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Chemo-enzymatic enantio-convergent asymmetric total synthesis of (*S*)-(+)-dictyoprolene using a kinetic resolution—stereoinversion protocol

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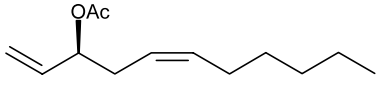
Abstract—A single enantiomer of a (stereo)chemically labile allylic-homoallylic alcohol was obtained in 91% e.e. and 96% yield from the racemate by employing a lipase-catalysed kinetic resolution coupled to in situ inversion under carefully controlled (Mitsunobu) conditions in order to suppress side reactions, such as elimination and racemisation. This technique was successfully applied to an enantio-convergent asymmetric total synthesis of the algal fragrance component (*S*)-dictyoprolene.

1. Introduction

Brown algae belonging to the genus *Dictyopteris prolifera* and *D. membranacea* are known to possess characteristic odors.[1,2] A component thereof resembling the scent of 'beach' is the doubly unsaturated *sec*-acetate ester (*S*)-dictyoprolene (*S*)-**1** (Scheme 1), isolated in 1979.[3] Besides its odoriferous properties, it represents a key intermediate in the biosynthesis of many C_{11} hydrocarbons from *Dictyopteris prolifera*.[4] Its structure and absolute configuration were determined by NMR and MS spectroscopy and independent synthesis in non-racemic form.[4] Herein, we describe a concise synthesis of (*S*)-dictyoprolene (*S*)-**1** using a chemo-enzymatic approach.[5] High synthetic efficiency is ensured by avoiding the occurrence of 'unwanted' stereoisomers via enantio-convergent transformations.



(*S*)-**1**

Scheme 1. Dictyoprolene (*S*)-**1**.

Our synthetic strategy was based on the racemic secondary alcohol *rac*-**6** (Scheme 2). We envisaged that the latter (or its corresponding acetate **1**) would be an ideal candidate for enantioseparation employing lipase-technology via acyl-transfer or ester hydrolysis, respectively.[6,5] Due to the apparent symmetry of ester hydrolysis versus acyl-transfer, the stereochemical outcome can be controlled towards the desired enantiomer by choosing the forward- and reverse-reaction mode.[7]

The most striking limitation of kinetic resolution is the maximum theoretical yield of 50% of each enantiomer. In order to circumvent this drawback, several approaches have been developed, which render an enantio-convergent process delivering a single enantiomeric product in 100% theoretical yield.[8] The most widely employed techniques are.

(i) Dynamic kinetic resolution implies in situ racemization of the starting material during kinetic resolution. The latter is achieved by using bio-[9–11] or chemo-catalysts,[12–14] which are often based on transition metals, such as Ru.[15,16]

(ii) Selective inversion of one enantiomer (in presence of the other) via a chemo-enzymatic protocol renders a single enantiomer.[17,18]

Since the allylic alcohol moiety in compound **6** is incompatible with Ru-complexes,[19] in situ racemization

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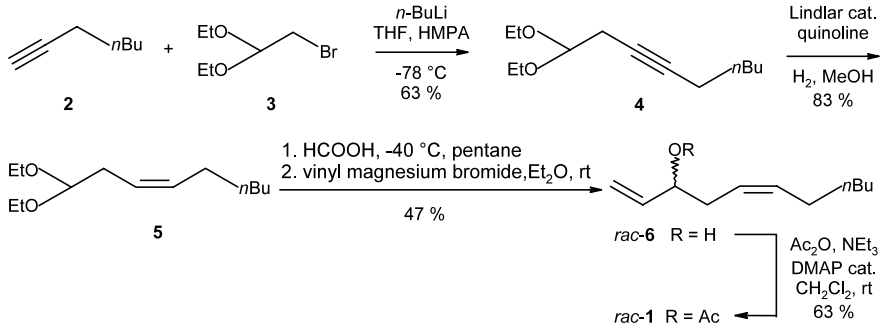


Scheme 2. Synthesis of *rac*-substrates.

