Ti-Catalyzed Synthesis of Exocyclic Allenes on Oxygenated Heterocycles

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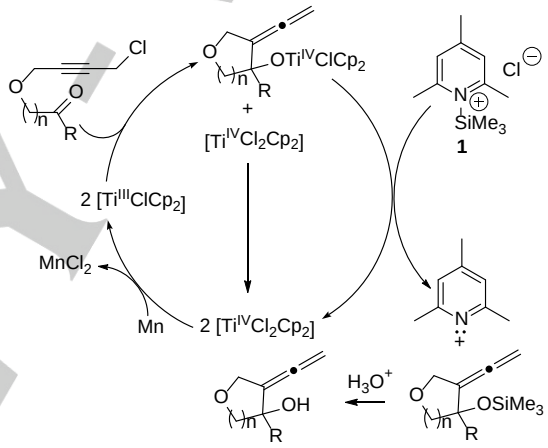
Abstract: A general method for the straightforward synthesis of exocyclic allenes on oxygenated five-, six-, seven- and eight-membered heterocycles is described. A Barbier-type titanocene(III) catalyzed cyclization of propargyl halides with a pendant carbonyl group is the key step of the process. This reaction is compatible with many functional groups and can be performed under smooth neutral and mild conditions at room temperature.

Introduction

For many years, allenes were considered highly unstable compounds or chemical curiosities for theoretical calculations. Nowadays, however, many natural products containing the allene group are known and, in many cases, they possess this peculiar unsaturated system on an exocyclic location.[1] In addition, allenes can be considered now as common building blocks in synthetic organic chemistry.[2] Due to the increasing versatility of allenes in pharmacy and contemporary chemistry, the number of methods for allene preparation is in continuous expansion.[3] In this context, we have recently reported the Barbier-type cyclization of propargyl halides catalyzed by [Cp_2TiCl] (Nugent-RajanBabu reagent).[4] This novel C-C bond forming reaction directly gave carbocycles and *N*-heterocycles with an exocyclic allene group and with ring sizes ranging from five to seven members.[5] Now, we have extended this method to the straightforward synthesis of oxygen-containing heterocycles bearing an exocyclic allene motif.

Results and Discussion

Titanium is a relatively inexpensive metal, one of the most abundant on the Earth crust, and many titanium derivatives are non-toxic and eco-friendly.[6] Moreover, based on our previous observations, we deemed that the Ti-catalyzed synthesis of oxygenated heterocycles bearing an exocyclic allene could be easily achieved by using the titanocene-regenerating agent **1**, developed in our laboratory,[7] to close the catalytic cycle depicted in Scheme 1.



Scheme 1. Anticipated catalytic cycle for the Ti-catalyzed synthesis of oxygenated heterocycles bearing an exocyclic allene.

To check our hypothesis, we treated ketone **2** with commercial Cp_2TiCl_2 in substoichiometric amount (0.2 equiv.), Mn dust and a mixture of TMSCl and 2,4,6-collidine, to allow the formation of **1**.[8] As expected, an acceptable 65% yield of the vinylidenetetrahydrofuran product **15** was obtained (Table 1, entry 1).

Subsequently, we checked the method for the synthesis of six-membered oxygenated heterocycles. Thus, treatment of aldehyde **3** under the above mentioned conditions gave the vinylidene hydroxychromane derivative **16** with a good 92% yield (Table 1, entry 2).

In a similar manner, titanocene(III)-catalyzed cyclization of dihalogenated aldehydes **4**-**7** provided halogenated vinylidenechromane derivatives **17**-**20** in yields ranging from a 84% to a 96% (Table 1, entries 3-6), confirming that the method is compatible with both aryl chlorides and aryl bromides. It should be noted that **17** and **18** were obtained as the trimethylsilyl ether derivatives of the expected alcohols, in accordance with the catalytic cycle depicted in Scheme 1. Moreover, secondary

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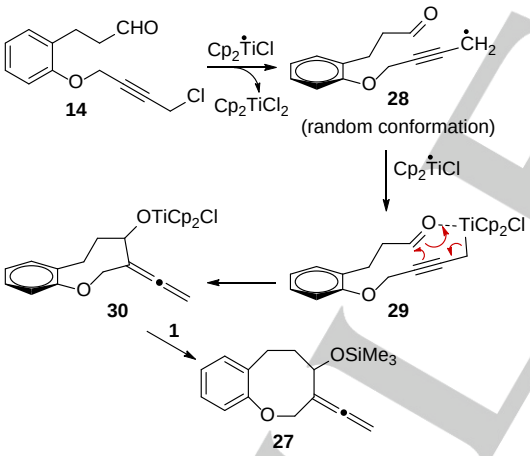
alcohols **16**-**20** might be easily transformed into chromone analogs by simple oxidation.

Titanocene(III)-catalyzed cyclization of ketone **8** lead to tertiary alcohol **21** with an excellent 94% yield (Table 1, entry 7). In a similar manner, Ti-catalyzed cyclization of aromatic ketones **9**-**12** gave vinylidenechromane derivatives **22**-**25** with yields ranging from 57% to 66% (Table 1, entries 8-11). Despite of the moderate yields obtained in these cyclizations, it should be noted that in all of these reactions relatively unstable tertiary and benzylic alcohols in α-position of an allene group were obtained, underlying the mild experimental conditions of the method. Synthesis of fluorinated benzopyran **23** (entry 9) also confirms that the method is compatible with aryl fluorides.

Ti(III)-catalyzed cyclization of aldehyde **13** gave vinylidenebenzoxepane derivative **26**. To the best of our knowledge, this is the first synthesis of an exocyclic allene on an oxygenated seven-membered heterocycle reported so far.

Eight-membered rings are considered as medium-size ones. Cyclization reactions leading to this kind of rings are generally hindered by both enthalpy and entropy factors.[9] Nevertheless, Ti(III)-catalyzed cyclization of aldehyde **14** gave an excellent 95% yield of vinylidenebenzoxocane derivative **27.** This is the first synthesis of an exocyclic allene on an eight-membered ring described to date, suggesting the potential usefulness of our method for the synthesis of medium-size rings. This unprecedented result may be rationalized if the mechanism depicted in Scheme 2 is accepted.

