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TOTAL SYNTHESIS OF CIS-6-METHOXY-1,1-DIMETHYLCARBAPEN-2-EM

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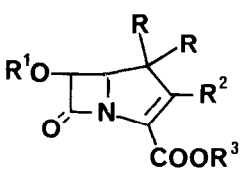
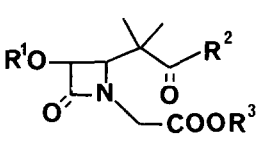
Summary: The total synthesis of the title compound via an intramolecular aldol condensation, and the novel use of the trimethylsilylethyl ester as a carboxyl protecting group in carbapenem systems, are reported.

The recent discovery of the potent antibiotic thienamycin[1] and its relatives[2] have stimulated considerable interest in the synthesis of carbapen-2-ems[3]. In contrast to the 6-alkylcarbapen-2-ems, the 6-alkoxycarbapen-2-ems 1 (and their dimethyl analogs 2) have received little attention. During our recent research on the synthesis of β-lactam antibiotics, we wished to synthesize 6-alkoxy-1,1-dimethylcarbapen-2-ems 2. Our synthetic strategy required an internal aldol condensation of a substituted azetidin-2-one 3. While our chemical investigation was in progress, a communication[4] described the preparation of the 6-alkoxy-carbapen-2-em ester 4 by an internal aldol condensation route[5]. However, deprotection of the ester function of 4 did not yield any identifiable β-lactam compound[4]. We now wish to report our chemical investigation leading to the total synthesis of cis-6-methoxy-1,1-dimethylcarbapen-2-em tetrabutylammonium salt (5).



1 R = H, R^3 = H
2 R = CH_3, R^3 = H
4 R = H, R^3 = 4-nitrobenzyl,
R^1 = CH_3, R^2 = H



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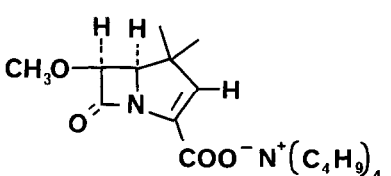

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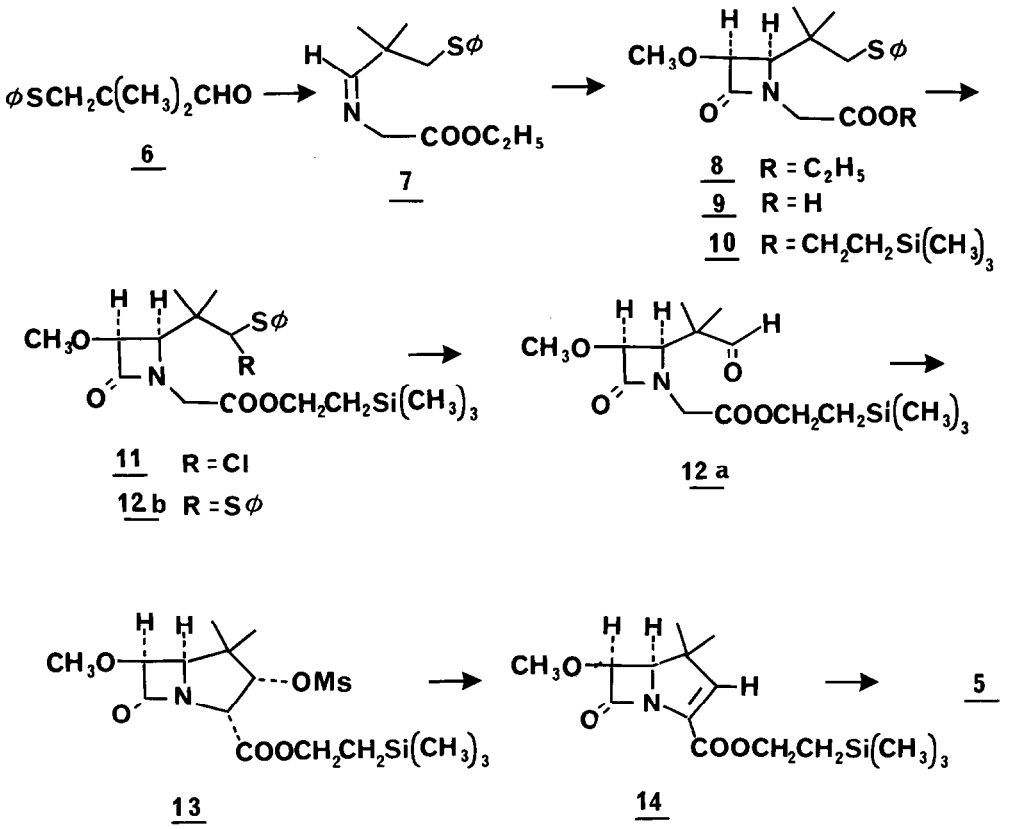
Our synthesis is characterized by the following: (1) the use of 3-thiophenoxy-2,2-dimethylpropanal (6)[6], in which the methylenephenylsulfide group serves as an aldehyde equivalent, (2) the very efficient formation of the azetidin-2-one using classical cycloaddition chemistry 7 → 8, (3) the equally efficient bicyclic ring formation by internal aldol condensation 12a → 13[5], and (4) the utilization of the trimethylsilylethyl ester[7] as protection for the carboxyl function. One of the major difficulties encountered in the synthesis of carbapenams or carbapenems is the removal of the ester moiety of intermediates[4,8]. This work shows that the trimethylsilylethyl ester is an attractive carboxyl protecting group[9] in the synthesis of carbapenems because it is readily cleaved without decomposition.



