A Regio and Stereospecific Synthesis of Carbacephem Antibiotics

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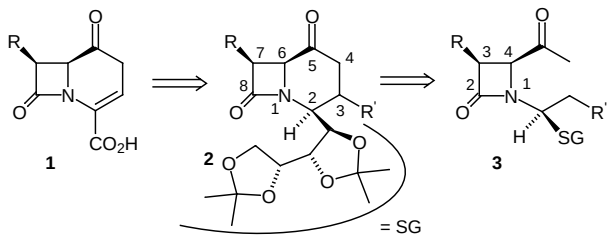
Dedicated to the late Dr. Stephan D. Gero with deep affection

Abstract: In this article we report a short and practical route to chiral carbacephems **1** based on an asymmetric Staudinger reaction for building the β-lactam ring, and on a tandem elimination-conjugate addition for making the second ring.

Key words: D-glucosamine, asymmetric Staudinger reaction, β-lactam, tandem ring-closure, carbacephem.

Carbacephems **1** are known to exhibit antibiotic activity and have increased chemical stability compared to cephalosporins.[1] They are usually synthesized[2,3] by making the β-lactam ring and then the six-membered ring, either by formation of the N-1/C-2[5] or the C-2/C-3 σ-bonds,[4] although a recent C-3/C-4 cyclization *via* alkene metathesis has been reported.[5]

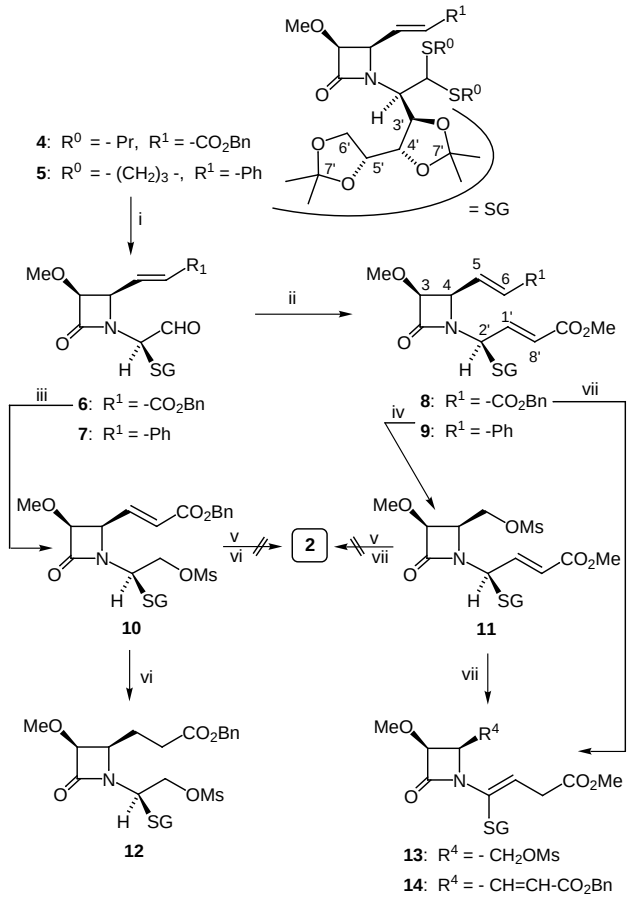


Scheme 1

In a previous paper[6] we described the attempts to synthesize carbacephams **2** (precursors of carbacephems **1**)[7] from some chiral 4-acetyl-*N*-substituted monobactams **3** by intramolecular displacement under ionic conditions at low temperature (Scheme 1). This strategy did not give the desired carbocycle **2** perhaps because of the steric requirements of the sugar residue SG.

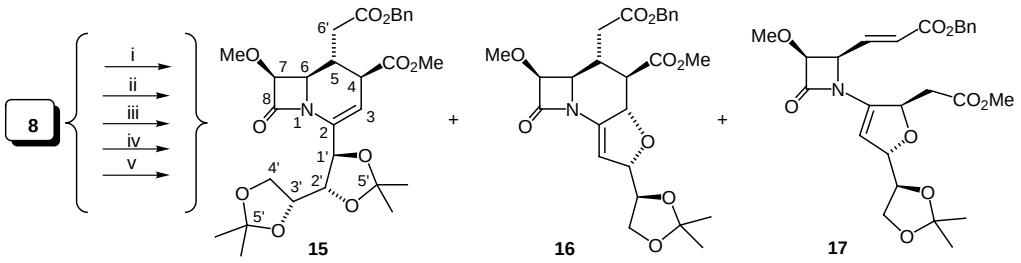
This sugar group introduced as a chiral auxiliary, is found as a substituent in several monocyclic β-lactams which act as selective inhibitors of human leukocyte elastase (HLE),[8] and this is the reason why we are interested in maintaining it in the carbocyclic β-lactam derivatives. Hence, we examined the viability of tandem conjugate additions in order to synthesize carbacepham and carbacephem systems with the sugar residue SG at C-2.

