

A SYNTHESIS OF OPTICALLY ACTIVE PLATYPHYLLIDE DETERMINATION OF ITS ABSOLUTE CONFIGURATION

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Abstract - The first enantioselective total synthesis of platyphyllide (**1**), based on the allenyl ether intramolecular cycloaddition strategy, is described, revealing the absolute configuration of this compound.

Platyphyllide (**1**) is the norsesquiterpene lactone, isolated from *Senecio platyphylloides*.¹ The spectral data and synthetic studies allowed the assignment of structure (**1**) (or enantiomer) to platyphyllide,^{2,3} but its absolute configuration could not be determined. As part of our research program on the allene intramolecular cycloaddition reaction,⁴ we have developed the synthetic route of (\pm)-**1**.³ Herein we described the first enantioselective route to (-)-platyphyllide (**1**). The results of this work may provide important information about the absolute configuration of natural platyphyllide (**1**).

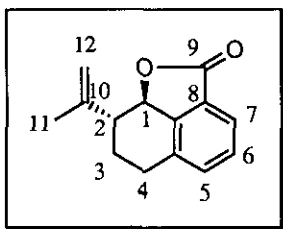
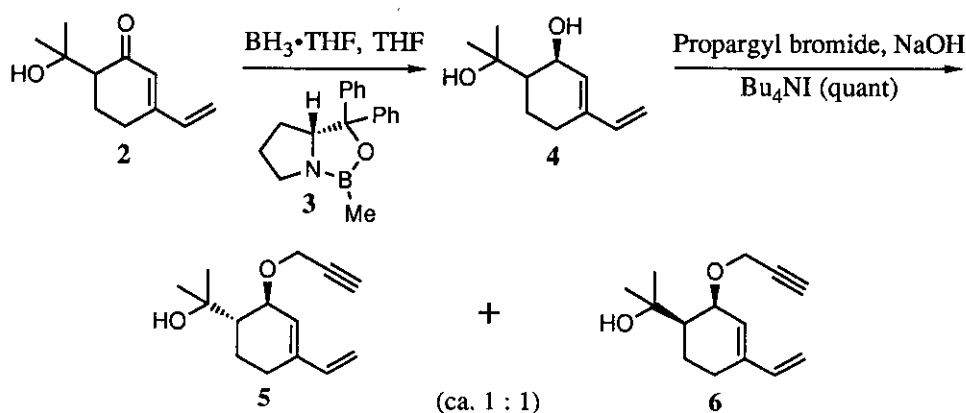


Figure 1. Structure of platyphyllide (**1**)

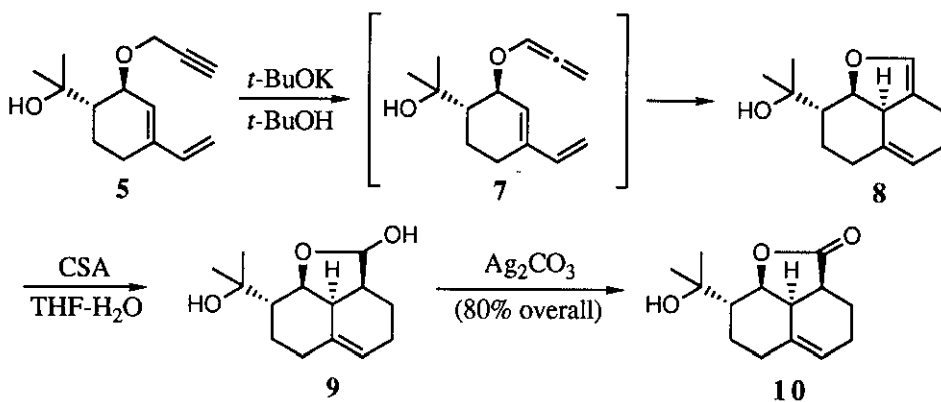
The synthetic sequence of the optically active starting material (**5**) is detailed in Scheme I.⁵ Enantioselective reduction of the aldol (**2**)³ using borane-tetrahydrofuran complex ($\text{BH}_3 \cdot \text{THF}$) with CBS catalyst [(*R*)-*B*-methylated oxazaborolidine (**3**)]⁶ gave a diastereomeric mixture of diols (**4**) which was directly propargylated

