3-Vinyl-2,5-dihydrofuran Derivatives via Enyne Metathesis

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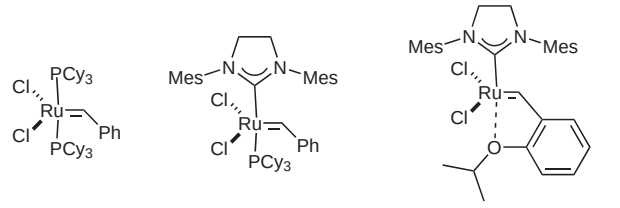
Abstract: Acyclic enynes having the alkyne moiety directly connected to the asymmetric carbon atom of an acetal were obtained in two steps. These reactive substrates were then subjected to ruthenium-catalyzed enyne metathesis to produce (5-ethoxy-4-vinyl-2,5-dihydrofuran-2-yl)methanol derivatives in racemic and enantiomerically pure form. These products are useful glycosyl donors for the preparation of d4T analogues.

Key words: enyne, metathesis, carbohydrate, cyclization, furan

Several nucleoside analogues have been shown to be highly effective as antiviral and antitumour agents. The 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns)[1] are effective nucleoside reverse transcriptase inhibitors (NRTIs), and form the most important class of compounds active against the human immunodeficiency virus (HIV), which causes AIDS. Among the NRTIs approved by the US Food and Drug Administration (US FDA) for the treatment of AIDS, the 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine)[2] is a very potent and selective inhibitor of HIV reverse transcriptase. In an attempt to investigate a wider structure–activity relationship for this type of NRTI, a number of d4N analogues 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[3,4] for the preparation of compounds **1**–**3** (Figure 1). The first one invoked the direct substitution of the 2′,3′-didehydro-2′,3′-dideoxynucleosides with organotin reagent[3a–c] or the formation of the tributyltinvinyl nucleoside followed by palladium-catalysed cross-coupling.[3a–c] The second one required convergent syntheses[3d–f,4] in which the final target functionalities in the 2′- and/or 3′-positions and π-character are present on the glycone precursor immediately prior to condensation by a base to effect nucleoside formation.

Metathesis[5] 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 (Figure 2).[5b] 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[6] and has been in use for several years. This work includes several examples which start from a stereochemically pure acyclic enyne as exemplified in carbohydrate chemistry.[7]



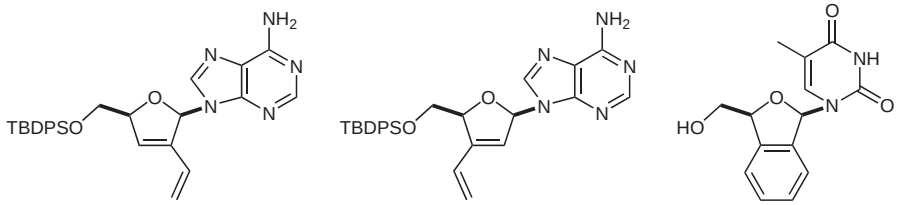
4 first-generation Grubbs catalyst

5 second-generation Grubbs catalyst

6 second-generation Hoveyda–Grubbs catalyst

Figure 2 Ruthenium catalysts for metathesis

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



1 **2** **3**

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

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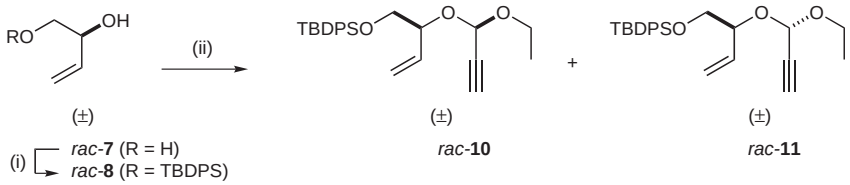
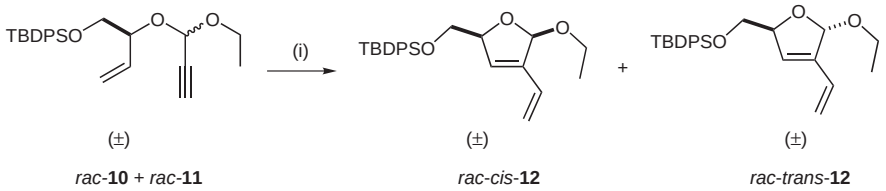


