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Hybrids of sugars and aromatics: A Pd-catalyzed modular approach to chromans and isochromans

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ABSTRACT

Herein we describe the synthesis of highly substituted chromans and isochromans using carbohydrates as starting materials. The key step of our synthetic approach is the annelation of the benzene moiety via a highly efficient Pd-catalyzed domino reaction. This powerful approach led to a small library of highly substituted chromans and isochromans by making use of a variety of different diynes and bromoglycals. We investigated several Pd-catalysts in order to improve the yields and to enlarge the scope of the domino reaction. Furthermore, we elucidated the mechanistic picture of the reaction with isotope-labelling experiments. Most probably the reaction proceeds via an oxidative addition followed by two carbopalladation steps and a final cyclization reaction.

1. Introduction

Chroman and isochroman motifs are widespread elements in natural products and have attracted much attention from a wide area of science including natural product chemistry as well as medicinal and synthetic organic chemistry. Chroman-derived natural products possess a broad array of biological activities such as antimicrobial, antiviral, antiproliferative, sex pheromone, antitumor and central nervous system activity.[1] Probably the most prominent example of such a biologically active compound with a chroman core is the vitamin E family [α-tocopherol (**1**)] (Fig. 1), which consists of eight naturally occurring compounds differing in the aliphatic side chain and the residues of the aromatic core leading to varying biological activity.[2] A representative example of a synthetic pharmaceutical agent with a chroman scaffold is cromakalin (**2**), a potent activator of ATP-dependent potassium channels that is known to induce apoptosis.[3] Also a plethora of natural products show the chroman core such as the potent anti-HIV agent daurichromenic acid (**3**), which was isolated from *Rhododendron dauricum* (Fig. 1). Its remarkable EC_{50} value of 5.67 ng/mL and the therapeutic index (TI) of 3710 encouraged a lot of synthetic organic chemists to establish a total synthesis.[4]

Among the numerous different synthetic strategies developed for the synthesis of chromans, chromens, isochromans and isochromens asymmetric transition metal- and organocatalyzed coupling reactions especially stand out.[5] Three of the most straightforward syntheses to build up the chroman framework are highlighted as follows.

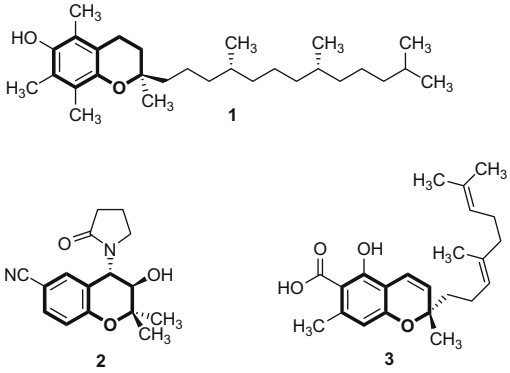

Figure 1. Examples for chroman systems with biological activity. The chroman core is shown in bold.

The first example deals with an organocatalytic domino oxa-Michael-Michael reaction.[6] The reaction between 2-hydroxy cinnamaldehyde **4** and a nitroolefin **5** discloses access to highly functionalized chromans containing multiple stereogenic centers (Scheme 1). As catalyst the chiral diphenylprolinol TMS ether (**6**) revealed to be the one of choice.

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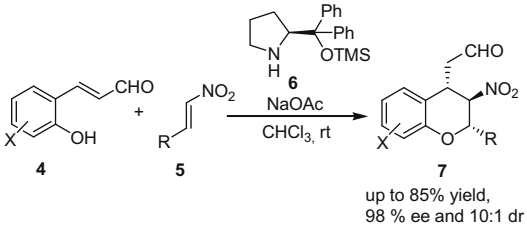
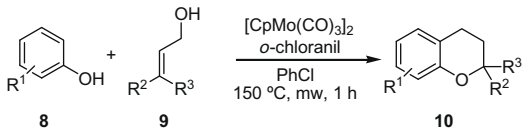


Scheme 1. Organocatalytic oxa-Michael–Michael domino reaction.

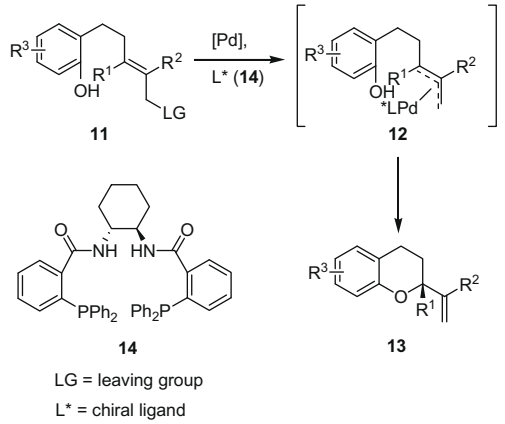
On the basis of the biosynthetic mechanism assembling the chroman skeleton that leads via a Friedel–Crafts-type allylation of a phenolic core with an allylic pyrophosphate and subsequent cyclization of the resulting O-allylated intermediate, one may assume that the cyclocoupling of phenols with allylic alcohols is a viable method to access chromans. Indeed, Yamamoto et al. reported a formal [3+3]-cyclocoupling catalyzed by a molybdenum complex and chloranil leading to various chromans in moderate to good yields (Scheme 2).[7]

At the beginning of the century the groups of Trost, Helmchen and Pfaltz have demonstrated that Pd-catalyzed asymmetric allylic alkylations (AAA) are powerful tools in organic synthesis.[8] Especially Trost et al. elucidated an *inter*molecular AAA of phenols with allyl carbonates for the synthesis of chiral chromans (Scheme 3). Unfortunately this approach lacks two aspects, namely the regio- and enantioselectivity. To address these issues an *intra*molecular AAA of phenol allyl carbonates was used. Best results were achieved by utilizing the Trost ligand **14**.

In recent years the design and the synthesis of new molecular platforms which are hybrids of two scaffolds have attracted much attention.[9] Chimeric frameworks such as **15** (Fig. 2) that are hybrids of benzodiazepins and β-D-glucopyranose have been synthesized to explore receptor space accessible neither to pyranoside nor to benzodiazepine scaffolds when applied individually. The continuing efforts in this field of medicinal chemistry should gain much importance in the near future due to commonly appearing resistances of bacteria against a variety of pharmaceuticals.



Scheme 2. [3+3]-Cyclocoupling of phenols with allylic alcohol.



Scheme 3. Intramolecular allylic alkylation (AAA) to access chiral chromans of type **13**.

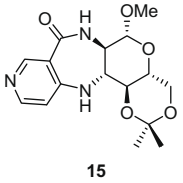
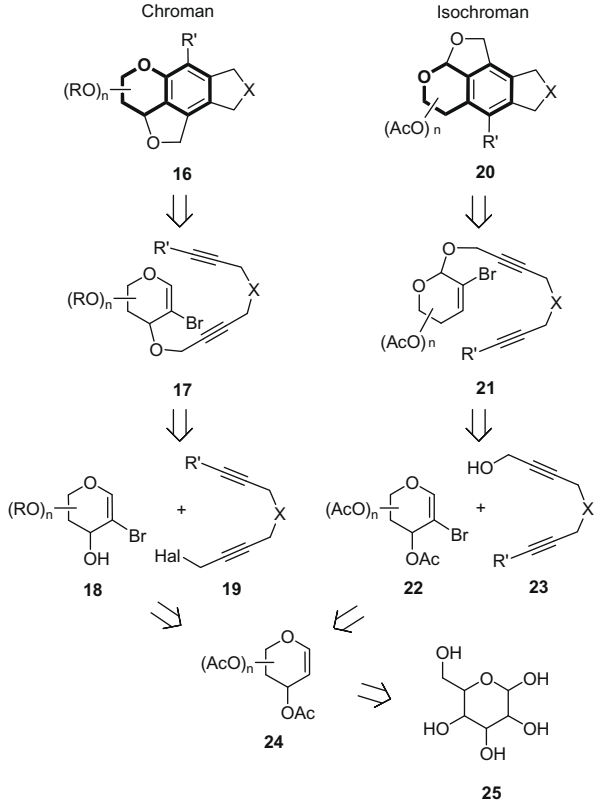


Figure 2. Hybrid **15** of sugar and benzodiazepine.

