# A SYNTHESIS OF THE C1–C9 FRAGMENT OF IONOMYCIN USING CATIONIC $\eta^3$-ALLYLICMOLYBDENUM AND -IRON COMPLEXES

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A key step in the synthesis of the C1–C9 fragment of the ionophore antibiotic ionomycin involves the addition of an alkylcopper(I) reagent to an ester-functionalised cationic $\eta^3$-allylicmolybdenum and an alkylzinc cuprate to the corresponding $\eta^3$-allyliciron complex. The reaction is regioselective and the metal directs enantiofacial attack (*anti*). The stereochemistry of the reactions is proven by an independent synthesis.

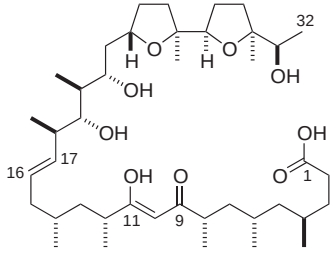
**Keywords**: Ionophores; Antibiotics; π-Allyl complexes; Molybdenum; Iron; Cuprates; Total synthesis; Stereoselective alkylations.

Ionomycin (**1**) is rare among the polyether antibiotics because it is a doubly charged ionophore that forms neutral hexacoordinate complexes with divalent cations, especially calcium. An X-ray crystal structure disclosed in 1979 [1,2] established the absolute stereochemistry of the 14 stereogenic centres and revealed the presence of an unusual β-diketone which, together with the carboxylate ion at C1, accounts for the preferential binding of divalent cations[3]. There have been three total syntheses of ionomycin from the groups of Evans[4], Hanessian[5] and Lautens[6] as well as numerous syntheses of various fragments[7–16]. We now report a synthesis of the C1–C9 fragment **2** which features the use of functionalised planar chiral cationic $\eta^3$-allylicmolybdenum and -iron complexes to install the carboxyl terminus and control the stereochemistry at C4 in a single operation. Such complexes have been rarely used in natural product synthesis. In the following account we (i) compare the relative merits of cationic molybdenum and iron complexes and (ii) investigate the optimum nucleophilic partners for the complexes.

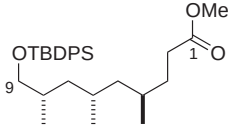
## RESULTS AND DISCUSSION

### *Synthesis of the Functionalised $\eta^3$-Allylicmolybdenum and -iron Complexes **5** and **8***

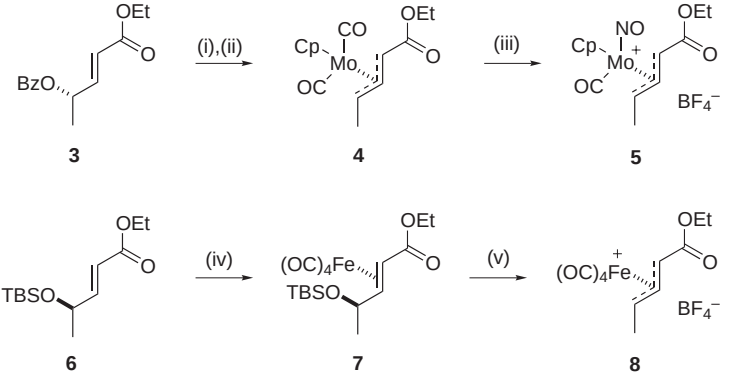
The $\eta^3$-allylmolybdenum complex **5** was prepared by a modification of a known route[17] as shown in Scheme 1. The sequence began with the reaction of the enantiopure allylic benzoate **3** (five steps from ethyl (*S*)-lactate) with $[Mo(CO)_4(thf)_2]$ generated in situ by the thermolysis of $[Mo(CO)_6]$ in THF. Oxidative addition occurred with clean retention of configuration to




ionomycin (**1**)




C1-C9 fragment (**2**)




SCHEME 1

(i) $[Mo(CO)_6]$, THF, reflux, 1 h, then add **3**, reflux 20 h; (ii) add LiCp, r.t., 2 h (92% from **3**); (iii) $NOBF_4$, DME, 0 °C; (iv) $[Fe_2(CO)_9]$, $Et_2O$, 20 °C, 3 days; (v) $HBF_4$, $Et_2O$, 20 °C, 1 h (72% from **6**)

give an intermediate which was treated with lithium cyclopentadienide (LiCp) to give the neutral $\eta^3$-allylmolybdenum complex **4** as an air-sensitive orange oil in 92% yield. The $[Mo(CO)_4(thf)_2]$ was superior in speed and efficiency to the $[Mo(CO)_4(py)_2]$ reagent used previously[18]. Neutral complex **4** was converted to the highly reactive cationic complex **5** by ligand exchange with nitrosonium tetrafluoroborate and generally used immediately though the complex can be isolated. The cationic complex **5** was obtained as a mixture of diastereoisomers (central chirality at Mo) owing to the indiscriminate nature of the ligand exchange[19].

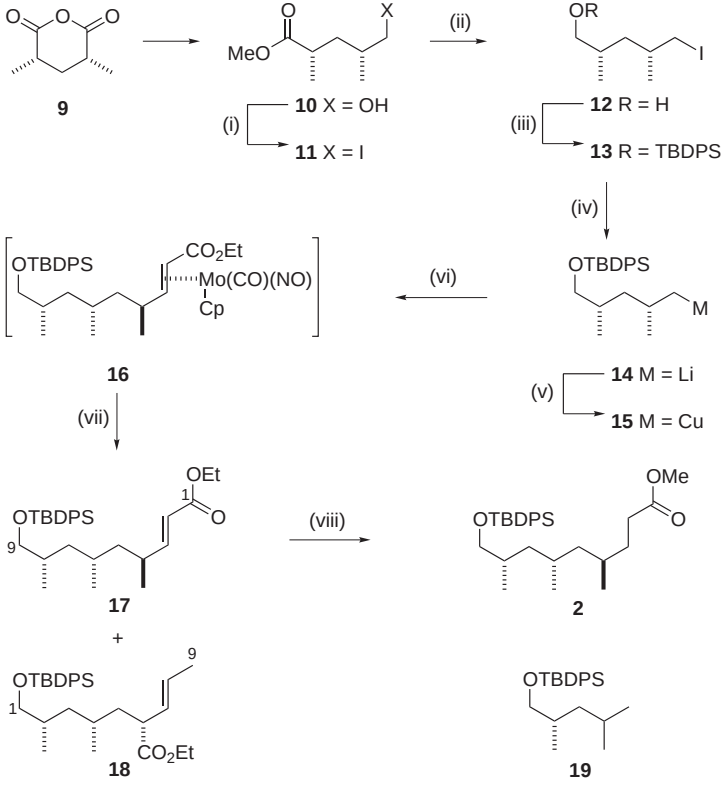
The $\eta^3$-allyliciron complex **8** was prepared according to the procedure of Enders and co-workers[20]. The *tert*-butyldimethylsilyl ether **6** (three steps from ethyl (*R*)-lactate)[17] was simply treated with $[Fe_2(CO)_9]$ in $Et_2O$ at room temperature to give the $\eta^2$-complex **7** which was then treated with $HBF_4$ to give the cationic complex **8** as a yellow powder in 71% yield. The cationic complex, suitably protected from exposure to air and moisture, could be stored for protracted periods at –20 °C.

