Synthesis of the C1–C16 fragment of ionomycin using a neutral (η^3-allyl)iron complex

John P. Cooksey, Philip J. Kocienski,* Ying-fa Li, Stefan Schunk and Thomas N. Snaddon

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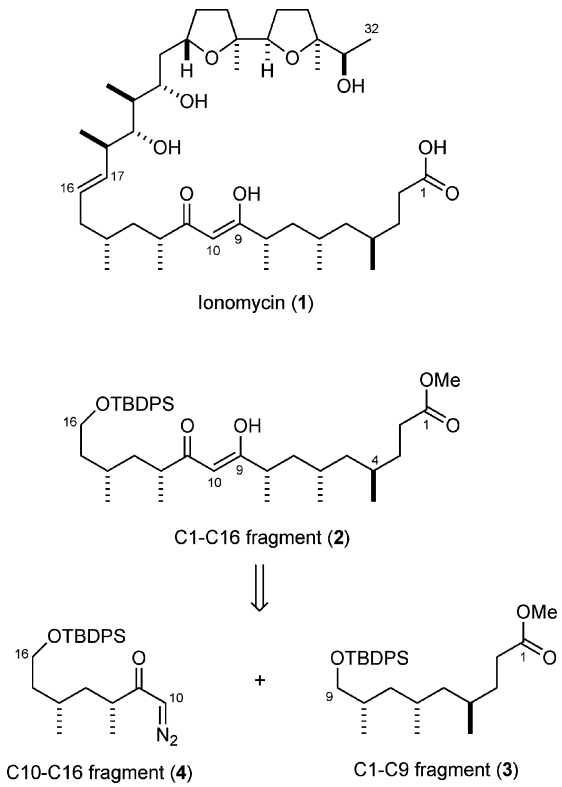
Key steps in the synthesis of the C1–C16 polyketide fragment of ionomycin were the nucleophilic addition of an organocuprate to a neutral (η^3-allyl)iron complex and the construction of a β-diketone moiety by the Rh-catalysed rearrangement of an α-diazo-β-hydroxyketone.

Introduction

Ionomycin (**1**, Scheme 1) is a doubly charged ionophore antibiotic that forms neutral hexacoordinate complexes with calcium and other divalent cations owing to the presence of a carboxylate ion at C1 and an unusual β-diketone at C9 and C11.[1,2] Total syntheses of ionomycin from the groups of Evans,[3] Hanessian[4] and Lautens[5] have been described as well as syntheses of various fragments.[6–17] We now report a synthesis of the C1–C16 fragment **2** which features the use of functionalised planar chiral *neutral* η^3-allyliron complex to install the carboxyl terminus and control the stereochemistry at C4 in a single operation. Such complexes have not been used previously in natural product synthesis.

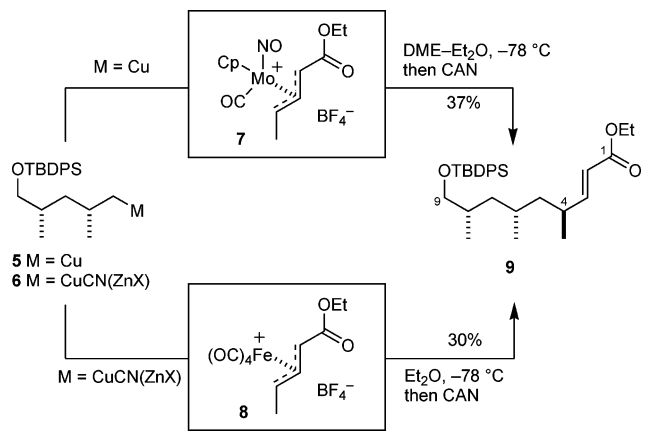


Scheme 1

In the following account we first describe the synthesis of the C1–C9 fragment **3**, then the synthesis of the C10–C16 fragment **4** and finally their union *via* the Pellicciari protocol to generate the β-diketone moiety.

Synthesis of the C1–C9 fragment 3

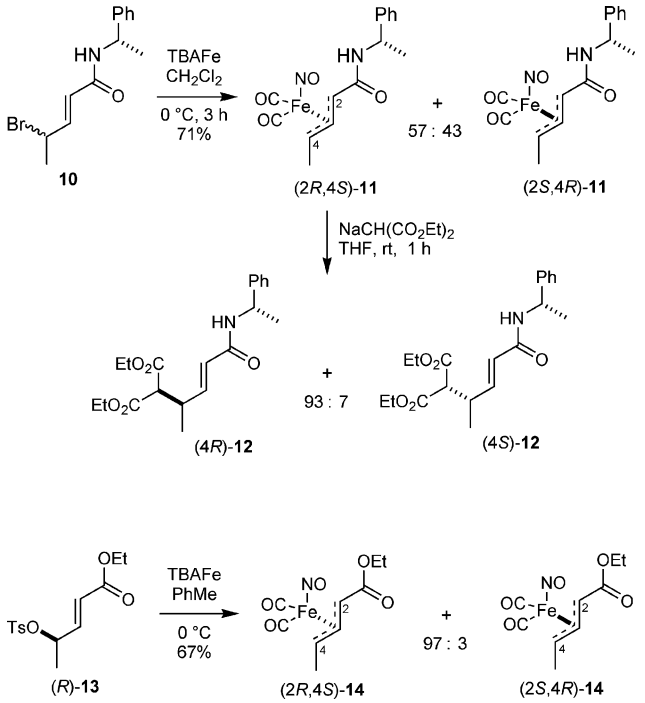
We recently reported two syntheses of the C1–C9 fragment **9**, a precursor to **3**, in which the key step was the addition of alkylmetal reagents to planar chiral *cationic* (η^3-allyl)metal complexes (Scheme 2).[18] The first approach entailed the addition of organocopper(I) reagent **5** to the (η^3-allyl)molybdenum complex **7**[19] to give the adduct **9** in 37% yield. In the second approach, the zinc cuprate **6** added to the (η^3-allyl)iron complex **8**[20] to give the adduct **9** in 30% yield. In both cases nucleophilic attack occurred regioselectively at C4 *anti* to the metal in accord with precedent[19–22] but variations in time, temperature, solvent and metal failed to improve the mediocre yields.[23]



Scheme 2

The one parameter we neglected in the previous optimisation study was the reactivity of the (η^3-allyl)metal complex and to that end we examined functionalised *neutral* (η^3-allyl)Fe(CO)$_2$NO complexes as electrophiles. Nakanishi and co-workers had previously made three key observations that were pertinent to our study (Scheme 3). Firstly, the diastereosiomeric mixture of allylic bromides **10** reacted with tetrabutylammonium tricarbonylnitrosylferrate (TBAFe) to give a chromatographically separable mixture of diastereoisomeric complexes (2*R*,4*S*)-**11** and

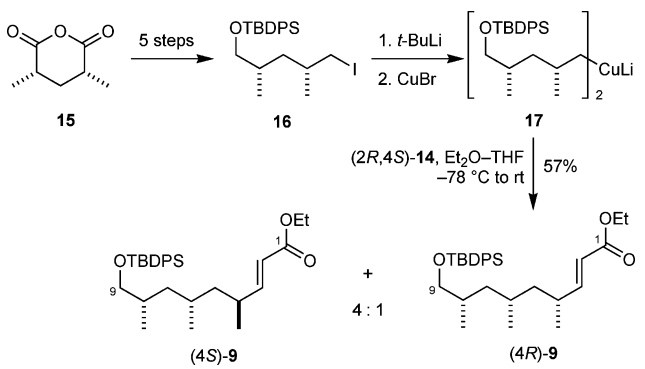
School of Chemistry, Leeds University, Leeds, UK LS2 9JT



Scheme 3

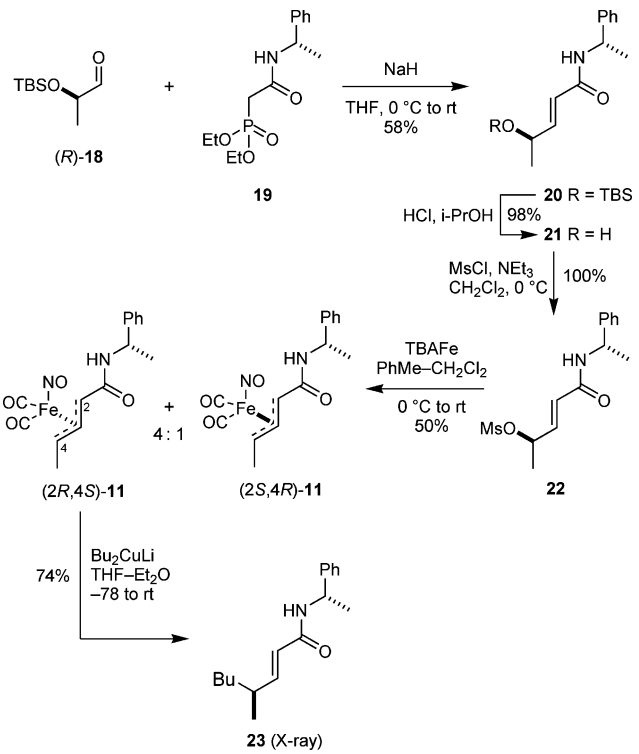
(2*S*,4*R*)-**11** and the absolute configuration of the complex (2*R*,4*S*)-**11** was secured by X-ray crystallography.[24] Secondly, soft carbon nucleophiles such as malonates reacted with complex (2*R*,4*S*)-**11** regioselectively at C4 *anti* to the iron.[25] Thirdly, the scalemic (*S*)-allylic tosylate **13** reacted with TBAFe under mild conditions to give the (η^3-allyl)iron complex (2*R*,4*S*)-**14** with clean inversion of configuration.[26] Taken together these observations suggested that the neutral (η^3-allyl)iron complexes could offer a convenient and readily accessible alternative to the cationic complexes shown in Scheme 2 provided the complexes reacted with suitable alkylmetal reagents.

The requisite alkylmetal reagent was prepared as shown in Scheme 4. The readily available *meso*-2,4-dimethylglutaric anhydride[27,28] was converted to the scalemic iodoalkane **16** in 5 easy, scalable steps. Halogen–metal exchange[29,30] afforded an organolithium reagent that was transmetallated to the organocopper(I) reagent **5** but it failed to react with (2*R*,4*S*)-**14**. However, the corresponding organocuprate **17** added to (2*R*,4*S*)-**14** to give an inseparable mixture of (4*S*)-**9** and (4*R*)-**9** (dr = 4 : 1) in 57% yield after oxidative demetallation. The disappointing dr suggested that either (a) the formation of (2*R*,4*S*)-**14** by reaction of enantiopure (*R*)-tosylate **13** with TBAFe did not proceed with clean inversion or (b) the reaction of the cuprate **17** with enantiopure (2*R*,4*S*)-**14** did not proceed with clean attack *anti* to the metal. Unfortunately we were unable to distinguish between these two prognoses because Nakanishi never disclosed the $[\alpha]_D$ of tosylate **13** and the assay of optical purity of **14** based on the chiral shift reagent $Eu(hfc)_3$[26] was precluded by extreme line broadening.



