the mixture heated to 70 °C for 24 h. After the mixture was cooled, water (100 mL) was added and the organic layer separated and dried over anhydrous Na_2SO_4. After concentration in vacuo, the resulting oil was dissolved in Et_2O and passed through a short alumina column to afford **18**, as a viscous oil: 450 mg (42%); ^1H NMR δ 1.38 (m, CH_2, 2 H), 2.04 (dd, CCH_2, J = 7.0, 7.0 Hz, 4 H), 3.65 (s, ϵ,ζ-OCH_2, 8 H), 3.69 (s, γ,δ-OCH_2, 8 H), 3.85 (m, ketal CH_2, 8 H), 4.00 (t, β-OCH_2, J = 7.0 Hz, 4 H), 4.47 (t, α-OCH_2, J = 7.0 Hz, 4 H), 6.66 (d, 5-py H, J = 7.7 Hz, 2 H), 7.03 (d, 3-py H, J = 7.7 Hz, 2 H), 7.50 (dd, 4-py H, J = 7.7, 7.7 Hz, 2 H); IR ($CHCl_3$) 2900, 1560, 1520, 1400, 1180, 1090, 980 cm^{-1}; MS, m/e 620 (0.5, M^+), 99 (100). Anal. Calcd for $C_{31}H_{44}N_2O_{11}$: C, 60.00; H, 7.10; N, 4.52. Found: C, 59.96; H, 7.38; N, 4.40.

Hydrolysis of Bis Ketal 18. A solution of **18** (100 mg, 0.16 mmol) and HCl (4 N, 25 mL) was warmed to 40 °C for 4 h. The solution was then neutralized with solid Na_2CO_3 and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford bis ketone **19**, as white microcrystals: 75 mg (88%); mp 99–100 °C (EtOH); ^1H NMR δ 2.08 (m, CH_2, 2 H), 3.20 (dd, $COCH_2$, J = 7.0, 7.0 Hz, 4 H), 3.58 (s, ϵ,ζ-OCH_2, 8 H), 3.65 (m, γ,δ-OCH_2, 8 H), 3.83 (t, β-OCH_2, J = 6.5 Hz, 4 H), 4.46 (t, α-OCH_2, J = 6.5 Hz, 4 H), 6.88 (dd, 5-py H, J = 7.7, 1.0 Hz, 2 H), 7.65 (m, 3,4-py H, 4 H); IR ($CHCl_3$) 2960, 1700 (C=O), 1560, 1390, 1190, 1150, 1090, 970 cm^{-1}; MS, m/e 532 (25, M^+), 313 (43), 176 (100). Anal. Calcd for $C_{27}H_{36}N_2O_9$: C, 60.90; H, 6.77; N, 5.26. Found: C, 60.52; H, 6.91; N, 5.43.

Reaction of Bis Ketone 19 with Ammonium Acetate. A mixture of **19** (100 mg, 0.19 mmol) and NH_4OAc (1.0 g) in MeOH (5 mL) was stirred and refluxed for 3 h. After cooling, the mixture was neutralized with solid Na_2CO_3, water (50 mL) was added, and the solution was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extract was dried over anhydrous Na_2CO_3, filtered, and concentrated in vacuo to give **20**, as colorless needles: 70 mg (72%); mp 127–128 °C; ^1H NMR (see Figure 1); IR ($CHCl_3$) 2950, 1580, 1540, 1395, 1230, 1130, 1050, 980 cm^{-1}; MS, m/e 511 (9, M^+), 292 (38), 266 (44), 265 (100). Anal. Calcd for $C_{27}H_{33}N_3O_7$: C, 63.41; H, 6.46; N, 8.22. Found: C, 63.18; H, 6.55; N, 7.99.

Acknowledgment. We thank the National Science Foundation and the Louisiana State University Center for Energy Studies for partial support of this work.

Studies on 6-Halo- and 6,6-Dihalopenicillins: The Rearrangement of Methyl 6,6-Dibromopenicillanate to 1,4-Thiazepine

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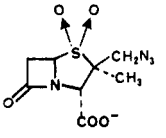
Methyl 6α-bromo- and 6β-bromopenicillanates underwent reductive dehalogenation with zinc and glacial acetic acid in acetonitrile or with zinc and ammonium acetate in tetrahydrofuran. Similarly methyl 6,6-dibromopenicillanate was reduced cleanly by zinc and ammonium acetate in THF to the corresponding 6,6-dihydropenicillanates; but with zinc and glacial acetic acid (or dilute hydrochloric acid) in acetonitrile or ethyl acetate, (3*S*)-6-bromo-2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylate was obtained as the major rearrangement product. However, oxidation of the sulfide to the sulfoxide (α or β) or sulfone stabilized the ring system to this rearrangement, the products being the 6,6-dihydropenicillanate 1-oxides or the sulfones. The 6,6-diiodopenicillanates, on the other hand, underwent extensive decomposition. These dissolving metal reductions have been used as a convenient route to either the 6,6-dihydropenicillanate 1α-oxides or the 6,6-dihydropenicillanate 1β-oxides, depending on the reaction sequence employed.

