Carbohydrate Research 345 (2010) 324–329

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Synthesis of 3-vinyl-2,5-dihydrofuran ring system via enyne metathesis

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ARTICLE INFO

Article history:
Received 19 April 2009
Received in revised form 9 September 2009
Accepted 22 September 2009
Available online 26 September 2009

Keywords:
Enyne metathesis
Glycosyl donor
Asymmetrical synthesis

ABSTRACT

An efficient route, starting from but-3-en-1,2-diol, is described to synthesize racemic diastereoisomeric (5-ethoxy-4-vinyl-2,5-dihydrofuran-2-yl) methanol derivatives. Acyclic enyne intermediates having the alkyne moiety directly connected to the asymmetric carbon atom of an acetal were obtained in two steps. These reactive substrates were then subjected to ruthenium-catalyzed enyne metathesis to produce the target compounds in racemic form. The relative configurations were determined by NOE proton NMR experiments. Similar strategy starting from (2*S*)-but-3-en-1,2-diol was proposed to provide pure enantiomers.

Nucleoside analogues have been shown to be highly effective antiviral and antitumor agents. D4T (Stavudine, 2′,3′-didehydro-2′,3′-dideoxythymidine)[1–3] is used in the treatment of human virus (HIV) infection.[4,5] Its mechanism of action is similar to that of other nucleoside HIV-reverse transcriptase (RT) inhibitors, and requires intracellular metabolization into the corresponding 5′-triphosphate derivative, which acts as a competitive inhibitor for the RT reaction and incorporation into viral DNA. With the aim of establishing structure–activity relationship for this type of NRTI, a number of d4N analogues[6] have been synthesized with the 2′- and 3′- protons replaced by a vinyl group (**1**, **2**) or the benzene ring of a benzo[*c*]furan core, **3**. Two strategies were employed[7–19] for the preparation of compounds **1**–**3** (Fig. 1). The first one invoked the direct substitution of the 2′,3′-didehydro-2′,3′-dideoxynucleosides with organotin reagent[7–9] or the formation of the tributyltinvinyl nucleoside followed by palladium-catalyzed cross-coupling.[7–9] The second one required convergent syntheses[10–19] in which the final target functionalities in the 2′- and/or 3′-positions and π-character are installed on the glycone precursor immediately prior to the condensation base to effect nucleoside formation.

Metathesis[20,21] is an extremely useful method in organic chemistry due to the development of selective catalysts such as the ruthenium carbenes **4–6**, which offer a good compromise between efficiency and tolerance to functional groups (Fig. 2).[21] The intramolecular enyne metathesis known as ring-closing enyne metathesis (RCEYM) is a particularly powerful method for the construction of various cyclic 1,3-diene systems.[22–25] Few examples of ruthenium-catalyzed enyne metathesis were described in the area of carbohydrate chemistry.[26–32] To the best of our knowledge, only one paper reported the synthesis of enantiomerically pure oxacyclic dienes starting from acyclic enyne having one asymmetrical carbon atom either in α position of the allyl group or in α position of the propargyl group.[33] The present work describes the first preparation of 4-vinyl-2,5-dihydrofuran derivatives with two asymmetric carbon atoms in positions 2 and 5, respectively.[34]

In order to prepare new nucleoside analogues of d4T an efficient synthesis of the enantiomerically pure glycosyl donors **12 *cis*** and **12 *trans*** have been sought (Scheme 2). Compounds **12 *cis*** and **12 *trans*** have potential as versatile intermediates that can undergo further selective transformations such as cycloaddition.

Retrosynthetic analysis suggested that but-3-en-1,2-diol (**7**) and 3,3-diethoxypropyne (**9**) were the most promising starting point. Compounds **7** and **9** had the advantage of being stable, inexpensive, and easily available. This strategy used an enyne having the alkyne moiety directly connected to the asymmetric carbon atom C-1 of an acetal which, to the best of our knowledge, was not reported as substrate for RCEYM. In the first part of this work, the target compounds were obtained in a racemic mixture and in the second part, application was repeated to prepare the enantiomerically pure form.

The primary hydroxyl group of the diol **7** was selectively protected using *tert*-butyldiphenylsilyl chloride in DMF in the presence of imidazole to give the corresponding ether **8** in 80% yield. Then, compound **8** was treated with the alkyne **9** and P_2O_5 in chloroform to afford the *tert*-butyldiphenylsilyl-protected 2-(1-ethoxyprop-2-ynyloxy)but-3-en-1-ol derivatives **10** and **11** (1:1) in 65% yield.[35,36] It was notable that the protection of the diol **7**, either by selective benzoylation or by silylation with

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doi:10.1016/j.carres.2009.09.023

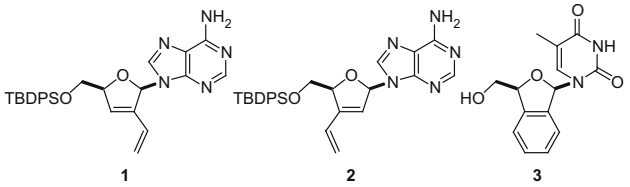


Figure 1. Nucleoside analogues **1–3** having 2′-vinyl or 3′-vinyl group or a benzo[*c*]furan core.

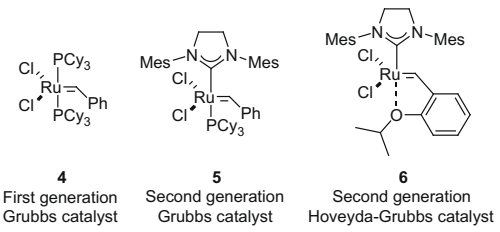
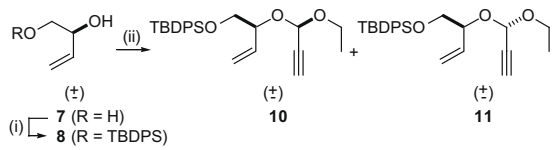


Figure 2. Ruthenium catalysts **4–6** for metathesis.