Scheme 4

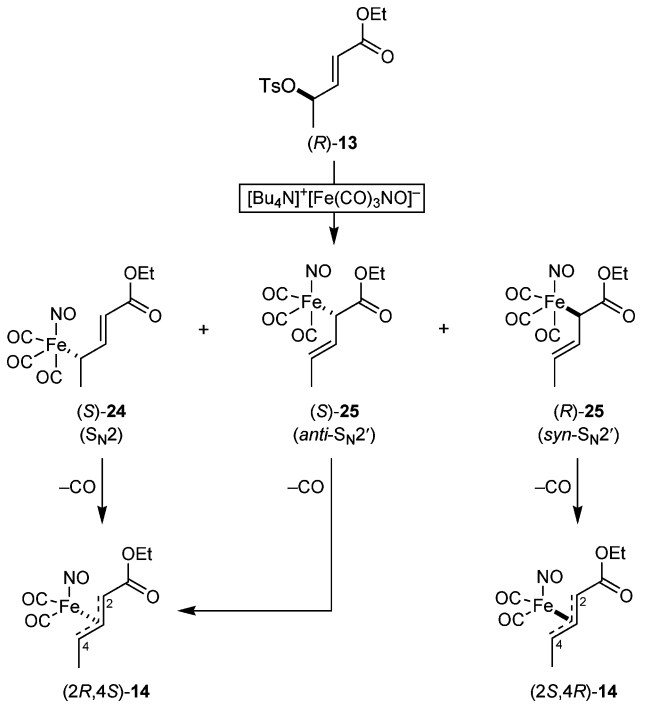
In order to address the stereochemical issues outlined above, we required an (η^3-allyl)iron complex whose stereochemical integrity was assured by an internal reference; therefore, we prepared (2*R*,4*S*)-**11** as shown in Scheme 5. A Horner–Wadsworth–Emmons reaction of the aldehyde (*R*)-**18** with the phosphonate **19** gave the enamide **20** in 58% yield. After cleavage of the TBS ether group, the alcohol **21** was activated as its mesylate ester **22** because preparation of the corresponding tosylate using Ts_2O and DMAP was slow and messy. By contrast the mesylate formed quickly with MsCl and triethylamine and it was more stable. Reaction of mesylate **22** with TBAFe in an 8 : 1 mixture of toluene and dichloromethane at 0 °C gave diastereoisomeric (η^3-allyl)iron complexes **11** in 50% yield. The dr (4 : 1) was ascertained by integration of the C2H signals in the ^{1}H NMR spectrum of the mixture (see the experimental data).[24] The red, air-sensitive complexes **11** were separable with difficulty by column chromatography but the major diastereoisomer was more easily obtained by crystallisation from pentane. Reaction of pure (2*R*,4*S*)-**11** with lithium dibutylcuprate gave a 74% yield of a single adduct **23** whose structure and stereochemistry was determined by X-ray crystallography. Thus the reaction of a carbonyl-functionalised neutral (η^3-allyl)iron complex with organocuprates appears to



Scheme 5

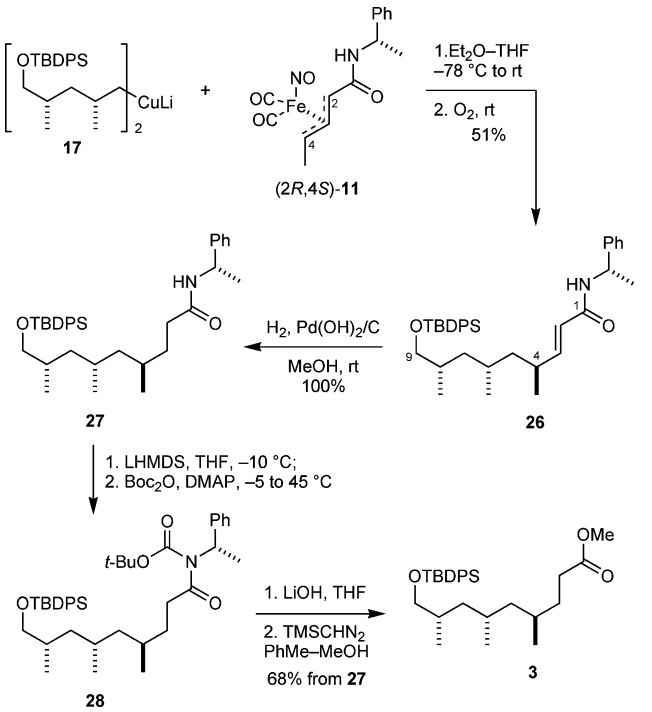
be both highly regioselective and stereospecific with nucleophilic attack occurring *anti* to the metal.

The foregoing experiments indicate that the formation of diastereoisomers (4*S*)- and (4*R*)-**9** from the reaction depicted in Scheme 4 was due to reaction of cuprate **17** with a 4 : 1 mixture of (2*R*,4*S*)-**14** and (2*S*,4*R*)-**14**, the mixture being generated during the reaction of TBAFe with tosylate (*R*)-**13** (Scheme 6). The stereochemistry can be rationalised in terms of the competition between the S_N2 and S_N2' pathways (*syn* and *anti*) leading to the η^1-allyl intermediates (*S*)-**24**, (*S*)-**25** and (*R*)-**25** which expel CO to form the enantiomeric (η^3-allyl)iron complexes **14**.[31] Precedent from the Nakanishi group[26] indicated that in nonpolar solvents such as toluene, (2*R*,4*S*)-**14** should have predominated (er = 97 : 3) whereas our results (er = 4 : 1) are less impressive.



Scheme 6

Proof that neutral (η^3-allyl)iron complexes react with organocuprates efficiently and with high *anti* stereoselectivity as detailed above paved the way for a satisfactory conclusion to the synthesis of the C1–C9 fragment **3** (Scheme 7). Reaction of cuprate **17** (2 equiv.) with (2*R*,4*S*)-**11** in Et_2O–THF at −78 °C followed by oxidative demetallation gave the adduct **26** as a single diastereoisomer in 51% yield. Hydrogenation of the enamide **26** gave the saturated amide **27** in quantitative yield but hydrolysis of the secondary amide was problematic. It was inert towards *N*-nitrosation thereby precluding cleavage *via* the *N*-nitrosamide using the procedure of Mori.[32] Base hydrolysis of the amide using 5 M KOH in MeOH at reflux for 2 d resulted in decomposition of the starting material. A 3-step procedure of Grieco[33] was successful. Formation of the *N*-Boc derivative **28** followed by base hydrolysis using 1 M LiOH and methylation of the resulting acid using trimethylsilyldiazomethane gave **3** in 68% yield from **27**. The structure and stereochemistry of **3** was proved by comparison of the ^1H and ^{13}C NMR spectra (500 and 125 MHz, respectively) with

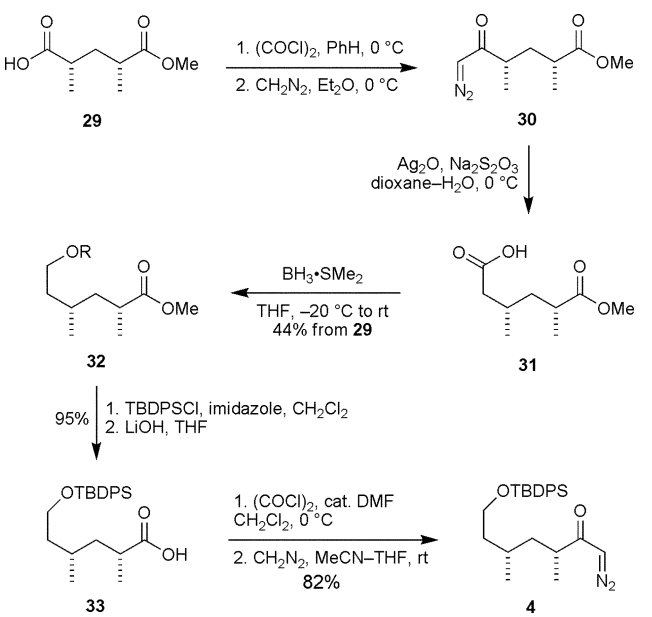


Scheme 7

an authentic sample prepared by a stereochemically unambiguous route.[18]

Synthesis of the C10–C16 fragment 4

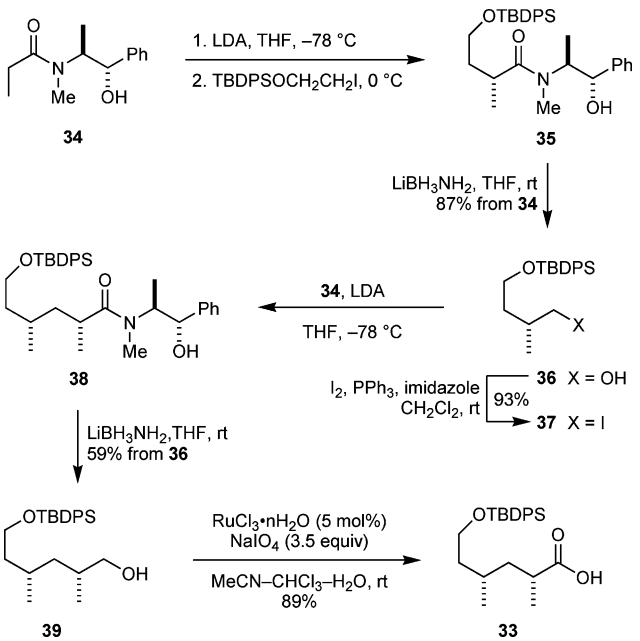
Three syntheses of the C10–C16 fragment were accomplished based on (1) a classical resolution, (2) the use of a chiral auxiliary and (3) a catalytic asymmetric process. The first route (Scheme 8) began with methanolysis of *meso*-2,4-dimethylglutaric anhydride (**15**) followed by resolution of the resultant carboxylic acid with (+)-α-methylbenzylamine.[34,35] The scalemic acid **29** was converted



Scheme 8

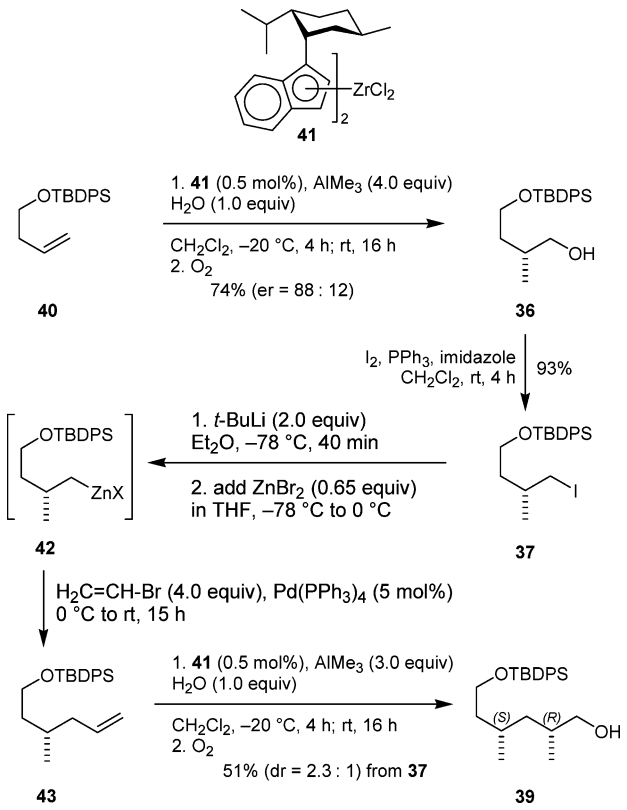
to the α-diazoketone **30** which underwent a Wolff rearrangement on treatment with silver(I) oxide at 0 °C to give the carboxylic acid **31**. Selective reduction of the carboxylic acid with borane dimethylsulfane complex generated the alcohol **32** (44% overall yield from **29**) whereupon four simple transformations were used to obtain the target α-diazoketone **4**. The first route benefits from easy scalability for all steps, except the Wolff rearrangement, and the low cost of the reagents.

