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# Radical cyclisation of epoxynitrile-2-azetidinones mediated by $Cp_2TiCl$

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**Abstract**—The reductive radical cyclisation of δ- and ε-epoxynitrile-2-azetidinones has been achieved using titanocene monochloride. The reaction was regioselective and afforded bicyclic β-lactams and tricyclic β-lactams containing an aryl group fused to a seven-membered ring.


## 1. Introduction

The increasing resistance of bacteria to classical β-lactam antibiotics[1] is well documented and this has provoked a growing interest in the synthesis of new β-lactams able to supersede the destructive action of β-lactamases.[2]

An approach to deactivate these enzymes consists in modifying the structure of classical β-lactam antibiotics, trying to make them insensitive to the β-lactamase attack. An alternative to avoid the enzymatic destruction of the antibiotics uses a substance that disables the β-lactamase in synergy with a β-lactam antibiotic. In this context, benzocarbapenems and benzocarbacephems have been designed as inactivators of β-lactamases (Fig. 1).

On the other hand, the interest in free radical reactions applied to synthetic problems continues to increase and these reactions have successfully been used for growing a number of synthetic targets, including the synthesis of five- and six-membered carbocyclic and heterocyclic compounds.[3]

In connection to our current research interest in the preparation[4] and biological activities[5] of β-lactams, we have recently reported a series of radical cyclisations on epoxy-olefin- and epoxyaldehyde-2-azetidinones, mediated by titanocene monochloride,[6] to afford chiral bi- and tricyclic β-lactams.[7] In this context, we report here the radical cyclisation of δ- and ε-epoxynitrile-2-azetidinones as a new route to the synthesis of new bi- and tricyclic β-lactams. The *n-exo* cyclisation process is based on the homolytic cleavage of an oxiranyl ring with titanocene monochloride followed by intramolecular addition to the cyano group. The resulting products after hydrolysis could be bi- and tricyclic hydroxy-keto-β-lactams. [8]


**Figure 1**. Structures of β-lactamase inactivators.

## 2. Results and discussion

The synthesis of δ- and ε-epoxynitrile-2-azetidinones **1**–**4** required for our study is illustrated in Scheme 1. The starting precursors, β-lactams **5**–**7**, were prepared by ketene–imine cycloaddition[9] between methoxyacetyl chloride in the presence of TEA and the imines obtained from *trans*-cinnamaldehyde and 2,2-dimethylaminoethanol or *o*-cyanoaniline. The Staudinger reaction carried out with 2,2-dimethylethanolamine afforded the racemic *cis*-2-azetidinone **5** in 77% yield. In contrast, the use of *o*-cyanoaniline as amine afforded in 91% yield a 2:3 cis/trans isomeric mixture from which the pure β-lactams **6** and **7** could be isolated by chromatography and crystallisation.[10]

The $^1$H NMR coupling constants between H-3 and H-4 shown by these 2-azetidinones clearly established the relative cis configuration for compounds **5** and **6** ($J \geq 4.4$) and the trans configuration for **7** ($J \geq 1.8$).[5,11]

Compound **5**, by desilylation and Swern oxidation gave the aldehyde **8** in 71% yield, which was transformed into the homologue aldehyde **9** in 45% yield through a Wittig reaction. Different pathways were examined to prepare the nitriles **10**

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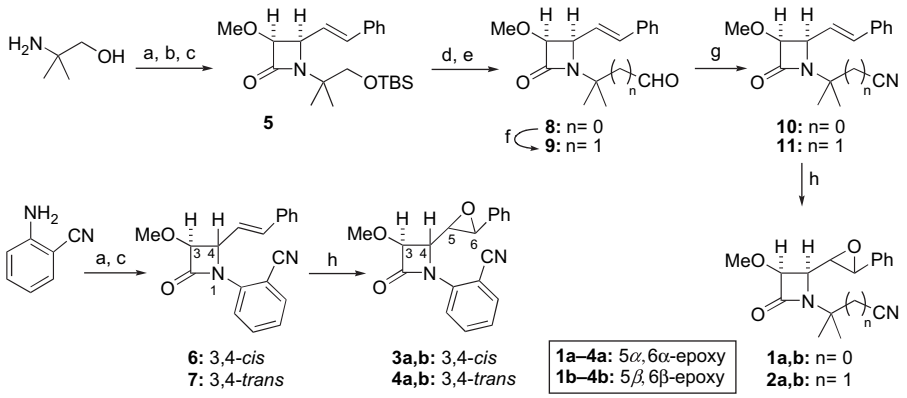



**Scheme 1**. Reagents and conditions: (a) *trans*-cinnamaldehyde, $CH_2Cl_2$, molecular sieve 4 Å, reflux, for **5**; *trans*-cinnamaldehyde, toluene, molecular sieve 4 Å, reflux, for **6** and **7**; (b) $^tBu(Me)_2SiCl$, pyr/DMAP, rt; (c) $MeOCH_2COCl$, TEA, rt; (d) HCl (0.1 M), MeOH, rt; (e) Swern oxidation; (f) $Ph_3P(Cl)CH_2OMe$, *n*BuLi, THF, −15 °C; then $HClO_4$ (30%), rt; (g) $Me_2N\text{-}NH_2$, MeOH, rt; then MMPP, 0 °C; (h) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, rt.

and **11**, and we found that the best yield (80%) was obtained by treatment of the aldehydes **8** and **9** with *N*,*N*-dimethylhydrazine, followed by oxidation with MMPP.[12]

The epoxidation of cyano-2-azetidinones **10** and **11** with *m*-CPBA gave diastereomeric mixtures of epoxylactams **1a/1b** (1:1) and **2a/2b** (3:2) in 74 and 85% yield, respectively. From these mixtures only the epoxide **1a** could be isolated as a pure substance by chromatography on silica gel.[13] Similar results were obtained in the epoxidation of the cis- and trans-isomers **6** and **7**. Treatment of these isomers with *m*-CPBA gave a 3:2 diastereomeric mixture of epoxylactams **3a/3b** in 85% yield and a 1:2 diastereomeric mixture of **4a/4b** in 90% yield, from which only the epoxide **3a** could be isolated as a pure substance.

The C-5 and C-6 configurations depicted in Scheme 1 for the epoxynitriles **1a**,**b** and **2a**,**b** were tentatively proposed by comparison of the respective polarities ($R_f$) and $^1H$ NMR data (Table 1) with those of the chiral epoxy-2-azetidinones **Ia** and **Ib** whose absolute configurations have been previously assigned as (5α,6α-epoxy) and (5β,6β-epoxy), respectively.[7b] From these data, it emerges that the less polar isomers of each pair of epoxides **1**, **2** and **I** show that the hydrogen atoms H-4 and H-6 are slightly unshielded and the proton H-5 is slightly shielded in comparison with those of the more polar isomers. Consequently, we propose the (5α,6α-epoxy) configuration for the less polar epoxynitriles **1** and **2** and the (5β,6β-epoxy) configuration for the more polar isomers.

