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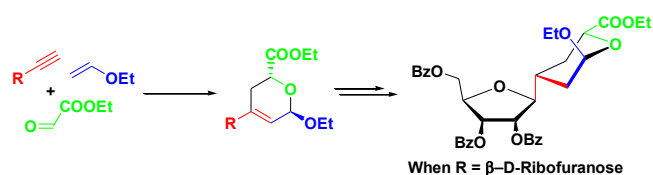
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One Pot Multicomponent Synthesis of 2,3-Dihydropyrans: New Access to furanose-pyranose 1,3-C-C-linked-Disaccharides.

Daniele Castagnolo, Lorenzo Botta and Maurizio Botta



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

Keywords: Enyne metathesis, Hetero Diels-Alder, Multicomponent Reaction, Dihydropyrans, Disaccharide.



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One Pot Multicomponent Synthesis of 2,3-Dihydropyrans: New Access to furanose-pyranose 1,3-C-C-linked-Disaccharides.

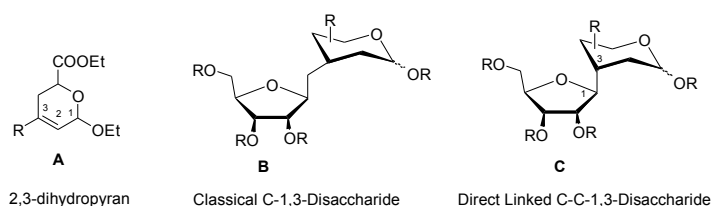
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Abstract— An efficient synthesis of 2,3-dihydropyrans from different terminal alkynes was developed. The 2,3-dihydropyrans were obtained in a few minutes through a microwave assisted multicomponent enyne cross-metathesis/heteroDiels-Alder reaction. Starting from C-ethynyl-ribofuranose a new multicomponent approach to furanose-pyranose 1,3-C-C-linked disaccharides was also developed. © 2013 Elsevier Science. All rights reserved

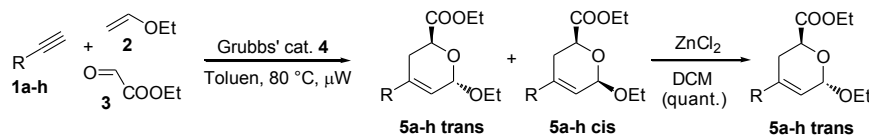
Multicomponent reactions (MCRs) have attracted considerable attention since their initial report in 1850 by Strecker,^{1a} who introduced a novel method for the synthesis of amino acids. In particular, multicomponent reactions that provide functionalized heterocyclic scaffolds in a single operation and 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** (Figure 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 centre 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 practical and efficient approach in the synthesis of furanose-pyranose 1,3-C-C-linked-disaccharides having general structure **C** (Figure 1). The furanose-pyranose C-disaccharides are compounds such **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 **C** having the two rings directly connected were 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.**

Different alkynes **1a-h** were mixed together with ethyl vinyl ether (EVE) **2** and ethyl glyoxalate **3** in degassed toluene and in

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Scheme 1.

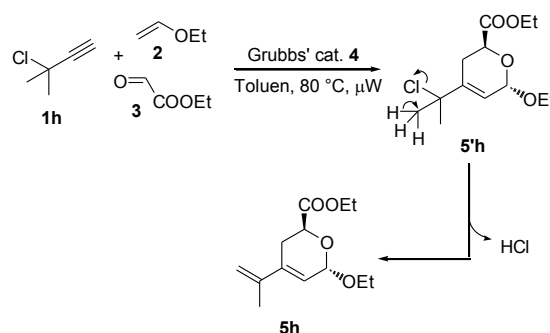
Table 1.

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) ₂ CH	5g	2 : 1	69
8	1h	Cl(CH ₂) ₂ C ^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 CH₂=CCH₃.

the presence of Grubbs' catalyst 2nd generation **4** and irradiated under microwaves at 80 °C for 20 minutes 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 ZnCl₂. The presence of a Lewis acid led to the formation in quantitative yield of trans-**5** compounds as the only products. 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

