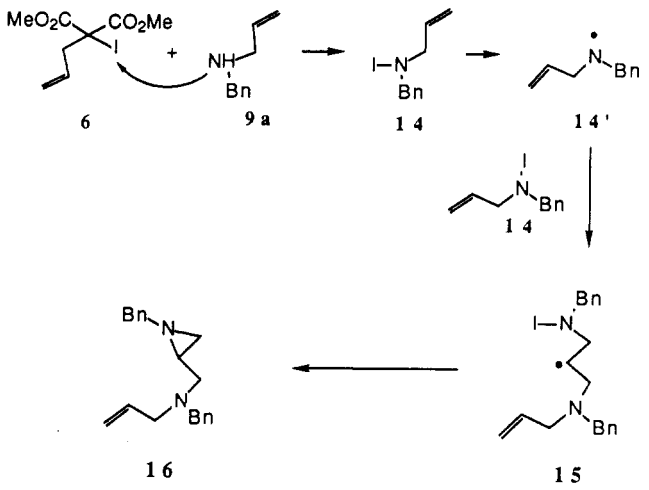
Scheme IV



forded **13c** in 59% isolated yield.

Thus, iodomalonate-mediated atom-transfer annulations can be performed to give azacyclic systems, provided the nucleophilic character of the allylamine is low. Further application of this methodology is being pursued to form a variety of azabicycles. This work will be reported in due course.

Experimental Section

All reactions were performed under an atmosphere of argon in flasks which were oven-dried overnight. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Benzene was degassed with argon. All reagents were purchased from Aldrich Chemical Co. and used without further purification. Merck silica gel 60 (230–400 mesh) was used for medium-pressure liquid chromatography (MPLC) and flash column chromatography. Macherey-Nagel precoated silica gel G/UV254 plates (0.25 mm) were used for thin-layer chromatography (TLC).

^{1}H NMR spectra were measured at 300 MHz on a General Electric QE-300 spectrometer in $CDCl_3$ using tetramethylsilane as a reference (0.00 ppm). ^{13}C NMR spectra were measured at 75 MHz on a General Electric QE-300 spectrometer in $CDCl_3$. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Microanalyses were conducted on a Control Equipment CEC240-XA instrument. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

***N*,1-Dibenzyl-*N*-allyl-2-(methylamino)aziridine (16).** To a solution of 250 mg (0.84 mmol) of allyliodomalonate **6**[6] in 2.5 mL of benzene were added 123 mg (0.84 mmol) of *N*-benzylallylamine **9a** and 53 μL (0.084 mmol) of bis(tributyltin). After exposing the homogeneous solution to light from a sunlamp (d = 8 cm) for 20 min, the brown-red homogeneous solution was cooled, diluted with 30 mL of dichloromethane, and washed with 20 mL of a 10% aqueous solution of potassium carbonate. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. MPLC (ethyl acetate–hexane, 1:3 to 1:1; 15 mm × 1000 mm diameter; flow rate 8 mL/min) provided 56 mg (45%) of aziridine **16** as an oil: R_f 0.27 (ethyl acetate–hexane, 1:2); ^{1}H NMR δ 1.38 (1 H, d, J = 6.4 Hz), 1.58 (1 H, d, J = 3.5 Hz), 1.70 (1 H, m), 2.45 (1 H, dd, J = 13.4, 6.3 Hz), 2.57 (1 H, dd, J = 13.4, 5.0 Hz), 3.02 (1 H, dd, J = 14.2, 6.6 Hz), 3.16 (1 H, dd, J = 14.2, 6.1 Hz), 3.40 (2 H, AB q, J = 13.2 Hz, $\Delta\nu$ = 41.6 Hz), 3.59 (2 H, AB q, J = 13.8 Hz, $\Delta\nu$ = 50.1 Hz), 5.13 (2 H, m), 5.84 (1 H, m), 7.30 (10 H, m); ^{13}C NMR 32.43, 38.00, 56.57, 58.02, 58.16, 64.66, 117.18, 126.70, 127.00, 128.06, 128.22, 128.29, 128.80, 135.88, 139.02, 139.54; HRMS $C_{20}H_{24}N_2$ M$^+$ calcd 292.1939, found 292.1936.

