Chinese Journal of Chemistry, **2004**, *22*, 377—383 **Article**

First Synthesis of (+)-2,14-Deoxyalatol from α-Santonin

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A novel and general approach for synthesis of the multi-oxygenated dihydrofuran sesquiterpenes has been developed starting from santonin. The key steps involve: the strategic acid-catalyzed double-bond shifting affording **4**, the novel base-promoted epoxide rearrangement of **5** generating two key functionals (the C5-OH and the $\Delta^{7,11}$ double bond), and the stereoselective cyclization of tetrahydrofuran ring without pre-controlling the stereochemistry of C-7. As an example of this approach, synthesis of (+)-2,14-deoxyalatol was described in detail.

Keywords first synthesis, dihydrofuran sesquiterpene, (+)-2,14-deoxyalatol

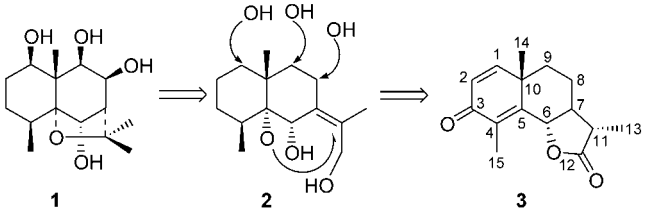
Introduction

A large number of the dihydroagarofuran sesquiterpenes, isolated from *Celastraceae* plants have been demonstrated to exhibit many important biological activities, such as cytotoxic,[1] antitumor,[2] immunosuppressive,[3] insecticided,[4] anti-HIV activities,[5] *etc*. Therefore, synthesis of this kind of compounds has been attracting the great interest of organic chemists, and some methods have been reported.[6] These approaches, however, are usually applicable to those compounds with the special hydroxyl group number and/or special hydroxyl substitution fashions (*i.e.*, substitution at special sites). Developing a general approach to synthesize as more as possible the target compounds is still a remaining challenging subject because this kind of natural sesquiterpenes indeed consists of a huge number of analogs and some un-natural derivatives have been proved to be of good biological activity.[7] In connection with our efforts for this purpose, we chose the naturally abundant santonin **3** as the starting material, which allows, to great extent, the differentiation of substitution number as well as substitution fashions due to that it possesses many functionization sites. This is required particularly for the synthesis of the most highly oxygenated *Celastraceae* target cores (*e.g.*, euonyminol).[6] In this paper, we wish to present in detail the concise synthesis of 2,14-deoxyalatol **1** to describe the generality of this approach. This target molecule was the core of many natural compounds, such as angulatueoidand.[8,9] The partial work was outlined in a previous paper.[10]

Results and discussion

The designed retro-synthesis is showed in Scheme 1, in which two major problems must be resolved: transforming the lactone moiety of **3** to the tetrahydrofuran ring without pre-reversing the stereochemistry of C-7 and, introducing the hydroxy functionality at the given sites. On the basis of this analysis, we initially tried to hydroxylyze directly at C-1, 2, 4 and 5 of **3** with a series of reagents such as OsO_4 or AD-mix-α or -β, *etc*., but did not succeed. The major problems were generation of the complicated products. Then we turned to another strategy (showed in Scheme 2), the first construction of the tetrahydrofuran moiety. For this purpose a temporary hydrogenation of C1-C2 double bond and protection of the C3-carbonyl were performed. Fortunately, a PTS-catalyzed protection of C3-carbonyl with glycol also shifted the C4-C5 double bond to C5-C6 to afford the compound **4**. That result was just what we hoped because if epoxide **5** could be prepared, the allylic alcohol intermediate **6** would be obtained after an acid-promoted rearrangement,[11] which would isomerize automatically to form the precursor **7,** a precursor for cyclization of tetrahydrofuran ring. Unfortunately, although a lot of acids, including the proton and Lewis acid, were tested, neither **6** nor **7** was identified from the mixed reaction systems.

Scheme 1



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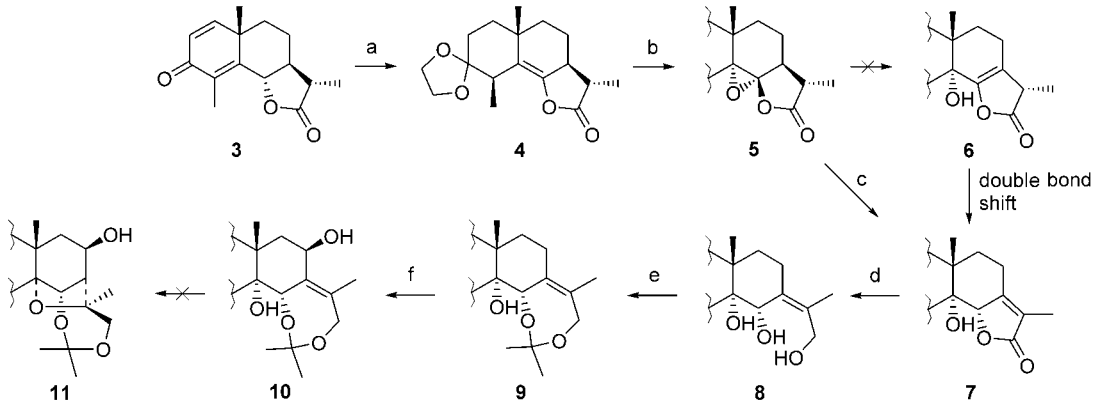
Scheme 2

