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Stereoselective synthesis of musclides A1, A2 and B

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Abstract—An expedient method for the stereoselective preparation of musclide A1, A2 and B, cardiotonic-potentiating principles from musk, has been achieved. The key step is the addition of the *O*-benzyl ethers of prop-2-yn-1-ol and (*R*)-but-3-yn-2-ol to aldehydes mediated by zinc triflate, Et_3N, and (+)- or (−)-*N*-methylephedrine. In some cases, the partial reduction of the resulting alkynols to *Z*-olefins has allowed us to remove the minor stereoisomer easily by chromatography to afford highly stereoenriched precursors of musclides.

1. Introduction

Musk, a dried secretion from the preputial follicles of the male musk deer (*Moschus moschiferus* L.), has been used not only as a precious perfume component but also as a traditional Chinese medicine since ancient times. Modern research has demonstrated that musk displays extensive pharmacological actions, including cardiotonic, sedative and anti-inflammatory properties.[1,2]

Kikuchi et al. have reported that the cardiotonic activity is due to the presence of three aliphatic 1,4-diol monosulfates, musclide A1, A2 and B.[3] Very recently, Tezuka et al. have established that the natural musclide A2 is the hydrogen sulphate **1** (Fig. 1).[4] In the same study, the structure of musclide B was assigned as (1*S*,4*R*)-4-hydroxy-1-(2-methylpropyl)pentyl hydrogen sulphate **2** by comparison of the natural product with the 1*R*,4*S* and 1*R*,4*R* stereoisomers obtained from ethyl (*S*)-leucinate. Shortly after, the same research group also confirmed that musclide A1 is a 7:3 mixture of (1*R*,4*R*)- and (1*S*,4*R*)-4-hydroxy-1-isopropylpentyl hydrogen sulphate [(1*R*,4*R*)-**3** and (1*S*,4*R*)-**3**].[5] Despite the doubtless interest of such compounds and the difficulty of their isolation from natural sources, synthetic studies aimed at preparing musclides and their precursors are limited to the aforementioned works.[3–5]

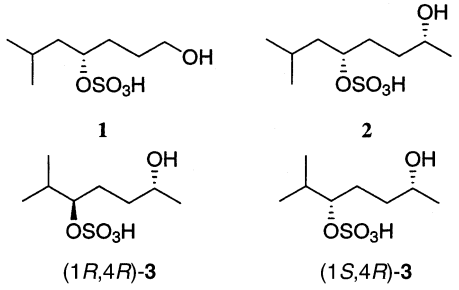

Figure 1.

In 2000, Carreira et al. reported the enantioselective addition of Zn–alkynylides to aldehydes using $Zn(OTf)_2$, (+)- or (−)-*N*-methylephedrine and Et_3N to afford highly enantioenriched propargylic alcohols.[6] Based on these studies, we have very recently extended this methodology to the stereoselective preparation of chiral monoprotected *syn*- or *anti*-2-alkyne-1,4-diols.[7] As a part of a project addressed to the application of this approach to the synthesis of natural products,[8] we wish to report herein the first stereoselective synthesis of musclides.

2. Results and discussion

In the light of our previous work, we envisaged that the required 1,4-diol motif present in musclides could be attainable through the stereoselective addition of 3-benzyloxyprop-1-yne **4** or (*R*)-3-benzyloxybut-1-yne **5** to the appropriate aldehyde.

