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Design and synthesis of useful intermediates for novel lipoxygenase substrates through enzymatic resolution

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Abstract—Unnatural lipoxygenase substrates carrying spacing modifiers with a non-ionic hydroxy terminus and with methylene (flanked by the *cis*,*cis* diene moiety) pro-(*S*)-hydrogen can be synthesized from the intermediates **1a**–**1c**. These intermediates are conveniently synthesized via enzymatic resolution with lipase in organic solvents.

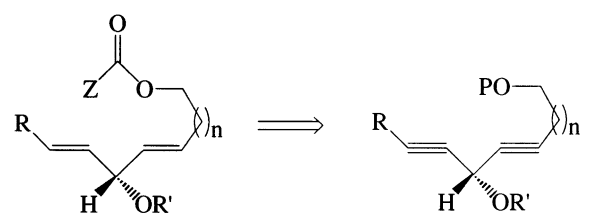
1. Introduction

Lipoxygenases (linoleate: oxygen oxidoreductase) are a group of non-heme iron containing dioxygenases which catalyze the addition of molecular oxygen to 1(*Z*),4(*Z*) polyunsaturated fatty acids in a regio- and stereospecific way.[1] The stereospecificity of lipoxygenases is characterized by the stereoselective removal of one of the two hydrogen atoms from the prochiral center.[2] It was earlier reported that lipoxygenase from soybean stereoselectively removes pro-(*S*)-hydrogen from the prochiral center.[3] Previous studies of modified substrates with soybean lipoxygenase reveal that the essential structural requirements are a single ω-6(*Z*), (*Z*)-1,4-pentadienyl moiety and an appropriately spaced proximal carboxyl group.[4] It had long been considered that the carboxyl groups of the fatty acid was important for enzymatic recognition and binding.[5]

However, research from several groups reveals that a carboxylic group or a charged head group in fatty acid analogues is not an essential structural requirement for binding and catalysis in soybean lipoxygenase catalyzed oxidations,[6] and substrates having a non-ionic hydroxy terminus are 'recognized' by soybean lipoxygenase. On the basis of this premise, we envisaged a synthetic route to obtain the unnatural lipoxygenase substrates **1a**–**1c** in enantiomerically pure form (Scheme 1) where the methylene hydrogen flanked by the (*Z*),(*Z*) diene moiety is pro-(*S*). Retrosynthetic analysis reveals that compounds **1a**–**1c** can be synthesized from the intermediate **2**. Here we wish to report the synthesis of **2a**–**2c** in enantiomerically pure form through a stereoselective enzymatic transesterification reaction in organic solvent medium (Scheme 2).

2. Results and discussion

In the first step of the synthesis 2-propyn-1-ol was deprotonated with $LiNH_2$ and the anion alkylated with 1-bromopentane to give 2-octyn-1-ol in 70% yield. Swern oxidation[7] of 2-octyn-1-ol then provided 2-octynal, and subsequent condensation of 2-octynal with the appropriate tetrahydropyranyl protected alkynol gave the di-acetylenic alcohols **3a**–**3c**. Removal of the tetrahydropyranyl protecting group with MeOH–PPTS[8] afforded the diols **4a**–**4c** and selective monoprotection of the primary alcohol function of **4a**–**4c** with TBDMS-



$R = C_5H_{11}$; $R' = OCOCH_3$
1a, n = 1, Z = $-(CH_2)_4OH$
1b, n = 2, Z = $-(CH_2)_3OH$
1c, n = 3, Z = $-(CH_2)_2OH$

2
P = Protecting group

Scheme 1. Substrates **1a**–**1c** having pro-(*S*)-hydrogen.