of the latter failed and dynamic resolution was inapplicable. As a consequence, the system of choice was based on stereo-inversion.[17,18] Thus, kinetic resolution furnishes an enantiomeric pair of alcohol **6** and the corresponding ester **1**. In order to obtain both compounds at a maximum of enantiomeric excess, the point of conversion—which is close to or slightly beyond 50%, depending on the enantioselectivity—has to be carefully chosen.[20,21] Without separation of the mixture of enantiomeric ester and alcohol, the latter is converted into an activated derivative bearing a good leaving group (i.e. mesylate,[22] sulfate,[23] triflate, nitrate,[24] borate,[24] etc.). This enantiomeric product mixture consisting of an activated and a non-activated *sec*-alcohol derivative can be (chemically) hydrolyzed through opposite stereochemical pathways: Whereas the carboxylate ester is hydrolyzed with retention of configuration, the activated enantiomeric derivative undergoes inversion, which furnishes the same enantiomeric *sec*-alcohol as the sole product in 100% theoretical yield. This so-called 'in situ inversion'-technique has been successfully employed to chemically rather stable *sec*-alcohols.

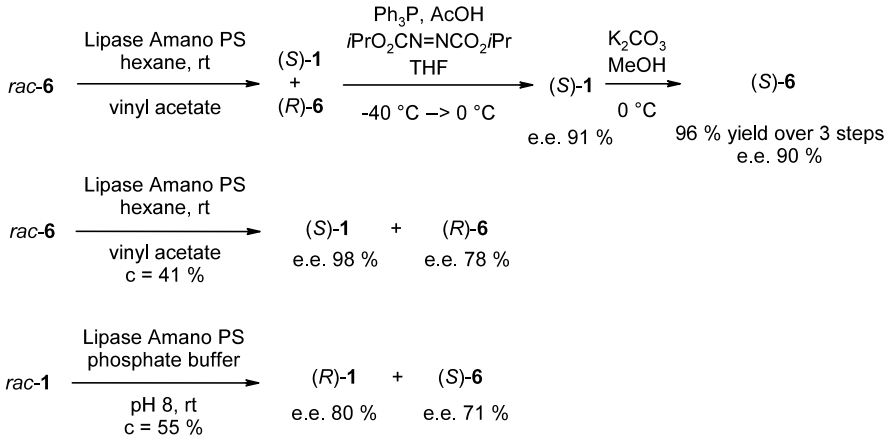
Taking the delicate chemical structure of the allylic-homoallylic alcohol *rac*-**6** into account, 'clean' inversion is not straightforward and several side reactions, such as racemisation and—most important—elimination forming a triply unsaturated conjugated system have to be expected. As a consequence, the use of triflate, mesylate or nitrate esters was avoided and Mitsunobu conditions were chosen.[25]

2. Results and discussion

Substrates alcohol *rac*-**6** or acetate *rac*-**1** for the lipase catalysed resolution were synthesized via the following sequence (Scheme 2). Coupling of the Li-anion of 1-heptyne **2** with bromoacetaldehyde diethylacetal **3** gave alkyne **4** in 68% yield. The latter was selectively hydrogenated with Lindlar-catalyst to give the corresponding *cis*-alkene **5** in 83% yield. In order to achieve absolute *cis*-selectivity, poisoning of the Lindlar catalyst with quinoline was required. Deprotection of acetal **5** (HCOOH at –40°C in pentane) gave the corresponding aldehyde, which was trapped in situ with vinyl magnesium bromide at room temperature to furnish alcohol *rac*-**6** in 47% yield. In order to avoid isomerization of the configurationally labile *E*-double bond, all of the former reactions had to be performed at low temperature. Acetylation of *rac*-**6** gave acetate *rac*-**1** according to literature procedures.[26]

Substrate *rac*-**6** was screened with several lipases (from *Geotrichum candidum*, *Rhizomucor miehei*, *Candida antarctica* and *Pseudomonas* sp.) for transesterification in hexane at room temperature using vinyl acetate as an acyl donor (Scheme 3). Table 1 shows the stereoselectivities denoted as the enantiomeric ratio (*E*)[27] obtained in the kinetic resolution of *rac*-**6** using various lipases. All reaction rates were in a reasonable range except lipase from *R. miehei* (Novo SP 524), which showed no conversion. Invariably, all fungal and bacterial lipases exhibited (*S*)-preference. In general, *rac*-**6** was converted with disappointingly low enantioselectivities, only Lipase Amano PS gave (*S*)-**1** in an e.e. up to 98% ($E > 200$).[5] These results clearly demonstrate that—depending on the substrate—enantioselectivities of lipases often vary to a great extent, even for lipases from a closely related microbial source: Lipase preparations AH, AK, PS, PS-C and SAM-II are all derived from *Pseudomonas* sp.

