PRACTICAL TOTAL SYNTHESES OF (*R*)-(+)- AND (*S*)-(-)-14-HYDROXY-4,14-*RETRO*-RETINOL

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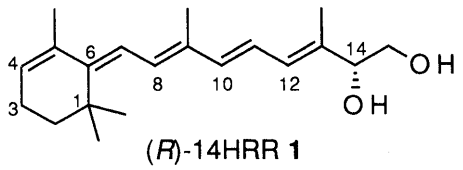
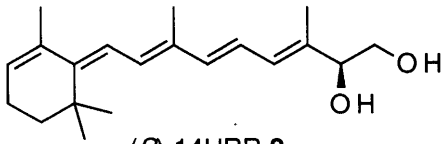
Practical and facile total syntheses of the remarkably unstable (*R*)-(+)-14-hydroxy-4, 14-*retro*-retinol [(*R*)-14HRR] **1** and of its enantiomer **2** have been achieved *via* an acid-catalyzed dehydration reaction of the respective tetraeneol intermediates **10** and its enantiomer obtained from (*R*)-(+)-1, 2-*O*-isopropylidene-butane-1, 2, 3-triol **3**.

KEYWORDS 14-hydroxy-4, 14-*retro*-retinol (14HRR); vitamin A; enantiomer

14-Hydroxy-4,14-*retro*-retinol (14HRR), one of the metabolites of vitamin A, was first isolated from B lymphocytes by Buck et al. in 1991.[1] It showed marked growth-supporting activity for B cells[1] and a functional activation of T cells,[2] and other related biological activity has been reported.[3-5] Because of its fascinating pharmacological activity and interesting chemical structure, much attention has been focused on 14HRR by biologists and chemists. In 1994, Derguini et al. reported the first synthesis of 14HRR[6] *via* Davalian's retroester.[7] Here we report alternative total syntheses of (*R*)-(+)-14HRR **1** and (*S*)-(-)-14HRR **2** *via* an acid-catalyzed dehydration reaction. Due to the instability of 14HRR,[1, 6] the latter steps of the synthesis need to be carried out under mild conditions. We have adopted an acid-catalyzed dehydration reaction and a deprotection reaction as the last two steps. Because the absolute configuration of 14HRR had not been determined,[1, 6] we developed a route to enable preparation of both enantiomers of the natural product.



