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Facile lipase catalysed syntheses of (*S*)-(+)-4-hydroxy-β-ionone and (*S*)-(+)-4-hydroxy-β-damascone: chiral flavorants and synthons

Gauri P. More, Sujata V. Bhat *

Laboratory for Advanced Research in Natural and Synthetic Chemistry, V.G. Vaze College, Mumbai University, Mithagar Road, Mulund (East), Mumbai 400 081, India

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ABSTRACT

Enantioselective syntheses of (*S*)-(+)-4-hydroxy-β-ionone and (*S*)-(+)-4-hydroxy-β-damascone have been achieved through pig pancreatic lipase catalysed *trans*-esterification. These molecules find utility as constituent in fruit-type fragrance and flavor formulations and as chiral synthons in asymmetric synthesis of bioactive terpenoids.

Ionones and damascones are established molecules among the most highly valued fragrance constituents as a result of their distinctive fine violet and rose odor.[1,2] Besides their use in the perfumery industry, ionones and damascones are also appreciated as synthetic building blocks.[3,4] Both of these C_{13} norterpenoids exist in nature as three distinct regioisomers, which differ in the position of the second double bond and are called as the α-, β-, and γ- isomers.

Abscisic acid (ABA, **1**) is one of the important phytochromes (Fig. 1).[5] In relation to this class of compounds, (*S*)-4-hydroxy-β-ionone **2** is a versatile synthon and has been converted into (*S*)-6-hydroxy-α-ionone.[6] Moreover, **2** has been also converted into a number of degraded carotenoids.[7,8] (±)-4-Hydroxy-β-ionone **2** was also used in the synthesis of forskolin (**4**).[9] A few methods for preparing optically active **2** have been demonstrated, which include epoxidation and rearrangement of optically resolved α-ionone to yield (*R*)-(−)-**2** (*ee* 97%)[10]; the separation of camphanoyl ester of (±)-**2** followed by hydrolysis,[10] asymmetric hydroxylation of β-ionone using *Aspergillus niger* to yield (*R*)-(−)-**2** (*ee* 74%)[11] as well as with cytochrome P450 (*ee* 3–8%).[12] Lipase LP from *Chromobacterium viscosum* (Tokyo Jozo) showed the highest enantioselectivity in the esterification of (±)-**2** with vinyl acetate at 40 °C for 12 h to yield (*S*)-(+)-**2** (yield 64%, ee 45%).[6] Asymmetric hydrolysis of (±)-**3** with the same lipase gave (*R*)-(−)-**2** (yield 51%, ee 96%).[6] Similarly, the hydrolysis of acetoacetyl ester of (±)-**2** using PLE yielded (*R*)-(−)-**2**, which was subjected to Mitsunobu inversion to yield (*S*)-(+)-**2** (88%), $[\alpha]_D = +5.8$.[13] These procedures are however unsatisfactory for obtaining (*S*)-(+)-**2** in high enantiomeric excess in a single step.

The members of damascone family extracted from Bulgarian roses constitute a popular class of perfumes.[14] The chemistry and synthetic applications of α- and β-ionone have been extensively studied,[10,14] whereas the isomeric α- and β-damascones have received much less attention. The biotransformation with species of *Aspergillus*, *Botryosphaeria,* and *Lasiodiplodia* gave a mixture of mono and di-hydroxylated β-damascone derivatives, which were found to be suitable for flavoring tobacco.[15]

The treatment of β-damascone with CYP101C1 from *Novosphingobium aromaticivorans* yielded two main products, 4-hydroxy-β-damascone (73%) and 3-hydroxy-β-damascone (18%) and four

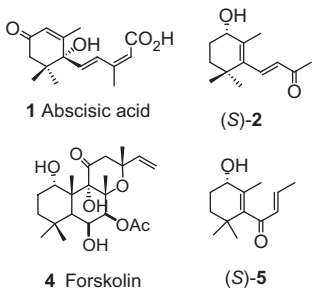

Figure 1. Abscisic acid (**1**), forskolin (**4**), (*S*)-(+)-4-hydroxy-β-ionone (**2**), and (*S*)-(+)-4-hydroxy-β-damascone (**5**).