For preparative-scale biotransformations Lipase Amano PS was used (Scheme 3). Thus, resolution of *rac*-**6** was terminated at 51% conversion to furnish (*S*)-**1** and (*R*)-**6** in 91% e.e. (*E* ca. 70). Without separation of products, this mixture was subjected to Mitsunobu inversion to give naturally occurring (*S*)-dictyoprolene (*S*)-**1** in 91% e.e. as the sole product in 96% yield. In order to prove the absence of racemisation during stereoinversion, (*S*)-**1** was hydrolysed under carefully controlled conditions (K_2CO_3 at 0°C in MeOH) to furnish (*S*)-**6** in 90% e.e. In order to provide access to the mirror-image enantiomers, kinetic resolution in the 'reverse direction' via ester hydrolysis of *rac*-**1** was performed. In this case, the enantioselectivity of lipase PS was considerably lower (*E* 14), although the same enzyme was used. Absolute configurations of dictyoprolene **1** and 1,5-undecadien-3-ol **6** were deduced from specific rotation values for (*S*)-**1**.[4]



Scheme 3. Biocatalytic synthesis of both enantiomers of dictyoprolene **1** involving lipase-catalysed resolution combined with in situ (Mitsunobu) inversion.

Table 1. Screening for the kinetic resolution of alcohol *rac*-**6**

Entry	Lipase	Conversion (%)	Time (h)	E.e.$_S$[a] (%)	E.e.$_P$ (%)	E[b]
1	Amano GC-4	15	2	n.d.	25 (*S*)	1.74
2	Amano GC-20	36	1	n.d.	26 (*S*)	2.0
3	*Candida antarctica* A	37	1	n.d.	25 (*S*)	1.9
4	*Candida antarctica* B	35	30	n.d.	37 (*S*)	2.6
5	Amano PS-C	42	1	n.d.	15 (*S*)	1.5
6	Amano AH	31	16	n.d.	43 (*S*)	3.0
7	Amano AK	40	4	n.d.	65 (*S*)	7.15
8	SAM-II	34	4	n.d.	78 (*S*)	12
9	Amano PS	41	7	78 (*R*)[c]	**98** (*S*)	**>200**

[a] E.e. values of alcohol **6** were not determined in the screening since no direct chiral separation method for alcohol *rac*-**6** could be developed.
[b] Calculated from e.e.$_P$ and c.
[c] Alcohol **6** was separated from **1** via column chromatography and analyzed as acetate **1**. n.d. not determined.

3. Conclusion

In summary, we have demonstrated that the combination of lipase-catalysed kinetic resolution coupled to in situ inversion is applicable to (stereo)chemically labile allylic-homoallylic *sec*-alcohols under carefully controlled (Mitsunobu) reaction conditions to avoid side reactions. The validity of this protocol was demonstrated by the enantio-convergent asymmetric total synthesis of (*S*)-dictyoprolene (*S*)-**1**, an algal fragrance component.

4. Experimental

4.1. General remarks

NMR spectra were recorded in $CDCl_3$ using a Bruker AMX 360 at 360 (^{1}H) and 90 (^{13}C) MHz and a Bruker DMX Avance 500 at 500 (^{1}H) and 125 (^{13}C) MHz. Chemical shifts are reported relative to TMS (δ 0.00) with $CHCl_3$ as internal standard [δ 7.23 (^{1}H) and 76.90 (^{13}C)], coupling constants (J) are given in Hz. TLC plates were run on silica gel Merck 60 (F_{254}) and compounds were visualized by spraying with Mo-reagent [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g/L), $Ce(SO_4)_2\cdot 4H_2O$ (4 g/L) in H_2SO_4 (10%)] or by dipping into a $KMnO_4$ reagent [2.5 g/L $KMnO_4$ in H_2O]. Compounds were purified either by flash chromatography on silica gel Merck 60 (230–400 mesh) or, for volatile substances, by Kugelrohr distillation. Petroleum ether (pet. ether.) had a boiling range of 60–90°C. GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID and either an HP1301 capillary column (both 30 m, 0.25 mm, 0.25 μm film, N_2). Enantiomeric purities were analyzed using a CP-Chirasil-DEX CB column ('column A', Chrompack, 25 m, 0.32 mm, 0.25 μm film). H_2 was used as a carrier gas. For programs and retention times vide infra. Optical rotation values were measured on a Perkin–Elmer polarimeter 341 at 589 nm (Na-line) in a 1 dm cuvette and specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Solvents were dried and freshly distilled by common practice. For anhydrous reactions,

