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# AN ALTERNATIVE SYNTHESIS OF THE 1-OXACEPHEM SKELETON

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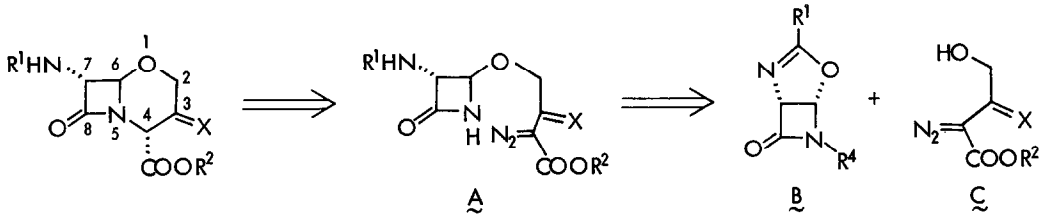
Summary: 1-Oxacephem skeletons were constructed in a convergent manner starting from building blocks B and C, which were easily prepared from penicillin and diketene, respectively, followed by intramolecular carbene insertion reaction of the resulting intermediate A.

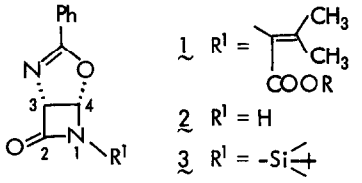
Reported methods[1] for the construction of the 1-oxacephem skeleton involve oxazine-ring cyclization either between $C_6$ and $O_1$, or $C_3$ and $C_4$, as the key steps, as originally reported by Wolfe[2] and by the Merck group,[3] respectively. Our highly stereocontrolled and industrially feasible synthesis[4] also involves intramolecular etherification between $C_6$ and $O_1$ as the key synthetic step. Our continuing studies on 1-oxacephem syntheses



A B C

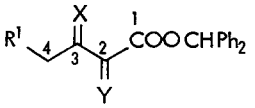
led us to an alternative, useful method featuring a convergent-type synthesis from two building blocks, B and C, to form intermediate A, followed by an intramolecular carbene insertion reaction[5] between $C_4$ and $N_5$. The synthesis is described here.

Building block B (3) was easily prepared from epi-oxazolinoazetidinone[6] by ozonolytic removal [$O_3$, $(CH_3)_2S$, then catalytic amounts of $NaOCH_3$] of the 3-methyl-2-butenoate side chain followed by $N_1$-H silylation (⫩Si-Cl, $Et_3N$-$CH_2Cl_2$) in 90% overall



1 $R^1$ = $CH_3$, $CH_3$, COOR
2 $R^1$ = H
3 $R^1$ = -Si⫩

yield. Building block C was prepared from diphenylmethyl 4-bromo-acetoacetate 4, which was readily derived from diketene.[7] 4-Hydroxyacetoacetate 6 was obtained directly when 4 was reacted with HCOONa in refluxing $CH_3OH$. However, this one-step conversion gave

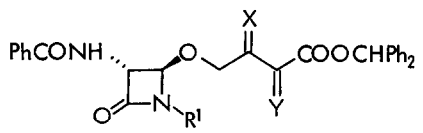


| | | | |
|---|---|---|---|
| 4 | $R^1$ = Br | X = O | Y =  |
| 5 | $R^1$ = OCHO | X = O | Y =  |
| 6 | $R^1$ = OH | X = O | Y =  |
| 7 | $R^1$ = OH | X = O | Y = $N_2$ |

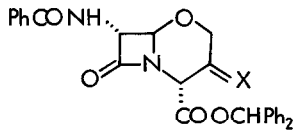
| | | | |
|---|---|---|---|
| 8 | $R^1$ = OH | X = O | Y = N~OH |
| 9 | $R^1$ = OTHP | X = O | Y = N~OSi  |
| 10 | $R^1$ = OTHP | X = $CH_2$ | Y = N~OSi  |
| 11 | $R^1$ = OTHP | X = $CH_2$ | Y = N~OH |
| 12 | $R^1$ = OH | X = $CH_2$ | Y = N~OH |
| 13 | $R^1$ = OTHP | X = $CH_2$ | Y = $N_2$ |
| 14 | $R^1$ = OH | X = $CH_2$ | Y = $N_2$ |