***N*-BOC-7,7-dicarbomethoxy-3-azabicyclo[3.3.0]octane (13b).** To a solution of 1.27 g (4.26 mmol) of allyliodomalonate **6** and 1.34 g (8.52 mmol) of *N*-BOC-allylamine **9b** in 10 mL of benzene was added via syringe 0.16 mL of bis(tributyltin). After the clear homogeneous solution was exposed to light from a sunlamp (d = 8 cm) for 30 min, the light source was removed and 5 mL of triethylamine was added. The solution was heated at reflux for 20 h, at which time the dark brown-red mixture was concentrated under reduced pressure. Flash chromatography on 150 g of silica gel (ethyl acetate–hexane, 1:5 to 1:3) provided 0.606 g (43%) of azabicycle **13b** as a clear oil: R_f 0.34 (ethyl acetate–hexane, 1:4); ^{1}H NMR 1.46 (9 H, s), 2.04 (2 H, dd, J = 13.2, 6.8 Hz), 2.56 (2 H, m), 2.72 (2 H, m), 3.25 (2 H, m), 3.44 (2 H, m), 3.72 (3 H, s), 3.74 (3 H, s); ^{13}C NMR 28.52, 39.29, 43.56, 52.77, 53.81, 62.25, 79.31; MS $C_{16}H_{25}NO_6$ M$^+$ 327. Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.69; H, 7.71; N, 4.28. Found: C, 58.25; H, 7.55; N, 4.06.

***N*-((*p*-Methoxyphenyl)sulfonyl)-7,7-dicarbomethoxy-3-azabicyclo[3.3.0]octane (13c).** Starting with 0.35 g (1.17 mmol) of **6** and 0.53 g (2.35 mmol) of *N*-((*p*-methoxyphenyl)sulfonyl)-allylamine **9c**, the crude product, formed from the identical reaction conditions described in the above paragraph, was purified on 30 g of silica gel (ethyl acetate–hexane, 1:2.5) to afford 0.275 g (59%) of azabicycle **13c** as a solid: mp 132.0–134.0 °C (ethyl acetate); ^{1}H NMR δ 1.98 (2 H, dd, J = 12.7, 7.4 Hz), 2.52 (2 H, m), 2.69 (2 H, m), 2.81 (2 H, m), 3.16 (2 H, br d, J = 8.8 Hz), 3.70 (3 H, s), 3.72 (3 H, s), 3.89 (3 H, s), 7.01 (2 H, d, J = 9.2 Hz), 7.73 (2 H, d, J = 9.2 Hz); HRMS $C_{18}H_{23}NO_7S$ M$^+$ calcd 397.1287, found 397.1222.

Acknowledgment. Thanks are extended to Professor D. P. Curran for helpful discussions regarding this work and for providing experimental details for the formation of the iodomalonate **6**.[6]

Stereoselective Synthesis of 6-Fluoropenicillanate Analogues of β-Lactamase Inhibitors†

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6β-Bromopenicillanic acid (**1a**)[2] and penicillanic acid 1,1-dioxide (**1b**)[3,4] have been extensively studied as β-lactamase inhibitors, and some aspects of the mechanism of action have been elucidated.[5-7]

The use of selectively fluorinated substrate is of considerable interest at the present time for the study of enzyme substrate interactions,[8] and the use of fluorinated analogues of biologically active compounds has recently been reviewed.[9] For these reasons the synthesis of regio- and stereospecifically fluorinated penicillanates is of interest. 6β-Fluoropenicillanates are known in the patent literature,[10] and we recently reported a procedure for the synthesis of (pivaloxyloxy)methyl (POM) 6α-fluoropenicillanate (**3d**).[11] We now describe new methods for the conversion of POM 6-diazopenicillanate (**2**) into POM 6β-bromo-6α-fluoro- and 6β-chloro-6α-fluoropenicillanates (**3a–b**) using a *N*-halosuccinimide and tetrabutylammonium bifluoride. In our hands these were considerably more efficient than the procedures currently available and may have application in other areas. We also describe the stereoselective conversion of these compounds into the POM 6β-fluoropenicillanate (**3e**) together with a procedure for the one-pot conversion of the POM 6-diazopenicillanate (**2**) into the 6α-fluoro compound **3d**.