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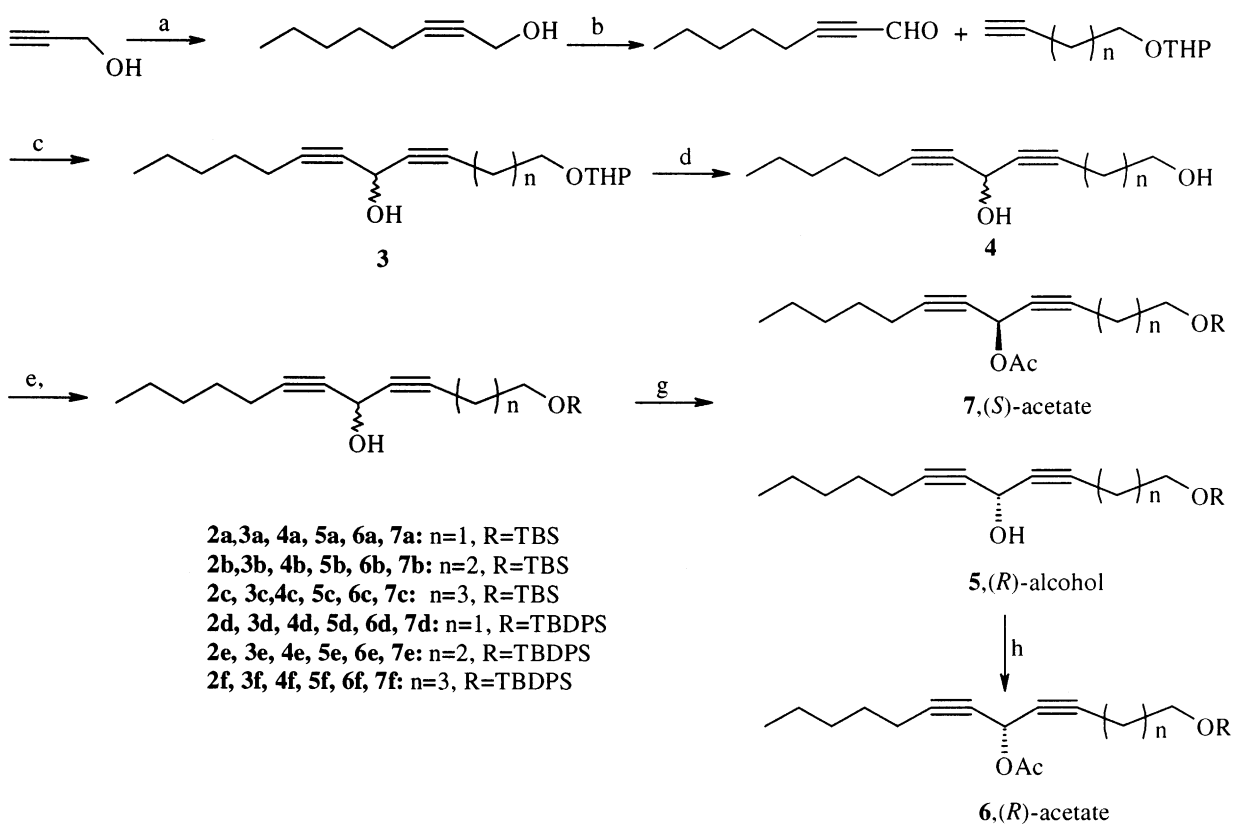

Scheme 2. Asymmetric synthesis of **2a–2f**. *Reagents and conditions*: (a) $LiNH_2$, $C_5H_{11}Br$, THF–HMPA (10:1), 70%; (b) $(COCl)_2$, DMSO, Et_3N, −78°C, 80%; (c) *n*-BuLi, THF–HMPA (6:1), −78°C, 1 h, then rt 6 h, 70%; (d) PPTS–MeOH, 80%; (e) imidazole, TBDMS–Cl, rt, 60%; (f) imidazole, TBDPS-Cl, rt, 60%; (g) vinyl acetate, diethylether; (h) Ac_2O, Et_3N, DMAP.

Cl or TBDPS-Cl under standard conditions afforded alcohols **2a–2f**. Transesterification of **2a–2f** with vinyl acetate in the presence of *Candida rugosa* lipase (CRL) in diethylether provided the required (*R*)-alcohols **5a–5f** in 33–46% yields (Table 1), which were then acetylated with Ac_2O, Et_3N to give the desired (*R*)-acetates **6a–6f**. The (*S*)-acetates **7a–7f** were obtained in 35–45% yield (Table 1). The absolute configurations of the alcohols and acetates were assigned according to a previous report.[9] Optical purity is in the range of 60–96% in both cases as determined by chiral HPLC analysis (Table 1, Scheme 2).