*Synthesis of C1–C9 Fragment **2** from the Cationic $\eta^3$-Allylicmolybdenum Complex **5***

The enantiopure hydroxyester **10**[21] was prepared in three steps from readily available 2,4-dimethylglutaric anhydride[22,23] (**9**) by a cheap and scalable resolution[21,24,25] (Scheme 2). The hydroxyl group was converted to the iodoalkane **11** using the procedure of Garegg and Samuelsson[26] and the ester function then reduced with DIBALH and the nascent hydroxy compound protected as its *tert*-butyldiphenylsilyl ether **13**. Halogen–lithium exchange with *t*-BuLi generated the lithium reagent **14** which was then transmetallated to the organocopper(I) reagent **15** with freshly recrystallised $CuBr{\cdot}SMe_2$. Addition of cold solution of the cationic complex **5** in 1,2-dimethoxyethane[27] to a solution of the organocopper(I) reagent **15** (1.1 equiv.) in $Et_2O$ at –78 °C gave the yellow $\eta^2$-complex **16** after aqueous work-up but this was not purified; rather, it was immediately treated with cerium(IV) ammonium nitrate[28] to give the desired product **17** in 37% overall yield for the four-step sequence from iodoalkane **13**. The regioisomer **18** (ca. 3%) was also tentatively identified as a component of an inseparable mixture of minor products. However, the major product (50%) was the protonated nucleophile **19**[29]. The spectroscopic data recorded for **17** established that nucleophilic attack had occurred at the $\gamma$-position[30] in agreement with an analogous reaction of an arylcopper(I) reagent with cationic complex **5**[17]. The stereochemistry at C4 was inferred from

precedented attack of various nucleophiles to cationic molybdenum complexes *anti* to the metal[31,32]. The stereochemistry was confirmed by unambiguous synthesis (see below). Reduction of the α,β-unsaturated ester **17** with an excess of magnesium in methanol was accompanied by transesterification to give the methyl ester **2** in 77% yield.

Attempts to improve the yield of **17** by varying the reaction conditions and the nature of the nucleophile were not successful. For example the cyanocuprate (RCu·LiCN) derived from organolithium **14** gave only a 5% yield of **17**; the zinc reagent (RZnX or $R_2Zn$) and the zinc cuprate (RCuCN·ZnX) did not react[33].

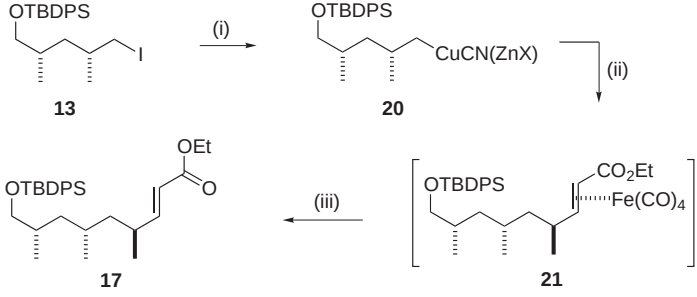



SCHEME 2

(i) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, 20 °C (93%); (ii) DIBALH, PhMe, –78 to 0 °C (94%); (iii) *t*-$BuPh_2SiCl$, imidazole, DMAP, $CH_2Cl_2$, 20 °C (99%); (iv) *t*-BuLi (1.7 equiv.), $Et_2O$, –78 °C; (v) $CuBr{\cdot}SMe_2$, $(i\text{-}Pr)_2S$–$Et_2O$, –78 °C; (vi) add complex **5** in DME to organocopper(I) reagent **15** in $Et_2O$, –78 to 20 °C; (vii) CAN, $Et_2O$–$H_2O$, 20 °C, 1 h (37% overall from **13**); (viii) Mg, MeOH, 0–20 °C, 12 h (77%)

*Synthesis of C1–C9 Fragment **2** from the Cationic $\eta^3$-Allyliciron Complex **8***

The iodoalkane **13** was converted to the corresponding organozinc halide by the method of Knochel[34] (Scheme 3) and thence to the alkylzinc cuprate **20** by addition of CuCN·2LiCl. The zinc cuprate **20** reacted with the cationic complex **8** at the γ-position *anti* to the metal, as amply demonstrated by Enders and co-workers[20,35], to give the α,β-unsaturated ester **17** in 30% yield after oxidative decomplexation of the $\eta^2$-complex **21** with oxygen or cerium(IV) ammonium nitrate. A similar sequence using the organocopper(I) reagent **15** and complex **8** gave **17** in 24% yield. Once again, attempts to improve the yield by varying the nucleophile and conditions failed.

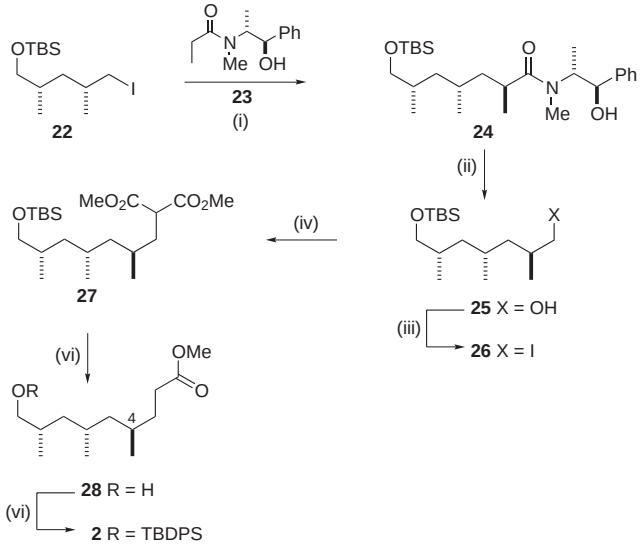



SCHEME 3
(i) Zn, 1,2-dibromoethane, TMSCl, THF, reflux; then add to CuCN·2LiCl, THF, –30 to 0 °C; (ii) add **20** to complex **8** in THF, –78 °C; (iii) CAN, THF–$H_2O$, 20 °C, 3 h (30% overall from **13**)

*Independent Synthesis of C1–C9 Fragment **2** as Proof of Stereochemistry*

In order to confirm that the reactions of the cationic complexes **5** and **8** had occurred *anti* to the metal to give the desired *R*-configuration at C4, an independent synthesis of fragment **2** was undertaken (Scheme 4). A reagent-controlled diastereoselective alkylation of the lithium enolate derived from *N*-propionyl-(1*R*,2*R*)-pseudoephedrine **23** with the iodoalkane **22** gave the alkylation product **24** (99%). Reductive cleavage of the auxiliary using the procedure of Myers[36] gave the alcohol **25** in 78% yield. $^1$H and $^{13}$C NMR spectroscopy of the crude reaction mixture indicated that the reaction was at least 97% diastereoselective. The alcohol was subsequently converted to the iodoalkane **26** using standard procedures. A two-carbon chain extension was performed in two steps beginning with alkylation of the sodium salt of dimethyl malonate by iodoalkane **26**. Krapcho

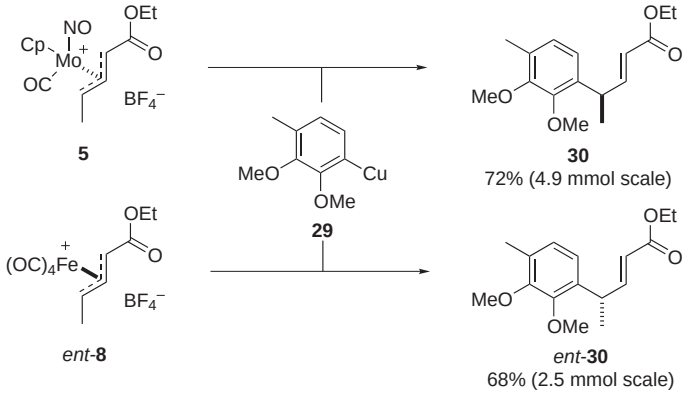
decarboxylation[37] of **27** was accompanied by deprotection of the *tert*-butyldimethylsilyl ether to afford alcohol **28** in 97% yield. Finally, re-protection of the alcohol as its *tert*-butyldiphenylsilyl ether afforded **2** that was identical by $^1$H and $^{13}$C NMR spectroscopy with the samples generated in Schemes 2 and 3.




