Cycloadditions of Cephalosporins. A Comprehensive Study of the Reaction of Cephalosporin Triflates with Olefins, Acetylenes, and Dienes To Form [2 + 2] and [4 + 2] Adducts

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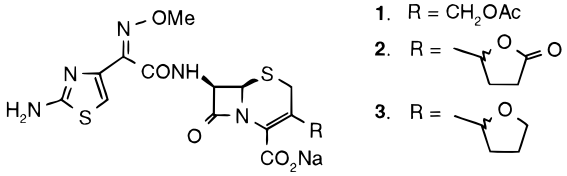
Novel polycyclic cephalosporins are formed by the reaction of cephalosporin triflates with various unsaturated compounds in the presence of Hunigs base. 2,3-Fused cyclobutane and cyclobutene cephems are obtained with olefins and acetylenes, respectively, whereas [4 + 2] cycloadducts are obtained with furan. The reaction has been rationalized by invoking the intermediacy of a strained 6-membered cyclic allene. The allene undergoes an orbital symmetry allowed concerted $_{\pi}2_{s} + _{\pi}2_{a}$ cycloaddition with olefins and acetylenes and a $_{\pi}4_{s} + _{\pi}2_{s}$ cycloaddition with furan. The regiochemistry of the [2 + 2] cycloadducts is independent of the substitution of the unsaturated component and of the oxidation state of the cephalosporin sulfur atom. However in the case of the [4 + 2] adducts, the sulfur oxidation state determines the regiochemistry of the addition. Carbacephalosporins also participate in this reaction with olefins but require a stronger base such as DBU. Thus the reaction described provides a facile, one-step procedure for the production of a rich variety of novel polycyclic cephalosporins.

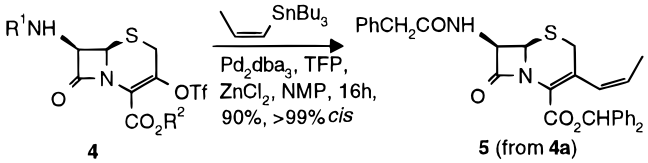
Introduction

Since the introduction of third-generation cephalosporins (e.g., cefotaxime **1**) there has been considerable interest in finding replacements for the metabolically unstable acetoxy group at C-3. Numerous modifications have been achieved by replacing the acetoxy group with a variety of nitrogen heterocycles and sulfur-based nucleophiles.[1] However, there are also several examples of carbon substituents at C-3 demonstrating that a leaving group at C-3 is not essential for antimicrobial activity.[2]



Recently Burton and co-workers reported on the synthesis and antimicrobial activity of C-3 lactonyl (**2**) and C-3 cyclic ether (**3**) cephalosporins.[3] They demonstrated that a lactone functionality retained cefotaxime-like activity and hoped that this would circumvent the problem of metabolism. Burton discovered that the introduction of C-3 cyclic ethers, groups known to confer good activity when attached to the C-2 of penems,[4] onto the cephem nucleus gave dramatically superior oral absorption in mice when dosed as prodrug esters, although the antibacterial activities of the sodium salts were not as potent as the C-3-lactonyl compounds.[5]

Scheme 1[a]



4a. R^1 = $PhCH_2CO$ R^2 = $CHPh_2$

4b. R^1 = $PhCH_2CO$ R^2 = pMB

4c. R^1 = PhCO R^2 = pMB

[a] TFP = tri(2-furyl)phosphine, NMP = *N*-methylpyrrolidone, pMB = *p*-methoxybenzyl.

Farina and others have developed organometallic methodologies for the formation of carbon−carbon bonds at C-3 of cephalosporins.[6] The Stille coupling of the readily accessible triflates (**4**)[7] with stannanes has been particularly successful for the introduction of unsaturated substituents at C-3 (Scheme 1). Although the introduction of sp^3-based substituents is generally not successful using the Stille coupling conditions, the reaction of organocuprates with the triflates (**4**) provides an alternative approach to alkyl substituents.[8]

We wished to investigate alternative methods for the introduction of the tetrahydrofuryl group onto the C-3 of the cephem nucleus via the triflates (**4**) with the ultimate goal of achieving the reaction stereoselectively. Treatment of the triflate **4a** with (2-tetrahydrofuryl)tri-

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(1) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.
(2) Kukolja, S.; Chauvette R. R. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, pp 93−198.
(3) Bateson, J. H.; Burton, G.; Fell, S. C. M. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2219.
(4) Ishiguro, M.; Iwata, H.; Nakatsuka, T.; Tanaka, R.; Maeda, Y.; Nishihara, T.; Noguchi, T. *J. Antibiot.* **1988**, *41*, 1685.
(5) Bateson, J. H.; Burton, G.; Fell, S. C. M.; Smulders H. C. *J. Antibiot.* **1994**, *47*, 253.
(6) Farina, V.; Kant, J. *Synlett* **1994**, 565, and references cited therein.
(7) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.
(8) Kant, J. *J. Org. Chem.* **1993**, *58*, 2296.

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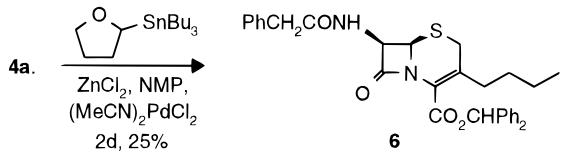
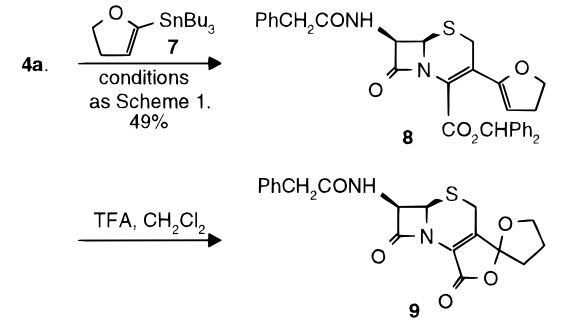
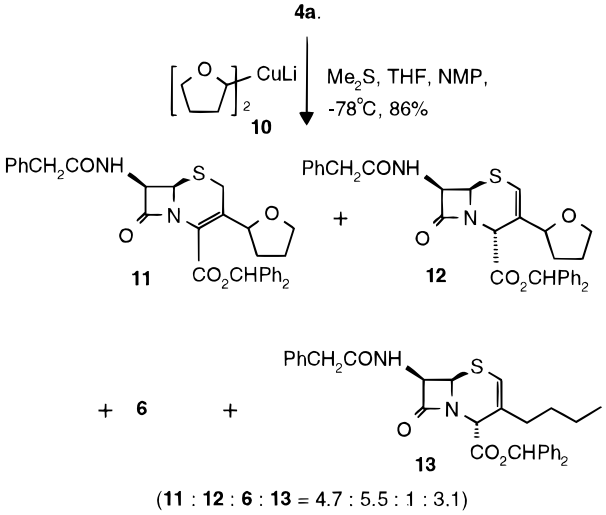
Scheme 2



Scheme 3



Scheme 4



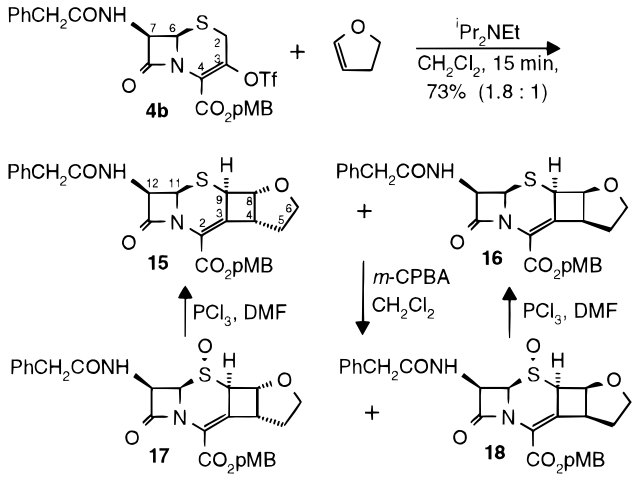
n-butylstannane[9] under palladium catalysis led to the unwanted transfer of a butyl group to give **6** after an extended reaction time (Scheme 2), whereas the unsaturated stannane **7** underwent a facile Stille coupling to give **8**. However we were unable to reduce the dihydrofuryl double bond. Attempts to deprotect **8** to the corresponding acid instead led to formation of a spiroacetal lactone (**9**) (Scheme 3).[10]

The tetrahydrofuryl group was successfully introduced at C-3 using the cuprate **10** (derived from (2-tetrahydrofuryl)tri-*n*-butylstannane). In addition to the desired Δ^3-cephem **11**, a considerable amount of the Δ^2 isomer **12** was obtained (Scheme 4). The 3-*n*-butyl analogues **13** and **6** were also obtained as a mixture of Δ^2 and Δ^3 isomers. These resulted from the presence of excess *n*-butyllithium in the preparation of the tetrahydrofurylcuprate. A potential solution to this problem would be the use of dialkylmagnesiocuprates (Normant's cuprates). These are less basic in nature than lithiocuprates and are reported by Kant to afford pure Δ^3 products.[8]

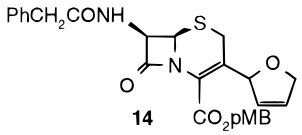
(9) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

(10) Bateson, J. H.; Burton, G.; Elsmere, S. A.; Elliott, R. L. *Synlett* **1994**, 152.

Scheme 5



An alternative approach for the introduction of a dihydrofuryl group appeared to be the asymmetric Heck reaction.[11] If applied to the cephalosporin triflate **4b**, the expected dihydrofuran **14** would now have the double



bond out of conjugation and therefore be more amenable to reduction. However this reaction took a totally unexpected course. Rather than the expected dihydrofuran **14**, two 2,3-fused polycyclic cephalosporins (**15** and **16**) were formed[12] (Scheme 5). We postulated that a cyclic allene intermediate was involved in the reaction, which underwent cycloaddition with the unsaturated component. We have reported on our initial findings,[13] and now report in full further investigations regarding the scope and mechanism of this remarkable reaction.

Results and Discussion

Treatment of the triflate **4b** with 2,3-dihydrofuran in *N*-methylpyrrolidone under conditions suitable for the asymmetric Heck reaction (^{i}Pr$_2$NEt, catalytic Pd(OAc)$_2$, (*R*)-BINAP) gave rise to a mixture of two isomeric products in 73% yield in a ratio of 1.8:1. Detailed NMR studies showed the products to be the fused cyclobutane adducts **15** and **16** and not the expected Heck product **14**. We subsequently discovered that the reaction could

(11) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem*. **1992**, *64*, 421. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. For a Heck reaction on carbapenems, see: Nishi, K.; Narukawa, Y.; Onoue, H. *Tetrahedron Lett*. **1996**, *37*, 2987.

(12) Conventional cephalsporin numbering has been used when referring to the bicyclic cephalosporin nucleus (see compound **4b**), and systematic nomenclature has been used for the cycloadducts (see compounds **15**, **19**, and **95**). α-Substituents are projected into the page while β-substituents are oriented out of the page.

(13) Elliott, R. L.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1993**, *58*, 6954. Elliott, R. L.; Nicholson, N. H.; Peaker, F. E.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem*. **1994**, *59*, 1606. Burton, G.; Elliott, R. L. (SmithKline Beecham plc) PCT Pat. Appl. WO 9318044, 16 Sept 1993; *Chem. Abstr*. **1994**, *121*, 57222. Burton, G.; Bateson, J. H.; Elliott, R. L.; Fell, S. C. M. (SmithKline Beecham plc) PCT Pat. Appl. WO 9400457, 6 Jan 1994; *Chem. Abstr*. **1994**, *120*, 191424. Elliott, R. L.; Nicholson, N. H.; Takle, A. K. (SmithKline Beecham plc) PCT Pat. Appl. WO 9421633, 29 Sept 1994; *Chem. Abstr*. **1995**, *122*, 31202. For other examples of polycyclic β-lactams, see: Niu C.; Pettersson T.; Miller M. J. *J. Org. Chem*. **1996**, *61*, 1014 and references therein.

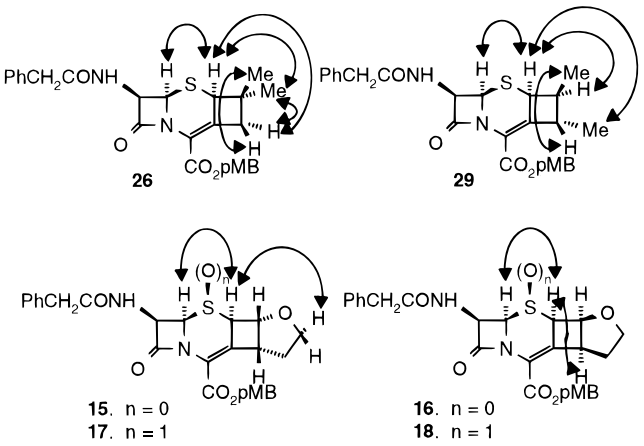


Figure 1. Observed NOEs.

be performed in CH_2Cl_2 and in the absence of any transition metal catalyst without affecting product yield or ratio (Scheme 5). The products **15** and **16** were most conveniently separated by silica gel chromatography after oxidation to the sulfoxides **17** and **18**. Reduction back to the respective sulfides was achieved with PCl_3 in DMF.

The reaction of the triflates **4** with olefins in the presence of a base to give fused cyclobutane products has proved to be extremely general (Table 1). In many cases the cyclobutane was obtained as a single isomer. The yields and purities of the products were often improved by the use of a large excess of the olefin.

The most facile cycloadditions in terms of highest yields and utilizing only 1−5 equiv of olefin occurred with the electron rich olefins (entries 12, 13, 14, 15, and 18) and styrene (entry 4). In general the monosubstituted olefins with conjugated π-systems gave mixtures of isomers with the substituents in the 5α- and 5β-positions (entries 4, 16, and 17) whereas the monosubstituted olefins with no extended π-system gave single isomers with the substituent in the 5β-position (entries 2, 12, 13, 15, 23, 24, and 30). 1,1-Disubstituted olefins also gave products with the substituents in the 5-position together with 3-substituted ceph-2-ems (entries 5 and 6). 1,1-Diphenylethylene, however, gave two isomeric products (entry 31) which have the 6-H in the α- (**60**) and β-positions (**61**). The two isomers were readily identified in the mixture by ^{1}H NMR. Particularly diagnostic was H-8 which appeared at 3.82 ppm in **61** and at 5.02 ppm in **60**. In an attempt to effect separation of the isomers, the mixture was oxidized with *m*-CPBA. This resulted in the isolation of only one product, the 6α-H isomer; the yield indicated that the 6β-H isomer must have isomerized to the 6α-H under the reaction conditions. Subsequent reduction gave the pure 6α-H isomer (**60**). Symmetrical *trans*-disubstituted olefins gave single products with the substituents at the 4α- and 5β-positions (entries 7 and 9); in unsymmetrical *trans*-olefins the electron rich substituent was found at the 5β-position in the product (entry 25). *trans*-2-Pentene gave two products with the substituents still occupying the 4α- and 5β-positions (entry 29). Acyclic *cis*-olefins gave predominantly the product with the substituents on the α-face (entries 8, 26, and 28). The products from *cis*-2-butene (entry 8) contained 34% of **29**, the exclusive product from *trans*-2-butene (entry 7). GC analysis of the *cis*-2-butene used showed the presence of 2.1% of the *trans* isomer. Thus **29** could be accounted for in two ways. Either a C-4−C-5 bond rotation occurred in some reaction intermediate or the cycloaddition reaction occurred faster with *trans*-2-butene than with the *cis* isomer (k_{rel} = 25:1). A competition reaction with *cis*-2-pentene (containing 0.9% *trans*) and *trans*-2-pentene also showed a k_{rel} of 22.7:1 (*trans*:*cis*) by integration of the NMR signals in the crude product. This strongly suggested a rate enhancement for the *trans* isomer over the *cis*. 5-Membered monocyclic olefins gave two isomeric products, with the fourth ring in the α- and β-orientations (Scheme 5 and entry 10), while the 6-membered monocyclic olefins gave products with the fourth ring exclusively on the α-face (entries 11 and 18). Benzo-fused 5-membered cyclic dienes also gave exclusive products with the benzo-fused rings on the α-face and the nonaromatic atom attached to position 4 (entries 19, 20, 21, and 22).

The novel polycyclic ring structures of these cephalosporin derivatives made unambiguous ^{1}H NMR assignment difficult. Therefore extensive ^{1}H and ^{13}C NMR studies were undertaken on several key compounds in order to fully elucidate their structures and define the stereochemistry. The 4-membered rings formed in this cycloaddition reaction were found to exhibit characteristic cross-ring $^4J_{H,H}$ couplings. In order to distinguish the *cis* and *trans* couplings, NOE difference experiments were performed (Figure 1).

In **26** strong NOEs were observed from H-6 to H-8 and to H-4α and also from Me-5α to H-6 and to H-4α. Since H-8 is known to be on the α-face of the molecule, H-6, H-4α, and Me-5α must also be α-oriented. This was supported by the large NOE from Me-5β to H-4β alone, which therefore confirmed both to be β-oriented. The cross-ring coupling constants were measured to be $^4J_{4\alpha,6}$(*cis*) = 1.3 Hz and $^4J_{4\beta,6}$(*trans*) = 2.7 Hz. In **29** there were strong NOEs from H-6 to H-8, H-5α, and Me-4α and also from H-4β to Me-5β. The coupling constants were $^3J_{5\alpha,6}$ = 9.5 Hz, $^3J_{4\beta,5\alpha}$ = 2.9 Hz, and $^4J_{4\beta,6}$ = 3.2 Hz. The NMR assignment of the stereochemistry of the products from olefins was confirmed by single-crystal X-ray diffraction analysis of the 5β-SPh derivative **62**[14] (Figure 2).

In one isomer (**15**) of the dihydrofuran reaction (Scheme 5) there is a large NOE between H-9 and H-11, confirming the α-orientation of H-9. Unfortunately, the proximity of the resonances H-9 (4.12 ppm), H-4 (4.15 ppm), and H-6α (4.18 ppm) prevented determination of the tetrahydrofuran ring stereochemistry from the NOE data. However H-9 exhibited a 3.1 Hz coupling to both H-4 and H-8, indicating that both were *trans* to H-9, and thus the tetrahydrofuryl ring was α-oriented. In the corresponding sulfoxide (**17**) an additional NOE was observed between H-9 (3.69 ppm) and H-6α (3.96 ppm) confirming the α-orientation of the tetrahydrofuryl ring. In the second isomer (**16**) strong NOEs were observed between H-9 and H-11 confirming the α-orientation of H-9. The coupling constant between H-8 and H-9 was 6.5 Hz, and that between H-9 and H-4 was small (<0.5 Hz). These values are indicative of a *cis* relationship between H-4, H-8, and H-9. There was reduced spectral crowding in the corresponding sulfoxide (**18**), and a weak NOE was observed between H-4 and H-9; but no NOE was observed between H-6 and H-9. These results indicated that the tetrahydrofuryl ring was oriented to the β-face.

