Stereochemistry of Base-Catalyzed Addition of Thiophenol to 3-H Carbacephalosporins

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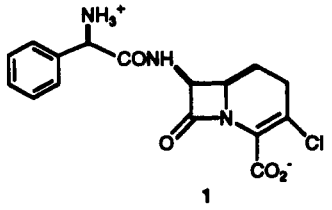
The stereochemistry of thiophenol addition to 3-H carbacephalosporins by the Michael addition reaction has been determined utilizing various NMR techniques. Detailed coupling information along with nuclear Overhauser enhancement studies indicate the thioadducts **8a–e** are formed by initial nucleophilic attack of the thiolate ion from the sterically more hindered β-face of the six-membered ring followed by proton delivery from the same face. The kinetic product has a trans disposition of the phenylthio and ester substituents which initially occupy axial positions in a chairlike conformation of the six-membered ring. In addition, preliminary data suggest the kinetic product slowly interconverts to the thermodynamic product through an elimination–addition mechanism affording the isomer where the thiolate ion has formally added from the α-face.

Loracarbef, **1**, the 1-carba analog of cefaclor, has recently been marketed as a new oral antibiotic.[1-3] A key challenge in the synthesis of **1** involves introduction of the 3-chloro



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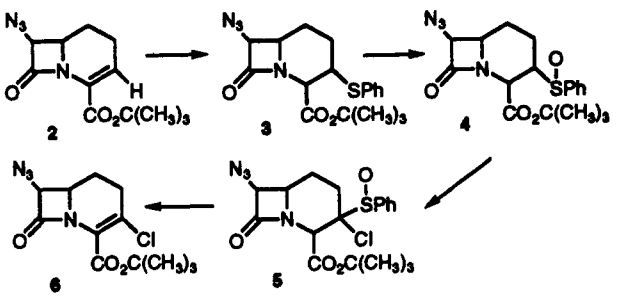
substituent in the 1-carba-1-dethiacephalosporin, or carbacephalosporin, nucleus. The Kyowa Hakko group has reported an interesting solution to this problem involving indirect chlorination of a 3-H carbacephem (Scheme 1).[4] In attempting to apply this process to 3-H carbacephems bearing different ester groups at C4 and nitrogen-based groups at C7, we have encountered some interesting results in the initial step involving the thiophenol addition to **7** (Scheme 2).

Treatment of **7b** with thiophenol and piperidine in methylene chloride led to rapid formation of the thiophenol adduct **8b** which could be isolated as a white crystalline solid.[5] ^{1}H NMR analysis showed the material to be a single isomer in accord with the previously reported results for **3** and **8a**.[4] HPLC monitoring confirmed that the Michael addition reaction is catalytic in base, with no reaction occurring in the absence of base. With slightly over 1 equiv of thiophenol and 0.2 equiv of base, starting material was nearly consumed within 30–60 min at 18–20 °C resulting in an *in situ* yield of **8b** which was greater than 95%.

Similar treatment of **7c–7e** with thiophenol and base resulted in nearly quantitative formation of the corresponding thiophenol adducts **8c–8e**. In each case, HPLC

Scheme 1



Scheme 2

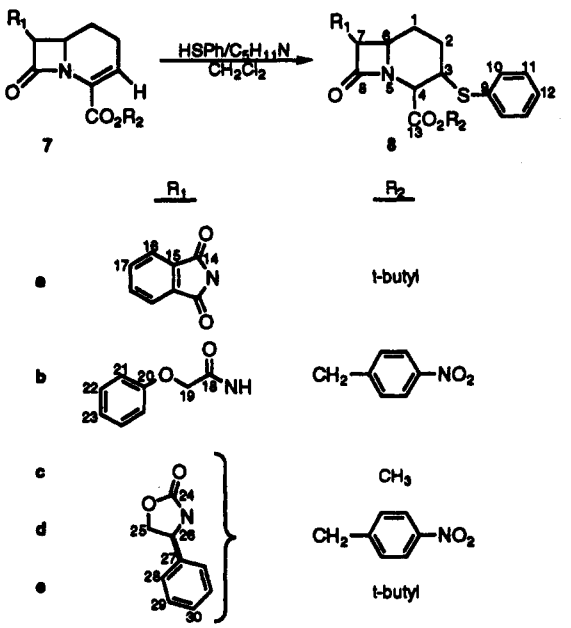


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Table 1. ^{1}H NMR Chemical Shifts and Coupling Constants of the Major Products of Thiophenol Addition

