Total synthesis of 14β-fluorosteroids via a transannular Diels–Alder reaction

Sylvie Beaubien and Pierre Deslongchamps

Abstract: 14β-Fluorosteroids **3** and **4** were synthesized to give a new class of unnatural cardenolides. The total synthesis of racemic 14β-fluorosteroids was accomplished using a highly diastereoselective transannular Diels–Alder reaction on a trans-cis-cis macrocyclic triene. The α-fluoro analog **4** provided a comparable inhibitory activity to natural digitoxigenin **1**.

Key words: fluorosteroid, bioisostere, cardiovascular diseases, transannular Diels–Alder reaction (TADA), macrocyclization.

Résumé : Les 14β-fluorostéroïdes **3** et **4** ont été synthétisés en vue d'obtenir une nouvelle classe de cardénolides non-naturels. La synthèse totale racémique des 14β-fluorostéroïdes a été accomplie en utilisant la réaction diastéréosélective de Diels–Alder transannulaire à partir d'un triène macrocyclique trans-cis-cis. L'α fluoro-analogue **4** donne une activité inhibitrice comparable à la digitoxigénine **1**.

Mots clés : fluorostéroïde, bioisostère, maladies cardiovasculaires, réaction de Diels–Alder transannulaire (DATA), macrocyclisation.

Introduction

The (+)-digitoxigenin **1** is derived from the biologically active trisaccharide digitoxin **2**, which is extracted from the *Digitalis purpura* plant (1) (Fig. 1). These cardenolide steroids belong to the large digitalis family, and the principal use of this type of molecule is the treatment of cardiovascular diseases (2).

Compounds from the digitalis family are considered to be dangerous because the therapeutic dose can correspond to up to 60% of the lethal dose. The therapeutic dose for cardiovascular disease is very small (1) (0.2 mg for digitoxin **2**). For this reason, many efforts have been made to synthesize cardenolide analogs to diminish the toxicity of this type of compound.

Bioisosterism is an approach used to decrease the toxicity of a drug (3). Based on this method, we decided to consider fluoro analogs of digitoxigenin **1**, since fluorine is a bioisostere of the hydroxyl group. In addition, some analogs of digitoxigenin **1** are known to possess an α,β-unsaturated ester instead of butenolide at the C-17 position (4). We, therefore, decided to synthesize the racemic fluoro analogs **3** and **4** of digitoxigenin **1** with a fluorine atom at the C-14 position and an α,β-unsaturated ester at the C-17 position. The biological activity of these analogs could then be measured and compared with that of digitoxigenin **1**.

To synthesize these two fluoro analogs, we used the transannular Diels–Alder (TADA) (5) reaction to construct the tetracyclic skeleton. Our past studies on the TADA reaction (6, 7) have shown that a 13-membered ring with a trans-cis-cis olefin geometry can lead to an A.B.C.[6.6.5] tricycle having a trans-syn-cis (TSC) ring junction configuration (8). In this reaction, four asymmetric centers are created simultaneously with high stereoselectivity. The challenging synthesis of the fluorinated compound, which represents a new class of unnatural cardenolides, is reported herein.

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Results and discussion

Retrosynthesis

The retrosynthetic analysis of fluoro analogs **3** and **4** is presented in Scheme 1. These fluoro analogs can be obtained by Birch reduction of the aromatic ring and by homologation of the C-17 ketone of tetracycle **5** to form the α,β-unsaturated esters **3** and **4**. Tetracycle **5** (TSC) can be obtained via the TADA reaction of trienic macrocycle **6** possessing an *E,E*-diene and an *E*-dienophile. Macrocycle **6** can be formed from the β-keto ester **7** by macrocyclization. This β-keto ester can be obtained from compound **8** by alkylation. Homologation of diol **9** with two different Horner–Emmons reactions can produce compound **8**. Finally, the diol **9** can be prepared from commercially available compound **10** in a few steps.

Synthesis of β-keto ester 7

The synthesis of β-keto ester **7** starts with the reduction of the commercially available ketone **10** with lithium aluminium hydride to give the corresponding alcohol followed

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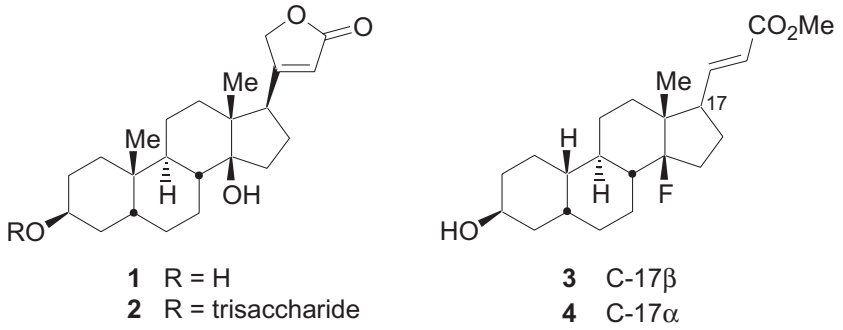
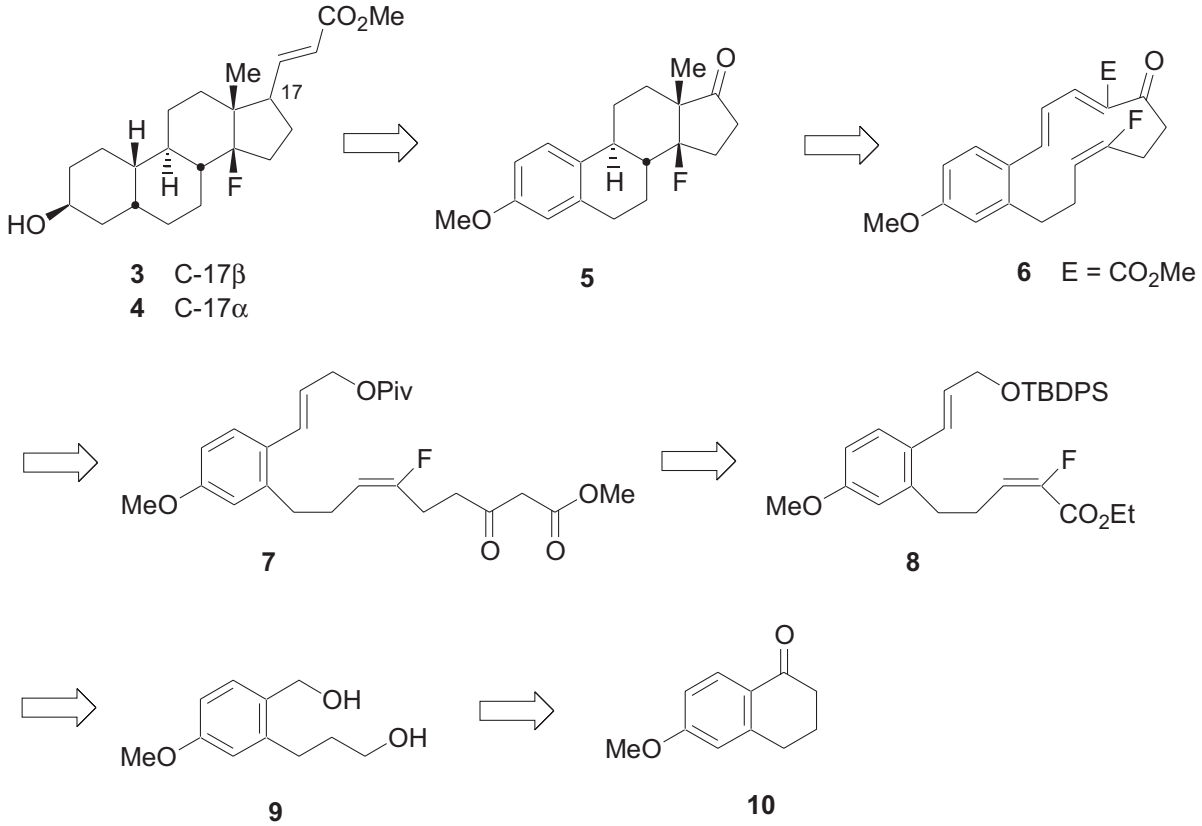
Fig. 1. Target structures.



1 R = H
2 R = trisaccharide

3 C-17β
4 C-17α

Scheme 1.



3 C-17β
4 C-17α

5

6 E = CO_2Me

7

8

9

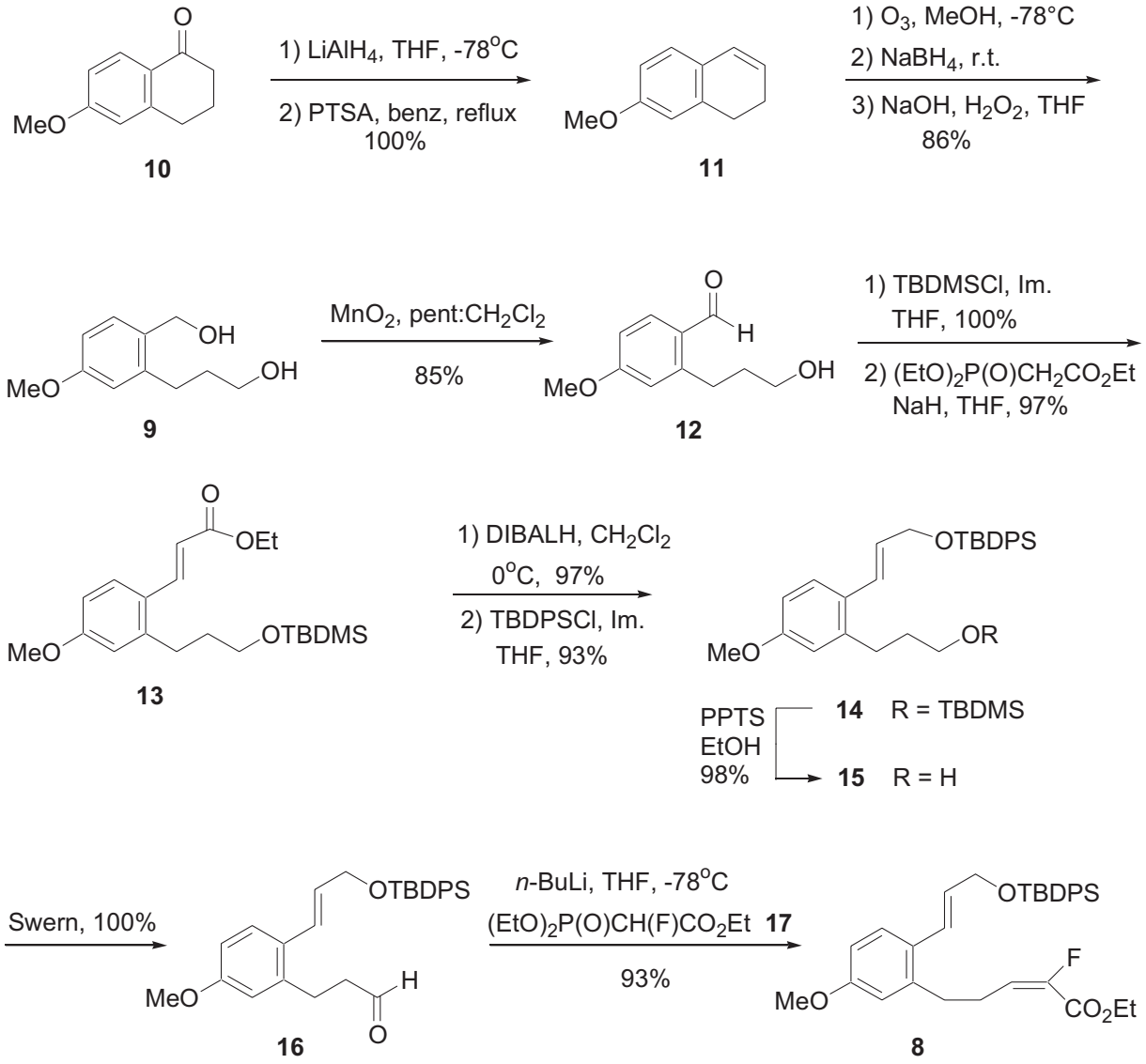
10

by dehydratation to produce the olefin **11** in a quantitative yield (Scheme 2). Ozonolysis of this olefin was performed followed by treatment with sodium borohydride (9) to give diol **9** in 86% yield. The selective oxidation of the benzylic alcohol of diol **9** was accomplished with manganese dioxide and the hydroxyaldehyde **12** was obtained in 85% yield. This hydroxyaldehyde was protected as a TBDMS ether and a Horner–Emmons (10) reaction was performed to produce the α,β-unsaturated ester **13** with very good yield as a single detectable geometrical isomer. Reduction with DIBALH of the α,β-unsaturated ester **13** afforded the corresponding alcohol, which was protected as a TBDPS ether to give disilylated compound **14**. The selective deprotection of TBDMS in the presence of the TBDPS ether was performed with a catalytic amount of PPTS in ethanol, and alcohol **15** was obtained in 98% yield. Swern oxidation (11) then led to aldehyde **16** in quantitative yield.

The fluorine atom, which is required at the 14β position in the final targets **3** and **4**, was introduced at this step with a Horner–Emmons (10) reaction. The aldehyde **16** was treated with the anion of fluorophosphonate **17** (12), and α,β-unsaturated ester **8** was obtained in 93% yield (Scheme 2). The isomer with the E geometry (12) was the only compound observed by ^{1}H NMR. With this key intermediate in hand, we could synthesize β-keto ester **7** for the macrocyclization reaction.

To this end, α,β-unsaturated ester **8** was reduced with lithium aluminium hydride to provide a quantitative yield of the alcohol, which was converted to the allylic chloride **18** with hexachloroacetone and triphenylphosphine (13). The introduction of the β-keto ester was accomplished by treating allylic chloride **18** with the dianion of methyl acetoacetate (14) to afford β-keto ester **19** in 65% yield. Deprotection of the silyl ether was carried out with TBAF, and the resulting

Scheme 2.



alcohol was converted to a pivaloate ester to give β-keto ester **7**, the desired macrocyclization precursor (Scheme 3).

Macrocyclization and TADA reaction

The key steps in this synthesis are the macrocyclization and the TADA reaction. To achieve macrocyclization, the silyl enol ether of β-keto ester **7** was prepared with *N*,*N*-bistrimethylsilylacetamide and subsequent slow addition (14 h) of this silyl enol ether to a solution of palladium catalyst at a high dilution (2 mmol/L). This concentration is essential to eliminate polymer formation. Under these reaction conditions (8, 15), the macrocyclization took place to afford the 13-membered ring macrocycle **20** in an excellent yield of 88% (Scheme 4). Now, we have to introduce an *E*-olefin to make the necessary diene for the TADA reaction. Macrocycle **20** was thus treated with benzeneseleninic anhydride (16, 17), and the trienic macrocycle **6** was obtained in 91% yield.

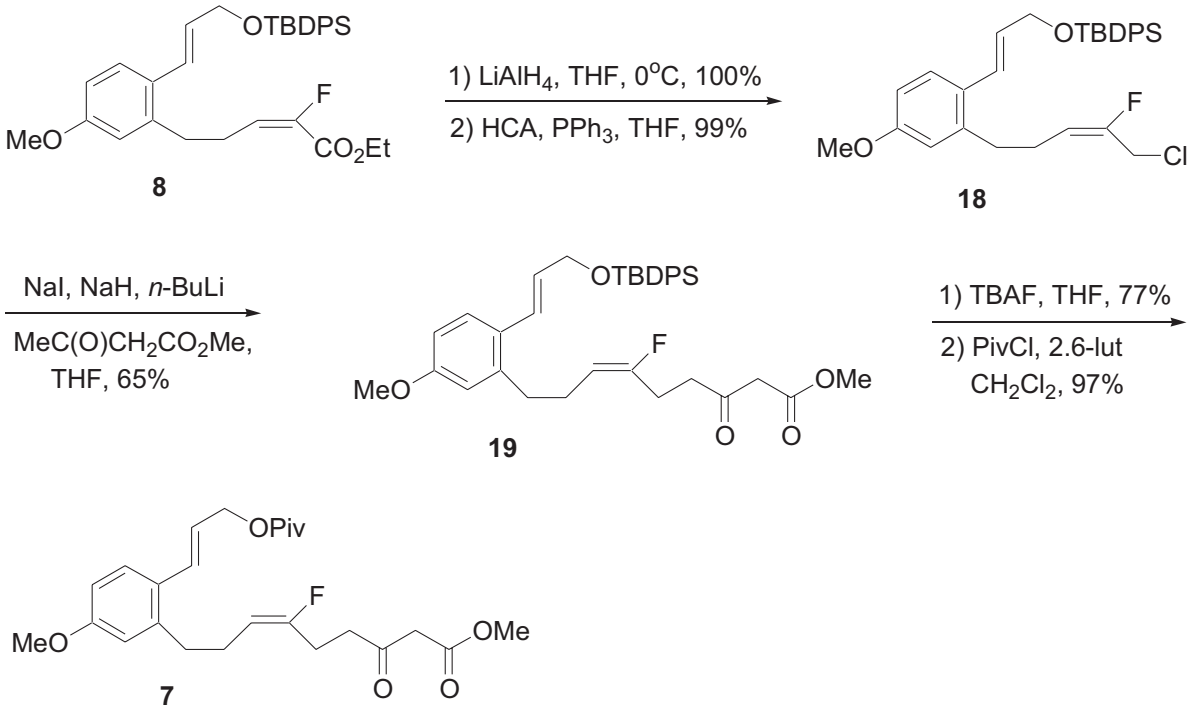
The macrocycle **6** contains the *E*-dienophile and *E,E*-diene that are necessary to obtain the TSC tetracycle after the TADA reaction. This key step was accomplished by heating macrocycle **6** at 165 °C in the presence of triethylamine in a sealed tube for 4 h. The TSC tetracycle **21** was obtained in 78% yield as a single isomer. In this step, four new chiral centers were formed simultaneously with a high degree of stereoselectivity.