* Corresponding author. Tel.: +91 02225423673.
E-mail address: sujata8b@gmail.com (S.V. Bhat).

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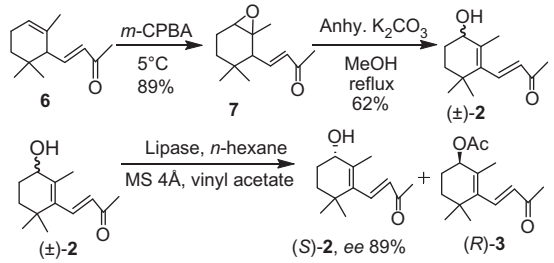
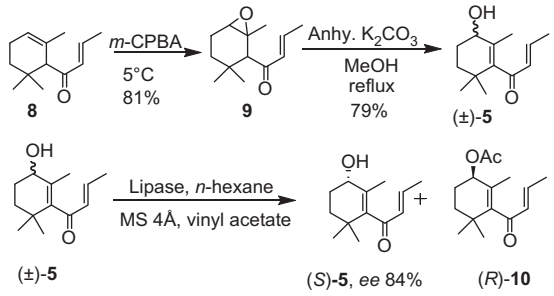


Scheme 1. Synthesis of (*S*)-(+)-4-hydroxy-β-ionone from α-ionone.



Scheme 2. Synthesis of (*S*)-(+)-4-hydroxy-β-damascone from α-damascone.

minor products (cumulative total ~9%).[16] Two of these were isolated from whole cell systems and were identified as 3-hydroxy-4-oxo-β-damascone and 3,4-epoxy-β-damascone. The other two products observed by GC were not produced in sufficient quantity to be characterized. Dehydrated decalone of (*S*)-4-hydroxy-β-damascone also represents valuable key intermediate for the elaboration of other *trans*-decalins.[17]

We report herein a new asymmetric synthesis of (*S*)-(+)-4-hydroxy-β-ionone **2** (Scheme 1) and (*S*)-(+)-4-hydroxy-β-damascone **5** (Scheme 2) starting from α-ionone and α-damascone respectively through pig pancreatic lipase (PPL) catalysed *trans*-esterification.

Thus, the epoxidation of α-ionone (**6**) with *m*-CPBA at 5 °C for 1 h in CH_2Cl_2 yielded 4,5-epoxide (**7**), which was subjected to a 5 °C base catalysed rearrangement by refluxing with K_2CO_3 in methanol for 4 h to give (±)-**2**. The latter compound was subjected to the PPL catalysed *trans*-esterification[18] to give (*S*)-(+)-4-hydroxy-β-ionone **2**, which was purified by silica gel column chromatography.[19] The structure of (*S*)-(+)-**2** was supported by IR, ^{1}H and ^{13}C NMR spectral values.[20] The presence of axial –OH group at C-4 position in (*S*)-(+)-**2** was indicated by peak at δ 4.03 (1H, t, J = 4.8 Hz) in ^{1}H NMR spectrum.

With the use of similar procedure (*S*)-(+)-4-hydroxy-β-damascone **5** from α-damascone was synthesized. The epoxidation of α-damascone (**8**) with *m*-CPBA at 5 °C for 1 h in CH_2Cl_2 yielded 4,5-epoxide (**9**), which was subjected to a base catalysed rearrangement by refluxing with K_2CO_3 in methanol for 4 h to give (±)-**5**. The latter compound was subjected to the PPL catalysed *trans*-esterification[18] to give (*S*)-(+)-4-hydroxy-β-damascone **5**, which was purified by silica gel column chromatography. The presence of axial –OH group at C-4 position in (*S*)-(+)-**5** was indicated by peak at δ 3.98 (1H, t, J = 5.0 Hz) in ^{1}H NMR spectrum.[19] The structure of (*S*)-(+)-**5** was supported by IR, ^{1}H and ^{13}C NMR spectral values, which are identical with those of sample reported earlier through hydroxylation of β-damascone with CYP101C1.[16] The enantiomeric excess (*ee* %) of (*S*)-(+)-4-hydroxy-β-ionone **2** and (*S*)-(+)-4-hydroxy-β-damascone **5** was determined using chiral HPLC on chiracel® OD analytical column and was found to be 89% and 84% respectively.