flasks were dried at 150°C and flushed with dry argon just before use. Organic extracts were dried over Na_2SO_4, and then the solvent was evaporated under reduced pressure. Compounds **2** and **3** were purchased from Aldrich. All lipases used were commercially available: Amano Enzyme Inc., Nagoya, Japan (GC-4, GC-20, PS-C, AH, AK, PS); Novozymes, Bagsvaerd, Denmark (*Candida antarctica* A, B); Aldrich (SAM-II).

4.2. Syntheses of substrates and biocatalytic transformations

4.2.1. 1,1-Diethoxy-3-nonyne 4. To a stirred solution of 1-heptyne **2** (12.0 g, 125 mmol) under argon in anhydrous THF (60 mL), *n*-BuLi (60 mL of a 2.5 M solution in hexane, 150 mmol) was added at −78°C. After 15 min, bromoacetaldehyde diethylacetal **3** (29.5 g, 150 mmol) was added dropwise at −78°C. When the reaction mixture reached rt HMPA (30 mL) was added and stirring was continued for 2 h reflux. The reaction was quenched by addition of H_2O (120 mL) and Et_2O (120 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2×80 mL). The combined organic phases were dried and evaporated. The residue was purified by flash chromatography (pet. ether/EtOAc, 20:1) to afford 1,1-diethoxy-3-nonyne **4** (18.0 g, 63%) as a colourless liquid. ^{1}H NMR (360.13 MHz, $CDCl_3$): $\delta = 0.88$ (3H, t, $J = 7.0$), 1.20–1.28 (6H, dd, $J_1 = 7.6$, $J_2 = 7.0$), 1.31–1.35 (4H, m), 1.46–1.48 (2H, m), 2.13–2.17 (2H, m), 2.47–2.50 (2H, m), 3.53–3.61 (2H, m), 3.66–3.72 (2H, m), 4.61 (1H, t, $J = 5.7$). ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 14.0$, 15.3, 18.8, 22.3, 25.1, 28.7, 31.1, 61.8, 75.2, 82.0, 101.4. Spectroscopic data were in full agreement with those previously reported.[28]

4.2.2. 1,1-Diethoxy-3(*Z*)-nonenal (*Z*)-5. To a solution of alkyne **4** (15 g, 72.0 mmol) in EtOH (150 mL), quinoline (4 mL) and Lindlar catalyst (3.5 g) were added and the resulting mixture was vigorously stirred under H_2 for 2 h at atmospheric pressure. Then the solids were removed by filtration through a plug of Celite-545 and the solvent was evaporated. Flash chromatography (pentane/EtOAc, 40:1) afforded pure *(Z)*-alkene (*Z*)-**5** as a colourless liquid (12.9 g, 83%). ^{1}H NMR (360.13 MHz, $CDCl_3$): $\delta = 0.89$ (3H, t, $J = 6.6$), 1.19–1.23 (6H, t, $J = 7.1$), 1.28–1.37 (6H, m), 2.01–2.07 (2H, m), 2.37–2.40 (2H, t, $J = 6.2$), 3.47–3.55 (2H, m), 3.61–3.68 (2H, m), 4.47 (1H, t, $J = 5.8$), 5.37–5.42 (1H, m), 5.48–5.51 (1H, m). ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 14.1$, 15.3, 22.6, 27.5, 29.3, 31.6, 32.1, 61.2, 102.7, 123.8, 132.4. Spectroscopic data were in full agreement with those previously reported.[29]

