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Free radical synthesis of benzofused tricyclic β-lactams by intramolecular cyclization of 2-azetidinone-tethered haloarenes

Benito Alcaide,[a,*] Pedro Almendros,[b] Alberto Rodríguez-Vicente[a] and M. Pilar Ruiz[a]

[a]*Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain*
[b]*Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain*

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Abstract—*o*-Halogenophenyl- and *o*-halogenobenzyl-4-alkenyl-β-lactams can be prepared both in the racemic form and in optically pure form using the ketene–imine cyclization. These 2-azetidinone-tethered haloarenes were used for the regio- and stereoselective preparation of benzofused tricyclic β-lactams including benzocarbapenems and benzocarbacephems via intramolecular aryl radical cyclisation.

1. Introduction

Since the discovery of penicillin, 2-azetidinone-based heterocycles have been one of the main classes of drugs used for the treatment of bacterial infections.[1] The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer.[2] In order to oppose the destructive action of β-lactamases, one strategy consists of modifying the structure of the β-lactam antibiotic, aiming to render it insensitive to the β-lactamase attack. A second approach uses a reagent, typically a β-lactam derivative, which incapacitates the β-lactamase, in synergy with the β-lactam antibiotic. Among others, benzocarbapenems and benzocarbacephems have been designed as suicide inactivators of β-lactamases. The preparation of benzocarbacephems has received more attention,[3] while the synthesis of benzocarbapenems is a less explored area. The first synthesis of these benzofused β-lactams was reported by Wakselman by using a copper-promoted intramolecular aryl substitution of 4-(*o*-bromophenyl)methyl-2-azetidinones.[4] A more recent contribution by Gilchrist described the preparation of benzocarbapenems by reduction and cyclization of 2-substituted indoles.[5] Both syntheses are racemic.

In connection with our current research interest in the preparation and synthetic utility of β-lactams,[6] here we examine the feasibility and efficiency of an approach (racemic and asymmetric) to benzofused tricyclic β-lactams including benzocarbapenems as well as benzocarbacephems, through intramolecular aryl radical cyclization of 2-azetidinone-tethered haloarenes.[7]

2. Results and discussion

Starting cyclisation substrates, alkenyl- and alkynyl-β-lactam-tethered haloarenes **1**–**8** (Scheme 1), were prepared both in the racemic form and in optically pure form using the ketene–imine cycloaddition as the key step.[8] 2-Azetidinones **1**–**4** were obtained from the corresponding imine[9] through Staudinger reaction with the appropriate acid chloride in the presence of Et_3N (Scheme 1, Table 1). Racemic compounds **1** bearing a *N*-(*o*-halophenyl) moiety were obtained as *cis*/*trans* mixtures with low *cis*-selectivity,[10] the *cis*-isomers being easily separated by fractional recrystallization of the mixtures. In contrast, racemic compounds **2** were obtained as single *cis*-diastereomers. Enantiomerically pure β-lactams (+)-**3a**, (+)-**3b** and (+)-**4** were prepared by reaction of the corresponding imines with the ketene derived from the Evans and Sjögren chiral oxazolidinone.[11] β-Lactams **3** and **4** were obtained exclusively as their *cis*-diastereoisomers with good to excellent stereoselectivity.[12]

Enantiopure β-lactam (+)-**9** was obtained as a single *cis*-enantiomer from the *o*-bromobenzyl imine of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with phenoxyacetyl chloride in the presence of Et_3N. Sequential acidic acetonide hydrolysis and oxidative cleavage of the resulting diol, followed by Wittig olefination

Keywords: Lactams; Nitrogen heterocycles; Radical reactions; Polycycles; Cycloaddition.
* Corresponding author. Tel.: +34 913 944 314; fax: +34 913944103; e-mail: alcaideb@quim.ucm.es

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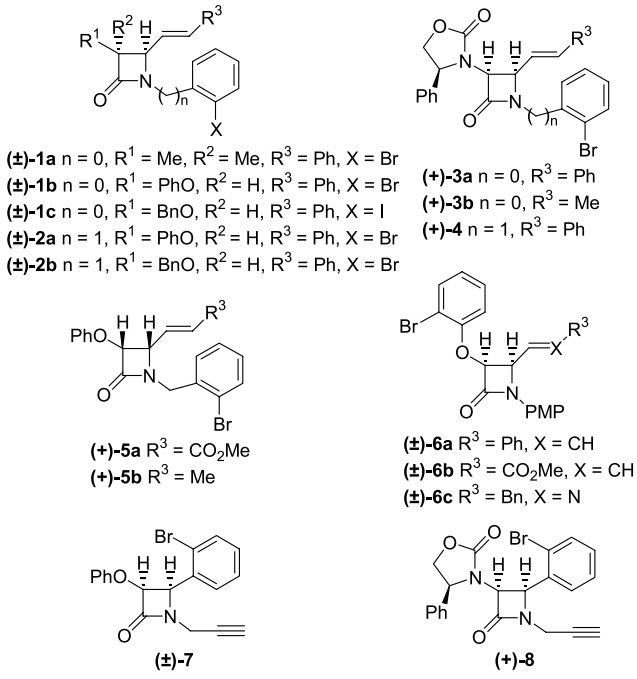
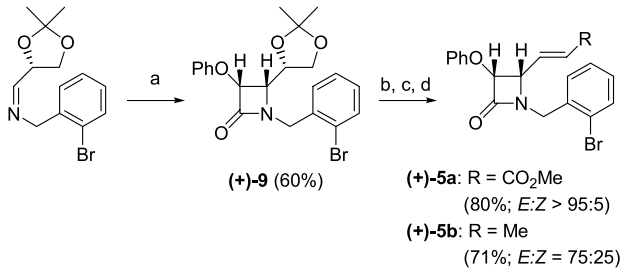
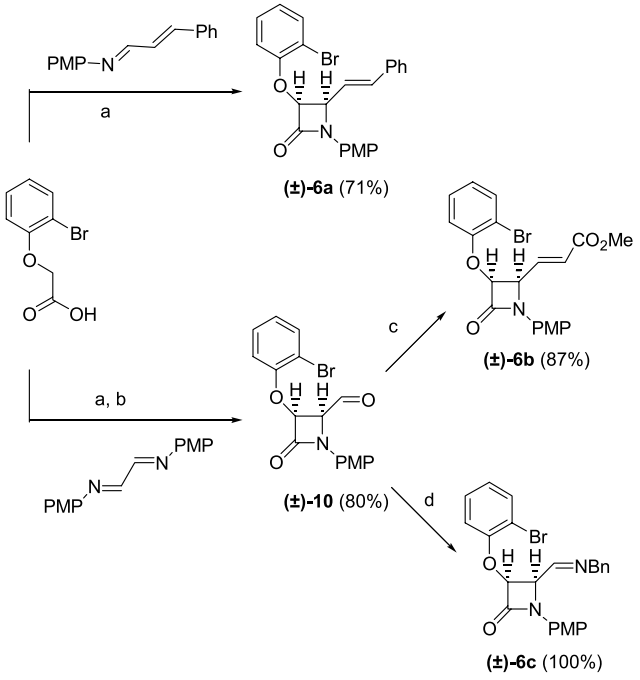


Scheme 1. Starting β-lactam-tethered haloarenes **1**–**8**.



Scheme 2. Reagents and conditions: (a) $PhOCH_2COCl$, Et_3N, dichloromethane, rt, 12 h; (b) PTSA, THF/H_2O, reflux, 3 h; (c) $NaIO_4$, $NaHCO_3$, dichloromethane, rt, 2 h; (d) for **5a**: $Ph_3P{=}CHCO_2Me$, THF, reflux, 3 h. For **5b**: $Ph_3(Et)PI$, LiBu, THF, rt, 16 h.



Scheme 3. Reagents and conditions: (a) $PhOP(O)Cl_2$, Et_3N, dichloromethane, rt, 16 h; (b) 5% aqueous HCl; (c) $Ph_3P{=}CHCO_2Me$, THF, reflux, 3 h.; (d) $BnNH_2$, $MgSO_4$, dichloromethane, rt, 16 h.

of the corresponding 4-oxoazetidine-2-carbaldehyde afforded the enantiopure alkenes (+)-**5a** and (+)-**5b** (Scheme 2). The preparation of cyclization precursors **6a**–**c** bearing the haloaryl moiety at C3 is shown in Scheme 3. Styryl-2-azetidinone **6a** was obtained with total *cis*-selectivity via direct Staudinger reaction of the *E*-cinnamaldehyde/*p*-anisidine derived imine and the ketene obtained from *o*-bromophenoxy acetic acid. Racemic β-lactam aldehyde **10** was obtained as a single *cis*-diastereoisomer, following our one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine.[13] Alkene **6b** was achieved through Wittig olefination of aldehyde **10**, while imine **6c** was prepared by condensation with benzylamine in the presence of magnesium sulphate.

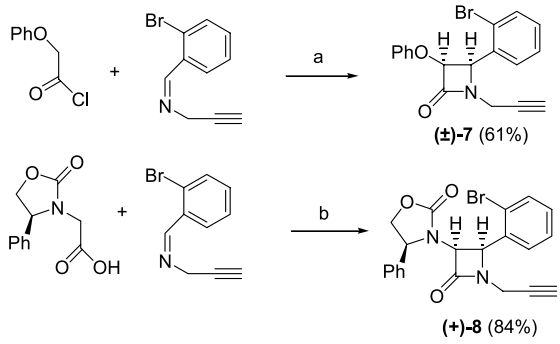
Alkynyl-2-azetidinones **7** and (+)-**8** were obtained with complete stereoselectivity in good yields, through the ketene–imine cycloaddition of the imine obtained from *o*-bromobenzaldehyde and propargylamine on reacting with the corresponding ketene (Scheme 4).