A study of the effect of solvents and bases on the reaction of triflate **4b** with 2,3-dihydrofuran was under-

(14) The author has deposited atomic coordinates for **62** and **86** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Table 1. Reaction of Triflates 4b or 4c with Olefins[a]

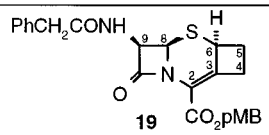
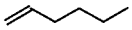
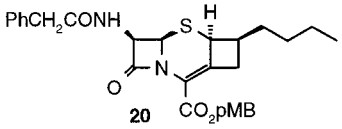
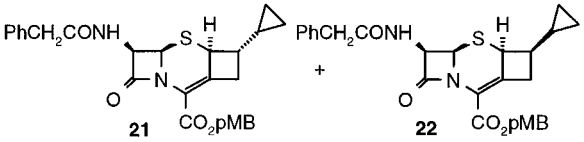
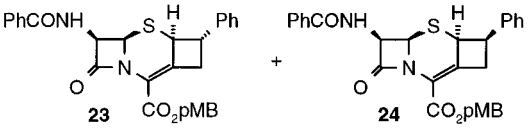
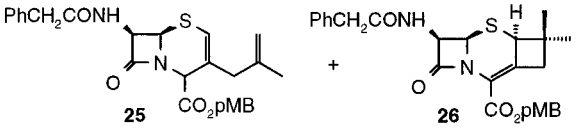
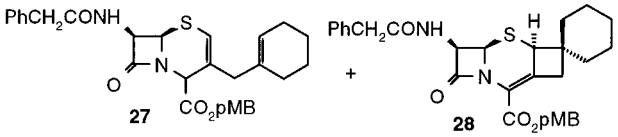
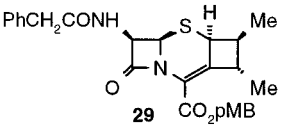
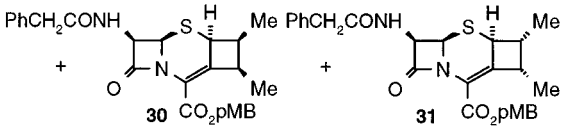
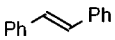
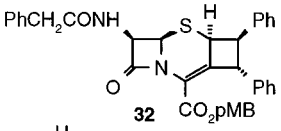
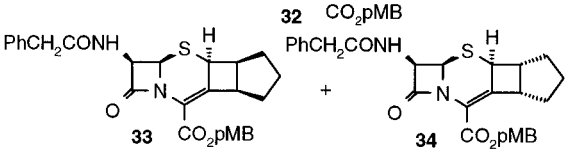
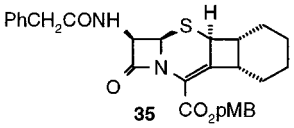
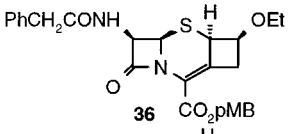
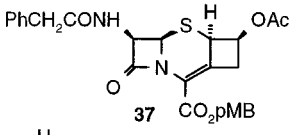
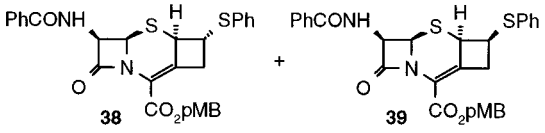
entry	olefin	equiv	products	yield % (ratio)
1	$CH_2=CH_2$	*b*	 **19**	60
2		5	 **20**	54
3		30	 **21** + **22**	56 (1 : 2.5)
4		5	 **23** + **24**	73 (1.3 : 1)
5		*d*	 **25** + **26**	88 (1 : 5.8)
6		5	 **27** + **28**	68 (1 : 2.2)
7		*d*	 **29**	88
8		*d*	**29** +  **30** + **31**	78 (4.3 : 1 : 7.3)
9		5	 **32**	91
10		200	 **33** + **34**	55 (1 : 1.75)
11		290	 **35**	39
12		5	 **36**	75
13		5	 **37**	74
14		1.1	 **38** + **39**	67 (1 : 3)

Table 1 (Continued)

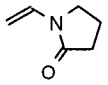
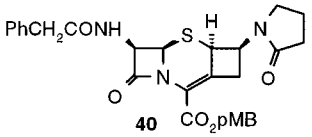
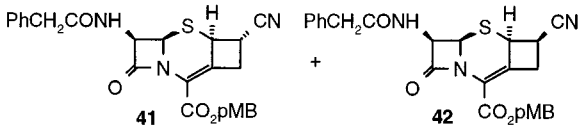
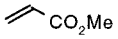
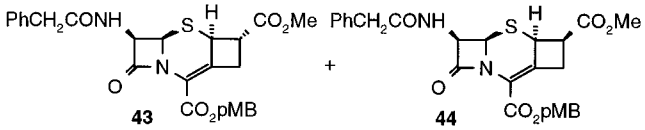
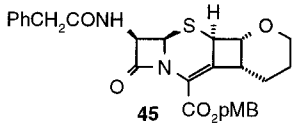
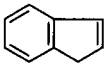
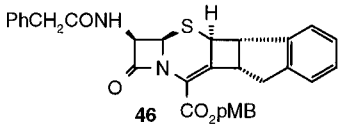
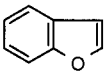
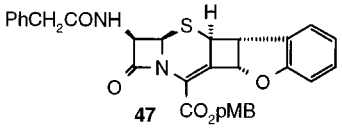
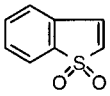
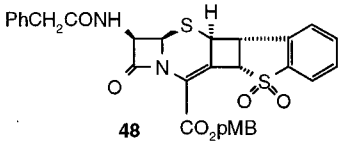
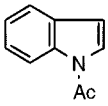
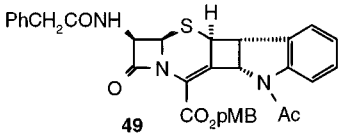
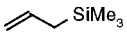
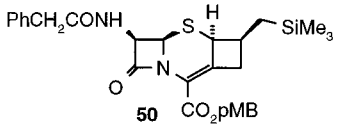
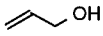
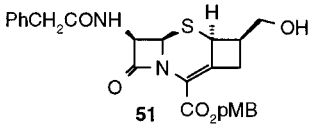
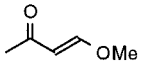
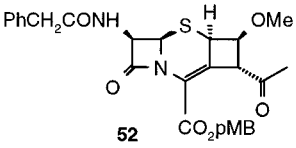
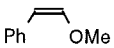
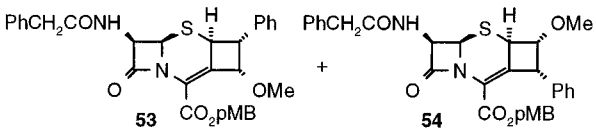
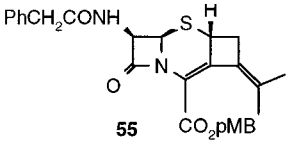
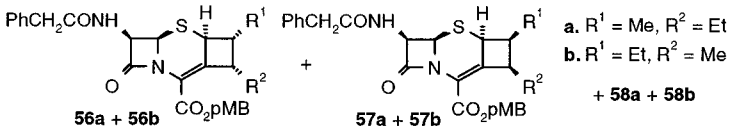
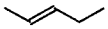
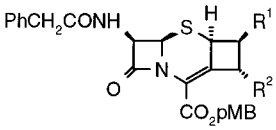
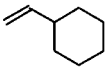
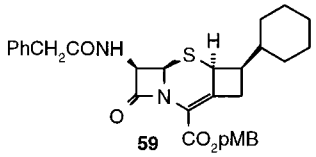
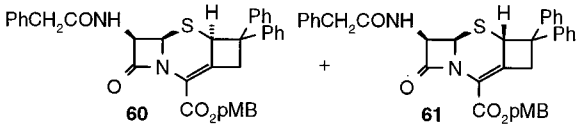
entry	olefin	equiv	products	yield % (ratio)
15		7	 **40**	100
16		50	 **41** + **42**	71 (1 : 2)
17		50	 **43** + **44**	76 (1 : 1.5)
18		5	 **45**	62
19		5	 **46**	90
20		25	 **47**	63
21		25	 **48**	34
22		5	 **49**	33
23		5	 **50**	71
24		5	 **51**	71
25		5	 **52**	56
26		5	 **53** + **54**	63 (3.3 : 1)
27		20	 **55**	34

Table 1 (Continued)

entry	olefin	equiv	products	yield % (ratio)
28		20	 **56a + 56b** + **57a + 57b** **a.** R^1 = Me, R^2 = Et **b.** R^1 = Et, R^2 = Me + **58a + 58b**	45 (46 : 41 : 3.6 : 2.6 : 3.6 : 3.2)
29		5	 **58a.** R^1 = Me, R^2 = Et **58b.** R^1 = Et, R^2 = Me	68 (1.4 : 1)
30		5	 **59**	74
31		3	 **60** + **61**	77 (1.4 : 1)

[a] Reaction conditions: triflate **4b** or **4c** (1 equiv), olefin, $^{i}Pr_2NEt$ (1 equiv), CH_2Cl_2, 15 min. [b] Ethylene passed into EtOAc solution of **4b**. [c] The benzamide derivative was used to simplify the NMR spectrum of the products. [d] Gas condensed into solution at −30 °C.

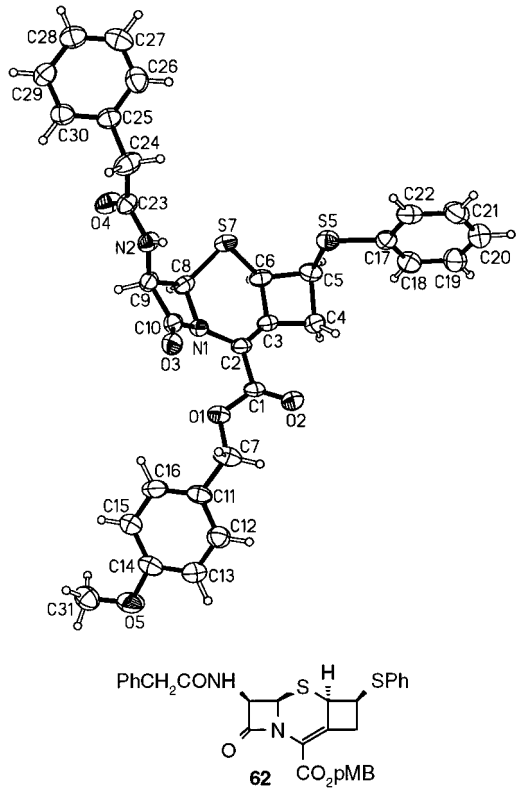


Figure 2. ORTEP view of **62** (the 5β-SPh product from **4b** and phenyl vinyl sulfide).

taken. In the presence of 1 equiv of $^{i}Pr_2NEt$ at room temperature, acetone and CH_2Cl_2 gave rapid reactions in 61 and 73% yields, respectively, whereas DMF and EtOH gave poorer yields (16 and 30%). Interestingly, however, EtOAc and THF gave much slower reactions, requiring *ca.* 1 h for complete disappearance of triflate (TLC monitoring) in 56 and 71% yields, respectively. Although CH_2Cl_2 was routinely used as solvent the lifetime of the triflate in the presence of $^{i}Pr_2NEt$ was relatively short. The use of EtOAc as solvent was particularly advantageous for the reaction with ethylene, when the gas was bubbled through a dilute solution of the triflate (**4b**) in EtOAc during slow addition of $^{i}Pr_2NEt$. $^{i}Pr_2NEt$ was routinely used as the base of choice. Bases with pK_a values higher than that of $^{i}Pr_2NEt$ (e.g., DBU) or less hindered bases (e.g., NEt_3) gave lower yields, Table 2, while bases with lower pK_a values (e.g., 2,6-lutidine) gave longer reaction times and also lower yields. Bases with even lower pK_a values failed to react, allowing recovery of the triflate. The use of K_2CO_3 gave superior yields to those of $^{i}Pr_2NEt$, but the reactions were much slower. The isomer ratio of the products did not alter significantly on changing the solvent or the base.

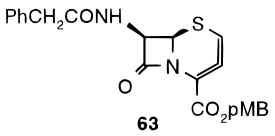
Table 2. Effect of Bases on the Reaction of Triflate 4b with 2,3-Dihydrofuran[a]

base	time, h	yield,[b] %
$^{i}Pr_2NEt$	0.25	73
DBU	3	31
NEt_3	0.5	36
2,6-lutidine	24	58[c]
K_2CO_3[d]	18	92[c]

[a] Reaction carried out at room temperature, ratio **4b**:2,3-dihydrofuran:$^{i}Pr_2NEt$ = 1:5:1. [b] Isolated yield after workup and chromatography. [c] Very little product observed by TLC after 0.5 h. [d] 2 equiv of K_2CO_3 used.

The existence of 6-membered cyclic allenes as intermediates which undergo cycloaddition reactions is well documented.[15] It is therefore proposed that the cephalosporin triflate eliminates triflic acid on treatment with base to form the allene (**63**). This allene is then trapped by olefins in a cycloaddition reaction. The polarized nature of the allene in **63**, having electron-donating sulfur and the electron-withdrawing ester substituents,

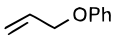
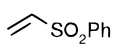
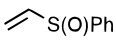
(15) Harnos, S.; Tivakornpannarai, S.; Waali, E. E. *Tetrahedron Lett.* **1986**, *27*, 3701. Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939. Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473. Angus, R. O., Jr.; Schmidt, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 532. Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997. Sütbeyaz, Y.; Ceylan, M.; Seçen, H. *J. Chem. Res., Synop.* **1993**, 293. Jamart-Grégoire, B.; Mercier-Girardot, S.; Ianelli, S.; Nardelli, M.; Caubère, P. *Tetrahedron* **1995**, *51*, 1973.



63

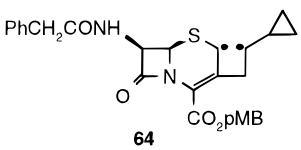
presumably allows it to react with an electronically diverse range of olefins. It is significant that there was found to be a number of monosubstituted olefins that did not successfully form cycloadducts. Examination of the ^{13}C resonances of the terminal carbon of the olefins revealed that the reactivity of the olefins fell into three catagories: (a) $\delta_C < 120$ ppm or (b) $\delta_C > 130$ ppm where successful reactions were achieved and the intermediate region (c) δ_C 120−130 ppm where no or very poor yields of cycloadducts were observed (Table 3).

Table 3. Olefins That Do Not Form Cycloadducts and Their $\delta(^{13}C)$ (=CH_2)

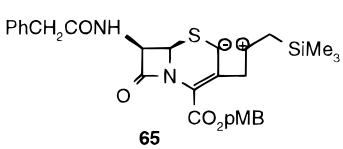
	121		128
	122		129
	125		129

Vinylpyridines also failed to give any cycloadducts despite falling in the predicted active region. However in these cases it is assumed that the pyridine nitrogen is preferentially reacting with the allene leading to decomposition. When a competition reaction was performed with a mixture of styrene and 4-vinylpyridine, this also resulted in decomposition and no styrene cycloadducts were observed.

Close inspection of the olefins used and their product distributions (see Table 1) has enabled us to speculate on the mechanism of this reaction leading to the proposal that the reaction is essentially a concerted process. For example, vinylcyclopropane (entry 3) gave a mixture of isomers **21** and **22** whereas vinylcyclohexane (entry 30) only gave one isomer (**59**). This result depicts the π-character of the cyclopropane ring, thus giving both isomers as observed when extended π-systems are present. However this result effectively rules out a stepwise biradical cycloaddition reaction (*via* intermediate **64**) as the cyclopropylcarbinyl radical has a very short lifetime and would result in cyclopropane ring opening rather than bond rotation followed by cyclobutane ring closure.[16] Olefins with electron-donating or electron-withdrawing substituents such as ethyl vinyl ether (entry 12) and methyl acrylate (entry 17) both give rise to products showing the same regiochemistry. Allyltrimethylsilane (entry 23) forms a single isomeric product (**50**). These results suggest that diionic intermediates are not involved as different regiochemistries might be expected for the electron-donating and -withdrawing olefins, and with allyltrimethylsilane the silyl group would stabilize a β-carbocation (**65**), allowing time for bond rotation to occur before ring closure.



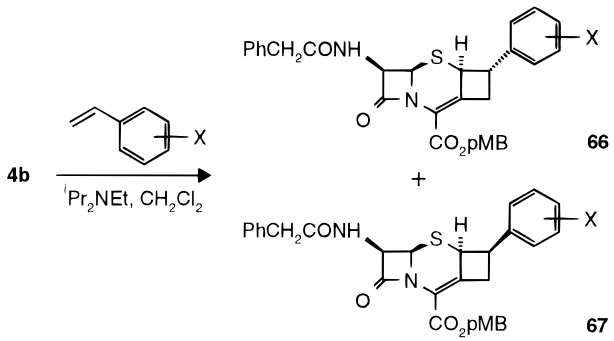
64



65

(16) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

Scheme 6



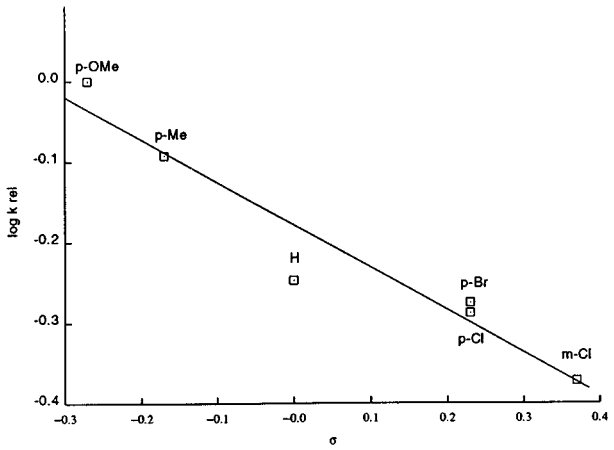


Figure 3. Plot of log k_{rel} *vs* σ.

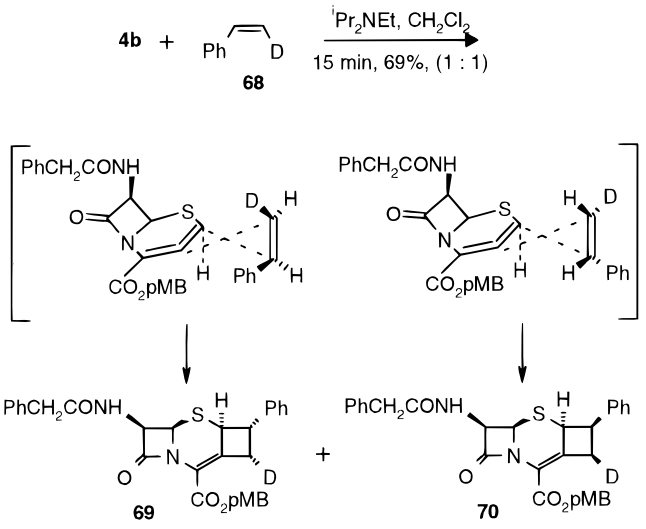
A Hammett study was conducted for the reaction of triflate **4b** with substituted styrenes in the presence of $^{i}Pr_2NEt$ (Scheme 6). A plot of relative rates (log k_{rel}) *vs* Hammett's σ-constants[17] gave a straight line with a reaction constant (ρ) of −0.54 (Figure 3). This result suggests that if the cycloaddition is the rate determining step then there is little charge separation in the transition state.

The most significant mechanistic result was that obtained with *cis*-β-deuteriostyrene (**68**). Only two products (**69** and **70**) were obtained in which the deuterium was *cis* to the phenyl group in both isomers as shown by ^1H, ^2H, and ^{13}C NMR spectroscopy. This indicates that bond rotation does not occur in the reaction and that the styrene is oriented in either of two directions as it approaches the cephalosporin allene to account for the two isomeric products (Scheme 7). This result contrasts that obtained by Waali who showed that the reaction of 1,2-cyclohexadiene (**72**) with *cis*-β-deuteriostyrene (**68**) is a stepwise diradical process in which bond rotation occurs in the diradical intermediate as all four possible isomers (**73**) are obtained[15] (Scheme 8). The Hammett ρ value for the reaction of **72** with styrenes is +0.79.[15]

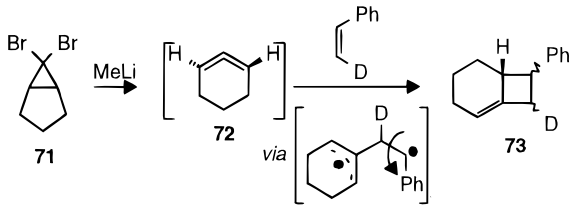
1,2-Dienes (e.g., 1,1-dimethylallene, Table 1, entry 27) also undergo [2 + 2] reactions to form cyclobutanes. However, this provided the only example observed so far in which a cycloadduct was formed with the substituent at the 4-position rather than the 5-position. The β-orientation of H-6 in **55** was shown by an NOE to the amide proton, while the UV spectrum (λ_{max} 304 nm) and the strong NOEs between H-6 and the H-5 protons rather than the methyl groups confirmed the regiochemistry. As allenes generally react at the central carbon, the

(17) Hansch, C.; Leo A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

Scheme 7



Scheme 8



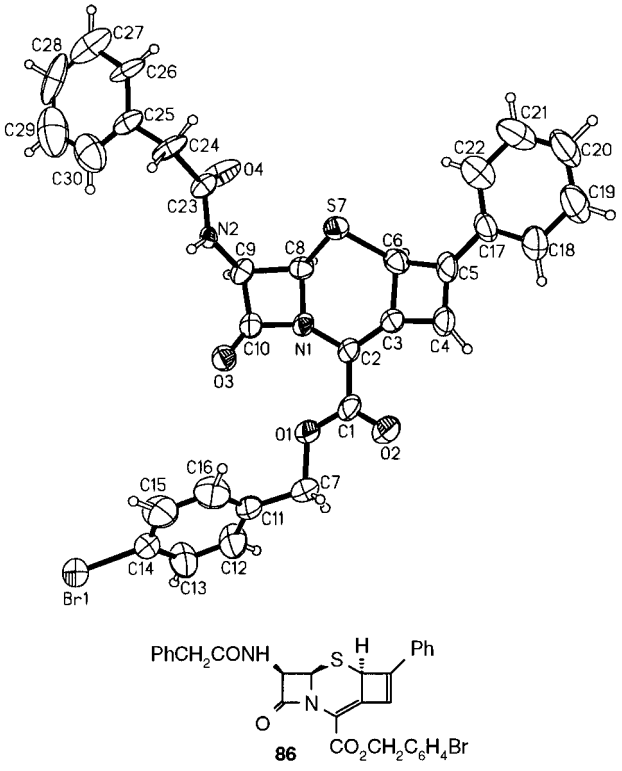
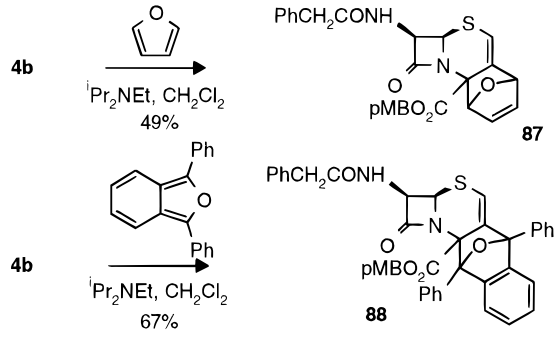


Figure 4. ORTEP view of **86** (the 6α-H product from **4b** and phenylacetylene as the *p*-bromobenzyl ester).

