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Cyclotrimerization of unsymmetrically bromo-substituted diynes: toward the synthesis of potential selective inhibitors of tyrosine kinase 2

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ABSTRACT

A study on transition metal catalyzed alkyne cyclotrimerization of unsymmetrically bromo-substituted diynes with ethynyltrimethylsilane was carried out to prepare bicyclic bromobenzene key intermediates for the total synthesis of five potential tyrosine kinase 2 inhibitors. Two different pre-catalysts (Cp*RuCl(cod) and $[Rh(cod)_2]BF_4$/BINAP) and different reaction conditions have been examined.

1. Introduction

Multiple myeloma (MM) is the second most common hematologic cancer, accounting for about 1% of all cancer deaths worldwide.[1] The median survival time after diagnosis is 3–4 years, and there are currently no cures. Tyrosine kinase 2 (Tyk2) has been identified as a potential target for MM cancer therapy.[2]

Based on computational work, Tøndel and co-workers suggested the 1,2,3,5-substituted benzene derivatives **1**–**5** as potential selective Tyk2-inhibitors (Fig. 1).[3,4] However, **1**–**5** are not readily available and must be synthesized before their biological activity can be evaluated. Structural similarities allow for common synthetic strategies. Retrosynthetic analyses pointed at compounds **6a**–**d** as key intermediates in the synthesis of **1**–**5** (Scheme 1).

The TMS-substituent of **6** can be converted to both OH- and NH_2-groups, making **6** masked phenol- and/or aniline compounds. Several methods for such transformations exist, typically utilizing electrophilic *ipso*-desilylation processes.[5,6] The bromo-substituent of **6** is a potential site for oxidative addition to palladium catalysts, and facilitating the linkage of the vinylic side chains of **1**–**5**. In general, bromobenzene derivatives can be prepared from already existing aromatic compounds by electrophilic aromatic substitution, directed *ortho*-metalation, or other conventional methods.[7] Transition metal catalyzed alkyne cyclotrimerization is a more straightforward strategy to highly substituted aromatic compounds from rather simple alkyne precursors.[8–13] The substitution pattern in the resulting benzene product is determined by the substituents of the parent alkynes, but regioselectivity has to be controlled. Both the steric- and electronic properties of the catalyst and substrates might influence the selectivity.[9,14] Today, several

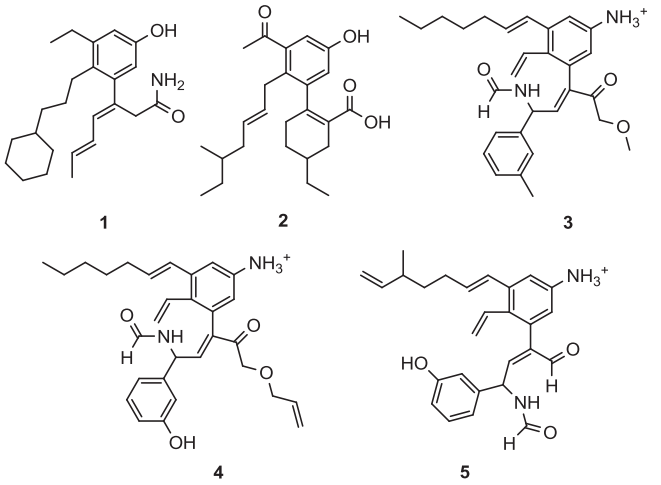

Fig. 1. Potential selective inhibitors of tyrosine kinase 2; **1**–**5**.

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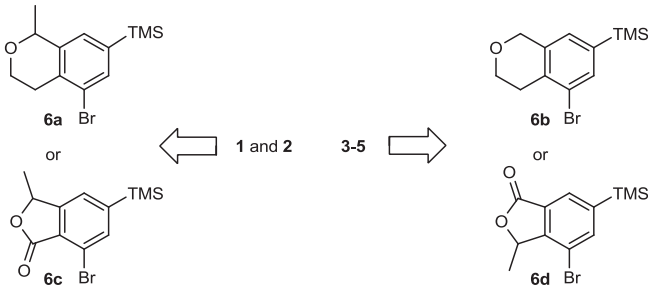
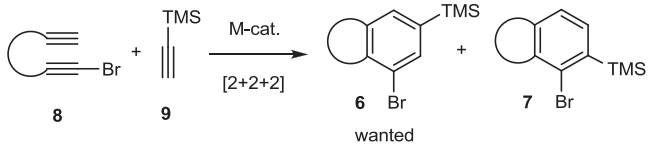


Scheme 1. Possible precursors to **1**–**5**.

catalysts and good methods exist for high yielding selective alkyne cyclotrimerization reactions.[8–13] Therefore, the compounds **6** might be available from the unsymmetrically bromo-substituted diynes (**8**) and ethynyltrimethylsilane (**9**) (Scheme 2) if the formation of regioisomers **7** can be suppressed.



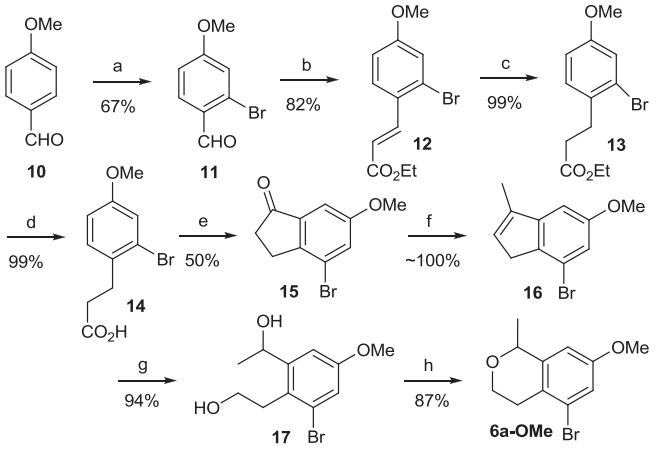
Scheme 2. The [2+2+2]-cyclotrimerization strategy for the preparation of **6**. 'M': transition metal catalyst.

In general, bromoalkynes are easily accessible from the corresponding terminal alkynes via mild and convenient methods, such as the silver catalyzed bromination with NBS developed by Hofmeister et al.[15] However, these compounds are most extensively used in reactions involving insertion of a metal to the C(sp)–Br bond. To the best of our knowledge, only two examples of cyclotrimerization reactions of bromo-substituted alkynes have been reported; an intramolecular co-catalyzed cyclization of a symmetrically dibromo-substituted triyne[16] and a Ru-catalyzed cyclotrimerization of a symmetrically substituted dibromodiyne with acetylene.[17] Concerning iodoalkynes, Yamamoto and co-workers have described Ru-catalyzed cyclotrimerization reactions of iododiynes with mono-alkynes[18] and used this methodology in the synthesis of spirocyclic *C*-arylribosides with potential biological activity.[19]

2. Results and discussion

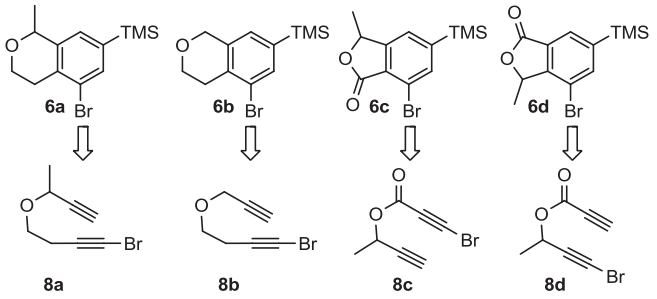
To compare the efficiency of a cyclotrimerization strategy to **6** (Scheme 2) with a classical approach, the methoxy-substituted variant of **6a** (**6a-OMe**) was prepared by eight classical steps from *p*-anisaldehyde (**10**) in 22% total yield (Scheme 3). Bromination with CBr_4 after the *ortho*-lithiation[20] of **10** gave **11** in 67% yield. A HWE-olefination of **11** provided pure *E*-**12** in 82% yield. Hydrogenation of **12** followed by hydrolysis of the ester **13**, yielded the acid **14** in 98%. The highest yield of **15** (50%) was obtained from an intramolecular Friedel–Craft acylation of **14** mediated by $AlCl_3$. Addition of MeMgBr to **15** followed by HCl-mediated elimination gave **16** in quantitative yield. Finally, ozonolysis of **16** with reductive work-up ($NaBH_4$) gave diol **17** in 94%, which easily cyclized to **6a-OMe** in the presence of acid (*p*-TsOH, 87%).

