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Enantioselective synthesis of (3*R*,4*E*)-19-methylicos-4-en-1-yn-3-ol, a bioactive metabolite of the marine sponge *Cribrochalina vasculum*

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Abstract

The first stereoselective synthesis of (3*R*,4*E*)-19-methylicos-4-en-1-yn-3-ol, an immunosuppressive and antitumoral metabolite isolated from the Caribbean sponge *Cribrochalina vasculum*, has been achieved and its stereostructure has been confirmed. The key step of the synthesis involves a borane-mediated reduction of the parent (*E*)-19-methyl-1-trimethylsilylicos-4-en-1-yn-3-one in the presence of a chiral oxazaborolidine.

1. Introduction

Marine sponges are rich sources of long-chain acetylenic metabolites.[1] Many of these compounds, frequently isolated from sponges of the genera *Siphonochaline*,[2] *Petrosia*,[3–10] *Cribrochalina*,[11,12] *Xestospongia*,[13] *Pellina*[14] and *Haliclona*,[15] show a variety of interesting biological activities (antimicrobial, antitumoral, enzyme inhibitory) as well as important ecological roles.[16] Recently, some acetylenic alcohols (**1**–**5**, Fig. 1) which exhibit remarkable immunosuppressive and antitumoral activities, were isolated in minute amounts from samples of the sponge *Cribrochalina vasculum* collected by Gunasekera et al.[11] in Belize and also by Aiello et al.[12] near the Bahamas Islands. From a structural point of view, these compounds possess unsaturated, long-chain backbones with a characteristic, terminal 4-alkene-1-yn-3-ol moiety. As far as the stereochemistry is concerned, Aiello et al.[12] assigned the configuration at C-3 of these compounds as *R* based on the CD spectra of the corresponding *p*-bromobenzoate derivatives. However, Hallock et al.[17] suggested that some acetylenic alcohols from *C. vasculum* collected at the Bahamas coast at much greater depths, including (+)-**1**, had the *S* configuration using the modified Mosher's NMR method; since they obtained a CD spectrum opposite in sign to that previously reported

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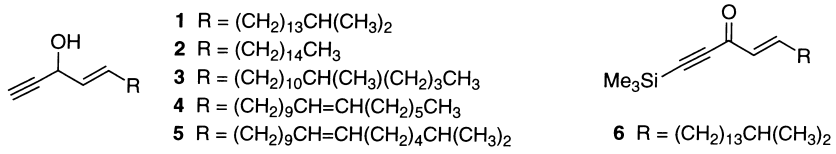


Figure 1.

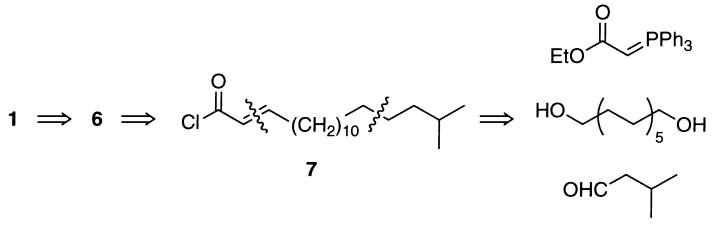
by Aiello et al.,[12] it was concluded that these metabolites can present either *R* or *S* configurations depending on the origin of the collection of *C. vasculum*.

Although these natural products appear to be attractive synthetic targets owing to their structural novelty and the strong bioactivity displayed, only a few stereoselective approaches to this kind of product have been very recently reported in which sugars are used as chiral pool starting materials,[17] or the stereocenters arise from an enzymatic resolution.[18–20]

In the context of studies directed toward the synthesis of marine natural products,[21,22] we wish to report herein the first stereoselective synthesis of (3*R*,4*E*)-19-methylicos-4-en-1-yn-3-ol, (*R*)-**1**, based on the stereoselective reduction of the parent (*E*)-19-methyl-1-trimethylsilylicos-4-en-1-yn-3-one, **6**. As a result, the stereochemistry proposed by Hallock et al.[17] for natural compound **1** has eventually been confirmed.

