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SYNTHESIS OF TRICYCLIC β-LACTAMS – FUNCTIONALLY AND TOPOLOGICALLY NOVEL CARBACEPHEMS

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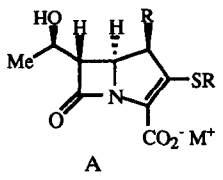
Abstract: The Lewis acid-catalyzed reactions of 1-trimethylsilyloxyfuran and the 4-methyl analog with 4-acetoxyazetidinone **1** are highly stereoselective, and give condensation products that can be elaborated into tricyclic β-lactams incorporating a carbacephem structure.

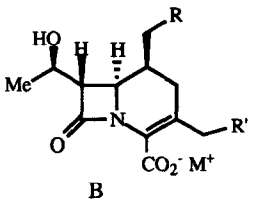
In the preceding Letter,[1] we described the synthesis of four 1-substituted 7-(*R*-1-hydroxyethyl) carbacephems (Figure 1, B) as hybrids of carbacephems[2] and carbapenems[3] of the thienamycin type.[4] Continuing our studies in the design and synthesis of novel β-lactam structural types,[5] we became interested in exploring the prospects of introducing a third ring in the carbacephem skeleton as illustrated in Figure 1,C. Such a prototypical tricyclic carbacephem would combine the structural and functional features of the "hybrid" structure reported in the preceding letter,[1] in addition to the incorporation of elements of constraint[6] as a part of a hitherto unexplored topological feature. There have been limited efforts in the synthesis of tricyclic or polycyclic β-lactam motifs,[7] the most successful and clinically promising example being the Glaxo "tribactams".[8]

Figure 1



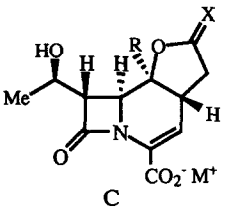
A

Carbapenem-type
R = H, Me, etc.