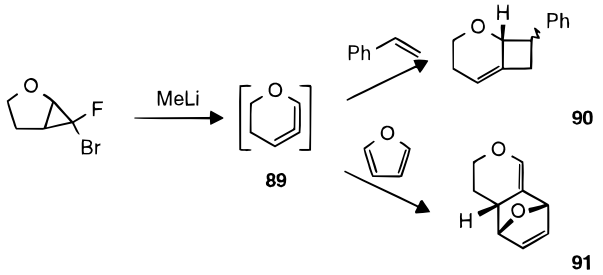
orientation of the ring formation probably supports a concerted process occurring at the least sterically congested double bond, since a radical or diion intermediate would be expected to be stabilized by the dimethyl group.

The reaction of the triflate **4b** with acetylenes has also been investigated and shown to result in the formation of fused cyclobutenes (Table 4). As with olefins, the monosubstituted acetylenes gave products with the substituent at the C-5 position. Generally a single stereoisomer is formed; however, in some cases, especially when extended π-systems are present, isomeric mixtures at C-6 are obtained (entries 1, 3, and 8). The structure and stereochemistry of the products was again determined by extensive NMR studies. Characteristically strong NOEs were observed between H-6 and H-8 when the former was on the α-face. Where two isomers were formed the β-orientation of H-6 was shown by the presence of an NOE between H-6 and the amide N-H. The structures were once again confirmed by single-crystal X-ray diffraction analysis of the *p*-bromobenzyl ester **86** (Figure 4). As seen previously with ethylene, a successful reaction with acetylene was achieved by bubbling the gas into a dilute solution of the triflate in EtOAc during the slow addition of $^{i}Pr_2NEt$.

Scheme 9



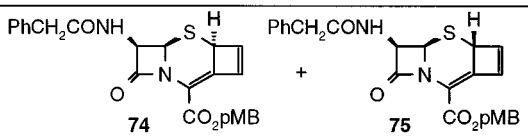
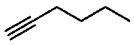
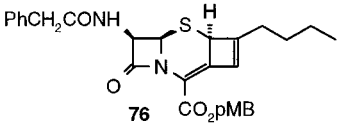
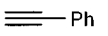
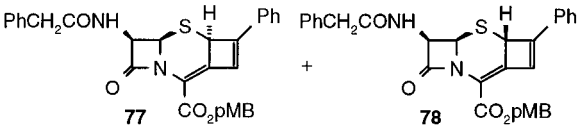
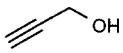
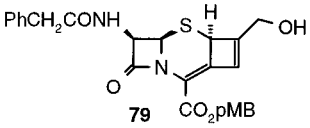
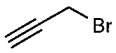
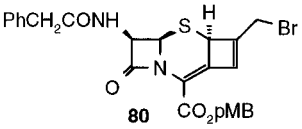
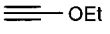
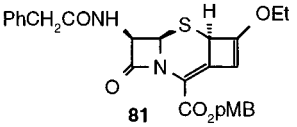
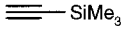
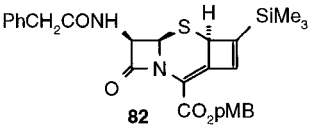
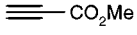
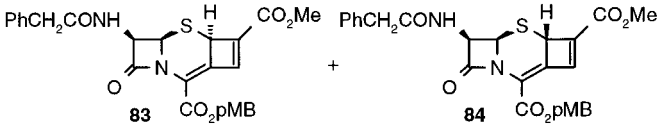
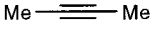
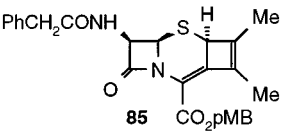
Scheme 10



To further extend our investigations of the reaction of the triflates **4** with unsaturated systems, we next turned our attention to 1,3-dienes. With 1,3-butadiene an unidentifiable mixture of products was obtained, but with furan a product of [4 + 2] addition was formed (Scheme 9). Extensive NMR studies assigned the structure as **87**, the product of addition to the C-3−C-4 bond of the cephalosporin. Unfortunately the stereochemistry of the three new chiral centers could not be unambiguously assigned by NMR and we were unable to grow crystals suitable for X-ray studies. 1,3-Diphenylisobenzofuran underwent a similar reaction to give **88**. Cyclopentadiene and 1,3-cyclohexadiene gave complex mixtures of products whose NMR spectra were consistent with the existence of both [2 + 2] and [4 + 2] cycloadducts; these products were not characterized further.

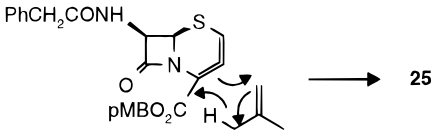
Christl has also observed changes in regioselectivity between [2 + 2] and [4 + 2] cycloadditions with 1-oxa-2,3-cyclohexadiene (**89**).[15] While [2 + 2] cycloaddition utilizes the 2,3-double bond to form the cyclobutane **90**, the [4 + 2] cycloaddition takes place at the less electron rich 3,4-double bond to give **91** (Scheme 10). An analogous change in regioselectivity is apparent with the cephalosporin allene **63**. These results enabled us to propose that the minor products seen in the reaction with 1,1-disubstituted olefins (Table 1, entries 5 and 6) are

Table 4. Reaction of Triflate 4b with Acetylenes[a]

entry	olefin	equiv	products	yield % (ratio)
1	CH≡CH	*b*	 **74** + **75**	42 (1 : 4.2)
2		87	 **76**	50
3		30	 **77** + **78**	95 (1 : 2.3)
4		50	 **79**	34
5		50	 **80**	16
6		10	 **81**	36
7		50	 **82**	69
8		10	 **83** + **84**	35 (2.5 : 1)
9		150	 **85**	57

[a,b] Reaction conditions as in Table 1.

Scheme 11

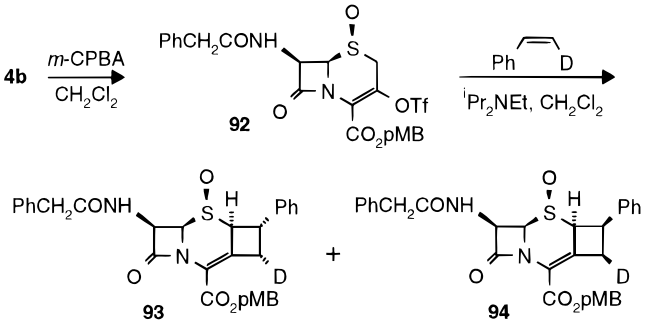


the result of a 6-electron electrocyclic ene reaction on the 3,4-double bond of the allene (Scheme 11).

Having examined the generality of the unsaturated component in this reaction, we then investigated modifications at the cephalosporin nucleus. Peracid oxidation of the triflate **4b** gave rise to the 1β-sulfoxide **92**.

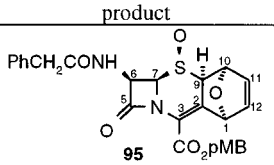
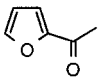
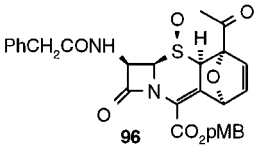
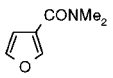
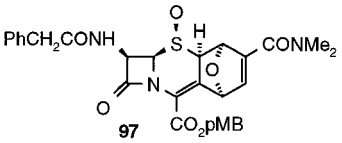
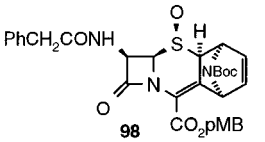
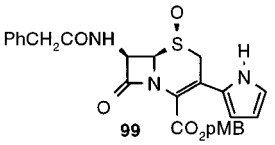
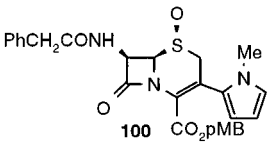
As with the sulfide triflate **4b**, the sulfoxide triflate **92** underwent cyclobutane formation with *cis*-β-deuteriostyrene (**68**) with retention of relative stereochemistry affording the isomeric cyclobutanes **93** and **94** (Scheme 12). However, with furan, although a [4 + 2] addition product was again formed, the addition was now across the 2,3-position of the cephalosporin nucleus to form **95**.

Scheme 12



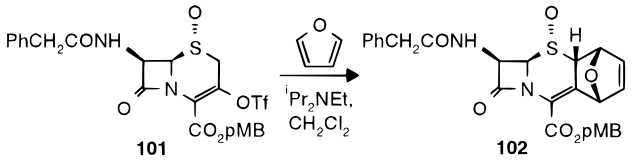
Once again extensive NMR studies were required to elucidate the structure of **95**. A large NOE between the C-7 and C-9 protons defined the C-9 stereochemistry, and the orientation of the oxygen bridge was deduced from the 4 Hz coupling observed between H-9 and H-10. Molecular modeling studies predicted a dihe-

Table 5. Reaction of Triflate 92 with Furans and Pyrroles[a]

entry	diene	product	yield %
1		 **95**	66
2		 **96**	10
3		 **97**	52
4		 **98**	29
5		 **99**	69
6		 **100**	79

[a] Reaction conditions as in Table 1 (5 equiv diene used).

Scheme 13

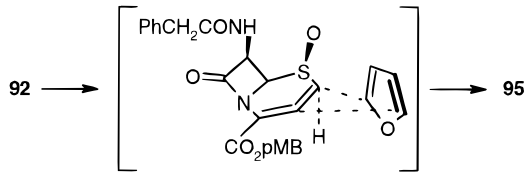


dral angle of 46° between H-9 and H-10 for an α-oxygen bridge and 91° for a *β*-oxygen bridge. This implies, from the Karplus equation, that the coupling constant should be approximately 4 Hz for an α-bridge and 0 Hz for a *β*-bridge. A limited number of substituted furans also underwent cycloaddition with **92** (Table 5). The cycloadduct **98** was formed in 29% yield with *N*-Boc-pyrrole in contrast to pyrrole or *N*-methylpyrrole which formed products of direct displacement of the triflate.

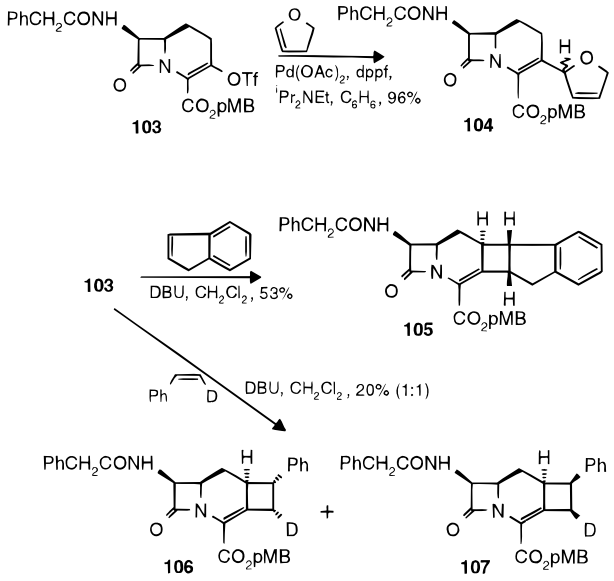
The cephalosporin α-sulfoxide triflate **101** could be prepared by *N*,*N*-dichlorourethane-mediated oxidation of **4b**.[18] Triflate **101** also underwent reaction with furan to yield the adduct **102** in 62% yield (Scheme 13). In this case the newly formed chiral centers have the opposite stereochemistry to that seen in **95**.

We propose that the [4 + 2] cycloaddition occurs to the more electron deficient double bond of the cephalosporin

Scheme 14



Scheme 15



allene (**63**). In the case of the sulfide this is the 3,4 double bond, whereas in the sulfoxides the 2,3 double bond is more electron deficient. Furthermore we propose that the stereochemistry of the addition products is due to the approach of the furan such that its oxygen atom is on the opposite face of the allene to the sulfoxide oxygen, thus reducing the electrostatic repulsion (Scheme 14).

The carbacephalosporin triflate **103**[19] was particularly remarkable in its reaction with olefins (Scheme 15). Under palladium-catalyzed, Heck type conditions, **103** reacted with 2,3-dihydrofuran in the presence of $^{i}Pr_2NEt$ to give two diastereomers (**104**) as the result of a conventional Heck reaction. However, in the presence of the stronger base (DBU) and in the absence of a palladium catalyst, **103** reacted with indene to give the [2 + 2] cycloadduct **105**. The products **106** and **107** were obtained from the reaction of *cis*-*β*-deuteriostyrene (**68**) and once again retained the relative stereochemistry of the deuterium and the phenyl group, suggesting a concerted cycloaddition onto a cyclic allene intermediate. We believe that the requirement for a stronger base reflects the relative acidities of the H-2 protons of the carbacephem compared to that of the cephem nucleus.[20]

Recently two other groups have postulated the intermediacy of cephalosporin allenes to account for observed products. Cainelli[21] described the formation of 3-chlorocephems from the 3-mesyloxy derivative in the presence of a base. In this case the corresponding sulfoxide did not undergo the reaction. Torii[22] also proposed that the

(18) Ochiai, M.; Aki O.; Morimoto, A.; Okada, T. *Tetrahedron Lett.* **1972**, 3241.

(19) Crowell, T. A.; Halliday, B. D.; McDonald J. H., III; Indelicato, J. M.; Pasini, C. E.; Wu, E. C. Y. *J. Med. Chem.* **1989**, *32*, 2436. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787. Bodurow, C.; Carr, M. A. *Tetrahedron Lett.* **1989**, *30*, 4081.

(20) The rate difference between the chlorination of 3-hydroxycarbacephems and 3-hydroxycephems has been attributed to sulfur neighboring group participation. Burks, J. E., Jr.; Chelius, E. C.; Johnson, R. A. *J. Org. Chem.* **1994**, *59*, 5724.

(21) Cainelli, G.; Contento, M.; Panunzio, M.; Sandri, S.; Umani-Ronchi, A.; Col, M. D. *Synlett* **1994**, 243.

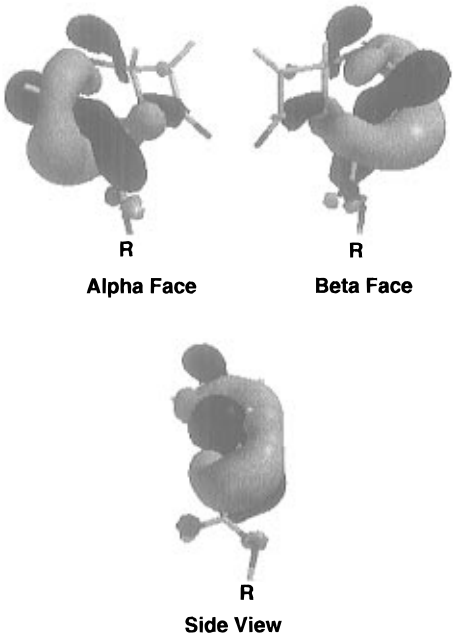


Figure 5. LUMO of the cephalosporin derived allene using PM3 (hydrogen atoms at C-7, R = pMB). The positive lobe is shown in dark grey and the negative lobe in light grey. The molecular orbital surface is contoured at a value of 0.032 e/au.

copper(I) chloride mediated alkenylation of cephem triflates with alkenyltributylstannes proceeds by the reaction of a vinylcopper species with an allene to give 3-alkenyl-Δ^2-cephems.

As previously stated 6-membered cyclic allenes have been generated by a number of routes and trapped through [2 + 2] and [4 + 2] cycloadducts. For 1,2-cyclohexadiene the twisted allene structure (**72**) appears to have the lowest energy. The [2 + 2] cycloadditions onto 1,2-cyclohexadiene can all be rationalized by a stepwise diradical mechanism.[15] However, we have obtained products that would not be consistent with the intermediacy of radicals or charged species. Our experimental evidence suggests that the [2 + 2] cycloadducts are obtained by a concerted $_\pi2_s + _\pi2_a$ mechanism[23] in which the olefin approaches the cephalosporin allene in an antarafacial manner.

In order to assess the relative stability of an allene intermediate and attempt to rationalize the observed chemoselectivity of selected reagents, we performed a number of MO calculations.[24] Model systems of putative allenic, allynic, and dipolar intermediates were generated and optimized using semiempirical MO methods. The calculated geometries were consistent with an allene type intermediate, with the cephem 2,3 and 3,4 bonds being similar in length (1.311 and 1.326 Å). Of note was the observation that the hydrogen at C-2 was oriented toward the α-face, suggesting that olefin attack was more likely from the *β*-face. Our results suggest that the reaction occurs between the LUMO of the cephalosporin allene **63** (Figure 5) and the HOMO of the unsaturated component. The HOMO of a simple dienophile, such as styrene, is concentrated on the two carbons of the reactive double bond. It could only react in a concerted manner with the allene through a suprafacial−antarafacial type mechanism. This would involve an antarafacial approach by the olefin (Figure 6). The observed regioselectivity of the cycloaddition is as explained with the larger orbital in the HOMO interacting with the large LUMO orbital on C-3 of the allene. The requirement for suprafacial−antarafacial overlap between the reagent and the allene also produces steric control at position 4 of the cyclobutane product. Any substituent which was attached to the reactive double-bond carbon with the greater HOMO density will be attached to C-4 of the product and on the α-face of the molecule.

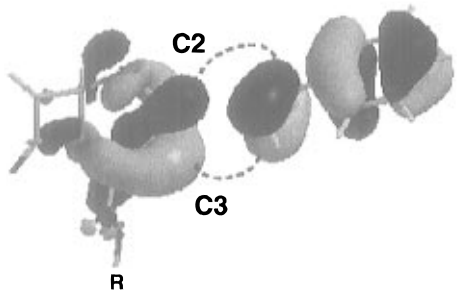


Figure 6. Schematic illustration of proposed approach of the cephalsporin allene and styrene. Molecular orbitals shown as calculated for the separate molecules.

Conclusion

The formation of fused polycyclic cephalosporins from the reaction of cephalosporin triflates with unsaturated compounds and a base is a remarkable process. In this paper we have described the results of our studies to determine the scope and mechanism of this reaction. These studies have suggested that the reaction proceeds via the intermediacy of a 6-membered cyclic allene which undergoes concerted $_\pi2_s + _\pi2_a$ cycladditions with olefins and acetylenes and $_\pi4_s + _\pi2_s$ cycloadditions with cyclic 1,3-dienes. These extremely rapid reactions, which occur under very mild conditions on readily available cephalosporin triflates, have produced numerous novel polycyclic cephalosporins bearing a wide range of functionality. The potential utility of this reaction is enormous. Indeed, a recent report has described the reaction of the cephalosporin triflate with silyl enol ethers and silylketene acetals. Subsequent fragmentation of the cyclobutane ring resulted in the formation of a variety of C3-substituted cephalosporins.[25] Additional studies from our laboratories have dealt with the introduction of more biologically relevant amino substituents at the cephalosporin C7 position. The results of these studies will be reported at a later date.

Experimental Section

General Methods. The ^{1}H and ^{13}C NMR spectra were referenced to TMS and the ^{2}H spectra referenced to $CDCl_3$ (7.28 ppm). Analytical TLC was performed on 0.25 mm silica gel 60F plates. Purification of the products was carried out using silica gel 60 (230−400 mesh) and the appropriate solvent system. Cephalosporin triflates **4a**−**c** were prepared by the methodology described in ref 7. The carbacephem triflate was prepared as described in ref 19.