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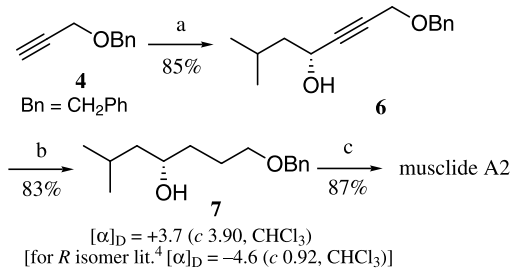
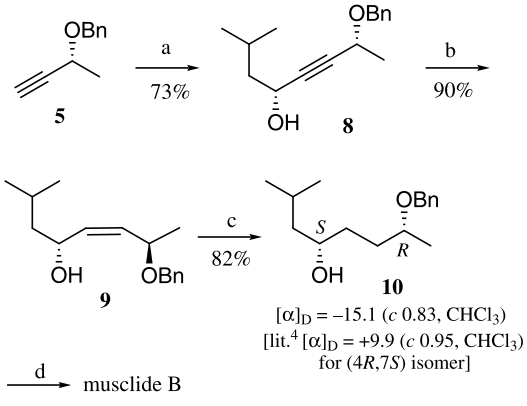
Our first efforts were directed to the preparation of monoprotected propargylic diol **6** (Scheme 1). The addition of alkyne **4** to 3-methylbutanal in the presence of $Zn(OTf)_2$, (+)-*N*-methylephedrine and Et_3N (65°C, 1 h) afforded **6** in 85% yield (91:9 *R*/*S* ratio).[9] Remarkably, when the reaction was performed at rt only a slight improvement in the enantioselectivity was noted but at the expense of longer reaction times and/or lower yields (e.g. 41% yield, 92:8 *R*/*S* ratio, 4 h). Subsequent hydrogenation of **6** cleanly afforded the known alcohol **7**, which, in turn, can be readily transformed into musclide A2.[4]



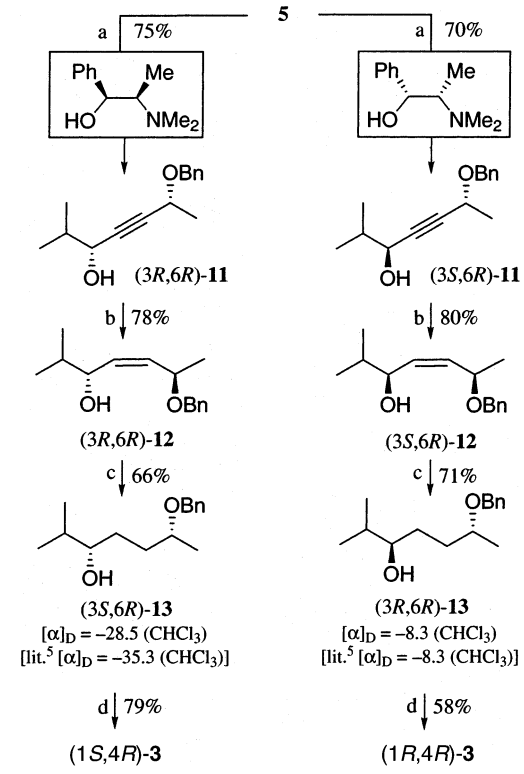
Scheme 1. *Reagents and conditions*: (a) $Zn(OTf)_2$ (1.1 equiv.), (+)-*N*-methylephedrine (1.2 equiv.), Et_3N (1.2 equiv.), 3-methylbutanal (1.1 equiv.), toluene, 65°C; (b) H_2 (1 atm), Pt/C cat., EtOAc, rt; (c) Ref. 4.

In a similar way, we examined the asymmetric alkynylation of 3-methylbutanal with the alkyne **5**, easily obtained from commercially available, inexpensive (*R*)-but-3-yn-2-ol. The slow addition of the aldehyde to the Zn–alkynylide derived from **5** in the presence of (+)-*N*-methylephedrine afforded the monoprotected diol **8** as a 90:10 (*R*,*R*)/(*R*,*S*) inseparable mixture of diastereomers (see Scheme 2).[10] Although the direct hydrogenation of **8** to **10** is obviously feasible, the partial reduction to **9** allowed us to remove the minor *R*,*S* stereoisomer by flash chromatography, increasing in this way the purity of the monoprotected diol.[11] Finally, hydrogenation of pure **9** gave the known saturated diol **10**. The efficient transformation of **10** into musclide B has been described previously.[4]



Scheme 2. *Reagents and conditions:* (a) $Zn(OTf)_2$ (1.1 equiv.), (+)-*N*-methylephedrine (1.2 equiv.), Et_3N (1.2 equiv.), 3-methylbutanal (1.1 equiv.), toluene, 65°C; (b) H_2 (1 atm.), Lindlar cat., EtOAc, rt; (c) H_2 (1 atm), Pt cat., EtOAc, rt; (d) Ref. 4.