As part of our ongoing studies on the facile modification of carbohydrates,[10] we gained interest in the synthesis of carbohydrate-derived chromans. We envisioned high structural diversity due to the sugar moiety bearing a high density of functional groups and chiral information. Furthermore, we anticipated biological activity against several protein targets on accounts of earlier studies, which were able to demonstrate that aromatic systems grafted to saccharides show significant carbohydrate–protein interactions.[11]

2. Results and discussion

Most of the previous chroman and isochroman syntheses annelate a pyrane moiety to an aromatic system. In contrast, our approach creates the benzene moiety starting from a pyrane derivative. In this paper, we report the full details of this highly efficient procedure to access chromans and isochromans of type **16** and **20** by utilizing an appropriately substituted 2-bromoglycal (**17** or **21**, respectively) as starting material of the domino reaction (Scheme 4).[12] Our method allows the facile introduction of defined stereocenters on the pyrane unit. The latter is easily accessible from monosaccharides of type **25** in a few steps. For the creation of the benzene moiety an intramolecular Pd-catalyzed domino



Scheme 4. Retrosynthetic analysis of chromans **16** and isochromans **20** leading to monosaccharides of type **25** as starting materials.

reaction[13] was used that employs a diyne chain attached to the pyrane core. Such a procedure allows the synthesis of heavily functionalized chroman and isochroman derivatives that are difficult to obtain by other routes. The target molecules may be regarded as hybrids between carbohydrates and aromatic compounds.

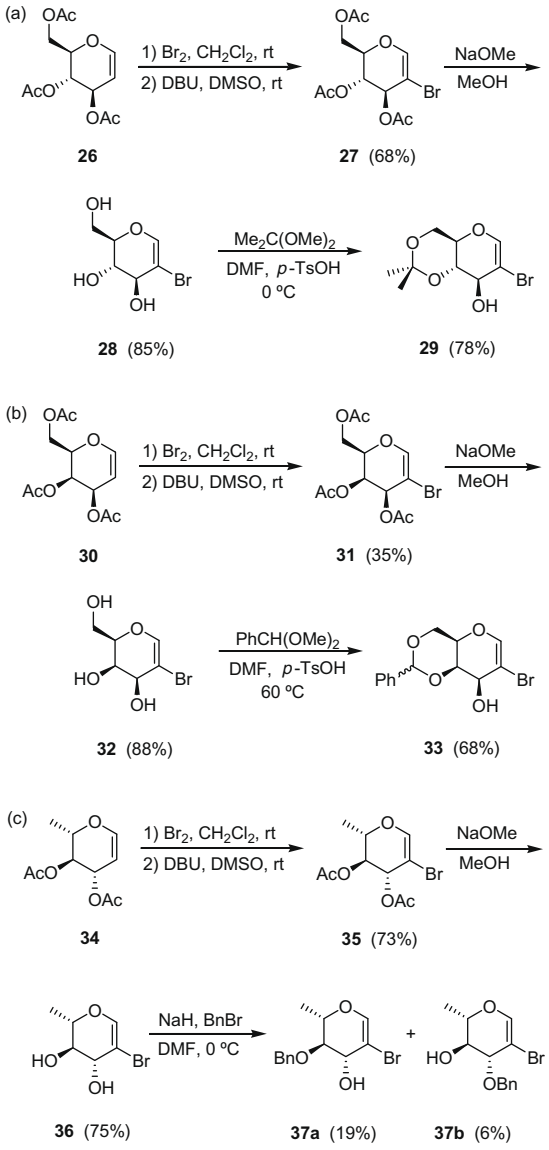
We began our studies for the synthesis of chromans by preparing a variety of 2-bromoglycals of type **18**, which are easily accessible from the corresponding peracetylated glycals (Scheme 5). The latter are either commercially available or can be synthesized from the native sugars (not shown). As carbohydrate precursors we used the hexoses D-glucose, D-galactose and L-rhamnose as well as the pentose D-arabinose. A bromination–elimination sequence afforded the peracetylated bromoglycals **27**, **31**, and **35**, respectively, in moderate yields. Saponification furnished the corresponding deprotected bromoglycals **28**,[14] **32**, and **36**. In the case of bromoglucal **28** (Scheme 5a) selective protection of the 4- and the 6-hydroxyl groups can be achieved by making use of the isopropylidene protecting group, whereas an analogous procedure led in the galactose series to protection of the 3- and 4-hydroxyl groups. Therefore, we utilized the benzylidene protecting group yielding the desired product **33** in 68%. A selective benzylation of one hydroxyl group of bromorhamnal **36** proved to be difficult; thus, a random benzylation followed by a chromatographic separation of the different regioisomers **37a** and **37b** was performed.

Recently, Bergman developed a highly enantioselective approach for the synthesis of kumarans[15] and we became interested in testing the notion whether we could also use five-membered bromoglycals as starting material for our domino method. However, efforts to synthesize 2-bromo-D-arabinal in furanoside form were in vain. Although there is literature evidence for the synthesis of the five-membered peracetylated arabinal **40** by starting from arabinose **39**, we did not succeed in preparing this compound. A closer look to our experiments gives the idea that this literature from the 1930s regarding the topic of selective synthesis of peracetylated five-membered arabinal is highly doubtable.[16] Simple analytical techniques to distinguish between five- and six-membered glycals were embryonic in these days. We were only able to isolate the six-membered arabinal **41** by using this procedure (Scheme 6). The latter could be converted to the corresponding bromoarabinal **42**.

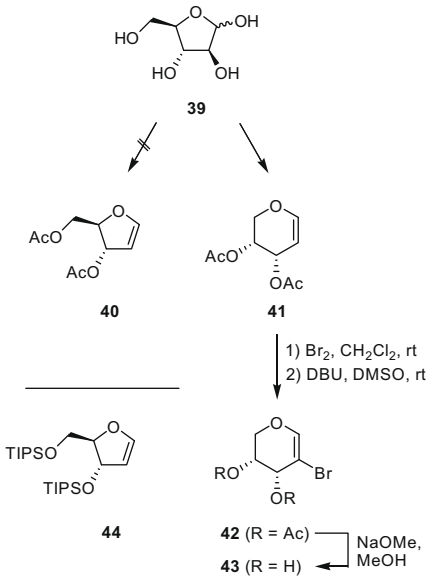
Townsend reported the preparation of a persilylated furanoside-arabinal **44**,[17] but our attempts to subject **44** to our bromination–elimination sequence lacked any success. The removal of the silyl groups—either with fluoride or under acidic conditions—furnished a furane derivative.[18]

To prepare a variety of diynes we started from the commercially available 1,6-heptadiyne (**47**). The major challenge was the desymmetrization of the symmetric structure in good yields. To address this problem either a chain elongation by one methylene unit utilizing *n*-BuLi/paraformaldehyde or a Sonogashira monocoupling with phenyl iodide was employed.[19] The sequence starting with the chain elongation by paraformaldehyde proved to be more efficient for the syntheses of the respective diynes. The elongated propargylic alcohol is either subjected to an Appel reaction yielding the bisalkyne **46** or its terminal triple bond can be further functionalized to give **45**, **48** and **49a**/**49b** (Scheme 7).

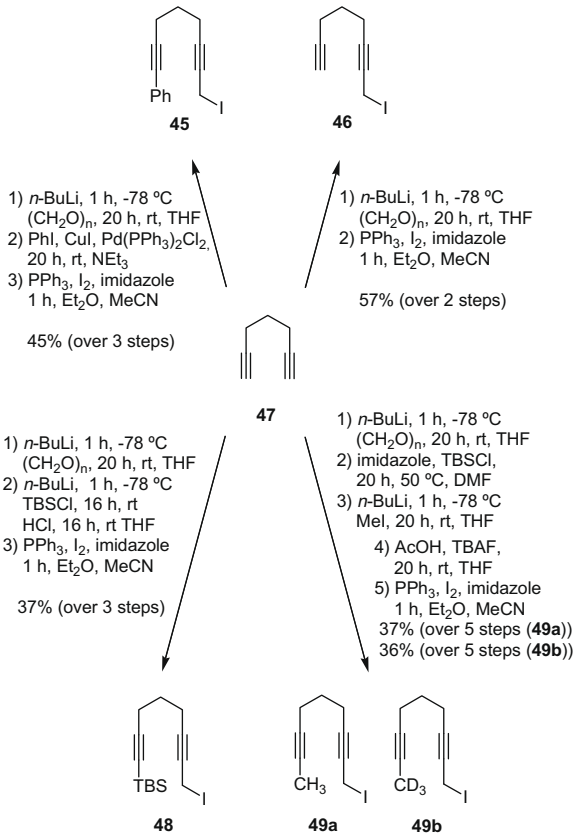
The synthesis of the propargylic iodide **50** with an oxygen atom in the tether commences with 2-butyne diol (**51**). The same starting material led via a double Appel reaction and nucleophilic substitution over two steps to the propargylic bromide **54** with geminal ester moieties (Scheme 8). Five steps were necessary to obtain the alkynyl cyanide **56**—a pseudodiyne—from propargylic alcohol **55** (Scheme 8).



Scheme 5. Synthesis of 2-bromoglycals.



