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Preparation of 9α-Fluorinated Sesquiterpenic Drimanes and Evaluation of Their Antifeedant Activities

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The preparation of 9α-fluoro analogues of both natural and unnatural drimane-type sesquiterpenes is described. Their synthesis began with the initial preparation of methyl 8-keto-12-nordriman-11-oate from β-ionone and entailed the electrophilic fluorination of C-9 for the stereoselective introduction of the fluorine atom. The drimane skeleton was completed from the intermediate 9α-fluoro-8-keto-12-nordrimane system by means of different reactions at the C-8 ketone carbonyl group, essentially Wittig methylenation, cyanohydrin formation or palladium-catalysed carbonylation of the corresponding enol triflate. Further manipulation of the functionalization derived from these key reactions allowed the preparation, among others, of 9α-fluorodrimanes, which are structurally and functionally related to albicanic acid, drimenin and olepupuane. Also described are the reactivities of some of the fluorine-containing systems prepared and a comparative study of the antifeedant activities of a selection of 9α-fluorodrimanes and the corresponding hydrogen analogues against several insect species with different feeding ecologies (*Spodoptera littoralis*, *Myzus persicae* and *Rhopalosiphum padi*), which revealed a significant increase in the antifeedant activities of some of the fluorinated drimane analogues.

Introduction

Fluorinated compounds are very rare in nature and, in contrast to other halogens found in many products isolated from natural sources, fewer than 20 naturally occurring fluorinated organic compounds have been isolated.[1] This contrasts with the very large number of non-natural fluorinated compounds that have been synthesized, particularly in the agrochemical and pharmaceutical fields. In fact, as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine.[2] This growing interest in fluorinated compounds is primarily motivated by the unique influence of the fluoro substituent on the chemical, physical and biological properties of these compounds.[3] In general, the fluorine atom is considered bioisosteric with both the hydrogen atom and the hydroxy group such that their replacement by a fluorine atom does not change the molecule's shape very much, exerting only a minor demand at receptor sites, at least for monofluoro analogues.[4] On the other hand, and owing to the peculiar characteristics of the fluorine atom, fluorine substitution affects the internal electronics of the molecule and can substantially alter its physiochemical properties. However, the analysis and even interpretation of this effect is not easy because fluorine produces different types of electronic effects which, depending on the situation, may compensate or reinforce each other. This situation is aptly described in an article by Schlosser on the effects of fluorine on OH, NH and CH acidities: "*Fluorine leaves nobody indifferent: it inflames emotion, be that affections or aversions. As substituent it is rarely boring, always good for a surprise, but often completely unpredictable*".[5]

Over the last few years there has been a growing interest in the synthesis of fluorine-containing analogues of natural products and a large number of fluorinated natural products with biological significance such as amino acids,[6] peptides,[7] glycosides,[8] nucleosides,[9] lipids,[10] oligosaccharides,[11] steroids,[12] prostaglandins,[13] vitamins,[14] antibiotics,[15] pheromones[16] alkaloids[17] and others[18] have been synthesized and some have subsequently been developed as pharmaceuticals and are marketed, registered or at the clinical development stage.[19] Also, a relatively significant number of fluoro derivatives of bioactive terpene-type compounds have bee reported and in many cases these show an increase in activity with respect to the corresponding hydrogen analogue. Although fluoro derivatives of practically all classes of terpenes, from mono- to triterpenes,[20] have been described, most of this research has focused on the preparation of fluorinated analogues of sesquiterpene-type compounds such as artemisinin and structurally related antimalarial compounds.[21]

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Drimanes are one of the main groups of sesquiterpenes with structures based on the hypothetical drimane skeleton **1** (Figure 1).[22] These compounds seem to play an important ecological role and some of them exhibit potentially useful biological activities, including antiviral [influenza A (H1N1)], anti-inflammatory, cytotoxic and, particularly, antifeedant properties.[23] This activity has been associated in most cases with the presence of a 1,4-dialdehyde moiety at C-11 and C-12, either as an actual aldehyde group or as a latent aldehyde existing as a γ-butenolide or furan ring. Representative biologically active examples of this type of sesquiterpene are albicanic acid (**2**) and the related albicanol (**3**), albicanyl acetate (**4**) and albicanal (**5**), polygodial (**6**), warburganal (**7**), cinnamolide (**8**), drimenin (**9**) and olepupuane (**10**; Figure 2).

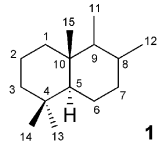

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Figure 1. Drimane skeleton.

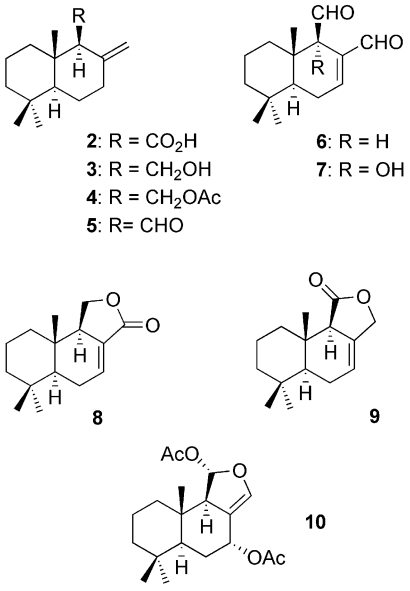
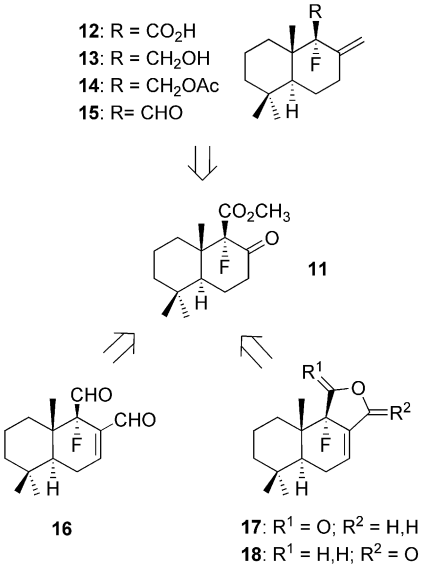


Figure 2. Representative biologically active natural drimanes.

In this article we describe the preparation of some C-9 fluoro analogues of the above-mentioned drimanes. As is the case for other closely related systems,[24] the biological activity of drimanes is generally enhanced by the presence of polar groups (i.e., OH, OAc, etc.) in the vicinity of the dialdehyde or butenolide moieties, a circumstance that may perhaps be due to a more favourable interaction with receptors. Therefore, we were interested in investigating how the modification of the 9-position in the drimane framework with a fluorine atom could influence their chemical and biological activity. In this work we have prepared C-9 fluoro analogues of several natural drimanes and other related non-natural ones and evaluated their antifeedant activity. Details of the work are given in the following sections of this article, including the change in the reactivity of some of these systems produced by the presence of the fluorine atom. A partial preliminary communication of this work has already been published.[25]

Results and Discussion

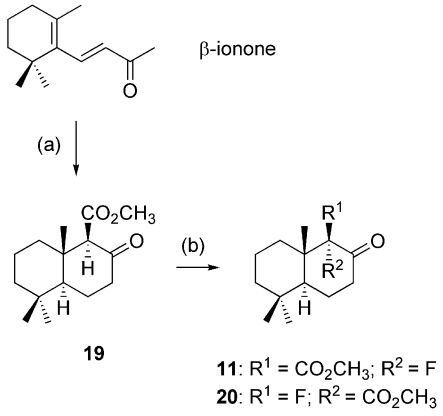
Much work has been carried out on the synthesis of drimanes.[26] The most common synthetic strategy for the preparation of the drimane skeleton is based on the use of a decalone system as the source of the AB rings into which the rest of the carbon atoms required to complete the drimane framework are incorporated. We followed the same strategy for the preparation of the 9α-fluorodrimanes, the syntheses of which begin with the initial preparation of the fluorodecalone **11** (Scheme 1). This decalone possesses a 12-nordrimane skeleton and, in principle, an appropriate functionalization for the ready elaboration of the different target fluorinated drimanes.



Scheme 1. 9α-Fluorodrimanes that could potentially be synthesized from decalone **11**.

Preparation of Fluorodecalone 11

Synthesis of the fluorodecalone **11** started with the initial preparation of non-fluorodecalone analogue **19** (Scheme 2). Different synthetic approaches to the preparation of the bicyclic system of this decalone have been described in the literature.[27] In this work we used the procedure based on the use of β-ionone as the starting material, which is transformed into decalone **19** through a three-step sequence involving Bu_3SnH regioselective hydrogenation to dihydro-β-ionone followed by methoxycarbonylation and stereoselective stannic chloride catalysed cyclization with an overall yield of 60%.[28]



Scheme 2. Reagents and conditions: (a) i. Bu_4SnH, AIBN, 80 °C (99%); ii. NaH, $(MeO)_2C{=}O$, dioxane, 105 °C (86%); iii. $SnCl_4$, CH_2Cl_2, 30 °C (71%); (b) i. NaH, NFSI, THF, room temp., (85% of **11**); ii. Selectfluor®, THF, room temp. (49% of **11** and 16% of **20**).

Hydrogen/fluorine interchange at the C-9[29] position of the decalone system was effected by electrophilic fluorination of the sodium enolate of β-keto ester **19** generated by the treatment of **19** with sodium hydride in THF. The efficiency and stereoselectivity of this electrophilic fluorination reaction depends on the nature of the electrophilic fluorinating agent used.[3b] The best results were obtained with *N*-fluorobenzenesulfonimide (NFSI, Figure 3),[3c] which stereoselectively afforded the fluorodecalone **11** in a yield of 85%. Use of the fluorinating reagent Selectfluor®[3d] furnished a 3:1 mixture of 9-epimeric fluorodecalones **11** and **20**, respectively, in a combined yield of 65% after their chromatographic separation. The stereochemistry at C-9 in decalones **11** and **20** was assigned on the basis of their spectroscopic data. Of particular relevance were the intense cross-peaks observed in the ^1H–^{19}F HOESY (Heteronuclear Overhauser Enhancement Spectroscopy) spectra of **11** between the fluorine and the 1α-, 5α- and 7α-hydrogen atoms, which unequivocally confirmed the α orientation (axial disposition) of the fluorine atom. A relatively small but significant shielding (ca. 0.5–1.5 ppm) of C-1, C-5 and C-7 is also observed in the ^{13}C NMR spectrum of **11** relative to the corresponding resonances of **20** due to the *syn* γ-effect of the axial fluorine atom.

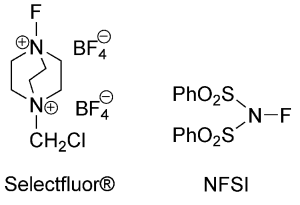
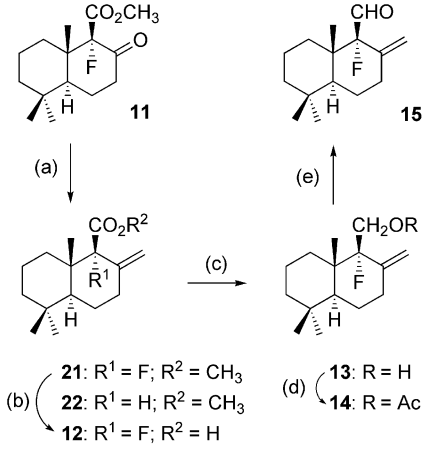


Figure 3. Electrophilic fluorinating reagents.

Elaboration of the Drimane Skeleton: Synthesis of 9α-Fluoroalbicanic Acid (12) and the Related 9α-Fluoroalbicanol (13), 9α-Fluoroalbicanyl Acetate (14) and 9α-Fluoroalbicanal (15)

With the desired fluorodecalone **11** in hand it was possible to complete the construction of the drimane framework by introducing the required additional C-12 carbon atom. One way of doing this was by methylenation of the carbonyl group of **11** by a Peterson or Wittig olefination reaction (Scheme 3). Although the reaction of the carbonyl group of **11** with $TMSCH_2MgCl$ to give the corresponding β-hydroxysilane was very efficient (99%), we could not find the conditions to efficiently induce the elimination of trimethylsilanol under a variety of both acidic and basic conditions or thermally. However, Wittig methylenation took place very efficiently when the ketone **11** was treated with methylidenetriphenylphosphorane in toluene at room temp. to afford the β,γ-unsaturated ester **21** in 85%yield. The influence of the fluorine atom on the reactivity of the carbonyl group is evidenced by the notable difference in reactivity between the fluorinated and non-fluorinated decalone systems (i.e., **11** → **21** vs. **19** → **22**), which may be attributed, at least partially, to the lowering of the LUMO energy of the π–CO bond produced by the fluorine atom.[30,31]

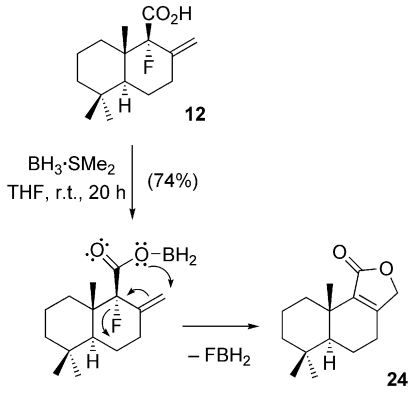


Scheme 3. Reagents and conditions: (a) Ph_3PCH_3Br, KHMDS, CH_3Ph, room temp., 2 h (85%); (b) NaH, PrSH, DMF, 80 °C, 2 h (87%); (c) $LiAlH_4{\cdot}2THF$, CH_3Ph, –40 °C (99%); (d) Ac_2O, DMAP, Py, room temp., 1.5 h, (95%); (e) DMP-py, CH_2Cl_2, room temp., 4.5 h (95%).