The selective formation of the TSC tetracycle can be explained by considering the transition state of the TADA reaction. As seen in Scheme 5, in transition state **22**, the olefins are perfectly aligned for the TADA reaction without any severe steric interaction. The other possible TADA product, CST tetracycle **21a**, cannot be obtained owing to improper orbital alignment (transition state **22a**). Thus, this transannular process allows complete control in the formation of TSC tetracycle **21** (18). The desired key 17β-fluoro racemic intermediate was thus obtained with a very good yield at each step.

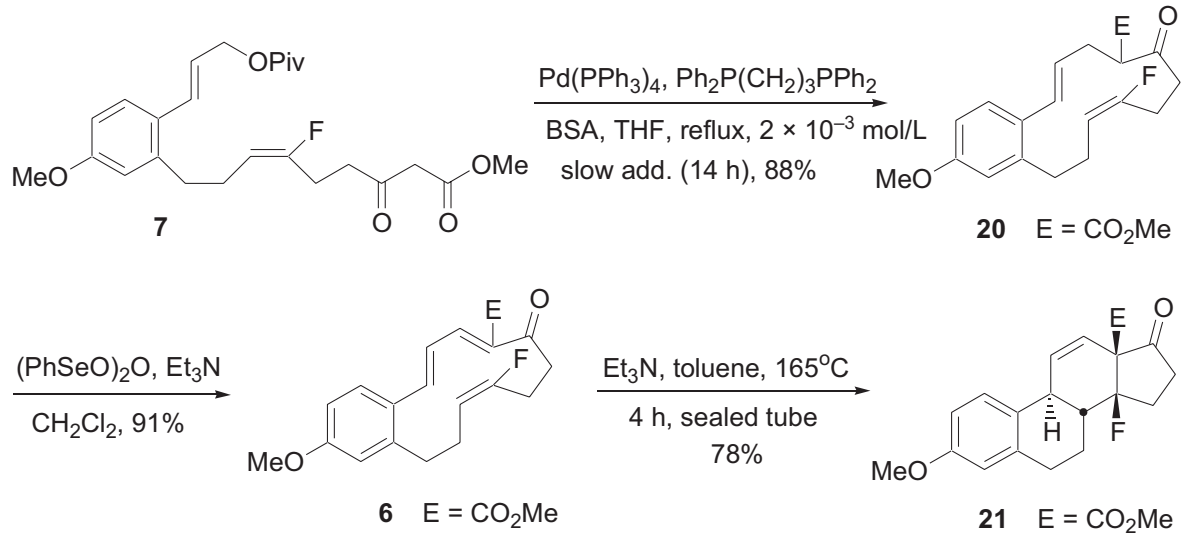
Installation of the C-13 methyl group and a model study for the homologation at the C-17 position

Having built the key intermediate **21**, the next step was to

Scheme 3.



Scheme 4.

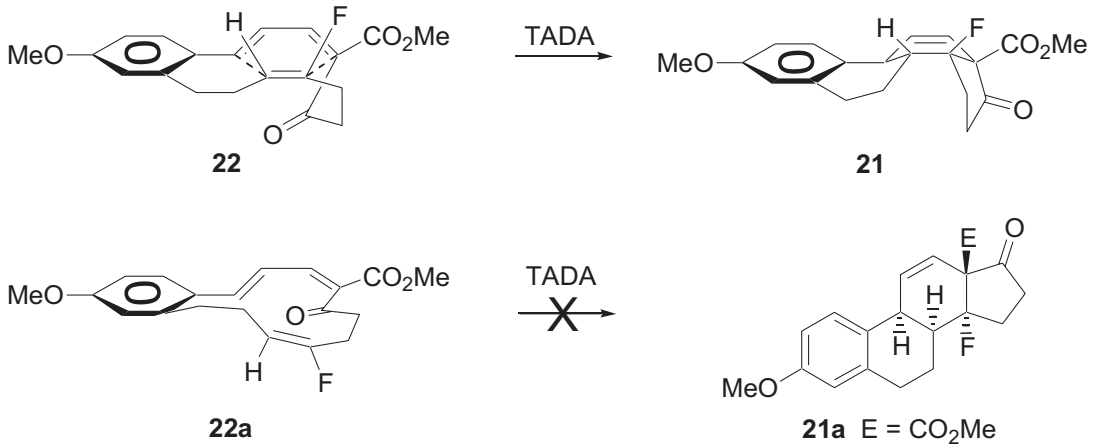


obtain a methyl group at the C-13 position and explore the homologation at the C-17 position.

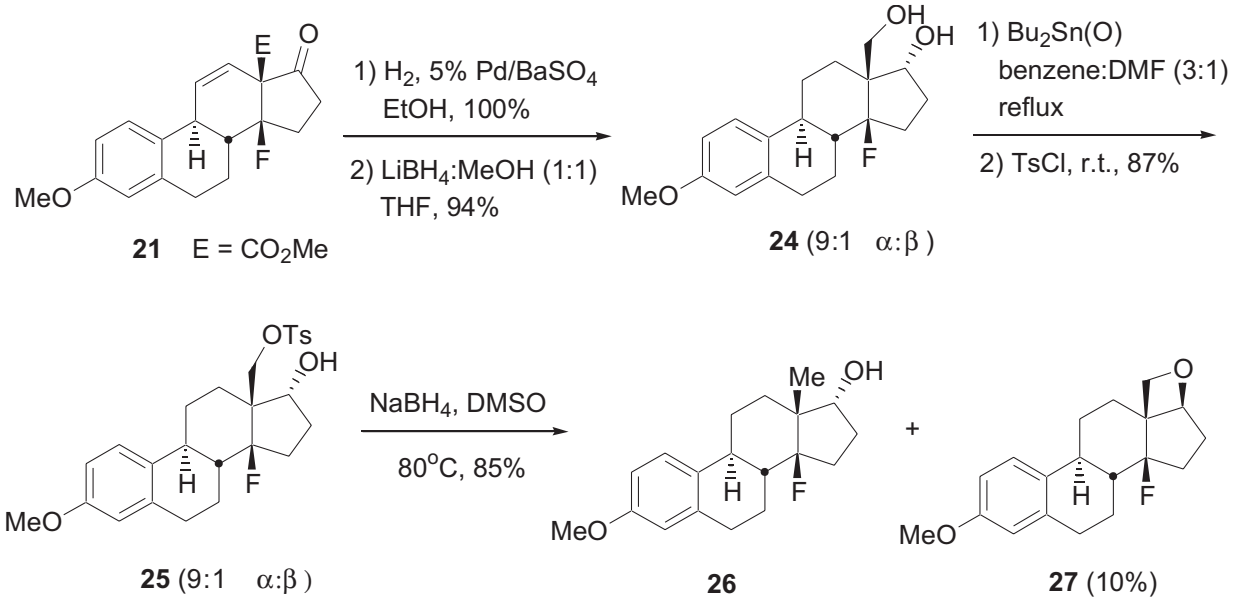
Hydrogenation of the olefin in tetracycle **21** (Scheme 6) was carried out, and compound **23** was obtained in quantitative yield. Reduction of the ester and ketone moieties was performed to give diol **24** as a 9:1 mixture of α:β isomers at C-17, which could not be separated. Selective tosylation of the primary alcohol of this diol mixture was then achieved in two steps (19). First, the diol **24** was treated with dibutyltin oxide at reflux in a mixture of benzene and DMF with a Dean–Stark trap and the corresponding ketal tin intermediate was formed. Tosyl chloride was then added to produce a 9:1 mixture (α:β isomers) of tosylate **25** in 87% yield. This mixture was reduced with sodium borohydride, and compound **26** was obtained pure in 85% yield after chromatography. Oxetane **27** was also obtained as a side product in 10% yield. This compound must come from the intramolecular displacement of the C-17 tosylate by the β-secondary alcohol of the minor β isomer of **25**.

Having tetracycle **26** with the desired methyl group at the C-13 position in hand, homologation at the C-17 position was then investigated. Many types of reactions for C-17 homologation of steroids are known in the literature (20). In our case, many attempts were made to add one carbon at this position. Several homologation methods were tried (Wittig (21), epoxidation (22, 23), S_N2 reaction, etc.), but the best results were obtained with a coupling reaction. The alcohol was first oxidized with TPAP–NMO (24) to give ketone **5** in 87% yield (Scheme 7). This ketone was treated with KHMDS to form the corresponding enolate. Comins reagent (25) was

Scheme 5.



Scheme 6.



then added, and the triflic enol ether **28** was obtained in 84% yield.

Palladium-catalyzed coupling of **28** was then investigated. Carbonylation (26) of compound **28** catalyzed by $Pd(OAc)_2$ led to the α,β-unsaturated ester **29** in 81% yield. This unsaturated ester was reduced with a catalytic amount of palladium to give ester **30** in a quantitative yield as a single isomer. Unfortunately, the isomer obtained at the C-17 center was α rather than the desired β isomer (confirmed by ^{1}H NMR shift of the β proton). To obtain the C-17 β isomer **31**, epimerization conditions were explored but without success. A survey of the literature (27) indicated that with an ester at C-17, both the kinetic and thermodynamic isomers correspond to the α isomer when the C–D ring junction is cis.

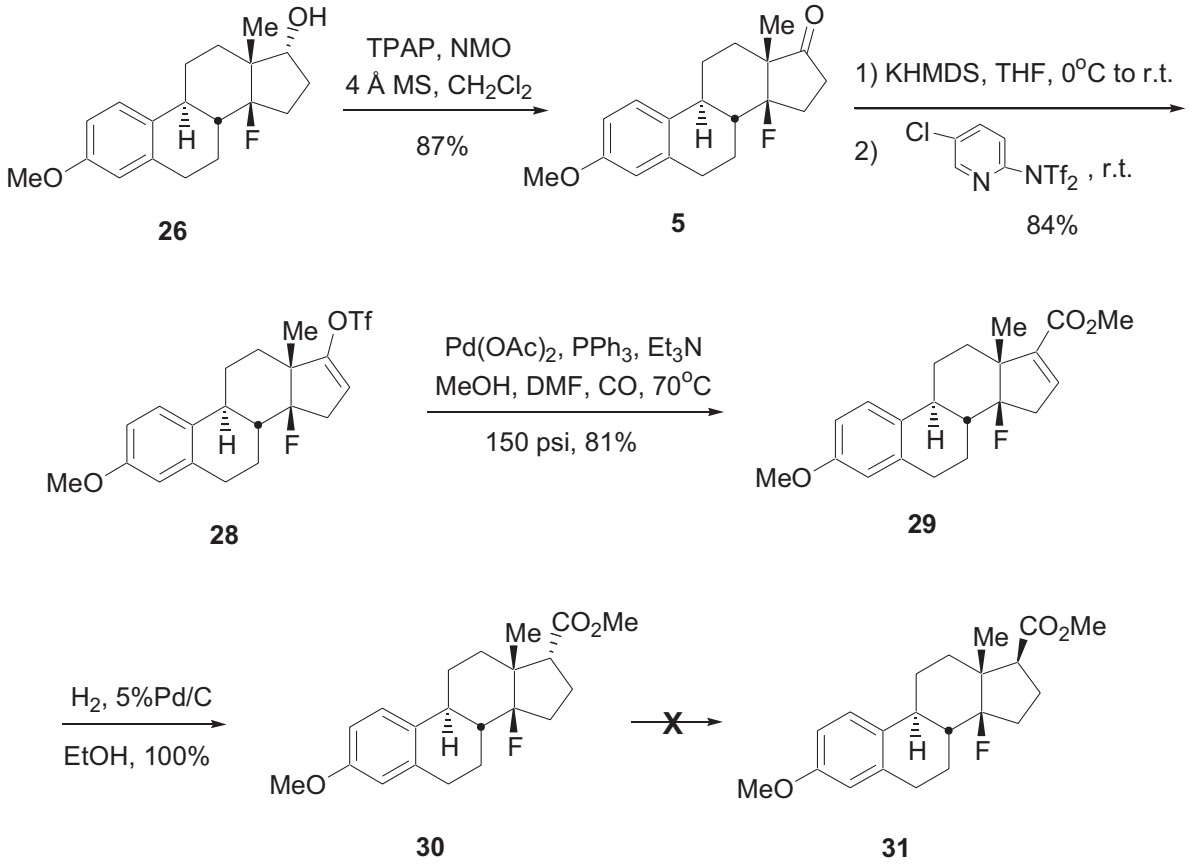
The only method to obtain the β C-17 center with the C–D cis ring junction is by using a nitrile (28). The coupling reaction was therefore performed on the triflic enol ether **28** with $Pd(PPh_3)_4$ and LiCN (29) from which α,β-unsaturated nitrile **32** was obtained in 79% yield (Scheme 8). Hydrogenation of this α,β-unsaturated nitrile provided a mixture of α- (**33a**, 37%) and β- (**33b**, 58%) nitriles, which were separated by chromatography. The structure of β-nitrile **33b** was confirmed by a X-ray diffraction analysis (Fig. 2). Having obtained the desired β-nitrile, the model study for the C-17 homologation was thus completed (Table 1).[2]

Functionalization of ring A

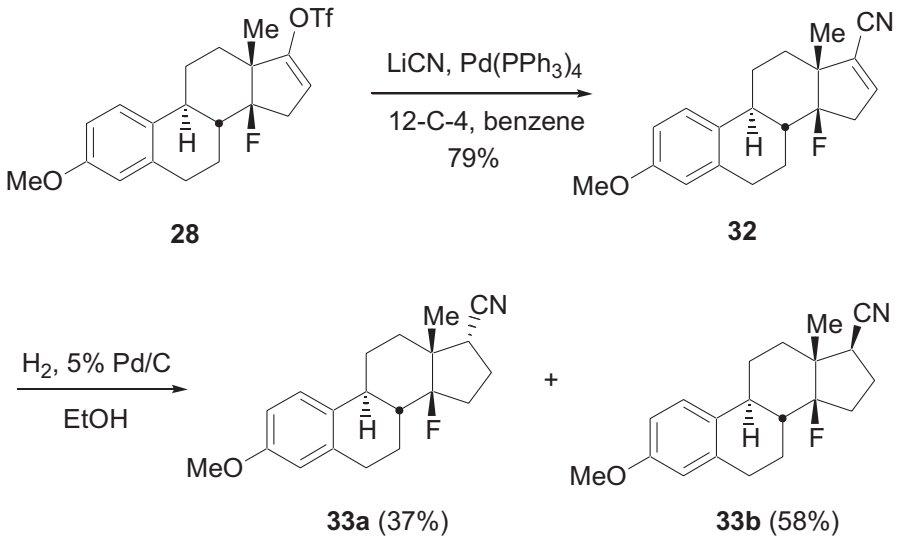
Starting from alcohol **26**, Birch reduction (30) with lithium metal was performed at –78 °C, and the corresponding enol ether was hydrolyzed with 1 N HCl to afford the α,β-

[2] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Building M-55, 1200 Montreal Road, Ottawa, ON K1A 0R6, Canada. DUD 4073. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 264404 and 264405 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Scheme 7.



Scheme 8.



unsaturated ketone **34** in 77% yield (Scheme 9). The proton at the C-10 position was β, as expected. We were pleased to see that the fluorine atom was not hydrogenolyzed at –78 °C, since this had occured at –30 °C.

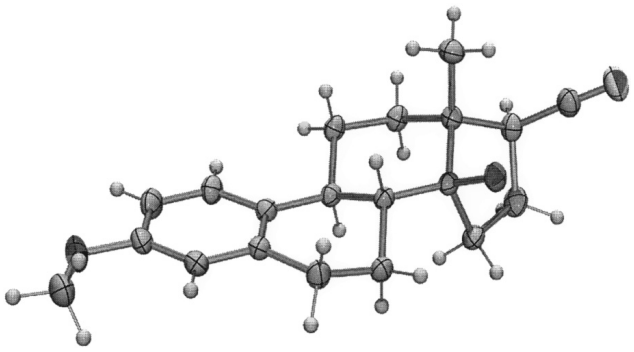
To obtain the desired cis A–B ring junction, hydrogenation of the α,β-unsaturated ketone **34** was accomplished with a catalytic amount of palladium (Scheme 9) to yield the cis and trans isomers **36** and **35** in 60% and 37% yields, respectively. The two isomers were easily separated and the synthesis was continued with tetracycle **36**, which had the A–B cis ring junction. Oxidation of tetracycle **36** with TPAP–NMO (23) furnished the diketone **37** in 99% yield.

