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A New Efficient Stereoselective Debromination Reaction with Trialkylgermanium Hydrides Useful in the Design of Short Synthetic Routes to β-Lactamase Inhibitor Prodrugs

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Abstract:

Prodrugs derived from the β-lactamase inhibitor 6-β-hydroxymethylsulbactam can be synthesized efficiently in a three-step process by making use of the highly stereoselective radical debromination utilizing tri-*n*-butylgermanium hydride. This reagent is capable of abstracting bromine from the C-6 position of pairs of epimers 6-hydroxymethyl-6-bromo-penicillate-1,1-dioxide esters and functionalized esters suitable for prodrug use in high yields. The bromine abstraction usually results in favoured formation of the 6-β-hydroxymethyl epimer relative to the 6-α-hydroxymethyl epimer in ratios that exceed 97:3. Reaction of pure 6-α-hydroxymethyl-6-β-bromo-penicillate-1,1-dioxide ester results in almost exclusive formation of 6-β-hydroxymethylsulbactam ester. This methodology conserves the C−C bond formation at C-6 by making use of both epimers resulting from formylation, which is difficult and nonstereoselective in the β-hydroxymethylsulbactam prodrug synthesis.

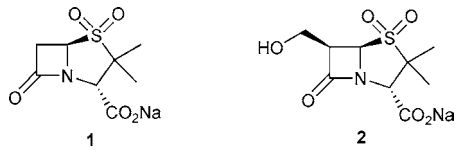
Introduction

Sulbactam sodium **1** was discovered[1] in 1980 and turned out to be a useful medicine for the treatment of bacterial resistance to penicillin-based antibiotics. Later in 1980 another potent β-lactamase inhibitor was discovered with a related, but more complicated, structure. This was 6-β-hydroxymethylsulbactam sodium, **2**,[2] (Scheme 1).

The need for the selective radical debromination was driven by the need to facilitate a short synthesis for prodrug molecules based on **2** and by the lack of options available to introduce a 6-β-hydroxymethyl functionality into the sulbactam nucleus. One method that gives useful yields, involves direct reaction of formaldehyde gas with the Grignard reagent derived from 6,6-dibromosulbactam esters such as **3** at cryogenic temperatures.[3] (Scheme 2).

In the sulfone penicillin benzyl ester series the yield of this reaction from **3** is about 30%. The formylation reaction is nonselective and gives rise to epimeric mixtures of **4** and **5**. The range can vary from approximately 1:1 to approximately 2:1 in favour of the β-hydroxymethyl epimer **5**. As a result, chromatographic separation is required to give pure 6-β-hydroxymethyl-6-α-bromosulbactam ester **5**. When benzyl is chosen as the ester blocking group, debromination can be concomitant with the blocking group removal and can be accomplished by hydrogenation; however, unless carefully optimised, it can easily result in significant loss of stereoselectivity at C-6, resulting in a mixture of the epimer 6-α-hydroxymethylsulbactam **6**[4] and the desired 6-β-hydroxymethylsulbactam **2**. For example, by using methodology reported in the recent patent literature[5] that starts with pure 6-β-hydroxymethy-6-α-bromo anomer **5**, the undesired 6-α-hydroxymethyl anomer **6** is formed to the extent of 25% when the hydrogenation is used to debrominate the C-6 position. Considering the difficulty of forming the carbon−carbon bond at C-6 in this series, 25% attrition of the desired molecular architecture is unwelcome. A recent account of the difficulties associated with the initial scale-up of prodrugs derived from **2** has been described.[6]

Scheme 1. **Sulbactam and 6-β-hydroxymethylsulbactam sodium salts**



1 **2**

Radical debromination with *n*-tributyltin hydride can lead to highly selective removal of bromine, favouring the desired β-hydroxymethyl stereochemistry.[7] This report describes an efficient three-step synthesis of the prodrugs **7** and **8**[8] that utilizes *n*-tributylgermanium hydride, which is a more suitable reagent for pharmaceutical use because of the lower toxicity of trace residual germanium compared to that of tin.[9]

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† Pfizer Inc.

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(1) Barth, W. E. U.S. Patent 4,234,579, November 18, 1980.

(2) Kellogg, M. S.; Hamanaka, E. S. U.S. Patent 4,397,783, August 9, 1983.

(3) Aimetti, J. A.; Kellogg, M. S. *Tetrahedron Lett.* **1979**, *20*, 3805.

(4) Kellogg, M. S. European Patent Application Publication No. 0 083 977 January 7, 1983.

(5) See example 2 (step 4) in World Patent Application WO 2004/018484 A1, March 4, 2004.

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(9) Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, *2*, 585.

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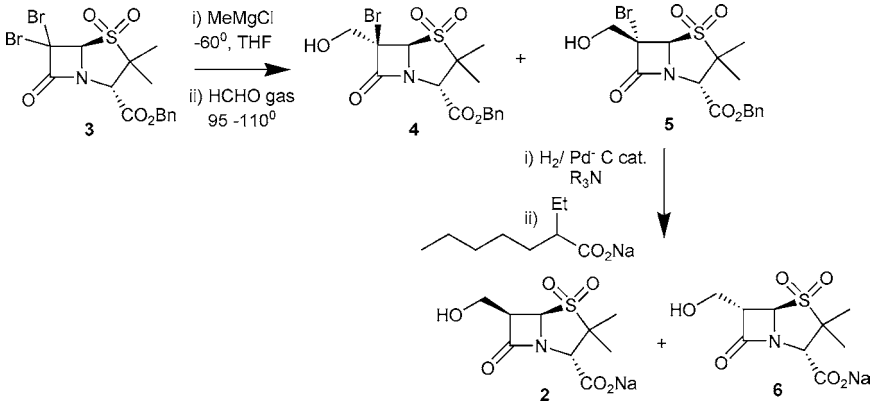
Scheme 2. **Synthesis of 6-β-hydroxymethylsulbactam sodium**



n-Tributylgermanium hydride proved to be very stereoselective and high yielding when developed for the synthesis of prodrugs derived from the β-lactamase inhibitor 6-β-hydroxymethylsulbactam sodium **2**.

