Use of the transannular Diels–Alder (TADA) reaction to probe biological receptors: Rational design and synthesis of tricyclic TADA adducts capable of rigidly holding pharmacophore parts

Yves A. Chantigny, Yves L. Dory, András Toró, and Pierre Deslongchamps

Abstract: Transannular Diels–Alder (TADA) adducts constitute a collection of rigid structures, whose conformational diversity is rich. It is possible to design such specifically functionalized molecules capable of binding to known biological targets by molecular modelling MCSS–HOOK (multiple copy simultaneous search). Here we show that such carefully designed compounds can be easily built from small synthons. TADA adducts are very interesting due to their huge conformational diversity, their rigidity (biological interest), and their ease of synthesis (chemical interest).

Key words: tricycles, synthesis, transannular Diels–Alder, macrocyclization, conformation, diversity.

Résumé : Les adduits de la réaction Diels–Alder transannulaire (DATA) constituent une banque de structures rigides dont la diversité conformationnelle est riche. Il est possible de concevoir de telles molécules spécifiques fonctionnalisées capables de se lier à des cibles biologiques connues, par modélisation moléculaire MCSS–HOOK. Nous montrons ici que de tels composés soigneusement sélectionnés peuvent être aisément assemblées à partir de petits synthons. L'intérêt de telles molécules se situe donc à trois niveaux : leur diversité conformationnelle étendue, leur rigidité (intérêt biologique), et leur relative facilité de synthèse (intérêt chimique).

Mots clés : tricycles, synthèse, Diels–Alder transannulaire, macrocyclisation, conformation, diversité.

Introduction

Generating molecular diversity constitutes an important tool for pharmaceutical chemists to discover new drug leads and to study biological targets (1). To date, nature is still one of the most important sources of original structures, although chemists have devised numerous ways to generate the sought-after diversity (2). We too have added milestones to this continuous and general synthetic effort by preparing libraries of macrocycles (3–7). By incorporating a diene and a dienophile within a macrocycle, a transannular Diels–Alder (TADA) reaction can occur (8–10). We have already made a thorough investigation of this reaction and showed that it is a powerful method in organic synthesis. In this work, we want to further demonstrate that the TADA reaction also offers a realistic potential for the creation of molecular diversity and for the synthesis of original structures.

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In memory of Professor Raymond U. Lemieux.

Y.A. Chantigny and A. Toró. Laboratoire de synthèse organique, Département de chimie, Institut de pharmacologie de Sherbrooke, Université de Sherbrooke, 3001, 12e avenue Nord, Sherbrooke, QC J1H 5N4, Canada.
Y.L. Dory and P. Deslongchamps.[1] Laboratoire de modélisation moléculaire, Département de chimie, Institut de pharmacologie de Sherbrooke, Université de Sherbrooke, 3001, 12e avenue Nord, Sherbrooke, QC J1H 5N4, Canada.

[1]Corresponding author (e-mail: pierre.deslongchamps@courrier.usherb.ca).

Molecular modelling design of our targets

The TADA macrocyclic precursors can be easily prepared from building blocks, and each of these macrocycles can be divided into four regions (Fig. 1). The reacting part includes two regions: the dienophile, which can be either *cis* (C) or *trans* (T), and the diene, which can be TT, TC, or CT, but not CC since no TADA adducts have ever been obtained from that particular diene geometry (11). The other two regions are the tethers, which define the size and shape of the resulting A and C rings of the TADA adducts. Our previous studies indicated that TADA adducts can reasonably be expected for five- to seven-membered rings for A and C (12). According to these limitations, there are 54 TADA macrocyclic precursors that can be prepared, which yield 144 tricycles after the reaction. The adducts are more numerous than the macrocyclic trienes because each TT diene can give rise to two products and because the enantiomers must also be included. It is obvious that many positions of these 54 bare macrocycles can be substituted so that the diversity expands accordingly. Such huge diversity can, in principle, be exploited in combinatorial libraries.

Another important aspect of the TADA approach resides in the rigidity of the resulting tricyclic frameworks. The 144 tricycles are sufficiently different from each other, so that conformational diversity arises as well. This important aspect can be fruitfully used when carrying out computa-

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Fig. 1. Diversity generated by means of the TADA reaction.

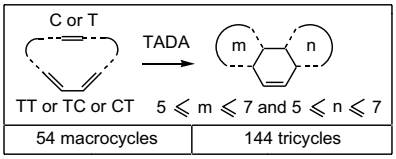
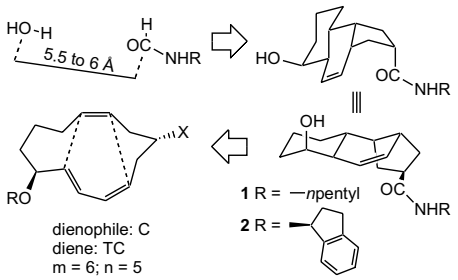


Fig. 2. Use of TADA tricyclic adducts to hold parts pharmacophores.

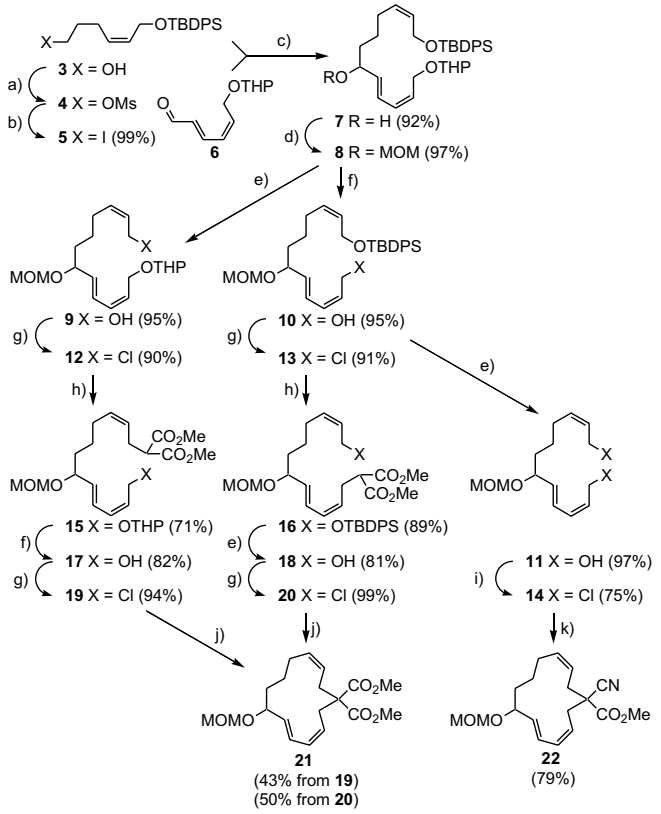


tional drug design, in particular by means of MCSS–HOOK (multiple copy simultaneous search) (13–15). A search on the stain P1/Mahomey of the polyovirus by means of the MCSS method yielded valuable information about the positions, where simple molecules such as water, methanol, amines, and amides, could best interfere with the virus (16). Given the positions and orientations of the suitable functional sites (Fig. 2), HOOK then systematically searched a database of our tricyclic adducts for skeletons that logically connected these binding sites in the presence of the virus. Two structures (**1** and **2**), having a *trans-syn-cis* (TSC) geometry, were obtained as result of that protocol. Both compounds differ only by the nature of their amine moiety; therefore, they can be prepared from the same adequately protected 13-membered tricycle bearing a *cis* (C) dienophile and a *trans–cis* (TC) diene, as previously shown in our model studies (17).

Synthesis

In terms of ease of synthesis, the macrocyclic trienes **21** and **22** (Scheme 1) were identified as being the most suitable TADA precursors. They were prepared in 10 and eight steps, respectively, from the same starting materials **3** and **6** (18, 19). Alcohol **3** was activated as its corresponding mesylate **4**, and subsequently treated with sodium iodide in acetone without purification. Resulting iodide **5** was obtained in 99% yield for the two steps. Upon treatment with *tert*-butyllithium at –78°C, iodide **5** was transformed into its corresponding anion. Addition of aldehyde **6** to the reaction mixture led to alcohol **7** as a mixture of diastereoisomers with a yield of 92%. The alcohol functionality was protected as methoxymethyl ether **8** in 97% yield. The silyl ether was then cleaved with tetrabutyl ammonium fluoride (TBAF) to yield allylic alcohol **9** (95% yield). Allylic chloride **12** was obtained from the preceding alcohol by means of hexachloroacetone (HCA) and triphenylphosphine (Ph_3P) (90%) (20). S_N2 nucleophilic attack of sodium dimethyl malonate onto the allylic iodide (formed in situ by sodium iodide) led to monosubstituted malonate **15** in 71% yield.

Scheme 1.

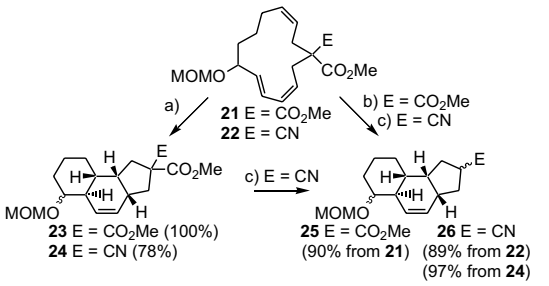


a) MsCl, Et_3N, CH_2Cl_2, 0ºC. b) NaI, acetone, reflux. c) *t*-BuLi, THF, -78ºC. d) KHMDS, MOMCl, THF, 0ºC to 70ºC. e) TBAF, THF, rt. f) PPTS, *i*-PrOH, reflux.g) Ph_3P, HCA, CH_2Cl_2, 0ºC. h) $CH_2(CO_2Me)_2$, NaH, NaI, THF 0ºC to 70ºC. i) Ph_3P, HCA, CH_2Cl_2, -20ºC. j) Cs_2CO_3, CsI, MeCN, 70ºC, slow addition. k) $NCCH_2CO_2Me$, Cs_2CO_3, THF:DMF (2:1), 80ºC, slow addition.

