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One-pot multicomponent synthesis of 2,3-dihydropyrans: new access to furanose-pyranose 1,3-*C*–*C*-linked-disaccharides

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ABSTRACT

An efficent synthesis of 2,3-dihydropyrans from different terminal alkynes was developed. The 2,3-dihydropyrans were obtained in a few minutes through a microwave-assisted multicomponent enyne cross-metathesis/hetero-Diels–Alder reaction. Starting from *C*-ethynyl-ribofuranose, a new multicomponent approach to furanose–pyranose 1,3-*C*–*C*-linked disaccharides was also developed.

Multicomponent reactions (MCRs) have attracted considerable attention since their initial report in 1850 by Strecker,[1a] who introduced a novel method for the synthesis of amino acids. In particular, multicomponent reactions that provide functionalized heterocyclic scaffolds in a single operation and in a stereodefined manner are of enormous importance in synthetic organic and medicinal chemistry.[1,2] Among heterocyclic compounds, 2,3-dihydropyrans represent an attractive challenge in organic synthesis being the key intermediates for the synthesis of many natural products.[3] Their olefin function particularly has great synthetic value for further functionalization to obtain polysubstituted tetrahydropyrans,[4] which constitute the structural core of most carbohydrates as well as many biologically important natural products and potential pharmaceutical agents.[5] Despite their potential importance to construct structurally complex molecules, the synthesis of dihydropyrans remains underutilized. Due to our previous experience in the field of enyne cross-metathesis (CM),[6] we reported herein a novel synthesis of 2,3-dihydropyrans having general structure **A** (Fig. 1) starting from different terminal alkynes through a microwave-assisted multicomponent enyne-CM/Hetero-Diels–Alder (HDA) reaction. These 2,3-dihydropyrans represent an attractive scaffold due to the presence of the ethoxy moiety at C1-anomeric center, which makes them the direct precursors of glycosides. As a consequence, we reasoned that starting from *C*-ethynyl-ribofuranose as the appropriate alkyne substrate, this multicomponent reaction could be a pratical and efficent approach in the synthesis of furanose-pyranose 1,3-*C*–*C*-linked-disaccharides having general structure **C** (Fig. 1). The furanose-pyranose *C*-disaccharides are compounds such as **B**, in which a methylene group replaces the exocyclic oxygen of the *O*-disaccharides. This substitution makes the *C*-disaccharides able to withstand enzymatic hydrolysis, and thus serve as a stable mimetic of the *O*-disaccharides.[7] There is evidence that they are capable of binding to proteins such as glycosyl hydrolases, glycosyl transferases, and lectins. Many routes to *C*-glycosides have been developed, and the applications to *C*-disaccharides and *C*-oligosaccharides are important extensions. However, only few routes to the synthesis of *C*-disaccharides such as **C** having the two rings directly connected have been reported so far.[8] The direct *C*-interglycosidic bond provides a unique structural motif, which may prove to be useful in controlling localized conformations and in affecting conformational properties, resulting also in compounds with new potential biological activities. In this work, an efficient synthesis of disaccharides having general structure **C** via the multicomponent enyne-CM/HDA reaction is presented.

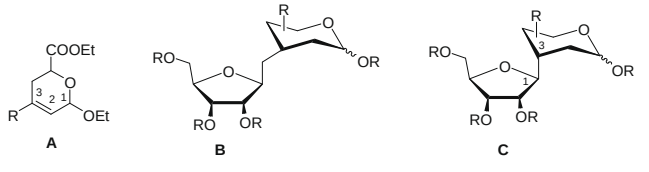

Figure 1.

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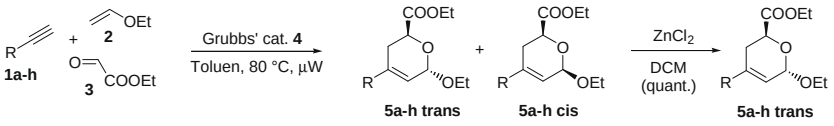


Scheme 1.

