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Structurally Novel Bi- and Tricyclic β-Lactams via [2 + 2] Cycloaddition or Radical Reactions in 2-Azetidinone-Tethered Enallenes and Allenynes

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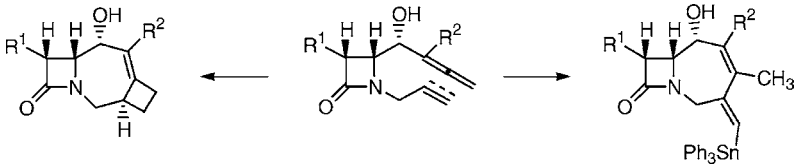
ABSTRACT



Thermolysis of β-lactam-tethered enallenyl alcohols gave tricyclic ring structures via a formal [2 + 2] cycloaddition of the alkene with the distal bond of the allene, while the tin-promoted radical cyclization in 2-azetidinone-tethered allenynes proceeded to provide bicyclic β-lactams containing a medium-sized ring. The access to cyclization precursors was achieved by regio- and stereoselective metal-mediated carbonyl allenylation of 4-oxoazetidine-2-carbaldehydes in an aqueous environment.

β-Lactam antibiotics have occupied a central role in the vigil against bacterial infections over the past several decades.[1] The various families of β-lactam antibiotics differ in their spectrum of antibacterial activity and in their susceptibility to β-lactamase enzymes, which constitute the most common and growing form of antibacterial resistance.[2] Bacterial resistance to β-lactam antibiotics caused by their widespread use over the past few decades has motivated a growing interest in the preparation and biological evaluation of new types of β-lactams that will overcome the defense mechanisms of the bacteria. Tricyclic β-lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases.[3] Besides, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition[4] to the use of these products as starting materials to develop new synthetic methodologies[5] has triggered a

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(1) For selected reviews, see: (a) Setti, E. L.; Micetich, R. G. *Curr. Med. Chem.* **1998**, *5*, 101. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (c) Neuhaus, F. C.; Georgeopapadakou, N. H. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J., Georgeopapadakou, N. H., Eds.; Chapman and Hall: New York, 1992.

(2) β-Lactamase enzymes catalyze the hydrolysis of β-lactams to give ring-opened β-amino acids that are no longer effective as inhibitors against their targets: bacterial membrane-bound transpeptidases enzymes. See, for example: (a) Sandanayaka, V. P.; Prashad, A. S. *Curr. Med. Chem.* **2002**, *9*, 1145. (b) Ritter, T. K.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508. (c) Díaz, N.; Suárez, D.; Merz, K. M. M., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4197. (d) Page, M. I. *Chem. Commun.* **1998**, 1609. (e) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (f) Hook, V. *Chemistry in Britain* **1997**, *33*, 34. (g) Spratt, B. G. *Science* **1994**, *264*, 388. (h) Davies, J. *Science* **1994**, *264*, 375.

(3) For selected references, see: (a) Kanno, O.; Kawamoto, I. *Tetrahedron* **2000**, *56*, 5639. (b) Hanessian, S.; Reddy, B. *Tetrahedron* **1999**, *55*, 3427. (c) Biondi, S.; Pecunioso, A.; Busi, F.; Contini, S. A.; Donati, D.; Maffeis, M.; Pizzi, D. A.; Rossi, L.; Rossi, T.; Sabbatine, F. M. *Tetrahedron* **2000**, *56*, 5649. (d) Ghiron, C.; Rossi, T. *The Chemistry of Trinems* in *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Societa Chimica Italiana: Rome, 1997; Vol. 1, pp 161−186. (e) Ngo, J.; Castañer, J. *Drugs Future* **1996**, *21*, 1238.