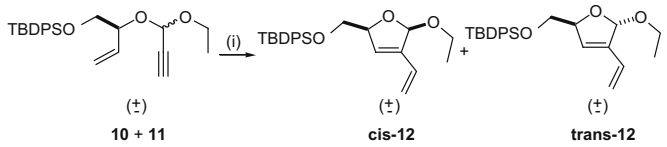
tert-butyldimethylsilyl chloride, gave a species which was prone to partial migration of the protecting group during the subsequent acetalization (see Scheme 1).

Starting from the mixture of acyclic enynes **10** and **11**, RCEYM was investigated for the formation of the conjugated oxacyclic 1,3-dienes, **12 *cis*** and **12 *trans***, using commercially available second-generation Grubbs catalyst **5** under various conditions (Scheme 2 and Table 1).

The RCEYM reaction, in the absence of an ethylene atmosphere, afforded the five-membered ring system but the yield was poor (Table 1, entry 1) and a large quantity of the starting material was recovered. The presence of an ethylene atmosphere (Table 1, entries 2–4), under Mori's conditions,[37] favored the RCEYM by ensuring a better turnover of the active catalyst with yne-then-ene mechanism[38–41] or ene-then-yne mechanism.[42] The use of a higher loading of catalyst (10% vs 3%) resulted in polymerization rather than enhancement of the yield of cyclic enynes **12 *cis*** and **12 *trans*** (Table 1, entries 2 and 3). Due to the presence of three oxygen atoms, addition of $Ti(OiPr)_4$ as Lewis acid using the protocol described by Fürstner[43] gave a moderate 26% yield (39% based on recovered **10** and **11**) (Table 1, entry 4). In our hands, the use of toluene or CH_2Cl_2 in 80 °C and 40 °C, respectively, did not afford the targets **12 *cis*** and **12 *trans*** but gave a polymerization mixture.



Scheme 1. Reagents and conditions: (i) TBDPSCl, imidazole, DMF, 20 °C, 24 h (80%); (ii) **9**, P_2O_5, $CHCl_3$, 45 °C, 2 d (65%).



Scheme 2. Reagents and conditions: (i) **5**, CH_2Cl_2, 20 °C, 5 d.

Table 1
RCEYM of enynes **10** and **11** using ruthenium carbenes **5** as catalyst

Entry	Catalyst (%)	**10** and **11** recovered yield (%)	**12 *cis*** yield (%)	**12 *trans*** yield (%)
1[a,b]	3	67	7	7
2[a,c]	3	—	25	25
3[a,c]	10	—	13	9
4[a,c,d]	3	32	13	13

[a] 0.03 M of **10** and **11**, **5**, CH_2Cl_2, 20 °C, 5 days.
[b] Under nitrogen atmosphere.
[c] Under ethylene atmosphere.
[d] $Ti(OiPr)_4$ 0.3 equiv.

Several N-glycosylations were attempted using the Vorbruggen methodology[44,45,36] to introduce the thymine moiety. However, it was demonstrated that such a methodology was ineffective. As an alternative approach the fusion procedure[46,47] was investigated but no nucleoside analogue was obtained. All attempts for the N-glycosylation afforded the decomposition of the dienes **12 *cis*** and **12 *trans***.

Unfortunately, the dienes **12 *cis*** and **12 *trans*** gave poor quality crystals thus, precluding the determination of their configurations by X-ray crystallography. Thus, the absolute configurations of the two asymmetric carbons C-2 and C-5 included in the furan core were determined by NMR experiments and independent chemical correlation. The relative configurations for the dienes **12 *cis*** and **12 *trans*** were assigned as 2*S*,5*R* (2*R*,5*S*) and 2*S*,5*S* (2*R*,5*R*), respectively, on the basis of the proton NMR NOE experiments (Fig. 3). Thus, in the racemic **12 *trans***, irradiation of H-5 proton gave enhanced signals for H proton of the methyloxy group. The same was true for H-5 proton when H proton of the methyloxy group was irradiated.

Conversely, no NOE effect was observed for the same protons of **12 *cis***. It was notable that, for compounds **12 *cis*** and **12 *trans***, irradiation of H-e proton of the vinyl group gave enhanced signals for H-5 proton and vice versa confirming the *s-trans* conformation of the dienes in solution. The comparison of the chemical shifts and coupling constants of H-2 and H-5 protons for the two diastereoisomers was also very interesting. The NMR spectra on the 2,5-dihydrofuran system have been investigated for several compounds with one or no substituent in the dihydrofuran ring.[13–19,48] In each case, the larger cross-ring coupling between H-2 and H-5 was assigned to the *trans* configuration and the smaller to the *cis* configuration. In agreement with the literature,[13–19,47] the observed coupling $J_{2,5}$ was 0 Hz for compound **12 *cis*** and 4.0 Hz for compound **12 *trans***.