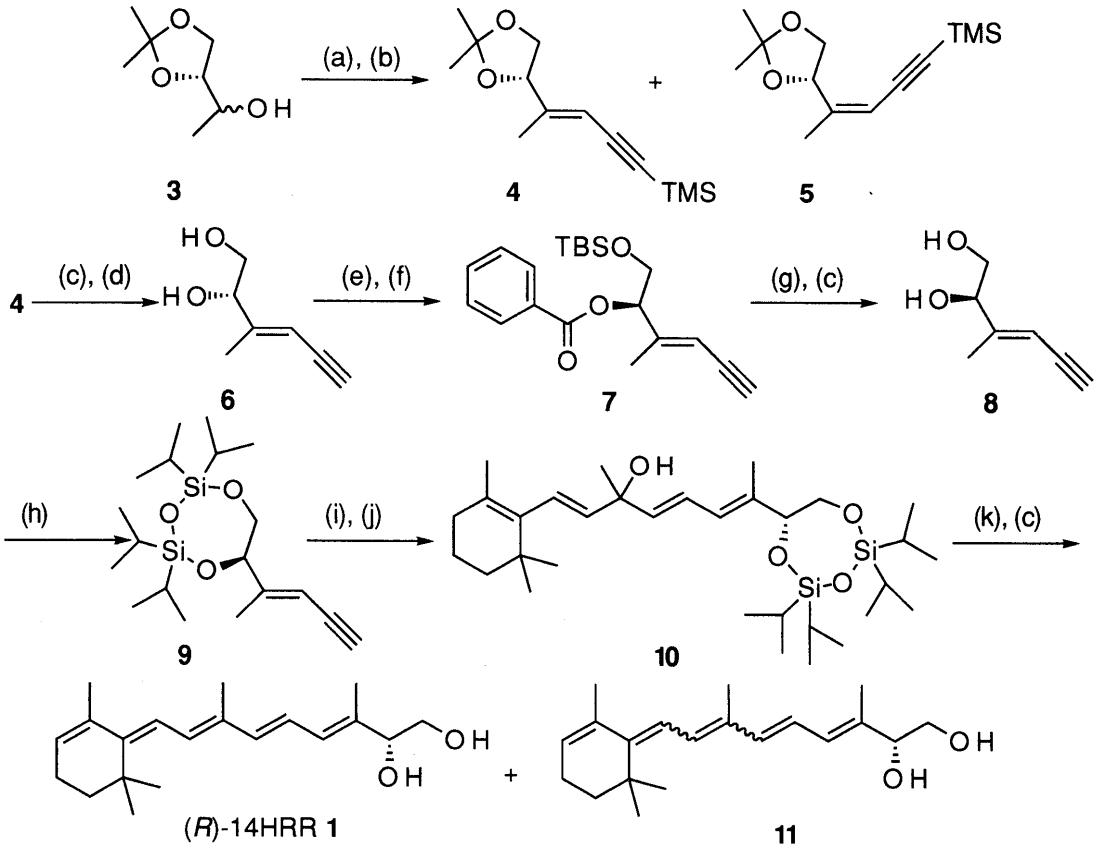
(*R*)-14HRR **1**



(*S*)-14HRR **2**

First, the synthesis of (*R*)-(+)-14HRR began with (*R*)-(+)-1,2-*O*-isopropylidene-butane-1, 2, 3-triol **3**,[8, 9] which was subjected successively to Swern oxidation ($(COCl)_2$, DMSO, Et_3N) and the Horner-Emmons reaction[10] ($NaN(TMS)_2$, diethyl (3-trimethylsilyl-2-propynyl) phosphonate) to give the *trans*-enyne **4** and the *cis*-enyne **5** in 63% yield in a ratio of 3 : 1. The structures of these products were determined on the basis of NOE experiments, in which the NOE between the methyne proton on the carbinol carbon and olefinic proton in *trans*-enyne **4** and the methyl proton and olefinic proton in *cis*-enyne **5** were observed. Next, inversion of the chiral center was accomplished as follows: (*S*)-(+)-3-hexen-5-yne-1, 2-diol **6** $[\alpha]_D^{24}$+3.06(*c*=2.32, MeOH) obtained from *trans*-acetonide **4** (*n*-Bu_4NF, THF, RT; AcOH, H_2O, 60°C) was protected selectively[11] (TBSCl, Et_3N, DMAP, CH_2Cl_2, RT) to give its mono-silyl ether in 75% yield, which on Mitsunobu reaction[12] afforded the benzoate **7** in 74% yield. Deprotection of the benzoate ester and silyl ether of compound **7** (1N KOH, MeOH, RT; *n*-Bu_4NF, THF, RT) afforded (*R*)-(-)-3-hexen-5-yne-1, 2-diol **8** $[\alpha]_D^{24}$-2.4 (*c*=1.49, MeOH) in 85% yield. The enantiomeric excesses of diols **6** and **8** were determined as follows: Treatment of diols **6** and **8** with MTPCl in pyridine gave di MTPA ester(*S*) and (*R*) respectively, whose ^{1}H-NMRs

showed their e.e.s to both be greater than 99%. Protection of the diol **8** with $TIPDSCl_2$,[13] which was an excellent protecting group not only for the acid dehydration reaction but also for its mild deprotection reaction, gave the silyl ether **9** in 81% yield. Alkylation of the enyne **9** with β-ionone followed by Red-Al reduction[14] gave the tetraene **10** selectively in 61% yield. Finally, the acid-catalyzed dehydration reaction[15-17] of the tetraene **10** was carried out with PPTS(0.3 eq) at 110°C in toluene for 3 min to give the *retro*-retinol derivative, which was then deprotected (*n*-Bu_4NF, THF, 10min) to furnish a mixture of (*R*)-(+)-14HRR **1** and its isomers **11** in 57% yield in a ratio of 7:3 after flash column chromatography, carried out on silica gel (Merck Kieselgel 60, mesh 70-230) containing 10% water. Purification of the mixture on a semipreparative reversed-phase C4 column (YMC, 300 Å) of 300 by 10mm internal diameter using water-methanol at 35/65 v/v as eluent gave pure (*R*)-(+)-14HRR **1**, whose spectral properties[18] were identical with those reported for natural 14HRR. The structures of two isomers **11** were assigned by ^1H-NMR.



