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Intermolecular Twofold Carbopalladation/Cyclization Sequence to Access Chromans and Isochromans from Carbohydrates

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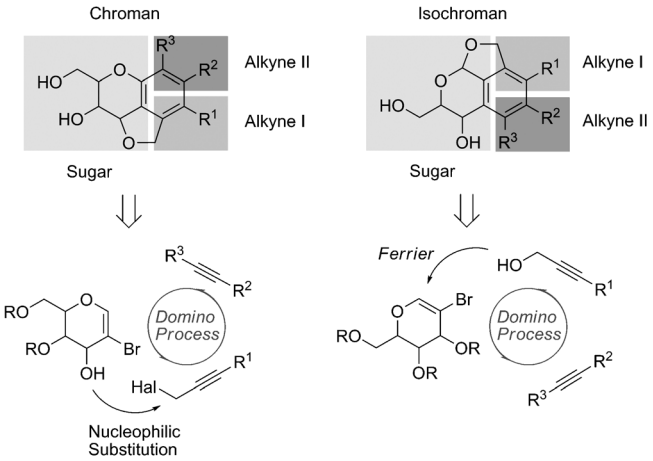
Dedicated to Professor Rolf Gleiter on the occasion of his 75th birthday

Due to vanishing petrochemical resources, the quest to find new pathways for efficient chemical synthesis from renewable feedstock has been intensified.[1] So far, major efforts have been achieved in the preparation of non-petroleum derived chemicals such as furfural from hemicellulose-rich biomass.[2] Advances using terpenes such as linalool as a starting material for alternative high-density fuels were also effectuated.[3] For the last decade the spotlight in green chemistry has been on biomass-derived energy sources and the development of novel and more efficient catalytic processes.[4] However, almost all fine chemicals are still derived from fossil resources. According to the technology roadmap of the U.S. Department of Energy for plant-based renewable resources in 1999, at least 10% of the fine chemicals should be based on non-fossil origin by 2020.[5] Recently, a report was published that makes use of terpene feedstock by converting it into polyketide architectures[6] and our group disclosed metal-catalyzed synthetic routes to spiroketals,[7] *C*-glycosides,[8] as well as chroman-type structures[9] starting from carbohydrates.

In contrast to our earlier studies, which showed limitations with respect to the substitution pattern due to the use of an intramolecular domino reaction,[9,10] our results for a much more flexible intermolecular variant are described in this report. The general idea is depicted in Scheme 1. In contrast to many other chroman and isochroman syntheses, which are confined to the annelation of the pyran moiety to the benzene ring,[11] our approach enables a synthesis of the aromatic core through a domino sequence consisting of a twofold carbopalladation followed by subsequent cyclization.[12,13,14]



Scheme 1. Retrosynthetic analysis of highly substituted chromans (left) and isochromans (right) leading to bromoglycals and two alkyne units.

The starting material is a 2-bromoglycal that can be easily derived from the native monosaccharide in several steps.[10,15] This six-membered ring can be employed either to give chroman- or isochroman-type structures. In the former case, an alkynyl chain is attached to C3, in the latter to C1. Propargylic bromides are utilized for chroman synthesis, whereas the corresponding propargylic alcohols are employed in a Ferrier reaction[16] to afford the starting materials for isochromans. The latter transformation consists of a Lewis acid-catalyzed S_N2' reaction of peracetylated or perbenzoylated bromoglycals resulting in a shift of the C=C double bond in the six-membered ring to give the corresponding 2-bromoglycals with an alkyne chain attached to the anomeric position. In all cases, the α anomer was the major product; the β anomer was detected only in minor amount ($\alpha/\beta = \approx 8:1$) and could easily be separated by column chromatography.