In order to study the influence of the protecting group on the cyclization, substrates **13–20** were prepared. At first, the silyl protection of **10** and **11** was removed using TBAF in THF at room temperature to afford the corresponding alcohols **13** and **14** in 84% yield. Then, the primary hydroxyl group of the alcohols **13** and **14** was protected: (i) using trityl chloride in pyridine to give the ethers **15** and **16** in 60% yield; (ii) using benzoyl chloride in pyridine to afford the esters **17** and **18** in 71% yield; and (iii) using

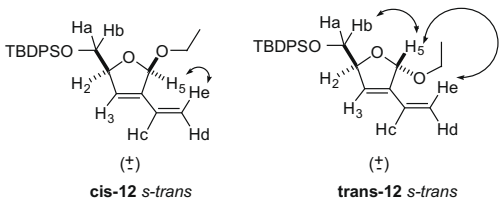
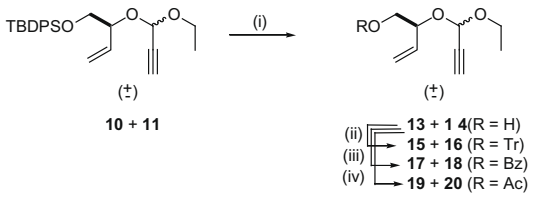
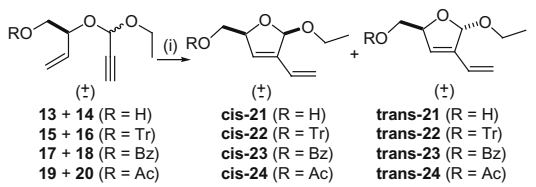


Figure 3. Proton NMR NOE interactions for compounds **12 *cis*** *s-trans* and **12** *trans s-trans*.



Scheme 3. Reagents and conditions: (i) TBAF 1 M, THF, rt, 16 h; (ii) TrCl, pyridine, rt, 7 d; (iii) BzCl, pyridine rt, 16 h; (iv) Ac_2O, pyridine, rt, 16 h.



Scheme 4. Reagents and conditions: (i) 3 mol % **5**, CH_2Cl_2 under ethylene atmosphere, 20 °C, 5 d.

Table 2
RCEYM of enynes **13**–**20** using ruthenium carbenes **5** as catalyst[a]

Entry	Starting materials	Enyne *cis* yield[b] (%)	Enyne *trans* yield[b] (%)
1	**13** and **14**	**21 *cis*** (7)	**21 *trans*** (20)
2	**15** and **16**	**22 *cis*** (30)	**22 *trans*** (20)
3	**17** and **18**	**23 *cis*** (16)	**23 *trans*** (32)
4	**19** and **20**	**24 *cis*** (20)	**24 *trans*** (15)

[a] 0.03 M, 3 mol % 5, CH_2Cl_2, 20 °C, 5 days under ethylene atmosphere.
[b] Obtained after flash chromatography.

acetic anhydride in pyridine to furnish the **19** and **20** in 74% yield (Scheme 3).

Under the optimized conditions starting from the acyclic enyne mixture **10** and **11** (Table 1, entry 2: 0.03 M, 3 mol % **5**, CH_2Cl_2, ethylene, 20 °C, 5 days), the dienes **21–24** were obtained in 27–50% yield (Scheme 4 and Table 2).

As reported,[26] unprotected alcohols **13** and **14** afforded the corresponding cyclic enynes **21 *cis*** and **21 *trans*** in rather poor yield (Table 2, entry 1). Among the different protecting groups, both the trityl and benzoyl derivatives **15–18** were obtained in better yields (Table 2, entries 2 and 3), similar to that for **10** and **11** (Table 1, entry 2). In our hands, the acetates **19** and **20** gave poor yields compared with those obtained with the corresponding benzoate **17** and **18** (35% vs 48%). The ratio *cis*:*trans* varied with the nature of the protecting group and was dependant probably on both stereoelectronic effects and potent π–π stacking.

It was notable that the formation of a six-membered ring (from *endo* selectivity) was not detected, nor was there any evidence of a dimer resulting from diene cross-metathesis (Tables 1 and 2). In our case, the formation of 1,3-substituted 1,2-dienes showed absolute *exo* selectivity for the RCEYM.[49,50]

In order to prepare the 1,3-diene in their enantiomerically pure forms, application of the above strategy was repeated starting from the commercial chiral (2*S*)-but-3-en-1,2-diol (**(2*S*)-7**). After selective silylation of **(2*S*)-7**, subsequent acetalization and cyclization afforded **(2*S*,5*R*)-12** and **(2*S*,5*S*)-12** with similar yields. The absolute configurations for the dienes **(2*S*,5*R*)-12** and **(2*S*,5*S*)-12** were assigned as 2*S*,5*R* and 2*S*,5*S*, respectively, on the basis of the proton NMR NOE experiments as determined above for the determination of the relative configurations of **12 *cis*** and **12 *trans***.

In summary, we have demonstrated a concise method using RCEYM reaction for the synthesis of 2,3-didehydro-2,3-dideoxyribo-D-ribofuranose derivatives. The reported strategy permitted the synthesis of enantiomerically pure carbohydrate analogues of the series D or L starting from the chiral (*S*)- or (*R*)-but-3-en-1,2-diols, respectively. To date these novel derivatives have not been used as potential glycosyl donors for the synthesis of new nucleosides.

1. Experimental

1.1. General methods

Melting points were determined on a digital melting-point apparatus (Electrothermal) and were uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1-dm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (internal Me4Si) at 300.13 MHz and at 75.47 MHz, respectively (Bruker Advance-300). TLC was performed on Silica F254 (Merck) and detection was by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was carried out on Silica Gel 60 (Merck, 230 mesh). EtOAc, diethyl ether, and petroleum ether were distilled before use. Bases and solvents were used as supplied.

