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Total synthesis of (±)-cocculolidine

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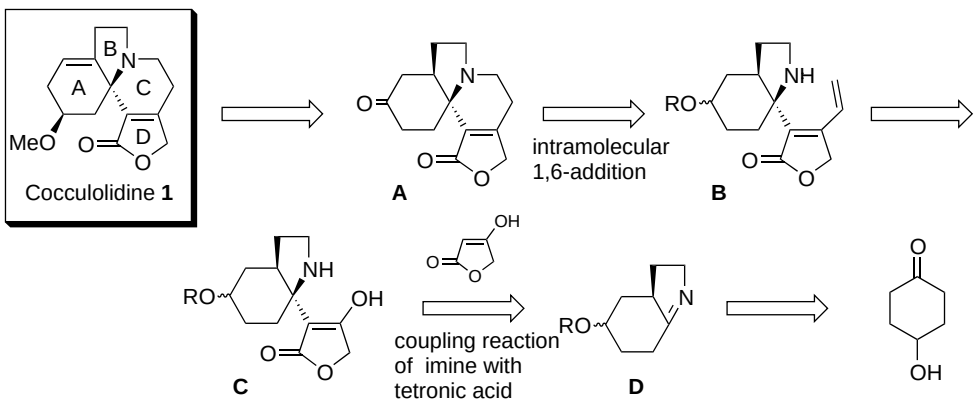
Abstract—A non-aromatic erythrina alkaloid, cocculolidine (**1**), which has insecticidal activity, was synthesized efficiently employing coupling reaction of imine with tetronic acid and intramolecular 1,6-addition as the key steps.

In 1966, Wada et al. isolated cocculolidine (**1**) from *Cocculus trilobus* DC as an insecticide.[1–4] It belongs to erythrina alkaloids which occur in the seeds and plant part of the erythrina species and causes paralysis of smooth muscles similar to the effect of curare.[5–7] Erythrina alkaloids are classified into two groups according to their structural features; those whose D-rings are aromatic, and the others whose D-rings are an unsaturated lactone. The synthesis of aromatic erythrina alkaloids has been achieved by many groups, but the synthesis of non-aromatic erythrina alkaloids had not been reported yet.[8] In this paper we describe the first total synthesis of cocculolidine (**1**), a non-aromatic erythrina alkaloid.

Our retrosynthetic analysis is illustrated in Scheme 1. We decided to utilize the key intermediate **A**, which could be transformed into cocculolidine (**1**) via introduction of olefin and methoxy groups using the carbonyl group in the A-ring. Compound **A** would be constructed by intramolecular 1,6-addition of **B** which would be given from **C** by vinylation. Compound **C** would be synthesized by a coupling reaction of tetronic acid with imine **D** which might be derived from 4-hydroxycyclohexanone.

The synthesis of imine (**6**) is outlined in Scheme 2. We started from known 4-*t*-butyldimethylsilyloxycyclohexanone[9] (**2**) and it was alkylated with bromoacetonitrile to give nitrile (**3**) (ca. 1:1 *cis*/*trans*) in good yield. Both isomers were separable. We employed both isomers for the successive steps without separation, because in the later stage this hydroxyl group will be oxidized to ketone. The carbonyl group was protected



Scheme 1. Retrosynthetic analysis of cocculolidine **1**.

Keywords: erythrina alkaloids; cocculolidine; coupling reaction of imine with tetronic acid; intramolecular 1,6-addition.
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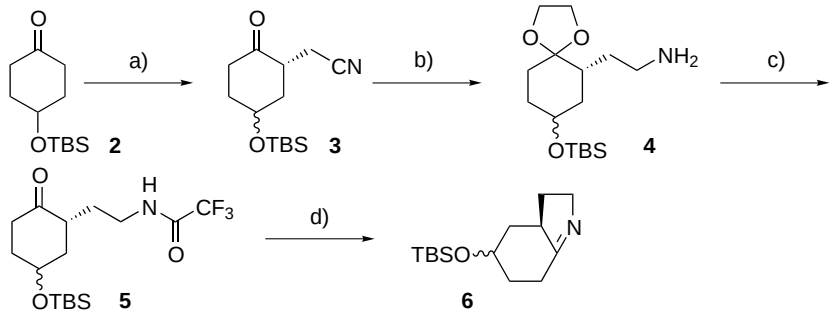


Scheme 2. (a) (i) LDA, bromoacetonitrile, THF −78 to 0°C (70% based on recovered **2**); (b) (i) TsOH, ethylenglycol, benzene reflux; (ii) LAH, $AlCl_3$, Et_2O 0°C; (c) (i) TFAA, pyr., CH_2Cl_2 0°C; (ii) TsOH, acetone reflux; (d) 5N NaOH, MeOH (five steps in 52%).

as an ethylenacetal, and reduction of nitrile with aluminum hydride afforded the corresponding amine (**4**). At first, we tried removal of ethylenacetal from amine (**4**), but the undesired removal of the TBS group occurred. On the other hand, after protection of the amino group with a trifluoroacetyl group, deprotection of ethylenacetal with catalytic TsOH in acetone was successful. The next intramolecular condensation took place to give imine (**6**) when the trifluoroacetyl group was removed.