Despite several high yielding steps in the synthesis of **6a-OMe** (Scheme 3), a more direct and less time-consuming route to **6** was desirable. Thus, the transition metal catalyzed alkyne cyclotrimerization strategy (Scheme 2) has been investigated. For this method to be superior to a classical total synthesis approach, some



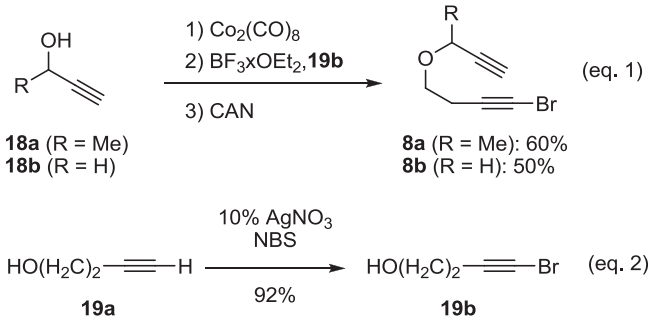
Scheme 3. Synthesis of **6a-OMe** from **10**. (a) (i) BuLi, $Me_2NCH_2CH_2NMe_2$ (ii) CBr_4 (b) $(EtO)_2POCH_2CO_2Et$, NaH (c) H_2, 5% $Rh–Al_2O_3$ (d) NaOH (e) (i) $SOCl_2$ (ii) $AlCl_3$ (f) (i) MeMgBr (ii) HCl (g) (i) O_3 (ii) $NaBH_4$ (h) *p*-TsOH.

requirements have to be fulfilled. First, the diyne precursors **8** (Scheme 4) should be easily accessible from commercially available starting materials. Second, the regioselectivity of the cyclotrimerization reactions of **8** and **9** must be controllable.



Scheme 4. Diynes **8**, precursors of **6**.

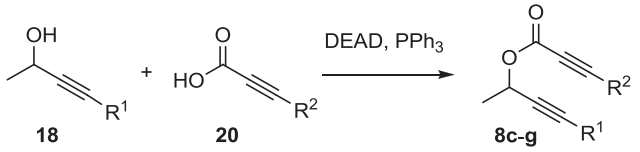
The ether linked 1,7-diynes **8a** and **8b** (Scheme 4) were prepared by the three step Nicholas reaction from the propargylic alcohols **18a** or **18b** and 4-bromo-3-butyn-1-ol (**19b**) (Scheme 5, Eq. 1) in 60% and 50% yield, respectively.[21] The brominated alkyne **19b**, was readily accessible by bromination of the terminal alkyne **19a** according to the method of Hofmeister et al. (Scheme 5, Eq. 2).[15]



Scheme 5. Preparation of **8a** and **b** by the Nicholas reaction (Eq. 1); preparation of **19b** from bromination of **19a** (Eq. 2).

For the preparation of ester-linked 1,6-diynes **8c** and **8d** (Table 1), the Mitsunobu reaction[22] of propargylic alcohols **18** with propargylic acids **20** was the initially planned strategy. Unfortunately, while **8d** was prepared from 4-bromobut-3-yn-2-ol (**18c**) and propiolic acid (**20a**) in 65% yield (Table 1, entry 2), only 22% yield of **8c** was

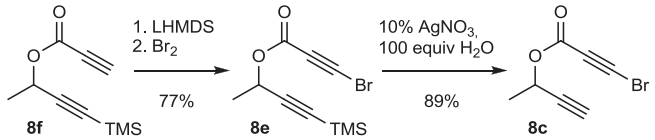
Table 1
Preparation of diynes **8c**–**g** by the Mitsunobu reaction[22]



Entry	**18** (R^1)	**20** (R^2)	Product (% yield)[a]
1	**18a** (H)	**20b** (Br)	**8c** (22%)
2	**18c** (Br)	**20a** (H)	**8d** (65%)
3	**18d** (TMS)	**20b** (Br)	**8e** (25%)
4	**18d** (TMS)	**20a** (H)	**8f** (73%)
5	**18a** (H)	**20c** (Me)	**8g** (77%)

[a] Isolated yield after column chromatography.

obtained by the same procedure applied on **18a** and 3-bromopropiolic acid (**20b**) (Table 1, entry 1). Attempts on esterification of **20b** with **18a** by other methods did not improve the isolated yield of the diyne. Only 20% yield of **8c** was isolated after a DCC/DMAP-mediated esterification,[23] and a standard acid catalyzed (*p*-TsOH) Fischer-esterification[24] with **18a** in excess showed only traces of product. In addition, the preparation of **20b** also turned out to be troublesome. Several methods were tried without success; bromination of **20a** by $AgNO_3$/NBS[15] and LHMDS/Br_2,[25] and basic hydrolysis of the corresponding ethyl ester (ethyl 3-bromopropiolate). The best result was obtained by bromination of **20a** with NaOBr,[26] which afforded **20b** in 37% yield. To examine the problem concerning the preparation of **8c**, a Mitsunobu test reaction of **20b** with the TMS-protected propargylic alcohol **18d** was preformed (Table 1, entry 3). The isolated 25% yield of the resulting diyne **8e** was not convincing, and decomposition or side reactions of **20b** were suspected. With this result in hand, an alternative route to **8c** employing the unsymmetrically TMS-protected diyne **8f** was investigated (Scheme 6). This diyne, **8f**, was prepared in 73% yield by the Mitsunobu reaction of **20a** and **18d** (Table 1, entry 4). Bromination of the terminal alkyne **8f** by LHMDS and Br_2 gave **8e** in 77% yield. Silver catalyzed TMS-deprotection of **8e** in the presence of water[27] gave **8c** in 89% yield. To compare with the 22% yield of **8c** obtained from the Mitsunobu reaction (Table 1, entry 1), this three step procedure gave a 50% total yield of **8c**.



Scheme 6. Preparation of **8c** from **8f**.

