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A STEREOSPECIFIC SYNTHESIS OF (±)-COCAINE

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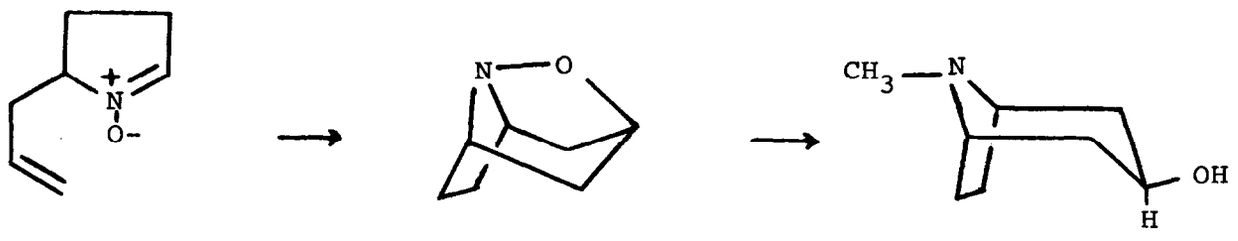
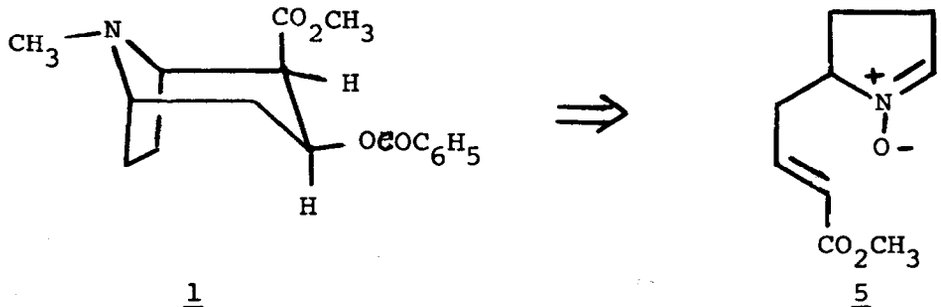
Efficient nitrone-based entries into the tropane skeleton have been described[1,2]. Thus, nitrone olefin 2 was efficiently converted into pseudotropine 4, via cycloadduct 3, according to the following scheme[2].



2 3 4

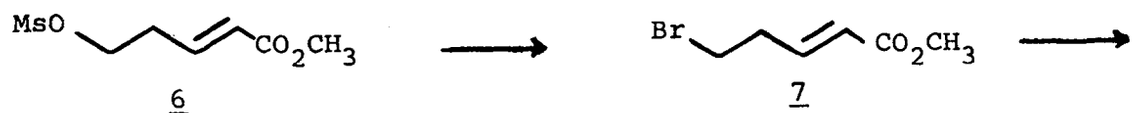
We wish to report herein an approach to cocaine (1) which emphasizes the high degree of regiochemical and stereochemical control possible using nitrone cycloadditions. Prior synthetic efforts toward cocaine have confronted severe difficulties relating to the relative stereochemistry of the two ester functions[3-6]. Our stereospecific approach depends on the synthesis of nitrone ester 5 as the key precursor of the natural product. Our initial



1 5

objective is therefore the synthesis of this nitrone ester (5). To accomplish this, we converted mesylate olefin 6[7] into the corresponding bromo ester 7 (80%) using lithium bromide in ether. The nitro compound 8 was then prepared from 7 using silver nitrite in

acetonitrile. Michael addition of nitro olefin 8 onto acrolein using sodium methoxide in methanol, followed in situ protection of the aldehyde functionality, provided acetal 9 in 90% overall yield.



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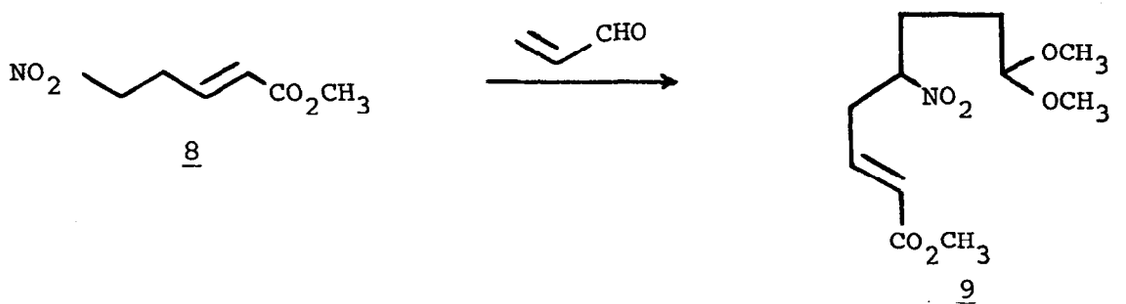
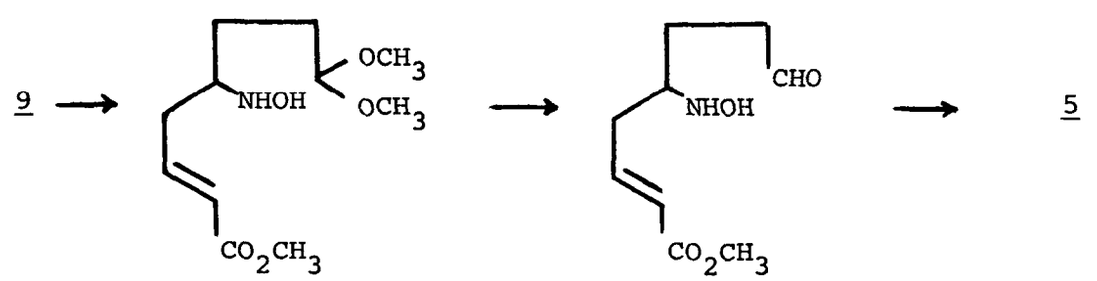
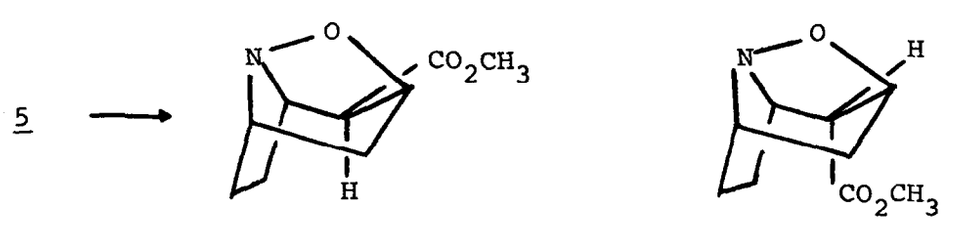


