

THE TANDEM BECKMANN AND HUISGEN-WHITE REARRANGEMENT AS
AN ALTERNATIVE TO THE BAEYER-VILLIGER OXIDATION OF THE
9-AZABICYCLO[3.3.1]NONAN-3-ONE SYSTEM: A FACILE ROUTE TO
(±)-DIHYDROPALUSTRAMIC ACID

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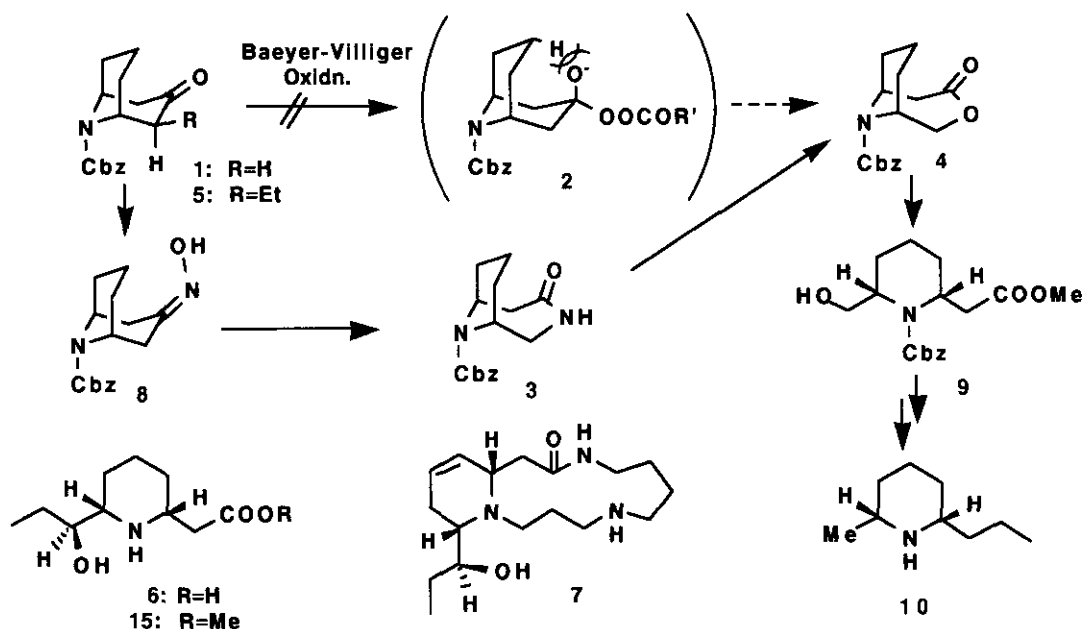
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Abstract - The transformation of the "fork head ketone" (1) into the corresponding bicyclic lactone (4) via the Beckmann followed by the Huisgen-White Rearrangement is described. An α -ethyl-substituted bicyclic ketone (5) was converted efficiently to dihydropalustramic acid (6), a degradation product from the alkaloid palustrine.

Although there are continuing interests in application of the Baeyer-Villiger oxidation to the stereo- and regio-specific synthesis of specifically substituted molecules, they have been investigated of its mechanistic aspects, especially on the migratory aptitude as well as its scope and limitations.² In the course of our exploratory study on applicability of the bicyclo[3.3.1]nonanone system (1) to natural product synthesis,³ we previously examined the Baeyer-Villiger oxidation of 1 and found an anomalous inactivity of the system.⁴ Thus, we have examined, as an alternative, the Huisgen-White rearrangement⁵ of the lactam, 3,10-diazabicyclo[4.3.1]decan-4-one (3), derived readily from 1 and found the sequence to lead to the desired lactone, 10-aza-3-oxabicyclo[4.3.1]decan-4-one

(4), in good yield. Application of the reaction to 2 α -ethyl-9-azabicyclo[3.3.1]nonan-3-one (5) provided a stereoselective route to ($\pm$)-dihydropalustramic acid (6).⁶