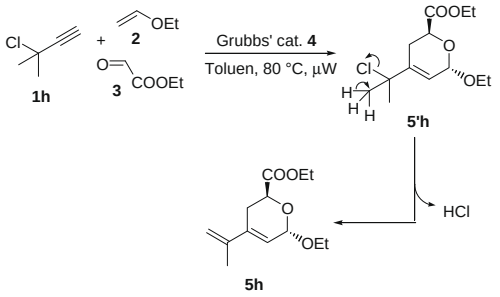
Table 1

Entry	Alkyne	R	Product	Trans/cis[a]	Yield[b] (%)
1	**1a**	TMS	**5a**	2:1	71
2	**1b**	$PMBOCH_2$	**5b**	2:1	51
3	**1c**	$TMSOCH_2$	**5c**	2:1	54
4	**1d**	Ph	**5d**	2:1	75
5	**1e**	$BocNHCH_2$	**5e**	2:1	62
6	**1f**	$BrCH_2$	**5f**	2:1	40
7	**1g**	$(EtO)_2CH$	**5g**	2:1	69
8	**1h**	$Cl(CH_3)_2C$[c]	**5h**[c]	2:1	45

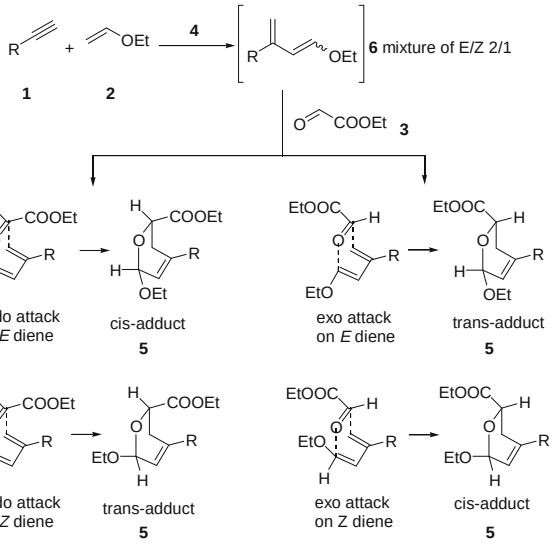
[a] Determined by ^1H NMR.
[b] Isolated yields were reported.
[c] Elimination of HCl was observed in the course of the reaction; hence, in compound **5h**, substituent R is $CH_2{=}CCH_3$.

Different alkynes **1a–h** were mixed together with ethyl vinyl ether (EVE) **2** and ethyl glyoxalate **3** in degassed toluene and in the presence of Grubbs' catalyst 2nd generation **4** and were irradiated under microwaves at 80 °C for 20 min affording the desired 2,3-dihydropyrans **5** as a mixture of cis/trans diastereoisomers (Scheme 1). The results are summarized in Table 1. All the dihydropyrans **5** were then equilibrated in the presence of $ZnCl_2$. The presence of a Lewis acid led to the formation of trans-**5** compounds as the only products in quantitative yield. The relative stereochemistry was assigned by NOESY experiments. When TMS-acetylene **1a** was reacted with EVE and glyoxalate (*entry 1*), a mixture of diastereoisomers **5a** was isolated in high yield in 2:1 trans/cis ratio. Alkynes **1b** and **1c** were also converted into adducts **5b** and **5c** in lower yields, but in the same trans/cis 2:1 ratio (*entries 2–3*). Compounds **1d–e** and **1g** were reacted with **2** and **3** under the same reaction conditions and led to products **5d–e** and **5g** in good yields (*entries 4, 5 and 7*). On the other hand, bromo-derivative **5f** was obtained only in 40% yield (*entry 6*). Attempts to improve the yield of **5f** failed. Finally, when alkyne **1h** was reacted with **2** and **3** under the same reaction condition, only the compound **5h** derived from the elimination of HCl was obtained (Scheme 2). It was supposed that derivative **5′h** was first formed from alkyne **1h**, and then converted into compound **5h** by elimination of HCl. The formation of the new conjugated double bond is the driving force for this elimination step.

The stereoselectivity results were unexpected and are in contrast with the data reported in the literature.[9] In fact the hetero Diels–Alder reactions generally proceed respecting the Alder rule and affording the cis-isomer (namely the *endo* product) as the



Scheme 2.