In the second route (Scheme 9) both stereogenic centres were generated by sequential alkylation of the lithium enolate derived from (1*S*,2*S*)-(+)-pseudoephedrine propionamide (**35**) according to the procedure of Myers.[36–38] Both alkylation reactions proceeded with high diastereoselectivity (dr = 98 : 2) and gave the alcohol **39** in 48% overall yield. Oxidation of **38** by the procedure of Sharpless and co-workers[39] gave carboxylic acid **33** which is an intermediate in route 1 described above. Route 2 is short and highly stereoselective but (1*S*,2*S*)-(+)-pseudoephedrine propionamide is expensive.



Scheme 9

The third and final route (Scheme 10) is in principle the most attractive because it exploits the Negishi–Kondakov zirconium-catalysed asymmetric carboalumination (ZACA) of terminal alkenes[40,41] to create the two stereogenic centres. The reaction is a rare example of an asymmetric catalytic carbometallation process and its prowess has been amply demonstrated in syntheses of polypropionates[17,42–45] and terpenoids.[46,47] We began with the known[48] methylalumination of the alkene **40** catalysed by 0.5 mol% of bis[(−)-1-neomenthylindenyl)zirconium dichloride (**41**).[49] After oxidation of the intermediate alane, the alcohol **36** was obtained in 74% yield and the Mosher ester revealed an er = 88 : 12. Attempts to displace the tosylate derived from **36** using vinylmagnesium bromide and dilithium tetrachlorocuprate failed but the corresponding iodoalkane **37** reacted slowly (44 h) at r.t. in the presence of one equivalent of dilithium tetrachlorocuprate to give the desired alkene **43** in <40% yield. A faster and more efficient route entailed a Negishi coupling[43] of the organozinc



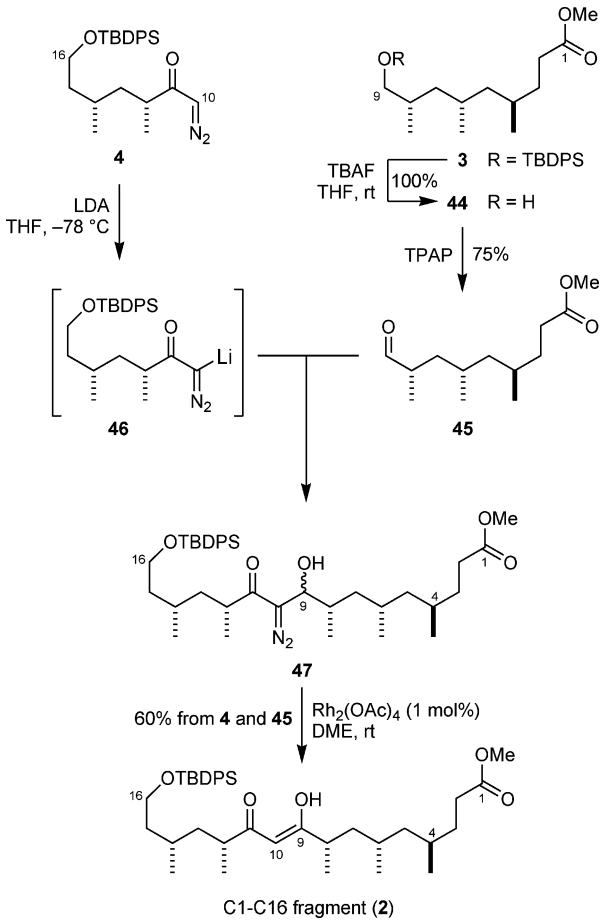
Scheme 10

derivative **42** with vinyl bromide in the presence of 5 mol% of Pd(0) to give the alkene **43** contaminated by the TBDPS ether of 3-methylbutanol (*ca.* 10 mol%). This mixture underwent a second ZACA reaction to give a diastereoisomeric mixture of alcohols (dr = 2.3 : 1) in 51% overall yield from **37**. Although the desired (2*R*,4*S*)-diastereoisomer **39** was the major product, it was difficult to separate from its (2*S*,4*S*)-diastereoisomer and so further optimisation of the ZACA route was abandoned.

Union of fragments 3 and 4 to give the C1–C16 fragment 2

In their total syntheses of ionomycin, Evans,[3] Hanessian[4] and Lautens[5] generated the β-diketone moiety spanning C9–C11 by consecutive aldol and oxidation reactions. We exploited a protocol devised by Pellicciari and co-workers[50] whereby LDA was added to a mixture of aldehyde **44** and α-diazoketone **4** at −78 °C (Scheme 11). The metallated α-diazoketone **46**, generated *in situ*, added to the aldehyde to form the β-hydroxy-α-diazoketone **47** which was then treated with $Rh_2(OAc)_4$ (1 mol%). The resultant carbene inserted into the adjacent C–H bond to generate the C1–C16 fragment **2** in 60% overall yield as a single diastereoisomer.

In conclusion, we have shown that functionalised neutral (η^3-allyl)iron complex (2*R*,4*S*)-**11** reacts with organocuprate nucleophiles regioselectively *anti* to the iron. Thus, a major limitation to the use of the related ester-functionalised cationic (η^3-allyl)-iron and -molybdenum complexes **7** and **8**, their inefficient reaction with alkylmetal nucleophiles,[18] has been addressed. But, there is a weevil in the wheat: the synthesis of the neutral complex (2*R*,4*S*)-**11** from scalemic allylic mesylate **22** is stereoselective and proceeds mainly by inversion but there is significant contribution from a



Scheme 11

pathway that proceeds by retention even in non-polar solvents—contrary to the report of Nakanishi and co-workers.[24] In the present case this vexation was inconsequential because the major complex could be obtained by crystallisation but extrapolation to other systems may be more difficult. Therefore, the synthetic potential of neutral (η^3-allyl)iron electrophiles will only be realised in full when the issue of their synthesis is resolved. A further markworthy feature of our approach to the C1–C16 fragment **2** of ionomycin is the use of the Pellicciari protocol[50] for the construction of the β-diketone moiety.

Experimental

All reactions requiring anhydrous conditions were conducted under a nitrogen atmosphere in flame-dried glassware. Where appropriate, solvents and reagents were dried by standard methods, *i.e.*, distillation from the usual drying agent under a nitrogen atmosphere prior to use: THF and Et_2O from sodium benzophenone ketyl; CH_2Cl_2, DME, MeCN, PhH and PhMe from CaH_2. Reactions were magnetically stirred and monitored by TLC using 0.25 mm E. Merck pre-coated silica gel plates and visualized with UV light followed by phosphomolybdic acid. All organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* using a Büchi rotary evaporator. Yields refer to chromatographically and spectroscopically pure products unless stated otherwise.

Infrared spectra were recorded neat on NaCl plates, details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, w = weak, br = broad. Magnetic resonance spectra were recorded on Bruker 300 and 500 MHz spectrometers in the solvents specified and the chemical shifts (δ) reported in ppm relative to the residual signals of chloroform ($\delta_H = 7.27$, $\delta_C = 77.2$) or benzene $\delta_H = 7.37$, $\delta_C = 128.4$). Coupling constants (J) are reported in Hz with multiplicities described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet and signal assignments based on COSY and HMQC correlation experiments. In the ^{13}C NMR spectra, multiplicities and signal assignments were elucidated using DEPT 135 and HMBC correlation experiments. Mass spectra are reported as values in atomic mass units followed by the peak intensity relative to the base peak (100%). Specific optical rotations were recorded at ambient temperature (22 ± 3 °C) on an AA 1000 polarimeter reported in 10^{-1}deg $m^{-2}g^{-1}$.

(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-iodo-2,4-dimethylpentane (16)

tert-Butyldiphenylsilyl chloride (1.8 g, 6.5 mmol) in CH_2Cl_2 (3 mL) was added to a solution of (2*S*,4*R*)-5-iodo-2,4-dimethylpentan-1-ol[18] (1.6 g, 6.5 mmol), imidazole (575 mg, 8.5 mmol) and DMAP (24 mg, 0.2 mmol) in CH_2Cl_2 (7 mL) and the resulting suspension was stirred at r.t. for 1 h. H_2O (10 mL) was added to the reaction mixture and the layers were separated. The aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography [SiO_2, hexanes] gave the title compound **16** (3.1 g, 6.45 mmol, 99%) as a colourless oil: $[a]_D = -8.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (4H, d, J 6.8, Ph), 7.46–7.38 (6H, m, Ph), 3.51 (1H, dd, J 9.8, 5.6, C1H_AH_B), 3.45 (1H, dd, J 9.8, 6.0, C1H_AH_B), 3.24 (1H, dd, J 9.6, 3.6, C5H_AH_B), 3.09 (1H, dd, J 9.6, 5.8, C5H_AH_B), 1.72 (1H, apparent oct, J 6.4, C2H), 1.53–1.46 (1H, m, C4H), 1.47 (1H, ddd, J 7.3, 6.6, 5.5, C3H_AH_B), 1.08 (9H, s, $(CH_3)_3Si$), 1.01 (1H, ddd, J 7.3, 6.6, 5.5, C3H_AH_B), 0.96 (3H, d, J 6.4, C2CH_3), 0.95 (3H, d, J 6.8, C4CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8 (4C, Ph), 134.1 (2C, Ph), 129.7 (2C, Ph), 127.8 (4C, Ph), 68.9 (C1H_2), 40.5 (C3H_2), 33.3 (C4H), 32.0 (C2H), 27.1 ((*C*H_3)$_3$CSi), 21.6 (C4*C*H_3), 19.5 ((CH$_3$)$_3$*C*Si), 18.3 (C5H_2), 17.5 (C2*C*H_3). IR (neat, NaCl plates): ν = 3070 s, 2958 s, 2929 s, 1472 m, 1427 m, 1389 m, 1378 m, 1194 m, 1111 s cm^{-1}. LRMS (ES mode) m/z = 481 [MH^+, 10%], 225 (100). HRMS (ES mode): m/z = 481.1441 [MH^+, 10%]; calculated for $C_{23}H_{34}IOSi$ [MH^+]: m/z = 481.1424. Anal. calcd for $C_{23}H_{33}IOSi$: C, 57.49; H, 6.92. Found: C, 57.6; H, 6.95.

