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Synthesis of Both Enantiomers of Halitunal

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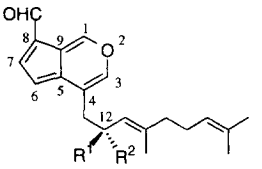
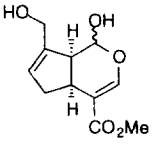
Abstract: Both enantiomers of halitunal (**1**), a novel diterpene aldehyde having an iridoid carbon framework with a heteroaromatic 10π-system, have been synthesized from (+)-genipin (**2**).

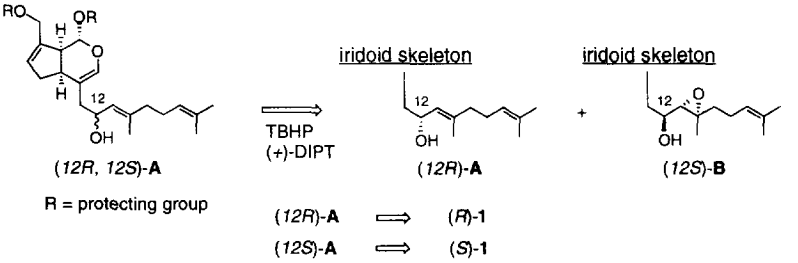
Halitunal (**1**), a diterpene aldehyde isolated from the marine algae *Halimeda tuna*, exhibits significant *in vitro* activity against a virus, namely, mourn coronavirus strain A59.[1] From the structural point of view, halitunal has an iridoid carbon framework with a 10π-aromatic cyclopentadieno[c]pyran ring system and one asymmetric carbon center at C12, the absolute configuration of which has not yet been assigned.[1] We wish to report herein the first synthesis of optically active halitunal ((*R*)-**1** and (*S*)-**1**, respectively).



Halitunal (1)
R: R^1 = H, R^2 = OAc
S: R^1 = OAc, R^2 = H

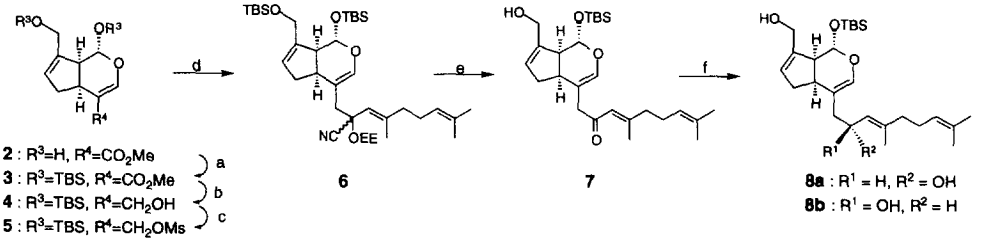


(+)-Genipin (2)



Scheme 1

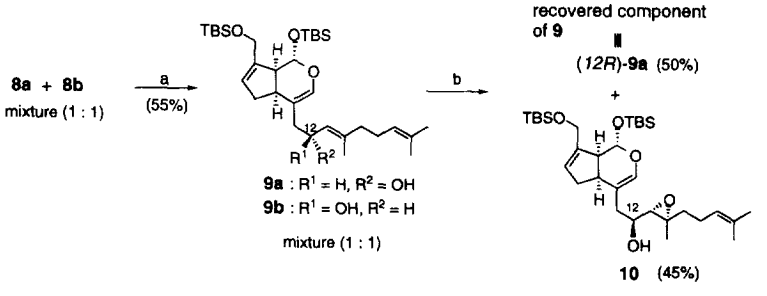
Our synthetic plan was the use of (+)-genipin (**2**) as the chiral starting material, which has the requisite iridoid carbon framework and is abundantly available from the water extract of *Gardenia jasminodes* Eills.[2-6] The present study, which targeted the synthesis of both enantiomers of **1**, required the introduction of the C12 hydroxyl group with an unambiguous absolute configuration. Therefore, the synthesis of a mixture of allylic alcohols **A** and a kinetic resolution of the mixture using the Sharpless asymmetric epoxidation method[7] was carried out first (Scheme 1). The presence of the chiral centers in the iridoid skeleton would be useful to certify the diastereomeric purity of the C12 hydroxyl group of the products. Thus, we started the synthesis of **A** from **2**.



a) TBSCl, $AgNO_3$, DMF (89%). b) DIBAH, CH_2Cl_2, -78 °C (91%). c) *n*-BuLi, MsCl, THF, -78 °C. d) **14**, LDA, THF, -78 °C. e) PPTS, MeOH. f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (26%, 4 steps).

