

A SYNTHETIC APPROACH TO IMPORTANT INTERMEDIATES OF RESERPINE AND  
 YOHIMBINE — SYNTHESIS OF NON-TRYPTAMINE COMPONENTS FROM  
 FURFURAL

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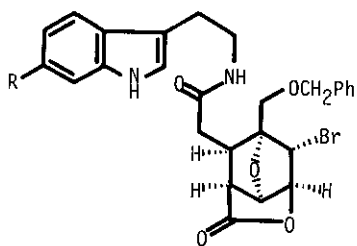
Abstract — A general method for the stereoselective synthesis of the non-tryptamine components of reserpine and yohimbine via the same compound (4) is described. This common intermediate was readily obtained by Diels-Alder reaction of the furfural derivative (10) with maleic anhydride.

We recently reported<sup>1</sup> a stereoselective synthesis of the intermediates (1) and (2) in the synthesis of Rauwolfia alkaloids, and cyclization of (2) followed by sodium borohydride reduction to form the unexpected lactam (3).

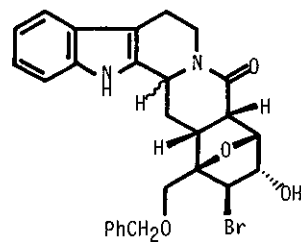
In continuing efforts towards the total synthesis of reserpine (6)<sup>1,2</sup> and yohimbine (9)<sup>3</sup>, we required a preparative route to the bromolactonic homoester (5) and the nitrile (8) which were considered to be potential intermediates in the synthesis of Rauwolfia alkaloids and yohimbine. It was envisaged that both of these compounds could be derived from the same compound.

Our strategy for the preparation of homoester (5) was basically the same of that previously reported by us<sup>1</sup>, whereas that for nitrile (8) involved sodium borohydride reduction of the Diels-Alder adduct (4) followed by catalytic hydrogenation, treatment of the resultant  $\gamma$ -butyrolactone (7) with potassium cyanide and finally epimerization.

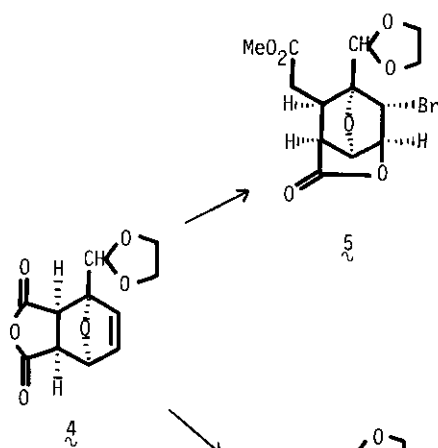
Diels-Alder reaction of maleic anhydride with the protected furfural (10) in dry benzene gave the desired endo adduct (4), m.p. 118 - 120<sup>o</sup>, in 47.9 % yield. Hydrolysis of this adduct (4) with H<sub>2</sub>O followed by halolactonization<sup>1</sup> afforded a



