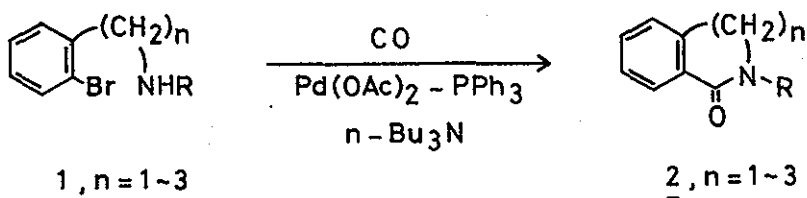


THE REACTIONS AND SYNTHESSES WITH ORGANOMETALLIC COMPOUNDS.
 VIII. THE TOTAL SYNTHESIS OF SENDAVERINE BY USE OF THE
 PALLADIUM CATALYZED INSERTION OF CARBON MONOXIDE

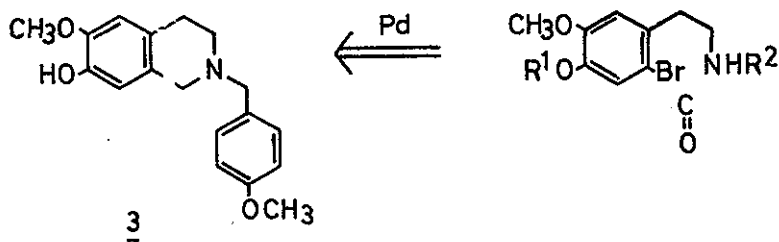
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The alkaloid, sendaverine(3), which was isolated from Corydalis aurea Willd. was synthesized from the 2-bromophenethylamine derivative(10) as an extension of the synthetic method of benzolactams by palladium catalyzed insertion of carbon monoxide.

We have recently reported the new synthesis of benzolactams by palladium catalyzed amidation.¹ The insertion of carbon monoxide toward o-bromo-alkylaminobenzene(1) easily occurred under mild condition such as an atmospheric pressure of carbon monoxide at 100°C by use of a catalytic amount of Pd(OAc)₂ and PPh₃ in the presence of a tertiary amine to afford the five, six, and seven membered benzolactams (2, n=1~3) in good yields.