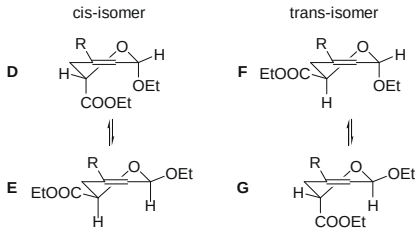


Scheme 3.

major compound. In our case. the trans-isomer was obtained as the major one, and its formation can be explained only if an *exo* attack is supposed. In fact, the first step of the reaction, the cross metathesis of alkyne **1** with EVE **2**, led always to a mixture of *E*/*Z*-diene **6** in a 2:1 ratio as previously described by us.[6b] Hence, if an *endo* attack happened on both *E*/*Z*-dienes **6,** a 2:1 cis/trans mixture of products **5** should have been expected. On the contrary, only an *exo* attack can explain the observed 2:1 trans/cis regioselectivity as illustrated in Scheme 3.

To confirm these assumptions, diene **6a** was synthesized separately as a 2:1 *E*/*Z* mixture[6b] and reacted with ethyl glyoxalate **3** under the standard conditions (rt for 12 h) also affording in this case **5a** as a 2/1 trans/cis mixture. The preference for the formation of trans-isomer could be explained if two factors are considered, namely the anomeric effect and the 1,3-diaxial interactions. It is known that dihydropyrans exist in rapidly inverting half-chair forms.

The anomeric effect favors the forms **D** and **F** over respectly **E** and **G** for both isomers (Scheme 4). However, form **D** is destabilized also by the additional 1,3-diaxal interactions between –OEt and –COOEt moieties which should lead cis-isomer to prefer a **E**-form counterbalancing the anomeric effect. On the other hand trans-isomer form **F** is the most stable since it is favored by both factors, the anomeric effect, and the pseudo-equatorial position of the ethyl-

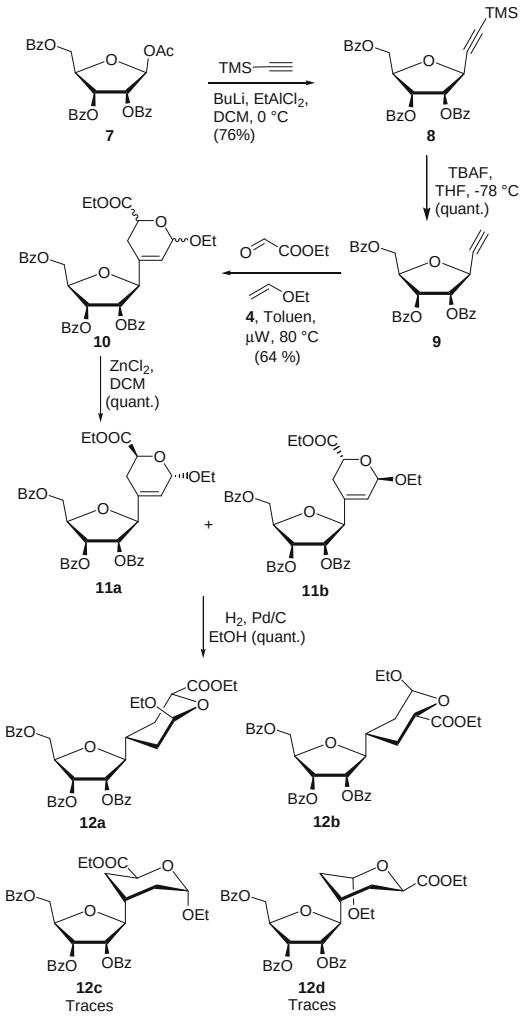


Scheme 4.

carboxylate moiety, which does not suffer of the 1,3-diaxal interactions.[10] Hence, these two factors can explain the stereoselectivity data observed for **5a–h**.[11]

We finally applied our multicomponent CM/HDA reaction to the synthesis of 1,3-*C*–*C*-linked furanose–pyranose disaccharides. We first focused on the synthesis of the precursor *C*-ethynyl-ribofuranose.