Three different approaches for elaborating the precursor carbacephams **2** from the readily accessible 1,3,4-trisubstituted azetidin-2-ones **4**[9] and **5**[10] were envisaged. They differ in the location of the Michael acceptor in the β-lactam nucleus that can be attached either to C-4 (**10**), to N-1 (**11**) or to both positions (**8**), as shown in Scheme 2. Deprotection of dithioacetal groups in **4** and **5** with $PhI(OCOCF_3)_2$[11] in the presence of $NaHCO_3$ afforded the respective aldehydes **6** (85%) and **7** (95%) which were reacted with $Ph_3P{=}CHCO_2Me$ to give **8** (54%) and **9** (63%) respectively. Reduction of aldehyde **6** with $NaBH_4$ in EtOH followed by methanesulfonation afforded **10** in 56% yield. Selective ozonolysis[6] of **9** using $NaBH_4$ as reducing agent gave an alcohol whose methanesulfonation provided **11** in 50% yield.



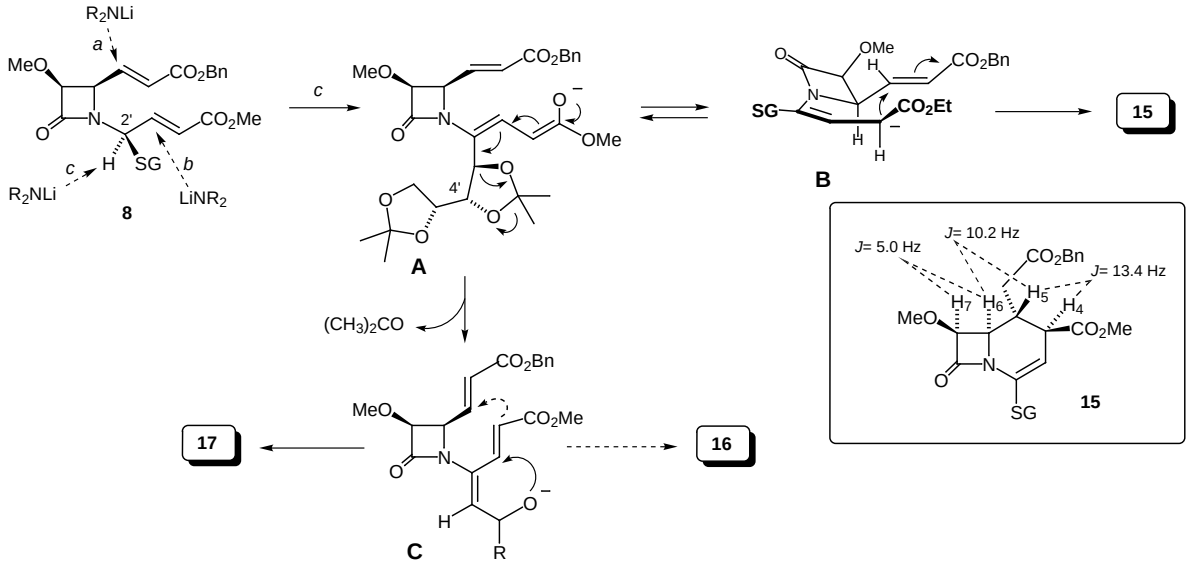
Reagents and conditions: i, $PhI(OCOCF_3)_2$ (1.5 mmol), $NaHCO_3$ (3.0 mmol), CH_3CN:H_2O (9:1), r.t.; ii, $Ph_3P{=}CH{-}CO_2Me$ (1.2 mmol), THF, r.t..; iii, $NaBH_4$, 0°C, then MsCl, pyridine/DMAP; iv, O_3, Sudan Red 19 (0.05 mmol%), CH_2Cl_2-MeOH (8:2), -78°C, $NaBH_4$, 0°C, then MsCl, pyridine/DMAP; v, Me_2CuLi, THF, -20°C; vi, Red-Al, CuBr, THF, -78°C; vii, $BnNH_2$, MeOH, r.t.

Scheme 2



Reagents: i, LDA ; ii, LHMDS; iii, NaHMDS; iv, LSA; v, phosphazene base P1-t-Bu. *Conditions:* THF, -78°C.

