Fluorination of Kaurenoic Acid Derivatives by Remote Functionalization

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Abstract: Kauranoids and related tetracyclic diterpenoids have recently shown an increasing interest because of the discovery of new biological activities that can be modified by the introduction of a fluorine atom. In this article it is described the stereospecific fluorination of the kauranols **6** and **7** by remote functionalization at the "unactivated" C-7 position.

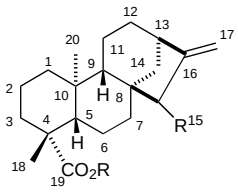
Key words: fluorination, kauranoids, natural products, synthetic methods, terpenoids.

The interest in kaurane diterpenoids has recently increased as some of them display various biological activities such as antimicrobial, antiinflammatory, anti-HIV, cytotoxic, antifertility, insect antifeedant, etc.[1] Kauranoids are also known to be the biological precursors of gibberellins, growth regulation plant hormones, and some of them have also shown gibberellin-like activity.[1,2] We reported in a recent paper the growth regulating activity of thirteen tetracyclic diterpene derivatives related to kauranoic acid which were isolated from several Spanish *Elaeoselinum* species.[3] In that study we observed that some of the tested substances were as active as or more active than gibberellic acid, GA_3. It was also concluded that the 7-hydroxykauranoids showed an increase of the gibberellin-like activity, so it seemed interesting to introduce a functional group at C-7 in natural kauranoids lacking in functionalization on the B ring.

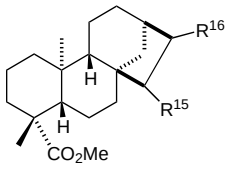
As part of a project on the transformation and synthesis of kauranoids and gibberellin analogues we report here our findings in the study of remote functionalization at C-7 in a tetracyclic diterpenoid skeleton. As starting material we selected kaurenoic acid **1**, major metabolite (40%) from the hexane extract of the aerial parts of *Elaeoselinum asclepium* subsp. *millefolium* (Umbelliferae).[4]

The introduction of fluorine atoms in biologically active substances can produce important modifications in their activity and hence the interest in the development of new stereospecific synthetic methods of fluorination.

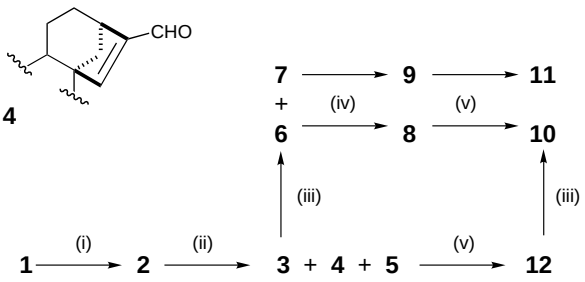
In a recent article Lawrence et al.[5] described the remote acetamidation of (–) menthol with the electrophilic fluorinating reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4 = Selectfluor[a]).[6]This prompted us to use this reactive to introduce a functional group in the B ring of kaurenoic acid for which we transformed **1** into the 15α- and 15β-hydroxy derivatives **6**, **7**, **10** and **11** in order to study the course of the reaction and the steric effects of that reagent on our substrate.



	R	R^{15}
1	H	H
2	Me	H
3	Me	α-OH
5	Me	=O
12	Me	β-OH



	R^{15}	R^{16}
6	α-OH	β-Me
7	α-OH	α-Me
8	=O	β-Me
9	=O	α-Me
10	β-OH	β-Me
11	β-OH	α-Me



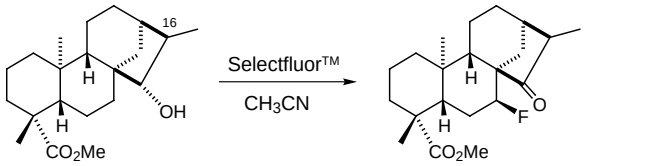
*Synthesis of kauranols **6**, **7**, **10** and **11**:* (i) CH_2N_2, Et_2O, room temp.; (ii) SeO_2 (1.2 mmol), *t*BuOOH (1.5 mmol), CH_2Cl_2, room temp.; (iii) H_2 (1.3 atm.), Pd(10%)/C, EtOH, room temp.; (iv) PDC (2.7 mmol), MeOH, CH_2Cl_2, room temp.; (v) $NaBH_4$ (0.5 mmol), THF/EtOH (95:5), 0° C.