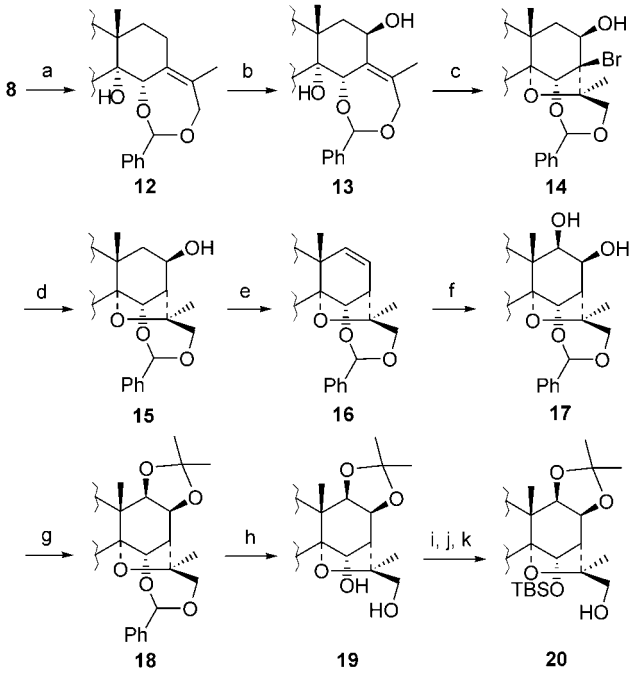


Reaction conditions: (a) H_2, Raney Ni, PhH; glycol (5 eq.), PTS, toluene, 53%; (b) *m*-CPBA, CH_2Cl_2, 68%; (c) NaOMe (50 eq.), MeOH, 83%; (d) $LiAlH_4$, THF, −78 ℃ to r.t., 95%; (e) acetone, PTS, r.t., 90%; (f) SeO_2, *t*-BuO_2H, dioxane, r.t., 95%.

In late continued efforts, an occasional test[12] using a basic system (50 equiv. NaOMe in MeOH) could readily perform the conversion of **5** to **7**. To our knowledge, this transformation has not been reported in this kind of compound. This transformation avoided the stereochemistry reversing of C-7 for the late tetrahydrofuran construction. Subsequently, the lactone ring of **7** was reduced with $LiAlH_4$, and for the late dihydroxylation at C-8 and -9, a functionality at C-8 must be introduced prior to cyclization of tetrahydrofuran ring. Therefore, two active hydroxyls at C-6 and -12 of **8** were selectively protected with acetone/PTS and then oxidized with SeO_2/*t*-BuO_2H to give the intermediate **10**. But the following cyclization of **10** did not work even with the well-established system $Hg(OAc)_2/NaBH_4$,[13] *m*-CPBA/NaBr,[14] and so on. A possible reason was the steric hinderance caused by the quaternary acetonide moiety.

Subsequently, benzoaldehyde-protecting group was used to replace acetone and the tetrahydrofuran closure precursor **13** (only one isomer, but we did not determine the stereochemistry of the acetal center) was prepared in 70% yield (Scheme 3) by treatment of triol **8** with $PhCHO/ZnCl_2$ followed by oxidation with SeO_2/*t*-BuO_2H. In the following tetrahydrofuran closure investigation, $Hg(OAc)_2$ was proved to be still not effective to **13** even though it worked well for the simple compound **8**.[15] A widespread search demonstrated that NBS/THF system could promote readily this closure at 0 ℃ and the tetrahydrofuran intermediate **14** was obtained in high yield (95%). Two characteristic signals at δ_C 92.0 (C-5) and 86.1 (C-11) indicated the successful cyclization of the tetrahydrofuran ring.[16] Debromination of compound **14** by a radical reaction with *n*-Bu_3SnH followed by dehydration gave the olefin **16**, which was subjected to dihydroxylation with OsO_4/NMO to give only the 8β,9β-diol product **17**. The stereochemistry of 8β,9β-diol (*i.e.*, 8a,9e-diol) was elucidated from the coupling constants $J_{7e,8e}$=4.0 Hz,[17] as the OsO_4 oxidation gave the *cis*-diol. No 8α,9α-diol was isolated possibly because of the steric hinderance from the tetrahydrofuran ring. For completing synthesis of the target molecule **1**, we need to remove two oxygenated groups at C-3 and -12 and introduce one hydroxyl at C-1. Thus two hydroxyls at C-8 and -9 were first protected, then C6-OH and C12-OH were released and after three steps (i—k in Scheme 3), the C12-OH free intermediate **20** was prepared. It should be particularly noticed that in our previous report,[10] the use of the acetone/PTS and other acetonization system for protection of C8,9-OH of