(1′*S*)-Diethyl 2-oxo-2-(1′-phenylethylamino)ethylphosphonate (19)

DMAP (4.9 g, 40 mmol) then EDCI·HCl (7.7 g, 40.0 mmol) were added to a colourless solution of diethylphosphonoacetic acid (3.2 mL, 20 mmol) and (*S*)-α-methylbenzylamine (2.6 mL, 20.0 mmol) in CH_2Cl_2 (500 mL) at r.t. The resulting colourless solution was strirred at r.t. for 2 h. HCl (1 M, 500 mL) was added to the reaction mixture and the layers separated. The organic layer washed with HCl (1 M, 500 mL), then brine (500 mL),

dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound **19** (5.7 g, 18.9 mmol, 94%) as a colourless oil: $[\alpha]_D$ −48.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.29 (4H, m, Ph), 7.26–7.21 (1H, m, Ph), 7.14 (1H, broad s, NH), 5.11 (1H, apparent quint, J 7.3, C1′H), 4.14 (2H, overlapping dq, J 15.0, 7.3, OCH_2CH_3), 4.02 (2H, overlapping dq, J 15.0, 7.3, OCH_2CH_3), 2.86 (1H, dd, J 20.9, 15.4, $C2H_AH_B$), 2.81 (1H, overlapping dd, J 20.5, 15.4, $C2H_AH_B$), 1.49 (3H, d, J 6.8, C1′CH_3), 1.34 (3H, t, J 7.3, OCH_2CH_3), 1.22 (3H, t, J 7.3, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (C=O), 143.1 (Ph), 128.5 (2C, Ph), 128.4 (Ph), 127.1 (Ph), 126.0 (3C, Ph), 62.6 (2C, ^2J (^{31}P-^{13}C) = 6.9, OCH_2CH_3), 49.1 (C1′H), 35.0 (d, ^1J (^{31}P–^{13}C) 131.0, C2H_2), 22.0 (C1′CH_3), 16.2 (2C, t, ^3J (^{31}P–^{13}C) 6.9, OCH_2CH_3). IR (neat): ν = 3280 s, 3064 s, 2981 s, 2932 s, 1651 s, 1552 s 1245 s cm^{-1}. LRMS (ES mode): m/z = 300 [MH$^+$, 100%], 197 (30), 196 (75), 179 (65), 168 (20).

(2*E*,1′*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)pent-2-enoic acid (1′-phenylethyl) amide (20)

Phosphonate **19** (2.9 g, 9.6 mmol) in THF (19 mL) was added *via* a cannula to a suspension of NaH (60% dispersion in mineral oil, 385 mg, 9.6 mmol) in THF (19 mL) at 0 °C. The resulting white suspension was stirred at r.t. for 2 h. The aldehyde (*R*)-**18**[51] (1.7 g, 9.2 mmol) in THF (10 mL + 3 mL rinse) was added *via* a cannula and the resulting suspension was stirred at r.t. for 18 h. The reaction was quenched with pre-mixed NH_4Cl (saturated aqueous, 25 mL) and brine (25 mL), the layers separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography [SiO_2, hexanes–Et_2O (3 : 1)] followed by recrystallisation from hexanes gave the title compound **20** (1.7 g, 5.4 mmol, 58%) as colourless needles: mp 70–72 °C; $[\alpha]_D$ −91.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (4H, m, Ph), 7.23–7.17 (1H, m, Ph), 6.78 (1H, dd, J 15.0, 3.9, C3H), 5.87 (1H, d, J 15.0, C2H), 5.63 (1H, broad s, NH), 5.15 (1H, apparent quint, J 7.3, C1′H), 4.42–4.36 (1H, m, C4H), 1.45 (3H, d, J 6.8, C1′CH_3), 1.17 (3H, d, J 6.4, C5H_3), 0.84 (9H, s, $(CH_3)_3CSi$), 0.00 (6H, s, $(CH_3)_2Si$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1 (C1), 148.4 (C3H), 143.3 (Ph), 128.8 (Ph), 127.6 (2C, Ph), 126.5 (2C, Ph), 120.9 (C2H), 67.9 (C4H), 48.9 (C1′H), 26.0 ($(CH_3)_3CSi$), 23.9 (C1′CH_3), 21.8 (C5H_3), 18.4 ($(CH_3)_3CSi$), −4.7 ($(CH_3)_2Si$). IR (neat): ν = 1668 s, 1633 s cm^{-1}. LRMS (ES mode): m/z = 334 [MH$^+$, 100%], 230 (20), 213 (65) 202 (35). Anal. calcd for $C_{19}H_{31}NO_2Si$: C, 68.5; H, 9.15; N, 4.3. Found: C, 68.5; H, 9.15; N 4.2.

(2*E*,1′*S*,4*R*)-4-Hydroxypent-2-enoic acid (1′-phenylethyl) amide (21)

Concentrated HCl (1 mL) was added dropwise to a solution of silyl ether **20** (1.4 g, 4.2 mmol) in *i*-PrOH (20 mL) at 0 °C and the resulting colourless solution stirred at r.t. for 18 h. Solid $NaHCO_3$ was added portionwise until no further gas evolution was observed. H_2O (10 mL) and CH_2Cl_2 (10 mL) was added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a clear, colourless oil. Purification by column chromatography [SiO_2, hexanes–EtOAc (1 : 5)] followed by recrystallisation from hexanes gave the title compound **21** (0.9 g, 4.1 mmol, 98%) as a colourless solid: mp 76–77 °C; $[\alpha]_D$ −159 (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.30 (4H, m, Ph), 7.28–7.24 (1H, m, Ph), 6.82 (1H, dd, J 15.2, 4.5, C3H), 6.10 (1H, broad s, NH), 5.96 (1H, dd, J 15.2, 1.7, C2H), 5.18 (1H, apparent quint, J 7.5, C1′H), 4.40 (1H, m, C4H), 2.53 (broad s, OH), 1.51 (3H, d, J 6.8, C1′CH_3), 1.28 (3H, d, J 6.6, C5H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1 (C1), 147.5 (C3H), 143.3 (Ph), 128.8 (2C, Ph), 127.6 (Ph), 126.4 (2C, Ph), 121.9 (C2H), 67.3 (C4H), 49.0 (C1′H), 23.0 (C1′CH_3), 21.8 (C5H_3). IR (neat): ν = 3469 s, 1658 s, 1633 s cm^{-1}. LRMS (ES mode): m/z = 220 [MH$^+$, 100%]. Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.25; H, 7.75; N, 6.4.

(2*E*,1′*S*,4*R*)-4-(Methanesulfonyloxy)pent-2-enoic acid (1′-phenylethyl) amide (22)

MsCl (0.35 mL, 4.6 mmol) was added dropwise to a colourless solution of the alcohol **21** (1.0 g, 4.6 mmol), Et_3N (0.63 mL, 4.6 mmol) and CH_2Cl_2 (65 mL) at 0 °C. The resulting clear, colourless solution was stirred at 0 °C for 1 h. The reaction was quenched with $NaHCO_3$ (saturated aqueous, 60 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with HCl (1 M, 60 mL, chilled using an ice-water bath), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the title compound **22** (1.4 g, 4.6 mmol, 100%) as a colourless solid that was used with no further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.24 (4H, m, Ph), 7.23–7.18 (1H, m, Ph), 6.73 (1H, dd, J 15.4, 5.6, C3H), 6.01 (1H, d, J 15.4, C2H), 6.59 (1H, broad s, NH), 5.27 (1H, apparent quint, J 6.4, C4H), 5.12 (1H, apparent quint, J 7.3, C1′H), 2.93 (3H, s, OSO_2CH_3), 1.46 (3H, d, J 7.3, C1′CH_3), 1.45 (3H, d, J 6.4, C5CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6 (C1), 142.9 (Ph), 140.6 (C3H), 128.9 (2C, Ph), 127.7 (Ph), 126.4 (2C, Ph), 126.4 (Ph), 125.1 (C2H), 77.3 (C4H), 49.3 (C1′H), 39.1 (OSO_2CH_3), 21.8 (C1′CH_3), 21.4 (C5CH_3). IR (neat): ν = 3332 br, 1671 s, 1630 s, 1531 s, 1445 s, 1338 s cm^{-1}. LRMS (ES mode): m/z = 320 [MNa$^+$, 80%], 298 [MH$^+$, 95], 265 (40), 236 (20), 224 (35), 202 (100).

Neutral iron complex (2*R*,4*S*)-11

Mesylate **22** (221 mg, 0.74 mmol) in CH_2Cl_2 (0.4 mL) was added in one portion to tetrabutylammonium tricarbonylnitrosylferrate[52] (TBAFe, 306 mg, 0.74 mmol) in PhMe (3.5 mL) at 0 °C. The resulting red–orange mixture was stirred at 0 °C for 1 h and at r.t. for a further 18 h. The reaction mixture was passed rapidly through a SiO_2 column under N_2 eluting with degassed CH_2Cl_2, the 2 characteristic red bands were collected and concentrated *in vacuo* to give a mixture of the title compounds (2*R*,4*S*)-**11** and (2*S*,4*R*)-**11** (128 mg, 0.37 mmol, 50%, dr = 4 : 1) as a red oily solid. Recrystallisation of the mixture from pentane (*ca.* 15 mL) gave (2*R*,4*S*)-**11** (86 mg) as a red solid: mp 130 °C (dec.); $[\alpha]_D$ −132 (c = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.28 (5H, m, Ph), 5.96 (1H, broad d, J 7.7, NH), 5.27 (1H, apparent quint, J 6.9, C1′H), 5.04 (1H, dd, J 12.0, 10.2, C3H), 4.22 (1H, overlapping dq, J 12.3, 6.2, C4H), 3.59 (1H, d, J 10.2, C2H), 2.01 (3H, d, J 6.1, C5H_3), 1.59 (3H, d, J 6.7, C1′CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.9 (CO), 217.4 (CO), 170.1 (C1), 143.3 (Ph), 128.8 (2C, Ph),

127.5 (Ph), 126.5 (2C, Ph), 96.8 (C4H), 77.0 (C3H), 60.5 (C2H), 49.4 (C1′H), 21.8 (C1′CH_3), 19.8 (C5H_3). IR (solid): ν = 3277 s, 3076 s, 3029 s, 2979 s, 2023 s, 1964 s, 1731 s, 1634 s, 1555 s cm^{-1}. LRMS (ES mode): m/z = 345 [MH$^+$, 5%], 330 (90), 300 (95), 289 (50), 259 (5), 242 (100).