2. Results and discussion

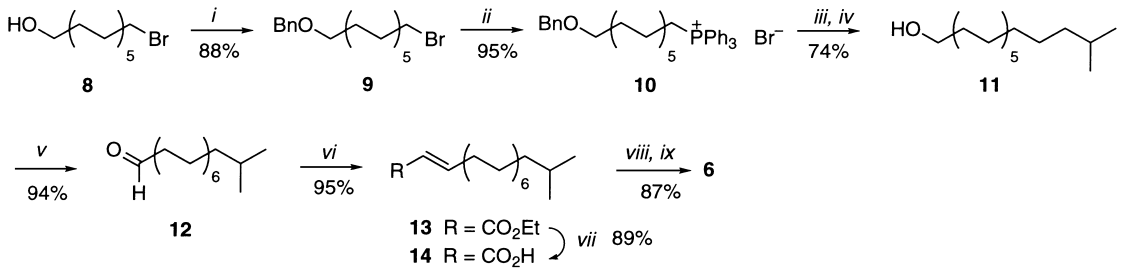
In our retrosynthetic analysis, compound **1** could arise from ketone **6** which, in turn, can be obtained from the α,β-unsaturated acid chloride **7** and bis(trimethylsilyl)acetylene by a Friedel–Crafts process. Compound **7**, as outlined in Scheme 1, could be further disconnected into three readily available fragments.



Scheme 1.

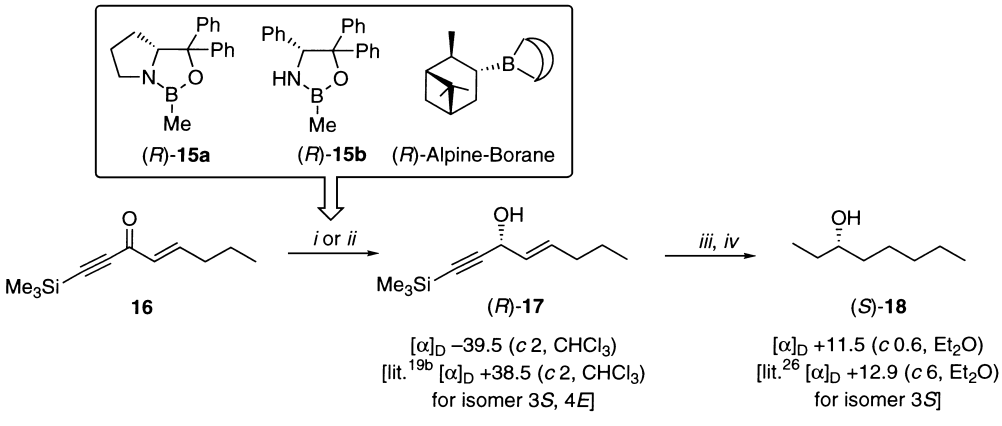
The synthesis of ketone **6** is summarised in Scheme 2. 12-Bromododecan-1-ol, easily obtained from dodecane-1,12-diol as described in the literature,[23] was protected as its *O*-benzyl derivative **9** and was then heated under nitrogen with triphenylphosphine to obtain the phosphonium salt **10** as a viscous oil. Treatment of **10** with BuLi, followed by addition of 3-methybutanal gave an olefin mixture, with the *Z*-isomer as the major product, which was hydrogenated without further purification to obtain saturated alcohol **11**. Swern oxidation of **11** followed by treatment of the resulting aldehyde with $Ph_3P{=}CHCO_2Et$ afforded (*E*)-α,β-unsaturated ester **13** in an *E*/*Z* ratio >30:1 according to the ^1H NMR spectrum of the crude product. Hydrolysis of ester **13** was accomplished with LiOH in refluxing dioxane:H_2O (3:1) overnight, which gave the unsaturated acid **14**. Finally, ketone **6** was readily obtained by transformation of **14** into its corresponding acid chloride followed by reaction of the crude product with $Me_3SiC{\equiv}CSiMe_3$ in the presence of $AlCl_3$.

Taking advantage of our previous experience of the enantioselective reduction of α,β-unsaturated ketones using chiral oxazaborolidines,[21,22,24,25] we assumed that treatment of **6** with BH_3:SMe_2 in the



Scheme 2. (i) $PhCH_2Br$, NaH, Et_2O, reflux; (ii) PPh_3, 120°C, neat; (iii) BuLi, THF, 0°C and then $(CH_3)_2CHCH_2CHO$; (iv) H_2, Pd/C, MeOH, rt; (v) Swern oxidn; (vi) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt; (vii) LiOH, dioxane:H_2O, 3:1, reflux; (viii) $(COCl)_2$, DMF cat., hexane; (ix) $Me_3SiC{\equiv}CSiMe_3$, $AlCl_3$, CH_2Cl_2, −20°C

