Divergent Strategy for the Diastereoselective Synthesis of the Tricyclic 6,7-Diaryltetrahydro-6H-benzo[c]chromene Core via Pt(IV)-Catalyzed Cycloaddition of o-Quinone Methides and Olefin Ring-Closing Metathesis

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INTRODUCTION

The tricyclic tetrahydro- and hexahydro-6H-benzo[c]-chromenes are the cores of naturally occurring as well as synthetic compounds, many of which display a wide range of interesting and important biological activities. Palodesangrens, a group of natural Diels–Alder products isolated from Brosimum rubescens Taubert, possess the common tetracyclic 6,7-Diaryltetrahydro-6H-benzo[c]chromene core structurally related to the tricyclic core of palodesangrens.

RESULTS AND DISCUSSION

Initially, we first considered the simplified tricyclic compound 8, where the substituent at C9 was a hydrogen atom instead of a methyl group. In addition, to facilitate the quinone methide chemistry, a methoxy group was placed at C3 while bromine was present at C2. Thus, our approach toward the synthesis of 8 where both Ar groups at C6 and C7 were 4-methoxyphenyl can be outlined retrosynthetically as shown in Scheme 1. While it is plausible to form 8 via an intramolecular [4 + 2] cycloaddition reaction of the diacetate precursor 9, the aldol condensation between benzaldehyde 10 and ketone 11 failed. The presence of an Ar group at the allylic position of 11 renders the proton at that position more acidic; the preformed

PtCl4 as the mediator/catalyst for the generation and [4 + 2] cycloaddition reactions of o-quinone methides (o-QMs) to prepare functionalized chromans and others. Herein we report, for the first time, the stereoselective synthesis of the 6,7-dihydro-6H-benzo[c]chromene core derivable from a 3,4-cyclohexenylfused chroman harbored as a 3,4-functionalized chroman. In recent years, we have investigated and reported the use of p-toluenesulfonic acid immobilized on silica (PTS-Si) as well as

Supporting Information

ABSTRACT: A divergent strategy for the synthesis of the tricyclic 6,7-dihydro-6H-benzo[c]chromene core was successfully developed. The 2,3-trans, 2,4-cis trisubstituted chroman moiety was formed via highly efficient and stereoselective Pt(IV)-catalyzed cycloaddition reactions of the corresponding quinone methides with chalcones. Subsequent steps provided the common diene alcohol, which underwent BF3·Et2O-mediated Et3SiH reduction and olefin ring-closing metathesis (RCM) using Ru(II) catalysts. The sequence of the final two steps provided a handle to diversify the stereochemical outcomes at C6 as well as C10a.

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enolate of 11 under basic conditions may be quenched by this proton, presumably via proton transfer. Thus, the intermolecular [4 + 2] cycloaddition reaction was considered as a means to install the requisite 2,3-trans,2,4-cis chroman core of 8. The olefin moiety of the cyclohexenyl ring of 8 could arise from the diene 12 via ring-closing metathesis (RCM). The allyl group of the diene 12 could be installed by allylation followed by reduction (or vice versa) of the ketone functional group in 13. As the quinone methide precursor, the corresponding benzyl acetates 14 and 15 could be prepared from the aldehyde 10 prior to its [4 + 2] cycloaddition reaction with the chalcone 16.

**Formation of Chroman.** The acetate 14, prepared in two steps from 10, was first considered as the quinone methide precursor to prepare 8 (Scheme 2). However, 14 did not provide the corresponding product 17 from the anticipated [4 + 2] cycloaddition reactions with simple styrene; decomposition of 14 as well as the allylic alcohol (the intermediate prior to acetylation) was observed under both PTS-Si and PtCl₄ conditions. Similarly, the [4 + 2] cycloaddition reactions of 14 with the diene 18 did not proceed to furnish the desired 2,3,4-trisubstituted chroman 19.