Scheme 3

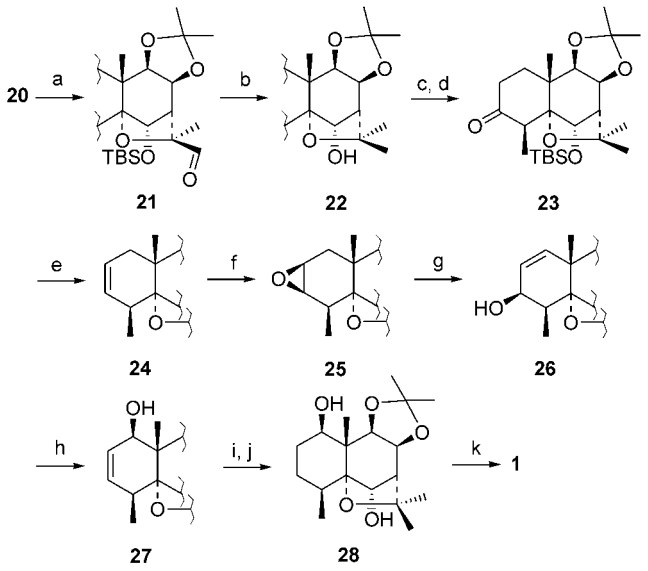


Reaction conditions: (a) PhCHO, $ZnCl_2$, r.t., 72%; (b) SeO_2, *t*-BuO_2H, 70%; (c) NBS, THF, 0 ℃, 95%; (d) *n*-Bu_3SnH, PhH; (e) Et_3N, MsCl; NaOMe, MeOH (44%, two steps); (f) OsO_4, NMO, acetone, r.t., 57%; (g) acetone, DMF, cat. PTS, r.t. 87%; (h) K, *t*-$BuNH_2$, THF, r.t., 89%; (i) BzCl, Py, 0 ℃; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (k) NaOMe (2 eq.), MeOH, r.t., 63% (three steps).

17 could not give the clear product, and MeI/NaH had to be used for the protection. As the demethylation was not successful, we were not actually able to obtain the natural product 2,14-deoxyalatol **1**. After our recent widespread tests, the acetone/PTS/DMF system was found to be effective for preparation of **18**.

For removal of the C12-OH of **20**, its sulfonate was prepared with MsCl and then reduced with $LiBHEt_3$. However, the reaction did not work at 0 ℃—r.t., and heating or refluxing would lead to a complicated mixture. Subsequently, the alcohol **20** was converted to an aldehyde **21**, and removed readily by Huang-Minlon reaction, but that reaction also removed the protecting group of C6-OH (as showed in Scheme 4). Reprotection of C6-OH of **22** with TBSOTf followed by treatment with PTSA in acetone gave a carbonyl compound **23**. Hydrozonization of **23** with $TsNHNH_2$ followed by treatment with CH_3Li led to an olefin **24** in high yield. Initially, compound **24** was subjected to oxidation with SeO_2 so as to directly introduce a hydroxyl at C-1, but no desired product could be obtained even by varying the reaction conditions. The major product was that with the hydroxyl located at C-4. It is a fact that introduction of C1-OH or C9-OH is generally difficult in the synthesis of this kind of compounds because of the steric hinderance from the adjacent quaternary C-10. Therefore **24** was first epoxidized with *m*-CPBA to afford a single product **25**, which was rearranged with the strong base LDA to generate the allylic alcohol **26** in 72% yield. A further isomerization of allylic alcohol **26** with 30% AcOH / THF[18] formed the compound **27** together with a small mount of unreacted **26**. The mixture of **26** and **27** was subjected to hydrogenation with 10% Pd/C to furnish **28** in 41% yield, with the C6-OTBS being deprotected. By a final deprotection of acetone group of **28** with MeOH/PTS, the natural product, 2,14-deoxyalatol **1** was produced in 86% yield.

Scheme 4



Reaction conditions: (a) PDC, CH_2Cl_2; (b) $NH_2NH_2 \cdot H_2O$, K_2CO_3, diethylene glycol, 170 to 220 ℃, 63% (two steps); (c) TBSOTf, 2,6-lutidine; (d) PTS, acetone, r.t., (73%, two steps); (e) *p*-$MeC_6H_4SO_2NHNH_2$, THF; CH_3Li, r.t.; (f) *m*-CPBA, CH_2Cl_2, r.t.; (g) *i*-Pr_2NLi (5 eq.), THF, −78 ℃ to r.t., (72%, three steps); (h) 30% AcOH, THF, r.t.; (i) 10% Pd/C, H_2; (j) *n*-$Bu_4N^+F^-$, THF, r.t., 41% (three steps); (k) PTS, MeOH, r.t. 86%.

Experimental

The ^1H NMR and ^{13}C NMR data were recorded in $CDCl_3$ or acetone-d_6 with Bruker ADANCE DXR-200 or AM-400 spectrometers. The chemical shifts were reported relative to TMS or $CDCl_3$. MS were measured on a HP-5988 spectrometer by direct inlet at 70 eV, and signals given in *m*/*z* with relative intensity (%) in brackets. HRMS were measured with ESI or EI technique. Optical rotations were determined on a Perkin Elmer Model 341 apparatus. Column chromatographies were generally performed on silica gel (200—300 mesh) eluting with petroleum ether (b.p. 60—90 ℃) and EtOAc.