Having obtained the monocyclic precursors, the next stage was set to carry out the key radical cyclisation step. The stereoselective synthesis of complex heterocycles and carbocycles by radical cyclisation has now been established as an efficient methodology in organic chemistry.[14] This wide research has been fostered by its operational simplicity and its tolerance to substrate functionalization. Furthermore, by a combination of stereoelectronic and molecular orbital

Table 1. Preparation of β-lactams **1**–**4**[a]

Product	R^1	R^2	R^3	X	n	Yield (%)[b]	*cis*/*trans* ratio[c]
1a	Me	Me	Ph	Br	0	40	
1b	PhO	H	Ph	Br	0	74	62:38
1c	BnO	H	Ph	I	0	70	64:36
2a	PhO	H	Ph	Br	1	40	100:0
2b	BnO	H	Ph	Br	1	60	100:0
(+)-**3a**	(*S*)-Ox[d]	H	Ph	Br	0	61	100:0
(+)-**3b**	(*S*)-Ox	H	Me	Br	0	69	90:10
(+)-**4**	(*S*)-Ox	H	Ph	Br	1	50	100:0

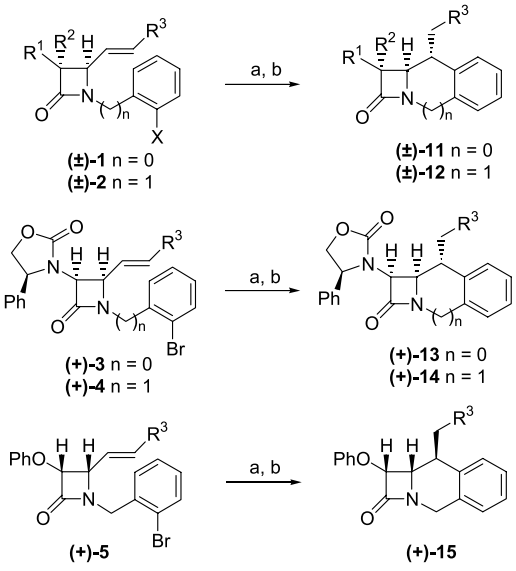
[a] Compounds **1** and **2** are racemic.
[b] Yield of pure, isolated product (or mixture of isomers, when applicable) with correct analytical and spectral data.
[c] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification.
[d] (*S*)-Ox= (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl.



Scheme 4. Reagents and conditions: (a) $PhOCH_2COCl$, Et_3N, dichloromethane, rt, 12 h; (b) $PhOP(O)Cl_2$, Et_3N, dichloromethane, rt, 16 h.

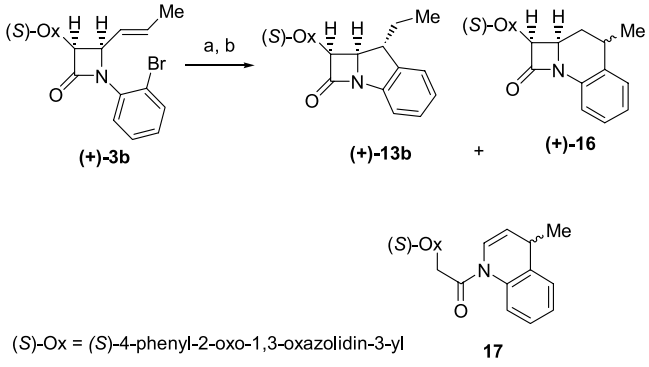
effects, radical cyclisations occur, in general, with high degrees of both regio- and stereo-control.

Haloaryl β-lactams **1**–**5** were reacted with tributyltin hydride and AIBN in benzene at reflux to give the expected benzocarbapenems **11** and **13** and benzocarbacephems **12**, **14** and **15** in good yields as single diastereomers after chromatographic purification (Scheme 5, Table 2). These intramolecular radical reactions were carried out under



Scheme 5. Reagents and conditions: (a) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1–2 h. (b) 10% aqueous KF, 30 min.

standard dilution conditions, and did not require the use of high dilution techniques. Removal of the organotin halides by a solution of KF in water is essential for an appropriate chromatographic purification of compounds **11**–**15**.[15] With the exception of the reaction of (+)-**3b**, neither cyclisation products different from **11**–**15** nor reduction products were detected in the ^1H NMR spectra of the crude reaction mixtures. The full stereoselectivity of the radical cyclisation is particularly attractive, being independent of the substitution at C3 or N1 on the β-lactam ring. In addition, 2-azetidinones bearing styryl or carboxymethyl substituents at C4 underwent 5(or 6)-*exo-trig* radical cyclization to benzocarbapenems and benzocarbacephems **11**–**15** in a totally regioselective fashion, as expected when the radical acceptor has a radical-stabilizing moiety at the β-position. The radical reaction of the crotonaldehyde-imine derived β-lactam (+)-**3b**, lacking a radical-stabilizing moiety, deserves special mention. Haloalkenyl β-lactam (+)-**3b** formed, along with benzocarbapenem (+)-**13b** (major product, 30%), benzocarbacephem (+)-**16** (minor product, 10%) and 1,4-dihydroquinoline **17** (relative proportions 3:1:2.5, respectively) (Scheme 6). Compounds (+)-**13b**, (+)-**16**, and **17** were obtained as single diastereoisomers, and thus it is clear that 6-*endo* cyclisation competes with 5-*exo* process when an unactivated double bond is used as the radical acceptor. However, this result is in sharp contrast with the radical reaction of compound (+)-**5b**, being obtained exclusively the 6-*exo* cyclisation product. In this case, independently of the substituent at the acceptor double bond, the 7-*endo* mode of cyclisation is not competitive.[16] Formation of compounds **11**, **13**, **16**, and **17** may be



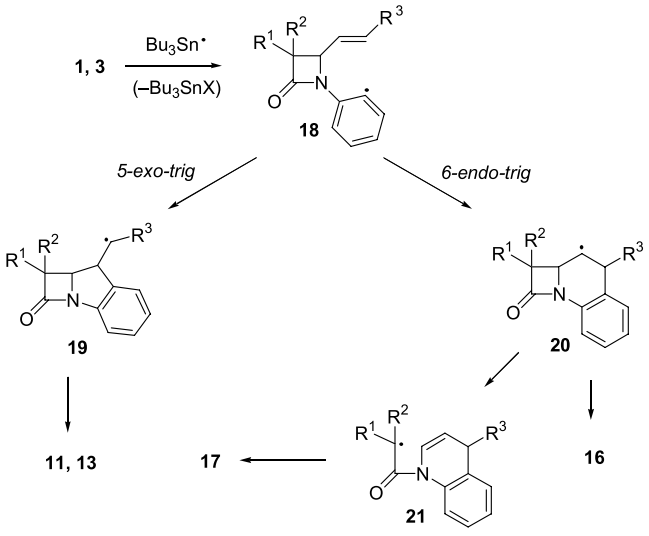
Scheme 6. Reagents and conditions: (a) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1.5 h. (b) 10% aqueous KF, 30 min.

Table 2. Preparation of fused tricyclic β-lactams **11**–**15**

Substrate[a]	R^1	R^2	R^3	X	n	Product[a]	Yield (%)[b]
1a	Me	Me	Ph	Br	0	**11a**	65
1b	PhO	H	Ph	Br	0	**11b**	66
cis-**1c**	BnO	H	Ph	I	0	*cis*-**11c**	60
trans-**1c**	BnO	H	Ph	I	0	*trans*-**11c**	65
2a	PhO	H	Ph	Br	1	**12a**	50
2b	BnO	H	Ph	Br	1	**12b**	61
(+)-**3a**			Ph		0	(+)-**13a**	70
(+)-**3b**			Me		0	(+)-**13b**	30
(+)-**4**			Ph		1	(+)-**14**	57
(+)-**5a**			CO_2Me			(+)-**15a**	64
(+)-**5b**			Me			(+)-**15b**	47

[a] Compounds **1**, **2**, **11** and **12** are racemic.
[b] Yield of pure, isolated product with correct analytical and spectral data.

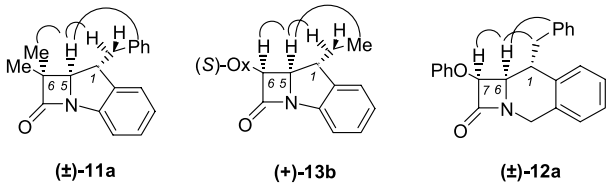
rationalized as shown in Scheme 7. Bromine abstraction by a stannyl radical followed by either 5-*exo*- or 6-*endo* cyclisation of radical **18** would form radicals **19** and **20**, respectively, depending on which of the two olefinic carbons is attacked. These radicals would lead to benzocarbapenems **11** and **13** or benzocarbacephem **16**, respectively, after hydrogen abstraction from tributyltin hydride. Formation of compound **17** may be explained by an homolytic C3–C4 bond cleavage in the 2-azetidinone nucleus of intermediate **20** to form radical intermediate **21**. This interesting process, which is an example of a radical C3–C4 bond breakage in the β-lactam ring,[17] is closely related to the cyclobutylcarbinyl radical cleavage, a useful methodology for the synthesis of medium size rings.[18] In our case, the driving force of the cleavage may be the stability of the captodative radical **21** together with the strain in the β-lactam ring.



Scheme 7.

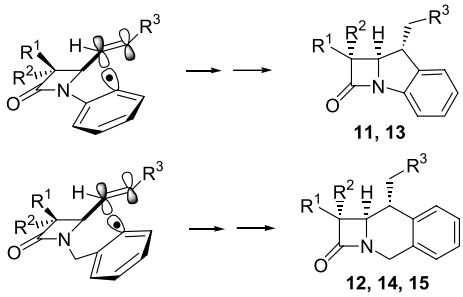
The relative stereochemistry of the 4-membered ring was established from the values of $J_{5,6}$ (benzocarbapenems) or $J_{6,7}$ (benzocarbacephems) vicinal proton couplings and it is transferred unaltered from the starting 2-azetidinone to the cyclized products. The stereochemistry of the new stereocenter at C1 in compounds **11**–**15** was derived from our previous results on stannylcarbapenams and stannylcarbacephams,[19] as well as by qualitative homonuclear NOE difference spectra on representative compounds. As an example, irradiation of the H5 hydrogen in compound **11a** resulted in a 5% increment on the proton signal 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 H5 hydrogen in compound (+)-**13b** 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 at C1. Similar figures were observed on performing NOE experiments in tricycle **12a** (Scheme 8). In this way, *anti* stereochemistries H1/H5 (benzocarbapenems) or H1/H6 (benzocarbacephems) were assigned.