Scheme 1

The starting diastereomeric hydroxykauranes were obtained as shown in the Scheme 1. The methyl ester **2** of the natural kaurenoic acid **1** was oxydized with selenium dioxide and *tert*-butyl hydroperoxide,[7] affording the 15α-alcohol **3** (72%) together with the 17-aldehyde **4** (2%), and the 15-ketone **5** (20%). Reduction of **3** with H_2 at 1.3 atm on 10% Pd/C in EtOH gave a mixture ca. 3:1 of the 16β- and 16α-methyl derivatives **6** and **7** in 85% yield. The conversion of these saturated 15α-alcohols into the respective epimeric alcohols **10** and **11** was carried out in 59% and 63% yield respectively by a two-step sequence,[8] i.e. oxidation with PDC and reduction of the ketones **8** and

9 with $NaBH_4$. We also tried to obtain these 15β-alcohols by $NaBH_4$ reduction of the ketone **5** followed by catalytic hydrogenation of the alcohol **12**, but only the 15β-hydroxy-16β-methyl isomer **10** was isolated in 35% yield.[9]

Once the starting diastereomeric alcohols were purified we explored the remote functionalization of each one using the Selectfluor™ reagent (Scheme 2). The treatment of 15α-hydroxy derivatives **6** or **7** with this reagent (2.2 mmol) in refluxing acetonitrile furnished a complex reaction mixture from which the ketones **8** (30%) or **9** (38%) and the 7β-fluoro derivatives **13** (10%) or **14** (12%) were isolated by column chromatography on silica gel. On the other hand, when the 15β-hydroxy isomers **10** or **11** were treated under the same reaction conditions, the starting material was recovered even after 16 h in refluxing acetonitrile.[10]



6: 16β
7: 16α

13: 16β + **8**
14: 16α + **9**

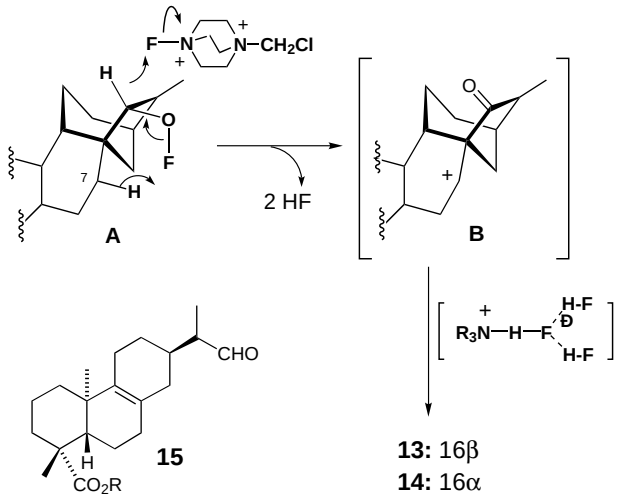
Reaction of **6** and **7** with Selectfluor™.

Scheme 2

The structures of both 7β-fluorinated isomers **13** and **14** were rigorously established by 2D COSY, HMQC and HMBC NMR experiments. The ^1H NMR signals of the geminal proton to the F atom in **13** (δ= 4.68, dd, $^3J_{7,6}$=4 and $^2J_{7,F}$= 54 Hz) and **14** (δ= 4.54, dd, $^3J_{7,6}$= 4 and $^2J_{7,F}$=54 Hz) let us assign the 7β-axial configuration for the fluor atom and this was confirmed by the γ-*gauche* shielding effects observed on the neighbouring carbon atoms C-5 and C-9 while the C-14 signal remained unaffected.

The *N*-fluoro quaternary salts such as Selectfluor™ are strong oxidizing and fluorinating agents but their reaction mechanism is not well understood and has been a subject of debate. They can deliver positive fluoride ions reponsable for the electrophilic fluorination reactions or compete with the production of radical species that can give radical coupling products.[11]

Although a reasonable radical process has been proposed to explain the acetamidation of menthol with Selectfluor™ in acetonitrile,[5] we think that in our case the observed fluorination should take place through a different process and a tentative explanation could be as depicted in Scheme 3. The first step may be the formation of an intermediate hypofluorite, which can reply as a electrophilic fluorinating reagent. In the case of the 15α-epimers **6** and **7** the F atom of the hypofluorite **A** can accede to the equatorial H-7α and progress by abstraction of this hydrogen atom to form HF (captured by the amine) and oxidation at C-15 to form the intermediate ketone **B**[12] in an enthalpic favoured process. This last intermediate would react with a complex amine·HF (similar to comercial TREAT HF)[13] from the less hindered side (backwards to the leaving H-7α) to give the fluoroderivatives **13** and **14** respectively. A process through a homolytic cleavage of the hypofluorite **A** can be discarded because the intermediate oxygen radical is rather apart from H-7. Such intermediate oxygen radical was generated by treatment of **6** with NIS under irradiation with a tungsten lamp and the main reaction product in this case was identified as the aldehyde **15**, a tricyclic abietane derivative which results from the cleavage of the C-8···C-15 bond as expected for a secondary oxygen radical.



