Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 11, pp. 2137-2140, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00292-4

The Use of Radical Decarboxylation in the Preparation of 1-Methylcarbapenem Antibiotic Precursors from *D*–Glucosamine

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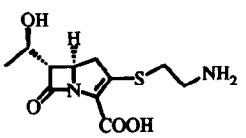
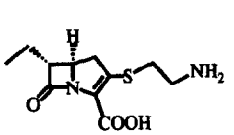
Abstract: The stereocontrolled synthesis of optically active 1-methylcarbapenams has been performed by radical cyclization and radical decarboxylation. 1,3,4-Trisubstituted-2-azetidinones, prepared by the Staudinger reaction with *D*-glucosamine as chiral auxiliary and sorbic acid were used as starting materials.

Carbapenems such as thienamycin[1] and PS-5 [2], generally show a broad antibiotic activity spectrum against Gram-positive and Gram-negative bacteria and are stable to β-lactamases, but a disadvantage of these compounds is their ready degradation in the kidney by dehydropeptidase I, (DHP-I)[3] to produce metabolites which are nephrotoxic. The synthesis of dehydropeptidase stable carbapenems is consequently a subject of therapeutic interest.

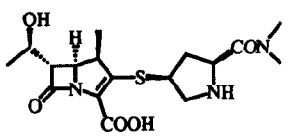
It has been found that the introduction of a methyl group into the 1-position of the carbapenem skeleton considerably improves the DHP-ase stability, as exemplified by meropenem.[4] For this reason we have studied the use of a radical decarboxylation in carbapenam systems in order to prepare 1-methylcarbapenem antibiotics according to the method recently disclosed by us.[5]



Thienamycin

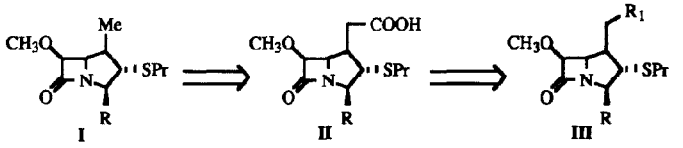


PS–5



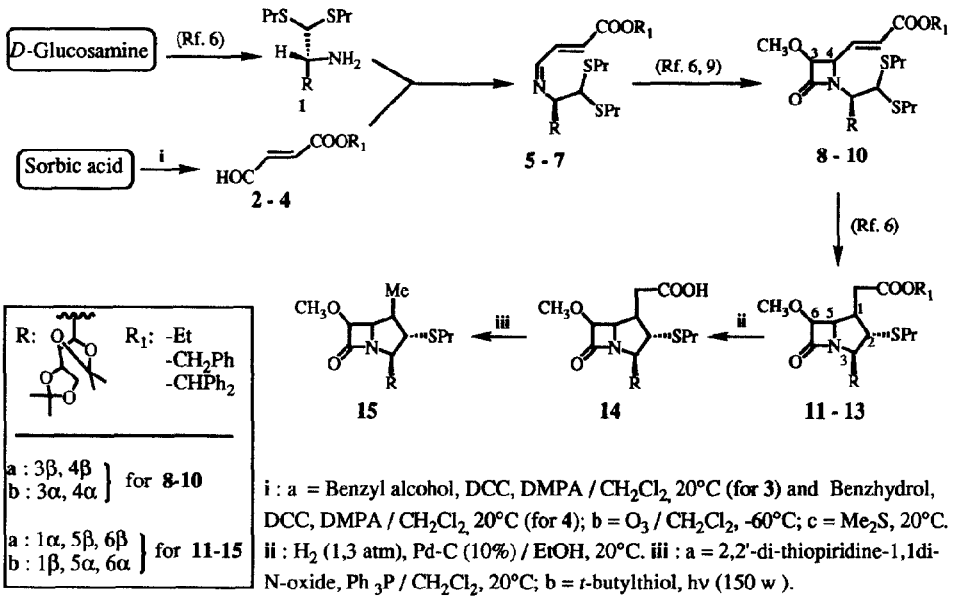
Meropenem

The retrosynthetic strategy for 1-methylcarbapenem precursors **I** is shown in Scheme 1. We first investigated the formation of the carboxymethylene carbapenams **II** from the readily available benzyl and furylmethyl carbapenams **III**[5,6] (R_1= -Ph or -Fur), but all attempts to achieve a specific oxidation of the phenyl and furyl groups were unsuccessful. Lastly the desired acid was obtained from the methylenecarboxylic esters of carbapenams **III** (R_1 = -COOR').



Scheme 1

In this paper, we describe the synthetic methods involved in the enantioselective preparation of 2-azetidinones **8-10** as well as their transformation into carbapenams **11-15**[7] (Scheme 2).



i : a = Benzyl alcohol, DCC, DMPA / CH_2Cl_2, 20°C (for **3**) and Benzhydrol, DCC, DMPA / CH_2Cl_2, 20°C (for **4**); b = O_3 / CH_2Cl_2, -60°C; c = Me_2S, 20°C. **ii** : H_2 (1,3 atm), Pd-C (10%) / EtOH, 20°C. **iii** : a = 2,2'-di-thiopiridine-1,1di-N-oxide, Ph_3P / CH_2Cl_2, 20°C; b = *t*-butylthiol, hν (150 w).