1.2. 1-(*tert*-Butyldiphenylsilanyloxy)but-3-en-2-ol (8)

To a solution of but-3-en-1,2-diol (**7**) (0.4 mL, 4.8 mmol) and imidazole (750 mg, 11 mmol) in DMF (4.4 mL) was added *tert*-butyldiphenylsilyl chloride (1.5 mL, 5.76 mmol) at 20 °C under nitrogen atmosphere. After 24 h at the same temperature, water was added and the mixture was extracted with toluene/EtOAc 1:2. The extract was worked up and the crude product was purified by flash chromatography (EtOAc/hexane 5:95) to yield **8** (1.25 g, 80%) as a colorless oil. R_f = 0.5 (AcOEt/hexane 5:95). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (m, 4H, Ph), 7.42 (m, 6H, Ph), 5.80 (m, 1H, H-3), 5.34 (dd, J = 1.5 Hz, J = 18 Hz, H-4), 5.21 (dd, 1H, J = 1.5 Hz, J = 12 Hz, H-4), 4.30 (m, 1H, H-2), 3.70 (dd, 1H, J = 4 Hz, J = 10 Hz, H-1), 3.68 (dd, 1H, J = 7 Hz, J = 10 Hz, H-1), 2.73 (d, 1H, J = 3.7 Hz, OH), 1.18 (s, 9H, 3CH3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5 (C-3), 135.5 (Ph), 133.1 (Ph), 129.8 (Ph), 127.8 (Ph), 116.5 (C-4), 73.5 (C-2), 67.6 (C-1), 26.8 ($3CH_3$), 19.2 (C-*t*Bu). HRMS (ESI) $[M+Na]^+$ calcd 349.1600, found m/z = 349.1606.

1.3. (1*R*,2*S*)- and (1*S*,2*R*)-(2-(1-Ethoxyprop-2-ynyloxy)but-3-enyloxy)-*tert*-butyldiphenylsilane (10) and (1*R*,2*R*)- and (1*S*,2*S*)-(2-(1-ethoxyprop-2-ynyloxy)but-3-enyloxy)-*tert*-butyldiphenylsilane (11)

To a solution of alcohol **8** (200 mg, 0.6 mmol) in $CHCl_3$ (2.3 mL) were added 3,3-diethoxypropyne (**9**) (0.21 mL, 1.5 mmol) and P_2O_5 (150 mg, 1.05 mmol). After stirring the mixture for 48 h at 45 °C, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated $NaHCO_3$. This extract was worked up and the crude product was purified by flash chromatography (EtOAc/hexane 3:97) to yield a mixture of **10** and **11** (159 mg, 65%) as a colorless oil. R_f = 0.8 (AcOEt/hexane 10:90). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (m, 4H, Ph), 7.44 (m, 6H, Ph), 5.78 (m, 1H, H-3), 5.56 (s, 0.5 H, 0.5 H-1′), 5.28 (m, 2.5 H, 0.5 H-1′, 2 H-4), 4.32 (m, 1H, H-2), 3.73 (m, 4H, 2H-1, OC*H*2CH_3), 2.56 (d, 0.5H, J = 2 Hz, H-3′), 2.52 (d, 0.5H, J = 2 Hz, H-3′), 1.19 (t, 3H, J = 8 Hz, CH_3), 1.06 (s, 9H, 3CH3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1 (Ph), 135.8 (C-3), 135.2 (C-3), 133.7 (Ph), 130.1 (Ph), 128.0 (Ph), 119.7 (C-4), 117.7 (C-4), 91.5 (C-1′), 89.0 (C-1′), 79.6 (C-2′), 79.0 (C-2), 78.6 (C-2), 74.0 (C-3′), 73.7 (C-3′), 67.3 (C-1), 66.7 (C-1), 60.5 (OCH_2CH_3), 59.7 (OCH_2CH_3), 27.2 ($C(CH_3)_3$), 19.6 ($C(CH_3)_3$), 15.4 ($6CH_3$). HRMS (ESI) $[M+Na]^+$ calcd 431.2018, found m/z = 431.2023.

1.4. (1*R*,2*S*)- and (1*S*,2*R*)-2-(1-Ethoxyprop-2-ynyloxy)but-3-en-1-ol (13) and (1*R*,2*R*)- and (1*S*,2*S*)-2-(1-ethoxyprop-2-ynyloxy)but-3-en-1-ol (14)

To a solution of **10** and **11** (850 mg, 2.1 mmol) in THF (50 mL) was added a solution of TBAF 1 M in THF (2.1 mL, 2.1 mmol) and the solution was stirred at rt for 16 h under nitrogen atmosphere. The volatiles were eliminated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 10:90) to yield **13** and **14** (300 mg, 84%) as a yellow oil. R_f = 0.2 (AcOEt/hexane 10:90). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (m, 1H, H-3), 5.38 (m, 3H, H-1′, 2H-4), 4.30 (m, 1H, H-2), 3.68 (m, 4H, OCH_2CH$_3$, 2H-1), 2.59 (d, 1H, J = 2 Hz, H-3′), 1.22 (t, 3H, J = 8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.1 (C-3), 134.2 (C-3), 120.2 (C-4), 118.6 (C-4), 91.4 (C-1′), 89.6 (C-1′), 79.3 (C-2), 79.2 (C-2), 79.0 (C-2′), 78.8 (C-2′), 74.8 (C-3′), 74.7 (C-3′), 65.6 (C-1), 62.3 (OCH_2CH$_3$), 60.4 (OCH_2CH$_3$), 15.3 (CH_3), 15.2 (CH_3). HRMS (ESI) [M+Na]$^+$ calcd 193.0841, found m/z = 193.0835.

