Tetrahedron Letters,Vol.27,No.50,pp 6091-6094,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

PRACTICABLE SYNTHESIS OF (1R,4R)-5-(ℓ-MENTHOXY)-2-AZABICYCLO[2.2.0]-HEX-5-EN-3-ONE AND ITS DERIVATIVES: NEW BUILDING BLOCKS FOR CARBAPENEM NUCLEI[1]

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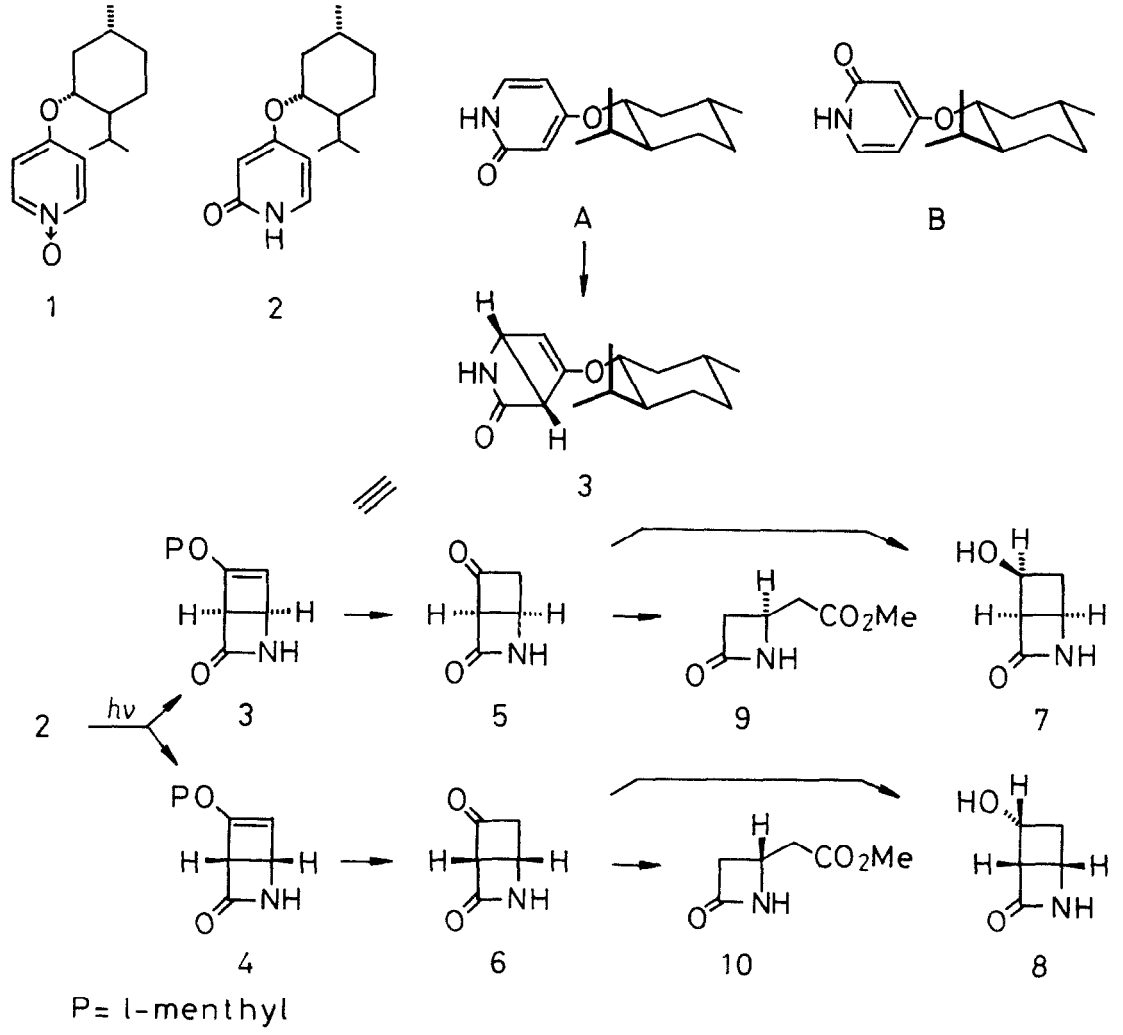
Abstract: Enantioselective synthesis of (1R,4R)-2-azabicyclo[2.2.0]-hexane-3,5-dione and (1R,4R,5S)-5-hydroxy-2-azabicyclo[2.2.0]hexan-3-one (new building blocks for carbapenems) from 4-(ℓ-menthoxy)-pyridin-2(1H)-one via photopyridone formation is reported.

The enormous commercial potential of thienamycin and other potent carbapenem antibiotics coupled with the challenging structural features has resulted in intense and varied synthetic effort.[2] Previously, we reported the synthesis of 2-azabicyclo[2.2.0]hexane-3,5-dione[3] and its 5-hydroxy derivative[4] (both crystalline compounds) via the photopyridone (2-azabicyclo[2.2.0]hex-5-en-3-one) obtained in almost quantitative yield from 4-alkoxypyridin-2(1H)-one by irradiation at ≥ 300 nm.[5] Furthermore, reactions of these two bicycles with a variety of reagents have demonstrated that the former serves as a chemical equivalent of azetidin-2-ones having an acetic acid or acylmethyl side-chain at the 4-position and the latter as 4-(2-oxoethyl)azetidin-2-one (an extremely unstable compound). While the synthesis of carbapenem nuclei using these two crystalline bicycles as intermediates has many advantageous features (short-step from pyridine, simplicity of the experimental procedure, high overall yield, and regio- and stereo-selective introduction of substituent),[3,6] a serious drawback is that it produces racemic products.