The mother liquors were concentrated *in vacuo* to give enriched (2*S*,4*R*)-**11** (42 mg) as a red oil. The dr was assigned from the ^{1}H NMR spectra by integration of the signals for the C2H at δ_H = 3.59 (d, *J* 10.2) for (2*R*,4*S*)-**11** and 3.57 (d, *J* 10.2) for (2*S*,4*R*)-**11**.[24]

(2*E*,1′*S*,4*S*)-4-Methyl-*N*-(1′-phenylethyl)oct-2-enamide (23)

A solution of CuBr·SMe_2 (215 mg, 1.05 mmol) in diisopropylsulfane (1 mL + 0.9 mL rinse) at 0 °C was added in one portion to *n*-BuLi (1.57 M in hexanes, 1.33 mL, 2.09 mmol) in Et_2O (21 mL) at −78 °C and the resulting red–brown solution was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to −50 °C for 30 min then recooled to −78 °C. Complex (2*R*,4*S*)-**11** (180 mg, 0.52 mmol) in THF (8.8 mL) at −50 °C was added dropwise to the reaction mixture at −78 °C and the resulting red-brown suspension stirred at −78 °C for 4 h and allowed to warm to r.t. slowly (16 h) forming a dark brown suspension. The reaction was quenched with pre-mixed NH_4OH (10 mL) and NH_4Cl (saturated aqueous, 10 mL) at r.t. and O_2 was bubbled through the reaction mixture for 1 h. The layers were separated and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow–orange oil. Purification by column chromatography [SiO_2, hexanes–Et_2O (2 : 1)] followed by recrystallisation from hexanes gave the title compound **23** (100 mg, 0.4 mmol, 74%) as colourless needles: mp 87–88 °C; $[a]_D$ −84.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.32 (4H, m, Ph), 7.30–7.24 (1H, m, Ph), 6.77 (1H, dd, *J* 15.2, 7.7, C3H), 5.71 (1H, d, *J* 15.2, C2H), 5.67 (1H, broad d, *J* 7.1, NH), 5.22 (1H, apparent quint, *J* 7.5, C1′H), 2.25 (1H, apparent sept, *J* 7.1, C4H), 1.53 (3H, d, *J* 6.8, C1′CH_3), 1.41–1.20 (6H, m, C5H_2/C6H_2/C7H_2), 1.04 (3H, d, *J* 6.6, C4CH_3), 0.88 (3H, t, *J* 6.6, C8H_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4 (C1), 150.8 (C3H), 143.4 (Ph), 128.8 (2C, Ph), 127.5 (Ph), 126.5 (2C, Ph), 121.9 (C2H), 48.8 (C1′H), 36.5 (C4H), 36.0 (C5H_2), 29.6 (C6H_2), 22.9 (C7H_2), 21.8 (C1′CH_3), 19.8 (C4CH_3), 14.8 (C8H_3). IR (neat): ν = 3282 s, 1666 s, 1623 s cm^{-1}. LRMS (ES mode): m/z = 282 [MNa$^+$, 10%], 260 [MH$^+$, 100]. HRMS (ES mode): m/z calculated for $C_{17}H_{26}NO$ [MH$^+$]: 260.2014; found: 260.2008. Anal. calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.60; H, 9.55; N, 5.35.

A single crystal X-ray analysis defined the relative stereochemistry of the amide **23** (Fig. 1). $C_{17}H_{25}NO$, monoclinic, space group $P2_1$, a = 11.2621(11) Å, b = 5.2062(5) Å, c = 14.3092(14) Å, V = 792.83(13) Å^3, Z = 2, ρ_{calc} = 1.087 Mg m^{-3}, μ = 0.066 mm^{-1}, crystal size: 0.38 × 0.15 × 0.10 mm, data collection range: 2.80 ≤ θ ≤ 25.99°, 33635 measured reflections, final $R(wR)$ values: 0.0319, (0.0818) for 1743 independent data and 178 parameters [$I > 2\sigma(I)$], largest residual peak and hole: 0.301, −0.145 e Å^{-3}.†

Hydrogen atoms were positioned geometrically with the following carbon–hydrogen distances: aromatic, 0.95 Å; olefinic, 0.95 Å; methyl, 0.98 Å; methylene, 0.99 Å; methine, 1.00 Å. H8 attached to N8 was positioned in a planar configuration and the distance N8-H8 refined to 0.85(3) Å. All Uiso(H) values were constrained to be 1.2 times Ueq of the parent atom. In the absence of significant anomalous scattering effects, the absolute stereochemistry could not be determined from the X-ray data and Friedel pairs were merged. The model was assigned on the basis of the known (*S*)-configuration of the phenethylamine.

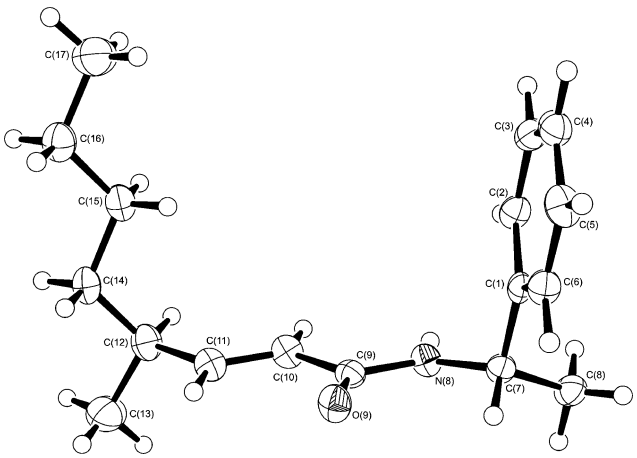


Fig. 1 X-Ray structure of amide **23**. The ellipsoid probabilities are 50%.

(2*E*,1′*S*,4*S*,6*S*,8*S*,)-9-(*tert*-Butyldiphenylsilyloxy)-4,6,8-trimethyl-*N*-(1′-phenylethyl)non-2-enamide (26)

t-BuLi (1.65 M in pentane, 4.0 mL, 6.6 mmol) was added dropwise to a solution of iodoalkane **16** (1.6 g, 3.3 mmol) in Et_2O (35 mL) at −78 °C and the resulting suspension stirred at −78 °C for 1 h. The mixture was allowed to warm to r.t. slowly (1 h) and the pale yellow solution then re-cooled to −78 °C. CuBr·SMe_2 (340 mg, 1.7 mmol) in diisopropylsulfane (2.5 mL, 0.5 mL rinse) was added rapidly to the reaction mixture at −78 °C, the resulting yellow suspension stirred at −78 °C for 1 h. The mixture was allowed to warm to −50 °C for 30 min forming a pale yellow–orange suspension of the cuprate **17**, and then recooled to −78 °C. Complex (2*R*,4*S*)-**11** (285 mg, 0.8 mmol) in THF (12 mL, 2 mL rinse) was added dropwise to the reaction mixture at −78 °C. The resulting orange–brown suspension was stirred at −78 °C for 4 h and allowed to warm to r.t. slowly (24 h) to give a dark brown suspension. The reaction was quenched with a solution composed of NH_4OH (25 mL) and NH_4Cl (saturated aqueous, 25 mL) at r.t. whereupon O_2 was bubbled through the reaction mixture for 2 h. The layers were separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow–orange oil. Purification by column chromatography [SiO_2, hexanes–Et_2O (5 : 1 → 3 : 1 → 2 : 1)] gave the title compound **26** (235 mg, 0.42 mmol, 51%) as a pale red oil: $[a]_D$ −42.9 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.64 (4H, m, Ph), 7.43–7.31 (10H, m, Ph), 7.29–7.25 (1H, m, Ph), 6.78 (1H, dd, *J* 15.2, 7.5, C3H), 5.64 (1H, dd, *J* 15.2, 1.1, C2H), 5.56 (1H, broad d, *J* 7.7, NH), 5.21 (1H, apparent quint, *J* 7.7, C1′H), 3.49 (1H, dd, *J* 9.8, 5.1, C9H_AH_B), 3.41 (1H, dd, *J* 9.8, 6.2, C9H_AH_B), 2.34 (1H, m, C4H), 1.71 (1H, apparent oct, *J* 6.6, C8H), 1.56–1.46 (1H, m, C6H), 1.52 (3H, d, *J* 7.1, C1′CH_3), 1.36 (1H, dt, *J* 13.7, 6.7, C7H_AH_B), 1.23 (1H, ddd, *J* 13.6, 8.9, 5.2, C5H_AH_B), 1.12 (1H, ddd, *J* 13.6, 8.9, 5.2,

† CCDC reference number 606362. For crystallographic data in CIF format see DOI: 10.1039/b606262h

C5H$_A$H$_B$), 1.05 (9H, s, (CH$_3$)$_3$CSi), 0.98 (3H, d, *J* 6.8, C4CH$_3$), 0.96–0.86 (1H, m, C7H$_A$H$_B$), 0.92 (3H, d, *J* 6.6, C8CH$_3$), 0.81 (3H, d, *J* 6.3, C6CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.4 (C1), 151.4 (C2H), 143.3 (Ph), 135.8 (4C, Ph), 134.3 (Ph), 134.2 (Ph), 129.7 (2C, Ph), 128.9 (2C, Ph), 127.8 (4C, Ph), 127.6 (Ph), 126.5 (2C, Ph), 121.3 (C2H), 69.1 (C9H$_2$), 48.9 (C1′H), 43.6 (C5H$_2$), 41.8 (C7H$_2$), 33.8 (C4H), 33.3 (C8H), 27.9 (C6H), 27.1 ((*C*H$_3$)$_3$CSi), 21.8 (C4*C*H$_3$), 20.4 (C6*C*H$_3$), 19.5 ((CH$_3$)$_3$*C*Si), 19.1 (C1′*C*H$_3$), 17.9 (C8*C*H$_3$). IR (neat): ν = 3266 br, 1665 m, 1626 s cm^{-1}. LRMS (ES mode): *m*/*z* = 578 [MNa$^+$, 65%], 556 [M$^+$, 30], 479 (80), 478 (100). HRMS (ES mode): *m*/*z* calculated for C$_{36}$H$_{49}$NO$_2$NaSi [MNa$^+$]: 578.3430; found: 578.3419.

(2*E*,1′*S*,4*R*,6*S*,8*S*)-9-(*tert*-Butyldiphenylsilyloxy)-4,6,8-trimethyl-*N*-(1′-phenylethyl)nonanamide (27)

A mixture of **26** (225 mg, 0.4 mmol) and Pd(OH)$_2$ (20% on activated charcoal, 10 mg) in MeOH (8 mL) at r.t. was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered through a celite pad washing the black residue with MeOH (10 mL) and CH$_2$Cl$_2$ (30 mL) and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography [SiO$_2$, hexanes–Et$_2$O (1 : 1)] to give the title compound **27** (229 mg, 0.4 mmol, 100%) as a colourless oil: [*a*]$_D$ −6.2 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.72–7.67 (4H, m, Ph), 7.47–7.33 (10H, m, Ph), 7.31–7.27 (1H, m, Ph), 5.63 (1H, broad s, NH), 5.18 (1H, apparent quint, *J* 6.6, C1′H), 3.52 (1H, dd, *J* 9.9, 5.5, C9*H*$_A$H$_B$), 3.44 (1H, dd, *J* 9.9, 6.4, C9H$_A$*H*$_B$), 2.22 (2H, m, C2H$_2$), 1.75 (1H, apparent oct, *J* 6.6, C8H), 1.51 (3H, d, *J* 6.8, C1′CH$_3$), 1.62–1.47 (3H, m, C4H/C6H/C3*H*$_A$H$_B$), 1.31 (1H, dt, *J* 13.7, 6.8, C7*H*$_A$H$_B$), 1.08 (9H, s, (CH$_3$)$_3$CSi), 1.12–1.05 (1H, m, C5*H*$_A$H$_B$), 0.95 (3H, d, *J* 6.6, C8CH$_3$), 1.02–0.91 (3H, m, C3H$_A$*H*$_B$/C5H$_A$*H*$_B$/C7H$_A$*H*$_B$), 0.85 (3H, d, *J* 6.2, C4CH$_3$), 0.80 (3H, d, *J* 6.6, C6CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.5 (C1), 143.4 (Ph), 135.8 (4C, Ph), 134.3 (2C, Ph), 129.7 (2C, Ph), 128.9 (2C, Ph), 127.8 (4C, Ph), 127.5 (Ph), 126.4 (2C, Ph), 69.2 (C9H$_2$), 48.7 (C1′H), 44.3 (C5H$_2$), 42.3 (C7H$_2$), 34.9 (C2H$_2$), 34.1 (C3H$_2$), 33.2 (C8H), 30.1 (C4H), 27.6 (C6H), 27.1 ((*C*H$_3$)$_3$CSi), 21.9 (C1′*C*H$_3$), 20.2 (C6*C*H$_3$), 19.5 ((CH$_3$)$_3$*C*Si), 19.1 (C4*C*H$_3$), 17.7 (C8*C*H$_3$). IR (neat): ν = 3282 br, 1639 s cm^{-1}. LRMS (ES mode): *m*/*z* = 580 [MNa$^+$, 55%], 558 [MH$^+$, 100], 481 (98), 480 (100). HRMS (ES mode): *m*/*z* calculated for C$_{36}$H$_{52}$NO$_2$Si [MH$^+$]: 558.3767; found 558.3782.

