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Stereospecific Synthesis of Polyfunctionalized Carbacephams Induced by Titanocene(III) Chloride

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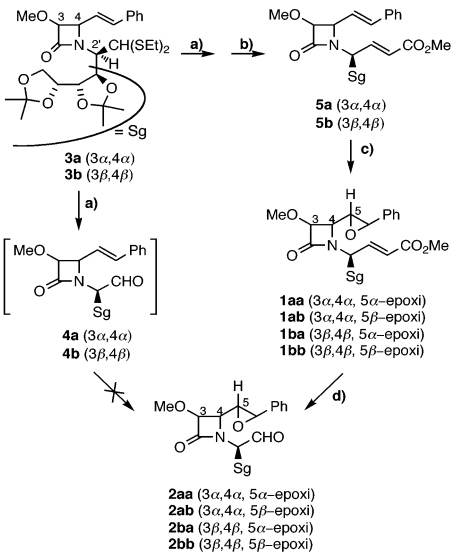
Abstract: Enantiomerically pure *N*-substituted epoxyalkene-2-azetidinones reacted with titanocene monochloride to give stereospecifically polyfunctionalized bicyclic β-lactams. Four isomeric epoxyaldehydes **2** reacted with $TiCp_2Cl$ to give exclusively the respective carbacephams **7** while under the same reaction conditions the epoxyesters **1**, which are more hindered for an intramolecular addition, gave the cyclization products **6** (only two isomers) and/or the elimination products **5** (all isomers).

In a previous paper[1] on the $TiCp_2Cl$-promoted reductive ring opening via single electron transfer[2] of enantiomerically pure epoxy-monobactams, we described the cyclization by 1,4 addition of benzyl radicals to a conjugated γ-lactone and by 1,2 addition to an amide and a lactone carbonyl functional group. These last additions were not described previously in the literature. To extend the application of these reactions and to compare the reactivity of the generated benzyl radicals on the conjugated alkenes, amides, and aldehydes,[2c] we report here the results obtained by reaction of enantiomerically pure epoxides **1** and **2** (Scheme 1)[3] with $TiCp_2Cl$.

The readily available *cis*-2-azetidinones **3a** and **3b**[4,5] (Scheme 1) were used as starting material to prepare the enantiomerically pure epoxides **1** and **2**. Deprotection of dithioacetal groups with [bis(trifluoroacetoxy)iodo]benzene yielded the aldehydes **4**, which were used without further purification in the next steps. Wittig reactions on the crude aldehydes **4a** and **4b** afforded in good yields the respective conjugated alkenes **5a** and **5b** and the regioselective epoxidation of the styryl group with *m*-CPBA followed by chromatography of the reaction products afforded the pure epoxides **1aa** (35%; $[\alpha]^{25}_D = +56$) and **1ab** (42%; $[\alpha]^{25}_D = +54$) from **5a** and **1ba** (40%; $[\alpha]^{25}_D = -33$) and **1bb** (49%; $[\alpha]^{25}_D = -21$) from **5b**.

SCHEME 1[a]



[a] Reagents and conditions: (a) $PhI(CF_3CO_2)_2/NaHCO_3$/85:15 CH_3CN/H_2O, rt; (b) $Ph_3P{=}CH{-}CO_2Me$, THF, rt; (c) *m*-CPBA, CH_2Cl_2, rt; (d) O_3, CH_2Cl_2, −78 °C; Me_2S, rt.

The instability of aldehyde functions to basic and acidic reaction media[6] prevents the direct conversion of the crude reaction products **4a** and **4b** into the respective epoxides **2aa** to **2bb**. However, the ozonolysis of each one of the pure epoxides **1** proceeded with very good yields to give the respective enantiomerically pure epoxyaldehydes **2aa** (100%; $[\alpha]^{25}_D = +52$), **2ab** (85%; $[\alpha]^{25}_D = +27$), **2ba** (100%; $[\alpha]^{25}_D = +22$), and **2bb** (90%; $[\alpha]^{25}_D = -29$).