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Preparation of the Cycloadducts. General Procedure. To a solution of triflate (**4a**−**c**) (1 equiv) and alkene or alkyne (see Tables 1, 4, and 5) in CH_2Cl_2 (30 mL per mmol) was added $^iPr_2NEt$ (1 equiv). After being stirred for 15 min, the mixture was chromatographed to afford the cycloadducts.

***p*-Methoxybenzyl (4*R*,8*R*,9*R*,10*S*,11*R*,12*R*)-13-Oxo-12-(phenylacetamido)-7-oxa-10-thia-1-azatetracyclo-[9.2.0.0^{3,9}.0^{4,8}]tridec-2-ene-2-carboxylate 10-Oxide (17) and *p*-Methoxybenzyl (4*S*,8*S*,9*R*,10*S*,11*R*,12*R*)-13-Oxo-12-(phenylacetamido)-7-oxa-10-thia-1-azatetracyclo[9.2.0.0.^{3,9}.0^{4,8}]-tridec-2-ene-2-carboxylate 10-Oxide (18).** A mixture of **15** and **16** was prepared from **4b** and 2,3-dihydrofuran by the general procedure in 73% yield (1.8:1): TLC R_f 0.30 (15% EtOAc in CH_2Cl_2). To a solution of the mixture of **15** and **16** (0.626 g, 1.236 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of *m*-CPBA (1.236 mmol) in CH_2Cl_2 (5 mL) dropwise over 5 min. The reaction mixture was washed with dilute $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$) and evaporated to give the sulfoxides which were separated by chromatography (50% EtOAc in CH_2Cl_2). **(4*R*,8*R*) isomer (17)** (0.245 g, 39%): TLC R_f 0.39 (50% EtOAc in CH_2Cl_2); mp 215 °C dec (EtOAc/CH_2Cl_2); IR (CH_2Cl_2) 1801, 1728, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 2H), 3.61 and 3.65 (ABq, J = 15.5 Hz, 2H), 3.69 (dt, J = 1.9, 3.2 Hz, 1H), 3.80 (s, 3H), 3.96 (dt, J = 6.7, 9.6 Hz, 1H), 4.11 (m, 1H), 4.25 (ddd, J = 9.6, 7.7, 3.1 Hz, 1H), 4.31 (dd, J = 4.9, 1.9 Hz, 1H), 4.99 (dd, J = 5.9, 3.2 Hz, 1H), 5.16 and 5.29 (ABq, J = 11.9 Hz, 2H), 5.92 (dd, J = 9.7, 4.9 Hz, 1H), 6.60 (d, J = 9.7 Hz 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.27−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 29.7, 43.5, 51.8, 55.3, 58.1, 61.5, 67.6, 69.2, 69.8, 74.9, 114.1 (2C), 124.0, 125.1, 127.1, 127.7, 129.2 (2C), 129.4 (2C), 130.5 (2C), 133.7, 159.7, 160.0, 163.7, 171.4. Anal. Calcd for $C_{27}H_{26}N_2O_7S$: C, 62.06; H, 5.02; N, 5.36; S, 6.14. Found: C, 62.00; H, 5.00; N, 5.40; S, 6.28. **(4*S*,8*S*) isomer (18)** (0.165 g, 26%): TLC R_f 0.32 (50% EtOAc in CH_2Cl_2); IR (CH_2Cl_2) 1800, 1729, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 1H), 2.61 (dd, J = 12.8, 5.0 Hz, 1H), 3.57 and 3.61 (ABq, J = 15.1 Hz, 2H), 3.66 (dd, J = 6.5, 1.9 Hz, 1H), 3.80 (s, 3H), 4.02 (m, 1H), 4.09 (m, 1H), 4.13 (m, 1H), 4.38 (dd, J = 4.8, 1.9 Hz, 1H), 5.15 (t, J = 6.3 Hz, 1H), 5.23 (s, 2H), 5.89 (dd, J = 9.8, 4.8 Hz, 1H), 6.78 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.27−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 32.4, 43.4, 52.5, 55.4, 58.5, 60.0, 67.7, 70.7, 70.9, 79.5, 114.1 (2C), 123.3, 127.0, 127.5, 129.0 (2C), 129.3 (2C), 130.6 (2C), 133.7, 134.0, 159.3, 160.0, 164.1, 171.4; mass spectrum *m*/*z* 522.1472, calcd for $C_{27}H_{26}N_2O_7S$ 522.1461.

***p*-Methoxybenzyl (4*R*,8*R*,9*R*,11*R*,12*R*)-13-Oxo-12-(phenylacetamido)-7-oxa-10-thia-1-azatetracyclo[9.2.0.0^{3,9}.0^{4,8}]-tridec-2-ene-2-carboxylate (15).** To a solution of sulfoxide **17** (0.22 g, 0.421 mmol) in DMF (6 mL) at −30 °C was added PCl_3 (74 μL, 0.85 mmol). The mixture was stirred at −30 °C for 30 min and then added to a mixture of ice, water, and ethyl acetate. The organic phase was washed with $NaHCO_3$, H_2O, and brine, and then dried ($MgSO_4$) and evaporated. The residue was chromatographed to give **15** (0.108 g, 50%): IR (CH_2Cl_2) 1788, 1723, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 1H), 2.08 (m, 1H), 3.59 and 3.64 (ABq, J = 16.0 Hz, 2H), 3.79 (s, 3H), 3.99 (m, 1H), 4.12 (t, J = 3.1 Hz, 1H), 4.15 (m, 1H), 4.18 (m, 1H), 4.56 (dd, J = 5.8, 3.1 Hz, 1H), 4.90 (d, J = 5.0 Hz, 1H), 5.12 and 5.25 (ABq, J = 11.9 Hz, 2H), 5.75 (dd, J = 8.8, 5.0 Hz, 1H), 6.15 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.26−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 29.8, 43.3, 45.6, 50.4, 55.3, 58.1, 61.2, 67.3, 69.1, 79.1, 114.0 (2C), 122.7, 127.3, 127.8, 129.2 (2C), 129.5 (2C), 130.5 (2C), 133.8, 133.9, 159.9, 160.7, 164.3, 171.3; mass spectrum *m*/*z* 506.1513, calcd for $C_{27}H_{26}N_2O_6S$ 506.1512.

***p*-Methoxybenzyl (4*S*,8*S*,9*R*,11*R*,12*R*)-13-oxo-12-(phenylacetamido)-7-oxa-10-thia-1-azatetracyclo[9.2.0.0^{3,9}.0^{4,8}]-tridec-2-ene-2-carboxylate (16)** (prepared from **18** by the above procedure (48% yield)): IR (CH_2Cl_2) 1787, 1723, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1H), 2.46 (dd, J = 12.7, 4.6 Hz, 1H), 3.58 and 3.63 (ABq, J = 15.9 Hz, 2H), 3.76 (m, 1H), 3.80 (s, 3H), 4.08 (m, 1H), 4.11 (m, 1H), 4.17 (d, 1H, J = 6.5 Hz), 4.92 (dd, J = 6.5, 5.2 Hz, 1H), 4.98 (d, J = 5.0 Hz, 1H), 5.15 and 5.18 (ABq, J = 11.9 Hz, 2H), 5.77 (dd, J = 8.9, 5.0 Hz, 1H), 6.19 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.27−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 31.3, 43.2, 45.1, 51.3, 55.3, 58.4, 61.1, 67.4, 70.8, 77.1, 114.0 (2C), 122.5, 127.1, 127.7, 129.1 (2C), 129.5 (2C), 130.6 (2C), 133.8, 140.7, 159.9, 160.1, 164.4, 171.3; mass spectrum *m*/*z* 506.1503, calcd for $C_{27}H_{26}N_2O_6S$ 506.1512.

Preparation of 19. Ethylene was passed through a sintered glass bubbler into a solution of triflate **4b** (0.50 g, 0.852 mmol) in EtOAc (500 mL) at room temperature while a solution of $^iPr_2NEt$ (0.15 mL, 0.852 mmol) in EtOAc (100 mL) was added dropwise over 1.5 h. The mixture was stirred under an ethylene atmosphere for a further 16 h and then concentrated. The residue was chromatographed to give *p*-methoxybenzyl (6*S*,8*R*,9*R*)-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (**19**) (0.24 g, 60%): IR (CH_2Cl_2) 1786, 1723, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (dddd, J = 10.4, 9.4, 8.8, 8.2 Hz, 1H), 2.46 (dtd, J = 10.4, 9.3, 3.2 Hz, 1H), 3.16 (dtd, J = 15.8, 9.4, 1.6 Hz, 1H), 3.28 (ddt, J = 15.8, 8.8, 3.0 Hz, 1H), 3.60 and 3.67 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.32 (dddd, J = 9.3, 8.2, 2.8, 1.5 Hz, 1H), 4.94 (d, J = 5.0 Hz, 1H), 5.15 and 5.20 (ABq, J = 11.9 Hz, 2H), 5.76 (dd, J = 8.8, 5.0 Hz, 1H), 5.97 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.24−7.37 (m, 7H); mass spectrum *m*/*z* 464.1411, calcd for $C_{25}H_{24}N_2O_5S$ 464.1406.

Spectral Data for the Cycloadducts Prepared. The General Procedure was followed unless indicated otherwise.

***p*-Methoxybenzyl (5*S*,6*S*,8*R*,9*R*)-5-butyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (20)** (from **4b** and 1-hexene): mp 160−161 °C; IR (CH_2Cl_2) 1785, 1722, 1686 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 270 (11 200), 226 (17 900) nm; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.18−1.50 (m, 6H), 2.66 (dquintet, J = 3.1, 8.4 Hz, 1H), 2.84 (dt, J = 16.2, 3.1 Hz, 1H), 3.22 (dd, J = 16.3, 9.2 Hz, 1H), 3.60 and 3.67 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.40 (dd, J = 9.3, 1.8 Hz, 1H), 4.92 (d, J = 4.9 Hz, 1H), 5.12 and 5.22 (ABq, J = 11.9 Hz, 2H), 5.76 (dd, J = 9.1, 4.9 Hz, 1H), 5.97 (d, J = 9.1 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.26−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 30.0, 30.6, 35.2, 36.4, 43.3, 44.0, 55.2, 58.2, 59.8, 66.9, 113.9 (2C), 120.9, 127.4, 127.6, 129.1 (2C), 129.5 (2C), 130.2 (2C), 133.7, 139.8, 159.7, 160.9, 164.0, 170.9. Anal. Calcd for $C_{29}H_{32}N_2O_5S$: C, 66.90; H, 6.20; N, 5.38; S, 6.16. Found: C, 67.12; H, 5.78; N, 5.49; S, 5.74.

***p*-Methoxybenzyl (5*S*,6*S*,8*R*,9*R*)-5-Cyclopropyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (21) and *p*-Methoxybenzyl (5*R*,6*S*,-8*R*,9*R*)-5-Cyclopropyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (22)** (from **4b** and vinylcyclopropane[26]). The (5*S*) isomer **21** was eluted first: IR (KBr) 1783, 1720, 1660, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.13−0.22 (m, 2H), 0.48−0.59 (m, 2H), 0.92−1.02 (m, 1H), 1.99 (dq, J = 8.9, 7.8 Hz, 1H), 2.80 (ddd, J = 1.6, 9.0, 15.9 Hz, 1H), 3.35 (ddd, J = 2.7, 8.0, 15.6 Hz, 1H), 3.61 and 3.68 (ABq, J = 16.4 Hz, 2H), 3.80 (s, 3H), 3.93 (ddd, J = 1.4, 2.7, 8.0 Hz, 1H), 4.92 (d, J = 4.9 Hz, 1H), 5.15 and 5.18 (ABq, J = 12.0 Hz, 2H), 5.74 (dd, J = 4.9, 8.8 Hz, 1H), 5.94 (d, J = 8.9 Hz, 1H), 6.85−6.92 (m, 2H), 7.21−7.40 (m, 7H); mass spectrum *m*/*z* 505 (MH^+). **(5*R*) isomer 22:** IR (KBr) 1785, 1720, 1665, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00−0.20 (m, 2H), 0.40−0.56 (m, 2H), 0.88−1.00 (m, 1H), 2.01 (dq, J = 3.2, 9.3 Hz, 1H), 3.02 (dt, J = 2.9, 16.2 Hz, 1H), 3.25 (ddd, J = 1.2, 8.9, 16.4 Hz, 1H), 3.61 and 3.67 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.38 (ddd, J = 1.2, 2.9, 9.2 Hz, 1H), 4.94 (d, J = 4.9 Hz, 1H), 5.13 and 5.24 (ABq, J = 12.0 Hz, 2H), 5.77 (dd, J = 4.9, 9.0 Hz, 1H), 6.06 (d, J = 9.0 Hz, 1H), 6.85−6.92 (m, 2H), 7.21−7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 3.9, 4.1, 12.5, 36.6, 40.7, 43.4, 45.2, 55.3, 58.3, 60.0, 67.0, 114.0 (2C), 120.8, 127.5, 127.7, 129.2 (2C), 129.5 (2C), 130.3 (2C), 133.8, 139.4, 159.8, 161.0, 164.2, 171.2. Anal. Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.65; H, 5.59; N, 5.55. Found: C, 66.43; H, 5.62; N, 5.41.

***p*-Methoxybenzyl (5*S*,6*S*,8*R*,9*R*)-9-Benzamido-10-oxo-5-phenyl-7-thia-1-azatricyclo[6.2.0.0.^{3,6}]dec-2-ene-2-carboxylate (23)** (from **4c** and styrene). The (5*S*) isomer **23** was eluted first: IR (CH_2Cl_2) 1787, 1724, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.33 (ddd, J = 5.0, 9.2, 1.4 Hz, 1H), 3.56 (q, J = 8.4 Hz, 1H), 3.80 (s + ddd, J = 15.0, 8.0, 2.5 Hz, 4H), 4.41 (ddd J

(26) Tsunoda, T.; Hudlicky, T. *Synlett* **1990**, 322.

= 7.9, 2.3, 1.4 Hz, 1H), 5.12 (d, J = 4.9 Hz, 1H), 5.24 (ABq, J = 11.9 Hz, 2H), 5.98 (dd, J = 8.4, 4.9 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.20−7.56 (m, 11H), 7.81 (d, J = 7.0 Hz, 2H). Anal. Calcd for $C_{30}H_{26}N_2O_5S$: C, 68.43; H, 4.98; N, 5.32; S, 6.09. Found: C, 68.42; H, 4.98; N, 5.46; S, 6.12. The later-eluting fractions contained the (5*R*) isomer **24** as a mixture comprising 27% **23**. **Data for 24:** IR (CH_2Cl_2) 1786, 1724, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.56 (dt, J = 16.8, 3.3 Hz, 1H), 3.65 (dd, J = 16.9, 9.2 Hz, 1H), 3.80 (s, 3H), 4.01 (td, J = 9.4, 4.0 Hz, 1H), 4.76 (ddd, J = 9.8, 2.5, 1.2 Hz, 1H), 5.08 (J = 5.0 Hz, 1H), 5.28 (ABq, J = 12.0 Hz, 2H), 5.96 (dd, J = 8.9, 5.0 Hz, 1H), 6.59 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.16−7.51 (m, 10H), 7.65 (d, J = 8.5 Hz, 2H); mass spectrum *m*/*z* 526.1583, calcd for $C_{30}H_{26}N_2O_5S$ 526.1562.

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-5,5-Dimethyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (26).** Isobutene (*ca*. 5 mL) was condensed into a solution of triflate **4b** (80 mg, 0.136 mmol) in CH_2Cl_2 (8 mL) at −30 °C. ^{i}Pr$_2$NEt (24 μL, 0.136 mmol) was added and the mixture allowed to warm to room temperature with stirring over 30 min. The mixture was concentrated then chromatographed. *p*-Methoxybenzyl (6*R*,7*R*)-3-(2-methyl-2-propenyl)-7-(phenylacetamido)ceph-2-em-4-carboxylate (**25**) was eluted first (9 mg, 13%): IR (CH_2Cl_2) 1780, 1741, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 2.69 and 2.87 (ABq, J = 15.3 Hz, 2H), 3.60 and 3.67 (ABq, J = 16.3 Hz, 2H), 3.82 (s, 3H),4.67 (s, 1H), 4.81 (s, 1H), 4.84 (s, 1H), 5.06 and 5.12 (ABq, J = 11.8 Hz, 2H), 5.23 (d, J = 4.0 Hz, 1H), 5.63 (dd, J = 9.1, 4.0 Hz, 1H), 5.94 (s, 1H), 6.15 (d, J = 9.1Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.23−7.37 (m, 7H); mass spectrum *m*/*z* 492 (M$^+$). **26** (50 mg, 75%); IR (CH_2Cl_2) 1786, 1723, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 3H), 1.33 (s, 3H), 2.85 (d, J = 15.7 Hz, 1H), 2.97 (dd, J = 15.6, 2.5 Hz, 1H), 3.59 and 3.68 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.02 (dd, J = 2.4, 1.2 Hz, 1H), 4.92 (d, J = 4.9 Hz, 1H), 5.10 and 5.23 (ABq, J = 12.0 Hz, 2H), 5.75 (dd, J = 8.9, 4.9 Hz, 1H), 6.04 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.19−7.36 (m, 7H); mass spectrum *m*/*z* 492.1715, calcd for $C_{27}H_{28}N_2O_5S$ 492.1719.

***p*-Methoxybenzyl (6*R*,7*R*)-3-(1-Cyclohexenylmethyl)-7-(phenylacetamido)ceph-2-em-4-carboxylate (27) and *p*-Methoxybenzyl (6*S*,8*R*,9*R*)-10-Oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-5-spirocyclohexane-2-carboxylate (28)** (from **4b** and methylenecyclohexane). **27** was eluted first (21%): IR (CH_2Cl_2) 1778, 1740, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53−1.96 (m, 8H), 2.63 and 2.77 (ABq, J = 15.1 Hz, 2H), 3.60 and 3.67 (ABq, J = 16.2 Hz, 2H), 3.82 (s, 3H), 4.79 (s, 1H), 5.07 and 5.12 (ABq, J = 11.8Hz, 2H), 5.21 (d, J = 4.0 Hz, 1H), 5.39 (br s, 1H), 5.63 (dd, J = 9.1, 4.0 Hz, 1H), 5.88 (s, 1H), 6.14 (d, J = 9.1 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.23−7.37 (m, 7H); mass spectrum *m*/*z* 532.2037, calcd for $C_{30}H_{32}N_2O_5S$ 532.2032. **28** (47%); IR (CH_2Cl_2) 1785, 1721, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42−1.65 (m, 10H), 2.74 (br d, J = 16.3 Hz, 1H), 3.00 (dd, J = 15.9, 2.8 Hz, 1H), 3.59 and 3.68 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 3.95 (dd, J = 2.7, 1.0 Hz, 1H), 4.90 (d, J = 4.9 Hz, 1H), 5.11 and 5.23 (ABq, J = 12.0 Hz, 2H), 5.74 (dd, J = 9.0, 4.9 Hz, 1H), 6.02 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.19−7.37 (m, 7H); mass spectrum *m*/*z* 532.2042, calcd for $C_{30}H_{32}N_2O_5S$ 532.2032.

***p*-Methoxybenzyl (4*S*,5*S*,6*S*,8*R*,9*R*)-4,5-dimethyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (29)** (from **4b** and *trans*-2-butene by the method described for the preparation of **26**): mp 172−173 °C; IR (CH_2Cl_2) 1786, 1721, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7.1 Hz, 3H), 1.25 (d, J = 7.3 Hz, 3H), 2.41 (ddq, J = 9.5, 7.1, 3.0 Hz, 1H), 3.04 (ddq, J = 7.3, 3.2, 3.0 Hz, 1H), 3.63 (ABq, J = 16.0 Hz, 2H), 3.79 (s, 3H), 4.47 (dd, J = 9.5, 3.2 Hz, 1H), 4.90 (d, J = 4.9 Hz, 1H), 5.08 (d, J = 11.9 Hz, 1H), 5.26 (d, J = 11.9 Hz, 1H), 5.76 (dd, J = 9.0, 4.9 Hz, 1H), 6.07 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.30 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 15.9, 17.9, 37.2, 43.1, 43.4, 47.0, 55.3, 58.3, 59.8, 67.0, 114.0 (2C), 121.7, 127.4, 127.7, 129.1 (2C), 129.5 (2C), 130.5 (2C), 133.8, 142.9, 159.8, 160.8, 164.2, 171.2. Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C, 65.84; H, 5.73; N, 5.68; S, 6.51. Found: C, 65.56; H, 5.49; N, 5.60; S, 6.22.