Results and Discussion

Synthesis design was aimed at conserving the carbon−carbon bond formed at C-6 on the penicillin ring system. Much effort in our and others' laboratories has not led to a new or improved bond formation methodology to produce hydroxymethyl derivatives of sulbactam. The most effective method so far known is that noted in Scheme 2, which utilizes the reaction of formaldehyde gas with the Grignard derivative of dibromo compound **3**. The yield of the conversion of **3** into **4**/**5** is rather low, ∼25−30%, and in addition is not stereoselective. Successful efficient synthesis of prodrugs based on Scheme 2 proved far from optimum as it also contained a protection strategy and a relatively inefficient debromination using hydrogenation even though significant advances were made from the 1980s technology.[10] The elimination of the protection strategy accompanied by the development of a highly stereoselective radical debromination procedure suitable for pharmaceutical use that would make use of both α- and β-hydroxymethyl epimers and conserve hard-won C−C bond formation at C-6 would improve synthetic efficiency and lead to an efficient three-step synthesis. The venture was successful, and the synthesis is outlined in Scheme 3.

The dibromo sodium salt **9** was esterified using chloromethyl derivatives of suitable prodrug side chains **10** and **11**, which contained other functional groups. The esters **12** and **13** were prepared by conventional but individually tailored means to provide the first new intermediates of the synthesis. Chloromethyl compound **10** was converted into the iodo derivative in situ using the Finkelstein reaction and was reacted with the TBA salt of **9** to yield the ester **12**. The TBA salt of **9** was reacted with the optically active secondary chloromethyl compound **11** ultrasonically to yield **13** to avoid racemization of the side chain's optically active centre. Magnesium derivatives of **12** and **13** were prepared in situ from methylmagnesium chloride Grignard reagent in the temperature range −100 to −50 °C. The 6-bromo-6-hydroxymethyl isomeric pairs **14a**/**14b** and **15a**/**15b** were synthesized by direct reaction with formaldehyde gas monomer generated by cracking paraformaldehyde at 80−110 °C. The yield of this procedure has a limit of about 40% in studies so far, and the product mixtures **14a**/**14b** and **15a**/**15b** contain ratios of the epimers in the range 1:1 to 2:1 in favour of the desired 6β-hydroxymethyl isomer, emphasising the requirement for a stereoselective debromination procedure that converts the α and the β epimer into exclusively β-hydroxymthyl debrominated products. Fortunately, the complex prodrug side chain survives the harsh conditions of the formaldehyde reaction, leaving the search to devise a methodology that would yield the target molecules **7** and **8** as exclusive products of debromination from the mixture of epimers **14a**/**14b** and **15a**/**15b**, respectively. The epimer mixtures **14a**/**14b** and **15a**/**15b** are chromatographically separated from 6-bromo 6-H analogue side products before being used in the radical debromination step to avoid contaminating the desired products **7** and **8** with sulbactam analogues.

On the basis of the results known for debromination with trialkyltin hydrides such as tri-*n*-butyltin hydride, we worked on developing germanium analogues. We focused on tri-*n*-butylgermanium hydride but also considered triethylgermanium hydride and tri-*iso*-propylgermanium hydride. The smaller alkyl germane reagents were more difficult to make although triisopropyl germanium hydride[11] was successfully prepared but in a lower yield (30%) than the tri-*n*-butylgermanium hydride (66%). It was not possible to pursue this particular option but is believed to give similar results. The intermediate **5** and more remarkably its epimer **4** (Scheme 4) and mixtures of **4** and **5** were found to yield exclusively the β-hydroxymethyl ester **16** when debrominated with tri-*n*-butylgermanium hydride and AIBN as a radical initiator. The optimized conditions developed for this reaction used a 30% molar excess of tri-*n*-butylgermanium hydride

(10) In Scheme 1 when $R_3N = Et_3N$, the ratio of **2** and **6** is 3:1 using specific hydrogenation conditions of defined solvent, Pd catalyst type, reaction temperature, and hydrogen pressure, but for $R_3N = i\text{-}Pr_2EtN$ under the same conditions of hydrogenation, the ratio of **2** and **6** is in the range 9:1−13:1. This study will be reported in detail elsewhere. See also: Quallich, G. J.; Bordner, J.; Elliott, M. L.; Morrissey, P.; Volkmann, R. A.; Wroblewska-Adams, M. M. *J. Org. Chem.* **1990**, *55*, 367.