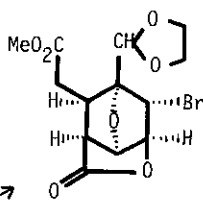
1: R=H  
2: R=OMe



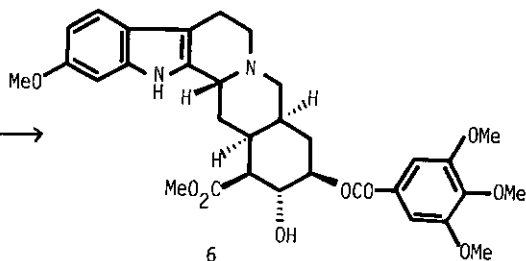
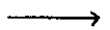
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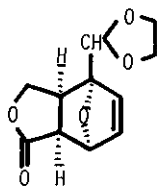
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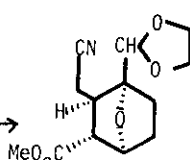
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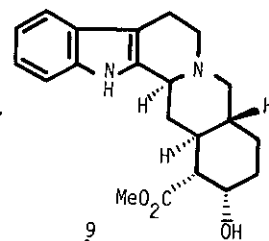
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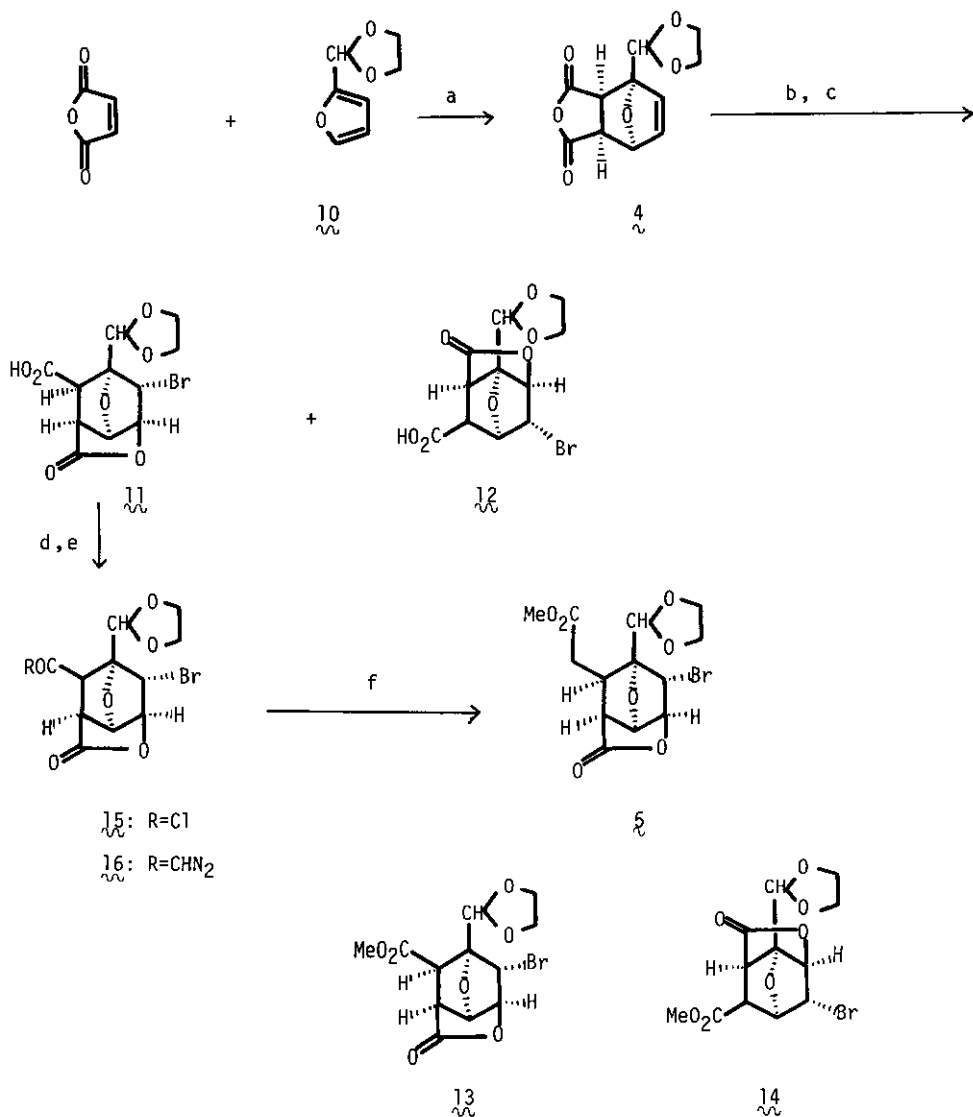
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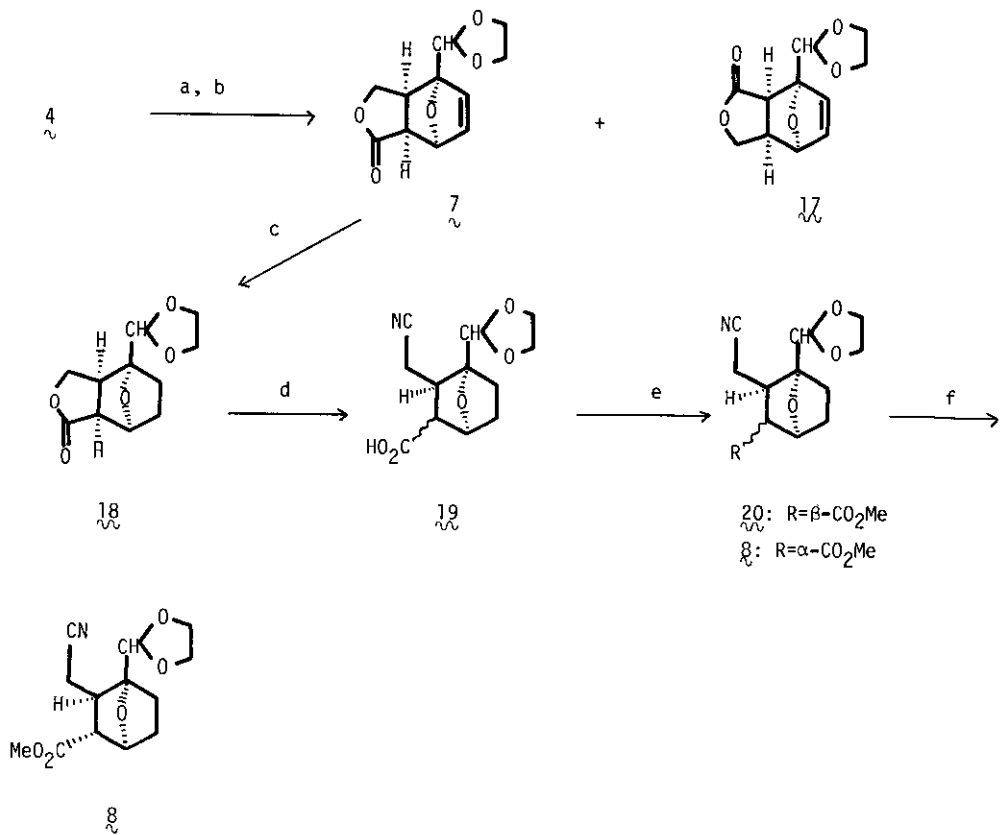
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9