Due to the apparently low stability of 14 under the PTS-Si/PtCl₄-mediated [4 + 2] cycloaddition reaction conditions, the benzyl acetate 15 bearing a TMS-protected acetylene moiety as a masked vinyl group was then considered. The benzyl acetate 15 was prepared in a straightforward manner from the aldehyde 10 via TMS acetylide addition followed by acetylation in quantitative yield over two steps (Scheme 3). With the benzyl acetate 15 in hand, its [4 + 2] cycloaddition reactions with styrene and 4-vinylanisole were carried out using PTS-Si; moderate yields (42–44%) of the desired chromans 20 and 21 were obtained, each as a mixture of inseparable 2,4-cis and 2,4-trans diastereomers. The corresponding ketone chroman 22 from a similar reaction using (E)-chalcone under PtCl₄ catalysis was also produced, presumably in low yield, as evidenced by the ¹H NMR of the semipurified product. Nevertheless, the results suggested that the PtCl₄-catalyzed [4 + 2] cycloaddition

![Scheme 2. Attempted Synthesis of the Chromans 17 and 19](image-url)

![Scheme 3. Synthesis of the Ketone Chroman 24a](image-url)
reaction between the benzyl acetate 15 as a quinone methide precursor and a chalcone as a dienophile was feasible. After some experimentation, upon reaction with chalcone 23a containing a 4-methoxy substituent on each aromatic ring, the benzyl acetate 15 gave the corresponding ketone chroman 24a in 85% yield as an inseparable 8:1 mixture of 2,4-cis and 2,4-trans diastereomers.\(^{24}\) Presumably, the ratio of 2,4-cis to 2,4-trans reflected the endo preference at the transition state of the [4 + 2] cycloaddition.\(^{16}\)

The scope of the [4 + 2] cycloaddition reactions between the benzyl acetate 15 and various substituted chalcones 23a–l was investigated. Chalcones 23a–l with different numbers and substitution patterns of the methoxy group were used; the results are summarized in Table 1.

**Table 1. PtCl₂-Catalyzed [4 + 2] Cycloaddition Reactions between Benzyl Acetate 15 and Various Chalcones 23a–l**

<table>
<thead>
<tr>
<th>entry</th>
<th>chalcone</th>
<th>Ar¹</th>
<th>product</th>
<th>H₂,H₃</th>
<th>yield (%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23a</td>
<td>(4-OMe)C₆H₄</td>
<td>24a</td>
<td>8:1</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>23b</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24b</td>
<td>8:1</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>23c</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24c</td>
<td>7:1</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>23d</td>
<td>(4-OMe)C₆H₄</td>
<td>24d</td>
<td>&gt;99:1</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>23e</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24e</td>
<td>&gt;99:1</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>23f</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24f</td>
<td>6:1</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>23g</td>
<td>(4-OMe)C₆H₄</td>
<td>24g</td>
<td>8:1</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>23h</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24h</td>
<td>9:1</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>23i</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24i</td>
<td>5:1</td>
<td>38</td>
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<tr>
<td>10</td>
<td>23j</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24j</td>
<td>&gt;99:1</td>
<td>53</td>
</tr>
<tr>
<td>11</td>
<td>23k</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24k</td>
<td>&gt;99:1</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>23l</td>
<td>(3,4,5-(OMe)₃)C₆H₂</td>
<td>24l</td>
<td>5:1</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^{a}\)Unless otherwise noted, the reactions were performed using PtCl₂ (10 mol %) and chalcone 23a–l (2 equiv) in CH₂Cl₂ as solvent.\(^{a}\)Isolated yields.

as shown in A. Subsequent TBAF-mediated desilylation followed by hydrogenation of the terminal acetylene using Lindlar’s catalyst produced the corresponding olefin 26 in 89% yield over two steps. However, allylation of 26 or its N-tosylated amine, under various conditions, did not proceed to give the desired diene 27.\(^{20,26}\)

At this point, allylation of the ketone via allyl Grignard followed by reduction of the corresponding tertiary alcohol using Et₃SiH was considered as an alternative to provide the diene 27. After some experimentation, it was found that desilylation of 24a could be smoothly affected by Cs₂CO₃ in methanol\(^{27}\) to furnish the corresponding ketone alkyne 28 in 91% yield as a single diastereomer (Scheme 5). Isomerization at C4 of the minor diastereomer may occur concomitantly under these basic conditions. Hydrogenation of 28 with Lindlar’s catalyst at 300 psi of hydrogen gas\(^{28}\) using a Paar apparatus provided the ketone olefin, which was then treated with allyl Grignard in a diethyl ether (Et₂O):THF (2:1) solvent mixture to provide the diene alcohol 29 in 82% yield over two steps as a 2:1 inseparable mixture of two diastereomers.\(^{29}\)

