Pergamon

Tetrahedron Letters 43 (2002) 627–630

TETRAHEDRON LETTERS

A novel approach for construction of the naturally occurring dihydroagarofuran sesquiterpene skeleton

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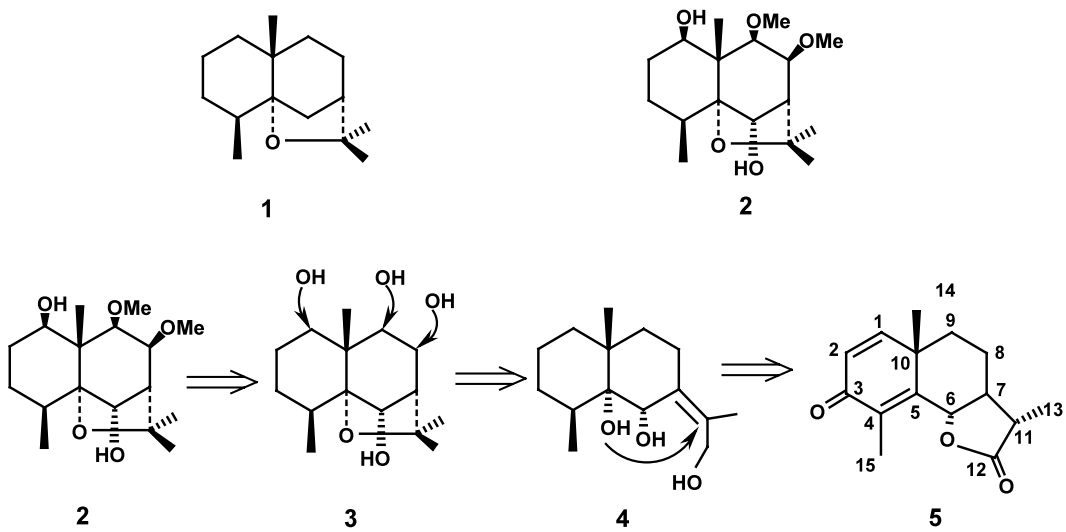
Received 11 October 2001; accepted 16 November 2001

Abstract—A general and efficient approach for the synthesis of a kind of dihydrofuran sesquiterpenes extensively present in the *Celastraceae* family of plants has been developed by a series of transformations from santonin. The key creative and versatile steps involve the strategic acid-catalyzed double-bond shifting affording **6**, the novel base-promoted epoxide rearrangement of **7** generating two key functions (the C5–OH and the $\Delta^{7,11}$ double bond) and the stereoselective construction of a tetrahydrofuran moiety without particularly controlling the stereochemistry of C7. In particular, this approach can introduce any number of hydroxyls at the required positions for synthesis of many natural dihydroagarofuran sesquiterpenes.

Numerous agarofuran sesquiterpenes with a different number of polyol esters bearing the skeleton **1**, isolated from the *Celastraceae* plants have attracted a great deal of interest from chemists on account of their wide range of biological activities, such as important cytotoxic,[1] antitumor,[2] immunosuppressive,[3] insecticidal[4] and anti-HIV activities.[5] However, few successful synthetic works on agarofuran sesquiterpenes have been reported up to now, because the multi-hydroxylation on the skeleton and construction of the tetrahydrofuran ring is challenging work. In 1997, White and co-workers reported the first successful total synthetic work.[6] However, it was very complicated and was only used for the synthesis of a few target compounds with some limited substitution fashions. In connection with our investigation of this field, our goal was to develop a general and efficient procedure for the synthesis of the agarofuran sesquiterpenes with a different number of hydroxyl



Scheme 1.

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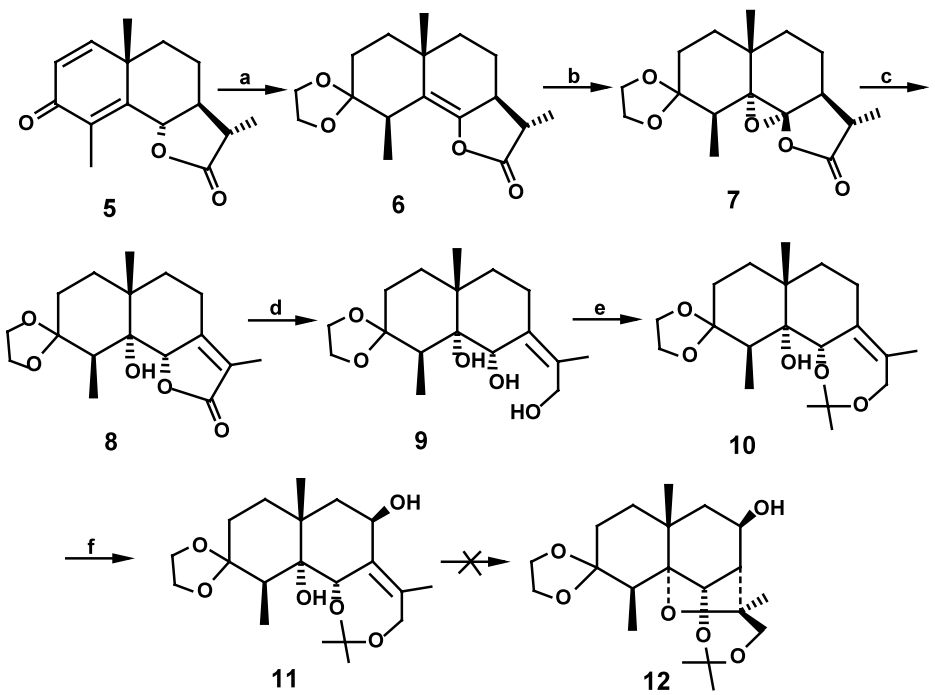
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02203-1