The complete selectivity observed in the formation of



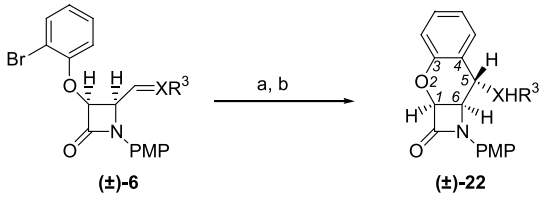
Scheme 8. Selected NOE effects and stereochemistry of compounds **11a**, (+)-**13b** and **12a**.

benzocarbapenems **11** and **13** and benzocarbacephems **12**, **14** and **15** must be due to the preference of the radical intermediates for the conformation depicted in Scheme 9 for these cyclisations.



Scheme 9.

Next, we decided to explore the extension of the above radical intramolecular cyclisation of *N*-haloaryl-β-lactams to 2-azetidinones bearing the proradical center at C3. The treatment of haloarenes **6a**–**c** under similar conditions for the preparation of benzocarbapenems and benzocarbacephems **11**–**15** gave the fused tricyclic β-lactams **22a**–**c** (Scheme 10, Table 3). Compounds **22a** and **22b** were obtained as mixtures of diastereomers, which are epimers at the newly formed C5 stereocenter, while the amino derivative **22c** could be prepared as a single isomer. The relative stereochemistry of the new chiral center of compounds **22** at C5 was determined by the value of coupling constants of H5–H6 protons (J=0–1.2 Hz for the major *anti*-isomers; J=3.6–4.2 Hz for the minor *syn*-isomers).[20]



Scheme 10. Reagents and conditions: (a) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1 h. (b) 10% aqueous KF, 30 min.

The slight variation in the diastereomeric ratio in the formation of compounds **22a** and **22b**, could be explained taking into account the higher bulkiness of the phenyl group in comparison to the carboxymethyl moiety. However, steric reasons can not be used to explain the nearly total stereoselectivity of the azaderivative **22c**.

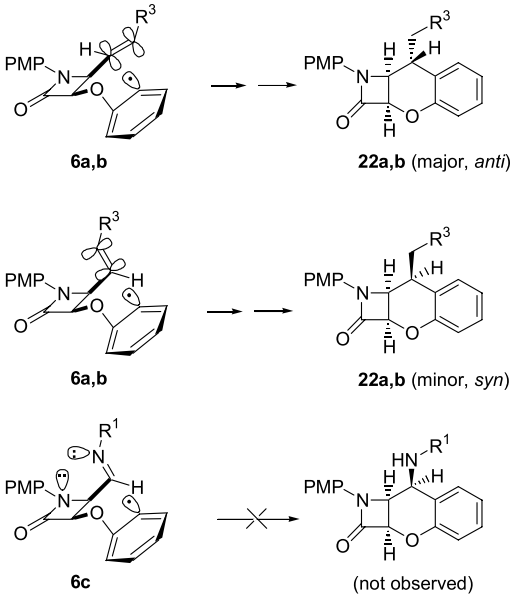
These cyclisations may be understood in terms of the

Table 3. Preparation of fused tricyclic β-lactams **22**[a]

Substrate[b]	R^3	X	dr[c]	Product[b]	Yield (%)[d]
6a	Ph	CH	85:15	**22a**	69
6b	CO_2Me	CH	70:30	**22b**	56
6c	Bn	N	>95:5	**22c**	60

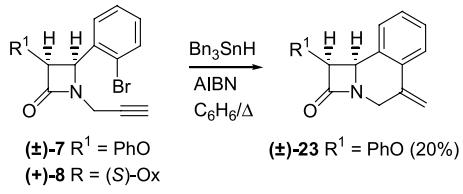
[a] PMP=4-$MeOC_6H_4$.
[b] Compounds **6** and **22** are racemic.
[c] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification.
[d] Yield of pure product (mixture of isomers).

possible conformations presented in Scheme 11. The highest overlap between the aryl radical and the π* orbital of the acceptor double bond is for the conformations giving rise to the major *anti*-isomers. For **22c**, the possible electronic repulsion between the unshared electronic pairs of the nitrogen atoms can be responsible of the destabilization of the conformation giving rise to the minor *syn*-isomer.



Scheme 11.

2-Azetidinones **7** and (+)-**8** were selected as monocyclic precursors with the aim of using a terminal alkyne as a proradical center in the synthesis of benzofused tricyclic β-lactams. Unfortunately, tricycle **23** was isolated in a poor 20% yield from the alkynyl haloarene **7**, while the radical reaction of (+)-**8** gave a complex mixture (Scheme 12).



Scheme 12. Reagents and conditions: (a) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux. (b) 10% aqueous KF, 30 min.

In conclusion, easily available 2-azetidinone-tethered haloarenes have proved to be appropriate substrates for the regio- and stereoselective intramolecular aryl radical cyclisation leading to different enantiopure or racemic benzocarbapenems, benzocarbacephems, as well as other fused tricyclic β-lactams. A new radical C3–C4 bond cleavage of the β-lactam ring has been also observed. Efforts to develop this methodology for the preparation of more elaborate benzocarbapenems and benzocarbacephems are currently underway in our research group.

3. Experimental

3.1. General methods

Melting points were taken using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Mass spectra were recorded on a Hewlett–Packard 5989A spectrometer. Microanalyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid). Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in deg cm^2 g^{-1} at 25 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na-benzophenone. Benzene, dichloromethane and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Identification of products was made by TLC (Kiesegel 60F-254). UV light (λ=254 nm), and a vanillin solution in sulfuric acid and 95% EtOH (1 g vanillin, 5 mL H_2SO_4, 150 mL EtOH) was used to develop the plates.

3.2. Materials

The following chemicals were prepared according to previously reported procedures: *N*,*N*-di-(*p*-methoxy-phenyl) glyoxaldiimine,[21] 2,3-*O*-(isopropylidene)-D-glyceraldehyde,[22] (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl-acetic acid,[23] (2-bromophenoxy)acetic acid.[24]

3.3. General procedures for the synthesis of cyclisation substrates 1–4, 6a, and 7–9

Method A. A mixture of aldehyde (10 mmol), 2-halogenoaniline (10 mmol) and a catalytic amount of $ZnCl_2$/α-phenylethylamine complex (0.1 mmol) in benzene (50 mL) was heated at reflux (2–4 h) on a Dean–Stark apparatus. Then, the mixture was filtered and the solvent

was removed under reduced pressure. To a cooled (0 °C) solution of the imine in anhydrous dichloromethane (50 mL), Et_3N (4.16 mL, 30 mmol), the corresponding acid or acid chloride (15 mmol), [and $PhOP(O)Cl_2$, only when (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl-acetic acid and 2-(*o*-bromophenyl)acetic acid are used, 2.25 mL, 15 mmol] were successively added under argon. The resulting mixture was allowed to warm to room temperature, and was stirred for 16 h. The crude mixture was diluted with dichloromethane (100 mL) and washed with saturated $NaHCO_3$ (2×20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

Method B. A solution of the corresponding aldehyde (10 mmol), and amine (10 mmol) in dichloromethane (50 mL) was stirred overnight at room temperature over $MgSO_4$ (100 mmol). Then, the $MgSO_4$ was filtered off, washed with an additional 15 mL of dichloromethane, and the resulting solution cooled at 0 °C under argon. Et_3N (4.16 mL, 30 mmol), the corresponding acid or acid chloride (15 mmol), [and $PhOP(O)Cl_2$, only when (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl-acetic acid and 2-(*o*-bromophenyl)-acetic acid are used, 2.25 mL, 15 mmol] were successively added under argon. The resulting mixture was allowed to warm to room temperature, and was stirred for 16 h. The crude mixture was diluted with dichloromethane (100 mL) and washed with saturated $NaHCO_3$ (2×20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

3.3.1. (±)-1-(2-Bromophenyl)-3,3-dimethyl-4-(*E*)-styryl-azetidin-2-one (1a). *Method A*. From 1.32 g (10 mmol) of *trans*-cinnamaldehyde, 1.67 g (10 mmol) of *o*-bromoaniline, and 1.59 g (15 mmol) of 2-methylpropanoyl chloride, 840 mg (40%) of compound **1a** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 2:1). ^{1}H NMR: δ 1.30 (s, 3H), 1.52 (s, 3H), 4.79 (d, 1H, J=8.7 Hz), 6.17 (dd, 1H, J=8.7, 15.9 Hz), 6.64 (d, 1H, J=15.9 Hz), 7.30 (m, 9H). ^{13}C NMR: δ 172.2, 135.8, 134.4, 133.7, 128.6, 128.2, 128.1, 128.0, 128.0, 127.4, 126.6, 124.3, 118.2, 68.7, 55.5, 22.6, 17.9. IR ($CHCl_3$, cm^{-1}): ν 1755, 1480. MS (EI), *m*/*z*: 357 (M^++2, 7), 355 (M^+, 7), 286 (41), 284 (36), 158 (100), 143 (94%). Anal. Calcd for $C_{19}H_{18}NOBr$: C, 64.06; H, 5.09; N, 3.93. Found: C, 64.18; H, 5.06; N, 3.91.

3.3.2. (±)-*cis*-1-(2-Bromophenyl)-3-phenoxy-4-(*E*)-styryl-azetidin-2-one (1b). *Method A*. From 790 mg (6.0 mmol) of *trans*-cinnamaldehyde, 1.0 g (6.0 mmol) of *o*-bromoaniline, and 1.53 g (9.0 mmol) of phenoxyacetyl chloride, 1.87 g (74%) of compound **1b** was obtained as a mixture of isomers *cis*/*trans* (62:38). The *cis* isomer was isolated by recrystallization as a colourless solid. Mp 130–132 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 5.50 (dd, 1H, J=4.8, 9.0 Hz), 5.59 (d, 1H, J=4.8 Hz), 6.32 (dd, 1H, J=9.0, 15.9 Hz), 6.74 (d, 1H, J=15.9 Hz), 7.30 (m, 14H). ^{13}C NMR: δ 164.4, 157.2, 137.7, 135.7, 133.7, 129.5, 128.7, 128.7, 128.5, 128.3, 128.1, 127.7, 126.7, 122.3, 121.7, 117.6, 115.6, 81.8, 64.0. IR ($CHCl_3$, cm^{-1}): ν 1750, 1480. MS (EI), *m*/*z*: 421 (M^++2, 1), 419 (M^+, 1), 328 (15), 286 (36), 246 (45), 222 (23), 128 (100%). Anal. Calcd for $C_{23}H_{18}NO_2Br$: C, 65.73; H, 4.32; N, 3.33. Found: C, 65.63; H, 4.34; N, 3.35.

