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Asymmetric total synthesis of (−)-isocelorbicol, a natural dihydroagarofuran sesquiterpenoid

Wei-Dong Z. Li,* Gang Zhou, Xiaolei Gao and Yulin Li*

National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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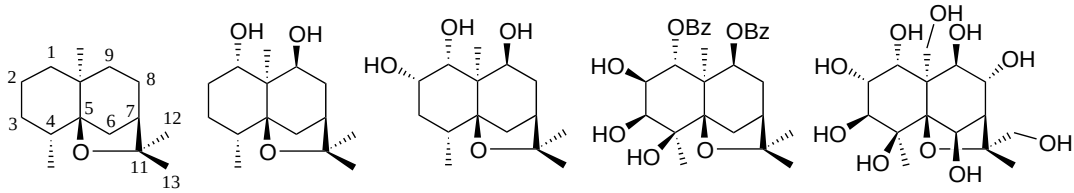
Abstract—The first enantioselective total synthesis of (−)-isocelorbicol, a naturally occurring sesquiterpene polyol of the agarofuran group, starting from optically active 9-oxo-10-*epi*-α-cyperone (**8**) is described.

In the past two decades, the plants of the *Celastraceae* family have attracted considerable attention and proven to be a rich source of characteristic hydroxylated sesquiterpene esters[1–5] bearing a tricyclic dihydroagarofuran skeleton **1**, which have been shown to exhibit significant cytotoxic,[6] immunosuppressive,[7] anticancer,[8] insect antifeedant[9] and potent anti-HIV[10] activities. The dense array of hydroxyl substitution on the decalin skeleton leads to the increasingly complex structures of this type of sesquiterpene natural products as illustrated for diol **2**,[11] triol **3** (isocelorbicol),[12] benzoate **4**[13] and euonyminol **5**.[14]



1 **2** **3** **4** **5**

Intrigued by their unique structure and remarkably wide range of biological activities, pioneering studies on the synthesis of agarofuran sesquiterpenoids have been reported by Büchi,[15] Marshall,[16] Deslongchamps,[17] Heathcock,[18] Huffman,[19] and more recently White,[20] which have stimulated a great deal of interests in this area.[21] The asymmetric synthesis of polyhydroxylated dihydroagarofuran represents a significant challenge for synthetic organic chemists. In connection with our interests in this subject and the ongoing project on the asymmetric synthesis of bioactive sesquiterpenoids, we have reported[22] in a previous Letter a stereocontrolled oxidative acetoxylation at sterically congested C-1 position of the decalin skeleton leading to a general approach for the construction of the tricyclic dihydroagarofuran skeleton **1**. Herein we describe the application of this method for the first enantioselective synthesis of isocelorbicol (**3**), a dihydroagarofuran triol isolated from the seeds of *Celastrus orbiculatus* by Smith and coworkers in 1976 with its structure elucidated[12] on the basis of spectral and chemical evidence. The racemic syntheses of **3** have been reported by Huffman and co-workers.[19d–f]

The retrosynthetic plan is outlined in Scheme 1, which involves (1) conversion of optically active 9-oxo-10-*epi*-α-cyperone (**8**)[22] to key intermediate enone **7**, (2) hydroxylation of **7** at C-1 and cyclization to form β-dihydroagarofuran **6**, and (3) stereocontrolled reduction of keto groups and hydrogenation of $\Delta^{3,4}$ olefin of **6**.

As reported[22] previously, 9-oxo-10-*epi*-α-cyperone (**8**) (54% ee), was transformed into enone **7** in four steps in good chemical yield, which was subjected to recrystal-

Keywords: isocelorbicol; dihydroagarofuran; sesquiterpenoid; asymmetric synthesis.

* Corresponding authors. E-mail: liwd@lzu.edu.cn

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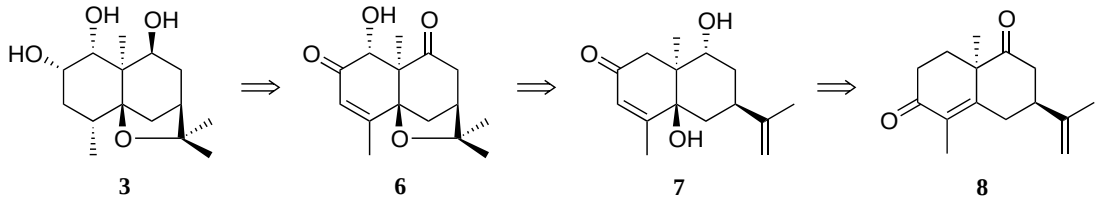


Scheme 1.