Among the organic solvents used for the transesterification, diethylether provided the best results with respect to both yield and ee (Table 2). Porcine pancreatic lipase (PPL) and lipase from *Pseudomonas* species were also used to mediate the same transesterification reaction, but no significant transesterification reaction occurred. The alcohols **2a–2f** have one small and one large group attached to the hydroxymethine functionality. The large group contains a bulky functionality (-OTBDMS, -OTBDPS) slightly removed from the asymmetric center. In all cases the (*S*)-isomer of **2a–2f** undergoes rapid transesterification compared to the corresponding (*R*)-isomer which remains unreacted. These findings are in perfect agreement with the previous work.[11] The total synthesis of lipoxygenase substrates **1a–1c** can be achieved from **5a–5f** after some simple reaction sequences which includes controlled hydrogenation of the di-acetylenic moiety using Lindlar catalyst, removal of the silyl protecting groups and attachment of the appropriate prosthetic group. We have just achieved the total synthesis of **1a–1c**, and we are currently engaged in the study of their reactivity with soybean lipoxygenase. These results will be communicated in due course.

3. Conclusion

The enantiomers of **1a–1c** having pro-(*R*)-hydrogen can be synthesized from compounds **7a–7c** by following the same sequence of reaction as described earlier. Due to the absence of pro-(*S*)-hydrogen these compounds may act as suitable substrate analog inhibitors for soybean lipoxygenase, which are of great biological interest. This study is currently under investigation. In conclusion an efficient and convenient enzymatic resolution has been carried out for the synthesis of a series of key intermediates for novel lipoxygenase substrates.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodium

Table 1. Transesterification of compounds **2a–2f** with CRL and vinyl acetate

Entry	Comp.	Time (h)	Conversion (c)	(*S*)-Acetate		(*R*)-Alcohol		E^b
				Ee_p[a]	Yield	Ee_s[a]	Yield	
1	**2a**	25	40	95	38	61	33	75
2	**2d**	28	38	96	42	58	40	90
3	**2b**	26	35	96	40	60	46	82
4	**2e**	40	42	94	40	67	41	66
5	**2c**	32	40	95	35	63	30	75
6	**2f**	26	45	95	39	77	37	92

[a] Ees were calculated by chiral HPLC (Diacel, Chiral OD column, hexane–isopropanol, 9:1).
[b] Enantioselectivities of the reactions (*E*)[10] were determined from the following equation; $E=\ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$, where ee_p = pdt·ee; $c=ee_s/(ee_s+ee_p)$%.

benzophenone ketyl. HMPA was distilled from BaO and stored over 3 Å molecular sieves. Dichloromethane (DCM) was distilled from calcium hydride. Lipase (from *Candida rugosa*, type VII, 1440 units/mg of protein), lipase (from Porcine pancreas, type II, 66 units/mg of protein) and lipase (from *Pseudomonas* species, type XIII, 60 units/mg of protein) were obtained from Sigma Co. (USA) and used as obtained. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian VXR 200 (200 MHz) instrument. Chemical shifts are reported as ppm downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer. For enzymatic reactions the solvents employed were desiccated over 4 Å molecular sieve powder for 50 h prior to use. Optical rotations were measured on a JASCO Dip 360 digital polarimeter. The abbreviation TF denotes the thin film.

4.2. 2-Octyn-1-ol

2-Propyn-1-ol (7 g, 100 mmol) was added to a stirred suspension of lithium amide (prepared from 1.4 g, 0.2 g atom of Li in liquid ammonia, 150 ml) over 15 min and stirred for an additional 1 h. 1-Bromopentane (15.6 g, 100 mmol) in THF–HMPA (60 mL, 10:1) was then added and the reaction mixture allowed to stir for a further 6 h. The reaction was quenched with solid NH_4Cl (10 g) and the excess ammonia was then allowed to evaporate. The residue was dissolved in water and extracted with ether. The combined organic layer was washed with water, brine and dried (Na_2SO_4). The crude product was purified by column chromatography to give 2-octyn-1-ol (9 g 70%). IR (TF): 3400, 1090 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 3H), 1.2–1.6 (m, 6H), 2.2 (t, $J=7$ Hz, 2H), 4.1 (s, 2H). EIMS (*m*/*z*): 126 (M^+).