Preparation of Cycloadducts from *cis*-2-Butene (from **4b** and a mixture of *cis*-2-butene + 2.1% *trans*-2-butene by the method described for the preparation of **26**). An inseparable mixture of **29**, the (4*R*,5*S*) isomer **30**, and the (4*S*,5*R*) isomer **31** was obtained in 78% yield (ratio 34:8:58): ^{1}H NMR ($CDCl_3$) (signals due to **31**) δ 1.12 (d, J = 7.5 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 2.47 (sextet, J = 7.5 Hz, 1H), 3.97 (dd, J = 8.2, 3.0 Hz, 1H); signals due to **30**, δ 0.93 (d, J = 7.2 Hz), 2.67−2.83 (m), 4.25 (d, J = 9.2Hz).

***p*-Methoxybenzyl (4*R*,5*R*,6*S*,8*R*,9*R*)-4,5-diphenyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (32)** (from **4b** and *trans*-stilbene): mp 167−168 °C; IR (CH_2Cl_2) 1788, 1724, 1687 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 273 (12 400) nm; ^{1}H NMR ($CDCl_3$) δ 3.50 and 3.60 (ABq, J = 16.2 Hz, 2H), 3.76 (s, 3H), 3.89 (dd, J = 9.9, 4.2 Hz, 1H), 4.83−4.89 (m, 2H), 5.03 (d, J = 11.9 Hz and d, J = 4.9Hz, 2H), 5.19 (d, J = 11.8 Hz, 1H), 5.78−5.83 (m, 2H), 6.70 (d, J = 8.7 Hz, 2H), 6.98−7.37 (m, 17H). Anal. Calcd for $C_{37}H_{32}N_2O_5S$: C, 72.06; H, 5.23; N, 4.54; S, 5.20. Found: C, 71.98; H, 5.18; N, 4.55; S, 4.87.

***p*-Methoxybenzyl (4*R*,8*S*,9*S*,11*R*,12*R*)-13-Oxo-12-(phenylacetamido)-10-thia-1-azatetracyclo[9.2.0.0^{3,9}.0^{4,8}]tridec-2-ene-2-carboxylate (33) and *p*-Methoxybenzyl (4*S*,8*R*,9*S*,-11*R*,12*R*)-13-Oxo-12-(phenylacetamido)-10-thia-1-azatetracyclo[9.2.0.0^{3,9}.0^{4,8}]tridec-2-ene-2-carboxylate (34)** (from **4b** and cyclopentene). The earlier-eluting fractions contained predominantly the (4*R*,8*S*) isomer **33**: IR (CH_2Cl_2) 1785, 1719, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35−1.48 (m, 1H), 1.50−1.69 (m, 4H), 2.25−2.29 (m, 1H), 3.13 (dtd, J = 9.8, 6.8, 2.7 Hz, 1H), 3.60 and 3.66 (ABq, J = 16.0 Hz, 2H), 3.79 (s, 3H), 3.86 (t, J = 6.8Hz, 1H), 4.31 (d, J = 9.8 Hz, 1H), 4.98 (d, J = 4.9 Hz, 1H), 5.12 and 5.19 (ABq, J = 12.0 Hz, 2H), 5.74 (dd, J = 9.0, 4.9 Hz, 1H), 6.00 (d, J = 8.7Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.25−7.37 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.8, 28.7, 31.9, 39.6, 42.6, 43.4, 50.5, 55.3, 58.3, 60.9, 67.1, 114.0 (2C), 121.1, 127.4, 127.7, 129.1 (2C), 129.5 (2C), 130.5 (2C), 133.8, 144.8, 159.8, 160.3, 164.1, 171.1; mass spectrum *m*/*z* 504.1729, calcd for $C_{28}H_{28}N_2O_5S$ 504.1719. The later-eluting fractions contained predominantly the (4*S*,8*R*) isomer **34**: IR (CH_2Cl_2) 1785, 1720, 1687cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56−1.94 (m, 6H), 2.85 (q, J = 6.0 Hz, 1H), 3.59 and 3.06 (ABq, J = 16.1 Hz, 2H), 3.77 (dd, J = 5.0, 3.3 Hz, 1H), 3.79 (s, 3H), 3.86−3.91 (m, 1H), 4.88 (d, J = 5.0 Hz, 1H), 5.11 and 5.23 (ABq, J = 11.9 Hz, 2H), 5.74 (dd, J = 8.8, 5.0 Hz, 1H), 6.06 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.25−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 25.7, 30.7, 32.9, 43.4, 43.5, 43.7, 49.4, 55.3, 58.4, 61.4, 67.0, 114.0 (2C), 120.7, 127.5, 127.7, 129.2 (2C), 129.5 (2C), 130.5 (2C), 133.8, 140.7, 159.8, 160.9, 164.3, 171.2; mass spectrum *m*/*z* 504.1719, calcd for $C_{28}H_{28}N_2O_5S$ 504.1719.

***p*-Methoxybenzyl (4*S*,9*R*,10*S*,12*R*,13*R*)-14-oxo-13-(phenylacetamido)-11-thia-1-azatetracyclo[10.2.0.0^{3,10}.0^{4,9}]-tetradec-2-ene-2-carboxylate (35)** (from **4b** and cyclohexene): mp 234−236 °C; IR (CH_2Cl_2) 1784, 1718, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97−1.08 (m, 1H), 1.30−1.74 (m, 6H), 1.93−2.00 (m, 1H), 2.39 (br q, J = 8.2 Hz, 1H), 3.47 (tdd, J = 9.3, 8.4, 2.6 Hz, 1H), 3.60 and 3.66 (ABq, J = 16.3 Hz, 2H), 3.80 (s, 3H), 4.26 (dd, J = 8.7, 2.6 Hz, 1H), 4.90 (d, J = 4.9 Hz, 1H), 5.11 and 5.23 (ABq, J = 11.9 Hz, 2H), 5.75 (dd, J = 8.9, 4.9 Hz, 1H), 5.98 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.25−7.37 (m, 7H); mass spectrum *m*/*z* 518.1882, calcd for $C_{29}H_{30}N_2O_5S$ 518.1875.

***p*-Methoxybenzyl (5*S*,6*R*,8*R*,9*R*)-5-ethoxy-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (36)** (from **4b** and ethyl vinyl ether): mp 181−183 °C; IR (CH_2Cl_2) 1787, 1724, 1685 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 225 (17 600), 270 (10 700) nm; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 3.17 (dt, J = 17.3, 2.3 Hz, 1H), 3.34 (dd, J = 17.3, 6.5 Hz, 1H), 3.39−3.48 (m, 2H), 3.60 and 3.66 (ABq, J = 16.0 Hz, 2H), 3.79 (s, 3H), 4.30 (dd, J = 6.6, 2.7 Hz, 1H), 4.40 (td, J = 6.6, 2.0 Hz, 1H), 4.94 (d, J = 5.0 Hz, 1H), 5.12 and 5.21 (ABq, J = 12.0 Hz, 2H), 5.76 (dd, J = 8.9, 4.9 Hz, 1H), 6.08 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.26−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 15.2, 38.7, 43.5, 45.7, 55.4, 58.5, 60.5, 66.1, 67.2, 73.7, 114.2 (2C), 121.6, 127.6, 127.8, 129.3 (2C), 129.7 (2C), 130.5 (2C), 133.9, 137.5, 159.9, 160.9, 163.7, 171.4.

Anal. Calcd for $C_{27}H_{28}N_2O_6S$: C, 63.76; H, 5.55; N, 5.51; 6.30. Found: C, 63.62; H, 5.31; N, 5.53; S, 6.30.

***p*-Methoxybenzyl (5*S*,6*R*,8*R*,9*R*)-5-acetoxy-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (37)** (from **4b** and vinyl acetate): mp 171−172 °C; IR (CH_2Cl_2) 1789, 1741, 1684 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 267 (10 700), 225 (17 500) nm; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 3.26 (ddd, J = 17.4, 2.6, 1.7 Hz, 1H), 3.49 (dd, J = 17.4, 6.5 Hz, 1H), 3.60 and 3.67 (ABq, J = 16.3 Hz, 2H), 3.79 (s, 3H), 4.50 (dd, J = 6.6, 2.6 Hz, 1H), 4.93 (d, J = 5.0, 1H), 5.13 and 5.23 (ABq, J = 11.9 Hz, 2H), 5.29 (td, J = 6.6, 1.7 Hz, 1H), 5.79 (dd, J = 9.1, 5.0 Hz, 1H), 5.96 (d, J = 9.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.24−7.37 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 20.7, 38.0, 43.4, 45.3, 55.3, 58.3, 59.8, 67.3, 69.1, 114.0 (2C), 121.8, 127.3, 127.7, 129.2 (2C), 129.7 (2C), 130.4 (2C), 133.7, 135.2, 159.9, 160.6, 164.0, 170.8, 171.1. Anal. Calcd for $C_{27}H_{26}N_2O_7S$: C, 62.06; H, 5.01; N, 5.36. Found: C, 61.99; H, 4.72; N, 5.35.

***p*-Methoxybenzyl (5*R*,6*R*,8*R*,9*R*)-9-Benzamido-10-oxo-5-(phenylthio)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (38) and *p*-Methoxybenzyl (5*S*,6*R*,8*R*,9*R*)-9-Benzamido-10-oxo-5-(phenylthio)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (39)** (from **4c** and phenyl vinyl sulfide). The (5*R*) isomer **38** was eluted first: IR (CH_2Cl_2) 1788, 1725, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.07−3.19 (m, 1H), 3.62−3.76 (m, 2H), 3.81 (s, 3H), 4.26−4.30 (m, 1H), 5.05 (d, J = 4.9 Hz, 1H), 5.21 (s, 2H), 5.95 (dd, J = 8.4, 4.9 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.10−7.59 (m, 10H), 7.78 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 39.4, 43.6, 48.9, 55.3, 58.9, 60.5, 67.3, 114.1 (2C), 120.4, 127.3 (3C), 128.2, 128.8 (2C), 129.4 (2C), 130.5 (2C), 132.4, 132.6 (2C), 132.8, 132.9, 133.1, 159.9, 160.8, 164.3, 167.4; mass spectrum *m*/*z* 558.1281, calcd for $C_{30}H_{26}N_2O_5S_2$ 558.1283. **(5*S*) isomer 39:** IR (CH_2Cl_2) 1788, 1725, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.31 (dt, J = 16.9, 3.0 Hz, 1H), 3.72 (ddd, J = 16.9, 8.4, 1.2 Hz, 1H), 3.81 (s, 3H), 4.30 (td, J = 8.4, 3.0 Hz, 1H), 4.86 (ddd, J = 8.4, 3.0, 1.2 Hz, 1H), 5.11 (d, J = 5.0 Hz, 1H), 5.18 and 5.28 (ABq, J = 12.0 Hz, 2H), 6.00 (dd, J = 8.6, 5.0 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.16−7.58 (m, 10H), 7.77 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 39.0, 42.3, 46.3, 55.3, 58.9, 60.6, 67.2, 114.0 (2C), 122.2, 126.9, 127.3, 127.4 (2C), 128.7 (2C), 129.2 (2C), 129.4 (2C), 130.3 (2C), 132.3, 132.9, 134.9, 136.0, 159.8, 160.8, 163.8, 167.5; mass spectrum *m*/*z* 558.1293, calcd for $C_{30}H_{26}N_2O_5S_2$ 558.1283

***p*-Methoxybenzyl (5*S*,6*R*,8*R*,9*R*)-10-Oxo-9-(phenylacetamido)-5-(phenylthio)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (62)** (from **4b** and phenyl vinyl sulfide) (84%, 35:65 ratio). The later-eluting (5*S*) isomer **62** was partially separated from the (5*R*) isomer by chromatography. Crystallization from ethyl acetate and hexane gave crystals of **62** suitable for X-ray diffraction analysis: mp 174−177 °C; ^{1}H NMR ($CDCl_3$) δ 3.23 (dt, J = 17.0, 3.0 Hz, 1H), 3.51−3.72 (m, 3H), 3.80 (s, 3H), 4.26 (td, J = 8.3, 3.0 Hz, 1H), 4.76 (dd, J = 8.3, 2.2 Hz, 1H), 4.90 (d, J = 5.0 Hz, 1H), 5.13 and 5.23 (ABq, J = 12.0 Hz, 2H), 5.76 (dd, J = 8.9, 5.0 Hz, 1H), 6.06 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.19−7.37 (m, 12H). Anal. Calcd for $C_{31}H_{28}N_2O_5S_2$: C, 65.02; H, 4.93; N, 4.89; S, 11.20. Found: C, 65.67; H, 4.95; N, 5.16; S, 10.89.

X-ray Structure Determination of 62. Light yellow plates suitable for the collection of X-ray diffraction data were obtained by recrystallization from a solution of **62** in ethyl acetate and hexane. A crystal of dimensions 0.70 × 0.30 × 0.02 mm was mounted on an Enraf Nonius CAD-4 diffractometer and flash cooled in a stream of N_2 gas to 223(2) K. Intensity data were collected on the diffractometer using graphite-monochromated Cu Kα radiation and an $\omega-2\theta$ variable speed scan technique. Final cell constants, and other information pertinent to data collection and refinement, were as follows: space group, $P2_1$; unit cell dimensions, a = 5.0900(10) Å, b = 18.831(4) Å, c = 14.422(3) Å, β = 98.13(3)°, V = 1368.5(5) Å^3; empirical formula, $C_{31}H_{28}N_2O_5S_2$; formula weight, 572.67 amu; Z = 2; density (calc) = 1.390 Mg m^{-3}; $F(000)$ = 600; linear absorption coefficient μ(Cu K) = 2.135 mm^{-1}; data collection range $3.10 \le \theta \le 62.47°$, $-5 \le h \le 1$, $-21 \le k \le 21$, $-16 \le l \le 16$; total number of reflections collected, 5084; unique independent reflections, 4325 (R_{int} = 0.102). The structure was solved by direct methods and refined with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were included in idealized positions riding on the atom to which they are attached with isotropic displacement factors assigned as a constant (1.2) times U_{eq} of the attached atom. The full-matrix least-squares refinement (on F^2) of 361 parameters converged (Δ/σ_{max} = 0.00) to values of the conventional crystallographic residuals R = 0.060 for 4117 observed data [$I > 2\sigma(I)$] and R = 0.065 (wR2 = 0.182) for all 4325 data.[14]

***p*-Methoxybenzyl (5*S*,6*R*,8*R*,9*R*)-10-oxo-9-(phenylacetamido)-5-(2-oxopyrrolid-1-yl)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (40)** (from **4b** and *N*-vinyl-2-pyrrolidone): IR (CH_2Cl_2) 1789, 1724, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80−1.98 (m, 2H), 2.34−2.39 (m, 2H), 3.31−3.40 (m, 2H), 3.42 (dt, J = 17.4, 2.8 Hz, 1H), 3.53 (dd, J = 17.2, 8.6 Hz, 1H), 3.61 and 3.68 (ABq, J = 16.4 Hz, 2H), 3.80 (s, 3H), 4.52 (dd, J = 8.0, 2.2 Hz, 1H), 4.98 (d, J = 4.9 Hz, 1H), 5.07 (dt, J = 8.4, 2.7 Hz, 1H), 5.15 and 5.22 (ABq, J = 12.0 Hz, 2H), 5.79−5.89 (m, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.23−7.35 (m, 7H); mass spectrum *m*/*z* 547.1788, calcd for $C_{29}H_{29}N_3O_6S$ 547.1777.

***p*-Methoxybenzyl (5*RS*,6*S*,8*R*,9*R*)-5-Cyano-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylates (41 and 42)** (from **4b** and acrylonitrile). An inseparable mixture of the (5*S*) (**41**) and (5*R*) (**42**) isomers (ratio 1:2) was obtained: IR (KBr) 1787, 1724, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.05−3.12 (m, 1H), 3.50−3.77 (m, 4H), 3.80 (s, 3H), 4.53−4.63 (m, 2H), 4.95 and 4.99 (2d, J = 5.0 Hz, 1H), 5.16, 5.20 and 5.18 (ABq + s, J = 12.0 Hz, 2H), 5.80 (2dd, J = 8.7, 5.0 Hz, 1H), 6.05 and 6.30 (2d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.24−7.41 (m, 7H); mass spectrum *m*/*z* 510 (MH^+).

***p*-Methoxybenzyl (5*RS*,6*S*,8*R*,9*R*)-5-(methoxycarbonyl)-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylates (43 and 44)** (from **4b** and methyl acrylate). An inseparable mixture of the (5*S*) (**43**) and (5*R*) (**44**) isomers (ratio 2:3) was obtained: IR (CH_2Cl_2) 1786, 1728, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (m, 0.4H), 3.33 (m, 0.6H), 3.67 (s, 1.8H), 3.70 (m, 4H), 3.75 (s, 1.2H), 3.79 (s, 3H), 4.58 (m, 1H), 4.94 (d, J = 5.0 Hz, 0.6H), 4.97 (d, J = 5.0 Hz, 0.4H), 5.17 (ABq, J = 12.0 Hz, 0.8H), 5.19 (ABq, J = 11.9 Hz, 1.2H), 5.77 (m, 1H), 6.06 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.22−7.39 (m, 7H); mass spectrum *m*/*z* 522.1482, calcd for $C_{27}H_{26}N_2O_7S$ 522.1461.

***p*-Methoxybenzyl (4*R*,9*R*,10*S*,12*R*,13*R*)-14-oxo-13-(phenylacetamido)-8-oxa-11-thia-1-azatetracyclo[10.2.0.0^{3,10}.0^{4,9}]-tetradec-2-ene-2-carboxylate (45)** (from **4b** and 3,4-dihydro-2*H*-pyran): IR (CH_2Cl_2) 1786, 1725, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49−1.66 (m, 3H), 2.00−2.15 (m, 1H), 3.59 and 3.67 (ABq, J = 16.0 Hz, 2H) and 3.60−3.74 (m, 3H), 3.80 (s, 3H), 4.10 (dd, J = 7.3, 6.6 Hz, 1H), 4.67 (dd, J = 6.6, 2.8 Hz, 1H), 4.94 (d, J = 5.0 Hz, 1H), 5.10 and 5.24 (ABq, J = 11.9 Hz, 2H), 5.76 (dd, J = 9.0, 5.0 Hz, 1H), 6.09 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.24−7.39 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 22.1, 23.5, 42.7, 42.9, 43.4, 55.3, 57.8, 60.0, 62.9, 67.2, 70.0, 114.0 (2C), 122.1, 127.3, 127.8, 129.2 (2C), 129.5 (2C), 130.5 (2C), 133.7, 134.7, 159.9, 160.7, 164.3, 171.3; mass spectrum *m*/*z* 520.1666, calcd for $C_{28}H_{28}N_2O_6S$ 520.1668.

***p*-Methoxybenzyl (4*S*,8*S*,9*S*,11*R*,12*R*)-13-oxo-12-(phenylacetamido)-10-thia-1-aza-6,7-benzotetracyclo-[9.2.0.0^{3,9}.0^{4,8}]trideca 2,6-diene-2-carboxylate (46)** (from **4b** and indene): IR (KBr) 1781, 1730, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.18 (dd, J = 17.6, 4.9 Hz, 1H), 3.30 (dd, J = 17.4, 10.3 Hz, 1H), 3.51 and 3.57 (ABq, J = 14.0 Hz, 2H), 3.76 (s, 3H), 3.95 (dd, J = 6.8, 5.7 Hz, 1H), 4.23−4.29 (m, 2H), 5.04 (d, J = 5.0 Hz, 1H), 5.19 and 5.24 (ABq, J = 11.9 Hz, 2H), 5.67 (dd, J = 8.3, 5.0 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 7.19−7.33 (m, 9H), 7.40 (d, J = 8.6 Hz, 2H), 9.08 (d, J = 8.3 Hz, 1H); mass spectrum *m*/*z* 552.1730, calcd for $C_{32}H_{28}N_2O_5S$ 552.1719.

