DOI: 10.1002/adsc.200900864

Divergent Reactivity of 2-Azetidinone-Tethered Allenols with Electrophilic Reagents: Controlled Ring Expansion *versus* Spirocyclization

Benito Alcaide,[a,*] Pedro Almendros,[b,*] Amparo Luna,[a] and M. Rosario Torres[c]

[a] Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain
Fax: (+34)-91-394-4103; e-mail: alcaideb@quim.ucm.es

[b] Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
Fax: (+34)-91-564-4853; e-mail: Palmendros@iqog.csic.es

[c] CAI Difracción de Rayos X, Facultad de Química, Universidad Complutense de Madrid, 28040 Madrid, Spain

Received: December 14, 2009; Published online: March 4, 2010

Dedicated to Prof. Dr. Antonio García Martínez on the occasion of his retirement.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900864.

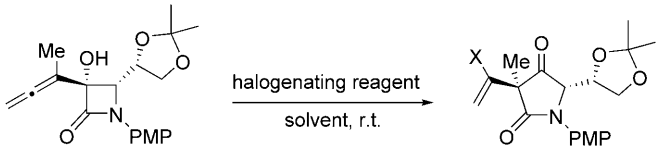
Abstract: A dual reactivity of 2-azetidinone-tethered allenols may occur by judicious choice of the electrophilic reagents, namely halogenating versus selenating reagents. Using common substrates, structurally different compounds, namely tetramic acids (from *N*-bromosuccinimide) or spirocyclic seleno-β-lactams (from *N*-phenylselenophthalimide), can be readily synthesized by these divergent protocols.

Keywords: allenes; chemoselectivity; heterocycles; rearrangement; regioselectivity

Allenes are a class of compounds with two cumulative carbon-carbon double bonds, which are versatile synthetic intermediates in organic synthesis.[1] On the other hand, in addition of the key role that β-lactams have played in medicinal chemistry, namely, the fight against pathogenic bacteria, enzyme inhibition, or gene activation,[2] the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[3] A process which involves a selective chemical reaction, even if the structure of the substrate suggests numerous possibilities for reactivity, represents an attractive strategy.[4] As part of a program aimed at expanding the use of allenes and β-lactams in organic synthesis,[5] we report herein an unprecedented example of control of the reactivity of 2-azetidinone-tethered allenols with electrophilic reagents [*N*-bromosuccinimide (NBS) *versus* *N*-phenylselenophthalimide (NPSP)] which permits the selective synthesis of pyrrolidine-2,4-diones (tetramic acids)[6] and spirocyclic seleno-β-lactams.[7,8] Tetramic acids were achieved through a chemo-, regio-, and diastereoselective ring expansion while spiranic 2-azetidinones were obtained by a regioselective selenocycloetherification.

We employed three different systems in our initial screening of halogenating reagents for the model system 2-azetidinone-tethered allenol **1a**.[9] Initially, the use of molecular bromine was tested. Next, both tribromoisocyanuric acid (TBCA)[10] and NBS were investigated. Substrate **1a** gave full conversion in all cases. Bromine gave a complex mixture of products (Table 1, entry 1). Interestingly, the use of TBCA as bromide source regiospecifically provided pyrrolidine-2,4-dione **2a**, but as a 80:20 mixture of diastereoisomers (Table 1, entry 2). To our delight, these results were improved with NBS, which afforded compound **2** as single isomer, in a totally selective fashion (Table 1, entry 3). Solvent screening demonstrated that dichloromethane was the best choice in the reaction (Table 1, entry 5). Next, we studied the reaction of allenol **1a** with different halogen sources such as molecular iodine, *N*-iodosuccinimide (NIS), and bis-(pyridine)iodonium tetrafluoroborate (Ipy_2BF_4).[11] However, only a small amount of iodotetramic acid derivative **2b** was isolated (Table 1, entries 6–8). Noticeably, the conversion of allenic β-lactam **1a** into tetramic acid **2a** occurs chemo-, regio-, and diastereospecifically. The chemospecificity arises from the exclusive cleavage of the C2–C3 bond of the four-mem-

Table 1. Selective ring expansion reaction of 2-azetidinone-tethered allenol **1a** to tetramic acid derivatives **2a** or **2b** under modified halogenation conditions.