Table 2. Transesterification of **2a** with CRL in different organic solvents

Entry	Solvent	Time (h)	Yield (%) (*S*)-acetate	Ee
1	Diethylether	25	40	95
2	Hexane	48	15	72
3	Cyclohexane	70	18	40
4	*t*-Butylmethylether	40	10	58
5	Tetrahydrofuran	42	22	60

4.3. 2-Octynal

2-Octyn-1-ol (2 g, 15 mmol) in DCM was added to oxallyl chloride (1.44 mL, 15 mmol) and DMSO (2.3 mL, 30 mmol) in DCM (50 mL) at −78°C. The temperature was maintained at −78°C for a further 1 h. Triethylamine (10 mL, 75 mmol) was then added and after stirring for 5 min the mixture was allowed to warm to 25°C and stirred for a further 30 min at the same temperature. Water was added to the solution, and the mixture was extracted with DCM. The organic extract was washed with water, brine and dried (Na_2SO_4). The organic extract was evaporated and purified by column chromatography to afford 2-octynal in 80% yield. IR (TF): 2820, 1700 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 3H), 1.2–1.5 (m, 4H), 1.6 (m, 2H), 2.4 (t, $J=7$ Hz, 2H), 9.1 (s, 1H). EIMS (*m*/*z*): 124 (M^+).

4.4. 1-(4-Tetrahydro-2*H*-pyranyloxy-1-butynyl)-2-octynyl alcohol 3a

2-(3-Butynyloxy)tetrahydro-2*H*-pyran (1 g, 6.6 mmol) was dissolved in THF–HMPA (6:1, 30 mL). *n*-BuLi (2.5 M in hexane, 2.6 mL, 6.6 mmol) was added dropwise to the solution at −78°C, and stirring was continued for a further 1 h at the same temperature. 2-Octynal (0.85 g, 6.75 mmol) was added slowly and the solution allowed to warm to room temperature. The mixture was stirred for a further 6 h at room temperature, and saturated NH_4Cl solution was added. The mixture was extracted with ethyl acetate and the organic extract was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to give **3a** in 60% yield. IR (TF): 3390 cm^{-1}; PMR: 0.9 (t, $J=7$

Hz, 3H), 1.2–1.4 (m, 6H), 1.6–1.8 (m, 6H), 2.2 (t, $J=7$ Hz, 2H), 2.5 (t, $J=7$ Hz, 2H), 3.5 (m, 2H), 3.8 (m, 2H), 4.6 (t, $J=4$ Hz, 1H), 5.0 (s, 1H). EIMS (m/z): 278 (M^+).

4.5. 3,6-Dodecadiyne-1,5-diol 4a

A solution of **3a** (0.5 g, 1.8 mmol) dissolved in methanol (10 mL) was treated with catalytic PPTS and stirred for 45 min at room temperature. The methanol was evaporated, and the crude product was dissolved in DCM, washed with 5% $NaHCO_3$ solution, water, brine and dried (Na_2SO_4). Purification by column chromatography gave **4a** in 80% yield. IR (TF): 3410 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 3H), 1.2–1.5 (m, 6H), 2.2 (t, $J=7$ Hz, 2H), 2.5 (t, $J=7$ Hz, 2H), 3.7 (t, $J=7$ Hz, 2H), 5.1 (s, 1H). EIMS (m/z): 194 (M^+).

4.6. (±)-1-(4-*O*-*tert*-Butyldimethylsilyl-1-butynyl)-2-octynyl alcohol 2a

A solution of **4a** (0.3 g, 1.54 mmol) in DCM (10 mL) was cooled to 0°C was treated with imidazole (0.16 g, 2.3 mmol) and stirred for 15 min. *tert*-Butyldimethylchlorosilane (0.25 g, 1.7 mmol) was added and the mixture stirred for a further 1 h at room temperature. Water was added to the reaction mixture, and extracted with DCM. Purification through column chromatography gave **2a** in 60% yield. IR (TF): 3380 cm^{-1}; PMR: 0.0 (s, 6H), 0.8–1.0 (brs, 12H), 1.2–1.6 (m, 6H), 2.2 (t, $J=7$ Hz, 2H), 2.5 (t, $J=7$ Hz, 2H), 3.7 (t, $J=7$ Hz, 2H), 5.1 (s, 1H). FABMS: 309 (M+1).