During the TBAF-mediated desilylation, a slight excess of TBAF was used to prevent further silylation of the diene alcohol 24a, a fact that was confirmed by ¹H NMR analysis of 24a, which showed a well-defined singlet for the &OH* signal of the TBAF-mediated desilylation product 24a in 89% yield over two steps. However, allylation of 26 or its N-tosylated amine, under various conditions, did not proceed to give the desired diene 27.\(^{20,26}\)

At this point, allylation of the ketone via allyl Grignard followed by reduction of the corresponding tertiary alcohol using Et₃SiH was considered as an alternative to provide the diene 27. After some experimentation, it was found that desilylation of 24a could be smoothly affected by Cs₂CO₃ in methanol\(^{27}\) to furnish the corresponding ketone alkyne 28 in 91% yield as a single diastereomer (Scheme 5). Isomerization at C4 of the minor diastereomer may occur concomitantly under these basic conditions. Hydrogenation of 28 with Lindlar’s catalyst at 300 psi of hydrogen gas\(^{28}\) using a Paar apparatus provided the ketone olefin, which was then treated with allyl Grignard in a diethyl ether (Et₂O):THF (2:1) solvent mixture to provide the diene alcohol 29 in 82% yield over two steps as a 2:1 inseparable mixture of two diastereomers.\(^{29}\)
the hydroxy group of the diene alcohol 29 could be effectively performed by using Et₃SiH in the presence of BF₃·O₂Et⁴⁵,⁵¹ to furnish the desired diene 27 in 86% yield as a single diastereomer, presumably via the transition state B, which delivered the hydride from Et₃SiH syn to the C₆a proton.

**Ring-Closing Metathesis.** With the diene 27 in hand, we next performed the RCM using the second-generation Grubbs ruthenium catalyst. After some experimentation, it was found that RCM of the diene 27 could be best carried out in toluene at 60 °C for 18 h, giving the desired tricyclic compound 30 in 79% yield as a single diastereomer. Surprisingly, from careful NMR analysis of 30, the unanticipated epimerization at the 6-position of the tetrahydro-6H-benzo[c]chromene (C2 of the chroman) took place under the RCM reaction conditions (Scheme 6).²⁵ Addition of 1,4-benzoquinone to suppress isomerization under the RCM conditions did not improve the outcome of the reactions.³² Thus, as an alternative, the sequence of alcohol reduction by Et₃SiH and RCM was investigated. When the diene alcohol 29 was subjected to the RCM conditions, a separable diastereomeric mixture of the tricyclic alcohols 31 and 32 was obtained in 29% and 48% yields, respectively.³₃ The alcohol 31 (7β-OH) then underwent BF₃·Et₂O-mediated Et₃SiH reduction to provide the tricyclic product 33 (H₁₀a) as a single diastereomer in 58% yield. Interestingly, when the alcohol 32 (7α-OH) underwent such reduction, a separable mixture of 33 and 3⁴,³⁵ (H₁₀β) was obtained in 18% and 38% yields, respectively. It should be noted that, under the reaction conditions, 34 was formed as a result of reduction at C7 as well as epimerization at C10α. This BF₃·Et₂O-mediated Et₃SiH reduction at C7 for both alcohols 31 and 32 was stereoselective, presumably due to the presence of the more rigid cyclohexenyl ring fused with the chroman system (transition state C), resulting in the delivery of the hydride syn to the C6a proton on the adjacent carbon. Thus, the sequence of BF₃·Et₂O-mediated Et₃SiH reduction and RCM of the diene alcohol 29 serves as a handle to provide differently stereodefined tricyclic products. In other words, generation of a specific diastereomer of the desired tricyclic product (30, 33, and 34) from the common diene alcohol 29 is under the reaction sequence control.