(+)-**1a**

(–)-**2a** X = Br
(–)-**2b** X = I

Entry	Reagent	Solvent	Time [h]	X	Yield [%][a]
1	Br_2	THF/H_2O (15:1)	1	Br	–
2	TBCA	THF/H_2O (15:1)	0.5	Br	(–)-**2a** (74)[b]
3	NBS	MeCN/H_2O (15:1)	1	Br	(–)-**2a** (58)
4	NBS	THF/H_2O (15:1)	6	Br	(–)-**2a** (81)
5	NBS	CH_2Cl_2	1.5	Br	(–)-**2a** (96)
6	I_2	THF/H_2O (15:1)	5	I	(–)-**2b** (20)
7	Ipy_2BF_4	DMSO	24	I	(–)-**2b** (10)
8	NIS	THF/H_2O (15:1)	48	I	(–)-**2b** (23)

[a] Yield of pure, isolated product with correct analytical and spectral data. TBCA = tribromoisocyanuric acid; NBS = *N*-bromosuccinimide; Ipy_2BF_4 = bis(pyridine) iodonium tetrafluoroborate; NIS = *N*-iodosuccinimide.
[b] A separable mixture (80:20) of diastereoisomers was observed.

bered nucleus, while the regiospecificity comes from the sole attack to the proximal allene carbon atom with concomitant placement of the bromine to the central allenic position. Besides, the reaction is diastereospecific so that just one diastereomer is formed.

The structure and stereochemistry of the tetramic acid **2a** was determined by X-ray diffraction analysis,[12] and its ORTEP drawing is shown in Figure 1.

Next, we investigated the substrate scope in this interesting rearrangement reaction. An additional challenge that exists in the development of selective ring

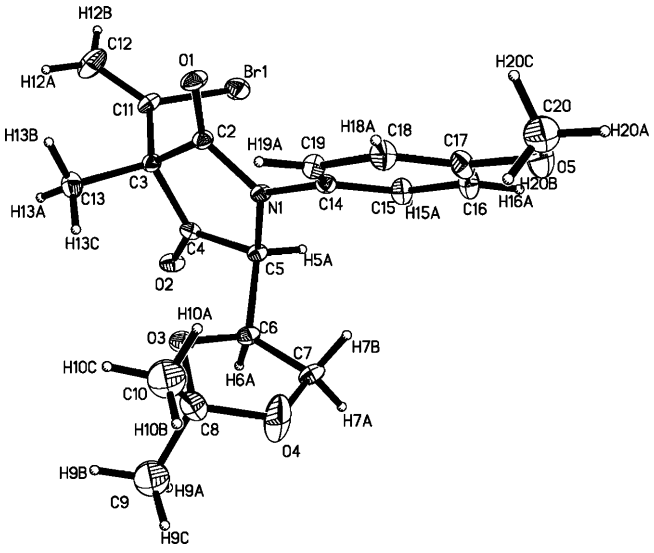
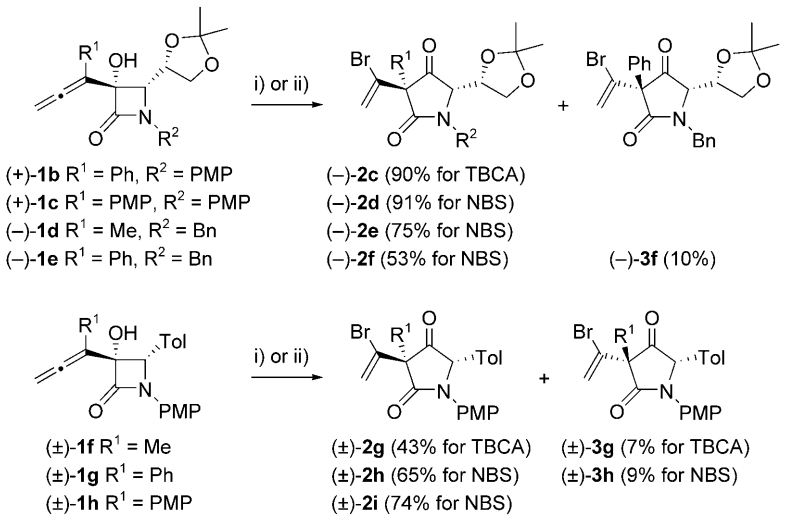