In this paper, we wish to report the photocyclization of 4-(ℓ-menthoxy)-pyridin-2(1H)-one 2 which can be synthesized from pyridine in four-step and successful separation of the photopyridone into chiral diastereomers 3 and 4 by fractional crystallization. Both diastereomers 3 and 4 are then converted to chiral 2-azabicyclo[2.2.0]hexane-3,5-diones 5 and 6 and their 5-hydroxy derivatives (7 and 8). Noteworthy features in the above synthetic method are asymmetric induction in the photocyclization step of the 2-pyridone and different solubility of diastereomers of the photopyridone, both of which make the method especially fit for practicable preparation of chiral bicycles 5 and 7 having desired absolute configurations.[7]

4-Nitropyridine-1-oxide was added to a solution of sodium ℓ-menthoxide in HMPA (prepared from ℓ-menthol and NaH in HMPA at 85 °C, 1 h) and the whole was kept standing overnight at room temperature. 4-(ℓ-Menthoxy)pyridine-1-oxide [1: mp 60-65 °C (hygroscopic), yield; 78%, $[\alpha]_D^{27}$ -118.6° (c=1.30, $CHCl_3$), picrate, mp 125-126 °C] thus obtained was treated with acetic anhydride (reflux, 1.5 h) to give the 2-pyridone [2: mp 220-222 °C, $[\alpha]_D^{28}$ -161.6° (c=1.24, $CHCl_3$)] in 63% yield. By irradiation at ≥300 nm in acetonitrile,[8] the photopyridone was obtained in almost quantitative yield as a mixture of diastereomers 3 and 4 in ca. 7:5 ratio.[9] The asymmetric induction is probably due to an unequal proportion of the rotamers (A and B), among which A (preferable to the formation of 3)[10] predominates over B. Recrystallization of



the mixture from pentane afforded the less soluble isomer [the major diastereomer: 3, mp 137-138 °C, $[\alpha]_D^{27}$ +75.5° (c=1.38, $CHCl_3$)] in a pure form in 45% yield. After repeated recrystallization of the mother liquor fraction, the more soluble isomer [the minor diastereomer: 4, mp 90-91 °C, $[\alpha]_D^{28}$ -200.6° (c=1.32, $CHCl_3$)] was obtained in 30% yield.

Deblocking of the menthoxy group from each diastereomer under acidic conditions (TsOH-aqueous THF, room temperature, 10 min) proceeded smoothly and in satisfactory yield (ca. 80%) to give chiral 2-azabicyclo[2.2.0]hexane-3,5-diones [5: mp 95-96 °C, $[\alpha]_D^{27}$ -340.9° (c=1.17, $CHCl_3$) and 6: mp 94-96 °C, $[\alpha]_D^{26}$ +338.5° (c=1.05, $CHCl_3$)], respectively.[11] Optical purity of each enantiomer was assured by their almost quantitative conversion in methanol (reflux, 2 h) to the corresponding (S)-[12] and (R)-4-(methoxycarbonylmethyl)-azetidin-2-ones [9: mp 70-71 °C, $[\alpha]_D^{29}$ +65.3° (c=1.11, $CHCl_3$) and 10: mp 69-71 °C, $[\alpha]_D^{27}$ -63.8° (c=1.28, $CHCl_3$)]. Reduction of 5 with sodium borocyanohydride in THF containing acetic acid (room temperature, 1 h) afforded (1R,4R,5S)-5-hydroxy-2-azabicyclo[2.2.0]hexan-3-one [7: mp 160-162 °C, $[\alpha]_D^{27}$ +113.1° (c=1.32, MeOH)] in 44% yield. Its enantiomer [8: mp 159-162 °C, $[\alpha]_D^{27}$ -112.0° (c=1.05, MeOH)] was obtained from 6 in the same manner.

In conclusion, we have achieved enantioselective synthesis of (1R,4R)-2-azabicyclo[2.2.0]hexane-3,5-dione (5) and (1R,4R,5S)-5-hydroxy-2-azabicyclo-[2.2.0]hexan-3-one (7) from pyridine and *l*-menthol by short-step, all of which can be carried out in a multigram scale. Since we have already demonstrated in racemic series that these bicycles (5 and 7) serve as chemical equivalents of azetidin-2-ones having an acetic acid, acylmethyl, or oxoethyl side-chain at the 4-position, it is obvious that they can serve as new building blocks for chiral carbapenem nuclei.

Acknowledgement —— This work was supported in part by a Grant-in-Aid for Special Research on Photochemical Process (61123005) from the Ministry of Education, Science and Culture, Japan. The authors thank Mr. Toshiyuki Sakamoto for his assistance in part of experiments.

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7. Previously, we reported that irradiation of 2',3',5'-tri-O-benzoyl-4-O-tert-butyldimethylsilyl-3-deazauridine gave the corresponding photopyridone as a mixture of diastereomers, which were separable by column chromatography. In this case, however, asymmetric induction was not observed. N. Katagiri, T. Haneda, and C. Kaneko, Nucleic Acids Research, Symposium Series, No. 16, 113 (1985).
8. Irradiation was performed by 400 W high-pressure mercury lamp with Pyrex filter.
9. The ratio of 3 and 4 was determined by HPLC analysis on μ-Porasil [hexane-THF, 5:1 (v/v)].
10. Since a rear face of the pyridone ring in A (or B) is less crowded, favorable twisting of the 2-pyridone ring of A in the photopyridone formation step should result in a predominant formation of 3, whose newly formed azetidinone ring occupies the reverse side of the isopropyl group.
11. Recovered ℓ-menthol retained its configuration as evidenced by the specific rotation value $[[\alpha]_D^{27}$ -47.5° (c=4.50, EtOH)].
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(Received in Japan 21 August 1986)