† Dedicated to the memory of Professor Orfeo O. Orazi.

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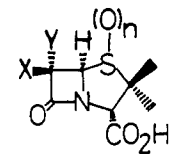
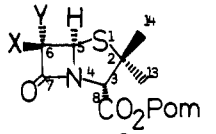
Results and Discussion

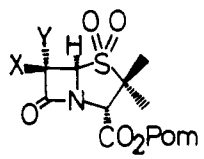
The conversion of 6-diazopenicillanates into 6-bromo-6-fluoropenicillanates using *N*-bromosuccinimide and hydrogen fluoride–pyridine has been reported.[10] In our hands the use of this procedure was unsatisfactory when applied to the POM ester **2**, giving rise to a complex mixture of products. We also investigated the use of mixtures of NBS and a range of other fluorides including KF-18-crown-6 complex,[12] CsF, and tetrabutylammonium fluoride (TBAF)[13] without success. However, after considerable experimentation the combination of tetrabutylammonium bifluoride (TBABF)[14] and *N*-bromosuccinimide in dichloromethane was found to be more reliable and gave the



1a X=Br, Y=H, n=0
1b X=H, Y=H, n=2



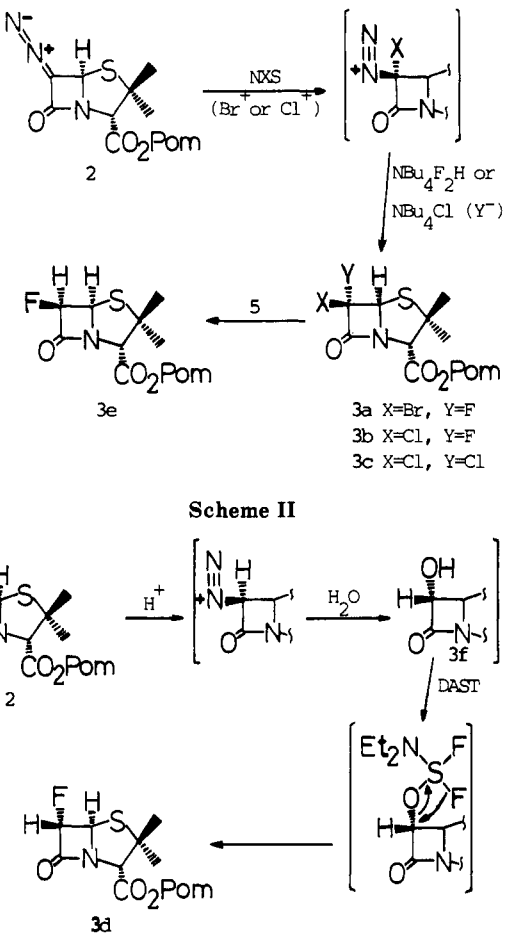
Pom= $-CH_2-O-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$



4a X=H, Y=F
4b X=F, Y=H

	X	Y
3a	Br	F
3b	Cl	F
3c	Cl	Cl
3d	H	F
3e	F	H
3f	H	OH
3g	OH	H
3h	H	SO_3CF_3

Scheme I



Scheme II

desired POM 6β-bromo-6α-fluoropenicillanate (**3a**) in 40% yield. Extension of the procedure to include *N*-chlorosuccinimide was also successful and gave the POM 6β-chloro-6α-fluoropenicillanate (**3b**) in 25% yield. The assignment of the cis H(5)–F(6) relationship is based upon ^{1}H NMR spectral evidence (see the Experimental Section).