Selective reduction of the ketone at the C-3 position should be possible with a hydride source sensitive to the steric hindrance (31). In addition, with such a hydride source, the reduction of the C-3 center to afford the β alco-

Table 1. X-ray crystallographic information for nitrile **33b** and nitro **47**.

Crystal	Nitrile **33b**	Nitro **47**
Empirical formula	$C_{20}H_{24}FNO$	$C_{26}H_{31}FN_2O_4$
Formula mass	313.40	454.53
Colour, habit	Colourless, plate	Colourless, plate
Crystal dimension (mm^3)	0.4 × 0.3 × 0.3	0.05 × 0.40 × 0.50
Crystal system	Prism	Triclinic
Space group	*P*1	*P*1
Z	4	2
a (Å)	9.601(2)	6.6631(10)
b (Å)	16.891(4)	9.5374(15)
c (Å)	10.3300(19)	18.128(3)
α (°)	90.00	92.969(3)
β (°)	98.40(4)	94.269(3)
γ (°)	90.00	102.600(3)
Collection ranges	$-11 < h < 11, 0 < k < 20, 0 < l < 12$	$-8 < h < 8, -12 < k < 11, -23 < l < 21$
Temperature (K)	293(2)	173(1)
Volume ($Å^3$)	1657.3(6)	1118.4(3)
D_{calcd} (Mg m^{-3})	1.256	1.350
Abs. coeff. (μ) (mm^{-1})	0.673	0.096
F(000)	672	484
θ Range for data collection (°)	5.05–71.76	2.19–27.50
No. of obsrvd. reflns.	3220	7872
No. of ind. reflns.	2873	4952
No. of data/restr./params.	3220/0/209	4952/0/422
Max. shift/error	0.002/0.000	0.000/0.000
Goodness-of-fit on F^2	1.031	1.083
Final *R* indices [$l > 2\sigma(l)$]	$R_1 = 0.0420$, $wR_2 = 0.1123$	$R_1 = 0.0491$, $wR_2 = 0.1362$
R indices (all data)	$R_1 = 0.0383$, $wR_2 = 0.1092$	$R_1 = 0.0617$, $wR_2 = 0.1429$
Max. diff. peak and hole (e $Å^{-3}$)	0.283 and –0.148	0.396 and –0.226

Fig. 2. Single crystal X-ray structure of nitrile β-**33b**.



hol should be favored (32). Indeed, the use of L-Selectride as the reducing agent on diketone **37** gave a quantitative yield of the β C-3 alcohol **38** (Scheme 9).

Fluoro analog synthesis and biological activities

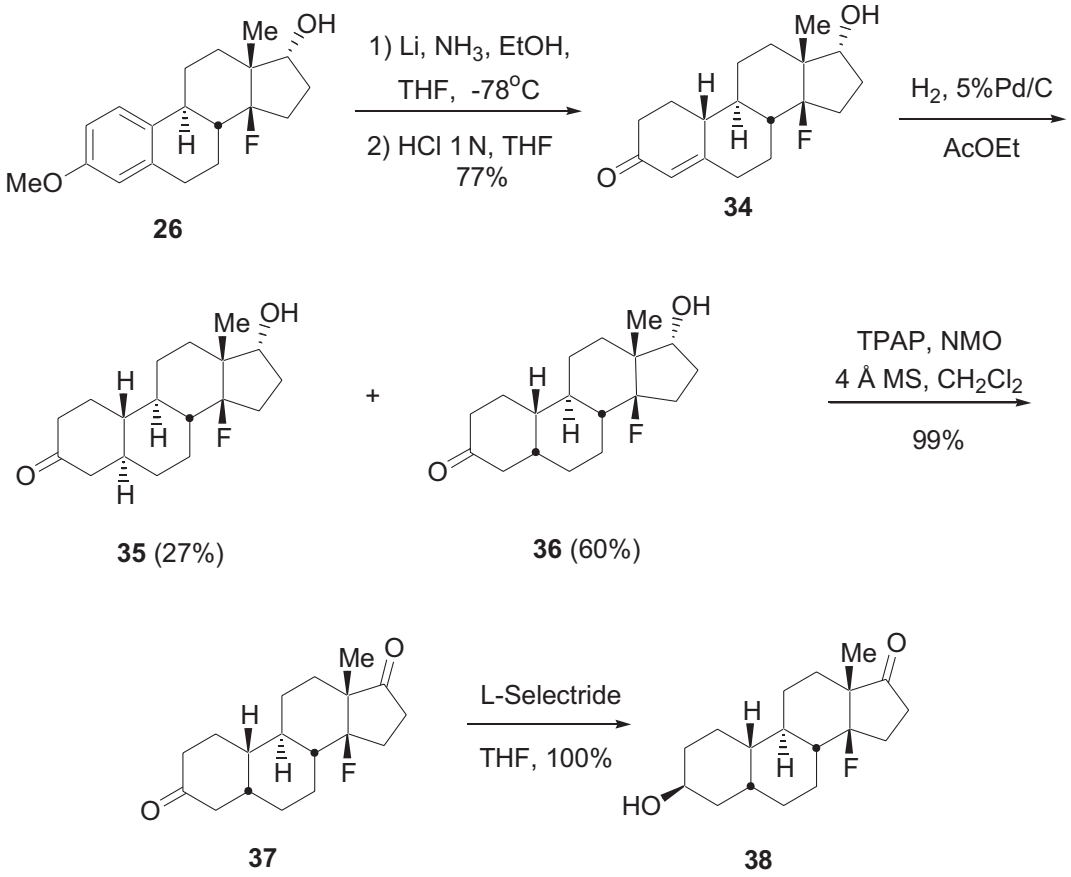
To complete the synthesis of the fluoro analogs, we had to carry out the nitrile homologation at the C-17 position developed in the model study and to introduce the α,β-unsaturated ester at the C-17 position.

Alcohol **38** was protected with TBDMSOTf (Scheme 10), and a mixture of the desired silyl ether **40** and silyl enol ether **39** was obtained. This mixture was treated with TBAF, and the silyl ether **40** was the only compound obtained in 92% yield for the two steps. This compound was treated under the same conditions used for the model compound **5** (Scheme 7) to prepare the triflic enol ether **41** without success. The starting material was recovered with some decomposition. We tried other bases (LiHMDS, NaHMDS, and LDA) to make this triflic enol ether, but the same negative results were obtained. We therefore looked for an alternative method via a vinyl iodide intermediate (33).

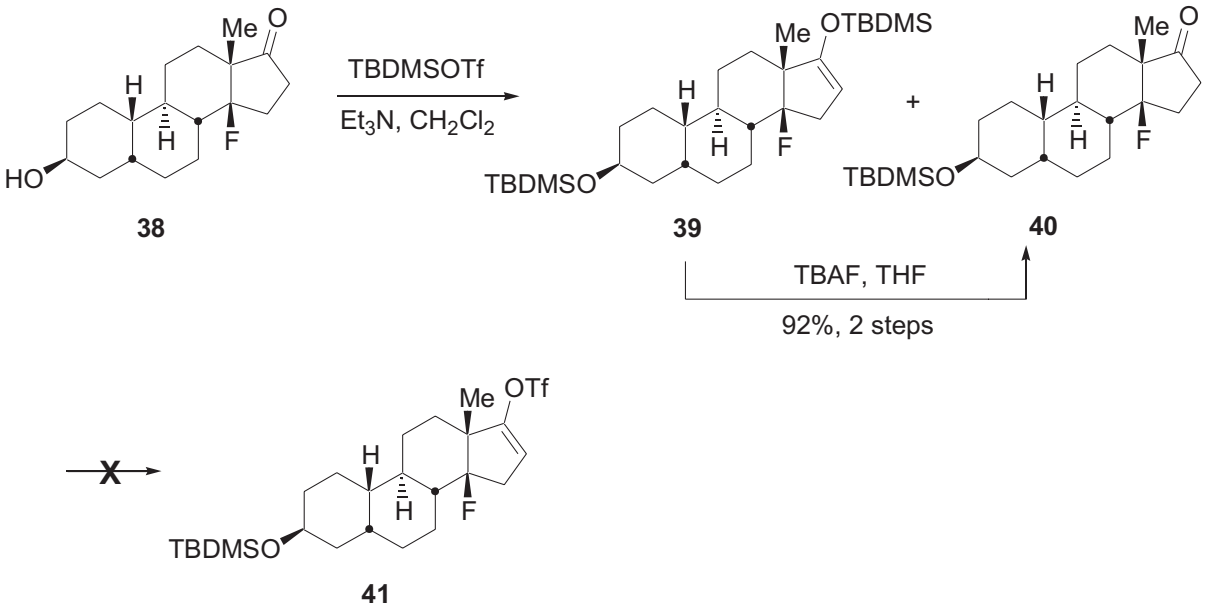
Starting with ketone **38**, the corresponding hydrazone was formed with hydrazine at reflux over 5 days, and this hydrazone was treated with iodine to provide the desired vinylic iodide **42** in 91% yield for the two steps (Scheme 11). The coupling reaction (LiCN, $Pd(PPh_3)_4$, 12-C-4) on this compound having a free alcohol was attempted, but gave a very poor yield. Thus, the alcohol was protected with TBDMSOTf to give compound **43** in a quantitative yield. The same coupling reaction (LiCN, $Pd(PPh_3)_4$, 12-C-4) was performed with vinylic iodide **43**, and the desired α,β-unsaturated nitrile **44** was obtained in 45% yield. This unsaturated nitrile was then hydrogenated to give the β-nitrile **45b** (53%) and the α-nitrile **45a** (47%), which were separated by chromatography.

Deprotection of the silyl ethers **45a** and **45b** was accomplished under acidic conditions to furnish the corresponding compounds **46a** and **46b** in a quantitative yield. To confirm the stereochemistry of the β-nitrile **46b**, the *p*-nitrobenzoate **47** was prepared and an X-ray diffraction analysis was ob-

Scheme 9.



Scheme 10.



tained, which confirmed the stereochemistry of all the asymmetric centers (Fig. 3).

To complete the synthesis, only two steps were required: the reduction of the nitrile to an aldehyde, and a Horner–Emmons reaction to introduce the α,β-unsaturated ester at the C-17 center. DIBALH was used to reduce the nitriles **46a** and **46b**. Reduction of the α-nitrile **46a** at 0 °C gave two compounds (Scheme 12), which were identified as aldehydes **48** and **49**, each containing an olefin. Clearly, the fluoride is sensitive to the presence of Lewis acid. In an attempt to resolve this problem, many other reducing agents were tried ($LiAlH(OEt)_3$, $LiAlH_4$, Raney Ni), but in each

Scheme 11.

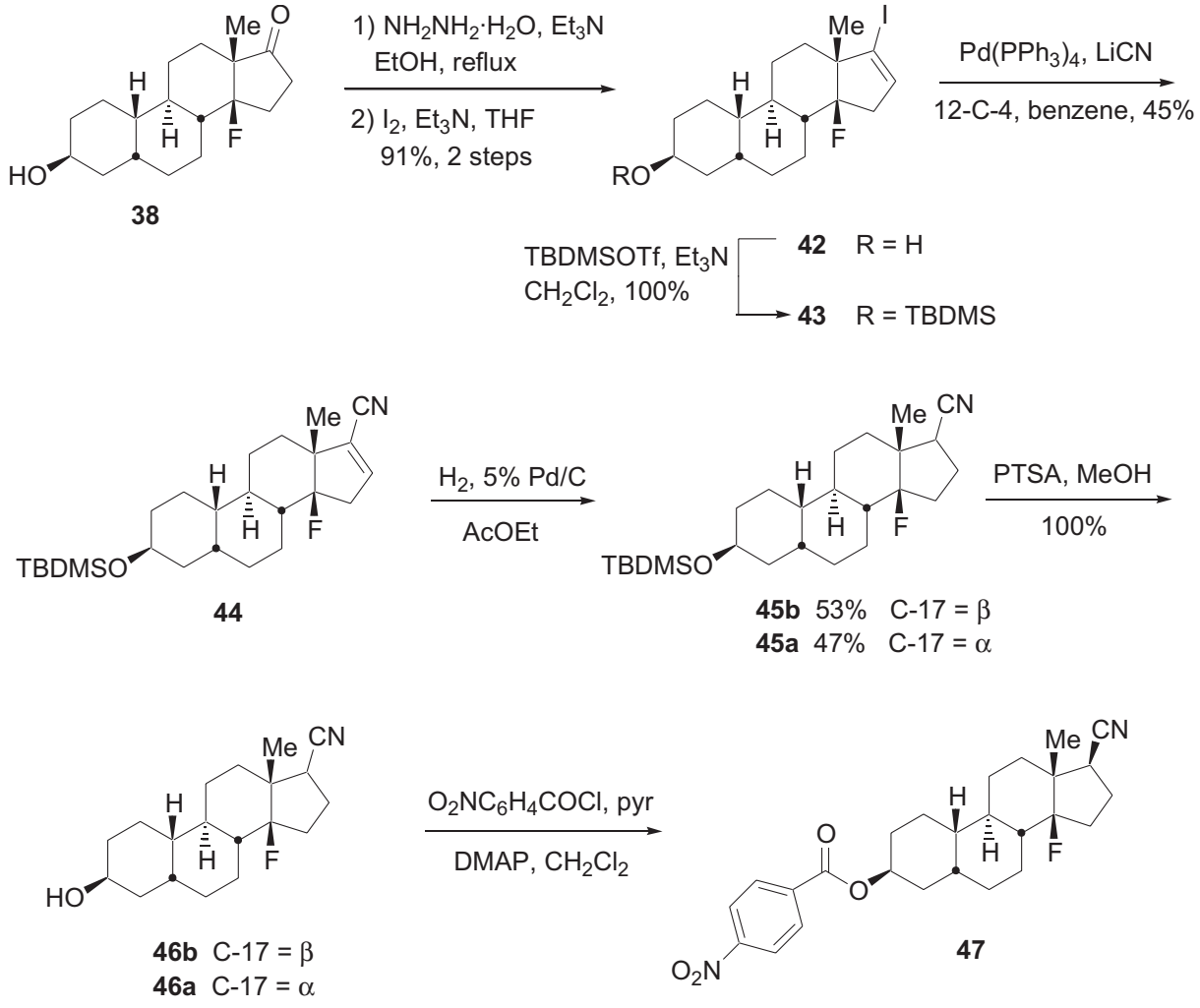
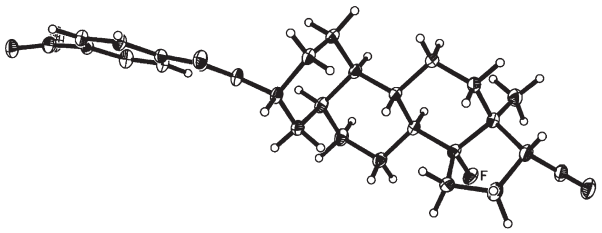


Fig. 3. Single crystal X-ray structure of *p*-nitrobenzoate **47**.



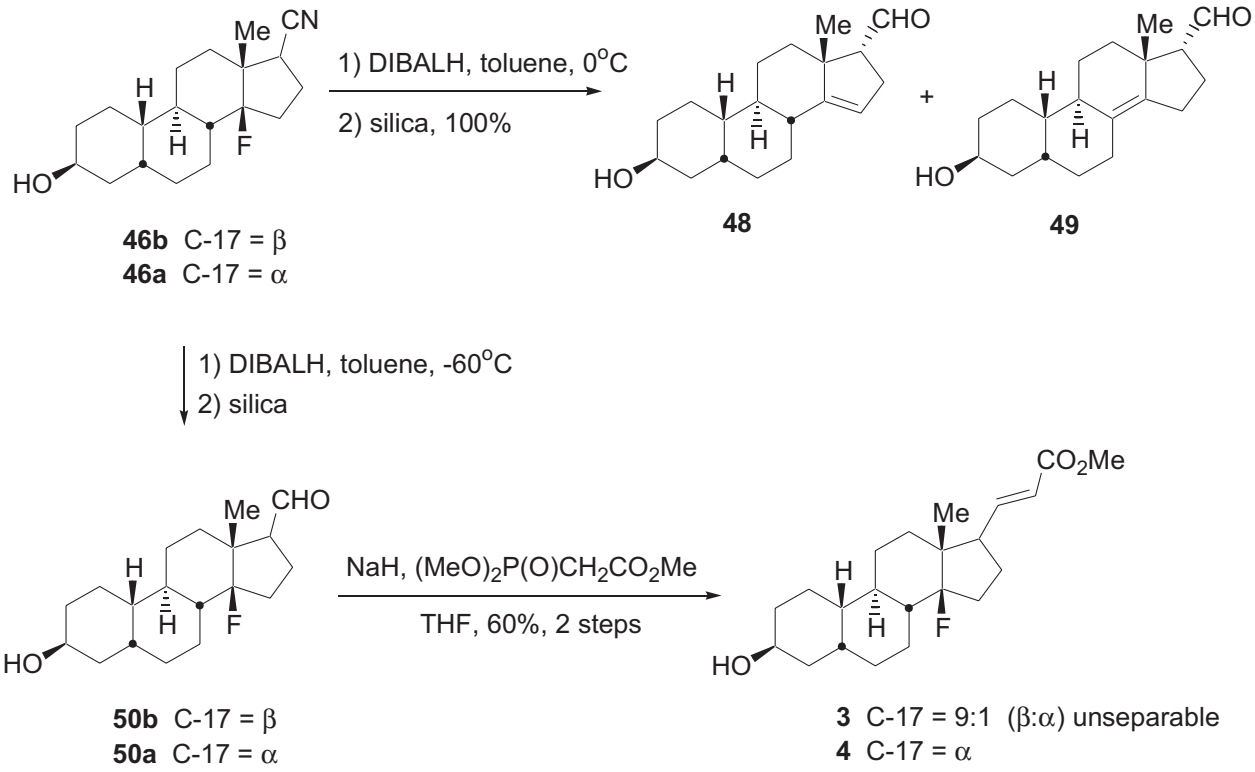
case, the starting material was recovered with some decomposition products. After considering these results, we decided to attempt the reduction of the α-nitrile **46a** with DIBALH at a lower temperature. When the reduction was performed at –78 °C, the starting material was recovered. The corresponding imine was obtained when the reaction was performed at –60 °C with 10 equiv. of DIBALH. To hydrolyze this imine, the residue was passed through a silica gel pad and α-aldehyde **50a** was obtained. The Horner–Emmons reaction was carried out on this aldehyde to furnish the desired α-fluoro analog **4** in 60% yield for the two last steps.