3.3.3. (±)-3-Benzyloxy-1-(2-iodophenyl)-4-(*E*)-styryl-azetidin-2-one (*cis*- and *trans*-1c). *Method A*. From 1.44 g (11.0 mmol) of *trans*-cinnamaldehyde, 2.39 g (11.0 mmol) of *o*-iodooaniline, and 3.04 g (16.5 mmol) of benzyloxyacetyl chloride, 3.70 g (70%) of compound **1c** was obtained as a mixture of isomers *cis*/*trans* (64:36). The *cis* isomer was isolated by recrystallization, while the *trans* isomer was purified by flash chromatography (hexanes/ethyl acetate, 2:1).

2-Azetidinone cis-**1c**. Colourless solid. Mp 139–141 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 4.68 (AB system, 2H, J=8.7 Hz), 4.97 (d, 1H, J=4.5 Hz), 5.13 (dd, 1H, J=4.5, 9.3 Hz), 6.34 (dd, 1H, J=9.3, 15.9 Hz), 6.61 (d, 1H, J=15.9 Hz), 6.90 (m, 1H), 7.20 (m, 12H), 7.75 (dd, 1H, J=1.2, 7.8 Hz). ^{13}C NMR: δ 165.6, 139.9, 137.3, 137.2, 136.5, 135.8, 129.3, 129.0, 128.6, 128.4, 128.4, 128.3, 128.3, 128.1, 127.8, 122.6, 93.7, 82.9, 73.0, 63.8. IR ($CHCl_3$, cm^{-1}): ν 1750, 1470. MS (EI), *m*/*z*: 390 (M^+−91, 6), 298 (12), 245 (10), 115 (32), 91 (100%). Anal. Calcd for $C_{24}H_{20}NO_2I$: C, 59.78; H, 4.21; N, 2.93. Found: C, 59.89; H, 4.19; N, 2.91.

2-Azetidinone trans-**1c**. Colourless oil. ^{1}H NMR: δ 4.57 (d, 1H, J=2.1 Hz), 4.64 (d, 1H, J=12.0 Hz), 4.85 (dd, 1H, J=2.1, 9.0 Hz), 4.88 (d, 1H, J=12 Hz), 5.96 (dd, 1H, J=9.0, 16.2 Hz), 6.44 (d, 1H, J=16.2 Hz), 6.9 (m, 1H), 7.25 (m, 12H), 7.75 (d, 1H). ^{13}C NMR: δ 164.7, 140.4, 137.6, 137.0, 135.6, 129.5, 129.1, 128.7, 128.6, 128.5, 127.7, 127.1, 126.8, 124.0, 122.8, 93.7, 87.3, 83.1, 73.2, 65.7. IR ($CHCl_3$, cm^{-1}): ν 1760, 1600. Anal. Calcd for $C_{24}H_{20}NO_2I$: C, 59.99; H, 4.16; N, 2.90. Found: C, 59.89; H, 4.19; N, 2.91.

3.3.4. (±)-*cis*-1-(2-Bromobenzyl)-3-phenoxy-4-(*E*)-styryl-azetidin-2-one (2a). *Method B*. From 260 mg (2.0 mmol) of *trans*-cinnamaldehyde, 370 mg (2.0 mmol) of *o*-bromobenzylamine, and 450 mg (3.0 mmol) of phenoxyacetyl chloride, 340 mg (40%) of compound **2a** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). ^{1}H NMR: δ 4.26 (d, 1H, J=15 Hz), 4.35 (dd, 1H, J=4.5, 9.0 Hz), 4.7 (d, 1H, J=15 Hz), 5.27 (d, 1H, J=4.5 Hz), 6.05 (dd, 1H, J=9.0, 15.6 Hz), 6.48 (d, 1H, J=15.6 Hz), 7.15 (m, 14H, Ar). ^{13}C NMR: δ 165.3, 157.2, 137.1, 135.9, 134.3, 133.0, 131.1, 129.7, 129.7, 129.4, 129.2, 128.5, 128.2, 127.8, 126.6, 122.1, 115.6, 82.0, 61.0, 44.7. IR ($CHCl_3$, cm^{-1}): ν 1760, 1600, 1500. Anal. Calcd for $C_{24}H_{20}NO_2Br$: C, 66.37; H, 4.64; N, 3.22. Found: C, 66.46; H, 4.66; N, 3.20.

3.3.5. (±)-*cis*-3-Benzyloxy-1-(2-bromobenzyl)-4(*E*)-styryl-azetidin-2-one (2b). *Method B*. From 260 mg (2.0 mmol) of *trans*-cinnamaldehyde, 370 mg (2.0 mmol) of *o*-bromobenzylamine, and 470 mg (3.0 mmol) of benzyloxyacetyl chloride, 540 mg (60%) of compound **2b** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). ^{1}H NMR: δ 4.11 (dd, 1H, J=4.5, 9.0 Hz), 4.21 (d, 1H, J=15.0 Hz), 4.56 (AB system, 2H, J=11.4 Hz), 4.64 (d, 1H, J=15.0 Hz), 4.74 (d, 1H, J=4.5 Hz), 6.09 (dd, 1H, J=9.0, 15.6 Hz), 6.44 (d, 1H, J=15.6 Hz), 7.20 (m, 14H). ^{13}C NMR: δ 166.8, 136.7, 136.6, 136.2, 134.7, 133.1, 131.1,

129.7, 128.7, 128.5, 128.4, 128.3, 128.2, 127.8, 126.8, 123.9, 123.2, 83.5, 72.9, 61.1, 44.5. IR ($CHCl_3$, cm^{-1}): ν 1755, 1600. Anal. Calcd for $C_{25}H_{22}NO_2Br$: C, 66.97; H, 4.95; N, 3.12. Found: C, 66.86; H, 4.98; N, 3.10.

3.3.6. (+)-(3*S*,4*R*)-1-(2-Bromophenyl)-3-[(*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl]-4-(*E*)-styryl-azetidin-2-one, (+)-3a. *Method A*. From 260 mg (2.0 mmol) of *trans*-cinnamaldehyde, 330 mg (2.0 mmol) of *o*-bromoaniline, 660 mg (3.0 mmol) of (*S*)-(2-oxo-4-phenyl-oxazolidin-3-yl)-acetic acid, and 440 μL (3.0 mmol) of phenyl dichlorophosphate, 600 mg (61%) of compound (+)-**3a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 169–171 °C (hexanes/ethyl acetate). $[\alpha]_D = +59.0$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 4.15 (dd, 1H, $J=7.5$, 8.7 Hz.), 4.61 (t, 1H, $J=8.7$ Hz), 4.64 (d, 1H, $J=5.1$ Hz), 4.87 (t, 1H, $J=8.7$ Hz), 5.24 (dd, 1H, $J=5.1$, 9.3 Hz), 6.12 (dd, 1H, $J=9.3$, 15.9 Hz), 6.63 (d, 1H, $J=15.9$ Hz), 7.02 (m, 1H), 7.35 (m, 13H). ^{13}C NMR: δ 163.0, 158.0, 138.0, 137.0, 135.7, 134.2, 133.5, 129.7, 128.8, 128.8, 128.7, 128.5, 128.3, 127.9, 127.0, 127.0, 122.6, 117.7, 71.1, 64.2, 62.8, 60.5. IR ($CHCl_3$, cm^{-1}): ν 1760, 1740. MS (EI), *m*/*z*: 490 ($M^+ +2$, 3), 488 (M^+, 3), 286 (100), 284 (70%). Anal. Calcd for $C_{26}H_{21}N_2O_3Br$: C, 63.81; H, 4.33; N, 5.72. Found: C, 63.93; H, 4.31; N, 5.75.

3.3.7. (+)-(3*S*,4*R*)-1-(2-Bromophenyl)-3-[(*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl]-4-[(*E*)-1-propenyl]-azetidin-2-one, (+)-3b. *Method A*. From 130 mg (1.95 mmol) of 2-butenal, 326 mg (1.95 mmol) of *o*-bromoaniline, 630 mg (2.85 mmol) of (*S*)-(2-oxo-4-phenyl-oxazolidin-3-yl)-acetic acid, and 420 μL (2.85 mmol) of phenyl dichlorophosphate, 570 mg (69%) of compound (+)-**3b** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 201–203 °C (hexanes/ethyl acetate). $[\alpha]_D = +97.2$ (*c* 0.6, $CHCl_3$). ^1H NMR: δ 1.65 (dd, 3H, $J=1.8$, 6.9 Hz), 4.26 (dd, 1H, $J=7.5$, 8.7 Hz), 4.65 (d, 1H, $J=5.4$ Hz), 4.73 (t, 1H, $J=8.7$ Hz), 4.96 (dd, 1H, $J=7.5$, 8.7 Hz), 5.07 (dd, 1H, $J=5.4$, 9.3 Hz), 5.25 (m, 1H), 5.80 (m, 1H), 7.25 (m, 9H). ^{13}C NMR: δ 163.0, 137.2, 135.5, 134.2, 133.5, 129.7, 129.6, 128.7, 128.5, 128.2, 128.0, 127.8, 124.3, 117.7, 71.1, 63.8, 62.3, 60.2, 18.3. IR ($CHCl_3$, cm^{-1}): ν 1752, 1748. MS (EI), *m*/*z*: 428 ($M^+ +2$, 3), 426 (M^+, 3), 229 (20), 224 (68), 184 (70), 144 (57%). Anal. Calcd for $C_{21}H_{19}N_2O_3Br$: C, 59.03; H, 4.48; N, 6.56. Found: C, 58.93; H, 4.51; N, 6.53.

