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Synthesis of the trichloroacetamide derivative of *enantio*-*iso*-ADDA methyl ester

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Dedicated to the memory of our esteemed colleague Dr. Andy Parkin

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ABSTRACT

The divergent syntheses of the trichloroacetamide derivatives of (2*S*,3*R*,8*R*,9*R*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-decadenoic acid (*enantio*-*iso*-ADDA), and (2*R*,3*R*,8*R*,9*R*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-decadenoic acid (*enantio*-ADDA), have been achieved. Our approach takes advantage of highly efficient non-aldol aldol, palladium catalysed aza-Claisen and cross-metathesis methodologies.

1. Introduction

iso-Motuporin **1** is a macrocyclic peptide isolated recently from the marine sponge *Theonella swinhoei*.[1] *iso*-Motuporin is closely related to motuporin **2**, nodularin **3** and the microcystins **4**. The key structural difference between them is that the unusual β-amino acid unit (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-decadenoic acid 'ADDA' present in the microcystins, nodularin and motuporin has been mutated into the isomeric β-amino acid unit (2*R*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-decadenoic acid '*iso*-ADDA' (Fig. 1).

Biologically, the microcystins, nodularin and motuporin exhibit significant activity as protein phosphatase inhibitors.[2] Protein phosphatases (PPs) are key proteins with significant roles in signal transduction pathways, and are involved in a variety of processes including cell division, neurotransmission, memory and learning.[3] However, the understanding of the relative pharmacological functions of the various phosphatase families remains fairly limited due to their structural similarities and the lack of selective inhibitors.[4]

Unfortunately, the high toxicity of the microcystins, nodularin and motuporin has kept them from being developed as potential therapeutic leads.[5] Importantly, truncation of the ADDA chain abolishes the PP inhibitory activity of the microcystins, nodularin and motuporin.

Interestingly, naturally occurring 6*Z*-ADDA nodularin and microcystin analogues display none of the toxicity associated with the parent compounds.[6]

The unique structure of ADDA as well as its biological relevance has inspired a number of synthetic approaches developed to date.[7]

Reports by Chamberlin and co-workers have demonstrated that microcystin analogues **6** incorporating the *N*-acylated ADDA chain and a single amino acid retain moderate activity as PP1/PP2A inhibitors (Fig. 2).[8,9] The recent discovery of *iso*-motuporin has not allowed any of these studies to be carried out with either *iso*-motuporin **1** or *iso*-ADDA **7**.

All this evidence suggests that stereoisomeric forms of the ADDA scaffold (and conversely peptides incorporating them) might provide an alternative starting point for the development of novel biological chemistry probes to study and dissect phosphatase activity.

2. Results and discussion

As part of our efforts towards the generation of novel ADDA isoforms that might help expand our knowledge of this important subunit, we would like to report the first total synthesis of fully protected *enantio*-*iso*-ADDA. An efficient total synthesis of *enantio*-*iso*-ADDA would allow us to compare its biological and physical properties to those of *enantio*-ADDA (recently synthesised by our group) and to evaluate its biological activity both on its own, and

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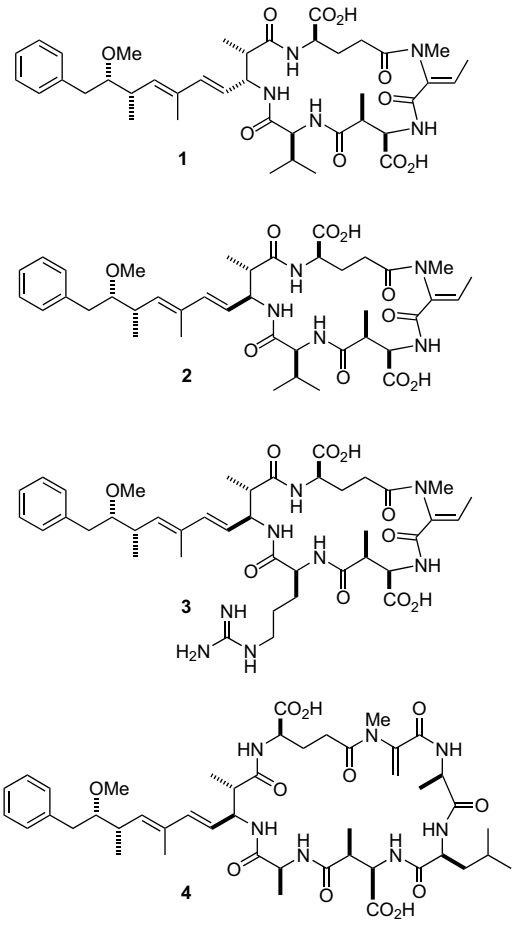


Figure 1. *iso*-Motuporin **1**, motuporin **2**, nodularin **3** and microcystin LA **4**.

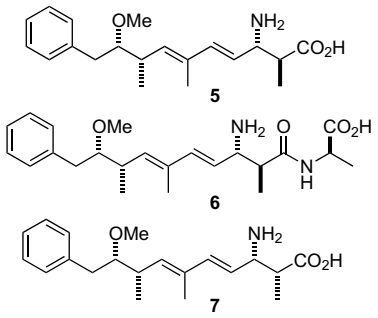
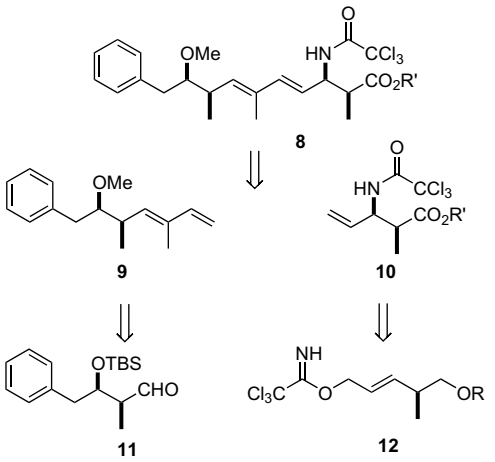


Figure 2. ADDA **5**, ADDA analogue **6** and *iso*-ADDA **7**.

