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The Asymmetric Synthesis of 2,3-Benzocarbapenems by Intramolecular Aryl Radical Cyclizations

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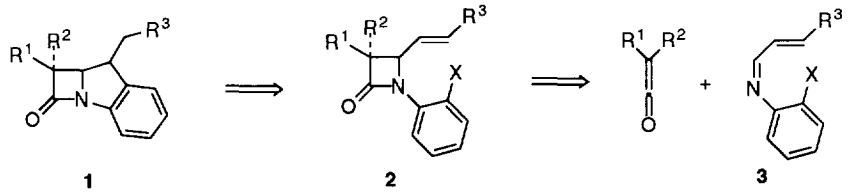
Abstract: Racemic and enantiomerically pure 2,3-benzocarbapenems **1** are obtained in good yields by the tin-mediated, intramolecular aryl radical cyclizations of the readily available 4-alkenyl-*N*-(2-halogenophenyl)-β-lactams **2**. Copyright © 1996 Elsevier Science Ltd

Increasing incidence of bacterial resistence to β-lactam antibiotics has promoted a growing interest in the development of effective β-lactamase inhibitors.[1] Among others, benzocarbapenems have been designed as suicide inactivators of β-lactamase. The first synthesis of these fused tricyclic β-lactams was reported by Wakselman by using a copper-promoted intramolecular aryl substitution of 4-(*o*-bromophenyl)methyl-2-azetidinones.[2] A recent paper by Gilchrist described the preparation of benzocarbapenems by reduction and cyclization of 2-substituted indoles.[3] This synthesis has prompted us to report our asymmetric approach to benzocarbapenems **1**, through intramolecular aryl radical cyclization of 4-alkenyl-*N*-(2-halogenophenyl)-β-lactams **2**.[4-6] 2-Azetidinones **2** are easily made by cycloaddition of ketenes[7] with α,β-unsaturated aldimines **3** (Scheme 1).

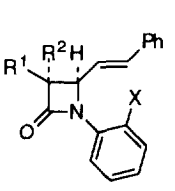


1 **2** **3**

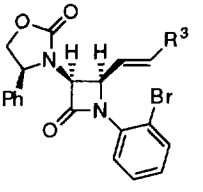
Scheme 1

Alkenyl imines **3** required in our work were formed by the condensation of an *o*-halogeno-aniline with the corresponding α,β-unsaturated aldehyde in the presence of the $ZnCl_2$/α-phenylethylamine complex as catalyst, using benzene or toluene as solvent and a Dean-Stark apparatus to remove the water formed during the reaction. A nearly quantitative yield of the Schiff base was obtained under these reaction conditions. Compounds **3** reacted with different ketenes to produce smoothly 2-azetidinones **2a-d**. Compound **2b** was obtained as a *cis/trans* mixture with low selectivity, although both isomers were easily separated by fractional recrystallization of the mixture. Enantiomerically pure β-lactams **2c** and **2d** were prepared by reaction of imines

3 with the ketene derived from the Evans and Sjögren chiral oxazolidinone.[8] β-Lactams **2c-d** were obtained exclusively as their *cis*-diastereoisomers with good to excellent stereoselectivity.[9]



2a: $R^1 = R^2 = Me$; X = Br (40%)
2b: R^1, R^2 = OBn, H; X = I (75%)
cis:trans = 62:38



2c: R^3 = Ph (61%) d.e. ≥ 95%
2d: R^3 = Me (70%) d.e. = 80%

Halogenated β-lactams **2** were reacted with tributyltin hydride and AIBN in benzene at reflux to give the expected benzocarbapenems **1** in good yields after chromatographic purification (Table 1).[10,11] Compounds **2a-2c** derived from cinnamaldehyde-imines (R^3 = Ph) underwent 5-*exo-trig* radical cyclization to products **1** in a totally regio- and stereoselective fashion as expected when the radical acceptor has a radical-stabilizing substituent at the β-position (in our case the phenyl group). Neither cyclization products different from **1** nor reduction products were detected in the ^{1}H-NMR spectra of the crude reaction mixtures. The stereoselectivity of the process is remarkably independent of the substitution at C-3 of the 2-azetidinone ring, and a single diastereomer of benzocarbapenems **1** is obtained in all cases. The relative stereochemistry of the 4-membered ring was established from the values of $J_{5,6}$, and is transferred unaltered from the starting 2-azetidinone to the cyclized products. The stereochemistry of the new stereocenter at C-1 in compounds **1** was derived from our previous results on stannylcarbapenams[6] and NOE experiments on representative compounds. Thus, irradiation of the H-5 hydrogen in compound **1a** resulted in a 5% increment on the proton of the methylene group at lower field (2.67 ppm), and a 5% increment on the phenyl group, and on the methyl group at lower field (1.18 ppm). Irradiation of the H-5 hydrogen in compound **1e** gave a 3% increment both on the most shielded proton of the methylene group (1.43 ppm), and on the methyl group corresponding to the ethyl substituent on C-1. In this way, an *anti* stereochemistry between C-1 and C-5 was assigned.