Several reaction conditions were evaluated for the hydrolysis of the methyl ester **21** to the corresponding carboxylic acid **12** (Scheme 3), the 9α-fluoro analogue of the natural drimane albicanic acid (**2**).[32] The conditions previously described for the hydrolysis of albicanic acid methyl ester (LiI, DMF)[33] failed and gave a complex reaction mixture, as did some of the other procedures assayed.[34] However, the hydrolysis of **21** to **12** was accomplished in good yield by using NaSPr in DMF, but limiting the heating temperature to 80 °C.

Note that although the acid **12** was relatively stable towards nucleophilic and basic reagents, it readily undergoes lactonization with elimination of the fluorine atom

under certain electrophilic conditions. Thus, treatment of **12** with diborane under the usual hydroboration conditions afforded the lactone **24** in 74% yield (Scheme 4). This compound is a naturally occurring drimanic sesquiterpenic lactone known as isodrimenin that was first isolated from the stem bark of the South American *Drimys* species[35] and exhibits significant feeding inhibition activity.[36] The formation of **24** in the above reaction represents an apparently intramolecular S_N2' process involving a disfavoured 5-*endo*-trig cyclization reaction. Although this type of cyclization is contrary to the generally accepted Baldwin rules, there are some examples in the literature of somewhat related anti-Baldwin cyclization reactions.[37] Comparatively, however, the above-mentioned 5-*endo*-trig process takes places under much milder reaction conditions.



Scheme 4. 5-*endo*-*trig* lactonization of 9α-fluoroalbicanic acid (**12**).

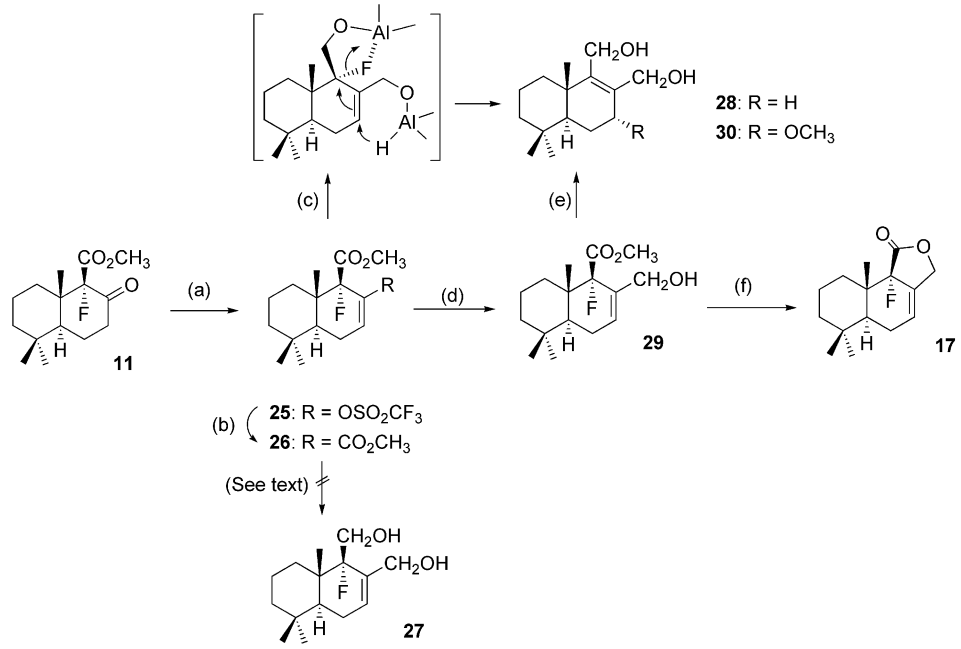
The 9α-fluoro analogues of other biologically active drimanes structurally related to albicanic acid were readily prepared from the ester **21** (Scheme 3). Thus, $LiAlH_4$ reduction of the ester moiety of **21** took place readily at low temperature to afford **13**, the 9α-fluoro analogue of the cytotoxic and potent fish antifeedant albicanol (**3**).[38] This latter compound can also be prepared by $LiAlH_4$ reduction of methyl albicanate (**22**), although higher temperatures were required in this case due to the significantly decreased reactivity of the ester moiety of this compound with respect to **21**. Acetylation of **13** under standard conditions gave **14**, the 9α-fluoro analogue of the also natural albicanyl acetate (**4**).[39] On the other hand, several conditions were examined for the conversion of 9α-fluoroalbicanol (**13**) to the corresponding aldehyde. The best results were obtained with the Dess–Martin periodinane reagent or tetrapropylammonium perruthenate (TPAP), which afforded an excellent yield of the relatively unstable drimanic aldehyde **15**, the 9α-fluoro analogue of albicanal (**5**).[40] The oxidation of **13** was significantly slower in comparison with the oxidation of albicanol (**3**) to albicanal (**5**). This is consistent with the mechanism suggested for this oxidation reaction and the slower formation rate of the perruthenate ester intermediate due to the lower nucleophilicity of the fluorinated alcohol.[41]

Alternative Elaboration of the Drimane Skeleton: Preparation of 9α-Fluorodrimenin (17)

In principle, a simple procedure for the elaboration of the 9α-fluorodrimane skeleton of some of the initial synthetic targets could imply the preparation of diester **26** from decalone **11** (Scheme 5), a strategy that has been used successfully for the preparation of functionally related natural compounds.[42] Following this approach, the decalone **11** was converted into the corresponding enol triflate **25** by treatment with potassium hexamethyldisilazane (KHMDS) at –78 °C and trapping of the enolate with *N*-phenyltriflamide. The enol triflate **25** was obtained in a yield of 70% after chromatography. The use of other bases or triflating agents such as triflic anhydride or Comins' reagent[43] was either totally unsuccessful or lower-yielding. The triflate thus obtained underwent palladium-catalysed carbonylation as described by Stille and co-workers[44] to give the methyl diester **26** in a yield of about 65%.

With diester **26** in hand we evaluated its transformation into the fluorinated diol **27** by reduction of the two ester moieties. This compound may be considered an appropriate intermediate for the preparation of the 9α-fluoro analogues of polygodial (**16**), drimenin (**17**) and cinnamolide (**18**). In fact, these natural compounds have been successfully prepared from the corresponding hydrogen analogue diol.[45,46] However, treatment of diester **26** with several reducing agents under a variety of conditions did not lead to the desired fluorinated diol **27**. Thus, treatment of **26** with $LiAlH_4$ at –78 °C exclusively afforded defluorinated diol **28**, a process that probably occurs by the previous reduction of both methoxycarbonyl groups to the corresponding methyleneoxyaluminium moieties followed by aluminium-assisted S_N2' elimination of the fluoride ion by inter- or, most probably, intramolecular hydride transfer (see Scheme 5).[47] The course of this reduction reaction contrasts with the result obtained in the above-mentioned reduction of ester **21** to alcohol **13** (see Scheme 3), which proceeded without detectable elimination of fluorine. On the other hand, reduction of the C-12 methoxycarbonyl moiety could only be achieved, albeit in low yield (30%), by treatment of **26** with 3–5 equiv of DIBAL-H in THF/cyclohexane at –78 °C for 4 h. In addition to the hydroxy ester **29**, the reaction also produced the diol **28** and recovered the starting diester, each one in a yield of around 30%. All attempts to improve the conversion of diester **26** to the hydroxy ester **29** under various conditions were unsuccessful. Longer reaction times or higher temperatures reduced the yield of **29** and gave larger amounts of diol **28**.

Not surprisingly, all attempts to reduce the methoxycarbonyl group of **29** to **27** were also unsuccessful. For example, reduction with $LiAlH_4$ under several conditions gave only diol **28**, whereas reduction with $LiBH_4$ in MeOH[48] afforded the methoxy diol **30**, a result that clearly shows the propensity of the allyl fluoride moiety of this system to participate in a S_N2' process. Similar results were obtained after derivatization of the hydroxy group of **29** to a methoxymethyl or a trialkylsilyl ether.[49]

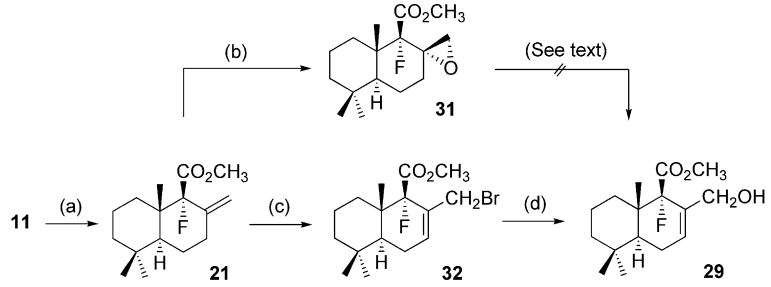


Scheme 5. Reagents and conditions: (a) KHMDS, $PhNTf_2$, THF, –78 °C (70%); (b) $Pd(OAc)_2$, PPh_3, iPr_2NEt, CO, CH_3OH, DMF, 65 °C (65%); (c) $LiAlH_4$, THF, –78 °C (90%); (d) DIBAL-H, THF/C_6H_{12}, –78 °C, (30% of **29** + 30% of **28** + 30% of **26**); (e) for **28**: $LiAlH_4$, CH_3Ph, –40 °C (83%); for **30**: $LiBH_4$, THF, MeOH, 65 °C, 1 h (65%); (f) DBU, 3 Å MS, C_6H_6, room temp. (85%).

Although obtained in low yield, the availability of the hydroxy ester **29** allowed the ready preparation of 9α-fluorodrimenin (**17**; Scheme 5), the 9α-fluoro analogue of the bioactive drimane sesquiterpene drimenin (**9**).[36,50] Thus, base-promoted lactonization of hydroxy ester **29** by treatment with 8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temp. in the presence of 3 Å molecular sieves afforded 9α-fluorodrimenin (**17**) in a yield of 85%.

The low yield obtained for allylic alcohol **29** prompted us to investigate an alternative route to improve the overall yield of 9α-fluorodrimenin from decalone **11**. We first tried to transform the *exo*-methylene compound **21** into **29** by epoxidation/epoxide ring-opening reactions (Scheme 6) as the same transformation has been described in the literature for the non-fluorinated analogue.[51] Epoxidation of the double bond of **21** was effected with *m*-chloroperbenzoic acid (MCPBA) under standard conditions, although due to the withdrawing effect of the allylic fluorine atom the reaction was considerably slower than the epoxidation of the corresponding non-fluorinate olefin. The smooth epoxidation reaction of **21** took place stereoselectively from the less hindered α face of the *exo*-methylene double bond to give the epoxide **31** in high yield (Scheme 6). The stereochemistry of epoxide **31** was confirmed by NOE experiments in which irradiation of the signal at δ = 3.41 ppm (12-H) gave enhancement of the signal at δ = 1.12 ppm, which corresponds to the axially disposed methyl group at C-10.

However, this epoxide proved to be thermally and chemically very stable and all attempts to promote the opening of the epoxide moiety to the allylic alcohol under acid (PTSA, toluene, reflux), basic (R_2NAlEt_2, benzene, room temp.) or even radical (Cp_2TiCl, benzene, room temp.) reaction conditions failed, the starting material being recovered unaltered under all the conditions assayed.[49] After these unsuccessful attempts to transform the *exo*-methylenic compound **21** into allylic alcohol **29**, this conversion was achieved quite efficiently by the sequence of allylic bromination/bromine substitution reactions. Thus, reaction of olefin **21** with *N*-bromosuccinimide (NBS) in a MeOH/CH_2Cl_2 medium re-



Scheme 6. Reagents and conditions: (a) as shown in Scheme 3, step a; (b) MCPBA, CH_2Cl_2, room temp., 20 h (82%); (c) NBS, CH_2Cl_2/CH_3OH, room temp. (75%); (d) $AgBF_4$, 2,6-lutidine, acetone/H_2O, 60 °C (85%).

gioselectively afforded the allyl bromide **32** in a yield of 75%. The required substitution of the bromine atom by a hydroxy group was not as easy as initially thought and most of the usual procedures used for the halogen/hydroxy exchange afforded only low yields of the allylic alcohol. Fortunately, treatment of allyl bromide **32** with silver tetrafluoroborate ($AgBF_4$) and 2,6-lutidine in a mixture of acetone/water at 65 °C satisfactorily furnished the desired allyl alcohol **29** in an excellent yield of 85%.[52] The preparation of **29** from decalone **11** by this route is considerably more efficient than the former, with an overall yield of 45% compared with about 15% for the former route.

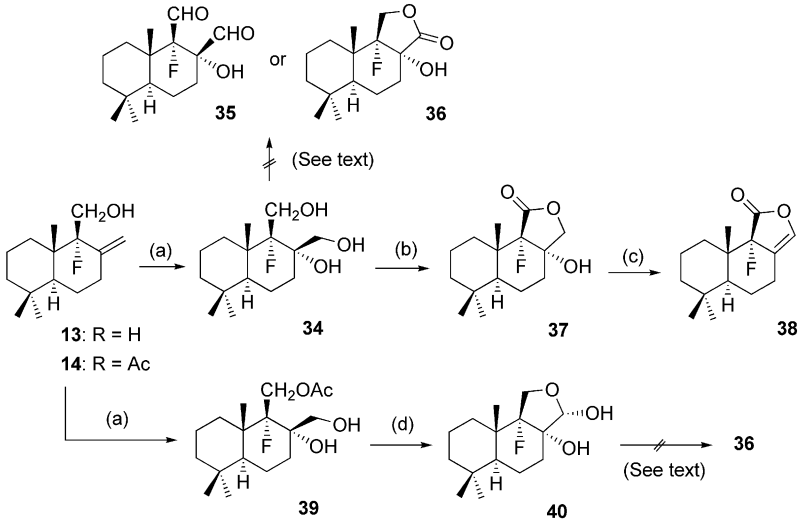
Preparation of Other 9α-Fluorodrimanes

We also undertook some additional transformations focusing on the preparation of other fluorinated drimanes including two of the initial targets, 9α-fluoropolygodial (**16**) and 9α-fluorocinnamolide (**18**; see Scheme 1). Unfortunately, the synthesis of these latter compounds could not be completed satisfactorily due to the "unexpected" effect produced by the fluorine atom on the reactivity of some key intermediates of their synthesis. This section briefly describes several of these transformations, some of which illustrate the difficulty of predicting the precise influence of fluorine on the reactivity of neighbouring functional groups.