The structure of the epoxy-β-lactams **1** and **2** was deduced from one- and two-dimensional NMR data, including COSY and HMQC experiments; however, it was not possible to assign the C-5 and C-6 configurations for these 2-azetidinones from the ^1H NMR data. The configurations depicted in Scheme 1 were deduced, as will be discussed below, from the configurational assignments of the cyclization products obtained from these epoxides (Table 1).

To explore the reactivity of the epoxides **1** and **2** with titanocene (III) monochloride, a THF solution of each pure epoxide (1.0 mmol) was added at room temperature

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(1) Ruano, G.; Grande, M.; Anaya, J. *J. Org. Chem.* **2002**, *67*, 8243−8245.

(2) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. (b) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101−103. (c) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607−609. (d) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788. (f) Li, J. J. *Tetrahedron* **2001**, *57*, 1−24. (e) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206−3208.

(3) The stereodescriptors α and β refers to the substituents below and above to the reference plane of the 2-azetidinone ring as it is depicted (IUPAC. *Pure Appl. Chem.* **1995**, *67*, 1307−1375).

(4) The *cis*-monobactams **3a** and **3b** were the only cyclization products obtained as a 1:2.1 mixture by Staudinger reaction of methoxyacetyl chloride with the imine produced from D-glucosamine and *trans*-cinnamaldehyde in the presence of Et_3N. No *trans* diastereomeric 2-azetidinone was detected. The absolute configuration of these compounds was deduced from their $[\alpha]_D$ data by comparison with the 1′,1′-dithyanyl derivative 3β,4β-disubstituted-2-azetidinone ($[\alpha]^{25}_D$ −102 (*c* 1.0, $CHCl_3$)) of known absolute configuration established by X-ray crystallography.[5]

(5) (a) Barton, D. H. R.; Gateau-Olesker, A.; Anaya-Mateos, J.; Cléophax, J.; Gero, S. D.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3211−3212. (b) Chiaroni, A.; Riche, C.; Anaya, J.; Gateau-Olesker, A.; Gero, S. D.; Hernando, J. I. M. *Acta Crystallogr.* **1994**, *C50*, 1470−1480. (c) Anaya, J.; Gero, S. D.; Grande, M.; Hernando, J. I. M.; Laso, N. M. *Bioorg. Med. Chem.* **1999**, *7*, 837−850.

(6) These aldehydes are very labile because of the acidity of the α-proton H-2′. The chromatographic grade silica gel is acidic enough to induce instantly the formation of the unsaturated aldehyde if not treated previously with TEA.[1]

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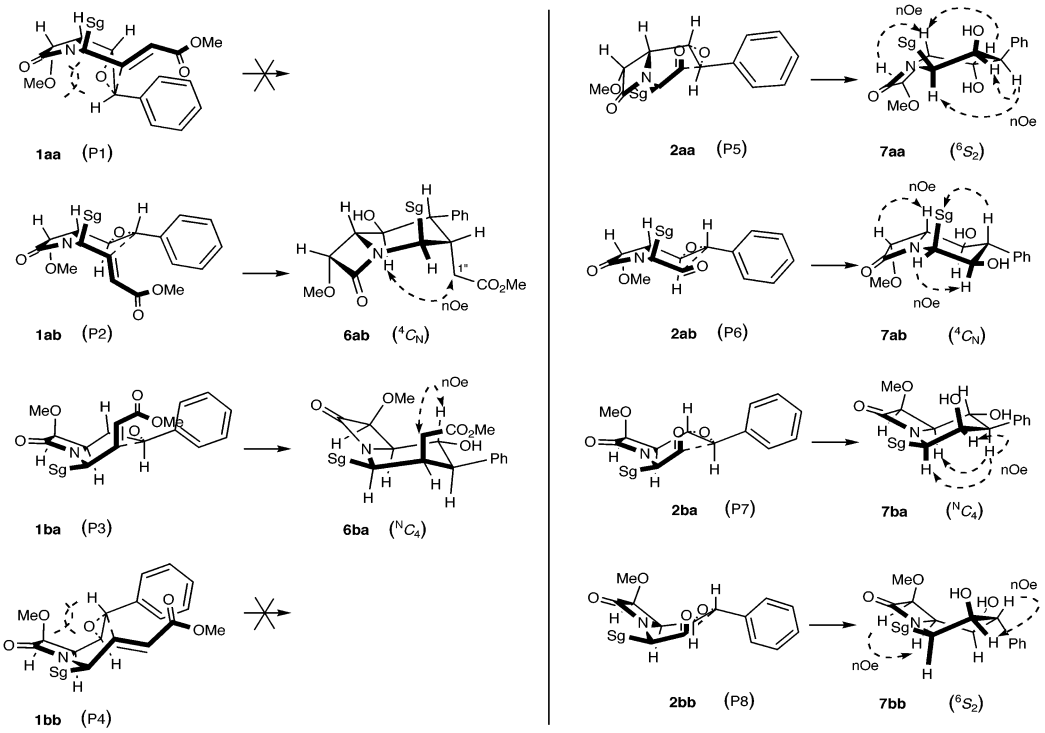
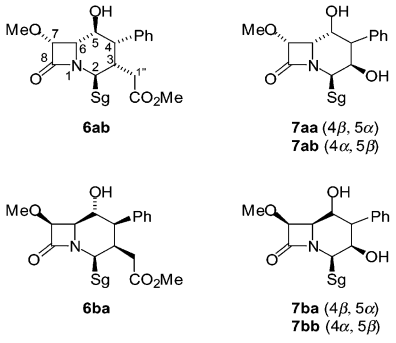