3.3.8. (+)-(3*S*,4*R*)-1-(2-Bromobenzyl)-3-[(*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl]-4-(*E*)-styryl-azetidin-2-one, (+)-4. *Method B*. From 260 mg (2.0 mmol) of *trans*-cinnamaldehyde, 370 mg (2.0 mmol) of *o*-bromobenzylamine, 660 mg (3.0 mmol) of (*S*)-(2-oxo-4-phenyl-oxazolidin-3-yl)-acetic acid, and 440 μL (3.0 mmol) of phenyl dichlorophosphate, 510 mg (50%) of compound (+)-**4** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 193–195 °C (hexanes/ethyl acetate). $[\alpha]_D = +35.9$ (*c* 2.0, $CHCl_3$). ^1H NMR: δ 4.10 (dd, 1H, $J=7.5$, 9.0 Hz), 4.20 (dd, 1H, $J=4.8$, 9.0 Hz), 4.28 (d, 1H, $J=15.6$ Hz), 4.47 (d, 1H, $J=4.8$ Hz), 4.55 (m, 2H), 4.80 (dd, 1H, $J=7.5$, 9.0 Hz), 5.84 (dd, 1H, $J=9.0$, 16.2 Hz), 6.43 (d, 1H, $J=16.2$ Hz), 7.20 (m, 14H). ^{13}C NMR: δ 170.0, 166.8, 152.2, 137.0, 135.7, 134.4, 132.8, 130.9, 129.6, 129.5, 129.4, 129.4, 128.6, 128.4, 127.8, 126.8, 123.6, 123.1, 70.8, 62.8, 61.6, 60.1, 45.2. IR ($CHCl_3$, cm^{-1}): ν 1760, 1750. Anal. Calcd for $C_{27}H_{23}N_2O_3Br$: C, 64.42; H, 4.61; N, 5.56. Found: C, 64.53; H, 4.63; N, 5.53.

3.3.9. (±)-*cis*-3-(2-Bromophenoxy)-1-(4-methoxyphenyl)-4(*E*)-styryl-azetidin-2-one (6a). *Method B*. From 130 mg (1.0 mmol) of *trans*-cinnamaldehyde, 120 mg (1.0 mmol) of *p*-anisidine, 350 mg (1.5 mmol) of (*o*-bromo)phenoxyacetic acid, and 220 μL (1.5 mmol) of phenyl dichlorophosphate, 320 mg (71%) of compound **6a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 80–82 °C (hexanes/ethyl acetate). ^1H NMR: δ 3.76 (s, 3H), 4.99 (dd, 1H, $J=4.8$, 8.7 Hz), 5.48 (d, 1H, $J=4.8$ Hz), 6.45 (dd, 1H, $J=8.7$, 16.2 Hz), 6.86 (m, 4H), 7.30 (m, 10H). ^{13}C NMR: δ 162.0, 156.7, 154.1, 137.2, 136.0, 133.6, 131.0, 128.8, 128.7, 128.5, 127.0, 123.6, 123.1, 118.9, 115.7, 114.5, 112.4, 82.1, 60.9, 55.6. IR ($CHCl_3$, cm^{-1}): ν 1750. Anal. Calcd for $C_{24}H_{20}NO_3Br$: C, 64.01; H, 4.48; N, 3.11. Found: C, 64.12; H, 4.45; N, 3.09.

3.3.10. (±)-*cis*-4-(2-Bromophenyl)-3-phenoxy-1-prop-2-ynyl-azetidin-2-one (7). *Method B*. From 370 mg (2.0 mmol) of *o*-bromobenzaldehyde, 100 mg (2.0 mmol) of propargylamine, and 510 mg (3.0 mmol) of phenoxyacetyl chloride, 450 mg (61%) of compound **7** was obtained as a pale orange oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). ^1H NMR: δ 2.28 (t, 1H, $J=2.5$ Hz), 3.77 (dd, 1H, $J=2.5$, 17.7 Hz), 4.47 (dd, 1H, $J=2.7$, 17.7 Hz), 5.50 (d, 1H, $J=4.7$ Hz), 5.56 (d, 1H, $J=4.7$ Hz), 7.15 (m, 9H). ^{13}C NMR: δ 165.6, 156.9, 132.9, 132.4, 130.0, 129.3, 128.9, 127.3, 124.1, 122.4, 115.9, 82.5, 75.6, 73.7, 60.8, 30.3. IR ($CHCl_3$, cm^{-1}): ν 3310, 1755. Anal. Calcd for $C_{18}H_{14}NO_2Br$: C, 60.69; H, 3.96; N, 3.93. Found: C, 60.60; H, 3.93; N, 3.96.

3.3.11. (+)-(3*S*,4*R*)-4-(2-Bromophenyl)-3-[(*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl]-1-prop-2-ynyl-azetidin-2-one, (+)-8. *Method B*. From 180 mg (1.0 mmol) of *o*-bromobenzaldehyde, 60 mg (1.0 mmol) of propargylamine, 330 mg (1.5 mmol) of (*S*)-(2-oxo-4-phenyl-oxazolidin-3-yl)-acetic acid, and 220 μL (1.5 mmol) of phenyl dichlorophosphate, 360 mg (84%) of compound (+)-**8** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). $[\alpha]_D = +145$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 2.17 (t, 1H, $J=2.7$ Hz), 3.77 (dd, 1H, $J=2.7$, 17.7 Hz), 3.92 (dd, 1H, $J=7.5$, 8.7 Hz), 4.22 (t, 1H, $J=8.7$ Hz), 4.35 (d, 1H, $J=4.8$ Hz), 4.53 (dd, 1H, $J=2.7$, 17.7 Hz), 4.66 (dd, 1H, $J=7.5$, 8.7 Hz), 5.15 (d, 1H, $J=4.8$ Hz), 7.40 (m, 9H). ^{13}C NMR: δ 164.0, 156.3, 136.5, 132.6, 132.2, 129.9, 129.7, 129.6, 128.0, 127.4, 127.3, 122.7, 75.9, 73.5, 70.3, 63.1, 61.8, 60.2, 30.9. IR ($CHCl_3$, cm^{-1}): ν 3300, 1750. Anal. Calcd for $C_{21}H_{17}N_2O_3Br$: C, 59.31; H, 4.03; N, 6.59. Found: C, 59.24; H, 4.10; N, 6.48.

3.3.12. (+)-(3*R*,4*S*)-1-(2-Bromobenzyl)-4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3-phenoxy-azetidin-2-one, (+)-9. *Method B*. From 980 mg (7.6 mmol) of 2,3-*O*-isopropylidene-D-glyceraldehyde, 1.42 g (7.6 mmol) of *o*-bromobenzylamine, and 1.70 g (11.4 mmol) of phenoxyacetyl chloride, 2.0 g (60%) of compound (+)-**9** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 3:1). Mp 95–97 °C (hexanes/ethyl

acetate). $[\alpha]_D = +56.7$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.25 (s, 3H), 1.27 (s, 3H), 3.53 (dd, 1H, $J=6.0$, 8.7 Hz), 3.61 (dd, 1H, $J=5.1$, 8.7 Hz), 4.05 (dd, 1H, $J=5.4$ Hz), 4.39 (m, 2H), 4.86 (d, 1H, $J=15.3$ Hz), 5.14 (d, 1H, $J=5.4$ Hz), 7.20 (m, 9H). ^{13}C NMR: δ 165.8, 157.3, 134.3, 133.0, 131.5, 129.6, 129.5, 127.3, 123.7, 122.5, 115.7, 109.7, 79.8, 76.9, 66.8, 59.9, 45.7, 26.5, 25.0. IR ($CHCl_3$, cm^{-1}): ν 1770. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.24; H, 5.19; N, 3.26.

3.4. Synthesis of other cyclisation substrates

3.4.1. (+)-(3*R*,4*S*)-1-(2-Bromobenzyl)-4-(*E*)-(2-methoxycarbonylethenyl)-3-phenoxy-azetidin-2-one, (+)-5a. To a solution of the corresponding acetonide β-lactam (+)-**9** (233 mg, 0.54 mmol) in THF/water (1:1, 12 mL) was added solid *p*-TsOH·H_2O (124 mg, 0.65 mmol) in a single portion. The resulting clear solution was heated under reflux for 3 h. The reaction mixture was allowed to cool to room temperature, and then was neutralized with solid $NaHCO_3$. The mixture was extracted with ethyl acetate, the organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product (colourless oil) was used for next step without any further purification. Saturated aqueous sodium hydrogen carbonate (0.05 mL) was added to a solution of the corresponding diol (196 mg, 0.5 mmol) in dichloromethane (10 mL), maintaining the temperature below 25 °C. Solid sodium periodate (214 mg, 1.0 mmol) was added over a 10 min period with vigorous stirring and the reaction was allowed to proceed for 2 h, while the temperature was maintained below 25 °C. The solid was removed by filtration, the filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford the crude aldehyde as a colourless oil (178 mg, 0.5 mmol) which was directly used without further purification. To a stirred solution of the aldehyde in THF (10 mL) at 0 °C a solution of methyl (triphenylphosphoranylidene)acetate (202 mg, 0.6 mmol) in THF (2 mL) was slowly added and the mixture was heated at reflux under an argon atmosphere for 3 h, before being concentrated under reduced pressure. Flash chromatography of the residue eluting with hexanes/ethyl acetate 3:1 mixture gave compound (+)-**5a** (185 mg, 82% overall yield from **9**) as a colourless solid. Mp 96–98 °C (hexanes/ethyl acetate). $[\alpha]_D = +7.4$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 3.62 (s, 3H), 4.25 (d, 1H, $J=15.3$ Hz), 4.31 (dd, 1H, $J=5.1$, 7.8 Hz), 4.72 (d, 1H, $J=15.3$ Hz), 5.26 (d, 1H, $J=5.1$ Hz), 5.91 (d, 1H, $J=15.9$ Hz), 6.73 (dd, 1H, $J=7.8$, 15.9 Hz), 6.88 (m, 3H), 7.20 (m, 5H), 7.50 (m, 1H). ^{13}C NMR: δ 165.4, 165.0, 157.2, 140.5, 134.0, 133.3, 131.5, 130.2, 129.7, 128.1, 126.8, 124.1, 122.6, 115.7, 82.3, 59.1, 51.9, 45.2. IR ($CHCl_3$, cm^{-1}): ν 1750, 1710. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.71; H, 4.36; N, 3.36. Found: C, 57.81; H, 4.33; N, 3.38.

