THE FIRST TOTAL SYNTHESIS OF FLOERKEIN B AND BARBILYCOPODIN

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Abstract—From functionalized iridoid and geranyl synthons, natural floerkein B and barbilycopodin, bicyclic diterpenoids containing an eleven-membered ring, have been totally synthesized via stereocontrolled Cope rearrangement of a dioxasilepine derivative.

In the line of our synthetic studies on the medium-ring containing higher terpenoids,¹ we have now extended the investigation to the dolabellane family,² which is consisted of bicyclo[9.3.0]tetradecane system. According to a biogenetic speculation, dolabellanes are precursors of fusicoocanes and dolastanes.

And, our strategy employed in the syntheses of 5-8-5-membered tricyclic compounds can be adopted with a slight modification; by changing one of the synthon pairs from iridoid to geranyl derivative, an intermediate, functionalized cyclopentene derivative having a long-chain substituent, could be obtained and its intramolecular condensation could furnish the carbon framework that found in dolabellanes, and subsequent adjustment of oxidation state should yield the natural products. Our target selected was floerkein B (1: R=H) and its diacetate, barbilycopodin (1: R=Ac), isolated by S. Huneck from Barbilophasia floerkei.³ Herein, we describe the first total synthesis of 1.

Starting iridoid (2) was prepared by chlorohydrin formation followed by LAH-reduction of (3S)-irida-1,8-dien-7-ol (3), and the counterpart, (E,E)-8-(tert-butyldimethylsilyloxy)geranyl chloride (4) was obtained.

This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.
without difficulty from geranyl acetate (5).

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{Ca(OC1)}_2/H^+} \text{CHO} \\
\text{CHO} & \xrightarrow{1. \text{LAH/THF}(84\%)} \text{CHO} \\
\text{CHO} & \xrightarrow{2. \text{MnO}_2/\text{CH}_2\text{Cl}_2(74\%)} \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{1. \text{BuOOH, Py (95\%)} } \text{CHO} \\
\text{CHO} & \xrightarrow{3. \text{LAH/THF (82\%)} } \text{CHO} \\
\text{CHO} & \xrightarrow{4. \text{MsCl, LICl/DMF, Py (92\%)} } \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{2 \xrightarrow{\text{CrCl}_2, \text{LAH}} + \text{CHO}} \text{CHO} \\
\text{CHO} & \xrightarrow{4 \xrightarrow{\text{DMF - THF}} \text{CHO}} \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{7 \xrightarrow{\beta-\text{OH}, \alpha-\text{vinyl (9\%)} } \text{CHO}} \\
\text{CHO} & \xrightarrow{8 \xrightarrow{\alpha-\text{OH}, \beta-\text{vinyl (3\%)} } \text{CHO}} \\
\text{CHO} & \xrightarrow{9 \xrightarrow{\alpha-\text{OH}, \alpha-\text{vinyl (2\%)} } \text{CHO}}
\end{align*}
\]

Scheme 2

The CrCl2-mediated coupling of 2 and 4 afforded all possible four diastereomers (6, 7, 8, and 9) in 53, 9, 3, and 2% yields, respectively; the major product (6) was temporarily assigned to be the expected product on the basis of the six-membered transitional geometry for the coupling reaction, and this assumption was confirmed through following results described below.

\[
\begin{align*}
\text{CHO} & \xrightarrow{1. \text{PDC/CH}_2\text{Cl}_2 (69\%)} \text{CHO} \\
\text{CHO} & \xrightarrow{2. \text{TMSCl/Py (92\%)} } \text{CHO} \\
\text{CHO} & \xrightarrow{1. \text{PDC/CH}_2\text{Cl}_2 (69\%)} \text{CHO} \\
\text{CHO} & \xrightarrow{2. \text{TMSCl/Py (92\%)} } \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{1. \text{DIBALH (96\%)} } \text{CHO} \\
\text{CHO} & \xrightarrow{2. \text{PPTS/aq.THF (70\%)} } \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{Me}_2\text{SiCl}_2/\text{C}_6\text{H}_6-\text{Py} (96\%)} \text{CHO} \\
\end{align*}
\]

Scheme 3

The Cope rearrangement of TBS ether (10) derived from 6 gave a single product (11), in 95% yield. From our earlier studies on Cope rearrangement of iridane derivatives, it is well established that the C-C bond formation occurs from the opposite direction of the bulky isopropyl group on the cyclopentene ring. Therefore, combined with the E-, Z-geometry of the enol and the trisubstituted double bonds which were confirmed with NOE experiments, the whole stereostructure of 11 was unambiguously elucidated as depicted. This result is consistent with the tentative structure of 6, since 11 should be obtained from a chair transition.
geometry in the rearrangement.
The stereochemistries of 11 are, however, not suitable for the synthesis of 1 in the following two points; in 11, the tertiary methyl and the hydroxylated-isopropyl groups have a cis-relationship and the trisubstituted double bond formed in the Cope rearrangement has a Z-geometry. To get opposite selectivity on these points, we again adopted our methodology used in the earlier studies. It is predictable that a dioxasilepine ring formation using tertiary and allylic hydroxy groups of an epimer (8) of 6, would place the migrating allyl group on the sterically-crowded α-face of the cyclopentene ring and, therefore, the required stereochemistry of tertiary methyl should be obtained. At the same time, an E-geometry of the trisubstituted double bond should also be realized if the rearrangement would proceed through a chair-geometry in such a transition structure.