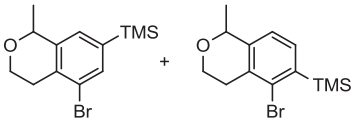
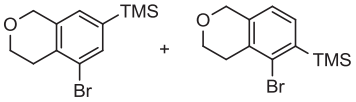
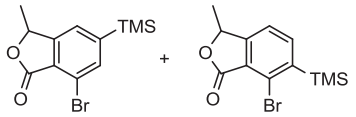
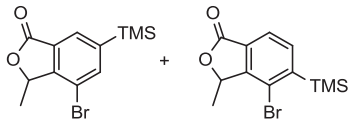
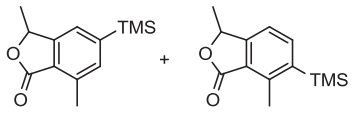
Ethynyltrimethylsilane (**9**) has been used extensively by Vollhardt and co-workers in co-mediated [2+2+2] cycloadditions.[28] Both the sterically demanding TMS substituent and the polarization of the C–Si bond,[6] might influence regioselectivity in the formation of cycloaddition products. With diynes **8a**–**d** in hand, cyclotrimerization of **8** with **9** was carried out using two different methods (A and B, Table 2). Method A refers to the cationic Rh(I)/BINAP-complex catalyzed alkyne cyclotrimerization procedure discovered by Tanaka and co-workers in 2003.[29,30] Under mild conditions, moderate to high yields of bicyclic products from cycloadditions of 1,6-diynes and, the in general less reactive, 1,7-diynes, have been obtained with both electron-deficient and electron-rich mono-alkynes.[30] Cationic Rh(I)/BINAP catalyzed cycloadditions of **9** with diethyl acetylenedicarboxylate has given only moderate yields, but excellent regioselectivity.[29,31] In general, regioselectivity is under electronic control and depends on the formation of the electronically favored rhodium metallacycle intermediate.[31] Method B was developed by Yamamoto and co-workers, and employs Cp*RuCl(cod) as a pre-catalyst.[32,33] Cycloadditions of unsymmetrical 1,6-diynes with terminal mono-alkynes in the presence of Cp*Ru(cod)Cl have displayed excellent selectivity for the sterically favored *meta*-products. The regioselectivity has its origin in steric interactions between the bulky Cp* ligand and the terminal alkyne substituents under formation of ruthenium metallacycle intermediates.[32,33] Opposite *ortho*-selectivity has been observed under reactions of terminal mono-alkynes with unsymmetrically substituted diynes bearing a conjugated carbonyl group in the tether. The inversed regioselectivity was explained by direct electronic effects from the electron-withdrawing group *para* to the electron-donating substituent on the mono-alkyne.[34] The results obtained from reactions of **8** with **9** by both methods, are given in Table 2.

Both **8a** and **b** reacted smoothly under the Rh-catalytic conditions applied in method A (Table 2, entries 1 and 3). High total yields of cyclotrimerization products were obtained (81 and 95%, respectively). In case of **8a**, the *ortho*-isomer **7a** was formed selectively over the wanted *meta*-product **6a** (*meta*/*ortho* 15:85, entry 1). However, low selectivity (43:57) was observed under the reaction of **8b**, where the *ortho*-isomer **7b** was formed in a slightly excess (entry 3). Method A required 10 equiv of compound **9** to provide the desired reaction. When the amount of **9** was reduced to 2 equiv, only self-trimerization products of **8a** and **b** were observed. It should also be noted that successful cyclotrimerization by method A was only achieved when dilution (c=0.1 M) and dropwise addition of **8** were employed. If the addition went too fast, and/or the solutions were more concentrated, considerable amounts of self-trimerization products of **8** were observed. Under the Ru-catalytic conditions in method B, the selectivity changed in favor of the wanted **6a** and **6b** (Table 2, entries 2, 4, and 5). The *meta*/*ortho* ratio of 9:1 was obtained in reactions of both **8a** and **b**, indicating a lesser importance of the methyl-substituent on **8a** regarding selectivity in method B compared to method A. However, higher yields were obtained of the methyl-substituted products **6a** and **7a** (28%, entry 2) compared to the unsubstituted products **6b** and **7b** (7%, entry 4), probably due to an increased Thorpe–Ingold effect[35] of **8a**. The yield of **6b**/**7b** was improved when a higher load of Ru-catalyst (10 mol %) and **9** (10 equiv) were applied on **8b** (23%, entry 5), but the selectivity remained 9:1.

Only moderate yields of cyclotrimerization products were obtained when applying method A on **8c** and **8d** (Table 2, entries 6 and 8), and formation of side products were observed by TLC and ^{1}H NMR-analyses of the crude. A 17:83 mixture of **6c** and **7c** was obtained from **8c** in 56% isolated yield (entry 6). Selectivity in slight favor of **6d** over **7d** was observed from the reaction of **8d**, where a 60:40 mixture of products were isolated in 40% yield (entry 8). More contrasting results on both reactivity and selectivity were observed for the cyclotrimerization of **8c** compared to **8d** by method B (Table 2, entries 7, 9, and 10). While **8c** reacted completely after 30 min (entry 7), **8d** needed an elevated temperature (80 °C) and higher load of both Ru-catalyst and **9** (10 mol %, 10 equiv) to react completely (compare entries 9 and 10). Excellent selectivity (97:3) from the reaction of **8c** was observed, and the wanted *meta*-product **6c** was isolated as a sole product in 64%. The reactions of **8d** gave a moderate selectivity in favor of **6d** over **7d** (77:23), and a total yield of 42%.

To illustrate the significance of the diyne bromo-substituent on the reaction outcome, the bromo-substituent of **8c** was replaced with a methyl group (**8g**). The diyne **8g** was prepared by the Mitsunobu reaction in 77% (Table 1, entry 5). Cyclotrimerization of **8g** with **9** by method B gave excellent *meta*-selectivity (97:3), and the product **6g** was isolated as a sole product in 97% yield (Table 2, entry 11).

Table 2
Cyclotrimerization of unsymmetrically bromo-substituted diynes **8** with ethynyltrimethylsilane (**9**)

Entry	8	Method[a]	% Conv. 8[b]	Products (6:7)[b]	% Yield[c]
				 **6a** **7a**	
1	**8a**	A	100	15:85	81
2	**8a**	B	100	90:10	28
				 **6b** **7b**	
3	**8b**	A	100	43:57	95
4	**8b**	B	58	90:10	7
5	**8b**	B[d]	100	90:10	23
				 **6c** **7c**	
6	**8c**	A	100	17:83	56
7	**8c**	B[e]	100	97:3	64
				 **6d** **7d**	
8	**8d**	A	100	60:40	40
9	**8d**	B	70	77:23	traces
10	**8d**	B[d,f]	100	77:23	42
				 **6g** **7g**	
11	**8g**	B	100	97:3	97

[a] Method A: 5% $[Rh(cod)_2]BF_4$/BINAP, 10 equiv **9** in DCE.[29,30] Method B: 5% Cp*Ru(cod)Cl, 5 equiv **9** in DCM or DCE.[32,33]
[b] Determined by ^1H NMR analysis of the crude.
[c] Total isolated yield of **6** and **7** after column chromatography.
[d] 10% catalyst, 10 equiv **9**.
[e] Reaction finished after 30 min.
[f] 80 °C.

3. Conclusion

Cyclotrimerization of unsymmetrically bromo-substituted diynes **8a**–**d** with ethynyltrimethylsilane (**9**) has been examined as a key step for the preparation of intermediates **6a**–**d** in the total synthesis of **1**–**5** (Fig. 1). The cationic Rh/BINAP catalyzed procedure developed by Tanaka (method A) gave moderate to excellent total yields of cyclotrimerization products (**6**+**7**), but the regioselectivity was in general favoring the *ortho*-isomers **7**. Using Yamamoto's method with Cp*RuCl(cod) as a pre-catalyst (method B), the regioselectivity shifted toward the *meta*-isomers **6**, but the isolated yields were in general lower. The best result regarding both yield and selectivity was obtained from the Ru-catalyzed cyclotrimerization of diyne **8c**, which gave **6c** as a sole product in 64%

isolated yield. A Ru-catalyzed test reaction with the methyl-substituted analogue **8g** gave **6g** in 97% yield, indicating that the bromo-substituted diynes might be labile under the reaction conditions. To compare cyclotrimerization to a classical approach, **6a** was prepared from **8a** and **9** by method B in 25% yield. An eight step synthesis of the methoxy-substituted analogue **6a-OMe** from *p*-anisaldehyde (**10**) was achieved in 22% total yield. This classical strategy included several high yielding steps, but it was time consuming compared to the more direct alkyne cyclotrimerization strategy. In addition, the cyclotrimerization strategy is a more general and faster approach to both the phenol- and aniline precursors **6a**–**d**.