3,3-Ethylenedioxy-5*α*,6*α*,12-triol-4*α*,6*β*-eudesm-7,11-ene (8)

Compound **7** (60 mg, 0.19 mmol) was dissolved in 5 mL of dried THF followed by addition of 50 mg of $LiAlH_4$ (1.33 mmol) at −78 ℃ under Ar atmosphere protection. The mixture was stirred at the same temperature for 1 h, then left to warm to the room temperature for one night. The excess $LiAlH_4$ was destroyed by acetal acetate and water. The mixture was extracted with acetal acetate. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (1∶1, *V*∶*V*) to give the compound **8** 60 mg in 95% yield. The spectral data of **8**: ^1H NMR δ: 4.31, 4.51 (dq, J=12.0 Hz, 5.0 Hz, each 1H), 4.04—3.91 (m, 5H), 1.73 (s, 3H), 2.50—1.20 (m, 9H), 1.10 (d, J=7.6 Hz, 3H), 1.04 (s, 3H); ^{13}C NMR δ: 136.3, 123.7, 112.9, 80.0, 70.2, 64.9, 64.5, 64.3, 43.2, 38.0, 37.7, 34.7, 27.7, 24.6, 22.5, 18.9, 13.6; EIMS *m*/*z* (%): 312 (M^+, 4), 294 (52), 184 (44), 140 (21), 109 (19), 99 (100), 87 (37), 67 (21), 55 (33); FAB-HRMS calcd for $C_{17}H_{28}O_5$+H: 313.2015, found 313.1966.

3,3-Ethylenedioxy-5*α*-hydroxy-6*α*,12-benzylidene acetal-4*α*,6*β*-eudesm-7,11-ene (12)

Compound **8** (150 mg, 0.48 mmol) was dissolved in 2 mL of benzyl aldehyde followed by addition of 150 mg of $ZnCl_2$. The mixture was stirred at r.t. for 0.5 h and then poured into saturated $NaHCO_3$, extracted with

CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (3∶1, *V*∶*V*) to give the compound **12** 138 mg in 72% yield. The spectral data of **12**: ^{1}H NMR δ: 7.50—7.31 (m, 5H), 5.93 (brs, 1H), 4.62 (d, *J*=15.0 Hz, 1H), 4.49 (brs, 1H), 4.01 (d, *J*=15.0 Hz, 1H), 3,89—3.80 (m, 4H), 2.90 (brs, 1H), 2.51—2.47 (m, 1H), 2.02—1.91 (m, 2H), 1.87—1.82 (m, 2H), 1.72 (s, 3H), 1.35—1.32 (m, 1H), 1.05—1.01 (m, 1H), 0.94 (s, 3H), 0.85—0.78 (m, 1H), 0.02 (d, *J*=4.0 Hz, 3H); ^{13}C NMR δ: 139.6, 134.7, 129.5, 128.9, 128.9, 128.9, 128.2, 128.2, 113.1, 101.4, 79.9, 72.0, 70.9, 64.9, 64.1, 42.0, 38.6, 37.1, 33.9, 27.2, 25.1, 21.0, 18.2, 12.6; EIMS *m*/*z* (%): 400 (M^+, 4), 385 (14), 294 (27), 276 (10), 216 (11), 184 (59), 107 (25), 99 (100); EI-HRMS calcd for $C_{24}H_{32}O_5$: 400.2250, found 400.2222.

3,3-Ethylenedioxy-5*α*,8*β*-diol-6*α*,12-benzylidene acetal-4*α*,6*β*-eudesm-7,11-ene (13)

Compound **12** (210 mg, 0.52 mmol) was dissolved in 4 mL of dioxane followed by addition of SeO_2 (29 mg, 0.26 mmol) and 0.1 mL of 75% *t*-BuO_2H. The mixture was stirred at r.t. for one night and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (1∶1, *V*∶*V*) to give the compound **13** 151 mg in 70% yield. The spectral data of **13**: $[\alpha]_D^{25}$ +29 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ: 7.60—7.38 (m, 5H), 5.94 (brs, 1H), 5.02 (d, *J*=4.9 Hz, 1H), 4.91 (brs, 1H), 4.81 (d, *J*=15.0 Hz, 1H), 4.17 (d, *J*=15.0 Hz, 1H), 4.00—3.91 (m, 4H), 2.15—2.10 (m, 2H), 2.08—2.05 (m, 1H), 1.90 (s, 3H), 1.89—1.87 (m, 1H), 1.74—1.71 (m, 1H), 1.39—1.36 (m, 1H), 1.33 (d, *J*=5.6 Hz, 3H), 1.21—1.19 (m, 1H), 1.11 (s, 3H); ^{13}C NMR δ: 137.8, 137.1, 136.2, 128.9, 128.3, 128.3, 127.1, 127.1, 112.5, 101.1, 79.2, 70.9, 68.4, 66.8, 64.1, 63.6, 42.7, 40.7, 37.1, 33.4, 26.0, 22.6, 17.3, 11.6; FABMS *m*/*z* (%): 417 (M^++H, 15), 398 (3), 311 (10), 293 (100), 276 (2), 231 (5), 99 (33); FAB-HRMS calcd for $C_{24}H_{32}O_6$+H: 417.2277, found 417.2291.

