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A General Synthetic Route of Dihydroagarofuran Sesquiterpenoid from α-(-)-Santonin

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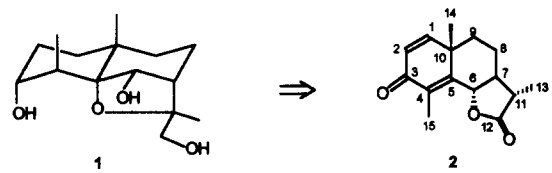
Abstract: A general and efficient approach for synthesis of dihydroagarofuran sesquiterpenoid, the core structure of the polyol esters extensively present in the *Celastraceae* plants, has been developed by a series of transformations, which mainly include three creative and synthetically valuable conversions: the strategic double-bond shifting of **3**, the versatile rearrangement of epoxide **5** generating two key functions, the C5-OH and 7,11-Double-bond, and the stereoselective cyclization/ reduction of **8** constructing the tetrahydrofuran ring of **11**. Thus the sesquiterpenoid 3α,6α,12-trihydroxy-dihydoagarofuran **1** was synthesized.

A variety of dihydroagarofuran sesquiterpene polyol esters, including the alkaloids, have been characterized from the *Celastraceae* plants during the past few decades,[1,2] many of which demonstrated the important cytotoxic,[3] immunosuppressive,[4] anticancer,[5] insecticidal[6] and insect antifeedant[7] activities, but less synthetic work about them was reported because of the challenging multi-hydroxylation on the skeleton and construction of the tetrahydrofuran moiety. Of few successful synthesis,[8-10] the procedure for synthesis of a compound possessing few hydroxyls appeared even quite long and complicated, and all requires the essential establishment of a specific configuration at C-7 for construction of the tetrahydrofuran ring. In our recent synthetic efforts, research interesting was focussed on searching for a short and efficient procedure by choice of α-(-)-santonin as starting material, a rich and synthetically versatile natural source,[11] because of the possible generation of multiple hydroxyls from its multi-functionality. This paper mainly describes the efficient synthesis of the core structure bearing three hydroxyls without the essential construction of the stereoselective carbon center C-7.



1 2

For mainly working on the ϒ-lactone moiety of santonin **2** to construct the tetrahydronfuran ring, our synthesis, as indicated in scheme **1**, was simplified to begin with the dihydro-santonin **3**, prepared by

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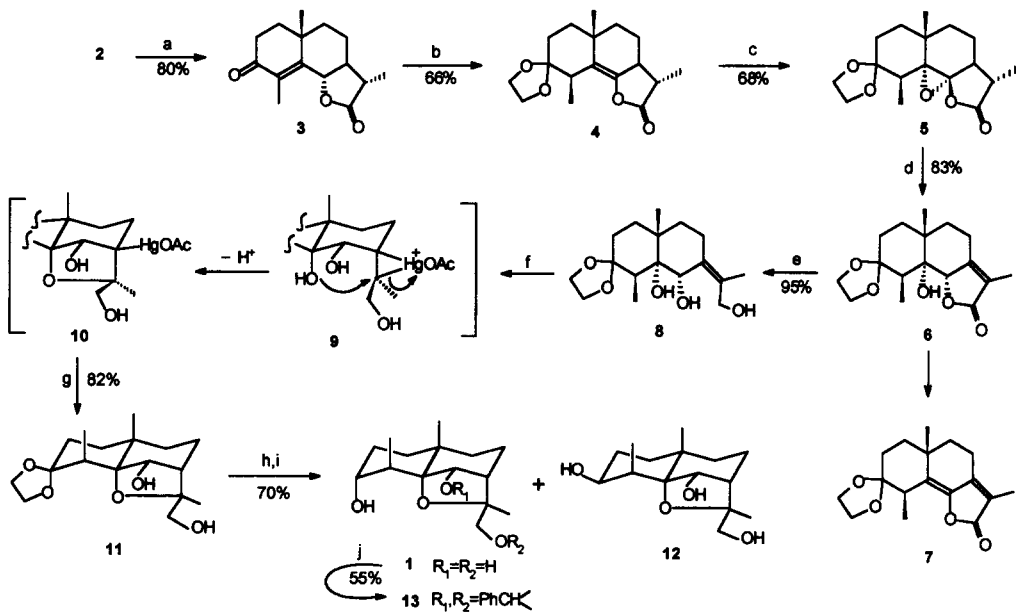
controlled hydrogenation of **2**.[12] Thus the acid-catalyzed contraction with glycol in dry benzene under Dean-Stark water trapping gave the major double-bond-shifting and carbonyl-protected product **4** in the 66% yield. The presence of a quartet at δ 3.03(J=7.5Hz) for 4-methine and the absence of a signal for H-6 in the ^{1}H NMR in **4** suggested that double bond migrated to C_5 and C_6. The axial direction of C_4-Me was assigned based on the ^{1}H NMR W couplings between H-2 and H-4 in the following **5** (J=3Hz) and **11**(J=1.7Hz). Then, epoxidation of **4** with m-CPBA in CH_2Cl_2 at r. t. formed only one epoxide in the 68% yield, whose ^{13}C NMR signals at δ 71.8 and 91.9 for two quaternary carbons and the molecular composition $C_{17}H_{24}O_5$ established by HRMS, indicated the 5,6-epoxide **5** was formed. The α-face direction of the epoxy oxygen in **5** was assigned based on the consideration that the oxygen attacked the double-bond from the α face of it due to the steric hindering caused by two β methyls, the C_4-Me and C_{10}-Me.



