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A short synthesis of (+) and (−)-falcarinol

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ABSTRACT

A short, practical synthesis of the bis-acetylenic natural product falcarinol **1** is reported. This method relies on the alternate functionalisation of bis-trimethylsilylbutadiyne **10**. This may be achieved in one-pot, however, better yields were obtained more conventionally. Lipase mediated enzymatic kinetic resolution of the racemic adduct in an organic solvent afforded (+)-**1** in 97% enantiomeric excess. The analogous process performed with racemic 3-acetoxy falcarinol **11** under aqueous conditions gave (−)-**1**. Oxidation of **1** with Dess–Martin periodinane gave falcarinone **2**.

1. Introduction

The so-called polyacetylenic class of fatty acid derived natural products is relatively widespread in the phytochemical kingdom. Aided by their characteristic absorption spectroscopy, members of this family have been detected and isolated from a range of plants.[1] Subsequently, studies have indicated that certain members also possess interesting biological profiles, including perturbation of cell proliferation,[2] anti-inflammatory and anti-platelet aggregatory effects.[3–5] One example, falcarinol **1** (also termed panaxynol and, in the past, carotatoxin), first reported by Takahashi from the widely used medicinal plant Panax ginseng C.A. Meyer in 1964,[6] represents a potentially novel lead for the development of compounds possessing anti-cancer activity.[7] Falcarinol **1** has generated renewed interest recently when it was shown that dietary amounts of the 3*R* enantiomer, isolated from carrots, delayed or retarded the development of large aberrant crypt foci and tumours in rats with azoxymethane induced colon preneoplastic lesions.[8] As a result some researchers are now suggesting that falcarinol may be responsible for the well known protective role of carrot consumption against the development of cancers[2b] rather than β-carotene, which has been shown not to confer protection against lung cancer in a dietary intervention study.[9] Related members of this family have also been isolated and possess altered oxygenation patterns whilst maintaining the C-17, bis-acetylenic backbone (Fig. 1).[1,2,10]

Optically active falcarinol **1** was first synthesised[11] from the chiral pool in 1999 by Cai and co-workers who relied on the Cadiot–Chodkiewicz, Cu(I) promoted sp–sp coupling reaction.[12] Thereafter, Faber and co-workers described an approach to **1** from 1,4-chlorobutyne and used enzymatic kinetic resolution to access either C-3 aptipode.[13] In relation to the single stereogenic centre, somewhat surprisingly both enantiomers of this natural product have been identified from different plants.[6,14] Historically this has contributed to making the task of determining the absolute configuration of the secondary alcohol within this series of compounds difficult. Ultimately this was unequivocally proven by comparison of naturally occurring material with that obtained from total synthesis, thus it is now confirmed that (+)-**1** possesses the 3S stereogenic centre.

Based on the reasonably arduous task of isolating these relatively fragile compounds from their natural source (in one isolation performed, 10 kg of carrots afforded 20 mg of **1**)[15] and their promising biological profile we became interested in developing a robust synthetic protocol that would enable access to either enantiomer of **1** to assist future isolation studies and to clarify their relative in vitro biological activities. We envisaged that racemic falcarinol might be synthesised in one-pot following the sequential reaction of an appropriately metallated butadiyne **7** with acrolein **8** and then an allylic halide **9**.[16,17] Subsequently, based on the precedent that truncated 3-hydroxyl enynes[13,18] may be efficiently resolved using lipases, we were reasonably confident that (±)-**1**, thus obtained, might be separated into the corresponding enantiomerically enriched materials for further biological evaluation Fig 2.

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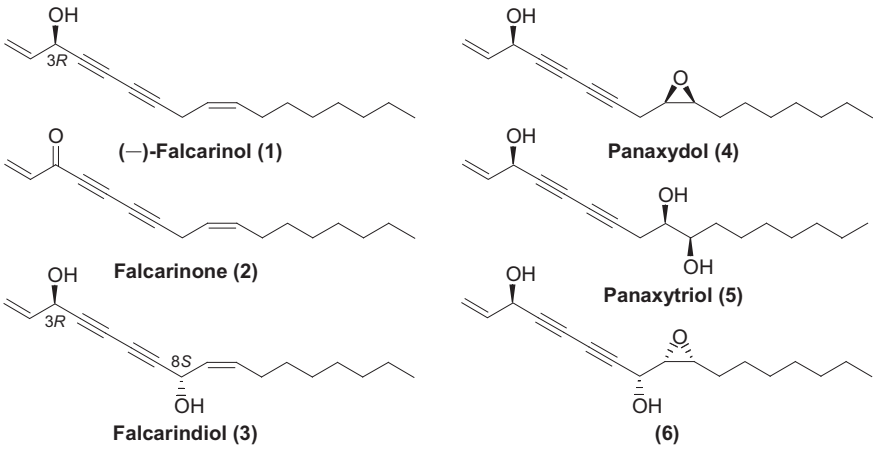


Fig. 1. Representative C-17 phytochemical bis-acetylenes.

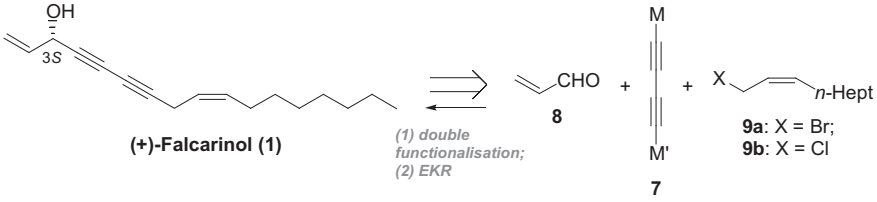


Fig. 2. Structure of (+)-falcarinol **1** and its retrosynthesis based on the double functionalisation-enzymatic kinetic resolution (EKR) of butadiyne (M, M′=metal).

