The combined CH_2Cl_2 extracts were washed with brine and then dried ($MgSO_4$). Product purification via flash silica gel chromatography (15% EtOAc - 85% hexane) afforded 5 gm (64%) product **4a** as a colorless solid : ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 4.63 (s, 1H, H-3), 5.63 (s, 1H, H-5), 6.92 (s, 1H), 7.36 (m, 10H); IR (KBr) cm^{-1} 3090, 3060, 3030, 2980, 2970, 1778, 1743; MS (DCI-Ammonia) (m/e): 591, 589 $(M + NH_4)^+$; Anal. Calcd. for $C_{21}H_{19}BrINO_3S$: C, 44.08; H, 3.35; N, 2.45; Br, 13.96; I, 22.18. Found : C, 43.91; H, 3.14; N, 2.17; Br, 13.12; I, 23.34.

Benzhydryl 6α-bromo-6-β-iodopenicillanate S, S-dioxide 4b. A CH_2Cl_2 solution (30 ml) of benzhydryl 6α-bromo-6-β-iodopenicillanate **4a** (5 gm - 8.7 mmol) was cooled to 0°C followed by the stepwise addition of acetic acid (4.5 ml) and $KMnO_4$ (2.8 gm - 17.7 mmol). The ice bath was removed and the reaction was stirred at 20° for 4h. Another portion of $KMnO_4$ (0.7 gm - 4.4 mmol) was added and the reaction was stirred overnight at which point tlc analysis indicated the reaction was complete (15% EtoAc - 85% hexane). The excess $KMnO_4$ was neutralized carefully with 37% formaldehyde solution (formaldehyde solution carefully added until wet filter paper, when spotted with the reaction mixture showed a brown color instead of purple). The reaction mixture was passed through a 5 cm pad of magnesium trisilicate, the filtrate was washed twice with water, dried, ($MgSO_4$) then purified via flash silica gel chromatography to give 2.7 gm

(57%) S, S-dioxide **4b** as a colorless solid: mp 140° (dec.); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 10H), 6.96 (s, 1H), 4.93 (s, 1H), 4.54 (s, 1H), 1.59 (s, 3H, CH_3), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 164.6, 138.3, 128.7 (2C), 128.6 (2C), 128.3 (2C), 127.4 (2C), 126.7 (2C), 79.4, 72.1, 6.4, 62.1, 19.1, 18.6; Opt. Rotation ($CHCl_3$) $[\alpha]_D^{25}$ = +171° ± 1, conc. = 1.014%; IR (KBr) cm^{-1}: 3088, 3064, 3032, 2982, 2937, 1805, 1744; MS (DCI-Ammonia) (*m/e*): 623, 621 $(M + NH_4)^+$; Anal. Calcd. for $C_{21}H_{19}BrINO_5S$: C, 41.74; H, 3.17; N, 2.32; Br, 13.22; I, 21.00. Found: 41.42; H, 3.10; N, 2.23; Br, 13.11; I, 20.84.

General Procedure for Reaction of Either Benzhydryl 6α-Bromo-6β-iodopenicillanate 4a or its S, S-dioxide 4b with Terminal Olefins. To a 0.35 M benzene solution of either the sulfide **4a** or the sulfone **4b** (1 equiv.) was added Me_6Sn_2 (0.1 equiv.) and the terminal olefin (1.2 equiv.). The solution was degassed with argon and then irradiated (300W lamp) under reflux. The progress of the reaction was monitored by tlc and/or hplc. Reaction times usually lasted from 2-6h. The crude reaction mixtures were absorbed directly onto silica gel, then purified (at least partially) by flash silica gel chromatography. More difficult separations of diastereomeric product components was accomplished via preparative hplc (EtOAc-hexane gradient). For inseparable product mixtures, diastereomeric ratios were usually determined from ^{1}H NMR data or analytical hplc analysis.