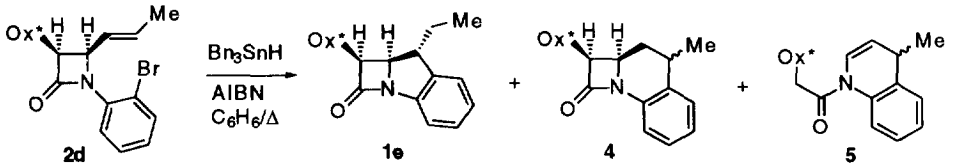
Table 1. Synthesis of 2,3-Benzocarbapenems **1** from 4-alkenyl-*N*-(2-halogenophenyl) β-lactams **2**

substrate	R^1	R^2	R^3	X	product	yield (%)[a]	M.p. (°C)[b]
2a	Me	Me	Ph	Br	**1a**	65	123-125
cis-**2b**	OBn	H	Ph	I	**1b**	60	oil
trans-**2b**	H	OBn	Ph	I	**1c**	65	87-89
(+)-2c	*S*-Ox	H	Ph	Br	**(+)-1d**	70	168-170
(+)-2d	*S*-Ox	H	Me	Br	**(+)-1e**	30	oil

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] Crystallyzed from ethyl acetate/hexanes. [c] *S*-Ox = (*S*)-4-Phenyl-2-oxo-1,3-oxazolidin-3-yl.

The presence of a phenyl group controls the exclusive 5-*exo* mode of cyclization. In fact, radical cyclization of β-lactam **2d** derived from crotonaldehyde-imine formed, along with benzocarbapenem **1e** (major product, 30%), benzocarbacephem **4** (minor product, 8%) and 1,4-dihydroquinoline **5** (relative proportions

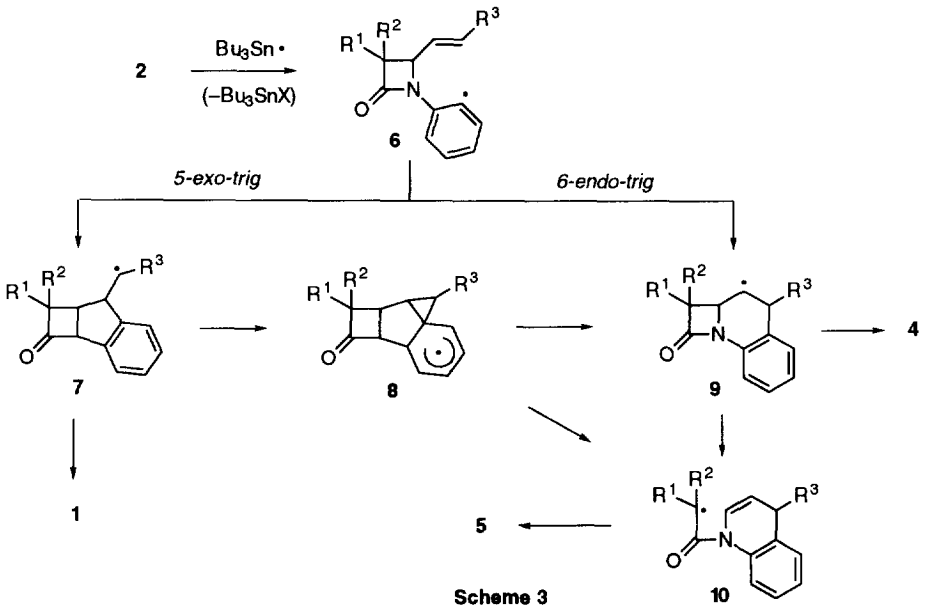
3:1:2.5, respectively)[12] (Scheme 2). Compounds **1e**, **4**, and **5** were obtained as single diastereoisomers, and thus it is clear that 6-*endo* cyclization competes with 5-*exo* process when an unactivated double bond is used as the radical acceptor.



