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Total synthesis of 3-azasteroids via the transannular Diels–Alder strategy

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This article is dedicated to Professor Jean François Normant on the occasion of his 65th birthday

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Abstract—The total synthesis of four new 3-azasteroids is described, using the transannular Diels–Alder (TADA) reaction. Elaboration of the acyclic trienes, macrocyclizations and TADA reactions are detailed, as well as the stereochemical outcome of the reaction.

1. Introduction

The total synthesis of natural as well as unnatural products has been one of the major endeavours of organic synthesis for a few decades, allowing for the refinement of both synthetic strategies and tactics, as well as the development of new synthetic methods addressing specific problems. Architecturally complex molecules have become accessible owing to the development of general or specific strategies.[1] In this respect, steroids have always represented an impressive synthetic challenge, owing to their polycyclic nature combined with complex stereochemical issues.

In the past few years, the transannular Diels–Alder (TADA) reaction has emerged as a robust tool to approach polycyclic diterpenes and steroids.[2] This strategy allowed for the synthesis of a large variety of tricyclic or tetracyclic terpenoids.[3] Its limits and potential have been very well delineated by extensive model studies.[4] The approach was also applied to the total synthesis of steroidal molecules.[5] Unnatural derivatives mimicking natural products, particularly steroid-like molecules possessing a heteroatom at the pro-C3 position (**1** and **2**, Fig. 1), are in principle within reach using such strategy.

Steroids containing one or several heteroatoms on their backbone have been the subject of several studies,[6] and were found to display a broad spectrum of biological activities. As far as azastaroids are considered, these activities range from antibacterial,[7] neuromuscular blockers,[8] androgenic activity,[9] to 5α-reductase inhibiting properties.[10]

In addition to its biological potential, this class of products holds an obvious synthetic challenge, and we felt in position to tackle its total synthesis using our unified approach towards steroids.[11] Accordingly, 3-aza-5β-steroid **1** and 3-aza-5α-steroid **2** (Fig. 1) were selected, having respectively the *cis-anti-trans-anti-trans* (CATAT) and the *trans-syn-cis-anti-trans* (TSCAT) stereochemistry.[12] These azasteroids are related to 5β-androsterone and adrenosterone respectively (Fig. 1).[13] The present article summarizes the total synthesis of 3-azasteroids **1** and **2**, as well as some interesting discoveries brought by this research.

2. Results and discussion

As indicated in Fig. 2, tetracycle **1** was envisioned to be the

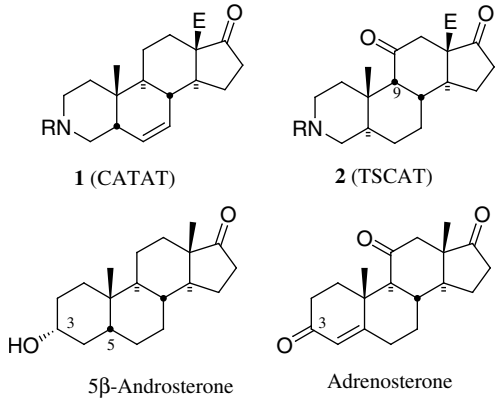

Figure 1. C3-modified steroidal targets.

Keywords: 3-azasteroids; transannular Diels–Alder strategy; acyclic trienes.

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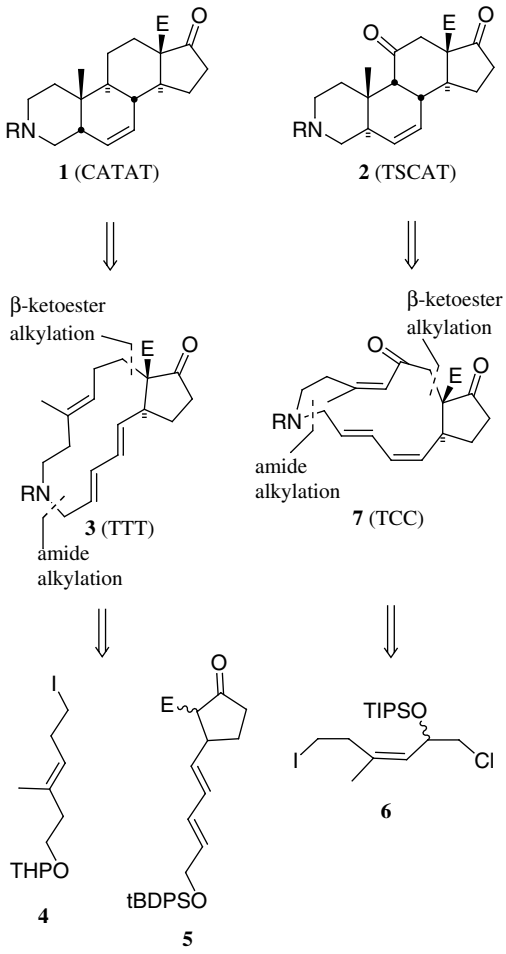
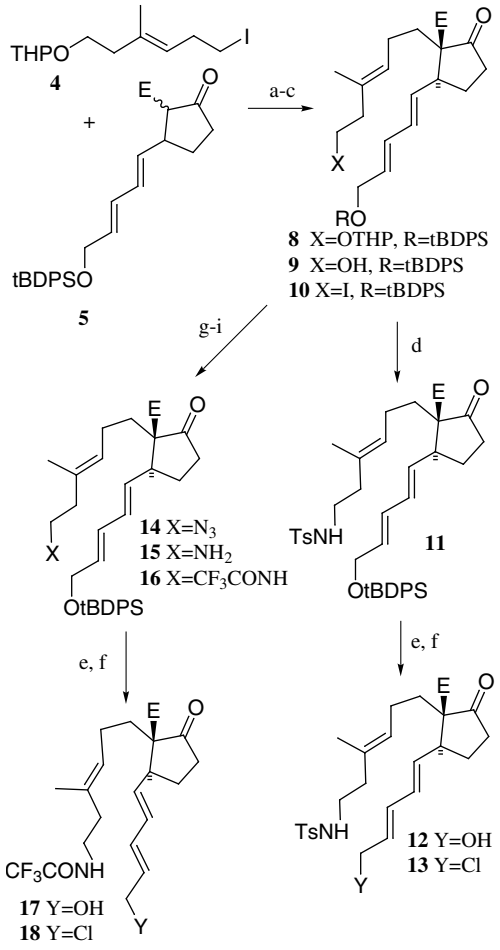


Figure 2. Retrosynthetic analysis



a. KH, toluene, rt then **4**, rfx (78%); b. PPTS, iPrOH, rfx (99%); c. PPh_3, DEAD, MeI, toluene, rt (90%); d. $TsNH_2$, NaH, 18-C-6, THF:DMF, 80°C (52%); e. TBAF, THF 0°C (82-95%); f. $(Cl_3C)_2CO$, PPh_3, THF -40°C (84-93%); g. NaN_3, DMSO rt (98%); h. PPh_3, H_2O, THF rt; i. TFAA, Et_3N, CH_2Cl_2 0°C (95% 2 steps).

Scheme 1.

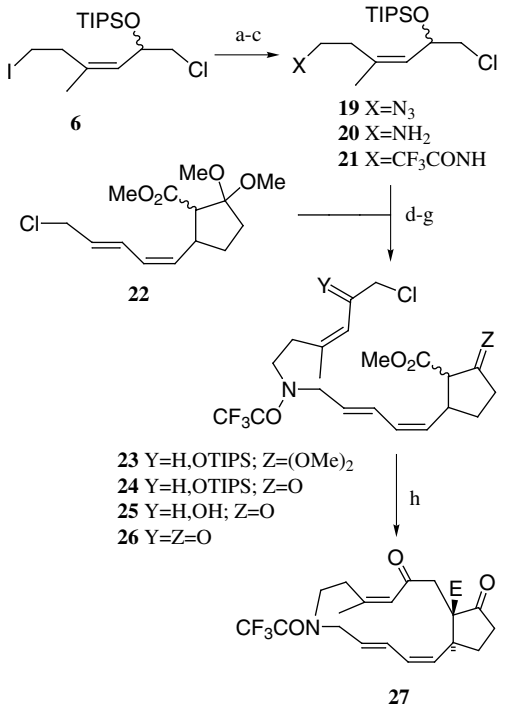
result of a TADA reaction on *trans-trans-trans* (TTT) trienic macrocycle **3**. The predicted major product of the cycloaddition was supposedly CATAT tetracycle **1**, according to our model studies on steroid synthesis.[11] Macrocycle **3** was in principle accessible from two main fragments, i.e. cyclopentanone **5** and iodide **4**, connected via alkylation of an amide. On the other hand, tetracycle **2** would be the TADA adduct obtained from *trans-cis-cis* (TCC) trienic macrocycle **7**. Here, only one geometry was to be expected. Macrocycle **7** could be obtained from two fragments, namely cyclopentanone **5** and iodide **6**.