3.4.2. (+)-(3*R*,4*S*)-1-(2-Bromobenzyl)-3-phenoxy-4-[1-(*E*)-propenyl]-azetidin-2-one, (+)-5b. The starting aldehyde obtained from β-lactam (+)-**9** as described in Section 3.4.1 was directly used without further purification. To a stirred suspension of ethyltriphenylphosphonium iodide (292 mg, 0.7 mmol) in THF (5 mL) under an argon atmosphere, BuLi (1.6 M in hexanes, 0.6 mmol) was added dropwise. After the addition was finished, the reaction mixture was stirred for further 30 min at room temperature. Then, a solution of crude aldehyde (178 mg, 0.5 mmol) in THF (5 mL) was added dropwise, and the reaction mixture was stirred for 16 h at room temperature. The crude mixture was diluted with brine and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Compound (+)-**5b** (143 mg, 77%) was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 5:1) as a mixture of isomers *E*/*Z* (75:25). A fraction containing analytically pure *E*-isomer could be isolated. $[\alpha]_D = +45.0$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 1.49 (dd, 3H, $J=1.8$, 7.0 Hz), 4.24 (d, 1H, $J=17.8$ Hz), 4.60 (dd, 1H, $J=4.5$, 10.2 Hz), 4.77 (d, 1H, $J=17.8$ Hz), 5.28 (d, 1H, $J=4.5$ Hz), 5.40 (m, 1H), 5.75 (m, 1H), 7.30 (m, 9H). IR ($CHCl_3$, cm^{-1}): ν 1750. Anal. Calcd for $C_{19}H_{18}NO_2Br$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.19; H, 4.84; N, 3.78.

3.4.3. (±)-*cis*-3-(2-Bromophenoxy)-4-[(*E*)-(2-methoxycarbonylethenyl)]-1-(4-methoxyphenyl)-azetidin-2-one (6b). To a stirred solution of aldehyde **10** (150 mg, 0.40 mmol) in THF (8 mL) at 0 °C a solution of methyl (triphenylphosphoranylidene)acetate (162 mg, 0.48 mmol) in THF (2 mL) was slowly added and the mixture was heated at reflux under an argon atmosphere for 3 h, before being concentrated under reduced pressure. Flash chromatography of the residue eluting with hexanes/ethyl acetate 1:1 mixture gave compound **6b** (150 mg, 87%) as a colourless oil. ^1H NMR: δ 3.66 (s, 3H), 3.72 (s, 3H), 4.91 (dd, 1H, $J=5.4$, 7.5 Hz), 5.40 (d, 1H, $J=5.4$ Hz), 6.14 (d, 1H, $J=16.5$ Hz), 6.81 (d, 2H, $J=9.0$ Hz), 6.86 (m, 1H), 7.04 (dd, 1H, $J=7.5$, 16.5 Hz), 7.22 (m, 4H), 7.45 (d, 1H, $J=7.8$ Hz). ^{13}C NMR: δ 165.5, 162.0, 157.0, 154.5, 151.6, 140.6, 133.7, 131.3, 128.8, 126.8, 124.1, 118.7, 116.2, 114.7, 82.4, 58.4, 55.6, 52.0. IR ($CHCl_3$, cm^{-1}): ν 1760, 1715. Anal. Calcd for $C_{20}H_{18}NO_5Br$: C, 55.57; H, 4.20; N, 3.24. Found: C, 55.68; H, 4.24; N, 3.21.

3.4.4. Synthesis of β-lactam imine (±)-6c. A solution of benzylamine (0.03 mL, 0.27 mmol) in dichloromethane (1 mL) was added dropwise to a stirred suspension of the 4-oxoazetidine-2-carbaldehyde **10** (100 mg, 0.27 mmol) and magnesium sulfate (320 mg, 2,7 mmol) in dichloromethane (5 mL) at room temperature. After stirring 16 h at room temperature, the mixture was filtered and the solvent was removed under reduced pressure to give 120 mg (100%) of compound **6c** which was directly used without further purification. Colourless oil. ^1H NMR: δ 3.80 (s, 3H), 4.70 (m, 2H), 4.90 (dd, 1H, $J=5.0$, 6.0 Hz), 5.50 (d, 1H, $J=5.0$ Hz), 6.90 (d, 2H, $J=9.0$ Hz), 6.95 (m, 1H), 7.25 (m, 6H), 7.40 (d, 2H, $J=9.0$ Hz), 7.55 (d, 1H), 8.0 (d, 1H, $J=4.0$ Hz). ^{13}C NMR: δ 161.3, 160.8, 156.8, 153.6, 137.7, 133.5, 130.8, 128.7, 128.6, 128.2, 127.3, 123.8, 118.5, 115.4, 114.5, 112.2, 81.6, 65.2, 60.6, 55.5. IR ($CHCl_3$, cm^{-1}): ν 1755, 1670.

3.5. General procedure for the radical cyclization reaction. Synthesis of tricyclic β-lactams 11, 12, 13a, 14, 15, 23, and 24

A solution of the corresponding *o*-halogenophenyl-β-lactam **1–7** (1 mmol), Bu_3SnH (1.2 mmol), and AIBN (0.1 mmol) in dry benzene (20 mL) was refluxed under argon

atmosphere until complete disappearance of the starting substrate (TLC, 1.5–3 h). The resulting crude reaction mixture was treated with 10% aqueous solution of KF (20 mL) for 30 min. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure tricyclic β-lactam.

3.5.1. Tricyclic β-lactam (±)-11a. From 300 mg (0.84 mmol) of compound **1a**, 149 mg (65%) of compound **11a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 123–125 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 0.79 (s, 3H), 1.18 (s, 3H), 2.72 (dd, 1H, J=10.8, 13.5 Hz), 3.44 (dd, 1H, J=4.8, 13.5 Hz), 3.66 (m, 1H), 3.79 (d, 1H, J=8.1 Hz), 7.20 (m, 9H). ^{13}C NMR: δ 179.6, 141.6, 140.4, 139.1, 128.8, 128.8, 128.8, 126.7, 125.0, 124.5, 116.8, 69.7, 52.8, 45.9, 39.9, 23.1, 18.1. IR ($CHCl_3$, cm^{-1}): ν 1760, 1600. MS (EI), *m/z*: 277 (M^+, 11), 208 (25), 186 (96), 158 (59), 91 (100%). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.12; H, 6.72; N, 5.28.

3.5.2. Tricyclic β-lactam (±)-11b. From 300 mg (0.71 mmol) of compound **1b**, 160 mg (66%) of compound **11b** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp >130 °C (decomp.) (hexanes/ethyl acetate). ^{1}H NMR: δ 2.92 (dd, 1H, J=8.4, 13.8 Hz), 3.30 (dd, 1H, $J_=$6.6, 13.8 Hz), 4.14 (m, 1H), 4.38 (dd, 1H, J=4.5, 7.8 Hz), 5.46 (d, 1H, J=4.5 Hz), 7.05 (m, 14H). ^{13}C NMR: δ 173.2, 157.2, 142.1, 141.1, 138.6, 129.8, 129.2, 128.8, 128.3, 126.8, 126.0, 125.2, 122.5, 117.9, 115.6, 80.7, 64.2, 43.0, 39.8. IR ($CHCl_3$, cm^{-1}): ν 1740, 1670. MS (EI), *m/z*: 341 (M^+, 6), 319 (19), 250 (8), 235 (44), 105 (76), 91 (100%). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.77; H, 5.53; N, 4.05.

3.5.3. Tricyclic β-lactam *cis*-(±)-11c. From 400 mg (0.92 mmol) of compound *cis*-**1c**, 170 mg (60%) of compound *cis*-**11c** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). This compound decomposed quickly on standing in solution at room temperature. ^{1}H NMR: δ 2.80 (dd, 1H, J=9.9, 13.8 Hz), 3.42 (dd, 1H, J=4.5, 13.8 Hz), 4.12 (m, 1H), 4.19 (dd, 1H, J=4.5, 4.8 Hz), 4.25 (AB system, 2H, J=12.0 Hz), 4.78 (d, 1H, J=4.8 Hz), 7.20 (m, 14H). IR ($CHCl_3$, cm^{-1}): ν 1775, 1650.

3.5.4. Tricyclic β-lactam *trans*-(±)-11c. From 200 mg (0.46 mmol) of compound *trans*-**1c**, 90 mg (62%) of compound *trans*-**11c** was obtained as a white solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 87–89 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 2.69 (dd, 1H, J=10.5, 13.8 Hz), 3.29 (dd, 1H, J=5.7, 13.8 Hz), 3.63 (m, 1H), 3.99 (m, 3H), 4.35 (d, 1H, J=2.4 Hz), 7.0–7.3 (m, 14H). ^{13}C NMR: δ 171.9, 141.0, 139.1, 138.8, 136.7, 129.3, 129.1, 128.6, 128.2, 127.9, 127.0, 125.6, 124.7, 116.6, 87.2, 71.9, 67.0, 48.0, 40.1, 25.3. IR ($CHCl_3$, cm^{-1}): ν 1770, 1650, 1600. MS (EI), *m/z*: 298 (27), 264 (5), 91 (100). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.98; H, 6.03; N, 3.86.

3.5.5. Tricyclic β-lactam (±)-12a. From 200 mg (0.46 mmol) of compound **2a**, 80 mg (50%) of compound **12a** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 1:1). ^{1}H NMR: δ 3.03 (dd, 1H, J=7.5, 14.7 Hz), 3.12 (dd, 1H, J=5.1, 14.7 Hz), 3.68 (m, 1H), 3.82 (dd, 1H, J=4.5, 8.1 Hz), 4.06 (d, 1H, J=15.6 Hz), 4.72 (d, 1H, J=15.6 Hz), 5.28 (dd, 1H, J=1.5, 4.5 Hz), 7.15 (m, 14H). ^{13}C NMR: δ 167.2, 157.6, 139.3, 136.7, 131.8, 129.7, 129.2, 128.7, 128.4, 127.5, 126.9, 126.7, 126.5, 122.4, 115.9, 81.8, 54.7, 40.9, 38.9, 36.3. IR ($CHCl_3$, cm^{-1}): ν 1760, 1600. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.22; H, 5.94; N, 3.94.