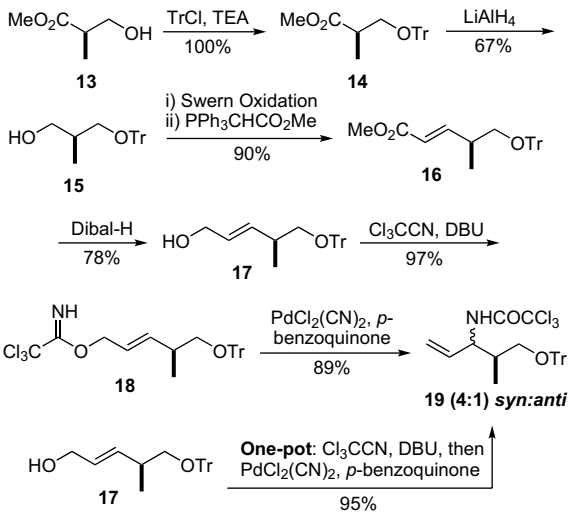
when attached to naturally occurring macrocyclic peptides and known pharmacophores.

Retrosynthetically, we envisioned *enantio-iso*-ADDA **8** as having originated through the convergent cross-metathesis coupling of the previously generated diene **9** with allylic amine **10**. Our convergent approach relies on the highly effective *E*,*E*-selective diene cross-metathesis, which has been utilised by Koide, Crimmins, and most recently by us.[10] As per our previous work, diene **9** could be readily secured through the olefination of aldehyde **11**, in turn easily accessible through Jung's non-aldol aldol methodology.[11] The allylic amide-coupling partner **10** on the other hand was envisioned as having originated through the Overman palladium catalysed rearrangement of trichloroacetimidate **12** (Scheme 1).[12]



Scheme 1.

Our synthesis of the right hand unit began with the commercially available methyl (*R*)-(−)-3-hydroxy-2-methylpropionate **13**, which was protected as the trityl ether **14** in quantitative yield. Lithium aluminium hydride reduction of the ester unit, then generated the mono-protected 1,3-diol **15** in high yield and with no epimerisation being observed (Scheme 2).



Scheme 2.

Swern oxidation of alcohol **15** followed by a Wittig olefination of the aldehyde intermediate afforded the desired conjugated ester **16** as a single double bond isomer in excellent yield and with no detectable epimerisation over the two-step sequence.

A selective 1,2-reduction of conjugated ester **16** then afforded the desired allylic alcohol **17** in good yield. Treatment of alcohol **17** with trichloroacetonitrile then gave the expected trichloroacetimidate intermediate **18** in nearly quantitative yield.

Treatment of the newly obtained trichloroacetimidate **18** under Overman's palladium(II) mediated aza-Claisen conditions proceeded to generate the expected allylic amide unit **19** in high yield and as a 4:1 mixture of *syn*/*anti* diastereomers.[12] Significantly, a novel one-pot trichloroacetamidate generation and aza-Claisen rearrangement further improved the overall transformation yield (95% from alcohol **17**) with similar diastereomeric ratios. The two diastereomers could be successfully separated through a selective recrystallisation of the major diasteromer **19*syn***, which corroborated the absolute stereochemistry of the amido-ether intermediate (Fig. 3).[13]

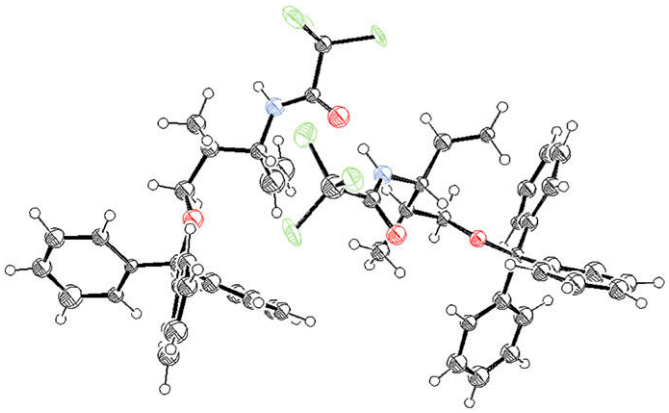
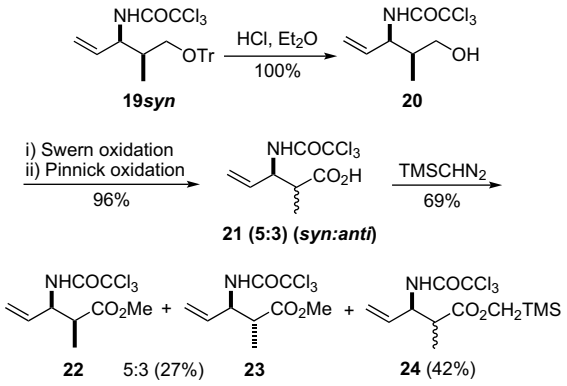


Figure 3. Crystal structure of allylic amine **19*syn***.

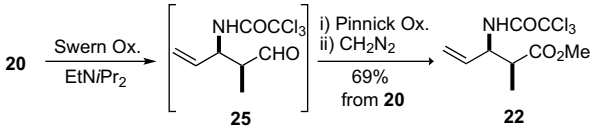
Treatment of trityl intermediate **19*syn*** with an etheral HCl solution proceeded to generate the desired primary alcohol **20**, which upon a sequential Swern–Pinnick oxidation procedure afforded the desired amido-acid intermediate **21** in excellent yield over the three-step process (Scheme 3). Interestingly, the use of triethylamine as part of the Swern procedure resulted in significant epimerisation of the aldehyde intermediate, which translated into the generation of an inseparable 5:3 mixture of *syn*/*anti* diastereomers.[14] Methylation of the carboxylic acid mixture using TMS-diazomethane in diethyl ether produced the *syn* and *anti* methyl esters **22** and **23** (5:3 ratio of diastereomers) as well as the TMS-methylene esters **24**. Separation by reverse phase semi-preparative HPLC allowed the isolation of esters **22**, **23** and the enriched TMS ester **24*syn***.



Scheme 3.

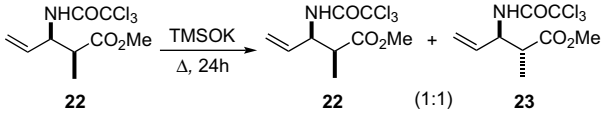
Although unexpected, the epimerisation observed during the triethylamine based Swern oxidation to generate the *anti* allylic amine unit **23** was a welcome result. This epimerization effectively allowed the generation of the non-trivial to generate *anti* allylic amide using these steps. Interestingly, all attempts to exclusively obtain the *anti* allylic amine through thermal conditions failed to yield any rearrangement products.