2.1. Synthesis of the triene precursors

Accordingly, the enolate of β-ketoester **5** was alkylated with iodide **4** to give acyclic triene **8** in 78% yield (Scheme 1).[14] The THP protection was removed, and the resulting alcohol transformed into the corresponding iodide **10** in excellent yields.[15] Reaction with tosylamide in basic conditions allowed for the introduction of the amide moiety and generated **11**. Desilylation was followed by allylic chloride formation in the presence of hexachloroacetone and triphenylphosphine[16] to give acyclic triene **13** ready for tandem macrocyclization-TADA cycloaddition (see the following section).

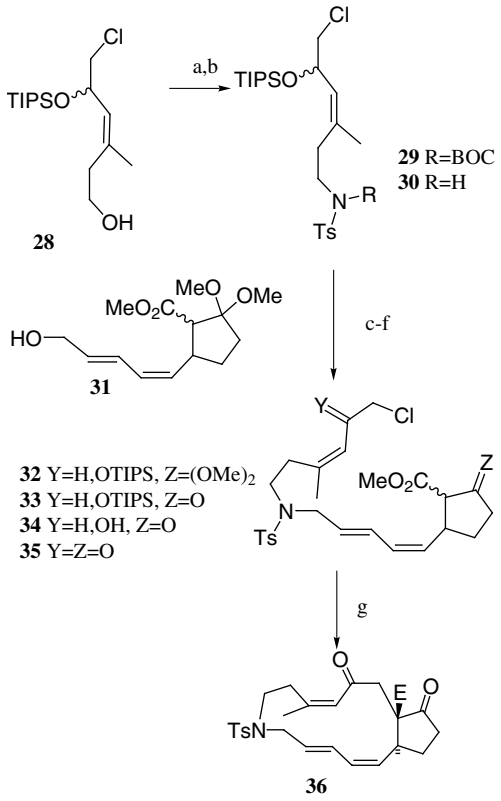
Similarly, reaction of iodide **10** with sodium azide led to the corresponding azide **14** in nearly quantitative yield. The latter underwent a Staudinger reduction to the free amine **15**, which was almost quantitatively transformed into trifluoroacetamide **16**. Subsequent deprotection of the silyl ether (82%) followed by chlorination led to allylic chloride **18** in 93% yield and completed the synthesis of the second acyclic TTT triene presursor.

The synthesis of TCC acyclic trienes involved a somewhat different approach. Starting from the known Z iodide **6** (Scheme 2),[17] displacement by sodium azide followed by LAH reduction and subsequent amidation led to trifluoroacetamide **21** in high yields. The latter was alkylated with allylic chloride **22**[5a] to connect the diene and dienophile parts together and produce acyclic triene **23** in 57% yield. The dimethoxycetal was then hydrolyzed to regenerate the cyclopentanone moiety **24**, and the silyl ether subsequently removed using TBAF to free alcohol **25** in 90% yield. The latter was oxidized with Dess–Martin periodinane[18] to yield



a. NaN_3, DMSO (91%); b. LAH, Et_2O; c. TFAA, pyridine (93% 2 steps); d. **22**, Cs_2CO_3, CH_3CN rfx (57%); e. TFA:H_2O, CH_2Cl_2 0°C (93%); f. TBAF, THF -20°C (90%); g. Dess-Martin periodinane (74%); h. Cs_2CO_3, CH_3CN 40°C (30%).

Scheme 2.



a. TsNHBOC, PPh_3, DEAD, THF (95%); b. DMSO, 180°C (95%); c. **31**, PPh_3, DIAD (75%); d. TFA:H_2O, CH_2Cl_2 0°C (93%); e. TBAF, THF -20°C (90%); f. Dess-Martin periodinane (74%); g. Cs_2CO_3, CH_3CN 40°C (60%).

Scheme 3.

chloroketone **26** ready for macrocyclization. Macrocyclization was carried out at low temperature under pseudo-high dilution,[19] by adding chloroketone **26** to a warm (40°C) suspension of cesium carbonate in acetonitrile during 1.7 h, followed by 2.5 h stirring at the same temperature (the final concentration being 2 mM). In this case, a modest 30% yield of the desired macrocycle **27** was obtained, attributed to the instability of the precursor chloroketone.

In a more convergent approach (Scheme 3), dienophile alcohol **28**[20] underwent a Mitsunobu reaction with TsNHBOC,[21] to give the corresponding carbamate **29** in 95% yield. The BOC group was subsequently pyrolyzed to regenerate tosylamide **30**,[22] which was coupled under Mitsunobu conditions with dienic alcohol **31**[5a] in 75% yield. Further elaboration of **32** as already mentioned led to chloroketone **35** in good yields. The latter underwent the macrocyclization smoothly in the above described conditions, giving access to TCC macrocyclic triene **36** in 60% yield.

2.2. TADA reactions (Scheme 4)

In the TTT series, when allylic chloride **18** was exposed to the macrocyclization conditions (12 h slow addition of the triene solution to a refluxing suspension of cesium carbonate in acetonitrile followed by 12 h reflux, final concentration 1 mM), a separable mixture of tetracycles was obtained in a 5.2:1 ratio and 55% overall yield. Selective crystallization of the major adduct **38**β allowed for a single crystal X-ray analysis and secured the assigned structure (see Fig. 3). Even though not isolated from the major adduct, the minor isomer was assigned TACST structure **38**α based on previous studies and molecular modeling calculations.[11,23,24] No trienic macrocycle remained as could be expected in the TTT series, as a consequence of the easily accessible *s-cisoid* geometry of the diene.[4a] When tosylamide

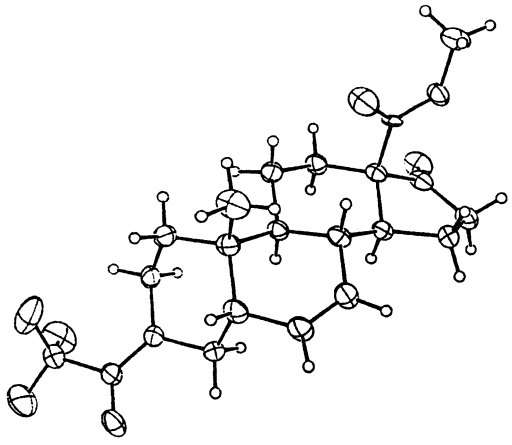


Figure 3. X-Ray analysis of tetracycle **38**β.

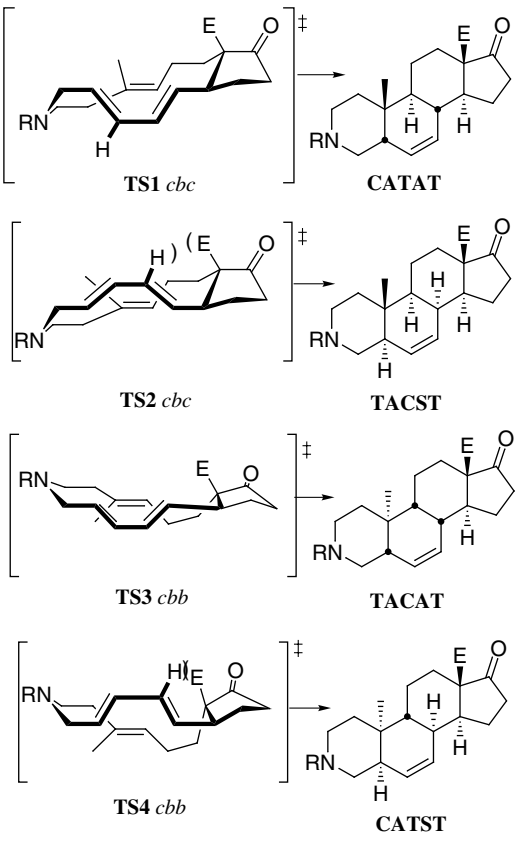
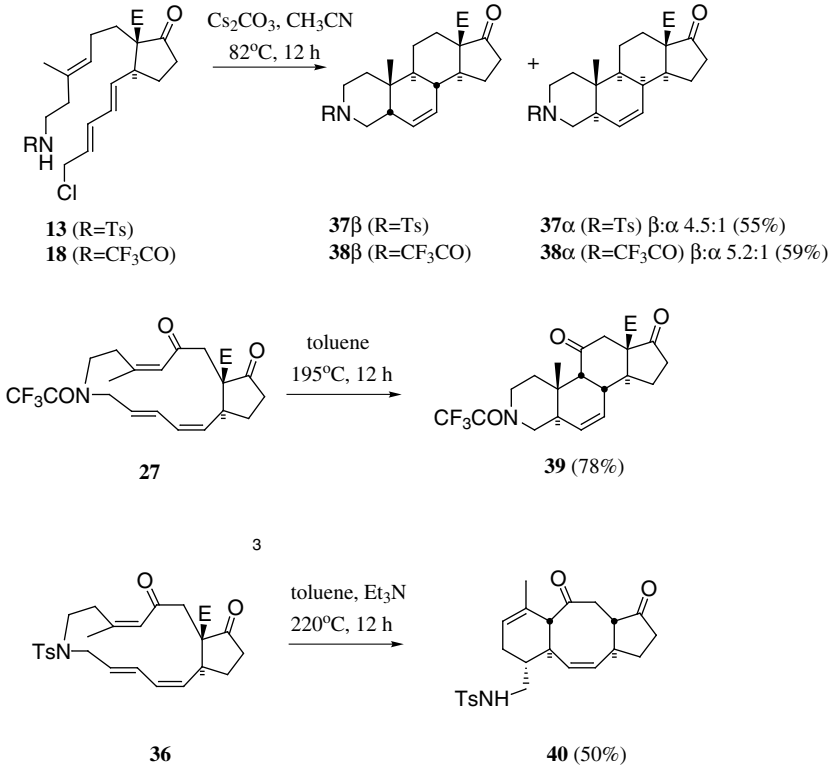


