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Synthesis of fluorinated drimanes. Preparation of 9αF-drimenin

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Abstract—A stereoselective approach to the 9α-fluorinated analogue of the natural drimane sesquiterpene drimenin starting from β-ionone is described. β-Ionone is transformed into a bicyclic β-cetoester from which 9αF-drimenin is prepared through stereoselective electrophilic fluorination at the C-9 with *N*-fluorobenzenesulfonimide followed by Wittig methylenation, allylic bromination, bromine-hydroxyl exchange and γ-lactonization.

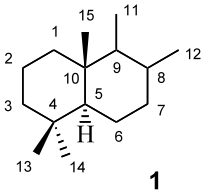
The replacement of a hydrogen atom by a fluorine atom in organic molecules is a strategy widely used for the development of new and more active pharmaceuticals and agrochemicals.[1] This strategy is inspired by the well-known 'fluorine effect', the fact that fluorine substitution can substantially alter the chemical properties[2] and disposition[3] of organic molecules while exerting only a minor steric demand at receptor sites, at least for monofluorinated analogues.[4]

Although very few fluorinated compounds have been isolated from living organisms,[5] a large number of fluorine-containing analogues of natural products with biological significance such as oligosaccharides, glycoconjugates, nucleosides, aminoacids, steroids and feromones have been synthesized.[6] However, only a few examples of fluorinated derivatives of bioactive terpene-type compounds have been reported, which in many cases show an increase in activity with respect to the corresponding hydrogen analogue.[7]

The drimanes are a group of sesquiterpenes isolated from various natural sources, which have structures based on the drimane bicyclic skeleton (**1**).[8] Many of these compounds show a wide spectrum of potentially useful biological properties[9] that may be associated in most cases with the presence of 1,4-dialdehyde or butenolide moieties at C11–C12. Representative examples are polygodial (**2**), warburganal (**3**), cinnamolide (**4**) and drimenin (**5**).

As with other related systems,[10] the presence of polar groups (i.e. OH, acetate, etc.) in the vicinity of the dialdehyde or butenolide moieties generally produces an increase in the biological activity, perhaps due to a more favourable interaction with the receptors. In this context, we were interested in investigating how the modification of 6-, 7- or 9-positions on the drimanes with a fluorine atom may influence their chemical and biological activity.

We describe in this communication the preparation, for the first time, of the 9α-fluorinated drimane framework and the synthesis of the fluorinated analogue of one the representative members of this group of sesquiterpenes, 9αF-drimenin (**6**).



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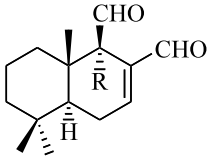

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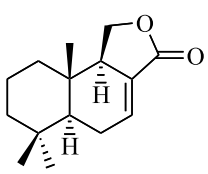
3: R = OH



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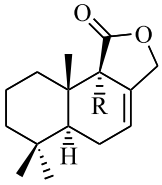

5: R = H

6: R = F

Our strategy for the preparation of the 9αF-drimane skeleton was based on the initial preparation of fluorinated decalone (**8a**) (Scheme 1). The required decalone

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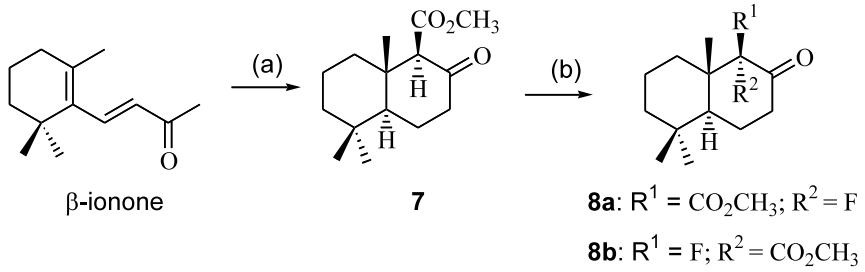


Scheme 1. *Reagents and conditions*: (a) i. Bu_3SnH, AIBN, 80°C; ii. NaH, $(MeO)_2CO$, dioxane, 105°C; iii. $SnCl_4$, CH_2Cl_2, 30°C, 60% overall yield. (b) NaH, NFSi, THF, rt, 85% of **8a**.

