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The Total Synthesis of the New Sesquiterpenoid (±)-Fulvanin 1 / Sollasin a

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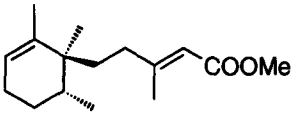
Key Words : stereoselective alkylation, allylic bromide, (±)-Sollasin a, (±)-fulvanin 1, Swern oxidation.

Abstract: *The reaction of 2,3-dimethylcyclohexan-1-one (2) with the functionalized allylic bromide 3 produced regio- and strereoselectively a precursor (4) of the new sesquiterpenoid sollasin a / fulvanin 1 (1). Functional group transformations then completed the synthesis.*

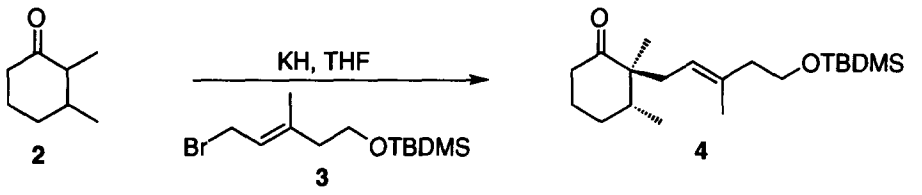
Recently, two independent research groups reported the isolation and characterization of a new sesquiterpenoid. One group described the isolation and structure elucidation of six new sesquiterpenes from a sample of sponge *Poecillastra sollasi*, collected from Little Inagua Island, and among which was sollasin a (**1**).[1] The other group collected a sample of sponge *Reniera fulva* from Egadi Islands and isolated fulvanin 1 (**1**).[2] It was found that fulvanin 1 and sollasin a have an identical structure, characterized by a rearranged cyclofarnesane skeleton.



1

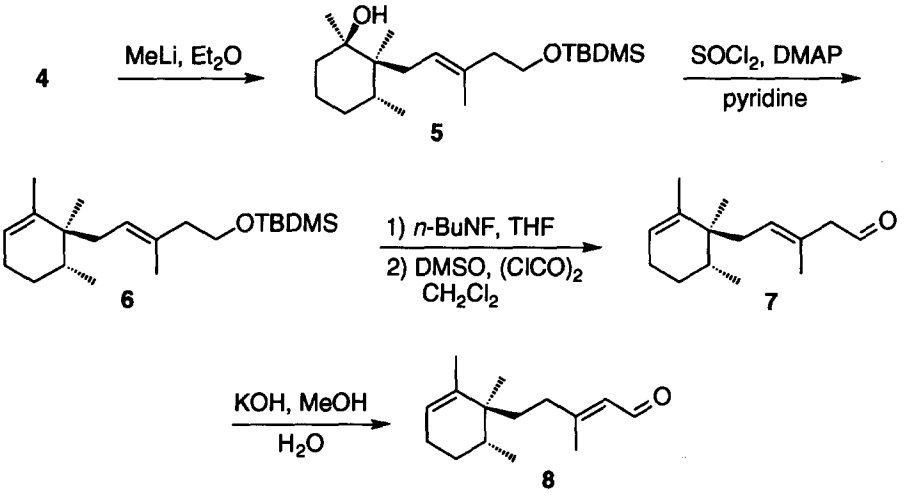
The stereocontrolled incorporation of the side chain and, consequently, the construction of the quaternary center is one of the primary problems we must solve in order to achieve the total synthesis of the target product, sollasin a / fulvanin 1. A synthesis can be based on the alkylation of 2,3-dimethylcyclohexan-1-one. Indeed, the results of previous studies showed that alkylation of conformationally mobile 1-enolates such as 3-alkyl- and 2,3-dialkylcyclohexanones provides stereoselectively the corresponding alkylated cyclohexanones which have the new alkyl group at C-2 *trans* with regards to the methyl at C-3.[3] Since enolates exist as an equilibrium mixture of conformations, the alkylation of the readily available 2,3-dimethyl-cyclohexanone (**2**)[4] with the *E*-functionalized allylic bromide **3**[5] provides an efficient stereoselective synthesis of compound **4** (scheme 1).