B

Carbacephem-type
R=H, OH, NHAc, R'=OAc, H

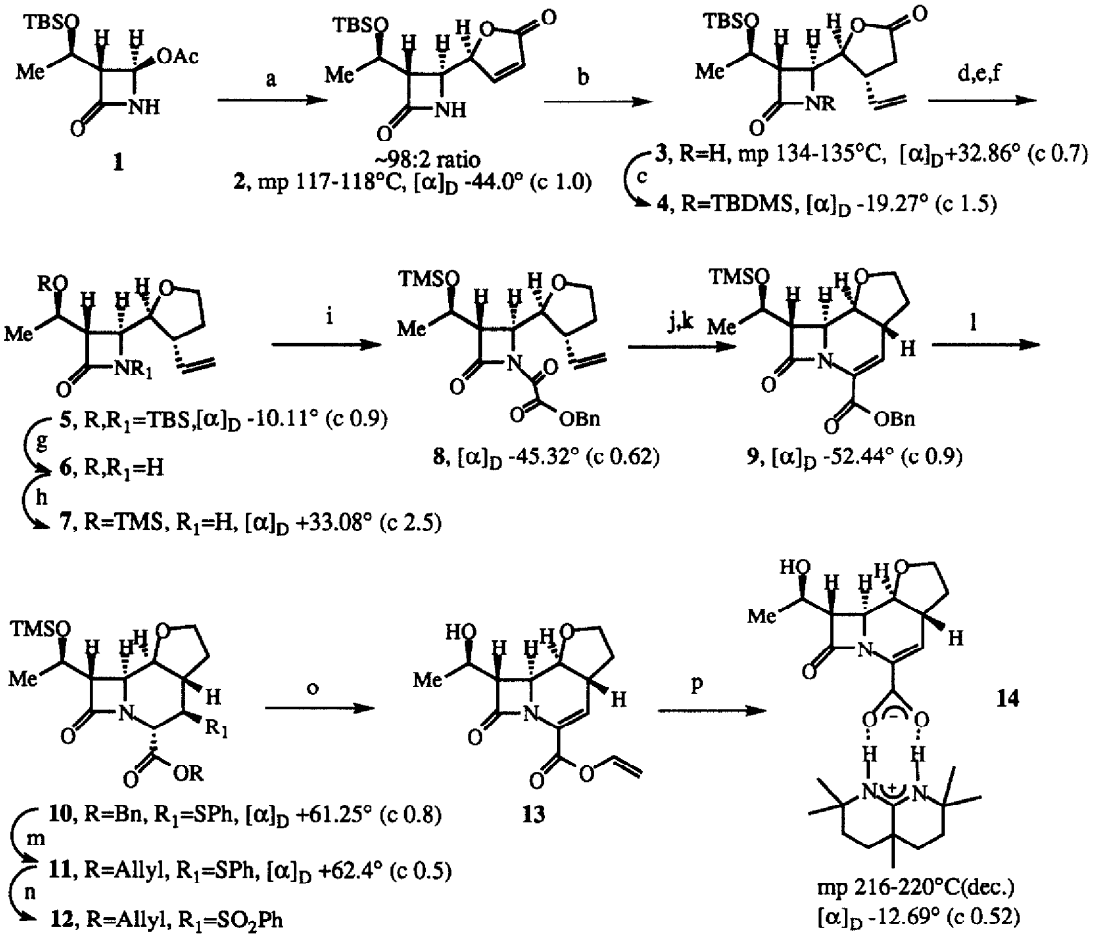


C

Tricyclic Carbacephems
R=Me or H, X=O or H, H

Treatment of the readily available azetidinone derivative **1**,[9] with 2-trimethylsilyloxyfuran[10,11] in the presence of zinc chloride gave the butenolide adduct **2** in excellent yield (Scheme 1). Conjugate addition of a vinyl moiety gave **3** as a crystalline solid. The structure of **3** was unambiguously established from an X-ray crystal structure of a related intermediate.[12] The lactone unit was transformed into the tetrahydrofuran unit as shown in expression **5**. At this point, it was necessary to exchange the TBS group for a TMS group because of the incompatibility of the functional groups with reagents utilized later in the synthetic sequence. Thus, the TMS derivative **7** was acylated to give the oxalimide derivative **8**.