1.5. (1*R*,2*S*)- and (1*S*,2*R*)-(2-(1-Ethoxyprop-2-ynyloxy)but-3-enyloxy)-triphenylmethane (15) and (1*R*,2*R*)- and (1*S*,2*S*)-(2-(1-ethoxyprop-2-ynyloxy)but-3-enyloxy)-triphenylmethane (16)

To a solution of **13** and **14** (500 mg, 2.94 mmol) in pyridine (10 mL) was added triphenylmethyl chloride (900 mg, 3.23 mmol). After stirring the mixture at rt for 7 days under nitrogen atmosphere, methanol was added and the volatiles were eliminated under reduced pressure. The residue was diluted in CH_2Cl_2 and the organic layer was washed successively with saturated NH_4Cl and water. The extract was worked up and the crude product was purified by flash chromatography (EtOAc/hexane 5:95) to yield **15** and **16** (720 mg, 60%) as a yellow oil. R_f = 0.8 (AcOEt/hexane 10:90). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (m, 6H, Ph), 7.27 (m, 9H, Ph), 5.75 (m, 1H, H-3), 5.57 (s, 0.5H, 0.5 H-1′), 5.27 (m, 2.5H, 0.5H-1′, 2H-4), 4.30 (m, 1H, H-2), 3.78 (m, 2H, OCH_2CH$_3$), 3.31 (m, 1H, H-1), 3.07 (m, 1H, H-1), 2.57 (d, 0.4H, J = 2 Hz, 0.4 H-3′), 2.51 (d, 0.6H, J = 2 Hz, 0.6H-3′), 1.18 (m, 3H, J = 8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.4 (Ph), 136.0 (C-3), 135.4 (C-3), 129.2 (Ph), 128.1 (Ph), 127.3 (Ph), 119.4 (C-4), 117.5 (C-4), 91.4 (C-1′), 89.1 (C-1′), 87.1 (C(Ph)$_3$), 87.0 (C(Ph)$_3$), 79.6 (C-2′), 77.1 (C-2), 76.7 (C-2), 74.0 (C-3′), 73.8 (C-3′), 67.2 (C-1), 66.7 (C-1), 60.7 (OCH_2CH$_3$), 59.8 (OCH_2CH$_3$), 15.4 (CH_3), 15.3 (CH_3). HRMS (ESI) [M+Na]$^+$ calcd 435.2018, found m/z = 435.1920.

1.6. (1*R*,2*S*)- and (1*S*,2*R*)-(2-(1-Ethoxyprop-2-ynyloxy)but-3-enyl)-benzoate (17) and (1*R*,2*R*)- and (1*S*,2*S*)-(2-(1-ethoxyprop-2-ynyloxy)but-3-enyl)-benzoate (18)

To a solution of **13** and **14** (100 mg, 0.59 mmol) in pyridine (5 mL) at 0 °C was added benzoyl chloride (0.07 mL, 0.65 mmol). After stirring the mixture at rt for 16 h, methanol was added and the volatiles were eliminated under reduced pressure. The residue was diluted in CH_2Cl_2 and the organic layer was washed successively with saturated $NaHCO_3$. The extract was worked up and the crude product was purified by flash chromatography (EtOAc/hexane 10:90) to yield **17** and **18** (115 mg, 71%) as a colorless oil. R_f = 0.6 (AcOEt/hexane 15:85). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (m, 2H, Ph), 7.55 (m, 1H, Ph), 7.42 (m, 2H, Ph), 5.81 (m, 1H, H-3), 5.38 (m, 3H, H-1′, 2H-4), 4.58 (m, 1H, H-2), 4.37 (m, 2H, OCH_2CH$_3$), 3.72 (m, 2H, 2H-1), 2.55 (d, 1H, J = 2 Hz, H-3′), 1.15 (m, 3H, J = 8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7 (CO), 134.9 (C-3), 134.0 (C-3), 133.4 (Ph), 130.4 (Ph), 130.1 (Ph), 128.8 (Ph), 120.5 (C-4), 118.8 (C-4), 91.3 (C-1′), 89.3 (C-1′), 79.1 (C-2′), 75.3 (C-2), 75.1 (C-2), 74.5 (C-3′), 74.2 (C-3′), 61.7 (OCH_2CH$_3$), 60.0 (OCH_2CH$_3$), 15.2 (CH_3). HRMS (ESI) [M+Na]$^+$ 297.1103, found m/z = 297.1102.

1.7. (1*R*,2*S*)- and (1*S*,2*R*)-(2-(1-Ethoxyprop-2-ynyloxu)but-3-enyl)-acetate (19) and (1*R*,2*R*)- and (1*S*,2*S*)-(2-(1-ethoxyprop-2-ynyloxu)but-3-enyl)-acetate (20)

To a solution of **13** and **14** (160 mg, 0.95 mmol) in pyridine (0.3 mL) was added acetic anhydride (0.1 mL, 1.14 mmol). After stirring the mixture at rt for 16 h under nitrogen atmosphere, a solution of 1 M HCl was added and the aqueous layer was extracted with EtOAc. The extract was worked up and the crude product was purified by flash chromatography (EtOAc/hexane 10:90) to yield **15** and **16** (150 mg, 74%) as a yellow oil R_f = 0.6 (AcOEt/hexane 15:85). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (m, 1H, H-3), 5.34 (m, 3H, H-1′, 2H-4), 4.30 (m, 1H, H-2), 4.13 (m, 2H, OCH_2CH$_3$), 3.75 (m, 2H, 2H-1), 2.56 (d, 1H, J = 2 Hz, H-3′), 2.07 (s, 3H, CH_3), 1.20 (m, 3H, J = 8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1 (CO), 134.9 (C-3), 133.8 (C-3), 120.4 (C-4), 118.6 (C-4), 91.5 (C-1′), 89.2 (C-1′), 79.1 (C-2′), 75.1 (C-2), 74.9 (C-2), 74.2 (C-3′), 73.4 (C-3′), 66.5 (C-1), 66.3 (C-1), 61.7 (OCH_2CH$_3$), 60.2 (OCH_2CH$_3$), 21.5 (*C*H$_3$CO), 21.2 (*C*H$_3$CO), 15.3 (CH_3), 15.2 (CH_3). HRMS (ESI) [M+Na]$^+$ calcd 235.0946, found m/z = 235.0946.