Recent reports have described many β-lactamase inhibitors such as clavulanic acid,[1] 6β-bromopenicillanic acid,[2] sulbactam[3] and its 6α-chloro analogue,[4] 6-(methoxymethylene)penicillanic acid,[5] and 2β-azidomethyl-substituted 6,6-dihydropenicillanate 1,1-dioxide (**1**)[6] and its triazolyl derivative **2** (YTR-830).[7]



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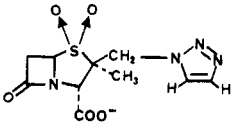

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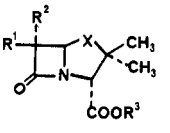
A part of our studies in this area was directed toward developing a high-yield, economical process for the preparation of 6,6-dihydropenicillanate 1β-oxide (**3**, $R^1 = R^2 = H$; X = SO), a useful intermediate for the synthesis of **1**. The key step in our approach was the efficient removal of the 6β-amido (or amino) group of the penicillin. Procedures useful for this purpose have generally relied on the catalytic hydrogenation of 6α-bromo-[8] or 6,6-dibromopenicillins,[3c,9] prepared from 6-aminopenicillanic acid while



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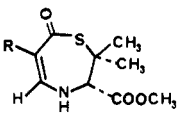

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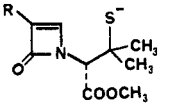

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† University of Alberta.
‡ Taiho Pharmaceutical Co. Ltd.

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other reductive debromination procedures involving tri-*n*-butyltin hydride[10] and sodium bisulfite[11] have been reported, particularly for the conversion of the 6,6-dibromopenams to the 6-monobromopenams. We, as well as others, have recently reported the dissolving metal reduction process for the removal of the C-6 bromine atom(s) of the penicillin nucleus.[6b,12]

Results and Discussion

To examine the general applicability of this dissolving metal procedure, studies on the displacement of both the halogen atoms of 6,6-dihalo (bromo or iodo) penicillanates and their corresponding sulfoxides (α or β) or sulfones by reductive cleavage with zinc and glacial acetic acid or under neutral conditions with ammonium acetate[13] were carried out. The rate of halide reduction was found to be dependent on the nature of the halogen atom.[6b] Thus with 6α-bromopenicillanates (**3**, R^1 = H; R^2 = Br; X = S) the reduction was complete within 2 h at 10 °C, while in the case of 6α-chloropenicillanates (**3**, R^1 = H; R^2 = Cl; X = S) the reaction was quite slow and incomplete, after 72 h at 40 °C only 35% of the reduced product being isolated. It is quite surprising that the dissolving metal reduction of 6,6-dihalopenicillins in acetic acid took a different course; cleavage of the β-lactam ring occurred in preference to the desired reaction, and a rearrangement product resulted. Thus, methyl (3*S*)-6-bromo-2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylate (**4**, R = Br; mp 100–102 °C) was isolated as the major product (after column chromatography) from the reaction of methyl 6,6-dibromopenicillanate (**3a**) with zinc and glacial acetic acid in acetonitrile or ethyl acetate at 0 °C; the minor product was the expected 6,6-dihydropenicillanate **3s**. The structure **4** was established on the basis of its IR and NMR spectra and by comparison to the related literature compounds. Kovacs and his co-workers[14] isolated thiazepinone **4** (R = Phth) during the C-6 epimerization of methyl 6β-phthalimidopenicillanate **3** (R^1 = Phth; R^2 = H; R^3 = CH_3; X = S). Thiazepinone formation under nonbasic condition has also been reported, for example, with antimony pentachloride.[15] In all cases the intervention of the enethiolate intermediate **5** has been suggested. A similar

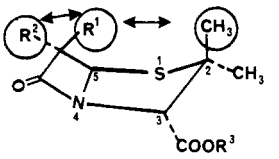
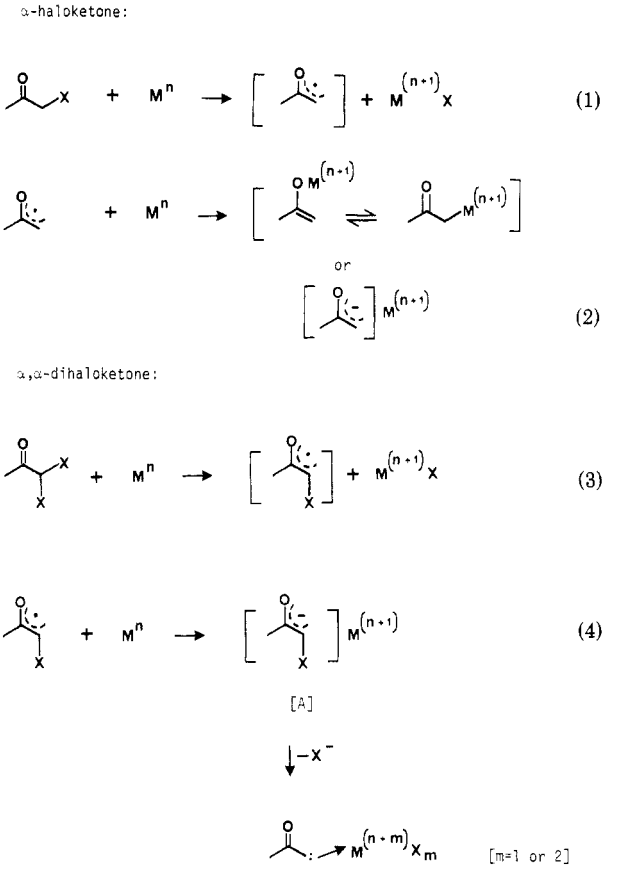


Figure 1.