The remaining allylic ether was then cleaved with PPTS to yield alcohol **17** (82%), which was transformed as before into its corresponding allylic chloride **19** (94%). The other macrocyclization precursor (**20**), which would lead to the same macrocycle (**21**), was prepared from the same triether (**8**) by a very similar pathway, with an overall yield of 62% for the five-step sequence. Alternatively, alcohol **10** (obtained from **8** with a yield of 95%) en route to **20**, was transformed into diol **11** by means of TBAF (97% yield). Dichloride **14** was then prepared in 75% yield by means of HCA and Ph_3P as before, but at lower temperature. All three allylic chlorides (**19**, **20**, and **22**) were then subjected to high-dilution macrocyclization conditions. Isomeric chlorides **19** and **20** yielded the same racemic macrocycle (**21**) with similar yields (43 and 50%, respectively) when slowly injected into a mixture of cesium carbonate in acetonitrile. A much better yield of 79% was obtained for the synthesis of macrocycle **22** (mixture of racemic diastereoisomers) when a mixture of methyl cyanoacetate and dichloride **14** in THF was added slowly to a suspension of cesium carbonate in THF and DMF (21). In summary, **21** was obtained from **3**, via **19** and **20**, with overall yields of 18 and 27%, respectively; the yield for **22**, however, was as high as 51%. Consequently, it proved easier to prepare substantial quantities of macrocycle **22** to carry on with the synthesis of **1** and **2**.

Both macrocycles **21** and **22** were heated at 140°C to provoke the TADA reaction (Scheme 2) — the expected TSC

Scheme 2.

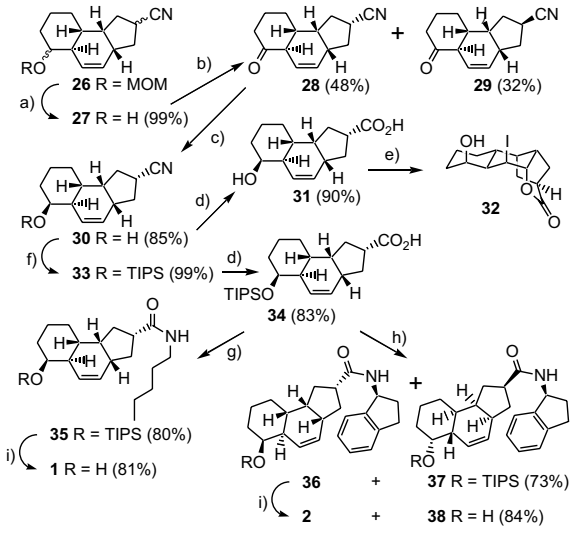


a) xylenes, 140ºC, 4h. b) NaCl, DMSO, 160ºC. c) NaCN, DMSO, 160ºC.

tricycles **23** and **24** were obtained with good yields of 100 and 78%, respectively. Tricycle **23** was produced as a 2:1 mixture (α or β at C4) of two racemic diastereoisomers, whereas **24** was obtained as a mixture of racemic diastereoisomers at C4 and C12. Demethoxycarbonylation of **24** was then performed at 160°C in dimethyl sulfoxide with sodium cyanide (97% yield) (22). Since demethoxycarbonylation occurs at high temperature, we tried successfully to induce both demethoxycarbonylation and TADA together by treating macrocycles **21** and **22** under demethoxycarbonylation conditions. Thus, **21** led to tricycle **25** (90%), when heated at 160°C in DMSO that contained sodium chloride (22); **22** gave **26** in 89% yield when it was treated under identical conditions previously used to prepare **26** from **24**. This confirmed our choice of selecting cyanide **26** (rather than methyl ester **25**) for further work, since it is obtained from **3** with an overall yield of 45%.

All that remained to be done were functional-group manipulations to introduce the amides at the nitrile position and to address the stereochemistry of the amide and the alcohol. To do this, methoxymethyl (MOM) ether **26** was cleaved by means of concentrated HCl to yield alcohol **27** (99% yield) (Scheme 3). Dess–Martin oxidation of this alcohol gave a separable mixture of two racemic ketones **28** (48% yield) and **29** (32% yield). To identify the relative stereochemistry of the nitrile, the major ketone (**28**) was first reduced with a bulky borohydride (lithium triisobutylborohydride) to give exclusively β-OH TSC tricycle **30** (85%) in which the secondary alcohol exists in the axial orientation. The nitrile was then hydrolyzed under basic conditions to corresponding acid **31** (90%), which could undergo iodolactonization to generate lactone **32**. The identities of nitriles **28** and **29** were inferred from that latter experiment, because no lactone can be obtained from the carboxylic acid derived from nitrile **29**. Alcohol **30** was protected as its triisopropyl silyl (TIPS) ether (**33**), with a yield of 99%, by means of TIPS triflate and 2,6-lutidine as a base. Hydrolysis of the nitrile, as before, yielded acid **34** in 83% yield. The acid group was activated as its acid chloride with oxalyl chloride (23). Amylamine was added to the crude acid chloride, and racemic amide-ether **35** was obtained in 80% yield. Alternatively, addition of (*S*)-(+)-1-aminoindane to the acid chloride provided the corresponding amide-ether as an inseparable mixture of racemic diastereoisomers **36** and **37** (73%). Finally, strong acidic conditions (6 N HCl) had to be used to cleave the silyl ethers to afford desired amide-alcohol **1**, together with its enantiomer (81%). The other target (**2**) was prepared in a similar manner from a mixture of **36** and **37**; it could not be separated from its diastereoisomer **38** (yield of 84%).

Scheme 3.



a) 6N HCl, MeOH, rt. b) Dess-Martin, CH_2Cl_2, rt. c) i Li tri-*i*butylborohydride, THF, -78ºC; ii NaOH, H_2O_2, rt. d) NaOH, H_2O_2, MeOH, reflux. e) Na_2CO_3, I_2, H_2O, THF, rt. f) TIPS-triflate, 2,6-lutidine, CH_2Cl_2, rt. g) i $(COCl)_2$, DMF, CH_2Cl_2, rt.; ii amylamine, Et_3N, CH_2Cl_2, rt. h) i $(COCl)_2$, DMF, CH_2Cl_2, rt.; ii (*S*)-(+)-1-aminoindane, Et_3N, CH_2Cl_2, rt. i) 6N HCl, MeOH, reflux

Conclusion

Compounds **1** and **2** proved not to have a significant affinity for the target virus, at least no better than the threshold of the assay, which was set in the sub-micromolar range. Nevertheless, our main goal during this preliminary work was first to demonstrate the chemical utility of TADA adducts for drug design. Thus, TADA tricycles could be used in combinatorial libraries, but the lack of mobility of the tricyclic framework is usually so severe that they should be more useful at the lead optimization stage. Rigidity, however, can be an asset when the shape of the target is precisely known from different theoretical sources (molecular docking or other computational techniques like MCSS–HOOK). In the latter case, rigid skeletons are necessary to hold binding sites (functional groups) uncovered by the theoretical protocol. A collection of reasonably rigid TADA-adduct tricyclic cores can easily provide the diversity necessary to ensure that any combination of two or three binding functional groups can be successfully held in the desired spatial arrangement (within the limits of the span of tricycles). In this work we have proven that, from MCSS–HOOK calculations, adequate tricycles capable of holding binding sites can be selected from a theoretical library of TADA-adduct structures. The resulting chemical targets can be synthesized in a reasonable number of steps, so that the suggested targets can be rapidly tested. In summary, TADA adducts are structurally attractive because their various geometries can cover a large conformational space; they are also chemically attractive because they come from macrocycles easily assembled from smaller pieces.

Experimental

The infrared (IR) spectra were taken on a PerkinElmer 1600 series FT-IR. The NMR spectra were recorded on a Brüker AC 300 instrument. The mass spectra (MS) were obtained on a ZAB-IF spectrometer. Flash chromatography was performed on silica gel Merck 60, 230–400 mesh.

Synthesis

Methanesulfonic acid 6-(*tert*-butyl-diphenyl-silanyloxy)hex-(4Z)-enyl ester (4)

To a solution of alcohol **3** (11.6 g, 32.6 mmol) and triethylamine (6.82 mL, 48.9 mmol) in dichloromethane (150 mL) at 0°C, was added methanesulfonyle chloride (2.78 mL, 35.9 mmol). The mixture was stirred for 1 h and a HCl 1 N solution (100 mL) was added. The mixture was extracted with dichloromethane (3 × 100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo to yield the crude title compound as an oil (used as is in the next step). IR (cm^{-1}): 3021, 2936, 2859, 1469, 1428, 1356, 1175, 1109, 936, 823, 704, 613. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyl), 5.65 (m, 1H, C*H*=CHCH$_2$OSi), 5.45 (m, 1H, CH=C*H*CH$_2$OSi), 4.26 (d, *J* = 6.5 Hz, 2H, C*H*$_2$OSi), 4.12 (t, *J* = 7.0 Hz, 2H, C*H*$_2$OMs), 2.92 (s, 3H, SO$_3$C*H*$_3$), 2.00 (q, *J* = 7.0 Hz, 2H, CH$_2$C*H*$_2$CH=CH), 1.71 (quintet, *J* = 6.5 Hz, 2H, C*H*$_2$CH$_2$CH=CH), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 135.4, 133.6, 130.7, 129.6, 128.6, 128.5, 69.0, 60.0, 37.1, 28.7, 26.7, 23.2, 19.0. MS *m*/*z*: 375 ([M – C_4H_9]$^+$). Exact mass (M – C_4H_9) calcd.: 375.1086; found: 375.1091.

tert-*Butyl-(6-iodo-hex-(2Z)-enyloxy)diphenyl silane (5)*

A solution of crude mesylate **4** (11.6 g, 32.6 mmol) and sodium iodide (48.9 g, 326 mmol) in acetone (250 mL) was heated to reflux for 1.5 h. The cooled mixture was concentrated under vacuo until saturation, diluted with water (150 mL), and extracted with hexanes (3 × 150 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered on Florisil, and concentrated under vacuo to yield the title compound as an oil (15.14 g, 99% 2 steps). IR (cm^{-1}): 3069, 3017, 2933, 2857, 1467, 1428, 1108, 822, 703, 612, 504. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyl), 5.65 (m, 1H, C*H*=CHCH$_2$OSi), 5.45 (m, 1H, CH=C*H*CH$_2$OSi), 4.26 (d, *J* = 6.5 Hz, 2H, C*H*$_2$OSi), 3.15 (t, *J* = 7.0 Hz, 2H, C*H*$_2$I), 2.00 (q, *J* = 7.0 Hz, 2H, CH$_2$C*H*$_2$CH=CH), 1.78 (quintet, *J* = 6.5 Hz, 2H, C*H*$_2$CH$_2$I), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 135.5, 133.7, 130.6, 129.6, 128.6, 128.5, 60.2, 33.1, 28.3, 26.8, 19.1, 6.9. MS *m*/*z*: 407 ([M – C_4H_9]$^+$).