3,3-Ethylenedioxy-8*β*-hydroxy-7*β*-bromo-6*α*,12-benzylidene acetal-5*α*,11-agarofuran (14)

Compound **13** (52 mg, 1.27 mmol) was dissolved in 10 mL of THF followed by addition of 5 mL of THF solution of 450 mg of NBS (2.53 mmol) at 0 ℃. The mixture was stirred at the same temperature for 1 h and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (3∶2, *V*∶*V*) to give the compound **14** 597 mg in 95% yield. The spectral data of **14**: ^{1}H NMR δ: 7.31—7.48 (m, 5H), 6.42 (s, 1H), 4.90 (brs, 1H), 4.22 (d, *J*=4.8 Hz, 1H), 4.04—4.01 (m, 4H), 3.89 (d, *J*=6.8 Hz, 1H), 3.81 (d, *J*=6.8 Hz, 1H), 2.53—2.51 (m, 1H), 1.91—1.78 (m, 3H), 1.65—1.63 (m, 1H), 1.52—1.50 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.31 (d, *J*=7.6 Hz, 3H), 1.24—1.22 (m, 1H); ^{13}C NMR δ: 139.5, 128.5, 128.3, 128.3, 125.8, 125.8, 110.9, 98.7, 92.0, 86.1, 79.9, 79.9, 77.8, 75.5, 64.6, 63.5, 42.9, 42.2, 40.6, 34.0, 26.1, 24.6, 17.2, 15.4; FABMS *m*/*z* (%): 495 (M^++H, 58), 417 (100), 311 (65), 293 (26), 249 (37), 122 (3), 99 (85); FAB-HRMS calcd for $C_{24}H_{31}O_6Br$+H: 495.1382, found 495.1378.

3,3-Ethylenedioxy-8*β*-hydroxy-6*α*,12-benzylidene acetal-5*α*,11-agarofuran (15)

Compound **14** (1.875 g, 3.78 mmol) was dissolved in 50 mL of benzene followed by addition of 2 mL of *n*-Bu_3SnH and a catalytic amount of AIBN. The solvent was evaporated *in vacuo* after the mixture was refluxed for 10 h. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (1∶1, *V*∶*V*) to give the compound **15** 1.132 g in 72% yield. The spectral data of **15**: $[\alpha]_D^{25}$ +54 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ: 7.41—7.18 (m, 5H), 6.12 (s, 1H), 5.00 (brs, 1H), 3.92—3.69 (m, 7H), 2.78 (d, *J*=7.2 Hz, 3H), 2.38—2.33 (m, 1H), 1.87—1.78 (m, 2H), 1.75—1.71 (m, 1H), 1.39—1.36 (m, 1H), 1.31 (s, 3H), 1.29 (d, *J*=7.2 Hz, 3H), 1.24—1.18 (m, 1H), 1.08—1.06 (m, 1H); ^{13}C NMR δ: 139.8, 128.3, 128.2, 128.2, 125.6, 125.6, 111.2, 99.5, 92.6, 84.3, 81.1, 78.9, 69.4, 64.5, 63.3, 53.6, 44.1, 41.9, 40.7, 34.2, 26.5, 25.2, 19.8, 15.6; FABMS *m*/*z* (%): 417 (M^++H, 100), 329 (9), 311 (90), 293 (23), 249 (5), 175 (2), 99 (86); FAB-HRMS calcd for $C_{24}H_{32}O_6$+H: 417.2277, found 417.2278.

3,3-Ethylenedioxy-8,9-oelfin-6*α*,12-benzylidene acetal-5*α*,11-agarofuran (16)

Compound **15** (1.200 g, 2.88 mmol) was dissolved in 20 mL of CH_2Cl_2 followed by addition of 1 mL of Et_3N and 0.5 mL of MsCl at −20 ℃. The mixture was stirred at the same temperature for 1 h, then water was added in excess and the resultant mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 100 mL of methanol followed by addition of 2 g of NaOMe. The mixture was refluxed for 24 h and the solvent was evaporated *in vacuo*. The residue was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (2∶1, *V*∶*V*) to give the compound **16** 500 mg in 44% yield. The spectral data of **16**: ^{1}H NMR δ: 7.41—7.30 (m, 5H), 6.21 (s, 1H), 5.57 (dd, *J*=6.8, 9.3 Hz, 1H), 5.22 (d, *J*=9.3 Hz, 1H), 4.80 (brs, 1H), 3.97—3.82 (m, 6H), 3.09 (d, *J*=6.8 Hz, 1H), 2.53—2.51 (m, 1H), 2.23—2.16 (m, 1H), 1.99—1.92 (m, 1H), 1.75—1.71 (m, 1H), 1.27 (d, *J*=7.6 Hz, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.14—1.11 (m, 1H); ^{13}C NMR δ: 140.0, 137.5, 128.3, 128.2, 128.2, 125.6, 125.6, 123.9, 111.1, 99.3, 91.2, 89.3, 81.4, 79.6, 64.4, 63.7, 48.5, 46.0, 42.7, 28.5, 28.4, 25.6, 22.6, 14.5; EIMS *m*/*z* (%): 398 (M^+, 6), 354 (1), 277 (2), 219 (6), 175 (14), 121 (25), 99 (100); FAB-HRMS calcd for $C_{24}H_{30}O_5$+H: 399.2171, found 399.2181.

3,3-Ethylenedioxy-8*β*,9*β*-diol-6*α*,12-benzylidene acetal-5*α*,11-agarofuran (17)