We then turned our attention to the synthesis of musclide A1. Our previous experience[7] suggested that either (3*R*,6*R*)-**11** or (3*S*,6*R*)-**11**, precursors of both constituents of musclide A1 [i.e. (1*R*,4*R*)-**3** and (1*S*,4*R*)-**3**] could be selectively obtained simply by switching from (+)- to (–)-*N*-methylephedrine in the alkynylation step (see Scheme 3). To our delight, the addition of the alkynylzinc reagent derived from **5** and (+)-*N*-methylephedrine to isobutyraldehyde readily afforded the desired monoprotected diol (3*R*,6*R*)-**11** with excellent stereochemical control (75%, 97:3 (*R*,*R*)/(*R*,*S*) ratio, matched case). As expected, when (–)-*N*-methylephedrine was used in a similar protocol, the 3*S*,6*R* isomer was obtained as the major product with good stereoselectivity (70%, 13:87 (*R*,*R*)/(*S*,*R*) ratio, mismatched case).[10] As in the case of musclide B, transformation of **11** in (*Z*)-**12** allowed us to remove the minor stereoisomer, improving in this way the stereochemical purity. Finally, hydrogenation of (3*R*,6*R*)-**12** and (3*S*,6*R*)-**12** afforded pure (3*S*,6*R*)-**13** and (3*R*,6*R*)-**13**, respectively. Since an efficient transformation of **13** into **3** has been described,[5] this approach constitutes a formal stereoselective synthesis of both components of musclide A1.



Scheme 3. *Reagents and conditions*: (a) $Zn(OTf)_2$ (1.1 equiv.), (+)- or (–)-*N*-methylephedrine (1.2 equiv.), Et_3N (1.2 equiv.), isobutyraldehyde (1.1 equiv.), toluene, 65°C; (b) H_2 (1 atm), Lindlar cat., EtOAc, rt; (c) H_2 (1 atm), Pt cat., EtOAc, rt; (d) Ref. 5.

3. Conclusion

In conclusion, we have disclosed herein a straightforward, stereoselective preparation of musclide A1, A2 and B from commercially available, low-cost starting materials. This formal synthesis of musclides explores and exemplifies the usefulness of the very recently described alkynylation of aldehydes in the synthesis of natural products.

4. Experimental

4.1. General methods

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 CH_2Cl_2, CH_2Cl_2/MeOH, hexane/EtOAc or CH_2Cl_2/hexane as the eluents, as indicated after the R_f values). NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz for ^1H, 50.3 MHz for ^{13}C, and 282.2 MHz for ^{19}F. Chemical shifts are given in ppm with respect to internal TMS. Infrared spectra were measured on a Perkin–Elmer 681 on NaCl plates (neat); only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Optical rotations were measured at 20±2°C. HRMS (FAB+) were obtained at the CACTI (Universidad de Vigo). $Zn(OTf)_2$ was dried overnight at 120°C under vacuum prior use. Acetylenic ether **4** was prepared according to a published procedure.[12]

4.2. (*R*)-3-Benzyloxybut-1-yne, 5

A solution of 890 mg (12.70 mmol) of (*R*)-but-3-yn-2-ol in 2 mL of dry THF was carefully added via cannula to a suspension of NaH (671 mg of 60% dispersion in mineral oil, 16.78 mmol), previously washed with dry hexane, containing a catalytic amount of tetrabutylammonium iodide, in 30 mL of dry THF. The mixture was stirred for 45 min and then 3.39 mL (28.50 mmol) of neat benzyl bromide were added dropwise and the resulting suspension was stirred at rt overnight. Fifteen hours later, TLC showed that the starting alcohol had almost disappeared and the reaction mixture was poured into CH_2Cl_2 and pH 7 phosphate buffer. 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 (99:1, hexane:EtOAc) to yield 1.694 g (83%) of (*R*)-3-benzyloxybut-1-yne, **5**: colourless oil; R_f 0.08 (1:1, hexane:CH_2Cl_2); $[\alpha]_D^{20}=+110.5$ (*c* 0.96, $CHCl_3$); ^1H NMR: δ 1.48 (d, $J=6.6$ Hz, 1H), 2.45 (d, $J=2.1$ Hz, 1H), 4.20 (qd, $J=6.6$, 2.1 Hz, 1H), 4.50 (A of an AB system, $J=11.8$ Hz, 1H), 4.79 (B of an AB system, $J=11.8$ Hz, 1H), 7.30–7.38 (m, 5H); ^{13}C NMR: δ 22.0, 64.2, 70.5, 73.1, 83.7, 127.7, 128.0, 128.4, 137.7; IR (neat): 698, 739, 1065, 1098, 1455, 1719, 2939, 2989, 3033, 3294. Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.64; H, 7.37.