SCHEME 4

(i) **23**, LDA, LiCl, THF, –78 to 0 °C; add **22**, 0 to 20 °C, 20 h (99%); (ii) LDA, $H_3B{\cdot}NH_3$, THF, 0 to 20 °C (78%); (iii) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, 20 °C (95%); (iv) dimethyl malonate, NaH, THF, 20 °C, then add **26** and reflux 20 h (91%); (v) NaCl, DMSO–$H_2O$, 160 °C, 7 h (97%); (vi) *t*-$BuPh_2SiCl$, DMAP, imidazole, $CH_2Cl_2$, 20 °C (91%)

In conclusion, we have synthesised the C1–C9 fragment **2** of ionomycin by two routes based on the reaction of relatively hard organometallic nucleophiles and cationic $\eta^3$-allyl complexes. With both the molybdenum and iron complexes **5** and **8**, the reaction occurred selectively at the γ-position *anti* to the metal in accord with precedent[32]. In the case of the molybdenum complex, the organocopper(I) nucleophile **15** gave the best yield (37%) whereas the zinc cuprate **20** was superior (30%) in the case of the iron complex. However, in neither case could the yield be raised to a level to justify celebration. It is likely that a combination of higher basicity of the alkylmetallic nucleophile and steric impedance of the α-branch were the root cause of the problem since we have already shown that complexes **5** and *ent*-**8** react with arylcopper(I) reagent **29** to give the products **30** and *ent*-**30** in 68–72% yield (Scheme 5)[17].




SCHEME 5

## EXPERIMENTAL

All reactions requiring anhydrous conditions were conducted under a nitrogen atmosphere in flame-dried glassware unless stated otherwise. Where appropriate, solvents and reagents were dried by 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 $CaH_2$. Freshly distilled light petroleum (b.p. 40–60 °C) was used. All reactions were magnetically stirred and monitored by TLC using 0.25 mm pre-coated silica gel plates visualized with UV light followed by phosphomolybdic acid unless stated otherwise. Organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo using a rotary evaporator. All yields refer to chromatographically and spectroscopically pure products unless stated otherwise.

Infrared spectra were recorded neat on NaCl plates, details are reported as $\nu_{max}$ in $cm^{-1}$, followed by an intensity descriptor. Magnetic resonance spectra were recorded 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 and signal assignments are 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. They are given in $10^{-1}$ deg $cm^2$ $g^{-1}$.

Dicarbonyl(η$^5$-cyclopentadienyl)[(2,3,4-η)-(2*R*,3*S*,4*S*)-5-ethoxy-5-oxopent-2(3)-en-2-yl]-molybdenum (**4**)

A flame dried two-necked flask equipped with a condenser and tap was charged with hexacarbonylmolybdenum (278 mg, 1.05 mmol) and THF (10.5 ml), and the resulting solution was heated under reflux for 1 h. A solution of ethyl (*S*)-4-(benzoyloxy)pent-2-enoate **3** (248 mg, 1.0 mmol) in THF (1.6 ml + 1 ml rinse) was added to the bright yellow reaction mixture via a syringe and the reaction mixture heated under reflux for 20 h forming a red/orange solution. *n*-BuLi (1.56 M solution in hexanes, 0.7 ml, 1.1 mmol) was added

dropwise to a solution of freshly distilled cyclopentadiene (0.1 ml, 1.15 mmol) in THF (1.3 ml) at 0 °C. The resulting white suspension was stirred at room temperature for 15 min, THF (1 ml) added and the pale yellow solution transferred to the reaction flask via a syringe at room temperature followed by a THF (0.5 ml) rinse. The reaction mixture was stirred at room temperature for 2 h forming an orange suspension, filtered through alumina under a nitrogen atmosphere (washing with anhydrous THF) and concentrated in vacuo to give the neutral complex **4** (319 mg, 0.92 mmol, 92%) as an orange oil. Spectroscopic data recorded for **4** are in accordance with those reported[17]. $[\alpha]_D$ –97.8 (*c* 0.1, $CHCl_3$).

Tetracarbonyl[(2,3,4-η)-(2*R*,3*S*,4*S*)-5-ethoxy-5-oxopent-2(3)-en-2-yl]iron(I) Tetrafluoroborate (**8**)

The title compound was obtained as a yellow powder (71%) on a 1.0 mmol scale by the procedure of Enders and co-workers[20].

Methyl (2*S*,4*R*)-5-Iodo-2,4-dimethylpentanoate (**11**)

Alcohol **10** (3.4 g, 20.9 mmol) in $CH_2Cl_2$ (57 ml) was added to a mixture of triphenylphosphine (6.0 g, 23.0 mmol), imidazole (3.3 g, 48.1 mmol), and iodine (5.8 g, 23.0 mmol) in $CH_2Cl_2$ (110 ml) at room temperature and the resulting white suspension stirred at room temperature for 4 h. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ ( 2 × 100 ml), brine (100 ml), dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 20:1) to give the iodoalkane **11** (5.3 g, 19.5 mmol, 93%) as a colourless oil. $^1$H NMR (300 MHz, $CDCl_3$): 3.69 (3 H, s, $CO_2CH_3$); 3.22 (1 H, dd, *J* = 9.7, 4.6, C5$\mathbf{H}_A$H$_B$); 3.13 (1 H, dd, *J* = 9.7, 6.2, C5H$_A$$\mathbf{H}_B$); 2.61–2.47 (1 H, m, C2H); 1.80 (1 H, ddd, *J* = 13.6, 9.2, 4.6, C3$\mathbf{H}_A$H$_B$); 1.55–1.40 (1 H, m, C4H); 1.27 (1 H, ddd, *J* = 13.7, 9.2, 4.5, C3H$_A$$\mathbf{H}_B$); 1.18 (3 H, d, *J* = 7.2, C2$CH_3$); 1.00 (3 H, d, *J* = 6.1, C4$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 177.0 (C1), 51.9 ($CO_2CH_3$), 40.9 (C3$H_2$), 37.4 (C2H), 32.7 (C4H), 20.5 (C4$CH_3$), 18.1 (C2$CH_3$), 17.4 (C5$H_2$). IR (neat): 2969 m, 1736 s, 1197 m. LRMS (ES mode), *m/z*: 271 [$MH^+$, 90%], 263 (75), 239 (10), 211 (7). HRMS (ES mode), *m/z*: 271.0184 [$MH^+$, 95%], calculated for $C_5H_{16}IO$ [$MH^+$]: 271.0190. $[\alpha]_D$ +15.1 (*c* 2.0, $CHCl_3$).

(2*S*,4*R*)-5-Iodo-2,4-dimethylpentan-1-ol (**12**)

DIBALH (1.5 M in PhMe, 30.4 ml, 21.7 mmol) was added dropwise to a stirred solution of ester **11** (5.9 g, 21.7 mmol) in PhMe (97 ml) at –78 °C. The resulting solution was stirred at –78 °C for 1 h, allowed to warm to 0 °C and stirred at 0 °C for a further 1 h. The reaction was quenched with saturated aqueous KNa tartarate (100 ml), the resulting solution stirred vigorously for 1 h, the layers separated and the aqueous layer extracted with $Et_2O$ (3 × 100 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 1:3) to give alcohol **12** (4.9 g, 20.4 mmol, 94%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 3.52 (1 H, dd, *J* = 10.5, 5.4, C1$\mathbf{H}_A$H$_B$); 3.44 (1 H, dd, *J* = 10.5, 6.4, C1H$_A$$\mathbf{H}_B$); 3.26 (1 H, dd, *J* = 9.7, 3.6, C5$\mathbf{H}_A$H$_B$); 3.16 (1 H, dd, *J* = 9.7, 5.6, C5H$_A$$\mathbf{H}_B$); 1.69 (1 H, apparent oct, *J* = 6.8, C2H); 1.54 (1 H, apparent oct, *J* = 6.4, C4H); 1.45 (1 H, ddd, *J* = 13.3, 7.2, 6.2, C3$\mathbf{H}_A$H$_B$); 1.37 (1 H, br s, OH); 1.10 (1 H, ddd, *J* = 13.1, 7.2, 6.3, C3H$_A$$\mathbf{H}_B$); 1.01 (3 H, d, *J* = 6.4, C4$CH_3$); 0.95 (3 H, d, *J* = 6.8, C2$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 68.3 (C1$H_2$), 40.3

($C3H_2$), 33.2 (C3H), 31.8 (C2H), 21.7 ($C4CH_3$), 18.4 ($C5H_2$), 17.3 ($C2CH_3$). IR (neat): 3600–3200 br m, 2957 s, 2923 s, 1457 m, 1378 m, 1194 m, 1036 m. LRMS (ES mode), *m/z*: 225 [$M^+$ – OH, 60%], 183 (30), 169 (10). HRMS (ES mode), *m/z*: 225.0137 [$M^+$ – OH, 10%], calculated for $C_7H_{14}I$ [$M^+$ – OH]: 225.0135. $[\alpha]_D$ –9.4 (*c* 1.5, $CHCl_3$).