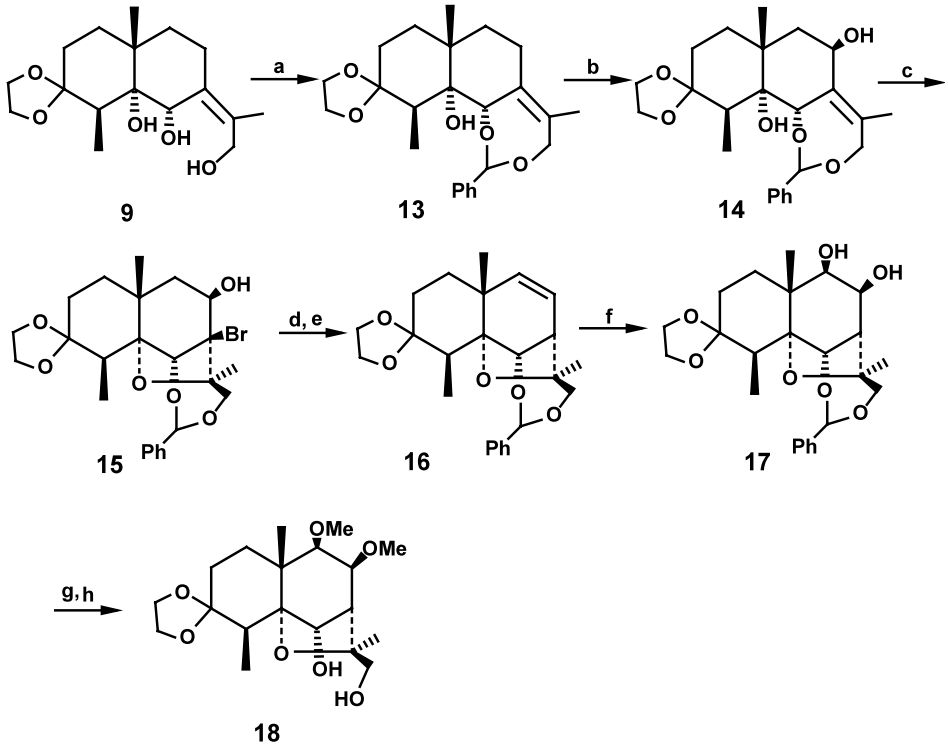
substituents. For this purpose, we chose the rich and synthetically versatile natural source α-santonin[7] as the starting material because of the possible generation of multiple hydroxyls from its multi-functionality such as carbonyl, double bond and hydroxyl. Here, as an example of our synthetic program to illustrate the generality of this approach, we want to report the synthesis of a natural product skeleton, the 8,9-dimethyletherified-2,14-dideoxyalatol **2**, which was the nucleus of many natural dihydroagarofuran sesquiterpenes, such as angulatueoidand,[8] several congeners,[9] and so on.

From the retro-synthetic analysis (Scheme 1), it was found that the key problems to be solved were focused on the construction of the tetrahydrofuran moiety by the conversion of the configuration on C7 and the multi-hydroxylation on the dihydroagarofuran sesquiterpene skeleton. In our previous paper, we reported the synthesis of the basic dihydroagarofuran sesquiterpene skeleton from α-santonin.[10] However, the reported ring-closure method with a $Hg(OAc)_2/NaBH_4$ system failed to synthesize the polyhydroxylated agarofuran sesquiterpene after many experiments. Thus, we need to develop a new method for the construction of the tetrahydrofuran moiety. As shown in Scheme 2, the triol **9** was first synthesized from α-santonin in a previous procedure.[10] However, direct oxidation of compound **9** with $SeO_2/^tBuO_2H$ only gave the complicated product possibly due to the existence of two allylic hydroxyls. Thus, we thought C6–OH and C12–OH of **9** should be protected before oxidation. From the molecular model inspection, it was found that the C12–OH was very adjacent to the C6–OH in comparison to the C5–OH and C5–OH was a tertiary alcohol. Protection of **9** with acetone successfully led to the single product **10** with C6–OH and C12–OH protected in 90% yield. The successive oxidation of **10** with $SeO_2/^tBuO_2H$ gave the exclusive product **11** in 95% yield.