4.7. (±)-1-(4-*O*-*tert*-Butyldiphenylsilyl-1-butynyl)-2-octynyl alcohol 2d

A solution of **4a** (0.2 g, 1 mmol) and DCM (6 mL) at 0°C was treated with imidazole (0.11 g, 1.5 mmol) and the solution was stirred for 15 min. *tert*-Butyldiphenylchlorosilane (0.31 g, 1.1 mmol) was added and the solution was stirred for a further 2 h at room temperature. After usual workup and purification, **2d** was obtained in 62% yield. IR (TF): 3390, 3010 cm^{-1}; PMR: 0.85 (t, $J=7$ Hz, 3H), 1.0 (s, 9H), 1.2–1.5 (m, 6H), 2.25 (t, $J=7$ Hz, 2H), 2.5 (t, $J=7$ Hz, 2H), 3.7 (t, $J=7$ Hz, 2H), 5.0 (s, 1H), 7.35–7.7 (m, 10H). FABMS: 433 (M+1).

4.8. 1-(4-*O*-*tert*-Butyldimethylsilyl-1-butynyl)-1(*S*)-2-octynyl acetate 7a

In a typical resolution experiment a solution of **2a** (100 mg) in dry ether (10 mL) was stirred with vinyl acetate (3 equiv.) followed by the addition of CRL (100 mg). The reaction mixture was stirred in an orbit shaker at 250 rpm at room temperature for 25 h. After 50% conversion (by GC analysis) the reaction mixture was filtered through Celite and evaporated to dryness. Compounds **7a** and **5a** were isolated after flash chromatography. The enzyme loses virtually no catalytic activity after each transesterification run at 30°C, and therefore can be used repeatedly. IR (TF): 1765 cm^{-1}; PMR: 0.0 (s, 6H), 0.9 (s, 12H), 1.2–1.6 (m, 6H), 2.1 (s, 3H), 2.25 (t, $J=7$ Hz, 2H), 2.45 (t, $J=7$ Hz, 2H), 3.7 (t, $J=7$ Hz, 2H), 5.9 (s, 1H). FABMS: 351 (M+1).

4.9. 1-(4-O-*tert*-Butyldiphenylsilyl-1-butynyl)-1(*S*)-2-octynyl acetate 7d

IR (TF): 3000, 1760 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 3H), 1.1 (s, 9H), 1.2–1.6 (m, 6H), 2.1 (s, 3H), 2.35 (t, $J=7$ Hz, 2H), 2.65 (t, $J=7$ Hz, 2H), 3.8 (t, $J=7$ Hz, 2H), 6.0 (s, 1H), 7.2–7.7 (m, 10H). FABMS: 475 (M+1)

4.10. 1-(5-Tetrahydro-2*H*-2-pyranyloxy-1-pentyl)-2-octynylalcohol 3b

IR (TF): 3385 cm^{-1}; PMR: 0.85 (t, $J=7$ Hz, 3H), 1.2–1.4 (m, 6H), 1.6–1.8 (m, 8H), 2.15 (t, $J=7$ Hz, 2H), 2.3 (t, $J=7$ Hz, 2H), 3.5 (m, 2H), 3.75 (m, 2H), 4.65 (t, $J=4$ Hz, 1H), 5.0 (s, 1H). EIMS (m/z): 292 (M^+).

4.11. 1-(6-Tetrahydro-2*H*-2-pyranyloxy-1-hexynyl)-2-octynylalcohol 3c

IR (TF): 3380 cm^{-1} PMR: 0.9 (t, $J=7$ Hz, 3H), 1.2–1.9 (m, 16H), 2.2–2.4 (m, 4H), 3.45 (m, 2H), 3.75 (m, 2H), 4.65 (t, $J=4$ Hz, 1H), 5.1 (s, 1H). EIMS (m/z): 306 (M^+).

4.12. 4,7-Tridecadiyne-1,6-diol 4b

PMR: 1.0 (t, $J=7$ Hz, 3H), 1.2–1.6 (m, 8H), 2.15 (t, $J=7$ Hz, 2H), 2.21 (t, $J=7$ Hz, 2H), 3.65 (t, $J=7$ Hz, 2H), 5.1 (s, 1H). EIMS (m/z): 208 (M^+).

