Stereocontrolled Synthesis of Optically Active β-D-Glucopyranosides of 3-Hydroxy-7,8-didehydro-β-ionol

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A stereocontrolled synthesis of optically active β-D-glucopyranosides 1—4 of 3-hydroxy-7,8-didehydro-β-ionol utilizing an asymmetric transfer hydrogenation to α,β-acetylenic ketones catalyzed by chiral ruthenium complexes as the key step is described.

Key words β-glucosides; 3-hydroxy-7,8-didehydro-β-ionol; asymmetric transfer hydrogenation; aroma precursor; chiral ruthenium complexes

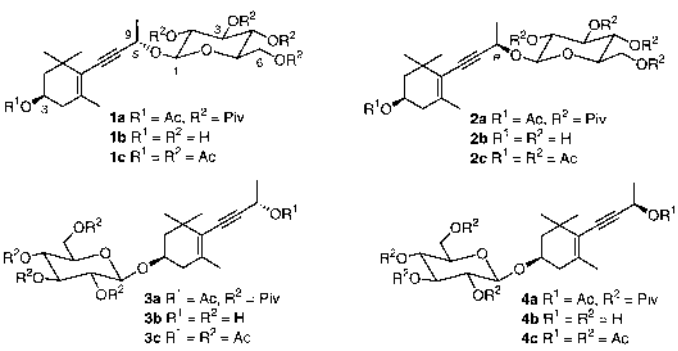
Damascenone and the related C_{13}-norisoprenoid aroma compounds have been suggested[1] to be produced through biodegradation of carotenoids in plants; however, the direct progenitors were not completely clarified. The titled compounds have been isolated from rose petals[2] and Riesling wine[3] as glucosidic aroma precursors. Especially, the 9-*O*-glucoside was considered[3] to be the more important damascenone progenitor, since its acid-treatment yielded a higher portion of damascenone compared to the free aglycon. The role of the glucosyl moiety in these glucosides is recognized[2,3] as stabilization of the hydroxy group. In intact plants, not only the position of the glucosyl moiety but also the stereochemistries of the hydroxy groups in these glucosides are considered to have influence on the behavior against enzymatic hydrolysis. Their stereochemistries at C-3 are considered to be *R*, because most xantophylls have *R* configuration for C-3.[4] However, their stereochemistries at C-9 have not been confirmed yet. Although the 9-*O*-β-glucoside of 3-hydroxy-7,8-didehydro-β-ionol has been prepared[5] as a diastereoisomeric mixture, there has been so far reported no stereocontrolled synthesis for the optically active glucoside. In order to clarify their roles as aroma precursors in plants, the confirmation of their stereochemistries including absolute configurations and the preparation of a diastereomeric pure sample is required. We have now accomplished the stereocontrolled synthesis of (3*R*,9*S*)- and (3*R*,9*R*)-9-*O*-β-D-glucopyranosides **1** and **2** as well as the corresponding 3-*O*-β-D-glucopyranosides **3** and **4** utilizing an asymmetric transfer hydrogenation[6] to α,β-acetylenic ketones catalyzed by chiral ruthenium complexes as the key step.

The known[7] (3*R*)-3-acetoxy terminal alkyne **5**, prepared (67%) from (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone,[8] was reduced with $LiAlH_4$ (93%) and then silylated (99%) to give the *tert*-butyldimethylsilyl (TBS) ether **6**. Reaction of the lithium derivative prepared from *n*-BuLi and **6** with acetaldehyde, followed by oxidation with MnO_2 provided α,β-acetylenic ketone **7** (88%), which was deprotected (99%) and then acetylated (96%) to give the acetate **8**. Asymmetric transfer hydrogenation[6] of α,β-acetylenic ketones **7** and **8** using chiral Ru(II) catalysts **15** or **16**[9] and 2-propanol as the hydrogen donor afforded the diastereomeric pure (>98% ee)[10] alcohol **9** or **10** as well as **11** or **12** in good isolated yields (>95%), respectively. The stereochemistries at C-9 of these alcohols were determined by the modified Mosher's method.[11] The (*S*)- and (*R*)-MTPA [α-methoxy-α-(trifluoromethyl)phenyl acetic acid] esters of **9** and **11** obtained by use of (*S*,*S*)-**15** were prepared. The positive $\Delta\delta$ values of δ_S–δ_R were observed on all protons except for the 9-methyl protons, indicating that **9** and **11** had *S* configuration for C-9. Thus, it was found that **10** and **12** obtained by use of (*R*,*R*)-**16** had *R* configuration for C-9. In the case of the TBS ether **7**, the (*S*)- or (*R*)-alcohol **11** or **12** could be also prepared *via in situ* formation of **15** or **16** by mixing $[RuCl_2(p\text{-cymene})]_2$, (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-toluenesufonyl)-1,2-diphenylethylenediamine (TsDPEN) and KOH in 2-propanol (Ru : diamine : KOH = 1 : 1 : 2.5).[6]

We next examined the glucosidation of alcohols **9** and **10** to prepare 9-*O*-β-D-glucopyranosides **1** and **2**. We have previously reported[12] that the reaction of 3-hydroxy-β-ionone with tetra-*O*-benzoyl-α-D-glucopyranosyl bromide using silver triflate as an activator and *N*,*N*-tetramethylurea as a proton acceptor gave the ortho ester, whereas the desired β-glucoside was obtained in the absence of *N*,*N*-tetramethylurea. In the cases of alcohols **9** and **10**, reaction with tetra-*O*-benzoyl-α-D-glucopyranosyl bromide using silver triflate in the absence of *N*,*N*-tetramethylurea provided complex mixtures, probably due to their instability against acidic conditions. β-Glucosidation of **9** and **10** was achieved[13] (**1a**: 72%; **2a**: 72%) by use of tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide[14] possessing a sterically bulky acyl group at C-2 position as a glucosyl donor and silver triflate as an activator in the presence of *N*,*N*-tetramethylurea. The acyl groups of **1a** and **2a** were removed under basic conditions to give the free alcohols (**1b**: 98%; **2b**: 99%), which were acetylated to provide pentaacetates **1c** (95%) and **2c** (87%).

