ORGANIC LETTERS

2001
Vol. 3, No. 26
4205−4208

Rapid Entry to Enantiopure Carbacepham Derivatives via Lewis Acid Promoted Carbonyl-Ene Cyclization of 2-Azetidinone-Tethered Alkenylaldehydes

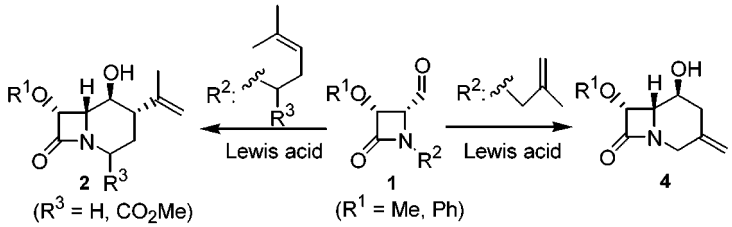
Benito Alcaide,* Carmen Pardo, Carolina Rodríguez-Ranera, and Alberto Rodríguez-Vicente

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040-Madrid, Spain

alcaideb@quim.ucm.es

Received October 8, 2001

ABSTRACT



Lewis acid promoted types I and II carbonyl-ene cyclizations of 2-azetidinone-tethered alkenylaldehydes are used for the rapid, highly diastereoselective synthesis of polyfunctionalized, enantiomerically pure carbacepham derivatives.

The Lewis acid promoted ene cyclizations of unsaturated carbonyl compound represent a valuable method for the stereoselective synthesis of functionalized cyclic compounds.[1] Similarly to other intramolecular cycloadditions, ene cyclization profits from entropic advantage, operational simplicity, and the fact that it proceeds usually with high degrees of regio- and stereocontrol. In addition, the development of new approaches to the stereocontrolled synthesis of β-lactam systems is a subject of interest in the context of their possible use as biologically active compounds[2] or as versatile chiral building blocks.[3] Our interest in the use of 4-oxoazetidine-2-carbaldehydes **1** as substrates for addition reactions and cyclization processes[4] prompted us to evaluate their ene reactions as a straighforward route to functionalized fused bicyclic 2-azetidinones. We reasoned that the presence of activated alkenyl groups attached to position N1 of the β-lactam ring might provide an opportunity to use such carbonyl-ene cyclization for the synthesis of bicyclic β-lactams of the carbapenam and carbacepham series, through both type I and type II cyclization modes (Scheme 1). Despite the great number of reported methodologies that have been developed for the synthesis of bicyclic β-lactams from a

(1) For reviews, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Snider, B. B. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 527. (c) Snieckus, V.; Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.

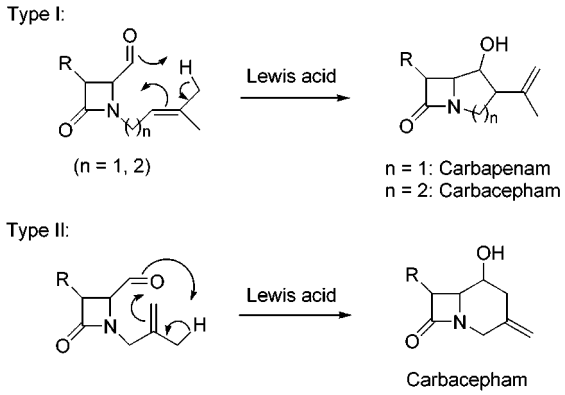
(2) See, for example: (a) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (b) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (d) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992A.

(3) See, for instance: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321. (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

(4) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226 and references therein.

