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Synthesis of 6,8,9,12-Tetrahydroxylated Dihydroagarofuran Sesquiterpenoid from α-Santonin

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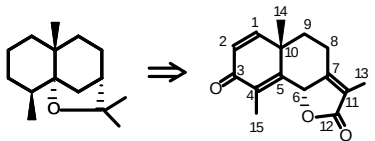
Abstract: The tittle compound has been synthesized successfully through the efficient and selective functional transformation of α-santonin. This procedure is the first successful approach developed for synthesis of the dihydroagarofuran kind of sesquiterpenoids from the eduesmanolide sesquiterpenoid α-santonin.

Keywords: Synthesis, dihydroagarofuran sesquiterpenoid, polyhydroxylation.

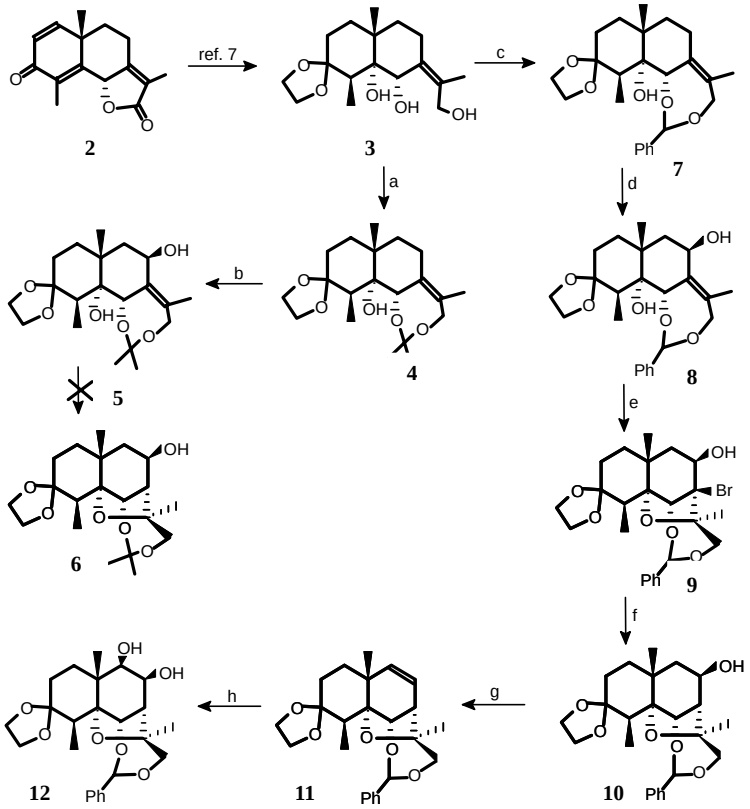
A variety of polyhydroxylated dihydroagarofuran sesquiterpenoids isolated from the *Celastraceae* plants contained the key skeleton **1**, with the hydroxyl number varying from two to nine[1]. Because of their significant biological activities, such as cytotoxic[2], antitumor[3], immumosuppressive[4], and insect antifeedant[5], and so on, organic chemists have paid high attention to the synthesis of this kind of compounds due to their poor content in natural source. To date, however, only few successful synthesis for the oligo-hydroxyl compounds have been achieved, and it was not reported until 1997 that a multi-hydroxylated dihydroagarofuran sesquiterpenoid, the euonyminol, was synthesized through an approach of more than twenty steps[6]. One of the challenges for synthesis of the polyhydroxyl compounds is the introduction of the multi-hydroxyl groups. For this reason, we have recently designed an alternative synthetic pathway which started from the naturally rich α-santonin, because it possesses several readily-oxygenated centers (*e.g.*C-1, 2, 3, 4, 6 and 12) and two chiral centers (*e.g.*C-6 and 10). This approach might be hopfully developed to be a general, short and efficient synthetic pathway for this kind of sesquiterpenoids with different hydroxyl substitution patterns. In our previous work[7], we developed a novel and efficient procedure for constructing the key tetrahydrofuran moiety, in which a successful synthesis of a trihydroxylated compound was achieved. Recently, we have made a further substantial progress in this synthetic program, *i.e.*, a key dihydroxylation at 8,9-positions. This paper mainly presents the successful synthesis of 6,8,9,12-tetrahydroxylated compound **12**.



