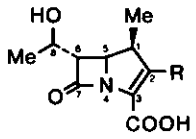
SYNTHESIS OF RACEMIC CARBAPENEMS WITH A 6β-METHYL GROUP

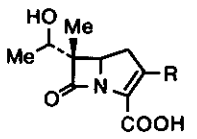
Hisao Satoh* and Teruji Tsuji
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku,
Osaka 553, Japan

Abstract —— The first total synthesis of some carbapenem antibiotics having a methyl group at the 6β position of the carbapenem nucleus is described.

Ever since the discovery of thienamycin, a variety of carbapenem antibiotics have appeared in the literature directed toward improvement of the chemical and biological stability of the highly strained ring system.[1a] Among them, 1β-methylcarbapenems[1b] have attracted considerable interest as a promising candidate for enhancing the stability toward renal dehydropeptidase-I. With the aim at such stabilization, we introduced a methyl group into the 6β position of the carbapenem nucleus. Here we report the first total synthesis of (±)-6β-methylcarbapenem derivatives and their antibacterial activity.

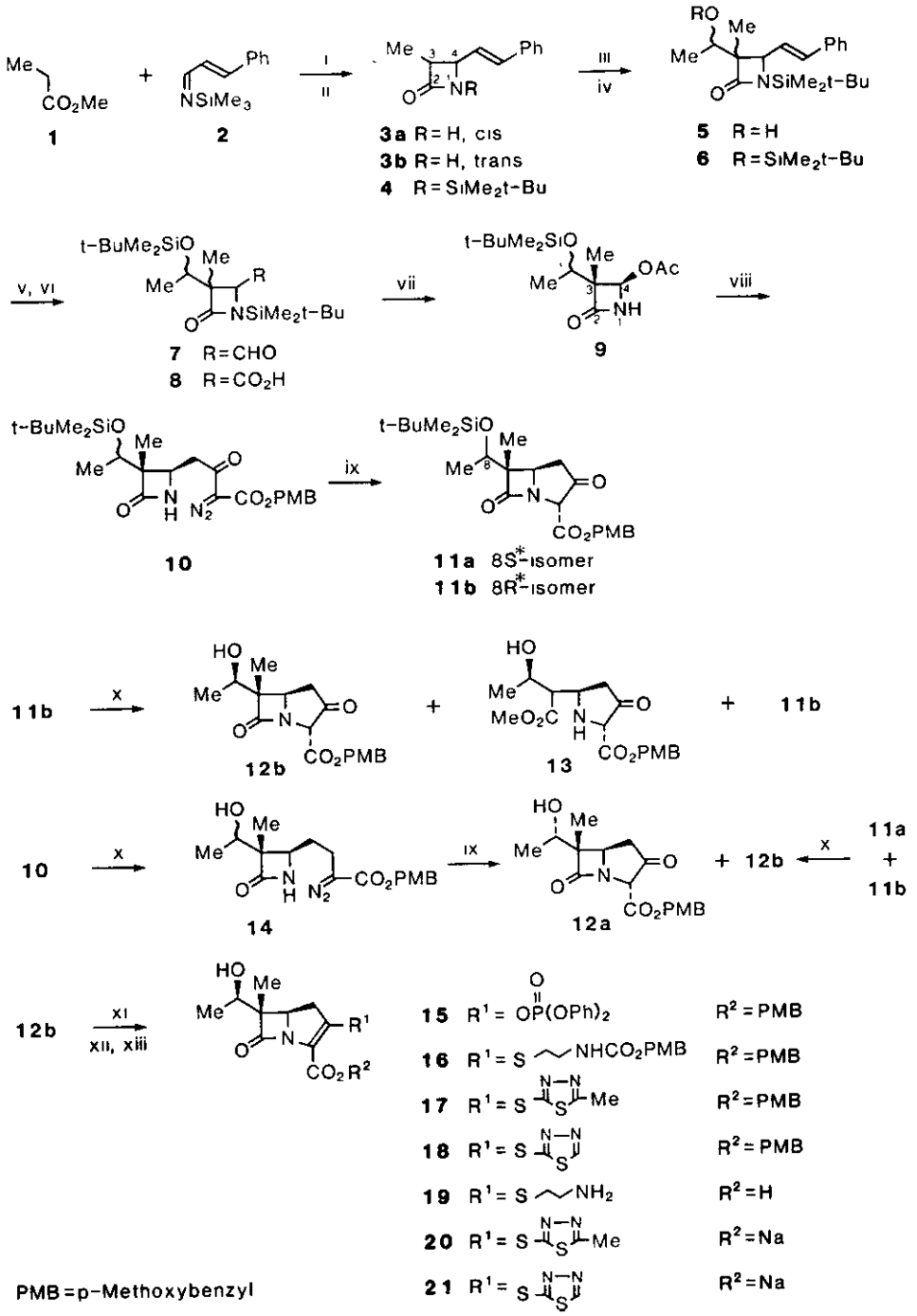


1β-Methylcarbapenems



6β-Methylcarbapenems

The enolate imine condensation between methyl propionate 1 and *N*-trimethylsilylimine 2[2] gave a 5:1 mixture of racemic *cis*- 3a and *trans*-β-lactam 3b[3] in 46-51% yield. The *cis-trans* mixture was converted to *N*-*t*-butyldimethylsilyl derivative 4 in 93% yield. Direct aldol condensation of the enolate derived from 4 with excess acetaldehyde gave an 80.9% yield of 5 as a mixture of diastereoisomers. Ozonolysis of *N,O*-bisprotected 6 followed by oxidation of the resulting aldehyde 7 gave the carboxylic acid 8. After oxidative decarboxylation with lead tetraacetate, we obtained the important key intermediate 9 (mp 51-58 °C)[4a] as an epimeric mixture at the C-1', accompanied by removal of the *N*-protecting group. For the relative configuration between substituents at the C-3 and C-4, Reider[4b], Georg,[4c] and Hart[4d] have independently pointed out that oxidative decarboxylation of 3-(1'-*t*-butyldimethylsilyloxy)ethyl-4-carboxy-2-azetidinone results in exclusive introduction of an acetoxy group at the C-4 from the less hindered side opposite the bulky substituent at the C-3. This procedure gave 9 from 5 in a 20% overall yield.



Scheme 1. Reagents and conditions. i, LDA, THF, -70 °C-room temp then HCl, ii, *t*-BuMe$_2$SiCl, Et$_3$N, cat *N*,*N*-dimethylaminopyridine, CH_2Cl_2, 0 °C – room temp , iii, 1.35 mol of LDA, 10 mol of MeCHO, THF, – 78 °C then 2.7 mol of AcOH; iv, *t*-BuMe$_2$SiCl, imidazole, DMF, room temp., 15 h; v, O_3, CH_2Cl_2, -78 °C then Me_2S; vi, pyridinium dichromate, DMF, 0 °C – room temp., 15 h, vii, $Pb(OAc)_4$, $Cu(OAc)_2$, DMF-AcOH, 70 °C, 0.5 h, viii, $H_2C{=}C(OSiMe_2t\text{-}Bu)\text{-}C(N_2)\text{-}CO_2PMB$, cat. ZnI_2; ix, cat. $Rh_2(OAc)_4$, PhH, 80 °C, x, aq. HCl, MeOH; xi, $(PhO)_2P(O)Cl$, *i*-Pr$_2$NEt; xii, R^{1}SH, *i*-Pr$_2$NEt, xiii, $AlCl_3$, anisole, CH_2Cl_2-$MeNO_2$.