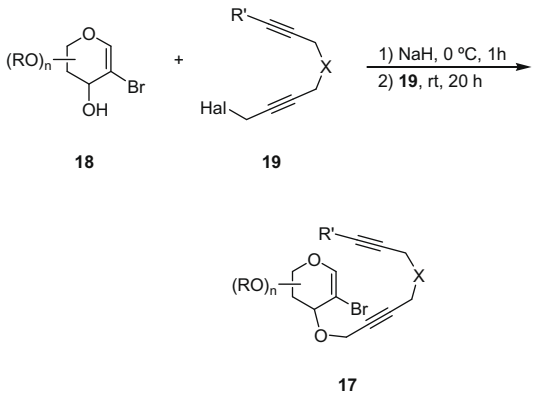
Scheme 6. Synthesis of bromoarabinals **42**–**43**.



Scheme 7. Synthesis of the different propargylic iodides.

With several propargylic halides of type **19** in hand the attachment of the diyne to the remaining 3-hydroxyl group of the bromoglycals was performed by using the typical reaction conditions for propargylic substitution reactions (Scheme 9). In order to investigate the scope of the Pd-catalyzed domino reaction a variety of different coupling products were prepared (Table 2) from propargylic halides of type **19** (Scheme 9) through alkylation of the remaining 3-hydroxyl group of bromoglycals **18**.

In order to optimize the reaction conditions for the desired domino reaction (Table 2) consisting of a *Heck*-carbopalladation–



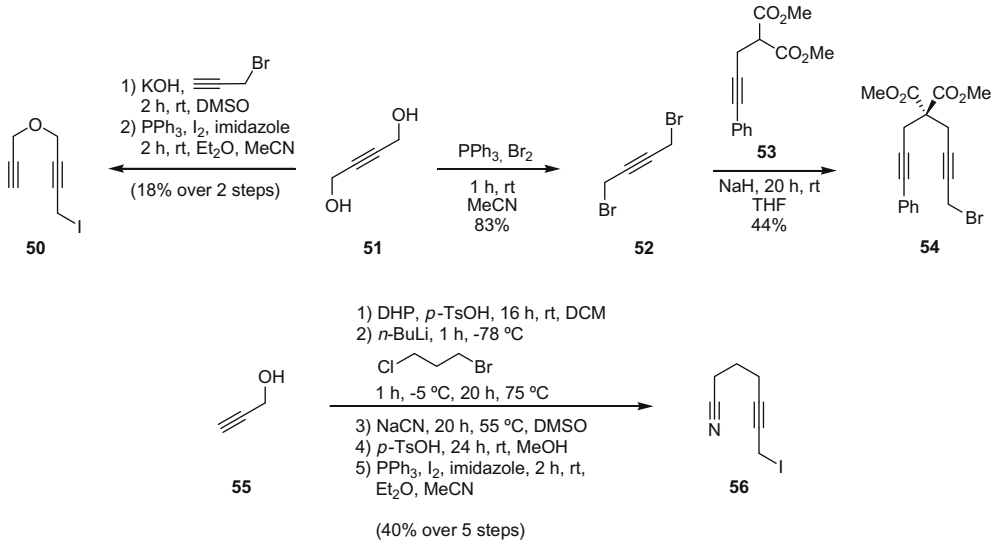
Scheme 9. Attachment of diynes **19** to bromoglycals **18** to afford the domino precursors **17**.

cyclization sequence we screened several catalytic systems as shown in Table 1 for the domino product **16c** using precursor **17c** as a test substrate. Utilizing 10 mol % of $Pd_2(dba)_3$ and 4.0 equiv of HN(*i*-Pr)$_2$ in DMF/MeCN/NMP (8:8:1) and stirring the reaction mixture for 30 min at 120 °C under microwave irradiation, we observed no conversion. Changing the catalytic system to $Pd(OAc)_2$ and davephos, the desired product was obtained in 56% yield. With the use of 6.0 equiv of HN(*i*-Pr)$_2$ and $Pd(dppf)Cl_2$ as cat-

Table 1
Optimization of the domino sequence using different catalytic systems for the synthesis of **16c**

Entry	Reagents	Yield (%)
1	$Pd_2(dba)_3$ (10 mol %), HN(*i*-Pr)$_2$ (4.0 equiv), DMF/MeCN/NMP (8:8:1), 30 min, 120 °C (mw)	Starting material
2	$Pd(OAc)_2$ (10 mol %), davephos (20 mol %), HN(*i*-Pr)$_2$ (4.0 equiv), DMF/MeCN/NMP (8:8:1), 30 min, 120 °C (mw)	56
3	$Pd(dppf)Cl_2$ (10 mol %), HN(*i*-Pr)$_2$ (6.0 equiv), DMF/MeCN/NMP (8:8:1), 30 min, 120 °C (mw)	72
4	$Pd(PPh_3)_4$ (10 mol %), HN(*i*-Pr)$_2$ (4.0 equiv), DMF/MeCN/NMP (8:8:1), 30 min, 120 °C (mw)	92

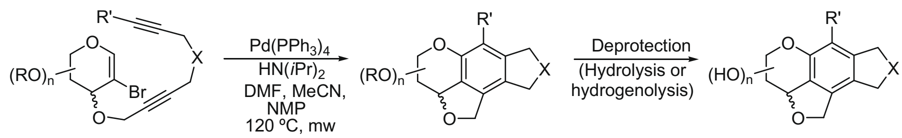
NMP = *N*-methyl-2-pyrrolidone; davephos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl.



Scheme 8. Synthesis of the different propargylic diynes.

Table 2

Carbohydrate diyne derivatives **17**, chroman products **16**, deprotected chromans **38** and yield of the domino sequence and deprotection, respectively



17 **16** **38**

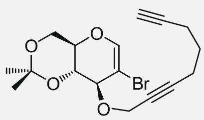
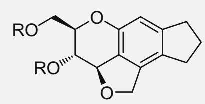
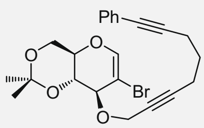
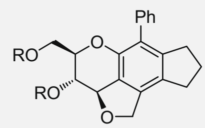
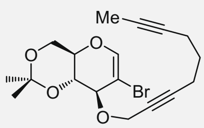
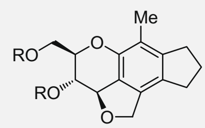
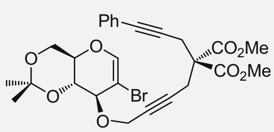
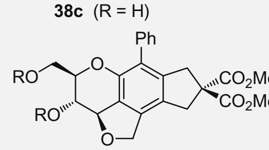
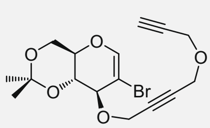
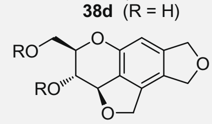
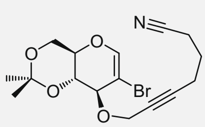
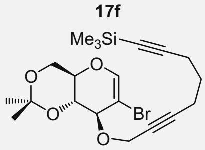
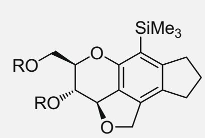
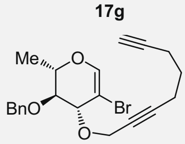
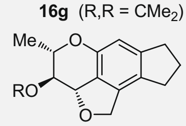
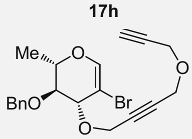
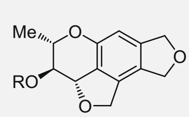
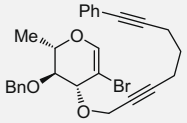
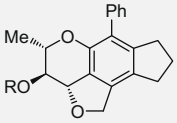
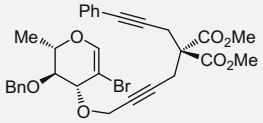
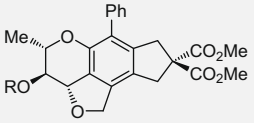
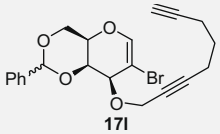
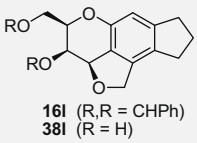
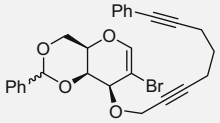
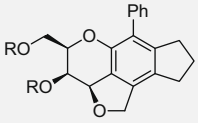
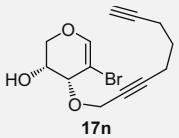
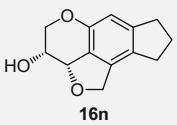
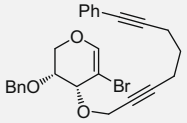
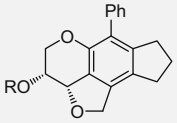
Starting material	Product	Yield (%)[a]
 **17a**	 **16a** (R,R = CMe_2) **38a** (R = H)	70 87
 **17b**	 **16b** (R,R = CMe_2) **38b** (R = H)	Quant. 83
 **17c**	 **16c** (R,R = CMe_2) **38c** (R = H)	92 88
 **17d**	 **16d** (R,R = CMe_2) **38d** (R = H)	86 33
 **17e**	 **16e** (R,R = CMe_2) **38e** (R = H)	52 99
 **17f**	No reaction	–
 **17g**	 **16g** (R,R = CMe_2)	92
 **17h**	 **16h** (R = Bn)	98
 **17i**	 **16i** (R = Bn) **38i** (R = H)	25[b] –