12-(*tert*-Butyl-diphenyl-silanyloxy)-1-(tetrahydropyran-2-yloxy)dodeca-(2Z,4E,10Z)-trien-6-ol (7) (diastereoisomers)

To a solution of *tert*-butyllithium 1.5 M (40 mL, 60 mmol) in ether (100 mL) at –78°C, was added dropwise over 10 min a solution of iodide **5** (14.82 g, 32 mmol) in ether (20 mL). After stirring for 10 min, a solution of aldehyde **6** (5.0 g, 25 mmol) in ether (20 mL) was added dropwise over 10 min. The mixture was allowed to warm to room temperature for 15 min, then cooled to –78°C, and a saturated NH_4Cl solution (40 mL) was added. The mixture was extracted with hexanes (3 × 20 mL). The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 1:1) to yield the title compound as an oil (14.2 g, 92%). IR (cm^{-1}): 3444 (br), 2934, 2858, 1428, 1113, 1077, 1024, 823, 703, 614. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyl), 6.49 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.10 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.72–5.55 (m, 3H, C*H*=CHCH$_2$OSi and C*H*=CHCH=C*H*), 5.39 (m, 1H, CH=C*H*CH$_2$OSi), 4.64 (t, *J* = 4.0 Hz, 1H, OC*H*O), 4.36 (dd, *J* = 6.5 Hz, 1H, C*H*HOTHP), 4.23 (d, *J* = 5.5 Hz, 2H, C*H*$_2$OSi), 4.21–4.08 (m, 2H, CH*H*OTHP and C*H*OH), 3.90 (m, 1H, OC*H*H of THP), 3.52 (m, 1H, OCH*H* of THP), 1.88 (q, *J* = 7.0 Hz, 2H, CH$_2$C*H*$_2$CH=CH), 1.84–1.25 (m, 10H, other CH$_2$), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 135.6, 133.8, 130.7, 129.5, 129.4, 127.6, 97.7, 72.2, 72.1, 62.7, 62.1, 60.2, 36.6, 30.5, 27.3, 26.7, 25.9, 25.2, 19.3, 19.0. MS *m*/*z*: 552 ([M + NH_4]$^+$), 517 ([M – OH]$^+$). Exact mass ([M + NH_4]$^+$) calcd.: 552.3509; found: 552.3500.

tert-*Butyl-[7-methoxymethoxy-12-(tetrahydropyran-2-yloxy)dodeca-(2Z,8E,10Z)-trienyloxy]diphenyl silane (8) (diastereoisomers)*

To a solution of alcohol **7** (1.294 g, 2.42 mmol) in THF (25 mL) at –78°C, was added a solution of potassium bis(trimethylsilyl) amide 0.5 M (5.81 mL, 2.9 mmol). After 15 min, methyl-methylether chloride (552 μL, 7.26 mmol) was added. After stirring for 2 h, a saturated NH_4Cl solution (30 mL) was added and the mixture was extracted with hexanes (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 3:1) to yield the title compound as an oil (1.35 g, 97%). IR (cm^{-1}): 2940, 2858, 1428, 1113, 1078, 1032, 822, 741, 703, 614, 503. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyl), 6.44 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.10 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.72–5.55 (m, 3H, C*H*=CHCH$_2$OSi and C*H*=CHCH=C*H*), 5.39 (m, 1H, CH=C*H*CH$_2$OSi), 4.65 and 4.48 (2d, *J* = 7.0 Hz, 2 × 1H, OC*H*$_2$O), 4.63 (t, *J*= 4.0 Hz, 1H, OC*H*O), 4.36 (m, 1H, C*H*HOTHP), 4.18 (m, 1H, CH*H*OTHP), 4.23 (d, *J* = 5.5 Hz, 2H, C*H*$_2$OSi), 3.99 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.87 (m, 1H, OC*H*H of THP), 3.52 (m, 1H, OCH*H* of THP), 3.33 (s, 3H, OC*H*$_3$), 1.88 (q, *J* = 7.0 Hz, 2H, CH$_2$C*H*$_2$CH=CH), 1.84–1.25 (m, 10H, other CH$_2$), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 135.5, 135.2, 133.8, 130.5, 130.4, 130.3, 129.5, 129.3, 127.6, 127.5, 127.2, 98.1, 97.8, 93.6, 76.1, 62.9, 62.8, 62.2, 62.1, 60.1, 55.3, 35.1, 30.6, 27.3, 26.7, 25.4, 25.3, 19.5, 19.4, 19.1. MS *m*/*z*: 596 ([M + NH_4]$^+$), 419 ([M – C_4H_9 – THPO]$^+$). Exact mass ([M + NH_4]$^+$) calcd.: 596.3771; found: 596.3763.

7-Methoxymethoxy-12-(tetrahydropyran-2-yloxy)-dodeca-(2Z,8E,10Z)-trien-1-ol (9) (diastereoisomers)

A solution of methoxymethyl ether **8** (1.3 g, 2.33 mmol) and tetrabutylammonium fluoride (1 M, 4.76 mL, 4.66 mmol) in THF (20 mL) was stirred at –20°C overnight. The mixture was diluted with water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 1:1 to 3:7) to yield the title compound as an oil

(744 mg, 95%). IR (cm^{-1}): 3460, 2941, 2882, 1455, 1387, 1349, 1205, 1120, 1031, 912. ^1H NMR ($CDCl_3$) δ: 6.44 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 6.10 (t, *J* = 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 5.68–5.50 (m, 4H, C*H*=C*H* and C*H*=CHCH=C*H*), 4.67 and 4.51 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.65 (t, *J* = 4.0 Hz, 1H, OC*H*O), 4.42–4.20 (m, 2H, CH_2OTHP), 4.18 (d, *J* = 6.5 Hz, 2H, CH_2OH), 4.07 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.87 (m, 1H, OC*H*H of THP), 3.52 (m, 1H, OCH*H* of THP), 3.38 (s, 3H, OCH_3), 2.13 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.90–1.35 (m, 10H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 134.8, 134.6, 128.9, 128.7, 127.0, 123.53, 123.5, 119.2, 98.7, 95.6, 92.0, 91.8, 91.3, 91.1, 77.9, 60.4, 56.3, 55.9, 26.8, 26.4, 25.0, 23.8, 23.6, 22.0, 19.0.

*12-(***tert***-Butyl-diphenyl-silanyloxy)-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-trien-1-ol (10)*

A solution of silylether **8** (1.57g, 2.72 mmol) and pyridinium *p*-toluenesulfonate (171 mg, 681 μmol) in isopropanol (50 mL) was stirred at reflux for 1 h. The solution was allowed to cool to room temperature and sodium bicarbonate (57.2 g, 681 μmol) was added. The mixture was concentrated under vacuo, water (50 mL) was added, and the mixture extracted with dichloromethane (3 × 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 3:1) to yield the title compound as an oil (1.09 g, 81%). IR (cm^{-1}): 3422, 2932, 2858, 1473, 1429, 1149, 1111, 1031, 824, 741, 702. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyl), 6.42 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.05 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.72–5.55 (m, 3H, C*H*=CHCH$_2$OSi and C*H*=CHCH=C*H*), 5.46–5.35 (m, 1H, CH=C*H*CH$_2$OSi), 4.65 and 4.49 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.30 (dd, *J* = 7.0, 1.0 Hz, 2H, CH_2OH), 4.24 (dd, *J* = 6.0, 1.0 Hz, 2H, CH_2OSi), 3.99 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.33 (s, 3H, OCH_3), 1.90 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.60–1.25 (m, 4H, other CH$_2$), 1.04 (s, 9H, SiC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 135.615, 135.527, 135.414, 133.979, 130.536, 130.109, 129.667, 129.527, 129.402, 127.590, 126.916, 93.597, 76.188, 60.176, 58.661, 55.345, 35.045, 27.344, 26.756, 25.308, 19.092. MS *m/z*: 512 ([M + NH$_4$]$^+$). Exact mass ([M + NH$_4$]$^+$) calcd.: 512.3196; found: 512.3197.

6-Methoxymethoxy-dodeca-(2Z,4E,10Z)-triene-1,12-diol (11)

To a solution of alcohol **10** (1.19 g, 2.41 mmol) in THF (35 mL) at 0°C was added a solution of tetrabutylammonium fluoride (1 M in THF, 4.81 mL, 4.81 mmol). The mixture was allowed to warm to room temperature and stirred for 1.25 h. A saturated NH_4Cl solution (50 mL) was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (ethyl acetate) to yield the title compound as an oil (599 mg, 97%). IR (cm^{-1}): 3372, 2944, 1460, 1440, 1150, 1095, 1029, 855. ^1H NMR ($CDCl_3$) δ: 6.45 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.06 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.66–5.45 (m, 4H, C*H*=C*H*, C*H*=CHCH=C*H*), 4.66 and 4.49 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.30 (d, *J* = 7.0 Hz, 2H, CH=CHCH=CHCH_2OH), 4.15 (d, *J* = 6.0 Hz, 2H, CH$_2$CH=CHCH_2OH), 4.05 (q, *J* = 7.0 Hz, 1H, C*H*OMOM), 3.35 (s, 3H, OCH_3), 2.10 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.70–1.30 (m, 4H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 135.2, 132.4, 130.3, 129.7, 128.8, 127.1, 93.6, 16.2, 58.6, 58.4, 55.4, 64.8, 27.1, 25.2. MS *m/z*: 225 ([M – OMe]$^+$), 211 ([M – MOM]$^+$). Exact mass ([M – OMe]$^+$) calcd.: 225.1491; found: 225.1485; ([M – C_2H_5O]$^+$) calcd.: 211.1334; found: 211.1340.