The β-D-ribofuranose **7** was reacted with trimethylsilylacetylene in the presence of $EtAlCl_2$ affording alkyne **8** as a 7:1 β/α mixture of diastereoisomers as revealed by ^1H NMR. Alkyne **8** was converted by TBAF desilylation[12] into precursor **9**, which was in turn reacted with EVE **2** and ethylglyoxalate **3** in the presence of **4** under microwave irradiation affording desired *C*-linked furanose-dihydropyrane **10** as a mixture of four diastereoisomers. Equilibration of **10** in the presence of $ZnCl_2$ led to a 1:1 mixture of two diastereoisomers **11a** and **11b** (61% yield over two steps) as revealed by HPLC–MS analysis.[13,14] Finally, hydrogenation of **11** led to desired 1,3-*C*–*C*-linked furanose–pyranose disaccharide **12** which was obtained as a mixture of the two diastereoisomers **12a** and **12b** having the furanose ring linked at the equatorial C3 position of pyranose as revealed by NMR and HPLC–MS analyses. (Scheme 5). Only traces of the two diastereoisomers **12c** and **12d** were detected by HPLC–MS analysis. Since the ethoxy moiety of **12a–d** is in the favored α-configuration due to the anomeric effect, the formation of **12c** and **12d** was disfavored by the 1,3-diaxal interactions of furanose ring and the ethoxy moiety itself.



Scheme 5.

In conclusion, an efficent synthesis of 2,3-dihydropyrans through a multicomponent enyne CM/HDA reaction was developed. Dihydropyrans **5** were obtained in high yields as mixture of trans/cis diastereoisomers.[13] Mechanistic explanation revealed that the cycloaddition step proceeds through an unusual *exo* attack. Finally, the multicomponent reaction was applied to the synthesis of furanose-pyranose *C*–*C*-linked disaccharide **12**, proving to be a very effective and versatile approach in the preparation of biologically interesting scaffolds as well as building blocks in carbohydrate chemistry. Synthetic application of this novel reaction is under investigation.

Acknowledgment

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10. It is known that the magnitude of anomeric effects related also to the nature of the alkoxy group. This might be the reason why in some cases HDA reaction carried out on similar substrates,[9a,b] but using butylvinylether as dienophile, led to endo adduct as the major product.
11. General procedure for the synthesis of **5.**Alkyne **1a–h** (1.0 mmol), ethylvinyl ether **2** (9.0 mmol), ethyl glyoxalate **3** (2.0 mmol), and Grubbs' catalyst **4** (0.1 mmol) were suspended in degassed toluene (4.0 mL) in a 10-mL glass vial equipped with a small magnetic stirring bar. The mixture was irradiated under microwaves for 2 × 10 minutes at 80 °C, using an irradiation power of 300 W. Microwave irradiations were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The mixture was then poured into a solution of $NaHCO_3$ (20 mL) and stirred for 10 minutes. The mixture was then extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography (SiO_2), using 1:2 Et_2O/hexanes as the eluent to yield the 2,3-dihydropyrans **5a–h** (as a 1:2 mixture of cis/trans-isomers) as tan oils.
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13. Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (methanol/water 70:30, flow rate 0.8 mL/min, UV-254 nm).
14. Characterization of **11** (1:1 mixture of diastereoisomers **11a** + **11b**; signals of both isomers are reported).^1H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.99 (m, 4H), 7.90–7.85 (m, 8H), 7.48–7.29 (m, 18H), 5.92–5.91 (m, 2H), 5.61 (m, 1H), 5.57 (m, 1H), 5.48 (m, 2H), 5.04–5.00 (m, 2H), 4.69–4.63 (m, 4H), 4.53–4.47 (m, 6H), 4.15–4.05 (m, 4H), 3.77 (m, 2H), 3.47 (m, 2H), 2.49–2.22 (m, 4H), 1.16 (m, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 166.2, 165.3, 165.2, 145.1, 136.1, 133.4, 133.2, 129.7, 129.5, 129.0, 128.4, 123.5, 122.0, 94.6, 94.5, 83.0, 82.7, 79.9, 79.2, 74.1, 73.4, 72.4, 72.0, 66.0, 65.9, 64.0, 63.9, 63.8, 63.7, 61.1, 29.6, 29.3, 15.3, 15.2, 14.0 ppm. MS (ESI): m/z = 644.9 [M+H], 666.9 [M+Na$^+$]. Elemental Anal. Calcd for $C_{36}H_{36}O_{11}$: C, 67.07; H, 5.63. Found. C, 67.32; H, 5.89.