(2*S*,4*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-5-iodo-2,4-dimethylpentane (**13**)

TBDPSCl (1.8 g, 6.5 mmol) in $CH_2Cl_2$ (3 ml) was added to a solution of iodoalkane **12** (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 room temperature for 1 h. $H_2O$ (10 ml) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum) to give **13** (3.1 g, 6.45 mmol, 99%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 7.68 (4 H, d, *J* = 6.8, Ph); 7.46–7.38 (6 H, m, Ph); 3.51 (1 H, dd, *J* = 9.8, 5.6, C1$\mathbf{H}_A$H$_B$); 3.45 (1 H, dd, *J* = 9.8, 6.0, C1H$_A$$\mathbf{H}_B$); 3.24 (1 H, dd, *J* = 9.6, 3.6, C5$\mathbf{H}_A$H$_B$); 3.09 (1 H, dd, *J* = 9.6, 5.8, C5H$_A$$\mathbf{H}_B$); 1.72 (1 H, apparent oct, *J* = 6.4, C2H); 1.53–1.46 (1 H, m, C4H); 1.47 (1 H, ddd, *J* = 7.3, 6.6, 5.5, C3$\mathbf{H}_A$H$_B$); 1.08 (9 H, s, $Me_3Si$); 1.01 (1 H, ddd, *J* = 7.3, 6.6, 5.5, C3H$_A$$\mathbf{H}_B$); 0.96 (3 H, d, *J* = 6.4, $C2CH_3$); 0.95 (3 H, d, *J* = 6.8, $C4CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 135.8 (4 C, Ph), 134.1 (2 C, Ph), 129.7 (2 C, Ph), 127.8 (4 C, Ph), 68.9 ($C1H_2$), 40.5 ($C3H_2$), 33.3 (C4H), 32.0 (C2H), 27.1 ($\mathbf{Me}_3$CSi), 21.6 ($C4\mathbf{C}H_3$), 19.5 ($Me_3\mathbf{C}Si$), 18.3 ($C5H_2$), 17.5 ($C2\mathbf{C}H_3$). IR (neat): 3070 s, 2958 s, 2929 s, 1472 m, 1427 m, 1389 m, 1378 m, 1194 m, 1111 s. LRMS (ES mode), *m/z*: 481 [$MH^+$, 10%], 225 (100). HRMS (ES mode), *m/z*: 481.1441 [$MH^+$, 10%], calculated for $C_{23}H_{34}IOSi$ [$MH^+$]: 481.1424. $[\alpha]_D$ –8.0 (*c* 1.0, $CHCl_3$).

Ethyl (2*E*,4*S*,6*S*,8*S*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-4,6,8-trimethylnon-2-enoate (**17**) via Molybdenum Complex **5**

*t*-BuLi (1.6 M in pentane, 0.69 ml, 1.10 mmol) was added dropwise to a solution of iodoalkane **13** (254 mg, 0.53 mmol) in $Et_2O$ (8.5 ml) at –78 °C and the resulting pale yellow solution of organolithium **14** stirred at –78 °C for 1 h. CuBr·$SMe_2$ (109 mg, 0.53 mmol) in diisopropyl sulfide (1.2 ml) at 0 °C was added in one portion to the reaction mixture at –78 °C and the resulting yellow/orange suspension stirred at –78 °C for 30 min.

$NOBF_4$ (59 mg, 0.50 mmol) was added in one portion to a solution of complex **4** (165 mg, 0.48 mmol) in DME (3 ml) at 0 °C whereupon gas evolution was observed. The resulting yellow suspension of **5** was stirred at 0 °C for 15 min and added dropwise to the reaction mixture at –78 °C. The resulting dark brown suspension was stirred at –78 °C for 4 h and allowed to warm to room temperature slowly (20 h) forming a dark brown solution. The reaction was quenched with pre-mixed $NH_4OH$ (10 ml) and saturated aqueous $NH_4Cl$ (10 ml) at room temperature, the layers separated, and the aqueous layer extracted with $Et_2O$ (2 × 20 ml). The combined organic layers were concentrated in vacuo to give a yellow oil containing the $\eta^2$-complex **16**.

Cerium(IV) ammonium nitrate (1.4 g, 2.55 mmol) was added in one portion to the $\eta^2$-complex **16** in THF (10 ml), $Et_2O$ (2.5 ml) and $H_2O$ (2.5 ml) at room temperature and the resulting yellow/orange solution stirred at room temperature for 1 h. $Et_2O$ (5 ml) and $H_2O$ (5 ml) were added, the layers were separated and the aqueous layer extracted with $Et_2O$ (2 ×

10 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 20:1) to give the title compound **17** (86 mg, 0.18 mmol, 37%) and **19** (85 mg, 0.24 mmol, 50%) as colourless oils.

Spectroscopic data for **17**: $^1$H NMR (500 MHz, $CDCl_3$): 7.67 (4 H, dd, *J* = 7.7, 1.3, Ph); 7.45–7.36 (6 H, m, Ph); 6.89 (1 H, dd, *J* = 15.6, 7.5, C3H); 5.76 (1 H, dd, *J* = 15.6, 1.1, C2H); 4.18 (2 H, dq, *J* = 8.6, 7.3, OC$\mathbf{H}_2$CH$_3$); 3.50 (1 H, dd, *J* = 9.8, 5.1, C9$\mathbf{H}_A$H$_B$); 3.41 (1 H, dd, *J* = 9.8, 6.6, C9H$_A$$\mathbf{H}_B$); 2.38 (1 H, apparent sept, *J* = 6.8, C4H); 1.71 (1 H, apparent sext, *J* = 6.4, C8H); 1.56–1.48 (1 H, m, C7$\mathbf{H}_A$H$_B$); 1.38–1.31 (1 H, m, C6H); 1.29 (3 H, t, *J* = 7.3, OCH$_2$C$\mathbf{H}_3$); 1.23 (1 H, ddd, *J* = 13.7, 8.5, 5.5, C5$\mathbf{H}_A$H$_B$); 1.12 (1 H, ddd, *J* = 13.7, 8.6, 5.4, C5H$_A$$\mathbf{H}_B$); 1.06 (9 H, s, Me$_3$Si); 0.99 (3 H, d, *J* = 6.8, C4CH$_3$); 0.96–0.89 (1 H, m, C7H$_A$$\mathbf{H}_B$); 0.93 (3 H, d, *J* = 6.8, C8CH$_3$); 0.82 (3 H, d, *J* = 6.4, C6CH$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 167.2 (C1), 155.5 (C3H), 135.8 (4 C, Ph), 134.2 (2 C, Ph), 129.7 (2 C, Ph), 127.8 (4 C, Ph), 119.1 (C2H), 69.0 (C9H$_2$), 60.3 (OCH$_2$CH$_3$), 43.4 (C5H$_2$), 41.7 (C7H$_2$), 34.0 (C4H), 33.3 (C8H), 27.9 (C6H), 27.1 (**Me**$_3$CSi), 20.4 (Me$_3$**C**Si), 19.5 (C4CH$_3$), 18.9 (C8CH$_3$), 17.9 (C6CH$_3$), 14.5 (OCH$_2$**C**H$_3$). IR (neat): 3683 m, 2959 s, 1720 s, 1461 m, 1427 m, 1366 m, 1264 m, 1179 m, 1112 m. LRMS (ES mode), *m/z*: 503 [MNa$^+$, 40%], 403 (100). HRMS (ES mode), *m/z*: 503.2982 [MH$^+$, 60%], calculated for $C_{30}H_{44}O_3NaSi$ [MNa$^+$]: 503.2957. $[\alpha]_D$ –4.7 (*c* 0.8, $CHCl_3$). For $C_{30}H_{44}O_3Si$ (400.8) calculated: 74.95% C, 9.22% H; found: 74.65% C, 8.95% H.