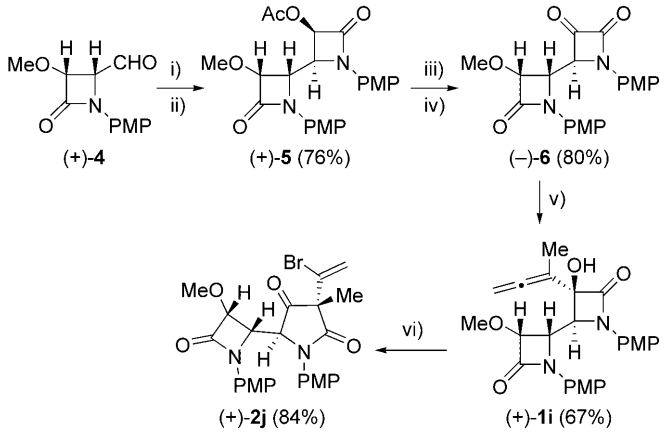
Figure 1. ORTEP-representation of the structure of pyrrolidine-2,4-dione **2a** in the solid state.

expansion reactions in substituted allenes of type **1** includes the control in the stereoselection during the formation of the all carbon stereocentres. Excellent yields and selectivities were achieved for the carbon-carbon bond cleavage in the electrophilic ring opening reaction of allenic β-lactams **1b–d** and **1h** to afford functionalized tetramic acids **2c-e** and **2i** (Scheme 1). Substrates **1e–g** gave a chromatographically separable mixture of major products **2f–h** and their corresponding minor diastereomers **3f–h**. Compounds **2** and **3** are remarkable since they bear a quaternary stereocentre, the formation of all carbon quaternary centres in an asymmetric manner being one of the most difficult problems in organic chemistry, not least because the process requires the creation of a new C–C bond at a hindered centre.[13]

To demonstrate that the above protocol can be considered in complex synthetic planning, it was successfully used for the mono-ring expansion of bis-β-lactam **1i**. The precursors were obtained in an optically pure form from 4-oxoazetidine-2-carbaldehyde **4**.[14] Thus, C4,C4′-bis-β-lactam **5** was prepared by treatment of aldehyde **4** with *p*-anisidine followed by ketene-imine cyclization. Acetoxy-bis-β-lactam **5** was conveniently converted into allenic bis-β-lactam **1i** by sequential transesterification, Swern oxidation, and indium-mediated Barbier-type carbonyl-allenylation reactions (Scheme 2). Worthy of note, the corresponding tetramic acid derivative **2j**, which show the selective bond breakage of the allenic β-lactam ring allowing differentiation between two chemically equivalent functional groups within the same molecule, could be exclusively obtained (Scheme 2). The results in



Scheme 1. Controlled ring expansion reaction of 2-azetidinone-tethered allenols **1b–h** to tetramic acid derivatives **2c–i** and **3f–h** under selective bromination conditions. *Reagents and conditions:* i) NBS, CH_2Cl_2, room temperature, **2d**: 0.5 h; **2e**: 1.5 h, **2i**: 1 h. ii) TBCA, THF/H_2O (15:1), room temperature, **2c**: 0.5 h; **2g**: 1 h. PMP = 4-$MeOC_6H_4$; Tol = 4-MeC_6H_4.