Figure 4.

analogue **13** was subjected to the same conditions, the results were essentially identical and tetracycles **37**β and **37**α were obtained as an unseparable mixture (CATAT: TACST 4.5:1, 59% yield). There again, macrocyclization and TADA occurred in a tandem fashion.

The obtention of a *ca* 5:1 ratio in favour of the CATAT geometry is also in agreement with our previous observations and theoretical studies,[11] as well as Takahashi's predictions in the 3-ketosteroid series (see Fig. 4).[25] Four transition states are actually competing. The more easily accessible one (**TS1**) possesses the *chair-boat-chair* (cbc) geometry in which the dienophile methyl group is oriented in a β fashion and the diene assumes the α orientation. This transition state leads to the major CATAT product. The second transition state (**TS2**) also has the *chair-boat-chair* conformation with the diene adopting this time the β orientation, albeit possesses an unfavourable transannular interaction and is thus slightly higher in energy. In the third transition state (**TS3**), the *chair-boat-boat* conformation accounts for higher energy. The last transition state (**TS4)** is excluded, suffering both from unfavourable steric interaction and from a *chair-boat-boat* conformation.

On the other hand, in the TCC series, diverging results were obtained. The TCC series exemplifies at its best the power of the TADA strategy, allowing for the Diels–Alder reaction of a *trans-cis* diene, which often is a poor coupling partner with respect to intermolecular and intramolecular settings.[25] Transannular effects force this diene to approach



Scheme 4.

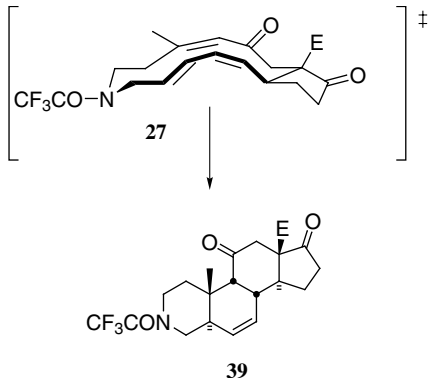


Figure 5.

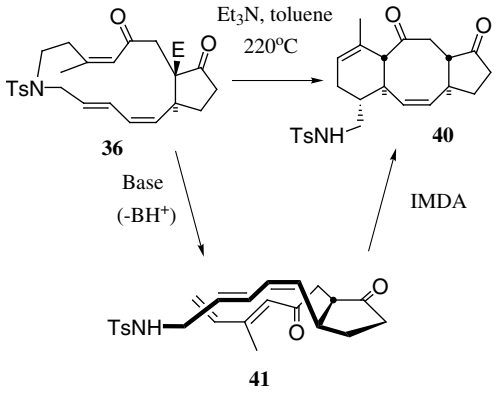


Figure 7.

the *s-cisoid* geometry, although the asynchronicity of the transition state[26] usually allows for slight deviation from the purely *s-cisoid* arrangement. Typically, TADA temperatures are higher than in the TTT series, where the *trans-trans* diene readily adopts a productive conformation.

Firstly, upon heating TCC macrocyclic triene **27** up to 195°C in toluene in a sealed tube, the desired azasteroid **39** was obtained in 78% yield after 12 h (Scheme 4). In the TCC series, only the *trans-syn-cis* (TSC) geometry can be obtained on the newly formed tricycle, based on geometrical constraints (Fig. 5). On the other hand, when TCC macrocyclic triene **36** was submitted to the TADA conditions in the absence of a base, only decomposition was observed. To our surprise, in the presence of triethylamine, 50% of rearrangement product **40** was obtained at 220°C. The stereochemistry of tricycle **40** was secured by a single crystal X-ray analysis (see Fig. 6). Moreover, the product was completely decarboxylated. The obtention of this rearrangement product could in principle be explained by the intervention of an intramolecular Diels–Alder reaction (IMDA) on the open product **41** derived from macrocycle **36** (Fig. 7). One may reasonably argue that in the presence of a base, elimination taking place via a retro-Michael reaction expels the tosyl-stabilized amide moiety of the molecule (Fig. 7). The newly created diene **41** would be in position to undergo an intramolecular Diels–Alder reaction with the *trans* olefin of the other diene moiety, resulting in the closure of the observed 8-membered ring and formation of [6.8.5] tricycle **40**. We assumed that the base was also responsible for the observed decarboxylation. The presence of the ester group on intermediate **41** would create an unfavourable interaction with the *cis* portion of the diene. Using more hindered bases than triethylamine (Hünig's base or 2,6-di-*tert*-butylpyridine) led to no reaction up to 260°C and degradation at higher temperatures, supporting this assumption.

Finally, similar precursors were prepared aiming at the 3-thio series. However, tandem macrocyclization-TADA on TTT triene derived from **18** ($CF_3CONH{=}SH$) met with failure. In the TCC series, a macrocycle analogous to **27** was synthesized ($CF_3CON{=}S$), but decomposed when heated up to the high temperatures required for the TADA reaction to occur.[27]

In conclusion, we have synthesized two new types of 3-azasteroids related to androsterone and adrenosterone. The synthesis makes use of the TADA strategy and emphasizes the direct link between the macrocyclic triene geometry and the stereochemistry of the resulting tetracycle, as well as the good stereocontrol associated with this strategy. Knowing that the precursor to the only chiral fragment cyclopentanone **5** can be produced in enantiomerically pure form,[28] this formally constitutes an enantioselective approach towards 3-azasteroids.

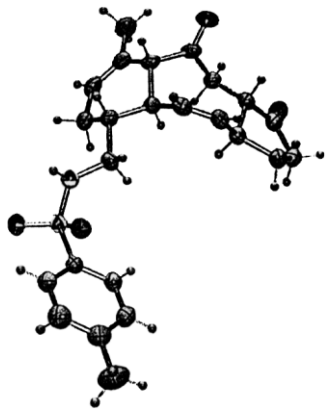


Figure 6. X-Ray analysis of tricycle **40**.

3. Experimental

3.1. General

All reactions were performed under N_2 atmosphere with oven or flame dried glassware. Solvents were distilled by the usual means. Analytical TLC were performed on precoated glass plates (0.25 mm) with silica gel 60F-250 (Merck). Flash chromatography was performed with 230–400 mesh silica gel 60 (Merck). Melting points were recorded on a Büchi Schmelz punk bestimmungs and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brüker AC-300 and are referenced with respect to the residual signals of the solvent; they are described using standard abbreviations. IR spectra were recorded on a

Perkin–Elmer 1600 FT-IR. Mass spectra were recorded on a ZAB-1F micromass spectrometer.

3.1.1. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-toluenesulfonamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-(*tert*-butyldiphenylsiloxy(penta-1,3-dien-1-yl]cyclopentanone (11). To a solution of Cs_2CO_3 (900 mg, 2.76 mmol) and tosylamide (525 mg, 3.07 mmol) in CH_3CN (4 mL) at 80°C, was added via canula a solution of iodide **10** (101 mg, 0.147 mmol) in CH_3CN (2 mL). The mixture was stirred for 15 h, cooled down to rt, filtered on celite and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes–ethyl acetate 7:3) to give **11** (54.5 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.75 (2H, d, J=8.0 Hz), 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 7.32–7.25 (2H, d), 6.26 (1H, dd), 6.17 (1H, dd, J=10.5 Hz, 14.5 Hz), 5.75 (1H, dt, J=7.0 Hz, 14.5 Hz), 5.58 (1H, dd, J=8.5, 14.5 Hz), 5.05 (1H, t, J=6.0 Hz), 4.52 (2H, t, J=6.0 Hz), 4.24 (2H, d, J=5.0 Hz), 3.67 (3H, s), 2.99 (2H, q, J=6.0 Hz), 2.87 (1H, q, J=8.5 Hz), 2.61–2.54 (1H, m), 2.42 (3H, s), 2.35–1.70 (8H, m), 1.45 (3H, s), 1.07 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.2, 170.2, 143.2, 136.8, 135.4, 133.5, 132.3, 132.2, 131.73, 131.42, 130.39, 129.60, 129.02, 127.59, 127.00, 63.93, 63.03, 51.96, 48.27, 40.5, 38.8, 38.4, 31.6, 26.7, 26.1, 25.2, 22.7, 21.4, 19.2, 15.3. IR ($CHCl_3$) ν 3368, 3028, 2952, 2859, 1731, 1428, 1375, 1248, 1160. MS (EI) 727 (M^+); 670 $(M\text{-}C_4H_9)^+$. HRMS (M^+) calc. for $C_{42}H_{53}NO_6SSi$: 727.3363; found: 727.3355.