These reactions proceed stereoselectively with the electrophilic halogen atoms being placed in a β-orientation and the nucleophilic halide atom in an α-orientation, in agreement with the proposed two-step mechanism for the displacement reaction.[15]

In addition, the regioselective introduction of two chlorine atoms at position 6 of the penam nucleus of **2**[16] was achieved using a combination of NCS and tetrabutylammonium chloride (TBAC), affording POM 6,6-dichloropenicillanate (**3c**) in 35% yield (Scheme I).

With the compounds **3a** and **3b** in hand, we investigated the very high chemo- and diastereoselective reduction with tris[2-methyl-2-phenylpropyl(neophyl)]tin hydride (**5**) to obtain the POM 6β-fluoropenicillanate (**3e**) in 68% isolated yield (Scheme I). The structure assigned to **3e** is consistent with its spectroscopic data. The stereochemistry of the fluorine substituent was determined to be β based on the cis coupling[11] of the protons on C-5 and C-6: δ 5.51 (t, $J_{5,6}$ = 4.0 Hz, $J_{5,F}$ = 4.0 Hz, C-5H), 5.74 (dd, $J_{5,6}$ = 4.0 Hz, $J_{6,F}$ = 55.8 Hz, C-6H). A detailed mechanistic rationale

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for this chemo- and diastereoselective reduction has been described elsewhere.[17]

Having synthesized the POM 6β-fluoropenicillanate, it was of interest to synthesize its 6α-isomer. Treatment of POM 6α-hydroxypenicillanate (**3f**), obtained from **2** by the method described by Sheehan et al.,[18] with diethylaminosulfur trifluoride (DAST)[19] afforded exclusively **3d** in 56% overall isolated yield. Furthermore, reaction of wet POM 6-diazopenicillanate (**2**) with 2 equiv of DAST readily provide **3d** in 65% yield. In this one-pot reaction we suppose that **3f** is generated in situ and then reacts with DAST (Scheme II). The ^1H, ^{13}C, and ^{19}F NMR spectral data (chemical shifts and coupling constants), along with the high-resolution mass spectrum, are in agreement with those previously reported.[11]

Compounds **3d** and **3e** were converted by a phase-transfer catalytic oxidation using potassium permanganate[20] into POM 6α-fluoropenicillanate 1,1-dioxide (**4a**) (80%) and POM 6β-fluoropenicillanate 1,1-dioxide (**4b**) (78%) respectively.

As an extension of the procedure for transforming **3f** into **3d**, we examined the reaction of DAST with POM 6β-hydroxypenicillanate (**3g**)[21] to test the stereoselective displacement of the hydroxyl group to provide POM 6β-fluoropenicillanate (**3e**). However, all attempts at this nucleophilic substitution were unsuccessful, with intractable mixtures of products being obtained. Similarly unsuccessful was the attempted displacement of the triflate group of POM 6α-((trifluoromethyl)sulfonyl)penicillanate (**3h**)[22] with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF).[23]

In conclusion, we have developed a stereoselective synthesis of 6,6-halofluoropenicillanates **3a** and **3b** from the readily available POM 6-diazopenicillanate (**2**). The novel POM 6,6-dichloropenicillanate (**3c**) was also prepared using related methodology. Compound **3a** was a very convenient substrate for chemo- and diastereoselective reductive dehalogenation with the hindered trineophyltin hydride (**5**) to afford the expected compound **3e** in good yield. On the other hand, reaction of wet diazo **2** with DAST produced exclusively the 6α-fluoro isomer **3d** in good yield, possibly via the S_Ni mechanism indicated in Scheme II.

Experimental Section

^1H, ^{13}C, and ^{19}F NMR spectra were taken at 80.13, 20.15, and 75.39 MHz, respectively. ^{19}F NMR spectra were referenced to external trifluoroacetic-*d* acid with all chemical shifts reported in ppm. Assignments for NMR peaks are given by positional numbers shown on structure **3** which are different from those shown in the *Chemical Abstracts* names in the headings. Low-resolution mass spectra were obtained by electron impact at 70 eV. Samples on which exact masses were obtained exhibited no significant peaks at *m/e* values greater than that of the parent. For compounds **3a**, **3b**, and **3c**, characteristic isotope peaks were observed in their mass spectra, with only the isotope lowest mass peaks are reported here. Silica gel 60 H (Merck) was utilized for column chromatography and silica gel GF_{254} (type 60 Merck) for TLC. The purity of all title compounds was shown to be at least 90% by proton NMR and TLC analyses.