presence of oxazaborolidines (*R*)-**15a** or (*R*)-**15b** would lead to the 1-trimethylsilyl-4-alken-1-yn-3-ol with the proper *R* configuration at C-3. In order to assess this assumption, reduction of the easily obtained (*E*)-1-trimethylsilyl-4-octen-1-yn-3-one, **16**, was first attempted since its derived chiral alcohol is known.[19b] As expected, **16** was efficiently transformed into (*R*)-**17** with BH_3:SMe_2 in the presence of 1 equiv. of either (*R*)-**15a** or (*R*)-**15b** (85–90% yield, 95% e.e.) in a few minutes.[22] As shown in Scheme 3, the configuration at C-3 in alcohol **17** was determined by comparison of its specific rotation, as well as the specific rotation of the 3-octanol derivative arising from **17**, with those described in the literature. It is noteworthy that long reaction times led to poorer chemical yields by concomitant side reactions, mainly hydroboration, of the alcohol first formed. Similarly, when only 0.2 equiv. of **15** were used the reaction became slower and the chemical yield also dropped. On the other hand, reduction of **16** with (−)-Alpine-Borane® proved to be as efficient as with **15** (93% yield, 92% e.e.) but longer reaction times were required.[26]



Scheme 3. (i) BH_3:SMe_2, (*R*)-**15**, THF, 0°C, 10 min (85−90%, 95% e.e.); (ii) (*R*)-Alpine-Borane®, neat, overnight (93%, 92% e.e.); (iii) K_2CO_3, MeOH, t.a., 1 h; (iv) H_2, Pt/C cat., MeOH (82% overall yield)

As far as the stereochemical course of the reaction is concerned, the observed configuration of alcohol **17** arising from reduction with oxazaborolidines was that expected according to the mechanism proposed by Corey et al.[27] for similar processes, by an arrangement such as **19** in which the double bond moiety — acting as a bigger group than $C{\equiv}CSiMe_3$ — is located far from the Me group on the boron atom (see Fig. 2). In a similar way, the stereochemical course of the reduction of **16** with Alpine-Borane® can be explained through a transition state such as **20** where the ethylene moiety also acts as a group 'larger' than the acetylenic one.

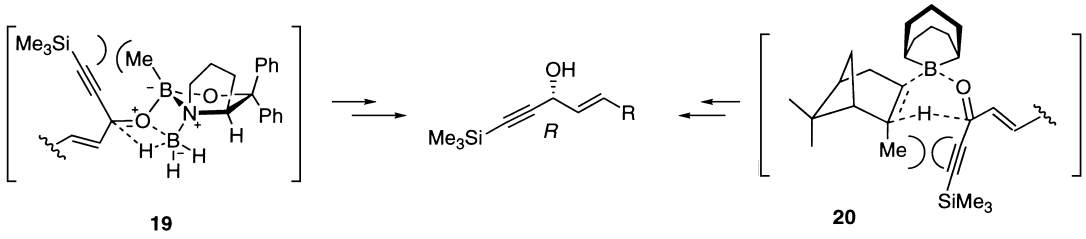
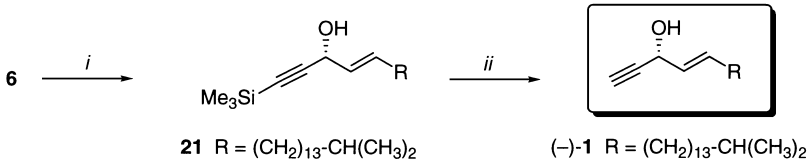


Figure 2.

Finally, we turned our attention to the synthesis of (+)-**1**. Reduction of ketone **6** was performed with BH_3:SMe_2 and (*R*)-**15b** to afford (*R*)-**21** (90% yield, 94% e.e.), which was easily desilylated by treatment with K_2CO_3 in MeOH/H_2O to obtain the desired unsaturated alcohol (−)-(*R*)-**1** (Scheme 4).



Scheme 4. (i) BH_3:SMe_2, (*R*)-**15**, THF, 0°C, 10 min (90%); (ii) K_2CO_3, MeOH, t.a., 1 h (82%)

3. Conclusions

In conclusion, we have disclosed an efficient approach to highly enantioenriched 4-alken-1-yn-3-ol moiety, present in many acetylenic metabolites isolated from sponges, which is based on the enantioselective reduction of the parent 1-trimethylsilyl-4-alken-1-yn-3-one followed by desilylation of the resulting alcohol. This strategy, obviously amenable to obtain either *R* or *S* enantiomers, has been applied to the first enantioselective synthesis of (3*R*,4*E*)-19-methylicos-4-en-1-yn-3-ol, (−)-(*R*)-**1**, an immunosuppressive and antitumoral acetylenic alcohol isolated from samples of the sponge *C. vasculum*. It is also worth noting that the correlation between the absolute configuration and the specific rotation determined in the present work confirm the *S* configuration proposed by Hallock et al. for samples of natural dextrorotatory **1**.