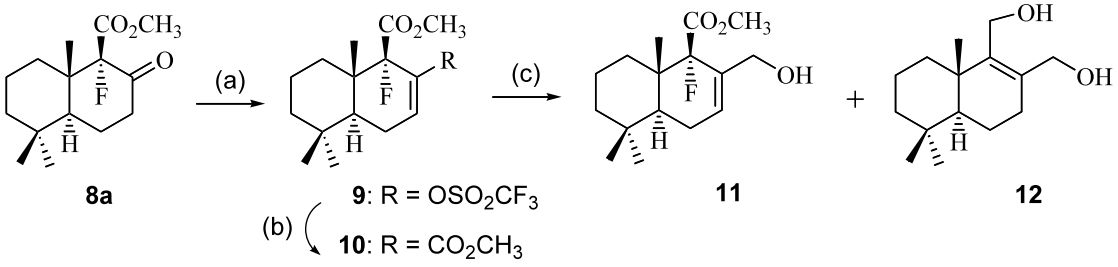
7 was first prepared from β-ionone in 60% overall yield, following the procedure previously described by Herlem and White.[11] Electrophilic fluorination of the sodium enolate of β-ketoester **7**, generated by treatment of **7** with sodium hydride in THF, with *N*-fluorobenzenesulfonimide (NFSi) afforded stereoselectively the fluorinated decalone **8a** in 85% yield. It is interesting to note that the use of the fluorinating reagent Selectfluor™ furnished a mixture of 9-epimeric fluorinated decalones **8a** and **8b** in 49 and 16% yield, respectively, after their chromatographic separation.

The configuration at C-9 of decalone **8a** was determined with the aid of Heteronuclear Overhauser Enhancement Spectroscopy (HOESY). Intense cross peaks were observed between the fluorine and 1α-, 5α- and 7α-hydrogens in the ^1H–^{19}F HOESY spectra of **8a**, which without doubt confirmed the α-orientation of the fluorine atom.

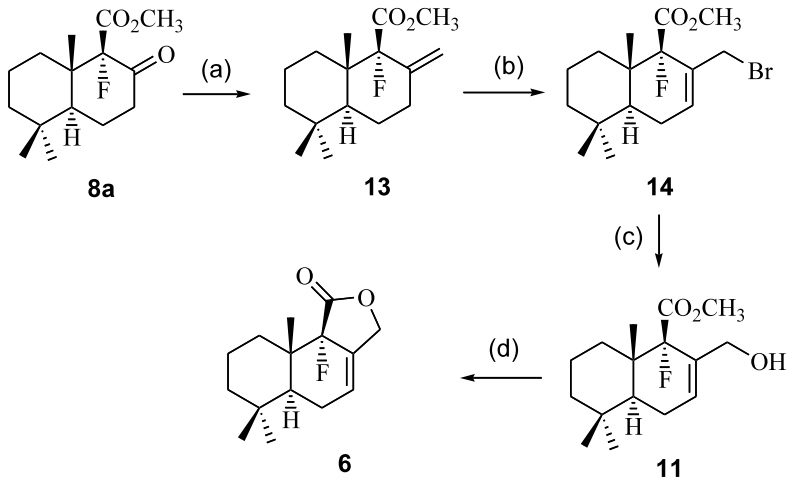
Sulfonylation of the enolate obtained by treatment of decalone **8a** with potassium hexamethyldisilazane (KHMDS) with *N*-phenyltriflamide gave vinyl triflate **9**, which in turn underwent palladium-catalysed carbonylation as described by Stille[12] to produce the methyl ester **10**, although only in a moderate 50% overall yield for the two steps. Once the drimane framework was completed, we directed our attention towards the transformation of diester **10** into hydroxy ester **11**, the immediate precursor of fluorinated drimenin (**6**). This transformation, that had been previously performed in high yield on the corresponding hydrogen analogue diester,[13] was more problematic than expected. Thus, $LiAlH_4$ reduction of diester **10** in THF at −78°C readily afforded (30 min) the diol **12** in 90% yield, a result that showed the lability of the axially orientated fluorine atom at C-9 and that parallels the result previously obtained by Ley in the reduction of the corresponding 9α-OH analogue of **10**.[14] Partial success in this transformation was achieved after studying the reduction of **11** with DIBAL-H under a variety of conditions. Thus, treatment of diester **10** with 3 equiv. of DIBAL-H in THF–cyclohexane at −78°C for 4 h afforded the hydroxy ester **11** (30%) together with starting material (30%) and diol **12** (30%), which were easily separable by conventional chromatography (Scheme 2).

Although the above route provided access to alcohol **11**, the low overall yield obtained prompted us to investigate an alternative route based on the initial methylenation of decalone **8a** (Scheme 3). It was thought that the fluorine atom on the ketone should have a beneficial effect in improving the ketone reactivity in the projected Peterson olefination.[14] Indeed, $TMSCH_2$–MgCl addition to the carbonyl group of **8a** proceeds readily to give the corresponding β-hydroxysilane in nearly quantitative yield. However, the methylenation reaction could not be completed since the intermediate β-hydroxysilane could not be induced to experience elimination under a variety of acidic conditions. In all cases the β-hydroxysilane was recovered unaltered, probably due to the β-cation-destabilizing effect of fluorine.[15] In contrast, Wittig olefination of **8a** with methylidenetriphenylphosphorane proceeded smoothly at ambient temperature to give the β,γ-unsaturated ester **13** in high yield (Scheme 3).

