An Efficient Synthesis of Bicyclic β-Lactams through Palladium Catalysed Ene–Halogenocyclization

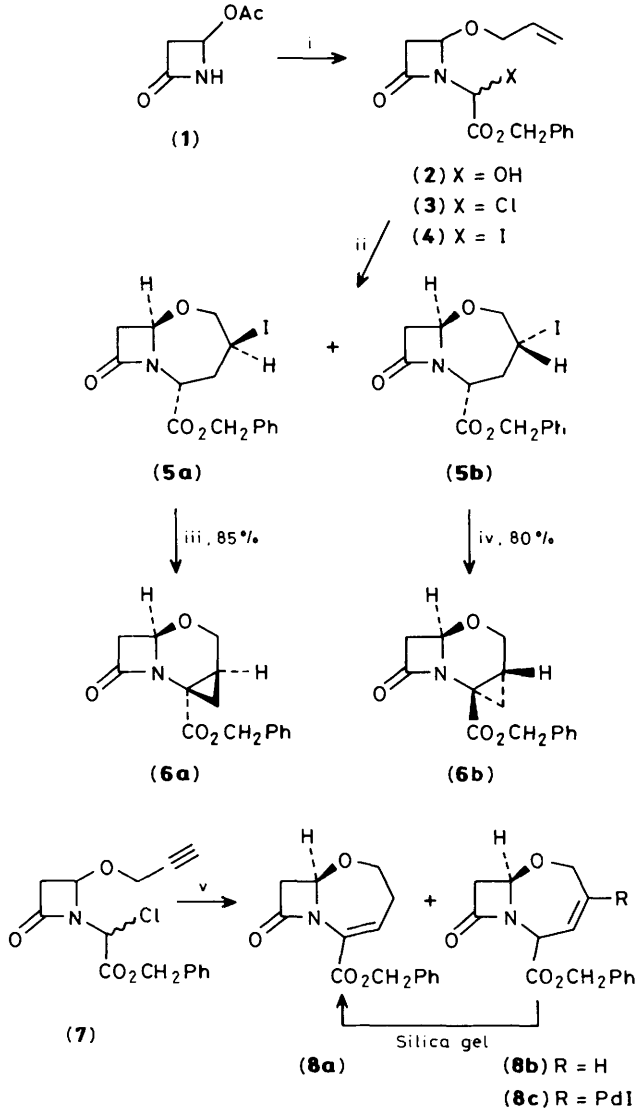
Miwako Mori,*[a] Nana Kanda,[a] and Yoshio Ban[b]

[a] *Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan*
[b] *School of Pharmaceutical Science, Toho University, Miyama 2-2-1, Funabashi 274, Japan*

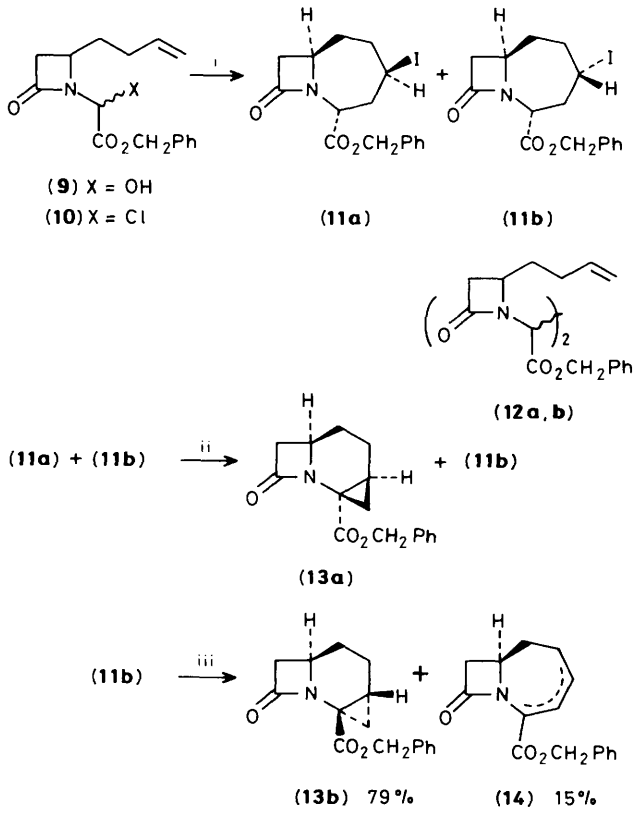
A new synthesis of oxa- and carba-cepham skeletons was developed by use of palladium catalysed ene–halogenocyclization followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