Reduction and Epimerization of 4b to form Benzhydryl 6α-Bromopenicillanate S, S-dioxide 6b and Benzhydryl 6β-Bromo-6α-iodopenicillanate S, S-dioxide 8b Respectively. To a 0.35 M benzene solution of benzhydryl 6α-bromo-6β-iodopenicillanate S,S-dioxide **4b** (604 mg-1.0 mmol) was added Me_6Sn_2 (32.8 mg-0.1 mmol). The solution was degassed with argon and then irradiated (300 W lamp) under reflux. Aliquots of the reaction were taken at 1,2 and 2.5 h intervals and analyzed by analytical hplc (Porasil; hexane - EtOAc; 90:10; 2 ml/min). At 2.5 h reaction time the reaction was stopped. Three distinct components were present by hplc. Two components, one of which was starting material, were poorly resolved by analytical hplc and they had a retention time of 6.1 min.. Another product with retention time of 7.8 min. was seen (85:15 EtOAc-hexane; 2 ml/min.). Partial purification of each product component was only achieved by flash chromatography (80:20) ethyl acetate : hexane). One major fraction weighing 266 mg was, from ^{1}H NMR analysis, a 2:1 mixture of starting material **4b** to benzhydryl 6α-bromopenicillanate S, S-dioxide **6b** (roughly 18% yield of **6b** and 29% recovery of **4b**). Since **6b** was inseparable from **4b**, its identity in this mixture was confirmed by comparing its ^{1}H NMR and hplc elution profile (co-injection) with an independently synthesized sample of **6b** (see next experimental procedure). The key diagnostic feature here was the coupling constant of 1.5 Hz between H(5) and H(6) indicating a relative trans orientation.

The other major fraction weighing 86 mg was, from ^{1}H NMR analysis, a 4:1 mixture of benzhydryl 6β-bromo 6α-iodopenicillanate S, S-dioxide **8b** and starting material **4b**(roughly 11% yield of **8b** and 3% recovery of **4b** (total **4b** recovery was 32%). Larger amounts of epimer **8b** were obtained relatively pure from a scale-up of the above reaction. Thus, a 0.35 M benzene solution of **4b** (2.44 g - 4 mmol) and Me_6Sn_2 (132 mg - 0.4 mmol) was irradiated (3h) as before. From flash silica gel chromatography a fraction enriched in **8b** was obtained. Repeated crystallizations from toluene-hexane gave 148 mg (6%) **8b** still mixed with 20% **4b** as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 4.6 (s, 1H, H-3), 5.08 (s, 1H, H-5), 6.95 (s, 1H), 7.36 (m, 10H); 20% impurity of **4b** with H-3 and H-5 absorbancies at 4.52 and 5.02 ppm respectively; IR (KBr) cm^{-1} 3080, 3060, 3015, 2980, 2925, 1803, 1755; Anal. Calcd. for $C_{21}H_{19}NO_5BrIS$: C, 41.74; H, 3.17; N, 2.32; Br, 13.23; I, 21.00. Found: C, 41.06; H, 2.99; N, 2.15; Br, 10.37; I, 24.78.

Synthesis of Benzhydryl 6α-Bromopenicillanate S,S-dioxide 6b. Benzhydryl 6α-bromopenicillanate **3a**,[16] (4.46g-10 mmol) was oxidized with m-chloroperbenzoic acid (3.8 g-22 mmol) in CH_2Cl_2 (60 ml) at 0°C (12 h period). The reaction mixture was filtered then the product was purified by flash silica gel chromatography (15% EtOAc - 85% hexane) to give 1.6 gm (33%) product **6b** as a colorless solid: mp 54-60°C; ^1H NMR ($CDCl_3$) δ 1.1 (s, 3H, CH_3), 1.6 (s, 3H, CH_3), 4.52 (s, 1H, H-3), 4.67 (d, 1H, H-5, $J_{H5,6}$ = 1.5 Hz), 5.15 (d, 1H, H-6, J = 1.3); IR (KBr) cm^{-1} 3631, 3577, 3512, 3373, 3093, 3066, 1811, 1761; Opt. Rotation ($CHCl_3$) $[\alpha]_D^{25}$ + 128°, conc. = 1.089% ± 1; MS (FAB - mNBA) (m/e) : 502 and 500 (M+ Na); Anal. Calcd. for $C_{21}H_{20}NBrSO_5$: C, 52.72; H, 4.18; N, 2.93; S, 6.69; Br, 16.74. Found: C, 56.60; H, 4.44; N, 2.88; S, 7.39; Br, 17.30.