	chem shift[a] (ppm)				coupling constants (Hz)				
compd	H3	H4	H6	H7	J_{H3-H4}	$J_{H3-H2\alpha}$, $J_{H3-H2\beta}$[b]	J_{H6-H7}	$J_{H6-H1\beta}$	$J_{H6-H1\alpha}$
8a	3.83	4.28	3.93	5.35	1.2	3.0	5.0	10.2	4.6
8b	3.74	4.51	3.96	5.19	1.1	3.3	4.6	10.6	5.6
8c	3.57	4.22	3.83	4.80	1.2	3.4	4.6	9.8	5.8
8d	3.54	4.29	3.83	4.79	1.2	3.4	4.6	9.6	5.8
8e	3.55	4.10	3.85	4.81	1.2	3.4	4.6	c	c

[a] Measured at 300 MHz in $CDCl_3$ (7.24 ppm) except for **8a** which was measured in $CD_3C(O)CD_3$ (2.04 ppm). Digital resolution of 0.17 Hz. [b] Coupling constants for H3 to H2α and H2β are unresolved at 300 MHz. The value provided here is an approximate value for each. [c] Not obtained due to overlapping of signals.

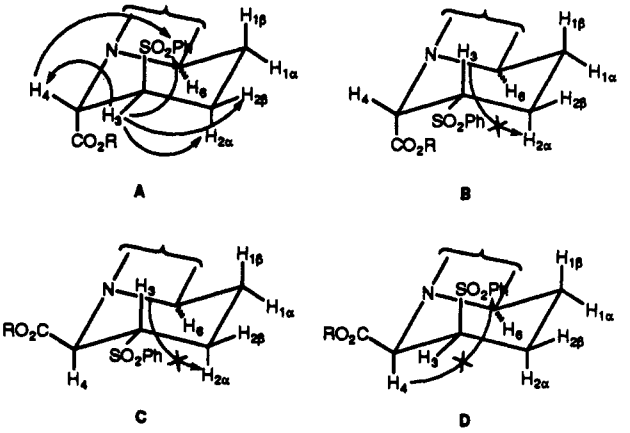
monitoring of the reactions showed rapid disappearance of starting material and virtually exclusive formation of a single isomeric product. Comparison of the ^{1}H NMR chemical shift and coupling data in Table 1, particularly the small coupling constant of H3–H4, suggests that all of the thiophenol adducts are structurally similar and share the same relative stereochemistry about the C3 and C4 centers. Reactions with **7c** and **7d** produced a very small amount of an additional product which was successfully isolated by flash chromatography. Mass spectral and ^{1}H NMR analysis showed this product to be an isomer of the major thiophenol adduct. Additionally, *in situ* ^{1}H NMR analysis of the reaction of **7e** with thiophenol indicated that a minor isomer also was formed, although the compound was never successfully isolated.

Investigation of the stereochemistry of the sulfide and ester groups became of vital interest not only to better define the mechanistic aspects of the thiophenol addition but also to understand the subsequent oxidation and chlorination chemistry of these compounds. Previously, the orientation of groups in **3** and **8a** had been assigned as 3αSPh-4$\alpha$$CO_2R$ based on the small H3–H4 coupling constant and presumed addition of the phenyl sulfide ion from the less hindered α-face.[4] The six-membered ring of the thioadducts was proposed to reside in a twisted chair conformation.

Structural analysis of **8b** by ^{1}H NMR was facilitated by oxidation to the sulfone **9**, wherein the shift differences in the C1 and C2 protons were magnified affording clean base-line separation of all four proton resonances. The signal due to H3 in **9** consisted of a triplet of doublets. The small 1.2-Hz coupling constant between H3 and H4 indicated these protons are not trans diaxial. In addition, the H3–H2 coupling constants were $J_{H3-H2\alpha}$ = 4.4 Hz and $J_{H3-H2\beta}$ = 3.1 Hz. These two values required that H3 reside in an equatorial position placing the phenylsulfone in an axial position. Preferential axial attack of the thiolate anion has been reported previously in a variety of six-membered-ring systems to afford the pseudoaxially disposed sulfenylated products.[6] In accordance with the observations of Abramovitch and co-workers,[7] the axial approach of the thiolate anion would be favored due to the almost continous overlap between the developing σ bond and the conjugated ester system in the formation of the transition state leading to the axial products.