only a low yield (20-30%) and the following two-step transformation gave a better one. Compound 4 was first subjected to a phase transfer reaction in which it was heated with HCOONa (3 equiv) in the presence of $H(OEt)_3$ (1 equiv) and catalytic amounts of n-$Bu_4N^+Br^-$ (0.1 equiv) in an EtOAc-$H_2O$ system at 50°C, from which 5 was obtained. Acid hydrolysis of 5 (HCl, EtOH-EtOAc) gave 6 in 49% overall yield from 4. Compound 6 was then converted into the diazo compound 7,[8] as a stable oil, in 70% yield by treatment with diazo transfer reagent ($TsN_3$, $Et_3N$) at room temperature. Our next task was to synthesize the five carbon side chain 14 in which the diazo and methylene groups were, respectively, at position 2 and 3 of 4-hydroxy acetoacetate 6. For this purpose, 6 was treated with $NaNO_2$ in aq. AcOH with ice-cooling and gave, in 70% yield, compound 8 (m.p. 117-118°C dec.), in which an oxime function was introduced at $C_2$ as a precursor of the future diazo group. Stepwise protection of the alcohol and oxime functions in compound 8 (  , p-TsOH·Pyr and then  SiCl, $Et_3N$-$CH_2Cl_2$) gave 9, which when subjected to the Wittig reaction with methylene triphenylphosphorane in the presence of hexamethyl phosphoramide[9] ($ph_3p^+CH_3Br^-$, n-BuLi, HMPA-$Et_2O$, 5-10°C), afforded the 3-methylene compound 10 in 65% yield. The t-butyldimethylsilyl-protecting group was selectively removed by fluoride ion ($Et_4N^+F^-$-THF, r.t.) to obtain 11 in 92% yield. Conversion of oxime 11 into the diazo compound 13, a crucial step in this synthesis, was achieved by treatment of 11 with O-mesitylenesulfonylhydroxylamine (MSH)[10] and n-BuLi in $CH_2Cl_2$ at -20°C, affording the diazo compound 13 in 60% yield. Mild deblocking of 13 by acid hydrolysis (p-TsOH·pry-$CH_3OH$, r.t.) gave the desired compound 14[11] in 50% yield. As 14 was sensitive to acid, the acid-stable oxime 12,[12] easily obtained from acid hydrolysis (HCl-$CH_3OH$, r.t.) of compound 10, was also used as one of the building blocks.

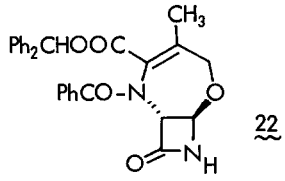
Intermolecular etherification between building blocks B (3) and C (7, 12, and 14) constituted a key step in this synthetic route. This was achieved by simply mixing 3 and 7 in EtOAc in the presence of catalytic amounts of $BF_3·Et_2O$ at room temperature. The reaction proceeded smoothly and in a completely stereospecific manner[13] to give ether 15[14] in 75% yield. Desilylation (aq. HCl-EtOH) followed by intramolecular carbene insertion reaction [catalytic $Rh_2(OAc)_4$-refluxing $C_6H_6$] converted 15 into 3'-nor-1-oxacephem 20[15,16] in 85% overall yield. The etherification between 3 and 14 was also carried out by the same method. This elaboration actually gave compound 18,[17] but in only low yield (34%) due to the instability[18] of 14 under acidic conditions. Therefore



15 $R^1$ = -Si(t-Bu)Me$_2$ X = O Y = $N_2$
16 $R^1$ = H X = O Y = $N_2$
17 $R^1$ = -Si(t-Bu)Me$_2$ X = $CH_2$ Y = N~OH
18 $R^1$ = -Si(t-Bu)Me$_2$ X = $CH_2$ Y = $N_2$
19 $R^1$ = H X = $CH_2$ Y = $N_2$



20 X = O
21 X = $CH_2$



22

the alternative two-step synthesis involving building blocks 3 and acid-stable 12 in place of 14 was used to obtain compound 18. Reaction of 3 and 12 under the same conditions (catalytic $BF_3 \cdot Et_2O$-EtOAc) gave the ether 17 in 75% yield, and its treatment with MSH and n-BuLi in EtOAc at -20°C afforded compound 18 in 55% yield. Deblocking of the t-butyldimethylsilyl group in 18 with $Et_4N^+F^-$ gave in 75% yield ether 19, which when subjected to ring closure reaction by refluxing its benzene solution in the presence of catalytic amounts of $Rh_2(OAc)_4$ gave the desired 1-oxacepham nucleus 21 in 53% yield, m.p. 155-156°C (from $Et_2O$), accompanied by a small amount of undesired compound 22.[19]

