Synthesis of a C-9 to C-18 Building Block of the Phenalamides

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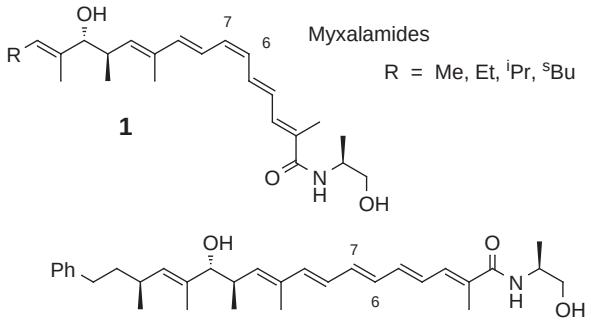
Abstract: In the context of a synthesis of phenalamide A2, the C-9 to C-18 building block **6** was synthesized. The stereogenic centers were generated by alkylation of an Evans oxazolidinone **12** and by a crotylboration reaction using the enantiomerically pure (*E*)-α-chlorocrotylboronate (**4**).

Key words: allylboration reaction, diastereoselectivity, natural products, stereoselective synthesis

The myxalamides (**1**) and the phenalamides (**2**) attracted the attention of medicinal chemists because these compounds are able to reverse the multidrug resistance of cancer cells (Scheme 1). It is their polyenic structure, which poses a challenge to efficient synthesis.



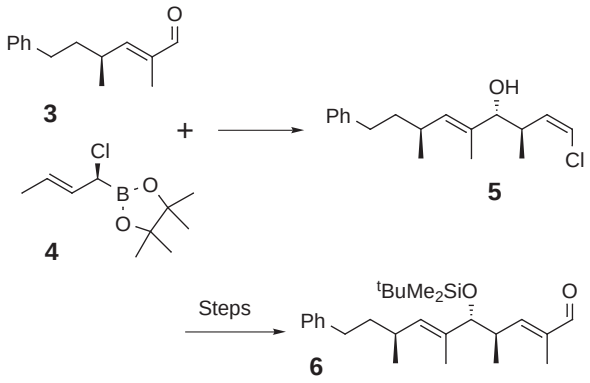
2a 6,7-Z: Phenalamide A_1 , Stipiamide

2b 6,7-E: Phenalamide A_2

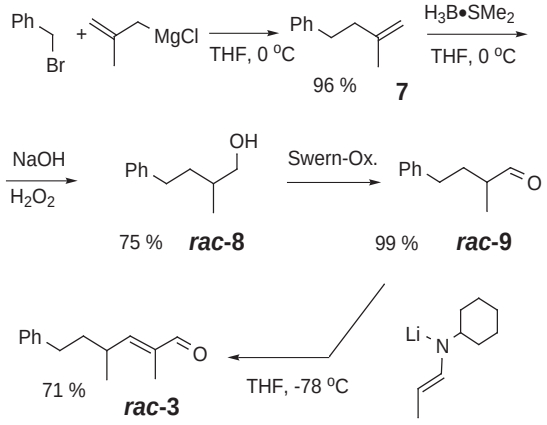
Scheme 1

Pioneering studies in this area resulted in the total synthesis of phenalamide A1 (stipiamide) and congeners by the Andrus group,[1–3] the synthesis of myxalamide A by Heathcock,[4] and our own synthesis of phenalamide A2.[5] A common building block for the synthesis of the phenalamides is the aldehyde **6**.[1,5,6] We describe here our route to generate this aldehyde **6**, using an allylation with the chiral (*E*)-α-chlorocrotylboronate (**4**) as key step to create the stereogenic centers at C-12 and C-13 (phenalamide numbering) (Scheme 2).

For initial screening we needed a good supply of the aldehyde **3** in racemic form. This was secured by the following reaction sequence (Scheme 3).



Scheme 2



Scheme 3

The sequence started with the Grignard coupling of methallylmagnesium chloride with benzyl bromide, which gave the hydrocarbon **7** much more effectively (96%) than the alternative coupling between benzylmagnesium chloride and methallyl bromide (44%). Hydroboration of **7** with borane·dimethylsulfide gave the alcohol **8**[7] in 75% yield. Alcohol **8** was readily oxidized to the aldehyde **9** using the Swern protocol.[8] The sequence was concluded by a Wittig directed aldol condensation.[9] This method is more effective (71%) than the related Corey/Enders (60%) approach.[10] However, the aldehyde *rac*-**3** obtained was always contaminated with minor amounts of the starting aldehyde **9**. While this was not a problem for model studies, it would be unacceptable for the synthesis of phenalamide A2 itself.