Scheme 1. a. H_2/Renay Ni/C_6H_6; b. Glycol(5eq)/PTS/ C_6H_6, reflux; c. m-CPBA(1.5eq)/CH_2Cl_2, r. t., overnight; d. NaOMe(50eq)/MeOH, r. t.; e. $LiAlH_4$(20eq)/THF, -40°C(3h)→r. t.(overnight); f. $Hg(OAc)_2$/THF/H_2O, 2h; g. $NaBH_4$(20eq)/NaOH, r. t., 3h; h. MeCOMe/PTS, r. t., 15 min; i. $LiAlH_4$(1.5eq)/Et_2O, -78°C, 4h; j. PhCHO/ $ZnCl_2$, r. t., 15h.

Epoxide **5**, when treated with NaOMe in MeOH at r. t., underwent an unusual rearrangement to give the important intermediate **6** in the 83% yield if the reaction was quenched with water upon the emerging of the further dehydration product **7**. The ^{13}C NMR of **6** displayed the signals at δ 120.8 and 161.3 for the tetrasubstituted and acyl-conjugated 7,11-double-bond, and that at δ 78.7 for oxygen-born quaternary C-5. The axial H-6 of **6** was assigned based on the similar literature stereochemistry consideration,[13] which was confirmed by NOESY technique for the following **1**. The α-configuration of C_5-OH of **6** was confirmed by

the later successful cyclization of **8**. Rearrangements of this epoxide under the typical conditions, for example with Al(O-*i*-Pr)$_3$/isopropanol or Al(O-*i*-Pr)$_3$/tolune in place of NaOMe/MeOH, proved to be ineffective.[14] Although the details of this rearrangement were unclear, the result was of synthetically significant importance not only because of the generation of C_5-OH and 7,11-double-bond for the following convenient tetrahydrofuran cyclization, but the possible hydroxylation at C-8 and C-9 through the appropriate functionization at the allylic position C-8 of this double-bond.