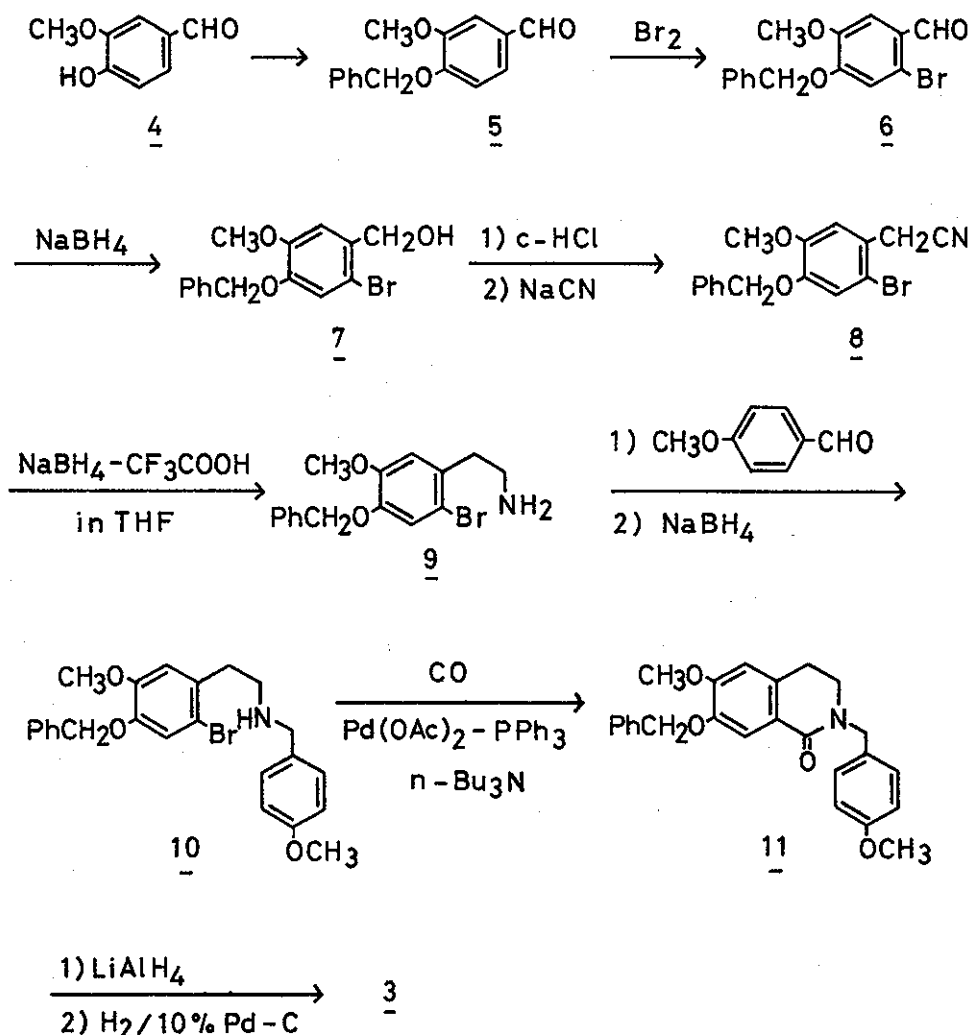


The synthesis of isoquinoline having no substituent at 1-position was fairly difficult. Recently, Tsuda et al. has reported the synthesis of isoquinolone via isocyanate by Bischler-Napieralski Reaction.² In our reaction, o-bromo-phenethylamine was directly converted to isoquinolone in a good yield and, moreover, the cyclization should take place exactly at the initial position of the halogen atom in the aromatic ring. An extension of the method to the synthesis of the natural alkaloid, sendaverine(3), was attempted with success, which is described in this paper.



Sendaverin(3) was isolated from Corydalis aurea Willd. by Manske³ and it possesses a tetrahydroisoquinoline skeleton.

The total synthesis of sendaverine(3) was already achieved by Kametani, who established the whole structure of this alkaloid.⁴ The successful new synthesis of this alkaloid is shown in the Chart 1.



Bromination of O-benzylvanillin (5) in acetic acid gave the bromo-derivative(6) in 70% yield,⁵ which was reduced with NaBH₄ to furnish the alcohol(7). 2-Bromo-4-benzyloxy-5-methoxybenzyl cyanide(8) was obtained on treatment of 7 with c. HCl and NaCN in 68% yield from 6. The reduction of the cyanide(8) was effected with the new reducing reagent [NaBH₃(OCOCF₃)] exploited by Umino, Iwakuma and N. Itoh,⁶ which could predominantly reduce the cyano group to the primary amine, leaving the halogen group at an aromatic ring intact. Thus, the cyanide(8) was converted by this reagent to the amine(9) as an oil in 40% yield [IR ν_{\max} (film) 3350, 3250 cm⁻¹; MS m/e 337, 335(M⁺)]. The amine(9) was condensed with 4-methoxybenzaldehyde by azeotropic distillation to eliminate the water produced on the reaction and was reduced with NaBH₄ to afford the compound(10) as the direct precursor available for this palladium-catalyzed carbonylation. The compound(10) was heated with Pd(OAc)₂ (2 mol%) and PPh₃ (4 mol%) in the presence of n-Bu₃N (1.1 mol) under carbon monoxide atmosphere at 100°C for 26 hr to afford the desired isoquinolone(11) as a colorless gummy substance in 34.5% yield [IR ν_{\max} (CHCl₃) 1640 cm⁻¹; MS m/e 403(M⁺), 211, 121 and 91; NMR δ (CDCl₃) 2.83 (t, J=6Hz, 2H), 3.45 (t, J=6Hz, 2H), 3.77 (s, 3H), 3.88 (s, (3H), 4.70 (s, 2H), 5.20 (s, 2H), 6.65 (s, 1H), 6.70-7.65 (9H), and 7.80 (s, 1H)]. The product (11) was reduced with LiAlH₄ in tetrahydrofuran, followed by hydrogenolysis with 10% Pd-charcoal to give the crude alkaloid, which was recrystallized

from hexane to afford sendaverine(3) as colorless prisms (mp 135-136°C, lit.⁴ 139-140°C). The spectral data of this synthetic product (nmr, ir, and mass) were fully identical with those described by Kametani⁴ [IR ν_{\max} (CHCl₃) 3544 cm⁻¹; MS m/e 299(M⁺), 298, 192, 191, 178, 150, 122, 121, and 107; NMR δ (CDCl₃) 2.62-2.87(m, 4H), 3.52(s, 2H), 3.61(s, 2H), 3.81(s, 3H), and 3.84(s, 3H)].

Thus, the new total synthesis of sendaverine(3) has been completed through the palladium-catalyzed insertion of carbon monoxide.

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