**Table 1**. Selected spectral data of epoxides **1**, **2** and **I**

| Compound ($R_f$) | $^1H$ NMR | | |
|---|---|---|---|
| | H-4 | H-5 | H-6 |
| **1a** (0.48)[a] | 3.72 | 3.20 | 3.95 |
| **1b** (0.46)[a] | 3.59 | 3.26 | 3.80 |
| **2a** (0.23)[b] | 3.78 | 3.20 | 3.81 |
| **2b** (0.22)[b] | 3.58 | 3.22 | 3.80 |
| **Ia** (0.30)[c] | 3.52 | 3.28 | 3.76 |
| **Ib** (0.25)[c] | 3.51 | 3.88 | 3.72 |

**Ia:** 5α, 6α-epoxy
**Ib:** 5β, 6β-epoxy

[a] Benzene/ethyl acetate 8:2.
[b] Benzene/ethyl acetate 9:1.
[c] Hexanes/ethyl acetate 7:3.

The stereochemistry depicted in Scheme 1 for the 5,6-epoxy-β-lactams **3** and **4** was deduced from the structures proposed for their cyclisation products **14a** and **15a/15b**, respectively (Table 2). The stereoselective formation of these homobenzocarbacephems (see below) suggests that the cyclisation could be a process analogous to those observed in our previous studies.[7] Hence, the epoxides **3a** and **4a**, precursors of **14a** and **15a** ($C^6$-αOH), respectively, should have the relative configuration 5α,6α and the epoxide **4b**, the precursor of the tricyclic β-lactam **15b** ($C^6$-βOH), should have the relative configuration 5β,6β.

Two procedures[6g] were checked to explore the reactivity of the epoxynitriles **1**–**4** (Table 2) with titanocene monochloride. *Method A*: a green solution of $Cp_2TiCl$ in THF, generated in situ from $Cp_2TiCl_2$ and $Zn^0$ at room temperature, was slowly added to a THF solution of the epoxide. *Method B*: the epoxide in THF solution was slowly added to the THF solution of titanium-III reagent.

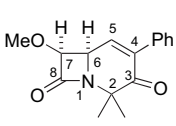
We first examined the 6-*exo*- and 7-*exo*-radical cyclisation process in the aliphatic δ- and ε-epoxynitrile-2-azetidinones **1** and **2** (Table 2), assuming that the reductive opening of epoxide ring with titanocene monochloride should firstly cause the formation of the C-6 benzylic radical intermediate. Thus, the addition of titanocene monochloride solution on the epoxynitrile-2-azetidinone **1a** solution (*Method A*) followed by acidic work-up proceeded with total regioselectivity to give the cyclisation product, the bicyclic β-lactam **12a**, in 60% yield (entry 1, Table 2).

Under the same conditions the reaction was carried out in a 4:5 isomeric mixture of **1a/1b** to give in 60% yield, a 3:4 mixture of $\Delta^{4,5}$-carbacephem **12a** and the starting epoxide **1b** (entry 2, Table 2). Similar results were obtained when a 3:2 isomeric mixture of the epoxides **2a/2b** was used as the starting material. In this case a 1:2:7 mixture of the compounds **13a/2a/2b** was obtained in 83% yield (entry 4, Table 2).

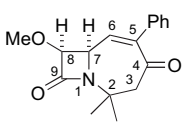
Under these conditions it seems that 5β,6β-epoxides **1b** and **2b** do not cyclise, so we decided to repeat the same reactions in the isomeric mixtures of the epoxides **1** and **2** but

**Table 2**. Reaction of epoxides **1–4** with $Cp_2TiCl$

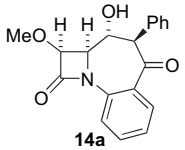
| Entry | Epoxide | Method (Time, h) | Products (yield, %)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Epoxide (%)[b] | Bilactam | | Alkene | Tribactam | |
| 1 | **1a** | A (3) | — | **12a** (60) | | — | | |
| 2 | **1a/1b** (4:5) | A (3) | **1b** (33) | **12a** (27) | — | — | | |
| 3 | **1a/1b** (4:5) | B (3) | **1b** (25) | **12a** (19) | — | **10** (13) | | |
| 4 | **2a/2b** (3:2) | A (1) | **2a** (16)[c], **2b** (57)[c] | **13a** (10)[c] | — | — | | |
| 5 | **2a/2b** (3:2) | B (3) | **2a** (12)[c], **2b** (55)[c] | **13a** (8)[c] | — | **11** (12)[c] | | |
| 6 | **3a** | A (2) | — | | | — | **14a** (56) | |
| 7 | **3a/3b** (1:1) | A (3) | — | | | **6** (25) | **14a** (35) | — |
| 8 | **3a/3b** (1:1) | B (5) | — | | | **6** (26) | **14a** (24) | — |
| 9 | **4a/4b** (1:2) | A (2) | **4a** (5) | | | — | **15a** (17) | **15b** (61) |
| 10 | **4a/4b** (1:2) | B (1) | — | | | **7** (22) | **15a** (11) | **15b** (34) |



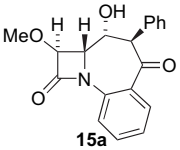
**12a**



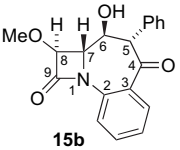
**13a**



**14a**



**15a**



**15b**

[a] Isolated yield after column chromatography.
[b] Recovered material.
[c] Calculated yield from GC/MS and $^1$H NMR.

reversing the order of addition of the reagents (*Method B*). Unfortunately, the 6-*exo*- and 7-*exo*-radical processes were not observed and lower yields for bicyclic β-lactams **12a** and **13a** were obtained in favour of the alkenes **10** and **11** (entries 3 and 5, Table 2).

The above results prove that a 7-*exo*-radical cyclisation of ε-epoxynitrile-2-azetidinones promoted by $Cp_2TiCl$ is possible and new tricyclic β-lactams could be synthesised. Thus, expecting that a planar geometry for the radical acceptors could be favourable for these cyclisation processes, we explored the reactivity of the benzoepoxynitriles **3** and **4**.

The reaction of pure cis-isomer **3a** with titanocene monochloride by the *Method A*, proceeded with total regio- and stereoselectivity to give the desired cyclisation product, the homobenzocarbacephem **14a** in 56% yield (entry 6, Table 2). But the same reaction carried out in a 1:1 mixture of the cis-isomers **3a/3b** afforded in 60% yield, a 5:7 mixture of elimination and cyclisation products **6/14a** (entry 7, Table 2). Different results were obtained when a 1:2 mixture of the *trans*-epoxynitriles **4a/4b** was used as the starting material. In this case, the homobenzocarbacephems **15a** and **15b** were obtained in 17% and 61% yield, respectively, and a small amount of the epoxide **4a** was also isolated (entry 9, Table 2). Also in these cases the reverse addition (*Method B*) does not improve the results. We found that the isomer **3b** does not cyclise and lower yields for homobenzocarbacephems **14a**, **15a** and **15b** were obtained in favour of the elimination products **6** and **7** (entries 8 and 10, Table 2).

The reaction products **12–15** were characterised by IR and NMR spectroscopies and FABHRMS analysis. These compounds show arylketone IR absorption bands while the IR cyanide group absorption bands and the NMR oxirane proton signals were absent. The NMR spectra of bicyclic β-lactams **12a** and **13a** are very similar, as both show signals for three methyl groups, three methynes (two $C_{sp^3}$ and one $C_{sp^2}$), and a phenyl group. The main difference is the presence of extra methylene group signal for the carbacephem **13a**.

