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Tetrahedron Letters 45 (2004) 6429–6431
Tetrahedron Letters

Metal-assisted synthesis of enantiopure spirocyclic β-lactams from azetidine-2,3-diones

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Received 17 May 2004; revised 17 June 2004; accepted 30 June 2004
Available online 19 July 2004

Abstract—A novel approach to enantiopure spirocyclic β-lactams has been developed by using different intramolecular metal-catalyzed cyclization reactions in monocyclic unsaturated alcohols. The access to cyclization precursors, 2-azetidinone-tethered homoallylic alcohols, (buta-1,3-dien-2-yl)methanols, and α-allenols was achieved by regio and stereoselective addition of stabilized organo-indium reagents to azetidine-2,3-diones in aqueous environment.

The importance of β-lactam antibiotics for the treatment of bacterial infections is well documented.[1] Besides, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition[2] to the use of these products as starting materials to develop new synthetic methodologies,[3] has triggered a renewed interest in the building of new β-lactam systems. In particular, spirocyclic β-lactams behave as β-turn mimetics,[4] as well as cholesterol absorption inhibitor,[5] they are precursors of α,α-disubstituted β-amino acids,[6] and the spiranic β-lactam moiety is present in chartellines, a family of marine natural products.[7]

Until now, relatively few efforts have been devoted to the synthesis of spiro β-lactams. Besides, all these syntheses were exclusively performed via cycloaddition reactions, mainly involving the ketene–imine cycloaddition.[8] The highly selective properties of metals would seem to recommend their application to the preparation of spirocycles. Consequently, as an alternative to the existing cycloaddition strategies, we thought in using metal-containing reagents for developing a novel and versatile entry to diversely functionalized spiranic-2-azetidinones. Based on our previous experience on the synthesis and synthetic applications of β-lactams,[9] in this contribution we wish to connect the chemistry of unsaturated alcohols with catalytic cyclization reactions for the synthesis of enantiopure spirocyclic β-lactams from azetidine-2,3-diones.

Starting substrates, enantiopure azetidine-2,3-diones (+)-**1a** and (+)-**1b**, were prepared from the corresponding (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imine, via Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation.[10] Homoallyl alcohol (+)-**2**, (buta-1,3-dien-2-yl) alcohol (+)-**3**, and α-allenyl alcohols (+)-**4a**–**d** were regiospecifically prepared through metal-mediated Barbier-type carbonyl-allylation, -1,3-butadien-2-ylation, or -allenylation reactions of α-keto lactams **1** in aqueous media, using our methodologies (Scheme 1).[10] Ring-closing metathesis (RCM) is one of the most powerful and reliable approaches to construct a ring system.[11] Indeed, transformation of alcohols **2** and **3** in diolefin precursors followed by RCM proved to be a straightforward access to spirocyclic β-lactams containing five- or six-membered oxacycles (Scheme 2). Of interest was the exposure of the triene derived from the butadienol (+)-**3** to Grubbs' catalyst. As expected from the literature precedent,[12] only the least substituted double bond of the 1,3-diene system reacted, to give the six-membered spiro compound (+)-**8**, which bears an exocyclic methylene. No traces of the five-membered regioisomer (+)-**7** could be detected.