Scheme I



intermediate **5** (R = Br) would also account for our rearranged product **4** (R = Br). Thiazepinone formation requires the cleavage of the 1–5 and 4–7 bonds of the penicillanoyl precursors, bond formation between the S atom and the CO moiety, and a proton transfer to the N atom. There was no evidence of this rearrangement when the 6,6-dibromopenicillanate **3a** was treated with acetic acid alone or with zinc in the absence of acetic acid. The reaction of the 6,6-dibromopenicillins with zinc under acidic conditions (glacial acetic acid or dilute hydrochloric acid in acetonitrile or ethyl acetate) resulted in extensive rearrangement to **4**. However under neutral conditions (zinc and ammonium acetate in THF) the 6,6-dihydropenicillins were obtained in high yields. Usually, reaction with Zn–NH_4OAc is much cleaner compared to the Zn–AcOH reaction. Again in the sulfide (6α-halo), sulfoxide (6α-halo or 6,6-dihalo), and sulfone (6,6-dihalo) series, the reaction of sulfone with Zn–AcOH gives a cleaner product than the sulfide and sulfoxide; in the last two cases the products are always associated with some (10–15%) decomposition products.

However, when the sulfur of the penicillin was oxidized to the sulfoxide (α or β) or sulfone, no rearrangement occurred in this zinc–acetic acid reaction. Instead, the corresponding 6,6-dihydro compounds were obtained in high yield. In contrast, under the reduction conditions used for methyl 6,6-dibromopenicillanate (**3a**), benzhydryl 6,6-diiodopenicillanate (**3i**) underwent extensive destruc-

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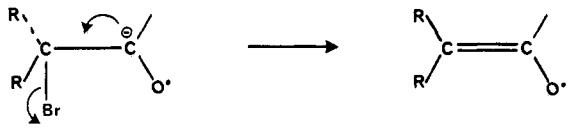
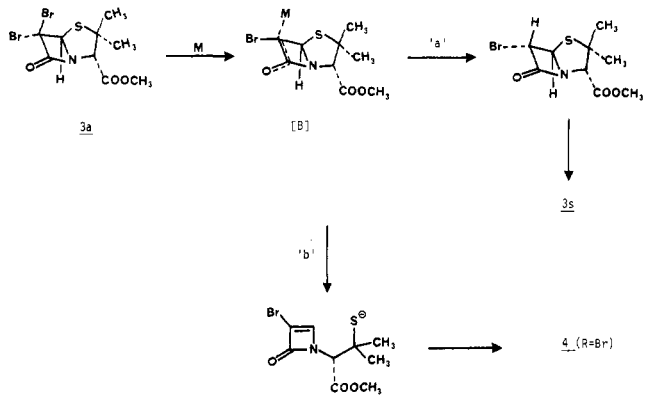
Scheme II



Scheme III



tion of the β-lactam, only a small quantity (<5%) of the dihydro compound **3w** was isolated from the complex reaction mixture.

An unusual feature of the foregoing reactions is that 6α- or 6β-bromopenicillins show no tendency to rearrange to thiazepinones. This large difference in chemical reactivity between the monohalo and dihalo derivatives is quite striking. A possible explanation could be the steric compression between the halogen atoms and the 2β-CH_3 group which probably facilitates the cleavage of the 1–5 bond (Figure 1).

In fact it has been observed [16] that 6β-phthalimidopenicillanate **3** (R^1 = Phth; R^2 = H, X = S) rearranges to the thiazepinone **4** (R = Phth) 300 times faster than its 6α-isomer **3** (R^1 = H; R^2 = Phth; X = S). Reductive dehalogenation of α-halo and α,α-dihalo ketones appears to proceed either by one-electron transfer (eq 1 and 3) or by two successive one-electron transfer reactions (eq 2 and 4) giving rise to the enolate intermediate[17] (Scheme I). The enolate intermediate A could further eliminate the remaining halogen atom to give the metal complex.

Reductive cleavage of α-substituted ketones proceeds readily if the molecule can adopt a conformation where the bond to the leaving roup is perpendicular to the plane of the carbonyl group.[18] Elimination of the substituent group is then eased by continuous overlap of the developing p-orbital at the α-carbon atom with the π-orbital system of the ion radical (Scheme II).

A consequence of this stereoelectronic requirement is that methyl 6β-bromopenicillanate (**3g**) was reduced faster (ca. 1 h) than its 6α-isomer **3f** (1.5 h). When the reduction of **3a** was repeated with smaller amounts of zinc and the reaction was quenched after a short period of time (40 min) the crude product was a mixture of the unchanged 6,6-dibromopenam **3a**, 6α-bromopenam **3f**, 6,6-dihydropenam **3s**, and the thiazepinone **4** (R = Br), which suggests that the β-substituent is preferentially reduced. The formation of the thiazepinone **4** (R = Br) and dihydro compound **3s** from compound **3a** presumably proceeds via the enolate species B,[19] which by protonation from the β-face gives the

Scheme IV

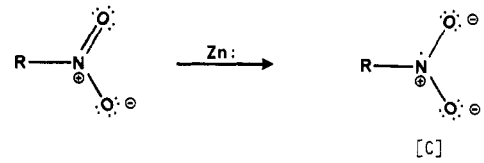
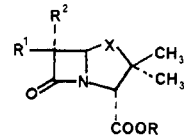


