Enantioselective Synthesis of (+)-Dihydroantirhine

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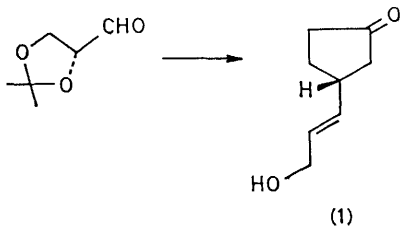
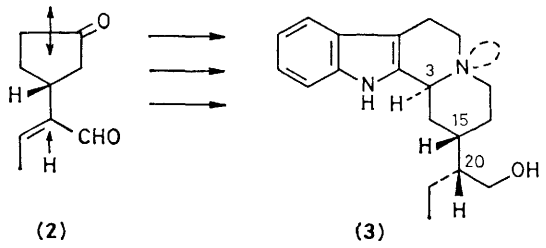
Enantioselective synthesis of (+)-dihydroantirhine (**3**) has been achieved from a readily available chiral starting material, (3*S*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**1**), *via* 2,3-sigmatropic rearrangement.

In a preceding paper,[1] we proposed that (3*S*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**1**) derived from (*R*)-1,2-isopropylideneglyceraldehyde could be a potentially versatile chiral synthon for natural products. In our continuous efforts



(1)

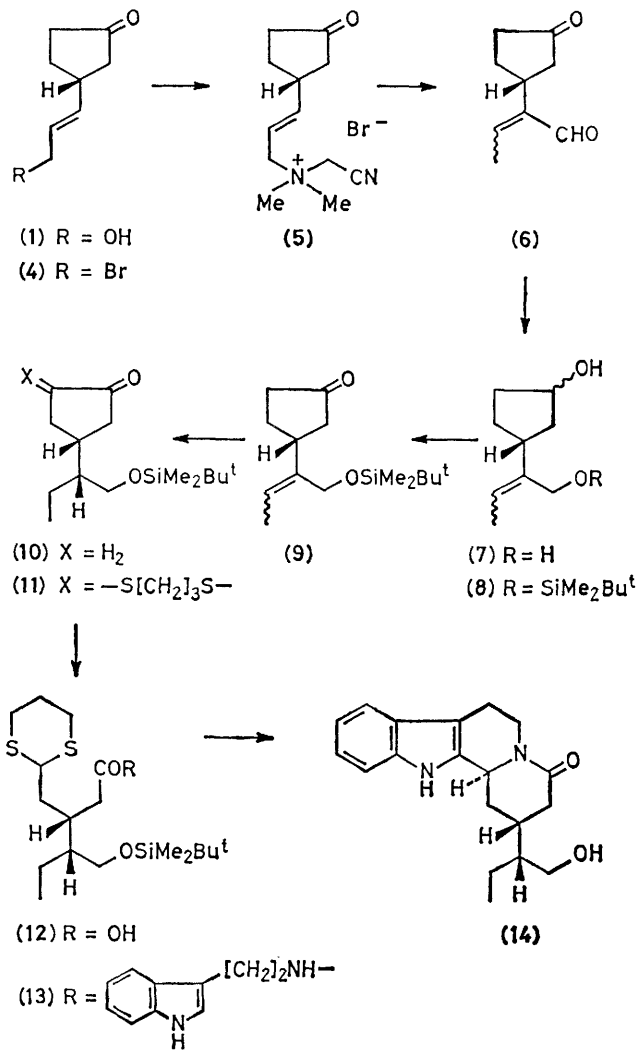


(2) (3)

towards the total synthesis of natural products starting from sugar,[1,2] we have been intrigued by the enantioselective synthesis of dihydroantirhine (**3**)[3] from (**1**). Here we report our successful results.

Our synthetic plan involves the stereoselective hydrogenation of the double bond and regioselective cleavage of the cyclopentanone unit in (**2**) as shown by the arrows. A molecule of type (**2**) should in turn result from 2,3-sigmatropic rearrangement of (**1**).