Synthesis of Benzhydryl 6β-Bromo-6α-iodopenicillanate 8a. To a 0.35 M benzene solution of benzhydryl 6α-bromo-6β-iodopenicillanate **4a**(322 mg - 0.56 mmol) was added Me_6Sn_2 (32 mg - 0.1 mmol). The solution was degassed with argon and then irradiated (300 W lamp) under reflux. Hplc analysis at 2,4 and 6h showed that the product to starting material ratio reached 1:2. The new product **8a** was preparatively inseparable from **4a**. Following flash silica gel chromatography (15% EtOAc - 85% hexane) 156 mg (50%) colorless solid was obtained; ^1H NMR ($CDCl_3$) 2:1 mixture of **4a** to **8a** δ: 1.23 and 1.25 (2s, 3H, CH_3), 1.60 and 1.66 (2s, 3H, CH_3), 4.61 and 4.64 (2s, 1H, H-3), 5.63 and 6.00 (2s, 1H, H-5), 6.93 (s, 1H, $CHPh_2$), 7.33 and 7.36 (2s, 10H, aromatic); MS (FAB - MB + Na) m/e: 594 MS (FAB - MB + TFA) m/e: 738 and 740; IR (KBr) cm^{-1} 1778, 1743; Anal. Calcd. for $C_{21}H_{19}NO_3SBrI$: C, 44.07; H, 3.35; N, 2.45; Br, 13.96; I, 22.18. Found: C, 44.56; H, 3.36; N, 2.24; Br, 13.65; I, 22.56.

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-3,3-dimethoxypropyl)]penicillanate S,S-dioxide, 5a (Entry a - Table 2). Two diastereomeric products were isolated via flash silica gel chromatography when sulfone **4b** (1.2 g - 2 mmol) was irradiated with acrolein dimethylacetal (225 mg - 2.2 mol) and Me_6Sn_2 (65 mg - 0.2 mmol) for 6h. The major diastereomeric product (308 mg - 22%) had hplc retention time of 6.1 min. (1.5 ml/min; 15% EtOAc - 85% hexane).
^1H NMR $CDCl_3$ δ 1.09 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.95 (ABX, 2H, CH_2) 3.49 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 4.52 (m, 2H, $CH(OMe)_2$ & CHI) 4.56 (s, 1H, H-3), 5.09 (s, 1H, H-5), 6.96 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3070, 3040, 2991, 2939, 2841, 1807, 1757; MS (FAB - mNBA) (m/e) : 728 (M + Na); 706 (M + H), 674 (M-OCH_3). The minor diastereomer (144 mg - 10%) had a hplc retention time of 8.6 min. ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.75 (ABX, 2H, CH_2), 3.44 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 4.24 (d, 1H, $CH(OMe)_2$, J = 4Hz), 4.4 (m, 1H, CHI), 4.58 (s, 1H, H-3), 5.23 (s, 1H, H-5), 6.97 (s, 1H), 7.36 (m, 10H); IR (KBr) cm^{-1} 3050, 3035, 3000, 2940, 2839, 1811, 1757; MS (FAB - m NBA) m/e : 728 (m + Na), 706 (M + H), 674 (M-OCH_3).

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-2-trimethysilylethyl)]penicillanate S, S-dioxide, 5b (Entry b - Table 2). Two inseperable diastereomeric products were isolated via flash silica gel chromatography (15:85 EtOAc-hexane) when **4b** (1.2 g-2mmol) was irradiated with vinyltrimethylsilane (251 mg-2.5 mmol) and Me_6Sn_2 (65 mg - 0.2 mmol) for 2.5 h. Two minor components were isolated together weighing 143 mg and proved to be a 1:1 mixture of the starting material **4b** and reduced sulfone **6b** by ^1H NMR analysis. The major product weighing 644 mg (46%) was a 3:2 mixture of product diastereomers. ^1H NMR ($CDCl_3$) δ 0.2, 0.22 (2s, 9H, $3CH_3$), 1.12, 1.18 (2s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.48, 2.92 (2M, 2H, CH_2), 3.2, 3.5 (2dd, 1H, CHI), 4.60, 4.61 (2s, 1H, H_3), 5.13, 5.44 (2s, 1H, H_5); IR (KBr) cm^{-1} 3093, 3068,

3035, 2958, 2904, 1811, 1755; MS (FAB - mNBA) - poor quality spectrum; Anal. Calcd. for $C_{26}H_{31}NO_5BrISSi$: C, 44.32; H, 4.44; N, 1.99. Found: C, 44.99; H, 4.56; H, 1.70.

