Convergent Synthesis of the Putative Biogenetic Precursor of Mycaperoxide B and a Norsesterterpene Triene Isolated from an Australian sponge[1]

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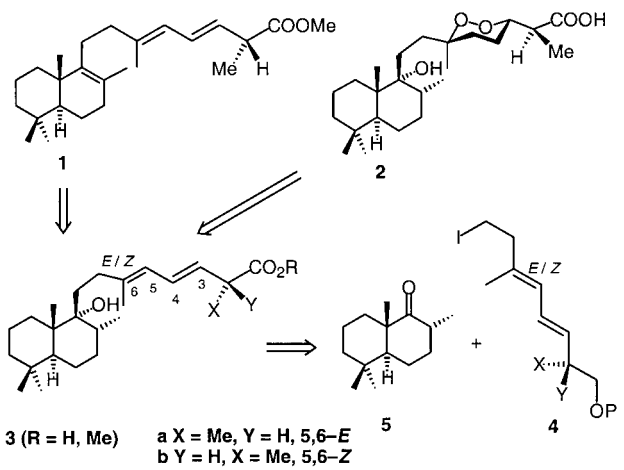
Abstract: The synthesis of enantiomerically pure norsesterterpene triene ester **1**, extracted from an Australian marine sponge *Latrunculia brevis*, has been achieved by preparation of *E,E*–diene **3a** *via* a Julia one-pot olefination and addition to 2,5,5,8a-tetramethyl-octahydro-napthalen-1-one **5**. The synthesis of *Z,E*–diene **3b**, the putative biogenetic precursor of mycaperoxide B **2** has also been achieved following the same methodology.

Key words: chiral synthesis, marine norsesterterpene, mycaperoxide

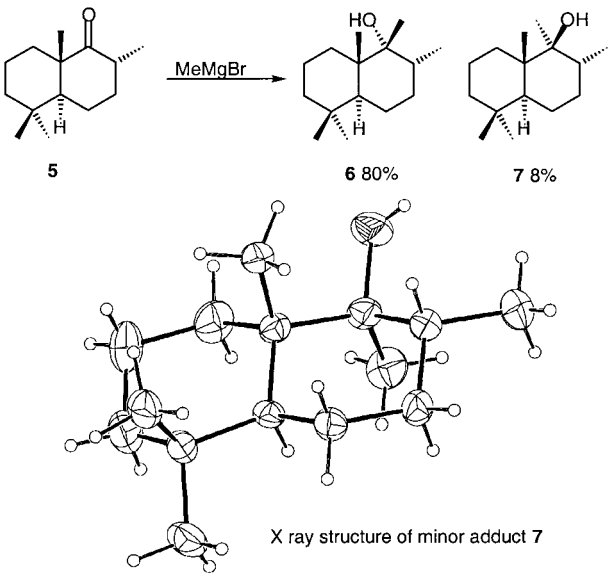
The norsesterterpene diene **1**, has been isolated from an Australian sponge, *Latrunculia brevis*.[2] It has been postulated that such materials might act as biosynthetic precursors to cyclic peroxides being elaborated by 4+2 singlet oxygen addition across the diene, followed by reduction of the unsaturated peroxide intermediate.[3] An example of such a cyclic peroxide, mycaperoxide B **2** has been isolated from a blue sponge of the genus *Mycale* inhabiting the waters off the coast of Thailand and has been found to show significant cytotoxicity and antiviral activity.[4] Mycaperoxide B is one of a family of seven cyclic peroxides which have been isolated from marine sponges,[5] and one of over twenty marine norsesterterpene cyclic peroxides which have been isolated and characterised so far.[6] A synthetic approach to triene **1** *via* tertiary alcohol **3a** would be equally applicable to synthesis of the putative mycaperoxide B biogenetic precursor **3b** (R = H), a substrate for singlet oxygen cycloaddition studies to lend support or otherwise for the proposition.



Scheme 1

Dienes **3a**, **3b** would be derived by equatorial attack of organometallic species derived from **4** on octahydronapthalen-1-one (–)–**5**, available in 33% yield over 4 steps from (–)–carvone (**Scheme 1**).[7]

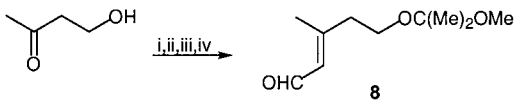
A literature survey of nucleophilic additions to decalones related to **5** indicated that the methyl groups flanking the carbonyl have a profound effect on the stereochemical outcome, making it difficult to predict whether axial or equatorial attack would predominate.[8] In a model study to examine alkylation of substrate **5**, treatment with MeMgBr gave a 10:1 mixture of isomeric tertiary alcohols **6**, **7** in almost 90% yield. Separation of the isomers by column chromatography afforded the minor isomer **7** as a crystalline solid. X-ray crystallographic analysis[9] showed the hydroxyl group to be in an equatorial configuration and hence demonstrating that the major isomer **6** was derived from equatorial attack of the Grignard reagent, in accordance with our requirements for synthesis of **3b** (**Scheme 2**).



