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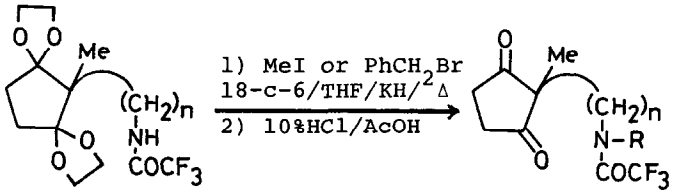
AN EFFICIENT SYNTHESIS OF MEDIUM-SIZED KETOLACTAMS THROUGH CONTROLLED *CRISSCROSS ANNULATION*: A SYNTHESIS OF (±)-DIHYDRODESOXYOTONECINE

Takeshi Ohnuma, Masaharu Nagasaki, Masayasu Tabe, and Yoshio Ban*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract: Controlled *crisscross annulation* was applied to the synthesis of (±)-dihydrodesoxyotonecine, a degradation product of secopyrrolizidine alkaloids.

In the preceding paper[1] has been described a new type of annulation reaction, the *crisscross annulation*, affording pyrrolizidines and indolizidines, which were readily utilized in alkaloid synthesis. This versatile *annulation* can be also controlled by using the protected secondary amine to capture the strained medium-sized ketolactams.[2] Generally, the known synthetic methods for these heterocycles are associated with difficulties: in operation by high dilution, low overall yields, and a lack of the regiospecificity at the cyclization stage. We here report the efficient synthesis of eight- and nine-membered ketolactams through the controlled *crisscross annulation*.

The diketones(3, 4, 5) for the *annulation* were readily prepared from the amides 1 and 2[1] by N-alkylation[3] with methyl iodide or benzyl bromide followed by acidic hydrolysis, respectively.