4.13. 5,8-Tetradecadiyne-1,7-diol 4c

PMR: 0.9 (t, $J=7$ Hz, 3H), 1.2–1.4 (m, 4H), 1.5–1.8 (m, 6H), 2.2–2.4 (m, 4H), 3.7 (t, $J=7$ Hz, 2H), 5.0 (s, 1H). EIMS (m/z): 222 (M^+).

4.14. 1-(5-*O*-*tert*-Butyldimethylsilyl-1-pentynyl)-2-octynylalcohol 2b

PMR: 0.1 (s, 6H), 0.9 (brs, 12H), 1.2–1.7 (m, 8H), 2.15 (t, $J=7$ Hz, 2H), 2.3 (t, $J=7$ Hz, 2H), 3.62 (t, $J=7$ Hz, 2H), 5.0 (s, 1H). FABMS: 323 (M+1).

4.15. 1-(6-*O*-*tert*-Butyldimethylsilyl-1-hexynyl)-2-octynylalcohol 2c

PMR: 0.0 (s, 6H), 1.0 (brs, 12H), 1.2–1.6 (m, 10H), 2.2–2.4 (m, 4H), 3.7 (t, $J=7$ Hz, 2H), 5.0 (s, 1H). FABMS: 337 (M+1).

4.16. 1-(5-*O*-*tert*-Butyldiphenylsilyl-1-pentynyl)-2-octynylalcohol 2e

IR (TF): 3380, 3005 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 2H), 1.1 (s, 9H), 1.3–1.8 (m, 8H), 2.1 (t, $J=7$ Hz, 2H), 2.28 (t, $J=7$ Hz, 2H), 3.7 (t, $J=7$ Hz, 2H), 5.1 (s, 1H), 7.3–7.7 (m, 10H). FABMS: 447 (M+1).

4.17. 1-(6-*O*-*tert*-Butyldiphenylsilyl-1-hexynyl)-2-octynylalcohol

PMR: 0.85 (t, $J=7$ Hz, 3H), 1.05 (s, 9H), 1.2–1.8 (m, 10H), 2.2–2.4 (m, 4H), 3.75 (t, $J=7$ Hz, 2H), 5.0 (s, 1H), 7.25–7.7 (m, 10H). FABMS: 460 (M+1).

4.18. 1-(5-*O*-*tert*-Butyldimethylsilyl-1-pentynyl)-1(*S*)-2-octynyl acetate 7b

IR (TF): 1760 cm^{-1}; PMR: 0.0 (s, 6H), 0.9 (brs, 12H), 1.2–1.6 (m, 8H), 2.1 (s, 3H), 2.2–2.3 (m, 4H), 3.6 (t, $J=7$ Hz, 2H), 6.1 (s, 1H). FABMS: 365 (M+1).

4.19. 1-(6-*O*-*tert*-Butyldimethylsilyl-1-hexynyl)-1(*S*)-2-octynyl acetate 7c

IR (TF): 1765 cm^{-1}; PMR: 0.1 (s, 6H), 1.0 (brs, 12H), 1.2–1.5 (m, 6H), 1.6 (m, 4H), 2.09 (s, 3H), 2.25 (m, 4H), 3.6 (t, $J=7$ Hz, 2H), 6.1 (s, 2H). FABMS: 379 (M+1).

4.20. 1-(5-*O*-*tert*-Butyldiphenylsilyl-1-pentynyl)-1(*S*)-2-octynyl acetate 7e

IR (TF): 1760 cm^{-1}; PMR: 0.85 (t, $J=7$ Hz, 3H), 1.0 (brs, 9H), 1.2–1.8 (m, 8H), 2.1 (s, 3H), 2.2–2.4 (m, 4H), 3.7 (t, $J=7$ Hz, 2H), 6.05 (s, 1H), 7.2–7.7 (m, 10H). FABMS: 489 (M+1).

4.21. 1-(6-*O*-*tert*-Butyldiphenylsilyl-1-hexynyl)-1(*S*)-2-octynyl acetate 7f

IR (TF): 1770, 3005 cm^{-1}; PMR: 0.9 (t, $J=7$ Hz, 3H), 1.1 (brs, 9H), 1.2–1.7 (m, 10H), 2.1 (s, 3H), 2.25 (m, 4H), 3.65 (t, $J=7$ Hz, 2H), 6.0 (s, 1H), 7.25–7.7 (m, 10H). FABMS: 503 (M+1).

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