4. Experimental section

4.1. General information

Chemicals were purchased from Sigma–Aldrich and used without further purification. All reactions sensitive to air or moisture were performed under argon or nitrogen atmosphere with dried solvents and reagents. DCM, THF, and Et_2O were dried using MBRAUN solvent purification system (MB SPS-800). DCE and toluene were dried by distillation after treatment with CaH_2, and stored over activated 4 Å molecular sieves. DCM and DCE were degassed with helium for 10–20 min prior to use in cyclotrimerization by method B (Ru-catalysis). Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 312 nm and a 5% solution of molybdophosphoric acid in 96% EtOH for detection. Column chromatography was performed with Silica gel (pore size 60 Å, 230–400 mesh particle size) purchased from Fluka. ^{1}H and ^{13}C NMR spectra were recorded from Bruker Advance DPX instruments (300/75 MHz and 400/100 MHz). Chemical shifts (δ) are reported in parts per million. Where $CDCl_3$ has been used, shift values for proton are reported with reference to TMS (0.00) via the lock signal of the solvent. Reference values for other NMR-solvents are taken from Silverstein.[36] Signal patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). ^{1}H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC). IR spectra were recorded from a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed (cm^{-1}). Accurate mass determination, EI and ESI, was performed on MAT95XL ThermoFinnigan and Agilent G1969 TOF MS instrument, respectively. For ESI analyses, samples were injected into the instrument using an Agilent 1100 series HPLC. A direct injection analysis without any chromatography was performed for the EI analyses.

4.2. Synthesis of 6a-OMe

*4.2.1. 2-Bromo-4-methoxybenzaldehyde (**11**).* 2-Bromo-4-methoxybenzaldehyde (**11**) was prepared in 67% from **10**, as described by Durst,[37] by the method of Comins and Brown.[20] Mp 77–79 °C; lit.[37] mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.21 (1H, d, *J* 0.8 Hz, CHO), 7.88 (1H, d, *J* 8.7 Hz, Ar–H5), 7.13 (1H, d, *J* 2.5 Hz, Ar–H3), 6.93 (1H, ddd, *J* 8.7, 2.5, 0.8 Hz, Ar–H6), 3.88 (3H, s, CH_3).

*4.2.2. (E)-Ethyl 3-(2-bromo-4-methoxyphenyl)-acrylate (**12**).* To a suspension of NaH (1.24 g, 51.7 mmol) in THF (300 mL) at 0 °C was added triethyl phosphonoacetate (7.20 mL, 36.6 mmol) dropwise over 5 min. The mixture was stirred at 0 °C for 1 h. A solution of **11** (6.90 g, 32.1 mmol) in THF (210 mL) was added dropwise over 1 h. The resulting solution was stirred at 0 °C for 30 min, warmed to rt, and stirred for additional 3 h. The reaction was quenched by addition of NH_4Cl (satd aq, 40 mL), and the solvent volume was reduced to ca. 50 mL under vacuum. The mixture was extracted with DCM (3×50 mL). The combined organic layers were washed with $NaHCO_3$ (satd aq, 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography (*n*-hexane/EtOAc, 9:1). The title compound was isolated as a colorless oil (7.50 g, 26.3 mmol, 82%), which transformed to a white solid when stored in freezer. Mp 39–40 °C; R_f (20% EtOAc/*n*-hexane) 0.37. IR (KBr): 3047 (w), 2975 (w), 2927 (w), 1697 (s), 1599 (s), 1488 (s), 1298 (s), 1276 (s), 1264 (s), 1231 (s), 1042 (s), 1025 (s), 975 (m), 858 (m), 809 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (1H, d, *J* 15.9 Hz, ArC*H*CHCO$_2$Et), 7.56 (1H, d, *J* 8.8 Hz, Ar–H6), 7.14 (1H, d, *J* 2.6 Hz, Ar–H3), 6.87 (1H, dd, *J* 8.8, 2.6 Hz, Ar–H5), 6.29 (1H, d, *J* 15.9 Hz, C*H*CO$_2$Et), 4.27 (2H, q, *J* 7.1 Hz, CH_2), 3.83 (3H, s, OCH_3), 1.34 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 161.2, 142.4, 128.4, 126.8, 126.3, 118.6, 118.1, 114.3, 60.5, 55.6, 14.3; HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}{}^{79}BrO_3$ $[M]^+$: 284.0043; found: 284.0044.

*4.2.3. Ethyl 3-(2-bromo-4-methoxyphenyl)-propanoate (**13**).* A solution of **12** (4.14 g, 14.5 mmol) in MeOH (110 mL) was added 5% Rh-alumina (414 mg, 10 wt %). The mixture was stirred under an atmosphere of H_2 (balloon) for 3 h. The catalyst was removed by filtration through a plug of silica packed with MeOH, and the solvent was removed under vacuum to give **13**, as a mixture of clear oil and white solid (4.10 g, 14.3 mmol, 99%). R_f (20% EtOAc/*n*-hexane) 0.37. IR (neat): 2979 (w), 2836 (w), 1730 (s), 1605 (m), 1492 (s), 1237 (s), 1179 (s), 1028 (s), 856 (m) cm^{-1}; ^{1}H NMR (300 MHz, MeOD): δ 7.17 (1H, d, *J* 8.6 Hz, Ar–H6), 7.09 (1H, d, *J* 2.6 Hz, Ar–H3), 6.82 (1H, dd, *J* 8.6, 2.6 Hz, Ar–H5), 4.09 (2H, q, *J* 7.2 Hz, CH_2CH$_3$), 3.74 (3H, s, OCH_3), 2.95 (2H, t, *J* 7.7 Hz, ArCH_2CH$_2$CO$_2$Et), 2.56 (2H, t, *J* 7.7 Hz, CH_2CO$_2$Et), 1.20 (3H, t, *J* 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, MeOD): δ 173.3, 160.3, 132.8, 132.0, 125.1, 119.1, 114.6, 61.6, 56.0, 35.4, 31.5, 14.5; HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}{}^{79}BrO_3$ $[M]^+$: 286.0199; found: 286.0203.

*4.2.4. 3-(2-Bromo-4-methoxyphenyl)propanoic acid (**14**).* A solution of **13** (2.80 g, 9.75 mmol) in MeOH (60 mL) was added NaOH (1 M in H_2O, 20 mL). The mixture was stirred at rt for 24 h. HCl (1 M in H_2O, ca. 30 mL) was added until pH ~2. The white precipitate was extracted into Et_2O (3×100 mL). The organic layers were washed with brine (200 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and **14** was isolated as a white solid (2.50 g, 9.65 mmol, 99%). Mp: 89–91 °C; R_f (20% EtOAc/*n*-hexane) 0.18. IR (KBr): 3063 (s, br), 2937 (w), 1714 (s), 1604 (s), 1489 (s), 1434 (s), 1317 (s), 1279 (s), 1233 (s), 1214 (s), 1037 (s), 810 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.34 (1H, br s, COOH), 7.16 (1H, d, *J* 8.5 Hz, Ar–H6), 7.10 (1H, d, *J* 2.6 Hz, Ar–H3), 6.80 (1H, dd, *J* 8.5, 2.6 Hz, Ar–H5), 3.78 (3H, s, OCH_3), 3.01 (2H, t, *J* 7.8 Hz, ArCH_2-CH$_2$CO$_2$H), 2.77 (2H, t, *J* 7.8 Hz, CH$_2$CH_2CO$_2$H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 158.8, 131.3, 130.8, 124.4, 118.1, 113.7, 55.5, 34.1, 30.2; HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}{}^{79}BrO_3$ $[M]^+$: 257.9886; found: 257.9889.