Scheme 2

Reduction of (+)-genipin bis(silyl ether) (**3**), obtained by silylation of both hydroxyl groups of **2**, with diisobutylaluminum hydride (DIBAH) gave allylic alcohol **4** in good yield (Scheme 2). After mesylation of the hydroxyl group of **4**, the resulting mesylate **5** was treated with the carbanion of cyano ether **14**[8] to afford **6** as a mixture of diastereomers (1 : 1). This was converted to the enone **7** by the following sequence of reactions: (1) hydrolysis of the ethoxyethyl ether moiety, (2) dehydrocyanation, and (3) selective removal of the silyl ether moiety on the primary position. Reduction of **7** with $NaBH_4$ in the presence of cerium(III) chloride afforded a diastereomeric mixture of allylic alcohols (**8a** and **8b** (1 : 1)), which were separated by silica gel column chromatography to give the less polar isomer **8a** and the more polar isomer **8b**, respectively.[9]



a) TBSCl, imidazole, DMF. b) (+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, -20 °C.

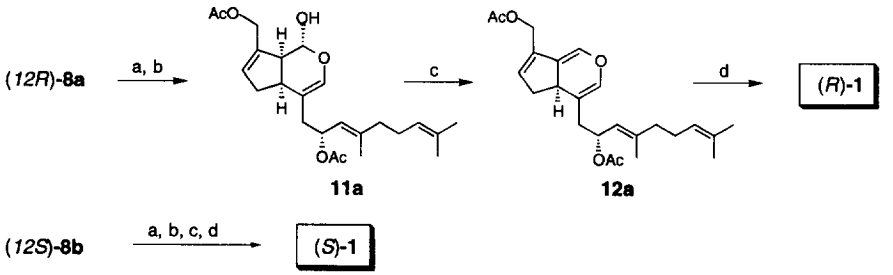
Scheme 3

It is well-known that a mixture of secondary allylic alcohols can be kinetically resolved under the Sharpless asymmetric epoxidation conditions where the rate of the formation of (*R*)-epoxide is much faster

than that of (*S*)-epoxide when (+)-diisopropyl tartrate (DIPT) was employed.[7] Thus, treatment of the mixture of the allylic alcohols **9a** and **9b**, prepared by silylation of **8**, with *tert*-butyl hydroperoxide (TBHP), (+)-DIPT, and titanium tetraisopropoxide ($Ti(O\text{-}i\text{-}Pr)_4$), gave a mixture of the unreacted allylic alcohol and the diastereomerically homogeneous epoxy alcohol **10** (Scheme 3). Thus, the absolute configuration at C12 of the recovered allylic alcohol **9a** was assigned to be *R* and that of the epoxide **10** to be *S* based on the above empirical method[7,10,11] Since the recovered **9a** corresponded to the less polar isomer **8a**, the absolute configuration at C12 was assigned to be *R*.

Finally, we examined the conversion of each isomer of **8** into optically pure (*R*)-**1** and (*S*)-**1** (Scheme 4). Acetylation of **8a** followed by removal of the silyl group gave the desired diacetate **11a** in quantitative yield. Dehydration of **11a** was carried out by treatment with 1,1'-thiocarbonyldiimidazole in benzene at room temperature to afford **12a**. Treatment of **12a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene at room temperature underwent dehydrogenation to give the desired (*R*)-**1** as a yellow oil. The conversion of **11a** to (*R*)-**1** was achieved in a one-pot process in 43% yield. The 12*S* enantiomer of **1** was synthesized from **8b** in the same manner as (*R*)-**1**. Synthetic (*R*)-**1** and (*S*)-**1** were completely identical with natural halitunal in all respects (^{1}H-NMR, ^{13}C-NMR, IR, UV, and high resolution mass spectra).[1,12] Unfortunately, the optical rotation of natural halitunal was not described in Koehn's report[1] and its authentic sample was not available.[13] However, it is obvious that either (*R*)-**1** or (*S*)-**1** is the natural product.