4. Experimental

All the solvents were distilled from an appropriate drying agent and stored under nitrogen atmosphere. The crude products were purified by column chromatography on silica gel of 230–400 mesh (flash chromatography). Thin-layer chromatograms were performed on HF 254 silica gel plates (using the eluents indicated after the R_f values). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 200 MHz and 50.3 MHz, respectively; chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in hertz. Infrared spectra were measured on a Perkin–Elmer 681 on NaCl plates (film) or in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Chemical ionisation mass spectra (NH_3) are given in *m*/*z*. Oxazaborolidines **15a**[28] and **15b**[25] were prepared according to published procedures.

4.1. Benzyl 12-bromododecyl ether **9**[29]

A solution of 1.75 g (6.57 mmol) of alcohol **8** in 5 mL of dry diethyl ether were carefully added via cannula to a suspension of NaH (375 mg of 60% dispersion in mineral oil, 9.7 mmol), previously washed with dry hexane, in 5 mL of dry diethyl ether. The mixture was heated at reflux for 45 min and then allowed to cool to room temperature. Afterwards, 1.12 mL (9.4 mmol) of neat benzyl bromide were added dropwise and the resulting suspension was stirred at room temperature. Twenty-four hours later, TLC showed that the starting alcohol **8** had almost disappeared and the reaction mixture was poured into diethyl ether and H_2O. The organic layer was separated and washed with brine. After drying (Na_2SO_4), the solvent was eliminated in vacuo and the crude product was purified by flash chromatography (2:1, hexane:CH_2Cl_2) to yield 2.052 g (88%) of **9**. Colourless oil. R_f 0.30 (1:2, hexane:CH_2Cl_2); ^{1}H NMR δ 1.27 (m, 16H), 1.60 (m, 2H), 1.86 (m, 2H), 3.40 (t, 2H, J=6.6 Hz), 3.46 (t, 2H, J=6.6 Hz), 4.50 (s, 2H), 7.30–7.40 (m, 5H); ^{13}C NMR δ 26.2, 28.2, 28.7, 29.5, 29.6, 32.8, 34.1, 70.5, 72.8, 127.4, 128.3, 129.0, 137.0; IR (film) 2900, 2820, 1440, 1100.

4.2. (12-Benzyloxidodecyl)triphenylphosphonium bromide **10**

A mixture of 170 mg (0.48 mmol) of **9** and 138 mg (0.53 mmol) of triphenylphosphine was heated in an oil bath at 120°C under N_2. The melt mixture was magnetically stirred for 3 h and then it was allowed to cool to room temperature. The crude product was purified by flash chromatography (9:1, CH_2Cl_2:MeOH) to afford 281 mg (95%) of phosphonium salt **10** as a thick oil. R_f 0.30 (9:1, CH_2Cl_2:MeOH); ^{1}H NMR δ 1.20 (m, 16H), 1.50–1.60 (m, 4H), 3.40 (t, 2H, J=6.6 Hz), 3.80 (m, 2H), 4.50 (s, 2H), 7.08–7.40 (m, 5H), 7.60–7.85 (m, 15H); ^{13}C NMR δ 22.3 (d, J_{CP}=52 Hz), 22.8, 25.6, 28.6, 28.9, 29.1, 29.7, 30.0, 30.9 (d, J_{CP}=16 Hz), 69.9, 72.2, 117.6 (d, J_{CP}=86 Hz), 126.9, 127.7, 128.5, 130.0 (d, J_{CP}=12.4 Hz), 133.1 (d, J_{CP}=9.8 Hz), 134.8 (d, J_{CP}=2.9 Hz), 138.1; IR (KBr) 3000, 2760, 1440, 1100. Anal. calcd for $C_{37}H_{46}BrOP$: C, 71.95; H, 7.51. Found: C, 71.71; H, 7.34.