*4.2.5. 4-Bromo-6-methoxy-2,3-dihydro-1H-inden-1-one (**15**).* A solution of **14** (0.740 g, 2.86 mmol) and $SOCl_2$ (20 mL) was refluxed under a flow of N_2 for 3 h. The solution was cooled to rt and $SOCl_2$ was removed under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 (60 mL), cooled to 0 °C, and added $AlCl_3$ (0.500 g, 3.75 mmol) against a positive N_2-flow. The mixture was warmed to rt and stirred for 20 h. The red suspension was cooled to 0 °C. HCl (1 M in H_2O, 15 mL) was added, followed by H_2O (40 mL). The phases were separated, and the water phase was extracted with DCM (2×50 mL). The organic extracts were treated with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The title compound **15** was isolated after column chromatography (10% EtOAc/*n*-hexane) as a white solid (0.345 g, 1.43 mmol, 50%). Mp

102–103 °C; R_f (20% EtOAc/*n*-hexane) 0.31. IR (KBr): 3049 (w), 2961 (w), 2927 (w), 2827 (w), 1705 (s), 1608 (m), 1479 (s), 1299 (s), 1257 (s), 1031 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (1H, d, *J* 2.3 Hz, Ar–H), 7.16 (1H, d, *J* 2.3 Hz, Ar–H), 3.83 (3H, s, OCH_3), 3.03–2.98 (2H, m, $ArCH_2CH_2CO$), 2.77–2.72 (2H, m, $ArCH_2CH_2CO$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 160.2, 147.2, 139.5, 125.9, 122.1, 104.9, 55.9, 36.8, 26.0; HRMS (EI): *m*/*z* calcd for $C_{10}H_9{}^{79}BrO_2$ $[M]^+$: 239.9785; found 239.9780.

*4.2.6. 7-Bromo-5-methoxy-3-methyl-1H-indene (**16**).* MeMgBr (3.0 M in Et_2O, 2.35 mL, 7.05 mmol) was added dropwise to a suspension of **15** (1.00 g, 4.15 mmol) in Et_2O (30 mL) at rt. The mixture transformed temporary into a yellow solution, before formation of a new suspension was observed. After stirring at rt for 30 min, the suspension was cooled to 0 °C, and added HCl (concn, 22 mL). The mixture was warmed to rt and stirred for 30 min, before H_2O (50 mL) and Et_2O (50 mL) was added. The phases were separated, and the water phase was extracted with Et_2O (2×50 mL). The collected organic extracts were treated with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated, to give **16** (0.991 g, 4.14 mmol, 100%) as a white solid. Mp 54–55 °C; R_f (20% EtOAc/*n*-hexane) 0.51. IR (neat): 3066 (w), 3004 (w), 2938 (w), 2830 (w), 1558 (m), 1473 (m), 1253 (m), 1213 (m), 1060 (s), 831 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (1H, d, *J* 2.2 Hz, Ar–H), 6.82 (1H, d, *J* 2.2 Hz, Ar–H), 6.28–6.24 (1H, m, alkene–H), 3.83 (3H, s, OCH_3), 3.23 (2H, app. p, *J* 2.1 Hz, CH_2), 2.11 (3H, app. q, *J* 2.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 148.3, 139.9, 136.5, 130.7, 118.3, 113.0, 104.7, 55.8, 38.5, 13.2; HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}{}^{79}BrO$ $[M]^+$: 237.9988; found: 237.9984.

*4.2.7. 1-(3-Bromo-2-(2-hydroxyethyl)-5-methoxyphenyl)ethanol (**17**).* A solution of **16** (3.03 g, 12.7 mmol) in DCM (50 mL) was cooled to −78 °C. A flow of O_3 was added, until a persisting blue color was observed. O_2 was bubbled through the solution until the color disappeared (ca. 5 min). $NaBH_4$ (4.81 g, 127 mmol) and MeOH (50 mL) was added, and the mixture was slowly warmed to rt and stirred for 18 h. The solvents were removed under reduced pressure, and the resulting white mass was stirred with $CHCl_3$ (100 mL) and NH_4Cl (satd aq, 100 mL) for 30 min. The phases were separated, the water phase extracted with $CHCl_3$ (2×100 mL), and the collected organic extracts were dried ($MgSO_4$), filtered and, concentrated, to yield **17** as a white solid (3.27 g, 11.9 mmol, 94%). Mp 115–117 °C; R_f (10% MeOH/DCM) 0.32. IR (neat): 3271 (br m), 2954 (w), 2869 (w), 1601 (m), 1468 (m), 1252 (s), 1037 (s), 1027 (s), 854 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (1H, d, *J* 2.7 Hz, Ar–H), 7.04 (1H, d, *J* 2.7 Hz, Ar–H), 5.14 (1H, q, *J* 6.4 Hz, CH), 3.94–3.82 (2H, m, CH_2CH_2OH), 3.79 (3H, s, OCH_3), 3.50 (1H, br s, OH), 3.16–3.03 (2H, m, CH_2CH_2OH), 2.30 (1H, br s, OH) 1.49 (3H, d, *J* 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 146.9, 127.1, 126.0, 117.6, 111.1, 66.3, 61.7, 55.5, 33.4, 23.1; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{15}{}^{79}BrNaO_3$ $[M+Na]^+$: 297.0097; found: 297.0088.

*4.2.8. 5-Bromo-7-methoxy-1-methylisochroman (**6a-OMe**).* A mixture of **17** (3.20 g, 11.6 mmol) and *p*-TsOH (0.227 g, 1.19 mmol) was added toluene (100 mL) and DCM (50 mL), and warmed to reflux for 24 h. The resulting dark red solution was cooled to rt and concentrated under vacuum. The crude oil was dissolved in DCM (50 mL), washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (2% EtOAc/*n*-hexane) gave **6a-OMe** as a yellow oil (2.59 g, 10.1 mmol, 87%). R_f (50% EtOAc/*n*-hexane) 0.59. IR (neat): 2933 (w), 2834 (w), 1604 (m), 1558 (m), 1474 (s). 1270 (s), 1118 (s), 1093 (s), 1042 (s), 854 (s), 793 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (1H, d, *J* 2.5 Hz, Ar–H), 6.60 (1H, d, *J* 2.5 Hz, Ar–H), 4.77 (1H, q, *J* 6.4 Hz, CH), 4.17 (1H, ddd, *J* 11.5, 5.8, 3.3 Hz, OCH_2CH_2Ar), 3.78 (3H, s, OCH_3), 3.74 (1H, ddd, *J* 11.5, 9.8, 4.2 Hz, OCH_2CH_2Ar) 2.87–2.77 (1H, m, OCH_2CH_2Ar), 2.72–2.64 (1H, m, OCH_2CH_2Ar), 1.51 (3H, d, *J* 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 142.6, 125.4, 125.2, 115.7, 110.1, 72.3, 63.6, 55.5, 29.1, 21.7; HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}{}^{79}BrO_2$ $[M]^+$: 256.0093; found: 256.0093.

4.3. Silver catalyzed bromination of terminal alkynes; preparation of 18c and 19b

The brominated alkynes **18c** and **19b** was prepared in according with a procedure developed by Hofmeister et al.[15]

*4.3.1. 4-Bromobut-3-yn-2-ol (**18c**).*[38] To a mixture of NBS (12.5 g, 70.2 mmol) and $AgNO_3$ (1.09 g, 6.42 mmol) in acetone (100 mL) was added **18a** (5.0 mL, 64 mmol). The suspension was stirred for 1 h at rt before it was concentrated under vacuum. The resulting gray mass was partitioned between ice water (100 mL) and Et_2O (100 mL). The phases were separated and the water phase was extracted with Et_2O (2×100 mL). The collected organic extracts were treated with brine (300 mL), dried ($MgSO_4$), filtrated, and concentrated under reduced pressure. The title compound (7.59 g, 50.9 mmol, 80%) was isolated as a yellow oil after column chromatography (10–20% EtOAc/*n*-hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 4.54 (1H, q, *J* 6.6 Hz, CH), 2.11 (1H, br s, OH), 1.46 (3H, d, *J* 6.6 Hz, CH_3).