The hydroxyl IR absorption bands as well as the presence of four $C_{sp^3}$–H methyne signals in NMR spectra are in agreement with the structures depicted in Table 2 for the tricyclic β-lactams **14a**, **15a** and **15b**. The stereochemistry of the benzofused tricyclic β-lactams **14a** and **15a** was deduced from the coupling constants of H-6 with the vicinal protons H-5 and H-7 ($J_{5,6}$=7.5 Hz, $J_{6,7}$=9.8 Hz in **14a**; $J_{5,6}$=8.4 Hz, $J_{6,7}$=4.3 Hz in **15a**). These coupling constants are characteristic of an *anti*-arrangement between these hydrogen atoms for compound **14a** and an *anti*/*syn*-arrangement for compound **15a**. The configuration of the tricyclic β-lactam **15b** was deduced from the coupling constant between H-6 and H-7 ($J_{6,7}$=9.4 Hz) as well as from NOE-difference spectrum data. Irradiation on the signal at $\delta$=4.25 ppm (m, H-5/H-6) in compound **15b** resulted in a 2.9% increment of the signal at $\delta$=4.06 ppm (dd, H-7) and a 2.1% increment of the signal at $\delta$=4.66 ppm (d, H-8). These data suggest a relative *syn*-relationship between H-6/H-8 and between H-5/H-7 and are consistent with the *trans*-arrangement of the H-5, H-6 and H-7 hydrogen atoms attached to the seven-membered ring. These configurational assignments are also supported by the dissimilar chemical shifts displayed by H-8 and C-8 in **15a** ($\delta_{H\text{-}8}$, 5.17 ppm; $\delta_{C\text{-}8}$, 84.0 ppm) and **15b** ($\delta_{H\text{-}8}$, 4.66 ppm; $\delta_{C\text{-}8}$, 87.3 ppm). The nearly *syn*-diaxial arrangement of H-8 and the hydroxyl group in **15a** (dihedral angle H–$C^8$–$C^6$–OH=−16°, $d_{H\text{–}O}$=2.4 Å) justifies the unshielding of H-8 ($\Delta\delta$ +0.51 ppm) in this isomer with respect to the chemical shift in **15b** (dihedral angle H–$C^8$–$C^6$–OH=50°, $d_{H\text{–}O}$=2.7 Å, Fig. 2). Also, the γ-shielding effect of the C-6 hydroxyl group on C-8 is more effective in **15a** (dihedral angle $C^8$–$C^7$–$C^6$–OH=−23°) than in **15b** (dihedral angle $C^8$–$C^7$–$C^6$–OH=55°), in agreement with the observed chemical shifts ($\Delta\delta$ −3.3 ppm).[14]

The evolution of the epoxy β-lactams **1–4** on reaction with $Cp_2TiCl$ could be explained as depicted in Scheme 2. The benzyl radicals *cis*/*trans*-**I** generated by homolytic cleavage of the oxirane ring can progress through two different pathways: (a) reduction to the benzyl anion followed by β-elimination of the titanium-oxo moiety to give the alkenes **6**, **7**,

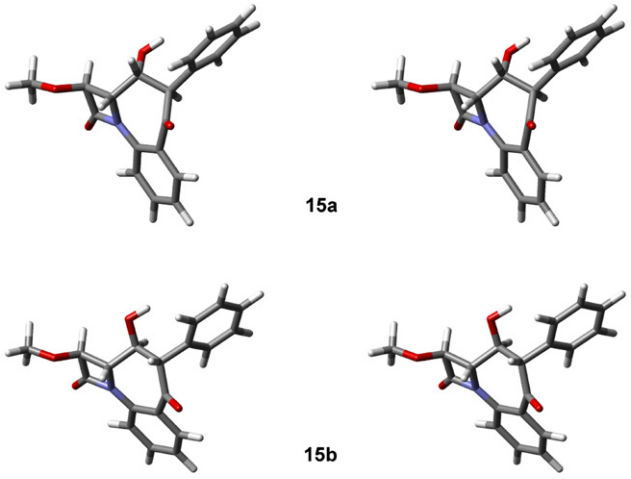
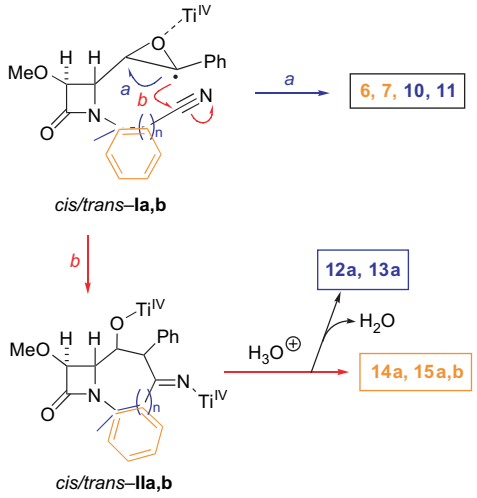



**Figure 2**. Energy minimised stereoscopic models for compounds **15a** and **15b**.[15]

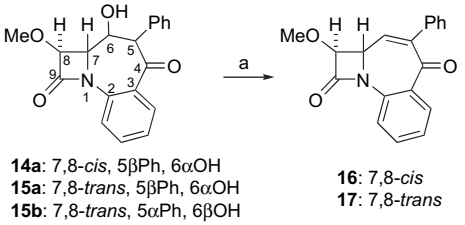
**10** or **11** and (b) radical trapping by the cyanide group to give the intermediate *cis*/*trans*-**II**, which progress after acid work-up to the desired homocarbacephems **14a**, **15a** or **15b** and, through subsequent dehydration, to the bicyclic β-lactams **12a** or **13a**.




**Scheme 2**. Proposed pathways explaining the formation of compounds **6**, **7** and **10**–**15**.

The product distribution in these reactions seems to be directed by stereoelectronic effects. The specific formation of the bi- and tricyclic β-lactams **12**–**15** could be explained if we consider that the addition of the benzyl radical to the nitrile group is quite slow,[8] thus the cyclisation process should go through a latter TS than in the case of alkyl radicals[16] so that it should lead to a higher selectivity as observed. The ability of the *cis*/*trans*-**Ia**,**b** radicals to cyclise depends on the accessibility of the triple bond by the benzyl radical and on the correct alignment of the C-6 $\sigma^{\bullet}$ and the nitrile $\pi^*$ orbitals. An analysis of the molecular models let us to verify that the *cis*/*trans*-**Ia**,**b** radicals can come close to the cyanide group (<4 Å), but the orientation of the $\sigma^{\bullet}$ and $\pi^*$ orbitals seems to be best arranged for cyclisation in isomers **1a**, **2a**, **3a** and **4b**, in agreement with the experimental results.

In order to evaluate the β-lactamase activity of these new bicyclic and tricyclic β-lactams, we also have prepared the unsaturated benzofused tricyclic β-lactams **16** and **17** by dehydration of the tricyclic β-lactams **14** and **15**, respectively (Scheme 3).




**Scheme 3**. Reagents and conditions: (a) *p*-$MeC_6H_4SO_2Cl$, TEA, DMAP, $CH_2Cl_2$, rt.

The reaction of the pure compound **14a** with *p*-toluenesulfonyl chloride in $CH_2Cl_2$ in the presence of TEA at room temperature, afforded in 36% yield the *cis*-homobenzocarbacephem **16**. The same reaction using a 1:3 mixture of compounds **15a**/**15b** as starting material, gave in 35% yield the *trans*-homobenzocarbacephem **17**.

The presence of the conjugated ketone in compounds **16** and **17** was evident from their IR and NMR spectral data, and also the molecular ions observed in their FABHRMS spectra ($[M^+ +23]$=328.0926 for **16** and 328.0936 for **17b**) support the structures depicted for these compounds in Scheme 3.