1.8. General procedure for the synthesis of the dienes 12, 21–24

The ruthenium catalyst **5** **(3 mol %)** was added into CH_2Cl_2 (26 mL) and ethylene gas was passed through the solution for 20 min. The enyne mixture (0.98 mmol) in CH_2Cl_2 (12 mL) was then added and the mixture was stirred under ethylene at 20 °C for 5 days. The volatiles were eliminated under reduced pressure and the residue was purified by flash chromatography to give the corresponding dienes.

1.8.1. (2*S*,5*R*)- and (2*R*,5*S*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethoxy)-*tert*-butyldiphenylsilane (12 *cis*) and (2*R*,5*S*)- and (2*S*,5*R*)-(5-ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethoxy)-*tert*-butyldiphenylsilane (12 *trans*)

Starting from enyne mixture of **10** and **11** (400 mg, 0.98 mmol), the flash chromatography (EtOAc/hexane 5:95) gave **12** ***cis*** (100 mg, 25%) and **12** ***trans*** (100 mg, 25%) in the order of fractions eluted. **12** ***cis***. R_f 0.50 (EtOAc/hexane 5:95); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (m, 4H, Ph), 7.45 (m, 6H, Ph), 6.48 (dd, 1H, J = 12 Hz, J = 18 Hz, =CH), 6.18 (s, 1H, H-3), 5.87 (s, 1H, H-5), 5.46 (d, 1H, J = 18 Hz, =CH), 5.23 (d, 1H, J = 12 Hz, =CH), 4.80 (m, 1H, J = 1 Hz, H-2), 3.68 (m, 4H, OCH_2CH$_3$, CH_2OSi), 1.23 (t, 3H, J = 8 Hz, CH_3), 1.06 (s, 9H, 3CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9 (C-4), 136.0 (Ph), 135.9 (Ph), 133.9 (C-3), 133.8 (Ph), 130.4 (=CH), 128.1 (Ph), 118.0 (=CH_2), 107.6 (C-5), 85.7 (C-2), 67.6 (CH_2OSi), 62.6 (OCH_2), 27.2 (C(*C*H$_3$)$_3$), 19.6 (*C*(CH$_3$)$_3$), 15.8 (CH_3). HRMS (ESI) [M+Na]$^+$ calcd 431.2018, found m/z = 431.2034. **12** ***trans*** R_f 0.20 (MeOH/CH_2Cl_2 5:95); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (m, 4H, Ph), 7.38 (m, 6H, Ph), 6.43 (m, 1H, J = 12 Hz, J = 18 Hz, =CH), 5.98 (s, 1H, H-3), 5.96 (d, 1H, J = 4 Hz, H-5), 5.43 (d, 1H, J = 18 Hz, =CH), 5.24 (d, 1H, J = 12 Hz, =CH), 4.90 (m, 1H, H-2), 3.72 (m, 4H, OCH_2CH$_3$, CH_2OSi), 1.26 (t, 3H, J = 8 Hz, CH_3), 1.04 (s, 9H, 3CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8 (C-4), 136.0 (Ph), 133.9 (Ph), 130.6 (C-3), 130.0 (Ph), 129.0 (=CH), 128.1 (Ph), 118.0 (=CH_2), 107.6 (C-5), 85.6 (C-2), 66.6 (CH_2OSi), 62.1 (OCH_2), 27.2 (C(*C*H$_3$)$_3$), 19.6 (*C*(CH$_3$)$_3$), 15.8 (CH_3). HRMS (ESI) [M+Na]$^+$ calcd 431.2018, found m/z = 431.2025.

1.8.2. (2*S*,5*R*)- and (2*R*,5*S*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-yl)-methanol (21 *cis*) and (2*R*,5*S*)- and (2*S*,5*R*)-(5-ethoxy-4-vinyl-2,5-dihydrofuran-2-yl)-methanol (21 *trans*)

Starting from enyne mixture of **13** and **14** (150 mg, 0.88 mmol), the flash chromatography (EtOAc/hexane 10:90) gave **21** ***cis*** (10 mg, 7%) and **21** ***trans*** (29 mg, 20%) in the order of fractions eluted. **12** ***cis***. R_f = 0.3 (EtOAc/hexane 20:80). ^{1}H NMR (acetone-

d_6, 300 MHz) δ 6.43 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 5.92 (s, 1H, H-5), 5.81 (s, 1H, H-3), 5.33 (d, 1H, J = 18 Hz, H-2′), 5.23 (d, 1H, J = 12 Hz, H-2′), 4.92 (m, 1H, H-2), 3.75 (m, 4H, OCH_2CH$_3$, CH_2OH), 1.28 (t, 3H, J = 8 Hz, CH$_3$). ^{13}C ($CDCl_3$, 75 MHz) δ 139.9 (C-4), 128.7 (C-3, C-1′), 118.2 (C-2′), 107.1 (C-5), 85.4 (C-2), 64.6 (CH_2OH), 63.8 (OCH_2CH$_3$), 15.8 (CH$_3$). HRMS (ESI) [M+Na]$^+$ 193.0841, found m/z = 193.0851. **12** ***trans***. R_f = 0.2 (EtOAc/hexane 20:80). ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.46 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.00 (d, 1H, J = 4 Hz, H-5), 5.95 (s, 1 H, H-3), 5.43 (d, 1H, J = 18 Hz, H-2′), 5.27 (d, 1H, J = 12 Hz, H-2′), 5.04 (m, 1H, J = 4 Hz, H-2), 3.65 (m, 4H, OCH_2CH$_3$, CH_2OH), 1.25 (t, 3H, CH$_3$). ^{13}C ($CDCl_3$, 75 MHz) δ 139.8 (C-4), 128.9 (C-3), 128.7 (C-1′), 118.5 (C-2′), 107.1 (C-5), 85.8 (C-2), 65.1 (CH_2OH), 62.4 (OCH_2CH$_3$), 15.7 (CH$_3$). HRMS (ESI) [M+Na]$^+$ 193.0841, found m/z = 193.0858.