2. Results and discussion

Initial investigations aimed at evaluating the proposed route outlined above (Fig. 2) focused on the use of inexpensive 1,4-bis-trimethylsilanylbuta-1,3-diyne **10** as a non-volatile butadiyne surrogate. Thus, treatment of a THF solution of **5** with 1 equiv of MeLi at 0 °C led to smooth lithium–silicon exchange. Subsequent cooling to −78 °C and addition of acrolein **2**, following work-up, led to the formation of 7-trimethylsilanylhept-1-ene-4,6-diyn-3-ol (not shown).[16b] Alternatively, simple addition of a 2 M solution of aqueous NaOH to a THF solution of the initial crude adduct, obtained following aqueous work-up led to cleavage of the sp-carbon silicon bond and **11** was isolated reproducibly, following purification by flash column chromatography, in approximately 73% yield (this may also be achieved by direct work-up with aqueous NaOH in 63% yield). Studies aimed towards the one-pot di-functionalisation of **10** began with an investigation into its double alkylation with **8**. Initally, this was effected following addition of 1 equiv of MeLi then **8** and then addition of the second equiv of MeLi followed by **8**. Although this did afford the double adduct **12** the yields were never above 25%. A much more efficient sequence was realised when **10** was treated directly with 5 equiv of MeLi followed by an excess of **8**. Thus, **12** was accessed in excellent yield. In relation to stereogenicity, even when analysed by high field nuclear magnetic resonance spectroscopy this material resembled a single diastereisomer. However, based on further studies (see discussion below), as might be expected this process generates a mixture of diastereoisomers (the C2 symmetric **12a** and the achiral, *meso*-**12b**), in which the 1,6-stereogenic centres are too far away to distinguish them spectroscopically.[19,20]

Subsequently, a one-pot approach to **1** was considered. The required electrophilic *Z*-allylic halides **9a** and **9b** were synthesised from propargyl alcohol **13** using standard transformations.[10a,13] Initial studies, which based on the successful formation of **12** and a report from Baldwin and co-workers,[16b] focused on either the sequential lithiation–alkylation of **10**, or formation of the dilithiated species and sequential addition of **8** and **9b**. However, all permutations of this approach and attempts to vary reaction parameters, such as temperature generated complex mixtures of products within which none of the hoped for product **1** was detected or isolable. Consequently, based on the report that transmetalation from lithium to copper may effectively enable the alkylation of acetylides with electrophilic allylic compounds we attempted to perform the analogous process, as shown, but with the inclusion of copper(I) iodide.[17] Following these conditions the formation of racemic falcarinol **1** was observed, however, despite attempts to optimise this process the yields were routinely poor. Nevertheless falcarinone **2** could be obtained from material thus prepared by oxidation with Dess–Martin periodinane. Yields using this reagent were higher than those obtained using the MnO_2-based conditions reported for **5**.[10c]

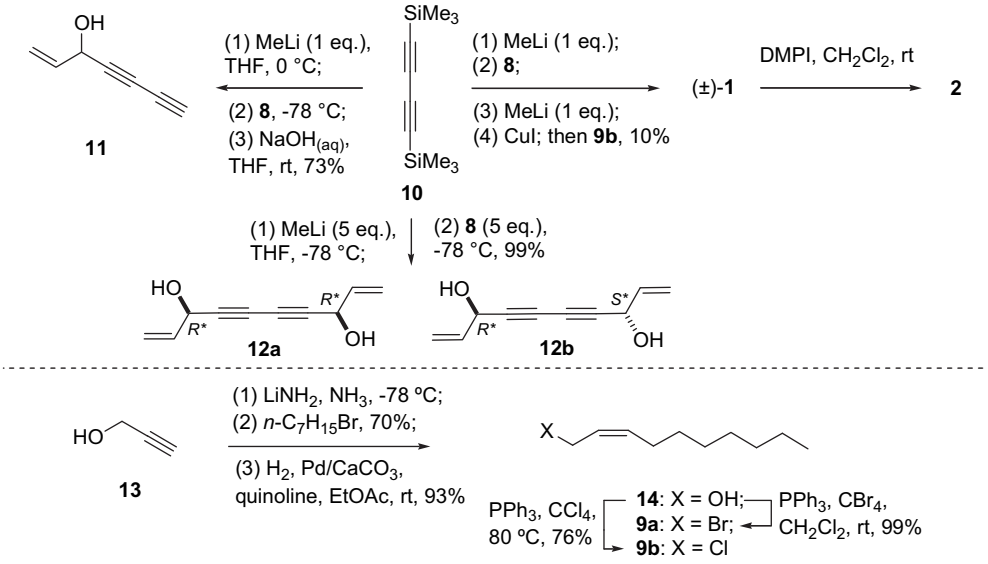
Due to the issues encountered with this one-pot approach we then decided to investigate a less ambitious two-pot approach. Thus, terminal bis-acetylene **11** was studied under the 'Jeffery' type[21] allylation conditions (cat. CuI, K_2CO_3, a quaternary ammonium salt as a phase transfer catalyst and DMF) previously reported in the context of falcarinol.[13] Treatment of **11** with bromide **9a** resulted in a relatively rapid reaction following, which **1** was isolated in 28% yield. This material was predominantly formed as the required *Z*-isomer and data was consistent with that found in the literature. However, some alkene isomerisation was detected (*Z*/*E*; 5:1). In addition a by-product was also formed, which proved challenging to separate from the target **1**.[22] Characterisation indicated that the structure of this material was **15**, presumably arising from an S_N2' type process. Subsequently the use of chloride **9b** in the alkylation reaction was studied and pleasingly it was found that although this reaction was slower than that with **9a**, reproducibly higher yields of **1** were obtained and additionally lower levels of alkene isomerisation were detected. Similar amounts, however, of **15** were produced. Performing the reaction with 8.20 mmol of **11** gave 0.92 g of **1** (3.77 mmol, 46%) after purification demonstrating the robustness of Faber's[13] method Scheme 2.

