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. The spectral data and synthetic studies allowed the assignment of structure (1) (or enantiomer) to platyphyllide, but its absolute configuration could not be determined. As part of our research program on the allene intramolecular cycloaddition reaction, we have developed the synthetic route of (±)-1. 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).

![Structure of platyphyllide (1)](image)

Figure 1. Structure of platyphyllide (1)

The synthetic sequence of the optically active starting material (5) is detailed in Scheme 1. Enantioselective reduction of the aldol (2) using borane-tetrahydrofuran complex (BH₃·THF) with CBS catalyst [(R)-B-methylated oxazaborolidine (3)] 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, \([\alpha]_D^{26} - 24.3^\circ (c = 0.7, \text{CHCl}_3)\), and (6), \([\alpha]_D^{24} - 77.5^\circ (c = 0.8, \text{CHCl}_3)\).

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), \([\alpha]_D^{25} + 13.9^\circ (c = 0.4, \text{CHCl}_3)\), in 80% overall yield from the propargyl ether (5).

Phenylselenenylation of 10 followed by oxidative elimination gave 11, \([\alpha]_D^{24} + 1.8^\circ (c = 0.5, \text{CHCl}_3)\), 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, CHCl₃) accompanied with over-dehydrogenated product (13), [α]Dₑ²⁵ +2.8° (c = 0.7, CHCl₃), 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-BrC₆H₄COBr, 4-dimethylaminopyridine (DMAP), pyridine] (Scheme IV). By the single crystal X-ray analysis, the absolute configuration of 14 assigned as 1R, 2S (Figure 2).
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 $^1$H 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 $[\alpha]_D^{24} -17.8^\circ$ ($c = 3.1$)). From this synthesis, therefore, the absolute configuration of platyphyllide was determined to be 1$R$, 2$R$ as depicted in Scheme V.

![Scheme V](image)

REFERENCES AND NOTES

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.
7. Crystal data for 14: (C$_{21}$H$_{19}$O$_4$Br): MW = 415.28; colorless, prismatic, dimensions 0.300 x 0.200 x 0.100 mm; orthorhombic, space group P2$_1$2$_1$2$_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$^3$, $\mu$(CuK$\alpha$) = 32.67 cm$^{-1}$, $F(000) = 848$. A total of 3338 reflections (2$\theta_{max} = 120.0^\circ$, $\omega$-2$\theta$ 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 CuK$\alpha$ radiation ($f_{Br} = -0.767$, $f_{Br} = 1.823$)].

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