Conversely, treatment of alcohol **20** under a Hunig's base derived Swern oxidation gave the aldehyde intermediate **25** with no observable epimerisation.[14] The crude aldehyde **25** was then converted to the diastereomerically pure methyl ester **22** through a Pinnick oxidation–diazomethane methylation sequence. Diazomethane provided a much cleaner methylation and in a higher yield than that performed with TMS-diazomethane. It should also be noted that Dess–Martin periodinane was also successful at avoiding epimerisation, however, required extensive purification to generate the clean methyl ester **22** (Scheme 4).[14]



Scheme 4.

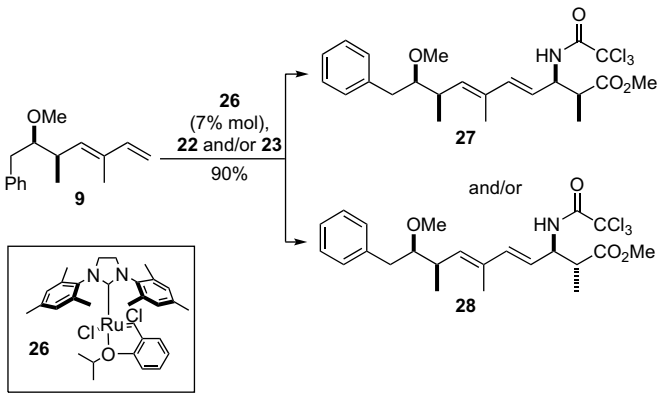
Interestingly, when the single diastereomer **22** was treated with TMSOK in THF, a significant amount of epimerisation was observed as well as partial decomposition (Scheme 5). This isomerisation raises the possibility that *iso*-motuporin might be the product of the biological isomerisation of motuporin rather than being produced through a different metabolic pathway entirely.



Scheme 5.

Having successfully achieved the synthesis of the amido ester unit **22**, the key cross-metathesis was attempted with diene **9** using our previously developed conditions.

We are pleased to report that treatment of diene **9** with allylic amides **22** and **23** (both as single components and as a mixture of diastereomers) in the presence of second generation Hoveyda–Grubbs catalyst **26** in THF generated the fully protected *enantio-iso*-ADDA and *enantio*-ADDA derivatives reproducibly in excellent yields and as single *E*,*E* diastereomers (Scheme 6). The cross-coupling, however, was found to be highly susceptible to the solvent used, and the yield dropped to 20% when the coupling was attempted in toluene.



Scheme 6.

It is important to highlight that in the case where the diastereomeric mixture was used in this coupling step, the products proved impossible to separate even through the use of HPLC methods. Furthermore, the spectroscopic and optical rotation data of both diastereomers were very similar to each other ($[\alpha]_D^{24}$ +12.4 for **27**, and $[\alpha]_D^{24}$ +11.2 for **28**) demonstrating the difficulty in separating, and identifying correctly different isoforms of the ADDA unit.

In conclusion, we have completed the first synthesis of fully protected *enantio-iso*-ADDA **27** as well as that of *enantio*-ADDA **28** utilising non-aldol aldol, palladium catalysed rearrangements and cross-metathesis methodologies to introduce the key functionalities.

Our convergent approach can be easily scaled up and allows for the generation of key ADDA isoforms, *enantio-iso*-ADDA and *enantio*-ADDA, taking advantage of an effective isomerisation

during the synthesis of the allylic amine coupling partner. Furthermore the methodology and procedures used as part of our syntheses allow for the rapid generation of all ADDA isoforms through the simple modification of the Jung non-aldol aldol rearrangement precursor, and through the use of the desired starting propionate.

We are currently in the process of comparing the biological properties of *enantio*-*N*-TAC-*iso*-ADDA and *enantio*-*N*-TAC-ADDA's full biological profile as potential lead compounds for selective phosphatase inhibition.

3. Experimental

3.1. General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether and dichloromethane (DCM) were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as-received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Buchi Rotavapor.

IR spectra were recorded as thin films on NaCl plates using a JASCO FT/IR410 Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were, respectively, recorded at 400 MHz and 100 MHz using a Bruker DPX Avance400 instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dm=double multiplet) and (3) coupling constant (*J*) quoted in hertz to the nearest 0.5 Hz.

High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15,000 full widths at half height.

Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40–63 μm) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

3.2. (*R*)-(−)-3-Trityloxy-2-methylpropionate, 14

To a solution of methyl (*R*)-(−)-3-hydroxy-2-methylpropionate **13** (91 mg, 0.77 mmol) in anhydrous dichloromethane (5 mL) was added anhydrous triethylamine (170 μL, 1.22 mmol) at room temperature. After stirring the mixture at room temperature for 5 min, the solution was cooled down to 0 °C and a previously prepared solution of tritylchloride (279 mg, 1.00 mmol) in dry dichloromethane (1 mL) was added slowly. The reaction mixture was then allowed to warm up to room temperature and stirred overnight. The reaction was then quenched by the addition of a saturated solution of ammonium chloride (4 mL), and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to afford a sticky yellowish oil (324 mg). Purification by flash chromatography (silica gel, 1% TEA, elution gradient 0–20% ethyl acetate in petroleum ether) yielded the pure trityl-protected ester **14** as a sticky, clear and colourless oil (277 mg, 100%), which tended to form white crystals upon storage. For multigram scale, the ester **14** was taken on crude in the next reaction without any purification. The spectroscopic data was in full agreement with that reported in the literature. $[\alpha]_D^{25}$ −19.7 (*c* 1.0, $CHCl_3$) compared to $[\alpha]_D^{23}$ +17.7 (*c* 1.9, $CHCl_3$) for the enantiomeric ester.[15]

3.3. (2*S*)-3-Trityloxy-2-methylpropan-1-ol, 15

A solution of crude ester **14** (36.52 g, 0.10 mol) in anhydrous diethyl ether (1100 mL), cooled down to −30 °C, was cautiously treated with small portions of solid lithium aluminium hydride (6.09 g, 0.16 mol). The reaction mixture was then allowed to warm up to room temperature, and the mixture was stirred overnight. The mixture was quenched slowly and carefully by the addition of water (6 mL), followed by a solution of sodium hydroxide (15 wt %, 6 mL). More water (18 mL) was then added, and the mixture was stirred until a white precipitate formed. The mixture was filtrated through Celite, and the solid was washed with ethyl acetate (1000 mL) until no product remained in the solid as indicated by TLC analysis. The organic filtrate was then dried over anhydrous sodium sulfate, and the solvents were evaporated under reduced pressure. Evaporation under high vacuum afforded the crude product as an extremely viscous yellowish oil (37.46 g) that tends to crystallise. Purification by flash chromatography (silica gel, 1% TEA, 20% ethyl acetate, 10% dichloromethane in 40–60 petroleum ether) provided alcohol **15** as an extremely viscous and yellowish clear oil (22.65 g, 67%), which can crystallise as a white powder after prolonged storage under high vacuum. Note: commercially available solutions of $LiAlH_4$ in diethyl ether can also be used with comparable yields. The spectroscopic data were in full agreement with that reported in the literature. $[\alpha]_D^{26}$ −32.7 (*c* 1.0, $CHCl_3$) compared to $[\alpha]_D^{29}$ +28.4 (*c* 1.0, $CHCl_3$) for the enantiomeric alcohol.[16]