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Bromo-6-fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)methyl Ester, [2*S*(2α,5α,6β)]- (3a). To a solution of **2** (200 mg, 0.59 mmol) in anhydrous dichloromethane (3 mL) at −40 °C was added dropwise and simultaneously 114 mg (0.65 mmol) of *N*-bromosuccinimide in a mixture of dichloromethane–acetonitrile (5 mL, 4:1) and 186 mg (0.65 mmol) of tetrabutylammonium bifluoride in anhydrous dichloromethane (2 mL). The cold bath was then allowed to warm to room temperature slowly and, after 1.5 h, the reaction was quenched by the addition of water (6 mL). The layers were separated, and the organic layer was dried (Na_2SO_4). The solvent was evaporated, and the crude product was subjected to column chromatography (silica gel, 70% chloroform, 30% hexane). The major product was identified as **3a** (97 mg, 40%), as an oil: IR (film) 1800 (β-lactam), 1765, and 1755 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.48 (s, 3 H), 1.59 (s, 3 H), 4.57 (s, 1 H, C-3H), 5.62 (d, 1 H, $J_{5,F}$ = 5.6 Hz, C-5H), 5.83 (s, 2 H, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.6 (C-10), 165.27 (C-8), 162.23 (d, $^2J_{C,F}$ = 23 Hz, C-7), 107.9 (d, $^1J_{C,F}$ = 306 Hz, C-6), 79.85 (C-9), 77.16 (d, $^2J_{C,F}$ = 27 Hz, C-5), 68.9 (C-3), 63.99 (C-2), 38.7 (C-11), 33.33 (C-14), 26.8 (C-12), 25.53 (C-13); ^{19}F NMR ($CDCl_3$) δ −109.14; LRMS *m/e* (relative intensity) 411 (M^+, 4.9), 297 (2.44), 252 (1.75), 197 (3.03), 114 (3.3), 85 (9.63), 57 (100); HRMS calcd for $C_{14}H_{19}BrFNO_5S$ 411.01512, found 411.01642. The minor product (24%) was identified as POM 6,6-dibromopenicillanate.[15]

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Chloro-6-fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)methyl Ester, [2*S*(2α,5α,6β)]- (3b). A solution of 300 mg (0.88 mmol) of **2** in anhydrous chloroform (5 mL) was stirred and cooled at −23 °C. A solution of *N*-chlorosuccinimide (118 mg, 0.88 mmol) in anhydrous chloroform (20 mL) and tetrabutylammonium bifluoride (250 mg, 0.88 mmol) in the same solvent (3 mL) were added slowly and simultaneously. After 4 h at room temperature, the reaction was quenched by addition of water (8 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel column by using dichloromethane–hexane (70:30). The major product was identified as **3b** (80 mg, 25%), as an oil: IR (film) 1800 (β-lactam), 1770, and 1750 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.50 (s, 3 H), 1.56 (s, 3 H), 4.56 (s, 1 H, C-3H), 5.66 (d, 1 H, $J_{5,F}$ = 5.6 Hz, C-5H), 5.83 (s, 2 H, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.63 (C-10), 165.29 (C-8), 162.7 (d, $^2J_{C,F}$ = 26 Hz, C-7), 112.86 (d, $^1J_{C,F}$ = 296 Hz, C-6), 79.74 (C-9), 76.7 (d, $^2J_{C,F}$ = 27 Hz, C-5), 68.68 (C-3), 63.73 (C-2), 38.67 (C-11), 33.25 (C-14), 26.73 (C-12), 25.17 (C-13); ^{19}F NMR ($CDCl_3$) δ −109.27; LRMS *m/e* (relative intensity) 367 (M^+, 5.9), 253 (3.25), 208 (1.7), 153 (2.4), 114 (2), 85 (7), 57 (100); HRMS calcd for $C_{14}H_{19}ClFNO_5S$ 367.06563, found 367.06635. The minor product (12%) was identified as POM 6,6-dichloropenicillanate (**3c**), described below.

