Tetrahedron Letters No. 40, pp 3867 - 3870.

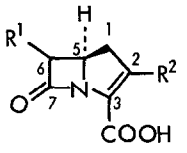
0040-4039/79/1001-3867$02.00/0

SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. PART 16.[1] SYNTHESIS OF 1-CARBA-2-PENEM-3-CARBOXYLIC ACID ESTERS FROM PENICILLINS UTILIZING A CARBON-CARBON COUPLING REACTION

Hiroshi Onoue, Masayuki Narisada,* Shoichiro Uyeo, Hiromu Matsumura,
Kyo Okada, Toshisada Yano, and Wataru Nagata
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Summary: Allylazetidinones 9, 10, prepared by coupling of allylcoppers 8 with chloroazetidinones 6, 7, were converted into carbapenem esters 16, 28-31 using an Emmons-Horner reaction to introduce the 6-side chain and an intramolecular Wittig reaction to form the carbapenem ring system.

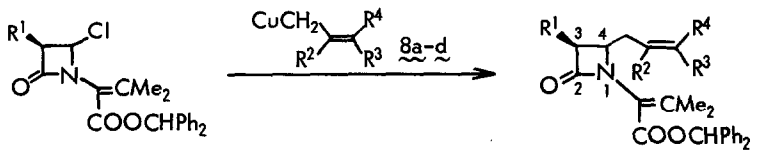
Recently, interest in the β-lactam chemistry has been focused on the syntheses[2,3] of the carbapenem ring system, the fundamental skeleton of thienamycin 1 and its analogues[4] 2-4. In this communication, we wish to describe a synthesis of some carbapenem esters 16, 28-31 involving a new coupling reaction of allylcoppers with chloroazetidinones derived from penicillins as a key reaction.



1, 4a R^1 = ---CH(OH)CH_3; R^2 = S⟨NH$_2$
2, 4b R^1 = ▬CH(OSO_3H)CH_3; R^2 = S⟨NHAc
3, 4b R^1 = ▬CH(OSO_3H)CH_3; R^2 = S(O)⟨NHAc
4, 4c R^1 = ▬CH(OSO_3H)CH_3; R^2 = S⟨NHAc
5, 4d R^1 = —CH_2CH_3; R^2 = S⟨NHAc

The chloroazetidinone 6[5] or 7[7] prepared from penicillins was allowed to react (THF, -35°C, 1-4 h then warmed to 0°C in 1 h) with allylcoppers 8a-d, prepared by mixing CuI(n-Bu_2S)$_2$ (ether, -76°C, N_2) with allyllithiums,[9] giving 9b or 10a-d respectively as shown in Table I. It is noteworthy that the coupling of either isomer of 7 (4β or 4α) with 8d yielded a mixture of 10d with the same isomer ratio (runs 5, 6). When lithium diallylcuprates were used in place of allylcoppers, conjugated addition products 11 were formed as the major products.

Epoxidation (m-chloroperbenzoic acid, rt) of 9b followed by hydrolysis (20% $HClO_4$-acetone, 0°C) and subsequent acetonidation of the resulting glycol proceeded smoothly to yield 12 (62%). Conversion of 12 into ylide 13 (70%) was performed by the method[10] developed in our laboratories



