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# The first asymmetric total synthesis of (*R*)-tuberolactone, (*S*)-jasmine lactone and (*R*)-δ-decalactone☆

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**Abstract**—A general synthetic approach has been developed for the first asymmetric total synthesis of tuberolactone **1**, jasmine lactone **2** and δ-decalactone **3**. The key step is the selective hydrogenation of triple and endocyclic double bonds in the key intermediate **4**.


Chiral lactones are functionalities commonly present in a number of natural products that function as pheromones or medicinal compounds.[1] They have often served as intermediates for the synthesis of other natural products.[2] Lactones possessing alkyl side chains have attracted much attention from synthetic and medicinal chemists due to their biological activity.[3] The short chain alkyl homologues are volatile and important aroma compounds in food and beverages. Natural perfumes[4] are obtained from plants by separation procedures such as distillation. They are mostly oily materials, and can be extracted from flowers, fruits, seeds, woods, branches and leaves, bark or roots. Flower scents have been popular among people of every period and culture. The most important of these scents are rose, jasmine, lilac, tuberose, gardenia, etc. The examples here are tuberolactone **1** and jasmine lactone **2**.

Tuberolactone **1** was identified as a trace constituent in tuberose oil,[5] from the flowers of *Polyanthes tuberose* L. This lactone has a close structural relationship to the well-known, olfactively interesting compound jasmine lactone found in the same oil, and therefore it is assumed to be of special olfactive importance. In comparison to the racemate, this enantiomer is more pleasant with regard to the tuberose note, but has less volume.[6] Both (−) and (+)-jasmine lactones **2** are present in jasmine[7] (*Jasminum grandiflorum* L.) and tuberose oils.[5] Jasmine lactone is also found in gardenia flowers. (±)-Tuberolactone[8] has been synthesized from (±)-jasmine lactone via sulfenylation-sulfoxide pyrolysis and from acrolein dimer.[9] Jasmine lactone[9,10] and its analogues[11] have been synthesized and their odour characteristics examined. δ-Decalactone **3** was identified for the first time in cashew apple products produced from the cashew tree (*Anacardium occidentale* L.), which is an indigenous Brazilian tree, found primarily in the northeastern coastal region.[12] It also occurs in products such as cheese, butter, coconut and strawberry, and the odour is sweet, creamy and milky. Racemic δ-decalactone is readily accessible from the Baeyer–Villiger reaction of the corresponding 2-substituted cyclopentanone. The resolution of jasmine lactone[13,14] and δ-decalactone[13] has been investigated.

Owing to their specific odour impressions and low threshold concentrations, these lactones play an important role as fragrant and flavouring materials, and therefore practical syntheses are in great demand.

To the best of our knowledge, there is no report on the asymmetric synthesis of these three lactones **1**–**3**. In connection with our studies on the synthesis of naturally occurring lactones,[15] the obvious structural similarities of **1**–**3** prompted us to develop a first asymmetric route for the total synthesis of (*R*)-(−)-tuberolactone, (*S*)-(+)-jasmine lactone and (*R*)-δ-decalactone, respectively (see Scheme 1).

The syntheses of tuberolactone, jasmine lactone and δ-decalactone began with the known epoxide **6**, prepared