10.1021/ol016871a CCC: $20.00
Published on Web 11/22/2001

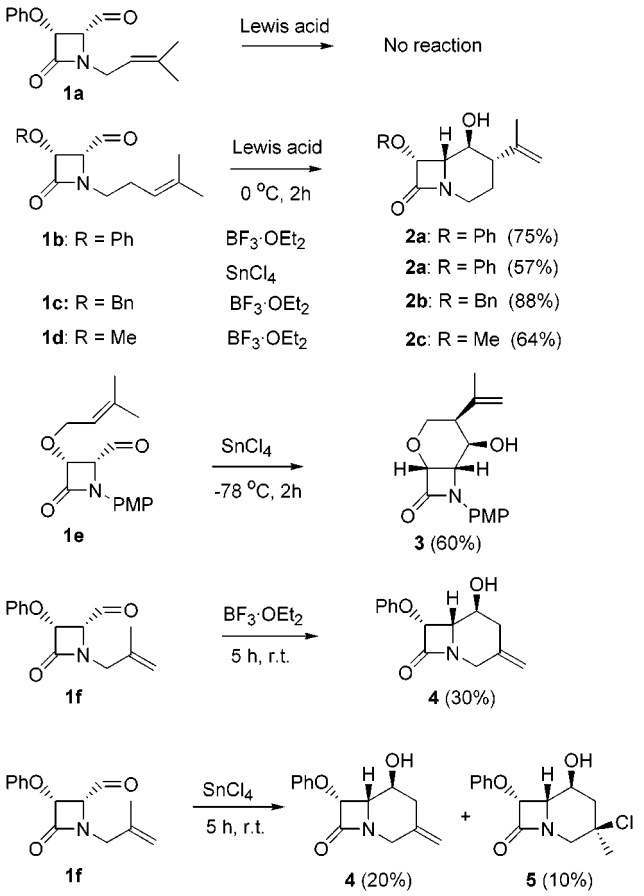
Scheme 1. Types I and II Carbonyl-Ene Cyclization Modes of 2-Azetidinone-Tethered Alkenyldehydes to Carbapenam and Carbacepham



preformed functionalized 2-azetidinone,[5] no reports refer to the carbonyl-ene cyclization.[6] We wish to report here the use of Lewis acid promoted carbonyl-ene cyclizations of 2-azetidinone-tethered alkenylaldehydes for the rapid synthesis of functionalized, enantiomerically pure carbacepham systems with extremely high diastereofacial selectivity.[7]

To evaluate the potential of intramolecular carbonyl-ene reaction for the synthesis of bicyclic β-lactams of the carbapenam and carbacepham series, we prepared several 2-azetidinone-tethered alkenylaldehydes **1** having variable length of the linking chain, different connectivity pattern of the reactive sites, and different substituted terminal or internal alkene moieties. Cyclization precursors, aldehydes **1**, were easily prepared as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylidene-propanal, through Staüdinger reactions with the corresponding acid chlorides in the presence of Et_3N,[8] followed by standard transformation of the acetal moiety.[9] Scheme 2 summarizes our results for the different enals **1** tested.[10] Reaction of **1a** with both $SnCl_4$ and BF_3·Et_2O failed to give the corresponding carbapenam system under different experimental conditions. However, homologous substrate **1b** proceeded smoothly to stereoselectively provide carbacepham **2a** in good yield as pure product both with $SnCl_4$ and BF_3·Et_2O.[11] Other tested Lewis acids such as Me_2AlCl, $TiCl_4$, and $ZnBr_2$ were less effective for the cyclization process. Apparently, because of the rigid angular disposition imparted by the planar lactam group, geometric constraints in reactive conformation arising from **1a** preclude an ene reaction to the 1,4-fused [4,5]-system. It is known that in type I ene cyclizations formation of cyclohexanols is

Scheme 2. Intramolecular Carbonyl-Ene Cyclization of 2-Azetidinone-Tethered Alkenylaldehydes **1**



(5) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: Weinheim, 1993; Chapter 3, p 121.

(6) To the best of our knowledge there is only one example of ene reaction for the synthesis of a cepham derivative via a transient sulfinyl cation: Kokulja, S.; Lammert, S. R.; Gleissner, M. R. B.; Ellis, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 5040.

(7) Carbacephems are a promising new family of β-lactam antibiotics closely related to the widely used cephalosporins, with similar antibacterial profiles but with greater chemical stability and enhanced pharmacokinetic properties. See, for example: (a) Cooper, R. D. G. In *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992; Chapter 8, p 272. See, also: (b) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170. (c) Palomo, C.; Ganboa, I.; Kot, A.; Dembkowski, L. *J. Org. Chem.* **1998**, *63*, 6398. (d) Ciufulini, M. A. *Chem. Commun.* **1996**, 881. (e) Lotz, B. T.; Miller, M. J. *J. Org. Chem.* **1993**, *58*, 618.

(8) (a) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227. (b) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: Weinheim, 1993; Chapter 3, p 295.

(9) See, for example: (a) Alcaide, B.; Almendros, P.; R.-Salgado, N. *J. Org. Chem.* **2000**, *65*, 3310. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612.