During our ongoing efforts on the intermolecular assembly of chromans and isochromans, we screened various palladium sources, ligands, bases, ratios of starting materials, but also the concentration of the reaction mixture. The catalysts $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(dppf)Cl_2$ were employed; however, improved catalytic yields were observed when Fu's salt ($[(t\mathrm{Bu})_3\mathrm{PH}]BF_4$) was added to the reaction mixture pro-

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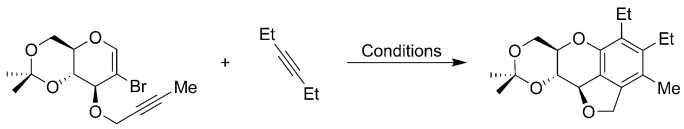
viding a sterically hindered ligand with a strongly σ-donating phosphorus atom.[17] This ligand proved to be superior to the previously used triphenylphosphine ligands. In our study, we finally found the equivalents of alkyne **2a** and the concentration of the reaction mixture to be the predominant effects on the yield of the reaction. The best results were accomplished with a 20-fold excess of alkyne **2a**, but also a lower amount of alkyne **2a** provided the desired product (Table 1). A lower concentration also proved to be beneficial. In highly concentrated reaction mixtures even traces of the respective cyclooctatetraene derivatives were found. With an optimized catalytic system in hand (DMF/MeCN/NMP = 8:8:1; $Pd(PPh_3)_4$, $[(tBu)_3PH]BF_4$, Cs_2CO_3 or HN(iPr)$_2$ as the base, $c = 10\ mmol\,L^{-1}$, and microwave irradiation), we investigated the scope of the intermolecular domino process.

Table 1. Optimization of the Pd-catalyzed intermolecular domino process.[a]



1b **2a** **3e**

	Catalyst [10 mol %]	Ligand [20 mol %]	Base [4.0 equiv]	**2a** [equiv]	c (**1b**) [mmol L^{-1}]	Yield [%]
1	$Pd(OAc)_2$	PPh_3	NBu_3	2.0	50	0
2	$Pd(PPh_3)_4$	–	HN(iPr)$_2$	3.0	35	23
3	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	HN(iPr)$_2$	10.0	35	36
4	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	HN(iPr)$_2$	20.0	35	44
5	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	35	49
6	$Pd(dppf)Cl_2$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	35	14
7	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	K_2CO_3	20.0	35	37
8	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	CsF	20.0	35	50
9	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	60	43
10	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	20	54
11	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	10	66
12	$Pd(PPh_3)_4$	P(tBu)$_3$[c]	Cs_2CO_3	20.0	10	65[b]

[a] General conditions: DMF/MeCN/NMP = 8:8:1, 2 h, 120 °C, microwave irradiation (mw). [b] 15 h, 120 °C, no microwave irradiation. [c] $[(tBu)_3PH]BF_4$ was employed.

2-Bromoglycals derived from glucose and galactose with different alkynes attached to the sugar core were investigated (alkyne I with R = H, Me, Ph). As coupling partners, internal and terminal alkynes (alkyne II) such as 3-hexyne (**2a**), bis(trimethylsilyl)acetylene (**2b**), tolane (**2c**) and (trimethylsilyl)acetylene (**2d**) were employed (Table 2).[18]

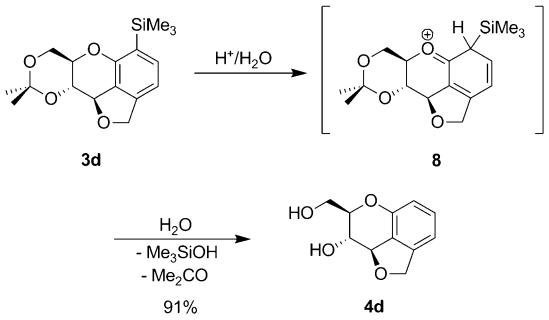
Notably, even highly sterically encumbered alkynes II such as **2b** and **2c** were successfully converted. Alkynes I with a sterically demanding substituent were found to be difficult substrates in the intermolecular domino reaction. With 3-hexyne we were able to isolate the desired product **3g** in only low yield (14 %); using the same substrate and tolane as alkyne II product formation could not be observed.

We suppose that the domino sequence is initiated by an oxidative addition of the Pd^0 into the C–Br bond of the respective bromoglycal. Intramolecular carbopalladation of the adjacent alkyne unit gives a diene system that reacts in a second intermolecular carbopalladation with alkyne II to afford a 1,3,5-triene. The final cyclization step generating the benzene unit may be regarded either as disrotatory electrocyclic 6π-electron ring-closure or as C–H activation (for a detailed reaction mechanism, see Supporting Information).