Scheme 1

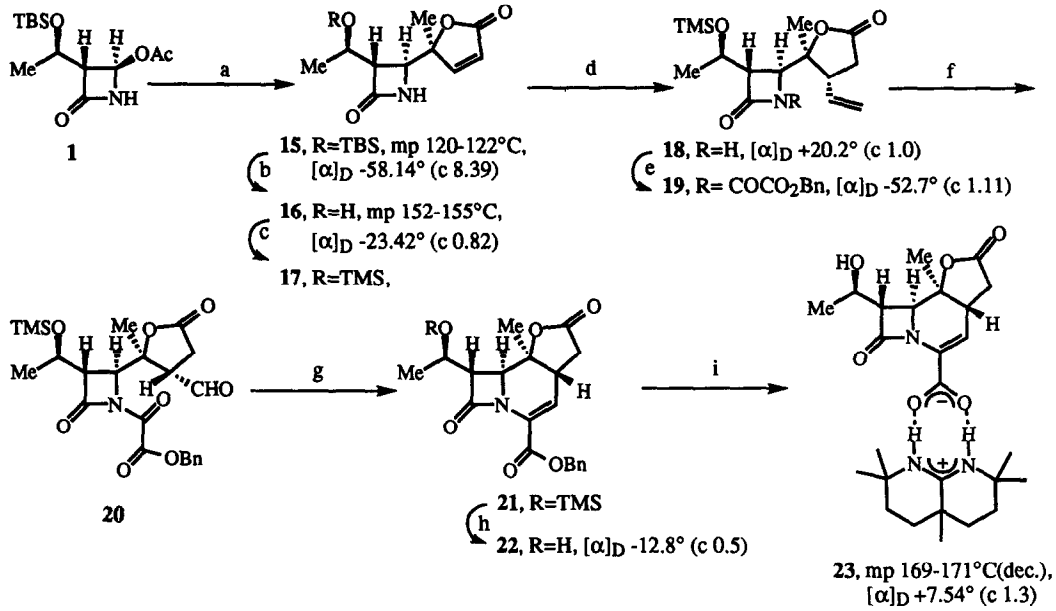


(a) $ZnCl_2$(20% mole), CH_2Cl_2, rt, slow addition of 2-trimethylsilyloxyfuran(1.5 eq) over 10 h, 85%; (b) vinylmagnesium bromide(3 eq), CuI(1.2 eq), Me_2S, THF, -78°C to -23°C, 1.5 h, 86%; (c) TBDMS-triflate (1.2 eq), 2,6-lutidine(1.5 eq), CH_2Cl_2, 0°C, 2 h, 84%; (d) DIBAL-H(1.2 eq), THF, -78°C to 0°C, 1.5 h, 84%; (e) Bu_3P(2.2 eq), PhSSPh(2.2 eq), CH_2Cl_2, rt, 18 h, 70%; (f) Bu_3SnH(2.7 eq), AIBN(2.7 eq), toluene, reflux, 1 h, 83%; (g) BF_3:Et_2O(2.9 eq), CH_3CN, rt, 12 h, 74% to 83%; (h) TMSCl(4eq), Et_3N(4 eq), CH_2Cl_2, 0°C, 5 h, 80%; (i) K_2CO_3(3.7 eq), pyridine(7 eq), BnOCOCOCl(1.4 eq), CH_2Cl_2, 0°C, 1 h, 58% to 70%; (j) O_3, $(MeO)_3P$(3 eq), CH_2Cl_2, -78°C to rt; (k) $(MeO)_3P$(5.5 eq), o-xylene, reflux, 10 h, 52%; (l) PhSH(2.4 eq), EtN-iPr_2(2.4 eq), PhSH(2.4 eq), benzene, rt, 1 h, 78%; (m) Ti-(isopropoxide)$_4$ (cat), allyl alcohol(excess), reflux, 2 h, 99%; (n) Oxone(3.5 eq), MeOH:H_2O, rt, 30 m, 91%; (o) DBU(cat), CCl_4, rt, 1 h, 90%; (p) pyrrolidine(1.2), $Pd(PPh_3)_4$ (15% mole), PPh_3, 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene(1 eq), CH_2Cl_2, rt, 30 m, 82%.

Ozonolysis of **8** led to the corresponding aldehyde without any epimerization as evidenced by NMR. Treatment of the dicarbonyl intermediate with trimethylphosphite in refluxing xylene[13] led to the tricyclic intermediate **9**, whose structure and stereochemistry were satisfactorily confirmed by detailed NMR analysis.

Having rapidly assembled the desired tricyclic structure, there remained the simple task of removing the benzyl ester and TMS groups. Unfortunately, all efforts at deesterification under a variety of hydrogenolysis conditions[14] led to the saturation of the double bond. Chemical methods of hydrolysis[15] were not successful. Thus, we were compelled to adopt an indirect route to the intended target. Addition of thiophenol to **9** under base catalyzed conditions occurred smoothly to give **10**. The benzyl ester was exchanged for an allyl ester[16] and the resulting product was oxidized with oxone to the corresponding sulfone, with concomitant loss of the TMS protective group. Elimination of the sulfone was effectively accomplished in the presence of DBU to give **13**. Palladium-catalyzed removal of the allyl ester[17] in the presence of pyrrolidine as base and a bulky amidine,[18] led to the tricyclic carbacephem **14**, as the amidinium salt.

Scheme 2



(a) $ZnCl_2$ (20% mole), CH_2Cl_2, rt, slow addition of 5-methyl-2-trimethylsilyloxyfuran (1.5 eq) over 10 h, 89-92%; (b) BF_3:Et_2O(3eq), CH_3CN, 0°C, 3 h, 82%; (c) TMSCl(3.5 eq), Et_3N(3.5 eq), CH_2Cl_2, 0°C, 5 h, 71%; (d) vinylmagnessium bromide(5 eq), CuI(2.5 eq), Me_2S, THF, -78°C to -23°C, 5 h, 92%; (e) BnOCOCOCl(1 eq), NaHMDS(1 eq), THF, -78°C, 30 m, 56%; (f), O_3, $(MeO)_3P$(1.9 eq), CH_2Cl_2, -78°C to rt; (g) $(MeO)_3P$(4.6 eq), o-xylene, reflux, 10 h, 40%; (h) PPTS(cat), THF:H_2O, 6 h, 93%; (i) Pd/C(10%), H_2, THF, 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene(1 eq), 81%.