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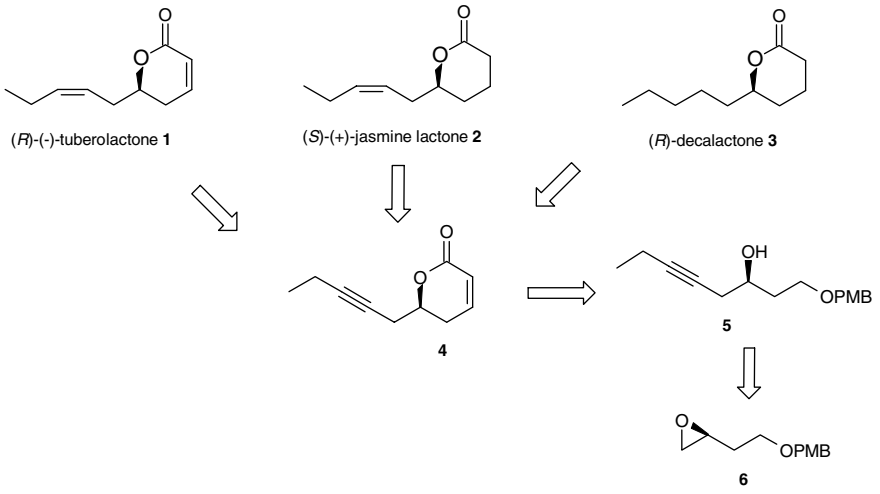
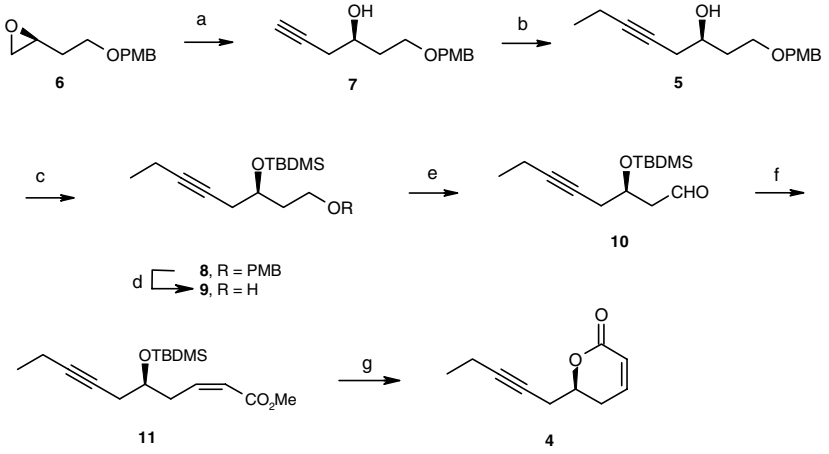
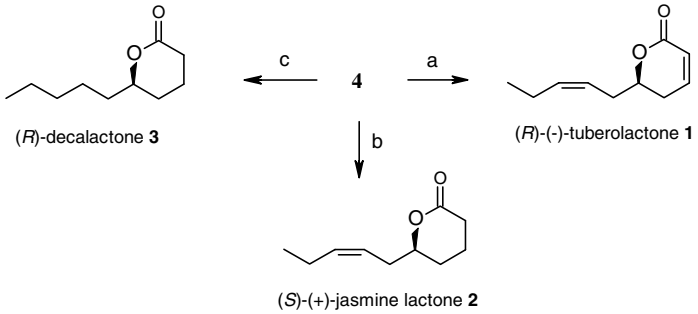



**Scheme 1.** Retrosynthetic plan.




**Scheme 2.** Reagents and conditions: (a) lithium acetylide, ethylenediamine complex, DMSO, 6 h, rt, 84%; (b) (i) Li/liq $NH_3$, dry THF, −78 °C, (ii) EtBr, THF, 3–4 h, 68%; (c) TBDMSCl, imidazole, DCM, rt, 1–1.5 h, 89%; (d) DDQ, DCM/$H_2O$ (9:1), rt, 30 min, 94%; (e) IBX, DMSO, 0 °C to rt, 1–2 h, 91%; (f) (i) NaH/THF, −78 °C, 30 min, (ii) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, THF, 30–45 min, 82%; (g) *p*-TSA/MeOH, rt, 3–4 h, 76%.




**Scheme 3.** Reagents and conditions: (a) $H_2$, Lindlar cat., EtOAc, quinoline, 2 h, 88%; (b) $H_2$, excess Lindlar cat., EtOAc, quinoline, 12 h, 38%; (c) $H_2$, 10% Pd/C, EtOAc, rt, 4 h, 87%.

by Jacobsen's hydrolytic kinetic resolution method.[16] The opening of enantiomerically pure epoxide **6** with lithium acetylide provided homopropargylic alcohol **7** (Scheme 2), which was subjected to alkylation with ethyl

bromide to afford alkylated compound **5** in 68% yield. The secondary hydroxyl group in compound **5** was silylated using TBDMSCl and imidazole in DCM to afford **8** in 89% yield. After removal of the PMB group with DDQ,[17] the alcohol **9** was oxidized to the corresponding aldehyde **10**. Aldehyde **10** was immediately subjected to Still–Gennari modification of the Horner–Emmons reaction,[18] to furnish *Z*-unsaturated carboxylic ester **11** in 82% yield. The cyclization of ester was achieved by treating with *p*-TSA in methanol to afford **4** by in situ deprotection of TBDMS group. This key intermediate was utilized for the synthesis of three target molecules (Scheme 3).[19] Thus, partial hydrogenation of the triple bond in compound **4** over Lindlar's catalyst afforded tuberolactone **1** in 88% yield. Whereas, treatment of **4** with excess Lindlar's catalyst in EtOAc, quinoline for 12 h yielded jasmine lactone **2** in 38% yield and hydrogenation of triple and endocyclic double bonds in the presence of 10% Pd/C in EtOAc furnished δ-decalactone **3** in 87% yield.