Compound **16** (500 mg, 1.26 mmol) was dissolved in 5 mL of acetone followed by addition of a catalytic amount of OsO_4 and 500 mg of NMO. The mixture was stirred at r.t. for 3 d. The solvent was evaporated *in vacuo*. And the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and acetone (2∶1, *V*∶*V*) to give the compound **17** 312 mg in 57% yield. The spectral data of **17**: $[\alpha]_D^{25}$ +82 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ: 7.46—7.31 (m, 5H), 6.12 (s, 1H), 5.01 (brs, 1H), 4.07 (m, 1H), 4.04—3.82 (m, 6H), 3.71 (brs, 1H), 3.00 (d, *J*=4.0 Hz, 1H), 2.44—2.42 (m, 1H), 2.27 (m, 1H), 2.22 (m, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.39 (d, *J*=7.6 Hz, 3H), 1.35 (s, 3H), 1.21 (s, 3H); ^{13}C NMR δ: 141.4, 128.7, 128.6, 128.6, 126.6, 126.6, 111.6, 100.4, 92.5, 84.9, 81.8, 79.4, 74.2, 71.9, 64.6, 63.9, 52.6, 45.2, 42.8, 32.5, 26.8, 18.6, 17.3, 16.1; EIMS *m*/*z* (%): 432 (M^+, 3), 414 (2), 365 (1), 308 (2), 253 (3), 149 (18), 99 (100); FAB-HRMS calcd for $C_{24}H_{32}O_7$+H: 433.2226, found 433.2260.

3,3-Ethylenedioxy-8*β*,9*β*-acetonide-6*α*,12-benzylidene acetal-5*α*,11-agarofuran (18)

Compound **17** (120 mg, 0.28 mmol) was dissolved in 3 mL of acetone and 1 mL of DMF followed by addition of a catalytic amount of PTS. The mixture was stirred at r.t. for one night and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and acetone (2∶1, *V*∶*V*) to give the compound **18** 112 mg in 87% yield. The spectral data of **18**: $[\alpha]_D^{25}$ +85 (*c* 1.7, $CHCl_3$); ^{1}H NMR δ: 7.47—7.32 (m, 5H), 6.02 (s, 1H), 5.00 (brs, 1H), 4.47—4.42 (m, 1H), 4.02—3.83 (m, 7H), 3.17 (d, *J*=3.2 Hz, 1H), 2.47—2.45 (m, 1H), 2.04—1.91 (m, 4H), 1.57 (s, 3H), 1.44 (s, 3H), 1.32 (d, *J*=7.2 Hz, 3H), 1.30 (s, 3H), 1.18 (s, 3H); ^{13}C NMR δ: 140.0, 128.4, 128.2, 128.2, 125.6, 125.6, 110.7, 109.4, 100.3, 92.0, 84.6, 81.1, 80.7, 78.6, 77.0, 64.4, 63.4, 47.7, 44.5, 42.8, 33.0, 27.2, 25.7, 25.5, 20.6, 20.3, 15.8; EIMS *m*/*z* (%): 472 (M^+, 2), 428 (1), 414 (12), 351 (1), 293 (1), 196 (1), 121 (20), 99 (100); EI-HRMS calcd for $C_{27}H_{36}O_7$: 472.2461, found 472.2478.

3,3-Ethylenedioxy-8*β*,9*β*-acetonide-6*α*,12-diol-5*α*,11-agarofuran (19)

Compound **18** (93 mg, 0.20 mmol) was dissolved in 2 mL of dried THF and 2 mL of *t*-$BuNH_2$ followed by addition of potassium (80 mg, 2.00 mmol) and two drops of *tert*-butyl alcohol. The mixture was stirred at r.t. for 8 h, then methanol was added in excess, and the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and acetone (1∶1, *V*∶*V*) to give the compound **19** 67 mg in 89% yield. The spectral data of **19**: $[\alpha]_D^{25}$ +83 (*c* 2.1, $CHCl_3$); ^{1}H NMR δ: 4.61 (brs, 1H), 4.54—4.52 (m, 1H), 3.85 (d, *J*=6.4 Hz, 1H), 3.74 (brs, 4H), 3.65 (d, *J*=12.0 Hz, 1H), 3.60 (d, *J*=12.0 Hz, 1H), 2.70—2.63 (m, 2H), 2.30—2.20 (m, 2H), 1.76—1.71 (m, 2H), 1.56 (s, 3H), 1.37 (d, *J*=7.8 Hz, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ: 109.6, 107.6, 94.5, 83.8, 81.1, 77.8, 77.2, 71.4, 69.7, 63.7, 51.3, 51.1, 44.6, 35.8, 34.6, 25.9, 25.4, 20.6, 19.5, 15.7; EIMS *m*/*z* (%): 366 (M^+-H_2O, 0.1), 353 (0.1), 325 (1), 309 (18), 249 (10), 209 (8), 191 (31), 99 (29), 43 (100); EI-HRMS calcd for $C_{20}H_{32}O_7$: 384.2148, found 384.2144.

3,3-Ethylenedioxy-8*β*,9*β*-acetonide-6*α*-*tert*-butyl dimethyl ether-12-hydroxy-5*α*,11-agarofuran (20)