The successful construction of the tricyclic carbacephem motif **14**, prompted us to explore the synthesis of a structural variant, namely a tricyclic carbacephem lactone (Figure 1 C, X = O) in which the angular position carried an "α-methyl" group. Treatment of **1** with 4-methyl-1-trimethylsilyloxyfuran in the presence of zinc chloride led to the corresponding butenolide adduct **15** in excellent yield. Exchange of the TBS group for TMS, conjugate addition of the vinyl group, and introduction of the oxalimide group gave **19** in good overall yield. The oxidative cleavage of the vinyl group gave the aldehyde derivative **20**, which was subjected to a trimethylphosphite mediated cyclization[13] uneventfully to give **21**. Removal of the TMS group and hydrogenolysis of **17** in the presence of the bulky amidine led to the desired tricyclic carbacephem lactone analog **23** in excellent yield. Evidently, unlike in the case of **9**, the C-1 α-oriented methyl group (carbacephalosporin numbering) in **22** prevents the catalyst from approaching the double bond, hence the selective hydrogenolysis of the benzyl ester only.

We have developed a versatile and stereocontrolled method for the functionalization of the 4-acetoxyazetidinone **1** with readily available furan derivatives. The resulting 4-substituted butenolide motifs lend themselves to a host of bond forming reactions, thus allowing the introduction of several functional groups. In one application, we have shown how such products can be transformed into tricyclic carbacephems of the types shown in expression C, Figure 1. In spite of their rather unique structures and topologies, the carbacephems **14** and **23** were inactive against a host of selected bacterial strains (MIC, >128μg/mL). This may be due to inherent structural, stereochemical and functional problems related to the "reactivity" of the β-lactam carbonyl group in these structures,[19] or simply due to the absence of an appropriate leaving group at C-3 as in the normal cephems. The methodology we have developed in the context of these novel β-lactam structures is amenable to modification in order to incorporate potential leaving groups on the carbacephem nucleus. Studies directed at such analogs are in progress and will be reported in due course.[20]

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References and Notes

1) S. Hanessian and M. Rozema, preceeding paper.

2) Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7582; Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584; Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett.* **1993**, 139.

3) For recent reviews, see: *The Organic Chemistry of β-Lactams*, Georg, G.I. Ed.; VCH Publications, Inc., New York, N.Y., **1993**. Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463.

4) Melillo, D.G.; Cretovich, R.J.; Ryan, K.M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498; Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.

5) Hanessian, S.; Couture, C. A.; Georgopapadakou, N. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2323; Sumi, K.; Di Fabio, R.; Hanessian, S. *Tetrahedron Lett.* **1992**, *33*, 749; Hanessian, S.; Sumi, K.; Vanasse, B. *Synlett* **1992**, 33; Hanessian, S.; Desilets, D.; Bennani, Y.L. *J. Org. Chem.* **1990**, *55*, 3098; Hanessian, S.; Desilets, D. in *Trends in Medicinal Chemistry* ; van der Groot, H.; Domany, G.; Pallos, L.; Timmerman, H. eds.; Elsevier, Amsterdam, 1989, p 165; Hanessian, S.; Alpegiani, M. *Tetrahedron*, **1989**, *45*, 941; Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438.

6) See Cohen, N. *Advan. Drug Res.* **1985**, *14*, 41; *J. Med. Chem.* **1983**, *26*, 259.

7) Schmidt, G.; Schrock, W.; Endermann, R. *Bioorg. Chem. Lett.* **1993**, *3*, 2193; Gunda, G.; Batta, G.; Jeko, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2451; Elliott, R. L.; Nicholson, N. H.; Peaker, F. E.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1994**, *59*, 1606; Sakagami, K.; Tashiro, M.; Takeuchi, Y.; Hatanaka, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 1766; Murakami, M.; Aoki, T.; Nagata, W. *Synlett.* **1990**, 684; Murakami, M.; Matsuura, M.; Aoki, T.; Nagata, W. *Synlett.* **1990**, 681; Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073; Finkelstein, J.; Holden, K. G.; Perchonock, C.D. *Tetrahedron Lett.* **1978**, *28*, 1629; Sendai, M.; Miwa, T. Eur. Pat. Appl. Ep 507,313 (cl. C07D477/00), **07 Oct 1992**. *Chem. Abstr., 118*, 124294y, **1993**; Gerlach, U.; Horlein, R.; Krass, N.; Lattrell, R.; Wollmann, T.; Limbert, M.; Marcus, A., Eur. Pat. Appl. Ep 517,065 A1 (cl. C07D477/00), **09 Dec 1992**. *Chem. Abstr.*, 118, 168890u, **1993**; Wollmann, T.; Gerlach, U.; Hörlein, R.; Krass, N.J. Lattreu, R.; Limbert, M.; Markus, A. in *Recent Advances in the Chemistry of Anti-Infective Agents*", Bentley, P.H.; Ponsford, R. eds., **1992**, p. 50, The Royal Society of Chemistry, T. Graham House, Cambridge, U.K. CB4 4WF.