**Scope of the Strategy.** The developed strategy was then applied to the synthesis of other 6,7-diaryltetrahydro-6H-benzo[c]chromenes from the corresponding chromans 24e,g,h (Scheme 7). With the exception of the diene 37a from the reduction of the diene alcohol 36a (3-OMePh as the Ar²), the other corresponding intermediates 35a−c, 36a−c, 37b,c, 39a−c, and 40a−c could be prepared in moderate to excellent yields en route to the desired tricyclic compounds 38b,c, 41b,c, and 42a−c (Table 2).³⁴ It should be noted that the BF₃·Et₂O-mediated Et₃SiH reduction of 36a (Ar¹ = 3-(OMe)₂Ph; Ar² = 3-OMePh) gave no desired product 37a; only a mixture of unidentified compounds could be obtained. Hence, without 37a, the subsequent Grubbs II RCM could not be performed to yield the tricyclic product 38a. In addition, when the tricyclic alcohol 39a underwent the BF₃·Et₂O-mediated Et₃SiH reduction, the expected tricyclic product 41a was not obtained. The tricyclic compound 42a, with concomitant 10a-isomerization, was produced from the reaction instead. Interestingly, when 40a was subjected to this reduction, 42a, one of the expected products, was obtained in low yield (15%) along with the nonreduced product with 10a,6a-isomerization 43 ³⁵ (Figure 2) in 19% yield. Interestingly, when 40c (Ar¹ = Ar² = 4-(OMe)₂Ph) underwent the BF₃·Et₂O-mediated Et₃SiH reduction, the tricyclic product 42c with 10a-isomerization was obtained; no 41c was observed.

Lindlar hydrogenation followed by methylation of the ketone alkyne 28 could install the requisite methyl group at C9 and furnish the corresponding alcohol 44 in 75% yield over two steps. After some experimentation, subsequent RCM of 44 using Grubbs II catalyst under various conditions proceeded more sluggishly than those of other similar dienes (29, 37b,c, 39a−c, and 40a−c) to give a separable mixture of the corresponding tricyclic alcohols 45 (7β-OH) and 46 (7α-OH) in 26% and 30% yields, respectively.³⁴ When the catalyst was changed to Hoveyda–Grubbs II, better yields of both 45 (35%) and 46 (38%) could be obtained. In the final step, hydride reduction of the alcohol 45 furnished the desired
product 47 (H₁₀α) in 84% yield as a single isomer while the alcohol 46 furnished a separable mixture of 47 and the nonreduced 10a,6a-isomerized tricyclic alcohol 48 (H₁₀αβ) in 35% and 22% yields, respectively. It should be noted that, while 44 could undergo the hydride reduction to give the corresponding diene 49, its subsequent RCM, under various RCM conditions, did not proceed to furnish the corresponding tricyclic product 50.

**CONCLUSION**

A synthetic approach for the tricyclic 6,7-diaryltetrahydro-6H-benzo[c]chromenes has been successfully developed employing simple benzaldehydes and acetophenones as building blocks. The skeleton of the tricyclic system comprises two units of benzaldehyde derivatives (one as the chroman aromatic ring and the other as the aryl group (Ar₁) on C₆), one unit of acetophenone (as the aryl group (Ar₂) on C₇), and one three-carbon (allylic) unit (as part of the cyclohexene ring). The chroman moiety was assembled first via a highly efficient and stereoselective [4 + 2] cycloaddition reaction between the o-QMs derived from the TMS-protected acetylene benzyl acetate and chalcones. Subsequent reactions on the TMS-protected alkyne group converted such a moiety to the corresponding olefin. The requisite allylic moiety was then added to the ketone via the Grignard reaction. The sequence of the remaining two steps of Grubbs RCM and BF₃·Et₂O-mediated Et₃SiH reduction on the resulting diene alcohol could be exploited to provide the final different tricyclic products in a stereodefined manner. Thus, through eight steps starting from the benzaldehyde building block 10, the desired complex 38b,c, 41b,c, 42a–c, and 47.
tricyclic 6,7-diaryltetrahydro-6H-benzo[c]chromenes containing four contiguous stereocenters could be obtained in good overall yields (up to 43%). Applications of the developed method have been further investigated for the total synthesis of palodosangrens, and the results will be reported in due course.