3.4. (2*E*,4*S*)-Methyl 5-trityloxy-4-methylpent-2-enoate, 16

A −78 °C solution of oxalyl chloride (414 μL, 4.89 mmol) in anhydrous dichloromethane (10 mL) was treated by the slow addition of anhydrous dimethylsulfoxide (845 μL, 11.90 mmol), and the mixture was stirred for 45 min under argon. A previously prepared solution of alcohol **15** (797 mg, 2.40 mmol) in dry dichloromethane (5 mL) was then added slowly at −78 °C and the resulting mixture was stirred for 1 h at −78 °C. The reaction mixture was treated with anhydrous diisopropylethylamine (1.50 mL, 8.61 mmol), and the solution was stirred for a further 45 min at −78 °C. The reaction mixture was then poured into a separatory funnel containing acidic water (20 mL H_2O+7 mL 1.0 M HCl). The layers were separated, and the organic fraction was washed with water (50 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated under vacuum to afford a very sticky yellowish oil (1.06 g), which showed few impurities by ^1H NMR spectroscopy. The crude was then dissolved in dry dichloromethane and used immediately without any further purification (50 mL, regular dichloromethane was preferred when the reaction was carried out in larger scale). Methyl(triphenylphosphoranylidene acetate) (1.76 g, 5.26 mmol) was then added to the dichloromethane solution and the resulting mixture was heated at reflux under argon for 3 days. The reaction mixture was then cooled down to room temperature and worked up by addition of enough 40–60 petroleum ether to force the triphenylphosphine oxide to precipitate out. The solid was discarded after filtration, and the process was repeated until no more triphenylphosphine oxide could be forced out of solution. Subsequent evaporation of the organic filtrates provided a very sticky orange oil (930 mg), which was used without any further purification in the next step. Purification by flash chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40–60 petroleum ether) yielded an analytically pure sample of the methyl ester **16** (835 mg, 90% over two steps) as an extremely viscous colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, d, J=6.8 Hz), 2.58 (1H, app sept, J=6.8 Hz), 3.02 (1H, dd, J=8.6, 6.3 Hz), 3.04 (1H, dd, J=8.8, 6.7 Hz), 3.69 (3H, s), 5.82 (1H, app dd, J=15.8, 0.8 Hz), 6.92 (1H, dd, J=15.8, 7.3 Hz), 7.17–7.41 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 37.2, 51.4, 67.1, 86.4, 120.4, 126.9, 127.7, 128.6, 144.0, 151.9, 167.1; $[\alpha]_D^{25}$ −3.4 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3087, 3059, 3023, 2963, 2952, 2915, 2872, 1720, 1658, 1598, 1491, 1448, 1437, 1275, 1218, 1196, 1180, 1153, 1072, 1033, 983, 765, 707, 632 cm^{-1}; HRMS (EI) observed M^+ 386.1886, calculated for $C_{26}H_{26}O_3$ 386.1882.

3.5. (4*S*,2*E*)-5-Trityloxy-4-methylpent-2-en-1-ol, 17

A 0 °C solution of ester **16** (17.15 g, 44.40 mmol) in anhydrous diethyl ether (1400 mL) was treated with the slow addition of Dibal-H (1.0 M in hexanes, 121.0 mL, 0.121 mol). The resulting mixture was then immediately removed off the cooling bath and was allowed to warm up to room temperature where it was stirred under argon until completion as indicated by TLC analysis (2 h). The reaction was then quenched by the dropwise addition of water (100 mL), followed by aq HCl (1.0 M, 10 mL). Ethyl acetate (500 mL) was added to the mixture, and the two phases were separated. The organic layer was subsequently washed with water (300 mL), acidic water (250 mL of water+50 mL of HCl 1 M) and finally with water (300 mL) one last time. The aqueous layers were then combined, and extracted with ethyl acetate (300 mL). The combined organic fractions were then dried over anhydrous sodium sulfate, and the solvent was evaporated under vacuum to yield a crude sticky yellowish oil residue (15.22 g). This crude oil was purified by flash chromatography (silica gel, 1% TEA, 20% ethyl acetate, 10% dichloromethane in 40–60 petroleum ether) to give the desired allylic alcohol **17** (12.41 g, 78%, 100% ee) as a clear yellowish oil. The enantiomeric excess was determined through Chiral HPLC analysis with a Chiracel AD column using hexane/isopropanol (99:1) at a flow rate of 0.75 mL/min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 1.26 (1H, br s), 2.50 (1H, app sept, J=6.4 Hz), 2.95 (1H, dd, J=8.7, 6.7 Hz), 3.03 (1H, dd, J=8.7, 6.4 Hz), 4.09 (2H, br s), 5.64–5.66 (2H, m), 7.21–7.46 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 36.9, 63.7, 68.0, 86.2, 126.8, 127.6, 128.5, 128.7, 135.6, 144.2; $[\alpha]_D^{23}$ +3.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3580, 3375, 3087, 3059, 3022, 2961, 2952, 2913, 2870, 1597, 1491, 1448, 1218, 1071, 973, 753, 707, 633 cm^{-1}.