Scheme 2

Encouraged by this finding we embarked upon the synthesis of *E,E*diene **4a**. The aldehyde **8** was prepared from 4–hydroxy–2–butanone in 30% overall yield by protection of the primary alcohol, Wadsworth-Emmons reaction and two–step conversion of the ester to the aldehyde (**Scheme**

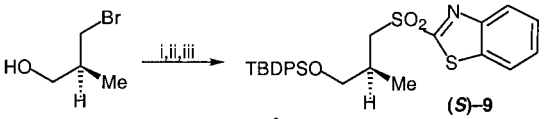
3).[10] NMR analysis of the material obtained from the Wadsworth Emmons reaction showed a mixture of isomers (*E* : *Z* 4 : 1) but these proved inseparable at this stage.[11]



i. 2-methoxypropene, $POCl_3$, 93%; ii. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 25°C, 47%; iii. DIBAL, Et_2O, -78°C, 88%; iv. TPAP, NMO, DCM, 25°C, 78%

Scheme 3

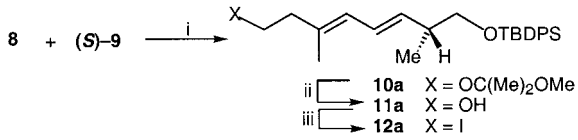
The synthesis of 2-[(3*S*)-6-*t*-butyldiphenylsilyloxy)-3-methylpropyl- sulfonyl]benzothiazole (*S*)–**9** was achieved in three steps from (*S*)-3-bromo-2-methyl propan-1-ol[12] in an overall yield of 83% (**Scheme 4**).



i. Imidazole, TBDPSCl, DMF, 25°C, 97%; ii. mercaptobenzothiazole, NaH, DMF, 25°C, 92%; iii. *m* -CPBA, DCM, 25°C, 93%

Scheme 4

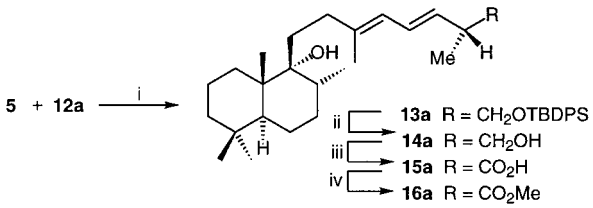
The stereochemical outcome of the one-pot olefination procedure developed by S. Julia[13] is often substrate dependent[13,14] but, when $LiN(TMS)_2$ (2 equivalents) was added to a mixture of **8** and (*S*)–**9** at –78°C, coupling was achieved in high yield and stereoselectivity (95%, no *Z*–isomer detectable) to produce **10a**.[15] Selective cleavage of the ketal permitted separation of the 4 : 1 mixture of alkene isomers resulting from the earlier Wadsworth Emmons reaction, furnishing pure *E*,*E*–alcohol **11a** in 52% yield which was converted to the iodide **12a** in 95% yield using triphenylphosphine / imidazole / I_2 (**Scheme 5**).[16]



i. $LiN(TMS)_2$, 2eq., THF, -78°C, 87% (>95/5 E:Z); ii. *p*-TSA, Ethanol, 25°C, 52%; iii. PPh_3, Imidazole, I_2, DCM, 25°C, 95%

Scheme 5

The coupling to form **13a** was achieved *via* organolithium generation by direct treatment of a mixture of **5** and **12a**, at –90°C with two equivalents of *t*-BuLi to furnish a 7:1 mixture of diastereoisomers.[17] Column chromatography furnished the major isomer **13a** in 56% yield and desilylation with TBAF furnished the primary alcohol **14a** in 95% yield. Finally, two step oxidation to the carboxylic acid **15a** and esterification with TMS–diazomethane without purification of intermediates gave methyl ester **16a** in 65% overall yield (**Scheme 6**).