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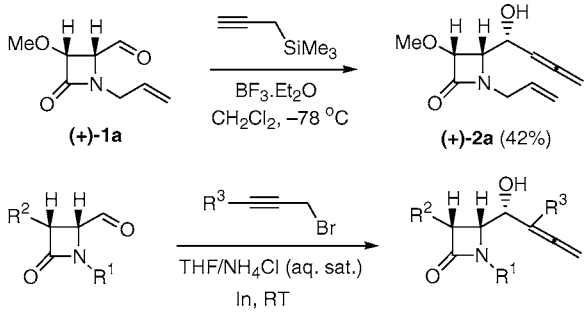
renewed interest in the building of new polycyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.[6] On the other hand, allenes have most certainly reached the status of important and useful functional groups in organic synthesis. Allenes can be transformed into other functional groups, such as olefins, alkynes, and α,β-unsaturated carbonyls and also participate in a variety of cycloaddition and transition metal-catalyzed cyclization reactions.[7] During the course of our ongoing project directed toward the synthesis of potentially bioactive 2-azetidinones,[8] we discovered a novel palladium-catalyzed domino reaction in allenynes.[8a] In this contribution, we wish to connect the chemistry of allenes with noncatalytic cyclization processes for the synthesis of enantiopure fused polycyclic β-lactams of nonconventional structure.

The starting substrates, 4-oxoazetidine-2-carbaldehydes **1a**−**d**, were prepared both in the racemic form and in optically pure form using standard methodology. Enantiopure 2-azetidinones (+)-**1a** and (+)-**1c** were obtained as single cis enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with methoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[8] Racemic compounds (±)-**1b** and (±)-**1d** were obtained as single cis diastereoisomers following our one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine.[9] α-Allenyl alcohol (+)-**2a** was prepared by boron trifluoride diethyl etherate-induced condensation of 4-oxoazetidine-2-carbaldehyde (+)-**1a** with propargyltrimethylsilane, while 2-azetidinone-tethered allenes **2b**−**h** were achieved via metal-mediated Barbier-type carbonyl-allenylation reaction of β-lactam aldehydes **1a**−**d** in aqueous media using our previously described methodologies (Scheme 1).[8a]

Scheme 1



(+)-1a R^1 = 2-propenyl, R^2 = MeO — **(+)-2b** R^3 = Me (75%)
(+)-1a R^1 = 2-propenyl, R^2 = MeO — **(+)-2c** R^3 = Ph (64%)
(±)-1b R^1 = 4-methoxyphenyl, R^2 = ethenyl — **(±)-2d** R^3 = Me (54%)
(±)-1b R^1 = 4-methoxyphenyl, R^2 = ethenyl — **(±)-2e** R^3 = Ph (80%)
(+)-1c R^1 = 2-propynyl, R^2 = MeO — **(+)-2f** R^3 = Me (75%)
(+)-1c R^1 = 2-propynyl, R^2 = MeO — **(+)-2g** R^3 = Ph (60%)
(±)-1d R^1 = 4-methoxyphenyl, R^2 = 2-propynyl — **(±)-2h** R^3 = Me (81%)

The intermolecular [2 + 2] cycloaddition reaction has been used to build tricyclic β-lactams bearing a four-membered ring fused to a cephalosporin, by treatment of a β-lactam enol triflate with different olefins, although in some cases a large excess of alkene was required to obtain reasonable yields.[10] Although, in theory, an intramolecular cycloaddition of β-lactam-dienes could be used to prepare tricycles, to our knowledge, there is no report involving intramolecular [2 + 2] cycloaddition reaction of 2-azetidinone-tethered alkenes.

The inherent instability imparted by the cumulated double bond in allenes[11] has been exploited by many research groups taking advantage of the facility in which cycloaddition reactions take place relative to that of an isolated double bond.[7b] However, positional selectivity problems are significant. Intramolecularization of the reactions, usually by placing the group at distances such that five- or six-membered rings are formed, automatically should solve the

(4) Some of the more notable advances concern the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus, protease, thrombin, and prostate-specific antigen. For selected examples, see: (a) Page, M. I.; Laws, A. P. *Tetrahedron* **2000**, *56*, 5631. (b) Haley, T. M.; Angier, S. J.; Borthwick, A. D.; Singh, R.; Micetich, R. G. *Drugs* **2000**, *3*, 512. (c) Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LaPlante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. G.; Deziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965. (d) Ogilvie, W. W.; Yoakim, C.; Do, F.; Hache, B.; Lagace, L.; Naud, J.; O'Meara, J. A.; Deziel, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1521. (e) Vaccaro, W. D.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313. (f) Borthwick, A. D.; Weingarte, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365. (g) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123.

(5) For reviews, see: (a) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (c) Alcaide, B.; Almendros, P. *Org. Prep. Proced. Int.* **2001**, *33*, 315. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321. (f) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (g) Ojima, I. *Adv. Asym. Synth.* **1995**, *1*, 95. (h) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

(6) For a recent review on bi- and tricyclic-β-lactams with nonclassical structures, see: Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.