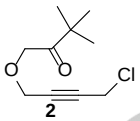
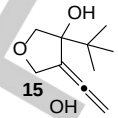
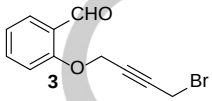
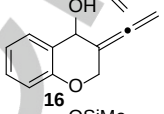
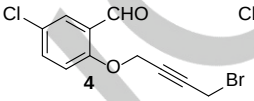
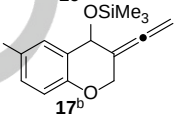
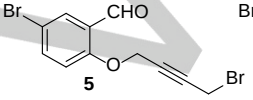
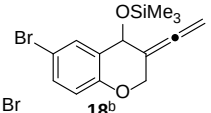
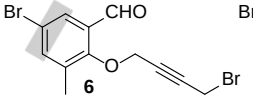
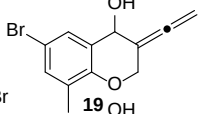
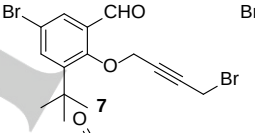
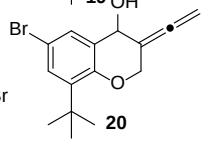
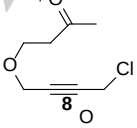
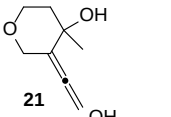
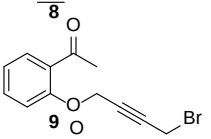
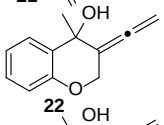
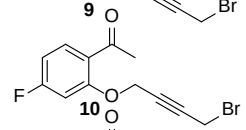
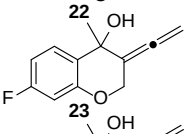
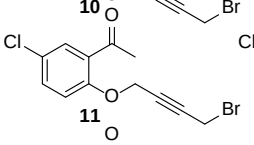
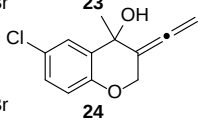
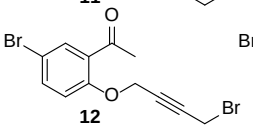
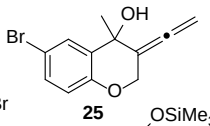
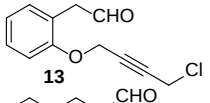
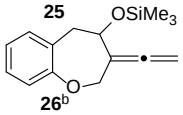
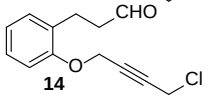
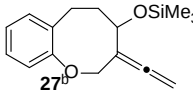


Scheme 2. Hypothetical mechanism for the titanocene(III)-catalyzed cyclization of **14** to **27**.

It is known that titanocene(III)-catalyzed cyclizations of propargyl halides take place in three steps: i) generation of a propargyl radical, ii) formation of an organometallic Ti(IV) complex and (iii) intramolecular nucleophilic attack to the carbonyl group.[5] In this way, formation of eight-membered ring **27** might proceed as depicted in scheme 2.

First, Cp_2TiCl would abstract the chlorine atom of **14** to give propargyl radical **28** (Scheme 2). Second, this radical would be

Table 1. Ti-catalyzed 5-, 6-, 7- and 8-cyclizations to oxygenated heterocycles with exocyclic allenes

Entry	Substrate	Product[a]	Yield [%]
1	 **2**	 **15**	65
2	 **3**	 **16**	92
3	 **4**	 **17**[b]	92
4	 **5**	 **18**[b]	96
5	 **6**	 **19**	95
6	 **7**	 **20**	84
7	 **8**	 **21**	94
8	 **9**	 **22**	63
9	 **10**	 **23**	60
10	 **11**	 **24**	57
11	 **12**	 **25**	66
12	 **13**	 **26**[b]	83
13	 **14**	 **27**[b]	95

[a] Free alcohol can also coexist with a lesser amount of the corresponding TMS ether, which can easily be converted into the alcohol by treatment with tetrabutylammonium fluoride. [b] Only the TMS ether was detected.

trapped by an additional Cp_2TiCl species to generate the alkyl-Ti(IV) organometallic intermediate **29**. In this key intermediate, coordination between titanium and the carbonyl oxygen closes a large-size twelve-membered ring in spite of unfavorable entropic factors.[10] Moreover, it is possible that the flat *o*-disubstituted benzene ring could exert some template effect, facilitating the cyclization to **29** by diminishing the entropy of the process. Finally, intramolecular nucleophilic attack to the carbonyl group, with concomitant extrusion of the allene moiety, would provide the eight-membered oxy-titanium ring **30,** which in the presence of the titanocene-regenerating agent **1**, would give product **27**.

Conclusions

In conclusion, we have demonstrated that the Cp_2TiCl-catalyzed cyclization of propargyl halides can also be used for the straightforward synthesis of exocyclic allenes on oxygenated five-, six-, seven- and eight-membered heterocycles. The reaction presumably follows the catalytic cycle depicted in Scheme 1. The present results, together with those previously described for carbocycles and nitrogen-containing heterocycles, suggest that this procedure might became a general and convenient method for the synthesis of exocyclic allenes.

Experimental Section

General experimental details. All reactions were performed under argon atmosphere, using oven-dried glassware in all cases. Dichloromethane was distilled from CaH_2 under argon. THF was distilled from Na/benzophenone under argon, and in all experiments involving titanocene (III) was deoxygenated prior to use. Dry distilled DMF was bought from Sigma-Aldrich supplier. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR, on a Varian Unity Inova operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR, and on a Varian Direct Drive operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, in $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) in hertzs (Hz). Chemical shifts are reported using $CDCl_3$ as internal reference. IR Spectra were recorded with a Bruker Alpha spectrometer and a Mattson Satellite FTIR. Mass spectra were recorded in a Waters Xevo by LC-QTof-MS and in a Bruker Autoflex by electrospray ionization. Analytical TLC was performed on 0.2 mm DC-Fertigfolien Alugram® Xtra Sil G/UV254 silica gel plates. Flash chromatography was performed on silicagel 60 (0.04 - 0.06 mm).