Table I



compd	R^1	R^2	R^3	X
3a[a]	Br	Br	CH_3	S
3b	Br	Br	CH_3	S---O
3c[b]	Br	Br	CH_3	SO
3d	Br	Br	CH_3	SO_2
3e[b]	I	I	CH_3	SO
3f[c]	H	Br	CH_3	S
3g[d]	Br	H	CH_3	S
3h[b]	Br	Br	$CHPh_2$	S
3i[b]	I	I	$CHPh_2$	S
3j[b]	Br	Br	$CHPh_2$	SO
3k[b]	I	I	$CHPh_2$	SO
3l[c]	H	Br	$CHPh_2$	S
3m[b]	H	Br	$CHPh_2$	SO
3n[b]	H	I	$CHPh_2$	SO
3o[c]	H	Br	CH_2Ph	S
3p[c]	H	Br	$CH_2C_6H_4NO_2$	S
3q[b]	I	I	CH_2CCl_3	S
3r[b]	H	I	CH_2CCl_3	S
3s	H	H	CH_3	S
3t	H	H	CH_3	SO
3u	H	H	CH_3	SO
3v	H	H	CH_3	SO_2
3w	H	H	$CHPh_2$	S
3x	H	H	$CHPh_2$	SO
3y	H	H	CH_2Ph	S

[a] 6-APA, Br_2, 2.5 (N) H_2SO_4, $NaNO_2$, CH_2Cl_2 (ref 3c). [b] Prepared via 6-diazo derivative (Scheme V). [c] 6-APA, KBr, 2.5 (N) H_2SO_4, $NaNO_2$, EtOH (ref 6b). [d] Prepared by Bu_3SnH reduction of **3a** (ref 10).

6α-bromopenicillanate, and finally the fully reduced dihydro product **3s** via path a, the thiazepinone **4** (R = Br) is formed via path b (Scheme III).

In this context another interesting observation was that while the methyl, benzhydryl, and benzyl esters of 6α-bromopenicillanic acids (**3f**, **3l** and **3o**, respectively) were reduced cleanly with Zn–AcOH, the corresponding *p*-nitrobenzyl ester **3p** was completely resistant to reduction. Even attempted reduction with tri-*n*-butyltin hydride in refluxing toluene was not successful. This is probably due to the fact that if the nitro group is present in the molecule it forms a relatively stable anion radical such as C and thus prevents the formation of the anion radical at the lactam carbonyl group (Scheme IV).

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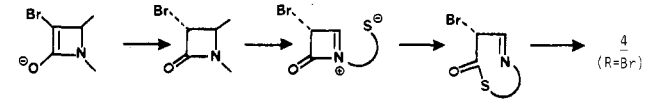


We found that the 6α-bromopenicillanate under the reaction conditions does not rearrange at all to the 1,4-thiazepine, suggesting that compound 4 is formed via path b.

Table II

reacn[a]	mol ratio of substrate:zinc:AcOH	temp, °C	time, h	yield,[b] %
3a → 3s	1:2:8	0–5	1.5	<10
3b → 3u	1:4:16	10	1.5	62
3c → 3t	1:4:16	10	1.5	81
3d → 3v	1:4:16	10	1.5	88
3e → 3t	1:4:16	10	1.0	82
3f → 3s	1:2:8	10	1.5	86
3g → 3s	1:2:8	10	1.0	86
3i → 3w	1:2:8	0–5	1.5	<5
3j → 3x	1:4:16	10	1.5	82
3k → 3x	1:4:16	10	1.0	81
3l → 3w	1:2:8	10	1.5	83
3m → 3x[c]	1:2:8	10	1.5	88
3n → 3x	1:2:8	10	1.0	82
3o → 3y	1:2:8	10	1.5	87

[a] Acetonitrile (6 mL/mmol of substrate) was used as the reaction solvent unless mentioned otherwise. [b] Isolated yield of pure product after column chromatography. [c] When two reactions (6-diazo → 6α-bromo → 6,6-dihydro) were superimposed, ethyl acetate was used as the solvent (see Experimental Section).

Use of excess zinc or increased reaction time or temperature resulted in complete loss of the β-lactam. The interference of the nitro group was further substantiated by repeating the reduction of benzyl 6α-bromopenicillanate (**3o**) with Zn–AcOH in presence of *m*-dinitrobenzene—in which case only starting bromo compound **3o** was recovered.

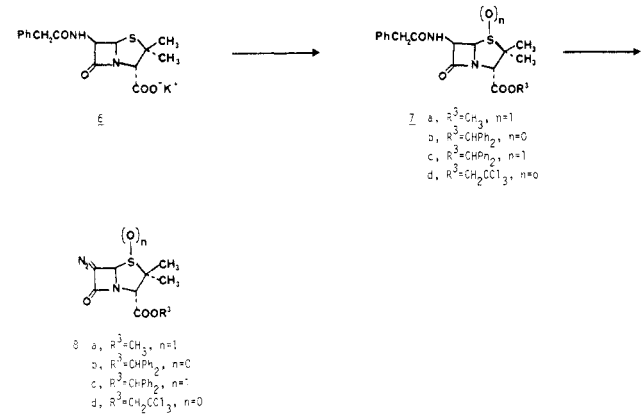
Table I is a list of the monohalo and dihalopenicillins prepared and the dihydropenicillins that have been obtained by reductive dehalogenation.