(7) For general reviews, see: (a) Patai, S. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Wiley: Chichester, 1980. (b) Schuster, H. F.; Coppola, G. M. In *Allenes in Organic Synthesis*; Wiley: New York, 1984. (c) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982. (d) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. For a review on transition metal-catalyzed reactions of allenes, see: (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2001**, *39*, 3590. For a review on palladium-allene chemistry, see: (f) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. For a review on transition metal-based cyclization of allenes, see: (g) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. For a selected recent paper on the asymmetric synthesis of oxygenated heterocycles from allenes, see: (h) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *8*, 5012.

(8) See, for instance: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *Chem. Commun.* **2002**, 1472. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 3646. (d) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F.; Pardo, C.; Sáez, E.; Torres, M. R. *J. Org. Chem.* **2002**, *67*, 7004. (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. *J. Org. Chem.* **2003**, *68*, 1426.

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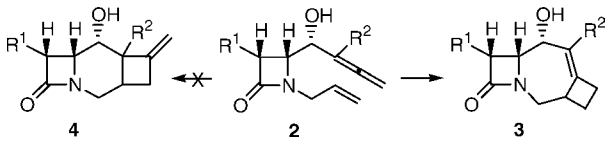
(10) Elliot, R. L.; Nicholson, N. H.; Peaker, F. E.; Takle, A. K.; Richardson, C. M.; Tyler, J. W.; White, J.; Pearson, M. J.; Eggleston, D. S.; Haltiwanger, R. C. *J. Org. Chem.* **1997**, *62*, 4998

(11) Allene moiety was originally thought to be very unstable (prior to the 1970s, allenes were regarded as curiosities) and, in fact, upon undergoing any addition reaction, experiences a relief in strain of about 10 kcal/mol: Padwa, A.; Filipkowski, M. A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Org. Chem.* **1994**, *59*, 591.

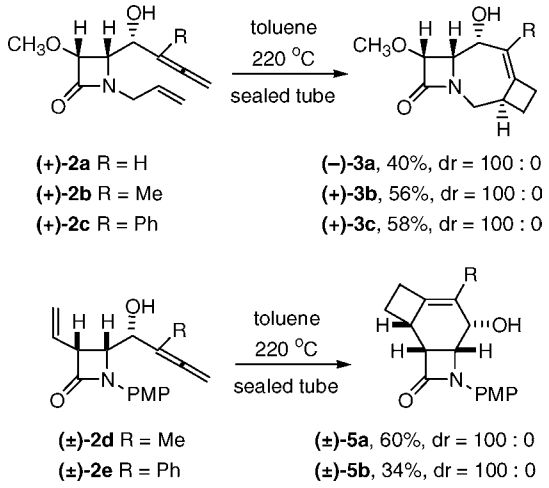
positional selectivity problems because larger rings are unfavored. Because allenes can react as 2π-electron donors in [2 + 2] cycloadditions, 2-azetidinone-tethered enallenyl alcohols **2** would be an ideal cyclization partner for the generation of a diverse array of tricyclic β-lactams containing a cyclobutane ring.[12] Equipped with an efficient synthesis of functionalized 2-azetidinone-tethered enallenes **2**, we attempted the thermolysis and succeeded in isolating tricyclic β-lactams **3** containing a cyclobutane ring. Substitution patterns on enallenes (+)-**2a**−**c** were selected in order to direct the regiochemical outcome of the cycloaddition to the six-membered central ring formation. However, we found that the thermal reaction produced tricycles **3** bearing a central seven-membered ring. No traces of the exocyclic methylene regioisomer **4** could be detected (Scheme 2).