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6,6-Dichloro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)methyl Ester, [2*S*(2α,5α)]- (3c). To a solution of **2** (280 mg, 0.82 mmol) in dry chloroform (4 mL) at −23 °C was added dropwise 250 mg (0.9 mmol) of tetrabutylammonium chloride in dry chloroform (3 mL) and then 120 mg (0.9 mmol) of *N*-chlorosuccinimide in the same solvent (20 mL). The mixture was slowly warmed to room temperature and, after 3 h, the reaction was quenched by addition of water (7 mL). The organic layer was dried (Na_2SO_4), and concentration in vacuo gave an oil which was chromatographed on silica gel column (chloroform–hexane, 80:20) to provide **3c** (110 mg, 35%) as a yellow oil: IR (film) 1800 (β-lactam), 1760, and 1750 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.50 (s, 3 H), 1.59 (s, 3 H), 4.56 (s, 1 H, C-3H), 5.69 (s, 1 H, C-5H), 5.80 and 5.88 (AB system, 2 H, *J* = 5.6 Hz, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.6 (C-10), 165.22 (C-8), 164.0 (C-7), 85.19 (C-6), 80.56 (C-5), 79.71 (C-9), 68.93 (C-3), 64.04 (C-2), 38.69 (C-11),

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(23) TASF has mainly been used as a source of anhydrous fluoride ion, and was successfully used for displacement of triflates in carbohydrates, see: Doboszewski, B.; Hay, G. W.; Szarek, W. A. *Can. J. Chem.* **1987**, *65*, 412.

33.21 (C-14), 26.73 (C-12), 25.35 (C-13); LRMS *m/e* (relative intensity) 383 (M^+, 3.52), 269 (2.47), 224 (1.5), 169 (2.12), 114 (3.7), 85 (8.9), 57 (100); HRMS calcd for $C_{14}H_{19}Cl_2NO_5S$ 383.03609, found 383.03542.

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)-methyl Ester, [2*S*(2α,5α,6β)]- (3e). To a solution of **3a** (69 mg, 0.17 mmol) and azobisisobutyronitrile (AIBN) (1 mg) in dry ether (5 mL) was added dropwise a solution of trineophyltin hydride (**5**) (104 mg, 0.2 mmol) in dry ether (2 mL) at room temperature. After the mixture was stirred for 5 h, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel column by using dichloromethane–hexane (60:40). The major fraction contained 38 mg (68%) of **3e** as an oil: IR (film) 1790 (β-lactam), 1770, and 1750 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.52 (s, 3 H), 1.66 (s, 3 H), 4.53 (s, 1 H, C-3H), 5.51 (t, 1 H, $J_{5,F}$ = 4 Hz, $J_{5,6}$ = 4 Hz, C-5H), 5.74 (dd, 1 H, $J_{6,F}$ = 55.8 Hz, $J_{5,6}$ = 4 Hz, C-6H), 5.77 and 5.88 (AB system, 2 H, J = 5.6 Hz, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.59 (C-10), 169.02 (d, $^2J_{C,F}$ = 29.6 Hz, C-7), 166.12 (C-8), 91.77 (d, $^1J_{C,F}$ = 255 Hz, C-6), 79.84 (C-9), 70.52 (C-3), 66.57 (d, $^2J_{C,F}$ = 22 Hz, C-5), 64.14 (C-2), 38.67 (C-11), 31.55 (C-14), 26.73 (C-12), 26.55 (C-13); ^{19}F NMR ($CDCl_3$) δ −128.04 (dd, $^2J_{H,F}$ = 55.8 Hz, $^3J_{H,F}$ = 4 Hz); LRMS *m/e* (relative intensity) 333 (M^+, 6.84), 219 (2.06), 174 (2.22), 119 (2.66), 114 (2.5), 85 (8.72), 57 (100); HRMS calcd for $C_{14}H_{20}FNO_5S$ 333.1046, found 333.1061. The minor fraction was identified as the corresponding 6α-isomer **3d** (3%).