4.3. General procedure for the addition of alkynes to aldehydes. Preparation of (*R*)-1-benzyloxy-6-methylhept-2-yn-4-ol, 6

A slurry mixture of dry $Zn(OTf)_2$ (408 mg, 1.1 mmol), (+)-*N*-methylephedrine (220 mg, 1.2 mmol), alkyne **5** (147 mg, 1 mmol), dry toluene (300 μL), and Et_3N (167 μL, 1.2 mmol) were vigorously stirred under Ar at rt. After 30 min, 3-methylbutanal (118 μL, 1.1 mmol) was added dropwise (ca. 5–10 min) by syringe to the mixture at 65°C. The reaction was monitored by TLC and, after completion (1 h), the mixture was poured directly into a silica gel column and purified by flash chromatography (9:1, hexane:EtOAc) to afford 197 mg (0.85 mmol, 85%) of **6**: colourless oil; R_f 0.23 (CH_2Cl_2); $[\alpha]_D^{20}=+10.7$ (*c* 1.16, $CHCl_3$); ^1H NMR: δ 0.92 (d, $J=6.6$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H), 1.60 (m, 2H), 1.85 (m, 1H), 2.15 (br s, 1H, OH), 4.20 (d, $J=1.4$ Hz, 2H), 4.45 (td, $J=7.2$, 1.4 Hz, 1H), 4.59 (s, 2H), 7.25–7.37 (m, 5H); ^{13}C NMR: δ 22.4, 22.5, 24.7, 46.7, 57.3, 60.9, 71.5, 80.5, 88.0, 127.8, 128.0, 128.4, 137.3; IR (neat): 698, 1028, 1071, 1111, 2871, 2958, 3033, 3405; HRMS calcd for $C_{15}H_{21}O_2$ (M^++1) 233.1542, found 233.1549. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.49; H, 8.88. The HPLC analysis (Chiralcel OD-H column, 9:1 hexane/Pr^{i}OH, 0.9 mL/min, $t_R(S)=13.2$ min, $t_R(R)=16.9$ min) revealed a 91:9 *S*/*R* ratio.

4.3.1. (4*R*,7*R*)-7-Benzyloxy-2-methyloct-5-yn-4-ol, 8. Alkynylation was performed according to the general procedure described in Section 4.3, to afford 73% yield of **8**: colourless oil; R_f 0.14 (9:1, hexane:EtOAc); $[\alpha]_D^{20}=+100.4$ (*c* 0.57, $CHCl_3$); ^1H NMR: δ 0.94 (d, $J=6.6$ Hz, 3H), 0.96 (d, $J=6.6$ Hz, 3H), 1.46 (d, $J=6.6$ Hz, 3H), 1.61 (m, 2H), 1.86 (m, 1H), 4.25 (qd, $J=6.6$, 1.6 Hz, 2H), 4.47 (td, $J=7.2$, 1.6 Hz, 1H), 4.50 (A of an AB system, $J=11.7$ Hz, 1H), 4.76 (B of an AB system, $J=11.7$ Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR: δ 22.2, 22.5, 22.6, 24.8, 46.9, 61.1, 64.5, 70.6, 84.6, 86.5, 127.7, 128.0, 128.4, 138.0; IR (neat): 699, 1028, 1053, 1086, 1106, 1162, 1328, 1455, 2871, 2935, 2958, 3066. Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.83; H, 9.12. An analytical sample was transformed into the corresponding Mosher ester derived from Mosher's (*R*)-acid. ^{19}F NMR analysis of the sample revealed as composition (2*R*,5*R*)/(2*R*,5*S*) = 9:1.