1.8.3. (2*S*,5*R*)- and (2*R*,5*S*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethoxy)-triphenylmethane (22 *cis*) and (2*R*,5*S*)- and (2*S*,5*R*)-(5-ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethoxy)-triphenylmethane (22 *trans*)

Starting from enyne mixture of **15** and **16** (100 mg, 0.24 mmol), the flash chromatography (CH_2Cl_2/hexane 40:60) gave **22** ***cis*** (30 mg, 30%) and **22** ***trans*** (20 mg, 20%) in the order of fractions eluted. **22** ***cis***. R_f = 0.6 (EtOAc/hexane 5:95). ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.50 (m, 6H, Ph), 7.28 (m, 9H, Ph), 6.46 (dd, 1H, J = 12 Hz, J = 18 Hz, H-3′), 6.10 (s, 1H, H-3), 5.90 (s, 1H, H-5), 5.43 (d, 1H, J = 18 Hz, H-2′), 5.22 (d, 1H, J = 12 Hz, H-2′), 4.90 (m, 1H, H-2), 3.65 (m, 2H, CH_2OTr), 3.16 (m, 2H, OCH_2CH$_3$), 1.21 (t, 3H, J = 8 Hz, CH$_3$). ^{13}C ($CDCl_3$, 75 MHz) δ 144.4 (Ph), 139.0 (C-4), 129.8 (C-3), 129.2 (Ph), 128.9 (C-1′), 128.1 (Ph), 127.3 (Ph), 118.1 (C-2′), 107.7 (C-5), 87.0 (CPh_3), 84.6 (C-2), 67.5 (CH_2OTr), 62.8 (OCH_2CH$_3$), 15.7 (CH$_3$). HRMS (ESI) [M+Na]$^+$ 435.1936, found m/z = 435.1951. **22** ***trans***. R_f = 0.5 (EtOAc/hexane 5:95). ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.43 (m, 6H, Ph), 7.25 (m, 9H, Ph), 6.36 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.13 (s, 1H, H-3), 5.90 (d, 1H, J = 4 Hz, H-5), 5.41 (d, 1H, J = 18 Hz, H-2′), 5.22 (d, 1H, J = 12 Hz, H-2′), 5.10 (m, 1H, H-2), 3.61 (m, 2H, CH_2OTr), 3.13 (m, 2H, OCH_2CH$_3$), 1.21 (t, 3H, J = 8 Hz, CH$_3$). ^{13}C ($CDCl_3$, 75 MHz) δ 144.4 (Ph), 138.6 (C-4), 130.7 (C-3), 129.1 (Ph), 128.9 (C-1′), 128.2 (Ph), 127.4 (Ph), 118.1 (C-2′), 107.5 (C-5), 86.9 (CPh_3), 84.3 (C-2), 66.8 (CH_2OTr), 61.9 (OCH_2CH$_3$), 15.7 (CH$_3$). HRMS (ESI) [M+Na]$^+$ calcd 435.1936, found m/z = 435.1938.

1.8.4. (2*S*,5*R*)- and (2*R*,5*S*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethyl)-benzoate (23 *cis*) and (2*R*,5*S*)- and (2*S*,5*R*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethyl)-benzoate (23 *trans*)

Starting from enyne mixture of **17** and **18** (100 mg, 0.36 mmol), the flash chromatography (EtOAc/hexane 5:95) gave **23** ***cis*** (20 mg, 20%) and **23** ***trans*** (15 mg, 15%) in the order of fractions eluted. **23** ***cis***. R_f = 0.3 (EtOAc/hexane 5:95). ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.06 (m, 2H, Ph), 7.50 (m, 3H, Ph), 6.46 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.21 (s, 1H, H-3), 5.90 (s, 1H, H-5), 5.46 (d, 1H, J = 18 Hz, H-2′), 5.23 (d, 1H, J = 12 Hz, H2′), 5.03 (s 1H, H-2), 4.42 (m, 2H, OCH_2Bz), 3.60 (m, 2H, OCH_2CH$_3$), 1.14 (t, 3H, J = 8 Hz, CH$_3$), ^{13}C ($CDCl_3$, 75 MHz) δ 166.4 (CO), 139.8 (C-4), 133.0 (Ph), 130.0 (C-3), 129.9 (Ph), 129.8 (Ph), 128.3 (Ph), 127.8 (C-1′), 118.4 (C-2), 107.4 (C-5), 82.6 (C-2), 66.8 (OCH_2Bz), 62.7 (OCH_2CH$_3$), 15.4 (CH$_3$). HRMS (ESI) (M+Na$^+$) calcd 297.1103, found m/z = 297.1100. **23** ***trans***. R_f = 0.2 (EtOAc/hexane 5:95). ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.01 (m, 2H, Ph), 7.58 (m, 3H, Ph), 6.46 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.21 (s, 1H, H-3), 6.02 (d, 1H, J = 4 Hz, H-5), 5.49 (d, 1H, J = 18 Hz, H-2′), 5.24 (d, 1H, J = 12 Hz, H-2′), 5.21 (m, 1H, H-2), 4.39 (m, 2H, OCH_2Bz), 3.60 (m, 2H, OCH_2CH$_3$), 1.14 (t, 3H, J = 8 Hz, CH$_3$), ^{13}C ($CDCl_3$, 75 MHz) δ 166.4 (CO), 139.6 (C-4), 133.1 (Ph), 129.9 (C-3), 129.8 (Ph), 129.7 (Ph), 128.4 (Ph), 128.1 (C-1′), 118.6 (C-4), 107.3 (C-5), 82.7 (C-2), 66.2 (OCH_2Bz), 62.1 (OCH_2CH$_3$), 15.3 (CH$_3$). HRMS (ESI) [M+Na]$^+$ calcd 297.1103, found m/z = 297.1103.