3.6. (4*S*,2*E*)-5-Trityloxy-4-methylpent-2-enyl-2,2,2-trichloroacetimidate, 18

To a −78 °C solution of allylic alcohol **17** (73 mg, 0.204 mmol) in anhydrous dichloromethane (5 mL) were added trichloroacetonitrile (30 μL, 0.30 mmol) and DBU (6.2 μL, 0.04 mmol). The mixture was slowly allowed to warm up to room temperature, where it was stirred under argon until completion as indicated by TLC analysis (3 h). The reaction was quenched by addition of water (5 mL), and diluted with diethyl ether (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The organic extracts were combined, and dried over sodium sulfate before being concentrated under vacuum to afford a crude yellowish oil (121 mg). Purification of oily residue by flash column chromatography (silica gel, 1% TEA, elution gradient 0–5% ethyl acetate in 40–60 petroleum ether) afforded the desired trichloroacetimidate **18** (99 mg, 97%) as a sticky colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, J=6.8 Hz), 2.53 (1H, app sept, J=6.5 Hz), 2.99 (1H, dd, J=8.7, 6.2 Hz), 3.03 (1H, dd, J=8.7, 6.7 Hz), 4.78 (2H, d, J=6.1 Hz), 5.72 (1H, dtd, J=15.6, 6.1, 0.9 Hz), 5.88 (1H, br dd, J=15.6, 7.0 Hz), 7.21–7.46 (15H, m), 8.29 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 37.1, 67.8, 69.9, 86.2, 91.5, 122.6, 126.8, 127.7, 128.7, 139.3, 144.2, 162.6; $[\alpha]_D^{24.5}$ −1.4 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3342, 3087, 3059, 3023, 2961, 2926, 2871, 1661, 1490, 1448, 1307, 1290, 1218, 1073, 974, 797, 763, 707, 649 cm^{-1}.

3.7. 2,2,2-Trichloro-*N*-((3*R*,4*S*)-5-trityloxy-4-methylpent-1-en-3-yl)acetamide, 19*syn*, and 2,2,2-trichloro-*N*-((3*R*,4*R*)-5-trityloxy-4-methylpent-1-en-3-yl)acetamide, 19*anti*

A solution of trichloroacetimidate **18** (9.84 g, 19.57 mmol) in anhydrous dichloromethane (435 mL) was treated with *p*-benzoquinone (3.12 g, 28.86 mmol) and bis(acetonitrile)dichloropalladium(II) (460 mg, 1.77 mmol, 9.1 mol%). The reaction mixture was stirred at room temperature until TLC analysis indicated completion (24 h). An initial filtration of the reaction mixture through a short pad of silica was then used to remove the main colouring agent. The silica pad was then flushed with diethyl ether and the combined organic flushes were concentrated to afford a crude residue that was purified by flash column chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40–60 petroleum ether) to afford the desired terminal alkene **19** as a mixture of two diastereoisomers (4:1, *syn*/*anti*) (8.71 g, 89%) as a very viscous and clear light brown oil. The two diastereoisomers were separated successfully by recrystallisation (ethanol/40–60 petroleum ether) to afford **19*syn*** as a white powder.

3.7.1. One-pot procedure

To a 0 °C solution of allylic alcohol **17** (812 mg, 2.27 mmol) in anhydrous dichloromethane (50 mL) was added DBU (67 μL, 0.43 mmol) followed by trichloroacetonitrile (320 μL, 3.19 mmol). The reaction mixture was then allowed to warm up to room temperature where it was stirred until completion as indicated by TLC analysis (2 h). *p*-Benzoquinone (315 mg, 2.91 mmol) and bis(acetonitrile)dichloropalladium(II) (63 mg, 0.24 mmol, 10.7 mol%) were then quickly added into the reaction mixture at the same time, and the reaction mixture was stirred under argon for 5 h. At this time, extra *p*-benzoquinone (158 mg, 1.46 mmol) and bis(acetonitrile)dichloropalladium(II) (47 mg, 0.18 mmol, 8.0 mol%) were added, and the reaction was stirred at room temperature until completion as indicated by TLC analysis (2 days). The reaction mixture was filtrated through a pad of silica gel and flushed with diethyl ether. Evaporation under reduced pressure of the organic solvent afforded a dark brown oil (1.46 g). Purification of the oily residue by flash chromatography (silica gel, 1% TEA, 10% ethyl acetate in 40–60 petroleum ether) gave the expected terminal alkene **19** (1.08 g, 95% over two steps) as a viscous and clear light brown oil. As in the two-pot procedure, the pure terminal alkene **19** was obtained as a 4:1 (*syn*/*anti*) mixture of diastereoisomers, which could be separated by recrystallisation to afford **19*syn*** as a white powder (ethanol/40–60 petroleum ether).

*Compound **19syn***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, J=7.2 Hz), 2.12 (1H, m), 3.12 (1H, t, J=9.8 Hz), 3.26 (1H, dd, J=10.0, 4.0 Hz), 4.38–4.46 (1H, m), 5.12 (1H, app dt, J=10.4, 1.2 Hz), 5.14 (1H, app dt, J=17.1, 1.3 Hz), 5.52 (1H, ddd, J=17.0, 10.4, 6.1 Hz), 7.23–7.45 (15H, m), 7.76 (1H, d, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 36.7, 57.2, 65.9, 87.9, 92.8, 117.8, 127.2, 127.9, 128.7, 132.4, 143.3, 161.1; $[\alpha]_D^{24}$ −1.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3368, 3086, 3058, 3022, 2967, 2927, 2883, 1706, 1492, 1448, 1218, 1036, 821, 759, 707, 633 cm^{-1}. Mp 140 °C.

*Compound **19anti***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, d, J=7.1 Hz), 2.00 (1H, m), 3.12 (1H, t, J=9.8 Hz), 3.26 (1H, dd, J=10.0, 4.0 Hz), 4.39–4.45 (1H, m), 4.98 (1H, br d, J=10.2 Hz), 5.01 (1H, d, J=17.0 Hz), 5.49 (1H, partially masked dd, J=17.0, 10.2 Hz), 7.23–7.46 (15H, m), 7.59 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 36.8, 57.5, 64.2, 87.4, 92.7, 116.0, 127.1, 127.9, 128.7, 135.0, 143.2, 161.7.