In order to unambiguously assign the stereochemistry at C3 and C4, nuclear Overhauser enhancement (NOE) studies were performed on **9**. When H3 was irradiated,

Chart 1



enhancements were observed in the signals for both C2 protons, the ortho proton of the phenyl sulfone, and H4 confirming the axial disposition of the phenyl sulfone (**A**, Chart 1). Additionally, irradiation of H4 revealed relatively strong NOE's to the ortho protons of the phenyl sulfone. These data contradict the previously proposed twisted chair conformation and resulting stereochemical assignment of 3αSPh-4$\alpha$$CO_2R$ for **3** and **8a** in which the phenyl sulfide and H4 are in a trans diaxial alignment and would not be expected to exhibit a strong NOE.

The configurations shown in **B–D** of Chart 1 further illustrate how the only stereochemical assignment compatible with the observed coupling constants and the various nuclear Overhauser enhancements for the thiophenol addition product is 3βSPh-4$\alpha$$CO_2R$. Structures **B** and **C** would not be expected to have an NOE from H2α and H3 due to their trans diaxial disposition. In addition, the coupling for these two protons would not fit the experimentally observed value of 4.4 Hz. Further analysis of the coupling data between H3 and H4 provides evidence that the stereochemical assignment shown in configuration **D** also is not likely. As has been observed previously with thiophenol adducts of six-membered-ring systems, coupling constants for equatorial–equatorial protons are less than 3 Hz while axial–equatorial coupling constants are 3 Hz and greater.[6c,7] Thus, the experimentally observed H3–H4 coupling constant of 1.2 Hz is consistent with H4 residing in the β position.

These results are also in agreement with those of Baldwin and co-workers[8] who assigned the stereochemistry at C3 and C4 of two isomeric 2,3-dimethyl-substituted cephalosporins through examination of the ^{1}H NMR coupling constants for H3 and the corresponding NOE experiments.

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(8) Baldwin, J. E.; Adlington, R. M.; Turner, N. J.; Domayne-Hayman, B. P.; Ting, H.-H.; Derome, A. E.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1167.

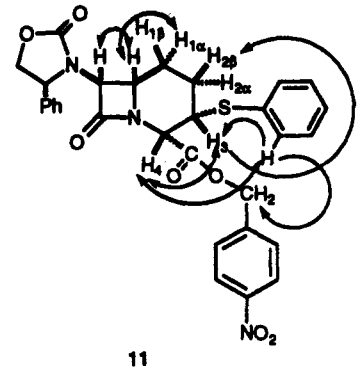
Relatively small H3–H4 coupling constants of 1.5 and 2.5 Hz were also observed for the cephalosporins, and subsequent NOE experiments determined the stereochemistry to be $3\beta CH_3$-$4\alpha CO_2H$ for each. Additionally, results on substituted cephalosporins having a $3\beta CH_3$ moiety indicate that the carboxyl group at C4 resides in the α position based upon the H3–H4 coupling constant of 2.0 Hz.[9]

Finally, the experimental coupling constants for H3 were compared to the theoretical values derived from molecular modeling experiments on **8b** having the various configurations illustrated in Chart 1. The coupling constants for H3 in **A**, obtained using the Quanta/CHARMm molecular modeling program[10] and the Karplus equation,[11] were 1.0, 2.8, and 4.0 Hz for H3–H4, H3–H2β, and H3–H2α, respectively. By modeling all of the other configurations at C3 and C4, the coupling data are only consistent with a stereochemical assignment of 3βSPh-$4\alpha CO_2$pNB.[12]

Further analysis of the coupling constants between the H6 and H1 protons and between the H1 and H2 protons in **9** provides insight into the conformation of the six membered ring. The coupling constants of 6.1 and 10.8 Hz between H6 and H1α and H6 and H1β, respectively, along with the nearly identical coupling constants observed between H2β and H1α of 3.2 Hz and H2β and H1β of 2.9 Hz, confirm that the ring system adopts a chairlike conformation. Inspection of models and NMR simulation techniques show that only the chairlike conformation can adequately fit the observed coupling constants and NOE data.

