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SYNTHESIS OF (+)-TRANS-WHISKY LACTONE, (+)-TRANS-COGNAC LACTONE AND (+)-ELDANOLIDE

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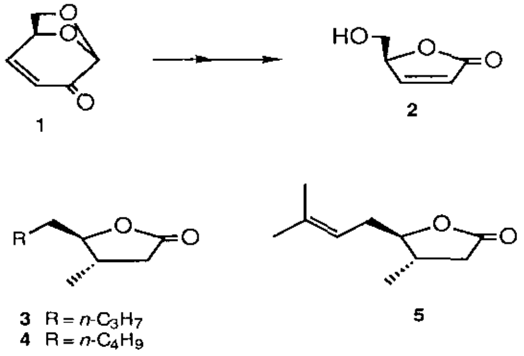
Abstract —— A new and useful synthesis of (+)-trans-whisky lactone (**3**), (+)-trans-cognac lactone (**4**) and (+)-eldanolide (**5**) starting from levoglucosenone (**1**) is described.

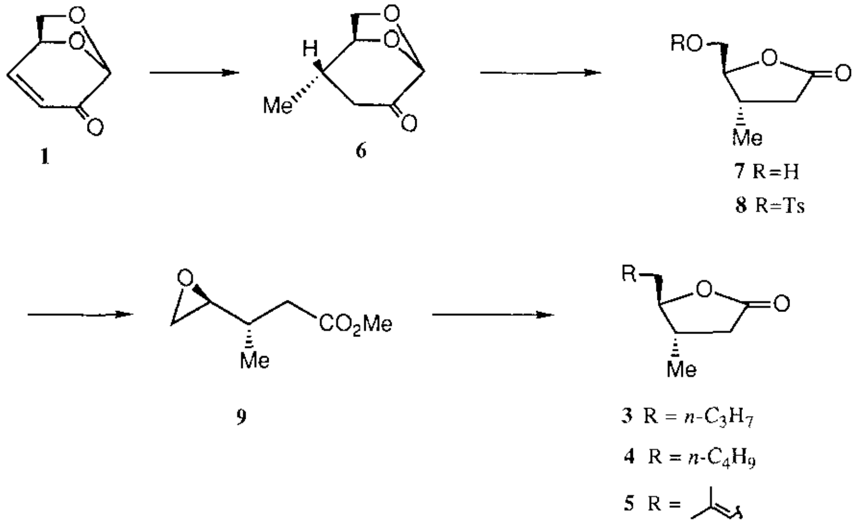
Levoglucosenone (**1**)[1](1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) is widely known as a pyrolytic product of cellulose. It is a very useful chiral source for synthesizing natural products[2] because of its highly functionalized structure, which contains one chiral center. We have recently reported an efficient method for the convenient preparation of (S)-5-Hydroxypenten-4-olide (**2**) from levoglucosenone (**1**)[3] by using the Baeyer-Villiger oxidation as a key step.(Scheme 1)



Scheme 1

In this paper, we describe a general method that permits easy access to 3,4-disubstituted γ-lactones, such as trans-whisky lactone (**3**) [(3S,4R)-3-methyl-4-octanolide], the key flavor of whisky and wine,[4,5] trans-cognac lactone (**4**) [(3S, 4R)-3-methyl-4-nonanolide], the key flavor of cognac,[6] and the natural eldanolide (**5**) [(3S,4R)-3,7-dimethyl-6-octen-4-olide], the pheromone produced by the male Eldana saccharina (Wlk.),[7] in an enantioselective manner using the chirality of levoglucosenone (**1**).

Our synthesis of **3**, **4** and **5** was straightforward, as illustrated in Scheme 2. Treatment of levoglucosenone (**1**) with Me_2CuLi gave **6** in 84.3 % yield {$[\alpha]_D^{23}$ -293° (Et_2O), lit.[2a] $[\alpha]_D^{23}$ -299° (Et_2O)}. It was shown to be 100 % diastereomerically pure when analyzed by glc and ^1H nmr. It was oxidized with AcOOH to give **7** in 86.0 % yield. The corresponding tosylate (**8**) was treated with K_2CO_3 in MeOH to give epoxide (**9**) in 66.4 % yield from **7**. Finally, treatment of **9** with n-Pr_2CuLi gave trans-whisky lactone (**3**)[8] in 76.2 % yield {$[\alpha]_D^{23}$ +79.5° (MeOH), lit.[9b] $[\alpha]_D^{20}$ +72.8° (MeOH)}. And similar treatment of **9** with n-Bu_2CuLi gave trans-cognac lactone (**4**)[10] in 78.3 % yield {$[\alpha]_D^{23}$ +79.5°(CH_2Cl_2), lit.[11] $[\alpha]_D^{15}$ +48.3° (CH_2Cl_2)}. And further, eldanolide (**5**)[12] was also synthesized in a similar manner using $Me_2C{=}CHMgBr$ and CuBr in 73.8 % yield {$[\alpha]_D^{23}$ +57.8° (EtOH), lit.[13b] $[\alpha]_D^{21}$ +55.9° (EtOH)}.



Scheme 2

In conclusion, we developed a new and useful synthesis of (+)-trans-whisky lactone (**3**), (+)-trans-cognac lactone (**4**) and (+)-eldanolide (**5**) starting from levoglucosenone (**1**).

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10. Physical data for our synthetic **4** are as follows; bp 101~103°C/6 torr; n_D^{23} 1.4431; ir (film) ν cm^{-1} 2962, 2936, 1779, 1212, 1172; ^{1}H-nmr (CDCl$_3$, 300 MHz): δ 0.90 (3H, t, J=6.8 Hz), 1.14 (3H, d, J=6.3 Hz), 1.21~1.75 (8H, m), 2.12~2.30 (2H, m), 2.60~2.75 (1H, m), 4.01 (1H, dt, J=4.0 and 7.7 Hz).
11. Only one synthesis of optically active trans-cognac lactone (**4**) has been reported; R. M. Ortuno, R. Merce, and J. Font, Tetrahedron, 1987, **43**, 4497.

12. Physical data for our synthetic **5** are as follows; bp 115~117°C/21 torr; n_D^{23} 1.4606; ir (film) ν cm^{-1} 2972, 2920, 1783, 1214, 1195; ^{1}H-nmr ($CDCl_3$, 300 MHz): δ 1.14 (3H, d, J=6.5 Hz), 1.64 (3H, s), 1.73 (3H, s), 2.10~2.50 (4H, m), 2.68 (1H, dd, J=7.5 and 16.6 Hz), 4.06 (1H, dd, J=6.5 and 12.2 Hz), 5.10~5.22 (1H, m).

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