Scheme 2

The imines **5-7** were prepared by condensation of 3,4;5,6-di-*O*-isopropylidene-*D*-glucosamine dipropylthioacetal,[6] **1**, with the aldehydes **2-4**. These aldehydes were prepared from esters of sorbic acid by

selective ozonolysis using Red 19 as indicator.[8] The imines, used without further purification, were reacted with methoxyacetyl chloride in the presence of triethylamine in the Staudinger reaction. After a short reaction time (15-30 min) the respective *cis*-2-azetidinones **8(a+b)**, **9(a+b)** and **10(a+b)** were obtained in good yields (Table 1, entries 1, 2 and 3). The absolute configuration of the reaction products **8a-10b** was deduced from the $[\alpha]_D$ data of these compounds by comparison with reference 2-azetidinones of known absolute configuration determined by X-ray crystal structure analysis.[9,10]

Treatment of the β-lactams **8a**, **9a**, **10a** and **10b** with Bu_3SnH-AIBN in toluene[6] provided the expected carbapenams **11a**, **12a**, **13a** and **13b** (Table 1, entries 4-7). Also in this case the absolute configuration at C-1 and C-2 was assigned by comparison of the $[\alpha]_D$ data with those of related carbapenams[5,6] of known absolute stereochemistry determined by single crystal X-ray analysis.[5,11]

To obtain the diastereomeric acids **14** from the esters **11**, **12** or **13**, several methods were attempted[12] and we found that the best yields in **14a** and **14b** (60%) were obtained by treatment of the benzhydryl esters **13a** and **13b** with H_2 at 1.3 atm on 10% Pd-C.

Table 1: Synthesis of β-lactams **8a - 10b**[a] and carbapenams **11a - 13b**[b]

Entry	Comp	R1	Yield[c]	ratio a:b	$[\alpha]_D$[d]
1	**8a, 8b**	Et	82%	66:34	-94, +17
2	**9a, 9b**	CH_2Ph	80%	66:34	-102, +15
3	**10a, 10b**	$CHPh_2$	80%	63:37	-83, +28
4	**11a**	Et	80%	---	-16
5	**12a**	CH_2Ph	77%	---	-8
6	**13a**	$CHPh_2$	79%	---	-11
7	**13b**	$CHPh_2$	80%	---	+30

[a]Reactions carried out on 7 mmol scale in toluene at room temperature (molar ratio CH_3OCH_2COCl : Imine : TEA = 1,5 : 1 : 3). [b]Reactions carried out on 6 mmol scale in toluene[7] (molar ratio β-lactam : Bu_3SnH (AIBN) = 1 : 1,5 (5%M)).[c]Yield of isolated pure products by column chromatography. [d]$[\alpha]_D$ measurements: c=1 in $CHCl_3$.

We were now prepared to attempt the radical decarboxylation in 1-carboxymethylene carbapenams **14**. The best way to perform this reaction[13] passes through the *N*-hydroxypyridine-2-thione esters of carboxylic acids.[14] These compounds could be formed under mild conditions by reaction with 2,2'-dithiopyridine-di-*N*-oxide and triphenylphosphine.[15] These mild conditions are necessary due to the chemical instability of the bicyclic carbapenam system.

Based on the two above mentioned methods, the 1-methylcarbapenams **15a** and **15b** were obtained in "one pot" two steps procedure as follows: the acids **14a** and **14b** were treated in the dark with 2,2'-dithiopyridine-1,1'-*N*-oxide and triphenylphosphine in CH_2Cl_2. After 30 minutes stirring at room temperature, 2 eq. of *t*-butylthiol (proton donor) were added and the solution was irradiated with a xenon lamp (150w) for 10 minutes. Solvent evaporation and further column chromatography allowed us to isolate the pure methylcarbapenams **15a** {$[\alpha]_D$= −35 (c= 0.5, $CHCl_3$)}and **15b** {$[\alpha]_D$= +41 (c= 0.7, $CHCl_3$)} in 58% and 60% yields respectively.

From the results reported here and those previously disclosed,[5] we have demonstrated that the use of radical cyclization and radical decarboxylation is a versatile approach for the synthesis of chiral 1-methylcarbapenem antibiotic precursors from chiral 1,3,4-trisubstituted-2-azetidinones.

Acknowledgement:
Financial support of this work by the Junta de Castilla y León (SA-49/12/92) is gratefully acknowledged.

References and notes:

1.- Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R.E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, 100, 6491.

2.- Okamura, K.; Hirata, S.; Okumura, Y.; Fukagawa, Y.; Shimauchi, Y.; Kuono, K.; Ishikura, T. *J. Antibiot.* **1978**, 31, 480.

3.- Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernández, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, 32, 1.

4.- Neu, H. C.; Novelli, A; Chin, N *Antimicrob. Agents Chemother.* **1989**, 33, 1009.

5.- Anaya, J.; Barton, D. H. R.; Gero, S. D.; Grande, M.; Martín, N.; Tachdijian C. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 867.

6.- An article describing the synthesis of imines, β-lactams and carbapenams from *D*-glucosamine is in preparation.

7.- All new compounds displayed satisfactory analytical and spectral data in agreement with their assigned structures.

8.- Veysoglu, T.; Mitscher, L. A.; Swayze, J. K.; *Synthesis* **1980**, 807.

9.- 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**, *11*, 3211.

10.- Anaya, J.; Gateau-Olesker, A.; Gero, S. D.; Hernando, J. I. M.; Chiaroni, A.; Riche, C. *Acta Chrystallogr., Sect. B*, **1994**, *in press.*

11.- Adonias, M.; Anaya, J.; Gero, S. D.; Tachdjian C.; Chiaroni, A.; Riche, C. *Acta Chrystallogr., Sect. B*, **1994**, *in press.*

12.- a) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.*, **1977**, *99*, 968. b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.*, **1979**, *44*, 1247. c) Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.*, **1979**, 2793. d) Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.*, **1978**, 5211.

13.- Neumann, W. P. *Synthesis*, **1987**, 665.

14.- a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Comm.*, **1983**, 939. b) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.*, **1986**, *58*, 675.

15.- Barton, D. H. R.; Samadi, M. *Tetrahedron*, **1992**, *48*, 7083.

(*Received* 28 *July* 1994)