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 (±)-**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**).

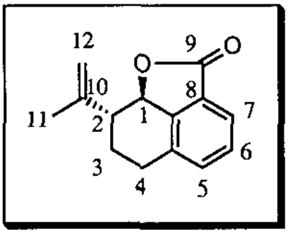
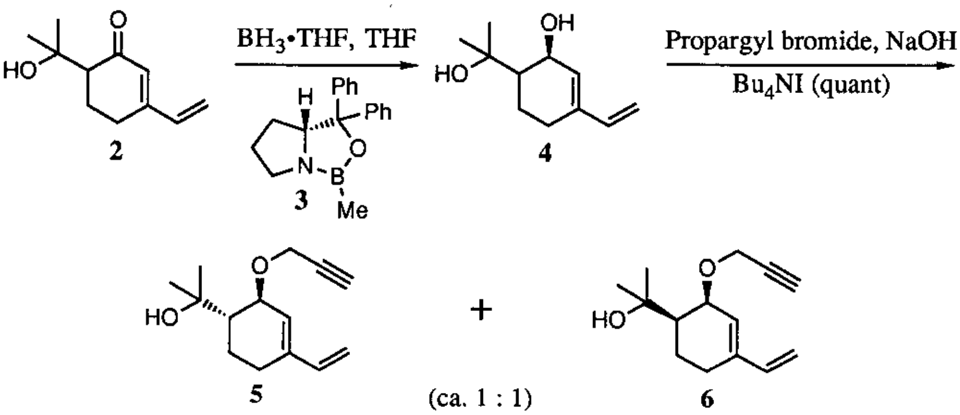


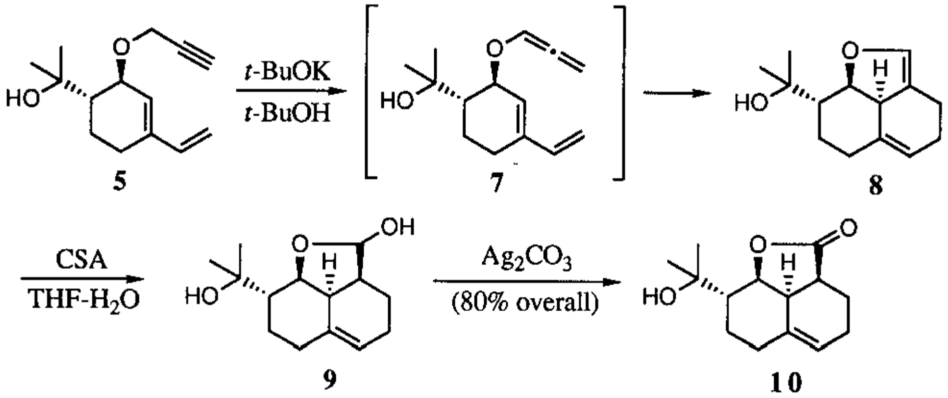
Figure 1. Structure of platyphyllide (**1**)

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 (BH_3•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° (c = 0.7, $CHCl_3$), and (**6**), $[\alpha]_D^{24}$ -77.5° (c = 0.8, $CHCl_3$).



Scheme I

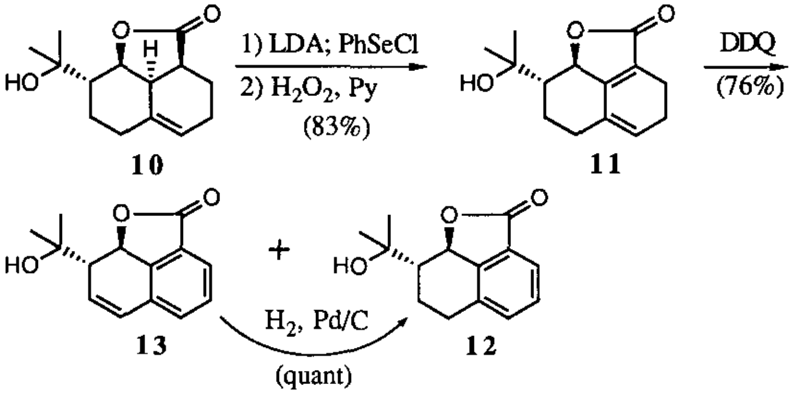
The *trans*-propargyl ether (**5**) was heated in *t*-BuOH in the presence of *t*-BuOK (excess) for 2 h; adduct (**8**) was obtained as the sole product, *via* the allenyl ether intermediate (**7**) (Scheme II). Treatment of **8** with 5% solution of 10-camphorsulfonic acid (CSA) in THF-H_2O (1:1) at 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° (c = 0.4, $CHCl_3$), in 80% overall yield from the propargyl ether (**5**).