4.3.2. (3*R*,6*R*)-6-Benzyloxy-2-methylhept-4-yn-3-ol, (3*R*,6*R*)-11. Alkynylation was performed according to the general procedure described in Section 4.3, to afford 75% yield of (3*R*,6*R*)-**11**: colourless oil; R_f 0.25 (85:15, hexane:EtOAc); $[\alpha]_D^{20}=+94.2$ (*c* 1.6, $CHCl_3$); ^1H NMR: δ 1.01 (d, $J=6.3$ Hz, 3H), 1.03 (d, $J=6.3$ Hz, 3H), 1.47 (d, $J=6.6$ Hz, 3H), 1.88 (m, 1H), 4.22–4.30 (m, 2H), 4.50 (A of an AB system, $J=11.7$ Hz, 1H), 4.77 (B of an AB system, $J=11.7$ Hz, 1H), 7.22–7.31 (m, 5H); ^{13}C NMR: δ 17.5, 18.1, 22.2, 34.6, 64.5, 67.9, 70.5, 84.9, 85.4, 127.7, 128.0, 128.4, 137.9; IR (neat): 698, 737, 1028, 1105, 1160, 1328, 1372, 1455, 2873,

2933, 2964, 3421; HRMS calcd for $C_{15}H_{21}O_2$ (M^++1) 233.1542, found 233.1531. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.76. An analytical sample was transformed into the corresponding Mosher ester derived from Mosher's (*R*)-acid. ^{19}F NMR analysis of the sample revealed as composition (3*R*,6*R*)/(3*S*,6*R*) = 97:3.

4.3.3. (3*S*,6*R*)-6-Benzyloxy-2-methylhept-4-yn-3-ol, (3*S*,6*R*)-11. Alkynylation was performed according to the general procedure described in Section 4.3, to afford 70% yield of (3*S*,6*R*)-**11**: colourless oil; R_f 0.25 (85:15, hexane:EtOAc); $[\alpha]_D^{20}$ = +118.5 (*c* 1.32, $CHCl_3$); ^{1}H NMR: δ 1.01 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.88 (m, 1H), 4.22–4.31 (m, 2H), 4.50 (A of an AB system, *J* = 11.7 Hz, 1H), 4.77 (B of an AB system, *J* = 11.7 Hz, 1H), 7.22–7.30 (m, 5H). ^{13}C NMR: δ 17.5, 18.2, 22.3, 34.5, 64.5, 67.9, 70.6, 84.9, 85.4, 127.6, 127.9, 128.3, 137.9; IR (neat): 699, 737, 1028, 1106, 1160, 1328, 1372, 1455, 2873, 2933, 2964, 3421; HRMS calcd for $C_{15}H_{21}O_2$ (M^++1) 233.1542, found 233.1553. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.61; H, 8.45. An analytical sample was transformed into the corresponding Mosher ester derived from Mosher's (*R*)-acid. ^{19}F NMR analysis of the sample revealed as composition (3*R*,6*R*)/(3*S*,6*R*) = 13:87.

4.4. (*S*)-1-Benzyloxy-6-methylheptan-4-ol, 7[4]

To a solution of 100 mg (0.43 mmol) of **6** (91:9 *S*/*R* ratio) in 5 mL of EtOAc, 30 mg of 5% Pt/C were added and the suspension was shaken under 1 atm of hydrogen for 4 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 pad of silica gel (98:2, CH_2Cl_2/MeOH) to yield 85 mg (83%) of **7**: colourless oil; R_f 0.15 (CH_2Cl_2); $[\alpha]_D^{20}$ = +3.7 (*c* 3.98, $CHCl_3$) [lit.[4] $[\alpha]_D^{20}$ +4.6 (c 0.92, $CHCl_3$) for the *R* isomer]; ^{1}H NMR: δ 0.92 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.21–1.84 (m, 7H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.69 (m, 1H), 4.53 (s, 2H), 7.27–7.39 (m, 5H, ArH); ^{13}C NMR: δ 22.1, 23.4, 24.6, 26.2, 35.2, 46.8, 69.5, 70.5, 73.0, 127.6, 127.7, 128.4, 138.2; IR (neat): 698, 735, 1028, 1099, 1366, 1455, 2869, 2927, 2954, 3423.