***p*-Methoxybenzyl (4*S*,8*R*,9*S*,11*R*,12*R*)-13-oxo-12-(phenylacetamido)-5-oxa-10-thia-1-aza-6,7-benzotetracyclo-[9.2.0.0^{3,9}.0^{4,8}]trideca-2,6-diene-2-carboxylate (47)** (from **4b** and 2,3-benzofuran): IR (CH_2Cl_2) 1785, 1729, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.62 and 3.70 (ABq, J = 16.3 Hz, 2H), 3.80 (s,

3H), 4.07 (dd, J = 6.3, 4.7 Hz, 1H), 4.24 (dd, J = 4.7, 1.7 Hz, 1H), 4.88 (d, J = 5.0 Hz, 1H), 5.23 and 5.30 (ABq, J = 11.9 Hz, 2H), 5.83 (dd, J = 8.7, 5.0 Hz, 1H), 5.93 (d, J = 8.9 Hz, 1H), 6.05 (dd, J = 6.3, 1.7 Hz, 1H), 6.87−6.94 (m, 4H), 7.17−7.39 (m, 9H); mass spectrum m/z 554 (M^+).

***p*-Methoxybenzyl (4*S*,8*S*,9*S*,11*R*,12*R*)-12-(phenylacetamido)-5,5,13-trioxo-5,10-dithia-1-aza-6,7-benzotetracyclo-[9.2.0.0^{3,9}.0^{4,8}]trideca 2,6-diene-2-carboxylate (48)** (from **4b** and thianaphthene 1,1-dioxide[27]): mp 270 °C dec (CH_2Cl_2/Et_2O); IR (CH_2Cl_2) 1798, 1734, 1690 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 278 (13 200) nm; ^{1}H NMR (DMSO-d_6) δ 3.51 and 3.56 (ABq, J = 14.1 Hz, 2H), 3.76 (s, 3H), 4.39 (dd, J = 5.6, 3.0 Hz, 1H), 4.65 (t, J = 6.6 Hz, 1H), 5.14 (d, J = 5.2 Hz, 1H), 5.25 and 5.31 (ABq, J = 12.0 Hz, 2H), 5.38 (dd, J = 7.5, 3.0 Hz, 1H), 5.77 (dd, J = 8.2, 5.2 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 7.22−7.33 (m, 5H), 7.43 (d, J = 8.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 9.14 (d, J = 8.3 Hz, 1H). Anal. Calcd for $C_{31}H_{26}N_2O_7S_2$: C, 61.78; H, 4.35; N, 4.65; S, 10.64. Found: C, 61.84; H, 4.24; N, 4.69; S, 10.66.

***p*-Methoxybenzyl (4*S*,8*R*,9*S*,11*R*,12*R*)-13-oxo-12-(phenylacetamido)-10-thia-1,5-diaza-6,7-benzotetracyclo-[9.2.0.0^{3,9}.0^{4,8}]trideca 2,6-diene-2-carboxylate (49)** (from **4b** and 1-acetylindole): IR (KBr) 1777, 1713, 1669, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 3.62 (d, J = 16.3 Hz, 1H), 3.70 (d, J = 16.3 Hz, 1H,), 3.81 (s, 3H), 3.98 (t, J = 6.4 Hz, 1H), 4.32 (dd, J = 6.4, 1.5 Hz), 4.88 (d, J = 5.0 Hz, 1H), 5.18 (d, J = 11.9 Hz, 1H), 5.33 (d, J = 11.9 Hz, 1H), 5.82 (dd, J = 6.8, 1.6 Hz, 1H), 5.85 (dd, J = 9.0, 5.0 Hz, 1H), 5.96 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.05 (t, J = 7.5 Hz, 1H), 7.18−7.42 (m, 10H); mass spectrum m/z (EI) 595 (M^+).

***p*-Methoxybenzyl (5*R*,6*S*,8*R*,9*R*)-10-oxo-9-(phenylacetamido)-5-[(trimethylsilyl)methyl]-7-thia-1-azatricyclo-[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (50)** (from **4b** and allyltrimethylsilane): IR (CH_2Cl_2) 1786, 1719, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.61−0.72 (m, 2H), 2.78−2.86 (m, 2H), 3.28 (br dd, J = 16.5, 9.5 Hz, 1H), 3.63 and 3.66 (ABq, J = 16.0 Hz, 2H), 3.80 (s, 3H), 4.41 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.96 (d, J = 4.9 Hz, 1H), 5.16 and 5.19 (ABq, J = 12.6 Hz, 2H), 5.77 (dd, J = 9.1, 4.9 Hz, 1H), 6.04 (d, J = 9.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.27−7.37 (m, 7H); mass spectrum m/z 550.1950, calcd for $C_{29}H_{34}N_2O_5SSi$ 550.1958.

***p*-Methoxybenzyl (5*R*,6*S*,8*R*,9*R*)-5-(hydroxymethyl)-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (51)** (from **4b** and allyl alcohol): IR (CH_2Cl_2) 1787, 1722, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.83−2.95 (m, 1H), 2.96 (dt, J = 16.8, 3.0 Hz, 1H), 3.22 (ddd, J = 16.2, 8.9, 1.2 Hz, 1H), 3.58 and 3.65 (ABq, J = 15.7 Hz, 2H), 3.65 (d, J = 7.2 Hz, 2H), 3.79 (s, 3H), 4.41−4.45 (m, 1H), 4.92 (d, J = 5.0 Hz, 1H), 5.11 and 5.23 (ABq, J = 12.0 Hz, 2H), 5.76 (dd, J = 8.9, 5.0 Hz, 1H), 6.32 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.16−7.34 (m, 7H); mass spectrum m/z 494.1528, calcd for $C_{26}H_{26}N_2O_6S$ 494.1512.

***p*-Methoxybenzyl (4*R*,5*S*,6*R*,8*R*,9*R*)-4-acetyl-5-methoxy-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (52)** (from **4b** and *trans*-4-methoxy-3-buten-2-one): IR (CH_2Cl_2) 1791, 1714, 1689 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 273 (10 200) nm; ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 3H), 3.31 (s, 3H), 3.49 and 3.56 (ABq, J = 13.9 Hz, 2H), 3.75 (s, 3H), 4.30 (dd, J = 2.8, 2.2 Hz, 1H), 4.50 (dd, J = 7.2, 1.9 Hz, 1H), 4.59 (dd, J = 7.3, 3.1 Hz, 1H), 5.13 (d, J = 5.1 Hz, 1H), 5.19 (s, 2H), 5.74 (dd, J = 8.5, 5.0 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 7.20−7.31 (m, 5H), 7.34 (d, J = 8.6 Hz, 2H), 9.13 (d, J = 8.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 28.7, 41.5, 44.5, 55.1, 56.9, 58.3, 60.2, 62.1, 66.5, 77.5, 113.8 (2C), 122.1, 126.4, 127.2, 128.2 (2C), 129.0 (2C), 130.2 (2C), 133.9, 135.8, 159.3, 160.0, 164.5, 171.0, 202.1. Anal. Calcd for $C_{28}H_{28}N_2O_7S$: C, 62.67; H, 5.26; N, 5.22; S, 5.98. Found: C, 62.40; H, 5.32; N, 5.17; S, 5.77.

***p*-Methoxybenzyl (4*S*,5*R*,6*S*,8*R*,9*R*)-4-Methoxy-10-oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo-[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (53)** (from **4b** and *cis*-β-methoxystyrene). After chromatography a mixture comprising the (4*S*)-methoxy-(5*R*)-phenyl compound **53** and the (5*R*)-methoxy-(4*R*)-phenyl compound **54** was obtained (63%, 3.3:1). **53** was obtained pure after recrystallization from EtOAc: mp 191−196 °C; IR (KBr) 1789, 1714, 1656 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 270 (13 000) nm; ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 3H), 3.52 (dd, J = 9.3, 6.0 Hz, 1H), 3.59 and 3.65 (ABq, J = 16.2 Hz, 2H), 3.79 (s, 3H), 4.76 (dd, J = 9.3, 1.7 Hz, 1H), 5.01 (d, J = 5.1 Hz, 1H), 5.12 (dd, J = 8.9, 5.1 Hz, 1H), 5.20 and 5.26 (ABq, J = 11.8 Hz, 2H), 5.85 (dd, J = 8.9, 5.1 Hz, 1H), 6.03 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.23−7.37 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 43.3, 45.2, 49.8, 55.2, 57.5, 58.5, 60.1, 67.6, 82.2, 114.0 (2C), 123.3, 126.8, 127.4, 127.7, 128.0 (2C), 128.4 (2C), 129.2 (2C), 129.4 (2C), 130.7 (2C), 132.6, 133.5, 135.4, 160.0, 160.4, 164.7, 171.1. Anal. Calcd for $C_{32}H_{30}N_2O_6S$: C, 67.35; H, 5.30; N, 4.91; S, 5.62. Found: C, 67.35; H, 5.11; N, 5.00; S, 5.38.

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-4-isopropylidene-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec 2-ene-2-carboxylate (55)** (from **4b** and 3,3-dimethylallene): IR (CH_2Cl_2) 1778, 1717, 1684 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 304 (9100) nm; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.86 (t, J = 1.8 Hz, 3H), 2.53 (ddqq, J = 12.8, 5.2, 1.8, 1.4 Hz, 1H), 2.90 (ddqq, J = 12.8, 8.2, 1.8, 1.4 Hz, 1H), 3.52 (dd, J = 8.2, 5.2 Hz, 1H), 3.65 (s, 2H), 3.79 (s, 3H), 5.07 (d, J = 4.1 Hz, 1H), 5.16 (s, 2H), 5.37 (dd, J = 8.2, 4.1 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.25−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 22.2, 23.6, 36.6, 36.8, 43.5, 55.3, 60.4, 62.4, 66.7, 114.0 (2C), 115.6, 127.5, 127.7, 128.4, 129.0 (2C), 129.7 (2C), 130.0 (2C), 134.3, 143.2, 156.7, 159.7, 161.6, 167.5, 171.2. Anal. Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.65; H, 5.59; N, 5.55; S, 6.35. Found C, 66.37; H, 5.27; N, 5.39; S, 6.17.

***p*-Methoxybenzyl (4*S*,5*R*,6*S*,8*R*,9*R*)-5-Ethyl-4-methyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (56b)** (from **4b** and *cis*-2-pentene + 0.9% *trans*-2-pentene). After chromatography a mixture of the (4*S*)-ethyl-(5*R*)-methyl isomer **56a**, **56b**, the (4*R*)-ethyl-(5*S*)-methyl isomer **57a**, the (5*S*)-ethyl-(4*R*)-methyl isomer **57b**, **58a**, and **58b** was obtained in 45% yield (ratio 46:41:3.6:2.6:3.6:3.2). Crystallization from EtOAc gave **56b**: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 7.5 Hz, 3H), 1.55 (quintet, J = 7.3 Hz, 2H), 2.23 (quintet, J = 8.1 Hz, 1H), 3.59 and 3.68 (ABq, J = 16.1 Hz, 2H) and 3.65 (m, 1H), 3.80 (s, 3H), 3.94 (dd, J = 8.3, 2.9 Hz, 1H), 4.89 (d, J = 4.9 Hz, 1H), 5.11 and 5.25 (ABq, J = 11.9 Hz, 2H), 5.75 (dd, J = 8.8, 4.9 Hz, 1H), 5.98 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.25−7.36 (m, 7H). ^{1}H NMR signals assigned to **56a**: δ 0.78 (t, J = 7.4 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 2.47 (sextet, J = 7.9 Hz, 1H). **57a**: 4.28 (d, J = 9.3 Hz). **57b**: 4.20 (d, J = 9.3 Hz).

***p*-Methoxybenzyl (4*S*,5*S*,6*S*,8*R*,9*R*)-5-Ethyl-4-methyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (58b)** (from **4b** and *trans*-2-pentene). After chromatography a mixture comprising the (4*S*)-ethyl-(5*S*)-methyl isomer **58a** and **58b** (68%, 1.4:1 ratio) was obtained. **58b** was obtained pure after crystallization from EtOAc/hexane: mp 158−159 °C; IR (CH_2Cl_2) 1786, 1719, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 1.25 (d, J = 7.3 Hz, 3H), 1.29−1.49 (m, 2H), 2.14−2.25 (m, 1H), 3.10 (qt, J = 7.2, 3.3 Hz, 1H), 3.60 and 3.69 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.50 (dd, J = 9.6, 3.3 Hz, 1H), 4.89 (d, J = 4.9 Hz, 1H), 5.08 and 5.29 (ABq, J = 11.9 Hz, 2H), 5.76 (dd, J = 9.1, 4.9 Hz, 1H), 5.98 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.26−7.37 (m, 7H). Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53; S, 6.33. Found: C, 66.40; H, 5.97; N, 5.65; S, 6.30. ^{1}H NMR signals assigned to **58a** in the mixture of **58a** and **58b**: δ 1.03 (d, J = 7.1 Hz), 1.56−1.64 (m), 2.41−2.54 (m), 2.85−2.94 (m), 4.40 (dd, J = 9.5, 3.1 Hz), 4.91 (d, J = 4.9 Hz).

***p*-Methoxybenzyl (5*R*,6*S*,8*R*,9*R*)-5-cyclohexyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (59)** (from **4b** and vinylcyclohexane): IR (KBr) 1786, 1704, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68−1.80 (m, 11H), 2.37 (dq, J = 4.0, 9.2 Hz, 1H), 3.03 (dt, J = 3.5, 16.9 Hz, 1H), 3.12 (ddd, J = 1.1, 9.1, 16.7 Hz, 1H), 3.61 and 3.69 (ABq, J = 16.2 Hz, 2H), 3.78 (s, 3H), 4.41 (ddd, J = 1.2, 2.7, 9.5 Hz, 1H), 4.87 (d, J = 4.9 Hz, 1H), 5.11 and 5.24 (ABq, J = 12 Hz, 2H), 5.77 (dd, J = 4.9, 9.2 Hz, 1H), 5.97 (d, J = 9.2 Hz,

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1H), 6.83−6.91 (m, 2H), 7.20−7.40 (m, 7H); mass spectrum *m*/*z* 546 (M^+).

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-5,5-Diphenyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (60)** (from **4b** and 1,1-diphenylethylene). After chromatography a mixture of **60** and the (6*R*) isomer **61** (77%, 58:42 ratio) was obtained. This mixture was treated with *m*-CPBA by the method described for the preparation of **17**/**18**. This gave, after chromatography, a single sulfoxide in 66% yield. Reduction with PCl_3 by the method described for the reduction of **17** gave **60** as the sole isomer in 75% yield. Spectral data for **60**: IR (CH_2Cl_2) 1788, 1726, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 and 3.58 (ABq, J = 16.4 Hz, 2H), 3.62 (dd, J = 16.4, 0.6 Hz, 1H), 3.81 (s, 3H), 4.31 (dd, J = 16.3, 2.6 Hz, 1H), 4.98 (dd, J = 2.3, 0.8 Hz, 1H), 5.02 (d, J = 4.9 Hz, 1H), 5.24 and 5.32 (ABq, J = 12.0 Hz, 2H), 5.72 (dd, J = 8.9, 4.8 Hz, 1H), 5.87 (d, J = 8.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.04−7.37 (m, 17H); mass spectrum *m*/*z* 616.2035, calcd for $C_{37}H_{32}N_2O_5S$ 616.2032. ^{1}H NMR signals assigned to **61** in the original mixture of **60** and **61**: δ 3.51 (d, J = 15.5 Hz, 1H), 3.82 (obscured by s at 3.81; but observed in a COSY experiment), 4.16 (dd, J = 15.5, 1.5 Hz, 1H), 4.89 (brs, 1H), 5.46 (dd, J = 9.3, 4.5 Hz, 1H), 6.17 (d, J = 9.3 Hz, 1H).

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-10-Oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (74) and *p*-Methoxybenzyl (6*R*,8*R*,9*R*)-10-Oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (75).** Acetylene, passed successively through a cold trap at −78 °C and then traps containing concentrated H_2SO_4 and soda lime, was bubbled through a sintered glass tube into a solution of triflate **4b** (1.0 g, 1.7 mmol) in EtOAc (500 mL) at room temperature while a solution of ^{i}Pr$_2$NEt (0.30 mL, 1.7 mmol) in EtOAc (100 mL) was added dropwise over 1.5 h. The mixture was stoppered and stirred for a further 16 h and then concentrated. The residue was chromatographed to give two isomers: **74** (63mg, 8%) and **75** (267 mg, 34%). The (6*S*) isomer **74** was eluted first: mp 197 °C dec; IR (CH_2Cl_2) 1787, 1723, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 and 3.68 (ABq, J = 16.2 Hz, 2H), 3.80 (s, 3H), 4.26 (t, J = 1.2 Hz, 1H), 4.82 (d, J = 4.9 Hz, 1H), 5.18 and 5.25 (ABq, J = 11.9 Hz, 2H), 5.96 (dd, J = 8.7, 4.9 Hz, 1H), 6.07 (d, J = 8.8 Hz, 1H), 6.73 (dd, J = 2.3, 1.3 Hz, 1H), 6.79 (dd, J = 2.1, 0.9 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.23−7.36 (m, 7H). Anal. Calcd for $C_{25}H_{22}N_2O_5S$: C, 64.92; H, 4.79, N, 6.06; S, 6.93. Found: C, 64.92; H, 4.75; N, 6.07; S, 6.65. **(6*R*) isomer 75:** IR (CH_2Cl_2) 1782, 1725, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2H), 3.80 (s, 3H), 4.42 (s, 1H), 5.11 and 5.17 (ABq, J = 12.0 Hz, 2H), 5.24 (dd, J = 8.0, 4.1 Hz), 5.70 (d, J = 4.1 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 2.3, 0.4 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.26−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 43.5, 44.1, 55.4, 59.8, 67.0, 73.5, 114.1 (2C), 114.3, 127.48, 127.51, 129.1 (2C), 129.6 (2C), 130.2 (2C), 134.3, 136.5, 147.7, 155.9, 159.9, 162.0, 166.3, 171.3; mass spectrum *m*/*z* 463 (MH^+).

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-5-butyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (76)** (from **4b** and 1-hexyne): mp 196−198 °C; IR (CH_2Cl_2) 1786, 1717, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.37 (sextet, J = 7.3 Hz, 2H), 1.50 (quintet, J = 7.2 Hz, 2H), 2.39 (t, J = 7.4 Hz, 2H), 3.63 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.19 (s, 1H), 4.81 (d, J = 4.8 Hz, 1H), 5.20 (ABq, J = 12.0 Hz, 2H), 5.89 (dd, J = 8.5, 4.8 Hz, 1H), 5.99 (d, J = 8.4 Hz, 1H), 6.47 (s, 1H), 6.88 (d, J = 8.5 Hz, 2H), 7.25−7.34 (m, 7H). Anal. Calcd for $C_{29}H_{30}N_2O_5S$: C, 67.16; H, 5.83; N, 5.40; S, 6.18. Found: C, 67.00; H, 5.75; N, 5.49; S, 5.98.

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-10-Oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (77) and *p*-Methoxybenzyl (6*R*,8*R*,9*R*)-10-Oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (78)** (from **4b** and phenylacetylene). The (6*S*) isomer **77** was eluted first: mp 240 °C dec; IR (CH_2Cl_2) 1787, 1720, 1688 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 350 (23 900) nm; ^{1}H NMR ($CDCl_3$) δ 3.59 and 3.63 (ABq, J = 15.8 Hz, 2H), 3.81 (s, 3H), 4.60 (d, J = 1.1 Hz, 1H), 4.98 (d, J = 4.6 Hz, 1H), 5.21 and 5.28 (ABq, J = 11.9 Hz, 2H), 5.88 (dd, J = 8.1, 4.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 1.3 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 7.24−7.50 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 43.0, 43.8, 55.3, 60.1, 63.2, 67.1, 113.7, 114.0 (2C), 126.6 (2C), 127.5, 127.6, 128.2, 129.0 (2C), 129.1 (2C), 129.4 (2C), 130.3 (2C), 130.7, 131.1, 133.8, 134.4, 152.6, 159.8, 161.4, 163.9, 171.8. Anal. Calcd for $C_{31}H_{26}N_2O_5S$: C, 69.13; H, 4.87; N, 5.20; S, 5.95. Found: C, 69.03; H, 4.63; N, 5.27; S, 5.97. **(6*R*) isomer 78:** mp 98−101 °C; IR (CH_2Cl_2) 1782, 1718, 1684 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 341 (22 300) nm; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 2H), 3.80 (s, 3H), 4.82 (s, 1H), 4.71 and 4.92 (ABq, J = 12.1 Hz, 2H), 5.34 (dd, J = 8.1, 4.1 Hz, 1H), 5.61 (d, J = 4.1 Hz, 1H), 6.55 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.1 Hz, 1H), 7.17−7.46 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 43.0, 43.7, 55.5, 60.0, 66.8, 71.3, 112.7, 114.2 (2C), 125.3, 127.5, 127.7, 127.8 (2C), 129.1 (2C), 129.3 (2C), 129.8 (2C), 130.0 (2C), 130.1, 132.0, 134.8, 154.0, 157.7, 159.9, 162.4, 168.8, 171.5. Anal. Found: C, 69.29; H, 4.87; N, 5.11; S, 5.79.