3-*O*-β-D-Glucopyranosides **3a** (64%) and **4a** (76%) were also prepared[13] by a similar glucosidation of alcohols **13** and **14**, which were obtained (**13**: 97% from **11**; **14**: 91% from **12**) by acetylation of **11** and **12** and subsequent desilylation. Deacylation (**3b**: 93%; **4b**: 99%) of **3a** and **4a** followed by acetylation afforded pentaacetates **3c** (82%) and **4c** (91%).

^{1}H- and ^{13}C-NMR spectra of 9-*O*-glucosides **1c** and **2c** were similar to each other but showed characteristic differences around C-9 as shown in the Table. Spectral data of the (9*S*)-glucoside **1c** were identical with those of the 9-*O*-glucoside isolated[3] from Riesling wine, while those of the (9*R*)-glucoside **2c** were accordance with those of the 9-*O*-glucoside isolated[2] from rose petals.



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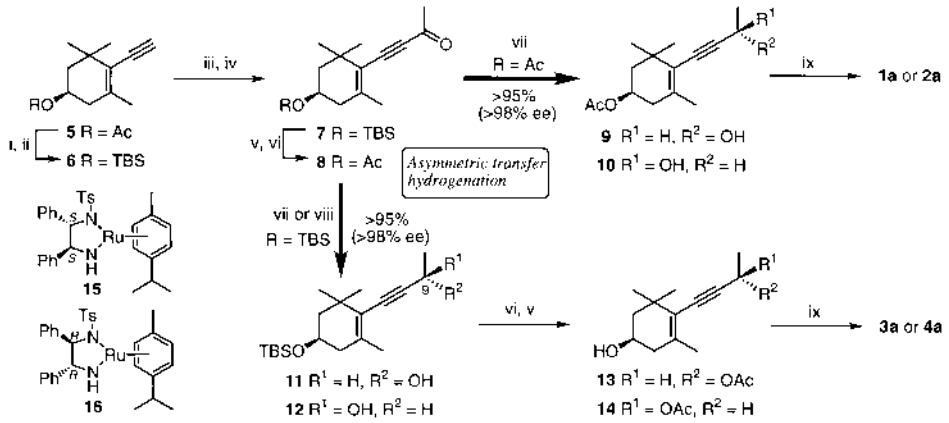

Reagents: i, $LiAlH_4$; ii, TBSCl, DMAP, Et_3N; iii, *n*-BuLi then CH_3CHO; iv, MnO_2; v, HF; vi, Ac_2O, Py; vii, cat. (*S*,*S*)-**15** or (*R*,*R*)-**16**, 2-PrOH; viii, cat. $[RuCl_2(p\text{-cymene})]_2$, cat. (*S*,*S*)- or (*R*,*R*)-TsDPEN, cat. KOH, 2-PrOH; ix, tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide, AgOTf, $Me_2NC(O)NMe_2$.

Chart 1

Table 1. Characteristic Spectral Data for Glucosides **1c**—**4c**

		1c (9*S*)	**2c** (9*R*)	δ (**1c**)—δ (**2c**)	**3c** (9*S*)	**4c** (9*R*)
^{1}H-NMR ($CDCl_3$, 500 MHz) δ: ppm	3-H	5.03	5.01	+0.02	3.92	3.92
	9-H	4.80	4.74	+0.06	5.60	5.59
	9-Me	1.48	1.51	−0.03	1.52	1.52
	1′-H	4.88	4.86	+0.02	4.62	4.62
^{13}C-NMR ($CDCl_3$, 125 MHz) δ: ppm	C3	67.74	67.77	−0.03	73.07	73.07
	C9	64.30	67.52	−3.22	61.10	61.10
	9-Me	22.35	23.12	+0.23	21.67	21.68
	C1′	97.78	98.88	−1.00	99.61	99.60
$[\alpha]_D^{26-7}$ (c=0.8—1.0, MeOH)		−62.1°	−6.8°	—	−108.6°	+14.6°

On the other hand, both ^{1}H- and ^{13}C-NMR spectra of 3-*O*-glucosides **3c** and **4c** did not show any differences, but their optical rotation data were quite different (Table). Although the ^{1}H-NMR data for the 3-*O*-glucoside isolated[3] from Riesling wine were in good agreement with those of **3c** and **4c**, the stereochemistry at C-9 is not confirmed yet as its optical rotation was not measured.

In conclusion, we have achieved a stereocontrolled synthesis of optically active β-D-glucopyranosides **1**—**4** of 3-hydroxy-7,8-didehydro-β-ionol. Synthetic studies of related C_{13}-norisoprenoid-glucosides and investigation toward the clarification of their role as aroma precursors are now in progress.

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