CHEMISTRY LETTERS, pp. 919-922, 1987.

A New Method of Formation of 9-Azabicyclo[4.2.1]nonane Skeleton and Its Application to Synthesis of (±)-Anatoxin a[1)]

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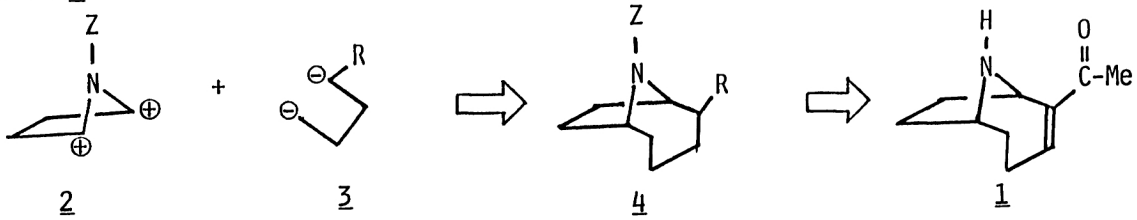
9-Azabicyclo[4.2.1]nonane skeleton was formed in one step by Lewis acid promoted reaction between 1-methoxycarbonyl-2,5-dimethoxypyrrolidine and 1-ethoxy-1-trimethylsiloxy-1,4-pentadiene, and it was converted to (±)-anatoxin a.

Anatoxin a (1), a potent postsynaptic depolarizing neuromuscular toxin produced by certain strains of *Anabaena flos-aquae*,[2)] has been an interesting target for organic synthesis, since it has significant biological activities and also it is the only naturally occuring alkaloid containing a 9-azabicyclo[4.2.1]-nonane (9-ABN) skeleton. Although some successful methods for the synthesis of racemic[3)] and optically active[4)] 1 have been reported in recent years, all of them require multiple steps for the formation of 9-ABN skeleton. We wish to report herein a new method of formation of the 9-ABN skeleton and its application to synthesis of (±)-1. Scheme 1 shows our strategy of synthesis of (±)-1, in which the annelation reaction between a dication 2 and a dianion 3 forms the 9-ABN skeleton 4.



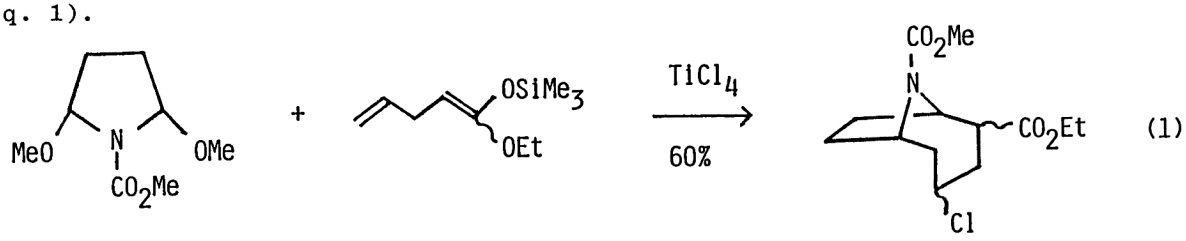
2 3 4 1

Z = protecting group

Scheme 1.

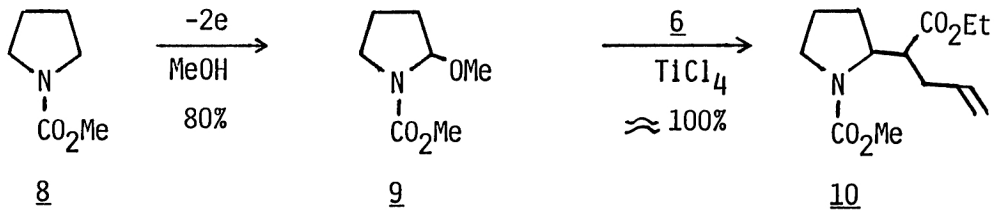
We have expected that 1-methoxycarbonyl-2,5-dimethoxypyrrolidine (5) would be

an appropriate precursor of 2, since we have already found that treatment of 5 with $TiCl_4$ forms an active species equivalent to 2 and it can be trapped with allyltrimethylsilane to form an 8-azabicyclo[3.2.1]octane skeleton.[5] It has also been presumed that 1-ethoxy-1-trimethylsiloxy-1,4-pentadiene (6)[6] could play as an equivalent of 3 owing to the well-known nucleophilic character of C-C double bonds of 6 toward acyliminium ions.[5,8] In fact, the annelation reaction of 5 with 6 catalyzed by $TiCl_4$ has successfully proceeded to give 7[9] in 60% yield (Eq. 1).