Synthesis of substrates 2, 8, 13, 14,

1-(4-Hydroxybut-2-ynyloxy)-3,3-dimethylbutan-2-one (2a). To a solution of but-2-yne-1,4-diol (1 g, 11.63 mmol) in dry DMF (30 mL) at 0 ºC, NaH 95 % (279 mg, 11.63 mmol) in dry DMF (5 mL) was added dropwise. The mixture was stirred for 1h, then 1-bromo-3,3-dimethylbutan-2-one (2.29 g, 12.79 mmol) was added and the mixture was stirred for 4 h at room temperature. Aqueous $KHSO_4$ saturated solution was added and the mixture extracted with Et_2O. The ethereal solution was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was submitted to flash chromatography (hexane/AcOEt 85:15) to give 985.6 mg (46%) of product **2a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ:4.42 (s, 2H), 4.31 (s, 4H), 1.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 211.3 (C), 85.5 (C), 80.9 (C), 69.7 (CH_2), 58.4 (CH_2), 51.0 (CH_2), 26.2 (CH_3). HRMS (TOF MS ES+) calc. for $C_{10}H_{17}O_3$ $[M+H]^+$: 185,1178; found 185,1153.

1-(4-Chlorobut-2-ynyloxy)-3,3-dimethylbutan-2-one (2). To a solution of compound **2a** (500 mg, 2.71 mmol) in Et_2O (30 mL), one drop of DMF and $SOCl_2$ (20 mL) were added. The mixture was stirred for 3 h, and then it was poured into a mixture of water-ice (40 mL) and AcOEt (60 mL). The organic layer was washed with aqueous $KHCO_3$ solution and with brine, dried over anhydrous Na_2SO_4. The solvent was removed and 538.3 mg (98%) of **2** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ:4.41 (br s, 2H), 4.31 (br s, 2H), 4.15 (br s, 2H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 211.1 (C), 82.0 (C), 81.7 (C), 69.6 (CH_2), 58.3 (CH_2), 42.9 (C), 30.2 (CH_2), 26.2 (CH_3). HRMS (TOF MS ES+) calc. for $C_{10}H_{16}ClO_2$ $[M+H]^+$: 203,0839; found 203,0835.

4-(4-Hydroxybut-2-ynyloxy)butan-2-one (8a). But-3-en-2-one (1 g, 14.26 mmol) was added to a mixture of but-2-yne-1,4-diol (1.23 g, 14.26 mmol) and DBU (4.57 mg, 0.03 mmol) in MeCN (43 mL) at room temperature. The mixture was stirred for 48h. The solvent was removed and the residue was submitted to flash chromatography (hexane/AcOEt 6:4) to give 1.78 g (80%) of product **8a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.31 (t, *J* = 1.7 Hz, 2H), 4.17 (t, *J* = 1.7 Hz, 2H), 3.77 (t, *J* = 6.2 Hz, 2H), 2.70 (t, *J* = 6.2 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 176.0 (C), 84.5 (C), 81.4 (C), 64.6 (CH_2), 58.3 (CH_2), 50.9 (CH_2), 43.2 (CH_2), 30.3 (CH_3). HRMS (TOF MS ES+) calc. for $C_8H_{13}O_3$ $[M+H]^+$: 157,0865; found 157,0886.

4-(4-Chlorobut-2-ynyloxy)butan-2-one (8). To a solution of compound **8a** (500 mg, 3.2 mmol) in Et_2O (30 mL), one drop of DMF and $SOCl_2$ (24 mL) were added. The mixture was stirred for 3 h, and then it was poured into a mixture of water-ice (50 mL) and AcOEt (70 mL). The organic layer was washed with aqueous $KHCO_3$ solution and with brine, dried over anhydrous Na_2SO_4. The solvent was removed and 547.5 mg (98%) of **8** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.21 (t, *J* = 1.8 Hz, 2H), 4.19 (t, *J* = 1.8 Hz, 2H), 3.78 (t, *J* = 6.2 Hz, 2H), 2.73 (t, *J* = 6.2 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 206.7 (C), 82.3 (C), 81.2 (C), 65.0 (CH_2), 58.5 (CH_2), 43.4 (CH_2), 30.4 (CH_3), 30.3 (CH_2). HRMS (TOF MS ES+) calc. for $C_8H_{12}ClO_2$ $[M+H]^+$: 175,0526; found 175,0551.

1-Allyl-2-(4-chlorobut-2-ynyloxy)benzene (13a). K_2CO_3 (1.5134 g, 11 mmol) and 1,4-dichlorobut-2-yne (1.8 mL, 17.5 mmol) were added to a solution of 2-allylphenol (1.5 mL, 11 mmol) in acetone (19 mL). The mixture was refluxed for 48 h. The reaction was quenched with HCl 5% (15 mL) and extracted with Et_2O. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduce pressure. Compound **13a** (1.3933 g, 6.32 mmol, 57%) was obtained as a colorless oil. IR (film) *v* (cm^{-1}): 1638, 1598, 1263, 1018.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.28-6.95 (4H, m), 6.02 (1H, ddt, *J*= 6.9 Hz, 10.2 Hz, 16.8 Hz), 5.09 (2H, m), 4.78 (2H, t, *J*= 1.8 Hz), 4.19 (2H, t, *J*= 1.8 Hz), 3.43 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 155.25 (C), 136.75 (CH), 130.01 (CH), 129.24 (C), 127.20 (CH), 121.52 (CH), 115.54 (CH_2), 112.02 (CH), 81.68 (C), 81.03 (C), 56.19 (CH_2), 34.16 (CH_2), 30.00 (CH_2). HRMS (QTof): calc. for $C_{13}H_{14}ClO$ $[M+1]^+$ 221.0733; found 221.0727.

2-(2-(4-Chlorobut-2-ynyloxy)phenyl)acetaldehyde (13). A 250 mL two-necked round-bottomed flask was charged with a mixture of **13a** (1 g, 4.5 mmol) and CH_2Cl_2 (100 mL). The flask was placed in a cooling bath (acetone/dry ice) at -78ºC, and a calcium chloride drying tube was used in one of the necks. Then O_3 was bubbled for 20 minutes until blue color appeared. N_2 was bubbled for 5 min. and Me_2S (343 µL, 4.5 mmol) was added. The mixture was stirred for 20 h, then the solvent was removed. The crude residue was purified by chromatography (gradient

hexane:AcOEt from 7:3 to 6:4). Compound **13** (0.1577 g, 0.7 mmol, 16%) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (1H, t, *J*= 2.1 Hz), 7.35-6.98 (4H, m), 4.78 (2H, t, *J*= 1.8 Hz), 4.16 (2H, t, *J*= 1.8 Hz), 3.70 (2H, d, *J*= 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 199.90 (CH), 155.56 (C), 131.49 (CH), 128.86 (CH), 121.79 (CH,C), 112.05 (CH), 82.16 (C), 81.10 (C), 56.11 (CH_2), 45.28 (CH_2), 30.07 (CH_2). HRMS (QTof): calc. for $C_{12}H_{12}ClO_2$ $[M+1]^+$ 223.0526; found 222.0520 $[M+1]^+$.