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C-R. T. (b) $NaN(TMS)_2$, diethyl (3-trimethylsilyl-2-propynyl)-phosphonate, THF, -78°C (c) *n*-Bu_4NF, THF, R. T. (d) AcOH, H_2O, 60°C (e) TBSCl, Et_3N, DMAP, CH_2Cl_2, R. T. (f) Ph_3P, DEAD, $PhCO_2H$, THF, R. T. (g) 1N KOH, MeOH, R. T. (h) $TIPDSCl_2$, imidazole, DMF, R. T. (i) *n*-BuLi, β-ionone, THF, -78°C (j) Red-Al, THF, 0°C-R. T. (k) PPTS, toluene, reflux.

The synthesis of (*S*)-(-)-14HRR **2**[19] was accomplished similarly in 37% yield from (*S*)-(-)-3-hexen-5-yne-1, 2-diol **6**. The CD spectra of (*R*)-(+)-14HRR **1** and (*S*)-(-)-14HRR **2** were mirror images of each other. Although the absolute configuration at C-14 is still ambiguous, data on these products should be important for determination of the absolute structure. Bioassays of (*R*)-(+)-14HRR **1** and (*S*)-(-)-14HRR **2** are under way.[20]

In summary, the total syntheses of (*R*)-(+)-14HRR and (*S*)-(-)-14HRR have been achieved *via* an acid-catalyzed dehydration reaction and mild deprotection reaction. We have developed a practical method for the synthesis of sufficient quantities of (*R*)-(+)- and (*S*)-(-)-14HRR for biological assay. Our process should be easily applicable to the synthesis of analogs of 14HRR .

ACKNOWLEDGMENTS We are grateful to Dr. T. Takakuwa and Mr. T. Ikedo (JASCO Co. Ltd.) for CD measurements. We also thank Dr. N. Asakawa, Dr. Y. Kawakami, Dr. T. Kawai and Dr. R. S. J. Clark (Eisai Co.) for helpful discussion.

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18) All new compounds were characterized by 400 or 600 MHz ^{1}H-NMR, IR and high-resolution mass spectrum. : Spectral data for (*R*)-(+)-14HRR **1** : $[\alpha]_D^{24}$+10.14 (*c*=0.55, MeOH) [JASCO DIP-360]; UV λmax (MeOH : H_2O= 6 : 4) nm(ε) 252 (2,900), 334 (34,100), 350 (50,300), 369 (43,700) [HITACHI U-3500]; CD (MeOH : H_2O= 6 : 4) Δε (nm) +0.49 (333), +0.63 (348), +0.49 (368) [JASCO J-720 spectropolarimeter]; IR ($CHCl_3$) cm^{-1} 3620-3480, 2929, 1650, 1620, 1600, 1425, 1375 [NICOLET 205 FT-IR spectrometer]; ^{1}H-NMR (400 MHz, CD_3CN) δ: 1.30 (s, 6H, 1-Me_2), 1.51 (t, 2H, *J*=6.4 Hz, 2-H_2), 1.78 (s, 3H, 5-Me), 1.90 (d, 3H, *J*=1.6Hz, 9-Me), 1.94 (s, 3H, 13-Me), 2.13 (m, 2H, 3-H_2), 2.74 (br s, 1H, O<u>H</u>), 3.10 (br s, 1H, O<u>H</u>), 3.40 (dd, 1H, *J*=7.2, 11.2Hz, 15-H), 3.52 (dd, 1H, *J*=4.4, 11.2Hz, 15-H), 4.05 (m, 1H, 14-H), 5.80 (t, 1H, *J*=4.4Hz, 4-H), 6.19 (d, 1H, *J*=11.0Hz, 12-H), 6.40 (d, 1H, *J*=12.3Hz, 7-H), 6.44 (d, 1H, *J*=16.0Hz, 10-H), 6.57 (dd, 1H, *J*=11.0, 16.0Hz, 11-H), 6.78 (d, 1H, *J*=12.3Hz, 8-H) [VARIAN UNITY 400]; MS m/z: 302.2247 (Calcd for $C_{20}H_{30}O_2$: 302.2246) [JEOL JMS-HX100].

19) Spectral data for (*S*)-(-)-14HRR **2** $[\alpha]_D^{24}$-11.36 (*c*=0.70, MeOH); CD (MeOH : H_2O= 6 : 4) Δε (nm) -0.50 (331), -0.64 (351), -0.44 (370); Other spectra of this sample are superimposable upon those of (*R*)-(+)-14HRR **1**.

20) 14HRR was stored at -70°C 3mM in EtOH - H_2O (1 : 1) which contained 1mM BHT as a stabilizer, and used for biological assays. Full details of these bioassays will be reported in due course.

(Received May 17, 1994; accepted June 9, 1994)