Treatment of 3-thiophenoxy-2,2-dimethylpropanal (6) with glycine ethyl ester hydrochloride in the presence of triethylamine and magnesium sulfate gave the Schiff base 7 (each 1 mol. equiv., CH_2Cl_2, 90%). Condensation of 7 with methoxyacetyl chloride in the presence of triethylamine yielded the cis-3-methoxy-azetidin-2-one 8 (CH_2Cl_2, r.t., 81%)[10] The stereochemistry at C3-C4 was confirmed to be cis by its PMR spectrum; the coupling constant for these protons is 5.5 Hz characteristic of cis disposition. Hydrolysis of 8 with one molar equivalent of sodium hydroxide yielded the acid 9 (0.5N NaOH, THF/H_2O, r.t., 98%). Esterification[11] of the acid 9 with trimethylsilylethanol gave the trimethylsilylethyl ester 10 in 85% yield. (To a solution of 3 mmole of 9 in 80 ml dimethoxyethane at ice temperature was added 6 mmole of pyridine, 4.5 mmole of phenyldichlorophosphate and 9 mmole of trimethylsilylethanol in sequence. After 15 hours at room temperature, the mixture was diluted with water and extracted with ehter. Purification of silica gel column yielded pure 10). Reaction of this ester with sulfuryl chloride (each 1 molar equiv., 0°C, CH_2Cl_2, 5 min.) gave the monochloro compound 11 which, upon purification in a water deactivated silica gel column, gave the aldehyde 12a (70%) and the disulfide 12b (15%)[6]. The disulfide 12b was conveniently converted to the aldehyde 12a by treatment with 1 molar equivalent of sulfuryl chloride at 0°C (90%). Cyclization of the aldehyde 12a with lithium bis(trimethylsilyl)amide (THF, -78°C) followed by quenching with methanesulfonyl chloride gave the mesylate 13 (65%). Using the same mechanistic consideration put forward by M. Shibuya, et al.[5] for the assignment of the relative stereochemistry of several carbapenam derivatives together with the fact that the coupling constant for the C2-C3 protons of 13 is 4.5 Hz, the configuration of 13 at C2-C3 was assigned to be cis. Dehydromesylation of 13 with 1,8-diazabicyclo-[5-4-0]-undec-7-ene (1 molar equiv., CH_2Cl_2, 85%) provided the carbapenem ester 14. Deprotection of the ester 14 with tetrabutylammonium fluoride (THF, r.t. one molar equivalent of each 3 hours) gave the 6-methoxy-1,1-dimethylcarbapen-2-em tetrabutylammonium salt (5) (85%). The above chemical transformation to carbapenems is efficient with an overall yield of about 30%. The antibacterial activities of 5 and related analogs will be reported in a future communication.

REFERENCES AND NOTES

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2. R.D.G. Cooper in "Topic in Antibiotic Chemistry", Vol. 3, ed. P. G. Sammes, Ellis Herwood Ltd., Chichester, 1979, p. 41.

3. For example: (a) L. Cama and B. G. Christensen, Tetrahedron Letters, 21, 2013 (1980); (b) R. J. Ponsford and R. Southgate, J. Chem. Soc. Chem. Commun., 1085 (1980); and references cited therein.

4. Michael W. Foxton, Robert C. Mearman, Christopher E. Newall and Peter Ward, Tetrahedron Letters, 22, 2497 (1981).

5. Masayuki Shibuya and Seiju Kubota, Tetrahedron Letters, 21, 4009 (1980).

6. Daniel T. W. Chu, submitted to for publication.

7. The use of the trimethylsilylethyl ester as a carboxyl protecting group is known [H. Gerlach, Helv. Chim. Acta, 60, 3039 (1977); P. Seiber, ibid, 60, 2711 (1977)]; however, its application for the protection of the carboxyl group of sensitive molecules such as carbapenems is new.

8. For example, L.D. Cama and B. G. Christensen, J. Amer. Chem. Soc., 100, 8006 (1978); H. Onoue, M. Narisoda, S. Uyeo, H. Matsumura, K. Okada, T. Yano and W. Nagota, Tetrahedron Letters, 3867 (1979).

9. A new method for deprotection of non-activated benzyl carboxyl protecting group in β-lactams have been reported. Masayuki Shikuga and Seijia Kubota, Tetrahedron Letters, 3611 (1981). However, because of the inability of the removal of p-nitrobenzyl group (activated benzyl group) in 6 alkoxy-carbapen-2-em (see reference 4) without cleavage of β-lactam ring, the use of this new method in our synthesis was not attempted.