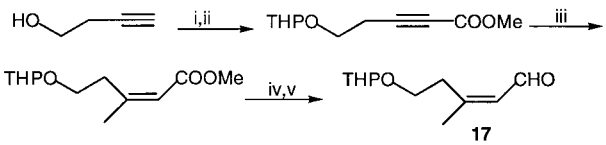
i. *t*-BuLi (2 eq.), Et_2O, -90°C, 56%; ii. TBAF, THF, 25°C, 95%; iii. a) Dess-Martin Periodinane, DCM, 25°C; b) $NaClO_2$, 2-methyl-2-butene, $Na_2PO_4.H_2O$, 25°C; iv. $TMS(CH_2N_2)$, toluene, methanol, 25°C, 65%

Scheme 6

The final dehydration of ester **16a** was accomplished with 50% H_2SO_4 to afford the natural product **1** in 65% yield. The ^1H and ^{13}C NMR data were identical with those reported for the natural product and the specific rotation $[\alpha]_D^{22}$ = +5.5 (c = 2.4, $CHCl_3$) was in accord with the reported value for the isolated material, $[\alpha]_D$ = +13.3 (c = 2.55, $CHCl_3$),[2,18] confirming the absolute configuration.

To underline the efficiency of this approach, we have also applied it to the synthesis of **3b** the proposed biogenetic precursor to mycaperoxide B which differs from **15a** in possessing the (*R*)–configuration at the side chain stereocentre and the *Z*–geometry of the 5–6 double bond.

The *Z*–2–methyl–5–hydroxypent–2–enal precursor for side chain construction was efficiently prepared as its THP ether **17** in five steps from 3-butyn-1-ol in an overall yield of 75% (**Scheme 7**).

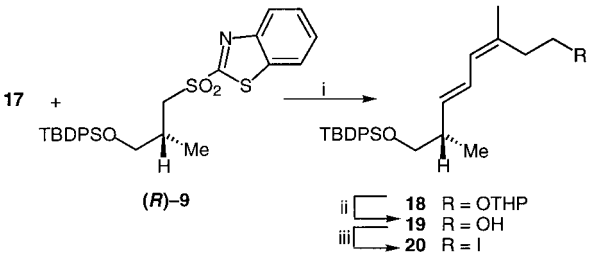


i. 3,4-DHP, PPTS, DCM, 25°C, 96%; ii. *n*-BuLi, ClCOOMe, THF, -60°C, 95%; iii. CuI, MeI, Et_2O, -78°C, 91%; iv. DIBAL, Et_2O, -78°C, 97%; v. TPAP, NMO, DCM, 93%

Scheme 7

Following the previously established conditions for Julia olefination, reaction of **17** and 2-[(3*R*)-6-*t*-butyldiphenylsilyloxy)-3-methylpropyl- sulfonyl]benzothiazole (*R*)–**9** with 2 equivalents of $LiN(TMS)_2$ gave *E*,*Z* –diene **18** in excellent yield and stereoselectivity. Removal of the THP ether and conversion of alcohol **19** to iodide **20** using previous conditions occurred in greater than 80% overall yield (**Scheme 8**).

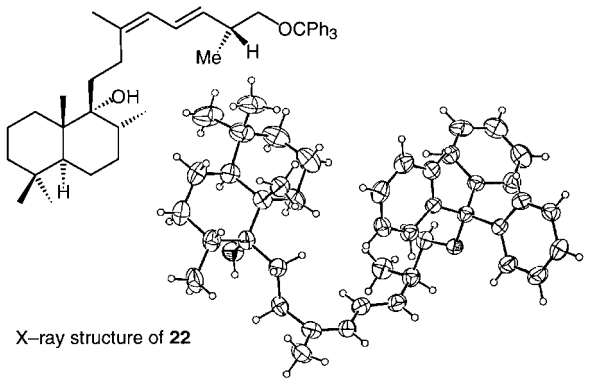
The coupling of decalone **5** and iodide **20** was achieved applying previously optimized conditions to afford **21** in 70% yield. Attempts to confirm the stereochemistry of the alkylative coupling step were thwarted by our inability to obtain crystals of sufficient quality for X–ray crystallographic analysis. However, the trityl ether of the of the



i. $LiN(TMS)_2$, 2eq., THF, -78°C, 95% (>95/5 E:Z); ii. PPTS, Ethanol, 55°C, 85%; iii. PPh_3, Imidazole, I_2, DCM, 25°C, 95%