The resolution of the falcarinol enantiomers was next considered. We have previously employed the immobilised lipase B from *Candida Antarctica* (CAL-B) to discriminate enantiomeric forms of cyclic alkanols,[23] additionally, the same enzyme was shown to resolve the truncated bis-acetylene **11**.[13] Therefore, following standard

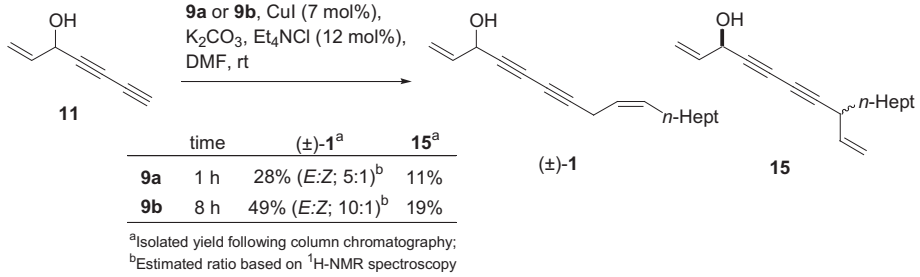
conditions[23] (±)-**1** was exposed to the solid supported enzyme in the presence of vinyl acetate. After 30 h NMR spectroscopic analysis indicated equal amounts of **1** and the corresponding ester **16** Scheme 3.

Separation of these compounds by column chromatography afforded (+)-**1** and (+)-**16** in 49% and 46% yields, respectively. Analysis of (+)-**1** by chiral HPLC indicated an enantiomeric excess of 97% for this material. Acetylation of (+)-**1** gave (−)-**16** that proved to be equal and opposite in terms of behaviour in plane polarised light to the sample of (+)-**16** obtained previously. Comparison of sign with literature values {*S*-**1**: +31.4 (*c* 1.12, $CHCl_3$)}[13] indicated that the *R*-enantiomer underwent acylation more rapidly, which is consistent with previously reported selectivities for this well studied enzyme. In order to access the final member of this series (±)-**1** was converted into (±)-**16** and then exposed to the same enzyme albeit in phosphate buffered aqueous solution. Following this protocol (−)-**1** was obtained in 33% yield and 98% ee along with (−)-**16** in 42% yield.

Based on the successful resolution study described above a similar approach was employed to probe the identity of the product(s) **12a** and **12b** obtained from the reaction of dilithiobutadiyne with acrolein **8** (Scheme 1). Thus, as illustrated in Scheme 4, in the presence of



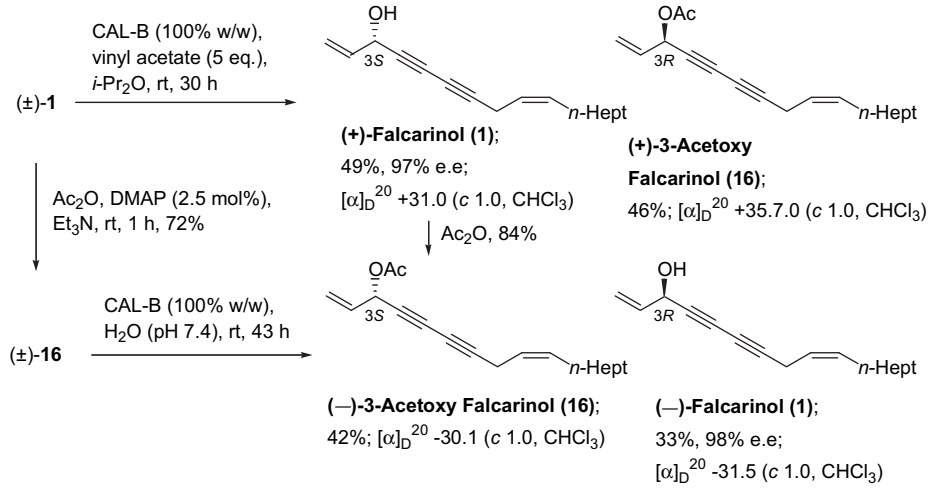
Scheme 1. Double functionalisation of butadiyne **10**, one-pot synthesis of **1** and its conversion to **2**.



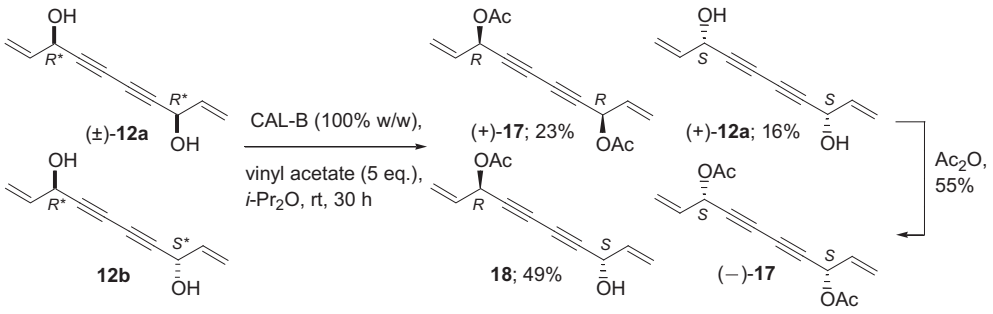
	time	(±)-**1**[a]	**15**[a]
9a	1 h	28% (*E*:*Z*; 5:1)[b]	11%
9b	8 h	49% (*E*:*Z*; 10:1)[b]	19%

[a]Isolated yield following column chromatography;
[b]Estimated ratio based on ^{1}H-NMR spectroscopy

Scheme 2. Alkylation of alkyne **11** in the synthesis of **1**.