2-(3-Hydroxypropyl)phenol (14a). To a solution of $NaBH_4$ (0.395 g, 10 mmol) in THF (6 mL), 3,4-dihydrochromen-2-one (841 µL, 6.7 mmol) was added. The mixture was refluxed for 2 h, then, it was cooled until room temperature and aqueous NH_4Cl saturated solution (5 mL) was added dropwise for 10 min. The mixture was stirred for 4 h. It was extracted with AcOEt and the organic layer was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduce pressure. Compound **14a** (0.6754 g, 66%) was obtained as a colorless oil. Spectral data are in agreement with literature values.[11]

3-(2-(4-Chlorobut-2-ynyloxy)phenyl)propan-1-ol (14b). K_2CO_3 (0.6081 g, 4.4 mmol) and 1,4-dichlorobut-2-yne (714 µL, 7.1 mmol) were added to a solution of **14a** (0.6754 g, 4.4 mmol) in acetone (4.5 mL). The mixture was refluxed for 24 h. The reaction was quenched with HCl 5% (15 mL) and extracted with Et_2O. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduce pressure and purified by column chromatography (gradient hexane:AcOEt from 9:1 to 65:35). Compound **14b** (0.5521 g, 2.3 mmol, 52%) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.24-6.93 (4H, m), 4.79 (2H, s), 4.19 (2H, s), 3.65 (2H, t, *J*= 6.3 Hz), 2.75 (2H, t, *J*= 7.5 Hz), 1.88 (2H, q, *J*= 6.9 Hz). HRMS (QTof): calc. $C_{13}H_{15}ClO_2$ 238.0761; found 238.0757 $[M+1]^+$.

3-(2-(4-Chlorobut-2-ynyloxy)phenyl)propanal (14). To a suspension of PCC (1.0184 g, 4.6 mmol) in CH_2Cl_2 (20 mL), a solution of **14b** (0.5520 g, 2.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The mixture was stirred for 1 h, then Et_2O (40 mL) was added and it was stirred for another hour. The whole was filtered on silica gel. Compound **14** (0.4412 g, 1.9 mmol, 81%) was obtained as a colorless oil. IR (film) *v* (cm^{-1}): 3065, 2928, 2725, 2252, 1720, 1600. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.83 (1H, t, *J*= 1.5 Hz), 7.28-6.93 (4H, m), 4.78 (2H, t, *J*= 1.8 Hz), 4.18 (2H, t, *J*= 1.8 Hz), 2.98 (2H, t, *J*= 7.5 Hz), 2.75 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 202.30 (CH), 155.34 (C), 130.20 (CH), 129.21 (C), 127.58 (CH), 121.51 (CH), 111.79 (CH), 81.92 (C), 81.44 (C), 55.91 (CH_2), 43.82 (CH_2), 30.17 (CH_2), 23.32 (CH_2). HRMS (QTof): calc. $C_{13}H_{13}ClO_2$ 236.0604; found 236.0610 $[M+1]^+$.

Synthesis of substrates 3, 4, 5, 6, 7, 9, 10, 11, 12. General procedure A for S_N2 reactions. Salicylaldehyde or 2-hydroxyacetophenone derivatives (1 equiv) were added to a stirred mixture of sodium hydride, 60 % dispersion in mineral oil, (1.2 equiv.) in dry DMF (3 mL/mmol) or THF (3 mL/mmol) at 0º C. Then, 15-crown-5 (1.2 equiv.) was added. After 15 min, 1,4-dibromobut-2-yne (1.2 equiv) was added quickly and the mixture stirred for 12h. at room temperature. Aqueous $NaHCO_3$ saturated solution was added and the mixture extracted with Et_2O. The ethereal solution was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was submitted to flash chromatography (hexane/Et_2O mixtures) to give the corresponding product.

2-((4-Bromobut-2-yn-1-yl)oxy)benzaldehyde (3). Reaction of salicylaldehyde (600 µL, 4.13 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 533 mg (51%) of product **3**, isolated as a white solid. mp 46.5-47.6 ºC. IR (film) *v* (cm^{-1}): 2871, 2252, 1684, 1474, 1208, 1121, 1000, 728. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.46 (s, 1H), 7.84 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.10 – 7.05 (m, 2H), 4.88 (t, *J* = 2.0 Hz, 2H), 3.92 (t, *J* = 2.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 189.3 (CH), 159.7 (C), 135.7 (CH), 128.5 (CH), 125.5 (C), 121.6 (CH), 113.2 (CH), 83.3 (C), 80.6 (C, C), 56.6 (CH_2,), 13.5 (CH_2). HRMS (QTof): calc. for $C_{11}H_{10}BrO_2$ $[M+1]^+$: 252.9864, 254.9844 ; found 252.9857, 254.9840.

2-((4-Bromobut-2-yn-1-yl)oxy)-5-chlorobenzaldehyde (4). Reaction of 5-chloro-2-hydroxybenzaldehyde (500 mg, 3.76 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 532 mg (59%) of product **4**, isolated as a white solid. mp 73.2-75.3 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) 10.41 (s, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 1H), 4.90 (t, *J* = 2.0 Hz, 2H), 3.93 (t, *J* = 2.0 Hz, 2H). δ: ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 188.1 (CH), 158.1 (C), 135.2 (CH), 128.2 (CH), 127.5 (C), 126.4 (C), 114.9 (CH), 83.8 (C), 80.1 (C), 57.0 (CH_2), 13.3 (CH_2). HRMS (QTof): calc. for $C_{11}H_9BrClO_2$ $[M+1]^+$: 286.9474, 288.9454; found 286.9365, 288.9449.