3.1.2. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-toluenesulfonamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-hydroxy-penta-1,3-dien-1-yl]cyclopentanone (12). To a solution of tosylamide **11** (66.5 mg, 0.0915 mmol) in THF (2 mL) at rt was added TBAF (1.0 M in THF, 0.101 mL, 0.101 mmol) and the mixture was stirred for 2 h at rt. The solvent was removed in vacuo and the product purified by flash chromatography (EtOAc:CH_2Cl_2:MeOH 30:70:1) to give **12** (43 mg, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.72 (2H, d, J=8.0 Hz), 7.33–7.25 (2H, d, J=9.0 Hz), 6.25–6.10 (2H, m), 5.81 (1H dt, J=5.5, 14.5 Hz), 5.58 (1H, dd, J=8.0, 14.5 Hz), 5.03 (1H, t, J=7.0 Hz), 4.51 (1H, t, J=6.0 Hz), 4.17 (2H, d, J=6 Hz), 3.65 (3H, s), 2.98 (2H, q, J=6.5 Hz), 2.85 (1H, q, J=8.0 Hz), 2.61–2.54 (1H, m), 2.42 (3H, s), 2.35–1.60 (9H, m), 1.43 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.2, 143.3, 136.8, 132.1, 131.8, 131.5, 131.2, 130.6, 130.2, 129.7, 127.1, 63.1, 52.0, 48.3, 40.6, 38.8, 38.3, 31.6, 26.1, 25.2, 22.7, 21.5, 15.3. IR (film) ν 3611, 3378, 3030, 2953, 1749, 1731, 1600, 1458, 1331, 1240, 1094. MS (EI): 489 (M^+); 471 $(M\text{-}H_2O)^+$. HRMS (M^+) calc. for $C_{26}H_{35}NO_6S$: 489.2185; found: 489.2178.

3.1.3. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-toluenesulfonamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-chloro-penta-1,3-dien-1-yl]cyclopentanone (13). To a solution of alcohol **12** (38.1 mg, 0.0779 mmol) in THF (1 mL) at −40°C were added PPh_3 (30.7 mg, 0.117 mmol) and 2,6-lutidine (13.6 mL, 0.117 mmol). Hexachloroacetone (17.7 mL, 0.117 mmol) was then added and the mixture was stirred for 30 min then heated up to rt. The solvent was removed in vacuo and the product purified by flash chromatography (hexanes–EtOAc 7:3) to give **13** (33 mg, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.70 (2H, d, J=8.0 Hz), 7.33–7.29 (2H, d, J=8.0 Hz), 6.43–6.11 (2H, m), 5.83–5.62 (2H, m), 5.04 (1H, brt, J=6.0 Hz), (2H, t, J=6.0 Hz), 4.10 (2H, d, J=6.5 Hz), 3.66 (3H, s), 2.98 (2H, q, J=6.5 Hz), 2.85 (1H, q, J=8.0 Hz), 2.65–2.56 (1H, m), 2.43 (3H, s), 2.35–1.60 (7H, m), 1.44 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 170.2, 136.9, 135.9, 134.4, 133.6, 133.4, 131.9, 131.2, 129.7, 128.3, 127.1, 127.0, 123.8, 52.1, 48.3, 40.5, 38.9, 38.3, 31.7, 26.1, 22.8, 21.5, 15.4. IR (film) ν 3031, 2955, 1750, 1731, 1599, 1435, 1405, 1331, 1240, 1160, 1094, 990. MS (EI): 507 (M^+), 471 $(M\text{-}HCl)^+$. HRMS (M^+) calc. for $C_{26}H_{34}ClNO_5S$: 507.1846; found: 507.1825.

3.1.4. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-6-azido-4-methylhex-3-en-1-yl]-3-[(1*E*,3*E*)-5-(*tert*-butyldiphenyl-siloxy)penta-1,3-dien-1-yl]cyclopentanone (14). To a solution of iodide **10** (159 mg, 0.233 mmol) in DMSO (1.7 mL) at rt was added NaN_3 (30.3 mg, 0.466 mmol). The mixture was stirred for 14 h. Water (3.4 mL) was added, and the mixture was extracted with ether (3× 10 mL). The combined organic layers were washed with water (2×10 mL), dried on $MgSO_4$, and the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes–EtOAc 6:4) to give azide **14** (132 mg, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (4H, m), 7.48–7.35 (6H, m), 6.30–6.10 (2H, m), 5.75 (1H dt, J=5.0, 14.5 Hz), 5.57 (1H, dd, J=8.0, 14.5 Hz), 5.25 (1H, t, J=6.5 Hz), 4.24 (2H, d, J=5 Hz), 3.67 (3H, s), 3.21 (2H, t, J=7.0 Hz), 2.89 (1H, q, J=9.0 Hz), 2.60 (1H, dt, J=5.5, 18.0 Hz), 2.28 (2H, t, J=7 Hz), 2.31–1.55 (7H, m), 1.64 (3H, s),1.08 (9H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 214.9, 170.2, 135.4, 133.5, 132.1, 131.9, 130.5, 130.3, 129.6, 129.1, 127.6, 126.5, 63.9, 63.2, 51.9, 49.6, 48.2, 38.6, 38.3, 31.5, 26.7, 26.1, 22.8, 19.2, 15.8. IR (film) ν 2946, 2867, 2845, 2099, 1750, 1727, 1428, 1224, 1162. MS (EI): 599 (M^+), 542 $(M\text{-}C_4H_9)^+$. HRMS $(M\text{-}C_4H_9)^+$ calc. for $C_{31}H_{36}N_3O_4Si$: 542.2475; found: 542.2469.

3.1.5. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-trifluoroacetamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-(*tert*-butyldiphenylsiloxy)penta-1,3-dien-1-yl]cyclopentanone (16). To a solution of azide **14** (82 mg, 0.136 mmol) in THF (1.5 mL) at rt, was added PPh_3 (71 mg, 0.27 mmol) and water (103 mL, 5.71 mmol). The mixture was stirred overnight at rt, then a solution of $NaHCO_3$ (5 mL) was added and the organic layer extracted with CH_2Cl_2 (3×10 mL). The organic layers were dried on $MgSO_4$ and the solvent removed in vacuo.

To a solution of the crude amine in CH_2Cl_2 (1.7 mL) at 0°C, was added pyridine (55 μL, 0.68 mmol) and TFAA (38 μL, 0.027 mmol). The mixture was stirred at 0°C for 15 min, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried on $MgSO_4$ and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes: EtOAc 7:3) to give amide **16** (88 mg, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (4H, m), 7.48–7.35 (6H, m), 6.58 (1H, s), 6.30–6.10 (2H, m), 5.75 (1H dt, J=5.0, 14.5 Hz), 5.56 (1H, dd, J=8.0, 14.5 Hz), 5.21 (1H, t, J=6.5 Hz), 4.25 (2H, d, J=5 Hz), 3.67 (3H, s), 3.43 (2H, q, J=6.5 Hz), 2.88 (1H, q, J=8.5 Hz), 2.65–2.52 (1H, m), 2.24 (2H,t, J=6.5 Hz), 2.31–1.70 (7H, m), 1.64 (3H, s),

1.08 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.2, 157.0 (q), 135.4, 133.5, 132.6, 132.3, 131.7, 130.3, 129.6, 129.0, 127.6, 127.1, 115.8 (q), 63.9, 63.0, 51.9, 48.5, 38.3, 37.4, 31.6, 29.5, 26.7, 26.1, 22.7, 19.2, 15.5. IR (film) ν 3340, 2953, 2857, 1750, 1719, 1555, 1458, 1428, 1209, 1164, 1112, 1056. MS (EI): 669 (M^+), 612 ($M\text{-}C_4H_9$)$^+$. HRMS ($M\text{-}C_4H_9$)$^+$ calc. for $C_{33}H_{35}F_3NO_5Si$: 612.2393; found: 612.2397.