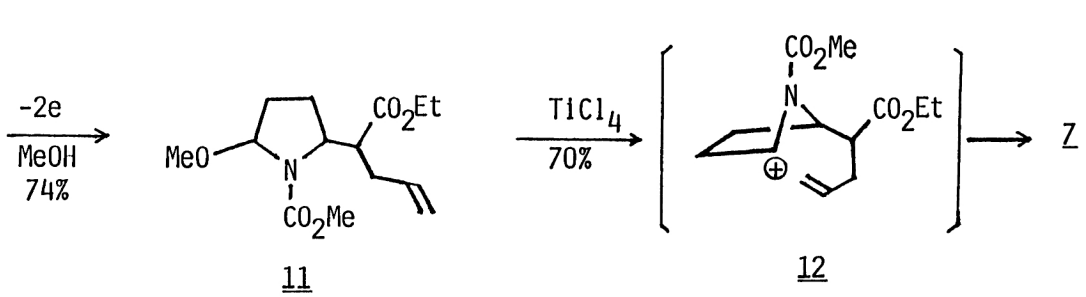


5 6 7 (1)

In order to elucidate the mechanism of this one step annelation yielding the desired 9-ABN skeleton, a stepwise preparation of 7 was also investigated (Eq. 2). Namely, the reaction of 6 with 1-methoxycarbonyl-2-methoxypyrrolidine (9)[10] prepared by the anodic methoxylation of 8 (80%) gave 10[11] in almost 100% yield. Subsequent anodic methoxylation of 10 (74%) followed by treatment of the α-methoxylated product 11[12] with $TiCl_4$ gave 7 in 70% yield. This result suggests that the annelation of 5 with 6 proceeds with stepwise mechanism involving intermediary formation of 12 which is the same intermediate formed in the step of conversion of 11 to 7.

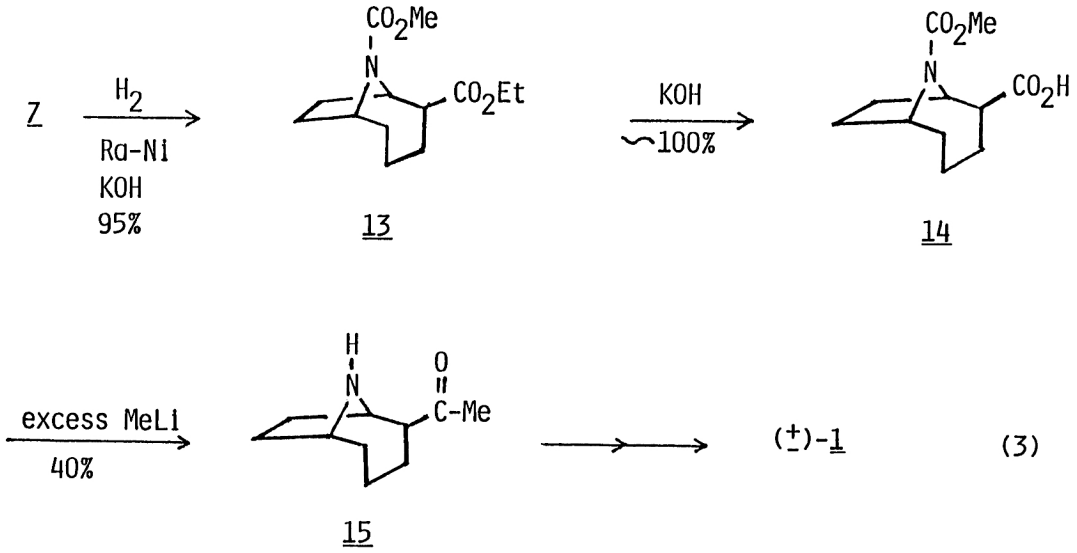


8 9 10



11 12 (2)