Table II summarizes the reaction conditions and the yields (after chromatography) of products from these reactions.

Methyl 6,6-dibromopenicillanate (**3a**) was readily obtained from 6-aminopenicillanic acid by diazotization–bromination[3c] followed by esterification[1] of the crude dibromo acid. Oxidation of **3a** with *m*-CPBA in CH_2Cl_2 at 20 °C for 30 min gave a mixture of the α-sulfoxide **3b** and β-sulfoxide **3c** in the ratio 90:10.[20] Crystallization from benzene–petroleum (bp 30–60 °C) gave the α-sulfoxide **3b**, mp 137–139 °C (lit.[9] mp 118–120 °C); which on treatment with Zn–AcOH in acetonitrile for 1.5 h at 10 °C followed by column purification gave the pure 6,6-dihydropenicillanate 1α-oxide **3u**, mp 142–145 °C (ethyl acetate), in about 60% yield.

The 6,6-dihydropenicillanate 1β-oxides were prepared by a different route (Scheme V). Esterification[1] of penicillin G (**6**) with CH_3I in presence of sodium bicarbonate in DMF at room temperature for 24 h gave the methyl ester, which on oxidation with H_2O_2–AcOH in methylene chloride[21] gave the corresponding 1β-sulfoxide **7a**, which was converted to the 6-diazopenicillanate **8a**, mp 130–135 °C, according to the procedure reported in the literature.[22] Treatment of the diazo compound **8a** with iodine in methylene chloride at 0 °C for 15 min gave the diiodide **3e**, which was converted to **3t**, mp 75–77 °C (>80% yield), by reduction with Zn–AcOH in acetonitrile. In a similar manner penicillin G (**6**) was conveniently and efficiently converted to **7c** in a one-step reaction with peracetic acid and benzophenone hydrazone.[23] The sulfoxide **7c** thus obtained was converted to its corresponding 6-diazo derivative **8c**, mp 140–145 °C, in good yield (~75%). The

Scheme V



diazo compound **8c**, dissolved in ethyl acetate and cooled to 0 °C, was treated with an equimolar amount of hydrogen bromide dissolved in ethyl acetate. Immediately, a brisk evolution of nitrogen ensued. After 20 min the resulting crude 6α-bromo compound **3m** was treated with 2.5 mol equiv of zinc in glacial acetic acid at 10 °C for 2 h. The resulting product after column purification gave pure benzhydryl 6,6-dihydropenicillanate 1β-oxide (**3x**), mp 145–148 °C (88%). Bromination of **8a** and **8c** gave the dibromides **3c** and **3j**, respectively; in these cases, however, some sulfoxides were unexpectedly reduced back to the sulfides **3a** and **3h** (~10% in each case, as judged from the ^1H NMR spectrum of the crude mixture). Oxidation[24] of **3a** with potassium permanganate gave the sulfone **3d**, which was smoothly reduced to **3v** in 88% yield.

The routes described above have hence produced either the 6,6-dihydropenicillanate 1α-oxide or the 6,6-dihydropenicillanate 1β-oxides in high yields, depending on the reaction sequence employed.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The ^1H NMR spectra were recorded on either a Varian EM-360 or Bruker AM-300 spectrometer and are reported in parts per million downfield from Me_4Si. Infrared spectra were recorded using a Nicolet DX FT-IR. Only significant maxima are listed. Microanalyses were performed by the Department of Chemistry, University of Alberta.

Methyl 6,6-Dibromopenicillanate (3a). In a 500-mL three-necked round-bottomed flask fitted with an overhead stirrer

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and thermometer, 125 mL of methylene chloride was taken and cooled to about 5 °C. To this were added bromine (30 g, 9.6 mL, 0.1877 mol), 2.5 N H_2SO_4 (50 mL), and sodium nitrite (8.6 g, 0.1246 mol). 6-APA (13.5 g, 0.06 mol) was added portionwise over a period of 20 min. The dark red solution was stirred for 30 min, with the pot temperature maintained at 5 °C. Excess bromine was destroyed by adding 10% sodium thiosulfate solution, which resulted in a light yellow solution. The organic layer was separated and the aqueous layer was saturated with sodium chloride and reextracted with methylene chloride (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford 6,6-dibromopenicillanic acid in 78% yield. This crude acid was directly used for further reaction.

A mixture of 6,6-dibromopenicillanic acid (4.5 g, 0.0125 mol), sodium bicarbonate (1.26 g, 0.015 mol), and methyl iodide (2.66 g, 0.01875 mol) in DMF (50 mL) was stirred at room temperature for 16 h. The mixture was poured into ice-cold water (200 mL) and extracted with ethyl acetate (3 × 50 mL), and the aqueous layer was saturated with sodium chloride and reextracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed with brine, dried, and evaporated to give a pale yellow solid (3.5 g, 75%). Crystallization from methylene chloride–hexane gave the desired ester **3a**, mp 98–102 °C, as light yellow solid: IR (KBr) 1790, 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 4.6 (s, 1 H, 3-H), 5.85 (s, 1 H, 5α-H). Anal. Calcd for $C_9H_{11}NO_3Br_2S$: C, 28.95; H, 2.95; N, 3.75; S, 8.58. Found: C, 29.18; H, 2.97; N, 3.88; S, 8.34.