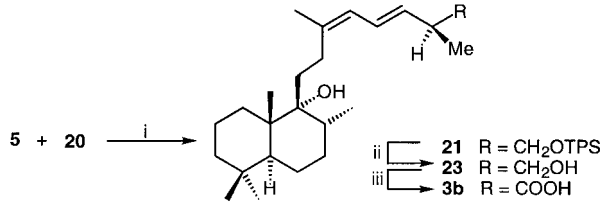
Scheme 8

side–chain epimer **22** did provide crystals which permitted X–ray crystallographic analysis to be carried out, confirming equatorial alkylation in this instance (**Figure**).[19]



Figure

Desilylation of **21** with TBAF afforded **23** in 94% yield and two–step oxidation of the primary alcohol as before furnished the target carboxylic acid **3b** in 80% yield (**Scheme 9**).



i. *t*-BuLi (2 eq.), Et_2O, -85°C, 70%; ii. TBAF, THF, 25°C, 94%; iii. a) Dess-Martin Periodinane, DCM, 25°C; b) $NaClO_2$, 2-methyl-2-butene, $Na_2PO_4.H_2O$, 25°C, 80%

Scheme 9

In conclusion, we have presented two illustrative examples of an efficient and flexible synthetic approach for the enantio– and diastereocontrolled construction of the carbon nucleus of a family of marine norsesterterpenes. We will report our studies on the photooxygenation behaviour of these compounds in due course.

Acknowledgement

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(7) J–P. Gesson, J–C. Jacquesy and B. Renoux, *Tetrahedron*, **1989**, *45*, 5853.
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(9) Crystal data for 7: $C_{15}H_{28}O$ M = 224.4, orthorhombic, $P2_12_12_1$ *a* = 11.264, *b* = 6.512, *c* = 19.53 Å, *V* = 1432 Å^3, *Z* = 4, *D* = 1.040 gcm–^{3}, *F*(000) = 1312. 2050 independent reflections were collected on a Marresearch Image Plate System. The structure was solved by direct methods and refined on F^2using Shelx97 (non–hydrogen atoms anisotropic and hydrogen atoms isotropic in calculated positions). Final *R* = 9.46, weighted *R* = 2.75. Crystal data have been deposited at the Cambridge Crystallographic Data Centre.
(10) For related synthetic approaches see R. Esmond, B. Fraser Reid and B. B. Jarvis, *J. Org. Chem.*, **1982**, *47*, 3358; A. Kanazawa, P. Declair, M. Pourashraf and A. E. Greene, *J. Chem. Soc., Perkin Trans 1*, **1997**, 1911.
(11) All novel compounds isolated gave spectroscopic data in accord with their assigned structures. Selected data for key intermediates and target compounds are given below:
(S)–9 $[\alpha]_D^{24}$ +25.3 (c = 1, $CHCl_3$); ν_{max} (film) 3070, 2959, 2858, 1770, 1589, 1330, 1148 cm^{-1}; δH (400 MHz; $CDCl_3$) 0.91 (9H, s), 1.04 (3H, d, *J* 6.8 Hz), 2.37 (1H, m), 3.22 (1H, dd, *J* 14.3, *J'*8.6 Hz), 3.38 (1H, dd, *J* 10.1, *J'*6.7 Hz), 3.57 (1H, dd, *J* 10.1, *J'*4.8 Hz), 3.86 (1H, dd, *J* 14.4, *J'*3.9 Hz), 7.22 (6H, m), 7.50 (4H, m), 7.90 (2H, m), 8.09 (2H, m); δC (100 MHz; $CDCl_3$) 16.6, 19.1, 26.7, 31.5, 57.6, 67.0, 122.4, 125.4, 127.5, 127.6, 127.9, 129.7, 133.0, 135.4, 136.8, 152.7, 165.8; $^m/_z$ (CI, NH_3) 510 $[MH]^+$; high resolution 510.1593, $C_{27}H_{32}NO_3S_2Si$ requires 510.1593 (*R*)–7 $[\alpha]_D^{23}$ –23.5 (c = 1, $CHCl_3$)
11a $[\alpha]_D^{24}$ –6.3 (c = 1, $CHCl_3$); ν_{max} (film) 3362, 3071, 3048, 3014, 2931 cm^{-1}; δH(400 MHz; $CDCl_3$) 1.07 (9H, s), 1.07 (3H, d, *J* 6.7 Hz), 1.77 (3H, d, *J* 1.1 Hz), 2.32 (2H, t, *J* 6.2 Hz), 2.45 (1H, m), 3.50 (1H, dd, *J* 9.7, *J'* 6.7 Hz), 3.56 (1H, dd, *J*