3: n=2, R=Me, 88%

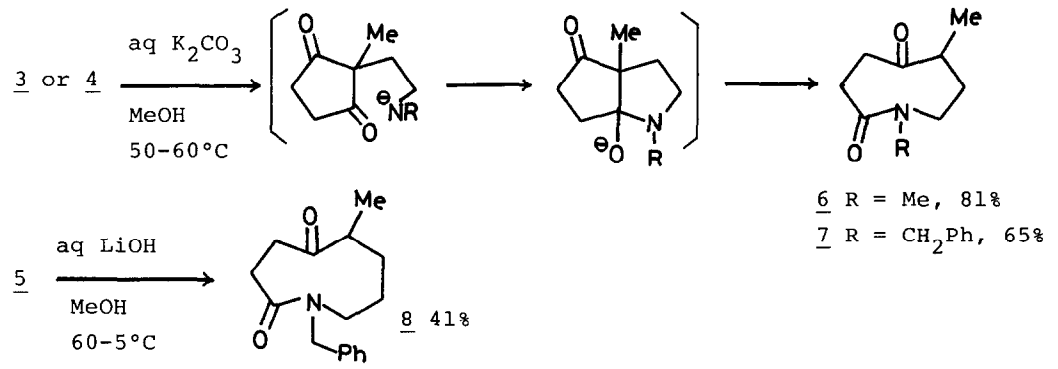
4: n=2, R=CH_2Ph, 89%

5: n=3, R=CH_2Ph, 51%

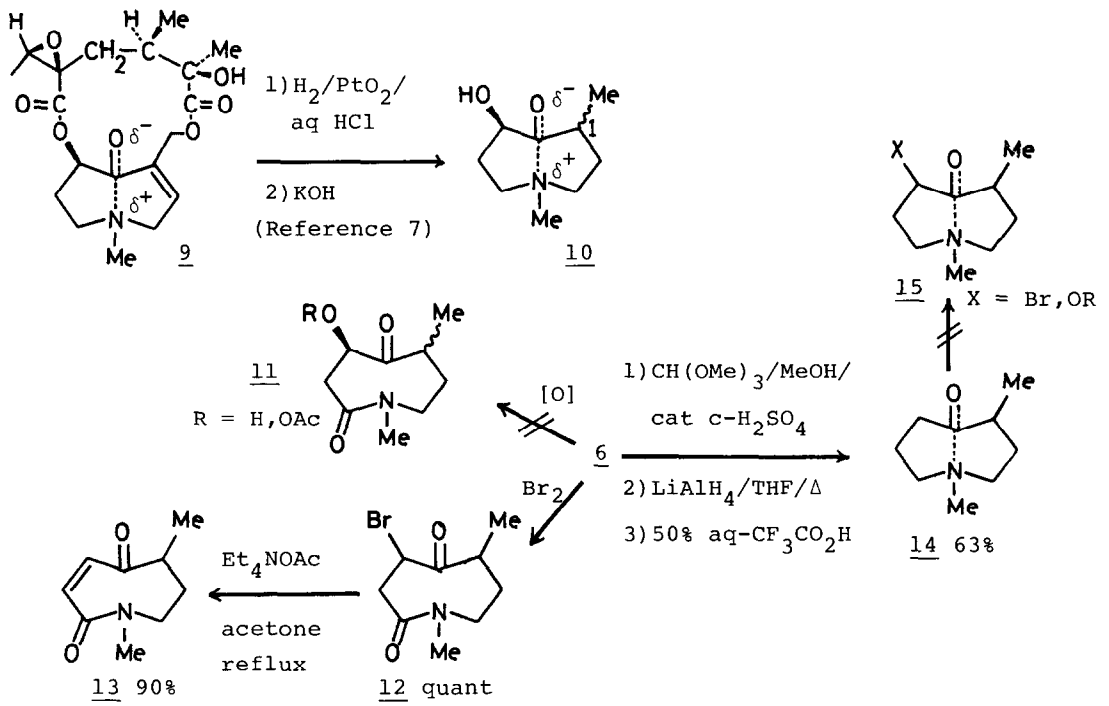
1: n=2

2: n=3

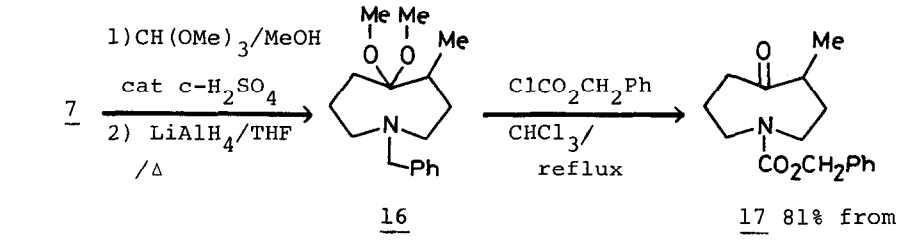
The *annulation* of 3 and 4 with potassium carbonate[5 equiv, 7% conc in MeOH-H_2O(5:2), 55-60°C for 20 min] smoothly produced the azacyclooctanones 6[4] and 7[5] in good yields. Similarly, the *annulation* of 5 with aqueous lithium hydroxide afforded the azacyclononanone 8.[6] Apparently, the present eight-membered ring-system should be useful in synthetic approaches to dihydrodesoxyotonecine(10) often obtained by degradation of the secopyrrolizidine alkaloids, e.g. fukinotoxin 9 and so on.[7]

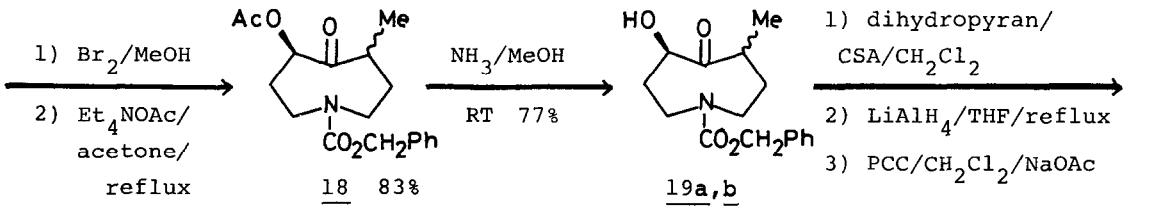


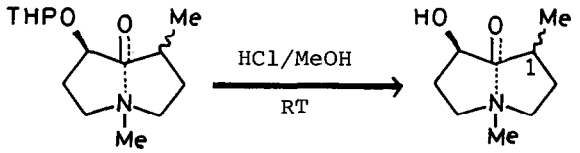
We had as our objective the first synthesis of 10 and the determination of the stereochemistry of the methyl group at C-1 position.[7] We initially used the N-methyl compound 6 as a starting azacyclooctanone; however, we failed to convert it to 11 by introducing the hydroxy or acetoxy groups to the α-carbon of carbonyl group using the various oxidizing agents.[8] These attempts did not succeed because 6 under strong basic or acidic conditions gave immediately the undefined ring-opened products. Moreover, the brominated ketone 12 afforded only the unsaturated ketone 13 during an attempt to introduce the acetoxy group. On the other hand, the bromination or oxidation of the aminoketone 14 prepared from 6 could not give the compound 15 because the usual ketonic properties were absent due to the transannular effect(14, $\nu_{max}^{CHCl_3}$ 1670 cm^{-1}).



