

TOTAL SYNTHESIS OF (-)-ANTIRHINE

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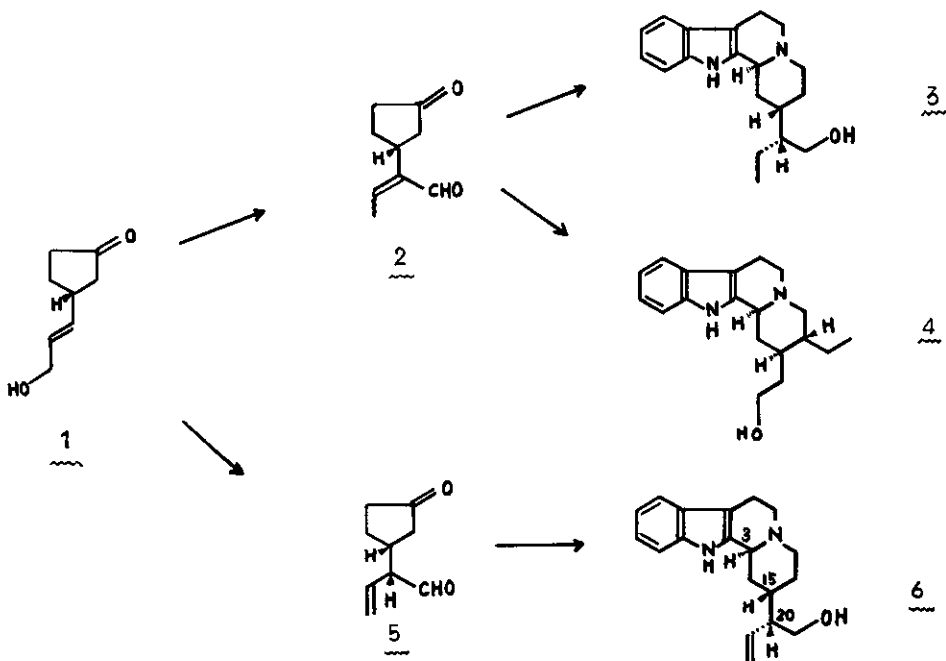
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Abstract — Total synthesis of (-)-antirhine (**6**) has been achieved from a potentially useful chiral synthon, (3S)-[3-hydroxy-(E)-prop-1-enyl]cyclopentanone (**1**), via β,γ -unsaturated aldehyde (**5**), which was obtained by mild hydrolysis of 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 (-)-antirrhine (**6**),^{4,5} the major alkaloid of *Antirhea putaminosa*. The synthetic strategy for the synthesis of (-)-antirrhine (**6**) centered around 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 (-)-antirrhine (**6**) via β,γ -unsaturated aldehyde (**5**).

