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SYNTHESIS OF A $\Delta^{1,6}$-1-CARBACEPHEM-4-CARBOXYLIC ACID DERIVATIVE AS PROTOTYPE FOR A NEW FAMILY OF FUSED BICYCLIC β-LACTAMS

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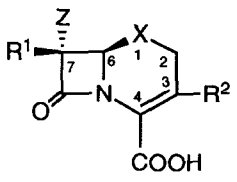
Abstract. The synthesis of 7-phenoxy-1-carbaceph-1,6-em-4-carboxylic acid **4** is described. The synthetic method involves the construction of a 8-oxo-1-azabicyclo[4.2.0]octane ring system through tri-n-butylstannane mediated free-radical annelation, and the introduction of the double bond at the bridgehead of a 8-oxo-1-azabicyclo[4.2.0]octene ring system by thermolysis of a sulfoxide group at position-6 .

Traditional views on structure-activity relationship of the classical $\Delta^{3,4}$-cephalosporins **1a** correlate the enamine resonance of cephalosporins (**Scheme I**) with their chemical and antibacterial activities.[1] Indeed $\Delta^{2,3}$-cephalosporins and dihydrocephalosporin **2a** have little or no antibacterial activity. A similar pattern is also observed in 1-oxa-$\Delta^{3,4}$-cephalosporins **1b** and 1-carba-$\Delta^{3,4}$-cephalosporins **1c**.[2] We therefore reasoned that some 1-carba-$\Delta^{1,6}$-cephalosporins **3** which have a similar, but differently oriented enamine system may



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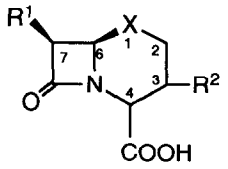

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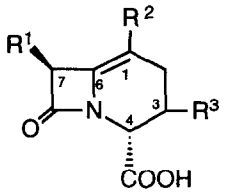

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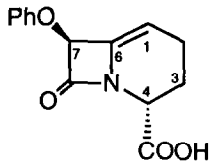

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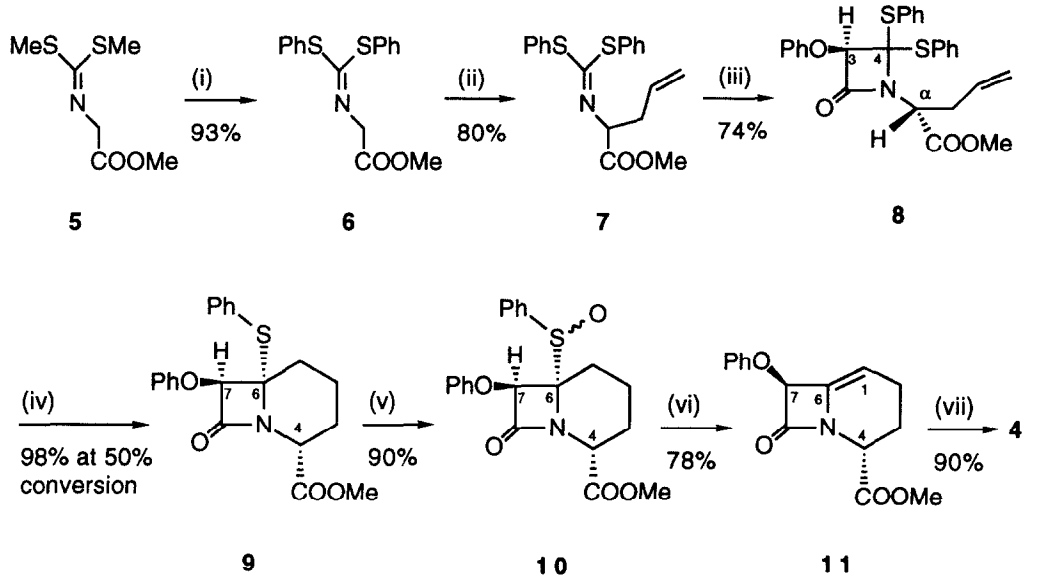
(a) R^1 = RCONH, R^2 = CH_2Y, X = S, Z = H
(b) R^1 = RCONH, R^2 = CH_2Y, X = O, Z = H or MeO
(c) R^1 = RCONH, R^2 = CH_2Y, X = CH_2, Z = H

Scheme I

exhibit antibacterial activity. In this case the chemical activation of the azetidinone system by the $\Delta^{1,6}$–double bond may derive from both steric and electronic factors.[3] Synthesis of bicyclic β–lactams of this new class required the development of a suitable synthetic methodology. We now report on the first synthesis of the first representative of this group namely, 7-phenoxy–1–carbaceph–1,6–em–4–carboxylic acid **4**.[4]