FIGURE 1. Proposed conformations for the carbacephams **6** and **7** and their precursors.

TABLE 1. Reaction of Epoxides 1 and 2 with $TiCp_2Cl$[a]

Entry	Epoxide	Alkene	Carbacepham
1	**1aa**	**5a** (72%)	----
2	**1ab**	**5a** (25%)	**6ab** (50%)
3	**1ba**	**5b** (23%)	**6ba** (52%)
4	**1bb**	**5b** (77%)	----
5	**2aa**	----	**7aa** (50%)
6	**2ab**	----	**7ab** (50%)
7	**2ba**	----	**7ba** (65%)
8	**2bb**	----	**7bb** (56%)



[a] In parentheses: isolated yield after column chromatography.

to a green solution of $TiCp_2Cl$, generated "in situ" from $TiCp_2Cl_2$ (2.2 mmol) and zinc (6.6 mmol) in THF.[2a]

The reactions of **1ab** and **1ba** with titanocene(III) chloride proceeded in a similar way to give a mixture of two products in 75% yield (entries 2 and 3, Table 1). In these reactions the major component was the expected cyclization product, the respective bicyclic β-lactam **6**, and the minor component was the elimination product, the alkene **5**. Different results were obtained when the isomers **1aa** and **1bb** were used as the starting material. In these cases, the deoxygenated monobactams **5a** or **5b** were isolated in 60 and 77% yield, respectively (entry 4, Table 1), and no cyclization product was observed.

On the contrary, all four isomeric epoxyaldehydes **2** under the above reaction conditions reacted with titanocene(III) chloride in the same way (entries 4−8, Table 1). In these cases, the reactions proceeded to give exclusively in a stereospecific manner the cyclization products, the respective bicyclic β-lactams **7**, with moderate yields (50−65%).

The proposed structures for the carbacephams **6** and **7** were deduced mainly from MS and NMR data, including NOE and two-dimensional experiments. The relative configurations *trans*-3,4,5-substituted in carbacephams[7] **7ab** and **7bb** or *cis*-3,4-*trans*-4,5-substituted in **6ab**, **6ba**, **7aa**, and **7ba** were deduced from the vicinal coupling constants between the hydrogen atoms of the six-membered ring (Table 2).[8]

The ^{1}H NMR data reported in Table 2 are in agreement with the conformations shown in Figure 1 for each one of the seven bicyclic β-lactams,[9] and the NOE observed in the compounds **6** and **7** also support these conformations. Consequently, as the configurations for C-2, C-6, and C-7 were known from the starting materials **3**,[4] we propose the following absolute configurations for the synthesized carbacephams: 2*S*,3*R*,4*R*,5*S*,6*S*,7*R* for **6ab** and **7ab**; 2*S*,3*S*,4*S*,5*R*,6*R*,7*S* for **6ba**; 2*S*,3*R*,4*S*,5*R*,6*S*,7*R* for **7aa**; 2*S*,3*R*,4*S*,5*R*,6*R*,7*S* for **7ba** and 2*S*,3*R*,4*R*,5*S*,-6*R*,7*S* for **7bb**.