Keywords: β-lactams; Metals; Oxacycles; Spirocycles.
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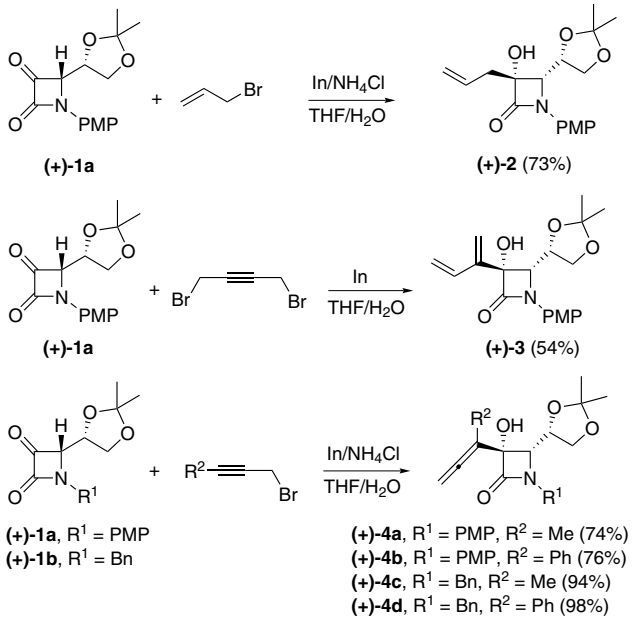
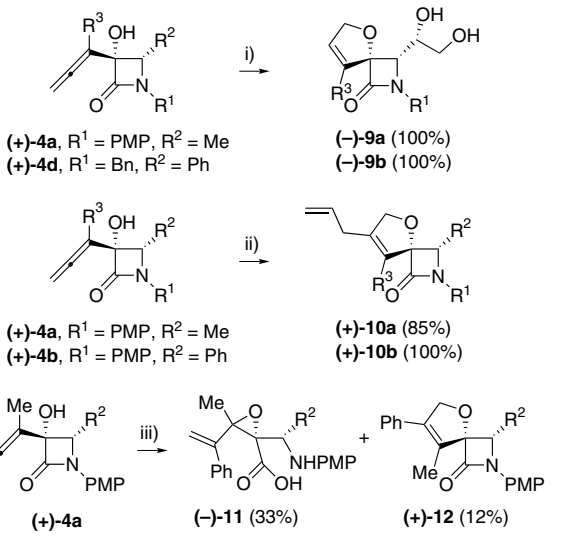
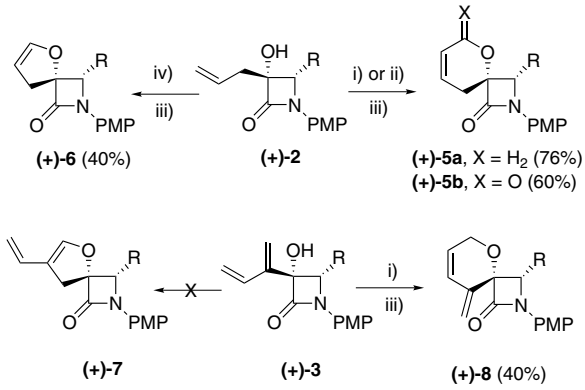
doi:10.1016/j.tetlet.2004.06.130



Scheme 1.



Scheme 3. Key: R^2 = [(*S*)-2,2-dimethyl-1,3-dioxalan-4-yl]. Reagents and conditions: (i) $AgNO_3$ (1 equiv), acetone–H_2O (1:1), reflux, **9a**: 3 h, **9b**: 6 h; (ii) allyl bromide (5 equiv), 5 mol% $PdCl_2$, DMF, rt, **10a**: 2 h; (iii) PhI (1:1 equiv), 5 mol% $Pd(PPh_3)_4$, K_2CO_3 (4 equiv), DMF, 85 °C, 45 h.



Scheme 2. Key: R = [(*S*)-2,2-dimethyl-1,2-dioxalan-4-yl]. Reagents and conditions: (i) allyl bromide (1.6 equiv), TBAI (cat), NaOH (aq 50%)–DCM (1:1), rt, 16 h; (ii) acryloyl chloride (2 equiv), HNa (2 equiv), THF, from 0 °C to rt, 16 h; (iii) 5 mol% $Cl_2(Cy_3P)_2Ru{=}CHPh$, toluene, reflux, **5a**: 7 h, **5b**: 33 h, **6**: 16 h, **8**: 12 h; (iv) methyl propiolate (1.2 equiv), Et_3N (2 equiv), DCM, 0 °C, 30 min.

Considering that allenes bearing a nucleophilic center can be cyclized on treatment with a wide variety of transition metal catalysts,[13] we turned our attention to metal-based cyclization reactions in our β-lactam-tethered α-allenic alcohols **4**. Our initial work began with the silver-induced reaction of α-allenols (+)-**4a** and (+)-**4d**, to give, with concomitant acetonide cleavage, the spirocyclic dihydrofurans (−)-**9a** and (−)-**9b** in quantitative yields. Next, we explored the palladium-catalyzed cyclizative coupling reaction of α-allenols (+)-**4a** and (+)-**4b** with unsaturated organic halides. Under optimized conditions, allyl bromide efficiently gave the disubstituted spiro dihydrofuran-β-lactams (+)-**10a** and (+)-**10b**,[14] while phenyl iodide afforded as main product the oxirane β-amino acid (−)-**11**, together with the regioisomeric spiranic five-membered ring (+)-**12** (Scheme 3). The formation of epoxide (−)-**11** involves concomitant ring opening of the β-lactam nucleus, probably because of the ring strain of the intermediate spirocyclic oxirane-β-lactam, which cannot survive under the reactions conditions.

In conclusion, a novel entry to enantiopure diversely functionalized spiranic β-lactams has been developed by using intramolecular metal-promoted cyclization reactions in monocyclic homoallylic alcohols, (buta-1,3-dien-2-yl)methanols, and α-allenols. The ring-closing metathesis of diolefin derivatives of the above alcohols proved to be a straightforward access to spirocyclic β-lactams containing five- or six-membered oxacycles. The metal-based cyclization reactions of the β-lactam-tethered α-allenic alcohols constitute a versatile entry to spiranic dihydrofuran- β-lactam derivatives. These results open up the possibility of future application to chiral building blocks other than 2-azetidinones. Other aspects of this chemistry are currently under investigation in our laboratory.