Only (trimethylsilyl)acetylene (**2d**) was tolerated as unsymmetrically substituted alkyne of type II. Notably, only regioisomer **3d** was found in moderate yield whereas the other regioisomer could not be detected. The use of phenylacetylene or 1-hexyne led only to traces of the desired products. The intermolecular carbopalladation occurs at the less hindered position of the terminal alkyne; thus, the silyl moiety is located adjacent to the pyran ring. Experiments with electron-poor alkynes such as acetylene carboxylic esters proved to be unsuccessful illustrating the electrophilic attack of the Pd species to the triple bond.

Similar experiments were performed with 1-alkynyl-substituted 2-bromoglycals **5a–5c**. The respective isochromans **6a–6e** were obtained in yields of 40–56 % (Table 3).

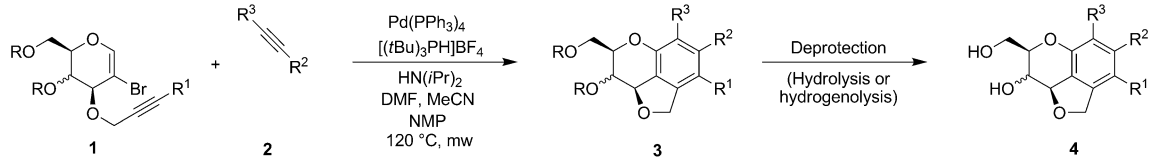
Deprotection reactions provided chromans and isochromans with free hydroxyls. Isopropylidene was removed by the action of acid and benzylidene protecting groups were cleaved under acidic conditions or by hydrogenolysis (Table 2). The acidic cleavage of isopropylidene also resulted in the removal of the TMS group adjacent to the pyran moiety in **3b** and **3d**. We rationalized this behavior by a stabilization of a positive charge in the *ortho* position (compound **8**) due to the neighboring oxygen atom of the pyran ring (Scheme 2). In this way, the chroman **4d** could be obtained in 91 % yield.



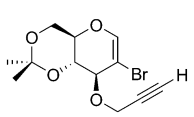
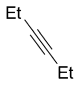
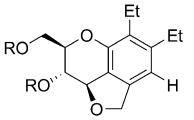
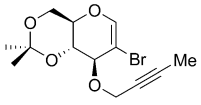
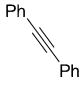
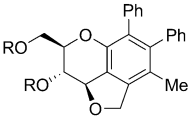
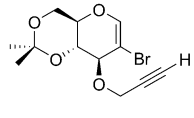
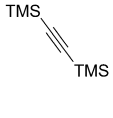
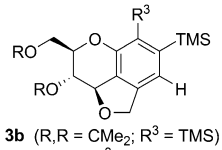
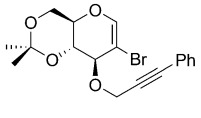
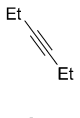
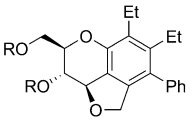
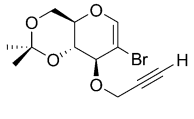
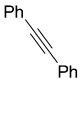
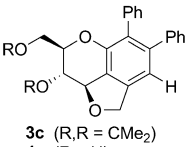
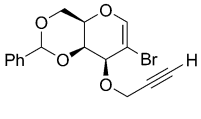
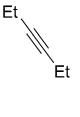
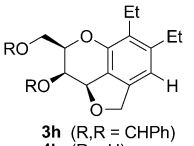
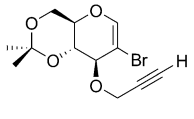
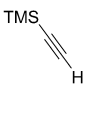
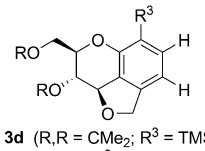
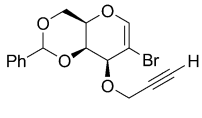
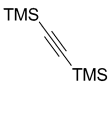
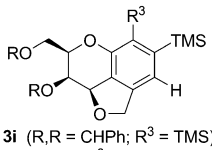
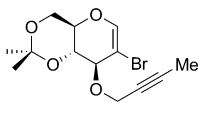
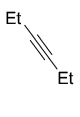
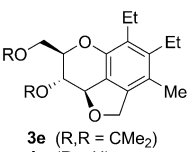
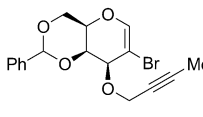
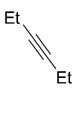
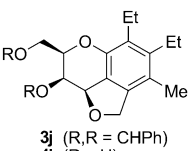
Scheme 2. Acidic cleavage of the TMS group adjacent to the pyran moiety leading to chroman **4d**.