4.3. 15-Methylhexadecan-1-ol **11**

To a magnetically stirred mixture of 444 mg (0.72 mmol) of phosphonium salt **10** in 10 mL of dry THF, 0.63 mL (1.0 mmol) of BuLi in hexanes were added dropwise at 0°C under N_2. After 45 min, 3-methybutanal (110 μL, 1.0 mmol) was added to the resulting red solution and the stirring was continued for a further 2 h at room temperature. The progress of the reaction was monitored by TLC. Work-up was done at 0°C by addition of 5 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with brine (5 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a crude product which was hydrogenated without further purification. To a solution of the crude product in MeOH (25 mL), 230 mg of 5% Pt/C were added, and the suspension was shaken under 1 atm of hydrogen. After 6 h, the mixture was filtered through a pad of Celite®. The solvent was eliminated in vacuo and the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to yield 136 mg (74% overall yield) of **11**: mp 42–44°C; R_f 0.20 (CH_2Cl_2); ^{1}H NMR δ 0.86 (d, 6H, J=6.6 Hz), 1.20–1.45 (m, 24H), 1.53 (m, 3H), 2.05 (bs, 1H), 3.63 (t, 2H, J=6.6 Hz); ^{13}C NMR δ 22.6, 25.7, 27.4, 27.9, 29.5, 29.6, 29.7, 29.9, 32.7, 39.0, 62.8; IR (KBr) 3360, 2920, 2840, 1460. Anal. calcd for $C_{17}H_{36}O$: C, 79.61; H, 14.15. Found: C, 79.88; H, 14.10.

4.4. 15-Methylhexadecanal **12**

DMSO (110 μL, 1.55 mmol) was added slowly to a solution of oxalyl chloride (70 μL, 0.80 mmol) in 2 mL of anh. CH_2Cl_2 at −40°C under Ar. After 10 min at this temperature, a solution of alcohol **11** (164 mg, 0.64 mmol) in 1 mL of anh. CH_2Cl_2 was added dropwise and the solution was stirred for 45 min. Afterwards, 418 μL (3.0 mmol) of Et_3N were added and the mixture was stirred for a further 15 min and then it was allowed to warm to room temperature. The suspension was poured into 130 mL of Et_2O:hexane (1:4) and 50 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), and the solvent was eliminated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2) to afford 153 mg (94%) of aldehyde **12**: mp 36–37°C; R_f 0.65 (CH_2Cl_2); ^{1}H NMR δ 0.86 (d, 6H, *J*=6.6 Hz), 1.20–1.45 (m, 22H), 1.53 (m, 1H), 1.63 (m, 2H), 2.42 (td, 2H, *J*=7.4, 1.8 Hz), 9.77 (t, 1H, *J*=1.8 Hz); ^{13}C NMR δ 22.6, 27.4, 28.0, 29.3, 29.5, 29.6, 29.7, 29.8, 29.9, 39.0, 43.9, 202.9; IR (KBr) 2920, 2840, 1730. Anal. calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.01; H, 13.63.

4.5. Ethyl (E)-17-methyl-2-octadecenoate **13**

A solution of 153 mg (0.60 mmol) of **12** and 251 mg (0.72 mmol) of ethyl(triphenylphosphoranylidene)acetate (previously dried at 50°C under vacuum for 2 days) in 1 mL of anh. CH_2Cl_2 was stirred at room temperature under N_2. The progress of the reaction was monitored by TLC. When full conversion of starting **12** was obtained (14 h), the solvent was removed and the crude product was purified by flash chromatography (CH_2Cl_2) to obtain 185 mg (95%) of unsaturated ester **13**. Colourless oil. R_f 0.72 (CH_2Cl_2); ^{1}H NMR δ 0.86 (d, 6H, *J*=6.6 Hz), 1.20–1.45 (m, 22H), 1.50 (m, 3H), 2.19 (dtd, 2H, *J*=7.0, 6.6, 1.6 Hz), 4.18 (q, 2H, *J*=7.2 Hz), 5.81 (dt, 1H, *J*=15.8, 1.6 Hz), 6.97 (dt, 1H, *J*=15.8, 7.0 Hz); ^{13}C NMR δ 14.3, 22.6, 27.4, 27.9, 28.0, 29.1, 29.4, 29.5, 29.7, 29.9, 32.2, 39.1, 60.1, 121.2, 149.5, 166.7; IR (film) 2900, 2820, 1720, 1650. Anal. calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.96; H, 12.40.