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Hydroxy-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)-methyl Ester, [2*S*(2α,5α,6α)]- (3f). This compound was prepared according to a method described by Sheehan[18] for other penicillins: yield 75%; IR (film) 3466 (OH), 1780 (β-lactam and ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.47 (s, 3 H), 1.55 (s, 3 H), 4.32 (br s, 1 H, OH), 4.49 (s, 1 H, C-3H), 4.83 (d, 1 H, J = 1.6 Hz, C-6H), 5.26 (d, 1 H, J = 1.6 Hz, C-5H), 5.79 and 5.85 (AB system, 2 H, J = 5.6 Hz, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.8 (C-10), 171.13 (C-7), 166.2 (C-8), 85.0 (C-6), 79.7 (C-9), 70.95 (C-5), 68.5 (C-3), 63.9 (C-2), 38.68 (C-11), 33.0 (C-14), 26.7 (C-12), 25.5 (C-13); LRMS *m/e* (relative intensity) 331 (M^+, 0.15), 274 (3.2), 244 (3), 217 (2.1), 160 (14.5), 144 (14), 85 (30), 57 (100).

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)-methyl Ester, [2*S*(2α,5α,6α)]- (3d).[11] **A: From 3f.** A solution of **3f** (215 mg, 0.65 mmol) in dry dichloromethane (2 mL) was added slowly to a solution of DAST (0.13 mL, 1.0 mmol) in dry dichloromethane (0.8 mL) at −23 °C under nitrogen. The reaction mixture was stirred for 6 h at room temperature, cooled to −10 °C, quenched with methanol (0.25 mL), and concentrated. Flash chromatography of the residue with chloroform–ether (95:05) as eluant yielded **3d** (164 mg, 75%) as white crystals, mp 62–64 °C. **B: From 2.** A 200-mg (0.59-mmol) sample of wet POM 6-diazopenicillanate (**2**) was dissolved in chloroform (4 mL) and cooled to 10 °C. DAST (0.147 mL, 1.173 mmol) in chloroform (1 mL) was added, and the mixture was stirred at this temperature for 15 h. After that the reaction mixture was cooled to −10 °C and methanol (0.25 mL) was added. Then the solvent was evaporated, and the crude product was purified by flash chromatography to give **3d** (195 mg, 65%).

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)-methyl Ester, 4,4-Dioxide, [2*S*(2α,5α,6α)]- (4a). To a solution of **3d** (133 mg, 0.4 mmol) in chloroform (10 mL) was added a solution of potassium permanganate (190 mg, 1.2 mmol) in water (10 mL). Then benzyltriethylammonium chloride (BTEAC, 10 mg, 0.04 mmol) was added, and the mixture was stirred vigorously at room temperature for 48 h. The mixture was filtered, the phases were separated, and the aqueous phase was extracted with chloroform (10 mL). The combined organic phase was washed with water containing hydrazine dihydrochloride (10 mL, 1 M) and brine (10 mL) and then was dried (Na_2SO_4). The solvent was removed to yield **4a** (116 mg, 80%) as a colorless oil: IR (film) 1810 (β-lactam), 1780 and 1755 (ester), 1330 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 s, 9 H), 1.43 (s, 3 H), 1.57 (s, 3 H), 4.45 (s, 1 H, C-3H), 4.67 (dd, 1 H, $J_{5,F}$ = 4.0 Hz, $J_{5,6}$ = 1.6 Hz, C-5H), 5.77 (dd, 1 H, $J_{6,F}$ = 53 Hz, $J_{5,6}$ = 1.6 Hz, C-6H), 5.75 and 5.96 (AB system, 2 H, J = 5.6 Hz, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.6 (C-10), 164.7 (C-8), 164.6 (d, $^2J_{C,F}$ = 22 Hz, C-7), 91.3 (d, $^1J_{C,F}$ = 238 Hz, C-6), 80.5 (C-9), 67.4 (d, $^2J_{C,F}$ = 25 Hz, C-5), 63.1 (C-2), 62.6 (C-3), 38.7 (C-11), 26.7 (C-12), 19.7 (C-14), 18.1 (C-13); ^{19}F NMR ($CDCl_3$) δ −127.22 (dd, $^2J_{H,F}$ = 53 Hz, $^3J_{H,F}$ = 4.0 Hz); LRMS (CI, ammonia) *m/e* (rel intensity) 383 ($M^+ + NH_4$, 47), 357 (100), 325 (15), 264 (52), 232 (63), 116 (35).