***p*-Methoxybenzyl (6*R*,8*R*,9*R*)-5-(hydroxymethyl)-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-deca-2,4-diene-2-carboxylate (79)** (from **4b** and propargyl alcohol): mp 190−197 °C; IR (KBr) 1776, 1709, 1660 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 299 (15 700)nm; ^{1}H NMR (DMSO-d_6) δ 3.48 and 3.54 (ABq, J = 14.0 Hz, 2H), 3.76 (s, 3H), 4.26 and 4.33 (ABq, J = 17.6 Hz, 2H), 4.47 (d, J = 1.0 Hz, 1H), 5.01 (d, J = 4.9 Hz, 1H), 5.18 and 5.22 (ABq, J = 12.0 Hz, 2H), 5.84 (dd, J = 8.4, 4.9 Hz, 1H), 6.57 (d, J = 1.2 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.20−7.31 (m, 5H), 7.37 (d, J = 8.7 Hz, 2H), 9.06 (d, J = 8.4 Hz, 1H). Anal. Calcd for $C_{26}H_{24}N_2O_6S$: C, 63.40; H, 4.91; N, 5.69; S, 6.51. Found: C, 63.42, H, 4.88; N, 5.81; S, 6.80.

***p*-Methoxybenzyl (6*R*,8*R*,9*R*)-5-bromomethyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (80)** (from **4b** and propargyl bromide): IR (CH_2Cl_2) 1790, 1723, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 and 3.68 (ABq, J = 16.1 Hz, 2H), 3.81 (s, 3H), 4.12 and 4.17 (ABq, J = 12.7 Hz, 2H), 4.34 (d, J = 0.7 Hz, 1H), 4.87 (d, J = 4.6 Hz, 1H), 5.17 and 5.25 (ABq, J = 11.9 Hz, 2H), 5.93 (dd, J = 8.7, 4.5 Hz, 1H), 5.99 (d, J = 8.7 Hz, 1H), 6.68 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.24−7.39 (m, 7H). Anal. Calcd for $C_{26}H_{23}N_2BrO_5S$: C, 56.22; H, 4.17; N, 5.04. Found: C, 56.42; H, 4.21; N, 5.11.

***p*-Methoxybenzyl (6*R*,8*R*,9*R*)-5-ethoxy-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (81)** (from **4b** and ethoxyacetylene): IR (CH_2Cl_2) 1782, 1733, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 3.59 (d, J = 16.1 Hz, 1H), 3.67 (d, J = 16.1 Hz, 1H), 3.80 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.37 (d, J = 1.2 Hz, 1H), 4.82 (d, J = 4.6 Hz, 1H), 5.15 (d, J = 12.0 Hz, 1H), 5.24 (d, J = 12.0 Hz, 1H), 5.54 (d, J = 1.0 Hz, 1H), 5.88 (dd, J = 8.5, 4.6 Hz, 1H), 6.02 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.24−7.39 (m, 7H); mass spectrum *m*/*z* 506.1513, calcd for $C_{27}H_{26}N_2O_6S$ 506.1512.

***p*-Methoxybenzyl (6*R*,8*R*,9*R*)-10-oxo-9-(phenylacetamido)-5-(trimethylsilyl)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (82)** (from **4b** and (trimethylsilyl)-acetylene): IR (CH_2Cl_2) 1787, 1720, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9H), 3.59 and 3.67 (ABq, J = 16.1 Hz, 2H), 3.80 (s, 3H), 4.23 (s, 1H), 4.80 (d, J = 4.2 Hz, 1H), 5.18 and 5.26 (ABq, J = 12.0 Hz, 2H), 5.90−5.96 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 7.25−7.35 (m, 7H); mass spectrum *m*/*z* 534.1650, calcd for $C_{28}H_{30}N_2O_5SSi$ 534.1645.

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-5-(Methoxycarbonyl)-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-deca-2,4-diene-2-carboxylate (84)** (from **4b** and methyl propiolate). The (6*R*) isomer **83** was eluted first: IR (CH_2Cl_2) 1792, 1721, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 (d, J = 16.3 Hz, 1H), 3.66 (d, J = 16.3 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.39 (s, 1H), 4.88 (d, J = 4.4 Hz, 1H), 5.20 (d, J = 11.9 Hz, 1H), 5.26 (d, J = 11.9 Hz, 1H), 5.99 (m, 2H), 6.89 (d, J = 4.8 Hz, 2H), 7.20 (s, 1H), 7.24−7.35 (m, 7H); mass spectrum *m*/*z* 520.1310, calcd for $C_{27}H_{24}N_2O_7S$ 520.1304. **(6*S*) isomer 84:** IR (CH_2Cl_2) 1783, 1724, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (d, J = 16.5 Hz, 1H), 3.74 (d, J = 16.5 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 4.43 (s, 1H), 5.13 (d, J = 11.3 Hz, 1H), 5.19 (m, 1H), 5.20 (d, J = 11.3 Hz, 1H), 5.67 (d, J = 4.1 Hz, 1H), 6.17

(d, J = 7.8 Hz, 1H), 6.86 (s, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.26−7.41 (m, 7H); mass spectrum m/z 520.1310, calcd for $C_{27}H_{24}N_2O_7S$ 520.1304.

***p*-Methoxybenzyl (6*S*,8*R*,9*R*)-4,5-dimethyl-10-oxo-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (85)** (from **4b** and 2-butyne): IR (CH_2Cl_2) 1783, 1716, 1684 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 298 (12 400) nm; ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H), 1.97 (s, 3H), 3.59 and 3.65 (ABq, J = 16.1 Hz, 2H), 3.79 (s, 3H), 4.07 (brs, 1H), 4.79 (d, J = 4.8 Hz, 1H), 5.17 and 5.23 (ABq, J = 11.8 Hz, 2H), 5.89 (dd, J = 8.6, 4.8 Hz, 1H), 6.06 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 7.24−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.2, 43.3, 45.6, 55.3, 59.8, 62.3, 67.1, 111.8, 113.9 (2C), 127.4, 127.7, 129.2 (2C), 129.5 (2C), 130.8 (2C), 133.7, 135.4, 142.5, 149.1, 159.9, 161.4, 164.6, 171.2; mass spectrum m/z 490.1562, calcd for $C_{27}H_{26}N_2O_5S$ 490.1562.

***p*-Bromobenzyl (6*S*,8*R*,9*R*)-10-Oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]deca-2,4-diene-2-carboxylate (86).** To a mixture of **77** and **78** (0.397 g, 0.737 mmol) in anisole (2 mL) at 0 °C was added TFA (4 mL). The mixture was stirred at 0 °C for 5 min and then evaporated under reduced pressure. Toluene was added to the residue, and it was evaporated under reduced pressure. The residue was dissolved in DMF (5 mL). *p*-Bromobenzyl bromide (0.32 g, 1.28 mmol) and K_2CO_3 (0.24 g, 1.73 mmol) were added, and the mixture stirred at room temperature for 1.5 h. Water (50 mL) was added, and the mixture was extracted with EtOAc (100 mL). The organic extract was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The (6*S*) isomer **86** (0.116 g, 27%) was separated from the (6*R*) isomer (0.184g, 42%) by chromatography: IR (KBr) 1777, 1708, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 and 3.68 (ABq, J = 16.3 Hz, 2H), 4.63 (d, J = 1.2 Hz, 1H), 5.00 (d, J = 4.5 Hz, 1H), 5.21 and 5.30 (ABq, J = 12.4 Hz, 2H), 5.90−5.99 (m, 2H), 6.90 (d, J = 1.0 Hz, 1H), 7.26−7.52 (m, 14H); mass spectrum m/z 586.0560, calcd for $C_{30}H_{23}{}^{79}BrN_2O_4S$ 586.0562.

X-ray Structure Determination of 86. Light yellow plates suitable for the collection of X-ray diffraction data were obtained by recrystallization from a solution of **86** in ethyl acetate and methanol. A crystal of dimensions 0.30 × 0.25 × 0.02 mm was mounted on an Enraf Nonius CAD-4 diffractometer and flash cooled in a stream of N_2 gas to 223(2) K. Intensity data were collected on the diffractometer using graphite-monochromated Cu Kα radiation and an $\omega-2\theta$ variable speed scan technique. Final cell constants, and other information pertinent to data collection and refinement, were as follows: space group $P2_1$; unit cell dimensions, a = 4.5760(10) Å, b = 12.727(3) Å, c = 22.942(5) Å, β = 93.29(3)°, V = 1333.9(5) Å^3; empirical formula, $C_{30}H_{23}BrN_2O_4S$; formula weight, 587.47; Z = 2; density (calc) = 1.463 Mg m^{-3}; $F(000)$ = 600; linear absorption coefficient μ(Cu K) = 3.155 mm^{-1}; data collection range $1.93 \le \theta \le 62.44°$, $-5 \le h \le 1$, $0 \le k \le 14$, $-23 \le l \le 26$; total number of reflections collected, 2548; unique independent reflections, 2223 (R_{int} = 0.092). The structure was solved by direct methods and refined with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were included in idealized positions riding on the atom to which they are attached with isotropic displacement factors assigned as a constant (1.2) times U_{eq} of the attached atom. The full-matrix least-squares refinement (on F^2) of 384 parameters converged (Δ/σ_{max} = 0.20) to values of the conventional crystallographic residuals R = 0.054 for 2072 observed data [$I > 2\sigma(I)$] and R = 0.058 (wR2 = 0.149) for all 2223 data.[14]

***p*-Methoxybenzyl (5*R*,6*R*)-4-oxo-5-(phenylacetamido)-13-oxa-7-thia-3-azatetracyclo[8.2.1.0^{2,9}.0^{3,6}]trideca-8,11-diene-2-carboxylate (87)** (from **4b** and furan): IR (CH_2Cl_2) 1777, 1739, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.57 (ABq, J = 15.9 Hz, 2H), 3.80 (s, 3H), 4.77 (dd, J = 4.0, 1.0 Hz, 1H), 5.11 (d, J = 11.9 Hz, 1H), 5.21 (d, J = 11.9 Hz, 1H), 5.28 (dt, J = 1.9, 1.0 Hz, 1H), 5.32 (dd, J = 8.6, 4.0 Hz, 1H), 5.67 (dt, J = 1.8, 1.0 Hz, 1H), 5.96 (d, J = 8.6 Hz, 1H), 6.07 (q, J = 1.0 Hz, 1H), 6.43 (dd, J = 5.6, 1.8 Hz, 1H), 6.47 (dd, J = 5.6, 1.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.22−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 43.3 (t), 55.3 (q), 56.4 (d), 59.7 (d), 64.5 (s), 68.1 (t), 81.7 (d), 83.0 (d), 113.4 (d), 114.2 (d), 127.1 (s), 127.6 (d), 129.0 (d), 129.5 (d), 130.1 (d), 131.1 (d), 131.1 (s), 133.9 (s), 138.5 (d), 160.0 (s), 160.3 (s), 167.0 (s), 170.8 (s); mass spectrum m/z 504.1369, calcd for $C_{27}H_{24}N_2O_6S$ 504.1355.

***p*-Methoxybenzyl (5*R*,6*R*)-1,10-diphenyl-4-oxo-5-(phenylacetamido)-13-oxa-7-thia-3-azatetracyclo[8.2.1.0^{2,9}.0^{3,6}]-trideca-8,11-diene-2-carboxylate (88)** (from **4b** and 1,3-diphenylisobenzofuran): IR (CH_2Cl_2) 1778, 1733, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.47 (d, J = 15.7 Hz, 1H), 3.54 (d, J = 15.7 Hz, 1H), 3.81 (s, 3H), 4.70 (d, J = 11.9 Hz, 1H), 4.83 (d, J = 4.3 Hz, 1H), 4.85 (d, J = 11.9 Hz, 1H), 5.37 (dd, J = 8.6, 4.1 Hz, 1H), 5.81 (d, J = 8.6 Hz, 1H), 6.11 (s, 1H), 6.78 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 7.15 (m, 3H), 7.21−7.30 (m, 5H), 7.37−7.41 (m, 3H), 7.47−7.51 (m, 3H), 7.60 (d, J = 7.5 Hz, 1H), 7.83−7.90 (m, 4H); mass spectrum m/z 706.2145, calcd for $C_{43}H_{34}N_2O_6S$ 706.2138.

***p*-Methoxybenzyl (1*S*,6*R*,7*R*)-1-Oxo-7-(phenylacetamido)-3-[(trifluoromethanesulfonyl)oxy]ceph-3-em-4-carboxylate (92).** To an ice-cooled solution of triflate **4b** (0.25 g, 0.43 mmol) in CH_2Cl_2 (5 mL) was added a solution of *m*-CPBA (0.106 g, 0.43 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature for 30 min, then diluted with CH_2Cl_2, washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was crystallized to give **92** (0.202 g, 80%): mp 148−150 °C (CH_2Cl_2/Et_2O); IR (CH_2Cl_2) 1793, 1735, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.46 (dd, J = 18.5, 1.6 Hz, 1H), 3.62 (ABq, J = 15.6 Hz, 2H), 3.81 (3H, s), 3.87 (d, J = 18.5 Hz, 1H), 4.53 (dd, J = 4.8, 1.4 Hz, 1H), 5.20 (d, J = 11.7 Hz, 1H), 5.36 (d, J = 11.7 Hz, 1H), 6.06 (dd, J = 9.8, 4.8 Hz, 1H), 6.65 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.25−7.36 (m, 7H); mass spectrum m/z 603 (MH$^+$).

***p*-Methoxybenzyl (1*S*,6*R*,7*R*,8*S*,9*R*,10*R*)-5,8-dioxo-6-(phenylacetamido)-13-oxa-8-thia-4-azatetracyclo-[8.2.1.0^{2,9}.0^{4,7}]trideca-2,11-diene-3-carboxylate (95)** (from **92** and furan): mp 202−203 °C (acetone); IR (CH_2Cl_2) 1801, 1725, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.41 (dd, J = 3.9, 1.6 Hz, 1H), 3.56 (d, J = 15.4 Hz, 1H), 3.63 (d, J = 15.4 Hz, 1H), 3.81 (s, 3H), 4.41 (dd, J = 4.8, 1.6 Hz, 1H), 5.24 (s, 2H), 5.39 (dt, J = 3.9, 1.1 Hz, 1H), 5.89 (brd, J = 2.6 Hz, 1H), 5.96 (dd, J = 9.7, 4.8 Hz, 1H), 6.27 (dd, J = 5.7, 1.6 Hz, 1H), 6.47 (dd, J = 5.7, 2.0 Hz, 1H,), 6.54 (d, J = 9.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H,), 7.22−7.33 (m, 5H), 7.36 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 43.6 (t), 55.6 (q), 57.7 (d), 57.9 (d), 68.3 (t), 70.4 (d), 79.4 (d), 81.4 (d), 114.4 (d), 122.4 (s), 127.0 (s), 127.8 (d), 129.1 (s), 129.3 (d), 129.5 (d), 130.9 (d), 131.2 (d), 134.0 (s), 135.4 (d), 160.1 (s), 160.3 (s), 164.5 (s), 171.5 (s); mass spectrum m/z 521 (MH$^+$). Anal. Calcd for $C_{27}H_{24}N_2O_7S$: C, 62.30; H, 4.65; N, 5.38; S, 6.16. Found: C, 62.18; H, 4.68; N, 5.28; S, 6.09.

***p*-Methoxybenzyl (1*S*,6*R*,7*R*,8*S*,9*R*,10*S*)-10-acetyl-5,8-dioxo-6-(phenylacetamido)-13-oxa-8-thia-4-azatetracyclo-[8.2.1.0^{2,9}.0^{4,7}]trideca-2,11-diene-3-carboxylate (96)** (from **92** and 2-acetylfuran): IR (CH_2Cl_2) 1803, 1721, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.31 (d, J = 1.5 Hz, 1H), 3.60 (br s, 2H), 3.81 (s, 3H), 4.40 (dd, J = 4.9, 1.5 Hz, 1H), 5.25 (s, 2H), 5.98 (d, J = 1.9 Hz, 1H), 5.99 (dd, J = 9.8, 4.9 Hz, 1H), 6.20 (d, J = 5.4 Hz, 1H), 6.49 (d, J = 9.8 Hz, 1H), 6.60 (dd, J = 5.4, 1.8 Hz, 1H), 6.90 (m, 2H), 7.24−7.38 (m, 7H); mass spectrum m/z 563 (MH$^+$).

***p*-Methoxybenzyl (1*S*,6*R*,7*R*,8*S*,9*R*,10*R*)-11-[(dimethylamino)carbonyl]-5,8-dioxo-6-(phenylacetamido)-13-oxa-8-thia-4-azatetracyclo[8.2.1.0^{2,9}.0^{4,7}]trideca-2,11-diene-3-carboxylate (97)** (from **92** and *N*,*N*-dimethyl-3-furamide): IR (KBr) 1795, 1716, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 3H), 3.10 (s, 3H), 3.50 (dd, J = 4.0, 1.2 Hz, 1H), 3.57 (s, 2H), 3.80 (s, 3H), 4.45 (dd, J = 5.0, 1.5 Hz, 1H), 5.24 (s, 2H), 5.73 (dd, J = 3.9, 0.9 Hz, 1H), 5.99 (dd, J = 10.0, 5.3 Hz, 1H), 6.03 (d, J = 1.4 Hz, 1H), 6.56 (d, J = 10.0 Hz, 1H), 6.60 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.23−7.38 (m, 7H); mass spectrum m/z 592 (MH$^+$).

***p*-Methoxybenzyl (1*S*,6*R*,7*R*,8*S*,9*R*,10*R*)-13-(*tert*-butoxycarbonyl)-5,8-dioxo-6-(phenylacetamido)-8-thia-4,-13-diazatetracyclo[8.2.1.0^{2,9}.0^{4,7}]trideca-2,11-diene-3-carboxylate (98)** (from **92** and *N*-Boc-pyrrole): IR (CH_2Cl_2) 1801, 1718, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.39 (dd, J = 3.4, 1.6 Hz, 1H), 3.60 (ABq, J = 15.4 Hz, 2H), 3.80 (s, 3H), 4.41 (dd, J = 4.8, 1.6 Hz, 1H), 5.14 (dd, J = 3.4, 1.7 Hz, 1H), 5.25 (s, 2H), 5.69 (brs, 1H), 5.94 (dd, J = 9.7, 4.8 Hz, 1H), 6.24

(dd, J = 5.6, 2.1 Hz, 1H), 6.41 (dd, J = 5.6, 2.6 Hz, 1H), 6.53 (d, J = 9.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.23−7.35 (m, 5H), 7.36 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5 (q), 43.70 (t), 55.6 (q), 57.9 (d), 58.0 (d), 61.8 (d), 64.2 (d), 68.4 (t), 70.3 (d), 82.2 (s), 114.4 (d), 122.7 (s), 127.1 (s), 127.7 (d), 129.4 (d), 129.6 (d), 129.7 (s), 131.0 (d), 131.5 (d), 134.0 (s), 135.3 (d), 153.9 (s), 160.2 (s), 160.3 (s), 164.5 (s), 171.5 (s); mass spectrum m/z 637 (MNH_4^+).

***p*-Methoxybenzyl (1*S*,6*R*,7*R*)-1-oxo-7-(phenylacetamido)-3-(2-pyrrolyl)ceph-3-em-4-carboxylate (99)** (from **92** and pyrrole): IR (CH_2Cl_2) 1792, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (dd, J = 17.9, 1.5 Hz, 1H), 3.62 (m, 2H), 3.81 (s, 3H), 4.27 (d, J = 17.9 Hz, 1H), 4.55 (dd, J = 4.6, 1.5 Hz, 1H), 5.23 (ABq, J = 11.8 Hz, 2H,), 5.97 (dd, J = 10.0, 4.6 Hz, 1H), 6.26 (m, 1H), 6.45 (m, 1H), 6.77 (d, J = 10.0 Hz, 1H), 6.90 (m, 3H), 7.34 (m, 7H), 11.32 (br s, 1H); ^{13}C NMR ($CDCl_3$/methanol-d_4) δ 42.6 (t), 46.7 (t), 58.1 (d), 55.0 (q), 66.9 (d), 68.4 (t), 109.8 (d), 112.5 (d), 113.7 (d), 116.7* and 116.8* (s), 117.3 (s), 121.4* and 121.5* (d), 126.3 (s), 126.5 (s), 127.1 (d), 128.6 (d), 129.0 (d), 130.5 (d), 133.8 (s), 159.7 (s), 163.2 (s), 164.1 (s), 172.0 (s), * signals split due to incomplete H−D exchange; mass spectrum m/z 520 (MH^+).