To complete the synthesis of the β-fluoro analog **3**, we had to repeat the last two steps previously discussed on the β-nitrile **46b**. Reduction of β-nitrile **46b** with DIBALH worked well to give the corresponding imine, but when this imine was passed through the silica gel pad, partial isomerization of the β- to α-aldehyde took place (Scheme 12).

To resolve this problem of epimerization, we tried to use aqueous conditions to hydrolyze the β-imine but with no success. Better results were obtained when the β-imine was passed rapidly through a short silica gel pad, and the corresponding aldehyde was obtained as a mixture of β-aldehyde **50b** and α-aldehyde **50a** (9:1). The Horner–Emmons reaction was performed on this mixture of aldehydes to give an unseparable 9:1 mixture of the β-fluoro analog **3** and α-fluoro analog **4**. This mixture was used to study the biological activity for the β-fluoro analog.

The biological activities of these two racemic fluoro analogs **3** and **4** were studied and compared with digitoxigenin **1**. Radioligand binding studies were performed to measure ligand–receptor affinities for **1**, **3**, and **4** at the ouabain receptor (i.e., ATPase (Na^+/K^+) expressed in the MDCK (dog kidney) cell line). [^{3}H]ouabain was used as the radioligand for competitive displacement. Compound binding affinities are reported as IC_{50} values, indicative of the drug concentration needed to inhibit 50% of [^{3}H]ouabain binding to the Na^+,K^+-ATPase. The results are very surpris-

Scheme 12.



ing. We expected that the inhibitory activity of the β-fluoro analog **3** would be superior to that α-fluoro analog **4**, but it was not the case. The β-fluoro analog **3** exhibited no activity, while the α-fluoro analog **4** had an IC_{50} of 12 μmol/L, in comparison to the natural product digitoxigenin **1** (IC_{50} of 0.35 μmol/L). No explanation can be provided to rationalize this result. However, the primary result obtained with the α-fluoro analog **4** has encouraged us to continue with the synthesis of other analogs to optimize the biological activity of this class of fluoro-steroids, and the results will be presented in another publication.

Summary

In summary, the synthesis of the fluoro analogs **3** and **4** was carried out via the formation of β-keto ester **7** with excellent yields. The macrocyclization reaction with this β-keto ester afforded the 13-membered macrocycle **6** with the trans-cis-cis olefin geometry, the precursor needed for the TADA reaction. The key step of the synthesis, the TADA reaction, was performed on this macrocycle to give the steroidal tetracycle **21** with the desired TSC configuration at the ring junction. With this TADA reaction, four new centers were created in one step to give the expected tetracycle **21**. This key tetracycle was obtained in 19 steps with very high yields and complete control of the diastereoselectivity. The functionalization of the A ring was accomplished and the homologation of the C-17 position was performed to give the desired α- and β-fluoro analogs.

The fluoro analog syntheses have been achieved in 35 steps in a linear sequence with 0.7% overall yield. The chemoselectivity, regioselectivity, and stereochemistry were controlled at each step of the synthesis except for the reduction of the β-nitrile **46b** to the corresponding aldehyde at the end of the sequence that gives 10% epimerization. The biological activity was measured for the two fluoro analogs. Surprisingly, the α-fluoro analog **4** provided 5% of the inhibitory potency of natural digitoxigenin **1**.

Experimental section

General

All reactions were performed under a nitrogen atmosphere with oven (150 °C) or flame-dried glassware. All solvents were distilled prior to use: ether and tetrahydrofuran from sodium–benzophenone; toluene, dichloromethane, and dimethyl sulfoxyde were distilled over calcium hydride, and methanol from magnesium–iodine. Most amines were dried over calcium hydride and distilled. All other starting materials and reagents were obtained commercially and used as such. For reaction workups, all organic phases were dried over magnesium sulphate. Analytical TLC was carried out on precoated glass plates (0.25 mm) with silica gel 60 (230–400 mesh). The following abbreviations were used for NMR data: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m), broad (br). Chemical shifts are reported in ppm δ units relative to chloroform (7.26 ppm for ^{1}H NMR and 77.0 ppm for decoupled ^{13}C NMR) as internal standard. ^{1}H and ^{13}C NMR spectra are referenced with respect to the residual signals of the solvent; they are described using standard abbreviations. ^{13}C NMR spectra of fluoro compounds give more carbon signals (one to five) owing to fluorine coupling with carbon. Melting points (mp) are uncorrected. Mass spectra (MS) were obtained with electronic ionization (70 eV).

Olefin 11

To a stirred solution of ketone **10** (20 g, 113 mmol) in tetrahydrofuran (500 mL) at –78 °C was added lithium aluminium hydride (2.2 g, 57 mmol). The mixture was stirred at –78 °C for 1 h and sodium sulfate decahydrate was added. The mixture was stirred at room temperature for 1 h and the precipitate was filtrated and washed with dichloromethane. The solvent was evaporated and crude alcohol was diluted in benzene. *p*-Toluenesulfonic acid (215 mg, 1.13 mmol) was added and the mixture was stirred at reflux with a Dean–Stark for 1.5 h. Satd. aq. $NaHCO_3$ was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The crude compound was filtered on a silica gel pad and washed with ethyl acetate – hexanes (3:7) to give olefin **11** as a colorless oil (19 g, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3030, 2933, 2830, 1606, 1569, 1500, 1464, 1428, 1253. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.96 (1H, d, J = 9.1 Hz, Ph), 6.71–6.68 (2H, m, Ph), 6.42 (1H, dt, J = 9.3, 1.9 Hz, PhCH=C*H*CH_2), 5.90 (1H, dt, J = 9.3, 4.4 Hz, PhC*H*=$CHCH_2$), 3.80 (3H, s, $ArOCH_3$), 2.78 (2H, t, J = 8.2 Hz, $PhCH_2CH_2$), 2.33–2.26 (2H, m, $PhCH{=}CHCH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.53, 137.08, 127.32, 127.14, 126.78, 125.81, 113.79, 111.02, 55.13, 27.97, 22.96. MS (*m*/*e*): 160 ($[M]^+$). HR-MS calcd. for $C_{11}H_{16}O_3$: 160.0888 ($[M]^+$); found: 160.0887 ± 0.0005.

Diol 9

To a stirred solution of olefin **11** (26.0 g, 160.3 mmol) in methanol (2 L) at –78 °C, O_3 was bubbled at –78 °C for 1.5 h. Nitrogen was bubbled for 15 min and sodium borohydride (12.1 g, 319.9 mmol) was added. The mixture was stirred at room temperature for 2 h and sodium borohydride (6.1 g, 160.0 mmol) was added. The mixture was stirred for 1 h and solvent was evaporated. The crude compound was diluted in tetrahydrofuran (1 L) and an aqueous solution of 2.5 mol/L NaOH (330 mL) and 30% hydrogen peroxide (230 mL) were added. The mixture was stirred at room temperature for 18 h. Aqueous sodium thiosulfate solution (10%) was added and the aqueous phase was extracted with chloroform. The combined organic phases were dried, filtered, and evaporated to give diol **9** as an amorphous white solid (27.1 g, 86%). IR ($CHCl_3$, cm^{-1}) ν: 3327, 2939, 2875, 1610, 1580, 1500, 1460, 1256, 1160, 1111, 1055, 1031, 942, 819. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (1H, d, J = 8.3 Hz, Ph), 6.78 (1H, d, J = 2.7 Hz, Ph), 6.72 (1H, dd, J = 8.3, 2.7 Hz, Ph), 4.63 (2H, s, $ArCH_2OH$), 3.80 (3H, s, $ArOCH_3$), 3.57 (2H, t, J = 5.9 Hz, CH_2CH_2OH), 2.82 (2H, t, J = 7.3 Hz, $ArCH_2CH_2$), 2.49 (2H, broad, $ArCH_2OH$, CH_2CH_2OH), 1.93 (2H, quint, J = 6.1 Hz, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 159.34, 142.05, 131.06, 130.80, 115.02, 110.88, 62.41, 60.74, 55.17, 33.63, 27.26. MS (*m*/*e*): 196 ($[M]^+$). HR-MS calcd. for $C_{11}H_{16}O_3$: 196.1099 ($[M]^+$); found: 196.1108 ± 0.0006.

Hydroxyaldehyde 12

To a stirred solution of diol **9** (9.5 g, 48.5 mmol) in a mixture of pentane–dichloromethane (4:1) (100 mL) was added MnO_2 (21.0 g, 242.5 mmol) and the mixture was stirred at room temperature for 30 min. MnO_2 was added in portions of 21.0 g every 30 min until the reaction was finished. The mixture was filtered on a silica gel pad and was further washed with ethyl acetate. The solvent was evaporated to give hydroxyaldehyde **12** as a yellow oil (8.0 g, 85%). IR ($CHCl_3$, cm^{-1}) ν: 3414, 2942, 2872, 1682, 1599, 1566, 1496, 1463, 1431, 1290, 1251, 1121, 1057, 1025, 813. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 10.06 (1H, s, C*H*O), 7.78 (1H, d, J = 8.6 Hz, Ph), 6.89 (1H, dd, J = 8.6, 2.5 Hz, Ph), 6.82 (1H, d, J = 2.5 Hz, Ph), 3.90 (3H, s, $ArOCH_3$), 3.68 (2H, t, J = 6.1 Hz, CH_2CH_2OH), 3.15 (2H, t, J = 7.8 Hz, $ArCH_2CH_2$), 2.06–1.85 (3H, m, $CH_2CH_2CH_2OH$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 191.54, 163.85, 147.53, 135.56, 127.29, 116.40, 111.68, 61.52, 55.44, 34.50, 28.93. MS (*m*/*e*): 194 ($[M]^+$). HR-MS calcd. for $C_{11}H_{14}O_3$: 194.0943 ($[M]^+$); found: 194.0948 ± 0.0006.

Ester 13

To a stirred solution of hydroxyaldehyde **12** (8.7 g, 44.8 mmol) in tetrahydrofuran (200 mL) were added imidazole (7.6 g, 112 mmol) and *tert*-butyldimethylsilyl chloride (10.1 g, 67.2 mmol). The mixture was stirred at room temperature for 45 min and satd. aq. NH_4Cl was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give the corresponding silyl ether as a yellow oil (13.8 g, 100%). IR ($CHCl_3$, cm^{-1}) ν: 2959, 2929, 2856, 2734, 1689, 1600, 1463, 1225, 1102, 1029, 836. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 10.14 (1H, s, C*H*O), 7.80 (1H, d, J = 8.6 Hz, Ph), 6.85 (1H, dd, J = 8.6, 2.6 Hz, Ph), 6.77 (1H, d, J = 2.6 Hz, Ph), 3.87 (3H, s, $ArOCH_3$), 3.68 (2H, t, J = 6.1 Hz, $CH_2CH_2OTBDMS$), 3.07 (2H, dd, J = 7.9, 6.1 Hz, $ArCH_2CH_2$), 1.84 (2H, dt, J = 9.5, 6.1 Hz, $CH_2CH_2CH_2OTBDMS$), 0.91 (9H, s, $Si\text{-}C(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 190.75, 163.7, 147.8, 134.31, 127.5, 116.18, 111.71, 62.19, 55.43, 34.84, 29.95, 25.95, 18.3, –5.3. MS (*m*/*e*): 251 ($[M - C_4H_9]^+$). HR-MS calcd. for $C_{13}H_{19}O_3Si$: 251.1103 ($[M - C_4H_9]^+$); found: 251.1108 ± 0.0007.

To a suspension of sodium hydride 60% in oil (2.5 g, 61.8 mmol) in tetrahydrofuran (350 mL) was added triethyl phosphonoacetate (12.3 mL, 61.8 mmol). The mixture was stirred at room temperature for 15 min and a solution of aldehyde (12.7 g, 41.2 mmol) in tetrahydrofuran (50 mL) was added. The mixture was stirred at room temperature for 20 min and satd. aq. NH_4Cl was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was filtered on a silica gel pad and washed with 10% ethyl acetate in hexanes to give ester **13** as a yellow oil (15.2 g, 97%). IR ($CHCl_3$, cm^{-1}) ν: 2954, 2857, 1712, 1603, 1495, 1464, 1366, 1295, 1257, 1159, 1105, 1032, 979, 837. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.95 (1H, d, J = 15.8 Hz, PhC*H*=CH), 7.56 (1H, d, J = 9.2 Hz, Ph), 6.76–6.73 (2H, m, Ph), 6.28 (1H, d, J = 15.8 Hz, PhCH=C*H*), 4.27 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.84 (3H, s, $ArOCH_3$), 3.77 (2H, t, J = 6.3 Hz, $CH_2CH_2OTBDMS$), 2.81 (2H, dd, J = 9.7, 6.1 Hz, $ArCH_2CH_2$), 1.81 (2H, dt, J = 9.7, 6.1 Hz, $CH_2CH_2CH_2OTBDMS$), 1.35 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 167.26, 161.01, 143.91, 141.48, 128.14, 125.57, 116.95, 115.15,

112.17, 62.17, 60.22, 55.16, 34.34, 29.67, 25.95, 18.30, 14.36, –5.31. MS (*m*/*e*): 363 [M – CH_3]$^+$, 321 ([M – C_4H_9]$^+$). HR-MS calcd. for $C_{20}H_{31}O_4Si$: 363.1991 ([M – CH_3]$^+$); found: 363.1995 ± 0.0011.

Disilyl ether 14

To a stirred solution of ester **13** (18.4 g, 48.7 mmol) in dichloromethane (450 mL) at 0 °C was added 1 mol/L diisobutylaluminium hydride in dichloromethane (121.8 mL, 121.8 mmol). The mixture was stirred at 0 °C for 1 h and sodium sulfate decahydrate was added. The mixture was stirred for 1 h. The precipitate was filtered and washed with dichloromethane. The solvent was evaporated to give the corresponding alcohol as a yellow oil (15.9 g, 97%). IR ($CHCl_3$, cm^{-1}) ν: 3356, 2952, 2857, 1607, 1494, 1464, 1256, 1098, 1033, 967, 836. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.43 (1H, d, *J* = 8.4 Hz, Ph), 6.83 (1H, d, *J* = 15.7 Hz, PhC*H*=CH), 6.77–6.72 (2H, m, Ph), 6.18 (1H, dt, *J* = 15.7, 6.0 Hz, PhCH=C*H*), 4.32 (2H, dd, *J* = 6.0, 1.3 Hz, CH_2OH), 3.82 (3H, s, ArOCH_3), 3.67 (2H, t, *J* = 6.2 Hz, CH_2CH_2OTBDMS), 2.76–2.71 (2H, m, ArCH_2CH_2), 1.79 (2H, dt, *J* = 9.9, 6.1 Hz, $CH_2CH_2CH_2$OTBDMS), 1.60 (1H, massif, CH_2O*H*), 0.94 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 159.13, 141.29, 128.50, 128.11, 128.06, 127.27, 114.85, 111.74, 64.06, 62.44, 55.18, 34.02, 29.76, 25.98, 18.35, –5.25. MS (*m*/*e*): 336 ([M]$^+$). HR-MS calcd. for $C_{19}H_{32}O_3Si$: 336.2121 ([M]$^+$); found: 336.2123 ± 0.0010.