After unsuccessful attempts to transform the exomethylenic compound **13** into allylic alcohol **11** via epoxidation/epoxide opening reactions, following previously established methodology for related transforma-



Scheme 2. *Reagents and conditions*: (a) KHMDS, $PhNTf_2$, THF, −78°C, 70%. (b) Ac_2Pd, iPr_2NEt, CO, CH_3OH, DMF, 65°C, 68%. (c) DIBAL-H, THF, −78°C, 30% of both **11** and **12** (30% of starting material recovered).



Scheme 3. *Reagents and conditions*: (a) KHMDS, Ph_3PCH_3Br, toluene, rt, 85%. (b) NBS, CH_2Cl_2–CH_3OH, rt, 75%. (c) $AgBF_4$, 2,6-lutidine, acetone–H_2O, 60°C, 85%. (d) DBU, 3 Å molecular sieves, C_6H_6, rt, 85%.

tion on the nonfluorinated analogue,[16] this conversion was achieved quite efficiently by a sequence of allylic bromination–bromine substitution reactions. Thus, reaction of olefin **13** with *N*-bromosuccinimide (NBS) in a MeOH–CH_2Cl_2 medium afforded regioselectively the allyl bromide **14** in 75%. Although the substitution of bromine by a hydroxyl group in **14** appeared simple, in practice, the presence of the fluorine atom at C-9 produced some unexpected problems that considerably limit the yield of most of the substitution reactions attempted with oxygenated nucleophiles. Fortunately, treatment of allyl bromide **14** with silver tetrafluoborate ($AgBF_4$) and 2,6-lutidine in a mixture of acetone–water at 65°C satisfactorily furnished the desired allyl alcohol **11** in 85% yield.[17] This new route for the preparation of hydroxy ester **11** from decalone **8a** was considerably more efficient than the former, giving a 49% global yield compared with about 12% for the former.

Finally, completion of the synthesis of the 9α-fluorinated analogue of natural drimenin **6** was accomplished by base-promoted lactonization of hydroxy ester **11**. Thus, when **11** was subjected to basic treatment with 8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane in the presence of 3 Å molecular sieves the 9αF-drimenin (**6**) was isolated in 85% yield.

Work is currently in progress in our group in order to prepare 9α-fluorinated analogues of other natural drimanes such as cinnamolide and polygodial.[18,19]

Acknowledgements

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18. The synthesized fluorinated drimane-type compounds described here are currently being tested in various in vitro biological experiments and the results will be reported elsewhere.
19. All compounds were characterised by ^{1}H, ^{13}C NMR, IR and HRMS. Selected data of more significant compounds are given:
Compound **6**: an oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1H, s, H-7), 4.91 (1H, d, *J* 11.8, H-12), 4.70 (1H, d, *J* 11.8, H-12′), 2.33 (1H, m, H-6), 2.17 (1H, m, H-1), 2.08 (1H, m, H-6′), 1.85 (1H, m, H-5), 1.81 (1H, m, H-1′), 1.54–1.68 (2H, m, H-2), 1.48 (1H, m, H-3), 1.34 (1H, m, H-3′), 0.95 (3H, s, H-13), 0.93 (3H, s, H-14), 0.88 (3H, s, H-15). ^{19}F NMR (282 MHz, $CDCl_3$) δ −145.3 (s).
Compound **8a**: an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s, CO_2CH_3), 2.80 (1H, dddd, *J* 10.8, 10.8, 5.4, 5.4, H-7α), 2.47 (1H, dddd, *J* 10.8, 3.6, 1.8, 1.8, H-7β), 1.98 (1H, m, H-6), 1.94 (1H, m, H-5), 1.68 (1H, m, H-6′), 1.64 (1H, m, H-1), 1.60 (1H, m, H-2), 1.52 (1H, m, H-2′), 1.42 (1H, m, H-3), 1.30 (1H, m, H-1′), 1.22 (1H, m, H-3′), 1.17 (3H, s, H-15), 0.98 (3H, s, H-14), 0.91 (3H, s, H-13). ^{19}F NMR (282 MHz, $CDCl_3$) δ 162.0 (s).
Compound **10**: an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, ddd, *J* 4.8, 2.4, 2.4, H-7), 3.76 and 3.72 (3H each, each s, 2×CO_2CH_3), 2.36 (1H, m, H-6), 2.19 (1H, m, H-6′), 0.97 (3H, s, H-15), 0.96 (3H, s, H-14), 0.92 (3H, s, H-13). ^{19}F NMR (282 MHz, $CDCl_3$): δ −143.8 (s).
Compound **11**: an oil; ^{1}H NMR (300 MHz, $CDCl_3$) 6.20 (1H, s, H-7), 4.13 (1H, d, *J* 12, H-12), 4.03 (1H, d, *J* 12, H-12′), 3.79 (3H, s, CO_2CH_3), 0.97 (3H, s, H-15), 0.95 (3H, s, H-14), 0.90 (3H, s, H-13). ^{19}F NMR (282 MHz, $CDCl_3$) δ −140.0 (s).