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Stereoselective total synthesis of a potent natural antifungal compound (6*S*)-5,6,dihydro-6-[(2*R*)-2-hydroxy-6-phenyl hexyl]-2*H*-pyran-2-one ☆

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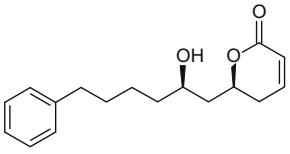
ABSTRACT

A practical stereoselective synthesis of (6*S*)-5,6,dihydro-6-[(2*R*)-2-hydroxy-6-phenyl hexyl]-2*H*-pyran-2-one (**1**), a potent natural antifungal compound, is described. The sequence involves diastereoselective iodine-induced electrophilic cyclization, epoxide ring opening with a vinyl Grignard reagent and ring closing metathesis (RCM) as the key steps.

Several natural products with α-pyrone (6-substituted 5,6-dihydro 2*H*-pyran-2-one or α,β-unsaturated-δ-lactone) structural units have been found to exhibit a wide range of biological activities.[1] They possess antifungal, antifeedent, antibacterial and cytotoxic properties.[2] Such important biological activities made them attractive targets to the total synthesis.[3] The simplest structure with a *syn*-1,3-diol/5,6-dihydro pyran-2-one moiety is (6*S*)-5,6,dihydro-6-[(2*R*)-2-hydroxy-6-phenyl hexyl]-2*H*-pyran-2-one (**1**) isolated by Hostettmann and co-workers from *Ravensara crossifolia*.[4] It exhibits an antifungal activity against the phytopathogenic fungus *Cladosporium cucumerinum* in bioautographic TLC assay and the minimum amount required to inhibit this fungal growth was 1 μg. This amount was comparable to the minimum quantity in the same assay of miconazole (1 μg) a commercially available reference antifungal compound.

Because of interesting antifungal activity and its structure containing an α,β-unsaturated δ-lactone moiety with a fixed *syn*-1,3-diol system **1** is an important target for total synthesis.[5] We have recently synthesized the compound **1** with an efficient approach, which we would like to mention here.

Our retrosynthetic analysis of **1** is depicted in Scheme 1, whose salient features involves the diastereoselective iodine-induced electrophilic cyclization of **4** to fix *syn*-1,3-diol system following the method developed by Bartlett and Cardillo. The cyclization product **5** can be converted into the epoxide **6** which can furnish the compound **9** by treatment with vinyl Grignard reagent followed by acrylation. Subsequently RCM of **9** can be used to construct the target molecule **1**.



1

The synthesis of **1** (Scheme 2) was initiated from commercially available 5-phenyl pentan-1-ol **2**, which was converted into the known homoallyl alcohol **3** (ee 97%) through oxidation under Swern conditions followed by Maruoka asymmetric allylation.[5a] Treatment of **3** with di-*tert*-butyl dicarbonate in the presence of DMAP in acetonitrile[6] formed the homoallylic *tert*-butyl carbonate **4** in 89% yield. The second stereogenic center with the required stereochemistry was established by using diastereoselective iodine-induced electrophilic cyclization of **4**. The compound **4** was treated with excess I_2 in CH_3CN at low temperature (−20 °C) to furnish the iodocarbonte **5** in 72% yield and with high diastereoselectivity (de 95%) favoring *syn*-isomer.[7] The pure *syn*-isomer was separated by column chromatography. The treatment of this compound with 3 equiv of K_2CO_3 in MeOH gave the desired *syn*-epoxy alcohol **6** (81%).[7] The secondary hydroxyl group of epoxide **6** was protected as its *tert*-butyl dimethylsilyl ether to form **7** in 88% yield. The Cu mediated opening[8] of the epoxide **7** with vinyl magnesium bromide in tetrahydrofuran (THF) at −78 to −40 °C yielded corresponding homoallyl alcohol **8** (80%).

☆ Part 30 in the series 'synthetic studies on natural products'.