Table 2 (*continued*)

Starting material	Product	Yield (%)[a]
 **17j**	 **16j** (R = Bn) **38j** (R = H)	81 75
 **17k**	 **16k** (R = Bn) **38k** (R = H)	88 89
 **17l**	 **16l** (R,R = CHPh) **38l** (R = H)	67 68
 **17m**	 **16m** (R,R = CHPh) **38m** (R = H)	75 57
 **17n**	 **16n**	38[b]
 **17o**	 **16o** (R = Bn) **38o** (R = H)	56[b] 76

[a] The first value is the yield of the domino reaction; the second value is the yield of the deprotection.
[b] The yield is given for a two-step procedure starting from 2-bromoglycal and diynyl halide.

alyst precursor the yield was improved to 72%. It has not escaped our notice that more equivalents of base are necessary for a better yield using Pd^{II} catalysts. However, the best results could be observed using 10 mol % of $Pd(PPh_3)_4$ and 4.0 equiv of $HN(i\text{-}Pr)_2$ (entry 4).

With the optimized reaction conditions in hand, scope and limitations of the reaction were investigated by employing different coupling products varying in the diyne chain as well as in the sugar core. The results are summarized in Table 2. The reaction generally proceeds in moderate to excellent yield (25% to quantitative yield) tolerating a broad range of functional groups in the diyne chain. Terminal phenyl moieties, hydrogen atoms, methyl and silyl units as well as ethers and esters as part of the tether were tolerated. Such a silyl group may give access to hydroxy-substituted chromans via Fleming–Tamao oxidation.[20] Summarizing the results one can conclude that oxygen heteroatoms in the tether decrease the yield (see **16e** and **16i**) whereas geminal ester functionalities seem to have no influence (see **16d** and **16k**). However, attempts to extend this reaction to a pseudodiyne, the nitrile **17f** that would afford a pyridine moiety attached to the sugar core were in vain. This might be due to the higher stability of the CN π-bond compared to the CC π -bond, which might lead to a σ-complex with the Pd-species. In the literature only rare examples are known in which Pd-species insert in a CN bond to create pyridine-like structures.[21]

In order to regenerate the native hydroxyl group pattern of the corresponding carbohydrates we deprotected the chromans **16a–16o**. The deprotection reactions were carried out under acidic conditions for removal of isopropylidene whereas hydrogenolysis was applied for the cleavage of benzyl moieties. With these efforts we were able to create hydroxylated chromans **38a–38o**, which are hardly accessible by other routes.

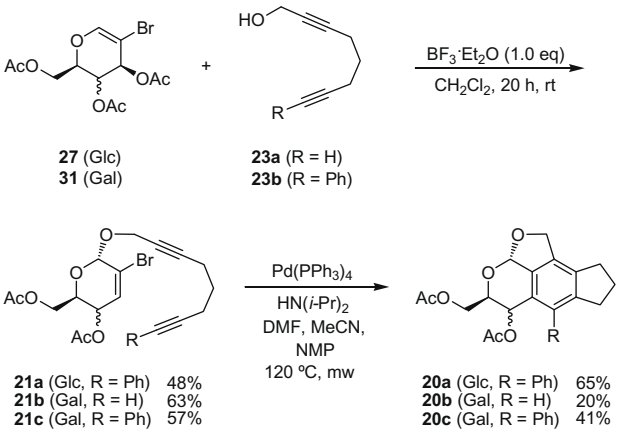
Due to the similar basic conditions of the domino reaction compared to a Pd-catalyzed propargylic substitution we became interested in testing the notion whether the complete synthesis from **18** and **19** to **16** could be streamlined in a one-pot operation. Since attempts to perform the diyne attachment by a Pd-catalyzed propargylic substitution—which is well known for soft nucleophiles[22]—did not afford the coupling product, we tried several other approaches for a one-pot domino sequence. Surprisingly, a non-sequential procedure proved to be the most successful. Thus, all reagents—the protected bromoglycal **29**, the diynyl halide **46**, sodium hydride and the Pd catalyst—were added at the same time and the microwave irradiation was started leading in 42% to the desired product **16a**. A consolidated view of all these factors indicates that the one-pot procedure turned out to be a considerable alternative to the conventional two-step procedure.

To elucidate the mechanistic picture of the domino reaction we synthesized a deuterium-labelled bromoglycal **17c(D_3)**. Relying upon our results it is supposed that the domino reaction is initiated

by the oxidative addition of the Pd^0 species into the C–Br bond of the respective bromoglycal to furnish intermediate **57c(D$_3$)**. Two intramolecular carbopalladation reactions of the Pd-species to the triple bonds generate triene **59c(D$_3$)** (Scheme 10). The final cyclization step affording the benzene unit may be regarded as electrocyclic 6 π electron ring-closure followed by the subsequent release of the catalytic species. A Heck-type transformation would also lead to the desired product; however an anti-dehydropalladation—due to the resulting aromatization possible, but rarely observed—would have to occur.

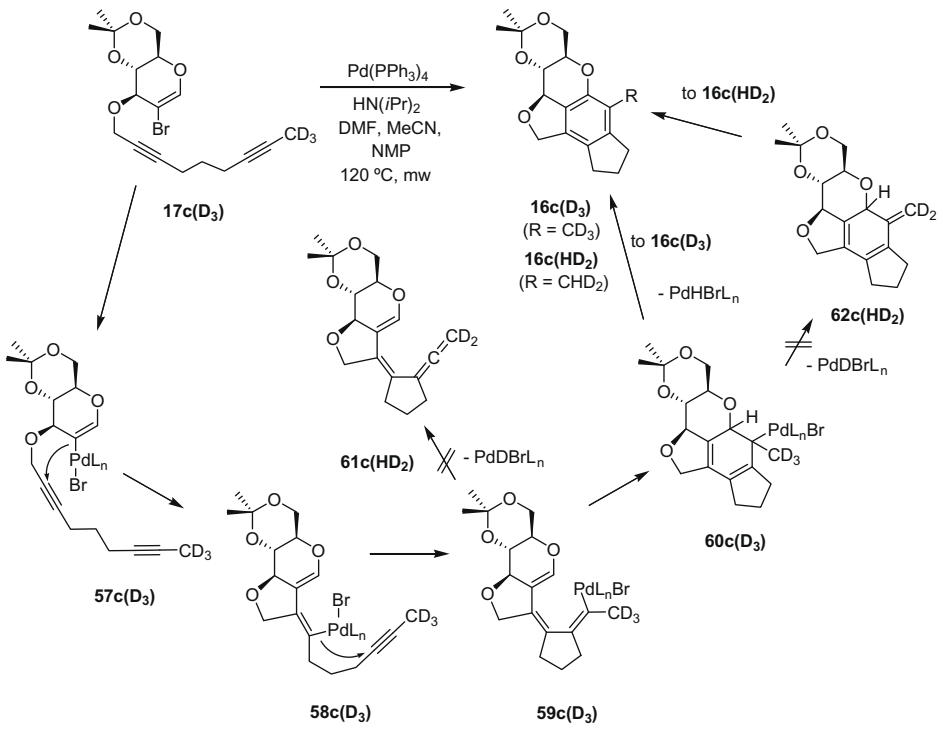
To answer the question whether the final ring-closure or a hypothetical β-hydride elimination is faster the product distribution of the reaction using the deuterated congener was analyzed. If a β-hydride elimination takes place leading to the intermediates **61c(HD$_2$)** and **62c(HD$_2$)**, respectively, followed by a cyclization one will observe a displacement of one deuterium atom by hydrogen (Scheme 10). However, we observed no scrambling (no occurrence of **16c(HD$_2$)**) leading to the assumption that the cyclization step via **60c(D$_3$)** to **16c(D$_3$)** is faster than a hypothetical β-hydride elimination.