Scheme 1 *Reagents and conditions*: (i) TBDPSCl, imidazole, DMF, 20 °C, 24 h (80%); (ii) **9**, P_2O_5, $CHCl_3$, 45 °C, 2 d (65%).



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

Retrosynthetic analysis suggested that but-3-en-1,2-diol (*rac*-**7**) and 3,3-diethoxypropyne (**9**) were the most promising starting point. Compounds *rac*-**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 that, to the best of our knowledge, was not reported as substrate for RCEYM.

At first, the synthesis of racemic acyclic enynes and the optimization of the RCEYM were explored. The selective silylation of the primary hydroxyl group of the diol *rac*-**7** with *tert*-butyldiphenylsilyl chloride in DMF in the presence of imidazole afforded the corresponding ether *rac*-**8** in 80% yield. Then, compound *rac*-**8** was treated with the alkyne **9** and P_2O_5 in chloroform to afford the *tert*-butyldiphenylsilyl (TBDPS)-protected 2-(1-ethoxyprop-2-ynyloxy)-but-3-en-1-ol derivatives, *rac*-**10** and *rac*-**11** (1:1) in 65% yield (Scheme 1). It was notable that protection of the diol *rac*-**7**, either by selective benzoylation or silylation with *tert*-butyldimethylsilyl chloride, gave a species which was prone to partial migration of the protecting group during the subsequent acetalisation.

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

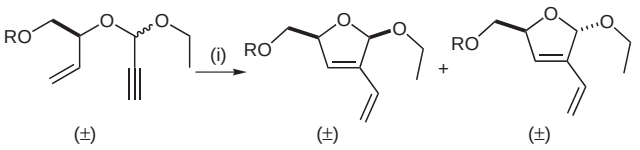
The RCEYM reaction, in the absence of an ethylene atmosphere, did afford the five-membered ring system but the yield was poor (Table 1, entry 1) and a large quantity of starting material was recovered. The presence of an ethylene atmosphere (Table 1, entries 2–4), under Mori's conditions,[8] favoured the RCEYM by ensuring a better turnover of the active catalyst with yne-then-ene mechanism[9] or ene-then-yne mechanism.[10] The use of a higher concentration of catalyst (10% vs. 3%) resulted in polymerisation and rather than enhancing the yield of the cyclic enynes *rac-cis*-**12** and *rac-trans*-**12** (Table 1, entries 2 and 3). Due to the presence of three oxygen atoms, addition of Ti(O*i*-Pr)$_4$ as Lewis acid using the protocol described by Fürstner,[11] gave a moderate 26% yield (39% based on recovered *rac*-**10** and *rac*-**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 target *rac-cis*-**12** and *rac-trans*-**12** but gave a polymerisation mixture.

To study the influence of the protecting group on the cyclization, substrates *rac*-**13**–*rac*-**20** were prepared. Under the conditions optimised for the acyclic enyne mixture *rac*-**10** and *rac*-**11** (Table 1, entry 2: 0.03 M, 3 mol% **5**, CH_2Cl_2, ethylene, 20 °C, 5 d), the dienes *rac*-**21**–*rac*-**24** were obtained in 27–50% yield (Scheme 3, Table 2).[12]

Table 1 RCEYM of Enynes *rac*-**10** and *rac*-**11** Using Ruthenium Carbenes **5** as Catalyst