Benzhydryl 6β-Bromo-6-[1-(R & S-2-iodo-3-(tert-butyloxycarbonylamino)propyl)]penicillanate S, S-dioxide, 5c (Entry c-Table 2). A preparatively inseparable mixture of diastereomeric products (1:3 ratio) isolated in 98% purity via hplc (20:80 EtOAc-hexane) when **4b** (1.2 g - 2 mmol) was irradiated with 1-(tert-butyloxycarbonylamino)-2-propene and Me_6Sn_2 (65 mg - 0.2 mmol) added in 4 equal portions at time intervals of 0, 0.5, 1 and 2h. The reaction was irradiated a total of 4.5 h. The mixture of iodine atom transfer adducts, a colorless solid, weighed 818 mg (54%). This mixture of diastereomers could be fractionally recrystallized (toluene-hexane) yielding 52 mg material which was 90% enriched in the major diastereomer. ^1H NMR ($CDCl_3$) δ 1.1 (s, 3H, CH_3), 1.45 (s, 9H, tert-butyl), 1.6 (s, 3H, CH_3), 2.65 (m, 2H, CH_2), 3.58 (m, 2H, CH_2), 4.46 (m, 1H, CHI), 4.6 (s, 1H, H-3), 5.23 (s, 1H, H-5), 6.97 (s, 1H), 7.37 (m, 10H, aromatic); IR (KBr) cm^{-1} 3425 (NH), 2977, 2931, 1807, 1751, 1711; MS (FAB) - poor quality spectrum; Anal. Calcd. for $C_{28}H_{34}N_2O_7SBrI$: C, 45.80; H, 4.51; N, 3.68; S, 4.22; Br, 10.51; I, 16.69. Found: C, 46.40; H, 4.53; N, 3.11; S, 4.41; Br, 9.45; I, 15.01.

The following reduced products were also isolated. Benzhydryl 6α-bromopenicillanate S, S-dioxide **6b** (163 mg-17%); ^1H NMR see above; Anal. calcd. for $C_{21}H_{20}NO_5SBr$: C, 52.72; H, 4.21; N, 2.93; Br, 16.71; S, 6.70. Found: C, 52.40; H, 4.16; N, 2.68; Br, 15.78; S, 6.36.

Benzhydryl 6α-iodopenicillanate S, S-dioxide **7** (189 mg-18%), tentative structural assignment; ^1H NMR ($CDCl_3$) δ 1.1 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 4.5 (s, 1H, H-3), 4.67 (d, 1H, H-6, $^JH_{5,6}$ = 1.5 Hz), 5.32 (d, 1H, H-5, $^JH_{5,6}$ = 1.5 Hz), 6.98 (s, 1H, $CHPh_2$), 7.36 (m, 10H); IR (KBr) cm^{-1} 3424 (H_2O), 3070, 3040, 2980, 2934, 1804, 1755; MS-(FAB)-poor quality spectrum; Anal. Calcd. for $C_{21}H_{20}NO_5SI$: I, 24.16. Found: I, 19.03; Br, 3.69.

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-3,3-dimethoxypropyl)]penicillanate, 5d (Entry d-Table 2). Two diastereomeric products were isolated after hplc purification (90:10 EtOAc-hexane) when sulfide **4a** (4.6 g - 8 mmol) was irradiated with acrolein dimethyl acetal (1.0 ml - 8.8 mmol) and Me_6Sn_2 (262 mg - 0.8 mmol) for 8h. There was 300 mg unreacted **4a** isolated. The least polar diastereomer weighed 1.72 gm (31%); ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.9 (ABX, 2H, CH_2), 3.4 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 4.35 (d, 1H, $CH(OMe)_2$, J = 2.4Hz), 4.45 (m, ABX, 1H, CHI) 4.56 (s, 1H, H-3), 5.64 (s, 1H, H-5), 6.94 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3068, 3027, 2984, 1781, 1747; MS(CI/NH_3) m/e (relative intensity) 691 and 693 (m + NH_4^+, 100), 642 and 644(100); Anal. Calcd. for $C_{26}H_{29}NO_5BrIS$: C, 46.30; H, 4.33; N, 2.04; S, 4.75. Found: C, 46.25; H, 4.75; N, 2.04; S, 4.75. The most polar diastereomer weighed 1.28 g (23%); ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.8 (ABX, 2H, CH_2), 3.44 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 4.23 (d, 1H, $CH(OMe)_2$, J = 4.2 Hz), 4.37 (m, ABX, 1H, CHI), 4.58 (s, 1H, H-3), 5.87 (s, 1H, H-5), 6.92 (s, 1H, $CHPh_2$), 7.4 (m, 10H); IR (KBr) cm^{-1} 3456 (H_2O), 3088, 3063, 3031, 2964, 1785, 1744; MS(CI/NH_3) m/e (relative intensity) 691 and 693 (M + NH_4^+, 20), 642 and 644(100).