3.8. 2,2,2-Trichloro-*N*-((3*R*,4*S*)-5-hydroxy-4-methylpent-1-en-3-yl)acetamide, 20

A solution of trityl-protected alcohol **19*syn*** (545 mg, 1.08 mmol) in dichloromethane (5 mL) was treated by the slow addition of a commercially available solution of HCl in anhydrous diethyl ether (1.0 M, 2.0 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred for 1 h, and was then concentrated under vacuum without any prior work up. The crude viscous oil (550 mg) was purified by flash chromatography (silica gel, elution gradient 5–10% ethyl acetate in 40–60 petroleum ether) to give the desired alcohol **20** (281 mg, 100%) as a very viscous, clear and colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, J=7.1 Hz), 2.18 (1H, m), 2.28 (1H, dd, J=5.5, 4.7 Hz), 3.53 (1H, app td, J=10.6, 4.6 Hz), 3.65 (1H, m), 4.58–4.64 (1H, m), 5.28 (1H, dm, J=17.2 Hz), 5.28 (1H, dm, J=10.6 Hz), 5.86 (1H, ddd, J=17.1, 10.7, 5.4 Hz), 7.80 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 38.6, 55.7, 65.1, 92.8, 117.3, 133.4, 161.8; $[\alpha]_D^{24}$ +15.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3468, 3427, 3321, 3085, 3017, 2966, 2934, 2882, 1698, 1644, 1516, 1241, 1036, 994, 928, 823, 757, 735, 683, 666 cm^{-1}; HRMS (CI) observed $(M+H)^+$ 260.0007, calculated for $C_8H_{13}O_2NCl_3$ 260.0012.

3.9. (2*R*,3*R*)-2-Methyl-3-(2,2,2-trichloroacetamido)pent-4-enoic acid, 21*syn*, and (2*R*,3*R*)-2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoic acid, 21*anti*

A −78 °C solution of oxalyl chloride (113 μL, 1.34 mmol) in anhydrous dichloromethane (12 mL) was treated by the slow addition of anhydrous dimethylsulfoxide (191 μL, 2.69 mmol), and the resulting mixture was stirred at −78 °C for 45 min. A previously prepared solution of alcohol **20** (210 mg, 0.806 mmol) in dry dichloromethane (6 mL) was then slowly added and the reaction mixture was stirred for a further 1 h at −78 °C. The reaction mixture was treated with anhydrous triethylamine (521 μL, 3.74 mmol), and the reaction mixture was allowed to warm up to room temperature and stirred for a further 1 h. The reaction was quenched by addition of water (10 mL), and the phases were separated. The organic layer was washed with water (2×10 mL) and the combined aqueous fractions were extracted with ethyl acetate (10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under vacuum to afford the crude aldehyde (237 mg) as a viscous orange oil, and as a 5:3 mixture of (*syn*/*anti*) diastereomers. The crude aldehyde was solubilised in *tert*-butanol (4.5 mL) and 2-methyl-2-butene (695 μL, 6.56 mmol) was added. This resulting solution was then treated slowly with a freshly made aqueous solution of sodium chlorite (555 mg, 6.14 mmol) and sodium phosphate monobasic dihydrate (816 mg, 5.23 mmol) in water (2.2 mL total volume) at room temperature. The reaction mixture was stirred overnight at room temperature and subsequently quenched by the dropwise addition of concd HCl (0.2 mL). The acidic mixture was then extracted with ethyl acetate (3×15 mL) and dichloromethane (30 mL). The combined organic extracts were dried over magnesium sulfate, and the solvent was removed under reduced pressure to give the crude acid mixture **21*syn*/*anti*** (545 mg) as a viscous yellow oil. Purification by flash chromatography (silica gel, 20% ethyl acetate in 40–60 petroleum ether) afforded the carboxylic acids **21*syn*** and **21*anti*** (213 mg, 96%) as an inseparable mixture of diastereomers (*syn*/*anti*, 5:3) as a viscous, clear and colourless oil.

Compound ***21syn***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, d, J=7.3 Hz), 2.87–2.94 (1H, m), 4.55–4.62 (1H, m), 5.33 (1H, app dt, J=10.3, 0.9 Hz), 5.35 (1H, app dt, J=17.1, 1.0 Hz), 5.84 (1H, ddd, J=17.0, 10.3, 6.6 Hz), 7.59 (1H, br d, J=8.0 Hz), 8.32 (1H, v br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 42.5, 55.3, 92.6, 119.4, 131.9, 161.2, 178.8; IR (thin film) ν_{max}=3411, 3344, 3201, 3088, 3021, 2986, 2927, 2855, 2651, 2552, 1709, 1510, 1265, 1216, 823, 755, 668 cm^{-1}. HRMS (CI) observed $(M+H)^+$ 273.9794, calculated for $C_8H_{11}O_3NCl_3$ 273.9805.

Compound ***21anti***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, d, J=7.3 Hz), 2.87 (1H, m), 4.56 (1H, m), 5.19 (1H, br dd, J=10.5, 1.2 Hz), 5.24 (1H, dd, J=15.9, 1.2 Hz), 7.77 (1H, ddd, J=15.9, 10.5, 5.3 Hz), 8.32 (1H, v br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 42.6, 54.9, 91.9, 117.5, 134.3, 161.9, 180.0.

3.10. (2*S*,3*R*)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, 22, and (2*R*,3*R*)-methyl 2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, 23

A solution of the acid diastereoisomeric mixture **21*syn*** and **21*anti*** (210 mg, 0.76 mmol) in anhydrous diethyl ether (4.5 mL) was treated with the dropwise addition of a commercial solution of TMS-diazomethane in hexanes (0.8 mL, 2.0 M, 1.6 mmol). The resulting yellow solution was stirred overnight, and was subsequently quenched by the sequential and careful addition of acetic acid (180 μL, 2.62 mmol) and potassium fluoride (50 mg, 0.86 mmol). After the mixture was stirred for 10 min, the solution was treated with aq HCl (1.0 M, 2×10 mL). The layers were separated and the organic phase was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to afford the crude esters (359 mg) as a yellow oil. Purification by flash column chromatography (silica gel, elution gradient 0–10% ethyl acetate in 40–60 petroleum ether) provided the desired methyl esters **22** and **23** as a viscous, clear oil and as an inseparable mixture (60 mg, 27%) of *syn*/*anti* (5:3) diasteromers. The TMS-methyl esters **24*syn*** and **24*anti*** (115 mg, 42%, d.r. 5:3) were also isolated as an inseparable mixture of diastereomers.

The diastereomeric mixture was then loaded onto a semi-preparative HPLC under reverse phase conditions as a MeCN/H_2O (50:50) stock solution (C18 column). The separation was achieved using the following elution profile: initial elution gradient increased the acetonitrile concentration from 25% to 45% over 20 min. The concentration was kept at 45% for 55 min and was then increased from 45% to 95% over 5 min. Finally, the concentration was kept at 95% for an additional 10 min at which point the run was terminated. Methyl ester **22** was isolated after 52.85 min. Methyl ester **23** was isolated after 55.90 min. Finally, the enriched fraction containing TMS-methylene ester **24*syn*** was isolated after 68.48 min (*syn*/*anti* 7.5:1.0). In all cases, the optimised detection wavelength was 214 nm.