4.6. (E)-17-Methyl-2-octadecenoic acid **14**

A solution of 185 mg (0.57 mmol) of ester **13** and 41 mg (1.71 mmol) of LiOH in 3 mL of dioxane and 1 mL of water was heated to reflux overnight. The solution was allowed to cool to room temperature and 2 M HCl was then added until the mixture reached pH 1. Afterwards, the mixture was extracted with CH_2Cl_2 (2×50 mL) and AcOEt (2×50 mL). The organic layers were washed with 0.2 M HCl (10 mL). After drying (Na_2SO_4), the solvent was eliminated in vacuo and the crude product was purified by flash chromatography (98:2, CH_2Cl_2:MeOH) to yield 150 mg (89%) of **14**: mp 58–59°C; R_f 0.55 (9:1, CH_2Cl_2:MeOH); ^{1}H NMR δ 0.86 (d, 6H, *J*=6.6 Hz), 1.20–1.45 (m, 22H), 1.50 (m, 3H), 2.22 (dt, 2H, *J*=7.0, 6.8 Hz), 5.82 (dt, 1H, *J*=15.8, 1.6 Hz), 7.08 (dt, 1H, *J*=15.8, 7.0 Hz); ^{13}C NMR δ 22.6, 27.6, 27.8, 29.1, 29.3, 29.6, 29.7, 29.9, 32.2, 39.0, 120.2, 153.0, 173.0; IR (KBr) 3300–3000, 2920, 2840, 1690, 1650. Anal. calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 77.21; H, 12.26.

4.7. (E)-19-Methyl-1-trimethylsilyl-4-icosen-1-yn-3-one **6**

Oxalyl chloride (46 μL, 0.52 mmol) was added to 141 mg (0.48 mmol) of acid **14** in 3 mL of anh. hexane at room temperature. A drop of anh. DMF was added and the mixture was stirred at room temperature overnight. The volatiles were removed under vacuum. The residue containing the crude acid chloride and 120 μL (0.53 mmol) of bis(trimethylsilyl)acetylene was dissolved in 1 mL of anh. CH_2Cl_2

and the solution was added dropwise to a suspension of 75 mg (0.56 mmol) $AlCl_3$ in 2 mL of anh. CH_2Cl_2 at −20°C. Thirty minutes later the mixture was warmed to 0°C and then stirred for a further 3 h at this temperature. The reaction was quenched by pouring the mixture into ice and pH 7 phosphate buffer followed by extractions with CH_2Cl_2 (2×50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by a short flash chromatography (CH_2Cl_2) to yield 155 mg (87%) of ketone **6** which was used immediately. Pale yellowish oil. R_f 0.64 (CH_2Cl_2); ^{1}H NMR δ 0.26 (s, 9H), 0.88 (d, 6H, *J*=6.6 Hz), 1.20–1.45 (m, 22H), 1.50 (m, 3H), 2.30 (dt, 2H, *J*=7.0, 6.6 Hz), 6.15 (dt, 1H, *J*=15.8, 1.4 Hz), 7.20 (dt, 1H, *J*=15.8, 7.0 Hz); ^{13}C NMR δ −0.7, 22.6, 27.4, 27.9, 28.0, 29.2, 29.3, 29.5, 29.6, 29.9, 32.6, 39.0, 99.0, 102.0, 132.0, 155.0, 179.0; IR (film) 2920, 2840, 2140, 1640. Anal. calcd for $C_{24}H_{44}OSi$: C, 76.52; H, 11.77. Found: C, 76.29; H, 11.84.

*4.8. (*E*)-1-Trimethylsilyl-4-octen-1-yn-3-one **16***

To a stirred solution of 0.83 mL (5.9 mmol) of trimethylsilylacetylene in 10 mL of anh. THF at −78°C, 3.47 mL (5.0 mmol) of a solution of BuLi in hexanes was added dropwise followed by 0.70 mL (6.0 mmol) of (*E*)-2-hexenal 10 min later. The reaction mixture was stirred for a further 10 min and then allowed to warm to room temperature. Then, the mixture was poured into pH 7 phosphate buffer and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to yield 0.94 g (96%) of crude, almost pure, (±)-**17** by TLC. The crude product was dissolved in 10 mL of dry hexane and 2.1 g of activated MnO_2 were added at once under N_2 and the suspension was stirred at room temperature. The progress of the reaction was monitored by TLC. After 1 h, a further 3.6 g of MnO_2 was added and the mixture was stirred overnight. Afterwards, TLC revealed the disappearance of the starting alkene. Filtration through a pad of Celite® and evaporation of the solvent gave a crude product which was purified by a short flash chromatography (2:1, CH_2Cl_2:hexane) to yield 783 mg (84%) of ketone **16** which was used immediately. Pale yellowish oil. R_f 0.48 (2:1, CH_2Cl_2:hexane); ^{1}H NMR δ 0.27 (s, 9H), 0.97 (t, 3H, *J*=7.3 Hz), 1.55 (m, 2H), 2.29 (m, 2H), 6.16 (dt, 1H, *J*=15.6, 1.5 Hz), 7.20 (dt, 1H, *J*=15.6, 6.8 Hz); ^{13}C NMR δ −0.7, 13.6, 21.1, 34.5, 98.0, 100.3, 132.1, 154.6, 178.2; IR (film) 2960, 2160, 1640. Anal. calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.33. Found: C, 68.26; H, 9.51. MS (CI) *m/z* (rel. int. %): 195 (M^++1, 100%).