(7) The numbering of the carbacepham system is given according to the IUPAC rules (*Pure Appl. Chem.* **1995**, *67*, 1307−1375).

(8) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

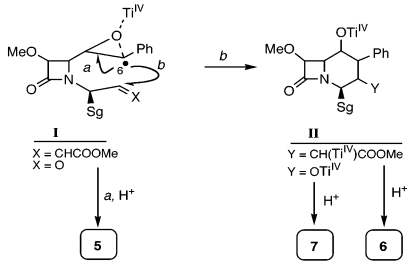
(9) The nomenclature for the six-membered ring conformation is given as proposed by Schwarz. Schwarz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505−508.

TABLE 2. Selected ^{1}H NMR Data on Compounds 6 and 7

compd	H-2	H-3	H-4	H-5	H-6	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{2,1'}$	$J_{3,1''}$
6ab	3.91 dd	2.61 ddt	3.59 dd	4.39 dd	3.77 dd	4.6	4.1	11.4	9.8	4.1	4.8	4.2, 4.2
6ba	3.78 dd	2.85 m	3.14 dd	4.37 dd	3.38 dd	3.6	3.6	11.5	8.2	4.3	3.8	3.4, 8.0
7aa	3.93 br s	4.25 dt[a]	2.82 br s	4.66 ddd[b]	4.33 dd	1.0	1.1	3.5	7.9	4.8		
7ab	4.34 dd	4.06 dt	3.30 dd	4.02 dd	3.87 dd	6.8	10.8	10.4	8.6	4.2	1.2	
7ba	3.25 dd	3.98 m	2.73 dd	4.68 dd	3.53 dd	0.5	0.4	11.2	8.0	4.4	8.8	
7bb	3.90 dd	4.59 ddd[c]	3.69 dd	4.37 dd	3.78 dd	9.8	5.9	3.5	2.1	4.9	8.4	

[a] $J_{3,OH} = 1.0$. [b] $J_{5,OH} = 2.9$. [c] $J_{3,OH} = 0.9$.

SCHEME 2. Possible Reaction Mechanism for the Formation of Compounds 5, 6, and 7



The reaction of the epoxy-β-lactams **1** and **2** upon treatment with $TiCp_2Cl$ could be rationalized as shown in Scheme 2. The benzyl radicals **I** generated by the homolytic cleavage of the epoxides **1** and **2** can evolve through the pathways *a* and *b*. The benzyl radicals **I** can give the alkenes **5a** and **5b** after β-elimination of the titanium−oxo moieties (pathway *a*)[2] or progress through pathway *b*, which implies the radical trapping by the conjugate electrophilic double bond or by the aldehyde carbonyl group for giving the carbacephams **6** or **7** after acidic workup. In these experiments, no cyclization products derived from the addition of the benzyl radicals to the amide carbonyl functional group were observed.

The stereospecific formation of the bicyclic β-lactams **6** and **7** suggests that the epoxide ring opening and the radical addition to C-1′ should be a concerted process with configuration inversion at C-6. A conformational analysis[10] of the epoxy-β-lactams **1** and **2** induced us to consider the conformers **P1** to **P8** (Figure 1) as the most appropriate precursors of the respective bicyclic β-lactams. In these conformers, the C-6−C-1′ distance and orientation are the best suited for cyclization.

In the case of the epoxide **1ab**, the benzyl radical **I** can access the *Re* face more easily than the *Si* face of the C-1′-conjugated alkene, as shown in the conformer **P2**, to give the 3α-substituted carbacephams **4ab**. Similarly, the best conformer of **1ba** for a conjugate addition is **P3**, in which the radical C-6 is close to the *Si* face of the C-1′ giving rise to the 3β-substituted carbacepham **4ba**. In contrast, the conformations for the epoxides **1aa** and **1bb** with a suitable distance C-6−C-1′ for cyclization (**P1** and **P4**) evidence severe crowding, mainly between the oxirane oxygen and the oxygen of the C-3 methoxyl group, apart from the steric interactions between the sugar residue with the β-lactam carbonyl group and the carboxylate−phenyl interactions. This could explain why no cyclization products were observed in these cases.

