

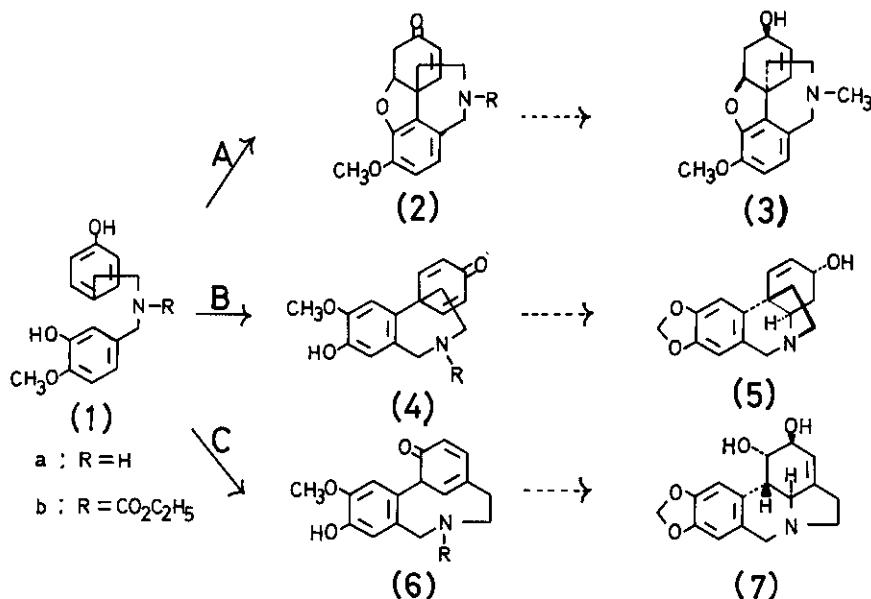
Studies on the Biomimetic Control of the Coupling Position in
the Oxidative Aryl-aryl Coupling Reactions of the Bridged Ether
Derivatives of O-Methylnorbelladine

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Oxidative aryl-aryl coupling reactions of the bridged ether derivatives (10a, 10b) of O-methylnorbelladine were investigated mimicking the enzymatic control of the reaction sites. Oxidation of (10b) by VOF_3 gave a para-metha coupling product (12), and (10a) afforded an ortho-metha coupling product (14) and a dimer (15).

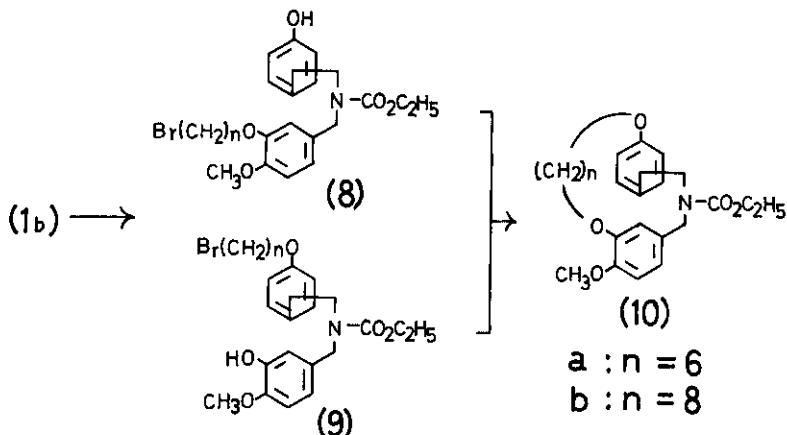
Although a number of successful results have been reported on the oxidative aryl-aryl coupling reactions connected with the biogenetic-type synthesis of natural products derived by those reaction in past two decades ¹⁾, only few reports on the control of the coupling position were recorded ²⁾. Amaryllidaceae alkaloids, which are classified to three groups, namely, the galanthamine type (3), the crinine type (5), and the lycorine type (7), and can be biosynthesized from O-methylnorbelladine (1a) by the oxidative phenol coupling reaction. That is, compounds (3), (5), and (7) may be synthesized through (2), the ortho-para coupling product by route A, through (4), the para-para coupling product by route B, and through (6), the para-ortho coupling product by route C, of O-methyl-norbelladine (1a), respectively. ³⁾ On the biogenetic-type synthesis of these Amaryllidaceae alkaloids, although several successful results have been reported on the crinine type alkaloids by various methods ¹⁾, only limited successes have been reported on the galanthamine type alkaloids ¹⁾ and none of the report has been recorded yet on the lycorine type alkaloids.

This paper deals with a preliminary investigation of the control of coupling position for the synthesis of these three types of Amaryllidaceae alkaloids by oxidative aryl-aryl coupling reaction mimicking the enzymatic control of the reaction sites ⁴⁾. The bridged ether derivatives of O-methyl-N-carbethoxy-norbelladine (1b) were chosen for these purpose, expecting with the sterical