Methyl [4*R*,6*S*,8*S*]-9-(*tert*-Butyldiphenylsilyloxy)-4,6,8-trimethylnonanoate (3)

LHMDS (2.0 M in THF, 0.14 mL, 0.14 mmol) was added dropwise to **27** (70 mg, 0.13 mmol) in THF (3 mL) at −10 °C and the resulting pale yellow solution stirred at −5 °C for 30 min. Boc$_2$O (82 mg, 0.38 mmol) in THF (1 mL, 0.4 mL rinse) was added to the reaction mixture and the resulting yellow solution stirred at r.t. for 30 min. DMAP (3 mg, 0.025 mmol) in THF (0.3 mL) was added to the reaction mixture at r.t. and the resulting yellow suspension stirred at r.t. for 1 h, then heated at 45 °C for 3 h. The reaction was quenched with NH$_4$Cl (saturated aqueous, 5 mL) and Et$_2$O (5 mL), the layers separated and the aqueous layer extracted with Et$_2$O (2 × 10 mL). The combined organic layers were washed with H$_2$O (10 mL) and brine (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the crude *N*-Boc amide **28** (and Boc$_2$O) as a yellow oil which was used with no further purification.

LiOH (1 M solution, 0.38 mL, 0.38 mmol) was added to the crude *N*-Boc amide **28** in THF (1 mL) and the resulting yellow mixture heated under reflux for 4 h. The THF was removed *in vacuo* and the aqueous solution poured into a stirred solution of HCl (1 M, 10 mL) and Et$_2$O (10 mL). The layers were separated and the aqueous layer extracted with Et$_2$O (2 × 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. The residue was dissolved in PhH (3 mL) and MeOH (1 mL) at 0 °C whereupon TMSCHN$_2$ (2 M solution in Et$_2$O, 0.66 mL, 1.3 mmol) was added dropwise. The resulting yellow solution was stirred at 0 °C for 2 h and concentrated *in vacuo*. The residue was purified by column chromatography [SiO$_2$, hexanes–Et$_2$O (10 : 1)] to give the title compound **3** (42 mg, 0.1 mmol, 68% over 3 steps) as a colourless oil. The ^{1}H and ^{13}C NMR data recorded at 500 and 125 MHz, respectively, were identical to those obtained on a sample of **3** prepared by an unambiguous route.[18]

(2*R*,4*S*)-6-Hydroxy-2,4-dimethylhexanoate (32)

Oxalyl chloride (0.75 mL, 8.7 mmol) was added dropwise to a solution of (2*R*,4*S*)-2,4-dimethylpentanedioic acid monomethyl ester **29** (500 mg, 2.9 mmol) in PhH (1 mL) at 0 °C and the resulting solution stirred at 0 °C for 4 h [gas evolution was observed]. The reaction mixture was concentrated *in vacuo* to give the acid chloride (1782 s, 1736 s cm^{-1}) as a colourless oil that was used with no further purification.

The acid chloride in PhH (2 mL) was added dropwise to a solution of diazomethane [prepared from Diazald (2.0 g, 9.3 mmol) in Et$_2$O (45 mL)] at 0 °C and the resulting yellow solution stirred at 0 °C for 2 h. The reaction mixture was concentrated *in vacuo* to give the *a*-diazoketone **30** (2106 s, 1732 s cm^{-1}) as an orange oil that was used in the next step with no further purification.

The *a*-diazoketone **30** in dioxane (10 mL) was added dropwise to a suspension of Ag$_2$O (672 mg, 2.9 mmol) and Na$_2$S$_2$O$_3$·5H$_2$O (720 mg, 2.9 mmol) in H$_2$O (15 mL) at 0 °C [gas evolution was observed]. The resulting dark suspension was stirred at 0 °C for 20 min and the reaction quenched with HCl (1 M, 30 mL). The reaction mixture was filtered, the layers separated, and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo* to give the acid **31** (1737 s, 1710 s cm^{-1}) as a yellow oil that was used in the next step with no further purification.

BH$_3$·SMe$_2$ (2.0 M in THF, 1.6 mL, 3.2 mmol) was added dropwise to a solution of the acid **31** in THF (10 mL) at −20 °C and the resulting solution stirred at −20 °C for 1 h and allowed to warm slowly to r.t. over 18 h. H$_2$O (10 mL) and EtOAc (10 mL) was added to the reaction mixture, the layers separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [SiO$_2$, hexanes–Et$_2$O (1 : 1)] to give the title compound **32** (219 mg, 1.3 mmol, 44% over 4 steps) as a colourless oil: [*a*]$_D$ −28.9 (*c* = 2.5, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.68 (1H, dt, *J* 10.7, 6.4, C6*H*$_A$H$_B$), 3.69–3.63 (1H, m, C6H$_A$*H*$_B$), 3.68 (3H, s, OCH$_3$), 2.62–2.54 (1H, m, C2H), 1.77 (1H, m, C3*H*$_A$H$_B$), 1.63 (1H, broad s, OH), 1.61–1.52 (1H, m, C4H), 1.55–1.49 (1H, m, C5*H*$_A$*H*$_B$), 1.46–1.39 (1H, m, C5H$_A$*H*$_B$), 1.16 (3H, d, *J* 7.3, C6CH$_3$), 1.18–1.11 (1H, m,

$C3H_AH_B$), 0.93 (3H, *J* 6.4, C4CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.8 (C1), 60.9 (C6H_2), 52.0 (OCH_3), 41.0 (C5H_2), 39.9 (C3H_2), 37.5 (C6H), 27.8 (C4H), 20.0 (C6CH_3), 18.4 (C4CH_3). IR (neat): ν = 3420 br, 1736 s cm^{-1}. LRMS (ES mode): *m*/*z* = 197 [MNa^+, 80%], 175 [MH^+, 95]. Anal. calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.80; H, 10.60.

Conversion of 32 to 33

TBDPSCl (302 mg, 1.1 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of alcohol **32** (188 mg, 1.08 mmol)), imidazole (88 mg, 1.3 mmol) and DMAP (13 mg, 0.11 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at r.t. for 5 h whereupon CH_2Cl_2 (15 mL) and H_2O (5 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was dissolved in THF (3 mL) to which was added methanolic LiOH (3.0 M, 2.0 mL) and the mixture stirred at ambient temperature until TLC indicated complete consumption of starting material (*ca.* 2 h). The reaction mixture was poured into iced 0.1 M HCl (10 mL) and the product extracted into CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2 Et_2O–hexanes (1 : 3)] to give carboxylic acid **33** (409 mg, 1.03 mmol, 95%) as a colourless oil. The spectroscopic data were identical to those recorded on a sample of **33** prepared by a different route (see below).

(3*R*,5*S*)-7-(*tert*-Butyldiphenylsilyloxy)-1-diazo-3,5-dimethylheptan-2-one (4)

Oxalyl chloride (35 μL, 0.4 mmol, 1.6 equiv) was added to a solution of **33** (100 mg, 0.25 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL). The reaction was stirred at r.t. for 2 min before cooling to 0 °C. DMF (1 drop) was added and immediate effervescence occurred. The reaction was stirred at 0 °C until effervescence had ceased (2 h). The resulting pale yellow solution was concentrated *in vacuo* giving a yellow oil that was dissolved in MeCN–THF (1 : 1, 2 mL). The resulting pale yellow solution was added dropwise to a solution of diazomethane [prepared from Diazald (1.5 g, 7.0 mmol) in Et_2O (22 mL)] at 0 °C. The reaction was stirred for 1 h. Thereafter, nitrogen was bubbled through the solution for 30 min at 0 °C to give a colourless solution. The solution was concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 5)] to give the title compound **4** (87 mg, 0.21 mmol, 82%) as a yellow oil: $[\alpha]_D^{24}$ −20.95 (*c* = 0.21, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (4H, dd, *J* 7.8 and 1.4), 7.45–7.38 (6H, m), 5.12 (1H, s, C1H) 3.75–3.66 (2H, m, C16H_2), 2.47–2.44 (1H, m, C12H), 1.72–1.57 (3H, m, C14H/C15H_2), 1.34–1.28 (1H, m, C13H_AH_B), 1.20–1.14 (1H, m, C13H_AH_B), 1.10 (3H, d, *J* 6.89, C12HCH_3), 1.06 (9H, s, C(CH_3)$_3$), 0.86 (3H, d, *J* 6.45, C14HCH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 199.3 (C2, C=O), 135.7 (4*C*H), 134.1 (2C), 129.7 (2*C*H), 127.8 (4*C*H), 62.0 (C16H_2), 41.7 (C12H_2), 39.6 (C14H_2) 27.5 (C13H), 27.0 (3C, C(CH_3)$_3$), 19.9 (C14CH_3), 19.4 (C, *C*(CH_3)$_3$), 18.0 (C12CH_3). IR (neat): ν = 2101 s, 1645 s cm^{-1}. LRMS (ES mode): *m*/*z* = 396.3 [(M–N_2 + 2H)$^+$, 45%], 395.2 (M–N_2 + H). HRMS (ES mode): *m*/*z* calcd for $C_{25}H_{35}O_2Si$: 395.2406; found: 395.2412 [M–N_2].