*4.9. Reduction of ketone **16** with BH_3:SME_2 catalysed by (*R*)-**15a***

A solution of **16** (155 mg, 0.80 mmol) in THF (1 mL) was added dropwise in ∼10 min to a solution of (*R*)-**15a** (0.80 mmol) and BH_3:SMe_2 (91 μL, 0.91 mmol) in THF (3 mL) at 0°C under Ar. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. Reaction was cautiously quenched by slow addition of MeOH (1 mL) at 0°C. The solution was stirred for 15 min at room temperature and the volatiles were then removed under vacuum. The residue was purified by flash chromatography (1:1, CH_2Cl_2:hexane) to yield 134 mg (85%) of alcohol (*R*)-**17**. Colourless oil; R_f 0.33 (2:1, CH_2Cl_2:hexane); $[\alpha]_D^{20}$ −39.5 (*c* 2, $CHCl_3$), [lit.[19b] $[\alpha]_D^{20}$ +38.5 (*c* 1, $CHCl_3$) for isomer 3*S*]; ^{1}H NMR δ 0.23 (s, 9H), 0.92 (t, 3H, *J*=7.2 Hz), 1.34–1.55 (m, 2H), 2.05 (m, 2H), 4.83 (m, 1H), 5.59 (ddt, 1H, *J*=15.3, 6.2, 1.4 Hz), 5.89 (dtd, 1H, *J*=15.3, 6.6, 1.0 Hz); ^{13}C NMR δ −0.2, 13.6, 22.0, 34.0, 63.3, 90.4, 105.0, 128.8, 133.8; IR (film) 3320, 2940, 2160, 1670. MS (CI) *m/z* (rel. int. %): 196 (M^+, 100%), 197 (M^++1, 19%). An analytical sample of the crude product was treated with an excess of (*S*)-Mosher acid chloride (derived from (*R*)-acid) to give the Mosher ester. The analysis by GC (Supelco Beta-DEX®) 120 capillary column, 130°C, t_R (*S*)=13.44 min, t_R (*R*)=14.01 min) as well as by ^{19}F NMR revealed a 95% e.e.

4.10. Reduction of ketone **16** with BH_3:SME_2 catalysed by (R)-**15b**

The reaction was performed as described above for (*R*)-**15a** to yield (*R*)-**17** in 90% yield and 95% e.e.

4.11. Reduction of ketone **16** with Alpine-Borane®

A commercial 0.5 M solution of (*R*)-Alpine-Borane® (5.2 mL, 2.60 mmol) in THF was placed in a round-bottom flask provided with a magnetic bar and the solvent was removed under vacuum in a vacuum manifold. The flask was then refilled with N_2, cooled in an ice bath and 181 mg (0.93 mmol) of neat ketone **16** were added dropwise. After 15 h, TLC revealed the disappearance of the starting ketone. To the crude product, 0.8 mL (14.3 mmol) of acetaldehyde in 2 mL of dry THF were added and the mixture was stirred at room temperature for 6 h before removing the solvents in vacuo. The residue was stirred with 0.10 mL of 2-aminoethanol in 2 mL of Et_2O. After 1 h, the precipitate was removed by filtration and washed with more diethyl ether. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (1:2, CH_2Cl_2:hexane) yielded 169 mg (93%) of (*R*)-**17**. The analysis of an analytical sample by ^{19}F NMR of the corresponding Mosher ester revealed a 92% e.e.

4.12. (S)-3-Octanol (S)-**18**[26]