The coupling constants, along with the proposed chairlike conformation, correlate well to those observed in earlier work with carbacephalosporins. Previously, Doyle and co-workers[13] determined the conformation at C1 for 2-bromo-substituted carbacephalosporins based upon the observed ^1H NMR coupling constants between H6 and H1β of 10.5 Hz and H6 and H1α of 5.0 Hz. They surmised, comparable to our analysis, that in order to fit the observed coupling constants, H1α must reside in the equatorial position with H1β occupying the axial position. Similar NOE enhancements and coupling constants are observed in spectra of **8d** supporting the assignment of an identical chairlike conformation. Likewise, difference NOE and NOESY NMR studies on **8b** are consistent with a similar chairlike conformation and trans diaxial disposition of the substituents at C3 and C4.

Upon completion of the stereochemical and conformational analysis of the major product of thiophenol addition, attention was focused on determining the stereochemistry of the minor isomer. In contrast to the major isomer **8d** where the NMR signal for H3 appears as a triplet of doublets, this same signal in the minor isomer **11** is composed of eight distinct peaks. Decoupling studies indicate H3 has a 6.2-Hz coupling to H4, a 12.2-Hz coupling to H2α, and a 3.9-Hz coupling to H2β, suggesting that H3 and H2α are trans diaxial. Theoretically derived coupling constants between the same protons using the Quanta/CHARMm molecular modeling program and the Karplus equation are 5.2, 12.2, and 3.8 Hz, respectively. Again,



11

Figure 1. Observed NOE's for the minor isomer **11**.

based upon modeling all the various configurations at C3 and C4, the coupling information is only consistent with a stereochemical assignment of 3αSPh-$4\alpha CO_2R$ for the minor isomers.

The NOE enhancements shown in Figure 1 further confirm that the thiolate anion has added from the equatorial face in the minor isomer with the subsequent protonation occurring from the β-face. The large coupling to H2α further suggests that the chairlike conformation argument imposed earlier for the major isomer is applicable here, although now H3 occupies the axial position. This stereochemical assignment and chairlike conformation is consistent with previous observations in which 3-substituted oxacephams were determined to have a 3αOC(O)-CH_3-$4\alpha CO_2CHPh_2$ configuration based upon the relatively large H3–H4 coupling constant of 6.9 Hz and the observed NOE enhancements.[14] Similar coupling constants of approximately 6 Hz have also been seen for cephalosporins having a $3\alpha CH_3$-$4\alpha CO_2R$ configuration.[9,15] Proton NMR coupling data for the minor isomers **10** and **11** are presented in Table 2.

Inspection of models shows that the trans diaxial disposition of the C3 and C4 substituents in **8** is sterically more congested than the cis alignment found in the minor isomers **10** and **11** suggesting the trans diaxial product could be epimerized to the corresponding cis isomer. Treatment of **8d** with 2.3 equiv of piperidine resulted in immediate formation of a small amount of thiophenol and **7d** accompanied by slow conversion of the initially isolated major isomer into the minor isomer. After 25 h at 18–20 °C, the percentage of minor isomer, calculated by integration of H3 in the ^1H NMR spectrum, had increased from 2 to 55%. This is consistent with thiophenol addition to **7d** resulting in initial formation of a kinetic product containing an axial phenylthio group which can slowly convert into a more stable thermodynamic product under basic reaction conditions wherein the –SPh has added equatorially. Rapid formation of both thiophenol and **7d** on treatment of **8d** with base shows that thiophenol addition is reversible and that interconversion of the kinetic and thermodynamic products most likely occurs through an elimination–addition mechanism. Work is currently underway to further understand the mechanistic aspects of the kinetic and thermodynamic forms of the thiophenol addition products.

In conclusion, the results are consistent with base-catalyzed Michael addition of thiophenol to 3-H carba-

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Table 2. ^{1}H NMR Chemical Shifts and Coupling Constants of the Minor Products of Thiophenol Addition

	chem shift[a] (ppm)				coupling constants (Hz)					
compd	H3	H4	H6	H7	J_{H3-H4}	$J_{H3-H2\alpha}$	$J_{H3-H2\beta}$	J_{H6-H7}	$J_{H6-H1\beta}$	$J_{H6-H1\alpha}$
10	2.81	4.52	3.89	4.43	6.2	12.5	3.7	4.5	11.5	4.8
11	2.93	4.65	3.89	4.41	6.2	12.2	3.9	4.5	11.4	4.7

[a] Measured at 300 MHz in $CDCl_3$ (7.24 ppm). Digital resolution of 0.17 Hz.