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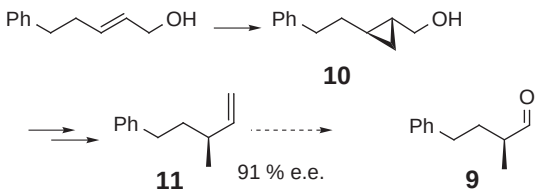
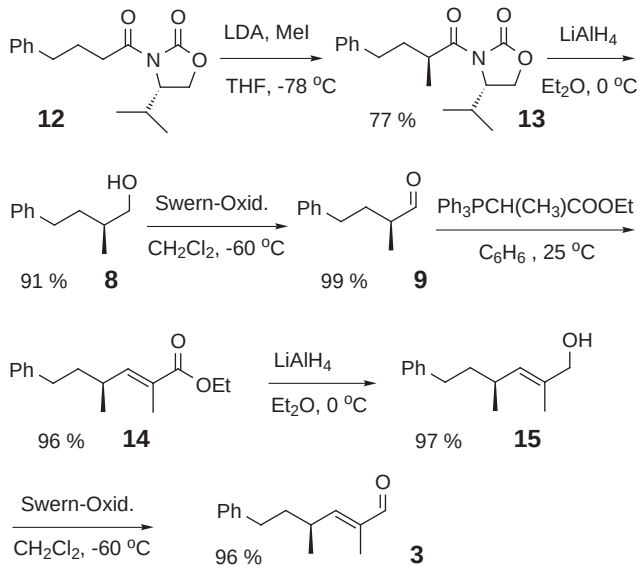
This endeavour required synthesis of the (*S*)-isomer of **9** and its conversion to (*S*)-**3**. After our studies were completed an elegant route to enantiomerically pure **9** was opened via an enantioselective cyclopropanation reaction[11] to **10** followed by transformation to the alkene **11**, a precursor for (*S*)-**9** (Scheme 4).



Scheme 4

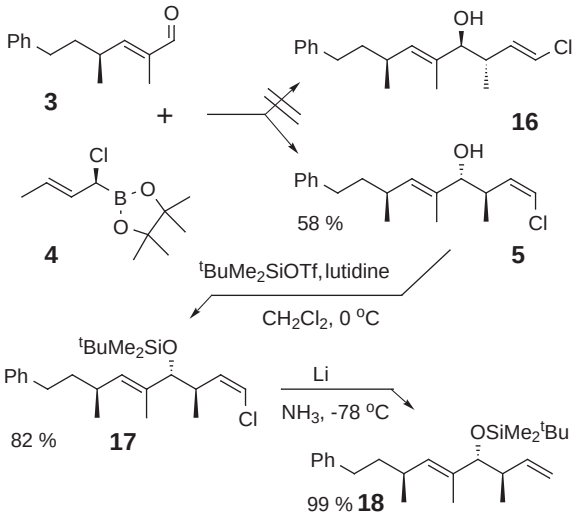
In comparison, the route used by Andrus and similarly by us is more conventional since it is based on the alkylation[12] of the Evans-enolate **12**. This led to the α-methylated compound **13** in 77% yield (Scheme 5).



Scheme 5

Removal of the chiral auxiliary was effected using lithium aluminium hydride to give the alcohol (*S*)-**8** in 91% yield. After oxidation to (*S*)-**9** as before, we used a Wittig reaction to generate ester **14**. This seemingly simple transformation was quite difficult, giving a poor yield of 40% when carried out in THF. Andrus[6] used toluene at 90 °C for the same transformation and obtained 55% of an 8:1 *E*:*Z*-mixture of **14**. We found that the reaction carried out in refluxing CH_2Cl_2 or in benzene at r.t. is higher yielding (93% to 96%) and furnishes product **14** free of the corresponding *Z*-isomer. Subsequent lithium aluminium hydride reduction (97%) and Swern oxidation (96%) routinely gave (*S*)-**3**.

For the chain extension of the aldehyde **3** to generate the next two stereogenic centers, Andrus used Brown's crotylboration[6] reaction with (−)-(ipc)$_2$-(*E*)-crotylborane,[13] which proceeded with 7:1 diastereoselectivity. The minor diastereomer likely resulted from insufficient reagent control of diastereoselectivity.[13] We chose α-chloro-(*E*)-crotylboronate (**4**)[14] hoping for higher reagent control of diastereoselectivity (Scheme 6).[15] The reaction with aldehyde **3** furnished the homoallylic alcohol **5** (53%). Traces of the other diastereomer **16** could easily be separated owing to opposite configuration of the vinyl chloride double bond.[14]

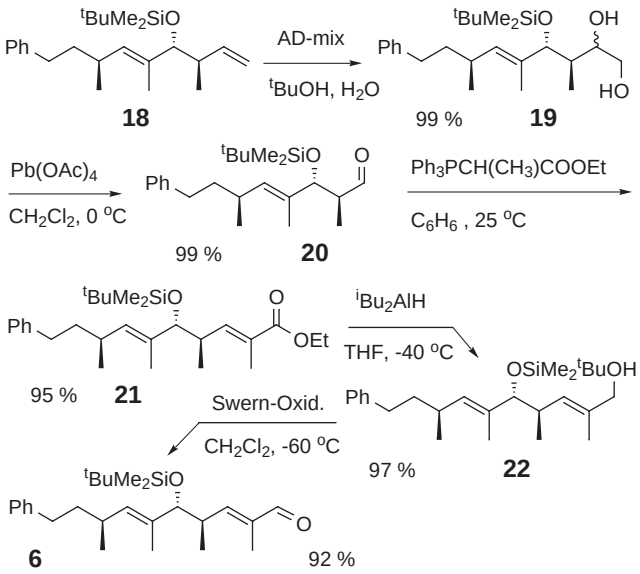


Scheme 6

Silyl-protection to give **17** was easily accomplished (82%). In order to generate the next aldehyde **20** in the reaction sequence, a selective cleavage of the terminal double bond had to be realized. Ozonolytic cleavage of a vinyl chloride is possible,[16] but the reaction conditions are too harsh to expect a differentiation between the two double bonds. Therefore, a reductive dechlorination of **17** to give **18** had to be performed. Fortunately, this step proceeded in essentially quantitative yield, a step which was necessitated due to the use of the α-chloro-(*E*)-crotyl-boronate. In comparison to the study of Andrus (conversion of **14** to **18** in four steps and 57% overall yield) we invested one additional step to reach a higher diastereoselectivity in the chain extension from **3** to **5**, but had to accept a lower overall yield of 44%.

