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

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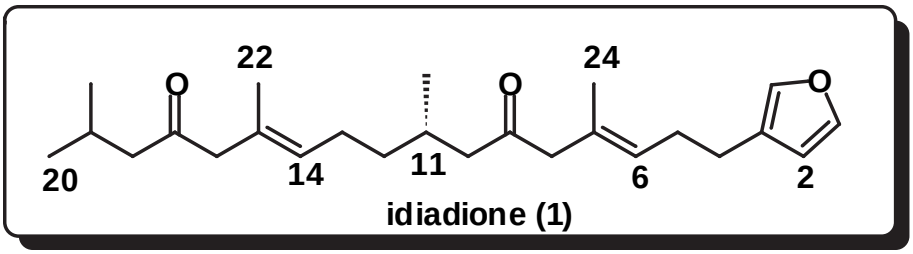
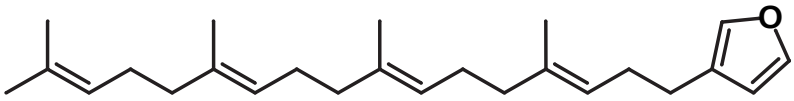
Abstract-(-)-Idiadione (**1**) , a furanosesterterpene isolated from a marine sponge *Spongia idia*, was synthesized, starting from (S)-(-)-citronellal (**2**) . The absolute configuration of naturally occurring **1** is established as (*S*) .

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 activity[2] 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[1] (furospinosuline 1[3]) (**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 .



idiadione (1)



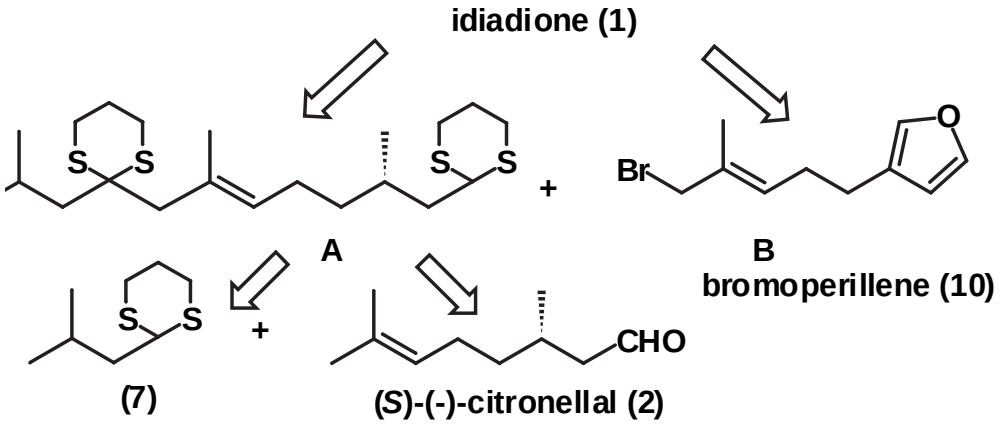
furospinulosin-1 (3)
(furospinosuline-1)

Scheme 1.

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

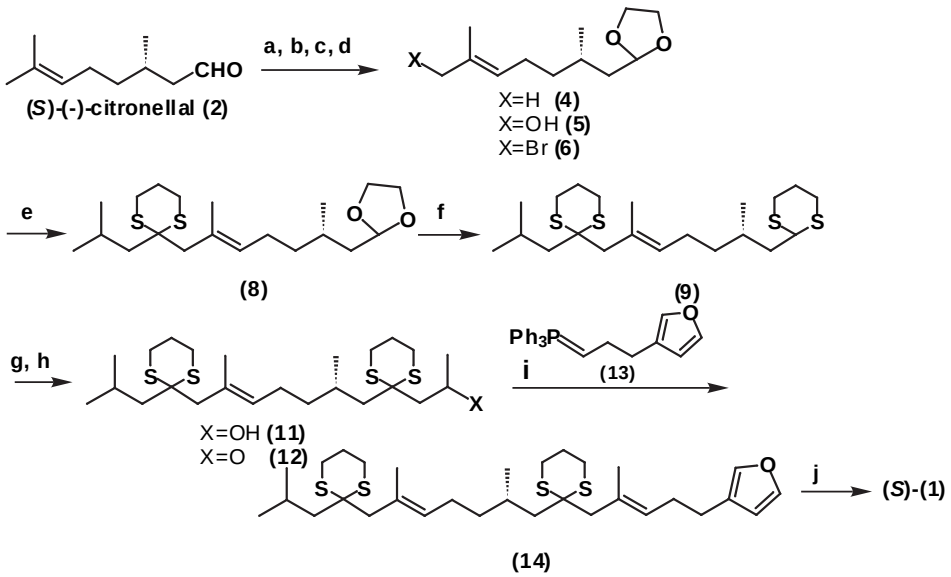
Scheme 2 shows retrosynthetic analysis for **1**. The target compound (**1**) is divided into left-hand part A and right-hand part (perillene part) B.

To produce the left-hand part A of the target molecule, we protected (*S*)-(-)-citronellal by ethylene glycol



Scheme 2. *Retrosynthetic analysis of idiadione (1)*

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 SeO_2[4] in CH_2Cl_2 at room temperature, afforded a mixture of aldehyde and alcohol. Without purification, the mixture was reduced by $NaBH_4$ 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 $Zn(OTf)_2$[5] in 77% yield.



Scheme 3. *Reagents and conditions:* (a) ethylene glycol, benzene, *p*-TsOH, reflux ; (b) SeO_2, 70%*t*-BuOOH, CH_2Cl_2, rt ; (c) $NaBH_4$, MeOH, rt, 50% for three steps; (d) CBr_4, Ph_3P, THF, rt, 82%; (e) 2-isobutyl-1,3-dithiane (**7**),n-BuLi, (**6**), THF, -20°C, 75%; (f) 1,3-propanedithiol, $Zn(OTf)_2$, CH_2Cl_2 , rt, 77%; (g) n-BuLi, propylene oxide, THF, -20°C, 58%; (h) TFAA, DMSO, Et_3N, CH_2Cl_2, -78°C, 82%; (i) Wittig reagent (**13**),THF, -30°C, 40%; (j) $HgCl_2$, $CaCO_3$, MeCN-H_2O, 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_3N in CH_2Cl_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** { $[a]_D^{21}$-6.6° (c 0.26 , $CHCl_3$) for synthetic , lit.,[1] $[a]_D$-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*.

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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**) {d 18.4,18.5}.
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