The Lewis acid-mediated reaction[5] *of the acetate* **9** *with the silyl enol ether*[6] *of p-methoxybenzyl* diazoacetoacetate resulted in stereospecific replacement of the C-4 acetoxy group to give the diazoester **10**[4b,7] (46-51%) which was cyclized[8] into two chromatographically separable bicyclic keto-esters **11a** (8*S**-isomer) and **11b** (8*R**-isomer) in 51.8% and 30.6% yields, respectively. The stereochemistry at the C-8 of **11a** and **11b** could be determined from the ^{1}H nmr spectra[4b,9] of carbapenems, i.e., the C<u>H</u>$_3$-CH(OH)-doublet signal in the 8*R**-isomer was always observed in a higher field than that in the 8*S**-one. The C<u>H</u>$_3$-CH(OSiMe$_2$-*t*-Bu)- signal in **11b** was observed at δ 1.183 (d, J = 6.0 Hz), whereas δ 1.267 (d, J = 6.0 Hz) was observed for **11a**. From these findings, the 8*S**-isomer was assigned to **11a** and the 8*R**-isomer to **11b**.

Careful treatment of **11b** with aq. HCl-MeOH at room temp. for 27.5 h[10] afforded the desired 8*R**-epimer **12b** ($\nu_{C=O}^{CHCl_3}$ 1760 cm^{-1}) as the major product with some recovered **11b** and ring-opened **13**. Desilylation of **10** followed by cyclization gave an inseparable mixture (crystals) of major **12a** and minor **12b**,[4b,9,11] in a ratio reflecting that of **11a** to **11b**, in 80.5% yield from **10** via **14**. They were also obtainable from a crude mixture of **11a** and **11b** upon exposure to the HCl-MeOH mixture in high yield.

The crude keto-ester **12b** derived from **11b** having the natural configuration at the C-8 position which is required for biological activity, was readily converted into carbapenems bearing the C-2-thia substitution pattern (**16**, foam, 82.2%; **17**, mp 150-154°C, 66.2%; **18**, mp 160-166°C, 29.8%) *via* enol-phosphate **15** (93.4%).[8,12] Final deprotection of these esters by treatment with aluminum trichloride and anisole under mild conditions[13] gave carboxylate derivatives **19**, **20** and **21**, as powders, respectively, in moderate yields. As anticipated, the chemical stabilities of **19**, **20** and **21** increased relative to the thienamycin series. However, *their antibacterial activities (in vitro) against both gram-positive and -negative bacteria diminished* relative to thienamycin. At present, it can only be said that the reduced antibacterial potency may result from the methyl substituent at the C-6 causing inactivation of the β-lactam carbonyl due to its inductive effect as well as making it difficult for the compound to approach the appropriate receptor sites due to its steric effect.