9.7, *J'* 6.2 Hz), 3.71 (2H, t, *J* 6.3 Hz), 5.55 (1H, dd, *J* 15.2, *J'* 7.5 Hz), 5.86 (1H, bd, *J* 10.7 Hz), 6.25 (1H, ddd, *J* 15.0, *J'* 10.8, *J"* 1.0 Hz) 7.38 (6h, m), 7.65 (4H, m); δC(100 MHz; $CDCl_3$) 16.3, 16.7, 19.2, 26.8, 39.6, 42.8, 60.3, 68.6, 125.9, 127.2, 127.5, 129.5, 132.5, 133.9, 135.4, 135.6; $^m/_z$ (CI, NH_3) 409 $[MH]^+$, 351; high resolution 409.2568, $C_{26}H_{36}O_2Si$ requires 409.2563.

16a ν_{max} (film) 1741 cm^{-1}; δH(400 MHz; $CDCl_3$) 0.84 (3H, s), 0.88 (3H, s), 0.89 (3H, d, *J* 6.4 Hz), 0.92 (3H, s), 1.17 (1H, dd, *J* 13.3, *J'* 3.4 Hz), 1.29 (3H, d, *J* 7.0 Hz), 1.30–1.62 (m, 12H), 1.72–1.80 (1H, m), 1.77 (3H, d, *J* 1.2 Hz), 2.07 (2H, m), 3.20 (1H, m), 3.69 (3H, s), 5.62 (1H, dd, *J* 15.1, *J* 8.1 Hz), 5.83 (1H, bd, *J* 10.8 Hz), 6.33 (1H, ddd, *J* 15.1, *J'* 10.8, *J'* 1.1 Hz); $^m/_z$ (CI, NH_3) 390 $[M]^+$; high resolution 390.3140, $C_{25}H_{42}O_3$ requires 390.3134.

1 $[\alpha]_D^{22}$ +5.5 (c = 1, $CHCl_3$); ν_{max} (film) 1736 cm^{-1}; δH(400 MHz; $CDCl_3$) 0.84 (3H, s), 0.89 (3H, s), 0.95 (3H, s), 1.11 (1H, dd, *J* 12.5 *J'* 2.1 Hz), 1.12–1.24 (2H, m), 1.29 (3H, d, *J* 7.0 Hz), 1.32–1.67 (5H, m), 1.58 (3H, s), 1.78–1.85 (1H, m), 1.79 (3H, d, *J* 1.1 Hz), 1.91–2.11 (6H, m), 3.21 (1H, m), 3.69 (3H, s), 5.64 (1H, dd, *J* 15.0, *J'* 8.1 Hz), 5.84 (1H, bd, *J* 10.8 Hz), 6.35 (1H, ddd, *J* 15.1, *J'* 10.8, *J"* 1.1 Hz); δC(100 MHz; $CDCl_3$) 16.7, 17.5, 19.0, 19.0, 19.5, 20.1, 21.7, 26.8, 33.3, 33.3, 33.6, 36.9, 39.0, 40.5, 41.8, 43.1, 51.9, 51.9, 125.3, 126.0, 127.9, 129.6, 140.0, 140.1, 175.2. $^m/_z$ (CI, NH_3) 373 $[MH]^+$.

17 ν_{max} (film) 2942, 2248, 1676 cm^{-1}; δH (400 MHz; $CDCl_3$) 1.47–1.76 (6H), 2.03 (3H, s), 2.85 (2H, t), 3.53 (2H, m), 3.78 (1H, m), 3.91 (1H, dt, *J* 9.7, *J'*6.4 Hz), 4.59 (1H, bs), 5.95 (1H, bd, *J* 8.1 Hz), 9.96 (1H, d, *J* 8.1 Hz); δC (100 MHz; $CDCl_3$) 19.1, 25.0, 25.0, 30.1, 32.7, 61.7, 64.6, 98.3, 129.5, 160.3, 191.0; $^m/_z$ (CI NH_3) 199 $[MH]^+$; high resolution 199.1335, $C_{11}H_{19}O_3$ requires 199.1334.