Spectroscopic data for (*S*)-*tert*-butyl[(2,4-dimethylpentyl)oxy]diphenylsilane (**19**). $^1$H NMR (300 MHz, $CDCl_3$): 7.68 (4 H, dd, *J* = 7.7, 1.3, PhH); 7.45–7.36 (6 H, m, PhH); 3.52 (1 H, dd, *J* = 9.8, 5.6, C1$\mathbf{H}_A$H$_B$); 3.42 (1 H, dd, *J* = 9.8, 6.4, C1H$_A$$\mathbf{H}_B$); 1.78–1.68 (1 H, m, C2H); 1.61 (1 H, m, C4H); 1.24 (1 H, ddd, *J* = 17.5, 8.0, 5.8, C3$\mathbf{H}_A$H$_B$); 1.08 (9 H, s, SiCMe$_3$); 1.01–0.94 (1 H, m, C3H$_A$$\mathbf{H}_B$); 0.93 (3 H, d, *J* = 6.8, C2CH$_3$); 0.87 (3 H, d, *J* = 6.4, C5H$_3$); 0.84 (3 H, d, *J* = 6.4, C4CH$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 135.8 (4 C, Ph), 134.3 (2 C, Ph), 129.6 (2 C, Ph), 127.7 (4 C, Ph), 69.5 (C1H$_2$), 42.9 (C3H$_2$), 33.6 (C2H), 27.1 (Si**C**(CH$_3$)$_3$), 25.4 (C4H), 23.6 (C4CH$_3$), 22.5 (C5H$_3$), 17.9 (Si**C**(CH$_3$)$_3$), 17.3 (C2CH$_3$). IR (neat): 3071 m, 3051 m, 2956 s, 2929 s, 2858 s, 1471 s, 1428 s. LRMS (ES mode), *m/z*: 355 [MH$^+$, 4%]. $[\alpha]_D$ –4.6 (*c* 1.0, $CHCl_3$).

Ethyl (2*E*,4*S*,6*S*,8*S*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-4,6,8-trimethylnon-2-enoate (**17**) via Iron Complex **8**

*A*. Using organocopper(I) reagent **15**: *t*-BuLi (1.63 M in pentane, 0.67 ml, 1.10 mmol) was added dropwise to a solution of iodoalkane **13** (279 mg, 0.58 mmol) in $Et_2O$ (9.5 ml) at –78 °C and the resulting pale yellow solution stirred at –78 °C for 2 h. CuBr·$SMe_2$ (119 mg, 0.58 mmol) in diisopropyl sulfide (1.3 ml) at 0 °C was added to the reaction mixture at –78 °C in one portion and the resulting yellow/orange suspension of organocopper(I) reagent **15** stirred at –78 °C for 30 min. Cationic iron complex **8** (200 mg, 0.52 mmol) was added in one portion to the reaction mixture at –78 °C. The resulting yellow/orange suspension was stirred at –78 °C for 5 h and allowed to warm to room temperature slowly (20 h) forming a dark brown solution. The reaction was quenched with pre-mixed $NH_4OH$ (10 ml) and saturated aqueous $NH_4Cl$ (10 ml) at room temperature, the layers separated, and the aqueous layer extracted with $Et_2O$ (2 × 20 ml). The combined organic layers were concentrated in vacuo to give an orange oil. $CHCl_3$ (20 ml) was added and the solution stirred vigorously open to the air for 3 days. The reaction mixture was concentrated in vacuo to give

an orange oil. Purification by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 20:1) gave the title compound **17** (56 mg, 0.12 mmol, 24%) as a colourless oil.

*B*. Using zinc cuprate **20**. 1,2-Dibromoethane (3 drops) was added to a suspension of zinc powder (316 mg, 4.8 mmol) in THF at room temperature and the mixture heated under reflux for 2 min. The dark suspension was allowed to cool to room temperature, TMSCl (2 drops) added and the resulting mixture stirred at room temperature for 25 min. Iodoalkane **13** (1.7 g, 3.6 mmol) in THF (2 ml) was added to the freshly activated zinc at room temperature and the resulting suspension stirred at room temperature for 20 h forming a pale grey suspension. The reaction mixture was added dropwise to a suspension of CuCN (318 mg, 3.6 mmol) and LiCl (301 mg, 7.1 mmol) in THF (6 ml) at –30 °C and the resulting pale grey suspension allowed to warm to 0 °C over 30 min. The reaction mixture was added dropwise to a suspension of cationic iron complex **8** (271 mg, 0.71 mmol) in THF (4 ml) at –78 °C. The resulting yellow suspension was stirred at –78 °C for 5 h and allowed to warm to room temperature slowly (20 h) forming a dark yellow/brown solution. CAN (1.5 g, 2.8 mmol) in $H_2O$ (10 ml) was added to the reaction mixture at room temperature and the resulting yellow/brown suspension stirred at room temperature for 3 h. $Et_2O$ (15 ml) was added to the reaction mixture, the layers separated, and the aqueous layer extracted with $Et_2O$ (2 × 15 ml). The combined organic layers were washed with pre-mixed $NH_4OH$ (20 ml) and saturated aqueous $NH_4Cl$ (20 ml), brine (40 ml), dried (anhydrous $Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 20:1) to give the title compound **17** (100 mg, 0.2 mmol, 30%) having spectroscopic data identical to those reported above.

Methyl (4*R*,6*S*,8*S*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-4,6,8-trimethylnonanoate (**2**)