1.8.5. (2*S*,5*R*)- and (2*R*,5*S*)-(5-Ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethyl)-acetate (24 *cis*) and (2*R*,5*S*)- and (2*S*,5*R*)-(5-ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethyl)-acetate (24 *trans*)

Starting from enyne mixture of **19** and **20** (100 mg, 0.47 mmol), the flash chromatography (CH_2Cl_2/hexane 30:70) gave **24** ***cis*** (16 mg, 16%) and **24** ***trans*** (32 mg, 32%) in the order of fractions eluted. **24** ***cis***. R_f = 0.2 (CH_2Cl_2/hexane 60:40). ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.43 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.11 (s, 1H, H-3), 5.86 (s, 1H, H-5), 5.47 (d, 1H, J = 18 Hz, H-2′), 5.23 (d, 1H, J = 12 Hz, H-2′), 4.88 (s, 1H, H-2), 4.10 (m, 2H, CH_2OAc), 3.63 (m, 2H, OCH_2CH$_3$), 2.04 (s, 3H, CH$_3$), 1.25 (t, 3H, J = 8 Hz, CH$_3$). ^{13}C ($CDCl_3$, 75 MHz) δ 170.9 (CO), 139.7 (C-4), 128.4 (C-3), 127.7 (C-1′), 118.4 (C-2), 107.3 (C-5), 82.6 (C-2), 66.5 (C-1), 62.6 (OCH_2CH$_3$), 20.9 (*C*H$_3$CO), 15.4 (CH$_3$). HRMS (ESI) [M+Na]$^+$ calcd 235.0946, found m/z = 235.0935. **24** ***trans***. R_f = 0.1 (CH_2Cl_2/hexane 60:40). ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.50 (dd, 1H, J = 12 Hz, J = 18 Hz, H-1′), 6.10 (s, 1H, H-3), 5.97 (d, 1H, J = 4 Hz, H-5), 5.44 (d, 1H, J = 18 Hz, H-2′), 5.25 (d, 1H, J = 12 Hz, H-2′), 5.05 (m, 1H, H-2), 4.08 (m, 2H, CH_2OAc), 3.56 (m, 2H, OCH_2CH$_3$), 2.05 (s, 3H, CH3), 1.24 (t, 3H, J = 8 Hz, CH$_3$), ^{13}C ($CDCl_3$, 75 MHz) δ 170.9 (CO), 139.7 (C-4), 128.4 (C-3), 127.7 (C-1′), 118.4 (C-2′), 107.2 (C-5), 82.3 (C-2), 66.2 (C-1), 62.4 (OCH_2CH$_3$), 20.9 (CH$_3$CO), 15.4 (CH$_3$). HRMS (ESI) [M+Na]$^+$ calcd 235.0946, found m/z = 235.0938.

1.9. 1-(*tert*-Butyldiphenylsilanyloxy)but-3-en-2-ol ((2*S*)-**8**)

The (2*S*)-but-3-en-1,2-diol ((**2*S***)-**7**) was converted to the silylated compound by the procedure employed above for the racemate to give the alcohol (**2*S***)-**8**; enantiomer (**2*S***)-**8** had NMR data identical to those for the racemic compound **8**, $[\alpha]_D^{22} = +0.6$ (c 1.0 in $CHCl_3$); HRMS (ESI) [M+Na]$^+$ calcd 349.1600, found m/z = 349.1604.

1.10. (1*R*,2*S*)-(2-(1-Ethoxyprop-2-ynyloxy)but-3-enyloxy)-*tert*-butyldiphenylsilane ((1*R*,2*S*)-**10**) and (1*S*,2*S*)-(2-(1-ethoxyprop-2-ynyloxy)but-3-enyloxy)-*tert*-butyldiphenylsilane ((1*S*,2*S*)-**11**)

Compound (**2*S***)-**8** was converted to the acyclic enynes by the procedure employed above for the racemate to give the acyclic enynes (**1*R*,2*S***)-**10** and (**1*S*,2*S***)-**11**; enantiomers (**1*R*,2*S***)-**10** and (**1*S*,2*S***)-**11** have NMR data identical to those for the racemic compounds **10** and **11**. HRMS (ESI) [M+Na]$^+$ calcd 431.2018, found m/z = 431.2016.

1.11. (2*S*,5*R*)-*tert*-Butyl-(5-ethoxy-4-vinyl-2,5-dihydrofuran-2-ylmethoxy)-diphenylsilane ((2*S*,5*R*)-**12**) and (2*S*,5*S*)-*tert*-butyl-(2-(1-ethoxyprop-2-ynyloxy)but-3-enyloxy)-diphenylsilane ((2*S*,5*S*)-**12**)

A mixture of compounds (***1R*,*2S***)-**10** and (***1S*,*2S***)-**11** was converted to the cyclic enynes by the procedure employed above for the racemate to give the cyclic enynes (***2S*,*5R***)-**12** and (***2S*,*5S***)-**12**; enantiomer (***2S*,*5R***)-**12** had NMR data identical to those for the racemic compound **12** ***cis***, $[\alpha]_D^{20} = -70.6$ (***c*** 0.3 in $CHCl_3$); HRMS (ESI) [M+Na]$^+$ calcd 431.2018, found m/z = 431.2034; enantiomer (***2S*,*5S***)-**12** had NMR data identical to those for the racemic compound ***12*** ***trans***, $[\alpha]_D^{20} = -30.9$ (***c*** 0.3 in $CHCl_3$); HRMS (ESI) [M+Na]$^+$ calcd 431.2018, found m/z = 431.2005.

Acknowledgment

This work was supported by regional program for invited researcher from the Région Poitou-Charentes, France.

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