In summary, we have achieved a convenient asymmetric synthesis of (*S*)-4-hydroxy-β-damascone and (*S*)-4-hydroxy-β-ionone through PPL catalysed *trans*-esterification.

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19. *General procedure*. A mixture of (±)-4-hydroxy-β-damascone **5** (1 g, 4.8 mmol), dry lipase (357 mg), activated molecular sieves 4 Å (286 mg), and vinyl acetate (825 mg, 9.6 mmol) in dry *n*-hexane (18 ml) was stirred at room temperature for 26 h. Reaction was monitored by GC and terminated at ~50% conversion. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified further by silica gel column chromatography and elution with a mixture of ethyl acetate and hexane (0.2:9.8) yielded (*R*)-**10** (472 mg, 39%) and (*S*)-**5** (503 mg, 51%).
Similarly synthesis of (*S*)-(+)-4-hydroxy-β-ionone **2** was also achieved.
20. *Analytical data for (S)-(+)-4-hydroxy-β-ionone (**2**) IR (CHCl$_3$, γ_{max}, cm^{-1}):* 3449, 3055, 2967, 2935, 1664, 1266, 739; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.21 (d, J = 16.4 Hz, 1H), 6.14 (d, J = 16.4 Hz, 1H), 4.03 (t, J = 4.8 Hz, 1H), 2.34 (s, 3H), 1.98–1.62 (m, 4H), 1.85 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 198.8, 143.1, 138.9, 134.6, 132.8, 69.6, 34.7, 28.7, 28.2, 27.5, 27.2, 18.4; GCMS: 208 (M$^+$), 193, 175, 165, 151, 137, 123, 109, 91, 77, 65, 55, 43; chiral HPLC (MeCN:H_2O—8:2), λ_{max} 254 nm, flow rate: 0.8 ml/min), t_R = 4.2 (major isomer), t_R = 5.7 (minor isomer), ee = 89%, $[\alpha]^{20}$ = 6.4 (c = 1, EtOH).
*Analytical data for (S)-(+)-4-hydroxy-β-damascone (**5**) IR (CHCl$_3$, γ_{max}, cm^{-1}):* 3410, 2937, 1692, 1643, 1442, 1364, 1291, 1172, 1136, 1079, 1023; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.76 (dq, J = 15.7, 6.9 Hz, 1H), 6.14 (dq, J = 15.7 Hz, 1.5 Hz, 1H), 3.98 (t, J = 5 Hz, 1H), 2.01–1.94 (m, 1H), 1.92 (dd, J = 6.9, 1.6 Hz, 3H), 1.79–1.70 (m, 1H), 1.69–1.62 (m, 1H), 1.63 (s, 3H), 1.43 (ddd, J = 13.1,7.5, 3.1 Hz, 1H), 1.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 18.0, 18.5, 27.7, 28.4, 28.9, 33.9, 34.7, 68.9, 131.2, 133.9, 143.4, 146.7, 201.2; GCMS: 208 (M$^+$), 193, 175, 139, 121, 105, 91, 69, 55, 41; chiral HPLC (MeCN:H_2O—8:2), λ_{max} 254 nm, flow rate: 0.8 ml/min), t_R = 4.1 (major isomer), t_R = 5.6 (minor isomer), ee = 84%, $[\alpha]^{20}$ = 3.7 (c = 1.8, EtOH).