*4.3.2. 4-Bromobut-3-yn-1-ol (**19b**).*[39] The title compound was obtained from **19a** (5.0 mL, 66 mmol) following the procedure described for **18c**. Purification by column chromatography (10–20% EtOAc/*n*-hexane) afforded **19b** (9.09 g, 61.0 mmol, 92%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (2H, app q, *J* 6.0 Hz, CH_2CH_2OH), 2.50 (2H, t, *J* 6.2 Hz, CH_2CH_2OH), 1.82 (1H, br t, *J* 6.1 Hz, OH).

*4.3.3. 3-Bromopropiolic acid (**20b**).*[26] The title compound was prepared from **20a** (6.15 mL, 99.9 mmol) and isolated as a white solid (5.45 g, 36.6 mmol, 37%), as reported by Morisawa and coworkers[26] Mp 84–85 °C; lit.[26] mp 84–85 °C. IR (neat): 2540 (m, br), 2186 (m), 1682 (s), 1605 (s), 1264 (s), 903 (s), 742 (s), 714 (s), 679 (s), 579 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.97 (br s, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.1, 73.6, 54.1; HRMS (EI) *m*/*z* calcd for $C_3H^{79}BrO_2$ $[M^+]$: 147.9154; found: 147.9157.

4.4. Preparation of diynes 8

*4.4.1. Preparation of **8a** and **b** by the Nicholas reaction.* Diynes **8a** and **b** were obtained from a Nicholas reaction procedure described by Martin, Martin and Ortega et al.[40]

*4.4.1.1. 1-Bromo-4-(but-3-yn-2-yloxy)but-1-yne(**8a**).* To a solution of $Co_2(CO)_8$ (6.71 g, 19.6 mmol) in DCM (70 mL) was added **18a** (1.38 mL, 17.6 mmol) at rt. The mixture was stirred for 2 h under a flow of N_2. The deep red solution was concentrated under reduced pressure. To the resulting oil was added a solution of **19b** (13.1 g, 87.9 mmol) in DCM (35 mL), and the solution was cooled to 0 °C under Ar-atm. $BF_3{\times}OEt_2$ (5.61 mL, 44.7 mmol) was added slowly, and the reaction mixture was stirred at 0 °C for 1 h. A solution of $NaHCO_3$ (satd aq, 30 mL) was added, the mixture was warmed to rt and stirred for 15 min. The phases were separated, and the water phase was extracted with DCM (3×30 mL). The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated to a deep red oil. The oil was dissolved in acetone (100 mL) and cooled to 0 °C. Ceric ammonium nitrate (CAN, 39.1 g, 71.3 mmol) was added in portions over 15 min. The mixture was warmed to rt and stirred until no gas evolution was observed (ca. 15 min). The resulting pink solution was concentrated to a solid pink residue, which was partitioned between Et_2O (70 mL) and H_2O (70 mL). The phases were

separated, and the water phase was extracted with Et_2O (2×70 mL). The collected organic phases were treated with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The title compound **8a** was isolated as a pale yellow oil (2.12 g, 10.5 mmol, 60%), after column chromatography (2% EtOAc/*n*-hexane). R_f (20% EtOAc/*n*-hexane) 0.60. IR (neat): 3295 (m), 2988 (w), 2870 (w), 1327 (m), 1104 (s), 636 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.20 (1H, dq, *J* 6.6, 2.1 Hz, CH), 3.82 (1H, dt, *J* 9.1, 7.0 Hz, OCH_2CH_2C), 3.53 (1H, td, *J* 9.1, 7.0 Hz, OCH_2CH_2C), 2.51 (2H, t, *J* 7.0 Hz, OCH_2CH_2C), 2.43 (1H, d, *J* 2.1 Hz, CCH), 1.45 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.5, 77.1, 73.3, 66.5, 65.4, 39.3, 22.1, 21.1; HRMS (EI): *m*/*z* calcd for $C_7H_7{}^{79}BrO$ $[M-CH_2]^+$: 185.9675; found: 185.9677. The excess of **19b** was recycled from column chromatography (R_f (20% EtOAc/*n*-hexane) 0.15).

*4.4.1.2. 1-Bromo-4-(prop-2-ynyloxy)but-1-yne (**8b**).* Diyne **8b** was obtained from **18b** (0.29 mL, 5.0 mmol) and **19b** (3.69 g, 24.8 mmol), following the procedure described for **8a**. Purification by column chromatography (2% EtOAc/*n*-hexane) gave **8b** (0.469 g, 2.51 mmol, 50%) as a pale yellow oil. R_f (10% EtOAc in *n*-hexane) 0.40. IR (neat): 3293 (m), 2870 (w), 1356 (m), 1097 (s), 634 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.19 (2H, d, *J* 2.4 Hz, OCH_2C), 3.65 (2H, t, *J* 6.9 Hz, OCH_2CH_2C), 2.52 (2H, t, *J* 6.9 Hz, OCH_2CH_2C), 2.45 (1H, t, *J* 2.4 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 79.5, 76.9, 74.8, 67.7, 58.3, 39.5, 21.0; HRMS (ESI): *m*/*z* calcd for $C_7H_{11}{}^{79}BrNO$ $[M+NH_4]^+$: 204.0019; found: 204.0020.

4.4.2. General procedure for the Mitsunobu reaction. A solution of **20** (1 equiv) and DEAD (40 wt % in toluene, 1 equiv) in Et_2O was added dropwise over 20 min to a cooled (0 °C) solution of PPh_3 (1 equiv) and **18** (1.5 equiv) in Et_2O (concn **20**=0.3 M). The resulting suspension was stirred and warmed to rt. After 20 h, the mixture was filtered through a silica-pad, pre-packed with Et_2O. The pad was washed with Et_2O. The filtrate was concentrated, and the crude product was purified by column chromatography.

*4.4.2.1. But-3-yn-yl 3-bromopropiolate (**8c**).* Diyne **8c** (0.496 g, 2.47 mmol, 22%) was prepared from **20b** (1.67 g, 11.2 mmol) and **18a** (1.32 mL, 16.8 mmol) in accordance with the general Mitsunobu procedure, and isolated as a yellow liquid after column chromatography (10% EtOAc/*n*-hexane). R_f (10% EtOAc/*n*-hexane) 0.36. IR (neat): 3297 (m), 2993 (w), 2215 (m), 2191 (m), 1709 (s), 1222 (s), 1022 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.48 (1H, dq, *J* 6.7, 2.1 Hz, CH), 2.52 (1H, d, *J* 2.1 Hz, alkyne–H), 1.56 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 80.9, 74.2, 72.5, 62.4, 53.9, 21.1; HRMS (EI): *m*/*z* calcd for $C_7H_5{}^{79}BrO_2$ $[M]^+$: 199.9467; found: 199.9464.

*4.4.2.2. 4-Bromobut-3-yn-2-yl propiolate (**8d**).* Diyne **8d** (0.554 g, 2.76 mmol, 65%) was prepared from **20a** (0.260 mL, 4.22 mmol) and **18c** (0.95 g, 6.4 mmol) in accordance with the general Mitsunobu procedure, and isolated as a yellow liquid after column chromatography (5% EtOAc/*n*-hexane). R_f (20% EtOAc/*n*-hexane) 0.42. IR (neat): 3289 (m), 2998 (w), 2214 (w), 2116 (m), 1712 (s), 1213 (s), 1032 (s), 753 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.50 (1H, q, *J* 6.6 Hz, CH), 2.94 (1H, s, alkyne–H), 1.56 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 77.1, 75.5, 74.2, 63.0, 47.1, 20.9; HRMS (EI): *m*/*z* calcd for $C_7H_5{}^{79}BrO_2$ $[M]^+$: 199.9467; found: 199.9465.