Methyl 6,6-Dibromopenicillanate 1,1-Dioxide (3d). Methyl 6,6-dibromopenicillanate (**3a**) (1 g, 0.00268 mol) was dissolved in 15 mL of glacial acetic acid, and 3 mL of water was added. To this mixture was added potassium permanganate 0.8470 g (0.00536 mol) portionwise over a period of 15 min. The mixture was stirred at room temperature for 3 h; excess permanganate was destroyed by dropwise addition of hydrogen peroxide. The mixture was poured into ice-cold water, and the precipitated solid was filtered off and dissolved in methylene chloride. The aqueous phase was saturated with sodium chloride and extracted with methylene chloride. The combined organic extracts were washed with saturated sodium bicarbonate solution, followed by brine, dried, and rapidly filtered through a small bed of silica. Concentration of the filtrate gave pure methyl 6,6-dibromopenicillanate 1,1-dioxide (**3d**) as white solid, mp 188–190 °C, in 60% yield: IR (KBr) 1808, 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 4.53 (s, 1 H, 3-H), 5.02 (s, 1 H, 5α-H). Anal. Calcd for $C_9H_{11}NO_5Br_2S$: C, 26.66; H, 2.71; N, 3.45; S, 7.90. Found: C, 26.62; H, 2.68; N, 3.42; S, 7.79.

Methyl 6,6-Dibromopenicillanate 1α-Oxide (3b). Oxidation of methyl 6,6-dibromopenicillanate (**3a**) (1.5 g, 0.004 mol) with *m*-chloroperbenzoic acid (85%, 0.8156 g, 0.004 mol) in methylene chloride at 20 °C for 30 min gave a mixture of the α- and β-sulfoxides in 95% yield (the α:β ratio was 90:10 as judged from the ^1H NMR spectrum of the crude reaction mixture). The crude mixture was directly crystallized from benzene–petroleum (bp 30–60 °C) to give pure methyl 6,6-dibromopenicillanate 1α-oxide: mp 137–139 °C (lit.[9] mp 118–120 °C); IR (KBr) 1802, 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 4.62 (s, 1 H, 3-H), 5.3 (s, 1 H, 5α-H). Anal. Calcd for $C_9H_{11}NO_4Br_2S$: C, 27.76; H, 2.82; N, 3.59; S, 8.22. Found: C, 28.11; H, 2.87; N, 3.63; S, 7.87.

6-Diazopenicillanate 1β-Oxide (8). Potassium 6β-(phenylacetamido)penicillanate (**6**) was converted to its methyl ester as described in the literature.[1] Oxidation of methyl 6β-(phenylacetamido)penicillanate with H_2O_2–AcOH in methylene chloride[21] at 25 °C for 48 h gave the corresponding 1β-sulfoxide **7a**. Dinitrogen tetraoxide (17.5 g) was dissolved in 182 mL of dry methylene chloride. In a 1-L three-necked round-bottomed flask equipped with an overhead stirrer, thermometer, and addition funnel, 16 g of anhydrous sodium acetate was covered with 70 mL of methylene chloride, the mixture was cooled to −5 °C, dinitrogen tetraoxide (87 mL of the above solution) was added, and the color of the mixture became canary yellow. A solution of methyl 6β-(phenylacetamido)penicillanate 1β-oxide (**7a**) (6 g, 0.0165 mol) in methylene chloride (70 mL) was added slowly over 20 min. Additional portions of N_2O_4 (22 mL, 73 mL) were added immediately after and 30 min after addition of the penicillin sulfoxide. The mixture was stirred at 0 °C for 2 h. Excess dinitrogen tetraoxide was destroyed by adding saturated sodium bicarbonate, and the layers separated. Aqueous layer was extracted with methylene chloride (2 × 50 mL). The combining methylene chloride extracts were washed with brine, dried (Na_2SO_4), and concentrated to about 150 mL. To this solution pyridine (2 mL) was added and refluxed gently for 3 h, cooled, washed with water, saturated sodium bicarbonate, and finally with brine, dried, and concentrated to give a brown syrup, which slowly solidified. Crystallization from methylene chloride–ether gave **8a**, 2.6 g (62%), mp 130–135 °C dec, as a light brown solid: IR (KBr) 2098, 1765, 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H, CH_3), 1.7 (s, 3 H, CH_3), 4.37 (s, 1 H, 3-H), 5.88 (s, 1 H, 5α-H). Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.02; H, 4.28; N, 16.34; S, 12.45. Found: C, 42.69; H, 4.37; N, 16.64; S, 11.54.

In a similar manner, benzhydryl 6-diazopenicillanate 1β-oxide (**8c**) was prepared in about 75% yield, mp 140–145 °C dec, from benzhydryl 6β-(phenylacetamido)penicillanate 1β-oxide (**7c**):[23] IR (KBr) 2106, 1761, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 4.48 (s, 1 H, 3-H), 5.8 (s, 1 H, 5α-H). Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.61; H, 4.64; N, 10.27; S, 7.82. Found: C, 61.12; H, 4.62; N, 10.00; S, 8.10.