(*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutan-1-ol (36)

n-BuLi (1.58 M in hexanes, 12.6 mL, 19.5 mmol, 4.0 equiv.) was added dropwise to a suspension of LiCl (2.62 g, 0.062 mol, 12.7 equiv.) and diisopropylamine (2.95 mL, 20.9 mmol, 4.3 equiv.) in THF (13.5 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 10 min and 0 °C for 10 min. The suspension was cooled to −78 °C and propionamide **34** (2.26 g, 10.2 mmol, 2.1 equiv.) in THF (31 mL) added dropwise at a rate sufficient to maintain the reaction temperature below −70 °C. The reaction was stirred at −78 °C for 1 h, 0 °C for 15 min and r.t. for 5 min. The reaction was cooled to 0 °C and 1-iodo-2-(*tert*-butyldiphenylsilyloxy)ethane[53] (1.5 g, 3.32 mmol, 1.0 equiv.) in THF (1.4 mL) added. The reaction was stirred at 0 °C for 14 h, slowly warming to r.t. Thereafter, the reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 3)] to give the amide **35** (2.56 g) as a colourless oil that was used directly in the next step.

n-BuLi (1.58 M in hexanes, 12.0 mL, 19.0 mmol, 3.9 equiv.) was added dropwise to a solution of diisopropylamine (2.9 mL, 20.45 mmol, 4.2 equiv.) in THF (22 mL) at −78 °C. The reaction was stirred at −78 °C for 10 min and 0 °C for 10 min. Borane–ammonia complex (0.6 g, 19.5 mmol, 4.0 equiv.) was added in one portion and the resulting suspension stirred at 0 °C for 10 min and r.t. for 15 min. The crude amide **35** (2.56 g) in THF (12.0 mL, 2.5 mL wash) was added dropwise at 0 °C. The resulting colourless solution was warmed to r.t. and stirred for 2 h. The reaction was cooled to 0 °C and HCl (2 M, 20 mL) added dropwise. The solution was stirred at r.t. for 30 min. The layers were separated and the aqueous layer extracted with Et_2O (4 × 30 mL). The combined organic layers were washed with HCl (2 M, 20 mL), NaOH (2 M, 20 mL) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 4)] to give the title compound **36** (1.46 g, 4.27 mmol, 87%) as a colourless oil: $[\alpha]_D$ +4.5 (*c* = 1.2, Et_2O, 20 °C). ^{1}H NMR, ^{13}C NMR and IR spectroscopic data agree with those reported.[54] The er of alcohol **36** (98 : 2) was established by ^{1}H and ^{19}F NMR spectroscopic analysis of the corresponding Mosher ester derivative which was prepared as follows:

Alcohol **36** (15 mg, 44 μmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (15 mg, 62 μmol, 1.4 equiv.), DCC (13 mg, 62 μmol, 1.4 equiv.) and DMAP (1 mg, 6.2 μmol, 0.1 equiv.) in CH_2Cl_2 (4 mL). The reaction was stirred at r.t. for 5 h whereupon TLC analysis showed remaining **36**. DCC (13 mg, 62 μmol, 1.4 equiv.) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (15 mg, 62 μmol, 1.4 equiv.) were added and the reaction stirred for a further 16 h whereupon TLC analysis showed complete consumption of **36**. Thereafter, the mixture was filtered and the filtrate washed with water (2 × 2 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2, Et_2O–petrol (1 : 4)] giving the Mosher ester of **36** (21 mg, 40 μmol, 83%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer):

δ = 7.66 (4H, dd, *J* 6.5 and 1.5), 7.52 (2H, m, ArH), 7.45–7.37 (9H, m and ArH), 4.29 (1H, dd, *J* 10.7 and 5.4, C13H_AH$_B$), 4.11 (1H, dd, *J* 10.7 and 6.5, C13H$_A$$H_B$), 3.74–3.66 (2H, m, C16H), 3.55 (3H, d, *J* 1.1, OCH_3), 2.12 (1H, m, C14H), 1.71–1.64 (1H, m, C15H_AH$_B$), 1.43–1.35 (1H, m, C15H$_A$$H_B$), 1.05 (9H, s, C($CH_3$)$_3$), 0.91 (3H, d, *J* 6.7, C14CH_3). ^{13}C NMR (300 MHz, $CDCl_3$, major isomer): δ = 166.8 (*C*O$_2$R), 135.7 (CH), 133.9 (C), 132.5 (C), 129.8 (CH), 129.76 (CH), 128.6 (CH), 127.9 (CH), 127.5 (CH), 71.5 (C13H$_2$), 61.6 (C16H$_2$), 55.6 (OCH_3), 35.9 (C15H$_2$), 29.6 (C14H), 27.0 (C(*C*H$_3$)$_3$), 19.3 (*C*(CH$_3$)$_3$), 16.8 (C14*C*H$_3$). A signal for the CF_3 group was not detected. ^{19}F NMR (470 MHz, $CDCl_3$): δ = −71.993 (major); −72.017 (minor). IR (neat): ν = 2923 s, 1749 s, 1169 s, 1111 s cm^{-1}. HRMS (ES mode) *m*/*z* = found: 581.2295 [MNa$^+$, 80%]. $C_{31}H_{37}O_4F_3NaSi$ requires: 581.2311.

(*R*)-4-Iodo-3-methyl-(*tert*-butyldiphenylsilyloxy)-butane (37)

Iodine (1.3 g, 3.8 mmol, 1.0 equiv.) was added in one portion to a colourless solution of PPh_3 (1.3 g, 4.94 mmol, 1.3 equiv.) and imidazole (0.67 g, 9.9 mmol, 2.6 equiv.) in CH_2Cl_2 (20 mL). The reaction was stirred at r.t. for 10 min giving a red–orange suspension. Alcohol **36** (1.3 g, 3.8 mmol, 1.0 equiv.) in CH_2Cl_2 (11 mL) was added dropwise and the reaction stirred at r.t. for 2 h. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 9)] to give the title compound **37** (1.61 g, 3.56 mmol, 93%) as a colourless oil: $[a]_D^{22}$ −0.6 (*c* = 1.3, Et_2O); lit.[54] $[a]_D^{22}$ − 0.50 (*c* = 1.2, Et_2O). ^{1}H NMR, ^{13}C NMR and IR spectroscopic data agree with those reported.[54]

(2*R*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol (39)

n-BuLi (1.6 M in hexanes, 8.3 mL, 13.3 mmol, 4.0 equiv.) was added dropwise to a suspension of LiCl (1.79 g, 42.2 mmol, 12.7 equiv.) and diisopropylamine (2.0 mL, 14.3 mmol, 4.3 equiv.) in THF (9 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 10 min and 0 °C for 10 min. The suspension was cooled to −78 °C and *N*-[(1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl]-*N*-methylpropionamide **34** (1.54 g, 7.0 mmol, 2.1 equiv.) in THF (21 mL) added dropwise at a rate sufficient to maintain the reaction temperature below −70 °C. The reaction was stirred at −78 °C for 1 h, 0 °C for 15 min and r.t. for 5 min. The reaction was cooled to 0 °C and iodoalkane **37** (1.5 g, 3.3 mmol, 1.0 equiv.) in THF (1.4 mL) added dropwise. The reaction was stirred at 0 °C for 14 h, slowly warming to r.t. Thereafter, the reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 3)] to give the amide **38** (1.18 g) as a colourless oil that was used directly in the next step.

n-BuLi (1.6 M in hexanes, 8.1 mL, 13.0 mmol, 3.9 equiv.) was added dropwise to a solution of diisopropylamine (2.0 mL, 13.9 mmol, 4.2 equiv.) in THF (15 mL) at −78 °C. The reaction was stirred at −78 °C for 10 min and 0 °C for 10 min. Borane–ammonia complex (0.41 g, 13.3 mmol, 4.0 equiv.) was added in one portion and the resulting suspension stirred at 0 °C for 10 min and r.t. for 15 min. The amide **38** (1.18 g) in THF (9 mL, 1 mL wash) was added dropwise at 0 °C. The resulting colourless solution was warmed to r.t. and stirred for 2 h. The reaction was cooled to 0 °C and HCl (2 M, 20 mL) added dropwise. The solution was stirred at r.t. for 30 min. The layers were separated and the aqueous layer extracted with Et_2O (4 × 30 mL). The combined organic layers were washed with HCl (2 M, 20 mL), NaOH (2 M, 20 mL) and brine (20 mL) before being dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 5)] to give the title compound **39** (0.75 g, 1.95 mmol, 59%, single diastereoisomer) as a colourless oil. This compound has been prepared previously,[55] but no spectroscopic data was reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (4H, dd, *J* 7.8 and 1.3), 7.45–7.38 (6H, m), 3.76–3.66 (2H, m, C6H$_2$), 3.51–3.49 (1H, m, C11H_AH$_B$), 3.39–3.36 (1H, m, C11H$_A$$H_B$), 1.77–1.61 (3H, m, C12H/C14H/C15H_AH$_B$), 1.32–1.24 (2H, m, C13H_AH$_B$/C15H$_A$$H_B$), 1.24 (1H, broad s, OH), 1.06 (9H, s, C(CH_3)$_3$), 0.97–0.90 (1H, m, C13H$_A$$H_B$), 0.92 (3H, d, *J* 6.7, C4HCH_3), 0.85 (3H, d, *J* 6.6, C12CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 135.8 (4C), 134.2 (2C), 129.7 (4C), 127.8 (4C), 68.6 (C1H$_2$), 62.1 (C16H$_2$), 41.2 (C13H$_2$), 39.3 (C15H$_2$), 33.2 (C12H), 27.0 (3C, C(*C*H$_3$)$_3$), 26.8 (C14H), 20.6 (C12H*C*H$_3$), 19.4 (*C*(CH$_3$)$_3$), 17.3 (C14H*C*H$_3$). IR (neat): ν = 3368 br s, 1111 s, 701 s cm^{-1}. LRMS (ES mode): *m*/*z* = 385 (M$^+$H, 20%). HRMS (ES mode): *m*/*z* calcd for $C_{24}H_{36}O_2NaSi$: 407.2382; found: 407.2373 [MNa]. Anal. calcd for $C_{24}H_{36}O_2Si$: C, 74.94; H, 9.43. Found: C, 75.0; H, 9.5.

(2*R*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexanoic acid (33)

$RuCl_3 \cdot nH_2O$ (17 mg) was added in one portion to a solution of **39** (0.62 g, 1.6 mmol, 1.0 equiv.) and $NaIO_4$ (1.21 g, 5.6 mmol, 3.5 equiv.) in CCl_4 (3.9 mL), MeCN (3.9 mL) and H_2O (6.2 mL). The reaction was stirred vigorously at r.t. for 3.5 h. Thereafter, Et_2O (5 mL) and H_2O (5 mL) were added and the layers separated. The organic layer was extracted with Et_2O (5 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The green residue was purified by column chromatography [SiO_2 Et_2O–hexanes (1 : 3)] to give the title compound **33** (0.57 g, 1.43 mmol, 89%) as a colourless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (4H, dd, *J* 7.8 and 1.5), 7.44–7.37 (6H, m), 3.74–3.65 (2H, m, C16H$_2$), 2.58–2.54 (1H, m, C12H), 1.74–1.67 (2H, m, C13H_AH$_B$/C14H), 1.64–1.57 (1H, m, C15H_AH$_B$), 1.36–1.29 (1H, m, C15H$_A$$H_B$), 1.23–1.16 (1H, m, C13H$_A$$H_B$), 1.17 (3H, d, *J* 6.91, C14HCH_3), 1.04 (9H, s, C(CH_3)$_3$), 0.86 (3H, d, *J* 6.4, C12HCH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 135.8 (4*C*H), 134.2 (2C), 129.7 (4*C*H), 127.8 (4*C*H), 61.9 (C16H$_2$), 41.4 (C13H$_2$), 39.6 (C15H$_2$), 37.2 (C12H), 27.5 (C14H), 27.0 (C(*C*H$_3$)$_3$), 19.7 (C12H*C*H$_3$), 19.3 (*C*(CH$_3$)$_3$), 17.2 (C14H*C*H$_3$). (C=O, not visible). IR (neat): ν = 3300–2200 m br, 1706 s, 1111 s cm^{-1}. LRMS (ES mode): *m*/*z* = 421.3 (MNa$^+$, 80%), 381.3 (67), 261.2 (100). HRMS (ES mode): *m*/*z* calcd for $C_{24}H_{34}O_3NaSi$: 421.2175; found: 421.2195 [MNa].