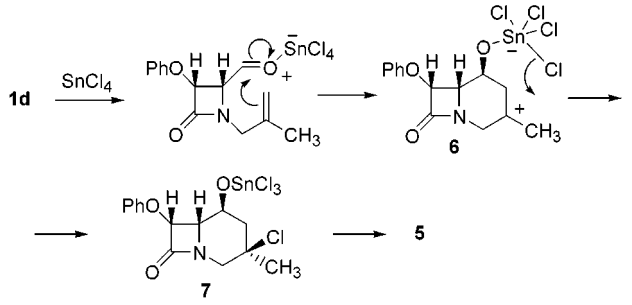
(10) **Representative experimental procedure** for the synthesis of carbacepham **2a**. To a solution of the starting β-lactam **1b** (1 mmol) in dry CH_2Cl_2 (10 mL) under argon at 0 °C was added BF_3·OEt_2 (1.2 mmol) dropwise, and the reaction mixture was stirred at this temperature for 2 h. The reaction was allowed to reach room temperature and quenched with $NaHCO_3$ (sat.). After extraction of the mixture with CH_2Cl_2 the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. After purification by flash chromatography, carbacepham **2a** was obtained in analytically pure form.

(11) All new compounds described herein were fully characterised by spectroscopic methods and microanalysis and/or HRMS. All yields refer to chromatographed, pure (NMR, TLC) compounds. Representative data are given for compound **2a**: mp 90−92 °C; $[\alpha]_D = +58.5$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2H), 1.73 (s, 3H), 1.94 (s, 1H), 2.24 (dt, J = 6.0, 10.0 Hz, 1H), 2.78 (m, J = 1.0, 6.0, 10.0, 13.7 Hz, 1H), 3.64 (dd, J = 3.9, 8.3 Hz, 1H), 3.77 (dd, J = 8.3, 10.0 Hz, 1H), 3.90 (ddd, J = 2.9, 3.9, 13.7 Hz, 1H), 4.91 (br s, 1H), 4.97 (t, J = 1.5 Hz, 1H), 5.33 (dd, 1H, J = 1.0, 3.9 Hz), 7.01−7.11 (m, 3H), 7.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.9, 157.2, 143.8, 129.4, 122.3, 115.7, 114.2, 81.6, 66.5, 59.1, 49.6, 37.8, 29.3, 19.2; IR (KBr, cm^{-1}) ν 3440, 1741; MS (EI) *m*/*z* 274 (M^++ 1, 2), 149 (100), 131 (47). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.50; H, 7.21; N, 5.08.

faster than formation of cyclopentanols as a result of the greater ring strain of cyclopentanols ($n = 6 > 5 \gg 7$).

Alkenylaldehydes **1c** and **1d** afforded compounds **2b** and **2c**, respectively, in good yields in their corresponding reactions with $BF_3{\cdot}Et_2O$. When alkene substituent was moved from position N1 to C3, as in 3,4-tethered enal **1e**, it also furnished the corresponding 3,4-fused [4,6]-system **3** in good yield and as only one isomer in its reaction with $SnCl_4$. However, use of $BF_3{\cdot}Et_2O$ yielded a complex mixture of products with complete disappearance of the starting material. Reaction of enal **1f** proceeded both with $SnCl_4$ and $BF_3{\cdot}Et_2O$ albeit in moderate to low yields of carbacepham **4**. Interestingly, along with compound **4**, chlorocarbacepham derivative **5** was also obtained as byproduct in the $SnCl_4$-promoted reaction. Formation of compound **5** with a cis disposition between chloro and hydroxyl groups suggests a stepwise mechanism and can be rationalized through initial participation of an aldehyde−$SnCl_4$ complex and further evolution to zwitterion **6** followed by intramolecular [1,5] chloride shift to chloro-alkoxide **7**, which finally gives chlorocarbacepham **5** after hydrolysis (Scheme 3). As far as

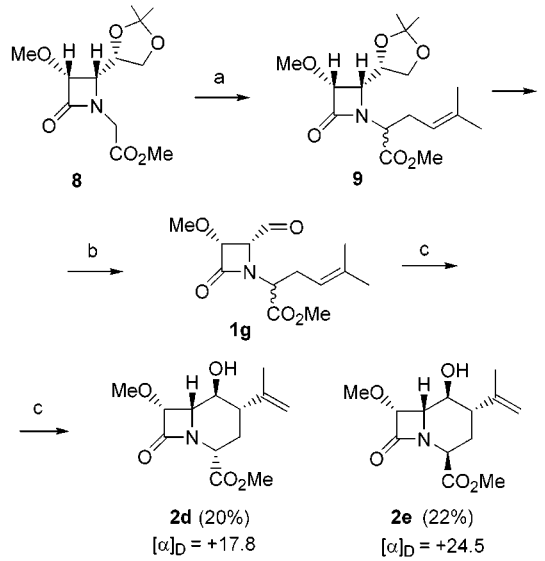
Scheme 3. Proposed Reaction Course for the Formation of Chlorocarbacepham **5**



we know this behavior known for Lewis acid catalyst such as Me_2AlCl or $TiCl_4$ is unprecedented for tin(IV) chloride.[12]