Thus, we succeeded in the synthesis of both enantiomers of halitunal ((*R*)-**1** and (*S*)-**1**) from (+)-genipin (**2**) in 10 steps (5% overall yield).



a) Ac_2O, Py, DMAP, CH_2Cl_2 (95%). b) TBAF, AcOH, THF, 0 °C (96%). c) 1,1'-Thiocarbonyldiimidazole, benzene, rt. d) DDQ, benzene, rt (47%, 2 steps).

Scheme 4

Acknowledgment

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References and Notes

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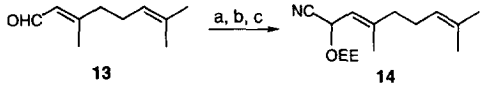
39, 3207. The compound **14** was prepared by (1) cyanosilylation of the geranyl aldehyde (**13**) with trimethylsilylcyanide (TMSCN) followed by KCN and 18-crown-6, and (2) exchange of the resulting silyl group to the ethoxyethyl group with pyridinium *p*-toluenesulfonate (PPTS) in excellent yield.



a) TMSCN, cat. KCN, cat. 18-crown-6, CH_2Cl_2, rt.
b) cat. PPTS, EtOH, rt.
c) Ethylvinylether, cat. PPTS, CH_2Cl_2, rt. (91%, 3 steps)

9. (*12R*)-**8a**: colorless oil, TLC R_f 0.32 (hexane : ethyl acetate = 3 : 1); $[\alpha]_D^{24}$ +16.4° (c = 0.867, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.23 (s, 1 H), 5.77 (s, 1 H), 5.20 (dd, 1 H, J = 7.9, 1.6 Hz), 5.09 (m, 1 H), 4.77 (d, 1 H, J = 7.9 Hz), 4.44 (ddd, J = 8.6, 8.6, 4.3 Hz, 1 H), 4.28 (s, 2 H), 2.94 (q, 1 H, J = 7.9 Hz), 2.69 - 2.59 (2 H), 2.22 - 1.98 (7 H), 1.69 (s, 6 H), 1.64 (s, 3 H), 0.93 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H). (*12S*)-**8b**: colorless oil, TLC R_f 0.26 (hexane : ethyl acetate = 3 : 1); $[\alpha]_D^{24}$ +8.0° (c = 0.929, $CHCl_3$); ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.77 (s, 1 H), 5.16 (d, 1 H, J = 8.6 Hz), 5.08 (m, 1 H), 4.69 (d, 1 H, J = 8.5 Hz), 4.45 (q, J = 6.7 Hz, 1 H), 4.28 (s, 2 H), 2.82 (q, 1 H, J = 8.5 Hz), 2.67 (m, 1 H), 2.55 (ddd, J = 8.5, 8.5, 1.4 Hz, 1 H), 2.31-1.97 (7 H), 1.68 (s, 3 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 3 H).
10. (*12R*)-**9a**: colorless oil, TLC R_f 0.78 (hexane : ethyl acetate = 4 : 1); ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.21 (s, 1 H), 5.76 (s, 1 H), 5.19 (d, 1 H, J = 7.9 Hz), 5.09 (m, 1 H), 4.80 (d, 1 H, J = 6.7 Hz), 4.42 (m, 1 H), 4.37 (m, 1 H), 4.21 (m, 1 H), 2.92 (m, 1 H), 2.65 - 2.53 (2 H), 2.19 - 1.95 (7 H), 1.68 (s, 6 H), 1.60 (s, 3 H), 0.92 (s, 18 H), 0.13 (s, 3 H), 0.11 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H). (*12S*)-**9b**: colorless oil, TLC R_f 0.75 (hexane : ethyl acetate = 4 : 1); ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.18 (s, 1 H), 5.78 (s, 1 H), 5.15 (d, 1 H, J = 8.6 Hz), 5.08 (m, 1 H), 4.68 (d, 1 H, J = 7.9 Hz), 4.44 (q, J = 7.3 Hz, 1 H), 4.38 (m, 1 H), 4.20 (m, 1 H), 2.80 (q, J = 8.5 Hz, 1 H), 2.64 (m, 1 H), 2.41 (dd, 1 H, J = 7.7, 7.7 Hz), 2.21 (dd, 1 H, J = 14.0, 7.3 Hz), 2.15 - 1.95 (6 H), 1.68 (s, 3 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 0.91 (s, 18 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H). **10**: colorless oil, ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.20 (s, 1 H), 5.76 (s, 1 H), 5.05 (m, 1 H), 4.66 (d, 1 H, J = 7.9 Hz), 4.36 (m, 1 H), 4.19 (m, 1 H), 3.56 (dd, 1 H, J = 14.0, 7.3 Hz), 2.79 (m, 1 H), 2.67 (d, 1 H, J = 7.3 Hz), 2.61 (m, 1 H), 2.52 (m, 1 H), 2.38 (dd, 1 H, J = 7.5, 1.4 Hz), 2.26 (dd, 1 H, J = 14.7, 7.3 Hz), 2.15 - 1.94 (6 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 0.89 (s, 21 H), 0.89 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H).
11. As shown in Table 1, the signs of the $\Delta\delta$ values clearly indicate the absolute configuration at C12 of **9b** to be *S*, which was in good agreement with the empirical rule reported by Kusumi, et al. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