bis[(−)-1-Neomenthylindenyl)zirconium dichloride (41)

The title compound was prepared by a modification of the procedure by Erker and co-workers.[49] *n*-BuLi (1.58 M

in hexanes, 7.37 mL, 11.65 mmol, 2.0 equiv.) was added dropwise to a solution of (+)-3-[1′*S*,2′*S*,5′*R*)-2′-isopropyl-5′-methylcyclohexyl]indene (2.96 g, 11.65 mmol, 2.0 equiv.) in THF (80 mL) at 0 °C. The reaction was stirred at r.t. for 2.5 h. The solution was cooled to −40 °C and transferred by cannula to a flask containing a suspension of $ZrCl_4(thf)_2$ (2.20 g, 5.82 mmol, 1.0 equiv.) in PhMe (30 mL) at −78 °C. The reaction mixture was gradually warmed to r.t. (over 4 h) and stirred for a further 16 h whereupon a bright yellow suspension was obtained. The solvent was removed *in vacuo* (vacuum quenched with N_2) giving a yellow–orange solid. The solid was washed with pentane (40 mL) and treated with CH_2Cl_2 (80 mL) under a nitrogen atmosphere. After stirring at r.t. for 2 h the precipitate was removed by filtration through a celite pad (under nitrogen). The yellow–orange filtrate was concentrated to saturation (solvent removal by distillation) and set in the freezer for 16 h. The mother liquor was removed *via* cannula and the crystals washed at −78 °C with CH_2Cl_2 (5 mL). After removal of the washings the crystals were dried under a stream of nitrogen for 2 h. The title compound (0.6 g, 0.9 mmol, 15%) was obtained as bright yellow needles (2 crops): mp 140–141.5 °C; lit.[49] mp 146 °C; $[\alpha]_D^{22}$ −67 ($c = 0.1$, $PhCH_3$); lit.[49] $[\alpha]_D^{22}$ −77 ($c = 0.23$, $PhCH_3$). ^{1}H NMR, ^{13}C NMR and IR spectroscopic data agree with those reported. [49]

(*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methyl-butan-1-ol (36) *via* carboalumination

Alcohol **36**, prepared on a 1.0 mmol scale (74%) from 4-(*tert*-butyldiphenylsilyloxy)-but-3-ene[48] according to literature procedure,[54] gave NMR and IR spectroscopic data that agree with those reported.[54] $[\alpha]_D^{22}$ +4 ($c = 1.5$, Et_2O). The er of **36** (88 : 12) was ascertained by integration of the ^{19}F signals of the Mosher ester derivative prepared as described above.

(2*R*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol (39) *via* carboalumination

t-BuLi (1.63 M in pentane, 2.17 mL, 3.54 mmol, 2.0 equiv.) was added dropwise to a solution of iodoalkane **37** (0.8 g, 1.77 mmol, 1.0 equiv.) in Et_2O (1.7 mL) at −78 °C. The mixture was stirred at −78 °C for 40 min whereupon $ZnBr_2$ (0.26 g, 1.15 mmol, 0.65 equiv.) in THF (17 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min and 0 °C for 10 min. A solution of freshly prepared $Pd(PPh_3)_4$ (0.104 g, 0.09 mmol, 5 mol%) in a 4 M solution of vinyl bromide in THF (1.77 mL, 4.0 equiv.) was added *via* syringe at 0 °C. The mixture was allowed to warm gradually to r.t. over 15 h whereupon H_2O (5 mL) was added and the resultant mixture filtered through celite. The layers of the filtrate were separated and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue, consisting of an inseparable mixture of **43** and the *tert*-butyldiphenylsilyl ether of 3-methylbutanol, was passed through a short column of silica gel eluting with hexanes. Evaporation of the solvent gave a colourless oil that was used immediately in the next step.

Neat $AlMe_3$ (0.51 mL, 5.31 mmol, 3.0 equiv.) was added to a solution of (−)-**41** (6.0 mg, 0.088 mmol, 0.5 mol%) in CH_2Cl_2 (7 mL). The resulting homogenous solution was cooled to −50 °C and H_2O (31 μL, 1.77 mmol, 1.0 equiv.) added dropwise with vigorous stirring. The reaction was warmed to r.t. (over 2 h) whereupon a dark orange–red solution was obtained. The solution was cooled to −20 °C and crude **43** in CH_2Cl_2 (1.0 mL) added dropwise. The reaction was stirred at −20 °C for 4 h and r.t. for 15 h. The reaction was cooled to 0 °C and O_2 bubbled through for 3 h. The solution was washed with NaOH (2 M, 2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 5)] to give the title compound **39** (348 mg, 0.9 mmol, 51%, dr 2.3 : 1) as a colourless oil. The dr of **39** varied between 2.2 : 1 to 3.7 : 1 and we were unable to identify an experimental procedure that gave consistent results.

The identity of the major product **39** and the dr was determined by comparison of the ^{13}C and ^{1}H NMR spectroscopic data recorded on the mixture with those recorded for the pure isomer prepared as described above.

Methyl [4*R*,6*S*,8*S*]-9-hydroxy-4,6,8-trimethylnonanoate (44)

TBAF·$3H_2O$ (61 mg, 0.23 mmol) was added in one portion to silyl ether **3** (100 mg, 0.2 mmol) in THF (1.0 mL) at r.t. and the resulting pale yellow solution was stirred at r.t. for 3 h. H_2O (2 mL) was added, the layers separated and the aqueous layer extracted with Et_2O (2 × 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography [SiO_2, hexanes–Et_2O (5 : 1) → (1 : 3)] gave the title compound **44** (49 mg, 0.2 mmol, 100%) as a colourless oil. $[\alpha]_D$ −20.1 ($c = 1.0$, $CHCl_3$); lit.[5] $[\alpha]_D$ −37.0 ($c = 1.0$, $CHCl_3$), Lit.[16] $[\alpha]_D$ −22.6 ($c = 1.0$, $CHCl_3$), Lit.[17] $[\alpha]_D$ −26.8 ($c = 1.0$, $CHCl_3$). Spectroscopic data are in accordance with those reported.[5,16,17]

Methyl (4*R*,6*S*,8*S*)-4,6,8-trimethyl-9-oxononanoate (47)

The aldehyde **45**, prepared on a 0.44 mmol scale (75% yield from **44**) according to a literature procedure,[5] gave spectroscopic data in accordance with those reported.[5,16,17] $[\alpha]_D = -10.1$ ($c = 1.0$, $CHCl_3$); lit.[5] $[\alpha]_D = -9.0$ ($c = 1.0$, $CHCl_3$).

Methyl (4*R*,6*S*,8*S*,12*R*,14*S*,*Z*)-16-(*tert*-butyldiphenylsilyloxy)-11-hydroxy-4,6,8,12,14-pentamethyl-9-oxohexadec-10-enoate (2)

n-BuLi (1.6 M in hexanes, 0.11 mL, 0.17 mmol, 1.0 equiv.) was added dropwise to a solution of diisopropylamine (27 μL, 0.19 mmol, 1.1 equiv.) in THF (0.16 mL) at −78 °C. The reaction was stirred at −78 °C for 10 min and 0 °C for 10 min. The solution was cooled to −20 °C and added dropwise to a pale yellow solution of α-diazoketone **4** (70 mg, 0.17 mmol, 1.0 equiv.) and aldehyde **45** (39 mg, 0.17 mmol, 1.0 equiv.) in THF (0.25 mL) at −78 °C. The resulting red–orange solution was stirred at −78 °C for 1 h before being quenched by dropwise addition of AcOH–Et_2O (1 : 5, 1.5 mL). The resulting pale yellow solution was warmed to r.t. and water (1 mL) added. The layers were separated and the organic layer washed with $NaHCO_3$ (saturated aqueous, 2 × 1 mL) and brine (1 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 5)] to give the α-diazo-β-hydroxy carbonyl compound **47** (80 mg) as a yellow oil and recovered **4** (15 mg, 0.036 mmol). The yellow oil was dissolved in DME (0.5 mL) whereupon $Rh_2(OAc)_4$

(1 mg, 2 μmol, 0.01 equiv.) was added. The resultant emerald green solution was stirred at r.t. for 100 min. The reaction mixture was filtered through a pad of celite eluting with hexanes (10 mL). The filtrate was concentrated *in vacuo.* The residue was purified by column chromatography [SiO_2, Et_2O–hexanes (1 : 5)] to give the title compound **2** (64 mg, 0.10 mmol, 60%) as a colourless oil: $[\alpha]_D^{25}$ −9.4 (c = 0.17, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): 15.74 (1H, s, OH), 7.67 (4H, d, J 7.7), 7.45–7.36 (6H, m), 5.46 (1H, s, C10H), 3.76–3.60 (2H, m, C16H_2), 3.67 (3H, s, CO_2Me), 2.45–2.38 (2H, m, C8H/C12H), 2.35–2.25 (2H, m, C2H_2), 1.69–1.41 (9H, m, C3H_2/C4H/C6H/C7H_2/C13H_2/C15$H_A$$H_B$), 1.36–1.28 (1H, m, C15$H_A$$H_B$), 1.20–1.09 (2H, m, C5$H_2$), 1.13–1.11 (6H, overlapping 2 × d, J 6.8 each, C8CH_3/C12CH_3), 1.05 (9H, s, (SiC(CH_3)$_3$), 0.92–0.81 (1H, m, C14H), 0.86–0.81 (9H, overlapping 3 × d, J 6.3, 6.4 and 6.5, C4CH_3/C6CH_3/C14CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 199.1, 198.6 (C9/C11), 174.6 (C1), 135.7 (4CH), 134.22 (2C), 129.7 (2CH), 127.8 (4CH), 97.2 (C10H), 62.0 (C16H_2), 51.7 (CO_2CH_3), 44.4 (C5H_2), 42.5 (C15H_2), 41.8 (C13H_2), 40.3, 40.1 (C8H/C12H), 39.7 (C7H_2), 32.9 (C2H_2), 32.0 (C3H_2), 29.8, 28.0, 27.5 (C4H/C6H/C14H), 27.0 (SiC(CH_3)$_3$), 19.9, 19.6, 19.1 (C4CH_3/C6CH_3/C14CH_3), 19.3 (SiC(CH_3)$_3$), 18.5 (2C, C8CH_3/C12CH_3). IR (neat): ν = 2929 s, 1741 s, 1603 br s, 1111 s, 702 s cm^{-1}. LRMS (ES mode): m/z = 645.5 [(MNa)$^+$, 55%], 546.4 (70), 545.4 (80), 468.4 (60), 467.4 (100). HRMS (ES mode): m/z calcd for $C_{38}H_{58}O_5NaSi$: 645.3951; found: 645.3964 (MNa). Anal. calcd for $C_{38}H_{58}O_5Si$: C, 73.27; H, 9.38. Found: C, 73.25; H, 9.5.

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