The present study shows that the δ- and ε-epoxynitrile radical cyclisations mediated by titanocene monochloride are stereocontrolled processes and can be applied to prepare new polycyclic β-lactams.

As far as we know, the 7-*exo*-radical cyclisation of ε-epoxynitriles mediated by titanocene monochloride has been applied for the first time to benzonitrile acceptors and the synthesised products, compounds **14** and **15**, are the first examples of homobenzocarbacephems reported in the literature. Further studies to optimise the yields and expand this approach to optically active benzofused tricyclic β-lactams as well as several biological activity tests are in progress and will be reported in due course.

## 3. Experimental section

### 3.1. General methods

Flash chromatographies were run on silica gel (Merck 60, 230–400 mesh) and thin layer chromatographies (TLC) on commercial silica gel plates (Merck $F_{254}$). Mass spectra (MS) were recorded on a VG TS-250 spectrometer: EI at 70 eV; FAB with xenon as ionisation gas; HRMS with *m*-nitrobenzyl alcohol matrix and 10 keV acceleration potential. IR spectra were recorded as neat film on a Bomem MB-100 instrument. $^1H$ and $^{13}C$ NMR spectra were obtained on Bruker instruments WP200SY and Advance 400DRX (200 and 400 MHz, respectively) in $CDCl_3$ solutions with tetramethylsilane as internal standard. Solvents and reagents were purified according to standard techniques.

### 3.2. Synthesis of mono-β-lactams 5, 6 and 7

*Method A*: a mixture of *trans*-cinnamaldehyde (10 mmol) and 2,2-dimethylaminoethanol (10 mmol) in $CH_2Cl_2$ (100 mL) with 4 Å molecular sieve was heated at 50 °C until the starting material disappeared in TLC. Then, the mixture was filtered through Celite® and the solvent was removed under reduced pressure. To a cooled (0 °C) solution of the imine and catalytic amount of DMAP in anhydrous pyridine (25.0 mL), *tert*-butyldimethylsilyl chloride (2.72 g, 20.0 mmol) was added under argon. The resulting mixture was allowed to warm to room temperature and stirred overnight. The crude mixture was poured into a cold solution of ammonium chloride and extracted with dichloromethane. The organic layer was washed with brine, dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure. To a solution of the crude silylated imine in anhydrous $CH_2Cl_2$ (100 mL), dry TEA (2.8 mL, 20 mmol,) and methoxyacetyl chloride (0.11 mL, 12.0 mmol) were successively added under argon. The reaction mixture was stirred at room temperature for 2 h and then poured into a cold ammonium chloride solution, neutralised to pH 7 and extracted with dichloromethane. The organic layer was washed with brine, dried (anhydrous $Na_2SO_4$) and the solvent removed under reduced pressure. Flash chromatography of the residue with hexanes/ethyl acetate 9:1 mixture as eluent gave compound **5** (3 g, 77%).

*Method B*: a mixture of *trans*-cinnamaldehyde (10 mmol) and *o*-cyanoaniline (10 mmol) in toluene (100 mL) was heated under reflux in a Dean–Stark apparatus until the starting material disappeared in TLC and then the solvent was removed under reduced pressure. To a solution of the crude imine in anhydrous $CH_2Cl_2$ (100 mL), dry TEA (2.8 mL, 20 mmol) and methoxyacetyl chloride (0.11 mL, 12.0 mmol) were consecutively added under argon. The reaction mixture was stirred at room temperature for 4 h and then same procedure as in *Method A* was followed. Flash chromatography of the residue with hexanes/ethyl acetate 9:1 mixture as eluent gave a 2:3 mixture of **6/7** (2.77 g, 91%). From this mixture, by crystallisation in pentane/ethyl ether, 890 mg of crystalline *trans*-2-azetidinone **7** was obtained together with 1.8 g of filtrate. A new flash chromatography of the filtrate with hexanes/ethyl acetate 95:5 mixture as eluent, afforded 350 mg of pure cis-isomer **6**.

**3.2.1. 1-(1′,1′-Dimethyl-2′-*tert*-butyldimethylsilyloxyethyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (5).** Colourless oil. IR (film): 1751, 1650, 1500, 760, 700 $cm^{-1}$; $^1H$ NMR (200 MHz): $\delta$ 0.04 (s, 6H), 0.90 (s, 9H), 1.24 (s, 3H), 1.33 (s, 3H), 3.39 (s, 3H), 3.52 (d, 1H, $J$=4.4 Hz), 3.67 (d, 1H, $J$=4.4 Hz), 4.40–4.50 (m, 2H), 6.30 (dd, 1H, $J$=8.3, 16.0 Hz), 6.70 (d, 1H, $J$=16.0 Hz), 7.30–7.50 (m, 5H); $^{13}C$ NMR (50 MHz): $\delta$ 18.2, 23.1, 23.4, 25.6, 58.2, 58.3, 60.7, 68.3, 83.9, 126.6, 126.8, 128.1, 128.6, 134.7, 136.4, 168.4; FABHRMS calcd for $C_{22}H_{33}NO_3Si$ ($M^+$+1): 390.2459; found: 390.2463.

**3.2.2. *cis*-1-(*o*-Cyanophenyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (6).** Colourless oil. IR (film): 2225, 1766, 1493, 755 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 3.53 (s, 3H), 4.90 (d, 1H, $J$=5.0 Hz), 5.60 (dd, 1H, $J$=5.0, 9.2 Hz), 6.25 (dd, 1H, $J$=9.2, 16.0 Hz), 7.05 (d, 1H, $J$=16.0 Hz), 7.25–7.45 (m, 7H), 7.60 (t, 1H, $J$=8.2 Hz), 8.10 (d, 1H, $J$=8.2 Hz); $^{13}C$ NMR (100 MHz): $\delta$ 58.9, 62.8, 85.6, 102.8, 117.2, 123.2, 125.3, 125.6, 126.8, 128.6, 133.8, 134.1, 135.3, 136.6, 137.5, 164.4; FABHRMS calcd for $C_{19}H_{16}N_2O_2Na$ ($M^+$+23): 327.1104; found: 327.1097.

**3.2.3. *trans*-1-(*o*-Cyanophenyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (7).** Colourless solid. Mp 60–61 °C (pentane/ethyl ether). IR (KBr): 2226, 1770 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.59 (3H, s), 4.60 (1H, d, $J$=1.8 Hz), 5.25 (1H, dd, $J$=1.8, 8.5 Hz), 6.20 (1H, dd, $J$=8.5, 15.9 Hz), 6.90 (1H, d, $J$=15.9 Hz), 7.25–7.45 (6H, m), 7.55 (1H, t, $J$=8.2 Hz), 7.60 (1H, d, $J$=8.2 Hz), 7.68 (1H, d, $J$=8.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 58.2, 63.9, 89.5, 103.1, 117.2, 123.4, 125.6, 126.7, 128.7, 133.8, 135.3, 136.6, 137.9, 164.4; FABHRMS calcd for $C_{19}H_{16}N_2O_2Na$ ($M^+$+23): 327.1104; found: 327.1108.