One of these approaches begins with the hydroxylation of the previously obtained 9α-fluoroalbicanol (**13**; Scheme 7). The *cis*-hydroxylation of the double bond of **13** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant proceeded stereoselectively from the less hindered side to afford the triol **34** in a yield of 85%. The stereochemistry of **34** was confirmed by the NOE enhancements observed between protons 12-H (irradiated) and CH_3-10 and 7β-H. Attempts to transform **34** into hydroxy dialdehyde **35**, a potential intermediate for 9α-fluoropolygodial, using several Swern oxidation conditions[53] only afforded complex reaction mixtures. Likewise, oxidation with some of the oxidizing reagents used for the oxidation of 1,4-diols to lactones did not give the hydroxy lactone **36**, the 9α-fluoro analogue of the antifungal drimane peniopholide[54] and a potential intermediate for 9α-fluorocinnamolide, but instead afforded the regioisomeric lactone **37**. Thus, oxidation with the Dess–Martin periodinane reagent (DMP) in pyridine at room temperature afforded **37** in a yield of 90%. The tertiary hydroxy group **37** was dehydrated regioselectively to the C8–C12 position by treatment with thionyl chloride in pyridine to give in nearly quantitative yield compound **38**, a 9α-fluorodrimane closely related to several naturally occurring olepupuane-type drimanes.[55]

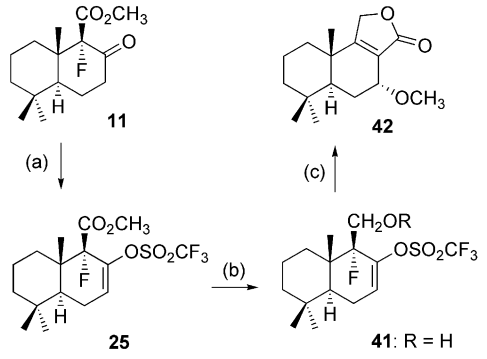
On the other hand, hydroxylation of 9α-fluoroalbicanol acetate (**14**) under the same conditions as described above for **13** gave the corresponding diol **39**. Initial attempts to oxidize the hydroxymethyl group (using, for example, NaOClO, $Me_2CH{=}CHMe_2$, *t*BuOH) to the corresponding carboxylic acid group failed. However, the diol **39** was readily transformed into the hydroxy lactol **40**, structurally and functionally related to some natural drimanes,[56] by oxidation of the hydroxymethyl group to the aldehyde followed by hydrolysis of the acetate group (Scheme 7). Nevertheless, all attempts to oxidize the lactol to the corresponding lactone (i.e., **36**) were unsuccessful. Swern reagent, *N*-iodosuccinimide[57] or silver carbonate/Celite[58] led only to the recovery of the starting material, whereas oxidation with DMP, PCC, Jones′ reagent or TPAP led to cleavage of the glycol moiety to give only the corresponding 11-formyloxy-8-keto derivative (see the Supporting Information).

An alternative approach to 9α-fluorocinnamolide (**18**) based on the method previously described in Scheme 5 for the preparation of 9α-fluorodrimenin (**17**) was also ex-



Scheme 7. Reagents and conditions: (a) OsO_4, NMO, acetone/H_2O, 3 d, room temp. (85% for **34** and 50% for **39**); (b) DMP, Py, room temp., 5 h (90%); (c) $SOCl_2$, Py, CH_2Cl_2, 20 h, room temp. (quantitative yield); (d) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C; ii. KOH, CH_3OH/H_2O, 0.5 h, room temp. (60%).

plored. This approach was initiated with the preparation of enol triflate **25** (Scheme 8), which was transformed into compound **41** by reduction of the ester to a primary alcohol group by treatment with $LiAlH_4$ at low temperature. No S_N2' elimination of fluoride was detected in this case, which is in direct contrast to what was observed in the related reductions of esters **26** or **29**. However, the palladium-mediated carbonylation of enol triflate **41** led to the formation of the expected γ-butyrolactone moiety and also to S_N2' displacement of fluoride by methoxide to afford the methoxy lactone **42**, the methyl ether of 7α-hydroxyconfertifolin, a drimanic lactone isolated from diverse natural sources.[54,59] Derivatization of the hydroxy group in **41** to a methoxymethyl (R = MOM) or triflate group (R = SO_2CF_3) did not circumvent the S_N2' reaction.[49] It is interesting to note that this reaction might involve a previous oxidative addition of the allyl fluoride moiety to Pd^0, a reaction that has yet to be thoroughly studied.[60] It is likely in this case that the intermediate η^3-allylpalladium(II) complex formed is stabilized by the oxygenated function at C-11, which favours the observed reaction. Although useless for the main objective of this work, the approach detailed in Scheme 8 could be of interest to elaborate the type of functionalization present in **42**, which is not only a characteristic of some drimanes but also of other polycyclic terpenes.

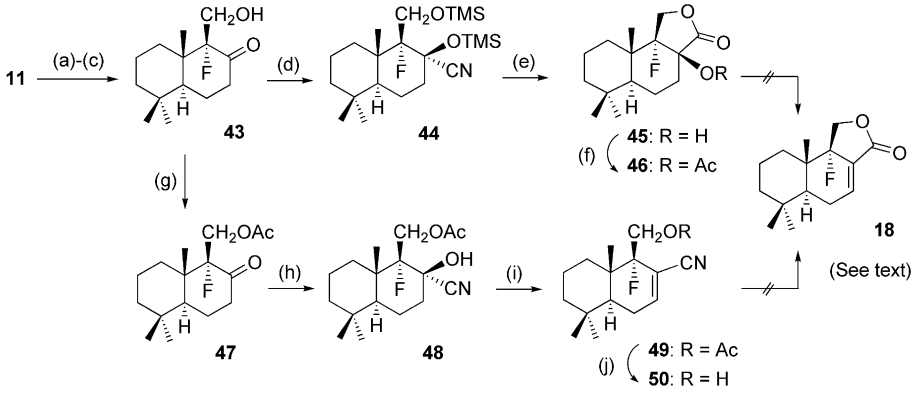


Scheme 8. Reagents and conditions: (a) as shown in Scheme 5, step a; (b) $LiAlH_4$, $PhCH_3$, –50 °C, 1 h (70%); (c) $Pd(OAc)_2$, PPh_3, iPr_2NEt, CO, CH_3OH, DMF, 65 °C, 20 h (75%).

Finally, another approach to the elaboration of the drimane framework was based on the cyanohydrin formation of β-hydroxydecalone **43** (Scheme 9). This decalone has already been prepared from β-keto ester **11** in three steps: formation of the ethylene ketal, reduction of the ester to the primary alcohol and regeneration of the carbonyl group. Treatment of **43** with excess trimethylsilyl cyanide (TMSCN) in the presence of ZnI_2 as catalyst provided the cyanohydrin trimethylsilyl ether **44**. The stereochemistry of the new stereogenic centre generated at C-8 was determined by a NOESY experiment. Significant NOE interactions were observed between the protons of the axially disposed trimethylsilyloxy group at C-8 and protons 11-H and CH_3-10. The trimethylsilyl ether groups of **44** were hydrolysed by mild acid treatment to give an intermediate β-hydroxy cyanohydrin, which cyclized in situ to give the drimanic hydroxy butyrolactone 9α-fluoro-8-epi-peniopholide (**45**)[54] in an overall yield of 85%.

With this compound in hand we then focused on the elimination of the tertiary hydroxy group. We were unable to obtain the elimination product **18** despite trying many different basic dehydration conditions such as $SOCl_2$/Py and DMAP or DBU, $POCl_3$/Py and DBU, MsCl/Et_3N in $ClCH_2CH_2Cl$, Martin's reagent and Burgess's reagent at temperatures that ranged from room temperature to 120 °C. Dehydration under acidic conditions, for example, PTSA/toluene or HCl/AcOH at reflux, also produced disappointing results. In all cases, the starting material was recovered nearly unaltered even after prolonged reaction times. Although the difficulty in promoting the elimination in acidic media could be accounted for on the basis of the strong electron-withdrawing nature of fluorine which destabilizes the partial positive charge generated at C-8, the unusual resistance to dehydration of the axial hydroxy group at C-8 under basic conditions is more difficult to understand. Treatment of **45** with Deoxo-fluor®, a nucleophilic fluorinating reagent, in pyridine at room temperature surprisingly caused the rapid dehydration of the tertiary hydroxy group and the elimination of HF to form 7,9(11)-dien-11,12-drimanolide after 2 h in a yield of 70% (see the Supporting Information). Although Deoxo-fluor® and other related *N*,*N*-dialkylaminosulfur trifluoride reagents are well known as powerful dehydrating agents,[3b] to the best of our knowledge no example of this type of dehydrofluorination reaction has been described in the literature. Attempts to dehydrate the tertiary alcohol by pyrolytic elimination of the corresponding acetate, that is, **46**, were also unsuccessful. Heating the acetate **46** in bulk up to 250 °C did not cause any reaction, but decomposition was observed upon heating at higher temperatures (approximately 270 °C).

In view of the difficulties encountered in the dehydration of hydroxy lactone **45**, we decided to invert the order of the last two steps by first dehydrating the hydroxy group and then subjecting the resulting unsaturated nitrile to lactonization (Scheme 9). Acetylation of the hydroxy group of **43** under standard conditions gave the β-acetoxydecalone **47**, which was converted into cyanohydrin **48** in an overall yield of about 83% by successive treatment with TMSCN/ZnI_2 and the HF/pyridine complex (Olah's reagent). Although initial experiments focusing on the elimination of the hydroxy group failed, it was eventually found that treatment of **48** with thionyl chloride in pyridine at room temperature for 4–5 h followed by very slow heating to 80 °C (ca. 4 h) and maintaining that temperature for a period of about 15 h provided the desired unsaturated nitrile **49** in an isolated yield of 90%. Hydrolysis of the acetate moiety of **49**, required for the subsequent lactonization step, was also more difficult than expected. Typical hydrolysis conditions, either acidic or basic, were unsuccessful leading to intractable mixtures. Even conditions that usually afford very easy hydrolysis, such as those involving the treatment of **49** with 3 equiv. of K_2CO_3 in MeOH/H_2O (3:2) at room temperature for 20 min or 3 equiv. of LiOH in THF/H_2O (2:1) at



Scheme 9. Reagents and conditions: (a) $(CH_2OH)_2$, PTSA, $PhCH_3$, reflux, 24 h (90%); (b) $LiAlH_4$, $PhCH_3$, –40 °C, 1 h (92%); (c) PTSA, acetone/H_2O, 55 °C, 4 h (89%); (d) TMSCN, ZnI_2, CH_2Cl_2, room temp., 15 h (76%); (e) PTSA, THF/H_2O, 55 °C, 20 h (85%); (f) Ac_2O, Py, 80 °C, 3 d (55%); (g) Ac_2O, Py, room temp., 2.5 h (99%); (h) i. TMSCN, ZnI_2, CH_2Cl_2, room temp., 5 h; ii. HF–Py, THF, room temp., 18 h (83% overall yield for the two steps); (i) $SOCl_2$, Py, see text, (90%); (j) DIBAL-H (2 equiv.), THF, –78 °C, 30 min then DIBAL-H (2 equiv.), THF, –78 °C, 1 h (97%).

room temperature overnight, led to a complex mixture in which only traces of the corresponding alcohol could be detected by TLC. Finally, and after much experimentation, we found that the transformation of **49** into hydroxy nitrile **50** could be achieved satisfactorily by reduction of the acetate moiety with DIBAL-H under quite specific, very mild conditions (see the Exptl. Sect.).

Having prepared **50**, its transformation to target 9α-fluorocinnamolide (**18**) seemed simple because, in addition to the related transformation of **44** into **45** described above, this type of lactonization has been described in the literature for non-fluorinated β-hydroxy nitriles.[61] However, all attempts to lactonize **50** failed. Reaction in neither acidic nor basic media produced any satisfactory results.

Evaluation of Antifeedant Activity

A comparative study of the antifeedant activities of a selection of the fluorinated compounds prepared above and the corresponding hydrogen analogues against several insect species with different feeding ecologies (*Spodoptera littoralis*, *Myzus persicae* and *Rhopalosiphum padi*) was carried out and the results are shown in Table 1. The fluorinated 12-nordrimane **11** and the non-fluorinated drimane **22** (see Scheme 3) showed sufficient antifeedant activity against *S. littoralis* to carry out dose-response experiments [percent feeding reduction (%FR) > 65], whereas **19** and **51** (the epoxidation product of methyl albicanate) had significant moderate effects, with activity levels similar to polygodial (**6**).[62] The effective antifeedant doses calculated for the four compounds were quite similar (EC_{50} values between 3.6 and 4.0 μg/cm^2). Most of the compounds tested had significant effects ($p < 0.05$, Wilcoxon signed rank test) on the settling behaviour of both aphid species. Fluorinated compounds **17** and **49** were very active against both aphid species, **31** only acted on *R. padi* [percent settling inhibition (%SI) ≥ 80], whereas **4** was moderately active on *M. persicae* (%SI = 74). Overall, *R. padi* was more sensitive to the active compounds than *M. persicae*. These three fluorinated compounds had similar or better antisettling activity towards *R. Padi* than polygodial, but with significantly narrower confidence levels.[62] Furthermore, none of these compounds exhibited phytotoxic effects when applied to the leaf surface.