In conclusion, the first asymmetric total synthesis of tuberolactone, jasmine lactone and δ-decalactone has been accomplished in eight steps from the same starting material. The selective hydrogenations are the key steps involved in the synthesis of these fragrant δ-lactones.

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19. *(6S)-6-(2-Pentynyl)-5,6-dihydro-2H-2-pyranone* **4**: yellow liquid, $[\alpha]_D^{25}$ −39.32 (*c* 1, $CHCl_3$); IR (neat): 2975, 2925, 1726, 1427, 1386, 1246, 1148, 1049 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.16 (t, $J = 7.5$ Hz, 3H), 2.12–2.25 (m, 2H), 2.40–2.76 (m, 2H), 4.44–4.56 (br s, 1H, CH–O), 6.04 (dd, $J = 9.8$, 1.5 Hz, 1H), 6.85–6.94 (m, 1H, CH=C–C=O); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 163.5, 144.7, 120.8, 84.9, 76.4, 75.6, 72.9, 27.9, 24.7, 13.7, 12.0; LCMS: *m/z* 165 (M+1); HRMS: *m/z* 170.226 (calcd for $C_{10}H_{18}O_2$, 170.250).
*(6R)-Tuberolactone* **1**: clear colorless liquid; $[\alpha]_D^{25}$ −30.16 (*c* 1, $CHCl_3$); IR (neat): 2964, 3015, 1725, 1635, 1386, 1247, 1150, 1048, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.78$ Hz, 3H), 2.02–2.57 (m, 6H), 4.36–4.44 (m, 1H, CH–O), 5.30–5.39 (m, 1H, CH=CH), 5.50–5.58 (m, 1H, CH=CH), 5.98 (dt, $J = 9.30$, 2.34 Hz, 1H, =CH–C=O), 6.82 (m, 1H, CH=C–C=O); $^{13}C$ NMR (75 MHz, $CDCl_3$):δ 164.2, 144.8, 135.4, 122.0, 121.3, 76.6, 37.8, 32.3, 29.6, 28.6, 20.6, 13.9; LCMS: *m/z* 189 (M+Na); HRMS: *m/z* 164.167 (calcd for $C_{10}H_{12}O_2$, 164.203).
*(6S)-Jasmine lactone* **2**: colorless liquid; $[\alpha]_D^{25}$ +18.9 (*c* 1, $CHCl_3$), lit.[13] +17.6 (*c* 0.38 $CHCl_3$); IR (neat): 2959, 1729, 1453, 1415, 1302, 1148, 1110, 1046, 906 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.99 (t, $J = 7.0$ Hz, 3H), 1.42–2.68 (m, 10H), 4.16–4.36 (br s, 1H, CH–O), 5.25–5.63 (m, 2H, CH=CH); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 171.8, 135.1, 122.3, 76.6, 33.3, 29.6, 29.4, 27.2, 20.7, 14.0; LCMS: *m/z* 191 (M+Na); HRMS: *m/z* 166.201 (calcd for $C_{10}H_{14}O_2$, 166.219).
*(R)-δ-Decalactone* **3**: colorless liquid; $[\alpha]_D^{25}$ +52.2 (*c* 1, $CHCl_3$), lit.[13] +56.7 (*c* 1.79 $CHCl_3$); IR (neat): 2931, 2861, 1736, 1463, 1379, 1340, 1243, 1184, 1118, 1036, 930; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0. 90 (t, $J = 6.80$ Hz, 3H), 1.21–2.62 (m, 14H), 4.19–4.30 (br s, 1H, CH–O); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 172.0, 80.5, 31.4, 29.3, 27.6, 24.4, 22.3, 18.3, 13.8; LCMS: *m/z* 193, (M+Na); HRMS: *m/z* 168.197 (calcd for $C_{10}H_{16}O_2$, 168.234).