The coupling reaction[10] of imine (**6**) with tetronic acid (**7**) was a key reaction, as shown in Scheme 3. To an ethereal solution of imine (**6**), a solution of tetronic acid in acetonitrile was added dropwise. The coupling reaction proceeded quickly, and the product (**8**) was precipitated as a white solid. So equilibration tends toward product (**8**), which was obtained by filtration in 91% yield. Secondary amine (**8**) was protected as *t*-butylcarbamate, and the enolic hydroxyl group was converted into trifluoromethanesulfonate which was transformed to a vinyl group under Stille's condition[11] to give **9**. The next intramolecular 1,6-addition of amine was also a key reaction. In the presence of TFA, the removal of *t*-butylcarbamate and subsequent intramolecular 1,6-addition proceeded successively to construct C-ring. Then water was added to the reaction mixture to give alcohol (**10**) in nearly quantitative yield. This alcohol was oxidized to key intermediate (**11**) with TPAP and NMO.[12] X-Ray analysis of (**11**) is shown in Fig. 1.

Next, we examined functionalization of the A-ring, as shown in Scheme 4. At first, we attempted the enolization of **11** by several methods, but the desired compounds were not obtained. So, after ketone (**11**) was transformed to dimethylacetal, elimination of methanol was executed by refluxing in *o*-dichlorobenzene to give methyl enyl ether (**12**, 74%) and its regioisomer (14%). The regioselectivity was changed to give methyl enyl ether (**12**, 4%) and its regioisomer (76%) by using TMSOTf and DIPEA.[13] Both isomers were separable by silica gel column chromatography. We attempted the conversion of **12** to α-selenoketone by treatment with phenylselenenyl chloride[14] followed by enolization

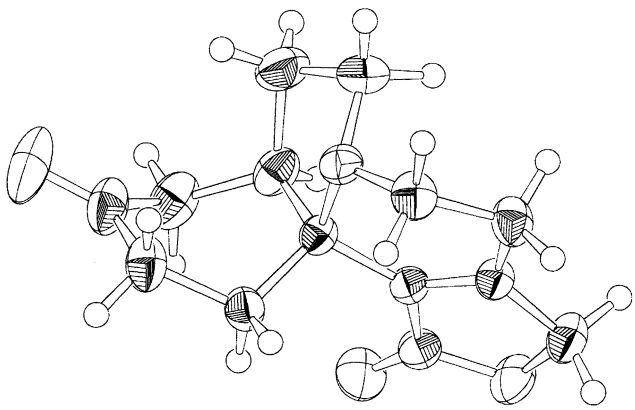
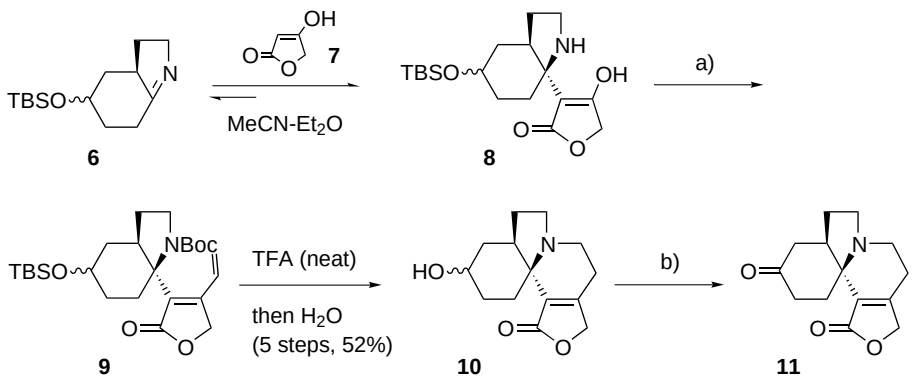
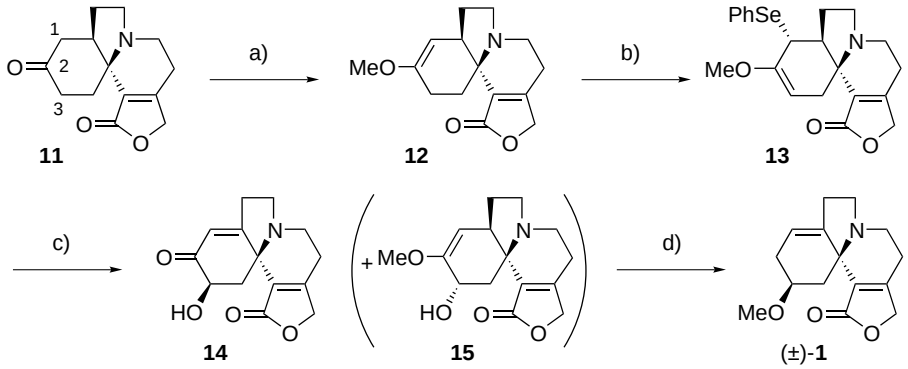


Figure 1. X-Ray analysis of **11**.



