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# Total synthesis of (±)-dihydrospiniferin-1 *via* a polyfluoro alkanosulfonyl fluoride induced tandem carbonium ion rearrangement reaction

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**A novel polyfluoroalkanosulfonyl fluoride induced carbonium ion rearrangement reaction of γ-hydroxymethyl cyclohexenone has been used for the total synthesis of (±)dihydrospiniferin 1.**

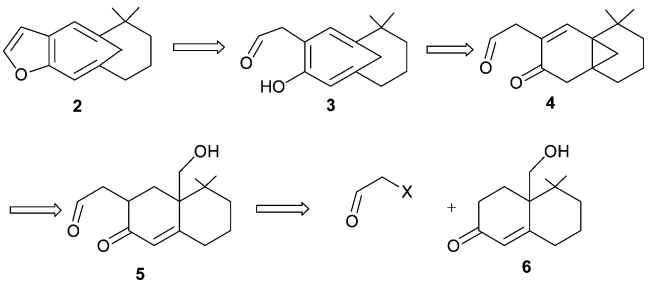
Spiniferin-1(**1**) is a structurally unique furanosesquiterpene, isolated by Cimino *et al*. in 1975 from the Mediterranean sponge *Pleraplysilla spinifera*, which is present in the Bay of Naples.[1] In 1978, its structure was reformulated as **1**[2] and supported by Marshall's rational synthesis of (±)-dihydrospiniferin-1(**2**) (Fig. 1).[3] Racemic **1** had also been synthesized[4] by Marshall by a similar strategy. Spiniferin-1 is the first and unique natural product with the skeleton of 1,6-methano[10]annulene up to now, although Vogel *et al*. prepared this kind of annulene in 1964.[5] The physical and chemical properties of 1,6-methano[10]annulene have been described in detail since it and its analogues were synthesized, but to the best of our knowledge no biological information has been reported. The biological secrets of spiniferin-1 make us interested in its total synthesis.

As a part of our research on the reaction of poly(per)-fluoroalkanosufonyl fluorides and their application in the synthesis of medicines and natural products,[6] we found a novel polyfluoroalkanosulfonyl fluoride induced carbonium ion rearrangement reaction[7] of γ-hydroxymethyl cyclohexenone recently. This rearrangement reaction provides a new and efficient synthetic method for dihydrospiniferin-1, spiniferin-1, as well as their analogues. In this paper, we will describe the total synthesis of (±)-dihydrospiniferin-1 *via* a novel polyfluoroalkanosulfonyl fluoride induced carbonium ion rearrangement reaction of γ-hydroxymethyl cyclohexenone.

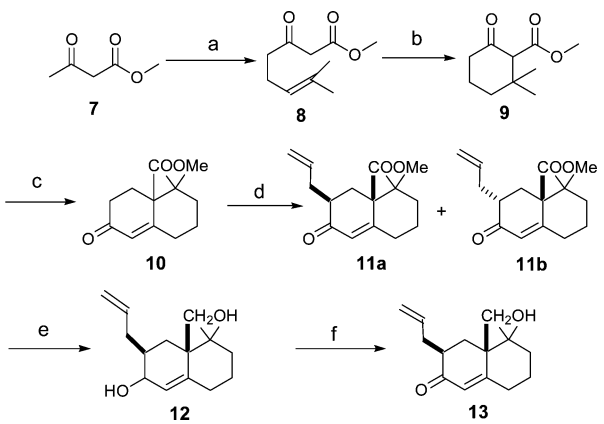
Our synthetic plan relied on the construction of 1,6-methano[10]annulene **3**, a key intermediate in Marshall's synthesis,[3] from polyhydro-4a,8a-methanonaphthalene **4**, which would be obtained by the rearrangement of γ-hydroxymethyl cyclohexenone **5** induced by polyfluoroalkanosulfonyl fluoride. Unsaturated ketone **5** was simplified into a readily available Robinson annulation product **6** and an α-halogen acetaldehyde (Scheme 1).

The Robinson annulation product **10** was obtained according to classical methods. The dianion[8] of ethyl acetoacetate **7**was generated when treated sequentially with NaH and n-BuLi in THF. Alkylation of the dianion with 4-bromo-2-methyl-2-butene gave the alkylated β-keto ester **8**, which was cyclized to 2-cyclohexanone carboxylate **9** in the presence of $SnCl_4$.[9] This sterically hindered β-keto ester underwent Michael addition when treated with a catalytic amount of freshly prepared potassium methoxide in THF, and the resulting Michael adduct further underwent Robinson annulation to afford **10** in 80% yield upon heating with methanolic potassium carbonate[4] (Scheme 2).

We planned to use $BrCH_2CH(OEt)_2$, the equivalent of α-halogen acetaldehyde, to introduce the side chain. Kinetic controlled enolation of enone **10** could be realized by using LDA[10]as the base at low temperature (−70 °C). But the subsequent alkylation did not occur even with the iodide due to the poor reactivity of enol anion. Fortunately, the alkylation of allylic bromide instead of $XCH_2CH(OEt)_2$(X = Br or I) gave two isomers **11a** and **11b** in 63% and 9% yields respectively. Treatment of **11a** with $LiAlH_4$ followed by selective oxidation of the allylic hydroxyl with DDQ[11] afforded hydroxymethyl enone**13**. Ozonolysis of **13** directly furnished the undesired ketal **14**, which supported the structural assignment of **11a** (Scheme 3).