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-2-trimethylsilylethyl)]penicillanate, 5e (Entry e-Table 2). The two diastereomeric products were isolated as a preparatively inseparable mixture (flash silica gel column 90:10 hexane to ethyl acetate). ^1H NMR ($CDCl_3$) (as a 1:2 mixture of diastereomers) δ 0.2 (s, 9H, $Si(CH_3)_3$), 1.27 (s, 3H, CH_3), 1.66, 1.68 (2 singlets, 3H, CH_3), 2.52 and 2.88 (ABX, 2H, CH_2-

CHI of both isomers), 3.2 and 3.4 (2dd, 1H, CHI, ABX), 4.6, 4.62 (2 singlets, 1:2 ratio, 1H, H-3 of both isomers), 5.67, 6.0 (2 singlets 2:1 ratio respectively, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3068, 3035, 2966, 1790, 1749; MS (FAB/mNBA + TFA) m/e 671 (M + H); Anal. Calcd. for $C_{26}H_{31}NO_3BrISSi$: C, 46.44; H, 4.65; N, 2.08, Br, 11.88; I, 18.87. Found: C, 46.71, H, 4.65; N, 1.91; Br, 12.00; I, 19.06.

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-3-(tert-butyloxycarbonylamino)propyl)] penicillanate 5f (Entry f-Table 2). The two diastereomeric products were isolated first via flash silica gel column, (75:25 hexane to ethyl acetate) to remove polar decomposition material, then via preparative hplc, (85:15 hexane to ethyl acetate) to isolate each product. Thus, the sulfide **4a**(4.6g - 8mmol) was irradiated 5h with N-(tert-butyloxycarbonyl)allylamine (1.38 g - 8mmol) and Me_6Sn_2 (262 mg - 0.8 mmol) to yield, after purification, 492 mg (10%) unreacted **4a**, 496 mg (8.5%) of one diastereomer as a tan solid and a more polar diastereomer (1.29 g - 22%) also a tan solid; ^1H NMR ($CDCl_3$) (less polar product) δ 1.25 (s, 3H, CH_3), 1.45 (s, 9H, $3CH_3$), 1.64 (s, 3H, CH_3), 2.95 (ABX, 2H, CH_2), 3.45 (broad multiplet, 2H, CH_2-N), 4.45 (pentet, 1H, CHI, ABX), 4.6 (s, 1H, H-3), 4.78 (broad, 1H, NH), 5.4 (s, 1H, H-5), 6.93 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3421 (NH), 3090, 3060, 3035, 2975, 2925, 1788, 1745, 1712; MS (CI/NH_3) m/e (relative intensity) 746 and 748 ($M + NH_4^+$) (75%); Anal. Calcd. for $C_{29}H_{34}N_2O_5SBrI$: C, 47.75; H, 4.70; N. 3.84; Br, 10.96; I, 17.40. Found: C, 48.35; H, 4.75; N, 3.60; Br, 10.32; I, 17.27.

^1H NMR ($CDCl_3$) (more polar product) δ 1.26 (s, 3H, CH_3), 1.45 (s, 9H, $3CH_3$), 1.66 (s, 3H, CH_3), 2.70 (ABX, 2H, CH_2), 3.57 (broad multiplet, 2H, CH_2N) 4.38 (m, 1H, CHI, ABX), 4.60 (s, 1H, H-3), 4.45 (broad, 1H, NH), 5.88 (s, 1H, H-5), 6.91 (s, 1H), 7.36 (m, 10H); IR (KBr) cm^{-1} 3415 (NH), 3090, 3060, 3035, 2975, 2925, 1785, 1747, 1714; MS (CI/NH_3) m/e (relative intensity) 746 and 748 ($M + NH_4^+$, 20); Anal. Calcd. for $C_{29}H_{34}N_2O_5SBrI$: C, 47.75; H, 4.70; N, 3.84; Br, 10.96; I, 17.40. Found: C, 49.10; H, 4.65; N, 3.48; Br, 10.35; I, 17.22.

Benzhydryl 6β-Bromo-6α-[1-(R & S-2-iodo-3-hydroxypropyl)]penicillanate 5g (Entry g-Table 2). Two diastereomeric products were isolated when sulfide **4a** (11.4 g - 10 mmol), allyl alcohol (1.3 g - 22 mmol) andMe_6Sn_2 (656 mg - 2 mmol) were irradiated at reflux for 4.5h. Filtration of the reaction mixture through a silica gel short column (1:1 EtOAc - hexane) followed by preparative hplc separation (4:1 hexane - EtOAc) yielded 3.2 g (25%) product and a more polar diastereomer 4.1 g (33%); ^1H NMR ($CDCl_3$) (less polar product) δ 1.25 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.95 (dd, 1H, OH), 3.0 (d, 2H, CH_2, J=7Hz), 3.58-3.90 (m, 2H, CH_2O), 4.54 (m, 1H, CHI), 4.58 (s, 1H, H-3), 5.61 (s, 1H, H-5), 6.92 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3407 (OH), 3060, 3030, 2965, 2930, 1785, 1760, 1746; MS (CI/NH_3) m/e (relative intensity) 647 and 649 ($M + NH_4^+$, 50); Anal. Calcd. for $C_{24}H_{25}NO_4BrIS$; C, 45.73; H, 4.00; N, 2.22; S, 5.09. Found: C, 45.74 H, 3.88; N, 2.09; S, 5.17.