Encouraged by the results shown above, we tried to extend our domino approach to the preparation of isochromans. We looked for a possibility to build up the precursors in an easy and modular manner. Starting from 2-bromoglucal **27**, 2-bromogalactal **31** and diynols of type **23** we were able to make use of a Lewis-acid promoted Ferrier reaction resulting in a shift of the C=C double bond in the six-membered ring (Scheme 11).[23] We tried different amounts of BF_3-etherate. It turned out that stoichiometric amounts of Lewis acid at room temperature and a long reaction time (20 h) are essential for a successful reaction.[24] In all cases the α-anomer was the major product and only traces of the β-anomer were detected that could easily be removed by silica gel column chromatography. Appling the same conditions as used in the synthesis of the chromans **16** the yields of the analogous domino reaction affording the isochromans **20a–20c** were poorer than for **16**.



Scheme 11. Synthesis of the isochromans **20a–20c**.

Two of the starting materials, the deprotected 2-bromoglucal (**28**)[14] as well as the deprotected 2-bromogalactal (**32**), could be crystallographically characterized. The molecular structure shows the typical half-chair form of six-membered alkenes as depicted for the bromogalactal **32** in Figure 3. It is interesting to note that the photochemical behavior of the two bromoglycal crystals was completely different. Whereas the colorless crystals of **28** were highly light-sensitive and got dark brown after several days, the colorless crystals of 2-bromogalactal were stable in sunlight for months. Indeed, a careful look at the solid-state structure of the crystals may give a hint for their different behavior. In the structure of **28** we found close intermolecular contacts (3.64 Å) between bromine centers being shorter than the sum of the van der Waals radii (3.7 Å)[25] as depicted in Figure 4, whereas in the solid-state structure of **32** no such interaction is observed. Only in the first case elemental bromine can be formed by light-induced cleavage



Scheme 10. Proposed mechanism for the annelation of the benzene unit to the sugar core shown for the synthesis of **16c(D$_3$)**.

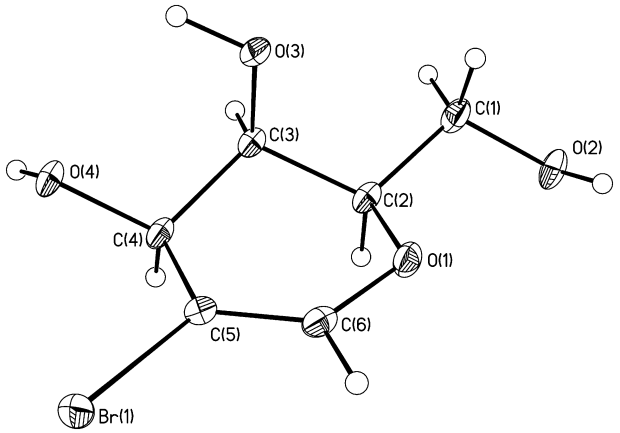


Figure 3. X-ray structure (ellipsoids drawn at 50% probability level) of the 2-bromogalactal (**32**).

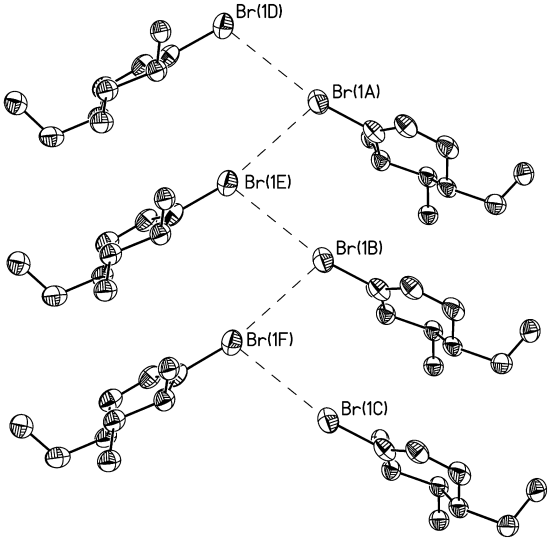


Figure 4. Packing of 2-bromoglucal (**28**) in the solid state showing close Br–Br interactions (dashed lines).

of the weak C–Br bond, whereas the discrete Br atoms in **32** cannot lead to any dimerisation. Intermolecular interactions between neutral halogen centers have been addressed in the literature.[26] These closed-shell interactions have at first been interpreted in terms of donor–acceptor interactions, however, later it was shown that electron correlation effects play a considerable role.[27]

3. Conclusion

In conclusion, we have successfully developed a highly efficient synthetic route to heavily substituted chromans and isochromanes via a Pd-catalyzed domino approach. We have demonstrated the versatility of this approach by using numerous monosaccharides with their rich stereochemistry and a variety of diynes differing in the tether. Our synthetic strategy allows the generation of complex oligocyclic structures with little effort. We were able to engender a high structural diversity, which provides access to a variety of carbohydrate-aromatic hybrids. Furthermore, the biological activity of many chromans suggests an exciting adventure into the realms of drug discovery. Our synthetic approach provides a facile access to novel molecular entities for explorations in chemical biology.

4. Experimental

4.1. General experimental

All solvents were distilled before use unless otherwise stated. Air and moisture sensitive reactions were carried out in oven-dried or flame-dried glassware, septum-capped under atmospheric pressure of argon. Commercially available compounds were used without further purification. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a 300, 500 or 600 MHz instrument using the residual signals from $CHCl_3$, δ 7.26 ppm and δ 77.0 ppm, and methanol, δ 4.87 ppm and δ 49.2 ppm, as internal references for ^{1}H and ^{13}C, respectively. ESI-HRMS mass spectrometry was carried out on a FTICR instrument. IR spectra were measured on conventional spectrometer. UV spectra were measured with a common photometer. Optical rotations were measured at 20 °C using a common optical rotation instrument. $HClO_4$–SiO_2 was prepared according to literature methods.[28] Analytical data of chromans and precursors not provided in this Experimental are given in our recent communication.[12a]

4.2. General procedure for the deacetylation of 2-bromoglycals

The peracetylated bromoglycal (10.0 mmol, 1.0 equiv) was dissolved in methanol (50 mL). A sodium methoxide solution (0.50 M in methanol, 7.00 mmol, 0.7 equiv) was slowly added until pH $\geqslant$12. The reaction was stirred for 3 h at rt. Then the reaction solution was neutralized by the addition of Amberlite IR-120 (H^+). The solution was filtered and the solvent was removed by rotary evaporation. The residue was purified by silica gel column chromatography (DCM/MeOH) to afford the desired compound as a white solid.

Analytical Data of **32**: yield: 88%. R_f: 0.16 (DCM/MeOH = 8:1). α = +61.2 (*c* 0.52, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 3.27–3.34 (m, 1H), 3.73 (dd, *J* = 5.2, 11.8 Hz, 1H), 3.82 (dd, *J* = 6.7, 11.8 Hz, 1H), 3.98–4.02 (m, 1H), 4.05 (d, *J* = 2.1 Hz, 1H), 4.27 (ddd, *J* = 1.6, 2.1, 4.6 Hz, 1H), 4.85 (s_{br}, 2H), 6.64 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 61.7, 67.8, 68.3, 79.7, 104.1, 144.8. IR (KBr): ν (cm^{-1}) = 3503, 3320, 3167, 3069, 1645, 1348, 1175. UV (MeOH): λ_{max} (lg ε) [nm] = 217 (3.77). MS (ESI): *m/z* (%) = 247.0 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M-H]^-$: 224.9611; found: 224.9592.

Analytical Data of **36**: yield: 75%. R_f: 0.38 (DCM/MeOH = 10:1). α = −43.8 (*c* 0.89, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.32 (d, *J* = 6.5 Hz, 3H), 3.42 (dd, *J* = 9.1, 6.5 Hz, 1H), 3.83–3.94 (m, 1H), 4.00 (dd, *J* = 6.5, 1.2 Hz, 1H), 4.88 (s_{br}, 2H), 6.60 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ = 17.3, 73.5, 76.1, 76.9, 103.6, 145.0. IR (KBr): ν (cm^{-1}) = 3002, 2363, 2330, 1777, 1265. UV (CH_3CN): λ_{max} (lg ε) [nm] = 216.0 (3.29). MS (ESI): *m/z* (%) = 209.0 (100) $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[M+H]^+$: 208.9642; found: 208.9648.

Analytical Data of **43**: yield: 70%. R_f: 0.06 (pentane/EtOAc 5:1). α = +125.0 (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 3.30 (m_c, 1H), 3.74 (m_c, 1H), 3.89 (m_c, 2H), 4.12 (dd, *J* = 1.4, 4.0 Hz, 1H), 6.66 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 65.5, 67.9, 69.5, 100.8, 146.0. IR (film): ν (cm^{-1}) = 2914, 1633, 1466, 1370. UV (MeOH): λ_{max} (lg ε) [nm] = 289.0 (2.81). MS (ESI): *m/z* (%) = 195.4 (96) $[M+H]^+$. HRMS (ESI): *m/z* calcd for $[M-H]^-$: 192.9501; found: 192.9515.