4.2.3. *rac*-1,5-Undecadien-3-ol *rac*-6. To a stirred solution of acetal **5** (7.0 g, 32.7 mmol) in pentane (100 mL), HCOOH conc. (20 mL) was slowly added at −40°C. After complete addition of HCOOH, the reaction mixture was allowed to warm up to rt. When first traces of side products were detected (ca. 30 min, monitored via TLC) work-up was immediately started although full conversion was not reached. The reaction mixture was cooled to −50°C and the solvent (containing product) was decanted. The solids (HCOOH) were washed with pentane (3×50 mL). The combined organic phases were concentrated in vacuo. The residue was dissolved in anhydrous Et_2O (100 mL) under argon and vinylmagnesium bromide (100 mL of a 0.5 M solution in Et_2O, 50 mmol) was added dropwise at rt. After 30 min the reaction was quenched with water (150 mL) and Et_2O (200 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2×200 mL). The combined organic phases were dried and evaporated. The residue was purified by flash chromatography (pet. ether/EtOAc, 30:1) to afford *rac*-**6** (2.54 g, 47%). ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 0.86$ (3H, t, $J = 5.8$), 1.27–1.37 (6H, m), 1.99–2.05 (2H, m), 2.14 (1H, s), 2.26–2.32 (2H, m), 4.10 (1H, s), 5.07 (1H, dd, $J_1 = 9.2$, $J_2 = 1.2$), 5.21 (1H, dd, $J_1 = 15.6$, $J_2 = 1.3$), 5.36 (1H, dt, $J_1 = 9.6$, $J_2 = 1.2$), 5.53 (1H, dt, $J_1 = 9.6$, $J_2 = 1.2$), 5.86 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 27.4, 29.3, 31.5, 35.1, 72.5, 114.6, 124.4, 133.4, 140.6. Spectroscopic data were in full agreement with those previously reported.[4]

4.2.4. *rac*-Dictyoprolene *rac*-1. To a stirred solution of alcohol *rac*-**6** (0.3 g, 1.8 mmol) in CH_2Cl_2, Ac_2O (0.24 g, 2.4 mmol), NEt_3 (0.26 g, 2.6 mmol) and DMAP (20 mg, cat.) were added. The resulting solution was stirred at 50°C for 20 h. After the reaction was complete it was quenched by addition of water (15 mL). After phase separation the organic phase was dried and concentrated. The residue was purified by flash chromatography (pet. ether/EtOAc, 25:1) to give *rac*-**1** (0.24 g, 63%) as a colourless liquid. ^{1}H NMR (360.13 MHz, $CDCl_3$): $\delta = 0.87$ (3H, t, $J = 6.5$), 1.26–1.36 (6H, m), 1.99–2.05 (5H, m), 2.32–2.41 (2H, m), 5.16 (1H, dd, $J_1 = 10.5$, $J_2 = 1.8$), 5.23 (1H, dd, $J_1 = 9.6$, $J_2 = 1.3$), 5.27–5.28 (1H, m), 5.30–5.33 (1H, m), 5.48–5.49 (1H, m), 5.75–5.80 (1H, m). ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 14.1$, 21.2, 22.6, 27.4, 29.3, 31.5, 32.2, 74.3, 116.7, 123.5, 133.2, 136.0, 170.3. Spectroscopic data were in full agreement with those previously reported.[4]

4.2.5. (*S*)-1,5-Undecadien-3-ol (*S*)-6 via biocatalytic in situ inversion. Lipase Amano PS (1.5 g) was dispersed in hexane (60 mL), and after addition of *rac*-**6** (1.0 g, 6.1 mmol) and vinyl acetate (2.0 g, 23.2 mmol) the mixture was agitated on an orbit shaker (rt, 120 rpm). The reaction was monitored by GC on a chiral stationary phase. When the conversion had reached 51% (8 h), the biocatalyst was filtered off and the solution was concentrated in vacuo. The residue was dissolved in anhydrous THF (100 mL), and AcOH (7.2 g, 120 mmol) and PPh_3 (31.4 g, 120 mmol) were added. The reaction mixture was immediately cooled to −40°C and a solution of diisopropyl azodicarboxylate (24.0 g, 120 mmol) in anhydrous THF (25 mL) was added. The solution was stirred at rt and after 30 min the reaction was quenched by addition of water (10 mL) and Et_2O (60 mL). After phase separation the organic phase was dried and concentrated to yield crude (*S*)-dictyoprolene (*S*)-**1** (e.e. 91%). Without further isolation, the residue was dissolved in MeOH (150 mL) and K_2CO_3 (6.0 g, 10 mmol) was added at 0°C. After 3 h at 0°C, the reaction mixture was filtered through a plug of Celite-545 and the solvent was evaporated. Flash chromatography

