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An enantioselective synthetic strategy toward the polyhydroxylated agarofuran

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Abstract—This paper describes a new approach for the enantioselective syntheses of naturally occurring polyhydroxylated dihydroagarofuran sesquiterpenoids starting from (–)-carvone. Through utilizing asymmetric Robinson annulation and acetoxylation as key steps, the agarofuran skeleton was enantioselectively constructed and an oxyfunctionalized group was introduced into the C-1 position. The important intermediate **23** to dihydroagarofuran was obtained in eleven steps.

In the sesquiterpenic family, a large number of β-dihydroagarofuran polyol esters based on dihydroagarofuran skeleton **1** have been isolated[1,2] from the species *Celastraceae*. These kind of compounds have been demonstrated to exhibit a wide spectrum of biological properties, including significant cytotoxic,[3] immunosuppressive,[4] anticancer,[5] insect antifeedant[6] and potent anti-HIV activity.[7] Their classic derivatives range from the least structurally complex diol **2**,[8] and the triol isocelorbicol **3**,[9] to complex polyols such as **4** (Fig. 1).[10]

Their highly oxygenated tricyclic frameworks, comprising a number of contiguous stereocenters, pose a formidable synthetic challenge and have attracted immense interest from synthetic chemists. Several racemic total syntheses of polyhydroxylated agarofurans have been reported since 1984.[11,12] However, there is no report on the total synthesis of optically active polyhydroxylated agarofuran to our knowledge. In our own quest for an enantioselective avenue toward a bioactive polyhydroxylated agarofuran, we are interested in developing a facile and general approach for the total synthesis of a polyhydroxylated agarofuran. Reported herein is an efficient approach for the enantioselective construction of a carbon skeleton and the introduction of an oxyfunctionalized group at the C-1 position.

In our earlier efforts, research interest was mainly focused on the introduction of an oxygenated group at the C-1 position. Our initial synthetic strategy was to employ (±)-9-keto-α-agarofuran **5** as a key intermediate, which was readily prepared from carvone in seven steps.[13] After considerable endeavor, several intermediates **6**–**12** have been obtained in several steps (Fig. 2). Unfortunately, attempted allylic oxidation or enone's α′-position oxidation of these compounds failed under various conditions, including PCC, SeO_2, CrO_3–SiO_2, PDC, CrO_3–*t*BuOOH, $Pb(OAc)_4$ and $Mn(OAc)_3$. Employing oxidative agents mentioned above only resulted in undesired products, complex mixtures or recovered substrates.

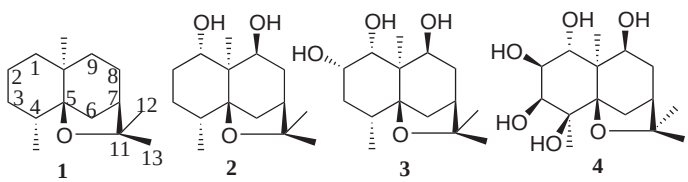

Figure 1.

Keywords: dihydroagarofuran; sesquiterpenoid; enantioselective synthesis.

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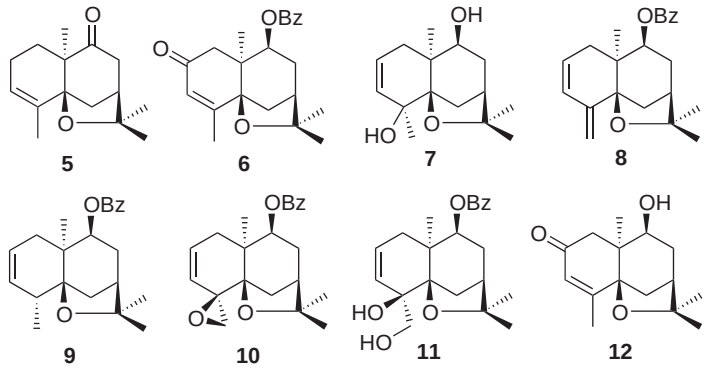
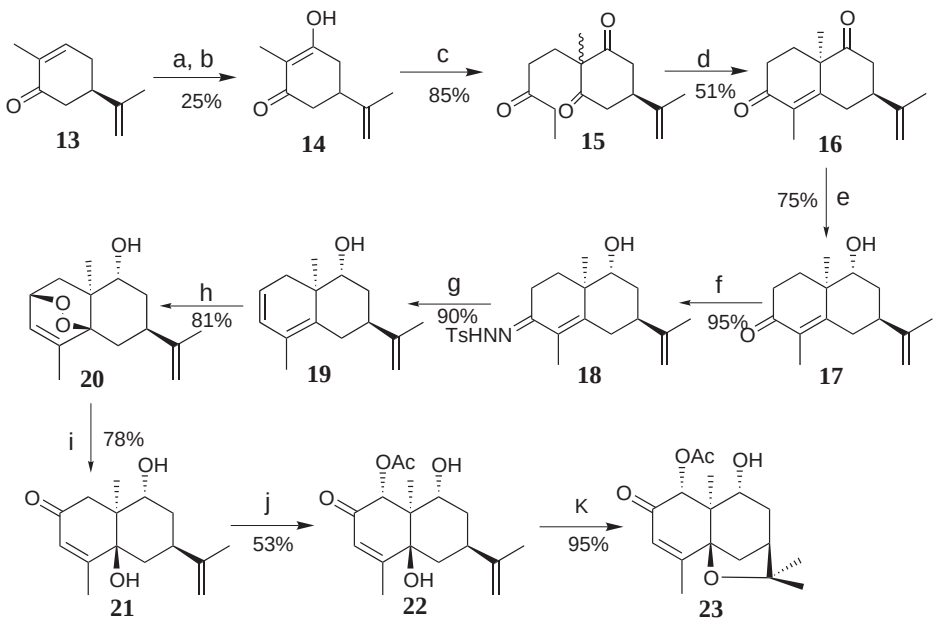


Figure 2.