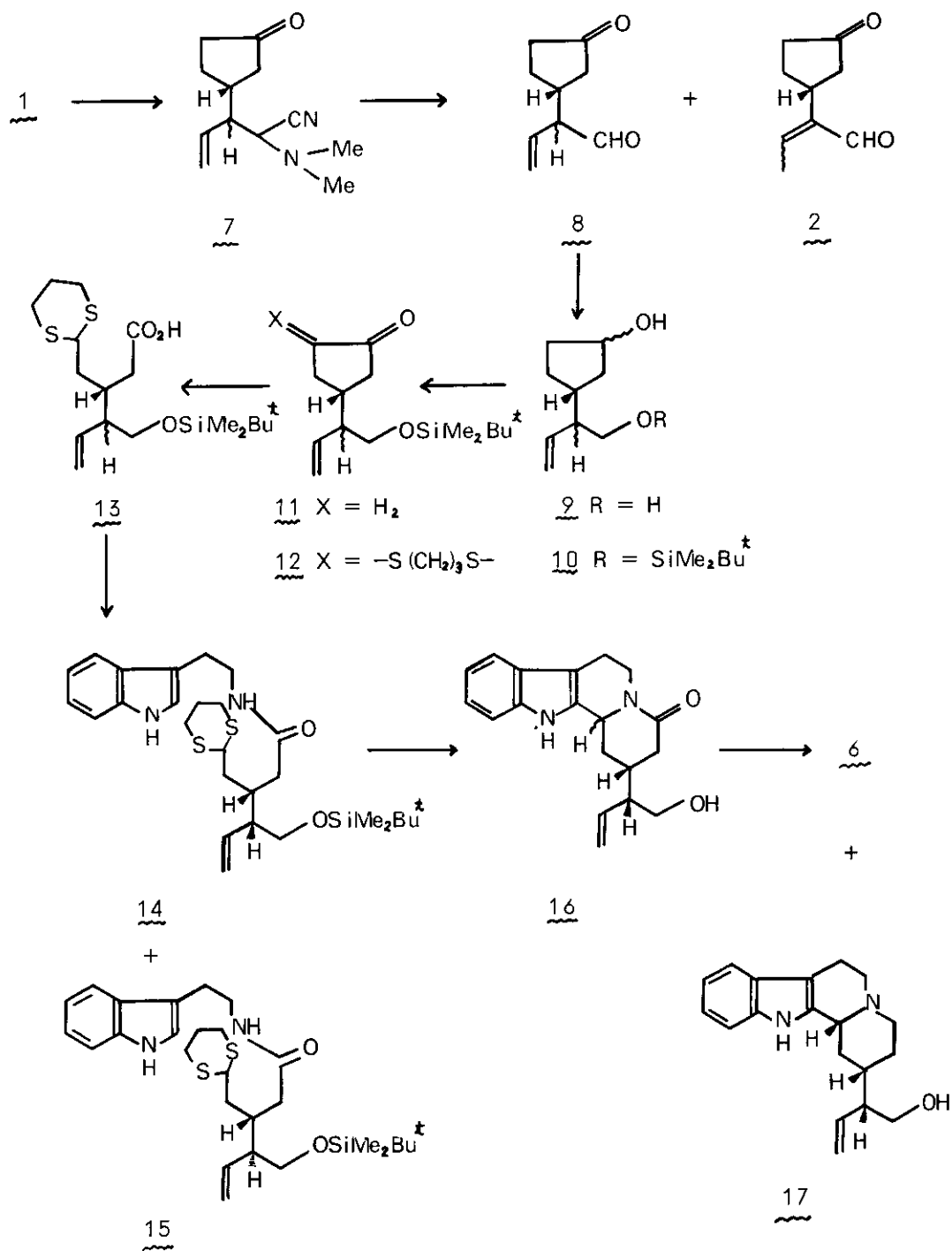
The synthetic procedure of **6** was carried out along the lines previously reported on **3**.¹ Hydrolysis⁶ of **7** prepared from **1** in 3 steps with cupric sulfate in ethanol at 80°C for 10 min provided the desired β,γ -unsaturated aldehyde (**8**) in addition to a small amount of the undesired α,β -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, CHCl₃), in 7 % overall yield from **1**.

Regioselective dithioacetalisation of **11** was performed to give the α -diketone monothioacetal **12**, $[\alpha]_D$ -46.4° (c = 0.625, CHCl₃), in 70.4 % yield with trimethylene dithiotoluene-*p*-sulphonate⁷ (1.5 equiv.) through the pyrrolidine enamine. Basic cleavage⁸ 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, CHCl₃) in 73.4 % yield. Treatment of **13** with methyl chloroformate in the presence of triethylamine⁹ gave the crude mixed anhydride, which on condensation with tryptamine in dichloromethane afforded the secondary amide (**14**), $[\alpha]_D$ 2.3° (c = 0.087, CHCl₃), and the undesired amide (**15**), $[\alpha]_D$ 1.7° (c = 0.349, CHCl₃), 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 acetonitrile¹⁰ resulted in cyclisation and simultaneous deprotection of the protecting group to give the lactam (**16**), $[\alpha]_D$ -10.3° (c = 0.116, CHCl₃), in 64.5 % yield.

Finally, **16** was reduced with lithium aluminium hydride to afford (-)-antirrhine (**6**), $[\alpha]_D$ -1.9° (c = 0.021, CHCl₃), lit.,⁴ $[\alpha]_D$ -2° (c = 0.23, CHCl₃), whose ir, nmr, mass spectra and t.l.c. behavior were identical with those of the authentic natural product, and (+)-C₃-*epi*-antirrhine (**17**) in 50.6 and 22.6 % yield, respectively.

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



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