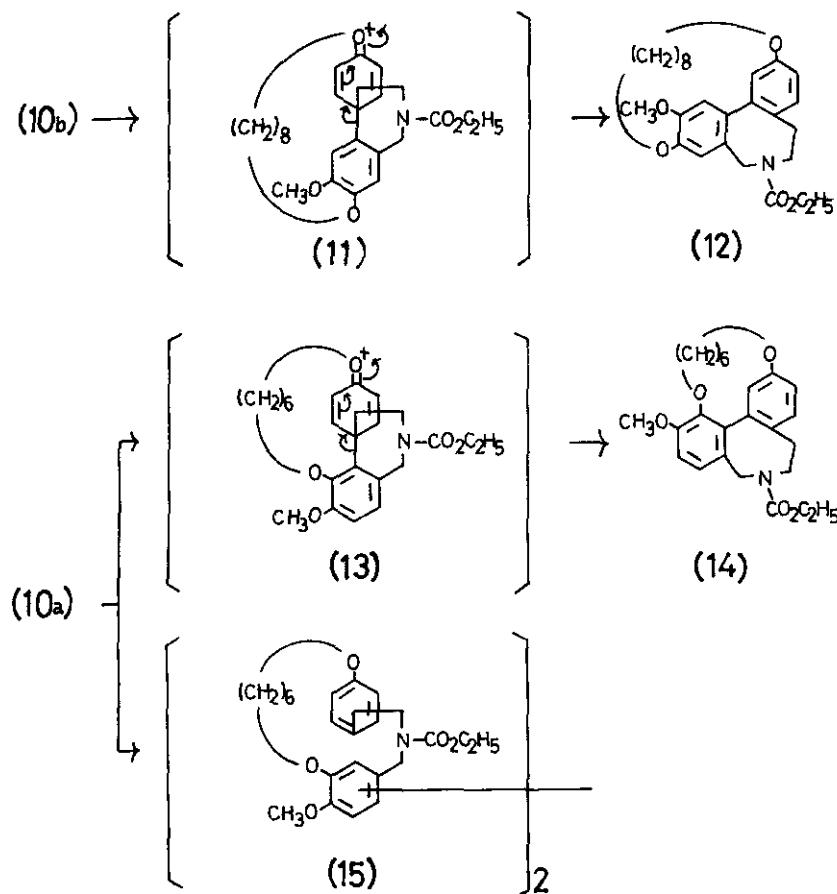
restriction between two aromatic rings.

The bridged ether derivatives (10a) and (10b) were synthesized in the following manner. Reaction of (1b) with hexamethylene dibromide in EtOH in the presence of K_2CO_3 at 80° for 40 min gave two mono alkylated products (8a) and (9a) in 21% (oil) and 13% (oil) yield ⁵⁾. Further treatment of (8a) and (9a) in the same fashion as above afforded the bridged ether compound (10a), oil, m/e: 427 (M^+), in 44% and 5% yield, respectively. Similar reaction of (1b) with octamethylene dibromide gave (8b) and (9b) in 16% (oil) and 9.5% (oil) yield ⁵⁾, and further reaction of (8b) and (9b) afforded the bridged ether compound (10b), oil, m/e:



455 (M^+), in 31% and 5% yield, respectively.

Oxidative coupling reaction of (10b) was carried out by the oxidation with VOF_3 in $CF_3CO_2H-CH_2Cl_2$ at -25° for 1 hr to give (12), mp. 152-155°, m/e: 453 (M^+), nmr ($CDCl_3$) ppm: 7.26 (d, $J=12$ Hz, 1H), 6.95 (dd, $J=12$ Hz, $J=3$ Hz, 1H), 6.82 (d, $J=3$ Hz, 1H), and 6.85 (s, 2H) (fine aromatic protons), in 58.6% yield. Oxidation of (10a) by VOF_3 in $CF_3CO_2H-CH_2Cl_2$ gave two compounds, an intramolecular coupling product (14), oil, m/e: 425 (M^+), nmr ($CDCl_3$) ppm: 7.07 (d, $J=7$ Hz, 1H), 6.9 (d, $J=10$ Hz, 1H), 6.76 (d, $J=3$ Hz, 1H), 6.68 (dd, $J=7$ Hz, $J=3$ Hz, 1H) and 6.50 (d, $J=10$ Hz, 1H) (fine aromatic protons), in 13% yield, and an intermolecular coupling product (15), mp. 138-139°, in 25% yield. On the other hand, oxidation



of (10a) by anode in the presence of HBF_4 as supporting electrolyte and by $\text{Ti}(\text{OCOCF}_3)_3$ in $\text{CF}_3\text{CO}_2\text{H}$ afforded only an intermolecular coupling product (15) as a sole product in 80% yield, respectively ⁶⁾.

Comparable reports in the synthesis of this type alkaloids from the norbelladine derivatives describe the main product is the crinine type compounds by the para-para coupling ¹⁾. The present results show that the ansa derivatives of O-methyl-norbelladine (10b, 10a) gave the different oxidative coupling products attributable to the methylene number of the bridged ether as anticipated. That is, (10b) gives the para-metha coupling product (12), which may be derived after the aryl rearrangement of the para-para coupled intermediate (11), whereas (10a) affords the ortho-metha coupling product (14), which may be derived after that of the ortho-para coupled intermediate (13) formed by the sterical restriction of the molecule, and the dimer (15) ⁷⁾.

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- 5) The structure of the monoalkylated products was not definitely identified either (8) or (9) yet.
- 6) The structures of (12) and (14) were postulated on the basis the aromatic proton signals in their nmr spectra.
- 7) In the rearrangement of the intermediates (11) and (13), the aryl group shift may be in preference to the alkyl group shift and the sterical requirement of the resulting products are preferable to (12) and (14).

Received, 13th August, 1980