TOTAL SYNTHESIS OF (-)-ANTIRHINE

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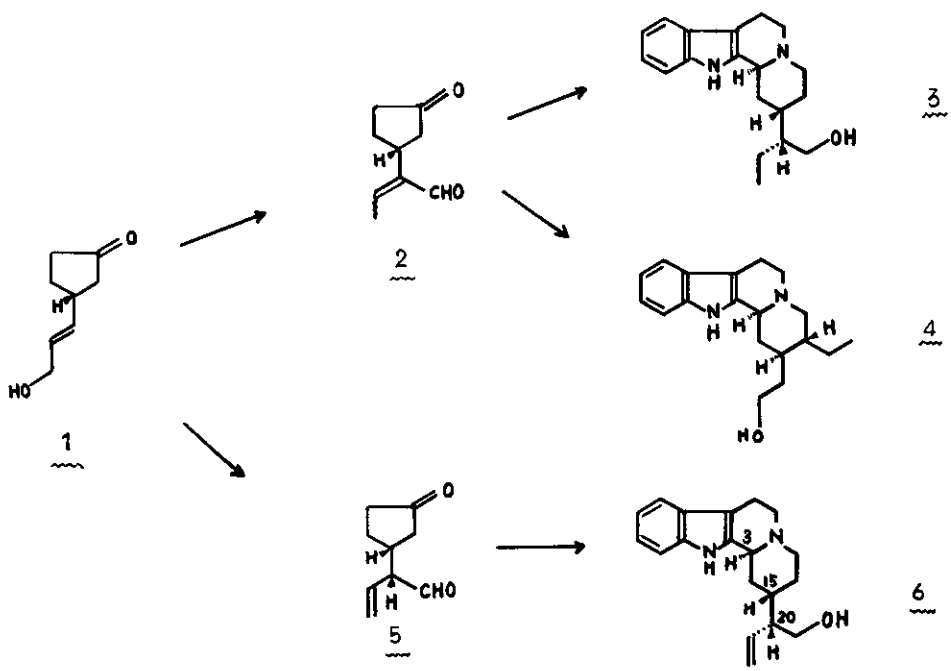
Abstract —— Total synthesis of (-)-antirhine (6) has been achieved from a potentially useful chiral synthon, (3S)-[3-hydroxy-(E)-prop-1-enyl]cyclopentanone (1), via β,γ-unsaturated aldehyde (5), which was obtained by mild hydrolysis of α-cyano-N,N-dimethylaminocyclopentanone (7).

Recently we reported the enantioselective synthesis of (+)-dihydroantirhine (3)[1] and (-)-dihydrocorynantheol (4)[2] using a potentially useful chiral synthon, (3S)-[3-hydroxy-(E)-prop-1-enyl]cyclopentanone (1)[3] derived from (R)-1,2-isopropylideneglyceraldehyde via α,β-unsaturated aldehyde (2). In our continuous



efforts toward the total synthesis of natural products using carbohydrates as a starting material, we studied an application of this chiral synthon (1) to the synthesis of (-)-antirhine (6),[4,5] the major alkaloid of Antirhea putaminosa. The synthetic strategy for the synthesis of (-)-antirhine (6) centered arround how to retain the double bond in 7 without migration during hydrolysis. This problem was easily resolved by mild hydrolysis of 7. We wish to report here successful total synthesis of (-)-antirhine (6) via β,γ-unsaturated aldehyde (5).