4.3. General procedure for the chroman domino precursors

The bromoglycal (1.50 mmol, 1.0 equiv) was dissolved in DMF (40 mL) and cooled to 0 °C, NaH (60% in mineral oil, 1.50 mmol, 1.0 equiv) was added and the solution was allowed to warm to

rt. The propargylic halide (1.65 mmol, 1.1 equiv), dissolved in DMF (15 mL), was added to the reaction mixture at 0 °C and stirred over night at rt. The reaction was stopped by the addition of water. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water and brine, 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 the desired compound as a yellow oil.

Analytical Data of **17c**: yield: 77%. R_f: 0.32 (hexane/EtOAc = 10:1). α = +74.0 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3H), 1.51 (s, 3H), 1.67 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.76 (t, *J* = 2.7 Hz, 3H), 2.23 (qt, *J* = 2.7, 7.2 Hz, 2H), 2.33 (tt, *J* = 2.3, 7.2 Hz, 2H), 3.74–3.86 (m, 2H), 3.87–3.98 (m, 1H), 3.99–4.08 (m, 1H), 4.20 (dd, *J* = 1.6, 7.2 Hz, 1H), 4.32 (td, *J* = 2.3, 15.0 Hz, 1H), 4.40 (td, *J* = 2.3, 15.0 Hz, 1H), 6.60 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 3.6, 18.0, 18.1, 19.1, 28.1, 29.0, 59.2, 61.4, 70.4, 72.8, 75.6, 76.1, 76.4, 78.2, 86.4, 99.6, 100.8, 144.8. IR (film): ν (cm^{-1}) = 2371, 1634, 1172. UV (CH_3CN): λ_{max} (lg ε) [nm] = 215.5 (3.85). MS (ESI): *m/z* (%) = 405.1 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 405.0672; found: 405.0667.

Analytical Data of **17e**: yield: 62%. R_f: 0.16 (hexane/EtOAc = 10:1). α = +76.0 (*c* 0.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3H), 1.50 (s, 3H), 2.43 (t, *J* = 2.5 Hz, 1H), 3.73–3.84 (m, 2H), 3.87–3.96 (m, 1H), 3.98–4.08 (m, 1H), 4.20 (dd, *J* = 1.6, 7.2 Hz, 1H), 4.25 (d, *J* = 2.5 Hz, 2H), 4.30 (t, *J* = 1.9 Hz, 2H), 4.39 (td, *J* = 1.9, 15.6 Hz, 1H), 4.47 (td, *J* = 1.9, 15.6 Hz, 1H), 6.60 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1, 29.0, 56.5, 56.8, 58.8, 61.3, 70.3, 72.8, 75.0, 75.9, 78.9, 81.6, 83.0, 99.6, 100.4, 145.0. IR (film): ν (cm^{-1}) = 3289, 3079, 2994, 2116, 1631, 1376. UV (CH_3CN): λ_{max} (lg ε) [nm] = 216.0 (3.86). MS (ESI): *m/z* (%) = 393.0 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 393.0308; found: 393.0294.

Analytical Data of **17j**: yield: 71%. R_f: 0.46 (hexane/EtOAc = 8:1). α = −27.8 (*c* 0.23, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.8 Hz, 3H), 1.77 (tt, *J* = 7.1, 7.2 Hz, 2H), 2.37 (tt, *J* = 2.3, 7.2 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 3.63 (dd, *J* = 4.7, 6.6 Hz, 1H), 4.10–4.22 (m, 2H), 4.34 (t, *J* = 2.3 Hz, 2H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 6.61 (d, *J* = 1.2 Hz, 1H), 7.17–7.43 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.6, 18.1, 18.7, 27.8, 58.5, 73.2, 73.8, 76.6, 77.2, 78.7, 81.3, 86.5, 88.6, 98.4, 123.7, 127.6, 127.8, 127.9, 128.1, 128.4, 131.5, 137.6, 144.2. IR (film): ν (cm^{-1}) = 3062, 2935, 2235, 1725, 1490, 1266. UV (CH_3CN): λ_{max} (lg ε) [nm] = 238.5 (4.29), 250.0 (4.23), 271.0 (3.42), 278.0 (3.36). MS (ESI): *m/z* (%) = 501.1 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 501.1036; found: 501.1019, $[M+Na]^+$ (ESI-HRMS).

Analytical Data of **17l**: yield: 77%. R_f: 0.17 (hexane/EtOAc = 4:1). α = +181.9 (*c* 0.16, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.72 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 2.30 (dt, *J* = 2.6, 7.0 Hz, 2H), 2.36 (tt, *J* = 2.2, 7.0 Hz, 2H), 3.98–4.01 (m, 1H), 4.04 (dd, *J* = 1.5, 12.5 Hz, 1H), 4.33 (dd, *J* = 1.5, 12.5 Hz, 1H), 4.36 (td, *J* = 2.2, 15.9 Hz, 1H), 4.40 (td, *J* = 2.2, 15.9 Hz, 1H), 4.44 (dd, *J* = 1.2, 5.0 Hz, 1H), 4.54 (dd, *J* = 1.2, 5.0 Hz, 1H), 5.63 (s, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 7.29–7.38 (m, 3H), 7.49–7.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 17.9, 27.4, 57.3, 69.0, 69.0, 69.3, 70.4, 72.0, 76.3, 83.3, 86.5, 98.8, 101.3, 126.2, 128.1, 129.0, 137.2, 144.4. IR (film): ν (cm^{-1}) = 3292, 2935, 2360, 1642, 1358. UV (CH_3CN): λ_{max} (lg ε) [nm] = 208.0 (4.11), 255.0 (2.65), 261.0 (2.57), 266.5 (2.44). MS (ESI): *m/z* (%) = 439.1 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 439.0515; found: 439.0516.

4.4. General procedure for isochroman domino precursors

The peracetylated bromoglycal (0.30 mmol, 1.0 equiv) and the corresponding propargylic alcohol (0.30 mmol, 1.0 equiv) were dissolved in dry dichloromethane (5 mL). After the addition of BF_3-etherate (0.30 mmol, 1.0 equiv), the reaction was stirred over night at rt and stopped by the addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the residue was purified by silica gel column chromatography (toluene/acetone) to afford the desired compound as a yellow oil.

Analytical Data of **21b**: yield: 63%. R_f: 0.46 (toluene/acetone = 10:1). α = −83.1 (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (tt, *J* = 7.0, 7.1 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.05 (s, 3H), 2.07 (s, 3H), 2.30 (dt, *J* = 2.6, 7.1 Hz, 2H), 2.36 (tt, *J* = 2.2, 7.0 Hz, 2H), 4.17–4.21 (m, *J* = 6.4 Hz, 3H), 4.30 (t, *J* = 2.2 Hz, 2H), 5.02 (dd, *J* = 2.7, 6.1 Hz, 1H), 5.26 (s, 1H), 6.42 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 17.9, 20.8, 20.8, 27.4, 55.8, 62.2, 64.8, 66.4, 69.0, 75.1, 83.3, 87.1, 95.0, 97.2, 126.8, 169.9, 170.3. IR (film): ν (cm^{-1}) = 2939, 2357, 1748, 1651. UV (CH_3CN): λ_{max} (lg ε) [nm] = 199.5 (4.10). MS (ESI): *m/z* (%) = 435.0 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 435.0414; found: 435.0414.

Analytical Data of **21c**: yield: 57%. R_f: 0.42 (pentane/EtOAc = 3:1). α = −76.5 (*c* 0.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (tt, *J* = 7.0, 7.1 Hz, 2H), 2.06 (s, 3H), 2.08 (s, 3H), 2.42 (tt, *J* = 2.1, 7.0 Hz, 2H), 2.53 (t, *J* = 7.1 Hz, 2H), 4.20 (d, *J* = 6.6 Hz, 2H), 4.33 (m, 2H), 4.36 (dd, *J* = 2.6, 6.6 Hz, 1H), 5.03 (dd, *J* = 2.6, 5.8 Hz, 1H), 5.29 (s, 1H), 6.43 (d, *J* = 5.8 Hz, 1H), 7.23–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1, 18.7, 20.8, 20.8, 27.7, 55.8, 62.2, 64.9, 66.4, 75.1, 81.3, 87.3, 88.9, 95.0, 126.7, 127.5, 128.9, 128.1, 128.1, 131.4, 169.9, 170.3. IR (film): ν (cm^{-1}) = 3021, 1746, 1372. UV (CH_3CN): λ_{max} (lg ε) [nm] = 202.0 (4.53), 239.0 (4.20), 249.5 (4.17), 271.5 (3.04), 278.0 (2.94). MS (ESI): *m/z* (%) = 511.07 (98) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 511.0732; found: 511.0727.