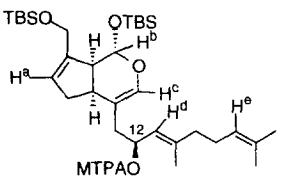


Table 1

		a	b	c	d	e
δ (ppm)	**9b**-(*S*)-MTPA	5.76	4.59	6.06	5.15	5.05
	9b-(*R*)-MTPA	5.79	4.61	6.15	5.01	5.03
$\Delta\delta = \delta_S - \delta_R$		-0.03	-0.02	-0.09	+0.14	+0.02

12. (*R*)-**1**: yellow oil, TLC R_f 0.64 (hexane : ethyl acetate = 2 : 1); CD λ_{max} (c = 0.005, MeOH) ($\Delta\varepsilon$) 256.6 (+0.98), 225.6 (-10.12) nm; ^{1}H-NMR (400MHz, C_6D_6) δ 9.96 (d, 1 H, J = 1.2 Hz), 9.05 (s, 1 H), 7.42 (d, 1 H, J = 3.7 Hz), 6.92 (s, 1 H), 6.67 (d, 1 H, J = 3.1 Hz), 6.02 (ddd, 1 H, J = 7.5, 7.5, 6.0 Hz), 5.14 (d, 1 H, J = 9.2 Hz), 5.01 (m, 1 H), 2.90 (dd, 1 H, J = 13.7, 5.8 Hz), 2.46 (dd, 1 H, J = 13.4, 7.9 Hz), 1.94 (m, 2 H), 1.85 (m, 2 H), 1.66 (s, 3 H), 1.64 (s, 3 H), 1.47 (s, 3 H), 1.35 (s, 3 H). IR ($CHCl_3$) 1730, 1640, 1475, 1400, 1250, 1030 cm^{-1}; High resolution MS calcd. for $C_{22}H_{26}O_4$ (M^+) 354.1831; found 354.1827. (*S*)-**1**: yellow oil, CD λ_{max} (c = 0.005, MeOH) ($\Delta\varepsilon$) 257.4 (-1.39), 227.6 (+4.53) nm.
13. We, at first, measured the specific rotation of (*R*)-**1** and (*S*)-**1**, though all $[\alpha]_\lambda$ values of (*R*)-**1** and (*S*)-**1** were almost ~0° (λ = 589, 577, 546, 435, and 365 nm, c = 1, $CHCl_3$). The signs of both enantiomers of **1** were indistinguishable, therefore, we measured CD spectra.[12]

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