4.5. General procedure for the partial hydrogenation of alkynols. Preparation of (4*R*,5*Z*,7*R*)-7-Benzyloxy-2-methyloct-5-en-4-ol, 9

To a solution of **8** (112 mg, 0.45 mmol) in EtOAc (3 mL), 5% Pd on calcium carbonate poisoned with lead (Lindlar catalyst, 30 mg) and quinoline (9 μL) were added and the suspension was shaken under 1 atm of hydrogen. The reaction was monitored by TLC. After 1 h, the mixture was filtered through a pad of Celite® using more EtOAc and CH_2Cl_2. The organic layer was washed with aq. HCl (5 mL, 0.1 M) and then dried over $MgSO_4$ and filtered. The solvent was eliminated in vacuo and the residue was purified by flash chromatography (96:4, hexane/EtOAc) to yield 102 mg (90%) of **9**: colourless oil; R_f 0.16 (85:15, hexane/EtOAc); $[\alpha]_D^{20}$ = +6.2 (*c* 0.40, $CHCl_3$); ^{1}H NMR: δ 0.89 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.42–1.58 (m, 2H), 1.64–1.80 (m, 1H), 4.30–4.47 (m, 2H), 4.37 (part A of an AB system, *J* = 11.7 Hz), 4.53 (part B of an AB system, *J* = 11.7 Hz), 5.46–5.58 (m, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR: 21.8, 22.2, 23.3, 24.4, 46.9, 66.1, 70.1, 70.7, 127.6, 128.4, 134.1, 134.8, 138.5; IR (neat): 697, 733, 1028, 1057, 1098, 1368, 1457, 2869, 2956, 3406. Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.17; H, 9.65%.

(4*S*,5*Z*,7*R*)-7-Benzyloxy-2-methyloct-5-en-4-ol: colourless oil; R_f 0.26 (85:15, hexane/EtOAc); $[\alpha]_D^{20}$ = −14.6 (*c* 1.21, $CHCl_3$); ^{1}H NMR: δ 0.88 (d, *J* = 6.6 Hz, 6H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.22 (m, 1H), 1.44–1.72 (m, 2H), 4.27–4.42 (m, 2H), 4.44 (part A of an AB system, *J* = 11.7 Hz), 4.58 (part B of an AB system, *J* = 11.7 Hz), 5.40–5.58 (m, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR: 21.5, 22.4, 23.0, 24.4, 46.6, 65.9, 70.0, 127.6, 127.7, 128.4, 133.1, 135.3, 138.5; IR (neat): 698, 737, 1028, 1057, 1098, 1368, 1455, 2871, 2930, 2957, 3422.

4.5.1. (3*R*,4*Z*,6*R*)-6-Benzyloxy-2-methylhept-4-en-3-ol, (3*R*,6*R*)-12. Reduction was performed according to the general procedure described in Section 4.5, to afford 78% yield of (3*R*,6*R*)-**12**: colourless oil; R_f 0.25 (85:15, hexane/EtOAc); $[\alpha]_D^{20}$ = −21.8 (*c* 0.76, $CHCl_3$); ^{1}H NMR: δ 0.91 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.69 (m, 1H), 4.02–4.07 (m, 1H), 4.35–4.42 (m, 2H, C*H*OBn plus the part A of an AB system, OC*H*$_2$Ph), 4.54 (part B of an AB system, *J* = 11.7 Hz, OC*H*$_2$Ph), 7.26–7.34 (m, 5H, ArH); ^{13}C NMR: δ 17.9, 18.3, 21.8, 34.2, 70.2, 70.9, 72.8, 127.5, 127.6, 128.4, 132.6, 135.7, 138.5; IR (neat): 698, 1028, 1072, 1369, 1455, 1498, 2873, 2929, 2961, 3432. HRMS calcd for $C_{15}H_{23}O_2$ (M^++1) 235.1698, found 235.1710. Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.72; H, 9.45%.