3.5.6. Tricyclic β-lactam (±)-12b. From 220 mg (0.49 mmol) of compound **2b**, 110 mg (61%) of compound **12b** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). ^{1}H NMR: δ 3.00 (br s, 2H), 3.56 (br s, 2H), 3.97 (d, 1H, J=18.3 Hz), 4.45 (d, 1H, J=11.7 Hz), 4.64 (d, 1H, J=18.3 Hz), 4.64 (br s, 1H), 4.72 (d, 1H, J=11.7 Hz), 7.15 (m, 14H). ^{13}C NMR: δ 168.5, 139.5, 137.1, 136.8, 131.6, 129.1, 128.7, 128.6, 128.5, 127.8, 127.2, 126.7, 126.6, 126.4, 126.2, 82.4, 72.7, 54.7, 40.4, 38.9, 35.9. IR ($CHCl_3$, cm^{-1}): ν 1750, 1640. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.40; H, 6.24; N, 3.81.

3.5.7. Tricyclic β-lactam (+)-13a. From 100 mg (0.20 mmol) of compound (+)-**3a**, 66 mg (70%) of compound (+)-**13a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 168–170 °C (hexanes/ethyl acetate). $[\alpha]_D$=+110.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 2.57 (dd, 1H, J=11.1, 13.2 Hz), 3.05 (t, 1H, J=7.8 Hz), 3.45 (dd, 1H, J=3.9, 13.2 Hz), 3.86 (dd, 1H, J=7.8, 8.7 Hz), 4.07 (m, 3H), 4.23 (t, 1H, J=8.7 Hz), 7.20 (m, 14H). ^{13}C NMR: δ 169.6, 157.3, 141.9, 140.8, 140.4, 136.6, 129.6, 129.5, 129.3, 129.2, 128.3, 127.3, 126.8, 125.7, 124.7, 117.4, 70.9, 65.5, 59.7, 59.5, 46.3, 39.5. IR ($CHCl_3$, cm^{-1}): ν 1795, 1755, 1600. MS (EI), *m/z*: 410 (M^+, 7), 319 (81), 207 (52), 130 (84), 104 (62), 91 (100%). Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.19; H, 5.43; N, 6.78.

3.5.8. Tricyclic β-lactam (+)-14. From 250 mg (0.50 mmol) of compound (+)-**4**, 120 mg (57%) of compound (+)-**14** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Mp 178–180 °C (hexanes/ethyl acetate). $[\alpha]_D$=+97.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR: δ 2.65 (dd, 1H, J=9.3, 13.8 Hz), 3.26 (br s, 1H), 3.41 (dd, 1H, $J_=$4.5, 13.8 Hz), 3.53 (br s, 1H), 3.65 (dd, 1H, J=4.5, 8.7 Hz), 3.91 (dd, 1H, J=5.7, 8.7 Hz), 4.04 (d, 1H, J=4.5 Hz), 4.06 (d, 1H, J=17.1 Hz), 4.28 (t, 1H, J=8.7 Hz), 4.70 (d, 1H, J=17.1 Hz), 7.20 (m, 14H). ^{13}C NMR: δ 162.9, 157.5, 140.2, 138.0, 135.6, 131.2, 129.6, 129.5, 129.3, 129.1, 128.3, 127.3, 127.2, 126.9, 126.8, 126.6, 70.9, 62.6, 59.3, 56.8, 41.0, 40.4, 36.2. IR ($CHCl_3$, cm^{-1}): ν 1760, 1750. Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.51; H, 5.68; N, 6.57.

3.5.9. Tricyclic β-lactam (+)-15a. From 70 mg (0.17 mmol) of compound (+)-**5a**, 40 mg (64%) of compound (+)-**15a** was obtained as a colourless oil after

purification by flash chromatography (hexanes/ethyl acetate, 4:1). $[\alpha]_D = +56.0$ (*c* 0.5, $CHCl_3$). ^1H NMR: δ 2.76 (dd, 1H, $J=6.0$, 16.5 Hz), 2.85 (dd, 1H, $J=5.1$, 16.5 Hz), 3.57 (s, 3H), 3.62 (m, 1H), 4.04 (dd, 1H, $J=4.2$, 9.3 Hz), 4.21 (dd, 1H, $J=1.8$, 16.8 Hz), 4.78 (d, 1H, $J=16.8$ Hz), 5.43 (dd, 1H, $J=1.8$, 4.2 Hz), 7.10 (m, 9H). ^{13}C NMR: δ 172.2, 166.8, 157.5, 135.1, 131.1, 129.7, 127.7, 127.1, 127.0, 126.6, 122.5, 115.7, 81.5, 54.0, 52.0, 40.8, 35.2, 33.3. IR ($CHCl_3$, cm^{-1}): ν 1775. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.09; H, 5.72; N, 4.12.

3.5.10. Tricyclic β-lactam (+)-15b. From 200 mg (0.54 mmol) of compound (+)-**5b**, 80 mg (47%) of compound (+)-**15b** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). $[\alpha]_D = +47.0$ (*c* 1.0, $CHCl_3$). ^1H NMR: δ 0.89 (t, 3H, $J=7.5$ Hz), 1.90 (m, 2H), 3.23 (m, 1H), 3.74 (dd, 1H, $J=4.2$, 8.9 Hz), 4.13 (d, 1H, $J=17.0$ Hz), 4.73 (d, 1H, $J=17.0$ Hz), 5.38 (dd, 1H, $J=1.6$, 4.2 Hz), 7.25 (m, 9H). ^{13}C NMR: δ 166.8, 157.8, 135.9, 131.5, 129.7, 127.7, 127.4, 126.9, 126.5, 122.4, 115.8, 81.9, 54.1, 40.6, 35.7, 24.0, 10.9. IR ($CHCl_3$, cm^{-1}): ν 1775. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.91; H, 6.49; N, 4.75.

3.5.11. Tricyclic β-lactam (±)-22a. From 220 mg (0.49 mmol) of compound **6a**, 120 mg (69%) of compound **22a** was obtained as a mixture (85:15) of epimers. The major isomer could be isolated after purification by flash chromatography (hexanes/ethyl acetate, 1:1). Colourless solid. Mp 155–157 °C (hexanes/ethyl acetate). ^1H NMR: δ 2.87 (d, 2H, $J=8.1$ Hz), 3.43 (t, 1H, $J=8.7$ Hz), 3.69 (s, 3H), 4.46 (dd, 1H, $J=1.2$, 5.1 Hz), 5.33 (d, 1H, $J=5.1$ Hz), 6.95 (m, 13H). ^{13}C NMR: δ 162.1, 156.5, 152.2, 138.5, 130.4, 129.7, 129.0, 128.9, 128.6, 126.8, 125.8, 123.5, 118.6, 118.5, 114.5, 79.6, 58.2, 55.4, 40.3, 39.9. IR ($CHCl_3$, cm^{-1}): ν 1755, 1590. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.73; H, 5.67; N, 3.75.

3.5.12. Tricyclic β-lactam (±)-22b. From 100 mg (0.23 mmol) of compound **6b**, 50 mg (56%) of compound **22b** was obtained as a mixture (70:30) of epimers. The major isomer could be isolated after purification by flash chromatography (hexanes/ethyl acetate, 3:1). Colourless oil. ^1H NMR: δ 2.49 (dd, 1H, $J=5.1$, 17.1 Hz), 2.70 (dd, 1H, $J=10.2$, 17.1 Hz), 3.68 (s, 3H), 3.71 (s, 3H), 3.78 (dd, 1H, $J=5.1$, 9.9 Hz), 4.59 and 5.30 (d, each 1H, $J=4.5$ Hz), 6.81 (d, 2H, $J=9.0$ Hz), 6.93 (m, 3H), 7.15 (m, 1H), 7.35 (d, 2H, $J=9.0$ Hz). ^{13}C NMR: δ 172.1, 161.8, 156.6, 152.4, 130.0, 129.8, 129.4, 125.1, 124.0, 118.9, 118.6, 114.6, 79.5, 58.5, 55.5, 52.0, 37.1, 34.3. IR ($CHCl_3$, cm^{-1}): ν 1760, 1750. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.87; H, 5.45; N, 3.98.

3.5.13. Tricyclic β-lactam (±)-22c. From 70 mg (0.14 mmol) of compound **6c**, 30 mg (60%) of compound **22c** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). ^1H NMR: δ 3.75 (s, 3H), 3.76 (br s, 2H), 4.13 (d, 1H, $J=1.2$ Hz), 4.73 (dd, 1H, $J=1.2$, 5.1 Hz), 5.4 (d, 1H, $J=5.1$ Hz), 6.80 (d, 2H, $J=9.0$ Hz), 7.0 (m, 2H), 7.18 (d, 2H, $J=9.0$ Hz), 7.35 (m, 7H). ^{13}C NMR: δ 161.9, 156.6, 152.4, 139.4, 130.6, 130.0, 129.8, 128.6, 128.2, 127.3, 124.9, 123.5, 119.2, 118.5, 114.6, 79.5, 59.9, 55.5, 53.6, 51.3. IR ($CHCl_3$, cm^{-1}): ν 3200, 1750, 1590. Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.70; H, 5.70; N, 7.20.

3.5.14. Tricyclic β-lactam (±)-23. From 500 mg (1.40 mmol) of compound **7**, 80 mg (20%) of compound **23** was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 3:1). ^1H NMR: δ 3.75 (d, 1H, $J=15.3$ Hz), 4.58 (d, 1H, $J=15.3$ Hz), 4.91 (d, 1H, $J=4.4$ Hz), 5.12 (s, 1H), 5.53 (d, 1H, $J=4.4$ Hz), 5.60 (s, 1H), 7.15 (m, 8H), 7.63 (d, 1H, $J=7.7$ Hz). ^{13}C NMR: δ 168.5, 157.5, 136.3, 133.3, 129.6, 129.5, 129.2, 128.6, 127.9, 125.4, 122.3, 115.7, 112.2, 82.0, 54.2, 43.7. IR ($CHCl_3$, cm^{-1}): ν 1760. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.84; H, 5.43; N, 5.08.