### 3.3. Synthesis of aldehydes 8 and 9

**3.3.1. 1-(1′,1′-Dimethyl-1′-formylmethyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (8).** To a solution of the silylated β-lactam **5** (5.0 g, 12.8 mmol) in methanol (193 mL), 0.1 M HCl (116 mL) was added. The resulting solution was stirred at room temperature for 2 h, then neutralised with solid $NaHCO_3$ and methanol was evaporated under reduced pressure. The resulting aqueous layer was extracted with ethyl acetate (3×15 mL), the organic combined extracts were washed with brine, dried (anhydrous $Na_2SO_4$) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate 4:1) and the resulting pure alcohol (2.72 g, 77%) was used for the next step. To a cooled (−78 °C) solution of oxalyl chloride (1.73 mL, 20.0 mmol) in anhydrous dichloromethane (55.2 mL), a solution of freshly distilled DMSO (3.9 mL, 54.9 mmol) in anhydrous dichloromethane (2.6 mL) was added dropwise under argon. The resulting mixture was stirred for 5 min keeping the temperature at −78 °C and then a solution of the above pure alcohol (2.75 g, 10.0 mmol) in anhydrous dichloromethane (13.0 mL) was added dropwise for a 1 h period. The reaction mixture was stirred for 30 min at −78 °C and then TEA (4.2 mL, 30 mmol) was added. The reaction was vigorously stirred for 40 min at −78 °C and then allowed to warm to 0 °C, and stirred for 2 h. The crude mixture was poured in water and extracted with ethyl acetate. The organic extract was washed with brine, dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure. Aldehyde **8** (2.6 g, 95%) was obtained as a colourless solid after crystallisation in hexanes/dichloromethane mixtures. Mp 90–91 °C (hexanes/dichloromethane). IR (KBr): 2840, 1755, 1717, 1660, 760, 700 $cm^{-1}$; $^1H$ NMR (200 MHz): $\delta$ 1.42 (s, 3H), 1.45 (s, 3H), 3.44 (s, 3H), 4.50 (dd, 1H, $J$=4.7, 9.3 Hz), 4.62 (d, 1H, $J$=4.7 Hz), 6.30 (dd, 1H, $J$=9.3, 16.0 Hz), 6.70 (d, 1H, $J$=16.0 Hz), 7.30–7.50 (m, 5H), 9.68 (s, 1H); $^{13}C$ NMR (50 MHz): $\delta$ 20.7, 21.0, 58.5, 60.6, 63.3, 84.2, 124.7, 126.6, 128.3, 128.6, 135.8, 136.0, 166.8, 198.4; FABHRMS calcd for $C_{16}H_{20}NO_3$ ($M^+$+1): 274.1438; found: 274.1429.

**3.3.2. 1-(1′,1′-Dimethyl-2′-formylethyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (9).** To a stirred suspension of methoxymethylenetriphenylphosphonium chloride (10.3 g, 30.0 mmol) in anhydrous THF (60 mL) at −15 °C under argon atmosphere, BuLi (1.6 M in hexanes, 30.0 mmol) was

added dropwise. After the addition was finished, the reaction mixture was stirred for further 10 min at −15 °C. Then, a solution of aldehyde **8** (2.73 g, 10.00 mmol) in anhydrous THF (6.0 mL) was slowly added, and the reaction mixture was stirred and slowly warmed to room temperature for 2 h. The crude mixture was poured into a cold ammonium chloride solution and extracted with ethyl acetate (3×25.0 mL). The combined organic extracts were washed successively with a saturated $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Compound **9** (1.30 g, 45%) was obtained as a colourless oil after purification by silica gel chromatography (hexanes/ethyl acetate 4:1). IR (film): 2834, 1748, 760, 700 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 1.42 (s, 3H), 1.43 (s, 3H), 2.74 (dd, 1H, $J$=2.0, 16.0 Hz), 3.07 (dd, 1H, $J$=2.0, 16.0 Hz), 3.42 (s, 3H), 4.49–4.50 (m, 2H), 6.30 (dd, 1H, $J$=9.4, 16.0 Hz), 6.72 (d, 1H, $J$=16.0 Hz), 7.25–7.45 (m, 5H), 9.80 (t, 1H, $J$=2.0 Hz); $^{13}C$ NMR (100 MHz): $\delta$ 25.7, 27.7, 52.8, 54.6, 58.6, 60.7, 83.7, 124.6, 126.6, 128.3, 128.7, 135.6, 136.0, 166.2, 200.2; FABHRMS calcd for $C_{17}H_{22}NO_3$ ($M^+$+1): 288.1594; found: 288.1579.

### 3.4. General procedure for the preparation of nitriles 10 and 11

To a stirred solution of the specific aldehyde (1.0 mmol) in methanol (5.7 mL) under argon atmosphere, *N*,*N*-dimethylhydrazine (0.11 mL, 1.43 mmol) was slowly added. After the completion of addition, the reaction mixture was stirred at room temperature until the starting material disappeared in TLC. The reaction mixture was cooled to 0 °C and a solution of magnesium monoperoxyphthalate (1.9 g, 3.0 mmol) in methanol (4.34 mL) was added and the resulting mixture was stirred for 10 min at 0 °C. Methanol was removed under reduced pressure and the crude residue was diluted with dichloromethane. The organic solution was washed twice with brine, dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure.

**3.4.1. 1-(1′,1′-Dimethyl-1′-cyanomethyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (10).** From 750 mg (2.75 mmol) of aldehyde **8**, 595 mg (80%) of nitrile **10** was obtained as a yellow oil after purification by flash chromatography (hexanes/ethyl acetate 4:1). IR (film): 2238, 1771, 1650, 1500, 700 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 1.74 (s, 3H), 1.81 (s, 3H), 3.45 (s, 3H), 4.52 (dd, 1H, $J$=4.8, 9.4 Hz), 4.59 (d, 1H, $J$=4.8 Hz), 6.32 (dd, 1H, $J$=9.4, 16.0 Hz), 6.81 (d, 1H, $J$=16.0 Hz), 7.30–7.50 (m, 5H); $^{13}C$ NMR (100 MHz): $\delta$ 26.0, 26.9, 50.2, 58.7, 61.3, 84.5, 119.6, 123.2, 126.8, 128.3, 128.6, 128.7, 135.7, 137.1, 162.6; FABHRMS calcd for $C_{16}H_{19}N_2O_2$ ($M^+$+1): 271.1441; found: 271.1439.

**3.4.2. 1-(1′,1′-Dimethyl-2′-cyanoethyl)-4-[(*E*)-styryl]-3-methoxy-2-azetidinone (11).** From 900 mg (3.14 mmol) of aldehyde **9**, 625 mg (70%) of nitrile **11** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate 7:3). IR (film): 2253, 1755, 1655, 1500, 755, 700 $cm^{-1}$; $^1H$ NMR (200 MHz): $\delta$ 1.47 (s, 6H), 2.74 (d, 1H, $J$=16.6 Hz), 3.05 (d, 1H, $J$=16.6 Hz), 3.42 (s, 3H), 4.55 (dd, 1H, $J$=4.4, 8.6 Hz), 4.57 (d, 1H, $J$=4.4 Hz), 6.35 (dd, 1H, $J$=8.6, 16.0 Hz), 6.75 (d, 1H, $J$=16.0 Hz), 7.30–7.40 (m, 5H); $^{13}C$ NMR (50 MHz): $\delta$ 25.4, 26.7, 29.5, 54.8, 58.7, 61.2, 84.1, 117.0, 125.0, 126.8, 128.6, 128.8, 136.0, 136.1, 166.6; FABHRMS calcd for $C_{17}H_{21}N_2O_2$ ($M^+$+1): 285.1598; found: 285.1577.