3.1.6. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-trifluoroacetamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dien-1-yl]cyclopentanone (17). The procedure for the synthesis of **12** was followed (on 87 mg of **16**). Purification by flash chromatography (EtOAc:CH_2Cl_2:MeOH, 30:70:0.5) gave alcohol **17** (46 mg, 82%) as a thick colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.25–6.08 (2H, m), 5.78 (1H dt, J=5.5, 14.5 Hz), 5.55 (1H, dd, J=8.0, 14.5 Hz), 5.15 (1H, t, J=6.5 Hz), 4.15 (2H, d, J=6.0 Hz), 3.63 (3H, s), 3.39 (2H, q, J=6.5 Hz), 2.85 (1H, q, J=8.0 Hz), 2.65–2.52 (1H, m), 2.20 (2H, t, J=7.0 Hz), 2.29–1.62 (8H, m), 1.59 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.2, 156.8 (q, J=39.0 Hz), 132.0, 131.9, 131.7, 131.3, 130.4, 126.9, 115.8 (q, J=288.0 Hz), 63.0, 52.0, 52.0, 48.3, 38.5, 38.2, 37.5, 31.6, 26.0, 22.6, 15.4. IR (film) ν 3402, 3342, 3097, 2953, 1749, 1716, 1558, 1448, 1456, 1213, 1192, 1160, 1087. MS (EI): 431 (M^+), 413 ($M\text{-}H_2O$)$^+$. HRMS ($M\text{-}H_2O$)$^+$ calc. for $C_{21}H_{26}F_3NO_4$: 413.1814; found: 413.1821.

3.1.7. (±)-(2*R*,3*S*)-2-Methoxycarbonyl-2-[(*E*)-4-methyl-6-trifluoroacetamidohex-3-en-1-yl]-3-[(1*E*,3*E*)-5-chloropenta-1,3-dien-1-yl]cyclopentanone (18). The procedure for the synthesis of **13** was followed (on 27 mg of **17**). Purification by flash chromatography (hexanes:EtOAc 7:3) gave chloride **18** (26 mg, 93%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (1H, s), 6.25–6.08 (2H, m), 5.75 (1H, q, J=7.5 Hz), 5.63 (1H, dd, J=8.0, 14.5 Hz), 5.16 (1H, t, J=6.5 Hz), 4.08 (2H, d, J=7.0 Hz), 3.64 (3H, s), 3.40 (2H, q, J=6.0 Hz), 2.86 (1H, q, J=8.0 Hz), 2.65–2.52 (1H, m), 2.21 (2H, t, J=7.0 Hz), 2.29–1.62 (7H, m), 1.60 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 170.1, 157.0 (q), 133.5, 133.2, 131,8, 131.1, 128.1, 127.0, 116.0 (q), 63.0, 52.0, 48.3, 44.8, 38.2, 37.4, 31.6, 26.9, 25.9, 22.6, 15.5. IR (film) ν 3344, 3102, 2953, 1749, 1722, 1556, 1436, 1283, 1211, 1177, 1064. MS (m/e): 418 ($M\text{-}OMe$)$^+$, 413 ($M\text{-}HCl$)$^+$. HRMS ($M\text{-}OMe$)$^+$ calc. for $C_{20}H_{24}ClF_3NO_3$: 418.1397; found: 418.1406.

3.1.8. (*Z*)-6-Azido-1-chloro-4-methyl-2-triisopropylsiloxyhex-3-ene (19). The procedure for the synthesis of **14** was followed (on 3.0 g of **6**). Purification by flash chromatography (hexanes:ethyl acetate 9:1), gave azide **19** as a clear oil (2.23 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (1H, d, J=7.5 Hz), 4.63 (1H, dt, J=6.0, 8.5 Hz), 3.57–3.37 (4H, m), 2.52–2.42 (1H, m), 2.32–2.22 (1H, m), 1.78 (3H,s), 1.08 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 129.6, 69.5, 49.5, 49.0, 32.0, 23.0, 17.9, 12.3. IR (film) ν 2933, 2865, 2095, 1461, 1380, 1255, 1066. MS: 302 ($M\text{-}C_3H_7$)$^+$, 274 ($M\text{-}N_2\text{-}C_3H_7$)$^+$. HRMS ($M\text{-}C_3H_7$)$^+$ calc. for $C_{13}H_{25}ClN_3OSi$: 302.1455; found: 302.1466.

3.1.9. (*Z*)-1-Chloro-4-methyl-6-trifluoroacetamido-2-triisopropylsiloxyhex-3-ene (21). To a solution of azide **19** (3.17 g, 9.2 mmol) in ether (70 mL) at 0°C, was added LAH (1.0 M in ether, 196 μL, 196 μmol). The mixture was stirred for 3 h at 25°C, treated with a saturated solution of $NaHCO_3$ (70 mL), then with 1 M NaOH (15 mL), then extracted three times with ether. The combined organic layers were dried on $MgSO_4$ and the solvent removed in vacuo. The amine was used as such for the following step.

To a solution of the amine (2.9 g, 9.09 mmol) in ether (100 mL) at 0°C, were added pyridine (3.67 mL, 45.5 mmol) and TFAA (2.57 mL, 18.2 mmol). The mixture was stirred at rt for 15 min, treated with water (80 mL), then extracted three times with CH_2Cl_2. The combined organic layers were dried on $MgSO_4$ and the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes:ethyl acetate 8:2), to give trifluoroacetamide **21** as a clear oil (3.53 g, 93% (two steps)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (1H, s), 5.32 (1H, d, J=8.0 Hz), 4.63–4.56 (1H, m), 3.60–3.30 (4H, m), 2.61–2.51 (1H, m), 2.31–2.20 (1H, m), 1.78 (3H,s), 1.06 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (q, J=20.0 Hz), 134.1, 130.2, 115.7 (q, J=280.5 Hz), 69.2, 48.5, 37.8, 31.2, 22.6, 17.8, 12.3. IR (film) ν 3302, 3105, 2945, 2867, 1704, 1557, 1463, 1383, 1342, 1308, 1184, 1116, 1065. MS (EI): 372 ($M\text{-}C_3H_7$)$^+$. HRMS ($M\text{-}C_3H_7$)$^+$ calc. for $C_{15}H_{26}ClF_3NO_2Si$: 372.1373; found: 372.1367.

3.1.10. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3,3-dimethoxy)cyclopentyl-7-trifluoroacetyl-2-triisopropylsiloxydodeca-3,9,11-triene (23). To a solution of amide **21** (2.79 g, 6.3 mmol) in acetonitrile (90 mL) at rt, were added Cs_2CO_3 (14.4 g, 44.1 mmol) and the diene solution (1.21 g, 4.21 mmol) in acetonitrile (10 mL). The solution was refluxed for 19 h, cooled down to rt, filtered on celite, rinsed with CH_2Cl_2 and dried on $MgSO_4$ then concentrated in vacuo. The product was purified by flash chromatography (hexanes:EtOAc 8:2), to give ketal **23** as a clear oil (1.61 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (1H, dd, J=11.0, 15.0 Hz), 5.96 (1H, t, J=11.0 Hz), 5.62–5.49 (1H, m), 5.35 (1H, t, J=10.0 Hz), 5.25 (1H, d, J=7.5 Hz), 4.66–4.52 (1H, m), 4.22–3.96 (2H, m), 3.67 (3H, s), 3.28, 3.21 (6H, 2s), 3.69–3.31 (4H, m), 2.73 (2H, d, J=8.5Hz), 2.63–2.40 (1H, m), 2.29–2.15 (1H, m), 2.10–1.84 (3H, m), 1.80 (3H, s), 1.60–1.42 (1H, m), 1.06 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 156.4 (q, J=20.0 Hz), 135.8, 134.5, 130.0, 129.2, 126.9, 116.4 (q, J=280.5 Hz), 111.6, 69.4, 57.9, 51.8, 50.1, 48.9, 48.4, 45.7, 40.8, 36.4, 32.0, 30.3, 30.0, 23.2, 17.9, 12.3. IR (film) ν 2946, 2867, 1739, 1694, 1462, 1436, 1360, 1316, 1256, 1201, 1143, 1086, 1050. MS (EI): 624 ($M\text{-}C_3H_7$)$^+$. HRMS ($M\text{-}C_3H_7$)$^+$ calc. for $C_{29}H_{46}ClF_3NO_6Si$: 624.2735; found: 624.2730.