Entry	Cat. (%)	Recovered yield (%) of *rac*-**10** and *rac*-**11**	Yield (%) of *rac-cis*-**12**	Yield (%) of *rac-trans*-**12**
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] *Reagents and conditions*: 0.03 M of *rac*-**10** and *rac*-**11**, **5**, CH_2Cl_2, 20 °C, 5 d.
[b] Under nitrogen pressure.
[c] Under ethylene pressure.
[d] Ti(O*i*-Pr)$_4$ (0.3 equiv).



rac-**13** + *rac*-**14** (R = H) *rac-cis*-**21** (R = H) *rac-trans*-**21** (R = H)
rac-**15** + *rac*-**16** (R = Tr) *rac-cis*-**22** (R = Tr) *rac-trans*-**22** (R = Tr)
rac-**17** + *rac*-**18** (R = Bz) *rac-cis*-**23** (R = Bz) *rac-trans*-**23** (R = Bz)
rac-**19** + *rac*-**20** (R = Ac) *rac-cis*-**24** (R = Ac) *rac-trans*-**24** (R = Ac)

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

Table 2 RCEYM of Enynes *rac*-**13** and *rac*-**20** Using Ruthenium Carbenes **5** as Catalyst[a]

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

[a] *Reagents and conditions*: 0.03 M, 3 mol% 5, CH_2Cl_2, 20 °C, 5 d under ethylene pressure.
[b] Obtained after flash chromatography.

As reported,[7a] unprotected alcohol *rac*-**13** and *rac*-**14** afforded the corresponding cyclic enynes *cis*-**21** and *trans*-**21** in rather poor yield (Table 2, entry 1). Among the different protecting groups, both the trityl and benzoyl derivatives *rac*-**15**–*rac*-**18** were obtained in better yields (Table 2, entries 2 and 3), similar to that for *rac*-**10** and *rac*-**11** (Table 1, entry 2). In our hands, the acetates *rac*-**19** and *rac*-**20** gave poor yields compared with those obtained with the corresponding benzoate *rac*-**17** and *rac*-**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 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.[13]

In order to prepare the 1,3-dienes 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 (**7**). After selective silylation of **7**, subsequent acetalisation and cyclisation afforded *cis*-**12**[14] and *trans*-**12**[15] with similar yields. Unfortunately, compounds *cis*-**12** and *trans*-**12** gave poor quality crystals thus precluding the determination of their configurations by X-ray crystallography. With the 2-*S* carbon configuration determined by the chiral diol **7**, the absolute configurations for the dienes *cis*-**12** and *trans*-**12** were assigned as 2*S*,5*R* and 2*S*,5*S*, respectively, on the basis of proton NMR NOE experiments. Thus, in compound *trans*-**12**, irradiation of H5 gave enhanced signals for protons of the methoxy group. The same was true for H5 when protons of the methoxy group were irradiated. Conversely, no NOE effect was observed for the same protons of compound *cis*-**12**. The study of the conformational analysis of the dienes *cis*-**12** and *trans*-**12** has been performed on the basis of ab initio gas-phase geometry optimisations using B3LYP 6-31G(d,p) in the Gaussian 03 program package by means of molecular modelling and confirmed this attribution (Figure 3). Thus, for the lowest energy conformer found for compound *trans*-**12** the proximity of H5 and H of the methyloxy group explained the NOE interaction observed (d = 2.942 Å).

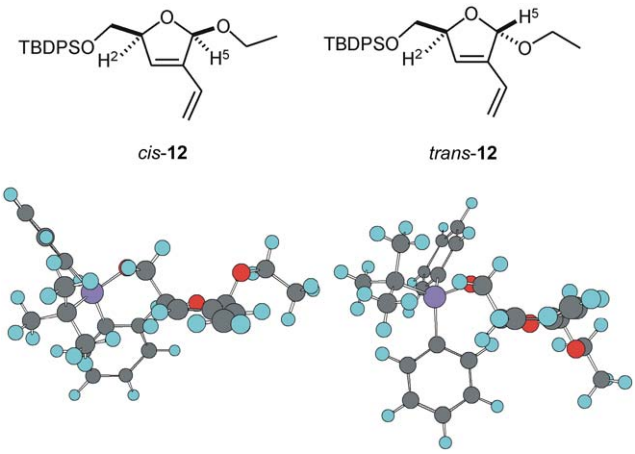


Figure 3 Target dienes *cis*-**12** and *trans*-**12** and the corresponding lowest energy conformers obtained on the basis of ab initio gas-phase geometry optimisations using B3LYP 6-31G(d,p) in the Gaussion 03 package