Methyl 6,6-Dibromopenicillanate 1β-Oxide (3c). To a stirred solution of freshly prepared methyl 6-diazopenicillanate 1β-oxide (**8a**) (257 mg, 1 mmol) in 10 mL of methylene chloride at 0 °C under a nitrogen atmosphere was added dropwise a solution of bromine (160 mg, 1 mmol) in 5 mL of methylene chloride. The mixture was stirred at that temperature for 15 min, washed with 10% sodium thiosulfate solution followed by brine, dried (Na_2SO_4), and concentrated. Purification by chromatography gave the corresponding dibromide **3c**, 300 mg (77%), as a light yellow foam: IR (KBr) 1794, 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H, CH_3), 1.7 (s, 3 H, CH_3), 4.72 (s, 1 H, 3-H), 5.3 (s, 1 H, 5α-H).

Reaction of 3a with Zn–AcOH. To a stirred solution of 1.0 g (0.0026 mol) of **3a** in 15 mL of acetonitrile at 0 °C was added 1.2 mL of glacial acetic acid. Zinc powder (0.357 g, 0.0052 mol) was added portionwise. The mixture was stirred at 0 °C for 1.5 h. The excess zinc was removed by filtration, and the filtrate was concentrated. The residue was dissolved in methylene chloride, washed successively with brine and dilute, aqueous sodium bicarbonate, dried, and concentrated. The residue was chromatographed on silica gel with ethyl acetate–hexane as eluant. Isolation of the fastest moving fraction gave methyl 6,6-dihydropenicillanate (**3s**) (0.230 g) as an oil. Crystallization from benzene–petroleum (bp 30–60 °C) gave pure **3s**: mp 48–50 °C; IR (KBr) 1774, 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 3.1 (dd, 1 H, J = 2, 16 Hz, 6β-H), 3.6 (dd, 1 H, J = 4.5, 16 Hz, 6α-H), 4.48 (s, 1 H, 3-H), 5.32 (dd, 1 H, J = 2, 4.5 Hz, 5α-H). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.23; H, 6.04; N, 6.51; S, 14.88. Found: C, 50.33; H, 6.18; N, 6.48; S, 14.79.

Isolation of the slower moving fraction gave 4 (R = Br), 0.650 g, as a white sticky foam. Further purification by crystallization from benzene–ether gave an analytically pure sample: mp 100–102 °C dec; IR (KBr) 3263, 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 3.82 (s, 3 H, $COOCH_3$), 4.41 (d, 1 H, J = 6 Hz, 3-H), 7.4 (br, m, 1 H, NH), 7.74 (d, 1 H, J = 9 Hz, vinylic 5-H). The signal at δ 7.4 disappeared when D_2O was added to the solution and the doublets collapsed to single lines. Anal. Calcd for $C_9H_{12}NO_3BrS$: C, 36.73; H, 4.08; N, 4.76; Br, 27.17; S, 10.88. Found: C, 36.93; H, 4.14; N, 4.74; Br, 27.09; S, 10.72.

Reaction of 3a with Zn–NH_4OAc. A solution of 373 mg (1 mmol) of **3a** in 10 mL of THF was treated with 5 mL of 1 M aqueous NH_4OAc and 262 mg (4 mmol) of powdered zinc. The resulting mixture was stirred at room temperature for 1 h and then filtered through a bed of Celite. The organic layer was separated from the aqueous layer, which was extracted twice with methylene chloride. The combined organic extracts were concentrated under reduced pressure. The residue was dissolved in methylene chloride, washed with brine, dried, and concentrated. Short-column chromatography gave **3s** in about 90% yield as an oil.

General Procedure for the Reductive Dehalogenation with Zn–AcOH. To a stirred solution of 6-halo- or 6,6-dihalopenicillin in acetonitrile (6 mL/mmol of substrate) at 0–10 °C (see Table II) in an ice bath was added glacial acetic acid. Zinc powder was added slowly. Within 10–15 min after the addition of zinc the color of the mixture turned yellow to deep orange (color

varies from compound to compound); the mixture was stirred at that temperature for 1.0–1.5 h. The excess zinc was removed by filtration through a bed of Celite, which was then washed with methylene chloride, and the combined filtrates were concentrated under reduced pressure. The sticky orange mass was redissolved in methylene chloride and washed three times with water. The aqueous extracts were combined, saturated with sodium chloride, and reextracted with methylene chloride. The organic layers were combined, washed two times with cold water followed by brine, dried, and concentrated to give a light yellow to orange sticky foam, which was purified over a short silica column with ethyl acetate–hexane as eluant.

The following compounds were made by this procedure.

Methyl 6,6-dihydropenicillanate 1,1-dioxide (3v): mp 118–120 °C; IR (KBr) 1809, 1758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.45 (dd, 1 H, J = 2, 16 Hz, 6β-H), 3.58 (dd, 1 H, J = 4.5, 16 Hz, 6α-H), 4.44 (s, 1 H, 3-H), 4.72 (dd, 1 H, J = 2, 4.5 Hz, 5α-H). Anal. Calcd for $C_9H_{13}NO_5S$: C, 43.72; H, 5.26; N, 5.67; S, 12.95. Found: C, 43.54; H, 5.22; N, 5.57; S, 12.95.

Methyl 6,6-dihydropenicillanate 1α-oxide (3u): mp 142–145 °C dec; IR (KBr) 1782, 1757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 3.42 (dd, 1 H, J = 2, 16 Hz, 6β-H), 3.65 (dd, 1 H, J = 4.5, 16 Hz, 6α-H), 4.44 (s, 1 H, 3-H), 4.65 (dd, 1 H, J = 2, 4.5 Hz, 5α-H). Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.75; H, 5.62; N, 6.06; S, 13.85. Found: C, 46.69; H, 5.73; N, 6.19; S, 13.78.