The saponification of the ester groups in isochromans **6a–6e** proved not to be possible with the commonly employed sodium methoxide in methanol. The strongly basic conditions also led to the abstraction of the slightly acidic anomeric proton resulting in decomposition of the desired product. Milder conditions utilizing potassium carbonate gave rise to the corresponding free hydroxyl groups in good to excellent yields (48–92 %). In some cases, such as in **7a** and **7e**, a

Table 2. Monoalkynylated 2-bromoglycals **1a–1e**, alkynes II **2a–2d**, chromans **3a–3j**, deprotected chromans **4a–4j** and corresponding yields of the domino sequence and the deprotection.



1 2 3 4

Starting materials	Product	Yield [%][a]	Starting materials	Product	Yield [%][a]
 **1a** +  **2a**	 **3a** (R,R = CMe_2) **4a** (R = H)	57 72	 **1b** +  **2c**	 **3f** (R,R = CMe_2) **4f** (R = H)	27 100
 **1a** +  **2b**	 **3b** (R,R = CMe_2; R^3 = TMS) **4b** (R = H; R^3 = H)	57 98	 **1c** +  **2a**	 **3g** (R,R = CMe_2)	14 –
 **1a** +  **2c**	 **3c** (R,R = CMe_2) **4c** (R = H)	25 79	 **1d** +  **2a**	 **3h** (R,R = CHPh) **4h** (R = H)	65 38
 **1a** +  **2d**	 **3d** (R,R = CMe_2; R^3 = TMS) **4d** (R = H; R^3 = H)	27 91	 **1d** +  **2b**	 **3i** (R,R = CHPh; R^3 = TMS) **4i** (R = H; R^3 = H)	69 78
 **1b** +  **2a**	 **3e** (R,R = CMe_2) **4e** (R = H)	66 73	 **1e** +  **2a**	 **3j** (R,R = CHPh) **4j** (R = H)	60 88

[a] The first value is the yield of the domino reaction; the second value is the yield of the deprotection.

slight anomeric isomerization was noticed ($\alpha/\beta = \approx 10:1$ and $\alpha/\beta = \approx 4:1$, respectively, Table 3).

The structure of deprotected isochroman **7d** could also be confirmed by X-ray crystallography. The absolute configuration of the anomeric stereocenter that was obtained by the diastereoselective Ferrier reaction was approved. In addition, it revealed a strongly distorted conformation of the corresponding pyran unit (Figure 1).

In conclusion, we have developed a convenient and general entry to carbohydrate-based chromans and isochromans by using an intermolecular Pd-catalyzed domino reaction in which three C–C bonds and two rings are formed. Starting materials are easily accessible monoalkynyl substituted 2-bromoglycals and terminal or internal alkynes being added in excess to the reaction mixture. We believe that the structural diversity of these carbohydrate derivatives will be useful in exploring differential avidity properties with chroman- and isochroman-binding enzymes.