Scheme 3. Lipase mediated resolution of (±)-**1** and (±)-**16**.



Scheme 4. Resolution of the mixture of **12a** and **12b**.

CAL-B the material, which was not spectroscopically distinguishable, was converted into 3 distinct compounds, which proved separable by standard chromatography.[20] Based on the typical lipase selectivity and the results obtained for **1** we assume that the *R*,*R*-**12a** undergoes double acylation, forming (+)-**17** and is the least polar member of these reaction products. Its enantiomer, *S*,*S*-**12a**, was recovered unchanged as the most polar species with chiroptical data consistent in sign to that reported in literature.[18] The symmetrical component, *meso*-**12b**, undergoes desymmetrisation and is converted into **18**, notably, this stereogenicity pattern matches that found in falcarindiol **3**. Further corroboration for this explanation was obtained following the acylation of (+)-**12a** into (−)-**17**.

3. Conclusion

In summary, we have developed and optimised a practical and scalable four-step synthesis for the assembly of both enantiomers of falcarinol **1** in order that their ability to interact with the processes of cell migration and proliferation may be determined. Additionally, oxidation of (±)-**1** afforded falcarinone **2**. Future work aims to employ the sequence outlined in Scheme 4 for the preparation of falcarindiol **3** and its stereoisomers.

4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian NMR systems (300–600 MHz spectrometers as indicated). Infrared spectroscopy was preformed on a Varian 3100 FTIR spectrometer. High resolution mass spectral data were acquired on a Waters GC time-of-flight (GCT Premier) instrument equipped with electron impact (EI) probe and on a Waters Quadrupole time-of-flight (Q-Tof Premier) mass spectrometer equipped with electrospray (ES) probe in the positive ionisation mode. Optical rotation measurements were recorded using a Perkin–Elmer Model 343 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography under moderate pressure was performed using Merck silica gel (60 Å, 0.040–0.063 mm).

4.2. 1-Heptene-4,6-diyn-3-ol 11

At 0 °C under N_2, a 1.7 M solution of MeLi in Et_2O (7.00 mL, 11.9 mmol, 1.00 equiv) was added dropwise to a solution of 1,4-bis (trimethylsilyl)butadiyne **10** (2.31 g, 11.9 mmol, 1.00 equiv) in dry THF (24 mL). After 3 h stirring at 0 °C the mixture was cooled to −78 °C. Acrolein **8** (0.80 mL, 11.9 mmol, 1.00 equiv) was added and the reaction was allowed to reach room temperature over 3 h. The pH of the reaction was adjusted to approximately 3 using 1.0 M aqueous solution of HCl (1.5 mL) and the reaction mixture was extracted with Et_2O (2×30 mL). The combined organic layers were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded crude hept-1-ene-4,6-diyn-7-trimethylsilyl-3-ol. The crude material was taken up in THF (25 mL) and a 1.0 M aqueous solution of NaOH (25 mL) was added. The mixture was stirred vigorously for 10 min. A 2.0 M aqueous solution of HCl (25 mL) was added and the reaction mixture was extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography (*c*-Hex–EtOAc; 6:1) afforded **11** (0.92 g, 73%) as a pale yellow oil.[13] R_f=0.30 (*c*-Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3406, 3091, 3023, 2964, 2920, 2859, 2217, 2045, 1700, 1644, 1146; *m*/*z* (EI) calcd for C_7H_6O 106.0419, found 106.0411; δ_H (400 MHz, $CDCl_3$) 2.22 (1H, s, CH), 2.40 (1H, br s, OH), 4.90 (1H, br s, CH), 5.25 (1H, d, *J*=10.0 Hz, CH), 5.46 (1H, d, *J*=17.0 Hz, CH), 5.90–5.96 (1H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 63.5 (CH), 67.5 (C), 69.3 (CH), 70.6 (C), 74.9 (C), 117.7 (CH_2), 135.7 (CH) ppm.

4.3. 1,9-Decadiene-4,6-diyne-3,8-diol 12a and 12b

At 0 °C under N_2, a 1.6 M solution of MeLi in Et_2O (2.10 mL, 3.36 mmol, 5.0 equiv) was added dropwise to a solution of 1,4-bis (trimethylsilyl)-butadiyne **10** (130 mg, 0.67 mmol, 1.0 equiv) in dry THF (5 mL). The mixture was stirred for 3 h maintaining the internal temperature of the reaction at 0 °C. The reaction mixture was cooled to −78 °C and acrolein **8** (0.25 mL, 3.74 mmol, 5.6 equiv) was added. The reaction was warmed to room temperature over 3 h. The pH of the reaction was adjusted to 3 using a saturated aqueous solution of HCl (4 mL) and the reaction mixture was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography (*c*-Hex–EtOAc; 3:1) afforded the *title compounds* **12a** and **12b** (105 mg, 99%) as colourless liquids. R_f=0.25 (*c*-Hex–EtOAc; 2:1); ν_{max} (neat/cm^{-1}) 3350, 2876, 2253, 2153, 1643, 1416, 1269, 1116, 1015, 930; *m*/*z* (EI) calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0678; δ_H (400 MHz, $CDCl_3$)* 2.69 (2H, br s, OH), 4.94 (2H, d, *J*=5.5 Hz, CH), 5.26 (2H, d, *J*=10.0 Hz, CH), 5.47 (2H, d, *J*=17.0 Hz, CH), 5.93 (2H, ddd, *J*=5.5, 10.0, 17.0 Hz, CH) ppm; δ_C (100 MHz, $CDCl_3$)* 63.6 (CH), 70.3 (C), 78.6 (C), 117.6 (CH_2), 135.9 (CH) ppm *Diastereoisomers indistinguishable spectroscopically.