The activities of these sesquiterpenes was species-dependent, as previously shown for other drimane-type compounds, including polygodial.[62] Family- and/or species-related differences in the drimane molecular target have been suggested.[63]

Several structure–activity trends can be deduced from the antifeedant effect of the test compounds on *R. Padi*. In general, fluorination of the C-9 position decreased the activity of compounds with an 8(12)-*exo*-methylene double bond (**13**, **14** and **21** vs. **3**, **4** and **22**, respectively) and increased the activity of compounds with a carbonyl group at C-11 (**11**, **17** and **31** vs. **19**, **9** and **51**, respectively), especially for 9α-fluorodrimenin (**17**) and epoxide **31**. The strong antisettling activity of **49** could be related to the Michael-type addition reactivity of the α,β-unsaturated nitrile moiety. A similar positive effect produced by the fluorine atom could be observed for the activity of the fluorinated analogues of albicanol and drimenin (**13** and **17** vs. **3** and **9**, respectively) on *M. persicae*. In contrast, *S. littoralis* was generally more sensitive to the non-fluorinated analogues. Similarly, previous results have shown the importance of the C-9 substituents on the antifeedant effects of drimanes.[62,63]

Oral cannulation of *S. littoralis* L6 larvae showed that the non-fluorinated derivatives **19** and **51** were moderate post-ingestive antifeedants whereas the fluorinated derivative of **19** (i.e., **11**) was toxic (pANCOVA2 < 0.05, see the Supporting Information). Post-ingestive effects against this insect have been reported for 3β-hydroxycinnamolide and 3β-acetoxydrimenin[64] and suggested for synthetic analogues (lactones) of polygodial (**6**) and warburganal (**7**) on *Pieris brassicae* and *L. decemlineata* larvae.[63] However, **6** did not affect orally injected *S. littoralis*.[62]

Table 1. Antifeedant activity [expressed as mean ± SE values of % feeding reduction (FR) and % settling inhibition (SI)] of 9α-fluoro compounds **11**, **13**, **14**, **17**, **21**, **31**, **45**, **47** and **49** and the corresponding 9α-hydrogen analogues on *S. littoralis* larvae and *R. padi* and *M. persicae* adults.

Spodoptera littoralis (%FR)[a]				*Rhopalosiphum padi* (%SI)[b]				*Myzus persicae* (%SI)[b]			
9αF compound		9αH analogue		9αF compound		9αH analogue		9αF compound		9αH analogue	
11	66.8 ± 8.9,[c] (3.6 ± 1.2)[d]	**19**	63.6 ± 10.4[c]	**11**	60.7 ± 5.5[c]	**19**	54.2 ± 7.0[c]	**11**	51.8 ± 10.7[c]	**19**	63.6 ± 7.0[c]
13	14.2 ± 5.3	**3**	40.4 ± 10.8	**13**	61.5 ± 9.7[c]	**3**	63.8 ± 8.2[c]	**13**	63.2 ± 5.5[c]	**3**	52.3 ± 11.0[c]
14	33.9 ± 12.2	**4**	63.5 ± 4.2[c]	**14**	56.9 ± 7.3[c]	**4**	74.0 ± 7.1[c]	**14**	37.0 ± 9.1	**4**	54.7 ± 6.9[c]
17	52.4 ± 17.4	**9**	53.9 ± 8.3	**17**	90.0 ± 1.9,[c] (1.8 ± 0.4)[d]	**9**	59.3 ± 9.7[c]	**17**	73.2 ± 9.3[c]	**9**	37.4 ± 6.9
21	37.2 ± 11.8	**22**	73.7 ± 8.8,[c] (3.9 ± 1.3)[d]	**21**	30.9 ± 10.0	**22**	51.7 ± 8.[c]	**21**	41.7 ± 9.1	**22**	56.7 ± 7.9[c]
31	41.61 ± 1.8	**51**[e]	63.2 ± 10.2[c]	**31**	89.3 ± 2.9,[c] (2.3 ± 0.3)[d]	**51**[e]	39.7 ± 8.7	**31**	47.3 ± 8.9[c]	**51**[e]	41.6 ± 9.5
45	38.9 ± 13.6	–	–	**45**	51.2 ± 8.7[c]	–	–	**45**	47.0 ± 8.7[c]	–	–
47	32.8 ± 11.8	–	–	**47**	40.7 ± 8.3[c]	–	–	**47**	40.8 ± 9.2	–	–
49	39.1 ± 7.7	–	–	**49**	79.9 ± 4.6,[c] (2.9 ± 0.5)[d]	–	–	**49**	71.5 ± 7[c]	–	–

[a] Feeding reduction as a percentage (FR) = $[1 - (T/C)] \times 100$[65] in which T = consumption of treated discs and C = consumption of control discs (n = 10 replicates). 100% indicates no consumption on treated leaf discs.[66] [b] Settling inhibition as a percentage (SI) = $[1 - \%T/\%C] \times 100$[67] in which $\%T$ = aphids settled on treated leaves and $\%C$ = aphids settled on control leaves (n = 20 replicates). [c] $p < 0.05$ (Wilcoxon signed rank test). [d] EC_{50} = effective dose (μg/cm^2) required to give a 50% feeding or settling inhibition (given at a 95% confidence level). [e] **51**: Methyl 8α(12)-epoxyalbicanate (see ref.[68]).

In the light of the above results it is safe to conclude that, in general, fluorination of the 9α-position produces a positive effect on the antifeedant activity of the drimane compounds against aphids. The presence of the fluorine atom at C-9 together with a double bond at C7–C8, either as such, as in **17** and **49**, or in a latent form, as in epoxide **31**, confers a considerable antifeedant activity on these molecules against both aphid species. On the other hand, compounds with a double bond between C-8 and C-12 also exhibit good activity, although in this case the presence of the fluorine atom has a detrimental effect on the antifeedant activity. In contrast, the antifeedant response of polyphagous *S. littoralis* larvae to these compounds indicates that the introduction of the fluorine atom on the drimane system resulted in a decrease in activity.

Conclusions

A synthetic approach for the elaboration of the 9α-fluorodrimane framework has been developed. This approach is based on the previous preparation of methyl 8-keto-12-nordriman-11-oate from β-ionone and involves the electrophilic fluorination of C-9 to stereoselectively introduce the fluorine atom. The drimane skeleton is completed from the intermediate 9α-fluoro-8-keto-12-nordrimane system by different reactions at the C-8 ketone carbonyl group, essentially Wittig methylenation, cyanohydrin formation or palladium-catalysed carbonylation of the corresponding enol triflate. Appropriate manipulation of the functionalization of the systems derived from these key reactions has allowed the preparation of 9α-fluorodrimanes structurally and functionally related to natural albicanic acid, drimenin, olepupuane and other 9α-fluorodrimane-type compounds.

A comparative study of the antifeedant activities of a selection of the fluorinated compounds prepared and the corresponding hydrogen analogues against several insect species has shown that fluorination of the 9α-position produces a positive effect on the antifeedant activity of the drimane-type compounds against aphids, particularly in the case of a double bond at C7–C8 conjugated with an electron-withdrawing group at C-12 (compound **49**), probably as a result of the enhanced Michael-type addition reactivity of the conjugate moiety.

These results also suggest that an increase in biological activity, particularly but not exclusively antifeedant, might occur with the fluorination of other higher terpenic systems structurally and functionally related to drimanes such as spongianes and scalaranes. This will be the subject of a further investigation in our laboratory.

Experimental Section

General: Except when specified otherwise, the TLC R_f values are given for a hexane/ethyl acetate (8:2) system. General experimental procedures and the details of the preparation and characterization of compounds **3**, **4**, **9**, **19**, **20**, **22**, **24**, **28**, **30**, **41**–**43**, **46**, **51** and the product formed from the reaction of **45** with Deoxo-fluor® are given in the Supporting Information.

(±)-Methyl 9α-Fluoro-8-oxo-12-nordriman-11-oate (11): A solution of β-keto ester **19** (2.56 g, 10.16 mmol) in anhydrous THF (10 mL) was added dropwise into a suspension of NaH (60% dispersion in mineral oil, 447 mg, 11.17 mmol, 1.1 equiv., prewashed with pentane) at 0 °C under argon. After 30 min of stirring at this temperature the reaction mixture was warmed to room temp. and stirred for 2 h. Then, a solution of NFSI (3.96 g, 12.19 mmol, 1.2 equiv.) in THF (20 mL) was added through a syringe.[3c] After stirring for 2 h at room temp., the reaction was quenched with water and worked up as usual using Et_2O to extract. The product was purified by chromatography (hexane/Et_2O, 8:2, as eluent) to give the 9α-fluoro-β-keto ester **11** (2.33 g, 85%) as a white solid. TLC: R_f = 0.44; m.p. 82–83 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}_{max}$ = 2950, 2927,

2867, 2848, 1751, 1716, 1633, 1600, 1459, 1434, 1380, 1348, 1195, 1166, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CO_2CH_3), 2.80 (dddd, J = 10.8, 10.8, 5.4, 5.4 Hz, 1 H, 7α-H), 2.47 (dddd, J = 10.8, 3.6, 1.8, 1.8 Hz, 1 H, 7β-H), 1.98 (m, 1 H, 6-H), 1.94 (m, 1 H, 5-H), 1.68 (m, 1 H, 6-H′), 1.64 (m, 1 H, 1-H), 1.60 (m, 1 H, 2-H), 1.52 (m, 1 H, 2-H′), 1.42 (m, 1 H, 3-H), 1.30 (m, 1 H, 3-H′), 1.22 (m, 1 H, 1-H′), 1.17 (s, 3 H, 15-H), 0.98 (s, 3 H, 13-H), 0.90 (s, 3 H, 14-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (d, J = 3.5 Hz, C-15), 18.1 (C-2), 21.9 (C-14), 22.3 (C-6), 32.6 (C-1), 33.5 (d, J = 5.4 Hz, C-13), 34.4 (C-4), 37.9 (d, J = 2.7 Hz, C-7), 41.1 (C-3), 44.4 (d, J = 5.6 Hz, C-5), 45.0 (d, J = 18.4 Hz, C-10), 52.3 (CO_2CH_3), 100.4 (d, J = 196.7 Hz, C-9), 165.7 (d, J = 25.6 Hz, C-11), 202.3 (d, J = 25.3 Hz, C-8) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –162.0 (s) ppm. MS (EI): m/z (%) = 270 (12) $[M]^+$, 252 (16), 237 (7), 217 (2), 203 (6), 179 (4), 163 (6), 137 (100), 123 (36), 109 (14), 95 (24), 69 (39), 55 (26). HRMS: calcd. for $C_{15}H_{23}FO_3$ 270.163123; found 270.162143.

(±)-9α-Fluoro-8(12)-drimen-11-oic Acid (9α-Fluoroalbicanic Acid, 12): A solution of ester **21** (40 mg, 0.15 mmol) in anhydrous DMF (1 mL) was added to a solution of sodium propanethiolate in DMF, generated by reaction of NaH (60% dispersion in mineral oil, 53 mg, 1.32 mmol, 9 equiv., prewashed with pentane) and propanethiol (135 μL, 1.48 mmol, 10 equiv.) in DMF (3 mL), at room temp. under argon.[69] The mixture was stirred at 80 °C for 2 h, cooled to 0 °C and treated with dilute aqueous HCl. Work-up as usual using EtOAc to extract followed by evaporation of the solvent afforded nearly pure 9α-fluoroalbicanic acid (**12**;33 mg, 87%) as an amorphous solid. TLC: R_f = 0.04. IR (NaCl): $\tilde{\nu}_{max}$ = 3113, 2934, 2864, 1719, 1630, 1455, 1431, 1386, 1117, 1062 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.08 (s, 1 H, COOH), 5.10 (dd, J = 4.2, 1.6 Hz, 1 H, 12-H), 5.04 (br. s, 1 H, 12-H′), 2.42 (m, 1 H, 7-H), 2.33 (m, 1 H, 7-H′), 1.72 (m, 1 H, 5-H), 1.65 (m, 1 H, 6-H), 1.60 (m, 1 H, 1-H), 1.60–1.47 (m, 2 H, 2-H), 1.41 (m, 1 H, 6-H′), 1.37 (m, 1 H, 3-H), 1.31 (m, 1 H, 1-H′), 1.18 (m, 1 H, 3-H′), 1.14 (s, 3 H, 15-H), 0.90 (s, 3 H, 13-H), 0.86 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (d, J = 2.8 Hz, C-15), 18.4 (C-2), 21.9 (C-14), 22.0 (C-6), 31.9 (C-7), 32.9 (C-1), 33.3 (C-4), 33.6 (C-13), 41.3 (C-3), 42.5 (d, J = 19.3 Hz, C-10), 45.4 (d, J = 4.8 Hz, C-5), 101.5 (d, J = 184.2 Hz, C-9), 113.3 (d, J = 7.5 Hz, C-12), 141.5 (d, J = 20.8 Hz, C-8), 170.1 (d, J = 27.8 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –153.7 (s) ppm. MS (EI): m/z (%) = 254 (7) $[M]^+$, 234 (23), 219 (46), 189 (26), 151 (25), 137 (85), 123 (63), 105 (40), 81 (44), 69 (100). HRMS: calcd. for $C_{15}H_{23}FO_2$ 254.168208; found 254.164104.