5-Bromo-2-((4-bromobut-2-yn-1-yl)oxy)benzaldehyde (5). Reaction of 5-bromo-2-hydroxybenzaldehyde (500 mg, 2.98 mmol) with 1,4-dibromobut-2-yne in DMF according to the general procedure A afforded 460 mg (56%) of product **5**, isolated as a white solid. mp 65.1-67.3 ºC. IR (film) *v* (cm^{-1}): 2877, 1684, 1472, 1003, 742, 620. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.37 (s, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.65 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 1H), 4.88 (t, *J* = 2.0 Hz, 2H), 3.92 (t, *J* = 2.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 188.0 (CH), 158.6 (C), 138.1 (CH), 131.2 (CH), 126.7 (C), 115.3 (CH), 114.6 (C), 83.8 (C), 80.1 (C), 56.9 (CH_2), 13.4 (CH_2). HRMS (QTof): calc. for $C_{11}H_9Br_2O_2$ $[M+1]^+$: 332.8949; found 332.8922.

5-bromo-2-(4-bromobut-2-ynyloxy)-3-methylbenzaldehyde (6). Reaction of compound **6b** (215 mg, 1 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded product **6** (51%), isolated as a light yellow-green oil. IR (film) *v* (cm^{-1}): 2870, 2254, 1685, 1470, 1208, 1120, 1003, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.30 (s, 1H), 7.81 (d, *J*= 2.5 Hz,1 H), 7.58 (d, *J*= 2.2Hz, 1H), 4.72 (t, *J*= 2.0Hz, 2H), 3.84 (t, *J*= 2.0Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (DEPT) δ: 188.8 (CH), 157.6 (C), 139.7 (CH), 135.0(C), 131.6(C), 129.0(CH), 118.3(C), 84.6 (C), 80.4 (C), 62.5 (CH_2), 15.7 (CH_3), 13.2 (CH_2). HRMS (QTOF ES+): calculated for $C_{12}H_{11}Br_2O_2$ $[M+H]^+$: 344.9121, 346.9100, 348.9080; found: 344.9117, 346.9097, 348.9086.

5-Bromo-2-(4-bromobut-2-ynyloxy)-3-*tert*-butylbenzaldehyde (7). Reaction of compound **7b** (257 mg, 1 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded product **7** (58%), isolated as a light yellow-green oil. IR(film) *v* (cm^{-1}): 2872, 2250, 1687, 1471, 1203, 1121, 1005, 725.^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.80 (d, *J* = 2.6 Hz, 1H), 7.66 (d, *J* = 2.6 Hz, 1H), 4.71 (t, *J* = 2.1 Hz, 2H), 3.89 (t, *J* = 2.1 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) (DEPT) δ: 188.4 (CH), 159.1 (C), 146.6 (C), 136.3 (CH), 131.8 (C), 130.5 (CH), 117.8 (C), 84.5 (C), 80.3 (C), 65.2 (CH_2), 35.16(C), 30.7 (CH_3), 13.2 (CH_2). HRMS (QTOF ES+): calculated for $C_{15}H_{17}Br_2O_2$ $[M+H]^+$: 388.9575, 386.9595, 390.9554; found: 388.9580, 386.9593, 390.9551.

1-(2-((4-Bromobut-2-yn-1-yl)oxy)phenyl)ethanone (9). Reaction of 2-hydroxyacetophenone (570 µL, 3.67 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 503 mg (51%) of product **9**, isolated as a white solid. mp 39.8-41 ºC. IR (film) *v* (cm^{-1}): 3002, 2249, 1688, 1291, 1003, 754. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.06 – 7.02 (m, 2H), 4.85 (t, *J* = 2.0 Hz, 2H), 3.92 (t, *J* = 2.0 Hz, 2H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 199.4 (C), 156.7 (C), 133.4 (CH), 130.4 (CH), 129.1 (C), 121.6 (CH), 113.2 (CH), 82.9 (C), 80.9 (C), 56.5 (CH_2), 31.8 (CH_3), 13.6 (CH_2). HRMS (QTof): calc. for $C_{12}H_{12}BrO_2$ $[M+1]^+$: 287.0021, 269.0000; found 287.0010, 268.9992.

1-(2-((4-Bromobut-2-yn-1-yl)oxy)-4-fluorophenyl)ethanone (10). Reaction of 4-fluoro-2-hydroxyacetophenone (500 mg, 3.18 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 352 mg (39%) of product **10**, isolated as a white solid. mp 58.8-60.3 ºC. IR (film) *v* (cm^{-1}): 3019, 1664, 1584, 1419, 1221, 1010, 827. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 – 7.80 (m, 1H), 6.80 – 6.74 (m, 2H), 4.87 (t, *J* = 2.0 Hz, 2H), 3.94 (t, *J* = 2.0 Hz, 2H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 197.6 (C), 164.2 (C), 158.3 (C), 132.7 (CH), 125.1 (C), 108.5 (CH), 100.9 (CH), 83.5 (C), 80.0 (C), 56.7 (CH_2), 31.8 (CH_3), 13.2 (CH_2). HRMS (QTof): calc. for $C_{12}H_{11}BrFO_2$ $[M+1]^+$: 284.9926, 286. 9906; found 284.9924, 286.9900.

1-(2-((4-Bromobut-2-yn-1-yl)oxy)-5-chlorophenyl)ethanone (11). Reaction of 5-chloro-2-hydroxyacetophenone (500 mg, 2.90 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 410 mg (47%) of product **11**, isolated as a white solid. mp 74.3-79.6 ºC. IR (film) *v* (cm^{-1}): 2885, 2256, 1670, 1473, 1180, 902, 640. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.85 (t, *J* = 2.0 Hz, 2H), 3.92 (t, *J* = 2.0 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 197.8 (C), 155.6 (C), 135.8 (CH), 133.0 (CH), 130.5 (C), 115.1 (CH), 114.2 (C), 83.4 (C), 80.3 (C), 56.8 (CH_2), 31.7 (CH_3), 13.3 (CH_2). HRMS (QTof): calc. for $C_{12}H_{11}BrClO_2$ $[M+1]^+$: 300.9631, 302.9610; found 300.9621, 302.9602.

1-(5-Bromo-2-((4-bromobut-2-yn-1-yl)oxy)phenyl)ethanone (12). Reaction of 5-bromo-2-hydroxyacetophenone (500 mg, 2.28 mmol) with 1,4-dibromobut-2-yne in THF according to the general procedure A afforded 347 mg (44%) of product **12**, isolated as a white solid. mp 78.3-81.2 ºC. IR (film) *v* (cm^{-1}): 3001, 2243, 1664, 1476, 1205, 1003, 806. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 2.6 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.86 (t, *J* = 2.0 Hz, 2H), 3.93 (t, *J* = 2.0 Hz, 2H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 197.87 (C), 155.60 (C), 135.82 (CH), 133.05 (CH), 130.49 (C), 115.13 (CH), 114.26 (C), 83.41 (C), 80.29 (C), 56.76 (CH_2), 31.70 (CH_3), 13.31 (CH_2). HRMS (QTof): calc. for $C_{12}H_{11}Br_2O_2$ $[M+1]^+$: 346.9105; found 346.9126.