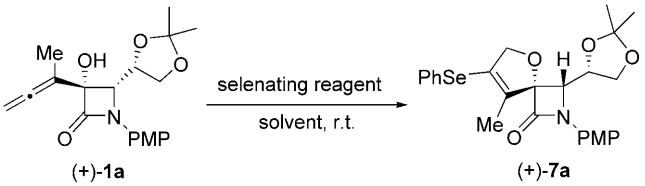
Scheme 2. Controlled ring expansion reaction of allenic bis-β-lactam **1i** to β-lactam/tetramic acid hybrid **2j** under selective bromination conditions. *Reagents and conditions:* i) $PMPNH_2$, $MgSO_4$, CH_2Cl_2, room temperature, 20 h. ii) $AcOCH_2COCl$, Et_3N, room temperature, CH_2Cl_2, room temperature, 14 h. iii) NaOMe, MeOH, 0 °C, 40 min. iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h. v) In, 1-bromobut-2-yne, THF/NH_4Cl (aqueous saturated), room temperature, 20 h. vi) NBS, CH_2Cl_2, room temperature, 45 min. PMP = 4-$MeOC_6H_4$.

Scheme 1 and Scheme 2 point to a steric effect of the substituents of the β-lactam ring at N1 and C4, indicating that bulky non-planar substituents at C4 have a positive influence on the diastereoselectivity of the reaction. Attached-ring adduct **2j** can be regarded as the hybrid of the pharmacologically relevant subunits of β-lactam and tetramic acid.

Next, we were attracted to the possibility that either heterocycle (tetramic acid or spirocycle) could be accessed by variation of the electrophilic reagent. We hypothesized that the product selectivity could be impacted by modulating the relative stability of the three-membered heterocyclic cation generated during the course of the reaction. An initial validation of our hypothesis included the exposure of 2-azetidinone-tethered allenol **1a** to different sources of seleniranium ion, an attractive challenge from both synthetic and biological points of view.[7,15] After extensive experimentation, gratifyingly, we found that treatment of substrate **1a** with the binary system consisting in an excess amount of NPSP (*N*-phenylselenophthalimide)[16] and catalytic amount of the Brønsted acid PTSA in dichloromethane at room temperature gave rise exclusively to the desired spirocyclic seleno-β-lactam **7a** (Table 2). In the absence of PTSA, adduct **7a** was obtained in lower yield. Solvent screening revealed that other solvents such as 1,2-dichloroethane and MeCN/H_2O (15:1) gave lower conversion, whereas retaining the selectivity towards spirocyclization. When *N*-phenylselenosuccinimide (NPSS) or PhSeBr were used instead NPSP under otherwise comparable conditions, the reaction proceeded less effectively to afford the desired selenaderivative **7a**.

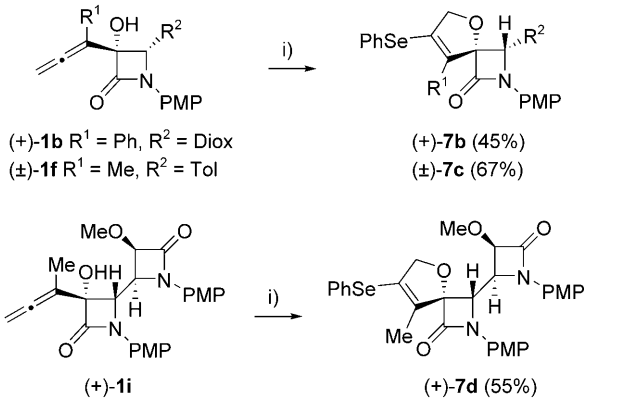
Under the optimized reaction conditions, we investigated the generality of the selenocycloetherification reaction. Differently functionalized 2-azetidinone-tethered allenes **1b**, **1f**, and **1i** cleanly underwent the spirocyclization to regiospecifically furnish selena-adducts **7b–d** in good yields (Scheme 3). The investigation of various allenic-β-lactam substrates in this reaction revealed that spiroadducts **7** were produced in all cases as the sole reaction products; tetramic acid derivatives not even being present in detectable amount.