*4.4.2.3. 4-(Trimethylsilyl)but-3-yn-2-yl 3-bromopropiolate (**8e**).* Diyne **8e** (0.240 g, 0.880 mmol, 25%) was prepared from **20b** (0.530 g, 3.56 mmol) and **18d** (0.90 mL, 5.4 mmol) in accordance with the general Mitsunobu procedure, and isolated as a pale yellow oil after column chromatography (2% EtOAc/*n*-hexane). R_f (10% EtOAc/*n*-hexane) 0.46. IR (neat): 2961 (w), 2210 (w), 2193 (w), 1716 (s), 1222 (s), 838 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.50 (1H, q, *J* 6.7 Hz, CH), 1.53 (3H, d, *J* 6.7 Hz, CH_3), 0.17 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 102.1, 91.1, 72.6, 63.1, 53.6, 21.4, −0.2; HRMS (EI): *m*/*z* calcd for $C_{10}H_{13}{}^{79}BrO_2Si$ $[M]^+$: 271.9863; found: 271.9865.

*4.4.2.4. 4-(Trimethylsilyl)but-3-yn-2-yl propiolate (**8f**).* Diyne **8f** (4.60 g, 23.7 mmol, 73%) was prepared from **20a** (2.00 mL, 32.5 mmol) and **18d** (8.20 mL, 48.8 mmol) in accordance with the general Mitsunobu procedure, and isolated as a colorless liquid after column chromatography (5% EtOAc/*n*-hexane). R_f (10% EtOAc/*n*-hexane) 0.39. IR (neat): 3267 (w, br), 2961 (w), 2117 (m), 1716 (s), 1218 (s), 839 (s), 755 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.51 (1H, q, *J* 6.7 Hz, CH), 2.92 (1H, s, alkyne–H), 1.54 (3H, d, *J* 6.7 Hz, CH_3), 0.18 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 102.1, 91.1, 75.4, 74.6, 63.0, 21.4, −0.17; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}NO_2Si$ $[M+NH_4]^+$: 212.1101; found: 212.1103.

*4.4.2.5. But-3-yn-2-yl but-2-ynoate (**8g**).* Diyne **8g** (0.621 g, 4.56 mmol, 77%) was prepared from **20c** (0.496 g, 5.90 mmol) and **18a** (0.69 mL, 8.8 mmol) in accordance with the general Mitsunobu procedure, and isolated as a pale yellow oil after column chromatography (5% EtOAc/*n*-hexane). R_f (10% EtOAc/*n*-hexane) 0.26. IR (neat): 3293 (m), 2994 (w), 2310 (w), 2240 (m), 1709 (s), 1242 (s), 1059 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.47 (1H, dq, *J* 6.7, 2.2 Hz, CH), 2.49 (1H, d, *J* 2.2 Hz, alkyne–H), 2.00 (3H, s, alkyne–CH_3), 1.55 (3H, d, *J* 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 86.5, 81.2, 73.6, 72.0, 61.4, 21.0, 3.8; HRMS (ESI): *m*/*z* calcd for $C_8H_{12}NO_2$ $[M+NH_4]^+$: 154.0863; found: 154.0862.

*4.4.3. But-3-yn-yl 3-bromopropiolate (**8c**) from **8f**.* A solution of **8f** (0.983 g, 5.06 mmol) in THF (15 mL) was cooled to −78 °C and added LHMDS-solution (1.0 M in THF, 6.1 mL, 6.1 mmol) dropwise over 15 min. The mixture was stirred at −78 °C for 1 h. Br_2 (0.31 mL, 6.1 mmol) was added dropwise over 5 min. The deep red solution was warmed to 0 °C, and stirred for 1 h. A solution of NH_4Cl (satd aq, 15 mL) was added to quench the reaction. The mixture was warmed to rt and the phases were separated. The water phase was extracted with Et_2O (2×15 mL). The collected organic extracts were treated with $Na_2S_2O_3$ (satd aq, 2×30 mL), dried ($MgSO_4$), filtered, and concentrated to a deep red oil. The crude was purified by column chromatography (2% EtOAc/*n*-hexane) to give **8e** as a pale yellow oil (1.063 g, 3.891 mmol, 77%). Spectroscopic data for **8e** are given in chapter 4.4.2.3.

To a solution of **8e** (0.955 g, 3.49 mmol) in acetone (25 mL) was added $AgNO_3$ (59.4 mg, 0.349 mmol) and water (6.30 mL, 0.349 mol). The mixture was stirred at rt in darkness. After 20 h, the yellow suspension was poured into brine (40 mL). The phases were separated and the water phase was extracted with Et_2O (3×40 mL). The collected organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The crude was purified by column chromatography (2% EtOAc/*n*-hexane) to afford **8c** (0.623 g, 3.10 mmol, 89%) as a yellow liquid. Spectroscopic data for **8c** are given in chapter 4.4.2.1.

4.5. Preparation of 6 by cyclotrimerization of 8 and 9

General procedures for each method are given under. Yields and selectivity data are given in Table 2. Characterization data and work-up details for the products are given under the general procedures.

4.5.1. Method A: Rh-catalyzed cyclotrimerization. The Rh-catalyzed alkyne cyclotrimerization reactions were performed as described by Tanaka and co-workers[29,30]

$[Rh(cod)_2]BF_4$ (15 mg, 0.037 mmol) and BINAP (23 mg, 0.037) were added DCM (5 mL) at rt, and the solution was stirred for 5 min. The flask was evacuated, and 1 atm of H_2 was introduced (balloon).

After stirring at rt for 1 h, the mixture was concentrated to dryness, re-dissolved in DCE (4 mL), and **9** (1.06 mL, 7.50 mmol) was added. A solution of **8** (0.75 mmol) in DCE (3.5 mL) was added dropwise over 10 min via cannula, and the mixture was stirred at rt for 20 h. The resulting crude solution was concentrated under vacuum, analyzed by ^{1}H NMR, and purified by column chromatography.

4.5.2. Method B: Ru-catalyzed cyclotrimerization. The Ru-catalyzed alkyne cyclotrimerization reactions were performed as described by Yamamoto and co-workers[32,33]

A degassed solution of **8** (0.75 mmol) and **9** (0.53 mL, 3.75 mmol) in DCE (3.75 mL) was added dropwise at rt over 10 min to Cp*Ru(cod)Cl (14.2 mg, 0.0375 mmol) via cannula. The deep red solution was stirred at rt for 20 h. The resulting crude mixture was concentrated under reduced pressure, analyzed by ^{1}H NMR, and purified by column chromatography.

*4.5.3. (5-Bromo-1-methylisochroman-7-yl)trimethylsilane (**6a**).* The title compound was prepared from **8a** and **9**, and isolated as a yellow oil after column chromatography (2% EtOAc/*n*-hexane) (Table 2, entries 1 and 2). R_f (10% EtOAc/*n*-hexane) 0.44. IR (neat): 2954 (w), 1370 (m), 1249 (s), 1116 (s), 835 (s), 753 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, s, Ar–H), 7.14 (1H, s, Ar–H), 4.82 (1H, q, *J* 6.4 Hz, CH), 4.17 (1H, ddd, *J* 11.5, 5.8, 3.5 Hz, OCH_2CH$_2$Ar), 3.77 (1H, ddd, *J* 11.5, 9.6, 4.2 Hz, OCH_2CH$_2$Ar), 2.94–2.84 (1H, m, OCH$_2$-CH_2Ar), 2.79–2.71 (1H, m, OCH$_2$CH_2Ar), 1.54 (3H, d, *J* 6.4 Hz, CH$_3$), 0.26 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 140.4, 134.7, 133.9, 128.4, 125.7, 72.2, 63.2, 30.0, 21.8, −1.2; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{23}{}^{79}BrNOSi$ $[M+NH_4]^+$: 316.0727; found: 316.0724.