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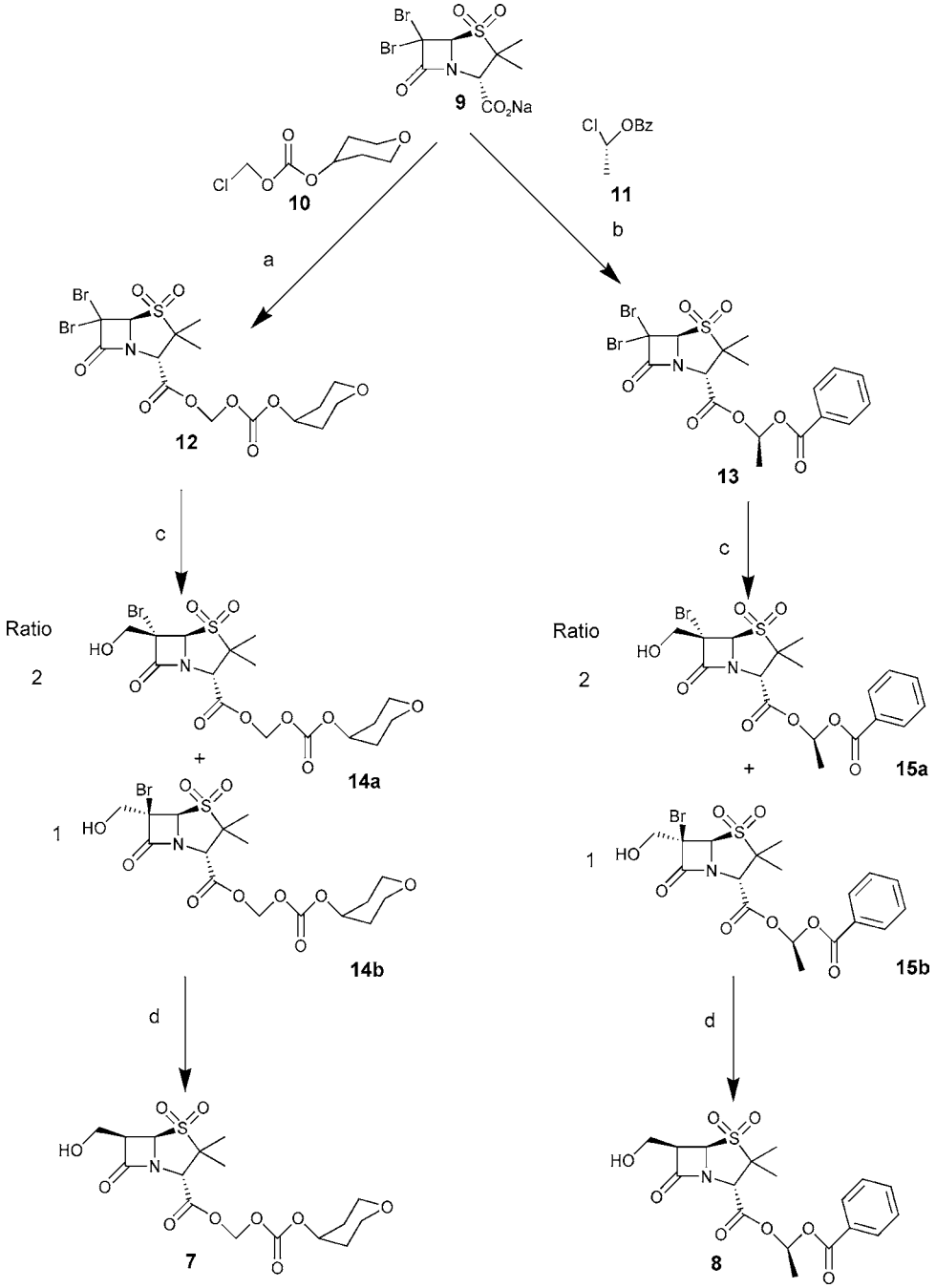
Scheme 3. **Efficient three-step prodrug synthesis using *n*-Bu_3GeH as a highly stereoselective debromination reagent[a]**



[a] Conditions: a) (i) **10**, KI, acetone, reflux, (ii) TBA·HSO_4, $NaHCO_3$, MeCN 25°; b) (i) TBA·HSO_4, $NaHCO_3$, CH_2Cl_2, (ii) **11**/acetone, ultrasound; c) (i) MeMgCl, THF −70°, (ii) HCHO gas 90°; d) *n*-Bu_3GeH, AIBN, MeCN reflux.

Scheme 4. **Conversion of 4 and/or 5 into 16**

in the presence of AIBN as radical initiator in refluxing acetonitrile. HPLC designed to separate both epimer pairs of starting materials **4** and **5** and potential products **16** and **17** showed that the debromination reaction was nearly quantitative, >99% conversion into **16**, and was complete after 1 h reaction.

The high yield and highly selective stereochemical outcome make tri-*n*-butylgermanium hydride or similar trialkylgermanium hydrides a good choice for syntheses of prodrugs such as **7** or **8**. In addition the simple clean work-up gives this class of reagent an advantage over the trialkyltin hydride series, which generate excessive tars and unacceptable levels of tin residues, along with the desired product. Trialkylsilicon hydrides such as triethylsilicon hydride do not give effective debromination under similar conditions or even with excess radical initiator. It was noted that, in contrast to tri-*n*-butylgermanium hydride, tri-*n*-butyltin hydride requires a minimal amount of AIBN radical initiator to effect reaction. Tris(trimethylsilyl)silane and AIBN can