The reasonably easy conversion of 7 to (±)-1 seems to make our annelation method more valuable. Thus, the hydrogenolysis of 7 using Ra-Ni catalyst under basic conditions gave dechlorinated product 13[13] (95%). The hydrolysis of the product to a carboxylic acid 14[14] (≃100%) and subsequent treatment of 14 with excess methyl lithium followed by hydrolysis afforded 15[15] (40%) (Eq. 3). The conversion of 15 to (±)-1 has already been reported.[4c]



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6) Ketene silyl acetal 6 was prepared according to the reported method[7] from ethyl 4-pentenoate. 68% yield; bp 92 °C/45 mmHg; IR (neat) 3090, 2990, 2914, 1687, 1645, 1380, 1260, 1190, 1100, 850 cm^{-1}; NMR (CCl_4) δ 0.18 (s, 9H), 1.15 (t, 3H, *J*=7.5 Hz), 2.48-2.73 (m, 2H), 3.20-4.14 (m, 1H), 3.72 (q, 2H, *J*=7.5 Hz), 4.66-4.99 (m, 2H), 5.45-5.91 (m, 1H).

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8) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 41, 4367 (1985).

9) 7: IR (neat) 2980, 2960, 2900, 1730, 1705, 1450, 1395, 1200, 1120, 790, 770 cm^{-1}; NMR (CCl_4) δ 1.25 (t, 3H, *J*=7.5 Hz), 1.41-2.65 (m, 9H), 3.56 and 3.66 (br s and s, 3H), 3.72-4.75 (m, 3H), 4.11 (q, 2H, *J*=7.5 Hz).

10) T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, 103, 1172 (1981).

11) 10: IR (neat) 3075, 2975, 2875, 1725, 1700, 1640, 1450, 1380, 1190, 1115, 910, 770 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3H, *J*=7.5 Hz), 1.55-2.73 (m, 6H), 2.73-3.66 (m, 3H), 3.68 and 3.69 (2s, 3H), 3.91-4.36 (m, 1H), 4.11 and 4.12 (2q, 2H, *J*=7.5 Hz), 4.86-5.23 (m, 2H), 5.50-6.06 (m, 1H).

12) 11: IR (neat) 3075, 2980, 2955, 2830, 1730, 1710, 1643, 1445, 1375, 1190, 1115, 1085, 915, 775 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3H, *J*=7.5 Hz), 1.53-2.66 (m, 6H), 2.77-3.41 (m, 1H), 3.27 and 3.33 (2s, 3H), 3.64 and 3.66 (2s, 3H), 3.81-4.27 (m, 1H), 4.11 (q, 2H, *J*=7.5 Hz), 4.77-5.27 (m, 3H), 5.56-6.08 (m, 1H).

13) 13: IR (neat) 2960, 2940, 2870, 1735, 1705, 1458, 1400, 1210, 1125, 1040, 775 cm^{-1}; NMR (CCl_4) δ 1.07-2.67 (m, 11H), 1.25 (t, 3H, *J*=7.5 Hz), 3.52, 3.63, and 3.66 (br s and 2s, 3H), 3.86-4.79 (m, 2H), 4.06 (q, 2H, *J*=7.5 Hz).

14) 14: IR (neat) 3100 (br), 2960, 2940, 2870, 1735, 1705, 1660, 1470, 1450, 1400, 1120 cm^{-1}; NMR (CCl_4) δ 1.07-3.28 (m, 11H), 3.58 and 3.68 (br s and s, 3H), 3.97-4.92 (m, 2H), 9.15 (br s, 1H).

15) 15: IR (neat) 3440 (br), 1710, 1640, 1460, 1410, 1365, 1220, 1200, 1175, 1130, 928 cm^{-1}; NMR ($CDCl_3$) δ 1.20-2.33 (m, 10H), 2.18 (s, 3H), 2.36-2.70 (m, 1H), 2.83 (s, 1H), 3.50-4.24 (m, 2H).

(Received February 23, 1987)