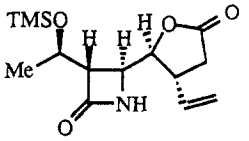
8) Padova, A.; Roberts, S. N.; Donati, D.; Perboni, A.; Rossi, T. *J. Chem. Soc., Chem. Commun.* **1994**, 441; Perboni, A.; Tamburini, B.; Rossi, T.; Donati, D.; Tarizia, G.; Gaviraghi, G.*"Recent Advances in the Chemistry of Anti-infective Agents"*, Bentley, P.H.; Ponsford, R. eds, **1992**, p. 21; The Royal Society of Chemistry, T. Graham House, Cambridge, U. K., CB4 4WF; Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso, R.; Bismara, C."Eur. Pat. Appl. Ep 416,953 (cl. C07D477/00), March 13, 1991, *Chem. Abstr., 116*, 235 337t, **1992**.

9) 4-Acetoxy-3-[(*R*)-1'-hydroxyethyl]-1'-[O-tert-butyldimethylsilyl]-2-azetidin-1-one **1**, is commercially available, Aldrich Chemical Company Inc., Milwaukee, Wis., and from Kaneka America Corp., New York, N.Y.

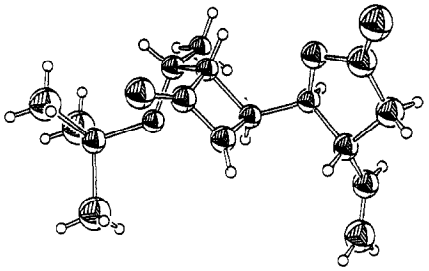
10) For the reactions of 2-trimethylsilyloxyfuran with carbonyl compounds, see: Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037; Rassu, G.; Spanu, P.; Casiraghi, G.; Pinna, L. *Tetrahedron* **1991**, *47*, 8025 and the references cited therein. For the reactions of 2-trimethylsilyloxyfuran with cyclic imines, see: Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697; Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, *55* and references cited therein.

11) This reaction was initially performed by Dr. V. Ratovelomanana in our laboratory using $BF_3.Et_2O$ leading to a mixture of **2** and its isomer in a ratio of 3:2.

12) The X-ray structure of compound **24** which is derived from **3**.



24



13) Afonso, A.; Hon, F.; Weinstein, J.; McPhail, A.T.; Ganguly, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6138; Battistini, C.; Scarafile, C.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2395.

14) Baldwin, J. E.; Cobb, J. E.; Sheppard, L. N. *Tetrahedron* **1987**, *43*, 1003; Ross Kelly, T.; McNutt, R. W.; Montury, M.; Tosches, N. P.*J. Org. Chem.* **1979**, *44*, 63.

15) Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1979**, *20*, 2793; Ohtani, M.; Watanabe, F.; Narisada, M. *J. Org. Chem.*, **1984**, *49*, 5271; Mangia, A.; Scandroglio, A. *Tetrahedron Lett.* **1978**, *19*, 5219; Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O.; *Tetrahedron Lett.* **1984**, *25*, 5397; Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, *21*, 2305.

16) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidman, B.; Züger, M. *Synthesis* **1982**, 138.

17) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, *20*, 613; Deziel, R.*Tetrahedron Lett.* **1987**, *28*, 4371; Jungheim, L.N. *Tetrahedron Lett.* **1989**, *30*, 1889; Jeffrey, P.D.; McCombie, S.W. *J. Org. Chem.* **1982**, *47*, 587; Kunz, H.; Waldmann, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 71.

18) Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron* **1982**, *38*, 2659; see also Heinzer, F.; Soukup, M.; Eschenmoser, A. *Helv. Chim. Acta* **1978**, *61*, 2851.

19) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B.; Rihs, G. *J. Am. Chem. Soc.* **1981**, *103*, 4526; Cohen, N.C. *J. Med. Chem.* **1983**, *26*, 259; *Adv. Drug. Res.* **1985**, *14*, 41 and refeerences therein.

20) All new compounds were adequately characterized by routine analytical and spectroscopic methods (HRMS, ^{1}H, ^{13}C NMR, 300 MHz). Optical rotations were recorded at 25°C in $CHCl_3$ and melting points are uncorrected.

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