Scheme 5. **α-CH_2OH structures**

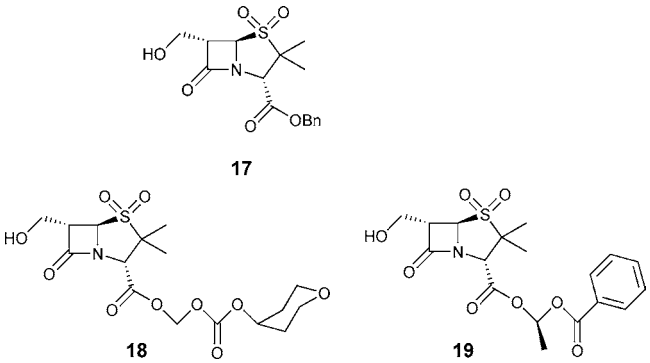


Table 1. **Comparison of various hydrides related to Bu_3GeH used for conversion[a] of 14a/14b mixtures into 7**

hydride reagent R_3MH	R_3MH (equiv)	AIBN (equiv)	**7** isolated (% yield)	HPLC purity (%)
Bu_3GeH	1.28	0.5	99.4	91.2[b]
$(TMS)_3SiH$	1.15	0.4	51.0	99.2[c]
Bu_3SnH	1.15	none	51.6	99.5[c]

[a] Reaction solvent MeCN, Bu_3GeH and $(TMS)_3SiH$ reactions carried out at reflux temperature, Bu_3SnH at 25 °C. [b] No chromatography. [c] After chromatography.

also be used to selectively debrominate **4** and **5** to yield principally **16**, but this option was not developed for prodrug synthesis.[12]

Similarly the epimer mixtures **14a**/**14b** and **15a**/**15b** respectively yielded the prodrugs **7** and **8** as almost exclusive products in high yield with tri-*n*-butylgermanium hydride and AIBN. In the case of **14a**/**14b** a 2:1 epimer mixture resulted in formation of **7** in 99% yield with minimal formation of its 6α epimer **18** (<3%), and for **15a**/**15b** a 2:1 epimer mixture resulted in formation of **8** in 65% yield with minimal formation of its 6α epimer **19** (<2%). (See Scheme 5 for α epimer structures).

Comparison Studies and Further Observations. It should be noted that although the main thrust of this project was directed at the use of Bu_3GeH, other related hydrides noted in Table 1 were shown to be effective in debromination of mixtures of **14a** and **14b** to yield principally **7**.

Further comparisons between Bu_3GeH and $(TMS)_3SiH$ show that pure **14a** or **14b** are converted into **7** in similar yields and selectivity (Table 2). These reactions were carried

Table 2. **Comparison conversions of pure 14a or 14b into 7 using Bu_3GeH or $(TMS)_3SiH$**

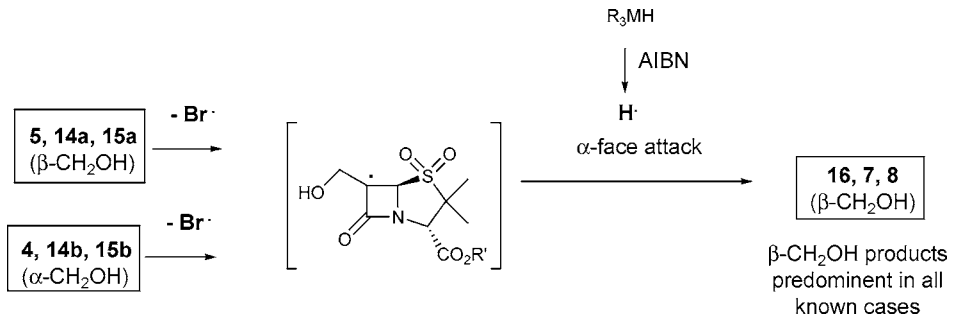
starting material	R_3MH reagent	R_3MH hydride (equiv)	AIBN initiator (equiv)	**7** (% yield)	**7** (β-CH_2OH) (% isomer excess[a])
14b (α-CH_2OH)	$(TMS)_3SiH$	1.22	0.46	72	96.6
14b (α-CH_2OH)	Bu_3GeH	1.45	0.46	81	89.4
14a (β-CH_2OH)	$(TMS)_3SiH$	1.22	0.46	66	93.5
14a (β CH_2OH)	Bu_3GeH	1.45	0.46	78	96.9

[a] HPLC area count calculation: Isomer excess % = [β-CH_2OH − α-CH_2OH/sum of α and β isomers] × 100.

out on small scale in a Carousel Reaction Station under the same conditions of solvent and temperature, MeCN at ∼70 °C. Tables 1 and 2 results show that Bu_3SnH and $(TMS)_3SiH$ also showed potential for use in the short prodrug synthesis described for Bu_3GeH, and with appropriate development or purification and work-up methodology these reagents could likely equal (or better) the performance of Bu_3GeH.

Reaction Mechanism of Debromination. The debromination of compounds **4**, **5**, **14a**, **14b**, **15a**, and **15b** to yield 6-β-hydroxymethylpenicillin esters, **16** (from **4** and **5**), **7** (from **14a** and **14b**), and **8** (from **15a** and **15b**) are almost certainly free radical in nature when caused by reagents of the type R_3MH (where M = Si, Ge, or Sn) and R = alkyl C_3 to C_4 or higher for Ge or Sn. In the case of Si, R is required to be TMS to be effective. Debromination effected by use of R_3MH is highly stereoselective and biased towards formation of the 6-β-hydroxymethyl series of products **16**, **7**, and **8**. The $R_3M^{\bullet}$ radical and the stereochemistry of the radical derived from the penicillin substrate could both play a role in the reaction stereoselectivity observed in the products. Debromination carried out with catalytic hydrogenation does not give such a strong bias towards 6-β-hydroxymethyl products as do bulky hydride reagents Bu_3GeH, Bu_3SnH, and $(TMS)_3SiH$. Pure α-hydroxymethyl starting materials such as **4**, **14b**, and **15b** give mainly β-hydroxymethyl products when treated with bulky hydride reagents, and β-hydroxymethyl starting materials (**5**, **14a**, **15a**) also give the same β-hydroxymethyl products (Scheme 6). The structure of the free radical substrate intermediate has not been studied mechanistically, but based on the evidence collected so far Scheme 6 shows what may be happening in the R_3MH-mediated debrominations. A com-

Scheme 6. **Postulated α-face attack of products penicillin substrate radical by H• generated from R_3MH to yield predominantly β-CH_2OH products from α- or β-CH_2OH starting materials[a]**



[a] R_3MH = $(TMS)_3SiH$, Bu_3GeH, or Bu_3SnH; R′ defined by **16**, **7**, and **8**.

mon substrate free radical is formed that then undergoes hydrogen free radical attack on the α-face of the penicillin to yield the β-CH_2OH products such as **16**, **7**, and **8**.