(±)-9α-Fluoro-8(12)-drimen-11-ol (9α-Fluoroalbicanol, 13): A 1 M solution of $LiAlH_4$ in toluene (820 μL, 0.82 mmol, 2 equiv.) was added dropwise into a solution of ester **21** (110 mg, 0.41 mmol) in anhydrous toluene (2 mL) at –40 °C under argon. After stirring for 30 min at this temperature, the mixture was carefully quenched with water and worked up using CH_2Cl_2 to extract. Chromatography of the crude product (hexane/EtOAc, 8:2, as eluent) afforded pure 9α-fluoroalbicanol (**13**; 98 mg, 99%) as a white solid. TLC: R_f = 0.24; m.p. 96–98 °C (benzene). IR (KBr): $\tilde{\nu}_{max}$ = 3371, 2975, 2931, 2865, 1650, 1631, 1456, 1444, 1384, 1085, 1062, 975, 892 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (s, 1 H, 12-H), 4.99 (d, J = 3.7 Hz, 1 H, 12-H′), 4.08–3.85 (m, 2 H, 11-H), 2.40 (ddddd, J = 13.2, 13.2, 5.3, 1.5, 1.5 Hz, 1 H, 7α-H), 2.24 (m, 1 H, 7β-H), 1.74 (m, 1 H, 5-H), 1.74 (m, 1 H, 6-H), 1.62 (m, 1 H, 1-H), 1.56–1.46 (m, 2 H, 2-H), 1.42 (m, 1 H, 1-H′), 1.36 (m, 1 H, 3-H), 1.32 (m, 1 H, 6-H′), 1.20 (m, 1 H, 3-H′), 0.91 (s, 3 H, 13-H), 0.85 (s, 3 H, 15-H), 0.83 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6 (d, J = 4.0 Hz, C-15), 18.8 (C-2), 21.9 (C-14), 23.2 (C-6), 32.4 (C-1), 33.0 (C-7), 33.5 (C-4), 33.7 (C-13), 41.2 (C-3), 42.2 (d, J = 18.9 Hz, C-10), 45.9 (d, J = 4.0 Hz, C-5), 60.3 (d, J = 23.5 Hz, C-11), 101.7 (d, J = 171.1 Hz, C-9), 112.8 (d, J = 7.5 Hz, C-12), 143.8 (d, J = 22.4 Hz, C-8) ppm. ^{19}F NMR (282 MHz, CDCl3): δ = –171.4 (s) ppm. MS (EI): m/z (%) = 240 (15) $[M]^+$, 225 (11), 137 (100), 123 (46), 109 (16), 95 (32), 81 (34), 69 (34), 55 (22). HRMS: calcd. for $C_{15}H_{25}FO$ 240.188944; found 240.189570.

(±)-9α-Fluoro-8(12)-drimen-11-ol Acetate (9α-Fluoroalbicanyl Acetate, 14): A mixture of albicanol (**13**; 210 mg, 0.87 mmol), DMAP (53 mg, 0.44 mmol, 0.5 equiv.) and Ac_2O (390 μL, 3.50 mmol, 4 equiv.) in anhydrous pyridine (1.6 mL) was stirred at room temp. for 1 h. Work-up as usual using CH_2Cl_2 to extract and column chromatography of the crude product (hexane/Et_2O, 8:2, as eluent) afforded 9α-fluoroalbicanyl acetate (**14**; 234 mg, 95%) as an oil. TLC: R_f = 0.54. IR (KBr): $\tilde{\nu}_{max}$ = 2941, 2869, 1743, 1650, 1558, 1457, 1386, 1367, 1240, 1047 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.05 (s, 1 H, 12-H), 4.73 (d, J = 3.8 Hz, 1 H, 12-H′), 4.57–4.36 (m, 2 H, 11-H), 2.37 (m, 1 H, 7-H), 2.20 (m, 1 H, 7-H′), 2.08 (s, 3 H, $COCH_3$), 1.80 (m, 1 H, 6-H), 1.74 (m, 1 H, 5-H), 1.60 (m, 1 H, 6-H′), 1.60 (m, 1 H, 2-H), 1.60 (m, 1 H, 1-H), 1.50 (m, 1 H, 2-H′), 1.42 (m, 1 H, 1-H′), 1.27 (m, 1 H, 3-H), 1.25 (m, 1 H, 3-H′), 0.90 (s, 3 H, 13-H), 0.89 (s, 3 H, 15-H), 0.83 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7 (d, J = 3.4 Hz, C-15), 18.8 (C-2), 21.0 ($COCH_3$), 21.8 (C-14), 23.1 (d, J = 1.1 Hz, C-6), 32.5 (C-1), 32.9 (C-7), 33.4 (C-4), 33.7 (C-13), 41.1 (C-3), 42.5 (d, J = 18.9 Hz, C-10), 45.6 (d, J = 4.4 Hz, C-5), 61.9 (d, J = 22.4 Hz, C-11), 99.4 (d, J = 176.3 Hz, C-9), 112.0 (d, J = 6.3 Hz, C-8), 143.8 (d, J = 22.4 Hz, C-12), 171.2 ($COCH_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –168.1 (s) ppm. MS (EI): m/z (%) = 282 (10) $[M]^+$, 222 (60), 207 (17), 189 (15), 137 (100), 123 (43), 109 (20), 95 (28), 81 (28), 69 (39), 55 (19). HRMS: calcd. for $C_{17}H_{27}FO_2$ 282.199509; found 282.199291.

(±)-9α-Fluoro-8(12)-drimen-11-al (9α-Fluoroalbicanal, 15): Dess–Martin periodinane (67 mg, 0.16 mmol, 1.5 equiv.) was added to a solution of alcohol **13** (25 mg, 0.10 mmol) in CH_2Cl_2 (0.3 mL) under argon. The flask was wrapped in aluminium foil to protect it from light, then cooled to 0 °C and dry pyridine (26 μL, 0.32 mmol, 3.1 equiv.) was added. The mixture was warmed up to room temp. and then stirred for 4.5 h. Work-up using CH_2Cl_2 to extract followed by purification by chromatography (hexane/Et_2O, 8:2, as eluent) gave 9α-fluoroalbicanal (**15**; 226 mg, 95%) as a colourless oil. TLC: R_f = 0.57. IR (KBr): $\tilde{\nu}_{max}$ = 2944, 2869, 2846, 2717, 1741, 1648, 1459, 1390, 1367, 1024, 916 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.83 (d, J = 9.0 Hz, 1 H, 11-H), 5.07 (d, J = 1.8 Hz, 1 H, 12-H), 4.84 (dd, J = 4.3, 1.8 Hz, 1 H, 12-H′), 2.43 (ddddd, J = 13.7, 13.7, 5.3, 1.7, 1.7 Hz, 1 H, 7α-H), 2.33 (ddd, J = 13.7, 5.1, 2.2 Hz, 1 H, 7β-H), 1.73 (m, 1 H, 1-H), 1.72 (m, 1 H, 5-H), 1.69 (m, 1 H, 6-H), 1.62–1.43 (m, 2 H, 2-H), 1.42 (m, 1 H, 6-H′), 1.40 (m, 1 H, 3-H), 1.22 (m, 1 H, 1-H′), 1.22 (m, 1 H, 3-H′), 1.13 (s, 3 H, 15-H), 0.91 (s, 3 H, 13-H), 0.86 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (d, J = 3.4 Hz, C-15), 18.3 (C-2), 22.0 (C-14), 22.1 (C-6), 32.3 (C-1), 32.8 (d, J = 2.3 Hz, C-7), 33.4 (C-4), 33.5 (C-13), 41.3 (C-3), 43.2 (d, J = 16.9 Hz, C-10), 45.4 (d, J = 2.9 Hz, C-5), 101.4 (d, J = 178.0 Hz, C-9), 113.6 (d, J = 7.5 Hz, C-12), 141.8 (d, J = 20.6 Hz, C-8), 201.0 (d, J = 40.7 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –164.1 (s) ppm. MS (EI): m/z (%) = 238 (60) $[M]^+$, 223 (28), 203 (9), 189 (12), 167 (28), 154 (20), 141 (26), 123 (86), 121 (25), 109 (31), 81 (46), 69 (100), 55 (42). HRMS: calcd. for $C_{15}H_{23}FO$ 238.173294; found 238.170834.

(±)-9α-Fluoro-7-drimen-11,12-olide (9α-Fluorodrimenin, 17): DBU (9 μL, 0.06 mmol, 1 equiv.) and a few grains of recently activated 3 Å molecular sieves (MS) were added to a solution of hydroxy

ester **29** (17 mg, 0.06 mmol) in anhydrous benzene (1.8 mL) under argon at room temp. The mixture was stirred for 3 h, filtered to separate the MS and worked up as usual using CH_2Cl_2 to extract. Purification of the crude product by chromatography (hexane/EtOAc, 8:2, as eluent) afforded 9α-fluorodrimenin (**17**; 12 mg, 85%) as an amorphous solid. TLC: R_f = 0.35. IR (KBr): $\tilde{\nu}_{max}$ = 2948, 2925, 2871, 1787, 1731, 1463, 1459, 1340, 1164, 1018 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.18 (s, 1 H, 7-H), 4.91 (d, J = 11.8 Hz, 1 H, 12-H), 4.70 (d, J = 11.8 Hz, 1 H, 12-H′), 2.33 (m, 1 H, 6-H), 2.17 (m, 1 H, 1-H), 2.08 (m, 1 H, 6-H′), 1.85 (m, 1 H, 5-H), 1.81 (m, 1 H, 1-H′), 1.68–1.54 (m, 2 H, 2-H), 1.48 (m, 1 H, 3-H), 1.34 (m, 1 H, 3-H′), 0.96 (s, 3 H, 14-H), 0.93 (s, 3 H, 13-H), 0.88 (s, 3 H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (d, J = 2.3 Hz, C-15), 17.6 (C-2), 21.7 (C-14), 24.3 (d, J = 3.4 Hz, C-6), 28.9 (d, J = 6.3 Hz, C-1), 32.9 (C-4), 33.1 (C-13), 37.0 (d, J = 19.5 Hz, C-10), 41.6 (C-3), 42.2 (C-5), 69.2 (C-12), 91.4 (d, J = 178.7 Hz, C-9), 128.3 (d, J = 16.1 Hz, C-8), 131.2 (d, J = 9.2 Hz, C-7), 170.9 (d, J = 27.6 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –145.3 (s) ppm. MS (EI): m/z (%) = 252 (2) $[M]^+$, 234 (100), 217 (20), 187 (20), 173 (12), 163 (12), 133 (13), 119 (50), 109 (38), 105 (27), 91 (20), 69 (33). HRMS: calcd. for $C_{15}H_{21}FO_2$ 252.152558; found 252.153496.

(±)-Methyl 9α-fluoro-8(12)-drimen-11-oate (21): A 0.5 M solution of KHMDS in toluene (13.5 mL, 6.75 mmol, 2.7 equiv.) was added dropwise into a suspension of Ph_3PCH_3Br (2.68 g, 7.50 mmol, 3 equiv.) in anhydrous toluene (15 mL) at room temp. under argon. After stirring for 30 min, a solution of decalone **11** (675 mg, 2.5 mmol) in toluene (10 mL) was added and stirring was continued for another 2 h. Work-up as usual using Et_2O to extract yielded an oily residue which was purified by column chromatography (hexane/Et_2O, 8:2, as eluent) to yield methyl 9α-fluoroalbicanate (**21**; 569 mg, 85%) as an oil. TLC: R_f = 0.54. IR (KBr): $\tilde{\nu}_{max}$ = 2989, 2948, 2869, 2846, 1739, 1650, 1459, 1434, 1390, 1288, 1263, 1068, 916 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.03 (dd, J = 4.2, 1.8 Hz, 1 H, 12-H), 4.95 (d, J = 1.8 Hz, 1 H, 12-H′), 3.78 (s, 3 H, CO_2CH_3), 2.45 (ddddd, J = 13.7, 13.7, 5.7, 2.6, 2.6 Hz, 1 H, 7α-H), 2.31 (dddd, J = 13.7, 4.7, 2.6, 2.6 Hz, 1 H, 7β-H), 1.78–1.56 (m, 2 H, 6-H), 1.75 (ddd, J = 12.5, 2.8, 2.6 Hz, 1 H, 5-H), 1.65 (m, 1 H, 1-H), 1.61 (m, 1 H, 2-H), 1.48 (m, 1 H, 2-H′), 1.39 (m, 1 H, 3-H), 1.21 (m, 1 H, 1-H′), 1.17 (m, 1 H, 3-H′), 1.15 (s, 3 H, 15-H), 0.92 (s, 3 H, 13-H), 0.88 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (d, J = 2.8 Hz, C-15), 18.5 (C-2), 22.0 (C-6), 21.9 (C-14), 31.9 (C-7), 32.9 (C-1), 33.3 (C-4), 33.6 (C-13), 41.3 (C-3), 42.8 (d, J = 19.5 Hz, C-10), 45.3 (d, J = 5.2 Hz, C-5), 51.8 (d, J = 1.1 Hz, CO_2CH_3), 101.1 (d, J = 187.8 Hz, C-9), 112.8 (d, J = 6.9 Hz, C-12), 142.1 (d, J = 21.2 Hz, C-8), 168.6 (d, J = 25.8 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –158.2 (s) ppm. MS (EI): m/z (%) = 268 (26) $[M]^+$, 253 (8), 233 (5), 137 (100), 123 (46), 109 (11), 95 (21), 69 (38), 55 (19). HRMS: calcd. for $C_{16}H_{25}FO_2$ 268.183859; found 268.183794.

(±)-Methyl 9α-Fluoro-8-trifluoromethanesulfonyloxy-7-drimen-11-oate (25): A solution of decalone **11** (107 mg, 0.39 mmol) in THF (2.5 mL) was slowly added dropwise to a 0.5 M solution of KHMDS in toluene (1.03 mL, 0.51 mmol, 1.3 equiv.) at –78 °C under argon. After stirring for 2 h at this temperature, a solution of $PhNTf_2$ (233 mg, 0.59 mmol, 1.5 equiv.) in THF (2.5 mL) was added and the stirring was continued for an additional 2 h. Work-up as usual using CH_2Cl_2 to extract and purification by column chromatography (hexane/EtOAc, 9:1, as eluent) gave the enol triflate **25** (110 mg, 70%) as a colourless oil. TLC: R_f = 0.47. IR (KBr): $\tilde{\nu}_{max}$ = 2956, 2933, 2875, 2850, 1762, 1753, 1681, 1421, 1213, 1143 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.23 (ddd, J = 5.8, 2.9, 2.9 Hz, 1 H, 7-H), 3.82 (s, 3 H, CO_2CH_3), 2.39 (m, 1 H, 6-H), 2.21 (m, 1 H, 6-H′), 1.85 (m, 1 H, 1-H), 1.73 (m, 1 H, 5-H), 1.63-1.49 (m, 2 H, 2-H), 1.47 (m, 1 H, 3-H), 1.36 (m, 1 H, 1-H′), 1.25 (m, 1 H, 3-H′), 1.05 (s, 3 H, 15-H), 0.97 (s, 3 H, 14-H), 0.96 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (d, J = 1.7 Hz, C-15), 17.8 (C-2), 22.3 (C-14), 23.0 (d, J = 2.3 Hz, C-6), 31.6 (d, J = 7.5 Hz, C-1), 32.9 (C-4), 33.1 (C-13), 41.0 (C-3), 41.9 (C-5), 42.2 (d, J = 18.4 Hz, C-10), 52.5 (CO_2CH_3), 96.7 (d, J = 193.2 Hz, C-9), 118.3 (q, J = 320.2 Hz, CF_3), 126.3 (d, J = 7.5 Hz, C-7), 142.9 (d, J = 20.7 Hz, C-8), 166.3 (d, J = 29.9 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.8 (d, J = 4.1 Hz), –149.5 (q, J = 4.1 Hz) ppm. MS (EI): m/z (%) = 402 (4) $[M]^+$, 335 (1), 307 (2), 267 (2), 252 (5), 217 (3), 124 (100), 109 (72), 69 (23), 55 (10). HRMS: calcd. for $C_{16}H_{22}F_4O_5S$ 402.112409; found 402.111205.