10. All the synthetic β-lactams are racemic mixtures, but only one enantiomer is depicted for convenience. Unless specified, compounds are isolated in pure form as an oil. Satisfactory spectral data (IR, NMR and MS) were obtained for all new compounds. Selected proton magnetic resonance data (δ value) taken in $CDCl_3$ includes:

7: 1.23 (s, 6, 2 CH_3), 1.27 (t, J = 7, 3, ethyl CH_3), 3.11 (s, 2, CH_2S), 4.08 (d, J = 1, 2, CH_2CO_2), 4.19 (q, J = 7, 2, ethyl CH_2), 7.28 (m, 5, C_6H_5), 7.56 (t, J = 1, 1, CH=N); 8: 1.13 (s, 6, 2 CH_3), 1.26 (t, J = 7, 3, ethyl CH_3), 2.97 (d, J = 12.5, 1, 1/2 CH_2S), 3.25 (d, J = 12.5, 1, 1/2 CH_2S), 3.51 (s, 3, OCH_3), 3.68 (d, J = 18, 1, 1/2 CH_2CO_2), 4.05 (d, J = 5.5, 1, C4H), 4.18 (q, J = 7, 2, ethyl CH_2), 4.40 (d, J = 18, 1, 1/2 CH_2CO_2), 4.46 (d, J = 5.5, 1, C3H), 7.23 (m, 5, C_6H_5); 9: 1.14 (s, 6, 2 CH_3), 2.98 (d, J = 12.5, 1, 1/2 CH_2S), 3.25 (d, J = 12.5, 1, 1/2 CH_2S), 3.50 (s, 3, OCH_3), 3.73 (d, J = 18, 1, 1/2 CH_2CO_2), 4.07 (d, J = 5.5, 1, C4H), 4.45 (d, J = 18, 1, 1/2 CH_2CO_2), 4.48 (d, J = 5.5, 1, C3H), 7.23 (m, 5, C_6H_5), 8.93 (b, 1, CO_2H); 10 0.05 (s, 9, $Si(CH_3)_3$, 0.95 (m, 2, CH_2Si), 1.09 (s, 6, 2 CH_3), 2.94 (d, J = 12.5, 1, 1/2 CH_2S), 3.22 (d, J = 12.5, 1, 1/2 CH_2S), 3.47 (s, 3, OCH_3), 3.62 (d, J = 18, 1, 1/2 CH_2CO_2), 4.01 (d, J = 5.5, 1, C4H), 4.18 (m, 2, CO_2CH_2), 4.35 (d, J = 18, 1, 1/2 CH_2CO_2), 4.42 (d, J = 5.5, 1, C3H), 7.20 (m, 5, C_6H_5); 12a: 0.05 (s, 9 $Si(CH_3)_3$), 0.97 (m, 2, CH_2Si), 1.14 (s, 3, CH_3), 1.18 (s, 3, CH_3), 3.52 (s, 3, OCH_3), 3.54 (d, J = 18, 1, 1/2 CH_2CO_2), 4.20 (m, 2, CO_2CH_2), 4.16 (d, J = 5.5, 1, C4H), 4.30 (d, J = 18, 1, 1/2 CH_2CO_4), 4.63 (d, J = 5.5, 1, C3H), 9.44 (s, 1, CHO); 13: 0.05 (s, 9, $Si(CH_3)_3$), 1.05 (m, 2, CH_2Si), 1.12 (s, 3, CH_3), 1.33 (s, 3, CH_3), 3.00 (s, 3, SO_2CH_3), 3.52 (s, 3, OCH_3), 3.82 (d, J = 5.0, 1, C5H), 4.26 (m, 2, CO_2CH_2), 4.71 (d, J = 5.0, 1, C6H), 4.78 (d, J = 4.5, 1, C3H), 5.15 (d, J = 4.5, 1, C2H); 14: 0.05 (s, 9, $Si(CH_3)_3$), 1.08 (m, 2H, CH_2Si), 1.24 (s, 3, CH_3), 1.36 (s, 3, CH_3), 3.52 (s, 3, OCH_3), 3.88 (d, J = 5.5, 1, C5H), 4.32 (m, 2, CO_2CH_2), 4.88 (d, J = 5.5, 1, C6H), 6.32 (s, 1, C2H); 5: 1.10 (mound, 12, 4 butyl CH_3), 1.17 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.55 (mound, 16, 4 butyl CH_2CH_2), 3.30 (mound, 8, 4 butyl N-CH_2), 3.50 (s, 3, OCH_3), 3.81, (d, J = 5.0, 1, C5H), 4.77 (d, J = 5.0, 1, C6H), 6.00 (s, 1, C2H).

11. Hsing-Jang Liu, Wing Hong Chan, and Sing Ping Lee, Tetrahedron Letters, 4461 (1978).

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