Conclusion

Radical debromination of either of the possible 6-bromo-6-hydroxymethylpenicillin-1,1-dioxide ester derivatives or mixtures of these esters gives almost exclusively β-hydroxymethyl products in high yield when performed with tri-*n*-butylgermanium hydride in the presence of radical initiators such as AIBN. This reaction is useful in devising efficient syntheses to prodrugs such as **7** and **8**. The nontoxic nature of germanium was considered a significant advantage over tin and gives the prospect of devising a very short commercial synthesis.

Experimental Section

6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate-4,4-dioxide, **9**, is manufactured by Pfizer Inc and can be obtained commercially from a variety of sources or synthesized from 6-aminopenicillanic acid.[13] Tri-*n*-butylgermanium hydride was made using literature (see ref 11) procedures and purified by fractional distillation. Mixtures of benzyl (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, **4** and benzyl (2*S*,5*R*,6*S*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, **5** were prepared according to methods similar to literature procedures.[14] **4** and **5** were separated by standard chromatographic techniques using silica gel and solvent gradients of increasing polarity made from heptane and ethyl acetate mixtures. Chloromethyl tetrahydro-2*H*-pyran-4-yl carbonate, **10** can be purchased from from Fontarome Chemical Inc., 70 S. Nevada Ave., St. Francis, WI 53235. (S)-1-Chloroethyl benzoate, **11** Can be made by literature procedures (see ref 6, example 1). NMR data was collected using an Oxford Instruments, Unity Inova 400 spectrometer, and FTIR data, with an ATI Mattson, Genesis series FTIR spectrometer. NOE experiments were performed to verify the relative positions of protons on 6-hydroxymethylsulbactam derivatives by irradiation of protons on C-3 or C-5.

{[(Tetrahydro-2*H*-pyran-4-yloxy)carbonyl]oxy}methyl-(2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4,4-dioxide, 12. Chloromethyl tetrahydro-2*H*-pyran-4-yl carbonate, **10** (3.54 g, 0.018 mol), potassium iodide (6.04 g, 0.036 mol), and acetone (50 mL) were refluxed at 56 °C for 10 h. The resulting salts were filtered off and washed with acetone (10 mL) to obtain an acetone solution of iodo derivative of **10**. Sodium (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4- -thia-1-azabicyclo [3.2.0]-heptane-2-carboxylate-4,4-dioxide, **9** (5.04 g, 0.012 mol), tetrabutylammonium hydrogen sulfate (4.2 g, 0.012mol), sodium bicarbonate (1.02 g, 0.012 mol), and acetonitrile (150 mL) were stirred for 2 h at 25 °C. The iodo derivative solution of **10** was added to the mixture over 20 min below 0 °C and then stirred at 25 °C for 1 h. The reaction mixture was quenched with ethyl acetate (250 mL) and water (150 mL) and stirred for 15 min, pH 6.6. The organic phase was washed with 1% w/v solution of sodium thiosulfate (150 mL) and 2% brine (4 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated to an oil. Crystallization from 2-propanol yielded a grey solid, **12** (g, 60%, HPLC purity 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) ppm, 1.44 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.78 (2H, m, THP−H), 2.02 (2H, m, THP−H), 3.57 (2H, m, THP−H), 3.96 (2H, m, THP−H), 4.58 (1H, s, H-2), 4.90 (1H, m, THP−H), 5.04 (1H, s, H-5), 5.81 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O), 5.93 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O). ν (cm^{-1}), Nujol,1806, 1758, 1272, 1181, 1090. The electron impact MS gave no molecular peak. The sample was dissolved in methanol, and the Applied Biosystems QSTAR Pulsari was used in electrospray mode to determine the accurate mass affording the following results. Triplets observed were consistent with the presence of two bromine atoms/molecule.

$(M+NH_4)^+$	
experimental mass	theoretical mass
564.9471	564.9490
566.9476	566.9471
568.9450	568.9452

$(M+Na)^+$	
experimental mass	theoretical mass
569.9086	569.9044
571.9002	571.9025
573.8991	573.9006

[(1*R*)-1-(Benzoyl)oxy]ethyl(2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 13. A mixture of sodium (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4- -thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate-4,4-dioxide, **9** (46.8 g, 0.11 mol), tetrabutylammonium hydrogen sulfate (38 g, 0.11 mol) and sodium bicarbonate (2.9 g, 0.136 mol) in dichloromethane (360 mL) was treated with water (96 mL) and stirred at 25 °C for 45 min. The aqueous phase was extracted with dichloromethane (120 mL), and the combined organics were dried over anhydrous Na_2SO_4, filtered, and placed in an ultrasound bath. A solution of (*S*)-1-chloroethyl benzoate, **11** (64.4 g, 0.34 mol) in acetone (96 mL) was added to the mixture over 20 min, with sonication. The mixture was sonicated for 20 h at 24−27 °C and concentrated to dryness. The residue was treated with ethyl acetate (760 mL) and water (280 mL) and stirred for 15 min. The aqueous phase was extracted with ethyl acetate (760 mL), and the combined organic phases were washed with saturated brine (96 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to an oil. Purification by column chromatography, using silica gel and ethyl acetate heptane mixtures as a solvent gradient, afforded a pale yellow noncrystalline solid, **13** (17.5 g, 29.4%): ^{1}H NMR ($CDCl_3$) ppm, 1.52 (s, 3H, 3-Me), 1.53 (s, 3H, 3-Me), 1.73 (d, J = 5.6 Hz, 3H, Me), 4.51 (s, 1H,