Possible reaction mechanism for the formation of **13** and **14.**

Scheme 3

The lack of reactivity in the case of the 15β-hydroxykauranoates could be ascribed either to the difficulty of the reactive in acceding from the β-face to form the hypofluorite or to the difficulty in binding the hypofluorite atom to the hydrogen atoms H-9 or H-11β along with the steric hindrance for a backwards attack of the nucleophilic fluoride complex.

Further studies are in progress to increase the yields and to try to understand the observed stereospecific fluorination with Selectfluor.™

Acknowledgement

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(9) All compounds were fully characterised by ^{1}H and ^{13}C NMR, IR and MS analyses. The relative configuration of the diastereomers **6**, **7**, **10** and **11** was assigned according to the δ_C of the following carbon atoms: C-9 (shielded in **10** and **11**), C-12 (shielded in **6** and **10**), C-15 (shielded in **7** and **10**), C-16 (shielded in **10**), C-17 (deshielded in **11**) and C-20 (shielded in **10**).
(10) *General procedure for the reactions with Selectfluor™:* To a solution of **7** (1.1 g, 3.3 mmol) in dry acetonitrile (50 mL) the reactive (7.3 mmol) was added and the reaction mixture was refluxed under argon atmosphere until dissapearence of the starting material (6 h). The reaction product was purified by column chromatography on silica gel with hexane/EtOAc mixtures as eluent and pure ketones **9** (173 mg) and **14** (58 mg) were isolated. Ketone **9**: mp 160-162°C; $[\alpha]_D^{23}$= – 107 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.64 (s, OMe), 2.29 (br d, *J* = 11.6 Hz, H-14), 1.16 (s, Me-18), 1.06 (d, *J* = 7.6 Hz, Me-17), 0.88 (s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 225.7 (C-15), 177.8 (C-19), 56.0 (C-5), 52.9 (C-8), 51.2 (C-9), 50.8 (OMe), 46.6 (C-16), 43.7 (C-4), 39.9 (C-10), 39.8 (C-1), 37.9 (C-14), 37.3 (C-13), 35.3 (C-7), 34.1 (C-3), 30.2 (C-12), 28.7 (C-18), 20.4 (C-6), 18.3 (C-2), 18.2 (C-11), 15.8 (C-17), 15.3 (C-20); MS (EI, 70 eV) *m/z* (%)= 332 (5) [M^+], 289 (3) [M^+–COMe], 274 (20) [M^+–CO_2Me], 121 (50), 107 (40), 91 (52), 79 (80), 55 (100). Fluoroketone **14**: mp 206-209ûC; $[\alpha]_D^{23}$= – 53 (c = 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.54 (dd, $^{3}J_{7,6}$ = 4.0 Hz; $^{2}J_{7,F}$ = 54.0 Hz, H-7), 3.65 (s, OMe), 1.17 (s, Me-18), 1.13 (d, *J* = 7.5 Hz, Me-17), 0.92 (s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 221.4 (C-15), 177.8 (C-19), 92.7 (d, $^{1}J_{C,F}$ = 180 Hz, C-7), 53.5 (C-8), 51.3 (OMe), 47.7 (C-5), 46.8 (C-9), 46.7 (C-16), 43.1 (C-4), 39.6 (C-1), 39.4 (C-10), 37.6 (C-14), 37.1 (C-13), 33.2 (C-3), 30.4 (C-12), 28.4 (C-18), 27.3 (C-6), 18.8 (C-2), 17.9 (C-11), 15.9 (C-17), 15.4 (C-20); MS (EI, 70 eV) *m/z* (%) = 330 (4) [MH^+–F], 290 (7) [MH^+–CO_2Me], 273 (3), 227 (10), 107 (50), 91 (54), 79 (53), 59 (52), 55 (100).
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