8 9

The conversion of 9 into the desired nitrone ester 5 was accomplished by reduction of the nitro group with zinc and ammonium chloride in dimethoxyethane-water solution. After acidification, the resulting oil was heated in toluene to afford ca. 10% of a white solid, identified as tricyclic ester 10[8]. The probable sequence of reactions involved is indicated below. The nitrone 5 was not characterized but, rather, directly cyclized to 10.

The ir spectrum of 10 exhibits a band at 5.80 μ, suggesting the retention of the ester functionality. The nmr spectrum exhibits a one-proton doublet at δ4.95 ppm (J 5.5 Hz)

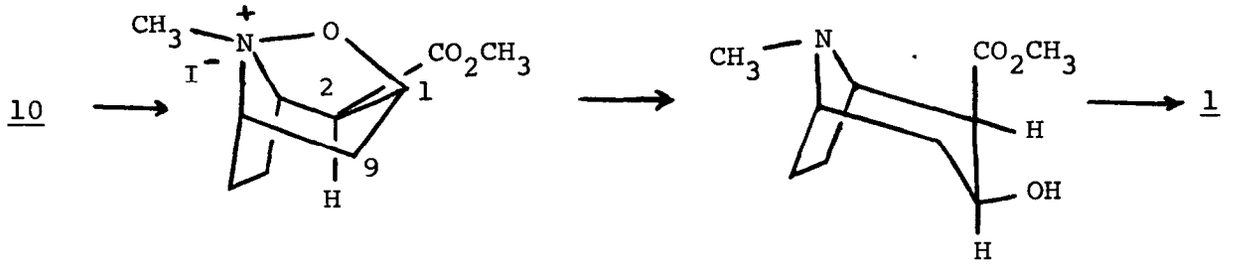




10 11

assignable to the C-1 proton since it is coupled only to the exo-proton at C-9. A dihedral

angle of 90° exists between the C-1 proton and the endo-protons at C-2 and C-9. This observation is consistent with the nmr spectrum of 3, the intermediate in the synthesis of pseudotropine[9]. One proton multiplets at δ 3.53 and 3.86 ppm were assignable to the two methine protons at C-3 and C-6. Methylation of the cycloadduct 10 with excess methyl iodide in methylene chloride and ether at reflux for 24 hours provided the methiodide 12.



12 13

The ir spectrum of 12 contained the ester carbonyl stretch at 5.79 μ. The nmr spectrum contained two three-proton singlets at δ3.70 and 3.80 ppm for the quarternary ammonium methyl group and the methyl ester, respectively, and two one-proton multiplets at δ4.42 and 4.76 ppm for the methine protons at C-3 and C-6, along with a characteristic one-proton doublet (J = 5.5Hz) at δ5.58 ppm for the C-1 proton. A primary advantage of the nitrone-based approach is the ability to control the stereochemistry of the ester function. Thus, as expected, no adduct (i.e. 11) with an endo-carbomethoxyl group was observed. The (Z)-configuration at the olefinic center in 5 fixes the sterochemistry of the carbomethoxyl group in 10 and 12. This in turn provides for the axial ester grouping in (±)-cocaine (vide infra).

The nitrogen oxygen bond of methiodide adduct 12 was cleaved with zinc and acetic acid to give a 47% yield of ecgonine methyl ester (13). The ir spectrum exhibited strong absorption at 2.60 μ confirming the presence of a free hydroxyl group, and a strong band at 5.86 μ, attributable to the ester carbonyl stretch. The nmr spectrum displayed the expected three-proton singlet at δ1.90 ppm (CH_3N) and another at δ3.28 ppm (CO_2CH_3).

Benzoylation of hydroxyester 13 using the method of de Jong[4] provided (±)-cocaine whose ir, nmr, and mass spectra were virtually identical with those of natural (-)-cocaine. Thus, the intramolecular nitrone cyclization has provided the first stereospecific total synthesis of (±)-cocaine.

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