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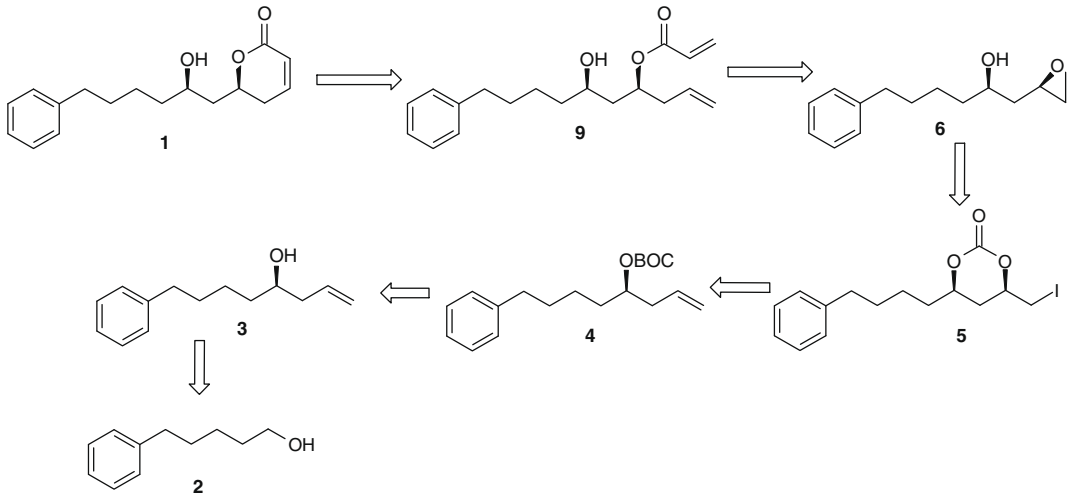
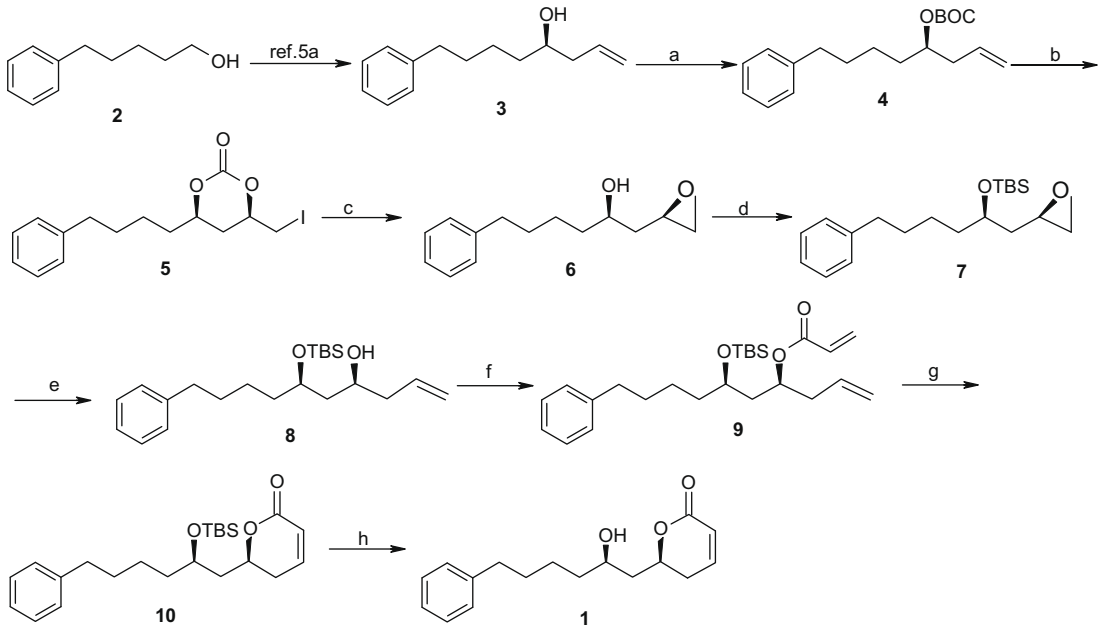