(±)-Dimethyl 9α-fluoro-7-drimen-11,12-dioate (26): $Pd(OAc)_2$ (22 mg, 0.09 mmol, 0.25 equiv.), Ph_3P (52 mg, 0.19 mmol, 0.5 equiv.) and iPr_2NEt (140 μL, 0.79 mmol, 2 equiv.) were added to a stirred solution of the enol triflate **25** (156 mg, 0.39 mmol) in a 1:1 mixture of DMF/MeOH (2.4 mL) and the resulting solution was stirred at 65 °C under CO balloon pressure for 20 h. The usual work-up using CH_2Cl_2 to extract and chromatography (hexane/EtOAc, 8:2, as eluent) afforded the diester **26** (80 mg, 65%) as a semi-solid. TLC: R_f = 0.27. IR (KBr): $\tilde{\nu}_{max}$ = 2950, 2927, 2871, 2846, 1760, 1724, 1656, 1436, 1272, 1255, 1137 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (ddd, J = 4.8, 2.4, 2.4 Hz, 1 H, 7-H), 3.76 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, CO_2CH_3), 2.33 (m, 1 H, 6-H), 2.16 (m, 1 H, 6-H′), 1.85 (m, 1 H, 1-H), 1.78 (m, 1 H, 5-H), 1.51 (m, 2 H, 2-H), 1.43 (m, 1 H, 3-H), 1.28 (m, 1 H, 1-H′), 1.25 (m, 1 H, 3-H′), 0.97 (s, 3 H, 14-H), 0.96 (s, 3 H, 15-H), 0.92 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (d, J = 2.3 Hz, C-15), 18.0 (C-2), 22.1 (C-14), 24.6 (d, J = 2.3 Hz, C-6), 31.8 (d, J = 6.9 Hz, C-1), 32.8 (C-4), 33.1 (C-13), 40.3 (d, J = 19.0 Hz, C-10), 41.1 (C-5), 41.5 (C-3), 51.9 and 52.1 ($2\times CO_2CH_3$), 94.8 (d, J = 193.8 Hz, C-9), 128.2 (d, J = 17.2 Hz, C-8), 147.8 (d, J = 6.3 Hz, C-7), 165.8 (C-12), 169.6 (d, J = 28.1 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –143.8 (s) ppm. MS (EI): m/z (%) = 312 (2) $[M]^+$, 280 (7), 260 (13), 242 (100), 227 (64), 212 (47), 196 (11), 169 (6), 153 (4), 124 (52), 109 (62), 92 (8), 69 (11). HRMS: calcd. for $C_{17}H_{25}FO_4$ 312.173688; found 312.173439.

(±)-Methyl 9α-Fluoro-12-hydroxy-7-drimen-11-oate (29): 2,6-Lutidine (580 μL, 5.0 mmol, 4 equiv.) was added to a solution of bromide **32** (434 mg, 1.25 mmol) and $AgBF_4$ (730 mg, 3.75 mmol, 3 equiv.) in acetone (12 mL) and water (24 mL) under argon. The resulting mixture was stirred at 60 °C for 3 h, then cooled to room temp., diluted with water and extracted with CH_2Cl_2. The extracts were washed with dilute HCl, 5% $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4. Evaporation of the solvent and chromatography (hexane/EtOAc, 8:2, as eluent) gave the hydroxy ester **29** (301 mg, 85%) as a solid. TLC: R_f = 0.12; m.p. 98–99 °C (hexane). IR (KBr): $\tilde{\nu}_{max}$ = 3434, 2987, 2950, 2923, 2869, 1737, 1681, 1461, 1434, 1390, 1274, 1207, 1076, 1056, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.20 (br. s, 1 H, 7-H), 4.14 (d, J = 12.9 Hz, 1 H, 12-H), 4.03 (d, J = 12.9 Hz, 1 H, 12-H′), 3.79 (s, 3 H, CO_2CH_3), 2.18 (m, 1 H, 6-H), 2.02 (m, 1 H, 6-H′), 1.78 (m, 1 H, 1-H), 1.77 (m, 1 H, 5-H), 1.51 (m, 2 H, 2-H), 1.42 (m, 1 H, 3-H), 1.23 (m, 1 H, 3-H′), 1.22 (m, 1 H, 1-H′), 0.98 (s, 3 H, 15-H), 0.95 (s, 3 H, 14-H), 0.91 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (d, J = 2.3 Hz, C-15), 18.2 (C-2), 22.0 (C-14), 23.7 (d, J = 2.8 Hz, C-6), 32.0 (d, J = 5.7 Hz, C-1), 32.9 (C-4), 33.0 (C-13), 40.3 (d, J = 18.9 Hz, C-10), 41.3 (C-3), 41.9 (C-5), 52.1 (CO_2CH_3), 64.2 (C-12), 98.0 (d, J = 190.0 Hz, C-9), 133.3 (d, J = 14.9 Hz, C-8), 134.3 (d, J = 8.6 Hz, C-7), 170.4 (d, J = 28.1 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –140.0 (s) ppm. MS (EI): m/z (%) = 284 (5) $[M]^+$, 266 (5), 232 (28), 187 (6), 124 (62),

109 (100), 91 (15), 69 (28). HRMS: calcd. for $C_{16}H_{25}FO_3$ 284.178773; found 284.178636.

(±)-Methyl 8α,12-Epoxy-9α-fluorodriman-11-oate (31): MCPBA (120 mg, 0.53 mmol, 2.3 equiv.) was added to a solution of **21** (63 mg, 0.23 mmol) in CH_2Cl_2 (7 mL) cooled in an ice–water bath. The reaction mixture was warmed up to room temp. and then stirred for 20 h, diluted with CH_2Cl_2 and successively washed with 5% aqueous solutions of KI, $Na_2S_2O_3$ and $NaHCO_3$ and then with brine. Drying over anhydrous $MgSO_4$ and evaporation of the solvent gave a residue that was purified by chromatography (hexane/EtOAc, 8:2, as eluent) to yield the epoxy ester **31** (55 mg, 82%). TLC: R_f = 0.45. IR (NaCl): $\tilde{\nu}_{max}$ = 3054, 2984, 2954, 1734, 1445, 1416, 1271, 1062, 898 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 3 H, CO_2CH_3), 3.41 (ddd, J = 4.5, 2.0, 2.0 Hz, 1 H, 12-H), 2.67 (dd, J = 4.5, 4.5 Hz, 1 H, 12-H′), 2.32 (ddddd, J = 13.2, 13.2, 5.1, 2.4, 2.4 Hz, 1 H, 7α-H), 1.76 (m, 1 H, 6-H), 1.68 (m, 1 H, 5-H), 1.61 (m, 1 H, 1-H), 1.57 (m, 1 H, 2-H), 1.53 (m, 1 H, 6-H′), 1.47 (m, 1 H, 2-H′), 1.39 (m, 1 H, 3-H), 1.26 (m, 1 H, 7β-H), 1.21 (s, 3 H, 15-H), 1.19 (m, 1 H, 3-H′), 1.05 (m, 1 H, 1-H′), 0.93 (s, 3 H, 13-H), 0.88 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (d, J = 3.2 Hz, C-15), 18.0 (C-2), 20.4 (C-6), 21.8 (C-14), 30.3 (d, J = 1.6 Hz, C-7), 32.7 (C-1), 33.2 (C-4), 33.7 (C-13), 41.1 (C-3), 44.1 (d, J = 18.4 Hz, C-10), 45.0 (d, J = 4.7 Hz, C-5), 52.2 (d, J = 0.9 Hz, CO_2CH_3), 53.4 (d, J = 4.6 Hz, C-12), 58.0 (d, J = 25.9 Hz, C-8), 101.5 (d, J = 195.4 Hz, C-9), 167.7 (d, J = 26.1 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –169.4 (s) ppm. MS (EI): m/z (%) = 284 (1) $[M]^+$, 269 (3), 239 (6), 193 (41), 178 (30), 161 (17), 137 (52), 123 (22), 109 (18), 95 (34), 73 (100). HRMS: calcd. for $C_{16}H_{25}FO_3$ 284.178773; found 284.180046.

(±)-Methyl 12-Bromo-9α-fluoro-7-drimen-11-oate (32): MeOH (10 mL) was added to a solution of compound **21** (447 mg, 1.67 mmol) and NBS (446 mg, 2.50 mmol, 1.5 equiv.) in CH_2Cl_2 (30 mL) and the resulting mixture was stirred at room temp. for 3 h.[70] The mixture was diluted with CH_2Cl_2 and worked up as usual. The crude product was purified by column chromatography (hexane/Et_2O, 8:2, as eluent) to give the bromo ester **32** (434 mg, 75%). IR (KBr): $\tilde{\nu}_{max}$ = 3450, 2950, 2927, 2869, 1733, 1654, 1457, 1440, 1390, 1280, 1074, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (s, 1 H, 7-H), 4.15 (d, J = 10.8 Hz, 1 H, 12-H), 3.91 (d, J = 10.8 Hz, 1 H, 12-H′), 3.82 (s, 3 H, CO_2CH_3), 2.28 (m, 1 H, 6-H), 2.06 (m, 1 H, 6-H′), 1.89 (m, 1 H, 5-H), 1.82 (m, 1 H, 1-H), 1.71–1.39 (m, 2 H, 2-H), 1.36 (m, 1 H, 3-H), 1.21 (m, 1 H, 1-H′), 1.18 (m, 1 H, 3-H′), 0.96 (s, 3 H, 15-H), 0.94 (s, 3 H, 14-H), 0.91 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (d, J = 1.7 Hz, C-15), 18.1 (C-2), 21.9 (C-14), 24.4 (d, J = 2.9 Hz, C-6), 32.0 (d, J = 5.2 Hz, C-1), 32.9 (C-4), 33.0 (C-13), 33.0 (C-12), 40.6 (d, J = 19.5 Hz, C-10), 41.1 (d, J = 2.3 Hz, C-5), 41.2 (C-3), 52.2 (CO_2CH_3), 97.5 (d, J = 194.2 Hz, C-9), 129.9 (d, J = 15.9 Hz, C-8), 138.1 (d, J = 7.5 Hz, C-7), 169.6 (d, J = 27.2 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –140.5 (s) ppm. MS (EI): m/z (%) = 349 (7) $[M + 1]^+$ (^{81}Br), 347 (8) $[M + 1]^+$ (^{79}Br), 267 (18), 247 (15), 245 (8), 215 (8), 207 (5), 187 (17), 177 (11), 145 (6), 137 (8), 131 (5), 124 (100). HRMS: calcd. for $C_{16}H_{25}{}^{79}BrFO_2$ $[M + H]^+$ 347.102195; found 347.100912.

(±)-9α-Fluorodrimane-8α,11,12-triol (34): NMO (24 mg, 0.21 mmol, 1.2 equiv.) and a catalytic amount of OsO_4 were added to a solution of fluorinated albicanol **13** (41 mg, 0.17 mmol) in a 4:1 mixture of acetone/water (1.9 mL) cooled to 0 °C. The flask was wrapped in aluminium foil to protect it from light and stirred at room temp. for about 3 d. The reaction mixture was worked up as usual using CH_2Cl_2 to extract and the crude product was purified by chromatography (hexane/EtOAc, 7:3, as eluent) to give the triol **34** (37 mg, 85%) as an amorphous solid. TLC: R_f = 0.14 (hexane/EtOAc, 1:1). IR (KBr): $\tilde{\nu}_{max}$ = 3396, 2981, 2942, 2869, 1648, 1637, 1456, 1388, 1375, 1363, 1265, 1025, 989, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.03–4.18 (m, 2 H, 11-H), 3.86 (d, J = 11.5 Hz, 1 H, 12-H), 3.76 (dd, J = 11.5, 1.7 Hz, 1 H, 12-H′), 1.88 (m, 1 H, 7-H), 1.62 (m, 2 H, 1-H, 2-H), 1.58 (m, 1 H, 7-H′), 1.56 (m, 1 H, 5-H), 1.54 (m, 1 H, 6-H), 1.46 (m, 1 H, 1-H′), 1.45 (m, 1 H, 2-H′), 1.34 (m, 1 H, 3-H), 1.29 (m, 1 H, 6-H′), 1.17 (m, 1 H, 3-H′), 1.05 (s, 3 H, 15-H), 0.88 (s, 3 H, 13-H), 0.83 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 17.8 (d, J = 5.1 Hz, C-15), 19.8 (C-2), 20.7 (C-6), 22.8 (C-14), 34.4 (d, J = 3.4 Hz, C-1), 34.6 (C-7), 34.7 (C-4), 34.8 (C-13), 42.9 (C-3), 43.4 (d, J = 18.4 Hz, C-10), 46.5 (d, J = 3.3 Hz, C-5), 48.5 (d, J = 3.3 Hz, C-5), 64.0 (d, J = 27.9 Hz, C-11), 66.6 (d, J = 5.5 Hz, C-12), 79.0 (d, J = 20.6 Hz, C-8), 102.9 (d, J = 182.0 Hz, C-9) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –173.1 (s) ppm. MS (EI): m/z (%) = 256 (54) $[M - 18]^+$, 243 (60), 225 (38), 203 (54), 163 (17), 123 (45), 95 (76), 81 (66), 69 (100), 55 (60). HRMS: calcd. for $C_{15}H_{25}FO_2$ $[M - H_2O]^+$ 256.183859; found 256.184792.