(pet. ether/EtOAc, 20:1) afforded (*S*)-**6** [0.96 g, 96%, $[\alpha]_D^{20} = -2.8$ (*c* 1.45, $CHCl_3$, e.e. 91%)].

4.2.6. Kinetic resolution of *rac*-1,5-undecadien-3-ol *rac*-6. Lipase Amano PS (2 g) was dispersed in hexane (70 mL), and after addition of *rac*-**6** (1.75 g, 10.4 mmol) and vinyl acetate (2.0 g, 23.2 mmol) the mixture was agitated on an orbit shaker (rt, 120 rpm). The reaction was monitored by GC on a chiral stationary phase. When the conversion had reached 41% (7 h), the biocatalyst was filtered off and the solution was concentrated in vacuo. The residue was purified via flash chromatography (pet. ether/EtOAc, 20:1) to afford (*S*)-**1** [0.45 g, $[\alpha]_D^{20} = +12.0$ (*c* 1.40, $CHCl_3$, e.e. 98%)] and (*R*)-**6** [0.71 g, $[\alpha]_D^{20} = +1.0$ (*c* 1.48, $CHCl_3$, e.e. 78%)]. Spectroscopic data of (*S*)-dictyprolene (*S*)-**1** were in full agreement with those previously reported.[4]

4.2.7. Kinetic resolution of *rac*-dictyoprolene *rac*-1. Lipase Amano PS (2 g) was dissolved in phosphate-buffer (200 mL, 100 mM, pH 8.0) and *rac*-**1** (1.0 g, 4.8 mmol) was added. The reaction was monitored by GC on a chiral stationary phase. When the conversion had reached 55% (30 min), the aqueous layer was extracted with Et_2O (3×40 mL) and the organic phase was dried and concentrated in vacuo. The residue was purified via flash chromatography (pet. ether/EtOAc, 20:1) to afford (*R*)-**1** [0.31 g, $[\alpha]_D^{20} = -14.4$ (*c* 1.53, $CHCl_3$, e.e. 80%)] and (*S*)-**6** [0.35 g, $[\alpha]_D^{20} = -2.0$ (*c* 1.32, $CHCl_3$, e.e. 71%)].

4.3. General procedure for the lipase-screening of *rac*-6

Alcohol *rac*-**6** (10 μL) was dissolved in hexane (1 mL) and lipase (100 mg) and vinyl acetate (120 μL) were added. The mixtures were incubated at 30°C with shaking at 120 rpm and the reactions were monitored by TLC and GC. For GC analysis the biocatalyst was removed by centrifugation and the organic phase was directly analyzed. Peak areas were corrected by the molar response factor of **6**/**1** on FID using a calibration curve.

4.4. Chiral analysis

Enantiomeric excesses were analyzed by GC on a chiral stationary phase. *rac*-dictyoprolene *rac*-**1** could be separated after following procedure: Column A [14 psi, H_2, 110°C (iso), $t_{R1} = 5.2$ min (3*R*), $t_{R2} = 6.2$ min (3*S*)]. For alcohol *rac*-**6** direct chiral separation was not possible and its enantiomeric composition was analyzed after derivatization as the corresponding acetate **1**.

4.5. Determination of absolute configuration

The absolute configuration of (*S*)-dictyoprolene (*S*)-**1** was elucidated by comparison of optical rotation values with literature data: $[\alpha]_D^{25} = +11.1$ (*c* 1.17, $CHCl_3$).[4] The absolute configuration of (*S*)-1,5-undecadien-3-ol **6** was deduced from that of (*S*)-**1**.

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