In the case of 7, the aminoketal 16 could be readily led to the N-carbobenzoxy derivative 17 in a good overall yield,[9] which kept the usual ketonic property($\nu_{max}^{CHCl_3}$ 1700 cm^{-1}) without involving a strong transannular effect. Acetoxylation of 17 via brominated intermediate afforded a mixture of the inseparable diastereomers 18. Deacetylation of 18 with NH_3 in MeOH produced the unstable alcohol 19a(higher R_f value on silica gel TLC) and 19b(lower one) in a 1:1 ratio after silica gel chromatography. Reduction of the tetrahydropyranyl ether derived from 19a gave the aminoalcohol, which was oxidized with PCC to furnish the ketoamine 20a. Removal of the tetrahydropyranyl group of 20a led to the water-soluble and unstable (±)-10a,[10] showing a carbonyl peak at 1610 cm^{-1}($CHCl_3$) due to a strong transannular effect. Similarly, the isomer 19b was converted to 10b,[10] which was apparently different from 10a. The spectral data(^1H NMR, IR, Mass) of the former isomer 10a were identical with those of the product from natural sources by degradation. Further, the study on the determination of the configuration at C-1 in 10a is now in progress.







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References and Notes:

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2. The related ring-enlargement methods for constructing the medium- or macro-sized lactones and polyazalactams were reported as follows. Formation of lactones: (a)J. R. Mahajan, Synthesis, 110(1976). (b)J. R. Mahajan, J. S. Resck, Ibid., 998(1980). (c)P. W. Scott, I. T. Harrison, S. Bittner, J. Org. Chem., 46, 1914(1981). (d)V. Bhat, R. C. Cookson, J. C. S. Chem. Comm., 1123(1981). (e)K. Kostova, A. Lorenzi-Riatsch, Y. Nakashita, M. Hesse, Helv. Chim. Acta, 65 , 249(1982). (f)E. Vedejs, D. W. Powell, J. Am. Chem. Soc., 104, 2046(1982). Formation of polyazalactams: (g)U. Kramer, A. Guggisberg, M. Hesse, H. Schmid, Ang. Chem. Int. Ed. Engl., 17,200(1978) (h)U. Kramer, A. Giggisberg, M. Hesse, Helv. Chim. Acta, 62, 2317(1979).
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4. Compound 6(mp 79-80°C): ^{1}H NMR($CDCl_3$) δ 1.08(d, J = 7 Hz, 3H), 1.5-1.9(m, 2H), 2.5-2.9(m, 5H), 2.95(s, 3H), 3.41(dd, J = 4.5, 7 Hz, 2H); IR(Nujol) 1705, 1630 cm^{-1}; Mass m/e 169(M^+), 114(base peak).
5. Compound 7(mp 107-8°C): ^{1}H NMR($CDCl_3$) δ 1.02(d, J = 7 Hz, 3H), 1.59(m, 2H), 2.76(m, 5H), 3.30(broad t, J = 6 Hz, 2H), 4.55(q, J = 14, 22 Hz, 2H), 7.22 (s, 5H); IR(Nujol) 1697, 1630 cm^{-1}; Mass m/e 245(M^+), 91(base peak).
6. Compound 8(mp 146-7°C): ^{1}H NMR δ 1.10(d, J = 7 Hz, 3H), 1.4-2.0(m, 4H), 2.4-3.0(m, 5H), 3.08(t, J = 6Hz, 2H), 4.53(broad s, 2H), 7.0-7.4(m, 5H); IR(Nujol) 1690, 1630 cm^{-1}; Mass m/e 259(M^+), 91(base peak).
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8. We attempted the following conditions: O_2/LDA, $PhI(OAc)_2$/KOH, $Tl(ONO_2)_3$, $Pb(OAc)_4$/AcOH.
9. (a)J. D. Hobson, J. G. McClusky, J. Chem. Soc.(C), 2015(1967). (b)K. C. Rice, J. Org. Chem., 40, 1850(1975).
10. Compound 10a(oil): ^{1}H NMR($CDCl_3$) δ 1.07(d, J = 6 Hz, 3H), 2.04(s, 3H), 1.8-2.3(m, 4H), 2.3-2.7(m, 4H), 3.34(broad, 1H), 3.78(m, 1H); IR($CHCl_3$) 3400, 1620 cm^{-1}; Mass m/e 171(M^+). Compound 10b(oil): ^{1}H NMR($CDCl_3$)δ 1.14(d, J = 7 Hz, 3H), 2.19(s, 3H), 1.8-2.8(m, 9H), 3.26(broad, 1H), 4.06(t, J = 4 Hz, 1H); IR($CHCl_3$) 3370, 1600 cm^{-1}; Mass m/e 171(M^+).

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