Table 3. ^{13}C NMR Assignments for the Phenylthio Adducts 8a–e, Thiosulfonyl Adduct 9, and Minor Phenylthio Isomer 11 in $CDCl_3$[a]

C[b]	8a	8b	8c	8d	8e	9	11
1	19.6	18.1	20.0	19.9	20.1	16.5	23.9
2	24.9	23.3	24.4	24.4	24.4	18.0	24.3
3	45.4	45.7	45.1	45.3	45.1	48.2	44.9
4	55.1	53.6	53.8	53.7	54.5	56.4	53.1
6	52.9	51.8	52.7	52.3	52.3	50.8	51.6
7	57.8	58.8	63.1	63.1	63.0	58.8	61.5
8	163.1	166.1	162.5	162.7	162.5	165.7	161.4
9	131.7	132.3	133.4	133.3	133.9	134.2	132.4
10	132.2	129.6	129.2	129.2	132.3	128.2	129.0
11	129.1	133.0	133.1	133.3	129.1	129.4	131.9
12	127.4	128.2	129.1	129.1	129.0	136.0	129.2
13	167.4	168.0	169.1	168.2	167.6	166.8	167.3
14	167.9						
15	134.4						
16	123.8						
17	134.4						
18		168.5				168.2	
19		65.6				66.1	
20		156.8				156.8	
21		114.5				114.4	
22		129.2				129.3	
23		122.1				121.7	
24			159.1	158.9	159.1		157.6
25			72.2	72.1	72.2		70.6
26			59.3	59.3	59.2		59.6
27			139.4	139.2	139.5		137.5
28			127.9	127.8	127.8		127.7
29			129.4	129.4	129.3		129.0
30			127.9	128.1	127.5		c
$C(CH_3)_3$	27.9, 82.9				82.8		
pNB		66.9, 123.7, 128.1, 141.7, 147.6		65.7, 123.9, 128.2, 141.9, 147.8		66.6, 123.5, 128.5, 141.2, 147.6	65.1, 123.4, 128.5, 141.9, 147.5
CH_3			52.3				

[a] Chemical shifts in ppm measured at 300 MHz in $CDCl_3$ (center peak at 77.0 ppm). Assignments were determined based upon the HETCOR spectrum of each. Quaternary carbons were assigned based upon a BAX[17] spectrum of **8b**. [b] Carbons are labeled as shown in Scheme 2. [c] A peak corresponding to this carbon was not evident in the spectrum but presumably falls under the 127.7 ppm peak.

cephalosporins occurring by initial nucleophilic attack of the thiolate ion from the sterically more hindered β-face coupled with proton delivery from the same face. This gives rise to an initial trans disposition of the C3 and C4 substituents, both of which initially occupy axial positions in a chairlike conformation of the six-membered ring. The initial kinetic product slowly interconverts to the thermodynamic product via the 3-H carbacephalosporin through an elimination–addition mechanism wherein the thiolate ion has added from the α-face. In addition, the subsequent protonation from the β-face in both isomers may be the result of a tight ion pair between the carbanion and the protonated base and is consistent with the solvation properties of methylene chloride.

Experimental Section

General. Analytical high-performance liquid chromatography (HPLC) was carried out using a Spectra Physics Model SP8800 pump, Applied Biosystems 757 absorbance detector, and a 4.6-mm × 25-cm Zorbax Rx C-8 (DuPont) column. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts for ^{1}H NMR (300 MHz) spectra are reported in ppm in $CDCl_3$ with residual $CHCl_3$ used as the internal standard (7.24 ppm) unless noted otherwise. ^{13}C NMR (75 MHz) spectra are reported in ppm relative to the $CDCl_3$ adsorption (77.0 ppm) unless noted otherwise. High-resolution mass spectra, obtained using Varian ZAB-3F (FAB$^+$), Varian ZAB-SE (FAB$^+$), or Varian MAT-731 (FD) spectrometers, and elemental analyses were performed at the Structural and Organic Chemistry Research Laboratory, Eli Lilly and Co., Indianapolis, IN. Melting points were determined on a Laboratory Devices Mel-Temp capillary melting point apparatus and are uncorrected. Flash chromatography refers to the technique described by Still, Kahn, and Mitra.[16] Reactions were carried out under an atmosphere of N_2.