Having secured compound **18,** selective cleavage of the terminal double bond was still a problem. Selectivity could be attained by an OsO_4 mediated dihydroxylation. Thus, reaction of the alkene **18** with potassium osmate and *N*-morpholine oxide followed by periodate cleavage gave 78% of the aldehyde **20** (Scheme 7).

We later turned to the AD-mix dihydroxylation of **18** reported by Andrus,[2] followed by cleavage of the diol **19** with lead tetraacetate to give aldehyde **20**, which was immediately converted to the α,β-unsaturated ester **21**. Wittig olefination of aldehyde **20** was again carried out in benzene at r.t. to give only the (*E*)-product **21**, whereas the reaction conditions used by Andrus (90 °C, toluene) led to

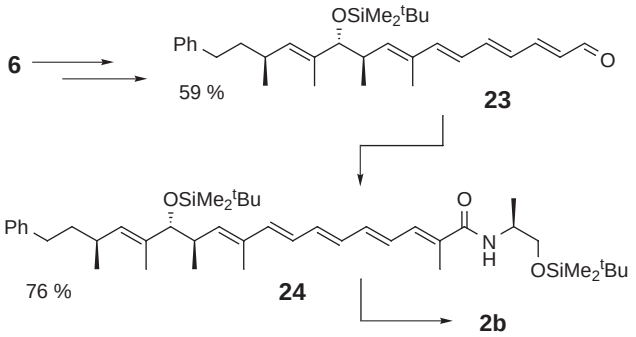


Scheme 7

8:1 *E*:*Z*-mixture. In our hands, the conversion of **18** into **21** could thus be realized with 94% overall yield.

The final steps to the target compound **6** were routine: lithium aluminium hydride reduction (77%) followed by Swern oxidation (92%). After the protocol of Andrus became available, we likewise used DIBAL-H reduction (97%) followed by Ley oxidation (80%) to obtain aldehyde **6** in high yield (Scheme 8).

At this point it should be mentioned that compound **6** was



Scheme 8

successfully converted[5] to the alkapentaenal **23** using the alkatrienal-homologation[17] developed specifically for this project. The aldehyde **23** was then transformed by Wittig olefination to phenalamide A2.

The experimental details of the latter transformations have already been published as supplementary material to ref.[5] All temperatures quoted are uncorrected. ^{1}H, ^{13}C NMR were recorded on a Bruker ARX-200, AC-300, AM-400, and AMX-500. Boiling range of petroleum ether (PE) was 40−60 °C. Flash chromatography was preformed with silica gel Si60, E. Merck KGaA, Darmstadt, 40–63 μm.

2-Methyl-4-phenyl-1-butene (7)

To magnesium turnings (40.4 g, 1.66 mol) in anhyd THF (400 mL) was added 2-methyl-2-propenyl chloride (10 mL) under a nitrogen atmosphere. Further methallyl chloride (116 mL, 1.19 mol in total) was added dropwise (the velocity of the reaction was controlled by cooling the reaction with an ice-bath). After reaction completion, the soln was transferred via canula to a storage vessel, titrated, and was found to be 1.47 M.

BnBr (78 g, 0.45 mol) was added at 0 °C over 5 h via a syringe pump to a soln of the Grignard reagent (1.47 M, 350 mL, 0.5 mol). After heating at reflux for 3 h, the mixture was cooled to 0 °C. Sat. NH_4Cl (200 mL) was added, the layers were separated and the aq layer was extracted with Et_2O (4 × 60 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), concentrated at 20 Torr, and fractionated to give compound **7** (63.0 g, 96%) as a colourless liquid.

Bp 74−76 °C, 12 Torr.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 3 H), 2.22–2.28 (m, 2 H), 2.66–2.71 (m, 2 H), 4.66 (m, 2 H), 7.08–7.23 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 34.3, 39.6, 110.2, 125.8, 128.28, 128.31, 142.2, 145.4

Anal. Calcd for $C_{11}H_{14}$ (146.2): C, 90.35; H, 9.65. Found: C, 90.22; H, 9.76.

2-Methyl-4-phenyl-1-butanol (8)

$BH_3{\cdot}SMe_2$ (10.0 M in DMS, 48.2 mL, 0.48 mol) was added dropwise at 0 °C to a soln of **7** (58.8 g, 0.40 mol) in THF (300 mL). The mixture was stirred for 1 h at 0 °C and then at r.t. for 12 h. After cooling to 0 °C aq NaOH (10%, 250 mL) and aq H_2O_2 (35%, 100 mL) were added dropwise resulting in the formation of a white precipitate. After stirring for 30 h at r.t., the mixture was transferred to a separatory funnel. K_2CO_3 was added to saturation and the mixture was extracted with *tert*-butylmethylether (4 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Distillation of the residue at 0.4 Torr furnished alcohol **8** (49.5 g, 75%) as a colourless liquid.