On the assumption that failure to introduce an oxy-functionalized group at the C-1 position was due to the steric hindrance of a rigid tetrahydrofuran ring, combined with a consideration of the enantioselective synthesis at the same time, we then turned our attention to an alternative synthetic approach. The detailed pathway of synthesis is summarized in Scheme 1.

By the published method,[14] an inseparable trione mixture **15** could be readily prepared from commercially available (−)-carvone **13** by epoxidation, cleavage of epoxide and condensation with ethyl vinyl ketone. D-(+)-Phenylalanine-catalyzed asymmetric Robinson annulation[15] of trione **15** afforded the (−)-9-oxo-10-*epi*-α-cyperone **16** (54% e.e.; $[\alpha]_D^{10}$ −25.5, *c* 2.54, $CHCl_3$) in 51% yield by Hagiwara's method. Selective reduction of the keto group of **16** by sodium borohydride in MeOH provided the hydroxyl enone **17**. The enantiomeric excess of **16** was determined by esterification of **17** with (*R*)-*O*-acetylmandelic acid.[16] Tosyl hydrazone formation followed by treatment with excess *n*-BuLi (6 equiv.) in anhydrous THF gave the conjugated diene **19** in 86% total yield.[17] Diels–Alder cycloaddition of diene[18] **19** to singlet oxygen generated from the adducts between triphenylphosphite and ozone[19] afforded the desired *endo*-peroxide **20** as a single product in 81% yield, in which the peroxide bridge was assigned as the β-configuration based on the consideration that the steric hindrance of the angular methyl group restricts the approach of oxygen from the site undergoing reaction. Rearrangement of peroxide **20** on K_2CO_3 in THF gave the hydroxyl ketone **21** in 78% yield. The β-configuration of the C-5 hydroxyl group in **21** was further confirmed by the latter's easy cyclization. Regioselective acetoxylation with $Mn(OAc)_3$ at the C-1 of enone **21** ultimately furnished the less polar acetate **22** in 53% yield.[20] The stereochemistry of the acetate **22** was confirmed via an NOE experiment. According to



Scheme 1. (a) 30% H_2O_2, KOH, MeOH–H_2O, 0°C, 2.5 h; (b) 1N NaOH, H_2O, reflux, 1 h; (c) EVK, KOH, MeOH, reflux, 6 h; (d) D-(+)-phenylalanine, D-(+)-CSA, 30–70°C, 6 days; (e) $NaBH_4$, MeOH, 0°C, 3 h; (f) $TsNHNH_2$, $BF_3{\cdot}Et_2O$, rt, 2 h; (g) *n*-BuLi, THF, −78°C to 0°C, 10 h; (h) O_3, $P(OPh)_3$, CH_2Cl_2, −78°C to 0°C, 2.5 h; (i) K_2CO_3, THF, 40°C, 24 h; (j) $Mn(OAc)_3$, benzene, reflux, 10 h; (k) TfOH, THF, rt, 5 min.

the literature method,[11a] treatment of **22** with trifluoromethanesulfonic acid smoothly afforded pure agarofuran **23** (60% e.e.;[16] $[\alpha]_D^{21}$ −12.9, *c* 0.78, $CHCl_3$) after chromatographic purification of the crude product on silica gel, which has shown identical spectral data with its structure.[21] The downfield ^{13}C NMR signals at δ 83.62 and 83.43 for two oxygen-linked quaternary carbons indicated the successful cyclization of the tetrahydrofuran ring.

In summary, we have presented a new enantioselective synthetic strategy to construct the skeleton and introduce an oxyfunctionalized group into the C-1 position as anticipated, which allows us to obtain the optically active important intermediate **23** to polyhydroxylated agarofuran starting from (−)-carvone in eleven steps. Application of the established method to the further syntheses of a number of naturally occurring polyhydroxylated agarofurans is under active investigation.

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21. Spectral data for **23**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.23 (s, 3H), 1.33 (s, 3H), 2.00 (s, 3H), 2.10 (s, 3H), 2.77 (d, $J=4.4$ Hz, 1H), 3.98 (m, 1H), 4.88 (s, 1H), 6.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 172.3, 158.5, 127.7, 83.6, 83.4, 75.5, 65.2, 46.3, 42.7, 34.2, 30.7, 29.9, 22.5, 21.0, 20.2, 17.5. EIMS (70 eV) *m*/*z* 308 (M^+, 3%), 293 (15%), 291 (50%), 290 (5%), 240 (13%), 149, 75 (100); IR (film): 3486, 2976, 2934, 1729, 1680 cm^{-1}; FAB-HRMS: found 331.1510, $C_{17}H_{22}O_5+Na^+$ requires: 331.1521.