Methyl 6,6-dihydropenicillanate 1β-oxide (3t): mp 75–77 °C; IR (KBr) 1781, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 3.38 (d, 2 H, J = 4 Hz, 6α-H + 6β-H), 4.52 (s, 1 H, 3-H), 5.03 (t, 1 H, J = 4 Hz, 5α-H). Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.75; H, 5.62; N, 6.06; S, 13.85. Found: C, 46.81; H, 5.63; N, 6.11; S, 13.81.

Benzhydryl 6,6-Dihydropenicillanate 1β-Oxide (3x). To a stirred solution of benzhydryl 6-diazopenicillanate 1β-oxide (**8c**) (4.407 g, 0.01076 mol) in 200 mL of ethyl acetate at 0 °C was added dropwise a solution of hydrogen bromide in ethyl acetate (6.3 mL, 0.95 g, 0.01183 mol). The mixture was stirred at 0 °C for 30 min. Excess hydrogen bromide was removed at reduced pressure. The mixture was again cooled to 10 °C; to this was added glacial acetic acid (6 mL). Zinc dust (1.75 g, 0.0267 mol) was added portionwise with stirring over 10 min. Stirring was continued for an additional 1.5 h. Filtration (through a bed of Celite) and evaporation gave a light brown oil, which was redissolved in 150 mL of ethyl acetate, washed with cold water, sodium bicarbonate solution, and finally with brine, dried (Na_2SO_4), and evaporated to give **3x** as a pale yellow foam, 3.89 g (94%). Purification by column chromatography eluted with hexane–ethyl acetate provided **3x** in 88% yield: mp 145–148 °C; IR (KBr) 1797, 1759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 3.32 (d, 2 H, J = 4 Hz, 6α-H + 6β-H), 4.6 (s, 1 H, 3-H), 4.9 (t, 1 H, J = 4 Hz, 5α-H). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.79; H, 5.48; N, 3.65; S, 8.35. Found: C, 65.83; H, 5.53; N, 3.74; S, 8.29.

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Registry No. **3** (R_1 = NH_2, R_2 = R_3 = H, X = S), 551-16-6; **3** (R_1 = R_2 = Br, R_3 = H, X = S), 24158-88-1; **3a**, 24138-27-0; **3b**, 25663-91-6; **3c**, 24138-29-2; **3d**, 61657-19-0; **3e**, 100298-36-0; **3f**, 34800-34-5; **3g**, 52354-06-0; **3h**, 75527-84-3; **3i**, 76517-35-6; **3j**, 100298-37-1; **3k**, 100298-38-2; **3l**, 74189-25-6; **3m**, 100349-41-5; **3n**, 100298-39-3; **3o**, 62263-89-2; **3p**, 100239-31-4; **3q**, 100298-40-6; **3r**, 100298-41-7; **3s**, 4027-61-6; **3t**, 61657-21-4; **3u**, 61657-20-3; **3v**, 65039-72-7; **3w**, 73968-83-9; **3x**, 100349-42-6; **3y**, 62263-72-3; **4** (R = Br), 100298-44-0; **7a**, 24652-72-0; **7a** (n = 0), 653-89-4; **7c**, 37591-56-3; **8a**, 100298-42-8; **8c**, 100298-43-9; **8d**, 51056-24-7.

Supplementary Material Available: ^1H NMR spectral data for compounds **3e–3n**, **3q**, **3r**, and **3w** (1 page). Ordering information is given on any current masthead page.

Synthesis of 7(8)-Desoxyasperdiol. A Precursor of the Cembranoid Asperdiol

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A convergent and highly stereoselective synthesis of 7(8)-desoxyasperdiol, a 14-membered synthetic precursor of the cembranoid asperdiol, is described starting from geraniol and the epoxide of *cis*-2-butene-1,4-diol acetonide (A1). The route from the geranyl fragment B2 proceeds in approximately 6% overall yield. Key transformations include a highly *E*-selective Wittig coupling of aldehyde A10 with the α-triphenylphosphorylidene ester B8 and macrocyclization of the iodo sulfone B14, possibly as the dianion. Desulfonylation and bis-debenzylation of the macrocycle B15 were achieved in one step with sodium in liquid NH_3–THF in 71% yield.

Asperdiol, a cembranoid antitumor agent derived from Caribbean gorgonians of the *Eunicea* genus, was isolated by Weinheimer and Matson and elucidated through single-crystal X-ray structure analysis.[1] Kato reported the first synthesis of this unusual cembranoid by a route involving Friedel–Crafts macrocyclization of a homologated farnesol and subsequent elaboration of key structural features through a fascinating series of selective transformations of macrocyclic intermediates.[2] Shortly thereafter, Still and Mobilio described a convergent synthesis in which the crucial C-1/C-14 hydroxyl–isopropenyl relationship was introduced in the context of a novel intramolecular allylchromium–enal macrocyclization step.[3] For several years now we have been exploring potential routes to asperdiol and related structures from readily available precursors. Our efforts have resulted in a straightforward and completely stereoselective synthesis of 7(8)-desoxyasperdiol B16 (II, Y = H), a key intermediate in the Kato synthesis of racemic asperdiol[2] (see Figure 1).

Central to our plan was the stereocontrolled assemblage of a protected erythro α-hydroxy aldehyde V and its ste-

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