Bp: 100−105 °C at 0.4 Torr.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.6 Hz, 3 H), 1.31–1.40 (m, 1 H), 1.46 (broad s, 1 H, OH), 1.50–1.73 (m, 2 H), 2.59 (ddd, *J* = 13.7, 9.9, 6.4 Hz, 1 H), 2.71 (ddd, *J* = 13.7, 10.0, 5.5 Hz, 1 H), 3.35 (dd, *J* = 10.6, 6.3 Hz, 1 H), 3.43 (dd, *J* = 10.6, 5.8 Hz, 1 H), 7.06–7.22 (m, 5 H). Cf. the data in ref.[7a]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5, 33.3, 34.9, 35.3, 68.1, 125.7, 128.3, 142.6

2-Methyl-4-phenyl-butanal (9)

A soln of oxalyl chloride (21.8 g, 0. 17 mol) in CH_2Cl_2 (400 mL) was cooled to –78 °C and a soln of DMSO (24.7 mL, 0.35 mol) in CH_2Cl_2 (30 mL) was added dropwise to the oxalyl chloride. After stirring for 10 min, the alcohol **8** (15.7 g, 0.10 mol) in CH_2Cl_2 (100 mL) was added dropwise. The mixture was stirred for further 20 min at –78 °C and Et_3N (62.8 mL, 0.45 mol) was added dropwise resulting in a thick suspension. The suspension was allowed to reach r.t., H_2O (300 mL) was added and the layers separated. The aq layer was extracted with Et_2O (3 × 175 mL). The combined organic layers were washed with HCl (1%, 175 mL), sat. $NaHCO_3$ (175 mL), brine (150 mL), dried ($MgSO_4$) and concentrated. Distillation of the residue furnished aldehyde **9** (13.9 g, 89%) as a clear liquid.

Bp: 54–57 °C/0.4 Torr.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 7.0 Hz, 3 H), 1.57–1.69 (m, 1 H), 1.97–2.09 (m, 1 H), 2.33 (qddd, *J* = 7, 7, 7, 1.7 Hz, 1 H), 2.56–2.67 (m, 2 H), 7.15–7.33 (m, 5 H), 9.58 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 32.0, 32.9, 45.4, 125.6, 128.2, 128.3, 141.2, 204.4.

(4*S*)-3-(4'-Phenyl-butyryl)-4-isopropyl-oxazolidin-2-one (12)

BuLi in hexane (1.43 M, 99.4 mL, 142 mmol) was added dropwise to a soln of (4*S*)-4-isopropyl-oxazolidin-2-one[12] (17.34 g, 135 mmol) in THF (500 mL) at –78 °C. After stirring for 30 min, a soln of 4-phenyl-butyryl chloride[18] (27.19 g, 149 mmol) in THF (150 mL) was added dropwise. The mixture was stirred for 30 min at –78 °C and allowed to reach r.t. over 8 h. Sat. $NaHCO_3$ (1 L) was added, the layers separated and the aq layer was extracted with *tert*-butylmethylether (3 × 100 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated to give **12** (36.4 g, 98%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 2.05 (m, 2 H), 2.41 (sept. d, *J* = 7.0, 3.9 Hz, 1 H), 2.74 (t, *J* = 7.7 Hz, 2 H), 3.02 (m, 2 H), 4.23 (dd, *J* = 9.1, 3.2 Hz, 1 H), 4.28 (t, *J* = 8.6 Hz, 1 H), 4.46 (td, *J* = 7.6, 3.8 Hz, 1 H), 7.24 (m, 3 H), 7.33 (t, *J* = 7.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 18.1, 26.2, 28.5, 35.1, 35.3, 58.5, 63.5, 126.1, 128.5, 128.6, 141.7, 173.1, 183.0.

HRMS: *m/z* calcd for $C_{16}H_{21}NO_3$ (M^+): 275.1521. Found: 275.1509.

(2'*S*,4*S*)-3-[2'-Methyl-4'-phenyl-butyryl]-4-isopropyl-oxazolidin-2-one (13)

BuLi in hexane (1.43 M, 110 mL, 157 mmol) was added dropwise at 0 °C to a soln of diisopropylamine (15.9 g, 157 mmol) in THF (140 mL). The mixture was cooled to –78 °C and a soln of **12** (36.4 g, 132 mmol) in THF (100 mL) was added dropwise. After stirring for 30 min at –78 °C methyl iodide (76.6 g, 540 mmol) was added dropwise and after 6 h stirring at –78 °C, the mixture was allowed to reach r.t. Sat. NH_4Cl (130 mL) was added, the layers separated and the aq layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with HCl (1 M, 200 mL), sat. $NaHCO_3$ (200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with pentane–*tert*-butylmethylether (1:1) furnished **13** (29.4 g, 77%) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 1.25 (d, *J* = 6.9 Hz, 3 H), 1.71 (m, 1 H), 2.12 (m, 1 H), 2.33 (sept,d, *J* = 7.0, 4.0 Hz, 1 H), 2.63 (m, 2 H), 3.81 (sext, *J* = 6.9 Hz, 1 H), 4.16 (dd, *J* = 9.1, 3.2 Hz, 1 H), 4.20 (t, *J* = 8.0 Hz, 1 H), 4.35 (td, *J* = 7.6, 3.8 Hz, 1 H), 7.17 (m, 3 H), 7.27 (t, *J* = 7.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.9, 18.2, 18.5, 28.2, 34.1, 35.1, 37.8, 58.6, 63.4, 126.1, 128.6, 128.7, 142.0, 153.9, 177.0.