(3*S*)-[3-Hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**1**),[1] prepared in 7 steps from (*R*)-1,2-isopropylideneglyceraldehyde, was allowed to react with phosphorous tribromide in the presence of pyridine (diethyl ether, 0 °C) to give the allyl bromide (**4**). Compound (**4**) was converted, without purification, into the α,β-unsaturated aldehyde (**6**) in 34.9% overall yield from (**1**) *via* 2,3-sigmatropic rearrangement[4] of the allylic ammonium ylide (**5**)[5] [dimethylaminoacetonitrile (1.1 equiv.), dimethyl sulphoxide, room temp., 15 h, KOBu^t (1.25 equiv.), tetrahydrofuran (THF), −10 °C, 2 h] and subsequent hydrolysis [30% $(CO_2H)_2$, THF, reflux, 1 h]. Reduction of (**6**) with sodium borohydride followed by protection of the primary alcohol group in (**7**) as the t-butyldimethylsilyl ether[6] [Bu^{t}Me$_2$SiCl (1.1 equiv.), imidazole (2 equiv.), dimethylformamide (DMF), −10 °C, 5 h] gave the monoprotected alcohol (**8**) in 82.4% yield which in turn was oxidized[7] [pyridinium chlorochromate (2 equiv.), sodium acetate (2 equiv.), CH_2Cl_2, room temp., 2 h] to the cyclopentanone (**9**) {$[\alpha]_D$ +69.0° (*c* = 0.168, $CHCl_3$)†}. The catalytic hydrogenation over Adam's catalyst of (**9**) proceeded stereoselectively in almost quantitative yield to provide (**10**) {$[\alpha]_D$ +92.6° (*c* = 0.497, $CHCl_3$)} possessing the desired stereochemistry at C(20) (numbering of dihydroantirhine). Regioselective thioacetalization [trimethylene dithiotoluene-*p*-sulphonate[8] (1.5 equiv.), triethylamine (2.5 equiv.), acetonitrile, reflux, 4 h] was achieved by treatment of the pyrrolidine enamine derived from (**10**) to afford the α-diketone monothioacetal (**11**) {$[\alpha]_D$ −35.3° (*c* = 0.216, $CHCl_3$)} in 68.3% overall yield from (**10**).



(1) R = OH
(4) R = Br

(5) (6) (10) X = H_2 (11) X = —S[CH_2]$_3$S— (9) (7) R = H (8) R = SiMe$_2$Bu^t (12) R = OH (14) (13) R =

Basic cleavage[9] of (**11**) [KOH (3.5 equiv.) in Bu^{t}OH, 60 °C, 2 h] followed by acidic work-up produced the carboxylic acid (**12**) {$[\alpha]_D$ +5.9° (*c* = 0.339, $CHCl_3$)} in 62.2% yield. Treatment of (**12**) with ethyl chloroformate in the presence of triethylamine[10] (CH_2Cl_2, room temp., 2.5 h) gave the crude mixed anhydride, which on condensation with tryptamine (CH_2Cl_2, room temp., 15 min) afforded the secondary amide (**13**) {$[\alpha]_D$ −6.2° (*c* = 0.13, $CHCl_3$)} in 84.5% overall yield.

Exposure of (**13**) to methyl iodide in aqueous acetonitrile[3a,11] (48 h, room temp.) resulted in cyclisation and simultaneous deprotection of the hydroxy-group to give the lactam (**14**) {$[\alpha]_D$ −21.7° (*c* = 0.12, $CHCl_3$)}. Finally, the lactam (**14**) was reduced with lithium aluminium hydride (THF, reflux, 3 h) to afford dihydroantirhine (**3**) in 81.1% yield. The synthetic substance had identical t.l.c. behaviour, rotation, i.r., ^{1}H n.m.r., and mass spectra to the authentic sample derived from natural antirhine. The transformation of (3*S*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**1**) into dihydroantirhine has thus been achieved.

† Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

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