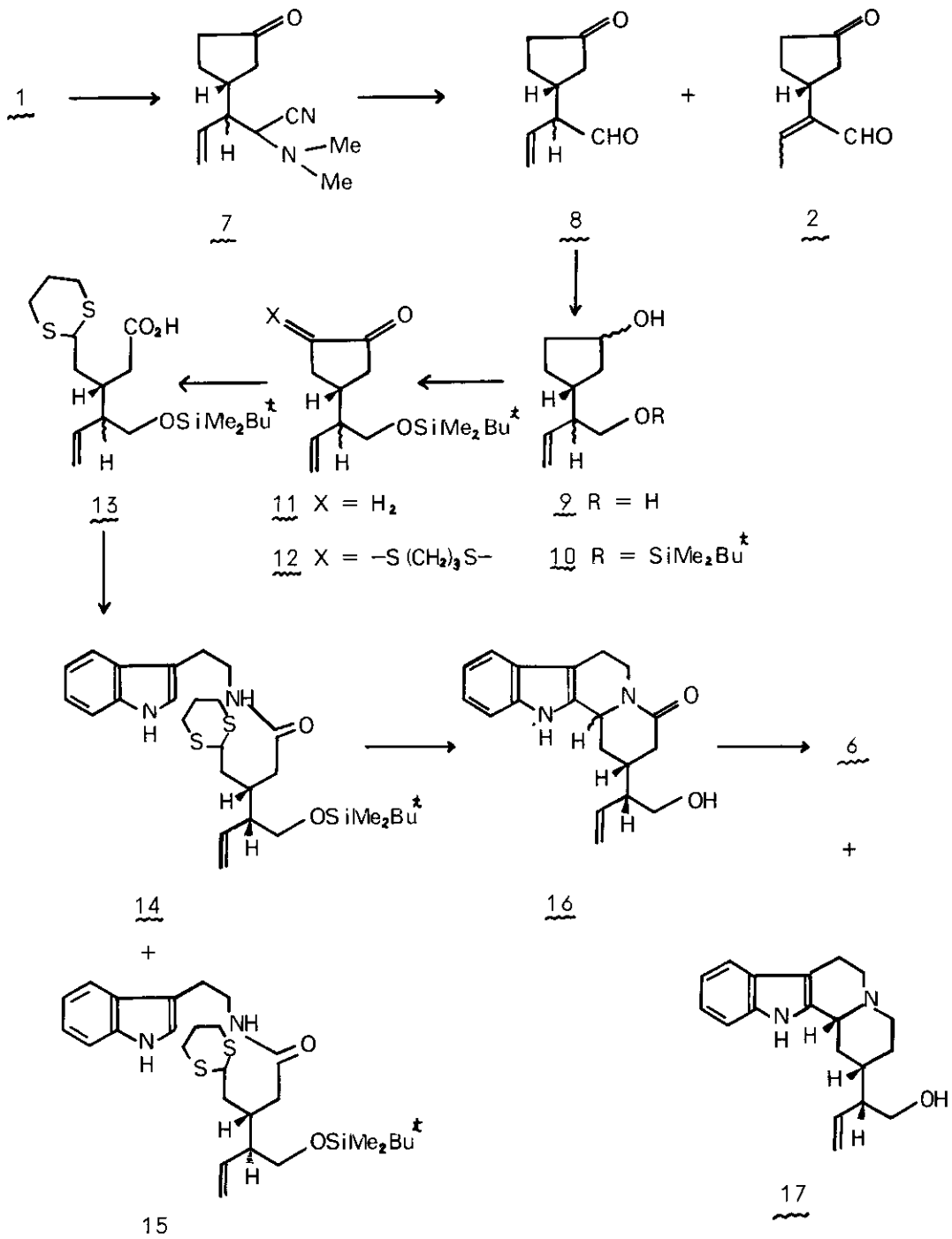
The synthetic procedure of 6 was carried out along the lines previously reported on 3.[1] Hydrolysis[6] of 7 prepared from 1 in 3 steps with cupric sulfate in ethanol at 80°C for 10 min provided the desired β,γ-unsaturated aldehyde (8) in addition to a small amount of the undesired α,β-unsaturated aldehyde (2) in the ratio 9:1. Reduction of 8 with sodium borohydride followed by protection of the primary alcohol in 9 as the tert-butyldimethylsilyl ether and then oxidation of 10 using pyridinium chlorochromate (2 equiv.) and sodium acetate (2 equiv.) in dichloromethane afforded the cyclopentanone (11), $[\alpha]_D$ 66.0° (c = 1.254, $CHCl_3$), in 7 % overall yield from 1.

Regioselective dithioacetalisation of 11 was performed to give the α-diketone monothioketal 12, $[\alpha]_D$ -46.4° (c = 0.625, $CHCl_3$), in 70.4 % yield with trimethylene dithiotoluene-p-sulphonate[7] (1.5 equiv.) through the pyrrolidine enamine. Basic cleavage[8] of 12 with potassium hydroxide (3.5 equiv.) in tert-butanol at 60°C for 2 h produced the carboxylic acid (13) $[\alpha]_D$ 2.6° (c = 0.453, $CHCl_3$) in 73.4 % yield. Treatment of 13 with methyl chloroformate in the presence of triethylamine[9] gave the crude mixed anhydride, which on condensation with tryptamine in dichloromethane afforded the secondary amide (14), $[\alpha]_D$ 2.3° (c = 0.087, $CHCl_3$), and the undesired amide (15), $[\alpha]_D$ 1.7° (c = 0.349, $CHCl_3$), as an easily separable mixture in 80.8 % yield, the formation ratio of both amides being 1:1.

Exposure of 14 to methyl iodide in aqueous acetonitrile[10] resulted in cyclisation and simultaneous deprotection of the protecting group to give the lactam (16), $[\alpha]_D$ -10.3° (c = 0.116, $CHCl_3$), in 64.5 % yield.

Finally, 16 was reduced with lithium aluminium hydride to afford (-)-antirhine (6), $[\alpha]_D$ -1.9° (c = 0.021, $CHCl_3$), lit.,[4] $[\alpha]_D$ -2° (c = 0.23, $CHCl_3$), whose ir, nmr, mass spectra and t.l.c. behavior were identical with those of the authentic natural product, and (+)-C_3-epi-antirhine (17) in 50.6 and 22.6 % yield, respectively.

The transformation of (3S)-[3-hydroxy-(E)-prop-1-enyl]cyclopentanone (1) into (-)-antirhine has thus been achieved.



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