Acknowledgements

Support for this work by the DGI-MCYT (Project BQU2003-07793-C02-01) is gratefully acknowledged. R.R.-A. thanks the MCYT for a predoctoral grant. T.M.-C. thanks the UCM and CSIC, for studentships ('beca de colaboración' and 'beca de introducción a la investigación', respectively).

References and notes

1. For selected reviews, see: (a) Hubbard, B. K.; Walsh, C. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 730; (b) Nau, R.; Eiffert,

A. *Clin. Microb. Rev.* **2002**, *15*, 95; (c) Setti, E. L.; Micetich, R. G. *Curr. Med. Chem.* **1998**, *5*, 101; (d) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993.

2. 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.
3. For reviews, see: (a) Alcaide, B.; Almendros, P. *Synlett* **2002**, *1*, 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.
4. Alonso, E.; López-Ortiz, F.; del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333.
5. Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282.
6. Alonso, E.; del Pozo, C.; González, J. *Synlett* **2002**, 69.
7. Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141.
8. (a) del Pozo, C.; Macías, A.; López-Ortiz, F.; Maestro, M. A.; Alonso, E.; González, J. *Eur. J. Org. Chem.* **2004**, 535; (b) Arjona, O.; Csák, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett.* **2002**, *34*, 6405; (c) Alonso, E.; del Pozo, C.; González, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 571; (d) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631; (e) DallaCroce, P.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1999**, *55*, 201; (f) Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369; (g) Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461; (h) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010; (i) Le Blanc, S.; Pete, J.-P.; Piva, O. *Tetrahedron Lett.* **1992**, *33*, 1993; (j) Dolle, R. E.; Li, C. S.; Novelli, R.; Kruse, L. I.; Eggleston, D. *J. Org. Chem.* **1992**, *57*, 128; (k) Dolle, R. E.; McNair, D.; Hughes, M. J.; Kruse, L. I.; Eggleston, D.; Saxty, B. A.; Wells, T. N. C.; Groot, P. H. E. *J. Med. Chem.* **1992**, *35*, 4875.
9. See, for instance: (a) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993; (b) Alcaide, B.; Almendros, R.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2004**, *69*, 826; (c) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793; (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795; (e) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415.
10. (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208; (b) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925.
11. For some reviews on olefin metathesis, see: (a) *Handbook of Metathesis*; Vols. 1–3, Grubbs, R. H., Ed.; Wiley–VCH: Weinheim, 2003; (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (c) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18; (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (e) Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2001**, *7*, 945; (f) Fürstner, A. *Synlett*, **1999**, 1523; (g) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211; (h) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (i) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 371; (j) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036.
12. (a) Mentink, G.; Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2002**, *4*, 3497; (b) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
13. For recent reviews on transition metal catalyzed cyclizations of allenes, see: (a) Hashmi, A. S. K. *Angew. Chem.* **2000**, *112*, 3737; (b) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12; (c) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701.
14. Representative experimental procedure for the synthesis of enantiopure spirocyclic β-lactams. General procedure for the palladium-catalyzed coupling reaction of α-allenols **4** with allyl bromide. Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding α-allenol **4** (0.10 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction mixture was stirred under argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being extracted with ethyl acetate (3×4 mL). The organic phase was washed with water (2×2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic 2-azetidinones **10**. Selected data: Spiranic dihydrofuran-β-lactam (+)-**10a**. From 64 mg (0.186 mmol) of the α-allenol (+)-**4a**, compound (+)-**10a** (61 mg, 85%) was obtained as a colorless oil. $[\alpha]_D$ +21.08 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.73 and 6.89 (d, each 2H, J = 9.3 Hz), 5.75 (m, 1H), 5.12 (dq, 1H, J = 6.8, 1.5 Hz), 5.05 (q, 1H, J = 0.7 Hz), 4.74 and 4.56 (dd, each 1H, J = 12.7, 2.0 Hz), 4.45 (m, 1H), 4.25 (dd, 1H, J = 8.5, 7.1 Hz), 4.08 (d, 1H, J = 8.5 Hz), 3.81 (s, 3H), 3.53 (dd, 1H, J = 8.8, 6.1 Hz), 2.92 (m, 2H), 1.65 (t, 3H, J = 2.0 Hz), 1.54 and 1.34 (s, each 3H). ^{13}C NMR ($CDCl_3$): δ 166.2, 156.5, 134.6, 133.6, 131.0, 125.4, 119.7, 116.7, 114.0, 109.8, 101.2, 78.3, 77.4, 66.6, 66.5, 55.4, 29.6, 26.6, 24.6, 8.5. IR ($CHCl_3$, cm^{-1}): ν 1747. MS (EI), *m*/*z*: 386 (M^++1, 22), 385 (M^+, 6), 149 (100). (Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.66; H, 7.01; N, 3.65).