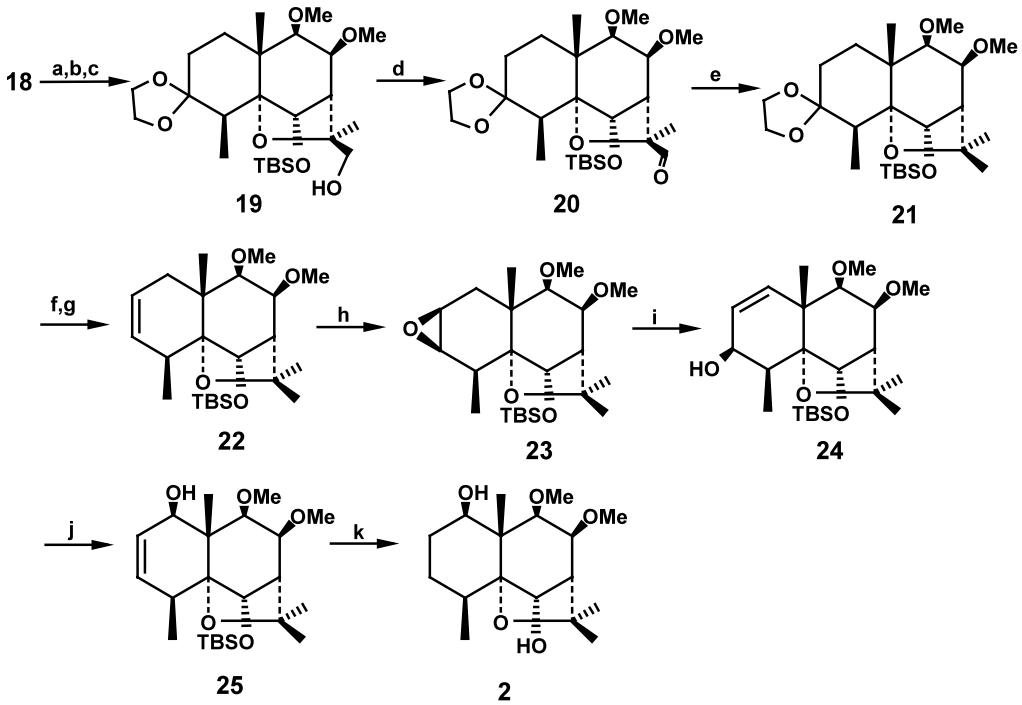
All attempts to cyclize **11** to the tetrahydrofuran derivative **12** with many reagents, such as NBS,[11] $Hg(OAc)_2/NaBH_4$,[12] *m*-CPBA/NaBr,[13] and so on, unfortunately, were not successful. The possible reason was steric hindrance of the quaternary acetonide. Subsequently, we had to change the protective group by protection of triol **9** with $PhCHO/ZnCl_2$ followed by oxidation to obtain the β-alcohol **14** in 75% yield (Scheme 3), and the other 8α-isomer was not detected. The stereoselective tetrahydrofuran ring closure of compound **14** with $NBS/CaCO_3$ readily afforded the product **15** in 95% yield. The two characteristic downfield ^{13}C NMR signals of **15** as δ 92.8(C5) and 84.7(C11) indicated the successful cyclization of the tetrahydrofuran ring as nearly all compounds of this kind have the similar shifting values.[14] Debromination of compound **15** by a radical reaction with tri-*n*-butyltin hydride followed by dehydration gave the product **16**, which was then converted to the 8β,9β-diol **17** by oxidation with OsO_4/NMO in acetone.[15] Furthermore, the proton coupling constants, $J=4.0$ Hz (H_7–H_8) and $J=4.8$ Hz (H_8–H_9), suggested the dihydroxylation was performed from the β-face. Several reagents, such as acetone and *tert*-butyldimethylsilyl chloride, were used for protection of 8,9-diol, but the protective groups at C8, C9 and C3 of these obtained compounds were easily removed in the next steps. Thus, we protected 8β,9β-diol of **17** as methyl ethers with sodium hydride and methyl iodide in



Scheme 2. *Reaction conditions*: (a) H_2, Raney Ni, PhH; Glycol (5 equiv.), PTS, toluene, 53%; (b) *m*-CPBA, CH_2Cl_2, 68%; (c) NaOMe (50 equiv.), MeOH, 83%; (d) $LiAlH_4$, THF, −78°C to rt, 95%; (e) acetone, PTS, rt, 90%; (f) SeO_2, $^tBuO_2H$, dioxane, rt, 95%.