To a stirred solution of alcohol (15.9 g, 47.3 mmol) in tetrahydrofuran (400 mL) were added imidazole (8.1 g, 118.3 mmol) and *tert*-butyldiphenylsilane chloride (18.5 mL, 71.0 mmol). The mixture was stirred at room temperature for 1.5 h and satd. aq. NH_4Cl was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (5% ethyl acetate, 95% hexanes) to give disilyl ether **14** as a yellow oil (25.0 g, 93%). IR ($CHCl_3$, cm^{-1}) ν: 3048, 2934, 2858, 1607, 1495, 1466, 1254, 1106, 1062, 967, 837. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.74 (4H, dd, *J* = 7.5, 1.7 Hz, Ph), 7.48–7.36 (7H, m, Ph), 6.87 (1H, d, *J* = 15.7 Hz, PhC*H*=CH), 6.76–6.72 (2H, m, Ph), 6.10 (1H, dt, *J* = 15.7, 4.9 Hz, PhCH=C*H*), 4.39 (2H, dd, *J* = 6.7, 1.8 Hz, CH_2OTBDPS), 3.82 (3H, s, ArOCH_3), 3.63 (2H, t, *J* = 6.3 Hz, CH_2CH_2OTBDMS), 2.71 (2H, dd, *J* = 9.7, 7.7 Hz, ArCH_2CH_2), 1.84–1.74 (2H, m, $CH_2CH_2CH_2$OTBDMS), 1.58 (9H, s, SiC(CH_3)$_3$), 1.11 (9H, s, SiC(CH_3)$_3$), 0.06 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.92, 141.09, 135.59, 133.79, 129.69, 128.22, 127.73, 127.65, 127.16, 126.46, 114.86, 111.77, 64.84, 62.45, 55.23, 33.97, 29.87, 26.91, 26.02, 19.32, 19.35, –5.20. MS (*m*/*e*): 574 ([M]$^+$). HR-MS calcd. for $C_{35}H_{50}O_3Si_2$: 574.3298 ([M]$^+$); found: 574.3303 ± 0.0017.

Alcohol 15

To a stirred solution of disilyl ether **14** (40.3 g, 70.2 mmol) in ethanol 95% (500 mL) was added *p*-toluenesulfonate pyridinium salt (1.8 g, 7.02 mmol) and the mixture was stirred at room temperature overnight. Satd. aq. $NaHCO_3$ was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (50% ethyl acetate, 50% hexanes) to give alcohol **15** as a yellow oil (31.5 g, 98%). IR ($CHCl_3$, cm^{-1}) ν: 3390, 3048, 2937, 2859, 1607, 1496, 1465, 1380, 1256, 1202, 1110, 1057, 967. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.75 (4H, dd, *J* = 7.5, 1.7 Hz, Ph), 7.48–7.38 (7H, m, Ph), 6.89 (1H, dt, *J* = 15.6, 1.7 Hz, PhC*H*=CH), 6.78–6.73 (2H, m, Ph), 6.11 (1H, dt, *J* = 15.6, 4.7 Hz, PhCH=C*H*), 4.41 (2H, dd, *J* = 4.7, 1.9 Hz, CH_2OTBDPS), 3.82 (3H, s, ArOCH_3), 3.65 (2H, t, *J* = 6.3 Hz, CH_2CH_2OH), 2.75 (2H, dd, *J* = 7.9, 6.2 Hz, ArCH_2CH_2), 1.89–1.80 (2H, m, $CH_2CH_2CH_2$), 1.61 (1H, massif, CH_2O*H*), 1.11 (9H, s, SiC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.94, 140.71, 135.56, 133.72, 129.71, 128.63, 128.35, 127.73, 127.25, 126.29, 114.84, 111.85, 64.68, 62.19, 55.25, 33.78, 29.74, 26.86, 19.32. MS (*m*/*e*): 403 ([M – C_4H_9]$^+$). HR-MS calcd. for $C_{25}H_{27}O_3Si$: 403.1729 ([M – C_4H_9]$^+$); found: 403.1734 ± 0.0012.

Aldehyde 16

To a stirred solution of DMSO (14.6 mL, 205.5 mmol) in dichloromethane (700 mL) at –78 °C were slowly added oxalyl chloride (12.0 mL, 137.0 mmol) and the alcohol **15** (31.5 g, 68.5 mmol) in dichloromethane. The mixture was stirred at –78 °C for 45 min and triethylamine (38.5 mL, 274.0 mmol) was added. The mixture was stirred at room temperature for 1 h and satd. aq. NH_4Cl was added. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was filtered on a silica gel pad and washed with 50% ethyl acetate in hexanes to give aldehyde **16** as a yellow oil (31.5 g, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3078, 2935, 2857, 2721, 1925, 1607, 1496, 1428, 1256, 1110, 967. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 9.78 (1H, s, C*H*O), 7.73 (4H, dd, *J* = 7.5, 1.6 Hz, Ph), 7.49–7.38 (7H, m, Ph), 6.83 (1H, dt, *J* = 15.6, 1.8 Hz, PhC*H*=CH), 6.77 (1H, dd, *J* = 5.8, 2.8 Hz, Ph), 6.71 (1H, d, *J* = 2.8 Hz, Ph), 6.11 (1H, dt, *J* = 15.5, 4.7 Hz, PhCH=C*H*), 4.41 (2H, dd, *J* = 4.7, 1.9 Hz, CH_2OTBDPS), 3.82 (3H, s, ArOCH_3), 2.98 (2H, dt, *J* = 7.4 Hz, ArCH_2CH_2), 2.71 (2H, t, *J* = 7.24 Hz, CH_2CH_2CHO), 1.11 (9H, s, SiC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 201.26, 139.06, 135.56, 133.68, 129.76, 129.03, 128.54, 127.83, 127.76, 127.67, 127.51, 125.70, 114.77, 112.26, 64.57, 55.27, 44.74, 26.87, 25.97, 19.33. MS (*m*/*e*): 458 ([M]$^+$), 401 ([M – C_4H_9]$^+$). HR-MS calcd. for $C_{29}H_{34}O_3Si$: 458.2277 ([M]$^+$); found: 458.2282 ± 0.0014.

Ester 8

To a stirred solution of fluorophosphonate **17** (10.2 g, 42.3 mmol) in tetrahydrofuran (700 mL) at –78 °C was added a 1.4 mol/L solution of *n*-butyl lithium in hexanes (32.0 mL, 42.3 mmol). The mixture was stirred at –78 °C for 10 min and aldehyde **16** (12.9 g, 28.2 mmol) in tetrahydrofuran was added. The mixture was stirred at –78 °C for 45 min and satd. aq. NH_4Cl was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give ester **8** as a colorless oil (14.3 g, 93%). IR ($CHCl_3$, cm^{-1}) ν: 3048, 2935, 2858, 1728, 1607, 1496, 1465,

1376, 1254, 1112, 1047, 967, 822. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.75 (4H, dd, *J* = 7.5, 1.6 Hz, Ph), 7.46–7.37 (7H, m, Ph), 6.89 (1H, dt, *J* = 15.6, 1.7 Hz, PhC*H*=CH), 6.78 (1H, dd, *J* = 8.5, 2.7 Hz, Ph), 6.72 (1H, d, *J* = 2.7 Hz, Ph), 6.12 (1H, dt, *J* = 15.5, 4.8 Hz, PhCH=C*H*), 5.97–5.84 (1H, m, CH_2CH=$CFCO_2Et$), 4.42 (2H, dd, *J* = 4.8, 1.8 Hz, CH_2OTBDPS), 4.26 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.83 (3H, s, $ArOCH_3$), 2.80–2.79 (4H, m, $ArCH_2CH_2$), 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.12 (9H, s, $SiC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.96, 148.99, 145.65, 139.41, 135.56, 134.84, 133.74, 129.72, 128.71, 127.73 127.36, 126.02, 122.35, 122.10, 114.87, 112.16, 64.68, 61.36, 55.25, 32.83, 26.87, 26.59, 19.33, 14.15. MS (*m*/*e*): 546 ($[M]^+$). HR-MS calcd. $C_{33}H_{39}O_4SiF$: 546.2601 ($[M]^+$); found: 546.2596 ± 0.0016.

Chloride 18

To a solution of ester **8** (33.4 g, 61.2 mmol) in tetrahydrofuran (600 mL) at 0 °C was added lithium aluminium hydride (2.32 g, 61.2 mmol). The mixture was stirred at 0 °C for 20 min and sodium sulfate decahydrate was added. The mixture was stirred for 1 h and the precipitate was filtered and washed with dichloromethane. The solvent was evaporated to give the alcohol as a colorless oil (30.8 g, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3433, 3047, 2936, 2858, 1735, 1607, 1496, 1429, 1253, 1111, 967, 854. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.77 (4H, dd, *J* = 7.5, 1.7 Hz, Ph), 7.50–7.40 (7H, m, Ph), 6.90 (1H, dt, *J* = 15.6, 1.6 Hz, PhC*H*=CH), 6.79 (1H, dd, *J* = 8.6, 2.7 Hz, Ph), 6.69 (1H, d, *J* = 2.7 Hz, Ph), 6.14 (1H, dt, *J* = 15.5, 4.6 Hz, PhCH=C*H*), 5.23 (1H, dt, *J* = 20.6, 8.4 Hz, CH_2CH=$CFCH_2OH$), 4.44 (2H, dd, *J* = 4.6, 1.9 Hz, CH_2OTBDPS), 3.98 (2H, d, *J* = 21.4 Hz, CH_2OH), 3.83 (3H, s, $ArOCH_3$), 2.76 (2H, t, *J* = 7.3 Hz, $ArCH_2CH_2$), 2.30 (2H, q, *J* = 7.6 Hz, $ArCH_2CH_2$), 1.49 (1H, massif, CH_2OH), 1.15 (9H, s, $SiC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 160.58, 158.82, 157.32, 139.64, 135.55, 133.65, 129.76, 128.77, 127.76, 127.40, 125.97, 115.45, 112.15, 107.54, 107.58, 65.00, 57.27, 56.87, 55.30, 33.68, 26.88, 19.34. MS (*m*/*e*): 504 ($[M]^+$). HR-MS calcd. for $C_{31}H_{37}O_3SiF$: 504.2496 ($[M]^+$); found: 504.2488 ± 0.0015.

To a stirred solution of the alcohol (8.6 g, 17.1 mmol) in tetrahydrofuran (200 mL) at –40 °C were added triphenylphosphine (4.9 g, 18.8 mmol) and hexachloroacetone (2.6 mL, 17.1 mmol). The mixture was stirred at –40 °C for 20 min and the solvent was evaporated. The residue was purified by flash chromatography (100% hexanes to 20% ethyl acetate, 80% hexanes) to give chloride **18** as a yellow oil (8.8 g, 99%). IR ($CHCl_3$, cm^{-1}) ν: 3017, 2936, 2859, 1732, 1607, 1496, 1465, 1429, 1254, 1217, 1111, 1047, 967. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.75 (4H, dd, *J* = 7.6, 1.6 Hz, Ph), 7.50–7.39 (7H, m, Ph), 6.87 (1H, dt, *J* = 15.6, 1.8 Hz, PhC*H*=CH), 6.79 (1H, dd, *J* = 8.6, 2.7 Hz, Ph), 6.68 (1H, d, *J* = 2.7 Hz, Ph), 6.13 (1H, dt, *J* = 15.6, 4.7 Hz, PhCH=C*H*), 5.31 (1H, dt, *J* = 18.8, 8.3 Hz, CH_2CH=$CFCH_2Cl$), 4.44 (2H, dd, *J* = 4.7, 1.9 Hz, CH_2OTBDPS), 3.94 (2H, d, *J* = 21.4 Hz, CH_2Cl), 3.83 (3H, s, $ArOCH_3$), 2.76 (2H, t, *J* = 7.3 Hz, $ArCH_2CH_2$), 2.30 (2H, q, *J* = 7.8 Hz, $ArCH_2CH_2$), 1.13 (9H, s, $SiC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.92, 156.83, 153.55, 139.27, 135.54, 133.67, 129.74, 128.86, 128.55, 127.74, 127.47, 125.88, 115.14, 112.17, 110.16, 109.89, 64.60, 55.29, 37.64, 37.20, 33.39, 26.86, 19.33. MS (*m*/*e*): 520 ($[M]^+$). HR-MS calcd. for $C_{31}H_{36}O_2SiFCl$: 522.2157 ($[M]^+$); found: 522.2153 ± 0.0016.

β-Keto ester 19

Solution 1

To a suspension of 60% sodium hydride in oil (592 mg, 14.8 mmol) in tetrahydrofuran (20 mL) at 0 °C was added methyl acetoacetate (2.8 mL, 26.3 mmol) and the mixture was stirred at 0 °C for 30 min. A solution of 1.6 mol/L *n*-butyl lithium in hexanes (8.6 mL, 13.8 mmol) was added and the mixture was stirred at 0 °C for 30 min.

Solution 2

To a stirred solution of chloride **18** (1.03 g, 1.97 mmol) in tetrahydrofuran (20 mL) was added sodium iodide (885 mg, 5.9 mmol) and the mixture was stirred at room temperature for 30 min.

Solution 1 was added to solution 2 and the mixture was stirred at room temperature overnight. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (30% ethyl acetate, 70% hexanes) to give β-keto ester **19** as a yellow oil (770 mg, 65%). IR ($CHCl_3$, cm^{-1}) ν: 3020, 2955, 2860, 1745, 1720, 1608, 1496, 1433, 1315, 1217, 1110, 967, 756. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 12.05 (RC(O)C*H*=C(OH)R′), 7.75 (4H, dd, *J* = 7.4, 1.7 Hz, Ph), 7.49–7.37 (7H, m, Ph), 6.92–6.87 (1H, m, CH=C*H*Ph), 7.77 (1H, dd, *J* = 8.5, 2.7 Hz, Ph), 6.70 (1H, d, *J* = 2.7 Hz, Ph), 6.11 (1H, dt, *J* = 15.5, 4.6 Hz, C*H*=CHPh), 5.06 (1H, dt, *J* = 21.7, 8.1 Hz, C*H*=CFR), 4.43 (2H, dd, *J* = 4.6, 1.8 Hz, CH_2OTBDPS), 3.82 (3H, s, $ArOCH_3$), 3.73 (3H, s, CO_2CH_3), 3.39 (2H, s, $C(O)CH_2C(O)$), 2.72 (2H, t, *J* = 7.3 Hz, $ArCH_2CH_2$), 2.55–2.20 (6H, m, $CH_2CH_2C(O)$, $CH_2CH_2C(O)$, CH_2CH=CFR), 1.13 (9H, s, Si-$C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 167.36, 160.38, 158.83, 157.12, 139.99, 135.54, 133.72, 129.71, 128.70, 128.61, 127.73, 127.25, 126.01, 115.17, 112.07, 105.57, 105.28, 64.58, 55.25, 52.35, 48.89, 39.14, 33.58, 26.86, 22.02, 21.65, 19.31. MS (*m*/*e*): 602 ($[M]^+$). HR-MS calcd. for $C_{36}H_{43}O_5FSi$: 602.2864 ($[M]^+$); found: 602.2870 ± 0.0018.

Pivaloate ester 7

To a stirred solution of β-keto ester **19** (1.72 g, 2.85 mmol) in tetrahydrofuran (30 mL) was added 1 mol/L tetrabutylammonium fluoride in tetrahydrofuran (5.7 mL, 5.70 mmol). The mixture was stirred at room temperature for 1.5 h and solvent was evaporated. The residue was purified by flash chromatography (70% ethyl acetate, 30% hexanes) to give the corresponding alcohol as a colorless oil (798 mg, 77%). IR ($CHCl_3$, cm^{-1}) ν: 3425, 2949, 2867, 1744, 1716, 1608, 1496, 1441, 1372, 1254, 1084, 1008, 912, 733. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.41 (1H, d, *J* = 8.6 Hz, Ph), 6.83 (1H, d, *J* = 15.7 Hz, CH=C*H*Ph), 6.76 (1H, dd, *J* = 8.6, 2.7 Hz, Ph), 6.68 (1H, d, *J* = 2.7 Hz, Ph), 6.18 (1H, dt, *J* = 15.6, 5.6 Hz, C*H*=CHPh), 5.10 (1H, dt, *J* = 21.6, 8.2 Hz, C*H*=CFR), 4.34 (2H, dd, *J* = 5.6, 1.5 Hz, CH_2OH), 3.82 (3H, s, $ArOCH_3$), 3.76 (3H, s, CO_2CH_3), 3.46 (2H, s, $C(O)CH_2C(O)$), 2.72 (2H, t, *J* = 8.0 Hz, $ArCH_2CH_2$),

2.63–2.58 (2H, m, $CH_2CH_2C(O)$), 2.48–2.36 (2H, m, $CH_2CH_2C(O)$), 2.23 (2H, q, J = 7.8 Hz, CH_2CH=CFR), 1.67 (1H, br, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 201.71, 167.53, 160.32, 158.96, 157.05, 140.21, 128.88, 128.38, 127.35, 115.10, 112.03, 105.68, 105.40, 63.56, 55.18, 52.39, 48.84, 39.12, 33.73, 26.81, 21.96. MS (*m*/*e*): 364 ($[M]^+$). HR-MS calcd. for $C_{20}H_{25}O_5F$: 364.1686 ($[M]^+$); found: 364.1683 ± 0.0011.