^1H NMR ($CDCl_3$) (more polar product) δ 1.27 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.09 (t, 1H, OH), 2.82 (ABX, 2H, CH_2), 3.85 (t, 2H, CH_2O), 4.48 (multiplet, 1H, CHI), 4.6 (s, 1H, H-3), 5.74 (s, 1H, H-5), 6.92 (s, 1H), 7.35 (m, 10H); Anal. Calcd. for $C_{24}H_{25}NO_4BrIS$; C, 45.73; H, 4.00; N, 2.22; S, 5.09. Found; C, 46.29; H, 3.91; N, 2.02; S, 4.92.

Synthesis of Benzhydryl 6β-(2-Trimethylsilylethyl)penicillanate S, S-dioxide 9. Benzhydryl 6β-bromo-6α-[1-(R & S-2-iodo-2-trimethylsilylethyl)]penicillanate S, S-dioxide **5b** (352 mg - 0.5 mmol), n-Bu_3SnH (320 mg - 1.1 mmol) and AIBN (16.4 mg - 0.1 mmol) were refluxed in benzene (3ml) for 1.25 h

under an argon atmosphere. On cooling, followed by preparative hplc (85:15 hexane-EtOAc) a crystalline product **9** was isolated (179 mg - 72%);
^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9H, $3CH_3$), 0.64 (m, 2H, CH_2-Si), 1.1 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.8 - 2.2 (m, 2H, CH_2), 3.84 (m, 1H, H-6), 4.54 (s, 1H, H-3), 4.56 (d, 1H, H-5, $^JH_{5,6}$ = 5 Hz), 6.98 (s, 1H), 7.35 (m, 10H); IR (KBr)cm^{-1} 3070, 3033, 2990, 2955, 2930, 1803, 1757; Anal. calcd. for $C_{26}H_{33}NOSSi$: C, 62.49; H, 6.66; N, 2.80; S, 6.42; Found: C, 62.60; H, 6.66; N, 2.53; S, 6.40.

Synthesis of Benzhydryl 6β-Bromo-6α-[(2-amino-5-thiazolyl)methyl] penicillanate 11 via the Iodoaldehyde 10. A mixture of benzhydryl 6β-bromo-6α-[1-(R & S-2-iodo-3-hydroxypropyl)]penicillanate (Entry g - Table 1) **5g** (3.02 g - 4.8 mmol) was dissolved in CH_2Cl_2 (75 ml) at 20°. To this was added pyridinium chlorochromate (3.1 g-14.4 mmol) and celite (20 g). The reaction was stirred while its progress was monitored by tlc (1:1 EtOAc-hexane). On completion, the reaction was filtered through magnesium trisilicate (CH_2Cl_2) and then the filtrate was concentrated to a foam to give 1.8 g (59%) crude aldehyde **10**; ^{1}H NMR (mixture of isomers) ($CDCl_3$) δ 1.25 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.3-3.3 (m, 2H, CH_2), 4.55 (s, 1H, H-3), 4.95 (m, 1H, CHI), 5.55 and 5.6 (2 singlets, 1H, H-5 of both isomers), 6.95 (s, 1H, CH), 7.3 (m, 10H), 9.35 (s, 1H, CHO).

The crude aldehyde **10** was then dissolved in DMF (50 ml) and thiourea was added (432 mg-6 mmol). The resulting reaction stirred overnight. On workup 5% $NaHCO_3$ (200 ml) and EtOAc (100 ml) were added. The organic portion was washed 3x with water, dried over Na_2SO_4, filtered and finally reduced in volume to a foam. Purification via hplc (1:1 EtOAc-hexane) produced the thiazole **11** (1.51 g-86% purity by analytical hplc). Another pass on the hplc produced pure **11** (842 mg - 31% for 2 steps); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 3.62 (broad dd, 2H, CH_2), 4.58 (s, 1H, H-3), 4.76 (broad singlet, 2H, NH_2), 5.4 (s, 1H, H-5), 6.90 (s, 1H, H-4' of thiazolyl), 6.92 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3444, 3378, 3065, 3032, 2970, 1784, 1744, 1611; MS (CI/NH_3) m/e (relative intensity) 558 and 560 (MH^+, 10), 480 (100); Anal. Calcd. for $C_{25}H_{24}N_3BrO_3S_2$: C, 53.75; H, 4.31; N, 7.52; S, 11.48. Found: C, 53.76; H, 4.29; N, 6.90; S, 11.13.