General experimental procedure B for the Ti(III) mediated cyclization. $[TiCp_2Cl_2]$ (0.2 equiv.) and Mn dust (8 equiv.) are placed in a Schlenk flask under an Ar atmosphere. Then, carefully deoxygenated, dry THF (20 mL) is added and the red suspension is stirred at room temperature until it turns lime green (after about 15 min). Next, a mixture of Me_3SiCl (4 equiv.) and 2,4,6-collidine (7 equiv.) in THF is added. Finally, a solution of the substrate (1 equiv.) in THF (2 mL) is added dropwise over a period of 15 min and the mixture stirred for another 6 h. The reaction is quenched with 2 N HCl and the organic solvent removed *in vacuo*. The residue is diluted in Et_2O, washed with brine, dried (anhydrous $MgSO_4$) and the solvent evaporated. Products were always purified by silica gel flash column chromatography (hexane/Et_2O mixtures).

3-(*tert*-Butyl)-4-vinylidenetetrahydrofuran-3-ol (15). Reaction of compound **2** (150 mg, 0.74 mmol) according to the general procedure B afforded 80.9 mg (65%) of product **15**, isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.06 (ddd, *J* = 11.0, 4.6, 3.8 Hz, 1H), 4.94 (ddd, *J* = 11.0, 4.7, 3.9 Hz, 1H), 4.58 (dt, *J* = 11.9, 3.8 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.01 (dd, *J* = 9.7, 0.4 Hz, 1H), 3.77 (d, *J* = 9.6 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 199.8 (C), 106.2 (C), 85.7 (C), 80.7 (CH_2), 77.0 (CH_2), 70.2 (CH_2), 25.3 (CH_3). HRMS (QTOF ES+): calc. for $C_{10}H_{17}O$ $[M+H]^+$: 169,1229; found 169,1235.

3-Vinylidenechroman-4-ol (16) Reaction of 2-((4-Bromobut-2-yn-1-yl)oxy)benzaldehyde (**3**) (100 mg, 0.395 mmol) according to the general procedure B afforded 63 mg (92%) of product **16**, isolated as colorless oil. Data corresponds to that quoted in the literature.[12]

6-Chloro-4-trimethylsilyloxy-3-vinylidenechromane (17). Reaction of 2-((4-bromobut-2-yn-1-yl)oxy)-5-chlorobenzaldehyde (**4**) (100 mg, 0.348 mmol) according to the general procedure B afforded 86 mg (0.32 mmol, 92%) of product **17**, isolated as colorless oil. IR (film) *v* (cm^{-1}): 2956, 1962, 1479, 1226, 1037, 838, 723. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 – 7.13 (m, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.12 (s, 1H), 4.98 – 4.97 (m, 2H), 4.78 (dt, *J* = 11.4, 2.8 Hz, 1H), 4.63 (dd, *J* = 11.4, 0.9 Hz, 1H), 0.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 204.5 (C), 152.7 (C), 129.3 (CH), 128.9 (CH), 126.0 (C), 125.4 (C), 118.4 (CH), 96.8 (C), 77.5 (CH_2), 66.0 (CH), 64.5 (CH_2), 0.3 (CH_3). HRMS (Qtof): calc. for $C_{14}H_{18}ClO_2Si$ $[M+1]^+$: 281.0759; found 281.0703.

6-Bromo-4-trimethylsilyloxy-3-vinylidenechromane (18). IR (film) *v* (cm^{-1}):2956, 1962, 1476, 1224, 998, 843, 815, 613. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 – 7.27 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 5.12 (s, 1H), 4.97 – 4.96 (m, 2H), 4.77 (dt, *J* = 11.4, 2.8 Hz, 1H), 4.62 (dd, *J* = 11.4, 0.9 Hz, 1H), 0.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 204.5 (C), 153.2 (C), 132.1 (CH), 131.8 (CH), 126.7 (C), 118.8 (CH), 112.6 (C), 96.9 (C), 77.4 (CH_2), 66.1 (CH), 64.5 (CH_2), 0.2 (CH_3). HRMS (Qtof): calc. for $C_{14}H_{18}BrO_2Si$ $[M+1]^+$: 325.0254; found 325.0224.

6-Bromo-3-vinylidenechroman-4-ol (18a). To a solution of **18** (65mg, 0.20 mmol) in THF (1 mL), 0.6 mL of *n*-Bu_4NF (1 M in THF) were added. The reaction mixture was stirred under reflux for 12 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in Et_2O, washed with brine, dried over $MgSO_4$ and filtered. The solvent was again removed. Compound **18a** (43mg, 0.17 mmol, 85%) was obtained after purification by flash chromatography SiO_2 (hexane/Et_2O 4:6). IR (film) *v* (cm^{-1}): 3358, 2921, 1961, 1478, 1001, 750. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 2.5 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.5 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 5.21 (s, 1H), 5.07 (dd, *J* = 4.2, 2.0 Hz, 2H), 4.78 (dd, *J* = 11.8, 2.4 Hz, 1H), 4.68 – 4.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 204.00 (C), 153.30 (C), 132.45 (CH), 131.53 (CH), 126.07 (C), 118.84 (CH), 113.03 (C), 97.33 (C), 78.88 (CH_2), 64.91 (CH_2), 64.85 (CH). HRMS (QTof): calc. for $C_{12}H_{11}BrO_2$ $[M+1]^+$: 252.9859; found 252.9849.