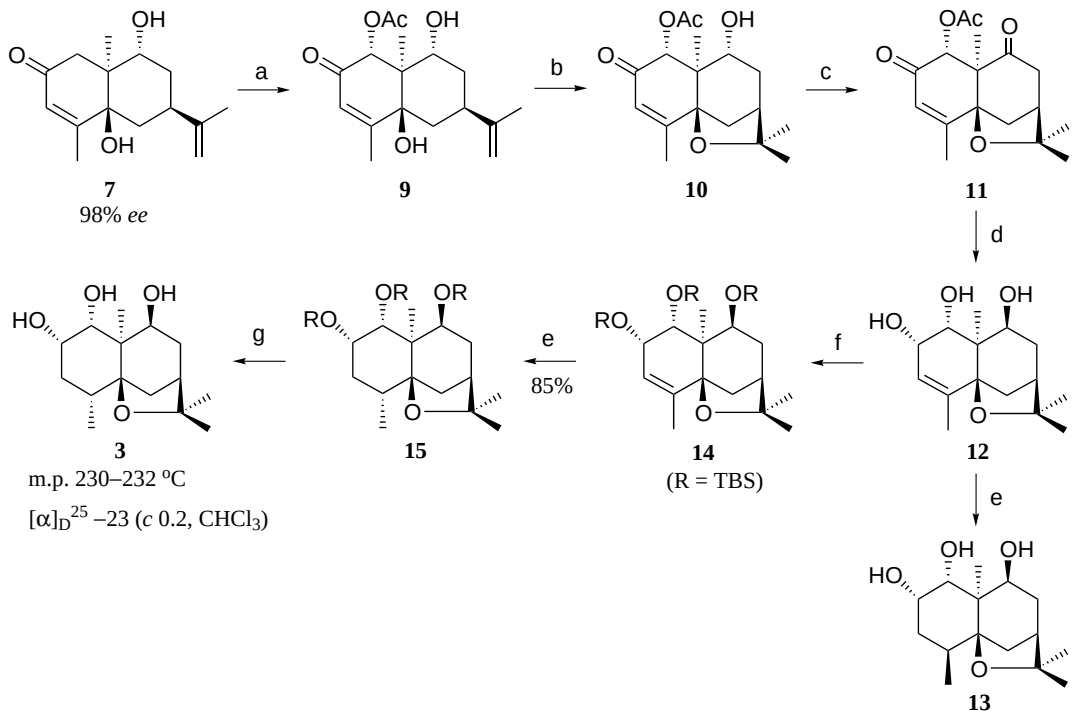
lization twice from a solvent mixture of ether and hexane (v/v 3:1) to afford practically optically pure **7** {mp 119–121°C, $[\alpha]_D^{14}$ –97.0 (*c* 0.25, $CHCl_3$), >98% ee[23]} in 67% yield. This crucial optical enrichment of **7** allows the synthesis of the natural **3** in a highly enantioselective fashion for the first time.

Detailed synthesis of **3** was outlined in Scheme 2. Acetoxylation [$Mn(OAc)_3$, C_6H_6, reflux][22] of optically pure enone **7** at C-1 followed by acid-catalyzed formation of dihydroagarofuran ring furnished the enone acetate **10**, which bears the tricyclic skeleton with desired β-configurated dihydroagarofuran ring of **3**.

The next stage of the synthesis requires the inversion of the hydroxyl configuration of **10** at C-9. Attempts for this purpose under Mitsunobu condition[24] met with failure presumably due to severe steric hindrance at C-9. An alternative way turned out to be ideal through the following two-step sequence: (1) Dess–Martin periodinane oxidation[25] to **11** (90%), (2) subsequent reduction with LAH in ether to give triol **12** and its C-2 epimer in a ratio of 3:1. To our disappointment, the catalytic hydrogenation (10% Pd-C, EtOH) of **12** afforded predominately 4-*epi*-isocelorbicol (**13**)[19d] in 95% yield.

Alternatively, hydrogenation of tris-TBS silyl ether **14** (68% from triol **12** by standard silylation) and subsequent desilylation gave the desired title compound **3** (27% yield from triol **12**) along with its 4β-epimer **13** in a ratio of ca. 10:1.[26] The spectral data and optical property of the synthetic **3** were consistent with those of reported for natural product.[27]

In summary, the synthesis of natural (–)-isocelorbicol (**3**) has been achieved enantioselectively from optically active 9-oxo-10-*epi*-α-cyperone (**8**) in 12 steps as well as its 4-epimeric isomer **13** by employing a general and efficient strategy based on the oxidative introduction of acetoxy function at C-1. The strategy demonstrated here is potentially applicable for the asymmetric synthesis of other polyhydroxylated dihydroagarofurans that is underway in our Laboratory.



Scheme 2. *Reagents and conditions*: (a) $Mn(OAc)_3$, C_6H_6, reflux, 53%; (b) TfOH, THF, rt, 5 min, 95%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 90%; (d) LAH, ether, 0°C, 62%; (e) H_2, 10% Pd-C, EtOH, rt, 24 h, 95%; (f) TBSOTf, Et_3N, CH_2Cl_2, rt, 2.5 h, 68%; (g) n-$Bu_4N^+F^-$, THF–H_2O, rt, 24 h, 47%. (rt = 20 ~ 25°C, TfOH = trifluoromethanesulfonic acid).

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27. An authentic sample is not available for direct comparison. Spectral data for **3**: IR (film) 3680, 3589, 3478, 2936, 2853, 1375, 1260, 1125, 1085,1045, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (6H, s, 10-CH_3, 11-CH_3), 1.25 (3H, d, J = 7.0 Hz, 4-CH_3), 1.47 (3H, s, 11-CH_3), 3.21 (1H, m, 9-H), 4.17 (1H, brs, 1-H), 4.21 (1H, m, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 90.5, 83.2, 79.3, 75.8, 66.7, 43.8, 35.5, 35.3, 34.1, 31.4, 30.1, 29.7, 24.8, 24.2, 15.5; MS (EI) m/z 270 (18%, M^+), 255(9), 252(10), 208(20), 179(12), 149(70), 125(55), 109(75), 69(100), 43(98); HRMS (EI): calcd for $C_{15}H_{26}O_4$: 270.1831, found 270.1825.