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(13) Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliott, M. L.; Moore, B. S. *J. Org. Chem.* **1982**, *47*, 3344. Dibromo compound **3**.
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H-2), 5.04 (s, 1H, H-5), 7.12 (q, 1H, O−CH−O, R-config), 7.50 (t, 2H, Ar−H), 7.65 (t, 1H, Ar−H), 8.05 (d, J = 7.2 Hz, 2H, Ar−H): ν (cm^{-1}), Nujol,1810, 1757, 1276, 1191, 1118,1053.

{[(Tetrahydro-2*H*-pyran-4-yloxy)carbonyl]oxy}methyl-(2*S*,5*R*,6*S*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 14a/{[(Tetrahydro-2H-pyran-4-yloxy)carbonyl]oxy}-methyl (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 14b. A mixture of paraformaldehyde (71.8 g, 2.34 mol, 9.0 equiv), toluene (70 mL), and silicone oil 200/200 cS (100 mL) was heated to reflux (∼108 °C), and the water separated from the azeotrope (1−2 mL) was collected in a Dean & Stark apparatus. When the moisture content of the mixture, measured by Karl Fischer titration, was below 0.03%, the heating was stopped. MeMgCl (3 M in THF, 140 mL, 0.42 mol, 1.61 equiv) was added under nitrogen to a cold (−70 °C) solution of **12** (143 g, 0.26 mol) in dry THF (1000 mL) at such a rate that the temperature was kept below −64 °C. The mixture was stirred under nitrogen at a temperature t < −65 °C for 30 min. The flask containing the dry paraformaldehyde mixture was connected to the cold flask containing Grignard solution by means of a heated (160 °C) glass tube, and the temperature of the paraformaldehyde flask was increased at such a rate as to ensure the gradual transfer of formaldehyde gas to the vigorously stirred Grignard solution over approximately 1.5 h. The temperature of the Grignard solution was kept below − 67 °C, and the progress of the reaction was followed by HPLC. At the end of the reaction the cold mixture was quenched with a solution of acetic acid (26 mL, 0.44 mol, 1.7 equiv) in THF (77 mL) and allowed to warm to room temperature overnight. Ethyl acetate (600 mL) and water (300 mL) were added, and the well-stirred mixture was titrated with H_2SO_4 (1 M, ∼193 mL) to pH = 3.5. Celite (50 g) was added with stirring, the suspension was filtered through a bed of Celite, and the filter cake was washed with ethyl acetate (145 mL). The layers were separated, the aqueous layer was extracted with ethyl acetate (3 × 140 mL), and the combined organic extracts were washed with brine (10% w/v NaCl, 3 × 286 mL) and saturated brine (286 mL). The solution was dried over anhydrous Na_2SO_4 (87 g), filtered, concentrated under vacuum at 37 °C, and dried under high vacuum overnight (10^{-4} bar), affording a dark-brown viscous oil (109.2 g). The crude oil was purified by column chromatography using silica gel and ethyl acetate/heptane mixtures as a solvent gradient to afford an off-white glassy foam **14a/14b** (57.7 g, 44.3%). The ratio of **14a/14b** was approximately 2:1. Small amounts of **14a** and **14b** were separated by further chromatography.

14a, 6-β, product: ^{1}H NMR ($CDCl_3$, 400 MHz) ppm, 1.44 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.76 (2H, m, THP−H), 2.01 (2H, m, THP−H), 2.67 (1H, dd, J_{8vic} 4.8 Hz, J_{8vic} 8.4 Hz, OH), 3.55 (2H, m, THP−H), 3.94 (2H, m, THP−H), 4.13 (1H, m, CH_2−OH), 4.58 (1H, s, H-2), 4.66 (1H, dd, J_{gem} 13 Hz, J_{OHvic} 8.4 Hz, CH_2−OH), 4.87 (1H, s, H-5), 4.90 (1H, m, THP−H), 5.81 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O), 5.92 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O). **14b, 6-α product:** ^{1}H NMR ($CDCl_3$, 400 MHz) ppm, 1.44 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.77 (2H, m, THP−H), 2.01 (2H, m, THP−H), 3.55 (2H, m, THP−H), 3.94 (2H, m, THP−H), 4.02−4.23 (1H, m, CH_2−OH), 4.58 (1H, s, H-2), 4.81 (1H, s, H-5), 4.85−4.96 (2H, m, CH_2−OH, THP−H), 5.78 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O), 5.92 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O).