4.4. 2-Decyn-1-ol[24]

Into a 3-necked 250 mL round bottom flask NH_3 (40 mL) was condensed at −78 °C under an inert atmosphere. Lithium (0.22 g, 31.7 mmol, 0.5 equiv) was added and the mixture was stirred for 20 min maintaining the internal temperature of the flask at approximately −50 °C. Iron(III) nitrate·9H_2O (0.26 g) was added and

the mixture was stirred for a further 30 min until a greyish white colour was obtained. Lithium (1.99 g, 287 mmol, 4.5 equiv) was added and the mixture was stirred for 3 h maintaining the internal temperature at −50 °C until a white suspension was observed. Propargyl alcohol **13** (4.40 mL, 75.6 mmol, 1.2 equiv) in THF (32 mL) was added slowly and the reaction was stirred for 2 h at −50 °C.1-Bromoheptane (10.0 mL, 63.6 mmol, 1.0 equiv) in THF (32 mL) was added and the reaction was warmed to room temperature over 16 h. The reaction was acidified to pH 1 using a 1.0 M aqueous HCl solution (ca. 60 mL) before extraction with DCM (2×50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by vacuum distillation afforded the *title compound* (6.96 g, 71%) as a colourless liquid.[24] R_f=0.35 (*c*-Hex–EtOAc; 4:1); bp 59–62 °C (0.1 mbar); ν_{max} (neat/cm^{-1}) 3370, 2919, 2857, 2289, 2261, 1466, 11,381,014; *m*/*z* (EI) 154 (M^+, 5%), 107 (50%), 93 (100%); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, *J*=7.0 Hz, CH_3), 1.22–1.36 (8H, m, CH_2), 1.47 (2H, pent, *J*=7.0 Hz, CH_2), 1.69 (1H, br s, OH), 2.17 (2H, tt, *J*=2.0, 7.0 Hz, CH_2), 4.21 (2H, t, *J*=2.0 Hz, CH_2) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.9 (CH_2), 22.8 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.05 (CH_2), 31.9 (CH_2), 51.6 (CH_2), 78.5 (C), 86.9 (C) ppm.

4.5. (*Z*)-Dec-2-ene-1-ol 14[24]

A solution of 2-decyn-1-ol (5.36 g, 34.8 mmol, 1.00 equiv) in EtOAc (220 mL) was treated with quinoline (0.50 mL, 4.23 mmol, 0.12 equiv) and Lindlar's catalyst (0.54 g, 10% w/w). The mixture was stirred under an atmosphere (ca. 1 atm) of H_2 for 9 h. The reaction mixture was then filtered through a plug of Celite. Solvent evaporation under reduced pressure and purification by flash column chromatography (*c*-Hex–EtOAc; 3:1) afforded the *title compound* (5.07 g, 93%) as a colourless liquid.[24] R_f=0.30 (*c*-Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3370, 3016, 2922, 2855, 1655, 1466, 1033; *m*/*z* (EI) calcd for $C_{10}H_{20}O$ 156.1514, found 156.1514; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J*=6.5 Hz, CH_3), 1.31–1.46 (10H, m, CH_2), 2.10 (2H, q, *J*=6.5 Hz, CH_2), 4.22 (2H, d, *J*=6.0 Hz, CH_2), 5.53–5.73 (2H, m, CH) ppm; δ_C (75 MHz, $CDCl_3$) 14.3 (CH_3), 22.9 (CH_2), 27.6 (CH_2), 29.35 (CH_2), 29.39 (CH_2), 29.8 (CH_2), 32.0 (CH_2), 58.8 (CH_2), 128.5 (CH), 133.4 (CH) ppm.

4.6. (*Z*)-1-Bromodec-2-ene 9a[25]

At 0 °C under N_2, a solution of (*Z*)-dec-2-ene-1-ol **14** (0.80 g, 5.12 mmol, 1.00 equiv) in dry DCM (20 mL) was treated with triphenylphosphine (1.71 g, 5.17 mmol, 1.01 equiv) and carbon tetrabromide (1.48 g, 5.64 mmol, 1.10 equiv). The reaction mixture was warmed to room temperature and stirred for 1.5 h. Solvent evaporation under reduced pressure and purification by flash column chromatography (*c*-Hex) afforded **9a** (1.11 g, 99%) as a colourless liquid. R_f=0.70 (*c*-Hex); ν_{max} (neat/cm^{-1}) 3026, 2909, 2842, 1648, 1465, 1204, 1145, 965, 752,658; *m*/*z* (ES^+) 231 (MNa^+, (^{79}Br) 50%), 233 (MNa^+, (^{81}Br) 50%); HRMS calcd for $C_{10}H_{19}{}^{79}Br$ 218.0670, found 218.0670; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=6.5 Hz, CH_3), 1.21–1.32 (8H, m, CH_2), 1.38 (2H, pent, *J*=7.0 Hz, CH_2), 2.11 (2H, q, *J*=7.0 Hz, CH_2), 3.99 (2H, d, *J*=8.0 Hz, CH_2), 5.55–5.61 (1H, m, CH), 5.67–5.74 (1H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.9 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 32.0 (CH_2), 125.4 (CH), 136.3 (CH) ppm (Broadening of peak at 29.3 ppm observed for two coincident CH_2 carbons).