To a solution of 120 mg (0.62 mmol) of (*R*)-**17** (95% e.e.) in 4 mL of MeOH:H_2O (10:1), K_2CO_3 (170 mg, 1.23 mmol) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (CH_2Cl_2, appearance of spot at R_f 0.29). When the reaction was completed (45 min), the mixture was poured into pH 7 phosphate buffer (8 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was dissolved in 30 mL of MeOH, 50 mg of 5% Pt/C was added, and the suspension was shaken under 50 atm of hydrogen for 3 h. Afterwards, the mixture was filtered through a pad of Celite®. The solvent was eliminated in vacuo and the residue was purified by flash chromatography through a short path of silica gel (9:1, CH_2Cl_2:AcOEt) to yield 66 mg (82%) of (*S*)-**18**, which was compared to a sample of commercial (±)-3-octanol. R_f 0.63 (9:1, CH_2Cl_2:AcOEt); $[\alpha]_D^{20}$ +11.5 (*c* 0.6, Et_2O) [lit.[26] $[\alpha]_D^{20}$ +12.9 (*c* 6, Et_2O) for isomer 3*S*]; ^1H NMR δ 0.79–1.00 (m, 6H), 1.20–1.60 (m, 10H), 1.72 (bs, 1H), 3.55 (m, 1H); ^{13}C NMR δ 9.9, 14.1, 22.7, 25.5, 30.2, 32.0, 36.1, 73.3.

4.13. Reduction of ketone **6** with BH_3:SME_2 catalysed by (R)-**15b**

A solution of **6** (78 mg, 0.21 mmol) in THF (1 mL) was added dropwise in ~10 min to a solution of (*R*)-**15b** (0.20 mmol) and BH_3:SMe_2 (30 μL, 0.30 mmol) in THF (2 mL) at 0°C under Ar. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. Reaction was cautiously quenched by slow addition of MeOH (0.1 mL) at 0°C. The solution was stirred for 10 min at room temperature and the volatiles were then removed under vacuum. The residue was purified by flash chromatography (2:1, CH_2Cl_2:hexane) to afford 71 mg (90%) of (3*R*,4*E*)-19-methyl-1-trimethylsilyl-4-icosen-1-yn-3-ol, (*R*)-**21**. Colourless oil; R_f 0.56 (CH_2Cl_2); $[\alpha]_D^{20}$ −23.3 (*c* 1, MeOH); ^1H NMR δ 0.19 (s, 9H), 0.88 (d, 6H, *J*=6.6 Hz), 1.20–1.45 (m, 22H), 1.50 (m, 3H), 2.08 (dt, 2H, *J*=6.6, 6.6 Hz), 4.83 (dd, 1H, *J*=6.0, 1.2 Hz), 5.60 (dd, 1H, *J*=15.4, 6.0 Hz), 5.90 (dtd, 1H, *J*=15.4, 6.6, 1.2 Hz); ^{13}C NMR δ −0.1, 22.8 27.6, 28.1, 29.0, 29.4, 29.6, 29.8, 30.1, 32.1, 39.2, 63.5, 90.6, 105.2, 128.8, 134.4; IR (film) 3340, 2940, 2860, 2200. Anal. calcd for $C_{24}H_{46}OSi$: C, 76.12; H, 12.24. Found: C, 76.22; H, 11.98. An analytical sample

of the crude product was treated with an excess of (*S*)-Mosher acid chloride (derived from (*R*)-acid) to give the Mosher ester. The analysis by ^{19}F NMR revealed a 94% e.e.

*4.14. (3*R,*4*E*)-19-Methyl-4-icosen-1-yn-3-ol (*R*)-**1***

A mixture of 48 mg (0.13 mmol) of (*R*)-**21**, 35 mg (0.26 mmol) of K_2CO_3, 2 mL of MeOH and two drops of water was stirred at room temperature. The progress of the reaction was monitored by TLC. When the reaction was completed (1 h), the mixture was poured onto a pH 7 phosphate buffer and extracted with CH_2Cl_2 (3×25 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by a short flash chromatography (CH_2Cl_2) to yield 33 mg (82%) of (*R*)-**1**: mp 35–37°C; R_f 0.42 (CH_2Cl_2); $[\alpha]_D^{20}$ −20.5 (*c* 1.1, MeOH) [lit.[17] $[\alpha]_D^{20}$ +22.2 (*c* 0.58, MeOH) for isomer 3*S*]; ^1H NMR δ 0.89 (d, 6H, *J*=6.6 Hz), 1.20–1.35 (m, 22H), 1.43 (m, 2H), 1.55 (m, 1H), 2.11 (dt, 2H, *J*=6.9, 6.9 Hz), 2.61 (d 1H, *J*=2.1 Hz), 4.88 (m, 1H), 5.65 (ddt, 1H, *J*=15.3, 6.0, 1.4 Hz), 5.96 (dtd, 1H, *J*=15.3, 6.9, 1.2 Hz); ^{13}C NMR δ 22.7, 27.4, 28.0, 28.8, 29.2, 29.5, 29.6, 29.7, 29.9, 31.9, 39.0, 62.8, 73.9, 83.3, 128.3, 134.6; IR (film) 3260, 2920, 2840, 2120.

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