### 3.5. General procedure for the synthesis of epoxynitrile-β-lactams 1–4

A solution of the specific alkene (1.0 mmol), *m*-CPBA (370 mg, 1.5 mmol) and $NaHCO_3$ (126 mg, 1.5 mmol) in dry dichloromethane (10.0 mL) was stirred under argon atmosphere at room temperature until the disappearance of the starting material was observed by $^1H$ NMR spectra. The reaction was then quenched with 10% v/v aqueous $Na_2S_2O_3$ and the aqueous layer was separated and extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and brine, dried (anhydrous $Na_2SO_4$) and the solvent was evaporated under reduced pressure.

**3.5.1. 1-(1′,1′-Dimethyl-1′-cyanomethyl)-4-[(1α,2α)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (1a) and 1-(1′,1′-dimethyl-1′-cyanomethyl)-4-[(1β,2β)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (1b).** Compound **10** (230 mg, 0.9 mmol) was reacted with *m*-CPBA for 5 days to gave a 1:1 diastereomeric mixture of products **1a** and **1b** (180 mg, 74%) after purification by flash chromatography (hexanes/ethyl acetate, 4:1). The isomer **1a** (80 mg) was isolated from enriched fractions by flash chromatography (benzene/ethyl acetate 9:1).

**3.5.1.1. Isomer 1a.** Colourless oil. IR (film): 2240, 1771, 1600, 1500, 750, 700 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 1.68 (s, 3H), 1.88 (s, 3H), 3.20 (dd, 1H, $J$=2.0, 8.0 Hz), 3.63 (s, 3H), 3.72 (dd, 1H, $J$=4.8, 8.0 Hz), 3.95 (d, 1H, $J$=2.0 Hz), 4.64 (d, 1H, $J$=4.8 Hz), 7.30–7.45 (m, 5H); $^{13}C$ NMR (100 MHz): $\delta$ 25.8, 27.2, 50.6, 58.1, 58.7, 59.6, 60.3, 83.8, 119.4, 125.6, 128.6, 128.7, 135.4, 165.3; FABHRMS calcd for $C_{16}H_{18}N_2O_3Na$ ($M^+$+23): 309.1215; found: 309.1122.

**3.5.1.2. Isomer 1b.** From a 4:5 mixture of **1a/1b**. $^1H$ NMR (400 MHz): $\delta$ 1.86 (s, 3H), 1.89 (s, 3H), 3.26 (dd, 1H, $J$=2.0, 8.2 Hz), 3.47 (s, 3H), 3.59 (dd, 1H, $J$=5.2, 8.2 Hz), 3.80 (d, 1H, $J$=2.0 Hz), 4.60 (d, 1H, $J$=5.2 Hz), 7.25–7.45 (m, 5H); $^{13}C$ NMR (100 MHz): $\delta$ 26.2, 26.6, 49.8, 57.3, 59.3, 60.1, 61.0, 83.1, 119.6, 125.7, 128.6, 128.6, 135.5, 165.7.

**3.5.2. 1-(1′,1′-Dimethyl-1′-cyanoethyl)-4-[(1α,2α)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (2a) and 1-(1′,1′-dimethyl-1′-cyanoethyl)-4-[(1β,2β)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (2b).** Epoxidation of compound **11** (250 mg, 0.9 mmol) throughout 6 days gave a 3:2 mixture of the compounds **2a** and **2b** (225 mg, 85%) after purification by flash chromatography (hexanes/ethyl acetate 7:3).

**3.5.2.1. Isomer 2a.** From a 3:2 mixture of **2a/2b**. $^1H$ NMR (400 MHz): $\delta$ 1.45 (s, 3H), 1.48 (s, 3H), 2.72 (d, 1H, $J$=16.7 Hz), 3.11 (d, 1H, $J$=16.7 Hz), 3.20 (dd, 1H, $J$=1.9, 7.7 Hz), 3.60 (s, 3H), 3.78 (dd, 1H, $J$=4.6, 7.7 Hz), 3.81 (d, 1H, $J$=1.9 Hz), 4.61 (d, 1H, $J$=4.6 Hz), 7.40–7.50 (m, 5H); $^{13}C$ NMR (100 MHz): $\delta$ 25.3, 26.8, 29.1, 54.2, 57.6, 59.3, 59.6, 60.7, 83.3, 116.9, 125.5, 125.7, 128.6, 128.7, 135.4, 166.4.

**3.5.2.2. Isomer 2b.** From a 3:2 mixture of **2a/2b**. $^1H$ NMR (400 MHz): $\delta$ 1.57 (s, 3H), 1.61 (s, 3H), 2.87 (d, 1H,

$J$=16.7 Hz), 3.06 (d, 1H, $J$=16.7 Hz), 3.22 (dd, 1H, $J$=2.0, 8.3 Hz), 3.45 (s, 3H), 3.58 (dd, 1H, $J$=5.0, 8.3 Hz), 3.80 (d, 1H, $J$=2.0 Hz), 4.58 (d, 1H, $J$=5.0 Hz), 7.30–7.40 (m, 5H); $^{13}$C NMR (100 MHz): $\delta$ 25.6, 26.5, 29.3, 54.3, 57.6, 58.2, 59.3, 60.8, 82.5, 117.0, 125.5, 125.7, 128.6, 128.7, 135.5, 166.2.

**3.5.3. *cis*-1-(*o*-Cyanophenyl)-4-[(1α,2α)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (3a) and *cis*-1-(*o*-cyanophenyl)-4-[(1β,2β)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (3b).** The epoxidation of compound **6** (260 mg, 0.9 mmol) during 5 days afforded a 3:2 diastereomeric mixture of compounds **3a/3b** (230 mg, 85%). After purification of the crude product by flash chromatography (hexanes/ethyl acetate 9:1), 50 mg of the pure isomer **3a** (18%) and 180 mg of a 1:1 mixture of **3a/3b** (66%) were isolated.

**3.5.3.1. Isomer 3a.** Colourless solid. Mp 138–139 °C (hexanes/$CH_2Cl_2$). IR (KBr) 2228, 1777, 1160 cm$^{-1}$; $^1$H NMR (400 MHz): $\delta$ 3.37 (dd, 1H, $J$=1.0, 7.6 Hz), 3.58 (s, 3H), 3.86 (d, 1H, $J$=1.0 Hz), 4.80 (dd, 1H, $J$=5.2, 7.6 Hz), 4.87 (d, 1H, $J$=5.2 Hz), 7.20–7.35 (m, 6H), 7.61 (t, 1H, $J$=8.2 Hz), 7.65 (t, 1H, $J$=8.2 Hz), 7.96 (d, 1H, $J$=8.2 Hz); $^{13}$C NMR (100 MHz): $\delta$ 56.2, 59.5, 59.8, 61.1, 84.0, 103.9, 117.1, 123.7, 125.7, 126.0, 128.5, 133.9, 135.6, 138.5, 165.2; FABHRMS calcd for $C_{19}H_{17}N_2O_3$ ($M^+$+1): 321.1239, found: 321.1201.

**3.5.3.2. Isomer 3b.** From a 1:1 mixture of **3a/3b**. $^1$H NMR (400 MHz): $\delta$ 3.35 (dd, 1H, $J$=1.9, 4.5 Hz), 3.64 (s, 3H), 3.74 (d, 1H, $J$=1.9 Hz), 4.75–4.80 (m, 2H), 7.15–7.35 (m, 6H), 7.62 (t, 1H, $J$=6.9 Hz), 7.68 (t, 1H, $J$=6.9 Hz), 7.85 (d, 1H, $J$=6.9 Hz); $^{13}$C NMR (100 MHz): $\delta$ 57.0, 58.3, 60.5, 61.0, 85.3, 103.2, 117.2, 122.8, 125.7, 125.8, 128.6, 128.7, 134.1, 135.2, 138.1, 164.2.