4.7. (*Z*)-1-Chlorodec-2-ene 9b[13]

A solution of (*Z*)-dec-2-ene-1-ol **14** (2.58 g, 16.5 mmol, 1.00 equiv) in CCl_4 (16.5 mL) was treated with triphenylphosphine (4.59 g, 17.5 mmol, 1.06 equiv). The mixture was stirred and heated to reflux for 9 h. The reaction was cooled to room temperature and CCl_4 was removed under reduced pressure. The resulting residue was taken up in *c*-Hex (20 mL) and stirred vigorously for 15 min. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography (*c*-Hex) afforded **9b** (2.18 g, 75%) as a colourless liquid.[13] R_f=0.60 (*c*-Hex); ν_{max} (neat/cm^{-1}) 3027, 2899, 2851, 1652, 1466, 1250, 1116, 966, 765; *m*/*z* (EI) calcd for $C_{10}H_{19}^{35}Cl$ 174.1175, found 174.1174; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=6.5 Hz, CH_3), 1.26–1.39 (10H, m, CH_2), 2.10 (2H, q, *J*=6.5 Hz, CH_2), 4.07 (2H, d, *J*=6.5 Hz, CH_2), 5.56–5.64 (2H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.9 (CH_2), 27.3 (CH_2), 29.33 (CH_2), 29.37 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 39.7 (CH_2), 125.3 (CH), 135.7 (CH) ppm.

4.8. (±)-Heptadeca-1,9*Z*-diene-4,6-diyn-3-ol 1 [(±)-falcarinol 1][13]

A solution of hept-1-ene-4,6-diyn-3-ol **11** (0.87 g, 8.17 mmol, 1.00 equiv) in dry DMF (10 mL) was transferred by cannula into a suspension of anhydrous K_2CO_3 (1.41 g, 10.2 mmol, 1.25 equiv), copper iodide (0.11 g, 0.59 mmol, 0.07 equiv) and Et_4NCl (0.16 g, 0.98 mmol, 0.12 equiv) in dry DMF (34 mL) under N_2. The mixture was stirred for 30 min at room temperature before (*Z*)-1-chlorodec-2-ene **9b** (1.57 g, 8.96 mmol, 1.10 equiv) in dry DMF (10 mL) was added. The reaction was left to stir at room temperature for 8 h. The reaction mixture was poured into water (250 mL) and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with a saturated solution of NH_4Cl (50 mL) and brine (50 mL) then dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude material as a mixture of two regioisomeric products. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded the *title compound* **1** (0.92 g, 46%), and **15** (0.38 g, 19%) as colourless liquids. Data for **1**: R_f=0.40 (*c*-Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3375, 3088, 3023, 2958, 2929, 2854, 2256, 1642, 1466, 1285, 1118; *m*/*z* (EI) calcd for $C_{17}H_{24}O$ 244.1827, found 244.1831; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=6.5 Hz, CH_3), 1.25–1.35 (10H, m CH_2), 1.86 (1H, d, *J*=6.5 Hz, OH), 2.01 (2H, q, *J*=7.0 Hz, CH_2), 3.01 (2H, d, *J*=7.0 Hz, CH_2), 4.89 (1H, t, *J*=5.5 Hz, CH), 5.22 (1H, d, *J*=10.0 Hz, CH), 5.32–5.38 (1H, m, CH), 5.42–5.52 (2H, m, CH), 5.92 (1H, ddd, *J*=5.5, 10.0, 17.0 Hz, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 17.9 (CH_2), 22.9 (CH_2), 27.4 (CH_2), 29.37 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 63.8 (CH), 64.2 (C), 71.5 (C), 74.3 (C), 80.5 (C), 117.3 (CH_2), 122.1 (CH), 133.3 (CH), 136.4 (CH) ppm. Data for **15**: R_f=0.42 (*c*-Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3362, 3087, 3011, 2928, 2253, 1664, 1640, 1465, 1406, 1264, 1224, 1118; *m*/*z* (ES^+) calcd for $C_{17}H_{24}ONa$ 267.1725, found 267.1725; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=7.0 Hz, CH_3), 1.26–1.56 (12H, m, CH_2), 1.89 (1H, br s, OH), 3.13 (1H, q, *J*=6.5 Hz, CH), 4.91 (1H, br s, CH), 5.08 (1H, dt, *J*=10.0, 1.5 Hz, CH), 5.23 (1H, dt, *J*=1.5, 10.0 Hz, CH), 5.25 (1H, dt, *J*=1.5, 17.0 Hz, CH), 5.45 (1H, dt, *J*=1.5, 17.0 Hz, CH), 5.70 (1H, ddd, *J*=6.5, 10.0, 17.0 Hz, CH), 5.93 (1H, ddd, *J*=5.5, 10.0, 17.0 Hz, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.9 (CH_2), 27.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 35.2 (CH_2), 36.2 (CH), 63.8 (CH), 67.2 (C), 71.4 (C), 75.3 (C), 82.7 (C), 116.0 (CH_2), 117.3 (CH_2), 136.3 (CH), 136.9 (CH) ppm.

4.9. Heptadeca-1,9*Z*-diene-4,6-diyn-3-one 2 [falcarinone 2]

A solution of **1** (86.0 mg, 0.35 mmol, 1.00 equiv) in DCM (1.5 mL) was treated with Dess–Martin periodinane (225 mg, 0.53 mmol, 1.50 equiv). The mixture was stirred at room temperature for 30 min before being quenched with a saturated $Na_2S_2O_3$ solution (10 mL). The resulting mixture was extracted with DCM (2×10 mL). Combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded the *title*