without separation, since the chromatographic separation could be much more easily achieved in **5**, $[\alpha]_D^{26} -24.3^\circ$ ($c = 0.7$, CHCl_3), and **(6)**, $[\alpha]_D^{24} -77.5^\circ$ ($c = 0.8$, CHCl_3).



Scheme I

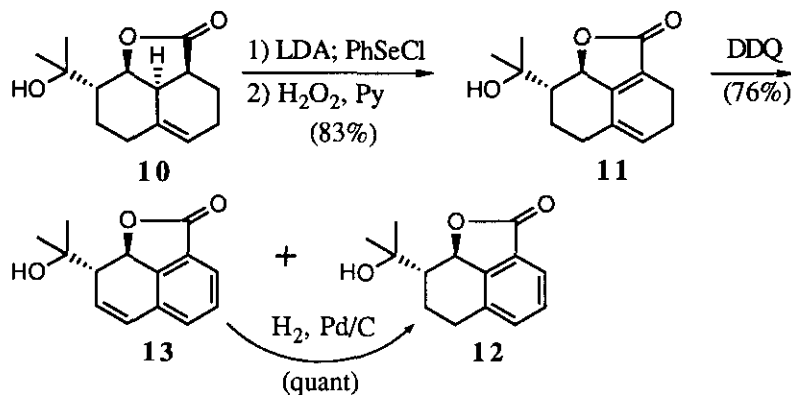
The *trans*-propargyl ether (**5**) was heated in *t*-BuOH in the presence of *t*-BuOK (excess) for 2 h; adduct (**8**) was obtained as the sole product, *via* the allenyl ether intermediate (**7**) (Scheme II). Treatment of **8** with 5% solution of 10-camphorsulfonic acid (CSA) in THF- H_2O (1:1) at room temperature for 1 h gave the lactol (**9**) which was readily oxidized by Fetizon's reagent (Ag_2CO_3 on Celite) to give the lactone (**10**), $[\alpha]_D^{25} -13.9^\circ$ ($c = 0.4$, CHCl_3), in 80% overall yield from the propargyl ether (**5**).



Scheme II

Phenylselenenylation of **10** followed by oxidative elimination gave **11**, $[\alpha]_D^{24} +1.8^\circ$ ($c = 0.5$, CHCl_3), in 83% overall yield (Scheme III). Treatment of the diene (**11**) with DDQ in benzene afforded compound (**12**), $[\alpha]_D^{25}$

+0.8° ($c = 0.6$, CHCl_3) accompanied with over-dehydrogenated product (**13**), $[\alpha]_{\text{D}}^{25} +2.8^\circ$ ($c = 0.7$, CHCl_3), which was easily converted to **12** by catalytic hydrogenation over Pd-C in quantitative yield.



In order to ascertain the absolute configuration, **12** was converted to its *p*-bromobenzoyl derivative (**14**) using standard method [*p*- $\text{BrC}_6\text{H}_4\text{COBr}$, 4-dimethylaminopyridine (DMAP), pyridine] (Scheme IV). By the single crystal X-ray analysis, the absolute configuration of **14** assigned as *1R, 2S* (Figure 2).⁷

