TOTAL SYNTHESIS OF (±)-ABRESOLINE VIA [3+2]CYCLOADDITION

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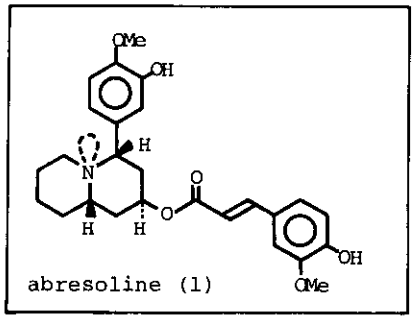
Abstract——A total synthesis of (±)-abresoline (1) has been achieved via stereoselective [3+2]cycloaddition of the homoallylic alcohol (2) with 3,4,5,6-tetrahydropyridine 1-oxide.

In the previous paper[1] we have described the general synthetic approach to the quinolizidine alkaloids via [3+2]cycloaddition reaction, wherein two naturally occurring arylquinolizidinols[2] have been synthesized. During the course of our investigation on the synthesis of the quinolizidine alkaloids, this approach has enabled us to synthesize efficiently (±)-abresoline (1)[3,4], a minor alkaloid of Heimia salicifolia.

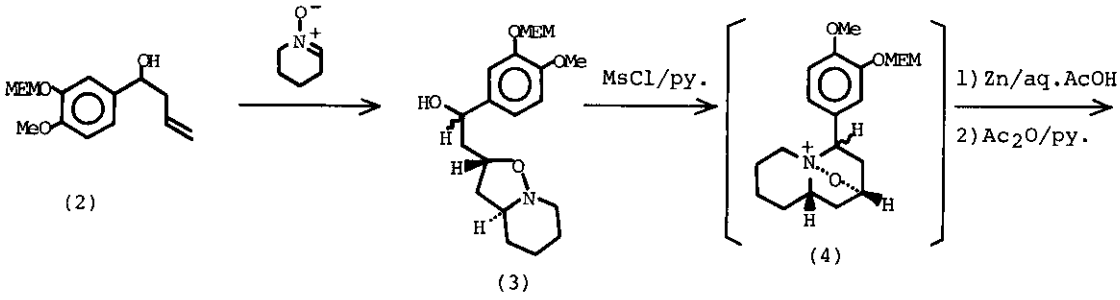
On heating the homoallylic alcohol (2)[5], in which the phenolic hydroxy was protected as β-methoxyethoxymethyl ethers[4], with 3,4,5,6-tetrahydropyridine 1-oxide in toluene under reflux for 2.5 h, the adduct (3)[6] was obtained in 99.1% yield as a mixture of two inseparable diastereomers. The stereochemistry of the adduct (3) was tentatively assigned as indicated and was later confirmed by its successful transformation to (±)-abresoline (1).

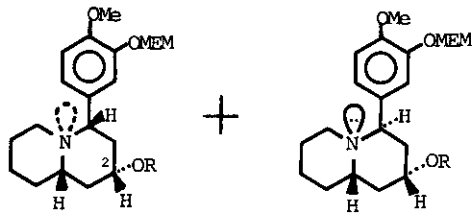
The adduct (3) was then treated with methanesulfonyl chloride in pyridine followed by reduction with Zn in 50% aqueous acetic acid to give the expected alcohols (5b) and (6b) through the quaternary salt (4). The alcohols were separated via the acetates (5a)[$\delta(CDCl_3)$ 2.00(3H, s), 3.02(1H, dd, J=12 and 3Hz), 4.87(1H, m); $\nu_{max}(CHCl_3)$ 2785 and 2740(Bohlmann bands), 1728 cm^{-1}; MS(m/e) 407(M^+, 100%)] and (6a)[$\delta(CDCl_3)$ 2.05(3H, s), 5.25(1H, m); $\nu_{max}(CHCl_3)$ 1728 cm^{-1}; MS(m/e) 407(M^+, 100%)] in 45.4% and 32.3% yield, respectively. The acetate (5a) was then hydrolysed to give the alcohol (5b), treatment of which with 3-methoxy-4-β-methoxyethoxymethyloxycinnamic acid in the presence of diethyl azodicarboxylate and triphenylphosphine[7] gave the C-2 inverted cinnamate(7)[$\delta(CDCl_3)$ 5.27(1H, m),

6.48(1H, d, J=16Hz), 7.78(1H, d, J=16Hz); $\nu_{max}(CHCl_3)$ 2825 and 2750(Bohlmann bands), 1700, 1630 cm^{-1}; MS(m/e) 629(M^+), 347(100%)] in 91% yield on the basis of consumed (5b). The Mitsunobu reaction using cinnamic acid has not yet been found in the literature so far. Completion of the synthesis from (7) was achieved by

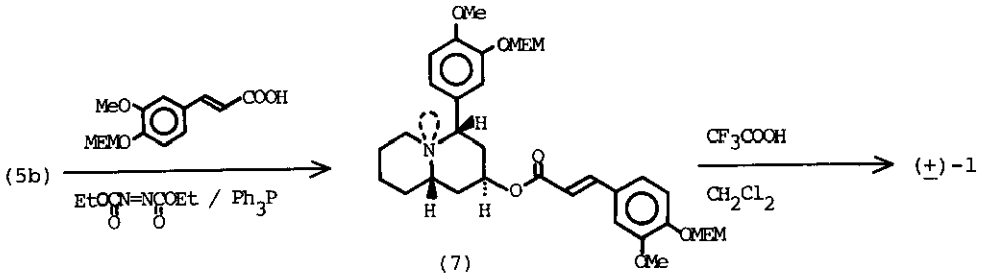


abresoline (1)





MEM=β-methoxyethoxymethyl



removal of the β-methoxyethoxymethyl group. Thus, treatment of (7) with trifluroacetic acid-CH_2Cl_2[4] at 0°C gave (±)-abresoline (1) in 77.8% yield which was identical with the natural substance[3] by comparison of IR and ^{1}H-NMR.

ACKNOWLEGEMENT

We thank Professor J.M. Edwards for kindly providing us with the spectral data (IR and ^{1}H-NMR) of abresoline (1).

REFERENCES AND NOTES

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5. The homoallylic alcohol (2) was readily prepared from 3-β-methoxyethoxymethyloxy-4-methoxybenzaldehyde with allylmagnesium bromide.
6. All new compounds exhibited satisfactory spectroscopic and analytical (combustion and/or high-resolution mass spectral) data consistent with the structures shown.
7. For a review on the uses of this reagent, see: O. Mitsunobu, Synthesis, 1981, 1.

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