Table 2. Selective selenocycloetherification reaction of 2-azetidinone-tethered allenol **1a** to spirocyclic β-lactam **7a** under modified selenation conditions.

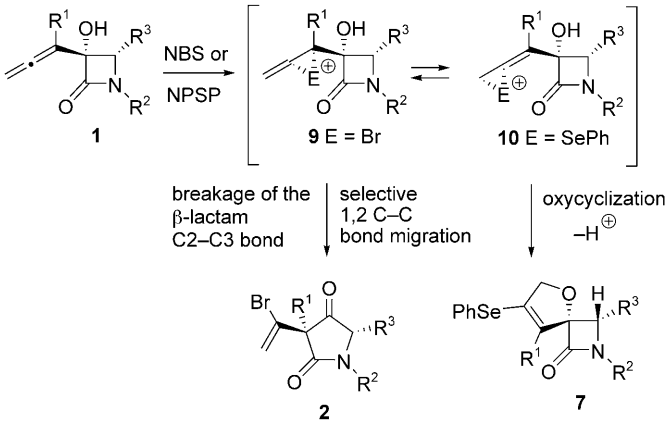


Entry	Reagent	Solvent	Time (h)	Catalyst	Yield [%][a]
1	PhSeBr	$MeCN/H_2O$ (15:1)	22	–	30
2	NPSS	$MeCN/H_2O$ (15:1)	40	–	–
3	NPSS	CH_2Cl_2	22	PTSA (15 mol%)	10
4	NPSP	$MeCN/H_2O$ (15:1)	40	–	–
5	NPSP	DCE	40	PTSA (15 mol%)	15
6	NPSP	CH_2Cl_2	40	–	17
7	NPSP	CH_2Cl_2	40	PTSA (10 mol%)	54
8	NPSP	CH_2Cl_2	40	PTSA (15 mol%)	64

[a] Yield of pure, isolated product with correct analytical and spectral data. NPSS = *N*-phenylselenosuccinimide; NPSP = *N*-phenylselenophthalimide; DCE = 1,2-dichloroethane; PTSA = *p*-toluenesulfonic acid.



Scheme 3. Controlled selenocycloetherification reaction of 2-azetidinone-tethered allenols **1b**, **1f**, and **1i** to spirocyclic seleno β-lactam derivatives under selective selenation conditions. *Reagents and conditions:* i) NPSP, 15 mol% PTSA, CH_2Cl_2, room temperature, **7b**: 48 h; **7c**: 40 h, **7d**: 48 h. PMP = 4-$MeOC_6H_4$. Diox = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl; Tol = 4-MeC_6H_4; NPSP = *N*-phenylselenophthalimide; PTSA = *p*-toluenesulfonic acid.



Scheme 4. Mechanistic explanation for the NBS- or NPSP-mediated preparation of tetramic acids **2** and spirocyclic seleno β-lactams **7** from common precursor allenols **1**.

A plausible mechanism for the formation of adducts **2** and **7** is illustrated in Scheme 4. It should be noted that *C*-attack and *O*-attack to the allene moiety could both be possible in this type of reaction. When NBS is used as the reactant, allenols **1** initially generate bromonium species **9**. Alternatively, the related seleniranium species **10** could also be formed in the presence of NPSP. Thus, cations **9** evolve to rearranged tetramic acids *via* intramolecular 1,2 C–C bond migration, which is chemospecific because of the exclusive breakage of the C2–C3 bond of the four-membered heterocycle. The stereoselectivity may be explained by the presence of the C4 substituent, which leads to the formation of the *anti* adduct to avoid steric repulsion between the C4 group and the bromoalkenyl moiety. On the other hand, cations **10** suffer highly regioselective nucleophilic attack of the oxygenated moiety to the former distal allenic carbon to afford the final spirocyclic products, rather than evolve by the activation of the strained C–C σ bond of the four-membered ring.