compound **2** (45 mg, 53%) as a viscous yellow liquid. R_f=0.55 (*c*-Hex–EtOAc; 8:1); ν_{max} (neat/cm^{-1}) 3024, 2957, 2929, 2855, 2234, 2164, 1646, 1611, 1467, 1401, 1269, 980; *m*/*z* (ES$^+$) 260 (MNH_4^+, 100%), 243 (MH^+, 100%); HRMS calcd for $C_{17}H_{23}O$ 243.1749, found 243.1740; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=6.5 Hz, CH_3), 1.26–1.44 (10H, m, CH_2), 2.02 (2H, q, *J*=7.0 Hz, CH_2), 3.10 (2H, d, *J*=7.5 Hz, CH_2), 5.33–5.39 (1H, m, CH), 5.52–5.58 (1H, m, CH), 6.15–6.19 (1H, m, CH), 6.34–6.42 (1H, m, CH), 6.50–6.56 (1H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.3 (CH_2), 22.9 (CH_2), 27.5 (CH_2), 29.36 (CH_2), 29.39 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 63.8 (C), 70.9 (C), 77.44 (C), 88.3 (C), 120.9 (CH), 134.19 (CH), 134.21 (CH_2), 138.1 (CH), 178.0 (CO) ppm.

4.10. (±)-3-Acetoxyheptadeca-1,9*Z*-diene-4,6-diyne 16 [(±)-3-acetoxy falcarinol 16]

A solution of **1** (110 mg, 0.45 mmol, 1.00 equiv) in acetic anhydride (2 mL) was treated with triethylamine (0.10 mL, 0.72 mmol, 1.60 equiv) and DMAP (ca. 3.0 mg, 0.024 mmol, 0.05 equiv). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with a saturated solution of NH_4Cl (2×5 mL). The organic layer was washed with brine (5 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation afforded the crude product. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded the *title compound* **16** (90.0 mg, 70%) as a colourless liquid. R_f=0.55 (*c*-Hex–EtOAc; 6:1); ν_{max} (neat/cm^{-1}) 3023, 2956, 2926, 2855, 2359, 2259, 1748, 1645, 1370, 1221, 1096, 1014, 975; *m*/*z* (ES$^+$) 309 (MNa^+, 100%); HRMS calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1926; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=6.5 Hz, CH_3), 1.25–1.37 (10H, m, CH_2), 2.00 (2H, q, *J*=7.0 Hz, CH_2), 2.07 (3H, s, CH_3), 3.00 (2H, d, *J*=7.0 Hz, CH_2), 5.29–5.38 (2H, m, CH), 5.46–5.54 (2H, m, CH), 5.80–5.89 (2H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 17.9 (CH_2), 21.1 (CH_3), 22.9 (CH_2), 27.4 (CH_2), 29.37 (CH_2), 29.40 (CH_2), 29.45 (CH_2), 32.0 (CH_2), 64.2 (C), 64.8 (CH), 71.0 (C), 72.1 (C), 80.7 (C), 119.7 (CH_2), 122.0 (CH), 132.5 (CH), 133.4 (CH), 169.7 (C) ppm; Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15%. Found: C, 79.38; H, 9.09%.

4.11. 3*S*-Falcarinol (+)-1 and 3*R*-acetoxyfalcarinol (+)-16

At room temperature lipase B from *Candida Antarctica* (0.25 g) was added to a solution of (±)-**1** (0.25 g, 1.02 mmol, 1.00 equiv) in DIPE (26 mL). Vinyl acetate (0.50 mL, 5.10 mmol, 5.00 equiv) was added and the reaction was agitated on a shaker (120 rpm) for 30 h. The reaction was filtered to remove the biocatalyst, which was sonicated in DIPE (3×20 mL) for 15 min to remove additional organic material product. The combined organics were evaporated under reduced pressure affording a mixture of the enantioenriched *title compounds*. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded (+)-**1** (0.12 g, 49%) and (+)-**16** (0.13 g, 45%) as colourless liquids whose data was in agreement with that reported above. (+)-**1**: $[\alpha]_D^{20}$ +31.0 (*c* 1.00, $CHCl_3$); {lit.,[12] $[\alpha]_D^{20}$ +33.8 (*c* 0.53, $CHCl_3$), lit.,[13] $[\alpha]_D^{20}$ +31.4 (*c* 1.12, $CHCl_3$)}; HPLC analysis (OJH column), *n*-heptane-EtOH; 95:5 (1.0 mL/min): (−)-**1** [(3*R*)-**1**]: t_r=6.9 min, (+)-**1** [(3*S*)-**1**]: t_r=7.8 min; 97% ee. (+)-**16**: $[\alpha]_D^{20}$ +35.7 (*c* 1.00, $CHCl_3$).

4.12. (−)-3-Acetoxyheptadeca-1,9*Z*-diene-4,6-diyne 16 [3*S*-acetoxyfalcarinol (−)-16]

A solution of (+)-**1** (52.0 mg, 0.21 mmol, 1.00 equiv) in acetic anhydride (1 mL) was treated with triethylamine (0.05 mL, 0.36 mmol, 1.71 equiv) and DMAP (ca. 1.0 mg, 0.008 mmol, 0.04 equiv). The mixture was stirred at room temperature for 40 min. The reaction mixture was diluted with Et_2O (5 mL) and washed with a saturated solution of NH_4Cl (2×3 mL). The organic layer was washed with brine (3 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation afforded the crude product. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded the *title compound* (51.0 mg, 85%) as a colourless liquid whose data was in agreement with that reported above. $[\alpha]_D^{20}$ −30.1 (*c* 1.00, $CHCl_3$).