Because a carboxy group contiguous to the lactam nitrogen is a prerequisite for biological activity, we also prepared the carbacepham precursor **1g** as 1:1 mixture of isomers (Scheme 4). Sequential reaction of β-lactam **8**[13] with LDA and methallyl bromide furnished an inseparable mixture (1:1) of epimers **9**.[14] After acetal deprotection and oxidative cleavage aldehyde **1g** was obtained as an inseparable mixture of isomers, which was used directly for carbonyl-ene experiments. Reaction of **1g** in the presence of $BF_3{\cdot}Et_2O$ afforded an easily separable 1:1 mixture of epimeric carbacephams **2d** and **2e**, which were obtained in 20% and 22% yield, respectively, as pure products after chromatography (42% overall yield from compound 9). Vicinal coupling constants

Scheme 4. Synthesis of Epimeric Carbacepham **2d** and **2e**[a]

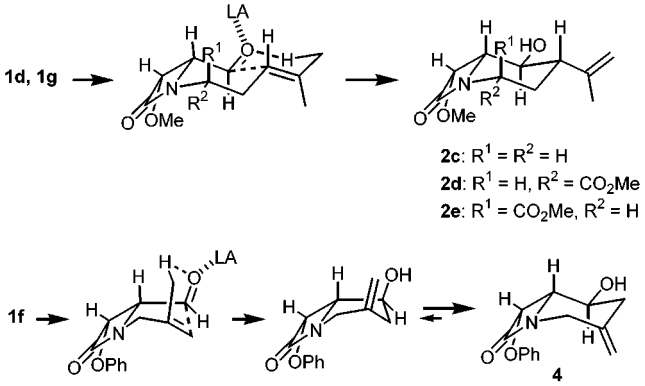


[a] (a) (i) LDA, THF, −78 °C, (ii) $Me_2CH{=}CHCH_2Br$, −78 °C to room temperature, 65%. (b) (i) $PPTS{\cdot}H_2O$, (ii) $NaIO_4$. (c) (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, (ii) SiO_2 separation, 42% from **9**.

and NOE experiments allowed assignment of **2d** and **2e** as the (4*R*)- and (4*S*)-diastereomers, respectively.

The stereochemical outcome in the present carbonyl-ene cyclizations leading to carbacephams **2** and **4** can be explained in terms of the six-membered, cyclic chairlike transition state models depicted in Scheme 5.[15]

Scheme 5. Proposed Models for Ene-Cyclization of Alkenyl Aldehydes **1d**, **1f**, and **1g** Leading to Carbacephams **2c**−**e** and **4**



In conclusion, we have demonstrated the utility of the reported methodology for the facile and diastereoselective elaboration of enantiopure bicyclic β-lactam systems relevant

(12) Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144.

(13) Alcaide, B.; Almendros, P.; R.-Salgado, N.; Martínez-Alcázar, M. P.; Hernández-Cano, F. *Eur. J. Org. Chem.* **2001**, 2001.

(14) The poor selectivity obtained in allylation of compound **8** is in clear contrast with the excellent stereoselectivity observed by Ojima for related type 2 alkylations in chiral 4-phenyl-β-lactam acetates. See, for example: Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770.

(15) For models on the carbonyl-ene cyclization reaction, see: (a) Braddock, D. Ch.; Hii, K. K.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1720. (b) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011. (d) Johnston, M.; Kwass, J. A.; Beal, R. B.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 5419.

to the synthesis of carbacephem antibiotics. The synthetic potential of these intramolecular processes as well as related intermolecular carbonyl-ene reactions are currently under investigation, and further aspects of this chemistry will be reported in due course.

Acknowledgment. We are grateful to the DGI (MCYT-Spain) for financial support of this research (project BQU2000-0645). C. Rodríguez and A. Rodríguez thank the DGI (CEC-Comunidad de Madrid-Spain) for a predoctoral and post-doctoral fellowship, respectively.

Supporting Information Available: Compound characterization data and experimental procedures for products **1a**, **1c**−**g**, **2a**−**e**, and **3**−**5.** This material is available free of charge via the Internet at http://pubs.acs.org.

OL016871A