Scheme 2



The tricyclic ring structures **3** arise from a formal [2 + 2] cycloaddition of the alkene with the distal bond of the allene, most likely via a diradical intermediate. Similar behavior patterns were observed on heating enallenes (±)-**2d** and (±)-**2e** to give fused tricycles **5**. Compounds **3** and **5** were obtained in moderate yields as single isomers. Selected examples are shown below in Scheme 3. An unsubstituted

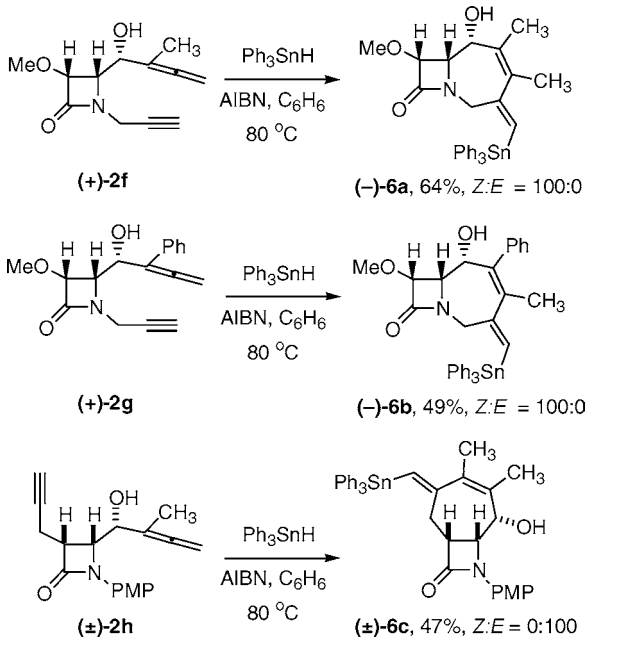
Scheme 3



allene results in a somewhat slower rate of reaction but with similar regiochemical preference. Our observed regiochemistry for the [2 + 2] cycloaddition is remarkable, because it is in sharp contrast with previously reported related examples in which the 2π-component was the internal double bond of the allene moiety;[13] only Padwa et al. have reported a similar regioselectivity from their study of intramolecular [2 + 2] cycloaddition reactions on (phenylsulfonyl)enallenes on preparing bicyclo[4.2.0]octene systems,[14] related to compounds **5**. However, these authors were not able to prepare bicyclo[5.2.0]nonenes, related to compounds **3**, obtaining instead monocyclic-substituted cyclooctenes.[14]

Recently, the use of radical cyclization for carbon−carbon bond-forming reactions has become widespread in organic chemistry for the construction of carbocycles and heterocycles.[15] The majority of commonly employed methods utilize tributyltin hydride to induce homolysis of an organic halide or alcohol derivative in forming the reactive carbon radical species. The addition of a free radical to two carbon−carbon double bonds, one double bond and one triple bond, or two triple bonds, constitutes an alternative approach that has the advantage of incorporating some useful additional functional groups into the cyclized products. Although the utility of this methodology using dienes, enynes, and diynes has been demonstrated, the radical reaction of allenic derivatives has received little attention,[16] because the addition reaction to allenes will be complicated in terms of chemo-, regio-, and stereoselectivity. The radical-induced cyclization of 2-azetidinone-tethered allenynes is appealing because useful functionality is introduced in one simple step in which new carbon−carbon bond formation occurs to afford bicyclic β-lactams of nonconventional structure.[6] The resulting cyclic compounds would be particularly useful to allow further synthetic transformations. This cyclization proceeded elegantly in enynes **2f**−**h** to provide the desired fused bicycles bearing a medium-sized ring **6a**−**c** as single isomers in fair yields (Scheme 4).[17] It is presumed that the addition of stannyl radical to the terminal position of the triple bond gives the vinylic radical intermediates in the propagation step, followed by cyclization toward the central carbon bond of

Scheme 4



the allene moiety to give bicycles **6** in a totally regio- and stereoselective fashion.

In conclusion, a novel entry to enantiopure nonconventional fused bi- and tricyclic β-lactams has been developed by using intramolecular [2 + 2] cycloaddition or radical reactions in monocyclic enallenes and allenynes. The thermolisis of β-lactam-tethered enallenyl alcohols gave tricyclic ring structures via a [2 + 2] cycloaddition of the alkene with the distal bond of the allene, while the tin-promoted radical cyclization in 2-azetidinone-tethered allenynes proceeded to provide bicyclic β-lactams in a totally regio- and stereoselective fashion. This opens up new prospects for the use of enallenes and allenynes as precursors of optically pure fused heterocycles without recourse to transition metal chemistry.

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Supporting Information Available: Spectroscopic and analytical data for compounds (+)-**3b**, (+)-**3c**, (±)-**5a**, (−)-**6a**, and (±)-**6c**, as well as general experimental procedures for compounds **3**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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