To a stirred solution of the alcohol (798 mg, 2.19 mmol) in dichloromethane (20 mL) were added 2,6-lutidine (765 μL, 6.57 mmol) and trimethylacetyl chloride (809 μL, 6.57 mmol) and the mixture was stirred at room temperature overnight. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (30% ethyl acetate, 70% hexanes) to give pivaloate ester **7** as a colorless oil (952 mg, 97%). IR ($CHCl_3$, cm^{-1}) ν: 3020, 2957, 2873, 1744, 1719, 1606, 1495, 1438, 1282, 1216, 1158, 1090, 1040, 695, 853, 756. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 12.05 (RC(O)C*H*=C(OH)R′), 7.40 (1H, d, J = 8.6 Hz, Ph), 6.83 (1H, d, J = 15.7 Hz, CH=C*H*Ph), 6.75 (1H, dd, J = 8.6, 3.0 Hz, Ph), 6.67 (1H, d, J = 2.7 Hz, Ph), 6.06 (1H, dt, J = 15.6, 6.2 Hz, C*H*=CHPh), 5.11 (1H, dt, J = 21.6, 8.1 Hz, C*H*=CFR), 4.73 (2H, dd, J = 6.2, 1.3 Hz, CH_2OPiv), 3.80 (3H, s, ArOCH_3), 3.73 (3H, s, CO_2CH_3), 3.41 (2H, s, C(O)CH_2C(O)), 2.71 (2H, t, J = 7.5 Hz, ArCH_2CH_2), 2.54–2.49 (2H, m, $CH_2CH_2C(O)$), 2.43–2.31 (2H, m, $CH_2CH_2C(O)$), 2.24 (2H, m, CH_2CH=CFR), 1.23 (9H, s, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 200.94, 167.35, 160.39, 159.29, 157.13, 140.38, 130.54, 127.90, 127.43, 123.48, 115.16, 112.11, 105.48, 105.19, 65.09, 55.22, 52.33, 48.89, 39.05, 38.79, 33.53, 27.21, 26.84, 21.96. MS (*m*/*e*): 448 ($[M]^+$). HR-MS calcd. for $C_{25}H_{33}O_6F$: 448.2261 ($[M]^+$); found 448.2270 ± 0.001.

Macrocycle 20

Solution 1

To a stirred solution of pivaloic ester **7** (1.67 g, 3.73 mmol) in tetrahydrofuran (15 mL) degassed with Ar was added *N*,*O*-bis(trimethylsilyl)acetamide (1.8 mL, 7.46 mmol). The mixture was stirred at reflux for 5 h.

Solution 2

To a stirred solution of tetrakis(triphenylphosphine) palladium(0) (1.07 g, 0.93 mmol) in tetrahydrofuran (1.9 L) degassed with Ar was added 1,3-bis(diphenylphospino)propane (384 mg, 0.93 mmol) and the mixture was stirred at reflux for 1 h.

Solution 1 was slowly added to solution 2 at reflux for 14 h and the resulting mixture was heated for 4 h. The solvent was evaporated and the residue was purified by flash chromatography (5% ethyl acetate, 35% dichloromethane, 60% hexanes) to give macrocycle **20** as a white solid (1.14 g, 88%); mp 129–131 °C. IR ($CHCl_3$, cm^{-1}) ν: 3020, 2956, 1743, 1714, 1607, 1493, 1436, 1250, 1216, 1165, 1115, 1078, 1041, 970, 762. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.21 (1H, d, J = 8.4 Hz, Ph), 6.73 (1H, dd, J = 8.4, 2.8 Hz, Ph), 6.67 (1H, d, J = 2.8 Hz, Ph), 6.57 (1H, d, J = 15.7 Hz, PhC*H*=CH), 5.77 (1H, ddd, J = 15.6, 8.6, 5.3 Hz, C*H*=CHPh), 5.00 (1H, dt, J = 20.7, 7.7 Hz, C*H*=CFR), 3.80 (3H, s, ArOCH_3), 3.77 (3H, s, CO_2CH_3), 3.80–3.75 (1H, m, C(O)C*H*C(O)), 3.04–1.86 (10H, m, PhCH_2CH_2CH=CFR, CH=C(F)CH_2CH_2C(O), CH_2C(H)CO_2Me). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 204.00, 169.54, 160.98, 159.09, 157.11, 140.77, 131.98, 129.24, 128.38, 126.07, 114.54, 111.63, 105.80, 105.52, 57.71, 55.19, 52.58, 39.06, 33.90, 32.01, 27.89, 22.42. MS (*m*/*e*): 346 ($[M]^+$). HR-MS calcd. for $C_{20}H_{23}O_4F$: 346.1580 ($[M]^+$); found: 346.1576 ± 0.0010.

Triene 6

To a stirred solution of 70% benzeneseleninic anhydride (10.2 g, 19.8 mmol) in dichloromethane (200 mL) was added triethylamine (4.6 mL, 32.9 mmol) and the mixture was stirred for 15 min. A solution of macrocycle **20** (2.30 g, 6.65 mmol) in dichloromethane was added and the mixture was stirred for 15 min. Satd. aq. $NaHCO_3$ was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (5% ethyl acetate, 95% dichloromethane) to give triene **6** as a yellow solid (2.05 g, 91%); mp 147–149 °C. IR ($CHCl_3$, cm^{-1}) ν: 3020, 2954, 1696, 1603, 1583, 1436, 1275, 1241, 1158, 1077, 1045. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.43 (1H, d, J = 11.5 Hz, PhCH=CH=C*H*), 7.21 (1H, d, J = 8.5 Hz, Ph), 6.96 (1H, d, J = 16.2 Hz, CH=C*H*Ph), 6.76 (1H, dd, J = 8.4, 2.7 Hz, Ph), 6.71 (1H, d, J = 2.7 Hz, Ph), 6.64 (1H, dd, J = 16.2, 11.5 Hz, PhCH=C*H*), 5.26 (1H, dt, J = 22.1, 8.7 Hz, C*H*=CFR), 3.82 (3H, s, ArOCH_3), 3.81 (3H, s, CO_2CH_3), 2.97–2.93 (2H, m, $CH_2CH_2C(O)$), 2.87–2.81 (2H, m, PhCH_2CH_2), 2.58 (2H, dt, J = 22.1, 6.9 Hz, $CH_2CH_2C(O)$), 2.22–2.14 (2H, m, PhCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 203.17, 164.94, 160.41, 159.01, 155.73, 144.16, 142.15, 136.13, 131.88, 126.46, 123.62, 117.45, 111.76, 107.23, 106.93, 55.29, 52.14, 39.48, 37.15, 26.02, 23.61. MS (*m*/*e*): 344 ($[M]^+$). HR-MS calcd. for $C_{20}H_{21}O_4F$: 344.1424 ($[M]^+$); found: 344.1426 ± 0.0010.

Tetracycle 21

To a solution of triene **6** (500 mg, 1.45 mmol) in toluene (70 mL) degassed with Ar was added triethylamine (1.0 mL, 7.25 mmol) and the mixture was heated in a sealed tube at 165 °C for 4 h. The solvent was evaporated and the residue was purified by flash chromatography (20% ethyl acetate, 80% hexanes) to give tetracycle **21** as a white solid (389 mg, 78%); mp 162–164 °C. IR ($CHCl_3$, cm^{-1}) ν: 3019, 2954, 1761, 1734, 1609, 1502, 1436, 1258, 1216, 1045. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.28 (1H, d, J = 8.9 Hz, *Ph*), 6.76 (1H, dd, J = 8.9, 2.7 Hz, *Ph*), 6.70 (1H, d, J = 2.7 Hz, *Ph*), 6.53 (1H, d, J = 9.9 Hz, CH=C*H*C(CO_2Me)R), 5.64 (1H, ddd, J = 9.9, 5.6, 3.0 Hz, C*H*=CHC(CO_2Me)R), 3.79 (3H, s, ArOCH_3), 3.72 (3H, s, CO_2CH_3), 3.23 (1H, d, J = 11.5 Hz, PhC*H*CH=CH), 3.00–2.94 (2H, m, PhCH_2CH_2), 2.91–2.77 (1H, m, C*H*C(F)R), 2.51–2.23 (4H, m, C(O)CH_2CH_2C(F)R), 2.14–1.92 (1H, m, PhCH_2CH*H*), 1.73–1.57 (1H, m, PhCH_2C*H*H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 209.92, 167.91, 157.95, 137.43, 132.10, 128.26, 125.88, 122.52, 114.30, 111.89, 105.07, 102.64, 65.61, 55.25, 52.88, 40.66, 40.37, 40.01, 35.60, 29.51, 26.43, 21.36. MS (*m*/*e*): 344 ($[M]^+$). HR-MS calcd. for $C_{20}H_{21}O_4F$: 344.1424 ($[M]^+$); found: 344.1413 ± 0.0010.

Diol 24

To a stirred solution of tetracycle **21** (594 mg, 1.73 mmol) in ethanol 95% (75 mL) was added 5% palladium(0) on barium sulfate (745 mg, 0.35 mmol) and hydrogen was bubbled through this solution for 15 min. The resulting mixture was stirred at room temperature overnight under a hydrogen atmosphere. N_2 was bubbled through this mixture and the solution was filtered on a silica gel pad to give the corresponding tetracycle as a beige solid (594 mg, 100%); mp 154–157 °C. IR ($CHCl_3$, cm^{-1}) ν: 3055, 2954, 1754, 1731, 1611, 1502, 1435, 1266, 1043, 896. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.19 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.7 Hz, *Ph*), 6.65 (1H, d, *J* = 2.7 Hz, *Ph*), 3.78 (3H, s, ArOCH_3), 3.73 (3H, s, CO_2CH_3), 2.94–2.89 (2H, m, PhCH_2CH_2), 2.83–2.70 (1H, m, PhC*H*), 2.58–2.49 (2H, m, RC(O)CH_2), 2.38–1.90 (7H, m), 1.65–1.77 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 211.61, 169.27, 157.77, 137.43, 130.21, 127.05, 113.72, 112.08, 106.08, 103.66, 62.19, 61.94, 55.16, 52.30, 42.70, 42.40, 39.37, 34.97, 30.05, 29.79, 26.73, 26.19, 22.04. MS (*m*/*e*): 346 ($[M]^+$). HR-MS calcd. for $C_{20}H_{23}O_4F$: 346.1580 ($[M]^+$); found: 346.1576 ± 0.0010.

To a stirred solution of this tetracycle (575 mg, 1.66 mmol) in tetrahydrofuran (40 mL) were added lithium borohydride (180 mg, 8.30 mmol) and methanol (336 μL, 8.30 mmol) and the mixture was stirred at room temperature for 2 h. Lithium borohydride (72 mg, 3.32 mmol) and methanol (134 μL, 3.32 mmol) were added and the mixture was stirred for 1 h. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (100% ethyl acetate) to give a mixture (α:β = 9:1) of diol **24** as a white solid (539 mg, 94%). Diol α-**24**: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (1H, d, *J* = 8.6 Hz, *Ph*), 6.72 (1H, dd, *J* = 8.6, 2.7 Hz, *Ph*), 6.64 (1H, d, *J* = 2.7 Hz, *Ph*), 4.74 (1H, t, *J* = 8.2 Hz, RR′C*H*OH), 4.00 (1H, d, *J* = 10.3 Hz, C*H*HOH), 3.90 (1H, d, *J* = 10.3 Hz, CH*H*OH), 3.78 (3H, s, ArOCH_3), 2.85 (2H, dd, *J* = 8.9, 3.8 Hz, PhCH_2CH_2), 2.47 (1H, t, *J* = 11.6 Hz, PhC*H*), 2.38–2.05 (5H, m), 1.92–1.62 (3H, m), 1.87 (2H, br, CHO*H*, CH_2OH), 1.50–1.28 (3H, m). MS (*m*/*e*): 320 ($[M]^+$). HR-MS calcd. for $C_{19}H_{25}O_3F$: 320.1788 ($[M]^+$); found: 320.1779 ± 0.0010. Diol β-**24**: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.18 (1H, d, *J* = 8.6 Hz, *Ph*), 6.73 (1H, dd, *J* = 8.6, 2.7 Hz, *Ph*), 6.64 (1H, d, *J* = 2.7 Hz, *Ph*), 4.18 (1H, d, *J* = 11.7 Hz, RC*H*HOH), 4.01 (1H, dd, *J* = 7.3, 2.2 Hz, RR′C*H*OH), 3.78 (3H, s, ArOCH_3), 3.71 (1H, d, *J* = 11.7 Hz, CH*H*OH), 2.86 (2H, dd, *J* = 8.6, 3.5 Hz, PhCH_2CH_2), 2.49–2.35 (2H, m), 2.31–1.83 (10H, m), 1.74 (1H, qd, *J* = 11.7, 2.0 Hz), 1.53–1.34 (1H, m), 1.05–0.96 (1H, m).

Tosylate 25

To a stirred solution of diol **24** (460 mg, 1.4 mmol) in a mixture of benzene–DMF (3:1, 12 mL) was added dibutylstannane oxide (430 mg, 1.73 mmol) and the mixture was stirred at reflux with a Dean–Stark for 1.5 h. The mixture was cooled down and *p*-toluenesulfonyle chloride (320 mg, 1.68 mmol) was added. The mixture was stirred at room temperature for 1 h. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ether–hexanes (1:1). The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (50% ethyl acetate, 50% hexanes) to give a mixture (α:β = 9:1) of tosylates **25** unseparable as a white solid (539 mg, 94%). Tosylate α-**25**: IR ($CHCl_3$, cm^{-1}) ν: 3602, 3551, 2951, 2872, 1610, 1501, 1464, 1361, 1176, 1097, 1045, 944, 816. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.78 (2H, d, *J* = 8.2 Hz, Ph), 7.34 (2H, d, *J* = 8.2 Hz, Ph), 7.16 (1H, d, *J* = 8.6 Hz, *Ph*), 6.72 (1H, dd, *J* = 8.6, 2.5 Hz, *Ph*), 6.62 (1H, d, *J* = 2.5 Hz, *Ph*), 4.81 (1H, massif, RR′CHO*H*), 4.57 (1H, t, *J* = 8.0 Hz, RR′C*H*OH), 4.30 (1H, d, *J* = 9.9 Hz, C*H*HOTs), 4.23 (1H, d, *J* = 9.9 Hz, CH*H*OTs), 3.78 (3H, s, ArOCH_3), 2.86–2.79 (2H, m, PhCH_2CH_2), 2.44 (3H, s, PhCH_3), 2.37–2.15 (2H, m), 2.08–2.01 (3H, m), 1.88–1.52 (4H, m), 1.46–1.33 (2H, m), 1.29–1.09 (1H, m). MS (*m*/*e*): 474 ($[M]^+$). HR-MS calcd. for $C_{26}H_{31}O_5FS$: 474.1876 ($[M]^+$); found: 474.1880 ± 0.0014.

Alcohol 26 and oxetane 27

To a stirred solution of tosylate **25** (650 mg, 1.37 mmol) in dimethylsulfoxide (80 mL) was added sodium borohydride (260 mg, 6.85 mmol) and the mixture was stirred at 80 °C overnight. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (50% ethyl acetate, 50% hexanes) to give alcohol **26** as colorless oil (353 mg, 85%) and about 10% of oxetane **27**. Alcohol **26**: IR ($CHCl_3$, cm^{-1}) ν: 3386, 2942, 2870, 1610, 1501, 1466, 1261, 1235, 1042. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (1H, d, *J* = 8.6 Hz, *Ph*), 6.73 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.65 (1H, d, *J* = 2.8 Hz, *Ph*), 4.28 (1H, t, *J* = 8.0 Hz, RR′C*H*OH), 3.78 (3H, s, ArOCH_3), 2.90–2.85 (2H, m, PhCH_2CH_2), 2.46–2.39 (1H, m, PhC*H*), 2.32–2.00 (4H, m), 1.90–1.74 (2H, m), 1.72–1.57 (3H, m), 1.53–1.36 (3H, m), 1.08 (3H, d, *J* = 1.3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.58, 137.76, 131.39, 126.83, 113.71, 111.88, 109.08, 106.71, 80.43, 55.21, 47.48, 47.25, 42.40, 42.11, 40.23, 29.97, 28.42, 28.22, 27.58, 27.24, 25.68, 22.13, 16.33. MS (*m*/*e*): 304 ($[M]^+$). HR-MS calcd. for $C_{19}H_{25}O_2F$: 304.1838 ($[M]^+$); found: 304.1843 ± 0.0009. Oxetane **27**: IR ($CHCl_3$, cm^{-1}) ν: 3018, 2945, 2882, 1610, 1502, 1465, 1215, 1038, 974. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.12 (1H, d, *J* = 8.6 Hz, *Ph*), 6.72 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.62 (1H, d, *J* = 2.8 Hz, *Ph*), 4.95 (1H, d, *J* = 5.9 Hz, C*H*HOCHRR′), 4.72 (1H, d, *J* = 5.9 Hz, CH*H*OCHRR′), 4.35 (1H, dd, *J* = 5.6, 4.7 Hz, RR′C*H*OCH_2), 3.78 (3H, s, ArOCH_3), 2.90–2.84 (2H, m, PhCH_2CH_2), 2.48–1.25 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.51, 137.58, 131.72, 127.84, 113.38, 112.33, 106.60, 104.18, 91.12, 74.36, 74.16, 55.20, 51.18, 50.95, 44.32, 43.97, 36.51, 32.33, 32.16, 32.12, 30.31, 29.05, 27.83, 23.94. MS (*m*/*e*): 302 $([M])^+$. HR-MS calcd. for $C_{19}H_{23}O_2F$: 302.1682 ($[M]^+$); found: 302.1399 ± 0.0009.