Synthesis of Benzhydryl 6β-[(2-amino-5-thiazolyl)methyl penicillanate 12. A solution containing **11** (112 mg - 0.2 mmol) n-Bu_3SnH(64 mg - 0.22 mmol), AIBN (3.3 mg - 0.02 mmol) and benzene (3 ml) was refluxed 0.75h under argon. The reaction was cooled and the solvent removed leaving a residue which was purified to give the product **12** (87 mg - 90%) via preparative hplc (25% EtOAc - 75% hexane); ^{1}H NMR ($CDCl_3$) n-Bu_3SnBr residues present δ 1.26 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 3.14 (m, 2H, CH_2), 3.8 (m, 1H, H-6), 4.5 (s, 1H, H-3), 4.8 (6s, 2H, NH_2), 5.44 (d, 1H, H-5, $^JH_{5,6}$ = 4.3 Hz); IR (KBr) cm^{-1} 3430, 3375, 3183, 3030, 2960, 1773, 1742; MS (CI/NH_3) m/e (relative intensity) 480 (MH^+, 100).

Synthesis of Benzhydryl 6β-Bromo-6α-[[1-(1-tert-butyloxycarbonyl)-2-aziridinyl]methyl]penicillanate 13. The minor diastereomeric component **5f** from Entry f-Table 1 (100 mg - 0.14 mmol) was dissolved in CH_3CN (5 ml). To this, Ag_2O was added (46 mg - 0.2 mmol). The resulting suspension was refluxed 2h before consumption of starting penicillanate was observed by tlc (1:1 hexane to EtOAc). The reaction was filtered and the filtrate was reduced to a residue which was then taken up in 1:1 EtOAc-hexane and passed through a 3 cm pad of silica gel and eluted with 1:1 EtOAc-hexane. Removal of the solvent gave a colorless foam 68 mg (83%); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.45 (s, 9H, $3CH_3$), 1.66 (s, 3H, CH_3), 1.98 - 2.1 (m, 2H, CH_2), 2.4 (d, 1H, aziridine H-3'), 2.62 (dd, 1H, aziridine-H-3'), 2.73 (m,

1H, aziridine-H-2'), 4.58 (s, 1H, penicillanate-H-3), 5.8 (s, 1H, penicillanate-H-5) 6.92 (s, 1H), 7.35 (m, 10H); IR (KBr) cm^{-1} 3065, 3030, 2977, 1786, 1745, 1720; MS (CI/NH_3) m/e (relative intensity) 601 and 603 (MH^+, 38); Anal. Calcd. for $C_{29}H_{33}N_2O_5BrS$: C, 57.50; H, 5.53; N, 4.66; S, 5.33; Br, 13.28. Found: C, 57.60; H, 5.42; N, 4.55; S, 5.27; Br, 11.95.

Acknowledgement: We thank Professor Dennis P. Curran for many helpful discussions and suggestions.