Anal Calcd for $C_{11}H_{23}NO_3$ (289.4): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.53; H, 8.03; N, 4 .89.

(2*S*)-2-Methyl-4-phenyl-butanol (8)

A soln of **13** (12.0 g, 41.5 mmol) in Et_2O (90 mL) was added dropwise at 0 °C to a soln of $LiAlH_4$ (4.72 g, 124 mmol) in Et_2O (200 mL). After stirring for 90 min at 0 °C, the mixture was allowed to reach r.t. After reaction completion, the mixture was cooled to 0 °C and EtOAc (20 mL) was added. Hydrolysis was affected by addition of H_2O (5 mL), aq NaOH (15%, 5 mL) and again H_2O (15 mL). The resulting precipitate was filtered and washed with *tert*-butylmethylether (50 mL). The filtrate was concentrated and the residue was purified by flash chromatography with pentane–*tert*-butylmethylether (1:1) to yield **8** (6.21 g, 91%) as a colourless liquid. For spectroscopic data see above.

$[\alpha]^{20}_D$ –20.0 (c, 5.0, $CHCl_3$).

(2*S*)-2-Methyl-4-phenyl-butanal (9)

The alcohol (*S*)-**8** (1.82 g, 11.1 mmol) was oxidized as described above to furnish aldehyde **9** (1.78 g, 99%), which was pure according to TLC and ^{1}H NMR. For the spectroscopic data see above.

(2*E*)-2,4-Dimethyl-6-phenyl-2-hexenal (3)

BuLi (1.51 M in hexane, 6.6 mL, 10.0 mmol) was added dropwise to a soln of diisopropylamine (1.01 g, 10.0 mmol) in anhyd THF (10 mL) at –78 °C. After maintaining the mixture for 40 min at –65 °C, a soln of *N*-cyclohexyl-*N*-propylidene-amine (1.39 g, 10.0 mmol) in THF (10 mL) was added dropwise. After stirring for 35 min, the mixture was cooled to –78 °C, a soln of aldehyde **9** (811 mg, 5.0 mmol) in THF (10mL) was added dropwise, and the mixture was allowed to reach r.t. After stirring for 2 d, a soln of oxalic acid dihydrate (1.25 g) in MeOH (20 mL) was added and the soln was heated to reflux for 2 h. H_2O (1mL) was added and heating was continued for 3 h. Sat. aq NH_4Cl (50 mL) was added resulting in the formation of a white precipitate. The mixture was extracted with *tert*-butylmethylether (3 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane–Et_2O (5:1) furnished a mixture (993 mg) of compound **3** and residual **9** as a colourless liquid corresponding to 715 mg (71% yield) of **3**.

Ethyl (2*E*,4*S*)-2,4-dimethyl-6-phenyl-2-hexenoate (14)

1-Ethoxycarbonylethylidene-triphenylphosphorane (12.0 g, 33 mmol) was added to a soln of (2*S*)-2-methyl-4-phenyl-butanal (**9**) (1.78 g, 11.0 mmol) in benzene (100 mL). The mixture was stirred until reaction completion (ca. 2 d). The soln was concentrated to ca. 50 mL and filtered over silica gel. The filtrate was concentrated and the residue was added into vigorously stirred pentane (300 mL), resulting in the slow precipitation of triphenylphosphine oxide and excess ylide. The mixture was filtered and the filtrate was concentrated. Flash chromatography of the residue with pentane–*tert*-butylmethylether (4:1) furnished compound **14** (2.54 g, 96%) as a colourless oil.

$[\alpha]^{20}_D$ +29.9 (c, 1.37, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.7 Hz, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.66 (m, 2 H), 1.81 (d, *J* = 1.4 Hz, 3 H), 2.57 (m, 3 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 6.59 (dq, *J* = 10.1, 1.4 Hz, 1 H), 7.18 (m, 3 H), 7.26 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.6, 14.3, 20.0, 32.8, 33.7, 38.5, 60.4, 125.8, 126.9, 128.3, 142.1, 147.4, 168.4, cf. the data reported by Andrus[6] (they give an additional methyl signal at 22.2 ppm, which could arise from the *Z*-isomer).

Anal. Calcd for $C_{16}H_{22}O_2$ (246.3): C, 78.01; H, 9.00. Found: C, 77.90; H, 9.16.