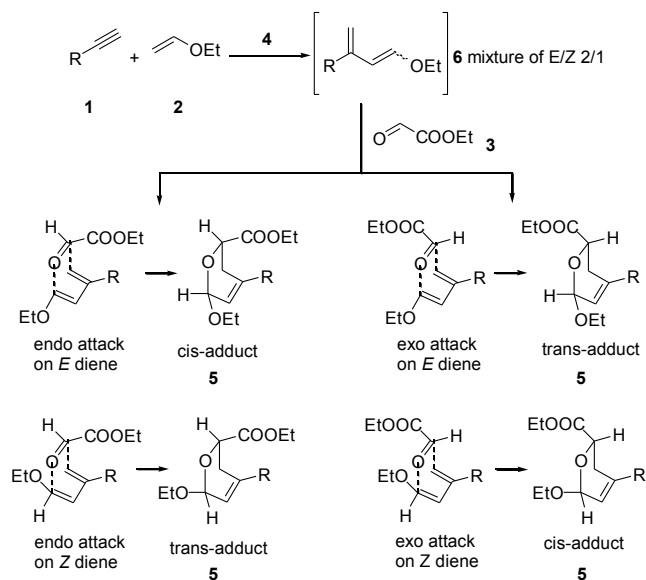
formed from alkyne **1h** and then converted into compound **5h** by elimination of HCl. The formation of the new conjugated double bond is the driving force for this elimination step.



Scheme 2.

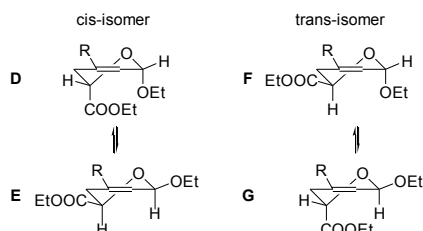
The stereoselectivity results were unexpected and are in contrast with data reported in the literature.⁹ In fact the hetero Diels Alder reactions generally proceed respecting the Alder rule and affording the cis isomer (namely the *endo* product) as the major compound. In our case the trans isomer was 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.



Scheme 3.

To confirm these assumptions, diene **6a** was synthesised separately as a 2:1 *E/Z* mixture^{6b} and reacted with ethyl glyoxalate **3** under standard conditions (rt for 12 hours) affording also 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.

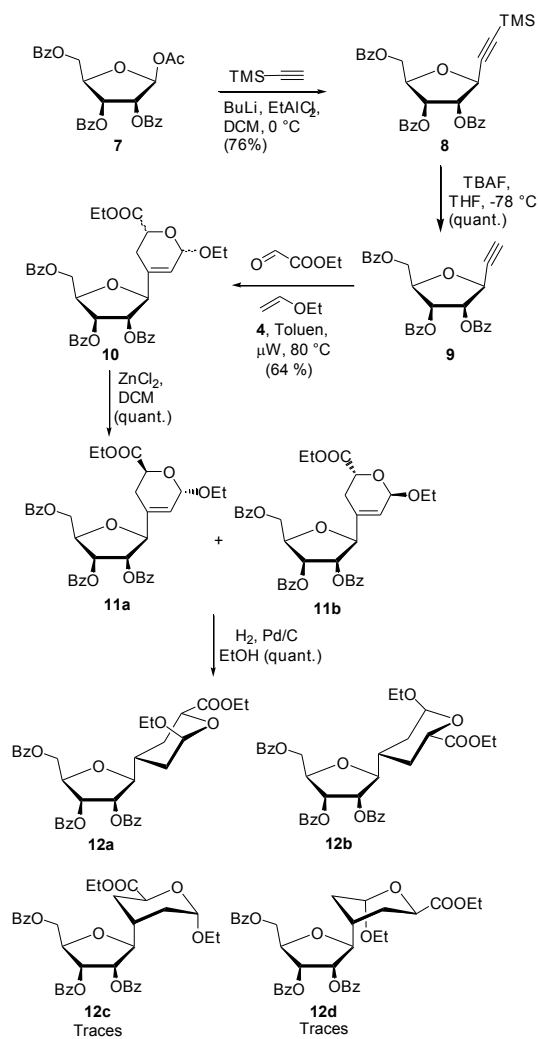


Scheme 4.

The anomeric effect favours the forms **D** and **F** over respectively **E** and **G** for both isomers (Scheme 4). However, form **D** is destabilized also by the additional 1,3-diaxial 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 favoured by both factors, the anomeric effect and the pseudo-equatorial position of the ethylcarboxylate moiety which does not suffer of the 1,3-diaxial 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.



Scheme 5.

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 desilylation¹² 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-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 favoured α -configuration due to the anomeric effect, the formation of **12c** and **12d** was disfavoured by the 1,3-diaxial interactions of furanose ring and the ethoxy moiety itself.

In conclusion, an efficient 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 biological interesting scaffolds as well as building blocks in carbohydrate chemistry. Synthetic application of this novel reaction are under investigation.

Acknowledgments

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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 x 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 NaHCO₃ (20 mL) and stirred for 10 minutes. The mixture was then extracted with Et₂O (2 x 10 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were purified by flash column chromatography (SiO₂) using 1:2 Et₂O/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 0.8mL/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, CDCl₃) 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. ¹³C-NMR (100 MHz, CDCl₃) 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 analysis for C₃₆H₃₆O₁₁: Calcd. C, 67.07; H, 5.63. Found. C, 67.32; H, 5.89.