Compound **19** (110 mg, 0.30 mmol) was dissolved in 4 mL of dried pyridine without purification followed by addition of 0.3 mL of benzoyl chloride at 0 ℃. The mixture was stirred at the same temperature for 1 h, then water was added in excess and the resultant mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in 3 mL of CH_2Cl_2 followed by addition of 0.3 mL of 2,6-lutidine and 0.3 mL of TBSOTf. The mixture was stirred at r.t. for one night and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 5 mL of methanol and 50 mg of NaOMe was added. The mixture was reacted at r.t. for 4 h and then extracted with EtOAc. The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (1∶1, *V*∶*V*) to give the compound **20** 90 mg in 63% yield. The spectral data of **20**: ^{1}H NMR δ: 4.70 (brs, 1H), 4.53—4.49 (m, 1H), 4.32 (d, *J* =10.0 Hz, 1H), 4.01—3.97 (m, 2H), 3.90—3.77 (m, 2H), 3.81 (d, *J*=5.2 Hz, 1H), 3.20 (d, *J*=10 Hz, 1H), 2.42 (d, *J*=3.2 Hz, 1H), 2.15—2.11 (m, 1H), 2.09—2.03 (m, 2H), 1.92—1.84 (m, 2H), 1.54 (s, 3H), 1.40 (brs, 6H), 1.12 (s, 3H), 1.10 (d, *J*=7.2 Hz, 3H), 0.93 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H); ^{13}C NMR δ: 111.2, 109.2, 92.5, 83.1, 82.0, 77.5, 73.9, 67.2, 64.7, 63.3, 49.3, 44.9, 42.2, 34.0, 27.5, 26.0, 26.0, 26.0, 25.9, 25.6, 20.0, 19.8, 17.9, 15.7, −3.4, −5.4; EIMS *m*/*z* (%): 498 (M^+, 1), 483 (3), 467 (74), 409 (35), 367 (4), 277 (11), 173 (7), 131 (64), 99 (100); EI-HRMS calcd for $C_{26}H_{46}O_7Si$: 498.3013, found 498.3000.

3,3-Ethylenedioxy-8*β*,9*β*-acetonide-6*α*-hydroxy-5*α*,11-agarofuran (22)

Compound **20** (360 mg, 0.74 mmol) was dissolved in 5 mL of CH_2Cl_2 followed by addition of 600 mg of PDC. The mixture was stirred at r.t. for 12 h and filtered through a thin pad of Al_2O_3. The solvent was evaporated *in vacuo* and the residue was dissolved in 5 mL of diethylene glycol without separation followed by addition of 0.3 mL of $NH_2NH_2 \cdot H_2O$ and 100 mg of K_2CO_3 (0.74

mmol). The mixture was reacted at 170 ℃ for 1 h then heated to 220 ℃ for 6 h and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (2∶1, *V*∶*V*) to give the compound **22** 172 mg in 63% yield. The spectral data of **22**: ^{1}H NMR δ: 4.72 (brs, 1H), 4.51—4.49 (m, 1H), 4.02—3.99 (m, 2H), 3.88—3.80 (m, 2H), 3.81 (d, *J*=6.4 Hz, 1H), 2.43 (d, *J*=3.2 Hz, 1H), 2.26—2.24 (m, 1H), 2.04—1.90 (m, 4H), 1.53 (brs, 6H), 1.37 (s, 3H), 1.34 (s, 3H), 1.19 (d, *J*=7.6Hz, 3H), 1.12 (s, 3H); ^{13}C NMR δ: 110.8, 109.0, 91.7, 81.8, 81.4, 77.6, 73.6, 64.2, 63.2, 51.6, 44.0, 41.3, 33.6, 30.3, 27.7, 26.0, 25.7, 20.2, 19.1, 15.7; EIMS *m*/*z* (%): 368 (M^+, 4), 310 (32), 256 (84), 213 (4), 195 (25), 166 (28), 133 (15), 99 (100); EI-HRMS calcd for $C_{20}H_{32}O_6$+H: 369.2272, found 369.2273.

3-Keto-8*β*,9*β*-acetonide-6*α*-*tert*-butyl dimethyl silyl-ether-5*α*,11-agarofuran (23)

Compound **22** (89 mg, 0.24 mmol) was dissolved in 3 mL of CH_2Cl_2 followed by addition of 0.1 mL of 2,6-lutidine and 0.1 mL of TBSOTf. The mixture was stirred at r.t. for 2 d, then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 2 mL of acetone and added in a catalytic amount of PTS. The mixture was stirred at r.t. for 1 h and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (2∶1, *V*∶*V*) to give the compound **23** 77 mg in 73% yield. The spectral data of **23**: ^{1}H NMR δ: 4.71 (brs, 1H), 4.54—4.49 (m, 1H), 3.81 (d, *J*=6.8 Hz, 1H), 2.81—2.73 (m, 2H), 2.43 (d, *J*=3.0 Hz, 1H), 2.24—2.05 (m, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.26 (brs, 9H), 0.92 (s, 9H), 0.15 (s, 6H); ^{13}C NMR δ: 214.0, 109.1, 93.1, 81.8, 81.3, 77.3, 73.4, 52.4, 51.5, 44.7, 36.0, 34.3, 30.2, 26.0, 26.0, 26.0, 26.0, 25.4, 25.4, 19.5, 17.9, 16.0, −3.4, −5.5; EIMS *m*/*z* (%): 438 (M^+, 20), 423 (7), 381 (30), 363 (9), 318 (48), 279 (100), 265 (63), 199 (38), 73 (96); EI-HRMS calcd for $C_{24}H_{42}O_5Si$: 438.2802, found 438.2802.