(2*E*,4*S*)-2,4-Dimethyl-6-phenyl-2-hexen-ol (15)

A soln of compound **14** (4.58 g, 18.6 mmol) in Et_2O (20 mL) was added dropwise at 0 °C into a suspension of $LiAlH_4$ (1.42 g, 37.5 mmol) in Et_2O (40 mL). After stirring for 15 min, TLC indicated the complete consumption of the starting material. EtOAc (10 mL), H_2O (2.5 mL), aq NaOH (15%, 2.5 mL), and again H_2O (7.5 mL) were added sequentially. The resulting precipitate was filtered and the filtrate was concentrated to give the alcohol **15** (3.69 g, 97%) as a colourless oil. The material was pure according to TLC and ^{1}H NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3 H), 1.35 (broad s, 1 H), 1.53 (m, 1 H), 1.56 (d, *J* = 1.3 Hz, 3 H), 2.34 (m, 1 H), 2.50 (td, *J* = 8.0, 2.3 Hz, 2 H), 3.93 (s, 2 H), 5.14 (dq, *J* = 9.6, 1.3 Hz, 1 H), 7.09 (m, 3 H), 7.17 (m, 2 H); signal for OH is missing.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 21.0, 31.8, 34.8, 39.2, 69.0, 125.6, 128.2, 128.3, 132.3, 133.7, 142.8.

For analysis, a small sample was subjected to flash chromatography with PE–Et_2O (4:1).

Anal. Calcd for $C_{14}H_{20}O$ (204.3): C, 82.03; H, 9.98. Found: C, 82.03; H, 10.03.

(2*E*,4*S*)-2,4-Dimethyl-6-phenyl-2-hexenal (3)

A soln of DMSO(2.07 g, 26.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise at –60 °C into a soln of oxalyl chloride (1.70 g, 13.4 mmol) in CH_2Cl_2 (30 mL). After stirring for 2 min, a soln of **15** (2.45 g, 12.0 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for an additional 15 min at –60 °C, Et_3N (6.07 g, 60 mmol) was added. The mixture was stirred for 5 min at –60 °C and then allowed to reach r.t. H_2O (20 mL) was added, the layers separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with aq HCl (2 M, 20 mL), sat. aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to furnish aldehyde **3** (3.33 g, 96%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.6 Hz, 3 H), 1.74 (d, *J* = 1.1 Hz, 3 H), 1.83 (m, 2 H), 2.62 (td, *J* = 7.9, 2.1 Hz, 2 H), 2.75 (m, 1 H), 6.32 (dq, *J* = 9.9, 1.5 Hz, 1 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.22 (d, *J* = 7.3 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 9.44 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.3, 19.8, 33.0, 33.6, 38.2, 125.9, 128.2, 128.3, 138.3, 141.6, 159.8, 195.4.

Anal. Calcd for $C_{14}H_{18}O$ (202.3): C, 83.12; H, 8.97. Found: C, 83.34; H, 9.10.

(1*Z*,2*R*,4*R*,5*E*,7*S*)-1-Chloro-3,5,7-trimethyl-9-phenyl-nona-1,5-dien-4-ol (5)

A soln of **3** (728 mg, 3.6 mmol) in PE (6 mL) was added to a soln of 2-([1'*S*,2'*E*]-1'-chloro-but-2'-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**4**) (1.125 g, 5.2 mmol) in PE (25 mL). After 4 d at r.t., the mixture was poured into sat. $NaHCO_3$ (10 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue furnished **5** (555 mg, 53%) as a colourless oil.

$[\alpha]^{20}_D$ –16.5 (c, 1.20, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 1.47 (m, 2 H), 1.56 (d, *J* = 1.3 Hz, 3 H), 1.59 (m, 1 H), 2.41 (m, 1 H), 2.48 (m, 2 H), 2.93 (sext, d, *J* = 7.5, 1.2 Hz, 1 H), 3.71 (d, *J* = 8.1 Hz, 1 H), 5.14 (d, *J* = 9.7 Hz, 1 H), 5.65 (dd, *J* = 9.4, 7.1 Hz, 1 H), 6.06 (dd, *J* = 7.1, 0.7 Hz, 1 H), 7.09 (m, 3 H), 7.21 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 16.7, 20.9, 31.9, 34.0, 36.0, 39.3, 81.8, 119.1, 125.6, 128.26, 128.29, 134.2, 134.3, 134.8, 142.7.

Anal. Calcd for $C_{18}H_{25}ClO$ (292.9): C, 73.83; H, 8.61. Found: C, 73.74; H, 8.71.

(1*Z*,3*R*,4*R*,5*E*,7*S*)-1-Chloro-4-(*tert*-butyldimethylsilyloxy)-3,5,7-trimethyl-9-phenyl-1,5-nonadiene (17)

tert-Butyl-dimethylsilyl triflate (1.41 g, 5.33 mmol) was added dropwise at r.t. to a soln of alcohol **5** (1.04 g, 3.55 mmol) and 2,5-lutidine (0.76 g, 7.1 mmol) in CH_2Cl_2 (4 mL). Additional *tert*-butyl-dimethyl-silyl triflate (0.5 mL) and 2,6-lutidine (0.5 mL) were added after 3 h at r.t. to bring the reaction to completion. After stirring for 12 h, MeOH (15 mL) was added and stirring continued for a further 20 min. the mixture was partitioned between *tert*-butylmethyl-ether (20 mL) and sat. aq NH_4Cl (20 mL). The layers were separated and the aq layer was extracted with *tert*-butylmethylether (4 × 25 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with PE furnished **17** (1.18 g, 82%) as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 1.53 (s, 3 H), 1.61 (m, 2 H), 2.38 (m, 1 H), 2.52 (quint, d, *J* = 10.0, 6.4 Hz, 2 H), 2.92 (sext, d, *J* = 6.8, 2.4 Hz, 1 H), 3.75 (d, *J* = 6.5 Hz, 1 H), 5.10 (d, *J* = 9.5 Hz, 1 H), 5.64 (dd, *J* = 9.4, 7.1 Hz, 1 H), 5.95 (d, *J* = 7.0 Hz, 1 H), 7.13 (m, 3 H), 7.22 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.3, 12.4, 17.1, 18.2, 21.1, 25.8, 31.7, 33.8, 36.9, 39.3, 81.2, 117.4, 125.5, 128.2, 128.3, 132.6, 134.7, 135.1, 143.0.