[(1*R*)-1-(Benzoyl)oxy]ethyl(2*S*,5*R*,6*S*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate-4,4-dioxide, 15a/[(1*R*)-1-Benzoyloxy]-ethyl-(2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 15b. [(1*R*)-1-(Benzoyl)oxy]ethyl(2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, **13** (10 g, 0.016 mol) in dry THF (100 mL) was cooled to −70 °C and treated with MeMgCl solution in THF (3 M, 9.1 mL, 0.0272 mol, 1.7 equiv) over 10 min, while maintaining cryogenic temperature. This was reacted with formaldehyde gas generated from paraformaldehyde (35 g), toluene (30 mL), and silicone oil (60 mL) in the manner described above. The reaction was stirred for 30 min when HPLC indicated that reaction was complete. Acetic acid (1.112 g, 0.018 mol, 1.14 equiv) was added, followed by ethyl acetate (110 mL) and sulfuric acid (1 M, 30 mL), pH noted as 0.91. The mixture was filtered through a Celite bed and washed with ethyl acetate (2 × 20 mL). The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to give a dark-yellow oil, 8.70 g. Traces of acetic acid were removed under high vacuum (10^{-4} bar), resulting in a foam, 5.80 g. Further purification by column chromatography (silica gel, ethyl acetate, and hexane) yielded (1-benzoyloxy)ethyl ester, 2*S*,5*R*,6*R*/*S*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide) (2:1, **15a**:**15b**), 2.0 g, 25.4%.

6-α,β product mixture: ^{1}H NMR ($CDCl_3$) ppm, 1.52 (t, 6H, 3-Me × 2) [β = s, 6H, Me × 2 and α = d, 6H, Me × 2], 1.73 (dd, 3H, Me) [β and α, 4.14 (m, 3H, CH_2−OH) [β = d, 1H, CH_2−OH and α = m, 2H, CH_2−OH], 4.51 (s, 1H, H-2) [β and α], 4.69 (d, J = 13 Hz, 1H, CH2−OH) [β], 4.81 (s, 1H, H-5) [α], 4.85 (s, 1H, H-5) [β], 7.12 (m, 1H, O−CH−O, R-config) [β and α], 7.50 (t, 2H, Ar−H) [β and α], 7.65 (t, 1H, Ar−H) [β and α], 8.05 (d, J = 7.2 Hz, 2H, Ar−H) [β and α]. ν (cm^{-1}), Nujol,1804, 1731, 1273, 1182, 1051[6-α, 15**b**].

15a, 6-β product: ^{1}H NMR ($CDCl_3$) ppm, 1.53 (s, 6H, 3-Me × 2), 1.73 (d, J = 5.4 Hz, 3H, Me), 4.14 (d, 1H, J = 13 Hz, CH_2−OH), 4.51 (s, 1H, H-2), 4.69 (d, J = 13 Hz, 1H, CH_2−OH), 4.85 (s, 1H, H-5), 7.12 (m, 1H, O−CH−O, R-config), 7.50 (t, 2H, Ar−H), 7.65 (t, 1H, Ar−H), 8.05 (d, J = 7.2 Hz, 2H, Ar−H). ν (cm^{-1}), Nujol,1805, 1729, 1270, 1160, 1051. Obtained by further chromatographic purification.

{[(Tetrahydro-2*H*-pyran-4-yloxy)carbonyl]oxy}methyl-(2*S*,5*R*,6*R*)-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 7. Tri-*n*-butylgermane (0.95 g, 3.87 mmol, 1.28 equiv) was added to a solution of **14a**/**14b** (2.0 g, assay 75.9%, 3.03 mmol) in

acetonitrile (30 mL). The mixture was heated to reflux and AIBN (0.3 g, 1.52 mmol, 0.5 equiv) added in one portion. The well-stirred reaction mixture was diluted with acetonitrile (40 mL) and hexane (50 mL), and the layers were separated. The hexane layer was extracted with acetonitrile (15 mL), and the combined acetonitrile layers were washed with hexane (3 × 30 mL), concentrated under vacuum at 40 °C, and dried under high vacuum (10^{-4} bar), affording crude product (1.89 g, assay 69.2%) as an oil. The crude oil was dissolved in EtOAc (9 mL) and heated to 60−68 °C, and heptane (20 mL) was added dropwise with stirring. The cloudy mixture was allowed to cool to room temperature, stirred at 0 °C for 2 h, filtered, washed with EtOAc/heptane 1:2 (1.5 mL) and heptane (5 mL), and dried under high vacuum (10^{-4} bar), affording **7** (1.27 g, 99.4%) as a white crystalline solid. HPLC assay 91.2%. Spectroscopic data noted below were identical with those of an authentic sample: ^{1}H NMR ($CDCl_3$, 400 MHz) ppm, 1.44 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.77 (2H, m, THP−H), 2.01 (2H, m, THP−H), 2.10 (1H, m, OH), 3.55 (2H, m, THP−H), 3.95 (2H, m, THP−H), 4.18 (2H, m, H-6, CH_2−OH), 4.34 (1H, m, CH_2−OH), 4.53 (1H, s, H-2), 4.71 (1H, d, J 4.8 Hz, H-5), 4.89 (1H, m, THP−H), 5.79 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O), 5.92 (1H, d, J_{gem} 5.6 Hz, O−CH_2−O). HPLC shows a main band corresponding to that for an authentic sample. Assay compared to authentic reference standard 97%.