6, R^1 = H
7, R^1 = NHTr

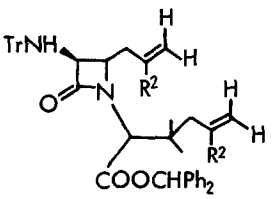
9b, R^1 = H
10a-d, R^1 = NHTr

	R^2	R^3	R^4
a	H	H	H
b	H	Me	H
c	H	Me	Me
d	Me	H	H

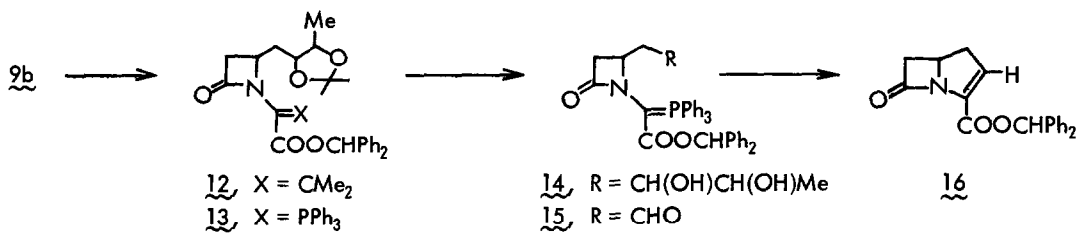
Table I. Coupling of Chloride 6, 7 with Allylcopper 8a-d

run	chloride	allylcopper	product	yield (%)	isomer ratio[a]
1	6	8b	9b	55.0	-
2	4β-7	8a	10a	12.4	33/67
3	4β-7	8b	10b	66.1	45/55
4	4β-7	8c	10c	64.0	55/45
5	4β-7	8d	10d	63.6	33/67
6	4α-7	8d	10d	48.2	33/67

[a] The ratio of 4β- to 4α-isomers was determined by nmr.



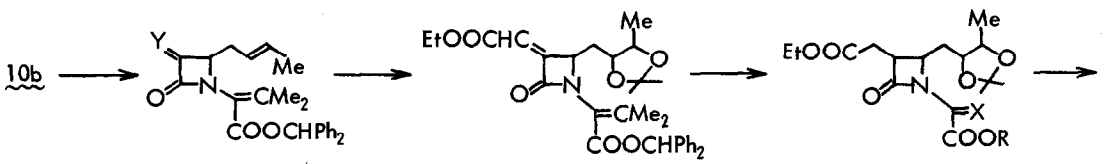
11 (R^2 = H, Me)



12, X = CMe_2
13, X = PPh_3

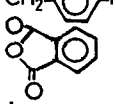
14, R = CH(OH)CH(OH)Me
15, R = CHO

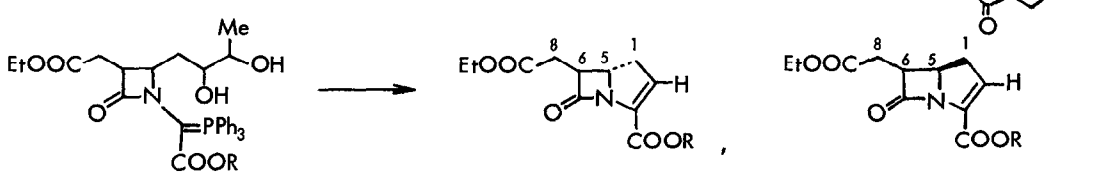
16

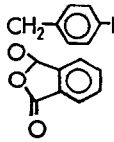


17, Y = H (3α), NH_2 (3β)
18, Y = O
19, Y = CHCOOEt

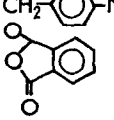
20

21, X = CMe_2; R = $CHPh_2$
22, X = PPh_3; R = $CHPh_2$
23, X = H, OH; R = CH_2-C_6H_4-NO_2
24, X = CMe_2; R = 



25, R = $CHPh_2$
26, R = CH_2-C_6H_4-NO_2
27, R = 

28, R = $CHPh_2$ (6β)
29, R = $CHPh_2$ (6α)

30, R = CH_2-C_6H_4-NO_2 (6α)
31, R =  (6β)

The acetonide group of 13 was deprotected by exposure to 2 N HCl in ethanol (rt, 16 h) to give 14. Glycol fission (HIO_4, H_2O-THF, rt, 0.5 h) of the latter gave aldehyde 15, which on neutralization (aq $NaHCO_3$-AcOEt) spontaneously cyclized, giving carbapenem ester 16[11] (51%).