3.6. Radical reaction of haloaryl β-lactam (+)-3b. Preparation of benzocarbapenem (+)-13b, benzocarbacephem (+)-16, and 1,4-dihydroquinoline 17

According to the general procedure described in Section 3.5. From 150 mg (0.35 mmol) of β-lactam (+)-**3b**, and after column chromatography eluting with hexanes/ethyl acetate (1:1), 40 mg (30%) of the less polar compound (+)-**13b**, 13 mg (10%) of compound (+)-**16**, and 33 mg (25%) of the more polar compound **17** were obtained.

3.6.1. Benzocarbapenem (+)-13b. Colourless oil. $[\alpha]_D = +126.0$ (*c* 0.7, $CHCl_3$). ^1H NMR: δ 0.98 (t, 3H, $J=7.5$ Hz), 1.43 (m, 1H), 1.95 (m, 1H), 3.0 (m, 1H), 4.01 (dd, 1H, $J=5.4$, 8.1 Hz), 4.35 (dd, 1H, $J=6.0$, 9.0 Hz), 4.75 (t, 1H, $J=9.0$ Hz), 4.96 (d, 1H, $J=5.4$ Hz), 5.02 (dd, 1H, $J=6.6$, 9.0 Hz), 7.15 (m, 9H). ^{13}C NMR: δ 170.6, 157.7, 141.6, 141.2, 137.9, 129.4, 129.3, 127.7, 127.7, 125.4, 124.7, 116.8, 71.0, 64.4, 61.9, 59.3, 44.3, 26.5, 11.8. IR ($CHCl_3$, cm^{-1}): ν 1760, 1600. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.28; H, 5.82; N, 8.07.

3.6.2. Benzocarbacephem (+)-16. Colourless solid. Mp >170 °C (decomp.) (hexanes/ethyl acetate). $[\alpha]_D = +114.6$ (*c* 0.5, $CHCl_3$). ^1H NMR: δ 1.09 (d, 3H, $J=7.2$ Hz), 1.7 (m, 2H), 2.72 (m, 1H), 3.87 (dddd, 1H, $J=1.5$, 4.2, 8.1, 12.0 Hz), 4.34 (dd, 1H, $J=5.4$, 8.7 Hz), 4.70 (t, 1H, $J=8.7$ Hz), 4.81 (d, 1H, $J=4.2$ Hz), 5.01 (dd, 1H, $J=5.4$, 8.7 Hz), 7.0–7.4 (m, 9H). ^{13}C NMR: δ 161.1, 157.9, 138.6, 132.6, 130.0, 129.4, 129.4, 128.0, 127.0, 126.5, 124.2, 118.5, 70.8, 63.2, 59.1, 54.1, 30.0, 29.3, 19.6. IR ($CHCl_3$, cm^{-1}): ν 1760, 1595. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.54; H, 5.83; N, 8.00.

3.6.3. 1,4-Dihydroquinoline 17. Colourless oil. ^1H NMR: δ 1.19 (d, 3H, $J=7.5$ Hz), 3.35 (m, 1H), 3.55 (d, 1H, $J=17.4$ Hz), 4.18 (t, 1H, $J=7.8$ Hz), 4.64 (d, 1H, $J=17.4$ Hz), 4.75 (t, 1H, $J=9.3$ Hz), 5.19 (t, 1H, $J=8.4$ Hz), 5.51 (dd, 1H, $J=5.1$, 7.2 Hz), 6.56 (d, 1H, $J=7.2$ Hz), 7.25 (m, 8H), 7.95 (d, 1H). IR ($CHCl_3$, cm^{-1}): ν 1750, 1650. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.52; H, 5.75; N, 8.08.

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References and notes

1. (a) *Recent Advances in the Chemistry of Anti-Infective Agents*; Bentley, P. H., Ponsford, R., Eds.; The Royal Society of Chemistry: Cambridge, 1993. (b) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In Lukacs, G., Ed.; Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products; Springer: Berlin, 1993; Vol. 2, p 621. (c) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman & Hall: London, 1992. (d) Morin, R. B., Gorman, M., Eds.; Chemistry and Biology of β-Lactam Antibiotics; Academic Press: New York, 1982; Vols. 1–3.
2. See, for example: (a) Ritter, T. K.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3508. (b) Díaz, N.; Suárez, D.; Merz, K. M. M., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 4197. (c) Page, M. I. *Chem. Commun.* **1998**, 1609. (d) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (e) Hook, V. *Chem. Br.* **1997**, *33*, 34. (f) Spratt, B. G. *Science* **1994**, *264*, 388. (g) Davies, J. *Science* **1994**, *264*, 375.
3. (a) Finkelstein, J.; Holden, K. G.; Perchonock, C. D. *Tetrahedron Lett.* **1978**, 1629. (b) Hakimelahi, G. H.; Just, G. *Can. J. Chem.* **1979**, *57*, 1939. (c) Bose, A. K.; Ram, B.; Hoffman, N. A.; Hutchinson, A. J.; Manhas, M. S. *J. Heterocycl. Chem.* **1979**, *16*, 1313. (d) Miyake, H.; Tokutake, N.; Kirisawa, M. *Synthesis* **1983**, 833. (e) Bachi, M. D.; Klein, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1925. (f) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680. (g) Ongania, K. H.; Wallnoefer, M. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 2. (h) Gilchrist, T. L.; Rahmam, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1203.
4. (a) Joyeau, R.; Yadav, L. D. S.; Wakselman, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1899. (b) Joyeau, R.; Dugenet, Y.; Wakselman, M. *J. Chem. Soc., Chem. Commun.* **1983**, 431.
5. (a) Coulton, S.; Gilchrist, T. L.; Graham, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1193. (b) Gilchrist, T. L.; Graham, K. *Tetrahedron Lett.* **1995**, *36*, 8693.
6. See, for instance: (a) Alcaide, B.; de Murga, R.; Pardo, C.; Rodríguez-Ranera, C. *Tetrahedron Lett.* **2004**, *45*, 7255. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2004**, *69*, 826. (d) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795. (f) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415.
7. For a preliminary communication of a part of this work, see: (a) Alcaide, B.; Moreno, A. M.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2203. (b) After the initiation of our efforts, a report appeared describing the aryl radical cyclization of *N*-allyl-4-(*o*-bromophenyl)-2-azetidinones leading to 1,2-benzocarbacephams. See: Banik, B. K.; Subbaraju, G. V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363.
8. (a) Staudinger, M. *Liebigs Ann. Chem.* **1907**, *356*, 51. For reviews on the ketene–imine approach to β-lactams, see: (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (d) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp 518–527. (e) 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. *N*-(2-Halogenophenyl)imines were prepared by the condensation of an *o*-halogenoaniline with the corresponding α,β-unsaturated aldehyde in the presence of the $ZnCl_2$/α-phenylethylamine complex as catalyst, using benzene as solvent and a Dean–Stark apparatus to remove the water formed during the reaction. Alternatively, *N*-alkylimines required in our work were smoothly prepared by the condensation of the appropriate aldehyde with the corresponding amine in dichloromethane at room temperature in the presence of anhydrous magnesium sulphate. A nearly quantitative yield of the Schiff base was obtained in all cases under these reaction conditions.
10. The assignment of relative stereochemistry was determined by the observed coupling constant for methine protons H3 and H4, which is a very well established criterium in β-lactam chemistry. See, for example: (a) Alcaide, B.; Aly, M. F.; Rodríguez, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453. (b) Ren, X. F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468. (c) Alcaide, B.; Domínguez, G.; Escobar, G.; Parreño, U.; Plumet, J. *Heterocycles* **1986**, *24*, 1579. (d) Zamboni, R.; Just, G. *Can. J. Chem.* **1979**, *57*, 1945.
11. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.
12. 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.
13. Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.
14. For selected references, see: (a) Zard, S. Z. *Radicals Reactions in Organic Synthesis*; Oxford University Press: New York, 2003. (b) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155. (c) Rousseau, G.; Homsi, F. *Chem. Soc. Rev.* **1997**, *26*, 453. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996. (e) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (f) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301–856. (g) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995.
15. Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449–450.
16. Although construction of five- and six-membered rings has received much attention, problems associated with the formation of medium-sized rings using free radical methodology are widely appreciated. Even the formation of seven-membered rings in the 7-*exo-trig* mode is likely to be unsuccessful in most cases (at 25 °C, $k_{7\text{-exo}} < 7 \times 10^{-1}\ s^{-1}$). However, we and others were able to prepare seven-membered rings by radical cyclization of β-lactam-tethered haloalkenes or alkynes. See: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612. (b) Penfold, D. J.; Pike, K.; Genge, A.; Anson, M.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 10347. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913. (d) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1237. (e) Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc.,*

Chem. Commun. **1986**, *1*, 78. (f) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.
17. For a review on the selective bond cleavage of the β-lactam nucleus, see: Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.
18. See, for example: (a) Crimmings, M. T.; Huang, S.; Guise-Zabacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519. (b) Horwell, D. C.; Morrell, A. I.; Roberts, E. *Tetrahedron Lett.* **1995**, *36*, 459.
19. Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377.
20. These values are in good agreement with previously reported data for related compounds obtained by different methods. See: Bertha, F.; Fetter, M.; Kajtár-Peredy, M.; Lempert, K.; Czira, G. *Tetrahedron* **1998**, *54*, 15227.
21. (a) Kliegman, J. M.; Barnes, R. K. *J. Org. Chem.* **1970**, *35*, 3140. (b) Kliegman, J. M.; Barnes, R. K. *Tetrahedron* **1970**, *26*, 2555.
22. Schmid, C.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.
23. Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. See, also Ref. 11.
24. Tako, A.; Ongania, K. H.; Wurst, K. *Monatsh. Chem.* **1997**, *128*, 1156.