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions, yields: (a) BOC_2O, DMAP, CH_3CN, 0 °C–rt, 10 h, 89%; (b) I_2, CH_3CN, −20 °C, 6 h, 72%; (c) K_2CO_3, MeOH, rt, 30 min, 81%; (d) TBSCl, imidazole, DCM, 0 °C–rt, 5 h, 88%; (e) vinyl magnesium bromide, CuBr, THF, −78 to 40 °C, 7 h, 80%; (f) acryloyl chloride, Et_3N, DMAP, DCM, 0 °C–rt, 4 h, 85%; (g) Grubb's 2nd generation catalyst (5 mol %), DCM, reflux, 6 h, 81%; (h) PTSA, MeOH, rt, 10 min, 82%.

The alcohol **8** was esterified with acryloyl chloride in presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **9** (85%).[9] Subsequently ring closing metathesis of ester **9** with commercially available Grubbs 2nd generation catalyst in refluxing DCM formed the α,β-unsaturated δ-lactone **10** (81%).[10] Finally deprotection of TBS group in **10** with PTSA in MeOH gave the target molecule **1** in 82% yield. The physical and spectroscopic data of **1** were in identical to those reported for natural product.[11] The overall yield of the compound was 17.4%.

In our present synthesis we have utilized Maruoka asymmetric allylation to generate the stereogenic center at C-2′ position[5a] and the diastereoselective iodine-induced electrophilic cyclization to generate the stereogenic center at C-6 position.[7b] The latter protocol has not been used earlier for the synthesis of **1** to install a new chiral carbon center. The advantage of the method is that the protected chiral homoallylic alcohol **4** was directly used to produce **5** with a second chiral center with *syn*-selectivity. In the earlier syntheses a chiral homoallylic alcohol was converted into a protected 1,3-hydroxyaldehyde[5a] or an unsaturated hydroxyester[5c] to install the stereogenic center at C-6 position. In an alternative approach the intermediate 1,3-diol with *syn*-selectivity was prepared by diastereoselective reduction of a protected 1,3-hydroxyketone which was obtained from a chiral epoxide (synthesized following a reported method[12]) through a sequence of reactions.[5b] Thus, only in the present synthesis of **1** a straightforward method for the generation of the second chiral center (with *syn*-stereochemistry) to a chiral homoallyl alcohol has been utilized. The method is easily accessible with a readily available reagent.

In conclusion the stereoselective total synthesis of the naturally occurring potent antifungal compound **1** has been achieved by employing diastereoselective iodine-induced electrophilic cyclization for installing 1,3 *syn*-system, followed by vinyl Grignard addition and RCM as key reactions.

Acknowledgments

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11. *Physical and spectral data of synthesized* **1**: melting point: 34–35 °C, $[\alpha]_D^{25} = -63.0$ (*c* 0.60, $CHCl_3$); IR (neat): 3450, 2926, 1720, 1636, 1456, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.24–7.03 (5H, m), 6.82 (1H, m), 5.97 (1H, d, $J = 9.0$ Hz), 4.59 (1H, m), 3.80 (1H, m), 2.55 (2H, t, $J = 7.0$ Hz), 2.37–2.28 (2H, m), 1.93–1.70 (2H, m), 1.62–1.41 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.9, 145.1, 142.4, 128.3, 128.2, 125.6, 121.2, 76.6, 69.1, 41.9, 37.4, 35.8, 31.3, 29.4, 25.0; Ms (ESI): *m*/*z* 297 $[M+Na]^+$; HRMS (ESI): *m*/*z* 297.1459 $[M+Na]^+$ calcd for $C_{17}H_{22}O_3Na$; *m*/*z* 297.1466.
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