**EXPERIMENTAL SECTION**

**General Experimental Methods.** Unless otherwise noted, reactions were run in oven-dried round-bottomed flasks. Tetrahydrofuran (THF) was distilled from sodium benzenophenone ketyl or purified by the solvent purification system, while dichloromethane (CH2Cl2) was also purified by the solvent purification system prior to use. All other compounds were used as received from the suppliers; PTS-Si (p-TsOH immobilized on silica) employed in these experiments possessed a surface area of 500 m²/g, as indicated by the supplier. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on a rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets. Chemical shifts for 1H nuclear magnetic resonance (NMR) spectra are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), doublet of doublets (dd), doublet of triplets (dt), and doublet of doublets of doublets (ddd). Resonances for infrared (IR) spectra are reported in wavenumbers (cm⁻¹). Low-resolution (LRMS) mass spectra were obtained using either electron ionization (EI) or time of flight (TOF), while high-resolution (HRMS) mass spectra were obtained using TOF via atmospheric-pressure chemical ionization (APCI) or electrospray ionization (ESI). Melting points are incorrect.

1-(5-Bromo-4-methoxy-2-(methoxymethoxy)phenyl)allyl Acetate (14). Allyltrimagnesium chloride (1.6 M in THF, 0.33 mL, 0.52 mmol) was added to a solution of benzaldehyde 10 (0.110 g, 0.40 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 4 h and then was quenched with saturated NH4Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 2 mL) and the combined organic phases were washed with water (3 mL), filtered, and concentrated under reduced pressure to give a crude product, which was used in the next step without further purification.

A solution of the benzyl alcohol and DMAP (1.50 g, 12.0 mmol) in DCM (40 mL) was cooled in an ice bath for 10 min before Et3N (1.70 mL, 20.0 mmol) and Ac2O (1.20 mL, 12.0 mmol) were added successively. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (10 mL), and the resulting mixture was extracted with DCM (3 × 20 mL). The combined organic phases were washed with water (3 × 20 mL) and brine (20 mL), dried over Na2SO4, and concentrated under reduced pressure to give a crude product which was purified by column chromatography on silica (15–20% EtOAc/hexanes) to give the desired product 15 as a white solid (3.31 g, 8.00 mmol, 100% over two steps). Mp (EtOAc/hexanes): 79.4–80.2 °C. 1H NMR (300 MHz, CDCl3): δ 0.20 (s, 9H), 2.08 (s, 3H), 3.48 (s, 3H), 3.89 (s, 3H), 5.20 (br s, 2H), 6.71 (s, 1H), 6.74 (s, 1H), 7.79 (s, 1H). 13C NMR (75 MHz, CDCl3): δ −0.28, 21.0, 56.2, 56.4, 60.1, 92.0, 94.7, 99.4, 101.1, 103.4, 115.3, 154.9, 157.2, 169.4. IR (UATR): νmax 2960, 2180, 1743, 1218, 843 cm⁻¹. LRMS (EI): m/z (rel intensity) 416 (1.45) [C6H13BrO3Si]⁺, 414 (1.16) [C6H13BrO3Si]⁺, 312 (92), 310 (87), 73 (100). TOF-HRMS: calc for C6H13BrO3Si (M + Na⁺) 437.0390, found 437.0379; calc for C6H13BrO3Si (M + Na⁺) 439.0722, found 439.0366.

**General Procedure for the PTS-Si-Mediated Generation of o-QM and the [4 + 2] Cycloaddition Reaction.** To a stirred solution of benzyl acetate 15 (1.0 equiv) in toluene (5 mL/mmol) was added the corresponding styrene (10 equiv) or its derivative (2 equiv in the case of 4-methoxystyrene) at room temperature. The resulting mixture was stirred at 0 °C for 10 min, and then PTS-Si (1.1 equiv) was added. The mixture was then slowly warmed to room temperature. The reaction mixture was stirred until the starting material was consumed, as indicated by TLC (typically 1–4 h). At that time, PTS-Si was filtered off and the resulting mixture was concentrated under reduced pressure to give a crude product mixture which was further purified by PTLC (10% EtOAc/hexanes) to furnish the desired product.

