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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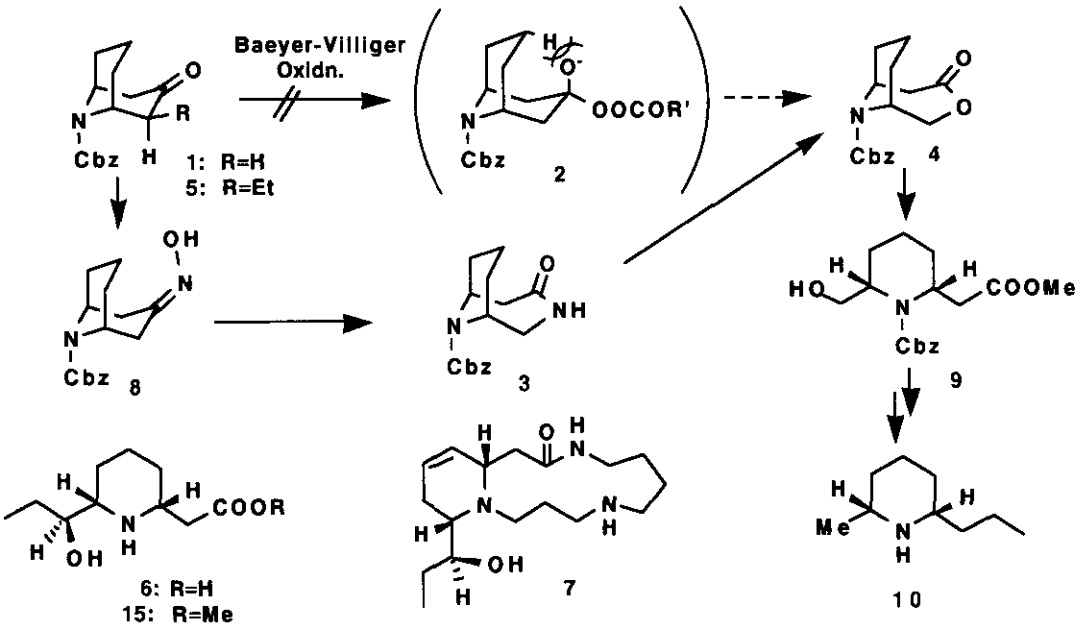
Abstract - The transformation of the "fork head ketone" (**1**) into the corresponding bicyclic lactone (**4**) *via* the Beckmann followed by the Huisgen-White Rearrangement is described. An α-ethyl-substituted bicyclic ketone (**5**) was converted efficiently to dihydropalustramic acid (**6**), a degradation 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 rearrangement[5] 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 2α-ethyl-9-azabicyclo[3.3.1]nonan-3-one (**5**) provided a stereoselective route to (±)-dihydropalustramic acid (**6**).[6]

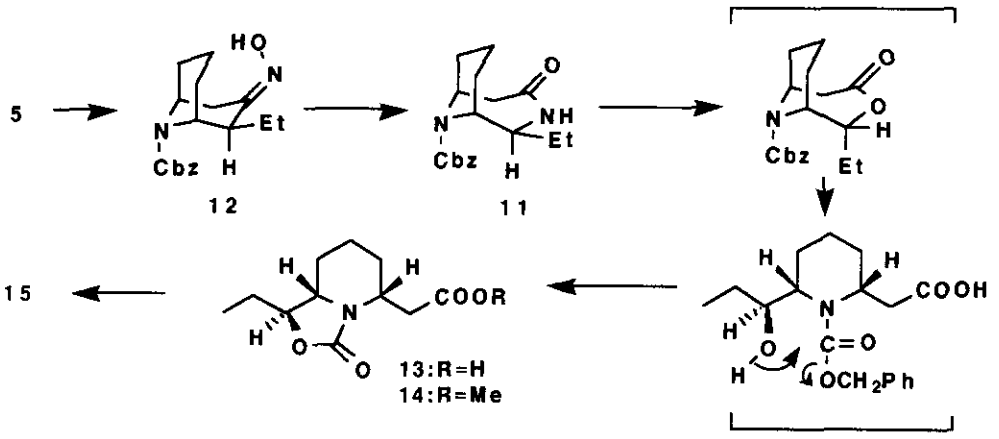
The acid (**6**) is a degradation product from palustrine (**7**),[7] the main alkaloid of *Equisetum palustre* L., and claimed to be a key intermediate for the synthesis of dihydropalustrine.[6,8] Because of the characteristic stereochemistry of the side chain (*threo-cis*) on the piperidine ring in **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 nitrogen[14] 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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3. The 2,6-disubstituted piperidine moiety consitutes a large family of naturally occurring alkaloids, see for example: a) G. M. Strunz and J. A. Findlay, 'The Alkaliods,' Vol. 26, ed. by A. Brossi, Academic Press, Inc., New York, 1985, p. 89; b) G. Massiot and C. Delaude, *ibid.*, Vol. 27, 1986, p. 269; c) A. Numata and T. Ibuka, *ibid.*, Vol. 31, 1987, p. 193.
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 ($CHCl_3$) ν_{max} 1735, 1691 cm^{-1}; ^{1}H-nmr ($CDCl_3$) 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 ($CHCl_3$) ν_{max} 1705, 1689 cm^{-1}; ^{1}H-nmr ($CDCl_3$) 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, ddddd, *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 ($CHCl_3$) ν_{max} 3397, 1690, 1666 cm^{-1}; ^{1}H-nmr ($CDCl_3$) 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).

12. T. Momose, N. Toyooka, and Y. Hirai, *Chem. Lett.*, **1990**, 1319.
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-2β-ethyl-9-azabicyclo[3.3.1]nonan-3-one-2α-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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