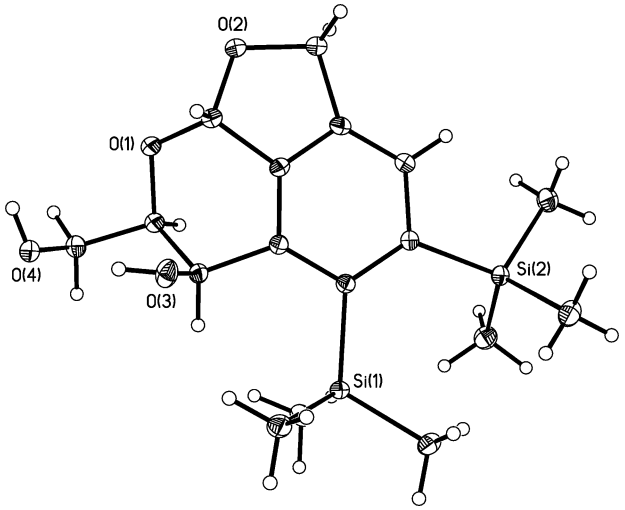
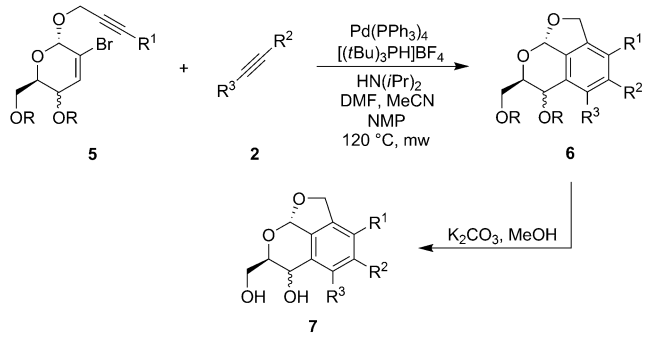
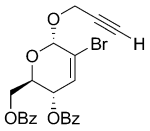
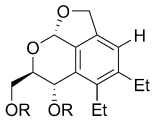
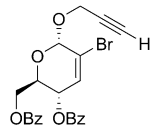
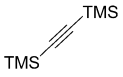
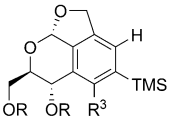
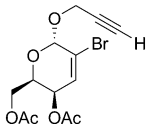
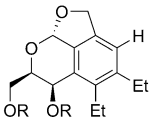
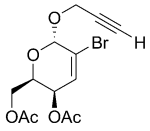
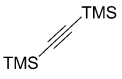
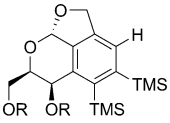
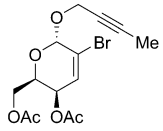
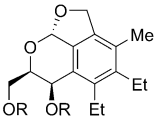


Figure 1. The structure of deprotected isochroman **7d**, depicted with anisotropic displacement parameters at the 50% probability level.

Table 3. Monoalkynylated 2-bromoglycals **5a–5c**, alkynes II **2a–2b**, isochromans **6a–6e**, deprotected isochromans **7a–7e** and corresponding yields of the domino sequence and the deprotection.



5 2 6 7

Starting materials		Product	Yield [%][a]
 **5a**	 **2a**	 **6a** (R = Bz) **7a** (R = H)	40 81[b]
 **5a**	 **2b**	 **6b** (R = Bz; R^3 = TMS) **7b** (R = H; R^3 = H)	54 84
 **5b**	 **2a**	 **6c** (R = Ac) **7c** (R = H)	40 78
 **5b**	 **2b**	 **6d** (R = Ac) **7d** (R = H)	52 92
 **5c**	 **2a**	 **6e** (R = Ac) **7e** (R = H)	56 48[c]

[a] The first value is the yield of the domino reaction; the second value is the yield of the deprotection. [b] Partial isomerization of the anomeric stereocenter ($\alpha/\beta = \approx 10:1$). [c] Partial decomposition and isomerization of the anomeric stereocenter ($\alpha/\beta = \approx 4:1$).

Experimental Section

General procedure: The alkynylated bromoglycal **1** or **5** (0.20 mmol, 1.0 equiv), respectively, and alkyne II (4.0 mmol, 20.0 equiv) were dissolved in a mixture of DMF/MeCN/NMP (9.0 mL, 9.0 mL, 1.2 mL). $Pd(PPh_3)_4$ (20 μmol, 0.1 equiv), $[(tBu)_3PH]BF_4$ (40 μmol, 0.2 equiv) and diisopropylamine or Cs_2CO_3 (0.80 mmol, 4.0 equiv) were added. The reaction was stirred in a microwave reactor for 2 h at 120 °C. The absorption level was set as "very high" and the prestirring time at 10 s. The reaction was stopped by the addition of brine. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the residue was purified by silica gel column chromatography (pentane/EtOAc) to afford chroman **3** or isochroman **6**, respectively, as a colorless to slightly yellow solid.

For the X-ray crystal structure of **7d** a single crystal was mounted with inert oil on a glass fiber.[19a] The data were collected at 100 K on a Bruker Smart Apex II with mirror optics. Data reduction was obtained from SAINT,[19b] and an empirical absorption correction with SADABS[19c] was applied. The structure was solved by direct methods (SHELXS-97)[19d] and refined by full-matrix least-squares methods against F^2 (SHELXL-97).[19d] The absolute structures was successfully determined by the Flack x parameter (zero within 3 esd's) during the refinement.[19e] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre.[20]

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Keywords: carbohydrates · chromans · cyclization · domino reactions · palladium

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[20] The crystal data and experimental details for the X-ray measurements are listed in the Supporting Information. CCDC-830678 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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