(±)-9α-Fluoro-8α-hydroxydriman-11,12-olide (37): Dess–Martin periodinane (154 mg, 0.36 mmol, 3.1 equiv.) was added to a solution of triol **34** (32 mg, 0.12 mmol) in CH_2Cl_2 (0.3 mL) under argon. The flask was wrapped in aluminium foil to protect it from light, then cooled to 0 °C and dry pyridine (60 μL, 0.73 mmol, 6.2 equiv.) was added. The mixture was warmed up to room temp. and stirred for 5 h, then diluted with CH_2Cl_2, washed successively with saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ followed by brine and dried with anhydrous $MgSO_4$. Elimination of the solvent and purification by chromatography (hexane/Et_2O, 8:2, as eluent) gave hydroxy lactone **37** (28 mg, 90%). TLC: R_f = 0.39. IR (KBr): $\tilde{\nu}_{max}$ = 3479, 2954, 2925, 2871, 1787, 1461, 1390, 1149, 1143, 1095, 1027, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.18 (app. AB system, J = 10.5 Hz, 2 H, 12-H), 2.12 (m, 1 H, 7-H), 1.79 (m, 1 H, 1-H), 1.70 (m, 1 H, 2-H), 1.65 (m, 1 H, 1-H′), 1.56 (m, 1 H, 7-H′), 1.53 (m, 2 H, 6-H), 1.43 (m, 1 H, 3-H), 1.29 (m, 1 H, 2-H′), 1.28 (m, 1 H, 5-H), 1.20 (m, 1 H, 3-H′), 1.09 (s, 3 H, 15-H), 0.94 (s, 3 H, 13-H), 0.85 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (d, J = 4.0 Hz, C-15), 17.6 (d, J = 1.7 Hz, C-6), 19.1 (C-2), 22.1 (C-14), 31.3 (d, J = 12.1 Hz, C-1), 33.1 (C-7), 33.3 (C-4), 33.4 (C-13), 40.8 (d, J = 20.7 Hz, C-10), 41.0 (C-3), 45.8 (C-5), 73.1 (d, J = 4.4 Hz, C-12), 75.0 (d, J = 18.9 Hz, C-8), 98.4 (d, J = 200.1 Hz, C-9), 171.8 (d, J = 26.4 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –184.8 (s) ppm. MS (EI): m/z (%) = 270 (76) $[M]^+$, 255 (100), 237 (49), 196 (71), 137 (75), 123 (91), 83 (36), 69 (98), 55 (56). HRMS: calcd. for $C_{15}H_{23}FO_3$ 270.163123; found 270.162215.

(±)-9α-Fluoro-8(12)-drimen-11,12-olide (38): A solution of hydroxy lactone **37** (69 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated sequentially with anhydrous pyridine (31 μL, 0.38 mmol, 1.5 equiv.) and $SOCl_2$ (28 μL, 0.38 mmol, 1.5 equiv.). The reaction mixture was warmed to room temp. and stirred for 15 h, then diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and brine and dried with anhydrous $MgSO_4$. Evaporation of the solvent and chromatographic purification (hexane/EtOAc, 9:1, as eluent) gave the lactone **38** (65 mg, 100%) as a viscous oil. TLC: R_f = 0.54. IR (KBr): $\tilde{\nu}_{max}$ = 2946, 2871, 1810, 1677, 1461, 1386, 1274, 1263, 1054, 1014, 995, 948 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.65 (t, J = 2.0 Hz, 1 H, 12-H), 2.45 (dddd, J = 15.6, 4.9, 1.3, 1.3 Hz, 1 H, 7β-H), 2.18 (m, 1 H, 7α-H), 1.85 (m, 1 H, 1-H), 1.77 (m, 1 H, 6-H), 1.77 (m, 1 H, 1-H′), 1.59 (m, 1 H, 5-H), 1.55 (m, 2 H, 2-H), 1.42 (m, 1 H, 3-H), 1.35 (m, 1 H, 6-H′), 1.26 (m, 1 H, 3-H′), 0.94 (s, 3 H, 13-H), 0.93 (s, 3 H, 15-H), 0.86 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (d, J = 2.9 Hz, C-15), 17.8 (C-

2), 21.8 (C-6), 21.9 (C-7), 21.9 (C-14), 29.4 (d, J = 5.5 Hz, C-1), 33.5 (C-13), 33.6 (C-4), 41.5 (C-3), 41.5 (d, J = 21.2 Hz, C-10), 45.6 (C-5), 95.4 (d, J = 192.3 Hz, C-9), 119.3 (d, J = 18.9 Hz, C-8), 137.6 (d, J = 12.1 Hz, C-12), 172.2 (d, J = 25.3 Hz, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –170.1 (s) ppm. MS (EI): m/z (%) = 252 (11) $[M]^+$, 237 (11), 142 (15), 137 (20), 124 (15), 123 (63), 109 (14), 95 (14), 81 (19), 69 (100). HRMS: calcd. for $C_{15}H_{21}FO_2$ 252.152558; found 252.148304.

(±)-11-Acetoxy-9α-fluorodrimane-8α,12-diol (39): Prepared by hydroxylation of albicanyl acetate (**14**; 124 mg, 0.44 mmol) with NMO (62 mg, 0.53 mmol, 1.2 equiv.) and catalytic OsO_4 in a 4:1 mixture of acetone/water (5 mL) as described above for **34**. The diol **39** was obtained in 50% yield (70 mg) after purification by column chromatography (hexane/EtOAc, 8:2, as eluent). TLC: R_f = 0.08. IR (KBr): $\tilde{\nu}_{max}$ = 3438, 2945, 2863, 2844, 1731, 1456, 1388, 1368, 1233, 1044, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (dd, J = 15.2, 12.6 Hz, 1 H, 11-H), 4.38 (dd, J = 17.9, 12.6 Hz, 1 H, 11-H′), 3.64 (s, 2 H, 12-H), 2.075 (s, 3 H, COCH_3), 2.07 (m, 1 H, 7-H), 1.64 (m, 1 H, 6-H), 1.63 (m, 1 H, 7-H′), 1.63 (m, 1 H, 2-H), 1.63 (m, 1 H, 1-H), 1.52 (m, 1 H, 5-H), 1.49 (m, 1 H, 2-H′), 1.47 (m, 1 H, 1-H′), 1.34 (m, 1 H, 3-H), 1.24 (m, 1 H, 6-H′), 1.16 (m, 1 H, 3-H′), 0.98 (s, 3 H, 15-H), 0.89 (s, 3 H, 13-H), 0.81 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (d, J = 5.2 Hz, C-15), 18.0 (C-2), 19.2 (C-6), 21.0 (COCH_3), 21.6 (C-14), 33.0 (d, J = 3.4 Hz, C-7), 33.2 (C-1), 33.2 (C-4), 33.4 (C-13), 40.9 (C-3), 42.4 (d, J = 18.9 Hz, C-10), 46.4 (d, J = 2.9 Hz, C-5), 61.5 (d, J = 23.5 Hz, C-11), 64.0 (d, J = 5.1 Hz, C-12), 76.7 (d, J = 21.8 Hz, C-8), 100.2 (d, J = 183.7 Hz, C-9), 170.5 (COCH$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –174.1 (s) ppm. MS (FAB): m/z (%) = 317 (100) $[M + 1]^+$, 298 (56), 281 (32), 221 (74), 201 (22), 109 (33). HRMS: calcd. for $C_{17}H_{30}FO_4$ $[M + H]^+$ 317.212813; found 317.213550.

(±)-11,12-Epoxy-9α-fluorodrimane-8α,12α-diol (40): DMSO (53 μL, 0.75 mmol, 5 equiv.) was added to a solution of oxalyl chloride (150 μL of a 2 M solution in CH_2Cl_2, 0.30 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (0.5 mL) at –60 °C. After 10 min of stirring at this temperature, a solution of glycol **39** (47 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction mixture was stirred for 30 min during which time the temperature of the reaction mixture was raised to –20 °C. Then the reaction mixture was cooled again to –60 °C and Et_3N (210 μL, 1.50 mmol, 10 equiv.) was added. After 1 h the reaction was worked up as usual using CH_2Cl_2 to extract to give an oily residue (44 mg), which was dissolved in a 1:1 mixture of MeOH/H_2O (3 mL) containing a catalytic amount of KOH. The mixture was stirred at room temp. for 30 min, diluted with water and worked up using CH_2Cl_2 to extract. Purification by chromatography (hexane/EtOAc, 8:2, as eluent) afforded the hydroxy lactol **40** (27 mg, 60%). TLC: R_f = 0.12. IR (NaCl): $\tilde{\nu}_{max}$ = 3405, 2950, 2919, 2863, 1726, 1454, 1393, 1091, 1024 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11 (s, 1 H, 12-H), 3.99 (dd, J = 14.4, 9.0 Hz, 1 H, 11-H), 3.88 (dd, J = 9.0, 2.7 Hz, 1 H, 11-H′), 2.10 (m, 1 H, 7-H), 1.63 (m, 1 H, 2-H), 1.61 (m, 1 H, 1-H), 1.60 (m, 1 H, 6-H), 1.48 (m, 1 H, 6-H′), 1.45 (m, 1 H, 7-H′), 1.41 (m, 1 H, 3-H), 1.34 (m, 1 H, 1-H′), 1.32 (m, 1 H, 2-H′), 1.32 (m, 1 H, 5-H), 1.17 (m, 1 H, 3-H′), 1.06 (s, 3 H, 15-H), 0.92 (s, 3 H, 13-H), 0.86 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (d, J = 5.8 Hz, C-15), 17.7 (C-6), 18.5 (C-2), 22.0 (C-14), 30.9 (C-7), 31.5 (C-1), 33.0 (C-4), 33.2 (C-13), 39.7 (d, J = 20.9 Hz, C-10), 41.3 (C-3), 45.3 (C-5), 68.3 (d, J = 29.8 Hz, C-11), 76.1 (d, J = 17.2 Hz, C-8), 99.7 (d, J = 5.7 Hz, C-12), 102.0 (d, J = 193.0 Hz, C-9) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –176.2 (s) ppm. MS (EI): m/z (%) = 272 (1) $[M]^+$, 206 (59), 191 (99), 163 (36), 137 (38), 123 (100), 109 (60), 95 (39), 69 (33). HRMS: calcd. for $C_{15}H_{25}FO_3$ 272.178773; found 272.177032.

(±)-9α-Fluoro-8β,11-bis(trimethylsilyloxy)drimane-12-carbonitrile (44): A mixture of hydroxy ketone **43** (129 mg, 0.53 mmol) and ZnI_2 (102 mg, 0.32 mmol, 0.6 equiv.) in CH_2Cl_2 (5.3 mL) was treated with trimethylsilyl cyanide (710 μL 5.33 mmol, 10 equiv.) at 0 °C under argon.[71] The reaction was allowed to slowly warm to room temp. and stirred for 15 h. The reaction mixture was diluted with CH_2Cl_2 and worked up as usual. Purification by column chromatography (hexane/Et_2O, 8:2, as eluent) afforded nitrile **44** (168 mg, 76%). IR (KBr): $\tilde{\nu}_{max}$ = 2956, 2902, 2871, 1459, 1444, 1251, 1126, 873, 844 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (dd, J = 29.0, 12.0 Hz, 1 H, 11-H), 3.91 (dd, J = 15.0, 12.0 Hz, 1 H, 11-H′), 2.15 (m, 2 H, 7-H), 1.58 (m, 1 H, 2-H), 1.57 (m, 1 H, 1-H), 1.48 (m, 2 H, 6-H), 1.48 (m, 1 H, 5-H), 1.46 (m, 1 H, 1-H′), 1.43 (m, 1 H, 2-H′), 1.35 (m, 1 H, 3-H), 1.18 (m, 1 H, 3-H′), 1.07 (s, 3 H, 15-H), 0.89 (s, 3 H, 13-H), 0.84 (s, 3 H, 14-H), 0.28 [s, 9 H, C8-OSi(CH_3)$_3$], 0.15 [s, 9 H, C11-OSi(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.6 [C11-OSi(CH_3)$_3$], 1.1 [C8-OSi(CH_3)$_3$], 16.4 (d, J = 4.0 Hz, C-15), 16.8 (C-6), 17.9 (C-2), 21.9 (C-14), 33.0 (C-13), 33.1 (d, J = 4.0 Hz, C-1), 33.7 (C-4), 38.6 (d, J = 1.4 Hz, C-7), 40.8 (C-3), 41.5 (d, J = 17.5 Hz, C-10), 46.2 (d, J = 1.9 Hz, C-5), 60.5 (d, J = 33.9 Hz, C-11), 71.5 (d, J = 20.1 Hz, C-8), 97.9 (d, J = 189.4 Hz, C-9), 121.4 (CN) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –172.7 (s) ppm. MS (EI): m/z (%) = 413 (25) $[M]^+$, 399 (32), 398 (100), 371 (33), 279 (16), 269 (14), 149 (84). HRMS: calcd. for $C_{21}H_{40}FNO_2Si_2$ 413.258165; found 413.259590.