(10) CS Chem3D Pro software (version 5.0, 1999, CambridgeSoft Corp., 100 Cambridge Park Drive, Cambridge, MA 02140-2317) using MM2 calculations.

Likewise, the stereospecific cyclization of the epoxyaldehydes **2** to form the carbacephams **7aa** to **7bb** may be explained assuming for the starting epoxides the conformers **P5**, **P6**, **P7**, and **P8** (Figure 1). In these cases, the smaller size of the aldehyde functional group in **2** as compared with the acrylate group in the epoxides **1** allows an easier approach of the benzyl radical **I** to the electrophile $C_{sp2}-1'$ for yielding the cyclization products, as confirmed by the observed results.

Thus, the four isomeric epoxyaldehydes **2** reacted with $TiCp_2Cl$ and gave exclusively the respective carbacephams. The epoxyesters **1** are too crowded, and their intermediate benzylic radicals progress under the same reaction conditions to the cyclization products **6** (only two isomers) and to the elimination products **5** (all isomers).

It is not clear to us why the attack of the benzyl radical takes place at only one of the faces (the *Re* face) of the aldehyde. Perhaps a steric effect caused by the coordination of the carbonyl group with the reagent and/or with the sugar residue could explain the observed face selectivity.

From these results and those previously disclosed,[1] we conclude that the reaction of $TiCp_2Cl$ with enantiomerically pure *N*-substituted 4-epoxyalkene-2-azetidinones is an efficient method for the stereospecific synthesis of very important polycyclic β-lactam compounds. Efforts to optimize the yields of the cyclization process are now under study.

Experimental Section

Preparation of Monobactams 3a and 3b.[5c] A solution of 3,4;5,6-di-*O*-isopropylidene-1,1-bis-ethylsulfanyl-D-glucosamine (10.0 mmol) and *trans*-cinnamaldehyde (10.0 mmol) in toluene was stirred at 110 °C for 4 h, and then the reaction product was concentrated to dryness. To a solution of the crude imine (10.0 mmol) and TEA (25 mmol) in dry toluene (100 mL) was added methoxyacetyl chloride (15.0 mmol) in toluene (6.0 mL) dropwise under argon atmosphere. The mixture was stirred at room temperature until the starting material disappeared (1 h). The reaction product was then poured onto a saturated NH_4Cl solution at 0 °C, neutralized with acetic acid, extracted with CH_2Cl_2, and washed with water (three times) and brine solution (twice), and the organic layer was concentrated to dryness. Purification by column chromatography (SiO_2, hexane/ethyl acetate mixtures) gave pure monobactams **3**. For NMR data, see the Supporting Information.

3a: isolated in 26% yield; R_f (8:2 hexane/ethyl acetate) 0.27; $[\alpha]^{25}_D$ +79 (*c* 1.0, $CHCl_3$); IR (neat) ν 1759, 1451, 1383, 1211, 1061 cm^{-1}. Anal. Calcd for $C_{28}H_{41}NO_6S_2$: C, 60.95; H, 7.49; N, 2.54; S, 11.62. Found: C, 60.76; H, 7.53; N, 2.65; S, 11.63.

3a: isolated in 53% yield; R_f (8:2 hexane/ethyl acetate) 0.30; mp 120−121 °C; $[\alpha]^{25}_D$ −118 (*c* 1.0, $CHCl_3$); IR (KBr) ν 1765, 1495, 1381, 1213, 1067, 733 cm^{-1}. Anal. Calcd for $C_{28}H_{41}NO_6S_2$: C, 60.95; H, 7.49; N, 2.54; S, 11.62. Found: C, 60.98; H, 7.48; N, 2.71; S, 11.62.