2-(12-Chloro-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-trienyloxy)-tetrahydro-pyran (12) (diastereoisomers)

To a solution of alcohol **9** (420 mg, 1.25 mmol) and hexachloroacetone (228 μL, 1.5 mmol) in dichloromethane (10 mL) at 0°C was added triphenylphosphine (492 mg, 1.9 mmol). The mixture was allowed to warm to room temperature and stirred 45 min. The mixture was concentrated under vacuo and purified by flash chromatography (hexanes–ether, 9:1) to yield the title compound as an oil (397 mg, 90%). IR (cm^{-1}): 2942, 1454, 1032. ^1H NMR ($CDCl_3$) δ: 6.44 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 6.10 (t, *J* = 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 5.68–5.50 (m, 4H, C*H*=C*H* and C*H*=CHCH=C*H*), 4.67 and 4.51 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.65 (t, *J* = 4.0 Hz, 1H, OC*H*O), 4.42–4.20 (m, 2H, CH_2OTHP), 4.07 (d, *J* = 7.0 Hz, 2H, CH_2Cl), 4.07 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.87 (m, 1H, OC*H*H of THP), 3.52 (m, 1H, OCH*H* of THP), 3.38 (s, 3H, OCH_3), 2.14 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.90–1.35 (m, 10H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 135.0, 134.9, 130.4, 127.8, 127.4, 125.5, 98.1, 97.9, 93.7, 76.1, 62.9, 62.8, 62.3, 62.2, 55.4, 39.4, 35.0, 30.6, 26.9, 25.4, 25.0, 19.5, 19.4.

tert*-Butyl-(12-chloro-7-methoxymethoxy-dodeca-(2Z,8E,10Z)-trienyloxy)diphenyl silane (13)*

Prepared similar to chloride **12** (91%). IR (cm^{-1}): 3016, 2932, 2858, 1472, 1428, 1149, 1112, 1031, 824, 703, 614. ^1H NMR ($CDCl_3$) δ: 7.70 and 7.40 (2m, 10H, 2 phenyls), 6.43 (dd, *J* = 15.0, 11.5 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.12 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.66–5.55 (m, 3H, CH=C*H*CH$_2$OSi and C*H*=CHCH=C*H*), 5.45–5.34 (m, 1H, C*H*=CHCH$_2$OSi), 4.65 and 4.50 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.22 (d, *J* = 6.5 Hz, 2H, CH_2OSi), 4.19 (d, *J* = 8.5 Hz, 2H, CH_2Cl), 4.03 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.34 (s, 3H, OCH_3), 1.89 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.60–1.24 (m, 4H, other CH$_2$), 1.06 (s, 9H, SiC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 137.1, 135.6, 135.5, 134.7, 133.8, 131.8, 130.5, 129.5, 129.4, 127.6, 125.9, 125.6, 93.7, 76.0, 60.1, 55.3, 39.3, 34.9, 27.3, 26.7, 26.5, 25.2, 19.1. MS *m/z*: 477 ([M – Cl]$^+$), 455 ([M – C_4H_9]$^+$), 451 ([M – CH_3OCH_2O]$^+$). Exact mass ([M – C_4H_9]$^+$) calcd.: 455.1809; found: 455.1812.

1,12-Dichloro-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-triene (14)

To a solution of diol **11** (599 mg, 2.34 mmol) and triphenylphosphine (1.72 g, 6.55 mmol) in dichloromethane (35 mL) at 0°C was added hexachloroacetone (426 μL, 2.81 μmol). The solution was allowed to warm to room temperature and stirred for 20 min. The mixture was concentrated under vacuo and purified by flash chromatography (100% hexanes then 95:5 hexanes–ether) to yield the title compound as an oil (514 mg, 75%). IR (cm^{-1}): 2931, 1453,

1251, 1031, 762. ^{1}H NMR ($CDCl_3$) δ: 6.47 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.15 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.7–5.58 (m, 4H, C*H*=C*H* and C*H*=CHCH=C*H*), 4.69 and 4.51 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.20 (dd, *J* = 8.0, 2.5 Hz, 2H, CH=CHCH=CHCH_2Cl), 4.10 (d, *J* = 7.0 Hz, 2H, CH=CHCH_2Cl), 4.15–4.00 (m, 1H, C*H*OMOM), 3.38 (s, 3H, OCH_3), 2.15 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.70–1.40 (m, 4H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 136.9, 134.7, 131.7, 126.0, 125.7, 125.5, 93.8, 75.8, 55.4, 39.3, 34.9, 26.7, 24.9. MS *m*/*z*: 310 ([M + NH_4]$^+$). Exact mass ([M + NH_4]$^+$) calcd.: 310.1340; found: 310.1333.

2-[7-Methoxymethoxy-12-(tetrahydropyran-2-yloxy)-dodeca-(2Z,8E,10Z)-trienyl]malonic acid dimethyl ester (15) (diastereoisomers)

To a suspension of sodium hydride 60% (200 mg, 5 mmol) in a DMF–THF solution (2:1, 15 mL) at 0°C, was added dropwise dimethylmalonate (640 μL, 5.6 mmol). The mixture was allowed to warm to room temperature and stirred 30 min. This solution was added to a solution of chloride **12** (397 mg, 1.12 mmol) and sodium iodide (168 mg, 1.12 mmol) in THF (10 mL) and heated to 70°C for 2 h. A saturated NH_4Cl solution (40 mL) was added to the cooled mixture and extracted with hexanes (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 9:1) to yield the title compound as an oil (358 mg, 71%). IR (cm^{-1}): 2949, 1738, 1437, 1343, 1272, 1234, 1201, 1150, 1030. ^{1}H NMR ($CDCl_3$) δ: 6.44 (dd, *J* = 15.0, 11.1 Hz, 1H, CH=CH-C*H*=CHCH$_2$), 6.10 (t, *J* = 11.0 Hz, 1H, CH=C*H*HC=CHCH$_2$), 5.65–5.40 (m, 3H, CH=C*H*CH$_2$CH and C*H*=CHCH=C*H*), 5.30 (m, 1H, C*H*=CHCH$_2$CH), 4.67 and 4.51 (2d, *J* = 6.5 Hz, 2 × 1H, OCH_2O), 4.65 (t, *J* = 3.0 Hz, 1H, OC*H*O), 4.42–4.15 (m, 2H, CH_2OTHP), 4.07 (q, *J* = 5.6 Hz, 1H, C*H*OMOM), 3.87 (m, 1H, OC*H*H of THP), 3.52 (m, 1H, OCH*H* of THP), 3.76 (s, 6H, CO$_2$CH_3), 3.40 (t, *J* = 4.0 Hz, 1H, C*H*(CO$_2$Me)$_2$), 3.36 (s, 3H, OCH$_2$OCH_3), 2.64 (t, *J* = 7.5 Hz, 2H, CH_2CH(CO$_2$Me)$_2$), 2.09 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.90–1.40 (m, 10H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 169.3, 135.1, 132.7, 130.3, 127.6, 127.1, 124.6, 98.0, 97.8, 93.5, 76.1, 62.8, 62.7, 62.2, 62.1, 55.3, 52.4, 51.5, 35.0, 30.5, 26.9, 26.6, 25.3, 25.2, 19.4.

2-[12-(tert-Butyl-diphenyl-silanyloxy)-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-trienyl]malonic acid dimethyl ester (16)

Preparation was similar to malonate **15** (89%). IR (cm^{-1}): 3014, 2953, 2859, 1739, 1429, 1344, 1150, 1033, 824, 703. ^{1}H NMR ($CDCl_3$) δ: 7.66 and 7.40 (2m, 10H, 2 phenyl), 6.43 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.04 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.67–5.29 (m, 4H, C*H*=C*H*CH$_2$OSi and C*H*=CHCH=C*H*), 4.66 and 4.49 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.24 (d, *J* = 6.5 Hz, 2H, CH_2OSi), 4.00 (q, *J* = 7.0 Hz, 1H, C*H*OMOM), 3.72 (s, 3H, CO$_2$*Me*), 3.73 (s, 3H, CO$_2$*Me*), 3.42 (t, *J* = 7.5 Hz, 1H, C*H*(CO$_2$Me)$_2$), 3.34 (s, 3H, OCH$_2$OCH_3), 2.77 (dt, *J* = 7.5, 1.0 Hz, 2H, CH_2CH(CO$_2$Me)$_2$), 1.89 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.60–1.20 (m, 4H, other CH_2), 1.06 (s, 9H, SiC(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 169.0, 135.5, 135.4, 134.8, 133.7, 130.5, 129.5, 129.4, 129.3, 127.5, 126.9, 126.5, 93.5, 76.1, 60.1, 55.2, 52.3, 51.4, 35.1, 27.3, 27.0, 26.7, 25.3, 19.0. MS *m*/*z*: 551 ([M – C_4H_9]$^+$). Exact mass ([M – C_4H_9]$^+$) calcd.: 551.2465; found: 551.2456.