Scheme II

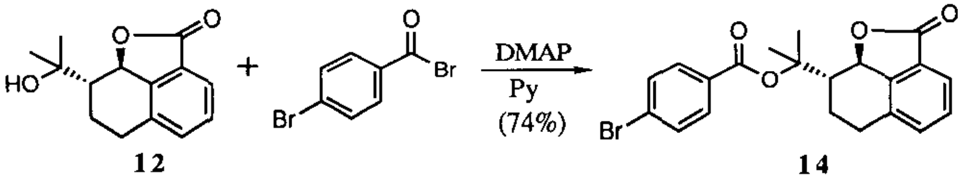
Phenylselenenylation of **10** followed by oxidative elimination gave **11**, $[\alpha]_D^{24}$ +1.8° (c = 0.5, $CHCl_3$), in 83% overall yield (Scheme III). Treatment of the diene (**11**) with DDQ in benzene afforded compound (**12**), $[\alpha]_D^{25}$

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



Scheme III

In order to ascertain the absolute configuration, **12** was converted to its p-bromobenzoyl derivative (**14**) using standard method [p-BrC_6H_4COBr, 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]



Scheme IV

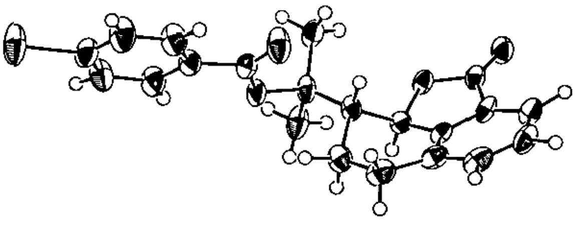
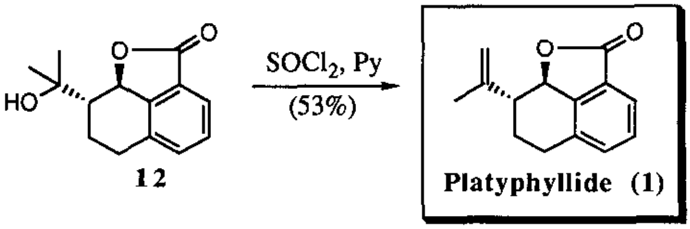


Figure 2. ORTEP diagram of **14**

Dehydration of **12** with thionyl chloride in pyridine gave (-)-platyphyllide (**1**), $[\alpha]_D^{24}$ -8.4° (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° (c = 3.1)}.[1] From this synthesis, therefore, the absolute configuration of platyphyllide was determined to be 1*R*, 2*R* as depicted in Scheme V.



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Platyphyllide (1)

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**: ($C_{21}H_{19}O_4Br$): MW = 415.28; colorless, prismatic, dimensions 0.300 x 0.200 x 0.100 mm; orthorhombic, space group $P2_12_12_1$ (#19); a = 8.198(2) Å, b = 38.372(3) Å, c = 5.812(2) Å, V = 1828.2(9) $Å^3$, Z = 4, d_{calc} = 1.509 g/cm^3, μ(CuKα) = 32.67 cm^{-1}, F(000) = 848. A total of 3338 reflections ($2\theta_{max}$ = 120.0°, 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 CuKα radiation (f_{Br} = -0.767, f'_{Br} = 1.823)].

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