General Procedure for the Preparation of Alkenes 5a and 5b. To a solution of monobactams **3** (1.00 mmol) and $NaHCO_3$ (4.00 mmol) in 85:15 CH_3CN/H_2O (10.0 mL) was added [bis(trifluoroacetoxy)iodo]benzene (1.50 mmol), and the mixture was stirred at room temperature until the starting material disappeared (20−30 min). The reaction product was then concentrated to dryness, the crude reaction products **4a** and **4b** were solved in dry THF (15 mL), and then a solution of methoxycarbonylmethylenetriphenylphosphorane (2.2 mmol) in THF (10.0 mL) was added dropwise under argon atmosphere. The mixture was stirred at room temperature until the starting material disappeared and then was poured into a cold ammonium chloride solution, extracted twice with ethyl acetate, and concentrated to dryness. Purification by column chromatography (SiO_2, 70% hexanes−ethyl acetate) gave the alkenes **5**. For NMR data, see the Supporting Information.

5a. Compound **5a** was isolated in 93% yield from the monobactam **3a** (1.10 g, 2.00 mmol) and also in 72% and 25% yield from the epoxy-*β*-lactams **1aa** and **1ab** by reductive opening of the epoxides (see below): R_f (6:4 hexane/ethyl acetate) 0.25; $[\alpha]^{25}_D$ +158 (*c* 1.0, $CHCl_3$); IR (neat) *ν* 1761, 1732, 1661, 1495, 1383, 1212, 1069, 970, 847, 754, 735 cm[1]; MS (FAB) *m*/*z* 502 ($M^+ + 1$, 13), 444 (10), 386 (6), 284 (25), 143 (100), 101 (44); HRMS (FAB) calcd for $C_{27}H_{36}NO_8$ ($M^+ + 1$) 502.2441, found 502.2475.

5b. Compound **5b** was isolated in 94% yield from **3b** (1.12 g, 2.03 mmol) and also in 23% and 77% yields from the epoxy-*β*-lactams **1ba** and **1bb**, respectively, by reductive opening of the epoxides (see below): R_f (6:4 hexane/ethyl acetate) 0.30; $[\alpha]^{25}_D$ −75 (*c* 1.0, $CHCl_3$); IR (neat) *ν* 1765, 1726, 1661, 1451, 1383, 1213, 1071, 972, 847 cm[1]; MS (FAB) *m*/*z* 502 ($M^+ + 1$, 8), 444 (12), 386 (5), 284 (30), 143 (100), 101 (50); HRMS (FAB) calcd for $C_{27}H_{36}NO_8$ ($M^+ + 1$) 502.2441, found 502.2416.

General Procedure for the Epoxidation of 5. To a solution of alkene **5** (1.00 mmol) in anhydrous CH_2Cl_2 (10.0 mL) was added *m*-CPBA (1.20 mmol), and the mixture was stirred at room temperature until the starting material disappeared. The reaction mixture was diluted in CH_2Cl_2, washed with a solution of sodium bicarbonate and water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The epoxidation of **5a** (520 mg, 1.04 mmol) for 15 h with *m*-CPBA (207 mg, 1.20 mmol) gave after column chromatography (7:3 hexane/ethyl acetate) the epoxides **1aa** (187 mg, 35%) and **1ab** (225 mg, 42%). Likewise, the epoxidation of **5b** (1.00 g, 2.00 mmol) for 15 h with *m*-CPBA (413 mg, 2.39 mmol) gave after column chromatography (7:3 hexane/ethyl acetate) the epoxides **1ba** (413 mg, 40%) and **1bb** (507 mg, 49%). For NMR data, see the Supporting Information.

1aa: R_f (6:4 hexane/ethyl acetate) 0.28; IR (neat) *ν* 1761, 1728, 1456, 1383, 1213, 1155, 1071, 914, 847, 733 cm[1]; HRMS (FAB) calcd for $C_{27}H_{36}NO_9$ ($M^+ + 1$) 518.2390, found 518.2388.