In summary, we have demonstrated for the first time that electrophilic reagents are capable of modulating 2-azetidinone-tethered allenol reactivity. These reactions can be tuned by using morphologically related NBS or NPSP as the reagents. From common substrates, structurally different compounds, namely tetramic acids or spirocyclic seleno-β-lactams, can be

readily synthesized by our divergent protocols. A more in-depth study of the reaction mechanisms involved in these processes and the understanding of their scope and limitations is underway.

Experimental Section

Typical Procedure for the Ring-Expansion Reaction to Tetramic Acids using 2-Azetidinone-Tethered Allenol 1a and *N*-Bromosuccinimide

To a solution of the 2-azetidinone-tethered allenol (+)-**1a** (50 mg, 0.15 mmol) in dichloromethane (6.5 mL) was added *N*-bromosuccinimide (35 mg, 0.196 mmol). The reaction mixture was stirred at room temperature for 90 min. Saturated aqueous sodium hydrogen carbonate (1.5 mL) was added, before being partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 2:1) to afford the product (−)-**2a** as a colorless solid; mp 137–139 °C; $[\alpha]_D$: −12.5 (*c* 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.32 and 6.95 (d, J = 8.8 Hz, each 2H), 6.03 and 5.85 (d, J = 3.0 Hz, each 1H), 4.65 (d, J = 2.3 Hz, 1H), 4.51 (td, J = 6.6, 2.2 Hz, 1H), 3.81 (m, 4H), 3.42 (dd, J = 8.9, 6.1 Hz, 1H), 1.60 and 1.42 (s, each 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.1, 171.7, 158.6, 129.8, 126.5, 125.7, 121.2, 114.4, 109.8, 75.1, 68.4, 64.5, 59.7, 55.4, 26.1, 24.6, 17.6; IR ($CHCl_3$): ν = 1760, 1703, 1513, 1251 cm^{-1}; HR-MS (EI): m/z = 424.0756, calcd for $C_{19}H_{23}BrNO_5$ $[M+H]^+$: 424.0760.

Acknowledgements

Support for this work by the DGI-MICINN (Projects CTQ2006-10292 and CTQ2009-09318), CAM (Project S2009/PPQ-1752), and UCM-BSCH (Grant GR58/08) are gratefully acknowledged. We thank Gonzalo Gómez-Campillos for his help in the preparation of some materials.

References

[1] For selected reviews, see: a) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; c) *Modern Allene Chemistry*, (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; d) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12; e) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; f) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.

[2] The β-lactam nucleus is the key structural motif in biologically relevant compounds such as antibiotics, enzyme inhibitors, and gene activators. For selected references, see: a) *Chemistry and Biology of* β-*Lactam Antibiotics*, (Eds.: R. B. Morin, M. Gorman), Academic Press, New York, **1982**, vols. 1–3; b) R. Southgate, C. Branch, S. Coulton, E. Hunt, in: *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, (Ed.: G. Lukacs), Springer Verlag, Berlin, 1993, vol. 2, p 621; c) G. Veinberg, M. Vorona, I. Shestakova, I. Kanepe, E. Lukevics, *Curr. Med. Chem.* **2003**, *10*, 1741; d) J. D. Rothstein, S. Patel, M. R. Regan, C. Haenggeli, Y. H. Huang, D. E. Bergles, L. Jin, M. D. Hoberg, S. Vidensky, D. S. Chung, S. V. Toan, L. I. Bruijn, Z.-z. Su, P. Gupta, P. B. Fisher, *Nature* **2005**, *433*, 73.

[3] For a review on the synthetic utility of β-lactams, see: B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437.

[4] For a review on chemoselective chemistry for the construction of complex molecules, see: R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.* **2009**, *42*, 530.