3.1.11. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-7-trifluoroacetyl-2-triisopropylsiloxydodeca-3,9,11-triene (24). To a solution of ketal **23** (296 mg, 444 μmol) in CH_2Cl_2 (3 mL) at 0°C, was added a solution of TFA (400 μL) in water (400 μL). The mixture was stirred for 45 min at 0°C, treated with $NaHCO_3$ then water and extracted three times with CH_2Cl_2. The combined organic layers were dried on $MgSO_4$ and the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes:EtOAc 8:2),

to give ketone **24** as a clear oil (256 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (1H, dd, J=11.0, 15.0 Hz), 6.08 (1H, t, J=11.0 Hz), 5.73–5.43 (1H, m), 5.38 (1H, q, J=10.0 Hz), 5.26 (1H, d, J=4.5 Hz), 4.66–4.52 (1H, m), 4.25–3.95 (2H, m), 3.73 (3H, s), 3.77–3.21 (4H, m), 3.00 (2H, d, J=11.5Hz), 2.62–2.18 (5H, m), 1.81 (3H, s), 1.75–1.61 (1H, m), 1.06 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 168.7, 156.6 (q, J=20.0 Hz), 134.5, 133.7, 133.5, 133.2, 129.3, 128.1, 116.4 (q, J=280.5 Hz), 69.5, 61.3, 52.5, 48.9, 45.9, 39.6, 38.0, 32.0, 29.8, 28.0, 23.2, 17.9, 12.3. IR (film) ν 2946, 2867, 1760, 1732, 1694, 1620, 1516, 1462, 1382, 1353, 1326, 1271, 1201, 1144, 1114, 1066. MS (EI) 578 $(M\text{-}C_3H_7)^+$. HRMS $(M\text{-}C_3H_7)^+$ calc. for $C_{27}H_{40}ClF_3NO_5Si$: 578.2316; found: 578.2321.

3.1.12. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-2-hydroxy-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-7-trifluoroacetyldodeca-3,9,11-triene (25). To a solution of protected chlorohydrine **24** (644 mg, 1.04 mmol) in THF (11 mL) at −20°C was added TBAF (1.0 M in THF, 2.1 mL, 2.1 mmol). The mixture was stirred for 5 h at rt, treated with NH_4Cl sat. (10 mL), heated up to rt and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried on $MgSO_4$ and the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes:ethyl acetate 6:4) to give chlorohydrine **25** as a clear oil (434 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (1H, m), 6.04 (1H, t, J=11.0 Hz), 5.65–5.54 (1H, m), 5.38–5.27 (2H, m), 4.51–4.40 (1H, m), 4.12–3.90 (2H, m), 3.66 (3H, s), 3.83–3.30 (4H, m), 2.95 (2H, d, J=11.5 Hz), 2.52–2.12 (5H, m), 1.75 (3H, s), 1.67–1.59 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 169.1, 156.8 (q, J=20.0 Hz), 138.5, 137.4, 133.3, 129.7, 127.9, 126.4, 116.5 (q, J=280.5 Hz), 68.1, 61.3, 52.6, 49.4, 45.8, 39.5, 38.0, 32.0, 27.8, 23.9, 20.4. IR (film) ν 3480, 2957, 1728, 1687, 1443, 1356, 1276, 1202, 1147, 1065. MS (EI) 447 $(M\text{-}H_2O)^+$. HRMS $(M\text{-}H_2O)^+$ calc. for $C_{21}H_{25}ClF_3NO_4$: 447.1424; found: 447.1417.

3.1.13. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-2-oxo-7-trifluoroacetyldodeca-3,9,11-triene (26). To a solution of chlorohydrine **25** (119 mg, 0.26 mmol) in CH_2Cl_2 (2.5 mL) at 0°C, was added Dess–Martin periodinane (141 mg, 0.33 mmol). The mixture was stirred for 2.5 h, treated with 1 M sodium thiosulfate and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried on $MgSO_4$ and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes:ethyl acetate 7:3), to give chloroketone **26** as a clear oil (54 mg, 74% corrected yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78–6.63 (1H, m), 6.27 (1H, d, J=11.5 Hz), 6.08–6.00 (1H, t, J=11.0 Hz), 5.73–5.56 (1H, m), 5.38–5.28 (1H, m), 4.32–4.05 (4H, m), 3.66 (3H, s), 3.75–3.34 (3H, m), 2.94 (2H, d, J=11.5 Hz), 3.00–2.72 (1H, m), 2.52–2.12 (3H, m), 1.99 (3H, d, J=13.0 Hz), 1.72–1.56 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 190.9, 168.8, 159.7, 157.9, 156.4 (q, J=20.0 Hz), 133.1, 130.0, 127.9, 121.3, 116.5 (q, J=280.5 Hz), 61.4, 52.3, 49.7, 43.9, 39.7, 38.0, 34.0, 31.5, 27.9, 26.3. IR (film) ν 2951, 1756, 1727, 1691, 1620, 1515, 1443, 1361, 1271, 1201, 1146. MS (EI): 463 (M^+). HRMS (M^+) calc. for $C_{21}H_{25}ClF_3NO_5$: 463.1373; found 463.1360.

3.1.14. (±)-(4*Z*,10*E*,12*Z*)(1*R*,14*S*)-8-Aza-5-methyl-1-methoxycarbonyl-3,17-dioxo-8-trifluoroacetylbicyclo[12.3.0]-heptadeca-4,10,12-triene (27). To a solution of cesium carbonate (1.61 g, 4.99 mmol) in CH_3CN (345 mL) at 40°C, was added, over a period of 7 h via syringe pump, a solution of chloroketone **26** (330 mg, 0.71 mmol) in CH_3CN (10 mL). The mixture was stirred for an additional 2.5 h, cooled down to rt, filtered on Celite, rinsed several times with CH_2Cl_2 and concentrated in vacuo. The product was purified by flash chromatography (hexanes:EtOAc 7:3), to give macrocycle **27** as a white solid, mp 139–141°C (90 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64–6.52 (1H, m), 6.30–6.20 (1H, q, J=10.5 Hz), 6.03 (1H, d, J=7.0 Hz), 5.61–5.48 (1H, m), 5.44–5.31 (1H, q, J=10.5 Hz), 5.02 (1H, m), 4.55–4.35 (2H, m), 3.71 (3H, s), 3.96–3.56 (2H, m), 3.47–3.29 (1H, m), 3.21 (1H, d, J=20.0 Hz), 3.16–3.05 (2H, m), 2.90 (1H, d, J=20.0 Hz), 2.87–2.50 (2H, m), 2.16–2.00 (2H, m), 1.87 (3H, d, J=11.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 201.1, 169.3, 156.5 (q, J=24.0 Hz), 145.6, 133.5, 132.0, 130.3, 128.3, 125.5, 116.5 (q, J=280.0 Hz), 52.4, 43.9, 43.7, 42.2, 40.8, 37.5, 30.2, 28.9, 26.1, 23.7. IR (film) ν 2955, 1752, 1728, 1691, 1640, 1457, 1370, 1300. MS (EI): 427 (M^+). HRMS (M^+) calc. for $C_{21}H_{24}F_3NO_5$: 427.1606; found: 427.1599.

3.1.15. (±)-*N*-(6-chloro-3-methyl-5-triisopropylsiloxy-hex-3-ene)-*N*-*t*-butoxycarbonyl-*N*-tosylamide (29). To a solution of alcohol **28** (298 mg, 0.928 mmol) in THF (10 mL) at 0°C, was added TsNHBOC (504 mg, 1.86 mmol) and triphenylphosphine (488 mg, 1.86 mmol). DEAD was then slowly added at 0°C, and the mixture was stirred for 24 h at rt. The solvent was removed and the crude directly purified by flash chromatography (hexanes:ethyl acetate 8:2) to give tosylamide **29** as a yellowish oil (506 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, J=8.4 Hz); 7.29 (2H, d, J=8.0 Hz); 5.28 (1H, dd, J=8.6, 1.1 Hz); 4.72 (1H, ddd, J=8.7, 5.8); 3.83 (2H, m); 3.53 (1H, dd, J=10.8, 5.9 Hz); 3.44 (1H, dd, J=10.8, 5.6 Hz); 2.68–2.59 (1H, m); 2.42 (3H, s); 2.42–2.33 (1H, m); 1.81 (3H, s); 1.35 (9H, s); 1.01 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 144.2, 137.3, 134.4, 129.2, 127.8, 84.3, 69.3, 49.5, 45.6, 33.7, 27.9, 23.3, 21.6, 18.0, 17.9, 12.3. IR (film) ν 2943, 2866, 1730, 1670, 1598, 1460, 1366, 1289, 1260, 1157. SM (m/e): 530 $(M\text{-}C_3H_7)^+$. HRMS $(M\text{-}C_3H_7)^+$ calc. for $C_{25}H_{41}O_5ClNSSi$: 530.2163; found: 530.2175±0.0016.