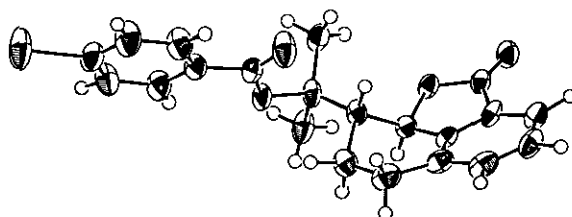
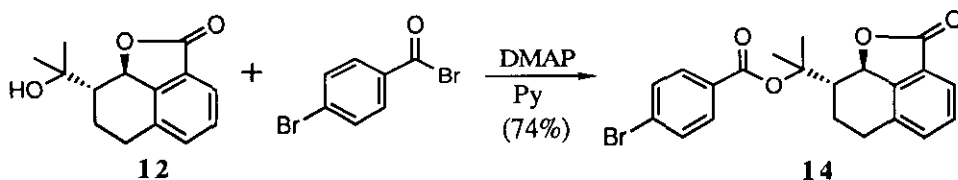
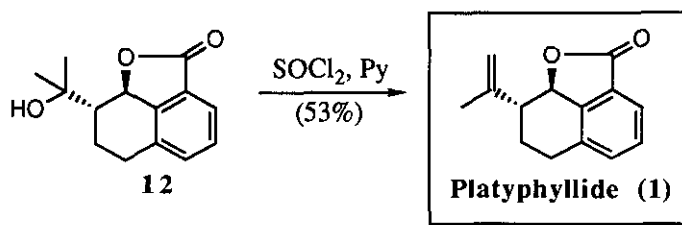


Figure 2. ORTEP diagram of **14**

Dehydration of **12** with thionyl chloride in pyridine gave (-)-platyphyllide (**1**), $[\alpha]_D^{24} -8.4^\circ$ ($c = 0.4$, CHCl_3 , in 53% yield (Scheme V). Although it was impossible to make a direct comparison of synthetic **1** with natural platyphyllide due to the deficiency of the natural product, the ^1H nmr spectral data of synthetic **1** were fully identical with those of natural platyphyllide: the sign of optical rotations of synthetic compound was the same as that reported in the literature $\{[\alpha]_D^{24} -17.8^\circ$ ($c = 3.1$) $\}$.¹ From this synthesis, therefore, the absolute configuration of platyphyllide was determined to be *1R, 2R* as depicted in Scheme V.



Scheme V

REFERENCES AND NOTES

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2. F. Bahlmann and E. Eickeler, *Chem. Ber.*, 1979, **112**, 2811.
3. K. Hayakawa, S. Ohsuki, and K. Kanematsu, *Tetrahedron Lett.*, 1986, **27**, 947.
4. We have already described the new access to an optically pure key intermediate of dihydromevinolin by analogous strategy, see: S. Nagashima, T. Taishi, and K. Kanematsu, *Ibid.*, 1994, **35**, 3577.
5. All new compounds gave satisfactory analytical and/or spectral data.
6. E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.
7. Crystal data for **14**: ($\text{C}_{21}\text{H}_{19}\text{O}_4\text{Br}$): MW = 415.28; colorless, prismatic, dimensions 0.300 x 0.200 x 0.100 mm; orthorhombic, space group $\text{P}2_12_12_1$ (#19); $a = 8.198(2)$ Å, $b = 38.372(3)$ Å, $c = 5.812(2)$ Å, $V = 1828.2(9)$ Å³, $Z = 4$, $d_{\text{calc}} = 1.509$ g/cm³, $\mu(\text{CuK}\alpha) = 32.67$ cm⁻¹, $F(000) = 848$. A total of 3338 reflections ($2\theta_{\text{max}} = 120.0^\circ$, ω - 2θ scans) were recorded on a Rigaku AFC7R diffractometer at $T = 293$ K. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1316 observed reflections ($I > 3.00\sigma(I)$) and 236 variable parameters and converged (largest parameter shift was 0.02 times its esd) with unweighted and weighted agreement factors of: $R = 0.038$, $R_w = 0.065$. The absolute configuration was definitely determined by Bijvoet method [the anomalous dispersion of bromine atom by $\text{CuK}\alpha$ radiation ($f_{\text{Br}} = -0.767$, $f'_{\text{Br}} = 1.823$)].