1 **2**

As shown in **scheme 1**, the intermediate **3** has been synthesized from santonin **2** in five steps, which was mentioned in our previous paper[7]. Initially we invested the direct allylic hydroxylation of **3** using SeO_2 in several mediums, but the results revealed that the reaction system was always complicated. So **3** was subjected to protection with acetone and an acetal **4** was obtained in 90% yield, which could be smoothly hydroxylated at C-8 by SeO_2/^{t}BuOOH/dioxane to afford **5** in 95% yield. A series of cyclization procedures for constructing the tetrahydrofuran ring, such as NBS/$CaCO_3$/THF[8], $Hg(OAc)_2$/THF[9], *m*-CPBA/NaBr/18-crown-6[10], were employed, but unfortunately, none of them could give the right product. So we have to change the protecting group.

Scheme 1



Reagents and Conditions: a)acetone/ PTS, 90%; b) SeO_2/ ^tBuOOH/dioxane, 95%; c) PhCHO/ $ZnCl_2$, 72%; d) SeO_2/^tBuOOH/dioxane, 82%; e) NBS/$CaCO_3$/THF/H_2O, 95%; f)$^nBu_3SnH$/benzene, reflux, 92%; g) $SOCl_2$/pyridine, 80 ^oC, 52%; h) NMO/ OsO_4(cat.)/ acetone, 87%.

Compound **3**, when treated with benzyldehyde[11], was converted to the acetal **7** in 72% yield, which was readily hydroxylated at C-8 position by SeO_2/^tBuOOH/dioxane to give the product **8** in a yield of 82%. Tetrahydrofuran cyclization of compound **8** was readily carried out just by stirring it at r.t. in NBS/$CaCO_3$/THF/H_2O for a period of 15min and the excellent yield 95% of bromo-tetrahydrofuran compound **9** was obtained, whereas the $Hg(OAc)_2$ mediated cyclization proved to be not effective to **8**. Interestingly, compound **9** could be reduced directly with $^nBu_3SnH$ in benzene without the AIBN initiator to afford the debromination product **10** in good yield (92%). The successive dehydration of the **10** with $SOCl_2$ in pyridine at 80 ^oC afforded **11** in 52% yield. Some other dehydration systems, such as $CuSO_4$/silica[12], was proved to be not favorable. Finally, compound **11** was dihydroxylated with NMO(4-methylmorpholine N-oxide)/OsO_4(cat.) in acetone[13] , and the target compound **12**[14] was obtained in 87% yield based on the recovery of **11**. The β-configuration for both hydroxyl groups at C-8 and 9 was assigned temporarily on the basis of the general stereoselectivity of OsO_4-dihydroxylation[15]. Further synthetic studies of the polyhydroxylated dihydroagarofuran sesquiterpenoids is still on going and will be published elsewhere.

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14. The spectral data of compound **12:** ^{1}HNMR (400M, $CDCl_3$) δ_H 7.32-7.48 (5H, m), 6.13 (1H, brs), 5.03 (1H, brs), 4.19 (1H, brs), 3.85-4.04 (6H, m), 3.71 (1H, brs), 3.03 (1H, d, J=4HZ), 1.55-2.46 (5H, m), 1.39 (3H, d, J=7.6HZ), 1.35 (3H, s), 1.24 (3H, s); ^{13}CNMR (400M, d^6-acetone) δ_C 16.1, 17.3, 19.6, 26.8, 32.5, 42.7, 45.2, 52.6, 63.9, 64.6, 71.7, 74.2, 79.4, 81.8, 84.9, 92.5, 100.4, 111.6, 126.6, 128.6 (2C), 128.7 (2C), 141.4.

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