Thiophenol Addition to 3-H Carbacephalosporins. General Procedure. To a solution of the 3-H carbacephalosporin in CH_2Cl_2 was added thiophenol followed by piperidine. This mixture was stirred at ambient temperature for 1.5–14 h (reaction time). In each experiment, completion of reaction was determined by *in situ* HPLC analysis: 60:40 0.1 M H_3PO_4 pH = 2.5/CH_3CN; 1.5 mL/min; 220 nm. The mixture was then washed successively with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated yielding a crude material which was further worked up.

7-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-8-oxo-3-(phenylthio)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid 1,1-Dimethylethyl Ester (8a). The 3-H carbacephalosporin **7a** was thiolated by means of the general procedure described above.

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Starting materials: **7a** (850 mg, 2.31 mmol), thiophenol (0.44 mL, 4.31 mmol), piperidine (195 mg, 2.29 mmol); CH_2Cl_2 (40 mL). Reaction time: 14 h. The crude product was purified by flash chromatography (2 cm × 17 cm with Kieselgel 60) eluting with 2:1 hexane–ethyl acetate. The 3-(phenylthio) adduct **8a** (770 mg, 77%) was obtained as a colorless solid: ^{1}H NMR ($CD_3C(O)CD_3$) δ 1.44 (s, 9H, *tert*-butyl), 1.48–1.68 (m, 2H, CH_2), 1.89–2.20 (m, 2H, CH_2), 3.83 (td, 1H, J = 1.2, 3.0, 3.0 Hz, H3), 3.93 (ddd, 1H, J = 4.6, 5.0, 10.2 Hz, H6), 4.28 (br s, 1H, H4), 5.35 (d, 1H, J = 4.9 Hz, H7), 7.23–7.37 (m, 1H, SPh H), 7.42 (t, 2H, SPh H), 7.62 (d, 2H, SPh H), 7.88–8.02 (m, 4H, Pt H); ^{13}C NMR data in Table 3; exact mass (FAB$^+$) calcd for $C_{26}H_{27}N_2O_5S$ 479.1641, found 479.1612.

***cis*-7-[(Phenoxyacetyl)amino]-8-oxo-3-(phenylthio)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (4-nitrophenyl)-methyl Ester (8b).** Starting materials: **7b** (50.0 g, 89.1 mmol), thiophenol (13.7 mL, 116 mmol), piperidine (1.2 mL, 16.4 mmol); CH_2Cl_2 (1 L). Reaction time: 3 h. Crystallization of **8b** was achieved by first concentrating the CH_2Cl_2 solution to *ca.* 300 mL. Then, methanol (250 mL) was added and the resultant solution was again concentrated until it remained permanently cloudy. Vigorous agitation of the mixture resulted in crystallization which was further completed by overnight storage at 0 °C. The solid was filtered, washed with methanol (300 mL) and hexanes (150 mL), and vacuum dried at 30 °C affording **8b** (53.3 g, 86%) as an off-white solid: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.46–1.72 (m, 2H, CH_2), 1.84–2.10 (m, 2H, CH_2), 3.74 (td, 1H, J = 1.1, 3.3, 3.3 Hz, H3), 3.96 (ddd, 1H, J = 4.6, 5.6, 10.6 Hz, H6), 4.51 (br s, 1H, H4), 4.58 (s, 2H, CH_2OPh), 5.19 (dd, 2H, CO_2CH_2), 5.32 (dd, 1H, J = 4.6, 7.3 Hz, H7), 6.97 (d, 2H, SPh H), 7.01–7.10 (t, 1H, SPh H), 7.22–7.37 (m, 5H, OPh H), 7.42 and 8.22 (dd, 4H, $PhNO_2$ H), 7.47–7.58 (m, 2H, SPh H); ^{13}C NMR data in Table 3; MS (FD) m/z 561 (M$^+$).

Anal. Calcd for $C_{29}H_{27}N_3O_7S$: C, 62.02; H, 4.85; N, 7.48. Found: C, 62.17; H, 5.08; N, 7.47.