Magnesium (14.1 mg, 0.6 mmol) was added in one portion to a colourless solution of ester **17** (28 mg, 0.06 mmol) in MeOH (0.5 ml) at 0 °C. The resulting grey suspension was stirred at 0 °C for 5 h, allowed to warm to room temperature slowly (18 h) and stirred at room temperature for a further 2 days. The reaction mixture was filtered and the residue rinsed with $Et_2O$ (2 × 5 ml). The solution was washed with 1 M HCl (10 ml), dried ($Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 20:1) to give ester **2** (21 mg, 0.05 mmol, 77%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 7.68 (4 H, dd, *J* = 8.1, 1.7, Ph); 7.45–7.36 (6 H, m, Ph); 3.67 (3 H, s, $OCH_3$); 3.51 (1 H, dd, *J* = 9.8, 5.1, C9$\mathbf{H}_A$H$_B$); 3.42 (1 H, dd, *J* = 9.8, 6.4, C9H$_A$$\mathbf{H}_B$); 2.36–2.26 (2 H, m, C2H$_2$); 1.73 (1 H, apparent sext, *J* = 6.4, C8H); 1.63–1.44 (5 H, m, C6H/C4H/C3H$_2$/C5$\mathbf{H}_A$H$_B$); 1.30 (1 H, apparent quint, *J* = 6.8, C7$\mathbf{H}_A$H$_B$); 1.06 (9 H, s, $Me_3Si$); 1.01–0.96 (1 H, m, C5H$_A$$\mathbf{H}_B$); 0.96–0.90 (1 H, m, C7H$_A$$\mathbf{H}_B$); 0.93 (3 H, d, *J* = 6.8, C8C$H_3$); 0.83 (3 H, d, *J* = 6.0, C4C$H_3$); 0.79 (3 H, d, *J* = 6.4, C6C$H_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 174.8 (C1), 135.8 (4 C, Ph), 134.3 (2 C, Ph), 129.7 (2 C, Ph), 127.7 (4 C, Ph), 69.2 (C9$H_2$), 51.7 ($OCH_3$), 44.2 (C5$H_2$), 42.2 (C7$H_2$), 33.3 (C8H), 33.2 (C2$H_2$), 32.1 (C3$H_2$), 29.9 (C4H), 27.6 (C6H), 27.1 ($\mathbf{Me}_3$CSi), 20.2 (C4$\mathbf{C}H_3$), 19.5 ($Me_3$C$\mathbf{Si}$), 19.1 (C6$\mathbf{C}H_3$), 17.8 (C8C$H_3$). IR (neat): 2956 s, 2929 s, 2858 s, 1742 s, 1472 s, 1462 s, 1428 s. LRMS (ES mode), *m*/*z*: 491 [M$Na^+$, 20%], 392 (70), 391 (100). For $C_{29}H_{44}O_3Si$ (468.8) calculated: 74.31% C, 9.46% H; found: 74.25% C, 9.30% H. $[\alpha]_D$ –18.1 (*c* 2.0, $CHCl_3$).

(2*S*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-iodo-2,4-dimethylpentane (**22**)

The TBS ether **22** (6.9 g, 19.3 mmol, 97%) prepared from alcohol **12** (4.8 g, 19.9 mmol) by the procedure of Hoffman and co-workers[38] gave spectroscopic data in accordance with those reported. $[\alpha]_D$ –4.0 (*c* 7.0, $CHCl_3$); lit.[38] $[\alpha]_D$ –4.2 (*c* 9.96, $CHCl_3$).

*N*-Propionyl (1*R*,2*R*)-Pseudoephedrine (**23**)

The title compound, prepared on a 60 mmol scale (90% yield from (1*R*,2*R*)-pseudoephedrine) according to a literature procedure, gave m.p. 115–116 °C; lit.[36] m.p. 114–115 °C. $[\alpha]_D$ –101.8 (*c* 1.0, MeOH); lit.[36] $[\alpha]_D$ –102 (*c* 1.0, MeOH).

(2*S*,4*S*,6*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethylheptan-1-ol (**25**)

BuLi (in 1.6 M hexanes, 14.0 ml, 22.4 mmol) was added dropwise to a mixture of diisopropylamine (3.4 ml, 24.1 mmol) and anhydrous LiCl (3.0 g, 71.1 mmol) in THF (16 ml) at –78 °C. The resulting pale yellow suspension was stirred at 0 °C for 10 min and then re-cooled to –78 °C. *N*-Propionyl (1*R*,2*R*)-pseudoephedrine (**23**) (2.6 g, 11.8 mmol) in THF (35 ml) was added via a cannula to the freshly prepared LDA solution at –78 °C and the resulting white suspension stirred at –78 °C for 1 h. The reaction mixture was warmed to 0 °C for 15 min, stirred at room temperature for 5 min and then recooled to 0 °C. Iodoalkane **22** (2.0 g, 5.6 mmol) in THF (2 ml) was added dropwise to the reaction mixture at 0 °C and the resulting suspension allowed to warm to room temperature slowly (20 h). The reaction was quenched with saturated aqueous $NH_4Cl$ (60 ml), the layers separated and the aqueous layer extracted with $Et_2O$ (3 × 60 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 1:1) to give the amide **24** (2.5 g, 5.6 mmol, 99%) as a pale yellow oil.

BuLi (1.6 M in hexanes, 13.7 ml, 21.8 mmol) was added dropwise to a solution of diisopropylamine (3.3 ml, 23.5 mmol) in THF (24 ml) at –78 °C. The resulting solution was stirred at 0 °C for 10 min. Borane–ammonia complex (691 mg, 22.4 mmol) was added in one portion to the freshly prepared LDA solution at 0 °C and the resulting white suspension stirred at 0 °C for 10 min, at room temperature for 15 min and then recooled to 0 °C. The amide **24** (2.5 g, 5.6 mmol) in THF (14 ml) was added dropwise via a cannula at 0 °C. The resulting colourless solution was stirred at room temperature for 2 h, quenched at 0 °C with the slow dropwise addition of 2 M HCl (50 ml) and stirred at room temperature a further 30 min. The layers were separated and the aqueous layer extracted with $Et_2O$ (4 × 50 ml). The combined organic layers were washed with 1 M HCl (80 ml), 2 M NaOH (80 ml) and brine (80 ml), dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 1:1) to give the alcohol **25** (1.30 g, 4.4 mmol, 78%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 3.47 (1 H, dd, *J* = 10.3, 6.0, C7$\mathbf{H}_A$H$_B$); 3.45 (1 H, dd, *J* = 9.8, 5.6, C1$\mathbf{H}_A$H$_B$); 3.43 (1 H, dd, *J* = 10.3, 6.4, C7H$_A$$\mathbf{H}_B$); 3.35 (1 H, dd, *J* = 9.8, 6.6, C1H$_A$$\mathbf{H}_B$); 1.78–1.65 (2 H, m, C2H/C6H); 1.65–1.56 (1 H, m, C4H); 1.34 (1 H, br s, OH); 1.30 (1 H, ddd, *J* = 13.6, 7.3, 6.7, C3$\mathbf{H}_A$H$_B$); 1.09 (2 H, apparent t, *J* = 6.8, C5H$_2$); 0.93 (1 H, ddd, *J* = 13.6, 7.3, 6.7, C3H$_A$$\mathbf{H}_B$); 0.90 (9 H, s, $Me_3$Si); 0.89 (3 H, d, *J* = 5.6, C2C$H_3$); 0.88 (3 H, d, *J* = 3.4, C4C$H_3$); 0.87 (3 H, d, *J* = 3.4, C6C$H_3$); 0.04 (6 H, s, $Me_2$Si). $^{13}$C NMR (75 MHz, $CDCl_3$): 69.4 (C7H$_2$), 68.5 (C1H$_2$), 42.1 (C3H$_2$), 40.5 (C5H$_2$), 33.4 (C2H), 33.2 (C6H), 27.4 (C4C$H_3$), 26.1 ($\mathbf{Me}_3$CSi), 20.4 (C4C$H_3$), 18.5 ($Me_3$C Si),

17.6 (C6$\mathbf{C}H_3$), 16.4 (C2$\mathbf{C}H_3$), –5.2 ($Me_2Si$). IR (neat): 3800–3000 br s, 2956 m, 2928 m, 2857 m, 1099 m, 836 s, 774 s. LRMS (ES mode), *m/z*: 289 [$MH^+$, 100%], 247 (10), 198 (25), 157 (10). HRMS (ES mode), *m/z*: 289.2570 [$MH^+$, 95%], calculated for $C_{16}H_{37}O_2Si$ [$MH^+$]: 289.2564. For $C_{16}H_{36}O_2Si$ (288.6) calculated: 66.60% C, 12.58% H; found: 66.5% C, 12.4% H. $[\alpha]_D$ –20.1 (*c* 1.0, $CHCl_3$).