Anal. Calcd for $C_{24}H_{39}ClOSi$ (407.1): C, 70.81; H, 9.66. Found: C, 70.79; H, 9.60.

(3*R*,4*R*,5*E*,7*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,5,7-trimethyl-9-phenyl-1,5-nonadiene (18)

A soln of **17** (470 mg, 1.15 mmol) in THF (5 mL) was cooled to –78 °C and gaseous NH_3 was introduced until the volume of the liquid increased by ca. 20 mL. Lithium-powder (ca. 100 mg) was added and the resulting blue soln was stirred for 3 h at –78 °C. Solid NH_4Cl was added in portions until the blue colour faded. The solvents were allowed to evaporate overnight and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to furnish **18** (430 mg, 100%), which was pure according to TLC and ^{1}H NMR.

^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 1.48 (m, 2 H), 1.53 (s, 3 H), 2.38 (m, 1 H), 2.52 (quint. d, *J* = 10.0, 6.4 Hz, 2 H), 2.92 (sext.d, *J* = 6.8, 2.4 Hz, 1 H), 3.75 (d, *J* = 6.5 Hz, 1 H), 4.90–5.10 (m, 2 H), 5.12 (m, 1 H), 5.85 (m, 1 H), 7.13 (m, 3 H), 7.22 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.9, –4.4, 11.4, 16.6, 18.3, 20.8, 25.9, 31.8, 34.1, 39.6, 42.0, 83.5, 113.6, 125.6, 128.2, 128.3, 133.7, 135.5, 142.3, 142.8.

For analysis, a small sample was subjected to flash chromatography with PE.

Anal. Calcd for $C_{24}H_{40}OSi$ (372.4): C, 77.35; H, 10.82. Found: C, 77.25; H, 10.85.

(2*RS*,3*R*,4*R*,5*E*,7*S*)-4-(*tert*-Butyldimethylsilyloxy)-1,2-dihydroxy-3,5,7-trimethyl-9-phenyl-5-nonene (19)

A soln of **18** (430 mg, 1.15 mmol) in *t*-BuOH (4 mL) was added to a mixture of potassium osmate(VI)dihydrate (5 mg, 0.01 mmol), hydroquinine-(1,4-phthalazine-diyl-diether) (46 mg, 0.06 mmol), potassium hexacyanoferrate (III) (1.16 g, 3.5 mmol), K_2CO_3 (534 mg, 3.86 mmol), H_2O (11 mL), and *t*-BuOH (7 mL). After stirring for 3.5 h, the reaction was terminated by addition of Na_2SO_3 (850 mg, 6.7 mmol). The layers were separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give **19** (468 mg, 99%) as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.00 (s, 3 H), 0.54 (d, *J* = 7.0 Hz, 3 H), 0.77 (s, 9 H), 0.81 (d, *J* = 6.9 Hz, 3 H), 1.39 (m, 1 H), 1.43 (d, *J* = 1.2 Hz, 3 H), 1.50 (m, 2 H), 1.71 (m, 1 H), 2.21–2.32 (m, 1 H), 2.45 (m, 2 H), 3.33–3.60 (m, 3 H), 3.75 (d, *J* = 9.2 Hz, 1 H), 4.49 (s, 1 H), 5.04 (d, *J* = 9.1 Hz, 1 H), 7.02 (m, 3 H), 7.13 (m, 2 H).

For analysis, a sample was purified by flash chromatography with PE–*tert*-butylmethylether (1:2).

Anal Calcd for $C_{24}H_{42}O_3Si$ (406.7.): C, 63.52; H, 11.33. Found: C, 63.30; H, 11.22

(2*S*,3*R*,4*E*,6*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyl-8-phenyl-4-octanal (20)

Na_2CO_3 (1.22 g, 11.5 mmol) and lead (IV)-acetate (510 mg, 1.15 mmol) were added sequentially into a soln of **19** (468 mg, 1.15

mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred for 2 h. When reaction was complete (TLC), the mixture was filtered over Kieselguhr and the filtrate was concentrated to give the crude aldehyde **20**, which was used in the next step without purification.

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2, –4.2, 11.1, 11.2, 18.1, 20.5, 25.7, 31.9, 33.9, 39.3, 50.0, 80.8, 125.7, 128.28, 128.31, 133.7, 135.4, 142.6, 205.2.

A sample was purified by flash chromatography with PE–ether (30:1).

Anal Calcd. for $C_{23}H_{38}O_2Si$ (374.6): C, 73.74; H, 10.22. Found: C, 73.63; H, 10.18.