3.10.1. (2S,3R)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, 22

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J=7.3 Hz), 2.84 (1H, qd, J=7.3, 4.7 Hz), 3.70 (3H, s), 4.49–4.53 (1H, m), 5.26 (1H, app dt, J=10.3, 1.0 Hz), 5.28 (1H, app dt, J=17.1, 1.0 Hz), 5.77 (1H, ddd, J=17.0, 10.3, 6.6 Hz), 7.71 (1H, br d, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 42.5, 52.1, 55.5, 92.6, 118.9, 132.2, 160.9, 173.8; $[\alpha]_D^{24}$ +65.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (ESI) observed $(M+H)^+$ 287.9956, calculated for $C_9H_{13}O_3NCl_3$ 287.9955.

3.10.2. (2R,3R)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, 23

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, d, J=7.2 Hz), 2.84 (1H, qd, J=7.2, 3.8 Hz), 3.71 (3H, s), 4.52–4.57 (1H, m), 5.20 (1H, ddd, J=10.5, 1.5, 0.5 Hz), 5.27 (1H, ddd, J=17.2, 1.6, 0.5 Hz), 5.80 (1H, ddd, J=17.2, 10.5, 5.2 Hz), 8.02 (1H, br d, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 42.4, 52.1, 55.2, 92.8, 116.9, 134.7, 161.9, 175.7; $[\alpha]_D^{24}$ +26.8 (*c* 1.0, $CHCl_3$).

3.10.3. (2S,3R)-(Trimethylsilyl)methyl-2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, ***24syn***

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (9H, s), 1.23 (3H, d, J=7.3 Hz), 2.84 (1H, qd, J=7.3, 4.6 Hz), 3.77 (1H, d, J=14.1 Hz), 3.88 (1H, d, J=14.1 Hz), 4.47–4.55 (1H, m), 5.28 (1H, app dt, J=10.4, 1.0 Hz), 5.31 (1H, app dt, J=17.2, 1.0 Hz), 5.79 (1H, ddd, J=17.1, 10.4, 6.7 Hz), 7.85 (1H, br d, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.1, 13.8, 42.7, 55.8, 58.6, 92.7, 119.1, 132.2, 161.0, 174.3. $[\alpha]_D^{24}$ +41.9 (*c* 1.0, $CHCl_3$) enriched fraction (*syn*/*anti* 7.5:1.0).

3.10.4. (2R,3R)-(Trimethylsilyl)methyl-2-methyl-3-(2,2,2-trichloroacetamido)pent-4-enoate, ***24anti***

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (9H, s), 1.29 (3H, d, J=7.2 Hz), 2.84 (1H, qd, J=7.2, 3.8 Hz), 3.81 (1H, s), 3.82 (1H, s), 4.47–4.55 (1H, m), 5.20 (1H, ddd, J=10.4, 1.5, 0.6 Hz), 5.26 (1H, ddd, J=17.1, 1.5, 0.6 Hz), 5.79 (1H, ddd, J=17.1, 10.4 Hz, one unresolved coupling), 8.14 (1H, br d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.1, 15.5, 42.5, 55.2, 58.6, 92.8, 116.8, 134.9, 162.0, 175.6. IR (thin film) ν_{max}=3340, 2958, 1718, 1509, 1298, 1252, 1180, 1154, 843, 822, 681 cm^{-1}; HRMS (FAB$^+$) observed $(M+H)^+$ 360.0355, calculated for $C_{12}H_{21}O_3NCl_3Si$ 360.0356.

3.10.5. (2S,3R)-Methyl 2-methyl-3-(2,2,2-trichloroacetamido) pent-4-enoate, ***22***

A −78 °C solution of oxalyl chloride (156 μL, 1.84 mmol) in anhydrous dichloromethane (3 mL) was treated with dimethylsulfoxide (317 μL, 4.46 mmol) and the mixture was stirred at −78 °C for 45 min. A previously prepared solution of alcohol **20** (235 mg, 0.902 mmol) in dry dichloromethane (2 mL) was then added slowly and the resulting mixture was stirred at −78 °C for a further 1 h. The reaction mixture was then treated slowly with anhydrous DIPEA (550 μL, 3.16 mmol) and the reaction mixture was stirred for an extra 45 min at −78 °C. The reaction mixture was then poured into an extraction funnel containing acidic water (8 mL H_2O+2.6 mL 1.0 M HCl). The phases were separated, and the organic fraction was washed with water (20 mL) one more time. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the desired aldehyde intermediate **25** as a viscous yellowish oil (311 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, d, J=7.5 Hz), 2.78 (1H, qd, J=7.4, 4.2 Hz), 4.61–4.66 (1H, m), 5.25–5.30 (2H, m), 5.82 (1H, ddd, J=17.10, 10.3, 6.7 Hz), 7.41 (1H, br d, J=8.9 Hz), 9.66 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 48.9, 54.4, 92.4, 119.1, 132.6, 161.1, 203.4.

The crude aldehyde **25** was dissolved in *tert*-butanol (5.0 mL) and 2-methyl-2-butene (773 μL, 7.30 mmol) was added to the solution. The mixture was then slowly treated with a freshly made aqueous solution of sodium chlorite (621 mg, 6.87 mg) and sodium phosphate monobasic dehydrate (913 mg, 5.85 mmol) in water (2.5 mL) at room temperature. The reaction mixture was stirred until completion as indicated by TLC analysis (1 h) and was then quenched by the dropwise addition of concd HCl (220 μL). Water (10 mL) was then added to the solution, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The organic fractions were combined and were dried over magnesium sulfate before being evaporated under reduced pressure to give the crude acid ***21syn*** (299 mg) as a very viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, d, J=7.3 Hz), 2.87 (1H, qd, J=7.2, 4.8 Hz), 4.55–4.62 (1H, m), 5.27 (1H, app dt, J=10.3, 0.9 Hz), 5.30 (1H, app dt, J=17.1, 1.0 Hz), 5.80 (1H, ddd, J=17.0, 10.4, 6.6 Hz), 7.72 (1H, br d, J=8.9 Hz), 9.40 (1H, v br s).