**3.5.4. *trans*-1-(*o*-Cyanophenyl)-4-[(1α,2α)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (4a) and *trans*-1-(*o*-cyanophenyl)-4-[(1β,2β)-epoxy-2-phenylethyl]-3-methoxy-2-azetidinone (4b).** The epoxidation of compound **7** (850 mg, 2.8 mmol) for 2 days afforded a 1:2 diastereomeric mixture of compounds **4a/4b** (805 mg, 90%) that was impossible to resolve chromatographically.

**3.5.4.1. Isomer 4a.** From a 1:2 mixture of **4a/4b**. $^1$H NMR (400 MHz): $\delta$ 3.36 (dd, 1H, $J$=2.0, 4.5 Hz), 3.64 (s, 3H), 3.75 (d, 1H, $J$=2.0 Hz), 4.74–4.82 (m, 2H), 7.20–7.35 (m, 6H), 7.63 (t, 1H, $J$=7.0 Hz), 7.65 (t, 1H, $J$=7.0 Hz), 7.82 (d, 1H, $J$=7.0 Hz); $^{13}$C NMR (100 MHz): $\delta$ 56.9, 58.3, 60.5, 60.9, 85.3, 103.1, 117.2, 122.8, 125.5, 125.7, 128.6, 128.7, 134.0, 135.2, 138.0, 164.2.

**3.5.4.2. Isomer 4b.** From a 1:2 mixture of **4a/4b**. $^1$H NMR (400 MHz): $\delta$ 3.31 (dd, 1H, $J$=1.9, 4.2 Hz), 3.62 (s, 3H), 4.04 (d, 1H, $J$=1.9 Hz), 4.66 (d, 1H, $J$=2.0 Hz), 4.87 (dd, 1H, $J$=2.0, 4.2 Hz), 7.20–7.35 (m, 6H), 7.60 (dt, 1H, $J$=1.5, 6.9 Hz), 7.62 (dt, 1H, $J$=1.5, 6.9 Hz), 7.90 (d, 1H, $J$=6.9 Hz); $^{13}$C NMR (100 MHz): $\delta$ 57.8, 58.3, 59.3, 61.4, 84.7, 102.2, 117.2, 123.2, 125.6, 125.5, 128.6, 128.7, 134.1, 135.2, 138.0, 164.2.

### 3.6. In situ generation of $Cp_2TiCl$

To 548 mg (2.2 mmol) of titanocene dichloride in anhydrous and strictly deoxygenated THF (12.5 mL), 262 mg (4.0 mmol) of activated zinc granules was added. The resulting red mixture was then vigorously stirred under argon with rigorous exclusion of oxygen until a green colour was observed (about 20 min).

### 3.7. General procedure for the radical cyclisation reaction. Synthesis of bi- and tricyclic β-lactams 12–15

*Method A*: a THF green suspension of $Cp_2TiCl$, generated as reported above, was added dropwise through cannula to the corresponding epoxide (1.0 mmol) in THF (17.0 mL). The reaction mixture was stirred at room temperature until a colour change from green to orange was observed and then the reaction is quenched with 10% v/v aqueous $KH_2PO_4$ (30.0 mL). The aqueous phase was extracted with ethyl acetate and the combined organic extracts were filtered through Celite®, dried (anhydrous $Na_2SO_4$) and concentrated in vacuo.

*Method B*: a solution of the corresponding epoxide (1.0 mmol) in THF (17.0 mL) was added dropwise through cannula to a green suspension of $Cp_2TiCl$, generated in situ from $Cp_2TiCl_2$ and $Zn^0$ as described above. The resulting reaction mixture was stirred until a colour change was observed and then worked up as reported in *Method A*.

**3.7.1. Bicyclic β-lactam 12a.** *Method A*. From 80 mg (0.3 mmol) of epoxynitrile **1a**, 46 mg (60%) of compound **12a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate 7:3). Likewise, from a 4:5 mixture of compounds **1a/1b** (180 mg, 0.63 mmol) a 4:3 mixture of compounds **1b/12a** (106 mg, 60%) was obtained. *Method B*. From a 4:5 mixture of compounds **1a/1b** (100 mg, 0.36 mmol) a 2:4:3 mixture of compounds **1b/10/12a** (55 mg, 57%) was obtained. Compound **12a**: mp 176–179 °C (hexanes/dichloromethane). IR: 1755, 1694, 1500, 745, 700 cm$^{-1}$; $^1$H NMR (400 MHz): $\delta$ 1.36 (s, 3H), 1.83 (s, 3H), 3.59 (s, 3H), 4.50 (dd, 1H, $J$=1.9, 4.9 Hz), 4.73 (d, 1H, $J$=4.9 Hz), 6.96 (d, 1H, $J$=1.9 Hz), 7.30–7.40 (m, 5H); $^{13}$C NMR (100 MHz): $\delta$ 21.2, 24.1, 50.7, 59.1, 62.0, 86.1, 128.0, 128.3, 128.8, 135.6, 139.2, 140.0, 167.4, 196.3; FABHRMS calcd for $C_{16}H_{18}NO_3$ ($M^+$+1): 272.1281; found: 272.1244.

**3.7.2. Bicyclic β-lactam 13a.** *Method A*. From a 3:2 mixture of compounds **2a/2b** (100 mg, 0.33 mmol) a 2:7:1 mixture of compounds **2a/2b/13a** (82 mg, 83%) was obtained. *Method B*. From a 3:2 mixture of compounds **2a/2b** (100 mg, 0.33 mmol) a 3:14:3:2 mixture of compounds **2a/2b/11/13a** (86 mg, 87%) was obtained. Compound **13a**: $^1$H NMR (400 MHz): $\delta$ 1.33 (s, 3H), 1.67 (s, 3H), 2.58 (d, 1H, $J$=11.4 Hz), 2.75 (d, 1H, $J$=11.4 Hz), 3.58 (s, 3H), 4.63 (d, 1H, $J$=5.1 Hz), 4.78 (dd, 1H, $J$=2.0, 5.1 Hz), 6.80 (d, 1H, $J$=2.0 Hz), 7.25–7.45 (m, 5H); $^{13}$C NMR (100 MHz): $\delta$ 24.8, 27.5, 29.1, 54.0, 59.0, 59.2, 83.5, 125.7, 128.1, 128.7, 135.5, 139.5, 141.0, 166.2, 200.0.