Scheme 3. (a) (i) Boc_2O, cat. DMAP, CH_2Cl_2 rt; (ii) Tf_2O, pyr., CH_2Cl_2 −78 to rt 8 h; (iii) *n*-$Bu_3SnCH{=}CH_2$, $(Ph_3P)_2PdCl_2$, DMF 35°C 4 h; (b) TPAP, NMO, 4 Å MS, CH_2Cl_2–MeCN (10:1) 0°C to rt (84%).



Scheme 4. (a) (i) TsOH, $CH(OMe)_3$, MeOH reflux (quant); (ii) *o*-dichlorobenzene reflux (74%); (b) PhSeCl, DIPEA, CH_2Cl_2 (70%); (c) OsO_4, H_2O_2, THF 0°C then NMO 40°C (52%); (d) (i) TsOH, ethanedithiol, MeOH reflux (90%); (ii) Ac_2O, pyr (95%); (iii) Raney-Ni, THF (47%); (iv) K_2CO_3, MeOH (72%); (v) CH_2N_2, SiO_2, CH_2Cl_2–Et_2O (34%).

to give compound (**13**). Although α-selenoketone was obtained, it could not be transformed into **13**. So phenylselenylation was carried out in the presence of DIPEA, and in this case concomitant deprotonation of the 3-position occurred to give **13**[15] in good yield. Selenide (**13**) was oxidized to selenoxide with a catalytic amount of OsO_4 and 1 equivalent of hydrogen peroxide. After the formation of selenoxide, 2.2 equivalents of NMO was added to give enone (**14**)[15] in 52% yield via dihydroxylation along with a side product (**15**)[15] in 42% yield via sigmatropic rearrangement of selenoxide. We tried to suppress this side reaction, but the yield of the desired **14** did not exceed 52%. All attempts for the methylation of the alcohol (**14**) to afford methyl ether were unsuccessful. Therefore, **14** was converted to the corresponding dithioacetal for removal of the ketone carbonyl group. The hydroxyl group was protected with an acetyl group to avoid the loss by absorption on Raney-Ni in the next reduction. After the desulfurization, the acetyl group was removed to give demethylcocculolidine, and we applied various conditions of methylation to this hydroxyl group. Under basic conditions, the desired cocculolidine (**1**) was not obtained and presumably tetra alkyl ammonium salt was formed because of high nucleophilicity of the tertiary amine. Fortunately, methylation was successful only under an acidic condition using CH_2N_2 and SiO_2[16] to give cocculolidine (**1**) in 34% yield. The synthetic (±)-**1** was completely identical with natural authentic sample.[17]

In conclusion, we have completed the first total synthesis of (±)-cocculolidine in 0.42% overall yield from 4-*t*-butyldimethylsilyloxycyclohexanone (**2**) through 21 steps. Work is now under way to improve the whole scheme of this synthesis, and the results will be reported in a full account.

Acknowledgements

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15. Although compounds (**13**), (**14**) and (**15**) were produced as single isomers, the related stereochemistry of them were not decided exactly. But we predicted that they had the stereochemistry shown in Scheme 4, because PhSeCl and OsO_4 approached from the less hindered face. Details will be discussed in a full account.
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17. IR and ^1H NMR (60 MHz) charts were kindly provided by Professor Yoji Sakagami. IR data of natural and synthetic samples were completely identical. Although ^1H NMR (300 MHz) data was consistent with its structure, it was impossible to compare with that (60 MHz) of a natural sample. We did not have full assurance. So, we isolated natural cocculolidine (250 mg) from fresh leaves of *Cocculus trilobus* DC (500 g) under a reported

procedure[2] and measured ^{1}H NMR (300 MHz). The ^{1}H NMR spectrum of our synthetic sample was identical with that of cocculolidine. IR data and 300 MHz ^{1}H NMR data of the synthetic sample are shown below.

IR (CCl_4, solution): ν 2930, 2836, 1766, 1653 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (1H, dd, $J = 11.4$, 12.0 Hz), 1.93–2.04 (1H, m), 2.16 (1H, dd, $J = 5.4$, 19.5 Hz), 2.27 (1H, dd, $J = 3.6$, 10.8 Hz), 2.31–2.52 (2H, m), 2.57–2.73 (2H, m), 2.75–2.86 (1H, m), 2.96 (1H, dt, $J = 3.6$, 8.7 Hz), 3.19–3.40 (2H, m), 3.35 (3H, s), 4.02–4.12 (1H, m), 4.64 (1H, dd, $J = 0.9$, 17.4 Hz), 4.73 (1H, d, $J = 17.4$ Hz), 5.69 (1H, m).