[5] See, for instance: a) B. Alcaide, P. Almendros, T. Martínez del Campo, M T. Quirós, *Chem. Eur. J.* **2009**, *15*, 3344; b) B. Alcaide, P. Almendros, R. Carrascosa, T. Martínez del Campo, *Chem. Eur. J.* **2009**, *15*, 2496; c) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 1901; d) B. Alcaide, P. Almendros, T. Martínez del Campo, *Chem. Eur. J.* **2008**, *14*, 7756; e) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem.* **2007**, *119*, 6804; *Angew. Chem. Int. Ed.* **2007**, *46*, 6684; f) B. Alcaide, P. Almendros, T. Martínez del Campo, R. Rodríguez-Acebes, *Adv. Synth. Catal.* **2007**, *349*, 749; g) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem.* **2006**, *118*, 4613; *Angew. Chem. Int. Ed.* **2006**, *45*, 4501.

[6] The substituted pyrrolidine-2,4-dione scaffold is a key pattern present in tetramic acids, a class of compounds exhibiting interesting biological properties ranging from antibacterial to antitumoral activities. For reviews, see: a) B. J. L. Royles, *Chem. Rev.* **1995**, *95*, 1981; b) A. Gossauer, *Prog. Chem. Org. Nat. Prod.* **2003**, *86*, 1; c) R. Schobert, A. Schlenk, *Bioorg. Med. Chem.* **2008**, *16*, 4203. For selected recent references, see: d) Y.-C. Jeong, M. G. Moloney, *Synlett* **2009**, 2487; e) C. A. Lowery, J. Park, C. Gloeckner, M. M. Meijler, R. S. Mueller, H. I. Boshoff, R. L. Ulrich, C. E. Barry, III, D. H. Bartlett, V. V. Kravchenko, G. F. Kaufmann, K. D. Janda, *J. Am. Chem. Soc.* **2009**, *131*, 14473; f) T. Yoshinari, K. Ohmori, M. G. Schrems, A. Pfaltz, K. Suzuki, *Angew. Chem.* **2010**, *122*, 893; *Angew. Chem. Int. Ed.* **2010**, *49*, 881.

[7] Spiro-β-lactams behave as β-turn mimetics, as well as enzyme inhibitors, they are precursors of α,α-disubstituted β-amino acids, and the spiranic β-lactam moiety is present in chartellines, a family of marine natural products. For selected recent references, see: a) S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Chem. Commun.* **2009**, 6265; b) A. Macías, A. Morán Ramallal, E. Alonso, C. del Pozo, J. González, *J. Org. Chem.* **2006**, *71*, 7721; c) H. Bittermann, F. Böckler, J. Einsiedel, P. Gmeiner, *Chem. Eur. J.* **2006**, *12*, 6315; d) P. S. Baran, R. A. Shenvi, C. A. Mitsos, *Angew. Chem.* **2005**, *117*, 3780; *Angew. Chem. Int. Ed.* **2005**, *44*, 3714. The biological and medicinal properties of organoselenium compounds are also increasingly appreciated, mainly due to their antioxidant, antimicrobial, antitumor, antihypertensive, enzyme modulator, and antiviral proper-

ties; e) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255; f) M. Soriano-García, *Curr. Med. Chem.* **2004**, *11*, 1657; g) T. G. Back, Z. Moussa, *J. Am. Chem. Soc.* **2003**, *125*, 13455. For recent reviews on organoselenium chemistry, see: h) D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi, T. Wirth, *Angew. Chem.* **2009**, *121*, 8559; *Angew. Chem. Int. Ed.* **2009**, *48*, 8409; i) D. M. Freudendahl, S. A. Shahzad, T. Wirth, *Eur. J. Org. Chem.* **2009**, 1649.

