SYNTHESIS OF (−)-IDIADIONE, A FURANOSESTERTERPENE ISOLATED FROM A MARINE SPONGE SPONGIA IDIA

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Abstract-(−)-Idiadione (1), a furanosesterterpene isolated from a marine sponge Spongia idia, was synthesized, starting from (S)-(−)-citronellal (2). The absolute configuration of naturally occurring 1 is established as (S).

The linear furanosesterterpene idiadione (1) was first isolated in 1980 by Faulkner et al.1 from a marine sponge Spongia idia (Leiosella idia). Faulkner reported that idiadione (1) is toxic to the sea star, brine shrimp and ectoproct. 1 has also antifeedant activity2 against fish. The structure of 1 has been elucidated by spectroscopic method and chemical degradation. Faulkner has also reported the isolation of a structure-related marine natural product, furospinulosin-1 (furospinosuline-13) (3), which was also isolated from the marine sponge Spongia idia. Idiadione (1) possesses one stereogenic carbon in a highly oxygenated furospinulosin-1(3) skeleton. No indication of the absolute configuration at the chiral center in 1 was mentioned by Faulkner.

We here describe the first enantioselective total synthesis of (S)-(−)-idiadione (1) using (S)-(−)-citronellal (2) as the starting material.

Scheme 2 shows retrosynthetic analysis for 1. The target compound (1) is divided into left-hand part A and right-hand part (perillene part) B.

To produce the left-hand part A of the target molecule, we protected (S)-(−)-citronellal by ethylene glycol
in the presence of a catalytic amount of p-toluenesulfonic acid in refluxing benzene and obtained the acetal (4). Oxidation of 4 with 70% t-BuOOH in the presence of SeO₂ in CH₂Cl₂ at room temperature, afforded a mixture of aldehyde and alcohol. Without purification, the mixture was reduced by NaBH₄ to the corresponding alcohol (5) (50%, three steps). Bromination of the alcohol (5) under the well-described conditions (tetrabromomethane / triphenylphosphine) afforded the bromide (6) in 82% yield. 2-Isobutyl-1,3-dithiane (7) was prepared from isovaleraldehyde and 1,3-propanedithiol in 70% yield. The bromide (6) was employed for the alkylation of 7 (n-BuLi / THF) to give 1,3-dioxolane (8) (75% yield), which was readily converted to 1,3-dithiane (9) by 1,3-propanedithiol and Zn(OTf)₂ in 77% yield.

Scheme 3. Reagents and conditions: (a) ethylene glycol, benzene, p-TsOH, reflux; (b) SeO₂, 70%-t-BuOOH, CH₂Cl₂, rt; (c) NaBH₄, MeOH, rt, 50% for three steps; (d) CBr₄, Ph₃P, THF, rt, 82%; (e) 2-isobutyl-1,3-dithiane (7), n-BuLi, (6), THF, -20°C, 75%; (f) 1,3-propanedithiol, Zn(OTf)₂, CH₂Cl₂, rt, 77%; (g) n-BuLi, propylene oxide, THF, -20°C, 58%; (h) TFAA, DMSO, Et₃N, CH₂Cl₂, -78°C, 82%; (i) Wittig reagent (13), THF, -30°C, 40%; (j) HgCl₂, CaCO₃, MeCN-H₂O, rt, 46%.
In the first attempt, alkylation of 9 with bromoperillene (10)\(^6\) (the right-hand part B) (n-BuLi / THF, -20°C) (LDA / THF, -78 to -30°C) was unsuccessful under these conditions.

We then turned our attention to another approach for the synthesis of idiadione (1). 1,3-Dithiane (9) was treated with n-BuLi and propylene oxide to give alcohol (11) (58% yield). The alcohol (11) was converted to the methyl ketone (12) by Swern oxidation\(^7\) (TFAA, DMSO, Et\(_3\)N in CH\(_2\)Cl\(_2\), 82% yield). We undertook coupling with the appropriate Wittig reagent (13).\(^8\) Treatment of the phosphonium salt with n-BuLi in THF led to the formation of a yellow solution of 13, which, upon addition of methyl ketone (12) at room temperature, furnished 40% yield of an inseparable mixture of the 6\(E\) and 6\(Z\) isomers of 14, 15 (ratio 6:1).\(^9\) Without purification, the mixture was hydrolyzed with HgCl\(_2\) in the presence of CaCO\(_3\) in aqueous MeCN.\(^10\) The hydrolyzed products can be separated by preparative TLC. The structural data of the major product (1) (46% yield) are in agreement with that of natural idiadione. Synthetic optically active 1 had identical specific rotation with that of natural 1 \{\([\alpha]_D^{21}\) -6.6° (c 0.26, CHCl\(_3\)) for synthetic, lit.\(^1\) \([\alpha]_D^{19}\)-6.6° (c 2.6, CHCl\(_3\)) for natural\} and from its relation to (S)-(−)-citronellal, the (S)-configuration for the natural product can be established.

In summary, we have accomplished the total synthesis of idiadione (1) in an optically active form from (S)-(−)-citronellal, and the absolute configuration of the natural product was determined to be 11\(S\).

**REFERENCES**

9. The 6\(E\) geometry of the olefinic bond was determined by comparison on the chemical shift data for the 22 (14\(E\)) and 24 methyl signals in the \(^{13}\)C-NMR spectrum of the major product (14) \{\([\alpha]_D^{19}\) 18.4, 18.5\}.