4.5. General procedure for the domino reaction leading to chromans and isochromans

The alkylated bromoglycal (0.10 mmol, 1.0 equiv) was dissolved in a mixture of DMF/MeCN/NMP (1.0 mL, 1.0 mL, 0.15 mL). $Pd(PPh_3)_4$ (10 μmol, 0.1 equiv) and diisopropylamine (0.40 mmol, 4.0 equiv) were added. The reaction was stirred in the microwave for 30 min 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, 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 the desired compound as a white solid.

Analytical Data of **16c**: yield: 92%. R_f: 0.32 (hexane/EtOAc = 6:1). α = +37.1 (*c* 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3H), 1.51 (s, 3H), 2.00–2.16 (m, 5H), 2.60–2.87 (m, 4H), 3.88–4.02 (m, 3H), 4.10–4.22 (m, 1H), 4.79 (dd, *J* = 2.6, 12.9 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6, 19.0, 25.6, 29.0, 30.6, 31.5, 62.4, 70.2, 72.6, 72.8, 79.2, 99.7, 117.9, 121.4, 129.2, 133.9, 146.3, 147.5. IR (KBr): ν (cm^{-1}) = 2997, 2953, 2896, 1610, 1476. UV (CH_3CN): λ_{max} (lg ε) [nm] = 206.5 (4.61), 284.0 (3.29). MS (ESI): *m/z* (%) = 325.2 (45) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 325.1410; found: 325.1408.

Analytical Data of **16g**: yield: 92%. R_f: 0.61 (hexane/EtOAc = 6:1). α = 23.9 (*c* 0.44, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.28 (s, 9H), 1.47 (s, 3H), 1.51 (s, 3H), 2.05 (tt, *J* = 7.3 Hz, 2H), 2.67 (dt, *J* = 4.0, 7.3 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 3.89–3.98 (m, 3H), 4.05–4.15 (m, 1H), 4.82 (dd, *J* = 2.3, 12.9 Hz, 1H), 4.99–5.06 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 1.3, 19.0, 25.9, 29.0, 29.6, 34.5, 62.3, 70.0, 72.4, 72.9, 79.4, 99.7, 118.5, 120.6, 129.5, 133.4, 153.1, 154.4. IR (film): ν (cm^{-1}) = 2953, 2361, 1618, 1593. UV (CH_3CN): λ_{max} (lg ε) [nm] = 209.5 (4.50), 289.5 (3.44), 295.0 (3.44). MS (ESI): *m/z* (%) = 383.2 (100) $[M+Na]^+$. HRMS (ESI): *m/z* calcd for $[M+Na]^+$: 383.1649; found: 383.1651.

Analytical Data of **16h**: yield: 98%. R_f: 0.47 (hexane/EtOAc = 8:1). $\alpha = -121.3$ (c 0.23, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.49$ (d, $J = 6.4$ Hz, 3H), 1.99–2.16 (m, 2H), 2.62–2.72 (m, 2H), 2.84 (t, $J = 9.4$ Hz, 2H), 3.38 (dd, $J = 8.1$, 9.3 Hz, 1H), 4.14 (qd, $J = 6.4$, 9.3 Hz, 1H), 4.71 (d, $J = 11.9$ Hz, 1H), 4.84 (dd, $J = 1.4$, 11.9 Hz, 1H), 4.96–5.14 (m, 3H, 3-H), 6.52 (s, 1H), 7.22–7.43 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.4$, 26.1, 30.1, 32.8, 72.6, 72.8, 74.9, 79.8, 82.9, 108.2, 127.5, 127.8, 128.2, 138.2, 121.7, 128.3, 136.5, 147.6, 149.9. IR (KBr): ν (cm^{-1}) = 2845, 1622, 1467, 1112. UV (CH_3CN): λ_{max} (lg ε) [nm] = 206.0 (4.66), 287.0 (3.52). MS (ESI): m/z (%) = 345.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 345.1461; found: 345.1457.

Analytical Data of **16l**: yield: 75%. R_f: 0.09 (hexane/EtOAc = 4:1). $\alpha = -145.0$ (c 0.10, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): $\delta = 1.90$–2.16 (m, 2H), 2.61–3.02 (m, 4H), 4.03–4.06 (m, 1H), 4.10–4.17 (m, 1H), 4.47 (dd, $J = 1.7$, 12.3 Hz, 1H), 4.62 (dd, $J = 1.1$, 3.5 Hz, 1H), 4.97 (dd, $J = 1.8$, 12.1 Hz, 1H), 5.15 (dd, $J = 2.6$, 12.1 Hz, 1H), 5.24 (m, 1H), 5.64 (s, 1H), 7.24–7.32 (m, 5H), 7.35–7.43 (m, 2H), 7.46–7.51 (m, 2H), 7.65–7.73 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.2$, 30.7, 32.9, 69.3, 70.0, 72.4, 73.6, 77.7, 101.3, 120.0, 122.8, 129.2, 134.4, 136.0, 137.6, 145.7, 146.5, 126.6, 126.7, 127.9, 128.1, 129.0, 129.9. IR (KBr): ν (cm^{-1}) = 2328, 1733, 1652, 1327. UV (CH_3CN): λ_{max} (lg ε) [nm] = 204.5 (4.65), 224.0 (4.34), 250.0 (4.04), 290.5 (3.59). MS (ESI): m/z (%) = 435.2 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 435.1567; found: 435.1568.

Analytical Data of **20a**: yield: 65%. R_f: 0.24 (pentane/EtOAc 3:1). $\alpha = +29.2$ (c 0.24, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (s, 3H), 1.90–2.03 (m, 2H), 2.07 (s, 3H), 2.39–2.51 (m, 1H), 2.76–2.92 (m, 3H), 3.90–3.97 (m, 1H), 4.22 (dd, $J = 3.2$, 12.1 Hz, 1H), 4.36 (dd, $J = 5.3$, 12.1 Hz, 1H), 5.10 (dd, $J = 1.9$, 12.7 Hz, 1H), 5.21 (d, $J = 12.7$ Hz, 1H), 6.12 (d, $J = 6.6$ Hz, 1H), 6.32 (s, 1H), 7.25–7.73 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.7$, 20.9, 25.5, 31.2, 32.3, 62.7, 65.7, 72.6, 76.5, 100.8, 126.0, 127.0, 128.9, 132.7, 134.5, 134.9, 137.1, 139.0, 146.4, 169.9, 170.6. IR (film): ν (cm^{-1}) = 2930, 1742, 1437, 1371. UV (CH_3CN): λ_{max} (lg ε) [nm] = 205.5 (4.56), 317.0 (3.04). MS (ESI): m/z (%) = 431.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 431.1471; found: 431.1465.

Analytical Data of **20b**: yield: 20%. R_f: 0.10 (toluene/acetone = 4:1). $\alpha = -58.2$ (c 0.73, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.06$ (s, 3H), 2.06 (s, 3H), 2.03–2.18 (m, 2H), 2.70–2.85 (m, 2H), 2.85–2.99 (m, 2H), 3.89 (dt, $J = 1.6$, 6.6 Hz, 1H), 4.34 (d, $J = 6.6$ Hz, 2H), 4.98 (d, $J = 12.6$ Hz, 1H), 5.13 (d, $J = 12.6$ Hz, 1H), 5.70 (d, $J = 1.6$ Hz, 1H), 6.44 (s, 1H), 7.26 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.9$, 21.0, 25.6, 30.8, 32.6, 62.8, 67.5, 71.8, 73.9, 101.4, 122.1, 127.8, 134.8, 135.3, 139.1, 146.8, 170.1, 170.5. IR (KBr): ν (cm^{-1}) = 2954, 1742, 1436, 1230. UV (CH_3CN): λ_{max} (lg ε) [nm] = 204.5 (4.58). MS (ESI): m/z (%) = 355.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 355.1152; found: 355.1162.

Analytical Data of **20c**: yield: 41%. R_f: 0.20 (pentane/EtOAc = 3:1). $\alpha = -25.4$ (c 0.24, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3H), 2.01 (s, 3H), 2.02–2.15 (m, 2H), 2.68–2.81 (m, 2H), 2.83–2.92 (m, 2H), 3.92 (td, $J = 1.6$, 5.5 Hz, 1H), 4.18 (d, $J = 5.5$ Hz, 1H), 4.20 (d, $J = 3.9$ Hz, 1H), 5.05 (d, $J = 12.6$ Hz, 1H), 5.19 (d, $J = 12.6$ Hz, 1H), 5.78 (d, $J = 1.6$ Hz, 1H), 6.58 (s, 1H), 7.30–7.75 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.9$, 20.9, 25.6, 31.4, 32.5, 63.4, 65.6, 72.0, 75.0, 101.7, 126.3, 127.6, 128.2, 130.4, 133.8, 135.5, 136.2, 136.9, 138.9, 145.4, 168.9, 170.5. IR (film): ν (cm^{-1}) = 2364, 1747, 1372, 1224. UV (CH_3CN): λ_{max} (lg ε) [nm] = 206.5 (4.58). MS (ESI): m/z (%) = 431.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 431.1471; found: 431.1465.