(2*S*,4*R*,6*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-iodo-2,4,6-trimethylheptane (**26**)

Alcohol **25** (1.20 g, 4.12 mmol) in $CH_2Cl_2$ (14 ml) was added to a mixture of triphenylphosphine (1.20 g, 4.53 mmol), imidazole (645 mg, 9.48 mmol), and iodine (1.15 g, 4.53 mmol) in $CH_2Cl_2$ (22 ml) at room temperature and the resulting orange suspension stirred at room temperature for 18 h. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ (2 × 30 ml), brine (30 ml), dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 60:1) to give the iodoalkane **26** (1.55 g, 3.9 mmol, 95%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 3.44 (1 H, dd, *J* = 9.8, 5.1, C1$\mathbf{H}_A$H$_B$); 3.37 (1 H, dd, *J* = 9.8, 6.4, C1H$_A\mathbf{H}_B$); 3.19 (1 H, dd, *J* = 9.4, 5.1, C7$\mathbf{H}_A$H$_B$); 3.14 (1 H, dd, *J* = 9.4, 6.0, C7H$_A\mathbf{H}_B$); 1.69 (1 H, apparent sext, *J* = 6.4, C2H); 1.64–1.55 (2 H, m, C4H/C6H); 1.31 (1 H, apparent quint, *J* = 6.8, C3H$_A\mathbf{H}_B$); 1.20–1.10 (2 H, m, C5$H_2$); 0.96 (3 H, d, *J* = 6.8, C4$CH_3$); 0.97–0.90 (1 H, m, C3H$_A\mathbf{H}_B$); 0.91 (9 H, s, $Me_3Si$); 0.88 (3 H, d, *J* = 6.8, C2$CH_3$); 0.87 (3 H, d, *J* = 6.8, C6$CH_3$); 0.05 (6 H, s, $Me_2Si$). $^{13}$C NMR (75 MHz, $CDCl_3$): 68.3 (C1$H_2$), 44.2 (C5$H_2$), 41.7 (C3$H_2$), 33.1 (C2H), 32.6 (C4H), 27.8 (C6H), 26.2 ($Me_3\mathbf{C}Si$), 20.5 (C4$\mathbf{C}H_3$), 20.4 (C6$\mathbf{C}H_3$), 18.9 (C7$H_2$), 18.5 ($Me_3\mathbf{C}Si$), 17.7 (C2$\mathbf{C}H_3$), –5.1 ($Me_2Si$). IR (neat): 2956 s, 2928 s, 2856 s, 1462 m, 1378 m, 1251 m, 1193 m, 1097 br m, 836 s, 775 s. For $C_{16}H_{35}IOSi$ (398.5) calculated: 48.23% C, 8.85% H; found: 48.3% C, 8.9% H. $[\alpha]_D$ –13.2 (*c* 1.0, $CHCl_3$).

Dimethyl 2-{(2*S*,4*S*,6*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethylheptyl}-malonate (**27**)

Dimethyl malonate (0.6 ml, 5.6 mmol) was added dropwise (gas evolution observed) to a stirred suspension of NaH (60% dispersion in mineral oil, washed with anhydrous pentane 2 × 2 ml, 198 mg, 5.0 mmol) in THF (18 ml) at room temperature and the resulting colourless solution was stirred at room temperature for 1 h. A solution of iodoalkane **26** (1.5 g, 3.7 mmol) in THF (4 ml) was added dropwise to the reaction mixture and the resulting solution heated under reflux for 20 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (20 ml), the layers separated and the aqueous layer extracted with $Et_2O$ (3 × 20 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 7:1) to give the malonate **27** (1.22 g, 3.4 mmol, 91%) as a colourless oil. $^1$H NMR (500 MHz, $CDCl_3$): 3.74 (6 H, s, 2 × OMe); 3.49 (1 H, apparent t, *J* = 7.7, C$\mathbf{H}(CO_2Me)_2$); 3.45 (1 H, dd, *J* = 9.4, 5.6, C7$\mathbf{H}_A$H$_B$); 3.32 (1 H, dd, *J* = 9.4, 6.8, C7H$_A\mathbf{H}_B$); 1.87 (1 H, ddd, *J* = 14.1, 7.7, 6.8, C1$\mathbf{H}_A$H$_B$); 1.76 (1 H, ddd, *J* = 14.1, 7.3, 7.3, C1H$_A\mathbf{H}_B$); 1.67 (1 H, apparent sext, *J* = 6.8, C6H); 1.62–1.55 (1 H, m, C4H); 1.53–1.43 (1 H, m, C2H); 1.24 (1 H, ddd, *J* = 13.7, 6.8, 6.8, C5$\mathbf{H}_A$H$_B$); 1.11 (1 H, ddd, *J* = 13.3, 9.8, 6.0, C3$\mathbf{H}_A$H$_B$); 1.01 (1 H, ddd, *J* = 13.7, 9.8, 5.8, C3H$_A\mathbf{H}_B$); 0.92 (1 H, ddd, *J* = 13.7, 7.1, 6.8, C5H$_A\mathbf{H}_B$); 0.90 (9 H, s, $Me_3Si$); 0.87 (6 H, d, *J* = 6.8, C6/C2$CH_3$); 0.82 (3 H, d, *J* = 6.8, C4$CH_3$); 0.04 (6 H, s, $Me_2Si$). $^{13}$C NMR (75 MHz, $CDCl_3$): 170.4 ($\mathbf{C}O_2CH_3$), 170.2 ($\mathbf{C}O_2CH_3$), 68.6 (C7$H_2$), 52.6 (CH($CO_2\mathbf{C}H_3$)$_2$), 49.8

(**C**H($CO_2CH_3$)$_2$), 44.0 (C3$H_2$), 42.2 (C5$H_2$), 37.1 (C1$H_2$), 33.2 (C6H), 28.5 (C4H), 27.5 (C2H), 26.1 (**Me**$_3$CSi), 20.2 (C4**C**$H_3$), 19.1 (C4**C**$H_3$), 18.5 ($Me_3$**C**Si), 17.5 (C4**C**$H_3$), –5.2 ($Me_2$Si). IR (neat): 2956 s, 2929 s, 2857 s, 1758 s, 1739 s, 1463 m, 1436 m, 1256 s. LRMS (ES mode), *m/z*: 425 [$MNa^+$, 50%], 403 [$MH^+$, 100], 272 (35), 271 (100), 239 (95), 221 (50), 207 (50). HRMS (ES mode), *m/z*: 403.2867 [$MH^+$, 100%], calculated for $C_{21}H_{43}O_5Si$ [$MH^+$]: 403.2880. For $C_{21}H_{42}IO_5Si$ (529.6) calculated: 62.64% C, 10.51% H; found: 42.45% C, 10.7% H. $[\alpha]_D$ –20.2 (*c* 1.0, $CHCl_3$).

Methyl (4*R*,6*S*,8*S*)-9-Hydroxy-4,6,8-trimethylnonanoate (**28**)