3.1.16. (±)-*N*-(6-chloro-3-methyl-5-triisopropylsiloxy-hex-3-ene)-*N*-tosylamide (30). A solution of sulfonamide **29** (52 mg, 0.09 mmol) in DMSO (1 mL) was heated up to 170–180°C for 20 min. The mixture was poured into water and extracted four times with a 1:1 mixture of hexanes and diethyl ether. The organic layers were dried on sodium sulphate, filtered and the solvents removed in vacuo. The product was purified by flash chromatography (hexanes–ethyl acetate 8:2), to give sulfonamide **30** as a yellow oil (34 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz), 5.21 (1H, d, J=8.8 Hz), 4.70 (1H, t, J=5.9 Hz), 4.50 (1H, ddd, J=12.5, 8.7, 0.8 Hz), 3.50 (1H, dd, J=10.7, 5.5 Hz), 3.15 (1H, dd, J=10.7, 6.9 Hz), 3.12–2.91 (2H, m), 2.42 (3H, s), 2.39–2.31 (1H, m), 2.17–2.09 (1H, m), 1.62 (3H, s), 1.01 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 136.8, 134.3, 129.9, 129.7, 127.1, 69.2, 48.8, 40.9, 32.5, 22.7, 21.5, 17.8, 12.3.

IR (film) ν 3282, 2944, 2888, 1668, 1599, 1463, 1382, 1159, 1094, 1015. SM (m/e): 430 $(M\text{-}C_3H_7)^+$. HRMS $(M\text{-}C_3H_7)^+$ calc. for $C_{20}H_{33}O_3ClNSSi$: 430.1639; found: 430.1629±0.0013.

3.1.17. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3,3-dimethoxy)cyclopentyl-7-*p*-toluenesulfonyl-2-triisopropylsiloxydodeca-3,9,11-triene (32). To a solution of sulfonamide **30** (2.8 g, 5.9 mmol) and triphenylphosphine (3.2 g, 12.2 mmol) in THF (58 mL) at 0°C, was added via canula alcohol **31** (1.1 g, 4.1 mmol), followed by DIAD (2.0 mL, 10.2 mmol). The mixture was stirred at rt for 3 h, and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes–ethyl acetate 9:1), to give the desired product as a yellowish oil contaminated with the starting tosylamide, which was removed during the subsequent step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (2H, d, J=8.1 Hz), 7.30 (2H, d, J=8.1 Hz), 6.50 (1H, dd, J=13.7, 12.2 Hz), 5.88 (1H, td, J=10.9, 2.3 Hz), 5.49 (1H, td, J=14.6, 7.5 Hz), 5.26 (1H, t, J=10.3 Hz), 5.18 (1H, d, J=9.0 Hz), 4.62–4.52 (1H, m), 3.97–2.70 (2H, m), 3.65 (3H, s), 3.58–3.40 (2H, m), 3.35 (1H, ddd, J=10.7, 6.2, 2.0 Hz), 3.26 (3H, s), 3.19 (3H, s), 3.19–2.95 (2H, m), 2.69 (1H, d, J=8.6 Hz), 2.52–2.35 (1H, m), 2.43 (3H, s), 2.28–2.08 (1H, m), 2.08–1.35 (4H, m), 1.68 (3H, s), 1.05 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 143.2, 134.9, 129.7, 129.0, 128.3, 127.2, 127.1, 111.5, 69.4, 69.2, 57.9, 51.8, 51.0, 50.8, 50.0, 49.2, 48.9, 45.9, 40.8, 36.3, 32.7, 30.0, 23.2, 22.6, 21.5, 17.9, 12.3. IR (film) ν 2945, 2866, 1738, 1461, 1437, 1348, 1255, 1159, 1119, 1093, 1050. SM (m/e): 682 $(M - C_3H_7)^+$. HRMS $(M - C_3H_7)^+$ caqlc. For $C_{37}H_{60}O_7ClNSSi$: 682.3000; found: 682.2991±0.0020.

3.1.18. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-7-*p*-toluenesulfonyl-2-triisopropylsilyloxydodeca-3,9,11-triene (33). The procedure for the synthesis of **24** was followed (starting on 2.9 g of impure **32**). Purification by flash chromatography (hexanes–ethyl acetate 8:2) gave ketone **33** as a colorless oil (1.8 g, 65% (2 steps).) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.0 Hz), 6.49 (1H, dd, J=14.0, 12.0 Hz), 6.01 (1H, td, J=11.0, 3.0 Hz), 5.61–5.52 (1H, m), 5.30 (1H, t, J=10.0 Hz), 5.18 (1H, d, J=8.5 Hz), 4.55 (1H, ddd, J=11.0, 8.5, 6.0 Hz), 3.93–3.53 (3H, m), 3.69 (3H, s), 3.50 (1H, ddd, J=11.0, 6.0, 1.5 Hz), 3.33 (1H, ddd, J=11.0, 6.0, 3.5 Hz), 3.18–2.96 (2H, m), 2.95 (1H, d, J=11.5 Hz), 2.51–2.10 (5H, m), 2.42 (3H, s), 1.72–1.59 (1H, m), 1.68 (3H, s), 1.03 (21H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 168.8, 143.3, 134.7, 132.3, 129.7, 128.9, 127.2, 69.5, 61.4, 52.5, 50.9, 50.6, 49.1, 46.7, 46.1, 45.8, 39.7, 38.0, 32.8, 32.6, 28.0, 23.2, 21.5, 17.9, 12.3. IR (film) ν 3029, 2946, 2867, 1758, 1729, 1462, 1438, 1339, 1220, 1210, 1158, 1091. SM (m/e): 636 $(M\text{-}C_3H_7)^+$. HRMS $(M\text{-}C_3H_7)^+$ calc. for $C_{32}H_{47}O_6ClNSSi$: 636.2582; found: 636.2589±0.0019.

3.1.19. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-2-hydroxy-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-7-*p*-toluenesulfonyldodeca-3,9,11-triene (34). The procedure for the synthesis of **25** was followed (starting with 1.74 g of **33**). Purification by flash chromatography (hexanes–ethyl acetate, 6:4) gave **34** as a clear oil (1.26 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (2H, d, J=8.1 Hz), 7.29 (2H, d, J=8.0 Hz), 6.49 (1H, dd, J=14.3, 11.5 Hz), 5.99 (1H, td, J=11.0, 3.2 Hz), 5.57–5.20 (3H, m), 4.50–4.38 (1H, m), 3.94–3.40 (4H, m), 3.68 (3H, s), 3.20–3.00 (1H, m), 3.20–1.90 (7H, m), 2.95 (1H, d, J=11.5 Hz), 2.40 (3H, s), 1.71 (3H, s), 1.70–1.50 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 169.1, 143.4, 138.2, 136.7, 132.4, 131.2, 129.8, 129.7, 129.1, 127.1, 126.2, 68.0, 61.3, 52.5, 50.5, 49.4, 46.0, 39.6, 38.0, 32.5, 27.7, 23.6, 21.5. IR (film) ν 3502, 2973, 2932, 2872, 1756, 1729, 1439, 1336, 1285, 1157, 1118. SM (m/e): 491 $(M - CH_4O)^+$. HRMS $(M\text{-}CH_4O)^+$ calc. for $C_{25}H_{50}O_5ClNS$: 491.1533; found: 491.1542±0.0014.

3.1.20. (±)-(3*Z*,9*E*,11*Z*)-7-Aza-1-chloro-4-methyl-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-2-oxo-7-*p*-toluenesulfonyldodeca-3,9,11-triene (35). The procedure for the synthesis of **26** was followed (starting on 1.02 g of **34**). Purification by flash chromatography (hexanes–ethyl acetate, 7:3) gave chloroketone **35** as a clear oil (810 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.1 Hz), 6.52 (1H, dd, J=14.8, 11.5 Hz), 6.18 (1H, s), 5.91 (1H, t, J=10.9 Hz), 5.45 (1H, dt, J=15.2, 6.8 Hz), 5.24 (1H, t, J=10.0 Hz), 4.07–4.00 (2H, m), 3.97–3.79 (2H, m), 3.67–3.51 (2H, m), 3.62 (3H, s), 3.29–3.11 (3H, m), 2.89 (1H, d, J=11.5 Hz), 2.80–2.69 (2H, m), 2.44–2.04 (1H, m), 2.35 (3H, s), 1.92 (3H, s), 1.65–1.53 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 190.7, 168.9, 159.8, 143.2, 137.0, 132.2, 129.6, 129.4, 129.3, 127.1, 127.0, 121.2, 61.5, 52.3, 49.5, 49.3, 45.4, 39.7, 38.0, 33.4, 27.9, 26.4, 21.4. IR (film) ν 2974, 2935, 2874, 1756, 1729, 1702, 1618, 1439, 1336, 1284, 1157, 1117, 1092. MS (m/e): 521 (M^+). HRMS (M^+) calc. for $C_{26}H_{52}O_6ClNS$: 521.1639; found: 521.1644±0.0016.