In conclusion, the present synthesis provides an alternative efficient synthetic route to the 1-oxacephem nucleus. With regard to the 3'-nor-1-oxacephem synthesis, the present method using building blocks, 3 and 7, appeared to be more advantageous than the previously developed one[15,20] because of the simplicity of the block 7 synthesis. Appropriate modifications at positions 3 and 7 in 20 and 21 should yield a variety of 7α-methoxy-1-oxacephem antibiotics including LMOX and 6315-S.[21]

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References and Notes

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8. 7: IR ($CHCl_3$) 1660, 1720, 2140 $cm^{-1}$; NMR ($CDCl_3$) δ 3.37 (t, 1H, J = 5.0 Hz, OH), 4.61 (d, 2H, J = 5.0 Hz, $CH_2OH$), 7.03 (S, 1H, $CHPh_2$), 7.2-7.5 (m, 10H, aromatic H).
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11. 14: Yellow oil; IR ($CHCl_3$) 1274, 1618, 1690, 2100, 3480 $cm^{-1}$; NMR ($CDCl_3$) δ 2.93 (br S, 1H, OH), 4.27 (br S, 2H, $CH_2OH$), 5.01 and 5.13 (each S, 1H, olefinic-H), 7.00 (S, 1H, $CHPh_2$), 7.2-7.4 (br S, 10H, aromatic-H).
12. 12: Mp 110-111°C; IR (Njujol) 995, 1237, 1584, 1612, 1624, 1715, 3170, 3230, 3400 $cm^{-1}$; NMR ($CDCl_3$) δ 2.98 (br S, 1H, OH), 4.29 (br S, 2H, $CH_2OH$), 5.03 and 5.48 (each S, 1H, olefinic-H), 7.10 (S, 1H, $CHPh_2$), ~7.3 (br S, 10H, aromatic-H), 9.38 (br S, 1H, =N-OH).
13. No undesired 3,4-cis isomer was isolated.
14. 15: IR ($CHCl_3$) 843, 1300, 1600, 1670, 1758, 2140, 3430 $cm^{-1}$; NMR ($CDCl_3$) δ 0.30 and 0.34 (each S, 6H, $Si(CH_3)_2$-), 0.97 (S, 9H, $Si(CH_3)_3$), 4.68 (d, 1H, J = 6.75 Hz, $C_7\beta$-H), 4.84 and 5.04 (ABq, 2H, J = 20 Hz, O-$CH_2$-), 5.08 (S, 1H, $C_6\alpha$-H), 6.69 (S, 1H, $CHPh_2$), 7.2-7.9 (m, 16H, aromatic-H and NH).
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16. After completion of our work (reported by W. Nagata in the Forth International Conference on Organic Synthesis, Tokyo Japan, 22-27 Aug., 1982) we noticed a similar carbene insertion reaction yielding a 3'-nor-1-oxacephem nucleus in patent literature (Meiji Seika Co., Ltd., Jpn. Kokai Tokkyo Koho JP 83 103,391).
17. 18: Foam; IR ($CHCl_3$) 1080, 1582, 1602, 1618, 1670, 1702, 1754, 2098, 3310-3430 $cm^{-1}$, NMR ($CDCl_3$) δ 0.15 and 0.23 (S, 6H, $Si(CH_3)_2$-), 0.93 (S, 9H, $Si(CH_3)_3$), 4.47 (S, 2H, $OCH_2$-), 4.64 (d, 1H, J = 6.5 Hz, $C_7\beta$-H), 4.87 (S, 1H, $C_6\alpha$-H), 5.21 and 5.57 (each S, 1H, olefinic-H), 6.99 (S, 1H, $CHPh_2$), 7.2-7.9 (m, 16H, aromatic-H and NH).
18. The instability maybe due to the free hydroxyl group on the same compound.
19. 22: Foam; IR ($CHCl_3$) 1080, 1584, 1604, 1672, 1727, 1784, 3330-3440 $cm^{-1}$; NMR ($CDCl_3$-$CD_3OD$) δ 1.57 (br S, 1H, NH), 1.97 (S, 3H, $CH_3$), 4.30 (br S, 2H, -$CH_2O$-), 4.95 (S, 1H, $C_6\alpha$-H), 5.27 (S, 1H, $C_7\beta$-H), 6.95 (S, 1H, $CHPh_2$), 7.7-7.9 (m, 15H, aromatic-H).
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