(Ox* = (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl)

Scheme 2

Formation of compounds **1**, **4**, and **5** may be rationalized as shown in Scheme 3. Bromine abstraction by a stannyl radical followed by either 5-*exo*- or 6-*endo* cyclization of radical **6** would form radicals **7** and **9**, respectively, depending on which of the two olefinic carbons is attacked. These radicals would lead to benzocarbapenems **1** or benzocarbacephem **4**, respectively, after hydrogen abstraction from tributyltin hydride. Alternatively, compound **4** may be formed from radical intermediate **7** *via* a ring expansion process through the radical intermediate **8**. Formation of compound **5** may be explained by an homolytic C3-C4 bond cleavage in the 2-azetidinone nucleus of intermediate **8** or **9** to form radical intermediate **10**. This interesting process, which is the first example of a radical C3-C4 bond breakage in the β-lactam ring,[13] is closely related to the



Scheme 3

cyclobutylcarbinyl radical cleavage, an useful methodology for the synthesis of medium size rings.[14] In our case, the driving force of the cleavage may be the stability of the captodative radical **10** together with the strain in the β-lactam ring.

In summary, β-lactams prepared from imines derived from cinnamaldehyde and *o*-halogenoanilines have proved to be easily available and appropriate substrates for aryl radical cyclization to different

enantiomerically pure substituted 2,3-benzocarbapenems. A new radical ring fragmentation of the β-lactam ring has been also observed. Work to determine the scope of this new synthetic strategy as well as its application for the asymmetric preparation of other different 3,4-benzofused polycyclic β-lactams is now underway in our laboratory.

Acknowledgements. Support for this work by the DGICYT (Project PB93-0442) is gratefully acknowledged. One of us (A.R.-V.) acknowledges the receipt of a predoctoral fellowship by the Ministerio de Educación y Ciencia (Spain).

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5. While this work was in progress a related aryl radical cyclization to 1,2-benzocarbacephams from *N*-allyl-4-(*o*-bromophenyl)-2-azetidinones has been reported. See: Banik, B. K.; Subbaraju, G. V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363-6.
6. We have previously reported the radical synthesis of tin-functionalized carbapenams from enyne-β-lactams: Alcaide, B.; Benito, J.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A.; Sierra, M. A.; García-Granda, S.; Gutíerrez-Rodríguez, A.*Tetrahedron: Asymmetry*, **1995**, *6*, 1055-8.
7. For a review on the ketene-imine approach to β-lactams, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers Inc., New York, 1993; Ch. 6, p 295-368
8. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.*, **1985**, *26*, 3783-3786.
9. Dichlorophenylphosphate was used as the condensating agent in these cases. See: Arrieta, A.; Lecea, B.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1988**, *53*, 3784-3791.
10. A typical experimental procedure follows. A solution of *N*-(*o*-halogenophenyl)-β-lactam **2** (1 mmol), Bu_3SnH (1.2 mmol), and AIBN (0.1 mmol) was refluxed in dry benzene (20 mL) under an argon atmosphere, until complete disappearance of the starting substrate (t.l.c., 1,5-3h). The resulting crude reaction mixture was treated with 10% aqueous solution of KF (20 mL) for 30 minutes. The organic layer was separated, dried and the solvent evaporated *in vacuo* to give the reaction mixture which was purified by flash chromatography. Partial decomposition was observed for 6-benzyloxy-2,3-benzocarbapenam **1b** while attempting purification. All pure compounds gave satisfactory spectroscopic and analytical data.
11. Removal of the organotin halides by a solution of KF in water is essential for an appropriate chromatographic purification of compounds **1**. See: Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449-450.
12. Data of compounds **4** and **5**. Compound **4**: M.p. >170º(dec.); $[\alpha]_D$ = +114.6º (c 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 1.09 (d, 3H, J =7.2), 1.7(m, 2H), 3.87 (dq, 1H, J_1=3.3; J_2=4.2; J_3=12.0), 4.34 (dd, 1H, J_1=5.4; J_2=9.0), 4.81 (t, 1H, J=4.2), 5.01 (dd, 1H, J_1=5.4; J_2=8.7), 7.0-7.4 (m, 9H). Compound **5**: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 1.19 (d, 3H, J =7.5), 3.35 (m,1H), 3.55 (d, 1H, J=17.1), 4.18 (t, 1H, J=7.8), 4.64 (d, 1H, J=17.4), 4.75 (t, 1H, J=9.3), 5.19 (t, 1H, J=8.4), 5.51 (dd, 1H, J=5.1; J=7.0), 6.56 (d, 1H, J=7.0), 7.1-7.9 (m,9H).
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