4.5.2. (3*S*,4*Z*,6*R*)-6-Benzyloxy-2-methylhept-4-en-3-ol, (3*S*,6*R*)-12. Reduction was performed according to the general procedure described in Section 4.5, to afford 80% yield of (3*S*,6*R*)-**12**: colourless oil; R_f 0.35 (85:15, hexane/EtOAc); $[\alpha]_D^{20}$ = +7.4 (*c* 0.96, $CHCl_3$); ^{1}H NMR: δ 0.83 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.64 (m, 1H), 1.76 (bs, 1H, OH), 3.99 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.26–4.35 (m, 1H), 4.42 (part A of an AB system, *J* = 12.2 Hz), 4.57 (part B of an AB system, *J* = 12.2 Hz), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR: δ 18.0, 18.1, 21.3, 34.0, 69.9, 70.0, 72.6, 127.6, 127.7, 128.3, 133.2, 134.1, 138.6; IR (neat): 698, 1028, 1073, 1094, 1370, 1457, 1498, 2873, 2930, 2962, 3448. HRMS calcd for $C_{15}H_{23}O_2$ (M^++1) 235.1698, found 235.1705. Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.63; H, 9.53%.

4.6. General procedure for the hydrogenation of *Z* alkenols to alkanols. Preparation of (4*S*,7*R*)-2-benzyloxy-7-methyloctan-5-ol, 10[4]

To a solution of **9** (100 mg, 0.40 mmol) in EtOAc (4 mL), 5% Pt/C (30 mg) were added and the suspension was shaken under 1 atm of hydrogen for 1 h. The

mixture was filtered through a pad of Celite® and the solvent was eliminated in vacuo. Column chromatography (hexane:EtOAc, 92:8) of the residue gave 81 mg (82%) of (4*S*,7*R*)-2-benzyloxy-7-methyloctan-5-ol, **10**: colourless oil; R_f 0.16 (85:15, hexane/EtOAc); $[\alpha]_D^{20} = -15.1$ (*c* 0.68, $CHCl_3$) [lit.[4] $[\alpha]_D = +9.9$ (*c* 0.95, $CHCl_3$) for (4*R*,7*S*) isomer]; ^{1}H NMR: δ 0.90 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 1.21 (d, $J = 6.0$ Hz, 3H), 1.34–1.81 (m, 7H), 3.52–3.70 (m, 2H), 4.45 (part A of an AB system, $J = 11.9$ Hz), 4.59 (part B of an AB system, $J = 11.9$ Hz), 7.23–7.35 (m, 5H, ArH); ^{13}C NMR: δ 19.5, 22.1, 23.5, 24.7, 32.8, 33.8, 46.8, 69.9, 70.3, 74.8, 127.5, 127.7, 128.3, 138.8; IR (neat): 697, 735 1028, 1065, 1090, 1374, 1455, 2869, 2929, 2956, 3423. HRMS calcd for $C_{16}H_{27}O_2$ (M^++1) 251.2011, found 251.2002.

4.6.1. (3*S*,6*R*)-2-Benzyloxy-6-methylheptan-5-ol, (3*S*,6*R*)-13[5]. Reduction was performed according to the procedure described in Section 4.6, to afford 66% yield of (3*S*,6*R*)-**13**: colourless oil; R_f 0.60 (65:35, hexane/EtOAc); $[\alpha]_D^{20} = -28.5$ (*c* 0.89, $CHCl_3$) [lit.[5] $[\alpha]_D = -35.5$ (*c* 0.93, $CHCl_3$]; ^{1}H NMR: δ 0.90 (d, $J = 6.9$ Hz, 6H), 1.21 (d, $J = 6.0$ Hz, 3H), 1.42–1.73 (m, 5H), 3.30–3.35 (m, 1H), 3.51–3.61 (m, 1H), 4.45 (part A of an AB system, $J = 11.7$ Hz), 4.59 (part B of an AB system, $J = 11.7$ Hz), 7.26–7.34 (m, 5H); ^{13}C NMR: δ 17.3, 18.8, 19.5, 29.9, 33.1, 33.6, 70.3, 74.7, 76.6, 127.5, 127.7, 128.3, 138.8; IR (neat): 697, 735, 1028, 1063, 1090, 1370, 1454, 2873, 2930, 2974, 3448. HRMS calcd for $C_{15}H_{25}O_2$ (M^++1) 237.1855, found 237.1855.