Ketone 5

To a stirred solution of alcohol **26** (312 mg, 1.03 mmol) in dichloromethane (50 mL) were added molecular sieve 4 Å (515 mg), 4-methylmorpholine-*N*-oxide (241 mg, 2.06 mmol), and tetrapropylammonium perruthenate (35 mg, 0.10 mmol). The resulting mixture was stirred at room temperature for

2 h and filtered on a silica gel pad. The solvent was evaporated and the residue was purified by flash chromatography (30% ethyl acetate, 70% hexanes) to give ketone **5** as an amorphous white solid (269 mg, 87%). IR ($CHCl_3$, cm^{-1}) ν: 2944, 2869, 1741, 1611, 1502, 1464, 1274, 1232, 1093, 1043, 936. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.19 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.67 (1H, d, *J* = 2.8 Hz, *Ph*), 3.79 (3H, s, $ArOCH_3$), 2.93 (2H, dd, *J* = 9.0, 3.9 Hz, $PhCH_2CH_2$), 2.59–2.48 (3H, m, PhC*H*, $RC(O)CH_2$), 2.42–2.13 (4H, m), 1.92 (1H, qd, *J* = 11.9, 2.1 Hz), 1.65–1.41 (4H, m), 1.13 (3H, d, *J* = 1.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 219.62, 157.80, 137.56, 130.58, 126.78, 113.82, 112.03, 107.01, 104.64, 55.21, 52.94, 52.67, 42.19, 41.90, 40.27, 33.30, 32.42, 29.90, 25.57, 25.21, 21.97, 12.72. MS (*m*/*e*): 302 ($[M]^+$). HR-MS calcd. for $C_{19}H_{23}O_2F$: 302.1682 ($[M]^+$); found: 302.1689 ± 0.0009.

Triflic enol ether 28

To a stirred solution of ketone **5** (22 mg, 0.073 mmol) in tetrahydrofuran (2 mL) at 0 °C was added 0.5 mol/L potassium bis(trimethylsilyl)amide in toluene (740 μL, 0.37 mmol) and the mixture was stirred at 0 °C for 15 min then at room temperature for 45 min. *N*-(5-Chloro-2-pyridyl)triflimide (93 mg, 0.22 mmol) in tetrahydrofuran (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (5% ethyl acetate, 95% hexanes) to give triflic enol ether **28** as a yellow oil (27 mg, 84%). IR ($CHCl_3$, cm^{-1}) ν: 2944, 2868, 1650, 1611, 1502, 1423, 1218, 1141, 1085, 1044, 884. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.7 Hz, *Ph*), 6.65 (1H, d, *J* = 2.7 Hz, *Ph*), 5.59 (1H, t, *J* = 2.7 Hz, C*H*=C(OTf)R), 3.79 (3H, s, $ArOCH_3$), 2.93–2.86 (2H, m, $PhCH_2CH_2$), 2.71 (1H, td, *J* = 17.1, 1.8 Hz, PhC*H*), 2.61–2.40 (2H, m), 2.30–2.05 (3H, m), 1.87 (1H, qd, *J* = 12.0, 2.1 Hz), 1.57–1.26 (3H, m), 1.18 (3H, d, *J* = 2.7 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.77, 155.04, 137.57, 130.16, 127.23, 120.65, 116.40, 113.76, 112.12, 108.48, 105.33, 102.86, 55.21, 49.48, 49.22, 43.00, 42.70, 40.25, 37.15, 34.05, 33.68, 29.57, 25.54, 22.27, 13.31. MS (*m*/*e*): 434 ($[M]^+$). HR-MS calcd. for $C_{20}H_{22}O_4F_4S$: 434.1175 ($[M]^+$); found: 434.1181 ± 0.0013.

α,β-Unsaturated ester 29

To a stirred solution of triflic enol ether **28** (20 mg, 0.046 mmol) in dimethylformamide (3 mL) were added triethylamine (32 μL, 0.23 mmol), methanol (233 μL, 4.60 mmol), triphenylphophine (0.7 mg, 0.0028 mmol), and palladium(II) acetate (0.3 mg, 0.0014 mmol). CO_2 was bubbled through the solution and the resulting mixture was stirred at 70 °C under a pressure of 150 psi (1 psi = 6.894 757 kPa) overnight. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ether. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give the α,β-unsaturated ester **29** as an amorphous white solid (13 mg, 81%). IR ($CHCl_3$, cm^{-1}) ν: 2944, 2565, 1717, 1612, 1501, 1436, 1336, 1243, 1191, 1044, 885. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.24 (1H, d, *J* = 8.7 Hz, *Ph*), 6.75–6.70 (2H, m, *Ph*, C*H*=CRCO_2Me), 6.65 (1H, d, *J* = 2.7 Hz, *Ph*), 3.78 (3H, s, $ArOCH_3$), 3.76 (3H, s, CO_2CH_3), 2.93–2.88 (2H, m, $PhCH_2CH_2$), 2.84–2.59 (2H, m), 2.46–2.32 (2H, m), 2.26–2.05 (2H, m), 2.00–1.86 (1H, m), 1.55–1.22 (3H, m), 1.35 (3H, d, *J* = 3.2 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 164.98, 157.64, 143.61, 137.89, 137.69, 130.70, 127.27, 113.71, 112.01, 108.74, 106.32, 55.21, 51.25, 42.52, 42.22, 40.58, 38.13, 37.70, 37.34, 30.03, 25.77, 23.07, 14.85. MS (*m*/*e*): 344 ($[M]^+$). HR-MS calcd. for $C_{21}H_{25}O_3F$: 344.1788 ($[M]^+$); found: 344.1779 ± 0.0010.

Ester 30

To a stirred solution of α,β-unsaturated ester **29** (15 mg, 0.044 mmol) in ethanol (2 mL) was added 5% palladium(0) on activated carbon (9 mg, 0.0044 mmol) and hydrogen was bubbled through the solution for 10 min. The mixture was stirred for 1 h under a hydrogen atmosphere and filtered on a silica gel pad. The solvent was evaporated to give ester **30** as a colorless oil (15 mg, 100%). IR ($CHCl_3$, cm^{-1}) ν: 2945, 2862, 1732, 1610, 1502, 1466, 1260, 1199, 1166, 1044, 961. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.18 (1H, d, *J* = 8.6 Hz, *Ph*), 6.72 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.64 (1H, d, *J* = 2.8 Hz, *Ph*), 3.78 (3H, s, $ArOCH_3$), 3.71 (3H, s, CO_2CH_3), 3.05 (1H, t, *J* = 9.2 Hz, C*H*CO_2Me), 2.91–2.86 (2H, m, $PhCH_2CH_2$), 2.50–2.42 (1H, m, PhC*H*), 2.29–1.78 (7H, m), 1.58–1.30 (4H, m), 1.21 (3H, d, *J* = 1.1 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 174.38, 157.62, 137.69, 131.23, 126.80, 113.69, 111.90, 110.58, 55.20, 53.16, 51.47, 42.10, 41.81, 40.05, 31.15, 30.06, 29.69, 29.29, 28.96, 26.05, 23.01, 22.22, 17.58. MS (*m*/*e*): 346 $([M])^+$. HR-MS calcd. for $C_{21}H_{27}O_3F$: 346.1944 ($[M]^+$); found: 346.1940 ± 0.0010.

α,β-Unsaturated nitrile 32

To a stirred solution of triflic enol ether **28** (41 mg, 0.094 mmol) in benzene (10 mL) were added lithium cyanide (18 mg, 0.56 mmol), tetrakis(triphenylphosphine) palladium(0) (11 mg, 0.0094 mmol), and 12-C-4 ether (2 μL, 0.0094 mmol). The resulting mixture was stirred at room temperature overnight and a catalytic amount of palladium (11 mg, 0.0094 mmol) was added. The mixture was stirred for an additional 24 h and water was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give α,β-unsaturated nitrile **32** as an amorphous solid (23 mg, 79%). IR ($CHCl_3$, cm^{-1}) ν: 3054, 2932, 2568, 2219, 1610, 1502, 1422, 1265, 1041, 883. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.7 Hz, *Ph*), 6.65 (1H, d, *J* = 2.7 Hz, *Ph*), 6.59 (1H, t, *J* = 2.6 Hz, C*H*=C(CN)R), 3.79 (3H, s, $ArOCH_3$), 2.93–2.88 (2H, m, $PhCH_2CH_2$), 2.84–2.68 (1H, m), 2.47–2.38 (1H, m), 2.31–2.10 (3H, m), 1.90 (1H, qd, *J* = 11.9, 2.1 Hz), 1.57–1.22 (4H, m), 1.31 (3H, d, *J* = 2.6 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.79, 142.09, 137.52, 130.03, 127.22, 125.12, 115.38, 113.78, 112.12, 107.07, 104.62, 55.22, 52.57, 52.31, 42.78, 42.48, 40.35, 38.99, 38.63, 37.93, 29.94, 25.69, 23.10, 14.96. MS

(*m*/*e*): 311 ([M]$^+$). HR-MS calcd. for $C_{20}H_{22}OFN$: 311.1585 ([M]$^+$); found: 311.1678 ± 0.0009.

Nitriles 33a and 33b

To a stirred solution of α,β-unsaturated nitrile **32** (20 mg, 0.064 mmol) in ethanol (2 mL) was added 5% palladium(0) on activated carbon (28 mg, 0.013 mmol) and hydrogen was bubbled through the solution for 10 min. The mixture was stirred for 2 h under a hydrogen atmosphere and filtered on a silica gel pad. The solvent was evaporated and the residue was purified by flash chromatography (20% ethyl acetate, 80% hexanes) to give nitrile α-**33a** as a white solid (7 mg, 35%) and nitrile β-**33b** as a white solid (12 mg, 60%). Nitrile β-**33b**: IR ($CHCl_3$, cm^{-1}) ν: 2932, 2868, 2238, 1610, 1501, 1466, 1236, 1161, 1038. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.16 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.65 (1H, d, *J* = 2.8 Hz, *Ph*), 3.78 (3H, s, ArOC*H*$_3$), 2.92–2.87 (2H, m, PhC*H*$_2$CH$_2$), 2.74 (1H, t, *J* = 7.7 Hz, R(CN)C*H*CH$_2$), 2.50–2.42 (1H, m, PhC*H*), 2.35–2.15 (5H, m), 2.10–2.03 (1H, m), 1.86 (1H, qd, *J* = 11.8, 2.2 Hz), 1.71–1.64 (1H, m), 1.57–1.36 (3H, m), 1.33 (3H, d, *J* = 1.1 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.76, 137.61, 130.64, 126.70, 121.71, 113.73, 112.05, 109.19, 106.78, 55.21, 48.52, 48.26, 42.03, 41.75, 39.93, 36.85, 30.32, 30.02, 26.64, 25.72, 23.17, 16.38. MS (*m*/*e*): 313 ([M]$^+$). HR-MS calcd. for $C_{20}H_{24}OFN$: 313.1842 ([M]$^+$); found: 313.1849 ± 0.0009. Nitrile α-**33a**: IR ($CHCl_3$, cm^{-1}) ν: 2938, 2239, 1610, 1502, 1467, 1320, 1236, 1043, 957. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.20 (1H, d, *J* = 8.6 Hz, *Ph*), 6.74 (1H, dd, *J* = 8.6, 2.8 Hz, *Ph*), 6.65 (1H, d, *J* = 2.8 Hz, *Ph*), 3.78 (3H, s, ArOC*H*$_3$), 3.04 (1H, t, *J* = 9.2 Hz, R(CN)C*H*CH$_2$), 2.91–2.86 (2H, m, PhC*H*$_2$CH$_2$), 2.47 (1H, td, *J*= 11.2, 3.5 Hz, PhC*H*), 2.36–1.77 (8H, m), 1.53–1.33 (3H, m), 1.18 (3H, d, *J* = 1.0 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.77, 137.47, 130.64, 126.78, 120.51, 113.78, 111.99, 55.21, 42.02, 41.73, 40.10, 39.13, 31.64, 29.90, 29.68, 29.35, 25.85, 24.31, 22.88, 16.81. MS (*m*/*e*): 313 ([M]$^+$). HR-MS calcd. for $C_{20}H_{24}OFN$: 313.1842 ([M]$^+$); found: 313.1849 ± 0.0009.

α,β-Unsaturated ketone 34

To a stirred solution of tetracycle **26** (227 mg, 0.75 mmol) in tetrahydrofuran (10 mL) at –78 °C was added 95% ethanol (1 mL), and gaseous ammonia was condensed (20 mL). Metallic lithium was added by portion until the solution was blue and the resulting mixture was stirred at –78 °C for 2 h. Solid NH_4Cl was added slowly until the blue color disappeared and ammoniac was evaporated at room temperature. Water was added and the aqueous phase was extracted with ether. The combined organic phases were dried, filtered, and evaporated. The residue was dissolved in tetrahydrofuran (10 mL) and 1 mol/L HCl (1 mL) was added. The mixture was stirred at room temperature overnight. Satd. aq. $NaHCO_3$ was added and the aqueous phase was extracted with ether. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (60% ethyl acetate, 40% hexanes) to give α,β-unsaturated ketone **34** as a colorless oil (168 mg, 77%). IR ($CHCl_3$, cm^{-1}) ν: 3611, 3432, 3016, 2949, 2874, 1662, 1619, 1454, 1364, 1220, 1067, 1007, 952. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 5.81 (1H, s, C*H*=CRR′), 4.18 (1H, t, *J* = 7.6 Hz, RR′C*H*OH), 2.52–1.46 (17H, m), 1.26–1.10 (3H, m), 1.05 (3H, s, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 199.85, 165.58, 124.76, 108.73, 106.36, 80.00, 47.23, 47.00, 45.78, 43.74, 43.45, 42.73, 36.36, 35.04, 27.91, 27.84, 26.34, 25.26, 25.02, 15.93. MS (*m*/*e*): 292 ([M]$^+$). HR-MS calcd. for $C_{18}H_{25}O_2F$: 292.1838 ([M]$^+$); found: 292.1832 ± 0.0008.

Ketones 35 and 36

To a stirred solution of α,β-unsaturated ketone **34** (126 mg, 0.43 mmol) in ethyl acetate (10 mL) was added 5% palladium(0) on activated carbon (91 mg, 0.043 mmol) and hydrogen was bubbled for 10 min. The mixture was stirred for 1 h under a hydrogen atmosphere and filtered on a silica gel pad. The solvent was evaporated and the residue was purified by flash chromatography (50% ethyl acetate, 50% hexanes) to give ketone **36** (cis) as a colorless oil (76 mg, 60%) and ketone **35** (trans) as a colorless oil (33 mg, 27%). Ketone **36** (cis): IR ($CHCl_3$, cm^{-1}) ν: 3444, 3019, 2932, 2882, 1706, 1466, 1216, 1077, 958. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.22 (1H, t, *J* = 7.8 Hz, RR′C*H*OH), 2.52 (1H, t, *J* = 13.9 Hz, RC(O)CH$_2$C*H*), 2.31–1.44 (19H, m), 1.39–1.10 (3H, m), 1.07 (3H, s, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 212.42, 108.91, 106.54, 80.33, 44.79, 44.51, 42.75, 40.31, 37.70, 36.43, 34.95, 30.10, 28.25, 28.00, 27.89, 27.80, 27.30, 24.42, 19.32, 16.12. MS (*m*/*e*): 294 ([M]$^+$). HR-MS calcd. for $C_{18}H_{27}O_2F$: 294.1995 ([M]$^+$); found: 294.1989 ± 0.0009. Ketone **35** (trans): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.23 (1H, t, *J* = 8.2 Hz, RR′C*H*OH), 2.44–0.89 (23H, m), 1.07 (3H, d, *J* = 0.8 Hz, C*H*$_3$). MS (*m*/*e*): 294 ([M]$^+$). HR-MS calcd. for $C_{18}H_{27}O_2F$: 294.1995 ([M]$^+$); found: 294.1989 ± 0.0009.

Diketone 37

To a stirred solution of alcohol **36** (76 mg, 0.26 mmol) in dichloromethane (5 mL) were added molecular sieve 4 Å (130 mg), 4-methylmorpholine-*N*-oxide (61 mg, 0.52 mmol), and tetrapropylammonium perruthenate (9 mg, 0.026 mmol). The resulting mixture was stirred at room temperature for 1 h and filtered on a silica gel pad. The solvent was evaporated to give diketone **37** as a colorless oil (76 mg, 99%). IR ($CHCl_3$, cm^{-1}) ν: 3020, 2930, 2879, 1740, 1708, 1461, 1215, 929, 746. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.59–2.37 (2H, m), 2.32–2.08 (6H, m), 1.88–1.05 (14H, m), 1.12 (3H, d, *J* = 1.5 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 219.46, 211.74, 106.80, 104.42, 44.52, 44.24, 42.63, 40.28, 37.45, 36.32, 35.06, 33.07, 31.91, 30.11, 27.20, 26.09, 25.75, 24.22, 19.10, 12.62. MS (*m*/*e*): 292 ([M]$^+$). HR-MS calcd. for $C_{18}H_{25}O_2F$: 292.1838 ([M]$^+$); found: 292.1844 ± 0.0008.