A 0 °C 3 M aq solution of sodium hydroxide (12.7 mL) topped up with diethyl ether (19 mL) was carefully treated by the addition of small portions of a suspension of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) (1.0 g in total, 50% in water, 3.40 mmol). After the bubbling has ceased (10 min), the yellow ethereal solution of diazomethane was transferred slowly and carefully using a polished glass pipette to a solution of the crude carboxylic acid ***21syn*** (299 mg) in diethyl ether (6 mL) at room temperature in an open air round bottom flask. The yellow solution was then stirred until completion as indicated by TLC analysis (30 min), and was subsequently quenched by the careful dropwise addition of acetic acid (150 μL, 2.62 mmol). After stirring the acidic mixture for 30 min, the solvent was evaporated under reduced pressure to give the crude methyl ester **22** (359 mg) as a viscous yellow oil. Purification by flash column chromatography (silica gel, elution gradient 0–10% ethyl acetate in 40–60 petroleum ether) provided the pure methyl ester **22** as a single diastereomer (180 mg, 69% over three steps) and as a colourless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J=7.3 Hz), 2.84 (1H, qd, J=7.3, 4.7 Hz), 3.70 (3H, s), 4.49–4.53 (1H, m), 5.26 (1H, app dt, J=10.3, 1.0 Hz), 5.28 (1H, app dt, J=17.1, 1.0 Hz), 5.77 (1H, ddd, J=17.0, 10.3, 6.6 Hz), 7.71 (1H, br d, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 42.5, 52.1, 55.5, 92.6, 118.9, 132.2, 160.9, 173.8; $[\alpha]_D^{24}$ +65.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3419, 3029, 2965, 2926, 2870, 1496, 1454, 1038, 742, 700 cm^{-1}; HRMS (ESI) observed $(M+H)^+$ 287.9956, calculated for $C_9H_{13}O_3NCl_3$ 287.9955.

3.11. (2*S*,3*R*,4*E*,6*E*,8*R*,9*R*)-Methyl 9-methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoate (*enantio*-*N*-TAC-*iso*-ADDA methyl ester), 27, and (2*R*,3*R*,4*E*,6*E*,8*R*,9*R*)-methyl 9-methoxy-2,6,8-trimethyl-10-phenyl-3-(2,2,2-trichloroacetamido)deca-4,6-dienoate (*enantio*-*N*-TAC-ADDA methyl ester), 28

3.11.1. General procedure

Neat methoxy diene **9**[10c] (140 mg, 0.608 mmol) and the diastereomeric mixture of methyl esters **22** and **23** (263 mg, 0.91 mmol) were placed in a round bottom flask equipped with a reflux condenser and wrapped up in aluminium foil. Second generation Hoveyda–Grubbs catalyst **26** (40 mg, 0.06 mmol, 7.0 mol %) was then quickly introduced to the reaction mixture followed by the fast addition of anhydrous tetrahydrofuran (20 mL). The mixture was then immediately placed in an oil bath pre-heated at 110 °C, and the reaction mixture was heated at reflux under argon until completion as indicated by TLC analysis (24 h). The reaction mixture was cooled down to room temperature, and it was diluted with hexanes (30 mL), which caused the catalyst derivatives to crash out of solution. Filtration of the solid residue followed by concentration of the remaining organic solvent under reduced pressure afforded a crude light brown oil. Note: when dealing with microscale amounts, a better work-up procedure involves the simple evaporation of the solvent under vacuum followed by purification of the crude residue.

The crude oil was purified by flash column chromatography (silica gel, elution gradient 0–10% ethyl acetate in 40–60 petroleum ether) to afford the heterodimers **27** and **28** as a light brown and very sticky clear oil. A second purification by flash column chromatography (silica gel, 100% toluene) was necessary to give the analytically pure heterodimers **27** and **28** (269 mg, 90%) as an inseparable 5:3 mixture of diastereomers.

The same procedure was repeated for the successful cross-coupling of each individual diastereomerically pure esters **22** and **23**.

3.11.2. enantio-N-TAC-iso-ADDA methyl ester, ***27***

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, J=6.8 Hz), 1.23 (3H, d, J=7.3 Hz), 1.62 (3H, d, J=1.2 Hz), 2.56–2.65 (1H, m), 2.68 (1H, dd, J=13.9, 7.4 Hz), 2.79 (1H, dd, J=13.9, 4.6 Hz), 2.88 (1H, qd, J=7.2, 4.5 Hz), 3.20 (1H, m), 3.24 (3H, s), 3.73 (3H, s), 4.57 (1H, app tm, J=7.9 Hz), 5.42 (1H, dd, J=15.3, 7.5 Hz), 5.43 (1H, d, J=10.6 Hz), 6.28 (1H, d, J=15.6 Hz), 7.17–7.29 (5H, m), 7.72 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 13.7, 16.1, 37.7, 38.2, 43.0, 52.1, 55.7,

58.6, 86.8, 92.8, 120.3, 126.0, 128.2, 129.4, 132.2, 137.4, 139.3, 139.7, 160.8, 174.2; $[\alpha]_D^{24}$ +12.4 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max}=3408, 3356, 3029, 2980, 2953, 2935, 2879, 1718, 1509, 1456, 1266, 1200, 822, 739, 702 cm^{-1}; HRMS (ESI) observed $(M+H)^+$ 490.1313, calculated for $C_{23}H_{31}O_4NCl_3$ 490.1313.

3.11.3. enantio-N-TAC-ADDA methyl ester, ***28***

^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J*=6.8 Hz), 1.30 (3H, d, *J*=7.2 Hz), 1.60 (3H, d, *J*=0.9 Hz), 2.55–2.63 (1H, m), 2.67 (1H, dd, *J*=13.9, 7.5 Hz), 2.79 (1H, dd, *J*=13.9, 4.6 Hz), 2.86 (1H, qd, *J*=7.2, 4.0 Hz), 3.16–3.22 (1H, m), 3.23 (3H, s), 3.72 (3H, s), 4.53–4.62 (1H, m), 5.41 (1H, d, *J*=9.5 Hz), 5.44 (1H, dd, *J*=15.8, 6.5 Hz), 6.24 (1H, d, *J*=15.6 Hz), 7.17–7.29 (5H, m), 8.01 (1H, d, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 15.3, 16.1, 36.7, 38.2, 43.3, 52.1, 55.3, 58.7, 86.9, 92.9, 122.9, 126.0, 128.2, 129.4, 132.1, 137.2, 137.6, 139.3, 161.7, 175.9; $[\alpha]_D^{24}$ +11.2 (*c* 1.0, $CHCl_3$).

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