A solution of malonate **27** (156 mg, 0.39 mmol), NaCl (30.0 mg, 0.51 mmol) and $H_2O$ (0.03 ml, 1.48 mmol) in DMSO (2 ml) was heated at 160 °C until no further evolution of gas was observed (7 h). The orange reaction mixture was allowed to cool to room temperature and $H_2O$ (10 ml) added. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 10 ml). The combined organic layers were washed with $H_2O$ (2 × 40 ml) and brine (40 ml), dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 10:1) to give the methyl ester **28** (87 mg, 0.37 mmol, 97%) as a pale yellow oil. The $^1$H and $^{13}$C NMR data recorded for **28** agreed with those reported by Lautens and co-workers[6]. $^1$H NMR (500 MHz, $CDCl_3$): 3.67 (3 H, s, $CO_2CH_3$); 3.51 (1 H, dd, *J* = 10.8, 5.6, C9**H**$_A$H$_B$); 3.43 (1 H, dd, *J* = 10.8, 6.7, C9H$_A$**H**$_B$); 2.39–2.27 (2 H, m, C2$H_2$); 1.72 (1 H, apparent sext, *J* = 6.8, C8H); 1.68–1.56 (2 H, m, C8H/C4H); 1.56–1.48 (1 H, m, C6H); 1.49–1.40 (2 H, m, C3$H_2$); 1.31 (1 H, apparent quint, *J* = 6.8, C7**H**$_A$H$_B$); 1.11 (1 H, ddd, *J* = 13.7, 9.0, 4.3, C5**H**$_A$H$_B$); 1.02 (1 H, ddd, *J* = 13.7, 9.0, 4.3, C5H$_A$**H**$_B$); 0.94 (1 H, apparent quint, *J* = 6.8, C7H$_A$**H**$_B$); 0.93 (3 H, d, *J* = 6.4, C8$CH_3$); 0.85 (6 H, d, *J* = 6.4, C4/C6$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 174.8 (**C**$O_2CH_3$), 68.4 (C9$H_2$), 51.7 ($CO_2$**C**$H_3$), 44.3 (C5$H_2$), 41.6 (C7$H_2$), 33.2 (C8H), 32.8 (C2$H_2$), 32.0 (C3$H_2$), 29.8 (C4H), 27.5 (C6H), 20.5 (C4**C**$H_3$), 19.3 (C6**C**$H_3$), 17.4 (C8**C**$H_3$). $[\alpha]_D$ –20.0 (*c* 1.0, $CHCl_3$); lit.[6] $[\alpha]_D$ –37.0 (*c* 1.0, $CHCl_3$).

Methyl (4*R*,6*S*,8*S*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-4,6,8-trimethylnonanoate (**2**)

TBDPSCl (142 mg, 0.52 mmol) in $CH_2Cl_2$ (1 ml) was added to a mixture of methyl ester **28** (119 mg, 0.52 mmol), imidazole (46 mg, 0.67 mmol), and DMAP (2 mg, 0.02 mmol) in $CH_2Cl_2$ (1 ml) at room temperature and the resulting pale yellow suspension stirred at room temperature for 1 h. $CH_2Cl_2$ (10 ml) and $H_2O$ (10 ml) were added to the reaction mixture, the layers separated and the aqueous layer extracted with $CH_2Cl_2$ (2 × 10 ml). The combined organic layers were dried (anhydrous $Na_2SO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography ($SiO_2$, light petroleum–$Et_2O$ 10:1) to give ester **2** (222 mg, 0.47 mmol, 91%) as a colourless oil giving spectroscopic data identical to those described above.

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## REFERENCES AND NOTES


1. Toeplitz B. K., Cohen A. I., Funke P. T., Parker W. L., Gougatas J. Z.: *J. Am. Chem. Soc.* **1979**, *101*, 3344.
2. Davies D. H., Snape E. W., Suter P. J., King T. J., Falshaw C. P.: *J. Chem. Soc., Chem. Commun.* **1979**, 1073.
3. Erdahl W. L., Chapman C. J., Taylor R. W., Pfeiffer D. R.: *J. Biol. Chem.* **2000**, *275*, 7071.
4. Evans D. A., Dow R. L., Shih T. L., Takacs J. M., Zahler R.: *J. Am. Chem. Soc.* **1990**, *112*, 5290.
5. Hanessian S., Cooke N. G., DeHoff B., Sakito Y.: *J. Am. Chem. Soc.* **1990**, *112*, 5276.
6. Lautens M., Colucci J. T., Hiebert S., Smith N. D., Bouchain G.: *Org. Lett.* **2002**, *4*, 1879.
7. Novak T., Tan Z., Liang B., Neghishi E.: *J. Am. Chem. Soc.* **2005**, *127*, 2838.
8. Spino C., Allan M.: *Can. J. Chem.* **2004**, *82*, 177.
9. Montana A. M., Garcia F., Grima P. M.: *Tetrahedron* **1999**, *55*, 5483.
10. von der Emde H., Langels A., Noltemeyer M., Brückner R.: *Tetrahedron Lett.* **1994**, *35*, 7609.
11. Guindon Y., Yoakim C., Gorys V., Ogilvie W. W., Delorme D., Renaud J., Robinson G., Lavalee J.-F., Slassi A., Jung G., Rancourt J., Durkin K., Liotta D.: *J. Org. Chem.* **1994**, *59*, 1166.
12. Taschner M. J., Chen Q. Z.: *Bioorg. Med. Chem. Lett.* **1991**, *1*, 535.
13. Nicoll-Griffith D. A., Weiler L.: *Tetrahedron* **1991**, *47*, 2733.
14. Spino C., Weiler L.: *Tetrahedron Lett.* **1987**, *28*, 731.
15. Schreiber S. L., Wang Z.: *J. Am. Chem. Soc.* **1985**, *107*, 5303.
16. Wuts P. G. M., D'Costa R., Butler W.: *J. Org. Chem.* **1984**, *49*, 2582.
17. Chow R., Kocienski P. J., Kuhl A., LeBrazidec J.-Y., Muir K., Fish P.: *J. Chem. Soc., Perkin Trans. 1* **2001**, 2344.
18. Kuhl A., Christopher J. A., Farrugia L. J., Kocienski P. J.: *Synlett* **2001**, 1765.
19. Faller J. W., Lambert C., Mazzieri M. R.: *J. Organomet. Chem.* **1990**, *383*, 161.
20. Enders D., Frank U., Fey P., Jandeleit B., Lohray B. B.: *J. Organomet. Chem.* **1996**, *519*, 147.
21. Hoffmann R. W., Zeiss H.-J., Ladner W., Tabche S.: *Chem. Ber.* **1982**, *115*, 2357.
22. Allinger N. L.: *J. Am. Chem. Soc.* **1959**, *81*, 232.
23. Wiley P. F., Gerzon K., Flynn E. H., Sigal M. V., Weaver O., Quark U. C., Chauvette R. R., Monohan R.: *J. Am. Chem. Soc.* **1957**, *79*, 6062.
24. Masamune S., Ali S. A., Suitman D. L., Garvey D. S.: *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.
25. Robinson J. A., Dyer U. C.: *J. Chem. Soc., Perkin Trans. 1* **1988**, *1*, 53.
26. Garegg P. J., Samuelsson B.: *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
27. Cosford N. D. P., Liebeskind L. S.: *Organometallics* **1994**, *13*, 1498.
28. Pearson A. J., Bruhn P., Richards I. C.: *Tetrahedron Lett.* **1984**, *25*, 387.
29. Compound **19** probably arises from deprotonation of the complex **5** by the organocopper(I) reagent **15** since quenching the reaction mixture with $D_2O$ did not lead to incorporation of deuterium.
30. Yu R. H., McCallum J. S., Liebeskind L. S.: *Organometallics* **1994**, *13*, 1476.
31. Adams R. D., Chodosh D. F., Faller J. W., Rosan A. M.: *J. Am. Chem. Soc.* **1979**, *101*, 2570.

32. Kocienski P. J., Bell R., Bourque E., Chow R., Christopher J. A., Gunn A., Kuhl A., Procter M., Uppal S., Yuen J.: *Pure Appl. Chem.* **2004**, *76*, 477.
33. Complex **5** reacts with BuCu to give an inseparable mixture of products in 55% yield (γ:α = 6:1). $Bu_2CuLi$ and $Bu_2CuLi{\cdot}LiCN$ gave <15% yield.
34. Knochel P., Yeh M.-C. P., Berk S. C., Talbert J.: *J. Org. Chem.* **1998**, *63*, 2392.
35. Enders D., Finkam M.: *Synlett* **1993**, 401.
36. Myers A. G., Yang B. H., Chen H., McKinstry L., Kopecky D. J., Gleason J. L.: *J. Am. Chem. Soc.* **1997**, *119*, 6496.
37. Krapcho A. P.: *Synthesis* **1982**, 893.
38. Hoffmann R. W., Schopfer U., Müller G., Brandl T.: *Helv. Chim. Acta* **2002**, *85*, 4424.