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Total Synthesis of (±)-Celaphanol A

Ping Yan BIE, Cheng Lu ZHANG, Xuan Jia PENG, Xin Fu PAN*

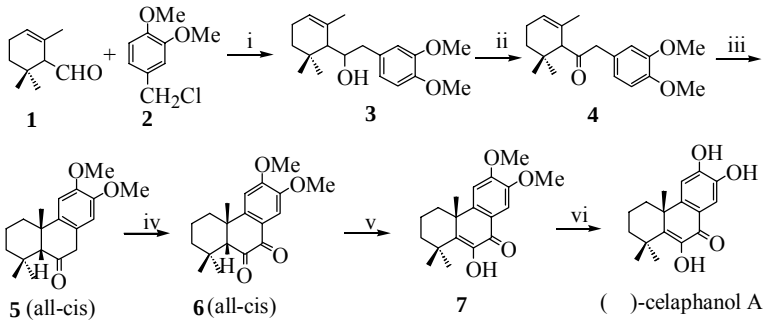
Department of Chemistry, National Laboratory of Applied Organic Chemistry,
Lanzhou University, Lanzhou 730000

Abstract: The first total synthesis of (±)-Celaphanol A was accomplished starting from α–cyclocitral and 3,4-dimethoxy benzyl chloride *via* a six-step process, in which the intramolecular cyclization of ketone 4 with $BF_3{\cdot}Et_2O$ afforded an all-*cis* isomer intermediate for synthesis of aromatic tricyclic diterpenes.

Keywords: Total synthesis, (±)-celaphanol A, diterpene.

Celaphanol A was a diterpene isolated from the stems of *Celastrus stephanotifolius*[1], which have been the subject of continued and growing interest, due to the range of biological activities shown by many members of this family[2]. Some have been used in traditional medicine[3] or as a stimulant[4] from ancient times. In order to further study the relationship between the structure and biological activity of the diterpene compound and as an extension of diterpenoid synthesis in our laboratory[5, 6], the first synthesis of the title compound was achieved through the AC-ABC ring construction synthetic strategy.

Scheme 1



Reagents and Conditions: (i) Mg, Et_2O, reflux, 2 h, 79%; (ii) PCC, CH_2Cl_2, r.t., 2.5 h, 85%; (iii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t., 93%; (iv) CrO_3/HOAc, r.t., 0.5 h, 90%; (v) t-BuOK/t-BuOH, r.t., 2 h, 80%; (vi) BBr_3, CH_2Cl_2, 0ºC, 0.5 h, 85%.

*E-mail: panxf@lzu.edu.cn

As shown in **Scheme 1**, α-cyclocitral **1** and 3,4-dimethoxy benzyl chloride **2** were used as the starting materials. The latter was prepared from readily available vanillin in three steps. The condensation of **1** and the Grignard reagent of **2** in dry diethyl ether under argon afforded the desired alcohol **3**, which was then oxidized with pyridinium chlorochromate in CH_2Cl_2 to yield ketone **4** in excellent yield. The intramolecular cyclization of **4** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature afforded all-*cis* isomer **5** in 93% yield and no *trans*-isomer was detected from its ^{1}H NMR spectrum.

The *cis*-configuration of A/B ring junction in **5** was characterized specifically by the upfield signal of the $C_{4\alpha}$ methyl group at 0.37ppm. According to the literature[7], when A/B ring is in *cis* junction, the $C_{4\alpha}$ methyl group remains within the sphere of magnetic influence of aromatic ring C, the chemical shift of $C_{4\alpha}$ methyl group appears at about 0.40 ppm. When A/B ring is in *trans* junction, the $C_{4\alpha}$ methyl group is deshielded by aromatic ring C, the chemical shift of $C_{4\alpha}$ methyl group will appear at about 1.00 ppm.

Oxidation of compound **5** with CrO_3/HOAc afforded diketone **6** in good yield. Treatment of **6** with *t*-BuOK/*t*-BuOH afforded the compound **7**[8] in 80% yield. Finally, demethylation of **7** with BBr_3 in CH_2Cl_2 furnished the target molecule (±)-Celaphanol A[9].

In conclusion, in the present work, a simple convergent synthetic route has been developed for the newly discovered diterpenoid.

Acknowledgments

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References and Notes

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8. **Compound 7:** white needles, mp: 119-121ºC. IR: ν (KBr) 1596, 1622, 3339cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$): δ ppm 1.43 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 1.75~2.35 (m, 6H), 3.94 (s, 3H), 3.96 (s, 3H), 6.90 (s, 1H), 7.12 (s, 1H), 7.56 (s, 1H). ^{13}C NMR (100MHz, $CDCl_3$): 17.5, 27.6, 28.0, 33.6, 34.7, 35.9, 37.6, 40.5, 56.1, 107.2, 107.3, 120.7, 141.3, 143.7, 148.0, 149.8, 153.6, 179.4. MS-EI (*m/z*): 316, 273, 247, 43. (Found: C, 72.21; H, 7.59. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.65%)
9. **(±)-Celaphanol A:** red solid, mp: 186-188ºC. IR: ν (KBr) 1650, 1700, 3413cm^{-1}. ^{1}H NMR (200MHz, CD_3COCD_3): δ ppm 1.36 (m, 1H), 1.50 (s, 3H), 1.54 (s, 3H), 1.60 (s, 3H), 1.59 (m, 1H), 1.75 (m, 2H), 1.89 (m, 1H), 2.39 (m, 1H), 7.05 (s, 1H), 8.24 (s, 1H). ^{13}C NMR (100MHz, CD_3COCD_3): 18.0, 27.9, 28.3, 33.9, 35.1, 36.3, 38.3, 40.8, 111.8, 112.4, 120.8, 140.6, 143.4, 144.9, 149.8, 151.8, 179.9. MS-EI (*m/z*): 288, 273, 245, 232, 218, 190. (Found: C, 70.92, H, 6.93. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%). The above data were consistent with the literature[1].

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