2-(12-Hydroxy-7-methoxymethoxy-dodeca-(2Z,8E,10Z)-trienyl)malonic acid dimethyl ester (17)

A solution of malonate **15** (693 mg, 1.54 mmol) and pyridinium *p*-toluenesulfonate (77 mg, 0.31 mmol) in methanol (8 mL) was heated to reflux for 3 h. The mixture was cooled to room temperature, sodium bicarbonate (26 mg) was added, and the mixture was concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 1:3) to yield the title compound as an oil (401 mg, 73%). IR (cm^{-1}): 3393, 2932, 1733, 1649, 1628, 1430, 1030. ^{1}H NMR ($CDCl_3$) δ: 6.45 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 6.08 (t, *J* = 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 5.68–5.40 (m, 3H, CH=C*H*CH$_2$CH and C*H*=CHCH=C*H*), 5.30 (m, 1H, C*H*=CHCH$_2$CH), 4.67 and 4.51 (2d, *J* = 6.5 Hz, 2 × 1H, OCH_2O), 4.32 (d, *J* = 7.0 Hz, 2H, CH_2OH), 4.07 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.73 (s, 6H, CO$_2$CH_3), 3.40 (t, *J* = 4.0 Hz, 1H, C*H*(CO$_2$Me)$_2$), 3.38 (s, 3H, OCH$_2$OCH_3), 2.64 (t, *J* = 7.5 Hz, 2H, CH_2CH(CO$_2$Me)$_2$), 2.09 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.70–1.35 (m, 4H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 169.3, 135.0, 132.6, 130.4, 129.3, 127.1, 124.7, 93.4, 76.1, 58.4, 55.3, 52.4, 51.5, 34.9, 26.9, 26.6, 25.4.

2-(12-Hydroxy-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-trienyl)malonic acid dimethyl ester (18)

Compound **18** was prepared similar to alcohol **9** (81%). IR (cm^{-1}): 3448, 3012, 2951, 1738, 1437, 1344, 1275, 1233, 1150, 1096, 1032, 919, 738. ^{1}H NMR ($CDCl_3$) δ: 6.45 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.06 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.7–5.48 (m, 3H, CH=C*H*CH$_2$OH and C*H*=CHCH=C*H*), 5.36 (dq, *J* = 11.0, 3.0 Hz, 1H, C*H*=CHCH$_2$OH), 4.68 and 4.52 (2d, *J* = 6.5 Hz, 2 × 1H, OCH_2O), 4.19 (d, *J* = 6.5 Hz, 2H, CH_2OH), 4.07 (q, *J* = 6.5 Hz, 1H, C*H*OMOM), 3.73 (s, 3H, CO$_2$*Me*), 3.72 (s, 3H, CO$_2$*Me*), 3.43 (t, *J* = 7.5 Hz, 1H, C*H*(CO$_2$Me)$_2$), 3.37 (s, 3H, OCH$_2$OCH_3), 2.78 (t, *J* = 7.5 Hz, 2H, CH_2CH(CO$_2$Me)$_2$), 2.12 (q, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH=CH), 1.70–1.40 (m, 4H, other CH$_2$). ^{13}C NMR ($CDCl_3$) δ: 169.1, 134.8, 134.5, 130.4, 127.2, 126.6, 125.4, 93.4, 76.1, 74.5, 55.3, 52.5, 51.3, 39.3, 34.9, 27.0, 26.7, 25.0. MS *m*/*z*: 308 ([M – MOMOH]$^+$), 325 ([M – MOM]$^+$), 338 ([M – CH_3OH]$^+$). Exact mass ([M – CH_3OH]$^+$) calcd.: 338.1729; found: 338.1737.

2-(12-Chloro-7-methoxymethoxy-dodeca-(2Z,8E,10Z)-trienyl)malonic acid dimethyl ester (19)

To a solution of alcohol **17** (294 mg, 80 mmol) and hexachloroacetone (155 μL, 1 mmol) in dichloromethane (10 mL) at 0°C, was added triphenylphosphine (334 mg, 1.28 mmol). After stirring for 1 h at room temperature, the mixture was concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 9:1 to 3:1) to yield the title compound as an oil (288 mg, 94%). IR (cm^{-1}): 2946, 1748, 1735, 1433, 1234, 1145, 1029. ^{1}H NMR ($CDCl_3$) δ: 6.45 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 6.08 (t, *J* = 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 5.68–5.40 (m, 3H, CH=C*H*CH$_2$CH and C*H*=CHCH=C*H*), 5.30 (m, 1H, C*H*=CHCH$_2$CH), 4.67 and 4.51 (2d, *J* = 6.5 Hz, 2 × 1H, OCH_2O), 4.20 (dd, *J* = 7.0, 2.0 Hz, 2H,

CH_2Cl), 4.07 (q, *J* = 5.5 Hz, 1H, C*H*OMOM), 3.73 (s, 6H, CO_2CH_3), 3.40 (t, *J* = 4.0 Hz, 1H, C*H*($CO_2Me)_2$), 3.38 (s, 3H, OCH_2OCH_3), 2.64 (t, *J* = 7.5 Hz, 2H, $CH_2CH(CO_2Me)_2$), 2.09 (q, *J* = 7.0 Hz, 2H, CH_2CH_2CH=CH), 1.70–1.35 (m, 4H, other CH_2). ^{13}C NMR ($CDCl_3$) δ: 169.3, 137.0, 132.6, 131.7, 126.9, 126.7, 124.7, 93.7, 76.0, 55.3, 52.4, 51.6, 39.3, 34.9, 26.9, 26.7, 25.1.

2-(12-Chloro-6-methoxymethoxy-dodeca-(2Z,4E,10Z)-trienyl)malonic acid dimethyl ester (20)

Compound **20** was prepared similar to chloride **19** (99 %). IR (cm^{-1}): 3016, 2951, 1754, 1738, 1435, 1345, 1233, 1149, 1031, 666. ^{1}H NMR ($CDCl_3$) δ: 6.46 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 6.06 (t, *J* = 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 5.7–5.56 (m, 2H, CH=CHCH=C*H*CH$_2$ and CH=C*H*CH$_2$Cl), 5.53 (dd, *J* = 15.0, 8.0 Hz, 1H, C*H*=CHCH=CHCH$_2$), 5.36 (dq, *J* = 10.5, 3.0 Hz, 1H, C*H*=CHCH$_2$Cl), 4.69 and 4.52 (2d, *J* = 6.5 Hz, 2 × 1H, OCH_2O), 4.09 (d, *J* = 5.0 Hz, 2H, CH_2Cl), 4.05 (m, 1H, C*H*OMOM), 3.73 (s, 3H, CO_2*Me*), 3.72 (s, 3H, CO_2*Me*), 3.43 (t, *J* = 7.5 Hz, 1H, C*H*($CO_2Me)_2$), 3.37 (s, 3H, OCH_2OCH_3), 2.78 (dt, *J* = 7.5, 0.5 Hz, 2H, CH_2CH($CO_2Me)_2$), 2.13 (q, *J* = 7.0 Hz, 2H, CH_2CH_2CH=CH), 1.70–1.30 (m, 4H, other CH_2). ^{13}C NMR ($CDCl_3$) δ: 169.1, 134.8, 134.5, 130.4, 127.2, 126.6, 125.4, 93.4, 76.1, 74.5, 55.3, 52.5, 51.3, 39.3, 39.3, 34.9, 27.0, 26.7, 25.0. MS *m*/*z*: 353 ([M – Cl]$^+$), 358 ([M – CH_3OH]$^+$). Exact mass (M^+) calcd.: 388.1653; found: 388.1647.

7-Methoxymethoxy-cyclotrideca-(3Z,5E,11Z)-triene-1,1-dicarboxylic acid (21)

A solution of chloride **19** (or **20**) (280 mg, 0.72 mmol) in acetonitrile (10 mL) was added over 12 h via a syringe pump, to a solution of cesium carbonate (2.4 g, 7.5 mmol) and cesium iodide (390 mg, 1.5 mmol) in acetonitrile (600 mL) at 70°C (final concentration = 1 mM). Three hours after the final addition, the mixture was cooled to room temperature, filtered on florisil, and concentrated under vacuo. Water (20 mL) was added to the residue and the mixture was extracted with a 1:1 ether–hexanes solution (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 9:1) to yield the final compound as an oil (113 mg, 43%). IR (cm^{-1}): 2951, 1737, 1437, 1208, 1037. ^{1}H NMR ($CDCl_3$) δ: 6.42 (dd, *J* = 15.0, 11.0 Hz, 1H, CH=CHC*H*=CHCH$_2$), 6.21 (t, *J* = 11.0 Hz, 1H, CH=C*H*CH=CHCH$_2$), 5.82 (dd, *J* = 16.0, 5.5, 1H, C*H*=CHCH=CHCH$_2$), 5.45 (m, 1H, C*H*=CHCH$_2$C), 5.10–4.95 (m, 2H, C*H*=CHCH$_2$C and CH=CHCH=C*H*CH$_2$), 4.62 and 4.67 (2d, *J* = 7.0 Hz, 2 × 1H, OCH_2O), 4.13 (m, 1H, C*H*OMOM), 3.75 (s, 6H, CO_2CH_3), 3.38 (s, 3H, OCH_2OCH_3), 2.69 (d, *J* = 8.5 Hz, 2H, CH=CHCH=CHCH_2), 2.51 (d, *J* = 7.0 Hz, 2H, CH=CHCH_2C), 2.20–1.30 (m, 6H, other CH_2). ^{13}C NMR ($CDCl_3$) δ: 171.3, 171.2, 135.6, 135.0, 133.0, 126.5, 124.7, 123.8, 94.4, 76.5, 56.9, 55.3, 52.6, 30.0, 29.2, 29.0, 25.9, 24.8.