The employed procedure was as follows. To a stirred suspension at 0 °C of potassium hydride (4.16 mmol)) in THF (5 mL), was added a solution of a mixture of two isomers of 2,3-dimethylcyclohexan-1-one (3.96 mmol)) in the same solvent (2.5 mL). After 1 h at 0 °C and 1 h at room temperature, the mixture was recooled to -78 °C and treated dropwise with a mixture of bromide **3** (3.57 mol)) and HMPA (1 mL), continuing to react at this temperature for 1 h and then allowed to warm to room temperature. Work-up and flash chomatography furnished the alkylated ketone **4** in 49 % yield.



scheme 1

Ketone **4** (1.45 mmol) in ether (10 mL) was then treated with methyllitium (2.9 mmol) at 0 °C for 2 h, yielding to tertiary alcohol **5** (51 %) (scheme 2). Iterative reaction of the organometallic reagent with isolated starting material increased the yield to 75 %. A 3.5 / 1 mixture of isomeric alcohols was obtained, with the compound bearing *cis* 1,3-dimethyl (**5**) as the major component. The stereochemistry was determined by comparison of chemical shifts of methyl groups of isomeric alcohol **5**, in ^{1}H NMR. For example, the value for methyl in position 1 is 1.15 ppm for the *cis* isomer and 1.21 ppm for the *trans* isomer.



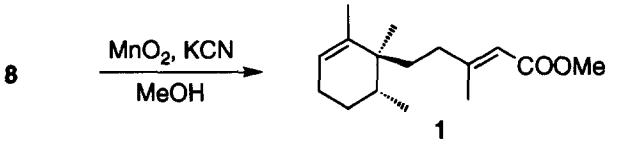
scheme 2

The dehydration of **5** (1.84 mmol) was performed with thionyl chloride (4.6 mmol)) in pyridine (25 mL), at 0 °C, and in the presence of DMAP (1.84 mmol),[6] leading to the formation of a mixture of dienes with an

endo /exo ratio of 3 / 1; the yield of *endo* isomer (**6**) was 62 %, after being separated by flash chomatography on silica gel impregnated with silver nitrate.[7]

The hydroxyl protecting group of **5** (0.88 mmol) was removed using tetra-*n*-butylammonium fluoride (1.75 mmol) in THF (7 mL)[8] and the obtained corresponding primary alcohol was then oxidized into the corresponding aldehyde. Swern oxidation[9] of primary alcohol (0.23 mmol) in the following conditions, oxalyl chloride (0.25 mmol)) and DMSO (0.54 mmol)) in methylene chloride (1 mL) at -83 °C for 20 min., successfully led to the aldehyde **7** in 68 % yield. The double bond conjugation was done at room temperature with potassium hydroxide, in a mixture of water and methanol.[10] The yield in conjugated aldehyde **8** was 52 %, after separation of the *E* / *Z* isomers, obtained in a 2 / 1 ratio.

Further oxidation to methyl ester was performed according to a procedure developed by Corey (scheme 3).[11] Thus, treatment of compound **8** (0.004 mmol) with manganese oxide (0.082 mmol), in presence of potassium cyanide (0.021 mmol) and in methanol (50 µL), achieved the synthesis of compound **1** in 60 % yield. The spectral data of this material proved identical to the natural fulvanin 1.[12]



scheme 3

The present study clearly demonstrates that the alkylated compound **4** may be readily prepared with full control of stereochemical relationships. The methodology is known to be general[3] and may be applied to the synthesis of other natural products of this class of sesquiterpenoids.[13]

The viability of the alkylation approach to the rearranged cyclofarnesane structure has been demonstrated by a first total synthesis of (±)-sollasin a / fulvanin 1. The regio- and stereocontrolled alkylation step of 2,3-dimethylcyclohexanone with allylic bromide **3** yielded the key intermediate **4** in the direct synthesis, with few functional group transformations, of this new sesquiterpenoid.

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4. Oxidation of commercially available 2,3-dimethylcyclohexan-1-ol with Jones's reagent afforded 2,3-dimethylcyclohexanone (**2**) in 80 % yield (b.p. 183-187 °C_{760}).
5. Bromide **3** was prepared from but-3-yn-1-ol as follows : protection of the hydroxyl group with TBDMSCl; acylation with methyl chloroformate;[14] Mukaiyama's procedure for stereocontrolled addition to a conjugated triple bond : sodium thiophenolate addition, followed by MeMgBr-CuBr and subsequent elimination;[15] reduction of the ester with DIBAl-H; bromination.[16]
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12. Data for compound **1** are as follows : Mass (m/e) :250 (3 %, M+), 235 (8 %), 127 (9 %), 124 (20 %), 123 (100 %), 121 (8 %), 109 (12 %), 95 (13 %), 81(21 %), 67 (7 %); Exact mass : found : 250.1930, calcd : 250.1933.
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