4.6.2. (3*R*,6*R*)-2-Benzyloxy-6-methylheptan-5-ol, (3*R*,6*R*)-13[5]. The reduction was performed according to the procedure described in Section 4.6, to afford 71% yield of (3*R*,6*R*)-**13**: colourless oil; R_f 0.60 (65:35, hexane/EtOAc); $[\alpha]_D^{20} = -8.3$ (*c* 0.89, $CHCl_3$) [lit.[5] $[\alpha]_D = -8.3$ (*c* 0.75, $CHCl_3$]; ^{1}H NMR: δ 0.91 (d, $J = 6.9$ Hz, 6H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.39–1.45 (m, 1H), 1.57–1.70 (m, 4H), 1.88 (bs, 1H), 3.30–3.36 (m, 1H), 3.52–3.62 (m, 1H), 4.46 (part A of an AB system, $J = 11.9$ Hz), 4.59 (part B of an AB system, $J = 11.9$ Hz), 7.26–7.34 (m, 5H); ^{13}C NMR: δ 17.4, 18.8, 19.5, 30.0, 33.1, 33.6, 70.4, 75.1, 76.7, 127.5, 127.7, 128.3, 138.8; IR (neat): 697, 735, 1028, 1063, 1090, 1373, 1454, 2873, 2931, 2963, 3448. HRMS calcd for $C_{15}H_{25}O_2$ (M^++1) 237.1855, found 237.1850.

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References

1. (a) Kimura, M. *Trends Pharmacol. Sci.* **1980**, *1*, 341–343; (b) Tokunaga, S.; Kimura, M.; Kimura, I. *J. Med. Pharm. Soc. Wakan-Yaku* **1987**, *4*, 276–277; (c) Kimura, M.; Kimura, I.; Uwano, T.; Isoi, Y.; Kadota, S.; Kikuchi, T. *Phytoter. Res.* **1991**, *5*, 159–162; (d) Kimura, I.; Takamura, Y.; Uwano, T.; Hata, Y.; Kimura, M.; Kikuchi, T. *Phytoter. Res.* **1995**, *9*, 16–20.
2. Musk is a important component of *Rokushingan*, a commercial cardiotonic sold in Japan.
3. Kadota, S.; Orito, T.; Kikuchi, T.; Uwano, T.; Kimura, I.; Kimura, M. *Tetrahedron Lett.* **1991**, *32*, 1733–1736.
4. Tezuka, Y.; Kudoh, M.; Hatanaka, Y.; Kadota, S.; Kikuchi, T. *Nat. Prod. Lett.* **1997**, *9*, 297–304.
5. Tezuka, Y.; Kudoh, M.; Hatanaka, Y.; Kadota, S.; Kikuchi, T. *Wakan Iyakugaku Zasshi* **1998**, *15*, 168–175.
6. (a) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381; (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; (d) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017–3020; (e) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606.
7. Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691–2694. See also: Sans, R.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341–8344.
8. Reported applications of Carreira's alkynylation to total syntheses are still scarce. See for instance: (a) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.*, **2001**, *66*, 6410–6424; (c) Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. *Org. Lett.* **2002**, *4*, 2977–2980.
9. *R*/*S* ratio of **6** was directly determined by HPLC analysis on a chiral column. The absolute configuration of the major enantiomer was assumed to be *R* on the basis of the work of Carreira et al. (Ref. 6) and confirmed later by chemical correlation with the known monoprotected diol **7**.
10. Stereoselectivities were determined by ^{19}F analysis of the corresponding Mosher esters. The configuration of the newly formed stereogenic centers was first determined by the Kakisawa method (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096) and it always agreed with that expected (Ref. 6). In addition, it should be noted that the absolute configurations were further confirmed by correlation with those of the known, saturated monoprotected diols **7**, **10** and **13**.
11. We found that the chromatographic separation of (*R*,*R*)- and (*R*,*S*)-**9** was more convenient than that of their corresponding *E* isomers, also accessible by $LiAlH_4$ reduction of **8** (see Ref. 7).
12. Manzocchi, A.; Fiecchi, A.; Santaniello, E. *Synthesis* **1987**, 1007–1009.