1-Cyano-7-methoxymethoxy-cyclotrideca-(3Z,5E,11Z)-trienecarboxylic acid methyl ester (22) (diastereoisomers)

A solution of bischloride **14** (720 mg, 2.25 mmol) and methyl cyanoacetate (298 μL, 3.38 mmol) in THF (20 mL) was added over 10 h using a syringe pump, to a solution of cesium carbonate (11.0 g, 33.8 mmol) in a THF–DMF solution (2:1, 800 mL) at 80°C. The DMF was purged with nitrogen for 1 h before use. One hour after the final addition, the solution was cooled to room temperature, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 8:2) to yield the title compound as an oil (568 mg, 79 %). IR (cm^{-1}): 2934, 2249, 1748, 1440, 1219. ^{1}H NMR ($CDCl_3$) δ: 6.47–6.26 (m, 2H, CH=C*H*C*H*=CHCH$_2$), 5.90 (dt, *J* = 15.0, 6.0 Hz, 1H, CH=CHCH=C*H*CH$_2$), 5.62–5.50 (m, 1H, CH_2CH_2CH=CH), 5.38 (q, *J* = 9.0 Hz, 1H, CH=C*H*CH$_2$C), 5.24 (m, 1H, C*H*=CHCH=CHCH$_2$), 4.62 (m, 2H, OCH_2O), 4.18 (q, *J* = 8.0 Hz, 1H, C*H*OMOM), 3.86 (s, 3H, CO_2CH_3), 3.37 (s, 3H, OCH_2OCH_3), 2.80–2.43 (m, 4H, CH=CHCH_2C), 2.22–1.30 (m, 6H, other CH_2). ^{13}C NMR ($CDCl_3$) δ: 168.7, 137.8, 137.4, 136.7, 134.8, 134.7, 126.8, 126.4, 123.6, 123.1, 122.8, 119.4, 95.1, 77.0, 76.7, 56.0, 54.2, 46.8, 42.9, 46.8, 42.9, 32.1, 31.6, 30.5, 30.2, 29.8, 26.8, 25.2, 24.9. MS *m*/*z*: 319 (M^+). Exact mass (M^+) calcd.: 319.1783; found: 319.1789.

6-Methoxymethoxy-1,3,3a,5a,6,7,8,9,9a,9b-decahydro-cyclopenta[a]naphthalene-2,2-dicarboxylic acid dimethyl ester (23) (diastereoisomers)

A solution of macrocycle **21** (61 mg, 173 μmol) in xylenes (1 mL) was stirred at 140°C for 4 h. The crude was purified by flash chromatography (hexanes–ether, 8:2) to yield the title compound as an oil (61 mg, 100%, OMOM, α:β = 2:1). ^{1}H NMR ($CDCl_3$) δ: 5.83 (d, *J* = 10.0 Hz, 1H, C*H*=CH), 5.48 (dt, *J* = 10.0, 3.0 Hz, 1H, CH=C*H*), 4.77 (d, *J* = 7.0 Hz, 0.66H, OCH_2OMe *alpha*), 4.70 (d, *J* = 7.0 Hz, 0.33H, OCH_2OMe *beta*), 4.63 (d, *J* = 7.0 Hz, 0.66H, OCH_2OMe *alpha*), 4.60 (d, *J* = 7.0 Hz, 0.33H, OCH_2OMe *beta*), 3.90 (m, 0.33H, C*H*OMOM *beta*), 3.72 (s, 3H, CO_2*Me*), 3.68 (s, 3H, CO_2*Me*), 3.39 (s, 2H, OCH_2O*Me*), 3.37 (s, 1H, OCH_2O*Me*), 3.20 (td, *J* = 10.5, 4.5Hz, 0.66H, C*H*OMOM *alpha*), 2.75 (m, 1H, C*H*CH=CH), 2.51 (m, 1H, C*H*CH=CH), 2.30–1.05 (m, 12H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 170.0, 129.2, 126.2, 95.6, 79.5, 76.5, 56.0, 53.01, 53.0, 41.9, 41.2, 39.4, 39.2, 33.3, 32.9, 31.0, 30.7, 30.1, 29.7, 24.3.

2-Cyano-6-methoxymethoxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]naphthalene-2-carboxylic acid methyl ester (24) (diastereoisomers)

A solution of macrocycle **22** (67 mg, 208 μmol) in xylenes (500 μL) was stirred at 140°C for 8 h. The crude was purified by flash chromatography (hexanes–ether, 8:2) to yield the title compound as an oil (52 mg, 78%). ^{1}H NMR ($CDCl_3$) δ: 5.92 (dd, *J* = 15.0, 6.5 Hz, 1H, C*H*=CH), 5.57 (m, 1H, CH=C*H*), 4.79 (d, *J* = 7.0 Hz, 0.66H, OCH_2OMe *alpha*), 4.71 (d, *J* = 7.0 Hz, 0.33H, OCH_2OMe *beta*), 4.63 (d, *J* = 7.0 Hz, 0.66H, OCH_2OMe *alpha*), 4.60 (d, *J* = 7.0 Hz, 0.33H, OCH_2OMe *beta*), 3.92 (m, 0.33H, C*H*OMOM *beta*), 3.82 (s, 1H, CO_2*Me*), 3.81 (s, 1H, CO_2*Me*), 3.80 (s, 1H, CO_2*Me*), 3.39 (s, 2H, OCH_2O*Me*), 3.38 (s, 1H, OCH_2O*Me*), 3.21 (td, *J* = 10.5, 4.5 Hz, 0.66H, C*H*OMOM *alpha*), 2.93 (m, 1H, C*H*CH=CH), 2.65–1.00 (m, 13H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 170.4, 169.4, 169.2, 130.0, 129.9, 129.6, 129.0, 127.5, 126.2, 95.4, 95.0, 79.0, 78.9, 74.9, 55.4, 55.2, 53.6, 53.4, 46.8, 46.6, 42.4, 42.3, 42.1, 41.0, 40.8, 40.7, 40.4, 39.3, 38.8, 38.6, 37.8, 36.4, 36.3,

36.0, 33.5, 32.8, 32.6, 30.8, 30.6, 30.3, 29.7, 24.1, 24.0, 20.7.

*6-Methoxymethoxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H-*cyclopenta[*a*]naphthalene-2-carboxylic acid methyl ester (25) (diastereoisomers)*

A solution of macrocycle **21** (92 mg, 261 μmol), sodium chloride (39 mg, 653 μmol), and water (10 μL) in DMSO (1 mL) was stirred at 160°C for 7 h. Water (10 mL) was added to the cooled solution and the mixture was extracted with a hexanes–ether solution (1:1, 3 × 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo to yield the title compound as an oil (66 mg, 90%). ^{1}H NMR (DMSO-d_6) δ: 5.75 (d, *J* = 6.5 Hz, 1H, C*H*=CH), 5.41 (m, 1H, CH=C*H*), 4.71–4.50 (m, 2H, OCH_2O), 3.82 (m, 0.33H, C*H*OMOM, H *alpha*), 3.65 (s, 2H, CO_2*Me*), 3.60 (s, 1H, CO_2*Me*), 3.28 (s, 2H, OCH_2O*Me*), 3.23 (s, 1H, OCH_2O*Me*), 3.10 (m, 0.66H, C*H*OMOM, H *beta*), 2.70 (m, 1H, C*H*CH=CH), 2.53–2.38 (m, 2H, C*H*CH=CH and C*H*CO_2), 2.20–1.00 (m, 12H, other CH_2 and CH).

*6-Methoxymethoxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H-*cyclopenta[*a*]naphthalene-2-carbonitrile (26) (diastereoisomers)*

A solution of macrocycle **22** (1.7 g, 5.43 mmol) and sodium cyanide (293 mg, 6 mmol) in DMSO (25 mL) was stirred at 160°C for 8 h. Water (100 mL) was added to the cooled solution and the mixture was extracted with a hexanes–ether solution (1:1, 3 × 100 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo to yield the title compound as an oil (1.27 g, 89%, OMOM, α:β = 2:1). Alternatively, a solution of tricycle **24** (50 mg, 157 μmol) and sodium cyanide (9.6 mg, 195.6 μmol) in DMSO (500 μL) was stirred at 160°C for 8 h. The mixture was diluted with water (15 mL) and extracted with a hexanes–ether solution (1:1, 3 × 15 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuo to yield the title compound as an oil (40 mg, 97%). IR (cm^{-1}): 2927, 2237, 1446, 1149, 1099, 1040. ^{1}H NMR ($CDCl_3$) δ: 5.92–5.88 (m, 1H, C*H*=CH), 5.60–5.42 (m, 1H, CH=C*H*), 4.80–4.57 (m, 2H, OCH_2O), 3.98–3.90 (m, 0.33H, C*H*OMOM, H_{ax}), 3.40 (s, 1H, OCH_2O*Me*), 3.39 (s, 1H, OCH_2O*Me*), 3.36 (s, 0.5H, OCH_2O*Me*), 3.35 (s, 0.5H, OCH_2O*Me*), 3.25–3.10 (m, 0.66H, C*H*OMOM, H_{eq}), 2.90–2.60 (m, 2H, C*H*CH=CHC*H*), 2.9–0.5 (m, 13H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 131.3, 131.0, 130.6, 130.1, 129.9, 128.6, 126.2, 123.4, 95.6, 95.1, 79.3, 75.2, 55.5, 55.3, 43.3, 43.2, 41.5, 41.2, 41.0, 40.6, 39.9, 39.6, 39.2, 39.1, 38.6, 36.7, 36.3, 33.7, 32.8, 31.1, 31.0, 30.7, 30.6, 30.3, 29.9, 29.6, 29.5, 27.3, 26.3, 24.3, 24.1, 21.0, 20.8. MS *m*/*z*: 261 (M^+), 246 ([M – CH_3]$^+$), 229 ([M – CH_3OH]$^+$), 216 ([M – MOM]$^+$). Exact mass (M^+) calcd.: 261.1729; found: 261.1733.