Reduction of **6** with $LiAlH_4$/THF at – 40°C→ r. t. gave the triol product **8** in the yield 95%, whose ^{13}C NMR exhibited the signals at δ 64.9 for the 12-methylene. Compound **8**, when treated with $Hg(OAc)_2$/THF followed by reduction with $NaBH_4$ *in situ*, smoothly gave the lone product **11** in total yield 82%,[15] and no other 11-epimerization product could be isolated and detected. Other cyclization conditions, such as NBS/THF, H_2SO_4/benzene and *p*-TsOH/benzene, proved to be ineffective, which all gave the very complicated mixtures. The down-field ^{13}C NMR signals at δ 92.8 and 84.7 indicated the successful cyclization of the tetrahydrofuran ring because nearly all compounds of this kind have the similar shifting values. The assignment of the possible configuration at C-11 in **10** was based on that the equatorially direct coordination of $Hg(OAc)_2$ with the double bond in **8** formed the triangle intermediate **9**,[16] which permitted that the C_5-OH attacked C-11 only from one side, the opposite one of the Hg atom, and thus led to the formation of β C_{11}-hydroxymethyl in **10**, which then was reduced to compound **11** with $NaBH_4$. Most important, this β direction of the C_{11}-hydroxymethyl was just required for synthesis of a number of bioactive micro-lactone alkaloids, such as Cathedulin K-19.[1]

For generation of an axial C_3-OH which was also essential for synthesis of this kind of micro-lactone alkaloids mentioned above, a series of diastereoselective reductions were tried, and $LiAlH_4$ reduction at low temperature proved to be effective. Thus compound **11** was subjected to deprotection with acetone/H^+ followed by reduction with $LiAlH_4$ at –78°C gave two separate products **1** and **12** in ratio 14/1, total yielding 70%. The axial direction of C_3-OH of the dominant **1** was assigned based on its ^1H NMR singlet at δ 3.75 and the singlet of the following **13** at δ 5.53 for H-3. For further confirming the stereochemical assignments of C-3, C-4 and C-6, a NOESY spectrum was taken, whose results were consistent with those mentioned above. Furthermore, compound **1** was readily contracted with PhCHO/$ZnCl_2$ to give the only acetal **13** in the 55% yield, supporting the above assignment of β C_{11}-hydroxymethyl because an α form hardly formed such a cyclic acetal due to the steric hindering. As a result, we have synthesized a dihydroagarofuran sesquiterpenoid **1** with three hydroxyls useful for further synthesis of natural products. All structures of these compounds described above were determined mainly by NMR, MS and HRMS analysis.[17]

The method reported above is in deed a new route for synthesis of dihydroagarofuran sesquiterpenoids. If the hydroxyls are introduced at appropriate stages of this synthetic scheme, a series of important chiral dihydroagarofuran sesquiterpene compounds or their enantiomers[18] could be synthesized.

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17. As a example, analysis data for **1**: $[\alpha]_D^{27}$= + 63.7° (c. 0.65, EtOH); δ_H(*ppm*) 1.14(3H, d, *J*=8Hz), 1.15, 1.28(each3H, 2s), 1.55-1.90(8H, m), 2.13(1H, t, *J*=2Hz), 2.35(1H, q, *J*=8Hz), 3.48, 3.57(each1H, ABq, *J*=12Hz), 3.75(1H, s), 4.08(1H, s); δ_C(*ppm*) 16.3, 19.9($2CH_3$), 2×24.2(CH_2, CH_3), 25.6, 31.7, 37.7($3CH_2$),38.6(CH), 40.0(C), 49.7(CH), 69.8(CH_2), 72.2, 77.6(2CH), 85.0, 94.5(2C); m/z(%) 270(M^+, 1), 238(82), 221(100), 203(15), 178(8), 161(12), 159(13), 95(5); FAB-HRMS: 271.1905, cacld for $C_{15}H_{26}O_4$+H: 271.1909.

18. Though the natural compounds are represented in the enantiomers of **1** in most cases, some of the actual absolute configurations are not determined, and in fact, some of the absolute configurations for the dihydroagarofuran ring systems have been determined to be (or depicted in) the same forms as **1**. As examples, please see: Budzikiewicz, H.; Romer, A. *Tetrahedron,* **1975**, 31, 1761-1767. Pailer, M.; Streicher, W.; Leitich, J. *Monatsh. Chem.* **1971**, 102, 1873-1897.