19 $[\alpha]_D^{20}$ +9.5 (c = 1, $CHCl_3$); ν_{max} (film) 3347, 3070, 3048, 3022, 2959 cm^{-1}; δH(400 MHz; $CDCl_3$) 1.07 (9H, s), 1.07 (3H, d, *J* 6.7 Hz), 1.79 (3H, d, *J* 1.0 Hz), 2.32 (2H, t, *J* 6.3 Hz), 2.46 (1H, m), 3.51 (1H, dd, *J* 9.7, *J'* 6.7 Hz), 3.58 (1H, dd, *J* 9.7, *J'* 6.2 Hz), 3.71 (2H, t, *J* 6.3 Hz), 5.55 (1H, dd, *J* 15.2, *J'* 7.5 Hz), 5.88 (1H, bd, *J* 10.7 Hz), 6.27 (1H, ddd, *J* 15.0, *J'* 10.8, *J"* 1.0 Hz), 7.39 (6H, m), 7.66 (4H, m); δC(100 MHz; $CDCl_3$) 16.8, 19.3, 23.7, 26.9, 35.5, 39.6, 60.8, 68.7, 125.6, 127.6, 128.5, 129.5, 132.6, 133.9, 135.6, 136.0; $^m/_z$ (CI, NH_3) 409 $[MH]^+$, 351; high resolution 409.2572, $C_{26}H_{36}O_2Si$ requires 409.2563.

3b $[\alpha]_D^{24}$ +17.8 (c = 1, $CHCl_3$); ν_{max} (film) 3455, 2934, 1713 cm^{-1}; δH(400 MHz; $CDCl_3$) 0.83 (3H, s), 0.87 (6H, s), 0.91 (3H, s), 0.93 (3H, s), 1.12-1.77 (m, 12H), 1.77 (3H, s), 2.16 (2H, bt *J* 8.8Hz), 3.17 (1H, m), 1.28 (3H, s), 5.63 (1H, dd, *J* 15.2, *J'* 7.9 Hz), 5.78 (1H, bd, *J* 11 Hz), 6.33 (1H, dd, *J* 15.2, *J'* 10.8 Hz); δC(100 MHz; $CDCl_3$) 16.1, 16.2, 16.9, 18.5, 21.5, 21.9, 23.6, 29.1, 31.2, 31.7, 32.9, 33.2, 33.6, 36.4, 41.6, 42.6, 43.2, 46.1, 77.2, 124.4, 127.6, 129.1, 140.0, 179.6; $^m/_z$ (CI, NH_3) 376 $[M]^+$; high resolution 376.2966, $C_{24}H_{40}O_3$ requires 376.2977.

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(15) *General procedure for Julia coupling*
A solution of sulfone (8.84 mmol) and aldehyde (9.09 mmol) in anhydrous THF (195 mL) was cooled to -78°C under nitrogen. $LiN(TMS)_2$ (18.0 mL, 1M in hexane) was added dropwise *via* syringe over a period of 25 minutes and the mixture was stirred for a further 90 min. The reaction mixture was warmed to room temperature, quenched with aqueous NH_4Cl (300 mL) and extracted with ether (250 mL). The aqueous layer was further extracted with ether (2 x 100 mL), the organic extracts combined, washed with brine (150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 15% ether in 30–40 petrol to furnish exclusively *E*–isomer.

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(17) *General procedure for coupling to decalone*
A solution of iodide (0.631 mmol) and 5 (0.663 mmol) in anhydrous ether (8 mL) was cooled to –90°C (ether–liquid nitrogen bath) under nitrogen. *t* -BuLi (0.75 mL, 1.7M in pentane) was added dropwise over a period of 5 minutes and the mixture was stirred for a further 30 minutes. The reaction was quenched with aqueous NH_4Cl (8 mL) and allowed to warm to room temperature. The aqueous layer was extracted with ether (2 x 10 mL), the organic extracts combined, washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by gradient flash column chromatography, eluting initially with 30-40 petrol, increasing to 5% ether : 95% 30-40 petrol afforded the coupled product as a colourless oil.

(18) We are grateful to Professor R. Capon of the University of Melbourne for providing us with copies of the spectra for this compound.

(19) Crystal data for **22**: $C_{43}H_{56}O_2$ M = 604.9, orthorhombic, $P2_12_12_1$ *a* = 10.040, *b* = 13.858, *c* = 26.100 Å, *V* = 3632 $Å^3$, *Z* = 4, *D* = 1.099 gcm^{-3}, *F*(000) = 1312. 4707 independent reflections were collected on a Marresearch Image Plate System. The structure was solved by direct methods and refined on F^2using Shelx97 (non–hydrogen atoms anisotropic and hydrogen atoms isotropic in calculated positions). Final *R* = 5.95, weighted *R* = 2.63. Crystal data have been deposited at the Cambridge Crystallographic Data Centre.