(±)-9α-Fluoro-8β-hydroxydriman-12,11-olide (45): A mixture of bis-(trimethylsilyloxy)nitrile **44** (239 mg, 0.57 mmol) and a catalytic amount of PTSA in 4% aqueous THF (5 mL) was heated at 55 °C for 20 h. Work-up of the reaction mixture as usual using CH_2Cl_2 to extract and chromatographic purification of the crude reaction product (hexane/EtOAc, 8:2, as eluent) afforded hydroxy lactone **45** (133 mg, 85%) as a white solid. TLC: R_f = 0.24; m.p. 146–147 °C (Et_2O). IR (NaCl): $\tilde{\nu}_{max}$ = 3444, 2950, 2871, 1778, 1712, 1461, 1392, 1365, 1261, 1184, 1051, 977 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.69 (dd, J = 35.8, 9.5 Hz, 1 H, 11-H), 4.25 (dd, J = 15.8, 9.5 Hz, 1 H, 11-H′), 3.19 (br. d, J = 1.5 Hz, 1 H, OH), 1.88 (m, 2 H, 7-H), 1.68 (m, 2 H, 6-H), 1.68 (m, 1 H, 1-H), 1.67 (m, 1 H, 2-H), 1.58 (m, 1 H, 5-H), 1.48 (m, 1 H, 2-H′), 1.41 (m, 1 H, 3-H), 1.22 (s, 3 H, 15-H), 1.21 (m, 1 H, 3-H′), 1.20 (m, 1 H, 1-H′), 0.91 (s, 3 H, 13-H), 0.89 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (d, J = 5.2 Hz, C-15), 16.7 (C-6), 17.4 (C-2), 21.4 (C-14), 27.6 (C-7), 32.0 (d, J = 3.4 Hz, C-1), 33.0 (C-4), 33.7 (C-13), 39.6 (d, J = 17.2 Hz, C-10), 41.5 (C-3), 46.6 (d, J = 3.4 Hz, C-5), 71.0 (d, J = 25.3 Hz, C-11), 74.6 (d, J = 32.7 Hz, C-8), 102.5 (d, J = 170.7 Hz, C-9), 176.1 (C-12) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –161.5 (s) ppm. MS (EI): m/z (%) = 270 (2) $[M]^+$, 238 (3), 209 (5), 160 (15), 137 (53), 136 (17), 125 (22), 123 (65), 95 (50), 81 (57), 73 (46), 69 (100). HRMS: calcd. for $C_{15}H_{23}FO_3$ 270.163123; found 270.162354.

(±)-11-Acetoxy-9α-fluoro-12-nordriman-8-one (47): A solution of hydroxy ketone **43** (165 mg, 0.68 mmol) and Ac_2O (300 μL, 2.72 mmol, 4 equiv.) in pyridine (1.2 mL) was stirred at room temp. for 2 h. The mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with dilute aqueous HCl, 5% aqueous $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4 and concentrated. Chromatographic purification (hexane/Et_2O, 8:2, as eluent) gave the keto acetate **47** (194 mg, 99%). TLC: R_f = 0.42. IR (KBr): $\tilde{\nu}_{max}$ = 2948, 2881, 1747, 1731, 1461, 1434, 1386, 1367, 1236, 1054 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.54 (dd, J = 32.0, 12.1 Hz, 1 H, 11-H), 4.30 (dd, J = 12.1, 10.6 Hz,

1 H, 11-H′), 2.90 (m, 1 H, 7-H), 2.36 (m, 1 H, 7-H′), 2.04 (s, 3 H, COCH_3), 2.02 (m, 1 H, 6-H), 1.99 (m, 1 H, 5-H), 1.75 (m, 1 H, 1-H), 1.59 (m, 1 H, 6-H′), 1.57 (m, 2 H, 2-H), 1.43 (m, 1 H, 1-H′), 1.40 (m, 1 H, 3-H), 1.24 (m, 1 H, 3-H′), 0.97 (s, 3 H, 13-H), 0.86 (s, 3 H, 15-H), 0.85 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (d, J = 4.3 Hz, C-15), 18.4 (C-2), 20.8 (COCH_3), 21.7 (C-14), 23.9 (C-6), 32.4 (C-1), 33.6 (C-4), 33.6 (C-13), 38.6 (d, J = 2.7 Hz, C-7), 41.0 (C-3), 44.8 (d, J = 4.6 Hz, C-5), 45.1 (d, J = 18.8 Hz, C-10), 59.9 (d, J = 20.2 Hz, C-11), 100.5 (d, J = 188.5 Hz, C-9), 170.8 (COCH$_3$), 206.7 (d, J = 27.0 Hz, C-8) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –173.3 (s) ppm. MS (EI): m/z (%) = 284 (10) $[M]^+$, 224 (46), 209 (15), 191 (9), 163 (12), 137 (57), 136 (42), 123 (100), 109 (38), 95 (61), 69 (90). HRMS: calcd. for $C_{16}H_{25}FO_3$ 284.178773; found 284.170853.

(±)-11-Acetoxy-9α-fluoro-8β-hydroxydrimane-12-carbonitrile (48): A mixture of keto acetate **47** (166 mg, 0.58 mmol) and ZnI_2 (111 mg, 0.35 mmol, 0.6 equiv.) in dry CH_2Cl_2 (5.5 mL) was treated with trimethylsilyl cyanide (385 μL, 3.0 mmol, 10 equiv.) at 0 °C under argon. The reaction mixture was stirred at room temp. for 5 h and then worked up as usual using CH_2Cl_2 to extract. The residue left after evaporation of the solvent (ca. 197 mg) was transferred to a Teflon tube, dissolved in anhydrous THF (2 mL) and treated with the HF/pyridine complex (ca. 500 μL). The mixture was stirred at room temp. until complete consumption of the silyl ether intermediate was observed by TLC analysis (ca. 18 h), then diluted with CH_2Cl_2, washed with dilute aqueous HCl, 5% $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. Evaporation of the solvent and chromatographic purification (hexane/EtOAc, 8:2, as eluent) gave the acetoxy nitrile **48** (150 mg, 83% overall yield from **47**). TLC: R_f = 0.16. IR (NaCl): $\tilde{\nu}_{max}$ = 3390, 2952, 2871, 1751, 1727, 1461, 1378, 1240, 1103, 1056 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.87 (dd, J = 31.3, 13.0 Hz, 1 H, 11-H), 4.41 (dd, J = 13.0, 11.6 Hz, 1 H, 11-H′), 2.30–2.09 (m, 2 H, 7-H), 2.21 (s, 3 H, COCH_3), 1.61–1.41 (m, 4 H, 2-H, 6-H), 1.61 (m, 1 H, 1-H), 1.44 (m, 1 H, 5-H), 1.44 (m, 1 H, 1-H′), 1.35 (m, 1 H, 3-H), 1.18 (s, 3 H, 15-H), 1.14 (m, 1 H, 3-H′), 0.91 (s, 3 H, 13-H), 0.85 (s, 3 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (d, J = 4.2 Hz, C-15), 16.5 (C-6), 17.7 (C-2), 21.2 (COCH_3), 21.9 (C-14), 33.0 (d, J = 4.5 Hz, C-1), 33.1 (C-4), 33.7 (C-13), 37.3 (C-7), 40.6 (C-3), 41.7 (d, J = 17.1 Hz, C-10), 45.9 (C-5), 61.7 (d, J = 21.6 Hz, C-11), 70.0 (d, J = 31.8 Hz, C-8), 96.5 (d, J = 190.7 Hz, C-9), 121.1 (CN), 173.1 (COCH$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –168.3 (s) ppm. MS (EI): m/z (%) = 311 (10) $[M]^+$, 306 (100), 285 (98), 225 (24), 219 (30), 207 (15), 167 (23), 165 (21). HRMS: calcd. for $C_{17}H_{26}FNO_3$ 311.189672; found 311.195612.

(±)-11-Acetoxy-9α-fluoro-7-drimene-12-carbonitrile (49): Anhydrous pyridine (122 μL, 1.51 mmol, 3.1 equiv.) and thionyl chloride (53 μL, 0.73 mmol, 1.5 equiv.) were added to a solution of hydroxy nitrile **48** (152 mg, 0.49 mmol) in dry toluene (5 mL). The mixture was stirred at room temp. for 4 h, heated progressively from room temp. to 80 °C over 4 h and then stirred at this temperature for 15 h. After work-up as described for **47**, the residue obtained was purified by column chromatography (hexane/EtOAc, 7:3, as eluent) to give the unsaturated nitrile **49** (130 mg, 90%) as a solid. TLC: R_f = 0.20; m.p. 72–73 °C (Benzene). IR (NaCl): $\tilde{\nu}_{max}$ = 2950, 2871, 2221, 1751, 1637, 1463, 1390, 1367, 1236, 1052, 981, 908 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (quint., J = 2.7 Hz, 1 H, 7-H), 4.43 (dd, J = 30.2, 12.3 Hz, 1 H, 11-H), 4.38 (dd, J = 27.9, 12.3 Hz, 1 H, 11-H′), 2.37 (m, 1 H, 6-H), 2.13 (s, 3 H, COCH_3), 2.13 (m, 1 H, 6-H′), 1.79 (ddd, J = 11.9, 4.6, 1.5 Hz, 1 H, 5-H), 1.58 (m, 2 H, 1-H), 1.58–1.47 (m, 2 H, 2-H), 1.43 (m, 1 H, 3-H), 1.22 (m, 1 H, 3-H′), 0.95 (s, 3 H, 14-H), 0.93 (s, 6 H, 13-H, 15-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (d, J = 2.9 Hz, C-15), 17.9 (C-2), 20.8 (COCH_3), 22.0 (C-14), 25.3 (d, J = 2.6 Hz, C-6), 31.1 (d, J = 6.4 Hz, C-1), 32.7 (C-4), 32.9 (C-15), 40.0 (d, J = 18.0 Hz, C-10), 40.8 (C-3), 41.3 (C-5), 62.2 (d, J = 33.5 Hz, C-11), 92.7 (d, J = 183.9 Hz, C-9), 112.4 (d, J = 20.3 Hz, C-8), 117.2 (CN), 153.9 (d, J = 6.3 Hz, C-7), 170.3 (COCH$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –145.4 (s) ppm. MS (EI): m/z (%) = 293 (1) $[M]^+$, 231 (10), 221 (15), 156 (6), 130 (12), 124 (91), 109 (100), 81 (12), 69 (24). HRMS: calcd. for $C_{17}H_{24}FNO_2$ 293.179107; found 293.174743.

(±)-9α-Fluoro-11-hydroxy-7-drimene-12-carbonitrile (50): A solution of acetoxy nitrile **49** (27 mg, 0.09 mmol) in anhydrous THF (1 mL) was treated with a 1 M solution of DIBAL-H in cyclohexane (190 μL, 0.19 mmol, 2 equiv.) at –78 °C under argon. The mixture was stirred at this temperature for 30 min, treated again with another identical portion of the DIBAL-H solution (190 μL) and then stirred under the same conditions for an additional 30 min. The reaction was quenched by the addition of acetone (1 mL), stirred for 15 min, diluted with CH_2Cl_2, washed with brine and dried with anhydrous Na_2SO_4. After evaporation of the solvent chromatographic purification (hexane/Et_2O from 8:2 to 6:4) gave the hydroxy nitrile **50** (23 mg, 97%) as a white solid. TLC: R_f = 0.16; m.p. 137–138 °C (hexane). IR (NaCl): $\tilde{\nu}_{max}$ = 3484, 2948, 2916, 2868, 2220, 1742, 1641, 1471, 1392, 1073 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (quint., J = 2.7 Hz, 1 H, 7-H), 4.00 (app. d, J = 13.2 Hz, 2 H, 11-H), 2.39 (m, 1 H, 6-H), 2.13 (m, 1 H, 6-H′), 1.90 (br. s, 1 H, OH), 1.77 (ddd, J = 12.0, 4.7, 1.5 Hz, 1 H, 5-H), 1.71–1.54 (m, 2 H, 1-H), 1.68–1.45 (m, 2 H, 2-H), 1.43 (m, 1 H, 3-H), 1.22 (m, 1 H, 3-H′), 0.96 (s, 3 H, 15-H), 0.95 (s, 3 H, 14-H), 0.92 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (d, J = 3.3 Hz, C-15), 17.9 (C-2), 22.0 (C-14), 25.4 (d, J = 2.7 Hz, C-6), 31.2 (d, J = 6.6 Hz, C-1), 32.8 (C-4), 33.0 (C-13), 39.9 (d, J = 18.0 Hz, C-10), 41.0 (C-3), 41.7 (C-5), 62.4 (d, J = 31.7 Hz, C-11), 94.2 (d, J = 181.3 Hz, C-9), 112.7 (d, J = 20.2 Hz, C-8), 117.2 (CN), 154.1 (d, J = 6.5 Hz, C-7) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –148.0 (s) ppm. MS (EI): m/z (%) = 251 (1) $[M]^+$, 221 (36), 206 (11), 186 (6), 130 (11), 124 (84), 109 (100), 69 (24). HRMS: calcd. for $C_{15}H_{22}FNO$ 251.168543; found 251.166264.

Bioassays: Selected compounds were evaluated in independent bioassays against three important agricultural insect pests. The antifeedant activity was tested with larvae of the generalist *Spodoptera littoralis* (Lepidoptera: Noctuidae). Aphid settling inhibition was evaluated with a grass specialist, *Rhopalosiphum padi*, and a feeding generalist, *Myzus persicae* (both Hemiptera: Aphididae). Compounds were assayed at an initial dose of 50 μg/cm^2 and those with higher deterrent activities were used to calculate EC_{50} values. Insect rearing, choice feeding assays and oral cannulations were conducted as described previously.[72]

Supporting Information (see also the footnote on the first page of this article): General experimental, details of the preparation of compounds **3**, **4**, **9**, **19**, **20**, **22**, **24**, **28**, **30**, **41**–**43**, **46** and **51**, reduction of diester **26** with DIBAL-H, dehydration of **45** with Deoxo-fluor®, oxidative fragmentation of **40**, oral cannulation data and characterization ^{1}H NMR spectra for compounds **11**–**15**, **17**, **21**, **31**, **37**, **38**, **45**–**47**, **49** and **50**.

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