6-Bromo-8-methyl-3-vinylidenechroman-4-ol (19). Reaction of compound **6** (173 mg, 0.5 mmol) according to the general procedure B afforded 134 mg (0.475mmol, 95%) of product **19**, isolated as a light brown-green oil. IR (film) *v* (cm^{-1}): 3230, 2922, 2005, 1731, 1646, 1251, 1193, 1097, 933, 843, 734, 591. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d, *J*= 2.5 Hz, 1H), 7.20 (d, *J*= 2.2 Hz, 1H), 5.18 (br s, 1H), 5.05 (br s, 2H), 4.78 (dt, *J*= 11.7, 2.5 Hz ,1H), 4.68 (dt, *J*= 11.7, 1.4 Hz, 1H), 2.17 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) (DEPT) δ: 203.9 (C), 151.4 (C), 133.2 (CH), 129.1 (CH), 128.7 (C), 125.2 (C), 112.4 (C), 97.2 (C), 78.9(CH_2), 65.1 (CH), 64.8 (CH_2), 15.8 (CH_3). HRMS (QTOF ES-): calculated for $C_{12}H_{10}BrO_2$ $[M-H]^-$: 264.9869, 266.9884; found: 264.9868, 266.9876.

6-Bromo-8-tert-butyl-3-vinylidenechroman-4-ol (20). Reaction of compound **7** (100 mg, 0.26 mmol) according to the general procedure B afforded 68 mg (84%) of product **20**, isolated as a light brown-green oil. IR (film) *v* (cm^{-1}): 3166, 2954, 1974, 1730, 1431, 1252, 1214, 1157, 1001, 871, 846, 733, 645, 519. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, *J*= 2.5 Hz, 1H), 7.30 (d, *J*= 2.5 Hz, 1H), 5.18 (br s, 1H), 5.06 (br s, 2H), 4.73 (dt, *J*= 11.8, 2.6 Hz, 1H), 4.68(dt, *J*= 11.8, 1.8 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) (DEPT) δ: 203.6 (C), 152.2 (C), 140.7 (C), 129.8 (CH), 129.4 (CH), 126.8 (C), 113.2 (C), 97.7 (C), 79.3 (CH_2), 65.2 (CH), 64.4 (CH_2), 35.01 (C), 29.5 (CH_3). HRMS (QTOF ES-): calculated for $C_{15}H_{16}BrO_2$ $[M-H]^-$: 307.0339, 309.0318; found: 307.0344, 309.0325

Tetrahydro-4-methyl-3-vinylidene-2H-pyran-4-ol (21). Reaction of compound **8** (150 mg, 0.68 mmol) according to the general procedure B afforded 90.3 mg (94%) of product **21**, isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.93 (d, *J* = 10.6 Hz, 1H), 4.88 (dd, *J* = 11.0, 2.1 Hz,

1H), 4.38 (dt, *J* = 12.1, 2.6 Hz, 1H), 4.15 (d, *J* = 12.1 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.79 (dt, *J* = 11.6, 4.4 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 201.6 (C), 104.3 (C), 78.4 (CH_2), 67.9 (C), 66.9 (CH_2), 64.7 (CH_2), 40.1 (CH_2), 27.98 (CH_3). HRMS (ES): m/z calc. for $C_8H_{13}O_2$ $[M+H]^+$: 141.0916; found 141.0922.

4-Methyl-3-vinylidenechroman-4-ol (22). Reaction of 1-(2-((4-bromobut-2-yn-1-yl)oxy)phenyl)ethanone (**9**) (45 mg, 0.168 mmol) according to the general procedure B afforded 20 mg (0.106 mmol, 63%) of product **22**, isolated as colorless oil. IR (film) *v* (cm^{-1}): 3431, 2927, 1961, 1484, 1219, 1006, 727 ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.2, 1.7 Hz, 1H), 7.00 (ddd, *J* = 7.8, 7.2, 1.3 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.11 (t, *J* = 2.1 Hz, 2H), 4.79 (dt, *J* = 11.9, 1.9 Hz, 1H), 4.79 (dt, *J* = 11.9, 2.2 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 202.8 (C), 153.5 (C), 129.1 (CH), 128.9 (C), 126.5 (CH), 121.3 (CH), 117.0 (CH), 103.4 (C), 80.0 (CH_2), 77.2 (C), 65.9 (CH_2), 29.6 (CH_3). HRMS (QTof): calc. for $C_{12}H_{13}O_2$ $[M+1]^+$: 189.0910; found 189.0900.

7-Fluoro-4-methyl-3-vinylidenechroman-4-ol (23). Reaction of 1-(2-((4-bromobut-2-yn-1-yl)oxy)-4-fluorophenyl)ethanone (**10**) (100 mg, 0.351 mmol) according to the general procedure B afforded 47 mg (0.21 mmol, 60%) of product **23**, isolated as colorless oil. IR (film) *v* (cm^{-1}): 2852, 1597, 1259, 1021, 703. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (dd, *J* = 8.8, 6.5 Hz, 1H), 6.70 (m, 1H), 6.56 (dd, *J* = 10.1, 2.5 Hz, 1H), 5.11 (m, 2H), 4.82 – 4.69 (m, 2H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (C), 164.5 (C), 161.2 (C), 127.8 (CH), 108.4 (CH), 103.7 (CH), 112.9 (C), 103.0 (C), 80.2 (CH_2), 67.1 (C), 66.1 (CH_2), 29.6 (CH_3). HRMS (QTof): calc. for $C_{12}H_{11}FO_2$ $[M+1]^+$: 206,0743; found 206.0453.

6-Chloro-4-methyl-3-vinylidenechroman-4-ol (24). Reaction of 1-(2-((4-bromobut-2-yn-1-yl)oxy)-5-chlorophenyl)ethanone (**11**) (70 mg, 0.232 mmol) according to the general procedure B afforded 30 mg (57%) of product **24**, isolated as colorless oil. IR (film) *v* (cm^{-1}): 3390, 2982, 1961, 1476, 1239, 1003, 806. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 2.5 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 5.13 – 5.11 (m, 2H), 4.77 (dt, *J* = 12.0, 2.0 Hz, 1H), 4.71 (dt, *J* = 12.0, 2.3 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 202.7 (C), 152.7 (C), 131.9 (CH), 131.0, (C), 129.2 (CH), 118.8 (CH), 113.1 (C), 103.0 (C), 80.3 (CH_2), 67.3 (C), 66.0 (CH_2), 29.7 (CH_3). HRMS (QTof): calc. for $C_{12}H_{12}ClO_2$ $[M+1]^+$: 223.0520; found 223.0510.