Scheme 3. *Reaction conditions*: (a) PhCHO, $ZnCl_2$, rt, 70%; (b) SeO_2, $^tBuO_2H$, 75%; (c) NBS, $CaCO_3$, THF, 0°C, 95%; (d) $^nBu_3SnH$, PhH; (e) $SOCl_2$, Py, 60% (two steps); (f) OsO_4, NMO, acetone, rt, 84%; (g) NaH, MeI, rt; (h) K, $^tBuNH_2$, THF, rt, 68% (two steps).



Scheme 4. *Reaction conditions*: (a) benzoyl chloride, Py, 0°C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (c) NaOMe (2 equiv.), MeOH, rt, 81% (three steps); (d) PDC, CH_2Cl_2; (e) $NH_2NH_2{\cdot}H_2O$, K_2CO_3, diethylene glycol, 150–220°C, 72% (two steps); (f) PTS, acetone, rt; (g) *p*-$MeC_6H_4SO_2NHNH_2$, MeOH; CH_3Li (3 equiv.), rt, 50% (two steps); (h) *m*-CPBA, CH_2Cl_2, rt, 88%; (i) *i*-Pr_2NLi (5 equiv.), THF, −78°C to rt, 72%; (j) HCl, THF, rt; (k) 10% Pd/C, H_2; $^nBu_4N^+F^-$, THF, rt, 47% (three steps).

THF followed by hydrogenation with $K/^tBuNH_2$/THF smoothly afforded the diol **18** in 68% yield. Having the diol in hand, we tried to remove C12–OH. Nevertheless, some attempts to dehydroxylate using many reagents, such as Ph_3P/NBS/$^nBu_3SnH$, MsCl/Py/$LiBHEt_3$ and so on, failed. Therefore, the C12–OH of **18** was first selectively protected with benzoyl chloride (Scheme 4), then we protected the hindered secondary alcohol at C6 with *tert*-butyldimethylsilyl trifluoro-methanesulfonate and finally removed the benzoyl group with NaOMe in MeOH to obtain compound **19** in 81% yield. Oxidation of **19** with PDC afforded the product **20** in quantitative yield, and the decarbonylation of compound **20** using a Huang-Minlon reduction was very effective to give **21** in 72% yield.[16] Thereafter, treatment of **21** with *p*-toluene sulphonic acid in acetone gave a carbonyl compound, hydrozonization of which with $TsNHNH_2$ followed by CH_3Li led to compound **22** in 43% yield (total yield from **21**).[17] To hydroxylate on C1, compound **22** was subjected to oxidation with SeO_2, but this did not lead to the desired product even when the reaction conditions were varied. Thus, compound **22** was epoxidized with *m*-CPBA to give **23** in 88% yield. We rearranged the epoxide **23** with a strong base to obtain the allylic alcohol **24** in 72% yield, which was further rearranged to another allylic alcohol **25** in the presence of acid.[18] Reduction of the $\Delta^{2,3}$ double bond by catalytic hydrogenation with 10% Pd/C and deprotection of the silyl group yielded the final product **2** in 47% yield. The structure of **2** was confirmed by 1D and 2D NMR technique and mass spectroscopy.[19]

In conclusion, the approach reported here is indeed a new route for the synthesis of the polyhydroxylated dihydroagarofuran sesquiterpenenes, which can be used for the synthesis of other agarofuran sesquiterpene derivatives. The application of this approach to the synthesis of other hydroxylated agarofurans for the biological activities test is ongoing and will be reported in due course.

Acknowledgements

We are grateful for financial support from NSFC (No. 29972019, 29925205 and QT program), FUKTME of China, the Young Teachers' Fund of the Ministry of Education and the Fund of the Ministry of Education (No. 99209).

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19. The spectral data of **2**: ^1H NMR: 4.75 (brs, 1H), 4.14 (m, 1H), 3.82 (dd, *J* 4.4, 4.8 Hz, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 3.27 (d, *J* 4.8 Hz, 1H), 2.41 (m, 2H), 1.60 (m, 4H), 1.53 (s, 3H), 1.32 (s, 3H), 1.12 (s, 3H), 1.11 (d, *J* 7.2 Hz, 3H); ^{13}C NMR: 92.5, 85.1, 81.0, 77.6, 73.4, 70.5, 58.1, 52.0, 44.2, 40.3, 34.3, 31.6, 31.6, 25.1, 24.0, 16.9, 10.9; HRMS for $C_{17}H_{30}O_5$: calcd 337.1986 $[M+Na]^+$, found 337.1985.