**3.7.3. Tricyclic β-lactam 14a.** *Method A*. From 50 mg (0.16 mmol) of epoxynitrile **3a**, 28 mg (56%) of compound **14a** was obtained as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate 8:2). Likewise, from a 1:1 mixture of compounds **3a/3b** (100 mg, 0.31 mmol), 24 mg (25%) of compound **6** and 35 mg

(35%) of compound **14a** were isolated by flash chromatography (hexanes/ethyl acetate 4:1). *Method B*. From a 1:1 mixture of compounds **3a/3b** (80 mg, 0.25 mmol), 20 mg (26%) of compound **6** and 19 mg (24%) of compound **14a** were isolated by flash chromatography (hexanes/ethyl acetate 4:1). Compound **14a**: Mp 178–180 °C (hexanes/$CH_2Cl_2$). IR (KBr): 3480, 1760, 1669 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 3.73 (s, 3H), 4.28 (d, 1H, $J$=7.5 Hz), 4.29 (dd, 1H, $J$=5.0, 9.8 Hz), 4.75 (dd, 1H, $J$=7.5, 9.8 Hz), 4.82 (d, 1H, $J$=5.0 Hz), 7.11 (dt, 1H, $J$=0.7, 7.6 Hz), 7.19 (d, 1H, $J$=7.6 Hz), 7.22–7.30 (m, 2H), 7.49 (ddd, 1H, $J$=1.5, 7.6, 8.2 Hz), 8.10 (dd, 1H, $J$=0.7, 8.2 Hz); $^{13}C$ NMR (100 MHz): $\delta$ 59.6, 60.1, 69.9, 72.4, 84.1, 119.3, 124.8, 127.8, 128.2, 128.9, 131.2, 133.3, 135.3, 137.0, 163.7, 199.9; FABHRMS calcd for $C_{19}H_{18}NO_4$ ($M^+$+1): 324.1230; found: 324.1224.

**3.7.4. Tricyclic β-lactams 15a and 15b.** *Method A*. From a 1:2 mixture of compounds **4a/4b** (380 mg, 1.19 mmol), 19 mg (5%) of epoxide **4a**, 65 mg (17%) of compound **15a** and 235 mg of **15b** (61%) were isolated by flash chromatography (hexanes/ethyl acetate 4:1). *Method B*. From a 1:2 mixture of compounds **4a/4b** (400 mg, 1.25 mmol), 84 mg (22%) of **7**, 44 mg (11%) of **15a** and 137 mg (34%) of **15b** were isolated by flash chromatography (hexanes/ethyl acetate 4:1).

**3.7.4.1. Isomer 15a.** IR (film): 3449, 1761, 1691 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 3.57 (s, 3H), 4.06 (dd, 1H, $J$=2.2, 4.3 Hz), 4.34 (d, 1H, $J$=8.4 Hz), 4.58 (dd, 1H, $J$=4.3, 8.4 Hz), 5.17 (d, 1H, $J$=2.2 Hz), 7.18 (t, 1H, $J$=7.4 Hz), 7.36–7.41 (m, 4H), 7.55 (ddd, 1H, $J$=0.9, 7.4, 8.2 Hz), 8.33 (d, 1H, $J$=8.2 Hz); $^{13}C$ NMR (100 MHz): $\delta$ 58.4, 64.4, 65.8, 74.6, 84.0, 119.0, 124.4, 128.2, 128.4, 128.8, 129.9, 133.1, 134.6, 139.3, 165.8, 196.6; FABHRMS calcd for $C_{19}H_{17}NO_4Na$ ($M^+$+23): 323.1050; found: 323.1047.

**3.7.4.2. Isomer 15b.** IR (film): 3449, 1762, 1671 $cm^{-1}$; $^1H$ NMR (400 MHz): $\delta$ 3.53 (s, 3H), 4.10 (dd, 1H, $J$=1.8, 9.4 Hz), 4.23–7.27 (m, 2H), 4.67 (d, 1H, $J$=1.8 Hz), 7.13 (t, 1H, $J$=7.2 Hz), 7.17 (d, 1H, $J$=7.9 Hz), 7.30–7.35 (m, 2H), 7.37 (dd, 1H, $J$=1.3, 7.2 Hz), 7.50 (ddd, 1H, $J$=1.3, 7.2, 8.2 Hz), 8.14 (dd, 1H, $J$=0.6, 8.2 Hz); $^{13}C$ NMR (100 MHz): $\delta$ 58.5, 65.3, 69.6, 71.8, 87.4, 120.0, 124.9, 128.1, 128.7, 128.9, 129.3, 131.1, 133.4, 135.4, 135.8, 163.7, 199.3; FABHRMS calcd for $C_{19}H_{17}NO_4Na$ ($M^+$+23): 323.1050; found: 323.1035.

### 3.8. Preparation of unsaturated tricyclic β-lactams 16 and 17

To a solution of the 10-hydroxy-tricyclic compound (1.0 mmol) in anhydrous dichloromethane (10 mL), dimethylaminopyridine, TEA (0.17 mL, 1.20 mmol) and tosyl chloride (229 mg, 1.20 mmol) were successively added under argon atmosphere. The resulting mixture was stirred at room temperature until the total disappearance of the starting material was observed in TLC. Then, the reaction mixture was poured into a cold saturated solution of $NH_4Cl$ and extracted with dichloromethane (10 mL×3). The combined organic extracts were dried (anhydrous $Na_2SO_4$) and concentrated under reduced pressure.

**3.8.1. Tricyclic β-lactam 16.** From **14a** (30 mg, 0.09 mmol), 10 mg (36%) of **16** was isolated after flash chromatography (hexanes/ethyl acetate 85:15). IR (film): 2928, 2846, 1767, 1657, 764 $cm^{-1}$; $^1H$ NMR (200 MHz): $\delta$ 3.72 (s, 3H), 4.80 (d, 1H, $J$=4.9 Hz), 4.92 (dd, 1H, $J$=3.8, 4.9 Hz), 6.64 (d, 1H, $J$=3.8 Hz), 7.25–7.35 (m, 6H), 7.57 (t, 1H, $J$=7.5 Hz), 7.93 (d, 1H, $J$=7.5 Hz), 8.06 (d, 1H, $J$=7.5 Hz); $^{13}C$ NMR (50 MHz): $\delta$ 55.0, 59.5, 83.7, 120.5, 125.0, 125.2, 127.1, 127.7, 128.5, 130.8, 134.5, 136.4, 137.5, 148.6, 163.2, 195.6; FABHRMS calcd for $C_{19}H_{15}NO_3Na$ ($M^+$+23): 328.0950; found: 328.0926.

**3.8.2. Tricyclic β-lactam 17.** From a 1:3 mixture of compounds **15a/15b** (90 mg, 0.28 mmol), 30 mg (35%) of **17** was isolated after flash chromatography (hexanes/ethyl acetate 85:15). IR (film): 3066, 2935, 2839, 1760, 1650, 771 $cm^{-1}$; $^1H$ NMR (200 MHz): $\delta$ 3.64 (s, 3H), 4.77 (d, 1H, $J$=1.9 Hz), 4.86 (dd, 1H, $J$=1.9, 3.4 Hz), 6.59 (d, 1H, $J$=3.4 Hz), 7.24 (t, 1H, $J$=7.8 Hz), 7.30–7.35 (m, 5H), 7.57 (t, 1H, $J$=7.8 Hz), 7.92 (d, 1H, $J$=7.8 Hz), 8.17 (d, 1H, $J$=7.8 Hz); $^{13}C$ NMR (50 MHz): $\delta$ 58.0, 59.1, 88.9, 120.4, 124.9, 127.1, 127.7, 128.3, 128.5, 130.9, 134.4, 136.5, 137.5, 148.3, 162.8, 194.1; FABHRMS calcd for $C_{19}H_{15}NO_3Na$ ($M^+$+23): 328.0950, found: 328.0936.

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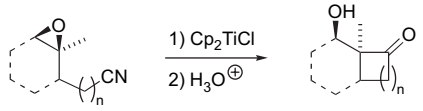


**Scheme 4.** Radical epoxynitrile cyclisations mediated by Ti(III) reagent.

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