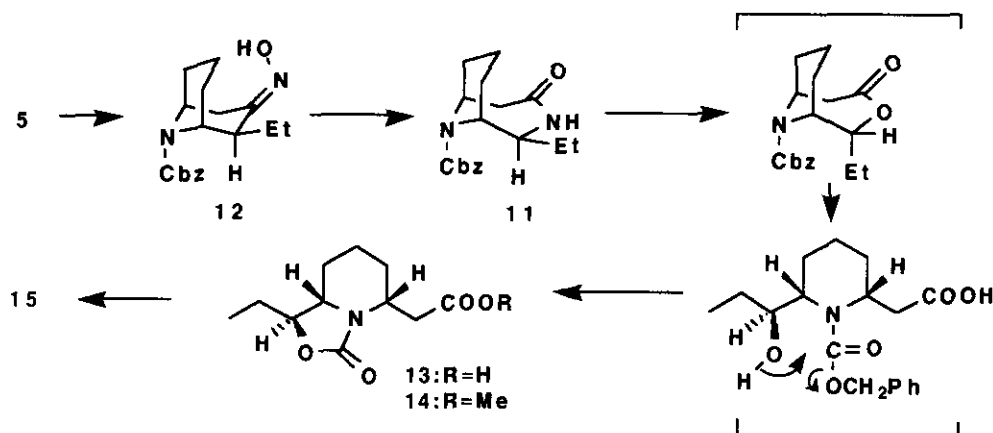
The acid (6) is a degradation product from palustrine (7),⁷ the main alkaloid of *Equisetum palustre* L., and claimed to be a key intermediate for the synthesis of dihydropalustrine.^{6,8} Because of the characteristic stereochemistry of the side chain (*threo-cis*) on the piperidine ring in 6 or 7, several approaches have been reported.⁶⁻⁹ Among them, we have been concerned with a design involving a stereoselective cleavage of a nitrogen-bridged bicyclic system.¹⁰



The ketone (1) was converted to the bicyclic lactam (3) via the Beckmann rearrangement of the corresponding oxime (8) in 92% overall yield from 1. The treatment of 3 with nitrogen peroxide gave the desired rearrangement product (4)¹¹ in 85% yield. Methanolysis of 4 afforded the α,α' -*cis*-substituted piperidine derivative (9), in 75% yield, spectral properties of which were satisfactorily in correlation with those of a methyl carbamate analog of 9.¹² Conversion of the methyl carbamate into dihydropinidine (10) has already been established.¹²

As 9 was obtained effectively, the sequence was applied to an α -ethyl analog (5).¹³ The ketone (5) was converted to the corresponding lactam (11) via the oxime (12) in the same manner as for the preparation of 3 in 85% overall yield from 5. Nitrosation of 11 with nitrogen peroxide and subsequent thermal elimination of nitrogen¹⁴ from the resulting nitroso lactam gave directly an

oxazolidinone (13), which was converted by Fischer's esterification into its methyl ester (14) in 40% yield from 11. The physical and spectral properties of 14 were in accordance with those reported.⁸ Hydrolysis of 14 with 47% aqueous HBr followed by Fischer's esterification furnished dihydropalustramic acid methyl ester (15)⁶ in 60% yield.



Recently we described the conversion of 1 into the *cis*-2,6-disubstituted piperidine system via asymmetric deprotonation and subsequent ozonolysis.¹² The present approach is another entry to the α -cleavage of the "fork head ketone" into the difunctionalized piperidine system.

REFERENCES AND NOTES

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4. A mechanism of the steric interference with formation of the tetrahedral intermediate (2) has been proposed: a) T. Momose, S. Atarashi, and O. Muraoka, *Tetrahedron Lett.*, 1974, 3697; b) T. Momose, O. Muraoka, S. Atarashi, and T. Horita., *Chem. Pharm. Bull.*, 1979, 27, 222.