For the synthesis of new β-lactam derivatives of more efficacious antibiotic activity, various methods have been reported for the construction of bicyclic β-lactam rings from azetidin-2-one.[1] We report here a novel simple method for the synthesis of oxa- and carba-homocepham skeletons by use of palladium catalysed ene–halogenocyclization.[2]

For the preparation of bicyclic β-lactams, the required compound (**3**) was prepared from 4-acetoxyazetidin-2-one (**1**) by the known method.[3] Though short column chromatography on silica gel afforded the pure chloride (**3**) in high yield (85%), the purification of the iodide (**4**) was difficult owing to its instability. Thus, compound (**3**) was treated with $Pd(PPh_3)_4$ (10 mol %) in the presence of KI (1.1 equiv.) and 'proton sponge' (1.1 equiv.) in hexamethylphosphoric triamide (HMPA) at 65 °C for 15 min to afford the oxahomocephams (**5a**) and (**5b**) (1:1.2) in 35% yield. The unexpected[2b] formation of the seven-membered ring was considered to be due to the effect of the strain of the azetidinone ring on the transition structure. The structural and stereochemical assignments of the two isomers were based mainly on analysis of coupling constants and chemical shifts[1b] from ^1H n.m.r. and two dimensional COSY measurements for each isomer.† Compound (**5a**) was treated with 1,8-diaza-



Scheme 1. *Reagents:* i, CH_2=$CHCH_2OH$, then $PhCH_2O_2CCHO$; ii, $Pd(PPh_3)_4$, HMPA, KI; iii, DBU, 15 min; iv, DBU, 48 h; v, $Pd(PPh_3)_4$, Bu^n_4NI, dioxane.



Scheme 2. *Reagents:* i, $Pd(PPh_3)_4$, dioxane, 90 °C, Pr^i_2NEt, Bu^n_4NI; ii, DBU, 5 min; iii, DBU, 24 h.

† Comparison of ^1H n.m.r. chemical shifts and coupling constants for oxahomocephams reported by Bachi[1b] with those for (**5a**) and (**5b**) indicates that the CO_2CH_2Ph groups are *cis* with respect to the bridgehead hydrogen atom. The orientation of the iodo group of compounds (**5a**) and (**5b**) was determined from coupling constant values.

bicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature to afford the cyclopropaoxacepham (**6a**) in 85% yield, and (**6b**) was obtained similarly from (**5b**) in 80% yield, but at a much slower rate.

Compound (**7**) was treated with $Pd(PPh_3)_4$ in the presence of Bu^n_4NI and di-isopropylethylamine as base in dioxane at 75 °C for 15 min to give the oxahomocephems (**8a**) and (**8b**) in 25% yield.‡ Compound (**8b**) was treated with silica gel in $CHCl_3$ at room temperature for several hours to convert it into (**8a**).

This palladium catalysed ene–halogenocyclization was further successfully extended to the formation of the carbacepham ring system. When compound (**10**) was treated with $Pd(PPh_3)_4$ in a similar manner in dioxane (0.15 M solution), the desired compound could not be obtained and a diastereoisomeric mixture of the dimers (**12a**) and (**12b**) (29 and 17% yield, respectively) was obtained along with (**9**) (4% yield). A 0.05 M solution of the substrate (**10**) in dioxane gave a mixture of the desired carbahomocephams (**11a**) and (**11b**) in 34% yield. When the mixture of (**11a**) and (**11b**) was treated with DBU in benzene at room temperature for 5 min, the carbacepham (**13a**) was obtained in 55% yield along with the starting carbahomocepham (**11b**) (45%). The remaining carbahomocepham (**11b**) was treated again with DBU for 24 h to give the carbacepham (**13b**) in 79% yield accompanied by compound (**14**) (15%; position of double bond uncertain). ^1H N.m.r. and 2D-COSY spectra, together with the behaviour towards DBU, demonstrate that the iodo group of (**11a**) should be β-oriented and that of (**11b**) α-oriented.

The present approaches demonstrate a possible pathway to various types of oxa- and carba-cephams.

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‡ The iodo compounds (**5a**) and (**5b**) are considered to be reductive elimination products formed from σ-alkylmetal complexes.[2] Compounds (**8a**) and (**8b**) would be obtained from the vinylpalladium complex (**8c**) with a small amount of water in the reaction mixture.

References

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