- a) Hydroquinone(cat.), dry benzene, r.t.  
 b) H<sub>2</sub>O, r.t. c) NaHCO<sub>3</sub>, Br<sub>2</sub>, r.t.  
 d)(COCl)<sub>2</sub>, dry benzene, reflux e) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, r.t.  
 f) absolute MeOH, dioxane, Ag<sub>2</sub>O, reflux



- a)  $\text{NaBH}_4$ , dry DMF, r.t.    b)  $2\text{N-H}_2\text{SO}_4$ , r.t.  
 c)  $\text{H}_2$ , 5%Pd-C, MeOH, r.t.    d) KCN, DMSO,  $160^\circ$   
 e)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$     f)  $\text{K}_2\text{CO}_3$ , absolute MeOH, r.t.

mixture of the bromolactonic acid (11) and its isomer (12) in almost quantitative yield. This mixture was converted, by treatment with excess diazomethane, to a readily separable mixture of the corresponding methyl esters (13), m.p. 149 - 150<sup>o</sup>, and (14), m.p. 187 - 189<sup>o</sup>, in the approximate ratio of 5.5 : 1.

The diazoketone (16) and its position isomer, derived via the corresponding acid chloride (15) and isomer from the bromolactonic acids (11 and 12), were refluxed in a mixture of absolute methanol and dioxane in the presence of freshly made silver oxide to provide the desired homomethyl ester (5), m.p. 130 - 132<sup>o</sup>, in 44.4 % yield after separation and purification by silica gel chromatography.

On the other hand, sodium borohydride reduction<sup>4</sup> of the Diels-Alder adduct (4) in dry dimethylformamide followed by acid treatment at room temperature afforded a separable mixture of the desired  $\gamma$ -butyrolactone (7), m.p. 114 - 116<sup>o</sup>, in 35.1 % yield and its isomer (17), m.p. 115 - 116<sup>o</sup>, in 35 % yield. Attempts to introduce the cyano group at this stage, by treatment of  $\gamma$ -butyrolactone (7) with potassium cyanide or sodium cyanide under various conditions, resulted in the formation of butenolide and the starting furfural derivative (10) due to facile retro Diels-Alder reaction. In order to circumvent this, the double bond was reduced. Catalytic hydrogenation of (7) on 5 % Pd-C in methanol afforded the dihydro- $\gamma$ -butyrolactone (18), m.p. 83 - 85<sup>o</sup>, in 89.2 % yield. Now introduction of the cyano group proceeded smoothly to give a diastereoisomeric mixture of carboxylic acids (19). Treatment of this mixture, without further purification, with an excess of diazomethane provided a separable mixture of the corresponding  $\beta$ -methyl ester (20), m.p. 96 - 98<sup>o</sup>, and the desired  $\alpha$ -methyl ester (8), m.p. 130 - 132<sup>o</sup>, in 69 % overall yield from the dihydro- $\gamma$ -butyrolactone (18), the ratio of the two compounds being approximately 1 : 1. Epimerization of the  $\beta$ -isomer (20) to the  $\alpha$ -isomer (8) using methanolic potassium carbonate at room temperature proceeded smoothly in almost quantitative yield.<sup>5,6</sup>

#### REFERENCES AND NOTES

1. T. Suzuki, A. Tomino, S. Kagaya, K. Unno, and T. Kametani, Heterocycles, 1979, 13, 203.
2. T. Suzuki, S. Kagaya, A. Tomino, K. Unno, and T. Kametani, Heterocycles, 1978, 9, 1749; for total synthesis, see R. B. Woodward, F. Bader, H. Bickel, and R. Kierstead, Tetrahedron, 1958, 2, 1; B. A. Pearlman, J. Amer. Chem. Soc., 1979, 101, 6404.

3. T. Suzuki, A. Tomino, K. Unno, and T. Kametani, Heterocycles, in press; for total synthesis, see E. van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, J. Amer. Chem. Soc., 1958, 80, 5006; L. Toke, K. Honty and Cs. Szántay, Chem. Ber., 1969, 102, 3248; G. Stork and R. N. Guthikonda, J. Amer. Chem. Soc., 1972, 94, 5109; T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, Chem. Pharm. Bull., 1975, 23, 2634; T. Kametani, Y. Hirai, and K. Fukumoto, ibid., 1976, 24, 2500.
4. B. Belleau and J. Puranen, Canadian J. Chem., 1965, 43, 2551; J. J. Bloomfield and S. L. Lee, J. Org. Chem., 1967, 32, 3919.
5. All structural assignments were supported by proton magnetic resonance, infrared and mass spectral data obtained using chromatographically purified and homogeneous samples. Elemental analyses were obtained for crystalline compounds.
6. All reported yields refer to isolated products.

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