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7. Palustrine was first isolated and identified by Eugster, *et al.*⁶ Later, the structure was revised by Natsume, *et al.*, (M. Natsume, M. Ogawa, I. Yoda, and M. Shiro, *Chem. Pharm. Bull.*, 1984, **32**, 812; M. Natsume and M. Ogawa, *ibid.*, 1984, **32**, 3789).
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9. a) T. Hamada, H. Sato, M. Hikota, and O. Yonemitsu, *Tetrahedron Lett.*, 1989, **30**, 6405; b) *Idem*, 18th Congress of Heterocyclic Chemistry, Fukuoka, Japan, 1986, Abstracts of Papers, p. 129.
10. T. Momose, S. Atarashi, and C. H. Eugster, *Heterocycles*, 1979, **12**, 41.
11. Satisfactory physical and spectral data were obtained for all new compounds: for example, for **4**: bp 134-136°C (0.02 mmHg); ir (CHCl₃) $\nu_{\max}$ 1735, 1691 cm⁻¹; ¹H-nmr (CDCl₃) δ 1.58-1.66 (2H, m), 1.76-1.91 (3H, m), 1.96-2.08 (1H, m), 2.77-2.88 (2H, m), 4.30-4.44 (2H, m), 4.51 and 4.62 (1H, each br m), 4.57 and 4.66 (1H, each br m), 5.16 (2H, s), 7.31-7.40 (5H, m). For **5**: bp 132-134°C (0.006 mmHg); ir (CHCl₃) $\nu_{\max}$ 1705, 1689 cm⁻¹; ¹H-nmr (CDCl₃) δ 0.94 and 0.98 (3H, each t, *J*=7.5 Hz), 1.14 and 1.21 (1H, each dqd, *J*=15.0, 7.5, 7.5 Hz), 1.37 (1H, dddd, *J*=14.5, 14.5, 14.5, 4.5, 4.5 Hz), 1.48-1.85 (5H, m), 2.01 (1H, dqd, *J*=15.0, 7.5, 7.5 Hz), 2.23-2.29 and ca. 2.33-2.39 (1H, each m), 2.33 and 2.35 (1H, each d, *J*=15.5 Hz), 2.60 and 2.67 (1H, each dd, *J*=15.5, 7.0 Hz), 4.60 and 4.68 (1H, each br t-like), 4.72, and 4.78 (1H, each br t-like), 5.17-5.24 (2H, m), 7.30-7.40 (5H, m). For **11**: mp 119-120°C (colorless prisms from benzene-ether); ir (CHCl₃) $\nu_{\max}$ 3397, 1690, 1666 cm⁻¹; ¹H-nmr (CDCl₃) δ 0.93 and 1.05 (3H, each t, *J*=7.5 Hz), 1.46-1.94 (7H, m), 2.01-2.14 (1H, m), 2.50-2.58 (1H, m), 2.78 and 2.84 (1H, each dd, *J*=15.0, 3.0

Hz), 3.48 and 3.56 (1H, each br m), 4.21 and 4.32 (1H, each br d, $J=6.8$ Hz), 4.48 and 4.54 (1H, each br m), 5.10-5.25 (2H, m), 5.58 (1H, br, exchangeable with D_2O), 7.31-7.40 (5H, m).

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13. The α -ethylated ketone (**5**) was synthesized as follows. The Claisen condensation of **1** with methyl carbonate in the presence of sodium hydride in dimethoxyethane and subsequent α -alkylation of the resulting β -keto ester with ethyl iodide afforded methyl *N*-carbobenzyloxy-2 β -ethyl-9-azabicyclo[3.3.1]nonan-3-one-2 α -carboxylate, which was subjected to the ketonic cleavage by action of a 3% solution of potassium hydroxide in dimethylsulfoxide-water to give **5** in 39% yield along with β -epimer (49%). The stereochemistry of **5** was determined by X-ray crystallographic analysis. Physical and spectral data of **5** are described in ref. 11.

14. The mechanism of the Huisgen-White rearrangement involving the retention or inversion of the stereochemistry has been described.^{5b}

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