*6-Hydroxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H-*cyclopenta[*a*]naphthalene-2-carbonitrile (27) (diastereoisomers)*

A solution of tricycle **26** (1.27 g, 4.85 mol) and HCl 6 N (750 μL) in methanol (125 mL) was heated to reflux for 8 h. The solution was concentrated under vacuo and purified by flash chromatography (hexanes–ether, 40% to 100% ether) to yield the title compound as an oil (1.06 g, 100%). IR (cm^{-1}): 3426, 2928, 2860, 2239, 1449, 1348, 1281, 1059, 1028. ^{1}H NMR ($CDCl_3$) δ: 6.05–5.40 (m, 2H, C*H*=C*H*), 4.10–4.07 (m, 0.33H, C*H*OMOM, H_{ax}), 3.37–3.22 (m, 0.66H, C*H*OMOM, H_{eq}), 2.90–2.60 (m, 2H, C*H*CH=CHC*H*), 2.5–2.3 (m, 1H, C*H*CN), 2.15–1.00 (m, 13H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 133.3, 130.8, 130.4, 130.0, 128.4, 128.2, 126.0, 123.5, 73.5, 69.7, 43.3, 43.0, 42.5, 41.4, 41.1, 40.3, 40.0, 39.8, 38.9, 38.7, 36.7, 36.3, 33.0, 32.9, 32.7, 31.2, 31.1, 30.8, 30.7, 30.4, 29.6, 29.2, 26.3, 24.4, 24.3, 20.6, 20.5. MS *m*/*z*: 216 ([M – H]$^+$). Exact mass ([M – H]$^+$) calcd.: 216.1388; found: 216.1392.

*6-Oxo-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H-*cyclopenta[*a*]naphthalene-2-carbonitrile (28) and (29)*

To a solution of alcohol **27** (145 mg, 671 μmol) in dichloromethane (22 mL) at 0°C, was added Dess–Martin periodinane (370 mg, 872 μmol). The solution was allowed to warm to room temperature and stirred for 30 min. A saturated $NaHCO_3$ solution (30 mL) and sodium thiosulfate (477 mg, 1.92 mmol) were added and stirred 30 min. The mixture was extracted with dichloromethane (3 × 30 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 9:1) to yield two racemic diastereoisomeres as oils (α-nitrile 66 mg and β-nitrile 50 mg, total yield: 80%).

Ketone **28** (α-nitrile). IR (cm^{-1}): 2928, 2850, 2335, 1709, 1450, 1360, 1240, 1145. ^{1}H NMR ($CDCl_3$) δ: 6.03 (d, *J* = 10.0 Hz, 1H, O=CCHC*H*=CH), 5.63 (dt, *J* = 10.0, 2.5 Hz, 1H, CH=C*H*), 2.82–2.70 (m, 3H, C*H*CH=CHC*H* and C*H*CN), 2.48–1.52 (m, 12H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 209.95, 131.54, 122.61, 121.91, 47.31, 42.91, 41.87, 41.22, 40.18, 38.31, 36.05, 30.41, 26.50, 26.28. MS *m*/*z*: 215 (M^+). Exact mass (M^+) calcd.: 215.1310; found: 215.1315.

Ketone **29** (β-nitrile). ^{1}H NMR ($CDCl_3$) δ: 6.07 (d, *J* = 10.0 Hz, 1H, O=CCHC*H*=CH), 5.51 (dt, *J* = 10.0, 3.0 Hz, 1H, CH=C*H*), 2.90–2.70 (m, 2H, C*H*CH=CHC*H*), 2.55 (qd, *J* = 9.0, 3.5 Hz, 1H, C*H*CN), 2.49–1.50 (m, 12H, other CH_2 and CH). ^{13}C NMR ($CDCl_3$) δ: 209.84, 130.75, 124.10, 123.0, 46.78, 41.80, 41.14, 39.54, 36.30, 30.22, 29.58, 28.91, 26.34, 26.15.

*6-Hydroxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H-*cyclopenta[*a*]naphthalene-2-carbonitrile (30)*

To a solution of ketone **28** (213 mg, 995 mmol) in THF (15 mL) at –78°C, was added lithium triisobutylborohydride (0.5 M, 2.8 mL, 1.4 mmol). After 3.5 h, NaOH (10%, 2.4 mL, 6 mmol) and H_2O_2 (35%, 583 μL, 6 mmol) were added and the mixture was stirred for 3 h at room temperature. A sodium thiosulfate solution (1 M) was then added and stirred for 30 min. The mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (100% ether) to yield the title compound as an oil (171 mg, 80%). IR (cm^{-1}): 3312, 2930, 2845, 2232, 1445, 1322, 1064. ^{1}H NMR ($CDCl_3$) δ: 5.63 (dt, *J* = 10.0, 2.5 Hz, 1H, OCHCHCH=C*H*), 5.52 (d, *J* = 10.0 Hz, 1H, OCHCHC*H*=CH), 4.10 (s, 1H, C*H*OH), 2.85–2.65 (m, 2H, C*H*CH=CHC*H*), 2.35 (dt, *J* = 13.5, 9.0 Hz, 1H, C*H*CN), 2.15–1.08

(m, 12H, other CH_2 and C*H*). ^{13}C NMR ($CDCl_3$) δ: 133.2, 128.1, 123.1, 69.7, 43.2, 40.3, 38.9, 36.1, 32.9, 32.7, 31.2, 30.4, 26.2, 20.6. MS *m*/*z*: 217 (M^+). Exact mass (M^+) calcd.: 217.1467; found: 217.1469.

6-Hydroxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid (31)

To a solution of alcohol **30** (12.5 mg, 58 μmol) in methanol (2 mL) was added an NaOH solution (25%, 416 μL, 2.6 mmol) and a H_2O_2 solution (30%, 600 μL, 12% v/v). The mixture was stirred at 65°C for 24 h and concentrated under vacuo to ~1 mL. The mixture was diluted with water (15 mL), the pH was adjusted to 2 with 1 N HCl, and the mixture extracted with dichloromethane (3 × 15 mL). The combined organics were dried over $MgSO_4$ and concentrated under vacuo. The residue was purified by flash chromatography (acetone–hexanes, 6:1) to yield the title compound as white crystals (12.4 mg, 90%). IR (cm^{-1}): 3400–2300, 3392, 2921, 2851, 1704, 1651, 1463, 1221. ^{1}H NMR (MeOD-d_4) δ: 5.54 (dt, *J* = 10.0, 2.5 Hz, 1H, OCHCHCH=C*H*), 5.42 (d, *J* = 10.0 Hz, 1H, OCHCHC*H*=CH), 3.99 (s, 1H, C*H*OH), 2.8–2.6 (m, 2H, C*H*CH=CHC*H*), 2.25 (dt, *J* = 13.5, 9.0 Hz, 1H, C*H*CO_2H), 2.15–1.12 (m, 12H, other CH_2 and CH).

Iodolactone 32

To a solution of acid **31** (1.5 mg, 3.8 μmol) in THF (0.5 mL) was added one crystal of iodide, one drop of water, and sodium bicarbonate (1 mg, 7.5 μmol). The solution was stirred 3 days at room temperature, then diluted with water (10 mL), and the pH adjusted to 2 with 1 N HCl. The mixture was extracted with dichlorometane (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuo to yield the title compound as a red oil (2 mg) (excess iodide). IR (cm^{-1}): 3557, 3006, 2956, 2880, 1743, 1601, 1454, 1365, 1244, 1163, 1066, 1002. ^{1}H NMR ($CDCl_3$) δ: 4.68 (t, *J* = 3.5 Hz, 1H, C*H*OC=O), 4.44 (t, *J* = 3.0 Hz, 1H, C*H*I), 4.02 (m, 1H, C*H*OH), 3.05 (q, *J* = 6.5 Hz, 1H, CH_2C*H*CHOC=O), 2.88 (dd, *J* = 7.5, 6.5 Hz, 1H, C*H*CO_2), 2.35–1.12 (m, 13H, other CH and CH_2). ^{13}C NMR ($CDCl_3$) δ: 174.0, 84.5, 69.2, 40.4, 39.8, 35.1, 34.9, 34.5, 34.3, 32.4, 30.8, 30.6, 29.9, 29.7, 18.4. MS *m*/*z*: 362 (M^+), 235 ([M – I]$^+$). Exact mass (M^+) calcd.: 362.0379; found: 362.0387; ([M – I]$^+$) calcd.: 235.1334; found: 235.1339.

6-Triisopropylsilanyloxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carbonitrile (33)

To a solution of alcohol **30** (55 mg, 254 μmol) and 2,6-lutidine (89 μL, 762 μmol) in dichloromethane (4 mL) at 0°C, was added slowly triisopropylsilane triflate (102 μL, 381 μmol). After 1 h at room temperature, a saturated NH_4Cl solution (30 mL) was added and the mixture extracted with dichloromethane (3 × 30 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ether, 95:5) to give the title compound as an oil (96 mg, 100%). IR (cm^{-1}): 2929, 2237, 1448, 1363, 1278, 1217, 1149, 1097, 1041, 917. ^{1}H NMR ($CDCl_3$) δ: 5.52 (d, *J* = 10.0 Hz, 1H, OCHCHC*H*=CH), 5.44 (dt, *J* = 10.0, 2.5 Hz, 1H, OCHCHCH=C*H*), 4.25 (br s, 1H, C*H*-OTIPS), 2.80–2.66 (m, 2H, C*H*CH=CHC*H*), 2.30 (dt, *J* = 13.5, 9.5 Hz, 2H, C*H*CN), 2.20–1.38 (m, 12H, CH and CH_2), 1.20–0.95 (m, 21H, OTIPS). ^{13}C NMR ($CDCl_3$) δ: 130.6, 130.1, 123.4, 70.8, 43.6, 41.5, 39.0, 36.2, 34.2, 32.6, 31.5, 30.3, 26.2, 20.8, 18.2, 13.3, 12.8, 12.4. MS *m*/*z* : 330 ([M – C_3H_7]$^+$). Exact mass ([M – C_3H_7]$^+$) calcd.: 330.2253; found: 330.2255.