REFERENCES AND NOTES

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2. (a) D. J. Hart, K. Kanai, D. G. Thomas, and T.-K. Yang, <u>J. Org. Chem.</u>, 1983, **48**, 289. (b) D.-C. Ha, D. J. Hart, and T.-K. Yang, <u>J. Am. Chem. Soc.</u>, 1984, **106**, 4819.
3. All new compounds have been fully characterized and their spectral data and elemental composition are in accord with their assigned structures. All yields were not optimized. All synthetic compounds were racemic mixtures, but only one isomer is depicted for convenience. Selected spectral data (^{1}H nmr in $CDCl_3$, 90 MHz; ir in $CHCl_3$; uv in H_2O): **3a**: ^{1}H Nmr $J_{3,4}$ = 5.5 Hz. **3b**: ^{1}H Nmr $J_{3,4}$ = 2.5

Hz. **7**: ^{1}H Nmr δ 9.83 (C*H*O, d, J = 2.0 Hz), IR 1742 cm^{-1}. **9**: ^{1}H Nmr δ 1.156 (CH_3·ĊH·O-, d, J = 6.0 Hz), 1.278 (CH_3·ĊH·O-, d, J = 6.0 Hz), 1.170 (C_3-CH_3, s), 1.217 (C_3-CH_3, s), 2.089 ($COCH_3$, s), 3.90 (>C*H*CH_3, q, J = 6.0 Hz), 3.96 (>C*H*CH_3, q, J = 6.0 Hz), 5.79 (C_4-*H*, s), 5.83 (C_4-*H*, s), 6.47 (N*H*, br). **10**: Ir 3400, 2135, 1753, 1705, 1642, 1290 cm^{-1}. **11a**: ^{1}H Nmr δ 1.200 (C_6-CH_3, s), 1.267 (C_8-CH_3, d, J = 6.0 Hz), 2.489 (C_1-*H*, d, J = 7.5 Hz), 2.567 (C_1-*H*, d, J = 7.5 Hz), 3.78 (OCH_3, s), 4.033 (C_8-*H*, q, J = 6.0 Hz), 4.100 (C_5-*H*, t, J = 7.5 Hz), 4.54 (C_3-*H*, s), 5.10 (CO_2CH_2-, s). **11b**: ^{1}H Nmr δ 1.111 (C_6-CH_3, s), 1.183 (C_8-CH_3, d, J = 6.0 Hz), 2.489 (C_1-*H*, d, J = 7.5 Hz), 2.567 (C_1-*H*, d, J = 7.5 Hz), 3.78 (OCH_3, s), 4.122 (C_8-*H*, q, J = 6.0 Hz), 4.155 (C_5-*H*, t, J = 7.5 Hz), 4.56 (C_3-*H*, s), 5.10 (CO_2CH_2-, s). **16**: Ir 1765, 1710 cm^{-1}. **17**: Ir 1768 cm^{-1}. **18**: Ir 1768 cm^{-1}. **19**: Uv λ_{max} 297 nm. **20**: Uv λ_{max} 290 nm. **21**: Uv λ_{max} 290 nm.

4. (a) The stereochemical assignment for **9** was performed on the basis of NOE difference experiments (200 M Hz in $CDCl_3$, 25°C), e.g., individual irradiation of the C-3 CH_3, C-4 H and C-1' H frequencies caused 4% enhancement of the OAc, C-1' H and C-4 H signals, respectively. Further support came from ^{13}C nmr spectral data. This result means that the acetoxy group introduced at the C-4 is in a trans-relationship to the (1-*t*-butyldimethylsilyloxy)ethyl group at the C-3 even in the presence of a methyl group at the C-3. (b) P. J. Reider and E. J. J. Grbowski, Tetrahedron Lett., 1982, **23**, 2293, and references cited in therein. (c) G. I. Georg and H. S. Gill, J. Chem. Soc., Chem. Commun., 1985, 1433. (d) D. J. Hart and D.-C. Ha, Tetrahedron Lett., 1985, **26**, 5493.
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6. This synthon was prepared from *p*-methoxybenzyl diazoacetoacetate as described in Y. Ueda, G. Roberge, and V. Vinet, Can. J. Chem., 1984, **62**, 2936.
7. Although we do not have any evidence for the stereochemistry at the C-4 of **10**, we assumed that a structure with a four-carbon unit introduced trans to the bulky Me(*t*-BuMe_2SiO)CH- group is preferable to a cis one, and thus depicted **10** as shown in the scheme.
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11. Since the major isomer **12a** has $\delta_{C8\text{-}CH_3}$ and $\delta_{C6\text{-}CH_3}$ at a lower field, than the corresponding proton signal in minor isomer **12b** in their ^{1}H nmr spectra, we felt it is reasonable to assume that **12a** also has the 8*S** configuration.
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