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SHORT REPORTS

STEREOSPECIFIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-RHODODENDROL*

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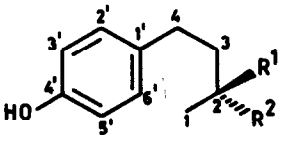
Key Word Index—*Rhododendron maximum*; *Acer nikoense*; (+)-rhododendrol; (−)-rhododendrol; absolute configuration; enzymatic reduction; baker's yeast.

Abstract—The stereospecific synthesis of (+)-rhododendrol, a constituent of *Rhododendron maximum* and *Acer nikoense*, by enzymatic reduction of 4-(4′-hydroxyphenyl)-2-butanone has shown that the absolute configuration of the molecule is *S*.

INTRODUCTION

(+)-Rhododendrol [(+)-4-(4′-hydroxyphenyl)-2-butanol] (**1**), mp 81–83° ($CHCl_3$), $[\alpha]_D$ +17.1° (EtOH; *c* 2.0), was isolated [1] for the first time from *Rhododendron maximum*. Later, it was isolated [2] along with its glucoside (**2**) from *Acer nikoense* and its absolute configuration was proposed to be *S* on the basis of the empirical rule on the relationship between optical rotation and chirality. There is no other report on the study on (+)-rhododendrol to determine its absolute configuration. It is interesting that its enantiomer, (−)-rhododendrol (**3**), and its glucoside (**4**) have been isolated [3] from *R. chrysanthum* and that these compounds have been reported [4] from different species of different genera. The absolute configuration of (−)-rhododendrol was proposed [5] as *S* by a biosynthetic method and more recently X-ray crystallographic analysis suggested [4] its absolute configuration to be *R*. The synthesis of **3** and (±)-rhododendrol has been achieved [6] but **1** has not yet been synthesized. Here we report the stereospecific synthesis of **1** by an enzymatic process which provides an easy method to determine its absolute configuration as *S*.



	R^1	R^2
1	OH	H
2	OGlc	H
3	H	OH
4	H	OGlc
5	O	O

RESULTS AND DISCUSSION

The stereospecific synthesis of **1** was achieved from 4-(4′-hydroxyphenyl)-2-butanone (**5**). The latter was synthesized by a reported method [6]. Chemical reduction of **5** with sodium and ethanol [6] or sodium borohydride [7] afforded the corresponding racemic alcohol. Earlier attempts [7] to resolve the racemic alcohol into its optically active forms were unsuccessful. However, it is now well documented [8–12] that the enzymatic reduction of an unsymmetrical carbonyl compound proceeds stereospecifically to an optically active alcohol and that a 4-aryl-2-butanone can be reduced with baker's yeast to afford in good yield and high optical purity the corresponding *S*-alcohol. We, therefore, treated **5** with baker's yeast under the conditions reported earlier for the reduction of a 4-aryl-2-butanone [12]. The product was characterized as 4-(4′hydroxyphenyl)-2-butanol from its spectral data (Experimental) and it showed an optical rotation of +13.6° (EtOH; *c* 0.4135). Hence it may be concluded that **1** possesses *S* configuration. This conclusion is supported by the result obtained from the X-ray crystallographic analysis [4] of **3** which confirmed the absolute configuration of the molecule as *R*. The enzymatic process discussed here offers a useful means for the determination of the absolute configuration of arylbutanols analogues of **1**.

EXPERIMENTAL

Mps: uncorr; IR: KBr; ^{1}H NMR: 200 MHz, $CDCl_3$ with TMS as int. standard; CC: silica gel (B.D.H.,

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100–200 mesh); TLC: silica gel G. The TLC spots were visualized by exposure of the plates to I_2 vapour. Baker's yeast (*Saccharomyces cerevisiae*, Type I, Sigma) was used for enzymatic reduction.

Synthesis of (+)-rhododendrol. Baker's yeast (3 g) was added to a vigorously stirred soln of sucrose (1.5 g) in tap H_2O (200 ml). The suspension was stirred for 0.5 hr at 30°. Compound **5** [6] (70 mg) was added and the stirring was continued. Three portions of fermenting baker's yeast [1.5 g in a soln of sucrose (750 mg) in tap water (50 ml)] were added during 72 hr and the suspension was stirred for another 48 hr at room temp. The mixt. was worked up by first adding celite and filtering through a sintered glass funnel. The filtrate was satd with NaCl and extracted with EtOAc (4 × 100 ml). The extract was dried, concd and purified by CC over silica gel to produce **1**, 48 mg, mp 80–81° ($CHCl_3$), $[\alpha]_D^{25}$ + 13.6° (EtOH; *c* 0.4135), IR ν_{max}^{nujol} cm^{-1}: 3330, 1595, 1500; ^1H NMR: δ 7.04 (2H, *d*, J = 8.0 Hz, H-3′ and H-5′), 6.72 (2H, *d*, J = 8.0 Hz, H-2′ and H-6′), 3.78 (1H, *m*, H-2), 2.64 (1H, *t*, J = 7.0 Hz, H_2-4), 1.79–1.58 (2H, *m*, H_2-3), 1.20 (3H, *d*, J = 8.0 Hz, Me); MS *m/z* (rel. int.): 166 $[M]^+$ (32), 148 (18), 133 (95), 107 (100).

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