6-Triisopropylsilanyloxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid (34)

To a solution of silyl ether **33** (67 mg, 180 mmol) in methanol (20 mL) was added NaOH (10%, 3.2 mL) and H_2O_2 (35%, 9 mL). The solution was heated to reflux for 24 h. The cooled solution was concentrated under vacuo to ~10 mL and acidified to pH 2 with HCl (1 N, 25 mL). The solution was extracted with dichloromethane (3 × 30 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by flash chromatography (hexanes–ethyl acetate, 6:4) to yield the title compound as an oil (58 mg, 83%). IR (cm^{-1}): 3450–2400, 2929, 2866, 1704, 1463, 1238, 1118, 1066, 882. ^{1}H NMR ($CDCl_3$) δ: 5.53 (d, *J* = 10.0 Hz, 1H, OCHCHC*H*=CH), 5.34 (dt, *J* = 10.0, 2.5 Hz, 1H, OCHCHCH=C*H*), 4.22 (m, 1H, C*H*OTIPS), 2.89–2.60 (m, 2H, C*H*CH=CHC*H*), 2.45–2.15 (m, 1H, C*H*CO_2H), 2.44–0.80 (m, 33H, other CH, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$) δ: 182.3, 131.6, 129.1, 70.9, 43.8, 42.6, 41.5, 38.8, 34.7, 34.3, 32.9, 31.6, 29.7, 28.9, 20.9, 18.3, 18.2, 12.8. MS *m*/*z*: 349 ([M – C_3H_7]$^+$). Exact mass ([M – C_3H_7]$^+$) calcd.: 349.2199; found: 349.2194.

6-Triisopropylsilanyloxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid pentylamide (35)

To a solution of acid **34** (22 mg, 56 μmol) in dichloromethane (3 mL) at 0°C was added oxalyle chloride (8 μL, 88 μmol) and DMF (1 μL, 11 μmol). The solution was warmed to room temperature. After 1.5 h, triethylamine (9 μL, 67 μmol) and amylamine (13 μL, 112 μmol) were added and stirred 24 h. The mixture was concentrated under vacuo and purified by flash chromatography (hexanes–acetone, 7:3) to yield the title compound as an oil (22 mg, 80%). IR (cm^{-1}): 3300, 2927, 2864, 1643, 1462, 1065. ^{1}H NMR ($CDCl_3$) δ: 5.5–5.3 (m, 3H, C*H*=C*H* and N*H*), 4.22 (br s, 1H, C*H*OTIPS), 3.21 (qd, *J* = 7.0, 1.0 Hz, 2H, CH_2NH), 2.73–2.46 (m, 2H, C*H*CH=CHC*H*), 2.20 (dt, *J* = 13.5, 9.5 Hz, 1H, C*H*CONH) 2.13–0.99 (m, 39H, other CH, CH_2 and CH_3) 0.89 (t, *J* = 7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR and DEPT-135 ($CDCl_3$) δ: 175.6 (s), 132.0 (d), 128.8 (d), 71.0 (d), 45.1 (d), 44.0 (d), 41.5 (d), 39.4 (t), 38.7 (d), 35.6 (t), 34.3 (t), 32.9 (d), 31.6 (t), 29.9 (t), 29.7 (t), 29.3 (t), 29.1 (t), 22.3 (t), 20.9 (t), 18.3 (q), 14.0 (q), 12.8 (d). MS *m*/*z*: 461 (M^+), 418 ([M – C_3H_7]$^+$). Exact mass (M^+) calcd.: 461.3689; found: 461.3680.

6-Triisopropylsilanyloxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid indan-(1*S*)-ylamide (36) and (37) (diastereoisomers)

Same procedure as for amide **35**, using (*S*)-(+)-1-aminoindane instead of amylamine. The title compound was obtained as an oil (18 mg, 73%) and recovered acid **34** (2 mg). IR (cm^{-1}): 3281, 2936, 2865, 1643, 1539, 1461, 1384, 1243, 1066, 881, 745, 674. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.15 (m, 4H, H-aryl), 5.72–5.33 (m, 3H, C*H*=C*H* and

CON*H*), 4.22 (br s, 1H, C*H*OTIPS), 3.07–0.80 (m, 40H, other CH, CH_2 and CH_3). ^{13}C NMR ($CDCl_3$) δ: 175.4, 143.4, 131.9, 128.9, 127.8, 126.7, 124.7, 123.9, 71.0, 54.5, 45.1, 44.0, 41.5, 38.7, 35.7, 35.5, 34.2, 32.9, 31.6, 30.2, 30.0, 29.8, 20.9, 18.3, 12.8. MS *m*/*z*: 507 (M^+). Exact mass (M^+) calcd.: 507.3532; found: 507.3541.

6-Hydroxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid pentylamide (1)

A solution of amide **35** (18 mg, 39 μmol) and HCl (6 N, 0.3 mL) in methanol (5 mL) was heated to reflux for 24 h. The cooled solution was concentrated under vacuo and purified by flash chromatography (hexanes–acetone, 7:3) to yield the title compound as an oil (7 mg, 81%). IR (cm^{-1}): 3300, 2927, 2860, 1647, 1548, 1456, 1372, 1249. ^{1}H NMR ($CDCl_3$) δ: 5.66 (dt, *J* = 10.0, 2.5 Hz, 1H, CH=C*H*), 5.49–5.37 (m, 2H, C*H*=CH and CON*H*), 4.06 (br s, 1H, C*H*OH), 3.21 (qd, *J* = 7.0, 1.0 Hz, 2H, CH_2NH), 2.80–2.65 (m, 1H, C*H*CH=CH), 2.63–2.45 (m, 1H, C*H*CH=CH), 2.22 (td, *J* = 13.5 Hz, 1H, C*H*CONH), 2.15–1.00 (m, 18H, other CH and CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 175.2, 134.8, 126.6, 69.9, 45.0, 43.5, 40.3, 39.5, 38.6, 35.5, 33.3, 32.7, 31.3, 29.8, 29.7, 29.3, 29.1, 22.3, 20.7, 14.0. MS *m*/*z*: 305 (M^+). Exact mass (M^+) calcd.: 305.2355; found: 305.2359.

6-Hydroxy-2,3,3a,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-2-carboxylic acid indan-(1*S*)-ylamide (2) and (38) (diastereoisomers)

Same procedure as for alcohol **1** but using a mixture of amides **36** and **37** instead of amide **35**. The title compounds were obtained as an oil (18 mg, 84%). IR (cm^{-1}): 3289, 3012, 2930, 2864, 1645, 1538, 1455, 1231, 1056, 988, 909, 732. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.17 (m, 4H, H-aryl), 5.71–5.41 (m, 3H, C*H*=C*H*, CON*H*), 4.08 (br s, 1H, C*H*OH), 3.05–2.50 (m, 5H, CH_2ArC*H*NH and C*H*CH=CHC*H*), 2.25–0.80 (m, 15H, other CH and CH_2). ^{13}C NMR ($CDCl_3$) δ: 175.1, 143.4, 134.8, 134.2, 129.7, 128.0, 126.7, 124.9, 123.9, 70.0, 54.5, 45.0, 43.7, 40.4, 38.7, 35.4, 34.2, 33.6, 33.4, 32.7, 31.3, 30.2, 29.9, 29.7, 20.8. MS *m*/*z*: 351 (M^+). Exact mass (M^+) calcd.: 351.2198; found: 351.2200.

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References

1. Y.C. Martin. J. Comb. Chem. **3**, 231 (2001).
2. E.J. Martin and R.E. Critchlow. J. Comb. Chem. **1**, 32 (1999).
3. M. Ramaseshan, M. Robitaille, J.W. Ellingboe, Y.L. Dory, and P. Deslongchamps. Tetrahedron Lett. **41**, 4737 (2000).
4. M. Ramaseshan, J.W. Ellingboe, Y.L. Dory, and P. Deslongchamps. Tetrahedron Lett. **41**, 4743 (2000).
5. R. Gagnon, Y.L. Dory, and P. Deslongchamps. Tetrahedron Lett. **41**, 4751 (2000).
6. P. Soucy, Y.L. Dory, and P. Deslongchamps. Synlett, **8**, 1123 (2000).
7. M. Ramaseshan, Y.L. Dory, and P. Deslongchamps. J. Comb. Chem. ***2***, 615 (2000).
8. S. Lamothe, A. Ndibwami, and P. Deslongchamps. Tetrahedron Lett. **29**, 1639 (1988).
9. S. Lamothe, A. Ndibwami, and P. Deslongchamps. Tetrahedron Lett. **29**, 1641 (1988).
10. T. Takahashi, K. Shimizu, T. Doi, J. Tsuji, and Y. Fukazawa. J. Am. Chem. Soc. **110**, 2674 (1988).
11. (*a*) P. Deslongchamps. Pure Appl. Chem. **64**, 1831 (1992); (*b*) E. Marsault, A. Toró, P. Nowak, and P. Deslongchamps. Tetrahedron Report, No. 565, **57**, 4243 (2001).
12. Y.L. Dory, P. Soucy, M. Drouin, and P. Deslongchamps. J. Am. Chem. Soc. **117**, 518 (1995).
13. A. Miranker and M. Karplus. Proteins: Structure, Function, and Genetics, **11**, 29 (1991).
14. M.B. Eisen, D.C. Wiley, M. Karplus, and R.E. Hubbard. Proteins: Structure, Function, and Genetics, **19**, 199 (1994).
15. D. Joseph-McCarthy, J.M. Hogle, and M. Karplus. Proteins: Structure, Function, and Genetics, **29**, 32 (1997).
16. A. Caflish, A. Miranker, and M.Karplus. J. Med. Chem. **36**, 2142 (1993).
17. G. Bérubé and P. Deslongchamps. Can. J. Chem. **68**, 404 (1990).
18. N. Hayashi, H. Noguchi, and S. Tsuboi. Tetrahedron, **56**, 7123 (2000).
19. Y.L. Dory, C. Ouellet, S. Berthiaume, A. Favre, and P. Deslongchamps. Bull. Soc. Chim. Fr. **131**, 121 (1994).
20. R. Appel. Angew. Chem. Int. Ed. Engl. **14**, 801 (1975).
21. Y. Chantigny, A. Toró, C.A. Lemelin, and P. Deslongchamps. Tetrahedron Lett. **39**, 7839 (1998).
22. A.P. Krapcho and J.F. Wemaster. J. Org. Chem. **45**, 4105 (1980).
23. G. Martin and M. Martin. Bull. Soc. Chim. Fr. 1637 (1963).