3.1.21. (±)-(4*Z*,10*E*,12*Z*)(1*R,14*S**)-8-Aza-5-methyl-1-methoxycarbonyl-3,17-dioxo-8-*p*-toluenesulfonylbicyclo-[12.3.0]heptadeca-4,10,12-triene (36).** To a solution of cesium carbonate (1.4 g, 4.3 mmol) and sodium iodide (0.65 g, 4.3 mmol) in acetonitrile (800 mL) at 45°C, was added over 1.5 h, with a syringe pump, a solution of chloroketone **35** (0.45 g, 0.86 mmol) in acetonitrile (10 mL). The mixture was stirred for 4 h at the same temperature, cooled down to rt, filtered on Celite, rinsed with methylene chloride and the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes:ethyl acetate, 8:2), to give macrocycle **36** as a white solid (250 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, J=8.2 Hz), 7.29 (2H, d, J=8.0 Hz), 6.35 (1H, dd, J=14.9, 10.7 Hz), 6.12 (1H, t, J=10.6 Hz), 5.97 (1H, s), 5.42 (1H, ddd, J=15.0, 9.9, 4.5 Hz), 5.25 (1H, t, J=10.8 Hz), 4.27 (1H, dt, J=10.5, 8.4 Hz), 4.14 (1H, dd, J=14.6, 4.4 Hz), 3.66 (3H, s), 3.46–3.30 (1H, m), 3.32 (1H, dd, J=14.6, 10.0 Hz), 3.21–3.07 (1H, m), 3.13 (1H, d, J=19.6 Hz), 2.84 (1H, d, J=19.6 Hz), 2.85–2.73 (1H, m), 2.67–2.46 (2H, m), 2.41 (3H, s), 2.09–1.99 (2H, m,), 1.82 (3H, s), 1.82–1.70 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 200.5, 169.4, 147.6, 143.6, 136.3, 130.7, 129.9, 129.7, 127.8, 127.4, 127.1, 61.6, 52.4, 49.0, 45.3, 42.3, 40.9, 37.5, 29.5, 26.0, 23.4, 21.5. IR (film), ν 3020, 2955, 1754, 1732, 1688, 1627, 1599, 1455, 1392, 1338, 1224, 1159, 1093. MS (m/e): 485 (M^+). HRMS (M^+) calc. for $C_{26}H_{31}O_6NS$: 485.1872; found: 485.1882 ±0.0014.

3.1.22. (±)-3-Aza-6,7-dehydro-18-methoxy-18-oxo-3-toluenesulfonylandrosterone (37β). To a solution of cesium carbonate (1.25 g, 3.84 mmol) in CH_3CN (750 mL) at 82°C, was added with a syringe pump over 12 h a solution of chloride **13** (31 mg, 0.0611 mmol) in CH_3CN. After 12 h additional stirring, the mixture was cooled down and filtered on Celite. The product was purified by flash chromatography (hexanes:EtOAc 6:4) to give an inseparable mixture of diastereomers (CATAT:TACST 4.5:1) (17 mg, 59%). Major adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.63 (2H, m), 7.34–7.28 (2H, m), 5.69 (1H, d, J=10.0 Hz), 5.56 (1H, dt, J=3.0, 10.0 Hz), 3.69 (3H, s), 3.59–3.53 (1H, m), 2.70–1.95 (12H, m), 1.91–1.10 (8H, m), 0.89 (3H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 212.2, 169.7, 143.4, 133.6, 129.7, 129.7, 128.7, 128.5, 127.6, 127.5, 60.9, 52.3, 51.6, 47.8, 43.4, 41.8, 39.0, 37.8, 37.3, 34.51, 32.5, 29.6, 22.5, 22.3, 21.6, 21.2. IR (film) ν 2953, 2870, 1748, 1723, 1648, 1599, 1456, 1340. MS (EI) 471 (M^+). HRMS (M^+) calc. for $C_{26}H_{33}O_5NS$: 471.2079; found: 471.2074.

3.1.23. (±)-3-Aza-6,7-dehydro-18-methoxy-18-oxo-3-trifluoroacetylandrosterone (38β). To a solution of cesium carbonate (4.60 g, 14.1 mmol) in CH_3CN (1100 mL) at 82°C, was added over 12 h, with a syringe pump, a solution of chloride **18** (456 mg, 1.02 mmol) in CH_3CN (9 mL). After stirring for 7 h at the same temperature, the mixture was cooled down, filtered on Celite and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes:EtOAc 6:4) to give a mixture of diastereomers (CATAT:TACST 5.2:1) (271 mg, 63%). The major adduct **38**β (CATAT) was crystallized from EtOAc:hexanes (mp 150–152°C), to give a crystal on which X-ray analysis was performed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, t, J=9.5 Hz), 5.61–5.52 (1H, m), 3.70 (3H, s), 3.30–2.80 (2H, m), 2.75–2.45 (4H, m), 2.35–1.80 (5H, m), 1.70–1.25 (7H, m), 0.92 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 169.7, 157.0 (q), 129 1, 126.7, 116.5 (q, J= 288.0 Hz), 60.9, 52.3, 51.7, 45.0, 43.2, 40.6, 39.3, 37.5, 37.2, 35.6, 34.4, 29.8, 22.3, 21.9, 21.5. IR (film) ν 3019, 2954, 2874, 1753, 1724, 1692, 1464, 1194, 1147. MS (EI): 413 (M^+). HRMS (M^+) calc. for $C_{21}H_{26}F_3NO_4$: 413.1814; found: 413.1821.

3.1.24. (±)-3-Aza-6,7-dehydro-4,5α-dihydro-18-methoxy-18-oxo-3-trifluoroacetyl-9β-adrenosterone (39). Macrocycle **27** (7 mg, 16.4 mmol) in solution in degassed toluene (1.0 mL) was heated up in a pyrex tube in vacuo at 195°C for 12 h. The solvent was removed in vacuo and the product purified by flash chromatography (hexanes:EtOAc 7:3) to give tetracycle **39** having the TSCAT stereochemistry as a thick oil (4 mg, 78% corrected yield). To be noted, the restricted rotation around the amide bond creates a doubling of certain signals by ^{13}C NMR, the appearance of which was temperature dependent. ^{1}H NMR (300 MHz $CDCl_3$) δ 5.94 (1H, dq, J=2.5, 12.0 Hz), 5.46 (1H, dt, J=2.5, 12.0 Hz), 4.3–3.6 (5H, m), 3.20 (1H, m), 3.057–2.70 (4H, m), 2.65–2.10 (5H, m), 1.98 (1H, dd, J=2.5, 13.0 Hz), 1.86 (3H, s), 1.60 (2H,s), 1.4–1.2 (1H, m), 0.92 (3H,s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 178.0, 173.0, 140.1 (q), 132.4, 128.7, 124.6, 116.1 (q, J= 288.5 Hz), 59.6, 51.2, 50.6, 50.1, 49.4, 47.8, 45.4, 43.7, 40.3, 37.7, 29.7, 24.7, 22.6. IR (film) ν 2927, 2856, 1766, 1739, 1692, 1460, 1388,1375, 1352. MS (EI): 427 (M^+). HRMS (M^+) calc. for $C_{21}H_{24}F_3NO_5$: 427.1606; found: 427.1602.

3.1.25. (±)-2β6α7α10α14β-3-methyl-6-tosylamidomethyltricyclo[4.9.0^{10,14}]pentadeca-3,8-dien-1,13-dione (40). A solution of macrocycle **36** (58 mg, 0.12 mmol) and triethylamine (50 μL, 0.36 mmol) in toluene (2 mL) was introduced in a pyrex tube, previously washed with ammonium hydroxide, water then acetone. The solution was degassed, the tube was sealed in vacuo then heated up for 12 h in an oven at 235°C. The tube was cooled down to rt, opened and the solvent removed in vacuo. The product was purified by flash chromatography (hexanes–ethyl acetate, 9:1) to give tricycle **40** (25 mg, 49%) as a clear oil, which was crystallized from methanol:hexanes (mp 199–202°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (2H, d, J=8.3 Hz), 7.32 (2H, d, J=7.9 Hz), 5.64 (1H, dd, J=10.5, 6.5 Hz), 5.55 (1H, m), 5.47 (1H, td, J=10.1, 1.5 Hz), 4.31 (1H, t, J=6.8 Hz), 3.06 (1H, ddd, J=13.1, 6.8, 3.9 Hz), 2.96–2,87 (1H, m), 2.87–2.67 (3H, m), 2.58 (1H, dd, J=11.8, 3.0 Hz), 2.44 (3H, s), 2.32–2.10 (3H, m), 2.08–1.87 (2H, m), 1.82–1.60 (2H, m), 1.60–1.50 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 143.6, 133.9, 133.4, 129.8, 129.2, 127.0, 127.0, 123.7, 77.2, 65.2, 54.2, 46.7, 42.0, 38.9, 36.8, 36.3, 29.8, 27.1, 21.5, 21.0. IR (film) ν 3285, 2922, 2853, 2357, 1733, 1454, 1378, 1322, 1158, 1085. MS (m/e): 427 HRMS (M^+) calc. for $C_{24}H_{29}O_4NS$: 427.1817; found: 427.1820±0.0013.

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