***cis*-7-(4-Phenyl-2-oxooxazolidinyl)-8-oxo-3-(phenylthio)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid Methyl Ester (8c).** Starting materials: **7c** (600 mg, 1.75 mmol), thiophenol (218 μL, 2.12 mmol), piperidine (30 mg, 0.35 mmol); CH_2Cl_2 (25 mL). Reaction time: 1.5 h. The crude product was purified by flash chromatography (2 cm × 18 cm with silica gel) eluting with 2:1 ethyl acetate–hexane to afford first the minor 3α-(phenylthio) isomer **10** (2 mg) followed by the 3β-(phenylthio) adduct **8c** (793 mg, 66%) as a colorless solid, mp 132–134 °C. **8c**: ^{1}H NMR ($CDCl_3$) δ 1.52–1.72 (m, 2H, CH_2), 1.74–1.97 (m, 2H, CH_2), 3.57 (td, 1H, J = 1.2, 3.4, 3.4 Hz, H3), 3.62 (s, 3H, CH_3), 3.83 (m, 1H, J = 4.6, 9.8, 5.8 Hz, H6), 4.22 (br s, 1H, H4), 4.26 (dd, 1H, OCH), 4.73 (t, 1H, OCH), 4.80 (d, 1H, J = 4.6 Hz, H7), 5.12 (dd, 1H, CHPh), 7.17–7.36 (m, 5H, SPh H), 7.36–7.51 (m, 5H, Ph H); ^{13}C NMR data in Table 3; exact mass (FAB$^+$) calcd for $C_{24}H_{25}N_2O_5S$ 453.1484, found 453.1471.

10: ^{1}H NMR ($CDCl_3$) δ 1.30–1.68 (m, 2H, CH_2), 1.72–2.08 (m, 2H, CH_2), 2.82 (ddd, 1H, J = 3.7, 6.2, 12.5 Hz, H3), 3.71 (s, 3H, CH_3), 3.89 (ddd, 1H, J = 4.5, 4.8, 11.5 Hz, H6), 4.30 (dd, 1H, OCH), 4.43 (d, 1H, J = 4.5 Hz, H7), 4.53 (d, 1H, J = 6.2 Hz, H4), 4.71 (t, 1H, OCH), 4.96 (dd, 1H, CHPh), 7.25–7.46 (m, 10H, SPh H and Ph H); ^{13}C NMR data in Table 3.

***cis*-7-(4-Phenyl-2-oxooxazolidinyl)-8-oxo-3-(phenylthio)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (4-Nitrophenyl)methyl Ester (8d).** Starting materials: **7d** (1.0 g, 2.16 mmol), thiophenol (0.28 mL, 2.73 mmol), piperidine (45 mg, 0.53 mmol); CH_2Cl_2 (20 mL). Reaction time: 3 h. The crude product was purified by flash chromatography (2 cm × 19 cm with silica gel) eluting with 2:1 ethyl acetate–hexane to afford the minor 3α-(phenylthio) isomer **11** followed by the 3β-(phenylthio) adduct **8d** (980 mg, 79%) as a colorless solid, mp 82–84 °C. **8d**: ^{1}H NMR ($CDCl_3$) δ 1.52–1.70 (m, 2H, CH_2), 1.70–2.01 (m, 2H, CH_2), 3.54 (td, J = 1.2, 3.4 3.4 Hz, 1H, H3), 3.83 (ddd, 1H, J = 4.6, 5.8, 9.6 Hz, H6), 4.27 (dd, 1H, OCH), 4.29 (br s, 1H, H4), 4.73 (t, 1H, OCH), 4.79 (d, 1H, J = 4.6 Hz, H7), 7.25–7.38 (m, 5H, SPh H), 7.38–7.50 (m, 5H, Ph H), 7.41 and 8.18 (dd, 4H, Ph-NO_2 H); ^{13}C NMR data in Table 3; exact mass (FAB$^+$) calcd for $C_{30}H_{28}N_3O_7S$ 574.1648, found 574.1651.

Anal. Calcd for $C_{30}H_{28}N_3O_7S$: C, 62.82; H, 4.74; N, 7.33. Found: C, 63.05; H, 4.87; N, 7.41.