Scheme 3



Possible mechanisme for the formation of compounds **15**, **16** and **17**.

Scheme 4

The monobactams **10** and **11** were first tested to study the role of different reagents and reaction conditions as well as the location of the nucleophile and Michael acceptor in the intramolecular cyclisations. Unfortunately, we did not succeed in the conversion of the above monobactams into the respective 4,5-disubstituted and 3,4-disubstituted carbacephams. Treatment of these monobactams **10** and **11** either with Me_2CuLi in ether[12] at -20 °C or with Red-Al® / CuBr in THF[13] at -78 °C gave the starting material together with β-lactam ring open products or the saturated monobactam **12**. Lastly, benzyl amine,[14] a softer base, was tested on **11** but apart from the starting material the sole reaction product isolated was identified as compoud **13** (44%). Similar results were obtained in the treatment of **8** with $BnNH_2$ under thermodynamic conditions to give **14** (80%).

In marked contrast with the above results, the diester **8** underwent a 6-[enol-*exo*]-*exo*-trig cyclisation when treated with LDA, LiHMDS, NaHMDS, lithium *N*-benzyl-*N*-trimethylsilylamide (LSA) and Phosphazene Base P_1-t-Bu[15] in THF at -78°C (Scheme 3). The best results were obtained when LSA[16] was used; in this case the carbacephem **15** was isolated in a non optimized 30% yield together with the compounds **16** (20%) and **17** (15%).

The structure of these compounds **15**, **16** and **17** were rigorously established by 2D COSY, HMQC, HMBC and 1D NOE experiments. The observed coupling constants (Scheme 4) and the NOE between H-6/H-4 and H-6/H-7 in **15** established the relative *trans* configuration for H-4, H-5 and H-6. As the absolute configuration for C-6 and C-7 was known, the configuration of the carbacephem skeleton was assigned (4*R*, 5*R*, 6*R*, 7*S*) for **15**.[17]

Although the LSA could react with **8** by conjugate addition[14] (Scheme 4, routes *a* and *b*), the formation of the observed reaction products can be explained by abstraction of the allyl hydrogen atom H-2' by the LSA under kinetic conditions (route *c*) with formation of the dienolate anion **A** which can adopt the geometry shown in **B** to give the carbacephem **15**. The diastereoselectivity of this last intramolecular cyclisation is in agreement with a chair-like conformation of the transition state in which the C-4 and C-5 substituents are equatorial.

On the other hand, the enolate **A** can progress through an alkoxide at C-4', **C**, to compounds **16** and **17** by intramolecular cyclisation.

The optimization of the above reported strategy for the preparation of carbacephem **15** as well as the study on the transformation of compound **16** into carbacephems **15** are in progress.