Ethyl (2*E*,4*R*,5*R*,6*E*,8*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6,8-tetramethyl-10-phenyl-2,6-decadienoate (21)

Ethoxycarbonyl-ethylidene-triphenyl-phosphorane (1.15 g, 3.16 mmol) was added to a soln of **20** (395 mg, 1.05 mmol) in benzene (20 mL). After stirring for 3 d at r.t., the soln was concentrated and the residue was introduced into pentane (50 mL) under vigorous stirring. This resulted in the precipitation of triphenylphosphine oxide and residual ylide. The mixture was filtered and the filtrate was concentrated. Flash chromatography of the residue with pentane–*tert*-butylmethylether (10:1) furnished **21** (458 mg, 95%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.86 (s, 9 H), 0.92 (s, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.58 (s, 3 H), 1.62–1.69 (m, 2 H), 1.86 (s, 3 H), 2.43 (sept, *J* = 6.2 Hz, 1 H), 2.50–2.56 (m, 1 H), 2.60–2.70 (m, 2 H), 3.78 (d, *J* = 7.7 Hz, 1 H), 4.17 (m, 2 H), 5.17 (d, *J* = 9.6 Hz, 1 H), 6.66 (d, *J* = 10.2 Hz, 1 H), 7.15–7.19 (m, 3 H), 7.26–7.29 (m, 2 H); signal for OH is missing.

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.0, –4.5, 11.4, 12.6, 14.3, 16.6, 18.1, 21.1, 25.7, 31.8, 33.9, 38.1, 39.3, 60.2, 82.8, 125.6, 127.3, 128.2, 128.3, 134.0, 134.9, 142.8, 146.0, 168.3

Cf. the data reported by Andrus[6] in which one methyl signal is missing, there is an additional signal at 38.6 ppm.

Anal Calcd. for $C_{28}H_{46}O_3Si$ (458.8): C, 73.31; H, 10.11. Found: C, 73.46; H, 10.22.

(2*E*,4*R*,5*R*,6*E*,8*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6,8-tetramethyl-10-phenyl-2,6-decadienol (22)

A soln of DIBAL-H (1.0 M, 0.52 mL) in PE was added at –40 °C slowly into a soln of compound **21** (80 mg, 174 μmol) in THF (2 mL). After stirring for 1 h at –40 °C MeOH (1 mL) was added and the soln was allowed to reach r.t. Sat. aq potassium sodium tartrate (2 mL) was added, the layers separated and the aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL) dried ($MgSO_4$) and concentrated. Flash chromatography of the residue with pentane–*tert*-butylmethylether (10:1) furnished **22** (70 mg, 97%) as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.12 (s, 3 H); –0.09 (s, 3 H), 0.75 (d, *J* = 5.8 Hz, 3 H), 0.77 (s, 9 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 1.36–1.54 (m, 2 H), 1.49 (d, *J* = 1.0 Hz, 3 H), 1.60 (d, *J* = 1.0 Hz, 3 H), 2.29–2.42 (m, 2 H), 2.42–2.59 (m, 2 H), 3.59 (d, *J* = 8.0 Hz, 1 H), 3.91 (s, 2 H), 5.01 (d, *J* = 9.8 Hz, 1 H), 5.16 (d, *J* = 9.8 Hz, 1 H), 7.05–7.10 (m, 3 H), 7.15–7.22 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.0, –4.5, 11.3, 14.1, 17.6, 18.1, 20.7, 25.7, 31.8, 34.0, 36.5, 39.5, 69.2, 83.6, 125.6, 128.2, 128.3, 130.5, 133.7, 134.2, 135.4, 142.8.

Anal. Calcd for $C_{26}H_{44}O_2Si$ (416.3): C, 74.94; H, 10.64. Found: C, 74.80; H, 10.68.

(2*E*,4*R*,5*R*,6*E*,8*S*)-5-(*tert*-Butyldimethylsilyloxy)-10-phenyl-2,4,6,8-tetramethyl-2,6-decadienal (6)

The alcohol **22** (138 mg, 0.33 mmol) was oxidized as described above for **3**. Flash chromatography of the crude product with PE–*tert*-butylmethylether (20:1) furnished the aldehyde **6** (126 mg, 92%) as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.08 (s, 3 H), –0.04 (s, 3 H), 0.76 (s, 9 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.44–1.65 (m, 2 H), 1.50 (d, *J* = 1.3 Hz, 3 H), 1.69 (d, *J* = 1.3 Hz, 3 H), 2.42–2.50 (m, 3 H), 2.74–2.90 (m, 1 H), 3.76 (d, *J* = 7.6 Hz, 1 H), 5.10 (d, *J* = 9.5 Hz, 1 H), 6.29 (dd, *J* = 10.0, 1.3 Hz, 1 H), 7.13 (m, 5 H), 9.33 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.3, –4.7, 9.3, 11.2, 16.4, 17.8, 20.4, 25.4, 31.6, 33.8, 37.9, 39.1, 82.6, 125.4, 128.0, 134.3, 138.8, 142.3, 158.2, 195.1.

Anal. Calcd for $C_{26}H_{42}O_2Si$ (414.7): C, 75.30; H, 10.21. Found: C, 75.21; H, 10.14.

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