REFERENCES AND NOTES

1. For examples, see: a) Alpegiani, M.; Hanessian, S.; Meinardi, G.; Perrone, E. *UK Patent Application GB 2,206,579* Farmitalia Carlo Erba **1987**. b) Chen, Y. L.; Hedberg, K.; Barrett, J. F. and Retsema, J. A. *J. Antibiotics* **1988**, *41*, 134. c) Chen, Y. L.; Hedberg, K.; Guarino, K.; Retsema, J. A.; Anderson, M.; Manousos, M. and Barrett, J. *J. Antibiotics* **1991**, *44*, 870. d) Reed, L. A.; Charleson, D. A. and Volkmann, R. A. *Tetrahedron Lett.* **1987**, *28*, 3431.
2. a) DiNinno, F.; Beattie, T. R. and Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960. b) Aimetti, J. A.; Hamanaka, E. S.; Johnson, D. A. and Kellogg, M. S. *Tetrahedron Lett.* **1979**, 1631. c) Aimetti, J. A. and Kellogg *ibid*, **1979**, 3805. d) Pirie, D. K.; Welch, W. M.; Weeks, P. D. and Volkmann, R. A. *ibid*, **1986**, *27*, 1549. e) Ref. 1d. f) Welch, W. M. and Guarino, K. J. C. *J. Org. Chem.*, **1987**, *52*, 4401.
3. a) Sacripante, G. and Just, G. *J. Org. Chem.* **1987**, *52*, 3659. b) Hanessian, S. and Alpegiani, M. *Tetrahedron* **1989**, *45*, 941. c) Recently, a Barton O-acyl 2-thiopyridylhydroxamate fragmentation has been described that compliments these other radical methods. See: Sumi, K.; DiFabio, R. and Hanessian, S. *Tetrahedron Lett.* **1992**, *33*, 749
4. a) Review: Curran, D. P. *Synthesis* **1988**, Part 2, 489. Pertinent references are limited to those iodine atom transfer examples relating to α-iodoamides and α-iodoesters. b) Jolly, R. S. and Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. c) Curran, D. P.; Chen, M-H; Spietzer, E.; Seong, C. M. and Chang, C-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. d) Yang, C. O. and Barth, F. *Tetrahedron Lett.* **1990**, *31*, 1121. e) Curran, D. P. and Chang, C-T. *J. Org. Chem.* **1989**, *54*, 3140. f) Flynn, D. L. and Zabrowski, D. L. *J. Org. Chem.* **1990**, 3673. g) Curran, D. P. and Tamine, J. *J. Org. Chem.*, **1991**, *56*, 2746. h) Curran, D. P.; Kim, D. and Ziegler, C. *Tetrahedron* **1991**, *47*, 6189.
5. a) Belinzoni, D. V.; Mascaretti, O. A.; Alzari, P. M.; Punti, G.; Faiman, C. and Pudgarny, A. *Can. J. Chem.* **1985**, *63*, 3177. b) The free acid of the penicillanate ester in ref. 5a was prepared by the method of Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliot, M. L. and Moore, B. S. *J. Org. Chem.* **1982**, *47*, 3344.
6. This downfield shift experienced by H-5 is likely due to an increase in steric compression. The same deshielding trend is seen for H_5 on going from pivaloyloxy methyl 6β-iodo-6α-chloropenicillanate to pivaloyloxy methyl 6β-iodo-6α-bromopenicillanate as seen in ref. 5a.
7. Independently synthesized phenyl 6α-bromo-6β-iodopenicillanate S,S-dioxide underwent identical reaction conditions as **4b** to form approximately 10% yield of the 6α-bromo-penicillanate S,S-dioxide.
8. One cannot exclude the possibility that the source of the hydrogen atom comes from an

uncharacterized decomposition pathway as the mass recovery is low in this experiment. Reduction under iodine atom transfer has been observed in other non-related systems involving α-iodoamides. See for example refs. 4b and 4g.

9. The role of the hexamethylditin in these reduction/epimerization studies seems to be minimal. In one experiment (data not reported in the experimental section) **4b** was irradiated in benzene (3h) to form similar ratios of **8b**, **6b** and recovered **4b** by ^{1}H NMR and hplc analysis. Only 51% mass recovery was realized.
10. The one exception is the reaction of the sulfone **4b** with allyl alcohol (data not shown). Complex reaction mixtures and substantial decomposition made product isolation and characterization impractical.
11. We propose that the stereochemistry of iodine transfer follows kinetic control since the isomer **5** ratio does not appreciably change throughout the reaction. Additionally, the starting iodide **4** is more likely to be a much better iodine donor than the product **5**. Therefore, any equilibration of **5** should be repressed as long as any **4** remains in the reaction mixture.
12. This class of compounds was of interest for biological evaluation.
13. Elimination of HI is the typical decomposition pathway for **10**. Initial attempts to oxidize **5g** using Swern conditions (oxalyl chloride, DMSO and Et3N at-70°C) resulted exclusively in HI elimination to form the α,β-unsaturated aldehyde (data not shown). This unsaturated aldehyde was extremely unstable at 20°C.
14. The major diastereomeric component from Table 2-entry f also underwent smooth cyclization to a single N-BOC-aziridine in 92% yield (data not shown).
15. Jensen, S. E.; Westlake, D. W. S.; Bowers, R. J. and Wolfe, S. *J. Antibiotics* **1982**, *35*, 1351.
16. Micetich, R. G.; Maiti, S. N.; Tanaka, M.; Yamazaki, T.; Ogawa, K. J. *J. Org. Chem.* **1987**, *51*, 853.