1ab: R_f (6:4 hexane/ethyl acetate) 0.30; mp 98 °C (hexane/CH_2Cl_2); IR (KBr) *ν* 1763, 1728, 1456, 1379, 1215, 1155, 1067, 912, 847, 735 cm[1]; HRMS (FAB) calcd for $C_{27}H_{36}NO_9$ ($M^+ + 1$) 518.2390, found 518.2335.

1ba: R_f (7:3 hexane/ethyl acetate) 0.30; IR (neat) *ν* 1761, 1730, 1456, 1381, 1215, 1160, 1071, 916, 849 cm[1]; MS (FAB) *m*/*z* 518 ($M^+ + 1$, 1), 460 (3), 307 (15), 154 (100), 107 (20), 77 (21); HRMS (FAB) calcd for $C_{27}H_{36}NO_9$ ($M^+ + 1$) 518.2390, found 518.2421.

1bb: R_f (7:3 hexane/ethyl acetate) 0.25; IR (neat) *ν* 1761, 1732, 1455, 1373, 1213, 1154, 1071 cm[1]; HRMS (FAB) calcd for $C_{27}H_{36}NO_9$ ($M^+ + 1$) 518.2390, found 518.2333.

General Procedure for the Ozonolysis of 1. A solution of epoxide **1** (1.00 mmol) in anhydrous CH_2Cl_2 (20.0 mL) was cooled to −78 °C, and ozone was bubbled through it until the solution had a permanent blue coloration. Dimethyl sulfide (2.0 mL) was added, and the solution was brought to room temperature and stirred for 30 min. Evaporation of solvent under reduced pressure gave the pure epoxides **2**. For NMR data, see the Supporting Information.

2aa: obtained in 100% yield from **1aa** (187 mg, 0.36 mmol); R_f (45:55 hexane/ethyl acetate) 0.2; IR (neat) *ν* 1763, 1458, 1375, 1215, 1154, 1065, 847, 731 cm^{-1}; MS (FAB) *m*/*z* 462 ($M^+ + 1$, 11), 434 (6), 404 (8), 346 (5), 286 (9), 143 (100), 91 (73).

2ab: obtained in 85% yield from **1ab** (200 mg, 0.39 mmol); R_f (45:55 hexane/ethyl acetate) 0.27; IR (neat) *ν* 1767, 1456, 1375, 1215, 1154, 1065, 845 cm^{-1}; MS (FAB) *m*/*z* 462 ($M^+ + 1$, 8), 404 (6), 307 (12), 189 (11), 154 (100), 136 (86), 91 (46); HRMS (FAB) calcd for $C_{24}H_{32}NO_8$ ($M^+ + 1$) 462.2128, found 462.2161.

2ba: obtained in 100% yield from **1ba** (210 mg, 0.41 mmol); R_f (1:1 hexane/ethyl acetate) 0.27; IR (neat) *ν* 1761, 1456, 1381, 1215, 1154, 1067, 847 cm^{-1}; MS (FAB) *m*/*z* 462 ($M^+ + 1$,7), 434 (3), 404 (5), 376 (5), 307 (8), 154 (100), 91 (76); HRMS (FAB) calcd for $C_{24}H_{32}NO_8$ ($M^+ + 1$) 462.2128, found 462.2144.

2bb: obtained in 90% yield from **1bb** (520 mg, 1.00 mmol); R_f (1:1 hexane/ethyl acetate) 0.20; IR (neat) *ν* 1759, 1458, 1373, 1215, 1154, 1069, 840 cm^{-1}; MS (FAB) *m*/*z* (%) 462 ($M^+ + 1$, 12), 434 (8), 404 (10), 376 (7), 286 (7), 143 (100), 91 (75). HRMS (FAB) calcd for $C_{24}H_{32}NO_8$ ($M^+ + 1$) 462.2128, found 462.2138.

General Procedure for Reductive Opening of Epoxides 1 and 2. A solution of the epoxide **1** or **2** (1.00 mmol) in THF (10.0 mL) was added to a green suspension of $TiCp_2Cl$, generated from $TiCp_2Cl_2$ (2.20 mmol) and Zn^0 (6.60 mmol) in dry and strictly deoxygenated THF (22.0 mL). The mixture was stirred at room temperature until the starting material disappeared (2−5 h) and then quenched with 10% v/v aqueous KH_2PO_4 (30.0 mL). The aqueous phase was separated and extracted with ethyl acetate, and the organic combined extracts were filtered through Celite, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography on silica gel using hexane/ethyl acetate mixtures as the eluent gave the products shown in Table 1. For NMR data, see Table 2 and the Supporting Information.