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(17) Selected physical data of key compounds **8** and **15**. *4β-(E-2-Benzyloxycarbonyl-1-ethene)-1[(1',2'-dideoxy-3',4';5',6'-di-O-isopropylidene-1',1'-(E-2-ethoxycarbonyl-1-ethenyl)-D-2'-glucosyl]-3β-methoxy-azetidin-2-one* (**8**): R_f= 0.25 (SiO_2, hexane/AcOEt 7:3). $[\alpha]_D^{23}$ = +60.4 (c= 1, $CHCl_3$). IR ν = 1767, 1728, 1661, 1516, 1383, 1260, 1067, 845. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.28, 1.31, 1.37 (3s, 12H, C(CH_3)$_2$); 3.40 (s, 3H, OCH_3); 3.61 (s, 3H, CO_2CH_3); 3.62 (dd, $J_{2',1'}$= 7.8 Hz, $J_{2',3'}$= 2.2 Hz, 1H, $H_{2'}$); 3.69 (t, $J_{4',3'}$= $J_{4',5'}$= 7.4 Hz, 1H, $H_{4'}$); 3.88 (dd, $J_{6'a,6'b}$ = 7.8 Hz, $J_{6'a,5'}$= 4.8 Hz, 1H, $H_{6'a}$); 3.92 (dd, $J_{6'b,6'a}$ = 8.0 Hz, $J_{6'b,5'}$= 5.6 Hz, 1H, $H_{6'b}$); 3.97-4.23 (m, 2H, $H_{3'}$, $H_{5'}$); 4.55 (dd, $J_{4,3}$ = 4.7 Hz, $J_{4,5}$ = 9.1 Hz, 1H, H_4); 4.64 (d, $J_{3,4}$ = 4.7 Hz, 1H, H_3); 5.15 (d, J = 12.4 Hz, 2H, CO_2CH_2Ph); 6.03 (dd, $J_{8',1'}$= 15.6 Hz, $J_{8',2'}$= 0.7 Hz, 1H, $H_{8'}$); 6.12 (d, $J_{6,5}$ = 15.7 Hz, 1H, H_6); 6.79 (dd, $J_{1',8'}$= 15.6 Hz, $J_{1',2'}$ = 7.8 Hz, 1H, $H_{1'}$); 6.90 (dd, $J_{5,6}$ = 15.7 Hz, $J_{5,4}$ = 9.2 Hz, 1H, H_5); 7.30-7.39 (m, 5H, H_{Ph}).^{13}C NMR (50.33 MHz, $CDCl_3$) δ = 25.1, 26.3, 27.1, 27.4 (4C, C(CH_3)$_2$); 51.5 (CO_2CH_3); 54.5 (C_4); 58.8 (OCH_3); 60.8 ($C_{2'}$); 66.4 (CO_2CH_2Ph); 67.7 ($C_{6'}$); 77.0, 79.2, 80.1 ($C_{3'}$, $C_{4'}$, $C_{5'}$); 85.5 (C_3); 110.2, 110.5 (2C, $C_{7'}$); 125.1 ($C_{8'}$); 126.4 (C_6); 128.1, 128.2, 128.5 (5C, CH_{Ph}); 135.8 (C_{Ph}); 141.3, 142.9 (C_1, C_5); 164.8, 165.6 (CO_2CH_2Ph, CO_2CH_3); 166.5 (C_2). *5α-Benzyloxycarbonylmethyl-2β[(1',2';3',4'-di-O-isopropylidene)-1,2,3,4-D-arabino-tetrahydroxybutyl]-7β-methoxy-4β-methoxycarbonyl-6β-carbacephem* (**15**): R_f= 0.27 (SiO_2, hexane/AcOEt 7:3). $[\alpha]_D^{23}$= +116 (c = 0.9, $CDCl_3$). IR ν = 1765, 1738, 1732, 1452, 1381, 1215, 1167, 1069, 843. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33, 1.36, 1.42, 1.45 (4s, 12H, C(CH_3)$_2$); 2.39-2.45 (m, 2H, $H_{6'a}$, H_5); 2.69 (d, $J_{6'b,6'a}$ = 13.4 Hz, 1H, $H_{6'b}$); 3.57 (s, 3H, OCH_3); 3.58 (s, 3H, CO_2CH_3); 3.58 (dd, $J_{4,3}$ = 6.0 Hz, $J_{4,5}$ = 13.4 Hz, 1H, H_4); 3.97 (dd, $J_{6,7}$ = 5.0 Hz, $J_{6,5}$ = 10.2 Hz, 1H, H_6); 4.00 (dd, $J_{4'a,4'b}$ = 8.4 Hz, $J_{4'a,3'}$= 5.2 Hz, 1H, $H_{4'a}$); 4.09 (dd, $J_{4'b,4'a}$ = 8.4 Hz, $J_{4'b,3'}$= 6.1 Hz, 1H, $H_{4'b}$); 4.11-4.15 (m, 1H, $H_{2'}$) 4.18-4.23 (m, 1H, $H_{3'}$); 4.61 (d, $J_{7,6}$ = 5.0 Hz, 1H, H_7); 4.73 (d, $J_{1',2'}$= 8.1 Hz, 1H, $H_{1'}$); 5.11 (d, J = 12.7 Hz, 1H, CO_2CHHPh); 5.13 (d, J = 12.7 Hz, 1H, CO_2CHHPh); 5.36 (d, $J_{3,4}$ = 6.0 Hz, 1H, H_3); 7.25-7.42 (m, 5H, H_{Ph}); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.3, 26.5, 26.7, 26.9 (4C, C(CH_3)$_2$); 30.7 (C_5); 33.0 ($C_{6'}$); 40.6 (C_4); 51.9 (CO_2CH_3); 52.2 (C_6); 58.9 (OCH_3); 66.0 ($C_{4'}$); 66.4 (CO_2CH_2Ph); 76.0 ($C_{3'}$); 77.0 ($C_{1'}$); 80.7 ($C_{2'}$); 83.9 (C_7); 105.7 (C_3); 109.4, 109.9 (2C, $C_{5'}$); 128.2, 128.3, 128.4, 128.5 (5C, CH_{Ph}); 135.2 (C_2); 135.7 (C_{Ph}); 164.9 (CO_2CH_3); 171.1 (CO_2CH_2Ph); 171.7 (C_8).

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