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid, 6-Fluoro-3,3-dimethyl-7-oxo-, (2,2-Dimethyl-1-oxopropoxy)-methyl Ester, 4,4-Dioxide, [2*S*(2α,5α,6β)]- (4b). Same procedure as **4a** using compound **3e** as the starting material. From 50 mg of **3e**, 43 mg (78%) of **4b** was obtained as a colorless oil: IR (film) 1820 (β-lactam), 1785 and 1765 (ester), 1340 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.43 (s, 3 H), 1.60 (s, 3 H), 4.64 (s, 1 H, C-3H), 4.79 (dd, 1 H, $J_{5,F}$ = 3.2 Hz, $J_{5,6}$ = 4.0 Hz, C-5H), 5.88 (dd, 1 H, $J_{6,F}$ = 52 Hz, $J_{5,6}$ = 4.0 Hz, C-6H), 5.72 and 5.95 (AB system, 2 H, J = 5.6 Hz, C-9H); ^{13}C NMR ($CDCl_3$) δ 176.67 (C-10), 168.71 (d, $^2J_{C,F}$ = 24 Hz, C-7), 165.23 (C-8), 89.25 (d, $^1J_{C,F}$ = 240.2 Hz, C-6), 80.55 (C-9), 64.98 (d, $^2J_{C,F}$ = 22 Hz, C-5), 64.20 (C-2), 63.92 (C-3), 38.72 (C-11), 26.75 (C-12), 19.92 (C-14), 17.66 (C-13); ^{19}F NMR ($CDCl_3$) δ −121.02 (dd, $^2J_{H,F}$ = 52 Hz, $^3J_{H,F}$ = 3.2 Hz); LRMS (CI, ammonia) *m/e* (rel intensity) 383 ($M^+ + NH_4$, 100), 319 ($M^+ - SO_2 + NH_4$, 18), 232 (63), 83 (14).

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Supplementary Material Available: ^{13}C and ^1H NMR spectra for the new compounds (7 pages). Ordering information is given on any current masthead page.

Cytotoxic Hydroperoxylepidozenes from the Actinia *Anthopleura pacifica* Uchida

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Marine organisms are excellent sources of biologically active substances with unique chemical structures.[1] In the course of our studies on the pharmaceutically active compounds from marine animals, we have isolated several cytotoxic sesquiterpenes, including hydroperoxides **1**, **6**, and **8** from the acetone extract of the Okinawan actinia *Anthopleura pacifica* Uchida. We describe herein their structures (Chart I).

1,10-Epoxy-14-hydroperoxy-4-lepidozene (**1**), $[\alpha]_D$ −143° (*c* 0.12, $CHCl_3$), an unstable colorless oil, exhibits a molecular peak at *m/z* 252, which corresponds to $C_{15}H_{24}O_3$, in the mass spectrum. The IR spectrum (film) shows the absorptions due to the hydroxy group at 3400 cm^{-1}. The ^1H NMR spectrum (500 MHz, C_6D_6) reveals an extremely shielded signal at δ 0.01 (1 H, ddd), which is apparently ascribable to a proton on a cyclopropane ring. The ^1H–^1H COSY-45[2] and ^1H–^{13}C COSY spectra established the vicinal relation of the proton and another shielded proton at δ 1.00. The 1D ^1H NMR spectrum shows that the

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