*4.5.4. (5-Bromo-1-methylisochroman-6-yl)trimethylsilane (**7a**).* The title compound was prepared from **8a** and **9**, and isolated in a mixture with the regioisomer **6a** as a yellow oil, after column chromatography (2% EtOAc/*n*-hexane) (Table 2, entries 1 and 2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (1H, d, *J* 7.8 Hz, Ar–H), 7.03 (1H, d, *J* 7.8 Hz, Ar–H), 4.81 (1H, q, *J* 6.5 Hz, CH), 4.19 (1H, ddd, *J* 11.5, 5.8, 3.3 Hz, OCH_2CH$_2$Ar), 3.77 (1H, ddd, *J* 11.5, 9.8, 4.2 Hz, OCH_2CH$_2$Ar), 2.94–2.84 (1H, m, OCH$_2$CH_2Ar), 2.81–2.74 (1H, m, OCH$_2$CH_2Ar), 1.52 (3H, d, *J* 6.5 Hz, CH$_3$), 0.39 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 139.7, 133.8, 133.5, 133.4, 123.1, 72.2, 63.6, 30.6, 21.7, −0.4.

*4.5.5. (5-Bromoisochroman-7-yl)trimethylsilane (**6b**).* The title compound was prepared from **8b** and **9**, and isolated as a yellow oil after column chromatography (2% EtOAc/*n*-hexane) (Table 2, entries 3, 4 and 5). R_f (10% EtOAc/*n*-hexane) 0.39. IR (neat): 2954 (w), 2851 (w), 1248 (m), 1235 (m), 1089 (m), 863 (s), 833 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, s, Ar–H), 7.05 (1H, s, Ar–H), 4.74 (2H, s, ArCH_2O), 3.99 (2H, t, *J* 5.8 Hz, OCH_2CH$_2$Ar), 2.81 (2H, t, *J* 5.8 Hz, OCH$_2$CH_2Ar), 0.25 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 137.0, 134.8, 133.6, 128.2, 125.7, 67.9, 65.5, 29.3, −1.2; HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}{}^{79}BrOSi$ $[M]^+$: 284.0227; found: 284.0224.

*4.5.6. (5-Bromoisochroman-6-yl)trimethylsilane (**7b**).* The title compound was prepared from **8b** and **9**, and isolated as a yellow oil in mixture with the regioisomer **6b**, by column chromatography (2% EtOAc/*n*-hexane) (Table 2, entries 3, 4, and 5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (1H, d, *J* 7.5 Hz, Ar–H), 6.93 (1H, d, *J* 7.5 Hz, Ar–H), 4.72 (2H, s, ArCH_2O), 3.99 (2H, t, *J* 5.9 Hz, OCH_2CH$_2$Ar), 2.81 (2H, t, *J* 5.9 Hz, OCH$_2$CH_2Ar), 0.39 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 138.5, 133.8, 133.4, 133.2, 122.8, 67.8, 65.7, 29.9, −0.3.

*4.5.7. 7-Bromo-3-methyl-5-(trimethylsilyl)iso-benzofuran-1(3H)-one (**6c**).* The title compound was prepared from **8c** and **9**, and isolated as a white solid after column chromatography (10% EtOAc/*n*-hexane) (Table 2, entries 6 and 7). Mp 95–97 °C; R_f (10% EtOAc/*n*-hexane) 0.20. IR (neat): 2953 (w), 1755 (s), 1319 (s), 1043 (s), 875 (s), 835 (s), 755 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H, s, Ar–H), 7.45 (1H, s, Ar–H), 4.48 (1H, q, *J* 6.7 Hz, CH), 1.64 (3H, d, *J* 6.7 Hz, CH$_3$), 0.33 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 153.0, 151.4, 138.3, 125.1, 124.5, 120.7, 76.2, 20.6, −1.2; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}{}^{79}BrNO_2Si$ $[M+NH_4]^+$: 316.0363; found: 316.0360.

*4.5.8. 7-Bromo-3-methyl-6-(trimethylsilyl)iso-benzofuran-1(3H)-one(**7c**).* The title compound was prepared from **8c** and **9**, and isolated as a yellow oil in mixture with the regioisomer **6c** after column chromatography (10% EtOAc/*n*-hexane) (Table 2, entry 6). R_f (10% EtOAc/*n*-hexane) 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (1H, d, *J* 7.5 Hz, Ar–H), 7.35 (1H, d, *J* 7.5 Hz, Ar–H), 4.45 (1H, q, *J* 6.6 Hz, CH), 1.62 (3H, d, *J* 6.6 Hz, CH$_3$), 0.45 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 154.5, 144.5, 141.2, 128.8, 124.2, 120.0, 75.4, 20.5, −0.2.

*4.5.9. 4-Bromo-3-methyl-6-(trimethylsilyl)iso-benzofuran-1(3H)-one (**6d**) and 4-bromo-3-methyl-5-(trimethylsilyl)iso-benzofuran-1(3H)-one (**7d**).* Cyclotrimerization experiments of **8d** and **9** (Table 2, entries 8, 9, and 10) afforded inseparable mixtures of **6d** and **7d**. The mixtures were isolated as yellow oils after column chromatography (5% EtOAc/*n*-hexane).

Analytical data for a 1:0.6 mixture of **6d** and **7d**: R_f (10% EtOAc/*n*-hexane): 0.28. IR (neat): 2954 (w), 1769 (s), 1317 (m), 1250 (m), 1095 (s), 1046 (s), 834 (s), 755 (s) cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}{}^{79}BrO_2Si$ $[M]^+$: 298.0019; found: 298.0013.

NMR data for **6d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, s, Ar–H), 7.87 (1H, s, Ar–H), 5.52 (1H, q, *J* 6.6 Hz, CH), 1.75 (3H, d, *J* 6.6 Hz, CH$_3$), 0.32 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 150.4, 146.0, 142.1, 129.7, 127.8, 116.8, 78.5, 18.7, −1.1.

NMR data for **7d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, d, *J* 7.5 Hz, Ar–H), 7.61 (1H, d, *J* 7.5 Hz, Ar–H), 5.53 (1H, q, *J* 6.5 Hz, CH), 1.77 (3H, d, *J* 6.5 Hz, CH$_3$), 0.46 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 150.3, 149.6, 137.0, 128.8, 124.1, 123.7, 79.1, 18.9, −0.4.

*4.5.10. 3,7-Dimethyl-5-(trimethylsilyl)isobenzo-furan-1(3H)-one (**6g**).* 3,7-Dimethyl-5-(trimethylsilyl)*iso*-benzofuran-1(3*H*)-one (**6g**) was prepared by the Ru-catalytic general procedure from **8g** and **9**, and isolated as a white solid after column chromatography (5% EtOAc/*n*-hexane) (Table 2, entry 11). Mp 77–78 °C; R_f (10% EtOAc/*n*-hexane) 0.34. IR (neat): 2953 (m), 1745 (s), 1329 (s), 1242 (s), 1046 (s), 877 (s), 825 (s), 752 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (1H,s, Ar–H), 7.34 (1H, s, Ar–H), 5.48 (1H, q, *J* 6.7 Hz, CH), 2.69 (3H, s, Ar–CH$_3$), 1.62 (3H, d, *J* 6.7 Hz, CH$_3$), 0.31 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 150.8, 148.5, 138.2, 135.4, 123.7, 123.4, 76.8, 20.6, 17.3, −1.3; HRMS (EI): *m*/*z* calcd for $C_{13}H_{18}O_2Si$ $[M]^+$: 234.1071; found: 234.1074.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.087. These data include MOL files and InChiKeys of the most important compounds described in this article.

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