Considering that introduction of some two carbon moiety at C_6 might affect antibacterial activity, we have undertaken synthesis of C_6-ethoxycarbonylmethylcarbapenems. The mixture of 4β- and 4α-10b was detritylated (p-TsOH·H_2O, acetone) and the desired product 4β-17 (31%) was separated by silica gel chromatography from 4α-17[12] (45%). These compounds were converted[13] into 4β-18 and 4α-18, respectively (70% each), by oxidation with 3,5-di-tert-butyl-1,2-benzoquinone (THF, 0°C, 18 h) and subsequent hydrolysis (oxalic acid-H_2O-THF, 0°C, 21 h).

First, a model experiment using 4α-18 of the unnatural configuration was carried out. Reaction of 4α-18 with lithium salt of triethyl phosphonoacetate anion (THF, -20°C, 15 min) and subsequent separation of the products by silica gel chromatography yielded Z-4α-19 (30%) and E-4α-19 (45%), the geometries being assigned based on the chemical shifts ($CDCl_3$) of relevant proton signals at δ 5.83 and δ 6.48, respectively. Conversions of the butenyl groups of both Z- and E-isomers into the corresponding acetonides proceeded similarly to the case of 9b, giving Z-4α-20 (74%) and E-4α-20 (86%), respectively. While selective hydrogenation[14] of E-4α-20 (H_2, 5% Pd on $CaCO_3$, AcOEt, then back-esterification with Ph_2CN_2) yielded an inseparable mixture (5:1) of 3β,4α- and 3α,4α-21 (97%), that of Z-4α-20 exclusively gave 3α,4α-21 (87%). The mixture of 3β,4α- and 3α,4α-21 was converted[10] into the corresponding ylides (86%), from which 3β,4α-ylide 22 was separated by silica gel chromatography. The deprotection of the acetonide group of 3β,4α-22 was carried out as described above giving 3β,4α-25 (95%). Similarly, 3α,4α-25 was obtained (78%) from 3α,4α-21 via 3α,4α-22. Periodic acid oxidation of 3β,4α- and 3α,4α-25 and subsequent neutralization of the resulting aldehydes produced carbapenem esters having the unnatural configuration, 28[16] (60%) and 29 (64%),[17] respectively. The stereochemistry of the C_6-side chain of both carbapenem esters was determined by comparison of their H and ^{13}C nmr spectra.

After several unsuccessful attempts to remove reductively the benzhydryl groups of esters 16, 28, and 29 and even the p-nitrobenzyl group of 30, prepared similarly from 4β-18 via 3α,4β-23, we tried to synthesize a carbapenem phthalidyl ester, which might be easily hydrolyzed by action of esterases existing in blood. Thus, carbapenem 31 was prepared from 4β-18 via 3β,4β-24 by the sequence of reactions used for converting 3α,4α-21 into 29. The phthalidyl ester 31 exhibited only moderate *in vitro* antibacterial activity[18] with horse blood serum, although interesting antibacterial activity of sodium C_2-unsubstituted carbapenem carboxylates has been reported recently.[3a,3b]

REFERENCES

1. Part 15: Hamashima et al., to be published.
2. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Am. Chem. Soc. 100, 313 (1978).
3. a) L. D. Cama and B. G. Christensen, J. Am. Chem. Soc. 100, 8006 (1978); b) D. H. Shih, J. Hannah, and B. G. Christensen, J. Am. Chem. Soc. 100, 8004 (1978); c) A. J. G. Baxter,

K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, J. Chem. Soc., Chem. Comm. 236 (1979).