**Scheme 1** Retrosynthetic analysis.




**Scheme 2** *Reagents and conditions*: (a) NaH, n-BuLi, 4-bromo-2-methyl-2-butene, THF, 0 °C, 79%; (b) $SnCl_4$, $CH_2Cl_2$, r.t., 81%; (c) $KOCH_3$, MVK, 0 °C; $K_2CO_3$, $CH_3OH$, reflux, 80%; (d) LDA, allylic bromide, −78 °C→r.t., 63% (**11a**),9% (**11b**); (e) $LiAlH_4$, THF, r.t., 76%; (f) DDQ, benzene, r.t., 70%.

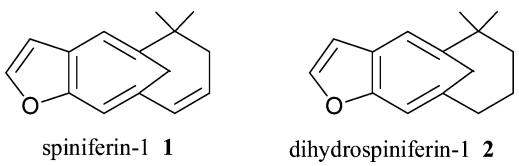
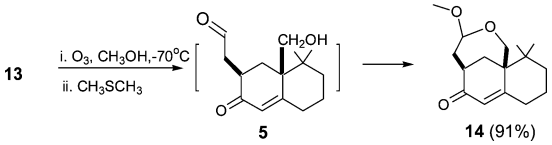



**Fig. 1** Structures of spiniferin-1 and dihydrospiniferin-1.




**Scheme 3** The confirmation of relative configuration of **11a**.

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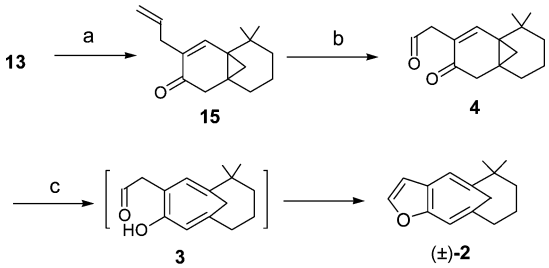


**Scheme 4** *Reagents and conditions*: (a) $HCF_2CF_2OCF_2CF_2SO_2F$, DBU, THF, 0 °C; $NEt_3$, reflux, 82%; (b) $O_3$, −70 °C, $CH_3OH$; $Me_2S$, r.t., 67%; (c) 12N HCl, THF, r.t. 69%.

Using a novel poly(per)fluoroalkanosufonyl fluoride induced tandem carbonium rearrangement which was recently found by us, γ-hydroxymethyl cyclohexenone **13** was transformed into our desired cyclopropyl enone **15** in 82% yield†. Selective ozonolysis[1,2] of compound **15** furnished aldehyde **4**. The latter in the presence of 12 N HCl rearranged to cycloheptatriene **3**, a unstable intermediate, which immediately cyclized to form (±)-**2** as a colorless oil (Scheme 4). Our synthetic material has identical $^1$H and $^{13}$C NMR data‡ as reported by Cimino[1,2] and Mashall.[3,4]

## Notes and references

† Synthesis of key intermediate **15**: To a stirred, cooled solution of 99 mg of enone **13** (0.4 mmol) in 2.5 ml of dry THF was added 119 µl (2 eq) of DBU and 144 µl (2 eq) of $HCF_2CF_2OCF_2CF_2SO_2F$. The solution was stirred for 30 min and was filtered through a short silica gel column with the aid of 2.5 ml of THF. The combined solution was added 280 µl (5 eq.) $NEt_3$ and was heated to reflux for 8 h. The solvent was removed under reduced pressure and the remainder was purified by column chromatography on silica gel to afford 75 mg (82%) of **15** as a colorless oil. IR (film): $\nu$ 1666, 1640 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.08 (s,1H), 5.77 (m,1H), 5.01 (m,2H), 2.92(m,1H), 2.84(d, $J$ = 8.6Hz, 1H), 2.51(d, $J$ = 8.6Hz, 1H), 1.11(s,3H), 1.10(s,3H), 0.51(d, $J$ = 4.0Hz, 3H); EIMS: m/e 230 ($M^+$, 100%)

‡ Procedure for the synthesis of (±)-**2**: To a stirred solution of 62 mg **4** (0.27 mmol) in 3 ml THF was added 0.6 ml 12 N HCl. The solution was stirred for 1 h and was extracted with ether. The combined organic layers was washed with brine and dried. The solvent was removed under reduced pressure and the remainder was purified by column chromatography on silica gel to afford 40 mg (69%) of (±)-**2** as a colorless oil. $^1$H NMR (300MHz, $CDCl_3$) $\delta$ 7.33(d, $J$ = 1.8Hz, 1H), 6.56(d, $J$ = 1.5Hz,1H), 6.29(s,1H), 6.28(s,1H), 3.14(d, $J$ = 10.8 Hz,1H), 2.2–2.5(m,2H), 1.7–1.9(m,2H), 1.3–1.5(m,1H), 1.32(s,3H), 1.14(d,$J$ = 10.8 Hz,1H), 1.05(s,3H), 0.6–0.8(m,1H); $^{13}$C NMR (75MHz, $CDCl_3$) $\delta$ 153.2, 140.3, 132.5, 129.4, 125.3, 112.2, 110.0, 109.1, 42.0, 37.8, 36.7, 35.0, 29.2, 27.1, 25.8.


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