6ab: R_f (4:6 hexane/ethyl acetate) 0.25; mp 159 °C (hexane−CH_2Cl_2); $[\alpha]^{25}_D$ +11 (*c* 1.0, $CHCl_3$); IR (KBr) *ν* 3439, 1748, 1454, 1377, 1260, 1211, 1103, 1070, 847 cm^{-1}; MS (FAB) *m*/*z* 520 ($M^+ + 1$, 48), 434 (23), 376 (8), 290 (42), 143 (38), 87 (100); HRMS (FAB) calcd for $C_{27}H_{38}NO_9$ ($M^+ + 1$) 520.2545, found 520.2542.

6ba: R_f (1:1 hexane/ethyl acetate) 0.25; $[\alpha]^{25}_D$ −41 (*c* 1.0, $CHCl_3$); mp 176 °C (hexane−CH_2Cl_2); IR (KBr) *ν* 3464, 1748, 1454, 1373, 1223, 1169, 1067, 841 cm^{-1}; MS (FAB) *m*/*z* 520 ($M^+ + 1$, 5) 307 (16), 154 (100), 107 (23), 69 (25); HRMS (FAB) calcd for $C_{27}H_{38}NO_9$ ($M^+ + 1$) 520.2545, found 520.2542.

7aa: R_f (3:7 hexane/ethyl acetate) 0.29; $[\alpha]^{25}_D$ +70 (*c* 1.4, $CHCl_3$); IR (neat) *ν* 3488, 1759, 1456, 1381, 1215, 1067, 914, 845, 753 cm^{-1}; MS (FAB) *m*/*z* 464 ($M^+ + 1$, 2), 434 (2), 307 (14), 154 (100), 91 (36); HRMS (FAB) calcd for $C_{24}H_{34}NO_8$ ($M^+ + 1$) 464.2284, found 464.2248.

7ab: R_f (3.7 hexane/ethyl acetate) 0.25; $[\alpha]^{25}_D$ +48 (*c* 1.1, $CHCl_3$); IR (neat) *ν* 3457, 1757, 1454, 1383, 1215, 1154, 1065, 845 cm^{-1}; MS (FAB) *m*/*z* 464 ($M^+ + 1$, 3), 307 (11), 154 (100), 91 (44); HRMS (FAB) calcd for $C_{24}H_{34}NO_8$ ($M^+ + 1$) 464.2284, found 464.2297.

7ba: R_f (3:7 hexane/ethyl acetate) 0.29; $[\alpha]^{25}_D$ +10 (*c* 0.6, $CHCl_3$); IR (neat) *ν* 3474, 1755, 1454, 1381, 1256, 1213, 1152, 1065, 847 cm^{-1}; MS (FAB) *m*/*z* 464 ($M^+ + 1$, 8), 391 (22), 279 (5), 149 (100), 113 (27), 91 (18); HRMS (FAB) calcd for $C_{24}H_{34}NO_8$ ($M^+ + 1$) 464.2284, found 464.2303.

7bb: R_f (3:7 hexane/ethyl acetate) 0.25; $[\alpha]^{25}_D$ +19 (*c* 6, $CHCl_3$); IR (neat) *ν* 3489, 1761, 1454, 1373, 1215, 1154, 1067, 840 cm^{-1}; MS (FAB) *m*/*z* 464 ($M^+ + 1$, 6), 391 (8), 307 (9), 154 (100), 91 (60); HRMS (FAB) calcd for $C_{24}H_{34}NO_8$ ($M^+ + 1$) 464.2284, found 464.2301.

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Supporting Information Available: ^1H and ^{13}C NMR data of **1**, **2**, **3**, and **5**−**7** as well as ^1H NMR and two-dimensional (COSY and/or HMQC) spectra of carbacephams **6** and **7** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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