Alcohol 38

To a stirred solution of diketone **37** (71 mg, 0.24 mmol) in tetrahydrofuran (10 mL) at –78 °C was added a solution of 1 mol/L L-Selectride in tetrahydrofuran (360 µL, 0.36 mmol). The mixture was stirred at –78 °C for 1.5 h. A 2 mol/L NaOH solution and a 30% hydrogen peroxide solution were added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (70% ethyl acetate, 30% hexanes) to give

alcohol **38** as an amorphous white solid (72 mg, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3611, 3451, 2933, 2878, 1739, 1447, 1266, 1061, 1001, 922. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.14 (1H, t, J = 2.7 Hz, RR′C*H*OH), 2.51–2.40 (2H, m), 2.29–2.05 (3H, m), 1.86–1.15 (18H, m), 1.08 (3H, d, J = 1.3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 220.09, 107.25, 104.88, 66.75, 44.74, 44.47, 41.27, 34.51, 33.18, 32.13, 30.81, 29.26, 26.95, 26.07, 25.74, 24.30, 20.97, 19.60, 12.62. MS (*m*/*e*): 294 ($[M]^+$). HR-MS calcd. for $C_{18}H_{27}O_2F$: 294.1995 ($[M]^+$); found: 294.2000 ± 0.0009.

Silyl ether 40

To a stirred solution of alcohol **38** (36 mg, 0.12 mmol) in dichloromethane (3 mL) were added triethylamine (84 μL, 0.60 mmol) and *tert*-butyldimethylsilane trifluoromethanesulfonate (41 μL, 0.18 mmol). The mixture was stirred at room temperature for 1 h. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was dissolved in tetrahydrofuran (2 mL) and tetrapropylammonium fluoride (1 mol/L) in tetrahydrofuran (60 μL, 0.060 mmol) was added. The mixture was stirred at room temperature for 15 min. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give silyl ether **40** as a colorless oil (46 mg, 92%). IR ($CHCl_3$, cm^{-1}) ν: 3020, 2931, 2882, 1739, 1471, 1446, 1252, 1212, 1050, 930. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.06 (1H, t, J = 2.6 Hz, RR′C*H*OTBDMS), 2.47–2.34 (2H, m), 2.29–2.05 (3H, m), 1.89–1.13 (17H, m), 1.09 (3H, d, J = 1.4 Hz, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 220.18, 107.37, 105.00, 67.10, 44.83, 44.57, 41.43, 34.70, 34.58, 34.14, 33.15, 32.21, 32.13, 31.10, 29.28, 27.70, 26.07, 25.84, 25.81, 25.73, 24.38, 21.01, 19.73, 18.06, 12.65, 12.55, –4.89. MS (*m*/*e*): 208 ($[M]^+$), 351 ($[M - C_4H_9]^+$). HR-MS calcd. for $C_{24}H_{41}O_2FSi$: 408.2860 ($[M]^+$); found: 408.2863 ± 0.0012.

Vinylic iodide 42

To a stirred solution of ketone **38** (101 mg, 0.34 mmol) in ethanol (7 mL) were added triethylamine (952 μL, 6.80 mmol) and hydrated hydrazine (165 μL, 3.40 mmol). The mixture was stirred at reflux for 5 days and water was added. The aqueous phases were extracted with dichloromethane and the combined organic phases were dried, filtered, and evaporated. The residue was dissolved in tetrahydrofuran (5 mL) and triethylamine (1 mL) was added. Iodide was added until a brown color appeared and the mixture was stirred for 5 min. Water was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium thiosulfate and the organic phase was dried, filtered, and evaporated. The residue was purified by flash chromatography (40% ethyl acetate, 60% hexanes) to give vinylic iodide **42** as an amorphous white solid (125 mg, 91%). IR ($CHCl_3$, cm^{-1}) ν: 3386, 2931, 2873, 1459, 1447, 1380, 1263, 1000. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.06 (1H, t, J = 2.5 Hz, C*H*=CIR), 4.14 (1H, t, J = 2.8 Hz, RR′C*H*OH), 2.62–2.40 (2H, m, CH_2CH=CIR), 2.19–2.13 (1H, m), 1.86–1.10 (16H, m), 1.08 (3H, d, J = 2.8 Hz, CH_3), 1.05–0.83 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 132.48, 109.80, 105.63, 103.18, 66.85, 45.97, 45.68, 40.96, 40.63, 40.27, 37.36, 34.93, 33.17, 30.90, 29.28, 27.03, 24.26, 21.13, 20.75, 17.11. MS (*m*/*e*): 404 ($[M]^+$). HR-MS calcd. for $C_{18}H_{26}OFI$: 404.1012 ($[M]^+$); found: 404.1008 ± 0.0012.

Silyl ether 43

To a stirred solution of alcohol **42** (148 mg, 0.37 mmol) in dichloromethane (10 mL) were added triethylamine (1.3 mL, 1.85 mmol) and *tert*-butyldimethylsilane trifluoromethanesulfonate (94 μL, 0.41 mmol). The mixture was stirred at room temperature for 1 h. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give silyl ether **43** as an amorphous white solid (190 mg, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3019, 2930, 2856, 1509, 1424, 1364, 1217, 1048. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.07 (1H, t, J = 2.4 Hz, C*H*=CIR), 4.05 (1H, t, J = 2.4 Hz, RR′C*H*OTBDMS), 2.62–2.43 (2H, m, CH_2CH=CIR), 2.22–2.13 (1H, m), 1.89–0.91 (17H, m), 1.08 (3H, d, J = 2.8 Hz, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 132.48, 109.92, 105.70, 103.24, 67.17, 54.23, 53.98, 46.08, 45.80, 41.13, 40.65, 40.29, 37.44, 35.11, 34.11, 31.20, 29.28, 27.80, 25.83, 24.35, 21.17, 20.90, 17.14, –4.87. MS (*m*/*e*): 461 ($[M - C_4H_9]^+$). HR-MS calcd. for $C_{20}H_{31}OFISi$: 461.1173 ($[M - C_4H_9]^+$); found: 461.1178 ± 0.0014.

α,β-Unsaturated nitrile 44

To a stirred solution of vinylic iodide **43** (47 mg, 0.091 mmol) in benzene (3 mL) were added lithium cyanide (18 mg, 0.55 mmol), tetrakis(triphenylphosphine) palladium(0) (11 mg, 0.0091 mmol), and 12-C-4 ether (2 μL, 0.0091 mmol). The resulting mixture was stirred at reflux for 30 min and water was added. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (7% ethyl acetate, 93% hexanes) to give α,β-unsaturated nitrile **44** as an amorphous white solid (17 mg, 45%). IR ($CHCl_3$, cm^{-1}) ν: 3019, 2930, 2546, 2127, 1610, 1504, 1368, 1215, 1168, 1086, 1049. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.54 (1H, t, J = 2.6 Hz, C*H*=C(CN)R), 4.05 (1H, massif, RR′C*H*OTBDMS), 2.83–2.54 (2H, m, CH_2CH=C(CN)R), 2.24–2.20 (1H, m), 2.03–1.96 (1H, m), 1.90–0.90 (16H, m), 1.26 (3H, d, J = 2.5 Hz, CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 141.97, 125.37, 115.51, 107.41, 104.95, 67.06, 52.47, 52.21, 45.28, 45.00, 41.02, 39.55, 39.18, 37.4, 34.81, 34.07, 31.10, 29.18, 27.76, 25.80, 24.33, 21.16, 18.06, 14.81, –4.89. MS (*m*/*e*): 402 ($[M - CH_3]^+$), 360 ($[M - C_4H_9]^+$). HR-MS calcd. for $C_{21}H_{31}OFNSi$: 360.2159 ($[M - C_4H_9]^+$); found: 360.2166 ± 0.0014.

Nitriles 45a and 45b

To a stirred solution of α,β-unsaturated nitrile **44** (15 mg, 0.036 mmol) in ethyl acetate (2 mL) was added a catalytic amount of 10% palladium(0) on activated carbon and hydro-

gen was bubbled through the solution for 15 min. The mixture was stirred for 2 h under a hydrogen atmosphere and filtered on a silica gel pad. The solvent was evaporated and the residue was purified by flash chromatography (10% ethyl acetate, 90% hexanes) to give nitrile β-**45a** as an amorphous white solid (8 mg, 53%) and nitrile α-**45b** as an amorphous white solid (7 mg, 47%). Nitrile α-**45a**: IR ($CHCl_3$, cm^{-1}) ν: 2930, 2856, 2363, 1460, 1444, 1252, 1216, 1047. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.05 (1H, t, J = 2.6 Hz, RR′C*H*OTBDMS), 2.98 (1H, t, J = 9.0 Hz, RR′C*H*CN), 2.27–0.95 (22H, m), 1.15 (3H, s, CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 120.70, 109.17, 106.76, 67.1, 48.42, 48.18, 44.74, 44.48, 41.38, 39.18, 34.52, 34.14, 31.27, 31.18, 30.25, 29.92, 29.26, 27.67, 25.81, 24.82, 24.14, 20.96, 18.07, 16.66, –4.90. MS (*m*/*e*): 404 ([M – CH_3]$^+$), 362 ([M – C_4H_9]$^+$). HR-MS calcd. for $C_{24}H_{39}OFNSi$: 404.2785 ([M – CH_3]$^+$); found: 404.2773 ± 0.0012. Nitrile β-**45b**: IR ($CHCl_3$, cm^{-1}) ν: 3019, 2930, 2856, 2240, 1527, 1477, 1426, 1215, 1048. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.05 (1H, t, J = 2.5 Hz, RR′C*H*OTBDMS), 2.65 (1H, t, J = 6.0 Hz, RR′C*H*CN), 2.28–1.96 (5H, m), 1.87–1.03 (17H, m), 1.30 (3H, s, CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 121.92, 109.58, 107.18, 67.10, 48.46, 48.21, 44.71, 44.44, 41.46, 40.04, 36.65, 34.25, 34.12, 31.23, 30.85, 30.51, 29.24, 27.69, 25.80, 25.59, 21.17, 20.97, 18.06, 16.20, –4.88. MS (*m*/*e*): 404 ([M – CH_3]$^+$), 362 ([M – C_4H_9]$^+$). HR-MS calcd. for $C_{24}H_{39}OFNSi$: 404.2785 ([M – CH_3]$^+$); found: 404.2773 ± 0.0012.

Alcohols 46a

To a stirred solution of nitrile **45a** (7 mg, 0.017 mmol) in methanol was added a catalytic amount of PTSA and the mixture was stirred at room temperature for 3 h. Satd. aq. $NaHCO_3$ was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (50% ethyl acetate, 50% hexanes) to give alcohol **46a** as an amorphous white solid (5 mg, 100%). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.15 (1H, t, J = 2.8 Hz, RR′C*H*OH), 2.98 (1H, t, J = 9.5 Hz, RR′C*H*CN), 2.23–2.16 (2H, m), 2.04–1.06 (21H, m), 1.15 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 120.68, 109.07, 106.67, 66.83, 48.46, 48.22, 44.70, 44.43, 41.27, 39.21, 34.38, 33.24, 31.33, 30.93, 30.29, 29.96, 29.29, 27.00, 24.80, 24.16, 20.97, 16.68. MS (*m*/*e*): 287 ([M – H_2O]$^+$). HR-MS calcd. for $C_{19}H_{26}FN$: 287.2049 ([M – H_2O]$^+$); found: 287.2045 ± 0.0008.

Alcohol 46b

The procedure used for the synthesis of alcohol **46a** was used with alcohol **46b** to give alcohol **46b** as an amorphous white solid (5 mg, 100%). IR ($CHCl_3$, cm^{-1}) ν: 3423, 3019, 2933, 2360, 1523, 1423, 1216, 928. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 4.14 (1H, t, J = 2.8 Hz, RR′C*H*OH), 2.66 (1H, t, J = 7.7 Hz, RR′C*H*CN), 2.28–1.96 (6H, m), 1.82–1.00 (17H, m), 1.30 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 121.86, 109.46, 107.42, 66.79, 48.45, 48.21, 44.62, 44.35, 41.30, 40.02, 36.56, 34.19, 33.22, 30.94, 30.51, 29.69, 29.23, 26.93, 25.51, 21.04, 20.94, 16.18. MS (*m*/*e*): 287 ([M – H_2O]$^+$). HR-MS calcd. for $C_{19}H_{26}FN$: 287.2049 ([M – H_2O]$^+$); found: 287.2045 ± 0.0008.

p-Nitrobenzoate 47

To a stirred solution of alcohol **46b** (1 mg, 0.0033 mmol) in dichloromethane (250 μL) were added pyridine (250 μL), *p*-nitrobenzoyle chloride (6 mg, 0.033 mmol), and 4-dimethylaminopyridine (catalytic amount). The resulting mixture was stirred at room temperature for 3 h. HCl (1 mol/L) was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (30% ethyl acetate, 70% hexanes) to give *p*-nitrobenzoate **47** as a white solid (1 mg); mp 210 to 211 °C. IR ($CHCl_3$, cm^{-1}) ν: 2934, 2856, 2244, 1719, 1280, 1118. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.30 (2H, d, J = 9.0 Hz, Ph), 8.21 (2H, d, J = 9.0 Hz, Ph), 5.40 (1H, t, J = 2.4 Hz, RR′C*H*OC(O)Ar), 2.68 (1H, t, J = 6.6 Hz, RR′C*H*CN), 2.31–1.07 (22H, m), 1.32 (3H, s, CH_3). MS (*m*/*e*): 472 ([MNH_4]$^+$). HR-MS calcd. for $C_{26}H_{35}O_4FN_3$: 472.2611 ([MNH_4]$^+$); found: 472.2623 ± 0.0014.

α,β-Unsaturated ester 4

To a stirred solution of nitrile **46a** (4 mg, 0.013 mmol) in toluene (1 mL) at –60 °C was added a 1.5 mol/L solution of DIBALH in toluene (26 μL, 0.039 mmol) and the mixture was stirred at –60 °C for 1 h. Sodium sulfate decahydrate was added and the mixture was stirred at room temperature for 1 h. The residue was filtered and the solvent was evaporated to give the corresponding imine. This imine was passed rapidly through a short silica gel pad to give aldehyde **50a** (4 mg) as a crude material. To a stirred suspension of 60% NaH in oil (5 mg, 0.13 mmol) in tetrahydrofuran (1 mL) was added trimethyl phosphonoacetate (21 μL, 0.13 mmol). The mixture was stirred at room temperature for 15 min and crude aldehyde **50a** (4 mg, 0.013 mmol) in tetrahydrofuran (1 mL) was added. The resulting mixture was stirred at room temperature for 30 min. Satd. aq. NH_4Cl was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (40% ethyl acetate, 60% hexanes) to give α,β-unsaturated ester **4** as a colorless oil (3 mg, 60% for two steps). IR ($CHCl_3$, cm^{-1}) ν: 3501, 2932, 2875, 1718, 1654, 1540, 1558, 1437, 1281, 1216, 1002. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.91 (1H, dd, J = 15.6, 8.7 Hz, C*H*=CHCO$_2$Me), 5.83 (1H, J = 15.6 Hz, CH=C*H*CO$_2$Me), 4.14 (1H, t, J = 2.6 Hz, RR′C*H*OH), 3.73 (3H, s, CO$_2$CH_3), 2.81 (1H, q, J = 8.7 Hz, RR′C*H*CH=CHCO$_2$Me), 2.22–1.03 (23H, m), 1.00 (3H, d, J = 1.1 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 149.70, 149.57, 121.97, 66.93, 51.45, 51.33, 49.00, 45.09, 44.81, 41.27, 34.39, 34.27, 33.26, 31.00, 30.41, 30.06, 29.96, 29.37, 26.97, 25.04, 24.69, 20.98, 20.74, 16.81. MS (*m*/*e*) (source temperature: 100 °C): 364 ([M]$^+$), 344 ([M – HF]$^+$). HR-MS (source temperature: 100 °C) calcd. for $C_{22}H_{33}O_3F$: 364.2414 ([M]$^+$); found: 364.2403 ± 0.0011.

α,β-Unsaturated ester 3

The procedure used for the synthesis of α,β-unsaturated ester **4** was used for α,β-unsaturated ester **3** to give an

unseparable mixture of α,β-unsaturated ester **3** and α,β-unsaturated ester **4** (9:1) as an amorphous white solid (3 mg, 60%). IR ($CHCl_3$, cm^{-1}) ν: 3501, 2931, 2865, 1718, 1654, 1541, 1458, 1437, 1269, 1221, 1000. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.01 (1H, ddd, J = 15.5, 10.7, 1.8 Hz, C*H*=CHCO$_2$Me), 5.65 (1H, J = 15.5 Hz, CH=C*H*CO$_2$Me), 4.14 (1H, t, J = 2.7 Hz, RR′C*H*OH), 3.71 (3H, s, CO$_2$C*H*$_3$), 2.38 (1H, td, J = 8.5, 3.2 Hz, R′RC*H*CH=CHCO$_2$Me), 2.17–1.03 (23H, m), 0.90 (3H, s, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 153.55, 153.49, 119.75, 66.93, 53.93, 51.35, 45.09, 44.81, 41.43, 38.08, 37.98, 34.18, 33.27, 31.09, 30.75, 29.37, 26.97, 26.66, 25.42, 21.09, 21.01, 15.63. MS (*m*/*e*) (source temperature: 100 °C): 364 ([M]$^+$), 344 ([M – HF]$^+$). HR-MS (source temperature: 100 °C) calcd. for $C_{22}H_{33}O_3F$: 364.2414 ([M]$^+$); found: 364.2403 ± 0.0011.

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