3*β*-Hydroxy-1,2-olefin-8*β*,9*β*-acetonide-6*α*-*tert*-butyl dimethylsilyl ether-5*α*,11-agarofuran (26)

Compound **23** (40 mg, 0.09 mmol) was dissolved in 4 mL of dried THF followed by addition of a catalytic amount of *p*-$MeC_6H_4SO_2NHNH_2$. The mixture was stirred at r.t. for 4 h and then the solvent was evaporated under reduced pressure. The residue was filtered through a thin pad of basic Al_2O_3, then redissolved in 2 mL of THF followed by addition of 1 mol/L CH_3Li solution in THF (0.90 mL). The mixture was stirred at r.t. for 6 h and then saturated NH_4Cl solution was added in excess, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in 3 mL of CH_2Cl_2 followed by addition of 21 mg of *m*-CPBA (0.09 mmol). The mixture was stirred at r.t. for 2 h then extracted with CH_2Cl_2. The organic layer was washed with $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to get the residue 23 mg. The solution of diisopropyl amine (0.04 mL, 0.27 mmol) in 2 mL of dried THF was slowly added in 0.13 mL of 2.13 mol/L *n*-BuLi solution in petroleum at −78 ℃. The mixture was stirred at the same temperature for 1 h then warmed to −50 ℃ for another 1 h. Subsequently, the mixture was recooled to −78 ℃ and the solution of 23 mg of **25** in 2 mL of THF was slowly added. The mixture was stirred at −78 ℃ for 1 h then warmed to r.t. for one night. After reaction, excess saturated NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and EtOAc (2∶1, *V*∶*V*) to give the compound **26** 29 mg in 72% yield. The spectral data of **26:** ^{1}H NMR δ: 5.71—5.68 (m, 1H), 5.61 (d, *J*=10.0 Hz, 1H), 4.80 (brs, 1H), 4.54—4.51 (m, 1H), 4.00 (d, *J*=4.0 Hz, 1H), 3.70—3.66 (m, 1H), 2.58—2.52 (m, 1H), 2.44 (d, *J*=3.0 Hz, 1H), 1.55 (brs, 6H), 1.38 (s, 3H), 1.27 (s, 3H), 1.11 (s, 3H), 1.04 (d, *J*=7.2 Hz, 3H), 0.93 (s, 9H), 0.15 (brs, 6H); ^{13}C NMR δ: 135.4, 124.3, 109.3, 92.6, 81.5, 78.7, 77.5, 72.9, 70.0, 51.6, 46.2, 39.9, 30.2, 25.8, 25.8, 25.8, 25.6, 25.6, 25.4, 22.5, 17.8, 17.8, −3.7, −5.6; EIMS *m*/*z* (%): 438 (M^+, 8), 381 (14), 305 (12), 255 (54), 199 (35), 125 (16), 73 (95), 43 (100); EI-HRMS calcd for $C_{24}H_{42}O_5Si$+H: 439.2874, found 439.2865.

1*β*, 6*α*-Diol-8*β*,9*β*-acetonide-5*α*,11-agarofuran (28)

Comound **26** (13 mg, 0.03 mmol) was dissolved in 2 mL THF followed by addition of a catalytic amount of 30% AcOH. The mixture was stirred at r.t. for 3 d and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in 1 mL of methanol followed by addition of 3 mg of 10% Pd/C. The mixture was reacted at r.t. under the hydrogen atmosphere for 2 h then filtered through a thin pad of silica gel to remove the Pd/C. The solvent was evaporated under reduced pressure and the residue was redissolved in 1 mL of THF followed by addition of 4 mg of *n*-$Bu_4N^+F^-$. The mixture was stirred at r.t. for 4 h then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluted with petroleum ether and acetone (1∶1, *V*∶*V*) to give the compound **28** 4 mg in 41% yield. The spectral data of **28**: ^{1}H NMR δ: 4.70 (brs, 1H), 4.50—4.48 (m, 1H), 4.21—4.17 (m, 1H), 3.76 (d, *J*=6.0 Hz, 1H), 2.46 (d, *J*=3.4 Hz, 1H), 2.44—2.42 (m, 1H), 2.18 (brs, 2H), 1.80—1.64 (m, 2H), 1.53 (s, 3H), 1.52 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.10 (d, *J*=7.2 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR δ: 109.0, 92.6, 82.0, 81.1, 77.6, 73.1,

70.0, 52.0, 43.9, 40.4, 35.1, 30.3, 25.8, 25.7, 25.6, 25.6, 19.9, 11.2; EIMS *m*/*z* (%): 326 (M^+, 13), 311 (13), 268 (31), 250 (23), 169 (57), 99 (31), 84 (100), 43 (66); EI-HRMS calcd for $C_{18}H_{30}O_5$: 326.2093, found 326.2103.

2,14-Deoxyalatol 1

Compound **28** (4 mg, 0.012 mmol) was dissolved in 1 mL of methanol followed by addition of 1 mg of PTS. The mixture was stirred at r.t. for 7 h, then filtered through a thin pad of basic Al_2O_3. The solvent was evaporated under reduced pressure to get the final product **1** 3 mg in 86% yield. The spectral data of **1**: $[\alpha]_D^{25}$ +31 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ: 4.74 (brs, 1H), 4.60 (m, 1H), 4.00 (m, 1H), 3.67 (m, 1H), 2.37 (m, 1H), 2.16 (brs, 1H), 1.59—1.53 (m, 4H), 1.48 (s, 3H), 1.25 (d, *J*=7.6 Hz, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ: 94.2, 82.4, 76.1, 73.1, 73.1, 71.3, 57.4, 44.9, 41.9, 35.7, 31.7, 25.6, 24.4, 17.5, 11.4; EIMS *m*/*z* (%): 286 (M^+, 25), 268 (19), 253 (23), 192 (73), 169 (32), 125 (100), 83 (74), 69 (29); EI-HRMS calcd for $C_{15}H_{26}O_5$: 286.1780, found 286.1817.

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