11: ^{1}H NMR ($CDCl_3$) δ 1.44–1.65 (m, 1H), 1.75–2.08 (m, 3H), 2.93 (ddd, 1H, J = 3.9, 6.2, 12.2 Hz, H3), 3.89 (ddd, 1H, J = 4.5, 4.7, 11.4 Hz, H6), 4.30 (dd, 1H, OCH), 4.42 (d, 1H, J = 4.5 Hz, H7), 4.65 (d, 1H, J = 6.2 Hz, H4), 4.72 (t, 1H, OCH), 4.94 (dd, 1H, CHPh), 5.22 (dd, 2H, CO_2CH_2), 7.28 (s, 5H, SPh H), 7.37 (m, 5H, Ph H), 7.47 and 8.18 (dd, 4H, Ph-NO_2 H); ^{13}C NMR data in Table 3; exact mass (FAB$^+$) calcd for $C_{30}H_{28}N_3O_7S$ 574.1648, found 574.1608.

***cis*-7-(4-Phenyl-2-oxooxazolidinyl)-8-oxo-3-(phenylthio)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid-1,1-Dimethylethyl Ester (8e).** Starting materials: **7e** (460 mg, 1.20 mmol), thiophenol (0.32 mL, 3.14 mmol), piperidine (300 mg, 3.52 mmol); CH_2Cl_2 (25 mL). Reaction time: 5 h. The crude product was purified by trituration in 4:1 hexanes–THF to afford **8e** (530 mg, 90%) as a colorless solid: mp 181–183 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H, CH_3), 1.55–1.72 (m, 2H, CH_2), 1.74–1.99 (m, 2H, CH_2), 3.55 (dt, 1H, J = 1.1, 3.4, 3.4 Hz, H3), 3.85 (ddd, 1H, J = 4.6 Hz, H6), 4.10 (br s, 1H, H4), 4.27 (dd, 1H, OCH), 4.73 (t, 1H, OCH), 4.81 (d, 1H, J = 4.6 Hz, H7), 5.12 (dd, 1H, CHPh), 7.17–7.35 (m, 5H, SPh H), 7.35–7.50 (m, 5H, Ph H); ^{13}C NMR data in Table 3; MS (FAB$^+$) m/z 495.2 (M$^+$).

Anal. Calcd for $C_{27}H_{30}N_2O_5S$: C, 65.57; H, 6.11; N, 5.66. Found: C, 65.30; H, 6.13; N, 5.44.

***cis*-7-[(Phenoxyacetyl)amino]-8-oxo-3-(phenylsulfonyl)-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (4-Nitrophenyl)methyl Ester (9).** To a solution of **8b** (1.0 g, 1.78 mmol) in CH_2Cl_2 (37 mL) was added a 35% solution of peracetic acid (0.68 mL, 3.54 mmol). The mixture was stirred for 5 h at room temperature and then was quenched to a negative starch iodide test with saturated aqueous $NaHSO_3$. The mixture was washed with $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated to afford **9** (1.04 g, 98%) as a colorless solid: mp 179–181 °C; ^{1}H NMR ($CDCl_3$,) δ 1.52–1.58 (m, 1H, H1β), 1.75–1.93 (m, 1H, H2β), 1.94–2.22 (m, 1H, H1α), 2.50–2.63 (m, 1H, H2α), 3.40 (dt, 1H, J = 1.2, 3.1, 4.4 Hz, H3), 3.97 (ddd, 1H, J = 4.6, 6.1, 10.8 Hz, H6), 4.55 (s, 2H, OCH_2), 4.88 (br s, 1H, H4), 5.17 (dd, 2H, CO_2CH_2), 5.44 (dd, 1H, J = 4.6, 8.8 Hz, H7), 6.85–7.06 (m, 3H, SPh H), 7.21–7.40 (m, 3H, SPh H and Ph H), 7.51 (d, 1H, J = 8.8 Hz, NH), 7.55–7.67 (m, 2H, Ph H), 7.67–7.78 (m, 2H, Ph H), 7.95 and 8.20 (dd, 4H, Ph-NO_2 H); ^{13}C NMR data in Table 3; MS (FD) m/z 593 (M$^+$).

Anal. Calcd for $C_{29}H_{27}N_3O_9S$: C, 58.68; H, 4.58; N, 7.08. Found: C, 58.66; H, 4.73; N, 7.02.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **8a-8e**, **9**, **10** and **11**, NOE difference spectra of **8b**, **8d**, **9**, and **11**, NOESY and BAX spectra of **8b**, and theoretical NMR methods and spectra of **8b** and **9** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.