***p*-Methoxybenzyl (1*S*,6*R*,7*R*)-1-oxo-7-(phenylacetamido)-3-[2-(*N*-methylpyrrolyl)]ceph-3-em-4-carboxylate (100)** (from **92** and *N*-methylpyrrole): IR (CH_2Cl_2) 1798, 1728, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (dd, J = 18.7, 1.8 Hz, 1H), 3.27 (s, 3H), 3.61 (d, J = 15.5 Hz, 1H), 3.68 (d, J = 15.5 Hz, 1H), 3.77 (d, J = 19 Hz, 1H), 3.80 (s, 3H), 4.52 (dd, J = 4.8, 1.6 Hz, 1H), 5.00 (s, 2H), 5.99 (dd, J = 3.7, 1.8 Hz, 1H), 6.09 (dd, J = 3.7, 2.7 Hz, 1H), 6.13 (dd, J = 9.9, 4.7 Hz, 1H), 6.57 (dd, J = 2.6, 1.8 Hz, 1H), 6.74 (d, J = 9.9 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.27−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 34.0 (q), 43.6 (t), 49.1 (t), 55.3 (q), 59.8 (d), 67.1 (d), 68.0 (t), 108.3 (d), 110.2 (d), 113.7 (s), 113.8 (d), 124.3 (d), 126.6 (s), 127.3 (s), 127.7 (d), 129.1 (d), 129.4 (d), 130.8 (d), 133.7 (s), 159.9 (s), 161.1 (s), 164.1 (s), 171.2 (s); mass spectrum m/z 533.1620, calcd for $C_{28}H_{27}N_3O_6S$ 533.1620. Anal. Calcd for $C_{28}H_{27}N_3O_6S$: C, 63.03; H, 5.10; N, 7.87. Found: C, 62.64; H, 5.15; N, 7.96.

***p*-Methoxybenzyl (1*R*,6*R*,7*R*)-1-Oxo-7-(phenylacetamido)-3-[(trifluoromethanesulfonyl)oxy]ceph-3-em-4-carboxylate (101).** To a solution of triflate **4b** (2.0 g, 3.4 mmol) in a mixture of THF (50 mL) and water (2 mL) was added *N*,*N*-dichlorourethane (0.54 g, 3.4 mmol). After being stirred for 45 min, the mixture was concentrated, and the residue was taken up in EtOAc, washed twice with water, and dried ($MgSO_4$). Purification by chromatography and trituration from Et_2O gave **101** (0.675 g, 33%): mp 74−75 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2) 1808, 1736, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.54 (d, J = 16.4 Hz, 1H), 3.66 (s, 2H), 3.80 (s, 3H), 4.38 (d, J = 16.4 Hz, 1H), 4.55 (d, J = 4.9 Hz, 1H), 5.19 (dd, J = 7.5, 4.9 Hz, 1H), 5.22 (d, J = 11.7 Hz, 1H), 5.32 (d, J = 11.7 Hz, 1H), 6.28 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.34 (m, 7H). Anal. Calcd for $C_{24}H_{21}F_3N_2O_9S_2$: C, 47.84; H, 3.51; N, 4.65; S, 10.64. Found: C, 47.97; H, 3.47; N, 4.64; S, 10.84.

***p*-Methoxybenzyl (1*R*,6*R*,7*R*,8*R*,9*S*,10*S*)-5,8-dioxo-6-(phenylacetamido)-13-oxa-8-thia-4-azatetracyclo-[8.2.1.0^{2,9}.0^{4,7}]trideca-2,11-diene-3-carboxylate (102)** (from **101** and furan): IR (CH_2Cl_2) 1796, 1724, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 2H), 3.81 (s, 3H), 4.09 (d, J = 5.0 Hz, 1H), 4.43 (d, J = 3.5 Hz, 1H), 4.79 (dd, J = 7.1, 5.0 Hz, 1H), 5.17 (d, J = 11.9 Hz, 1H), 5.26 (d, J = 11.9 Hz, 1H,), 5.27 (ddd, J = 3.7, 1.7, 0.8 Hz, 1H,), 6.17 (dd, J = 2.0, 0.8 Hz, 1H), 6.30 (dd, J = 5.6, 2.0 Hz, 1H), 6.37 (d, J = 7.1 Hz, 1H), 6.68 (dd, J = 5.6, 1.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.25−7.40 (m, 7H); mass spectrum (NOBA−Na) m/z 543 (MNa^+).

***p*-Methoxybenzyl (4*S*,5*S*,6*S*,8*R*,9*R*)-[4-^{2}H$_1$]-10-Oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]-dec-2-ene-2-carboxylate (69) and *p*-Methoxybenzyl (4*R*,5*R*,6*S*,8*R*,9*R*)-[4-^{2}H$_1$]-10-Oxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene (70)** (from **4b** and *cis*-β-deuteriostyrene[28]) (69%, 1:1 ratio). **69** was eluted first: mp 211−212 °C (EtOAc); IR (KBr) 1785, 1705, 1677, 1649cm^{-1}; UV (EtOH) λ_{max} (ϵ) 268 (13 100) nm; ^{1}H NMR ($CDCl_3$) δ 3.51 (t, J = 8.1 Hz, 1H), 3.61 and 3.67 (ABq, J = 16.1 Hz, 2H), 3.73 (dd, J = 8.3, 2.5 Hz, 1H), 3.79 (s, 3H), 4.36 (dd, J = 8.1, 2.6 Hz, 1H), 4.99 (d, J = 5.0Hz, 1H), 5.18 and 5.23 (ABq, J = 11.9 Hz, 2H), 5.78 (ABq, J = 8.7, 4.9 Hz, 2H), 6.10 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.20−7.38 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 38.2 (t, J = 20.4 Hz), 43.1, 43.4, 47.4, 55.4, 58.5, 60.4, 67.2, 114.1 (2C), 120.3, 126.2 (2C), 127.42, 127.44, 127.8, 128.9 (2C), 129.3 (2C), 129.6 (2C), 130.5 (2C), 133.8, 135.2, 141.0, 159.9, 161.1, 164.3, 171.3; ^{2}H NMR ($CHCl_3$) δ 3.32; mass spectrum m/z 542 (MH^+). **70**: mp 185−186 °C (EtOAc); IR (KBr) 1779, 1717, 1654 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 273 (11 100) nm; ^{1}H NMR ($CDCl_3$) δ 3.47 and 3.54 (ABq, J = 16.1 Hz, 2H), 3.59 (d, J = 9.7 Hz, 1H), 3.79 (s, 3H), 3.97 (t, J = 9.7 Hz, 1H), 4.68 (dd, J = 9.7, 0.9 Hz, 1H), 4.95 (d, J = 4.9 Hz, 1H), 5.19 and 5.29 (ABq, J = 12.0 Hz, 2H), 5.71 (dd, J = 9.1 and 4.9 Hz, 1H), 5.82 (d, J = 9.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.07−7.35 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 36.3 (t, J = 20.9 Hz), 40.0, 43.3, 46.4, 55.4, 58.4, 60.5, 67.3, 114.1 (2C), 120.6, 127.4 (2C), 127.67, 127.73 (2C), 128.6 (2C), 129.1 (2C), 129.5 (2C), 130.4 (2C), 133.6, 138.0, 138.4, 159.9, 160.9, 164.1, 171.2; ^{2}H NMR ($CHCl_3$) δ 3.55; mass spectrum m/z 542 (MH^+).

***p*-Methoxybenzyl (4*S*,5*S*,6*S*,7*S*,8*R*,9*R*)-[4-^{2}H$_1$]-7,10-Dioxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo-[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (93) and *p*-Methoxybenzyl (4*R*,5*R*,6*S*,7*S*,8*R*,9*R*)-[4-^{2}H$_1$]-7,10-Dioxo-5-phenyl-9-(phenylacetamido)-7-thia-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (94)** (from **92** and *cis*-β-deuteriostyrene) (43%, 1:1 ratio). The earlier-eluting fractions contained predominantly the (4*S*,5*S*) isomer **93**: ^{1}H NMR ($CDCl_3$) δ 3.60 and 3.66 (ABq, J = 15.4 Hz, 2H), 3.66 (dd, J = 8.3, 2.1 Hz, 1H), 3.79 (s, 3H), 3.93 (t, J = 8.2 Hz, 1H), 4.00 (dt, J = 8.4, 1.9 Hz, 1H), 4.37 (dd, J = 4.9, 1.7 Hz, 1H), 5.20 and 5.25 (ABq, J = 11.8 Hz, 2H), 5.96 (dd, J = 9.7, 4.9 Hz, 1H), 6.65 (1H, d, J = 9.7 Hz), 6.89 (d, J = 8.7 Hz, 2H), 7.15−7.39 (m, 12H); ^{2}H NMR ($CHCl_3$) δ 3.38. The later-eluting fractions contained predominantly the (4*R*,5*R*) isomer **94**: ^{1}H NMR ($CDCl_3$) δ 3.41 and 3.47 (ABq, J = 15.2 Hz, 2H), 3.60 (brd, J = 10.7 Hz, 1H), 3.79 (s, 3H), 4.05 (dt, J = 10.0, 1.5 Hz, 1H), 4.29 (t, J = 10.1 Hz, 1H), 4.35 (dd, J = 4.9, 1.8 Hz, 1H), 5.23 and 5.31 (ABq, J = 11.9 Hz, 2H), 5.84 (dd, J = 9.8, 4.9 Hz, 1H), 6.51 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.15−7.39 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 35.3 (m), 40.6, 42.9, 55.2, 58.2, 60.6, 67.4, 70.7, 114.0 (2C), 122.2, 127.1, 127.2, 127.6, 127.9 (2C), 128.5 (2C), 128.9 (2C), 129.3 (2C), 130.1, 130.4 (2C), 133.9, 135.5, 159.9 (2C), 163.6, 171.2; ^{2}H NMR ($CHCl_3$) δ 3.76; mass spectrum m/z 557 (M^+).

***p*-Methoxybenzyl (4*S*,5*R*,6*S*,8*R*,9*S*)-[4-^{2}H$_1$]-10-Oxo-5-phenyl-9-(phenylacetamido)-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (106) and *p*-Methoxybenzyl (4*R*,5*S*,-6*S*,8*R*,9*S*)-[4-^{2}H$_1$]-10-Oxo-5-phenyl-9-(phenylacetamido)-1-azatricyclo[6.2.0.0^{3,6}]dec-2-ene-2-carboxylate (107).** To a solution of triflate **103** (30 mg, 0.0528 mmol) and *cis*-β-deuteriostyrene (0.12 mL, 0.80 mmol) in CH_2Cl_2 (2 mL) was added a solution of DBU (8 μL, 0.0528 mmol) in CH_2Cl_2 (0.5 mL). After being stirred at room temperature for 1 h, the mixture was chromatographed to give the products **106** and **107** (5.4 mg, 20%) as a 1:1 mixture: IR (CH_2Cl_2) 1772, 1720, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.33 (q, J = 11.7 Hz, 0.5H), 1.02 (q, J = 11.4 Hz, 0.5H), 1.46 (ddd, J = 12.4, 6.7, 3.5 Hz, 0.5H), 2.10 (ddd, J = 12.3, 6.3, 3.5 Hz, 0.5H), 3.07−3.19 (m, 1H), 3.42−3.51 (m + ABq, J = 16.2 Hz, 2H), 3.58 and 3.63 (ABq, J = 15.7 Hz, 1H), 3.78−3.86 (m, 5H), 5.12 (t, J = 5.7 Hz, 0.5H), 5.16 and 5.22 (ABq, J = 12.0 Hz, 1H), 5.19 (t, J = 5.9 Hz, 0.5H), 5.19 and 5.26 (ABq, J = 12.0 Hz, 1H), 5.54 (d, J = 6.3 Hz, 0.5H), 5.93 (d, J = 6.0 Hz, 0.5H), 6.87 (d, J = 8.6 Hz, 2H), 6.95 (brd, J = 8.0 Hz, 1H), 7.09 (brd, J = 7.8 Hz, 1H), 7.16−7.36 (m, 10H); ^{2}H NMR ($CHCl_3$) δ 3.20 and 3.30; mass spectrum m/z 523 (MH^+).

***p*-Methoxybenzyl (4*S*,8*R*,9*S*,11*R*,12*S*)-13-Oxo-12-(phenylacetamido)-1-aza-6,7-benzotetracyclo[9.2.0.0^{3,9}.0^{4,8}]-trideca-2,6-diene-2-carboxylate (105).** To a solution of triflate **103** (0.203 g, 0.357 mmol) and indene (0.63 mL, 5.40 mmol) in CH_2Cl_2 (8 mL) was added a solution of DBU (54 μL, 0.36 mmol) in CH_2Cl_2 (2 mL). After being stirred at room temperature for 1 h, the mixture was chromatographed to give

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105 (0.101 g, 53%): mp 241−242 °C (CH_2Cl_2/EtOAc); IR (CH_2Cl_2) 1770, 1719, 1684 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 275 (9600) nm; ^1H NMR ($CDCl_3$) δ 1.07 (brq, J = 11.6 Hz, 1H), 2.05 (ddd, J = 12.3, 6.7, 3.4 Hz, 1H), 2.91−3.02 (m, 1H), 3.23 and 3.30 (dABq, J = 17.3, 10.1, 6.1 Hz, 2H), 3.50 (brt, J = 6.2 Hz, 1H), 3.59 and 3.66 (ABq, J = 16.1 Hz, 2H), 3.68−3.76 (m, 1H), 3.80 (s, 3H), 4.04−4.13 (m, 1H), 5.13 and 5.26 (ABq, J = 12.0 Hz, 2H), 5.18 (brt, J = 5.5 Hz, 1H), 6.03 (d, J = 6.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.15−7.39 (m, 11H). Anal. Calcd for $C_{33}H_{30}N_2O_5$: C, 74.14; H, 5.66; N, 5.24; *m/z* M 534.2155. Found: C, 73.56; H, 5.68; N, 5.30; M^+ 534.2155.

***p*-Methoxybenzyl (6*R*,7*S*)-3-(2,5-Dihydrofur-2-yl)-7-(phenylacetamido)-1-carba-1-dethiaceph-3-em-4-carboxylate (104).** To a stirred solution of triflate **103** (20 mg, 0.035 mmol) and 2,3-dihydrofuran (13.3 μL, 0.176 mmol) in benzene (0.5 mL) were added $Pd(OAc)_2$ (0.4 mg), 1,1′-bis(diphenylphosphino)ferrocene (2.0 mg), and $^iPr_2NEt$ (6.1 μL, 0.035 mmol). The reaction mixture was heated at 45 °C for 24 h. Chromatography gave the product **104** (16.4 mg, 96%) as a mixture of diastereomers (1:1): IR (CH_2Cl_2) 1769, 1720, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00−1.17 and 1.17−1.32 (2m, 1H), 1.86−2.53 (m, 3H), 3.58 (s, 2H), 3.69−3.81 and 3.79 (m+s, 4H), 4.67−4.70 (m, 2H), 5.16−5.27 (m, 3H), 5.55 (dd, J = 6.0, 1.7 Hz, 0.5H), 5.71 (dd, J = 5.5, 2.4 Hz, 0.5H), 5.96−6.00 (m, 1.5H), 6.07−6.18 (m, 1.5H), 6.86 (d, J = 8.7 Hz, 2H), 7.16−7.35 (m, 7H); mass spectrum *m/z* 511 (MNa^+).

Diphenylmethyl (6*R*,7*R*)-7-(Phenylacetamido)-3-(2-tetrahydrofuryl)ceph-3-em-4-carboxylate (11). To a solution of (2-tetrahydrofuryl)tri-*n*-butylstannane[9] (3.0 g, 8.3 mmol) in THF (20 mL) at −78 °C was added *n*-butyllithium (6.23 mL, 9.97 mmol, 1.6 M solution in hexanes). After 15 min this solution was transferred *via* a cannula to a suspension of copper(I) bromide−dimethyl sulfide complex in a mixture of dimethyl sulfide (15 mL) and THF (30 mL) at −78 °C. The dark brown mixture was stirred for 30 min at −78 °C and then transferred *via* a cannula to a solution of triflate **4a** (1.9 g, 3.0 mmol) in a mixture of *N*-methylpyrrolidone (20 mL) and THF (50 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h and then quenched by the addition of saturated NH_4Cl. The mixture was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. The 3-butyl compounds (0.403 g, 25%), as a 3.3:1 mixture of Δ^2- and Δ^3-cephems **13** and **6**, were separated from the 3-(2-tetrahydrofuryl) products (1.014 g, 61%) as a 1.2:1 mixture of Δ^2- and Δ^3-cephems **12** and **11** by chromatography. **Ceph-2-em 13:** ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 7.1 Hz, 3H), 1.10−1.50 (m, 4H), 1.92−2.12 (m, 2H), 3.63 (s, 2H), 4.87 (s, 1H), 5.21 (d, J = 4.0 Hz, 1H), 5.62 (dd, J = 9.1, 4.0 Hz, 1H), 5.87 (d, J = 0.9 Hz, 1H), 6.16 (d, J = 9.1 Hz, 1H), 6.87 (s, 1H), 7.26−7.42 (m, 15H). The 3-(2-tetrahydrofuryl) products were treated with *m*-CPBA and the resulting Δ^3-sulfoxide reduced with PCl_3 by the procedure described for the preparation of **15** to give the title compound **11** as a 1:1 mixture of diastereomers: IR (KBr) 1780, 1723, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23−1.96 (m, 2.5H), 2.21−2.32 (m, 0.5H), 2.99−3.92 (m, 6H), 4.84 (dd, J = 9.1, 6.7 Hz, 0.5H), 4.95 (d, J = 4.8 Hz, 1H), 5.01 (brt, J = 8.0 Hz, 0.5H), 5.76 and 5.85 (2dd, J = 8.9, 4.8 Hz, 1H), 6.01 and 6.08 (2d, J = 8.9 Hz, 1H), 6.86 and 6.94 (2s, 1H), 7.26−7.38 (m, 15H); mass spectrum *m/z* 554 (M^+).

Example of a Reaction of Triflate 4a with (2-Tetrahydrofuryl)tri-*n*-butylstannane under Pd Catalysis. Formation of 3-*n*-Butylceph-3-em (6). To a solution of triflate **4a** (100 mg, 0.158 mmol) in *N*-methylpyrrolidone (1 mL) was added (2-tetrahydrofuryl)tri-*n*-butylstannane (67 mg, 0.186 mmol), $(MeCN)_2PdCl_2$ (8 mg), and $ZnCl_2$ (0.336 mL, 1 M solution in Et_2O). The mixture was stirred at room temperature for 2 days and then partitioned between EtOAc and water, and the organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed to give diphenylmethyl (6*R*,7*S*)-3-*n*-butyl-7-(phenylacetamido)ceph-3-em-4-carboxylate (**6**) (23 mg, 25%): ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 6.9 Hz, 3H), 1.14−1.45 (m, 4H), 2.21−2.50 (m, 2H), 3.17 and 3.38 (ABq, J = 18.0 Hz, 2H), 3.61 and 3.69 (ABq, J = 16.2 Hz, 2H), 4.94 (d, J = 4.6 Hz, 1H), 5.76 (dd, J = 8.9, 4.7 Hz, 1H), 6.11 (d, J = 8.9 Hz, 1H), 6.92 (s, 1H), 7.26−7.38 (m, 15H); mass spectrum *m/z* 540 (M^+).

Kinetic Studies. To the individual styrenes (10 equiv) and triflate **4b** (10 mg, 0.017 mmol) in CH_2Cl_2 was added $^iPr_2NEt$ (3 μL, 0.017 mmol). After being stirred for 10 min, the reaction mixture was analyzed by HPLC (eluent 15%MeCN in CH_2Cl_2, detection at 270 nm). Competitive reactions were performed as above but with a mixture of 4-methoxystyrene (10 equiv) and another styrene (10 equiv). Only the later-eluting isomer of the 4-methoxystyrene product and the earlier-eluting isomer of the other styrene product were resolved. The information on the product isomer ratios of the individual reactions allowed the determination of the total product ratios. The relative rates of reactions were determined by the formula: $k_{rel} = k_X/k_{OMe} = P_X/P_{OMe}$, where X is the other substituted styrene and P_X/P_{OMe} is the product ratio.

Supporting Information Available: ^1H, ^2H, and ^{13}C NMR spectra of selected compounds (77 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.

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