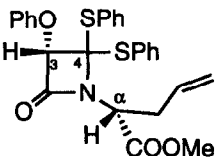
The synthesis of 7-phenoxy–1–carbaceph–1,6–em–4–carboxylic acid **4** is described in **Scheme II.**[5] It is based on four main stages: preparation of the non-fused β–lactam **8** which carries the required appendages and functionalities, formation of the fused bicyclic system **9** through tri–*n*–butylstannane/AIBN mediated free–radical annelation,[6] introduction of the bridgehead double in 1–carba–$\Delta^{1,6}$–cephalosporins **11** via thermal elimination of phenylsulfenic acid, and finally removal of the acid protecting group.[7]

Scheme II



(i) PhSH in F_3CCH_2OH, 80 °C.
(ii) CH_2=$CHCH_2Br$, *n*-Bu_4NCl, in mixture of CH_2Cl_2 and 10% aqueos NaOH, 20 °C.
(iii) $PhOCH_2COCl$, Et_3N, in toluene, 55 °C.
(iv) *n*-Bu_3SnH, AIBN, in C_6H_6, 80 °C.
(v) *m*-Chloroperbenzoic acid, in CH_2Cl_2, – 40 °C.
(vi) in toluene, 110 °C.
(vii) NaOH (1 equivalent) in H_2O/THF 1:10, 20 °C.

Our original working plan was based on the use of 4,4–dimethylthioazetidin–2–one **13** which was obtained in two steps from the *N*-bis[(methylthio)methylene] derivative **5**, but it was found to be insufficiently



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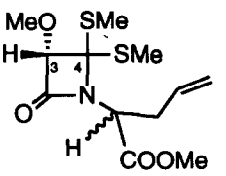

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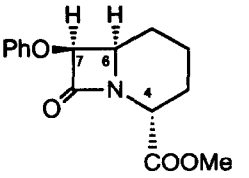

14

stable. Like some other 4,4–dimethylthioazetidin–2–ones [8] it undergoes decomposition during chromatography (silica gel and alumina), and the impure product is not suitable for free radical cyclization. In order to increase the stability of the 4-membered ring system the relatively small geminal methylthio groups in **13** were substituted by the more bulky phenylthio groups in **8**. Indeed the 4,4–diphenylthioazetidin–2–one **8** which was obtained from **7** in good yield,[9a] proved to be an excellent substrate for the tri–*n*–butylstannane/AIBN mediated cyclization to the fused bicyclic β-lactam **9**. This reaction was performed under high dilution conditions using the syringe pump technique. For optimal results the reaction should be discontinued at 50% conversion.[9b] When the reaction was prolonged beyond this point the bicyclic β-lactam was accompanied by its reduction product **14**.[10] The stereochemistry of the non–fused β-lactam **8** was determined by X–rays crystallographic analysis,[11] a small amount of its epimer **12** (7%) was also obtained. The relative stereochemistry at positions–6,7 of β-lactams **9** and **10** was assigned on the grounds of the strong downfield shift (1ppm), in the ^{1}H NMR spectrum, induced by the sulfoxide group on the hydrogen atom at position –7.

The carbonyl infrared stretching frequency of β-lactam **4** appears at 1806 cm^{-1}. Relatively high carbonyl frequency is characteristic for most antibacterial β-lactams. The figure observed for β-lactam **4** is higher than those reported for penicillins and cephalosporins,[12] and falls in the range of those recorded for penems.[13] The synthesis of 7-phenoxy–1–carbaceph–1,6–em–4–carboxylic acid **4** opens an avenue to a new class of fused bicyclic β-lactams. We plan to synthesize additional compounds **3** with various groups R^1, R^2, and R^3, and to screen their antibacterial activity.

References and Notes:

(1) For review and references see: Boyd, D. B. in *The Chemistry and Biology of β–Lactam Antibiotics*; Morin, R. B. Gorman, M. Eds.; Academic Press, New York, 1982; Vol. 1, p 437.
(2) For review and references see: *Topics in Antibiotic Chemistry*, P. G. Sammes Ed.; Ellis Horwood Ltd., Chichester, 1980; Vol.4, p 51.
(3) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.* **1980**, *45*, 1481.
(4) This material is taken from the Ph. D. thesis of Nira Bar–Ner The Weizmann Institute of Science, Rehovot, January 1988.
(5) All chiral compounds in this work are racemic; only one enantiomer of each pair has been displayed in the formulae.
(6) For other examples of free-radical annelations in the synthesis of bicyclic β-lactams see:
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(7) (a) All new compounds gave IR, ^{1}H NMR, and elemental analyses consistent with the assigned structures.
(b) Selected spectral data: **$\Delta^{1,6}$-1-Carbacephem-4:** IR (CH_2Cl_2) 1805 (C=O), 1757 (C=O), and 1701 (C=C) cm^{-1}; ^{1}H NMR (270 *MHz*, $CDCl_3$) : δ 1.89-1.98 (m, 2H, NCHC**H**$_2$), 2.09-2.18 (m, 2H, NCHCH$_2$C**H**$_2$), 4.63 (ddd, *J* = 5.29, 2.7, 0.6 Hz, 1H, NCH), 4.33 (br, CO_2H), 5.13 (dd, *J* = 4.5, 2.3 Hz, 1H, HC=C), 5.65 (s, 1H, OCH), 7.01-7.34 (m, OPh). **4,4-Diphenylthioazetidin-2-one 8**: IR (CH_2Cl_2) 1781 (C=O), 1730 (C=O) cm^{-1}; ^{1}H NMR (400 *MHz*, $CDCl_3$) : δ 2.78 (ddd, *J* =13.85, 6.75, 6.73 Hz, 1H, CHH), 3.03 (ddd, *J* =14.0, 8.67, 8.26 Hz, 1H, CHH), 3.77 (s, 3H, CH_3), 4.06 (dd, *J* = 9.48, 5.91 Hz, 1H, NCH), 5.11 (s, 1H, OCH), 5.16 (dd, *J* =10.12, 1.12 Hz, 1H, C=CHH), 5.22 (dd, *J* =17.0, 1.40 Hz, 1H, C=CHH), 5.80 (ddt, *J* =17.04, 10.15, 7.10 Hz, 1H, HC=C), 7.06-7.63 (m, OPh+SPh). **4-Methoxycarbonyl-$\Delta^{1,6}$-1-Carbacephem-11**: IR (CH_2Cl_2) : 1806 (C=O), 1744 (C=O), 1701 (C=C) cm^{-1} ; 1H NMR (400 *MHz*, $CDCL_3$) : δ 1.83-2.35 (m, 4H, CH_2CH_2), 3.79 (s, 3H, CH_3), 4.61 (dd, *J* = 5.60, 2.85 Hz, 1H, NCH), 5.12 (dd, *J* = 5.56, 2.35 Hz, 1H, C=CH), 5.66 (s, 1H, OCH), 7.03-7.34 (m, OPh) ; UV (EtOH) λ_{max} 268 nm (ε = 2575). **4,4-Diphenylthioazetidin-2-one 12**: IR (neat) :1784 (C=O), 1745 (C=O) cm^{-1}; ^{1}H NMR (400 *MHz*, $CDCl_3$) : δ 1.88 (dddt, *J* =13.99, 6.77, 5.49, 1.32 Hz, 1H, CHH), 2.71-2.81 (m, 1H, CHH), 3.76 (s, 3H, CH_3), 3.90 (dd, *J* =9.84, 5.40 Hz, 1H, NCH), 5.02 (d, *J* =17.02 Hz, 1H, C=CHH), 5.04 (d, *J* = 9.51 Hz, 1H, C=CHH), 5.06 (s, 1H, OCH), 5.55(dddd, *J* =17.09, 10.0, 7.31, 6.76 Hz, 1H, HC=C), 7.02-7.77 (m, OPh+SPh).

(8) Sullivan, D. F.; Scopes, D. I.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1976**, *41*, 1112.

(9) Selected experimental conditions:
(a) Triethylamine (3 mmol) in toluene (20 mL) was slowly (4 h) added to a mixture of *N*-bis[(phenylthio)methylene] derivative **7** (1.5 mmol) and phenoxyacetyl chloride (3.0 mmol) at 55 °C.
(b) Individual solutions of *n*-Bu_3SnH(0.65 mmol) and AIBN(0.065 mmol) in 10 mL of benzene were slowly (2 h) added to a boiling solution of **8** (0.65 mmol) in benzene (30 mL). The reaction mixture was boiled for additional 5 h, and worked up by standard methods to give the bicylic β-lactam **9** (52%) and recovered **8** (46%).

(10) The *cis* stereochemistry of β-lactam **14** ($J_{6,7}$ = 4.2 Hz) results from hydrogen atom transfer from *n*-Bu_3SnH to the radical centered on carbon atom-6 from the less hindered α-side.

(11) We thank Dr. Felix Frolow for the X-ray diffraction analysis of compound **8**.

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