4.6. General procedure for the deprotection of D-glucose based chromans

The protected chroman (60 μmol, 1.0 equiv) was suspended in methanol (5 mL) and water (0.5 mL). By addition of a 0.1 M HCl solution (0.5 mL) the pH value was set to pH 3. The mixture was stirred for 24 h at 40–50 °C. The reaction was stopped by the addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water 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 the desired compound as a white solid.

Analytical Data of **38b**: yield: 83%. R_f: 0.12 (hexane/EtOAc = 1:1). $\alpha = +18.3$ (c 0.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (tt, $J = 7.1$, 7.7 Hz, 2H), 2.53 (s_{br}, 1H), 2.69–2.82 (m, 4H), 3.90 (d, $J = 3.4$ Hz, 2H), 3.93–3.99 (m, 2H), 4.46 (s_{br}, 1H), 4.86 (d, 10.8 Hz, 1H), 5.03–5.09 (m, 2H), 7.21–7.44 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.4$, 30.7, 32.7, 61.9, 69.5, 73.0, 79.3, 82.3, 121.7, 123.2, 129.6, 135.1, 135.9, 146.1, 146.5, 126.9, 128.0, 129.7. IR (KBr): ν (cm^{-1}) = 2929, 2360, 1628, 1417. UV (CH_3CN): λ_{max} (lg ε) [nm] = 206.0 (4.44), 250.0 (3.96), 291.0 (3.52). MS (ESI): m/z (%) = 347.2 (58) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 347.1254; found: 347.1255.

Analytical Data of **38c**: yield: 88%. R_f: 0.13 (hexane/EtOAc = 1:1). $\alpha = +31.0$ (c 0.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (s_{br}, 1H), 1.96–2.15 (m, 5H), 2.55–2.86 (m, 4H), 3.80–3.81 (m, 1H), 3.94–4.08 (m, 3H), 4.16 (s_{br}, 1H), 4.80 (d, $J = 11.1$ Hz, 1H), 4.95–5.10 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.6$, 25.6, 30.6, 31.4, 62.2, 69.8, 72.9, 79.0, 82.2, 117.8, 120.8, 128.8, 133.0, 146.2, 147.5. IR (KBr): ν (cm^{-1}) = 2921, 2843, 1615, 1102. UV (CH_3CN): λ_{max} (lg ε) [nm] = 207.0 (4.56), 284.0 (3.33). MS (ESI): m/z (%) = 285.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 285.1097; found: 285.1099.

4.7. General procedure for the deprotection of L-rhamnose based chromans

The protected chroman (50 μmol, 1.0 equiv) was dissolved in methanol (3 mL) and dichloromethane (1.0 mL). $Pd(OH)_2/C$ (*Pearlman's Catalyst*) (5 mg) was added to the reaction mixture. Then a hydrogen atmosphere was generated in the reaction reservoir. The mixture was stirred over night at rt. The solvent was removed by rotary evaporation and the residue was purified by silica gel column chromatography (pentane/EtOAc) to afford the desired compound as a white solid.

Analytical Data of **38c**: yield: 89%. R_f: 0.18 (hexane/EtOAc = 1:1). $\alpha = -12.4$ (c 0.17, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (d, $J = 6.2$ Hz, 3H), 3.05 (d, $J = 3.3$ Hz, 1H), 3.33–3.53 (m, 4H), 3.53–3.66 (m, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 3.98–4.09 (m, 1H), 4.86 (d, $J = 12.0$ Hz, 1H), 4.97 (d, $J = 8.3$ Hz, 1H), 5.08 (d, $J = 12.0$ Hz, 1H), 7.26–7.44 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.7$, 38.3, 40.2, 53.0, 53.0, 60.8, 72.7, 73.9, 76.0, 82.3, 122.9, 123.0, 124.8, 135.1, 135.1, 141.3, 147.4, 127.0, 128.0, 129.7, 171.7, 171.7. IR (KBr): ν (cm^{-1}) = 2956, 1736, 1630, 1271. UV (CH_3CN): λ_{max} (lg ε) [nm] = 206.5 (4.42), 288.5 (3.52). MS (ESI): m/z (%) = 447.1 (100) $[M+Na]^+$. HRMS (ESI): m/z calcd for $[M+Na]^+$: 447.1414; found: 447.1425.

4.8. General procedure for the deprotection of D-galactose based chromans

Chroman (40 μmol, 1.0 equiv) was dissolved in acetonitrile (2 mL) and $HClO_4$–SiO_2 (10 mg) was added. The mixture was stirred over night at rt. The reaction was stopped by the addition of saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water 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 the desired compound as a white solid.

Table 3
Crystal data and structure refinement for bromoglycals **28**[14] and **32**

Compound	**28**	**32**
CCDC number	759503	757984
Empirical formula	$C_6H_9BrO_4$	$C_6H_9BrO_4$
Formula weight	225.04	225.04
Crystal system	Monoclinic	Orthorhombic
Space group	*C*2	$P2_12_12_1$
Temperature (K)	100(2)	100(2)
Wavelength (pm)	154.178	71.073
Unit cell dimensions		
a (Å)	25.0428(11)	4.7279(5)
b (Å)	4.7361(2)	11.5640(11)
c (Å)	6.7198(2)	13.9128(14)
α (°)	90	90
β (°)	94.5086(18)	90
γ (°)	90	90
Z	4	4
Volume (Å^3)	794.54(5)	760.66(13)
D_{calc} (g/cm^3)	1.881	1.965
μ (mm^{-1})	6.827	5.366
Max./min. transmission	0.3851/0.1890	0.4550/0.6652
θ range for data coll. (°)	3.54–71.15	2.29–27.31
Index ranges	$-30 \le h \le 30$ $-4 \le k \le 5$ $-8 \le l \le 8$	$-6 \le h \le 6$ $-14 \le k \le 14$ $-17 \le l \le 17$
Reflections collected	5790	13,579
Independent reflections	1280	1707
Data/restraints/parameters	1274/1/104	1707/9/127
R_{int}	0.0434	0.0226
Goodness-of-fit on F^2	1.126	1.11
$R_1(F)$ [$I > 2\sigma(I)$]	0.0481	0.0119
$wR(F^2)$ (all data)	0.1326	0.0319
Flack *x* parameter	0.12(5)	0.014(6)
Highest diff. peak/hole (e Å^{-3})	1.388/−1.004	0.388/−0.206

Analytical Data of **38l**: yield: 68%. R_f: 0.08 (hexane/EtOAc = 1:1). α = +14.0 (*c* 0.15, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.92–2.07 (m, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H), 3.70 (d, *J* = 7.4 Hz, 2H), 3.99–4.05 (m, 2H), 4.18 (dd, *J* = 3.5, 3.5 Hz, 1H), 4.69–4.77 (m, 1H), 4.79–4.88 (m, 1H), 4.94–5.02 (m, 2H), 6.44 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.5, 29.4, 32.3, 60.4, 62.5, 72.0, 78.3, 78.6, 107.3, 121.3, 127.7, 136.4, 145.7, 149.9. IR (KBr): ν (cm^{-1}) = 2927, 1750, 1622, 1468. UV (CH_3CN): λ_{max} (lg ε) [nm] = 205.5 (4.35), 225.0 (3.71), 286.5 (3.28). MS (ESI): *m/z* (%) = 271.1 (100) [M+Na]$^+$. HRMS (ESI): *m/z* calcd for [M+Na]$^+$: 271.0941; found: 271.0941.

5. X-ray investigations

The data for **28**[14] and **32** were collected from shock-cooled crystals at 100 K mounted with inert oil on glass fibers.[29] The data of **28** was collected on a Bruker Smart 6000-Cu rotating anode with INCOATEC Helios mirror optics. The data of **32** was collected on a Bruker TXS-Mo rotating anode with D8 goniometer and INCOATEC Helios mirror optics. Both were equipped with a low-temperature device. The data was integrated with SAINT,[30] and an empirical absorption correction with SADABS[31] was applied. Both structures were solved by direct methods (SHELXS-97)[32] and refined by full-matrix least-squares methods against F^2 (SHELXL-97).[32] The correctness of the absolute structures was successfully determined by the Flack x parameter (zero within 3 esd's) during the refinement.[33]

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. The CCDC numbers, crystal data and experimental details for the X-ray measurements are listed in Table 3. CCDC-759503 and -757984 contain 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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