It was notable that the stereochemistry for compounds *cis*-**12** and *trans*-**12** was based on the magnitude of the coupling between the dihydrofuran ring protons. The NMR spectra on the 2,5-dihydrofuran system have been investigated for several compounds with one or no substituent in the dihydrofuran ring.[4,16] In each case, the larger cross ring coupling between H2 and H5 was assigned to the *trans*-configuration and the smaller to the *cis*-configuration. In agreement with the literature,[4,16] the observed coupling $J_{2,5}$ was 0 Hz for compound *cis*-**12** and 4.0 Hz for compound *trans*-**12**.

In summary, we have demonstrated a concise method using RCEYM reaction for the synthesis of 2,3-didehydro-2,3-dideoxyribo-D-ribofuranose derivatives as potential glycosyl donors for different glycosidation routes to new nucleosides. 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.

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(12) **RCEYM Reaction of *rac*-15 and *rac*-16 – Typical Procedure**
The ruthenium catalyst **5** (3% mol) was dissolved in CH_2Cl_2 (26 mL) and ethylene gas was passed through the solution for 20 min. The enyne mixture of *rac*-**15** and *rac*-**16** (400 mg, 0.98 mmol) in CH_2Cl_2 (12 mL) was then added and the mixture was stirred under ethylene at 20 °C during 5 d. The volatiles were eliminated under reduced pressure and the residue was purified by flash chromatography (5% EtOAc in hexane) to give *rac*-*cis*-**22** (100 mg, 25%) and *rac*-*trans*-**22** (100 mg, 25%) in order of fractions eluted.

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(14) Selected physico-chemical data for compound *cis*-**12**: R_f = 0.50 (5% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (m, 4 H, Ph), 7.45 (m, 6 H, Ph), 6.48 (dd, 1 H, *J* = 12, 18 Hz, =CH), 6.18 (s, 1 H, H^3), 5.87 (s, 1 H, H^5), 5.46 (d, 1 H, *J* = 18 Hz, =CH), 5.23 (d, 1 H, *J* = 12 Hz, =CH), 4.80 (m, 1 H, *J* = 1 Hz, H^2), 3.68 (m, 4 H, OCH_2CH_3, CH_2OSi), 1.23 (t, 3 H, *J* = 8 Hz, CH_3), 1.06 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_3 of *t*-Bu), 19.6 (Cq of *t*-Bu), 15.8 (CH_3) ppm. ESI-HRMS: *m/z* calcd [M + Na^+]: 431.2018; found: 431.2034.

(15) Selected physico-chemical data for compound *trans*-**12**: R_f = 0.20 (5% MeOH–CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 4 H, Ph), 7.38 (m, 6 H, Ph), 6.43 (m, 1 H, *J* = 12, 18Hz, =CH), 5.98 (s, 1 H, H^3), 5.96 (d, 1 H, *J* = 4 Hz, H^5), 5.43 (d, 1 H, *J* = 18, =CH), 5.24 (d, 1 H, *J* = 12 Hz, =CH), 4.90 (m, 1 H, H^2), 3.72 (m, 4 H, OCH_2CH_3, CH_2OSi), 1.26 (t, 3 H, *J* = 8 Hz, CH_3), 1.04 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_3 of *t*-Bu), 19.6 (Cq of *t*-Bu), 15.8 (CH_3). ESI-HRMS: *m/z* calcd [M + Na^+]: 431.2018; found: 431.2025.

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