[(1*R*)-1-(Benzoyl)oxy]ethyl(2*S*,5*R*,6*R*)-3,3-dimethyl-6-(hydroxymethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, 8. Tri-*n*-butylgermane (0.62 g, 2.52 mmol) was added to a solution of **15a/15b** (1 g, 2.0 mmol) in acetonitrile (15 mL). The mixture was heated to reflux, and AIBN (0.17 g, 1.0 mmol) added in one portion. The well-stirred reaction mixture was diluted with acetonitrile (28 mL) and hexane (70 mL), and the layers were separated. The hexane layer was extracted with acetonitrile (7 mL), and the combined acetonitrile layers were washed with hexane (3 × 15 mL) and concentrated under vacuum at 40 °C, affording crude product (1.2 g) as a solid. The crude solid was dissolved in isopropyl alcohol (12 mL) at 70 °C, and heptane (24 mL) was added dropwise with stirring. The clear mixture was allowed to cool to room temperature and filtered; the precipitate was washed with heptane (5 mL) and dried under vacuum, affording **8** as a white solid (0.56 g, 68%). Spectroscopic data noted below were identical with those of an authentic sample: ^{1}H NMR (*d*-DMSO, 400 MHz): 7.96 (d, 2H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.5 Hz), 7.55 (t, 2H, J = 7.5 Hz), 7.07 (q, 1H, J = 5.4 Hz), 5.19 (d, 1H, J = 5 Hz), 5.15 (m, OH), 4.54 (s, 1H), 4.18 (m, 1H), 4.01 (m, 1H), 3.72 (m, 1H), 1.62 (d, 3H, J = 5.4 Hz), 1.44 (s, 3H) 1.35 (s, 3H). MS (*m*/*z*): 410 (M^- −1, 100). HPLC shows main band corresponding to an authentic sample. Assay compared to authentic reference standard 98%

Improved Method for Preparation of Benzyl (2*S*,5*R*)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]-heptane-2-carboxylate-4,4-dioxide, 3. Sodium (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, **9** (3820 g) was dissolved in DMF (5.7 L), and benzyl bromide (1400 g) was added over a 1 h to the DMF solution. The reaction mixture was stirred overnight at 25−30 °C. Water (4.5 L) and ethyl acetate (15.0 L) were added to the reaction mixture. The aqueous phase was washed with ethyl acetate (2 × 600 mL), and the combined organic phases were washed sequentially with a saturated aqueous $NaHCO_3$ solution (2 × 1 L) and an aqueous NaCl solution (2 × 1 L). The organic layer was dried over $MgSO_4$ and concentrated to give **3** (3566 g, 90%) as crystals, mp 146−147 °C. ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 3H), 1.5 (s, 3H), 4.5 (s, 1H), 4.9 (s, 1H), 5.16 (d, 1H, J = 12 Hz), 5.29 (d, 1H, J = 12 Hz), 7.35−7.40 (m, 5H), identical to an authentic sample.

Demonstration That Either Epimer 4 or 5 Can Be Debrominated with *n*-Bu_3GeH To Yield Exclusively *β*-Hydroxymethyl Isomer 16. *Preparation of Benzyl (2S,5R,6R)-3,3-Dimethyl-6-(hydroxymethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide,* ***16****, from* ***4****.* Benzyl (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide, **4** (2.0 g, purity 60%; 2.78 mmol), acetonitrile (30 mL), and tri-*n*-butylgermanium hydride (1.5 mL, purity 99.3%, 5.77 mmol) were heated to reflux. 2,2′-Azo-bis-isobutyronitrile (0.4 g, 2.39 mmol) was added in one portion, and heating at ∼81 °C continued for 10 min to 2 h or until reaction was completed as indicated by disappearance of starting material. HPLC indicated in situ yield >99%. The reaction mixture was cooled, diluted with acetonitrile (40 mL), and extracted with hexane (50 mL); the hexane layer was washed with acetonitrile (15 mL), and the combined acetonitrile fractions were re- extracted with hexane (3 × 30 mL). The washed acetonitrile solution was concentrated under vacuum on a rotary evaporator at ∼37 °C and the resulting oil dried under vacuum (10^{-4} bar) overnight affording crude product (1.75 g) which was purified by chromatography over silica gel using ethyl acetate/hexane mixtures to yield 16 (0.71 g, 72% yield). The ^{1}H NMR spectrum was consistent with that of a reference standard: ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.37 (1H, m, OH), 4.15 (2H, m, H-6, CH_2−OH), 4.32 (1H, m, CH_2−OH), 4.50 (1H, s, H-2), 4.69 (1H, d, J 4.4 Hz, H-5), 5.17 (1H, d, J_{gem} 12 Hz, Ph-CH_2), 5.92 (1H, d, J_{gem} 12 Hz, Ph-CH_2), 7.39 (5H, m, Ph-H).

From ***5****.* Benzyl (2*S*,5*R*,6*S*)-6-bromo-3,3-dimethyl-6-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide 5 (2.0 g, purity 78%; 3.61 mmol), acetonitrile (30 mL), and tri-*n*-butylgermanium hydride (1.5 mL, purity 99.3%, 5.77 mmol) were heated to reflux. 2,2′-Azo-bis-isobutyronitrile (0.4 g, 2.39 mmol) was added in one portion, and heating at ∼81 °C continued for 10 min to 2 h or until reaction was completed as indicated by disappearance of starting material. HPLC indicated in situ yield >99%. %. The reaction mixture was cooled, diluted with acetonitrile (40 mL), and extracted with hexane (50 mL); the hexane layer was washed with acetonitrile (15 mL), and the combined acetonitrile fractions were reextracted with hexane (3 × 30 mL). The washed acetonitrile solution was concentrated under vacuum on a rotary evaporator at ∼37

°C and the resulting oil dried under vacuum (10^{-4} bar) overnight, affording crude product (2.0 g) that was purified by chromatography over silica gel using ethyl acetate/hexane mixtures to yield **16** (0.69 g, 53% yield). The ^{1}H NMR spectrum was identical to that obtained from the product of the previous experiment and also consistent with that of a reference standard.

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