Thus, 6 was converted to an α,β-unsaturated ketone and its TMS ether (12) consecutively. The DIBALH-reduction of 12 in toluene at -78 °C and the deprotection of the TMS group with PPTS in CH2Cl2 afforded a single product, which was identical with a minor condensate (8). Treatment of 8 with dichlorodimethylsilane in benzene with pyridine formed cyclic ether (13), a dioxasilepine derivative. Subsequent Cope rearrangement of 13 afforded two products (14 and 15) in 75 and 20% yields, respectively. Intactness of the dioxasilepine system assured the cyclic intermediacy of the rearrangement and, therefore, the C-C bond formation occurred from more sterically hindered face to give a desired stereochemistry at the quaternary carbon in both products. From the NOE experiments, the trisubstituted double bond has an E-geometry in 14 and a Z-geometry in 15 via a chair and a boat transition states, respectively; crowded circumstances must be the reason for the reduced chair-boat selectivity.

Scheme 4

A brief hydrolysis of the dioxasilepine moiety of 14 by tetrabutylammonium fluoride (BAF) gave an unstable hydroxy aldehyde (16), which was directly treated with acetone cyanohydrin with DIBALH to form diastereomeric cyanohydrins (17 and 18), 43 and 33% yields, respectively, both of which were used for further transformations. Allyl chlorides (19 and 20) derived from 17 and 18 in three steps were independently treated with potassium hexamethyldisilazanide in THF and then quenched with D2O at room temperature; only 20 showed an incorporation of the deuterium. Thus, after the base-treatment, 20 was...
heated at 80 °C in anhydrous benzene to form a stereoisomeric mixture of cyclizates, which was hydrolyzed with aqueous HCl to remove ethoxyethyl groups, and aqueous NaOH to remove cyano group to give an eleven-membered ketone (21).

\[
\text{21} \xrightarrow{\text{LiAlH}_4/\text{THF}} \text{22} \xrightarrow{\text{m-CPBA/CH}_2\text{Cl}_2} \text{1}
\]

**Scheme 5**

The LAH-reduction of 21 gave an alcohol (22) in 90% yield, whose β-orientation was assured by NOE measurement in the \( ^1\text{H} \) NMR spectrum. Epoxidation of 22 with \( m \)-chloroperbenzoic acid afforded a bis-epoxide (1; \( R=\text{H} \)) in 95% yield with a high stereoselectivity. The \( ^1\text{H} \) NMR spectrum and the melting point of 1 (\( R=\text{H} \)), mp 230-231 °C (lit., 3 232-233 °C), confirmed the identity with natural floerkein B. Thus, its first total synthesis has been accomplished.

\[
\text{1} (R=\text{H}) \xrightarrow{\text{Ac}_2\text{O}, \text{DMAP}, \text{Py}} \text{23} \xrightarrow{\text{Ba(OH)}_2, \text{EtOH}} \text{24:} \ R=\text{H} \ \ \ \text{1':} \ R=\text{Ac}
\]

**Scheme 6**

In order to convert it into a congener, barbilycopodin (1; \( R=\text{Ac} \)), an acetylation of synthetic 1 (\( R=\text{H} \)) was also attempted. However, although the secondary hydroxyl was easily acetylated, the tertiary alcohol resisted to the reaction and this was converted into the enol acetate of the acetoacetate (23) in forced conditions. Saponification of 23 with barium hydroxide behaved parallel. However, after an easy hydrolysis of the secondary acetoxy group, the acetoacetyl group could be transformed to the acetyl group in very low yield. The resultant monoacetyl derivative (24) was reacetylated to the diacetate which was identical with natural 1 (\( R=\text{Ac} \)). Thus, barbilycopodin have been totally synthesized, too.

**REFERENCES**

6. Prolonged hydrolysis reaction of 14 caused epimerization of the aldehyde of the product (16) to form a thermodynamically stable hemiacetal (25).
8. The structures of 17 and 18 were deduced from 1H NMR evidences; in 17, methine and hydroxyl protons of the cyanohydrin moiety appeared at 4.47 and 6.19 ppm, respectively, both as broad singlets. This fact was only explainable with hydrogen bond between two hydroxyl groups and S-configuration of the cyanohydrin moiety in 17.
10. Low-valent titanium salt mediated cyclization on a diformyl derivative to form the eleven-membered ring was also successful, but the presence of an extra oxygen function seems to be disadvantageous.
11. 1H NMR δ(CDCl3)=1.24, 1.30, 1.38, 1.40, and 1.44(each 3H, s), 2.93 (1H, d, J=9 Hz), 3.06 (1H, dd, J=10.5, 3 Hz), 4.18(1H, ddd, J=12, 6, 2 Hz) [lit.,3 δ(CDCl3-CD3OD)=1.20, 1.26, 1.37, 1.39, and 1.43(each 3H, s), 2.94(1H, d, J=9 Hz), 3.10(1H, dd, J=10, 4 Hz), and 4.13(1H, ddd, J=12, 6, 2 Hz)].
12. 1H NMR δ(CDCl3)=1.32, 1.39, 1.45, 1.50, 1.57, 2.01, and 2.09(each 3H, s), 2.88(1H, d, J=9.5 Hz), 3.06(1H, dd, J=9.5, 3.5 Hz), and 5.36(1H, ddd, J=12, 6, 1.5 Hz) [lit.,3 δ(CDCl3-CD3OD)=1.29, 1.36, 1.42 1.48, 1.54, 1.99, and 2.06(each 3H, s), 2.87(1H, d, J=8 Hz), 3.04(1H, dd, J=9, 5 Hz), and 5.38 1H, ddd, J=12, 6, 2 Hz)].

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