4.13. (3*R*)-Falcarinol (−)-1 and (3*S*)-acetoxyfalcarinol (−)-16

Lipase B from *C. Antarctica* (0.25 g) was added to a 0.075 M aqueous solution of Na_2HPO_4 (3.8 mL) in acetone (0.6 mL). At room temperature (±)-**16** (90.0 mg, 0.31 mmol, 1.00 equiv) was added and the reaction was gently stirred for 43 h. The reaction mixture was extracted with DCM (2×12 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded a mixture of the enantioenriched *title compounds*. Purification by flash column chromatography (*c*-Hex–EtOAc; 98:2) afforded (−)-**1** (30.0 mg, 40%) and (−)-**16** (40.0 mg, 45%) as colourless liquids whose data was in agreement with that reported above. (−)-**1** [(3*R*)-**1**]: $[\alpha]_D^{20}$ −31.5 (*c* 1.00, $CHCl_3$); {lit.,[12] $[\alpha]_D^{20}$ −36.6 (*c* 0.92, $CHCl_3$), lit.,[13] $[\alpha]_D^{20}$ −35.3 (*c* 1.45, $CHCl_3$)}; HPLC analysis (OJH column), *n*-heptane–EtOH; 95:5 (1.0 mL/min): (−)-**1** [(3*R*)-**1**]: t_r=6.9 min, (+)-**1** [(3*S*)-**1**]: t_r=7.8 min; 98% ee.

4.14. (3*S*,8*S*)-1,9-Decadiene-4,6-diyne-3,8-diol (+)-12a, (1*R*,6*S*)-acetic acid 6-hydroxy-1-vinyl-oct-7-ene-2,4-diynyl ester (+)-18 and (1*R*,6*R*)-acetic acid 6-acetoxy-1-vinyl-oct-7-ene-2,4-diynyl ester (+)-17

At room temperature lipase B from *C. Antarctica* (0.10 g) was added to a solution of 1,9-decadiene-4,6-diyne-3,8-diol **12a** and **12b** (100 mg, 0.62 mmol, 1.00 equiv) in DIPE (11 mL). Vinyl acetate (0.30 mL, 3.25 mmol, 5.25 equiv) was added and the reaction was agitated on a shaker (120 rpm) for 42 h. The reaction was filtered to remove the biocatalyst, which was sonicated in DIPE (3×10 mL) for 15 min. Solvent evaporation under reduced pressure afforded a mixture of the enantioenriched *title compounds*. Purification by flash column chromatography (*c*-Hex–EtOAc; 3:1) afforded (3*S*,8*S*)-1,9-decadiene-4,6-diyne-3,8-diol[13] (+)-**12a** (16.0 mg, 16%), (1*R*,6*S*)-acetic acid 6-hydroxy-1-vinyl-oct-7-ene-2,4-diynyl ester (+)-**18** (62.0 mg, 49%) and (1*R*,6*R*)-acetic acid 6-acetoxy-1-vinyl-oct-7-ene-2,4-diynyl ester (+)-**17** (35.0 mg, 23%) as colourless liquids. Data for (+)-**12a**: $[\alpha]_D^{20}$ +61.0 (*c* 1.00, $CHCl_3$); {lit.,[18] $[\alpha]_D^{20}$ +122.0 (*c* 0.30, $CHCl_3$)} with other data as reported above. Data for (+)-**18**: R_f=0.45 (*c*-Hex–EtOAc; 2:1); $[\alpha]_D^{20}$ +57.7 (*c* 2.00, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3502, 3093, 3026, 2989, 2924, 2853, 2362, 2156, 1748, 1646, 1423, 1372, 1221; *m*/*z* (EI) calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0781; δ_H (400 MHz, $CDCl_3$) 1.98 (1H, d, *J*=6.5 Hz, OH), 2.10 (3H, s, CH_3), 4.94 (1H, t, *J*=5.0 Hz, CH), 5.26 (1H, d, *J*=10.0 Hz, CH), 5.35 (1H, d, *J*=11.0 Hz, CH), 5.48 (1H, d, *J*=15.0 Hz, CH), 5.55 (1H, d, *J*=16.0 Hz, CH), 5.83–5.98 (3H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 63.7 (CH), 64.6 (CH), 70.2 (C), 70.9 (C), 75.3 (C), 78.8 (C), 117.7 (CH_2), 120.0 (CH_2), 132.1 (CH), 135.8 (CH), 169.7 (CO) ppm. Data for (+)-**17**: R_f=0.70 (*c*-Hex–EtOAc; 2:1); $[\alpha]_D^{20}$ +77.0 (*c* 1.00, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3093, 3028, 2924, 2852, 2259, 2162, 1752, 1644, 1421, 1370, 1220; *m*/*z* (EI) calcd for $C_{14}H_{14}O_4$ 246.0892, found 246.0895; δ_H (400 MHz, $CDCl_3$) 2.07 (6H, s, CH_3), 5.33 (2H, d, *J*=9.0 Hz, CH), 5.52 (2H, d, *J*=15.5 Hz, CH), 5.80–5.90 (4H, m, CH) ppm; δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3), 64.5 (CH), 70.7 (C), 75.4 (C), 120.1 (CH_2), 132.0 (CH), 169.6 (CO) ppm.

4.15. (1*S*,6*S*)-Acetic acid 6-acetoxy-1-vinyl-oct-7-ene-2,4-diynyl ester (−)-17

A solution of (+)-**12a** (34.0 mg, 0.21 mmol, 1.00 equiv) in acetic anhydride (2 mL) was treated with triethylamine (0.09 mL, 0.63 mmol, 3.00 equiv) and DMAP (ca. 3.0 mg, 0.0025 mmol,

0.10 equiv). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with a saturated solution of NH_4Cl (2×6 mL). The organic layer was washed with brine (6 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation and purification by flash column chromatography (*c*-Hex–EtOAc; 3:1) afforded the *title compound* (−)-**17** (30.0 mg, 55%) as a yellow liquid whose data was in agreement with that reported above. $[\alpha]_D^{20}$ −71.8 (*c* 1.00, $CHCl_3$).

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.10.049. These data include MOL files and InChIKeys of the most important compounds described in this article.

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