4. a) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E.-A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratchliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, J. Am. Chem. Soc. 100, 6491 (1978); b) A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, J. Chem. Soc., Chem. Comm. 523 (1977); c) D. F. Corbett, A. J. Eglington, and T. T. Howarth, J. Chem. Soc., Chem. Comm. 953 (1977); d) K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura, and J. Lein, J. Antibiotics 31, 480 (1978).
5. Prepared by metal exchange[6] followed by protonation (aq NH_4Cl) of benzhydryl 6α-iodo-penicillanate and subsequent chlorination of the resulting penicillanate.
6. F. DiNinno, T. R. Beattie, and B. G. Christensen, J. Org. Chem. 42, 2960 (1977).
7. Obtained as crystalline 4β- (mp 172-174°C, decomp) and non-crystalline 4α-isomers from the tritylated products of the corresponding mixture of 3β-amino-4-chloroazetidinones.[8]
8. M. Narisada, H. Onoue, and W. Nagata, Heterocycles 7, 839 (1977).
9. Prepared by treatment of allyl, triphenyltins with phenyllithium: see, D. Seyferth and M. A. Weiner, J. Org. Chem. 26, 4797 (1961).
10. The original method was slightly modified: i) ozonolysis followed by immediate reduction (HOAc-Zn, 0°C); ii) chlorination ($SOCl_2$, Me_2NPh, 0°C); iii) ylide formation (Ph_3P, Me_2NPh, CH_2Cl_2, reflux, 1 h): see, S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, Heterocycles 8, 283 (1977).
11. 16. IR ν ($CHCl_3$) 1780, 1725 cm^{-1}. NMR (T-60, $CDCl_3$) δ 2.67-3.0 (2H, m, C_1-H); 2.92 (1H, dd, J = 3 and 16 Hz, $C_{6\alpha}$-H); 3.47 (1H, dd, J = 6 and 16 Hz, $C_{6\beta}$-H); 4.22 (1H, m, C_5-H); 6.50 (1H, t, J = 3 Hz, C_2-H).
12. The trans configuration was assigned based on the nmr spectrum of its N-phenylacetyl derivative: NMR ($CDCl_3$) δ 3.82 (1H, dt, J = 2 and 6 Hz, C_3-H); 4.65 (1H, dd, J = 2 and 8 Hz, C_4-H).
13. E. J. Corey and K. Achiwa, J. Am. Chem. Soc. 91, 1429 (1969).
14. Analogous reductions of 6-exomethylene penicillins[15] and dehydrothienamycin[4a] took somewhat different stereochemical courses.
15. a) J. C. Sheehan and Y. S. Lo, J. Org. Chem. 38, 3223 (1973); b) J. C. Sheehan, A. Buku, E. Chacko, T. J. Commons, Y. S. Lo, D. R. Ponzi, and W. C. Schwarzel, J. Org. Chem. 42, 4045 (1977).
16. 28. IR ν ($CHCl_3$) 1775, 1720 cm^{-1}. NMR (100 M/C, $CDCl_3$) δ 2.55-3.03 (4H, m, C_1-H, C_8-H); 3.50 (1H, ddd, J = 3, 5, and 10 Hz, C_6-H); 4.04 (1H, dt, J = 3 and 9 Hz, C_5-H); 6.47 (1H, t, J = 3 Hz, C_2-H). C^{13} NMR ($CDCl_3$) δ 33.2 (C_1), 35.9 (C_8), 55.2 (C_6), 58.3 (C_5).
17. 29. IR ν ($CHCl_3$) 1780, 1720 cm^{-1}. NMR (100 M/C, $CDCl_3$) δ 2.42-2.95 (4H, m, C_1-H, C_8-H); 3.99 (1H, m, C_6-H); 4.44 (1H, dt, J = 6 and 9.5 Hz, C_5-H); 6.53 (1H, t, J = 3 Hz, C_2-H). C^{13} NMR ($CDCl_3$) δ 29.9 (C_1), 31.3 (C_8), 48.6 (C_6), 55.5 (C_5). $[\alpha]_D^{25}$ -38.8° (EtOH). CD (θ) (EtOH) 266 nm (-7730).
18. The assay for antibacterial activity of the ester was carried out through the courtesy of Dr. T. Yoshida of this laboratory.

(Received in Japan 27 June 1979)