[8] For a review on the electrophilic addition to allenic derivatives, see: a) W. Smadja, *Chem. Rev.* **1983**, *83*, 263. For selected references on the interaction of allenes with halogenated reagents, see: b) J. Barluenga, E. Campos-Gómez, A. Minatti, D. Rodríguez, J. M. González, *Chem. Eur. J.* **2009**, *15*, 8946; c) J. Li, W. Kong, Y. Yu, C. Fu, S. Ma, *J. Org. Chem.* **2009**, *74*, 8733; d) J. L. García-Ruano, V. Marcos, J. Alemán, *Angew. Chem.* **2009**, *121*, 3201; *Angew. Chem. Int. Ed.* **2009**, *48*, 3155; e) B. Lü, X. Jiang, C. Fu, S. Ma, *J. Org. Chem.* **2009**, *74*, 438; f) F. Yu, X. Lian, J. Zao, Y. Yu, S. Ma, *J. Org. Chem.* **2009**, *74*, 1130; g) X. Jiang, C. Fu, S. Ma, *Chem. Eur. J.* **2008**, *14*, 9656; h) J. Li, C. Fu, G. Chen, G. Chai, S. Ma, *Adv. Synth. Catal.* **2008**, *350*, 1376. For selected references on the interaction of allenes with selenating reagents, see: i) G. He, Y. Yu, C. Fu, S. Ma, *Eur. J. Org. Chem.* **2010**, 42; j) G. He, H. Guo, R. Quian, Y. Guo, C. Fu, S. Ma, *Tetrahedron* **2009**, *65*, 4877; k) G. Chen, C. Fu, S. Ma, *J. Org. Chem.* **2006**, *71*, 9877; l) S. Ma, F. Pan, X. Hao, H. Huang, *Synlett* **2004**, 85; m) P. L. Beaulieu, V. M. Morisset, D. G. Garratt, *Tetrahedron Lett.* **1980**, *21*, 129.

[9] Starting allenols, were prepared using our methodology: a) B. Alcaide, P. Almendros, R. Carrascosa, M. C. Redondo, *Chem. Eur. J.* **2008**, *14*, 637; b) B. Alcaide, P. Almendros, C. Aragoncillo, R. Rodríguez-Acebes, *J. Org. Chem.* **2001**, *66*, 5208; c) B. Alcaide, P. Almendros, C. Aragoncillo, *Org. Lett.* **2000**, *2*, 1411.

[10] a) M. Eissen, D. Lenoir, *Chem. Eur. J.* **2008**, *14*, 99830; b) L. S. DeAlmeida, P. M. Esteves, M. C. S. De Mattos, *Synlett* **2006**, *2*, 1515.

[11] a) J. Barluenga, M. Trinchado, E. Rubio, J. M. González, *Angew. Chem.* **2003**, *115*, 2508; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406.

[12] X-ray data of **2a**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{19}H_{22}BrNO_5$ (M_r = 424.29); orthorhombic; space group: *P*2(1)2(1)2(1); a = 7.7011(7) Å, b = 9.4066(9) Å; c = 27.809(3) Å.; β = 90 deg.; V = 2014.5(3) Å^3; Z = 4; cd = 1.399 mg m^{-3}; μ = 2.068 mm^{-1}; F(000) = 872. A transparent crystal of 0.313 × 0.424 × 0.460 mm^3 was used. 4380 [R(int) = 0.0422] independent reflections were collected on a Bruker Smart CCD difractomer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3 in ω. The cell parameter were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final R(Rw) values were $R1$ = 0.0433, $wR2$ = 0.1082. CCDC 711362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax (+44)-1223–336033; or deposit@cccdc.cam.ac.uk].

[13] For recent selected reviews, see: a) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969; b) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; d) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127; e) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[14] a) B. Alcaide, P. Almendros, A. Luna, M. R. Torres, *J. Org. Chem.* **2006**, *71*, 4818; b) B. Alcaide, P. Almendros, J. M. Alonso, *J. Org. Chem.* **2004**, *69*, 993.

[15] The spiroether structural motif contains two rings joined by a single chiral oxo quaternary carbon centre; a biologically relevant moiety present in a variety of natural products and pharmaceuticals. For selected references, see: a) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572; b) S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku, M. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3148; c) F. A. Macías, J. L. G. Galindo, R. M. Varela, A. Torres, J. M. G. Molinillo, F. R. Fronczek, *Org. Lett.* **2006**, *8*, 4513.

[16] K. C. Nicolau, D. A. Claremon, W. E. Barnette, S. P. Seitz, *J. Am. Chem. Soc.* **1979**, *101*, 3704.