6-Bromo-4-methyl-3-vinylidenechroman-4-ol (25). Reaction of 1-(5-bromo-2-((4-bromobut-2-yn-1-yl)oxy)phenyl)ethanone (**12**) (100 mg, 0.289 mmol) according to the general procedure B afforded 51 mg (66%) of product **25**, isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 5.13 (t, *J* = 2.0 Hz, 2H), 4.77 (dt, *J* = 12.0, 1.9 Hz, 1H), 4.71 (dt, *J* = 12.0, 2.3 Hz, 1H) 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 202.7 (C), 152.6 (C), 131.9 (CH), 130.9 (C), 129.3 (CH), 118.8 (CH), 113.3 (C), 102.8 (C), 80.4 (CH_2), 67.3 (C), 66.0 (CH_2), 29.7 (CH_3). HRMS (QTof): calc. for $C_{12}H_{12}ClO_2$ $[M+1]^+$: 267.0015; found 267.0013.

2,3,4,5-tetrahydro-4-trimethylsilyloxi-3-vinylidenebenzo[*b*]oxepine (26). Reaction of compound **13** (40 mg, 0.18 mmol) according to the general procedure B afforded 38 mg (0.15 mmol 83%) of product **26**, isolated as colorless oil. IR (film) *v* (cm^{-1}): 3065, 2923, 2857, 1958, 1489, 1226, 1044, 988. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23-6.98 (4H, m), 4.85 (2H, m), 4.62 (1H, dt, *J*= 1.8 Hz, 12.3 Hz), 4.52 (1H, m), 4.45 (1H, dt, *J*= 0.9 Hz, 12.3 Hz), 3.06 (2H, m), 0.11 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 206.36 (C), 159.32 (C), 131.78 (CH), 129.80 (C), 127.76 (CH), 123.51 (CH), 120.78 (CH), 104.57 (C), 77.15 (CH_2), 70.69 (CH_2), 69.41 (CH), 42.62 (CH_2), -0.10 (CH_3). HRMS (QTof): calc. for $C_{15}H_{21}O_2Si$ $[M+1]^+$: 261.1311; found 261.1320.

3,4,5,6-tetrahydro-4-trimethylsilyloxi-3-vinylidene-2H-benzo[*b*]oxocine (27). Reaction of compound **14** (100 mg, 0.42 mmol) according to the general procedure B afforded 109 mg (0.40 mmol, 95%) of product **27** isolated as colorless oil. IR (film) *v* (cm^{-1}): 2928, 2865, 1953, 1490, 1215, 1037, 984. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35-7.03 (4H, m), 4.64 (1H, m), 4.54 (2H, m), 4.50 (1H, m), 4.33 (1H, m), 2.91 (1H, m), 2.67 (1H, m), 1.93 (2H, m), 0.14 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ (ppm) 206.93 (C), 156.01 (C), 137.07 (C), 129.95 (CH), 127.64 (CH), 124.54 (CH), 121.78 (CH), 103.61 (C), 76.33 (CH_2), 74.92 (CH_2), 71.87 (CH), 40.30 (CH_2), 26.26 (CH_2), 0.05 (CH_3). HRMS (QTof): calc. for $C_{16}H_{23}O_2Si$ $[M+1]^+$: 275.1467; found 275.1475.

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[1] A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004***, 116*, 1216–1236; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196-1216.

[2] For a recent review on the use of allenes in asymmetric synthesis and natural product syntheses, see: S. Yu. S. Ma, *Angew. Chem.* **2012***, 124*, 3128–3167; *Angew. Chem. Int. Ed.* **2012**, *51*, 3074-3112.

[3] a) For an extensive survey on allene synthesis: *Modern Allene Chemistry, Vol. 1* (Eds.: N. Krause and S. K. Hashmi). Wiley-VCH, Weinheim, **2004**. For recent reviews on the preparation of allenes: b) M. Periasamy, N. Sanjeevakumar, M. Dalai, R. Gurubrahamam, P. O. Reddy, *Org. Lett.* **2012**, *14*, 2932-2935; c) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519−528; d) D. Tejedor, G. Méndez-Abt, L. Cotos, F. García-Tellado, *Chem. Soc. Rev.,* **2013**, *42*, 458-471; e) S. Yua, S. Ma, *Chem. Commun.*, **2011**, *47*, 5384–5418.

[4] a) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986-997; and cited work; b) A. Rosales, I. Rodríguez-García, J. Muñoz-Bascón, E. Roldan-Molina, N. M. Padial, L. P. Morales, M. García-Ocaña, J. E. Oltra, *Eur. J. Org. Chem*. **2015**, 4567-4592.

[7] J. Muñoz-Bascón, C. Hernández-Cervantes, N. M. Padial, M. Álvarez-Corral, A. Rosales, I. Rodríguez-García, J. E. Oltra, *Chem., Eur. J.* **2014**, *20*, 801-810.

[6] D. J. Ramón, M. Yus, *Chem. Rev.* **2006**, *106*, 2126-2208.

[7] A. F. Barrero, A. Rosales, J. M. Cuerva, J. E. Oltra, *Org. Lett*. **2003**, *5*, 1935-1938.

[8] In order to reuse the excess of 2,4,6-collidine and Mn dust, a simple filtration and acid-base extraction allowed us to recover both materials.

[9] E. L. Eliel, S. H. Wilen, M. P. Doyle, *Basic Organic Stereochemistry*, John Wiley & Sons, New York, 2001, pp 429-433.

[10] It is generally accepted that in large rings there are neither Baeyer strain nor transannular strain (see Ref. 9).

[11] A. Gridnev; C.A. Simoneau, S.D. Allen, J.J. Farmer, A.S. Godleski. *PCT Int. Appl*. 2012075277, **2012**.

[12] H.Y. Kang, Y.T. Kim, Y.K. Yu, J.H. Cha, Y.S. Cho, H.Y. Koh. *Synlett* **2004**, 45-48.

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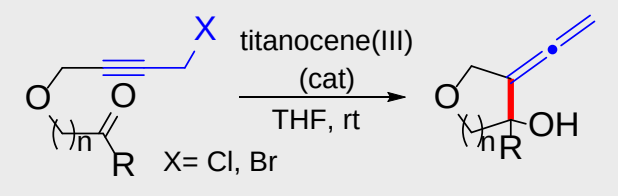

Synthesis of exocyclic allenes on oxygenated 5-, 6-, 7- and 8-membered heterocycles can be achieved through a Barbier-type titanocene(III) catalyzed cyclization of propargyl halides with a pendant carbonyl group.

Key Topic* Exocyclic Allenes.

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Ti-Catalyzed Synthesis of Exocyclic Allenes on Oxygenated Heterocycles