(6-Bromo-7-methoxy-2-phenylchroman-4-yl)ethynyltrimethylsilane (20). Following the general procedure for the PTS-Si-mediated o-QM/[4 + 2] cycloaddition reaction, benzyl acetate 15 (0.029 g, 0.070 mmol) furnished the chroman product 20 as an 81:24:4:2:4:2:trans inseparable mixture of diastereomers as a colorless oil (0.019 g, 0.044 mmol, 44%). 1H NMR (300 MHz, CDCl3): δ 0.17 (s, 9H, minor), 0.18 (s, 9H, major), 2.17 (dt, J = 13.7, 11.8 Hz, 1H, major), 2.21–2.28 (m, 2H, minor), 2.46 (ddd, J = 13.7, 5.3, 1.9, 1H, major), 3.74 (t, J = 4.5 Hz, 1H, minor), 3.83 (s, 3H, major), 3.84 (s, 3H, minor), 4.07 (ddd, J = 11.8, 5.0, 0.9 Hz, 1H, major), 5.00 (dd, J = 11.8, 1.9 Hz, 1H, major), 5.34 (dd, J = 9.0, 3.0, 1H, minor), 6.46 (s, 1H, minor), 6.51 (s, 1H, minor), 7.31–7.45 (m, 5H, SiH), 7.66 (d, J = 0.9 Hz, 1H, major). 13C NMR (75 MHz, CDCl3): δ: 0.0 (major), 0.1 (minor), 27.0 (major), 29.3 (major), 35.6 (minor), 36.8 (major), 56.2 (minor), 56.3 (major), 75.0 (minor), 78.0 (major), 86.9 (major), 100.9 (major), 101.1 (major), 102.6 (major), 106.3 (major), 107.9 (minor), 114.7 (major), 123.9 (major), 126.1 (minor), 128.1 (major), 128.4 (major), 128.7 (major), 132.7 (major), 133.3 (minor), 140.2 (major), 140.5 (minor), 154.2 (major), 154.3 (major), 155.8 (major). TOF-HRMS: calc for C6H13BrO3Si (M + Na⁺) 437.0543, found 437.0537; calc for C6H13BrO3Si (M + Na⁺) 439.0525, found 439.0519.

(6-Bromo-7-methoxy-2-(4-methoxystyryl)ethynyltrimethylsilane (21). Following the general procedure for the PTS-Si-mediated o-QM/[4 + 2] cycloaddition reaction, benzyl acetate 15 (0.029 g, 0.070 mmol) furnished the chroman product 21 as an 81:24:4:2:4:2:trans inseparable mixture of diastereomers as a colorless oil (0.019 g, 0.044 mmol, 44%). 1H NMR (300 MHz, CDCl3): δ 0.17 (s, 9H, minor), 0.19 (s, 9H, major), 2.18–2.26 (m, 2H, minor), 2.49 (dt, J = 13.7, 11.8 Hz, 1H, major), 2.44 (ddd, J = 13.7, 5.4, 1.9, 1H, major), 3.75 (t, J = 4.4 Hz, 1H, minor), 3.82 (s, 3H, major), 3.84 (s, 3H, minor), 4.06 (ddd, J = 11.8, 5.4, 0.9 Hz, 1H, major), 5.00 (dd, J = 11.8, 1.9 Hz, 1H, major), 5.34 (dd, J = 9.0, 3.0, 1H, minor), 6.46 (s, 1H, minor), 6.51 (s, 1H, minor), 7.31–7.45 (m, 5H, SiH), 7.66 (d, J = 0.9 Hz, 1H, major).
General Procedure for the PtCl4-Catalyzed Generation of o-QM and the [4 + 2] Cycloaddition Reaction with Chalcones 23a–I. To a stirred solution of benzyl acetate 15 (1.0 equiv) in DCM (10 mL/mmol) was added chalcone 23a–I (2 equiv) at room temperature. The resulting mixture was stirred at 0 °C for 10 min, and then PtCl4 (10 mol %) was added. The mixture was then slowly warmed to room temperature. The reaction mixture was stirred until the starting material was consumed, as indicated by TLC (typically 2–4 h). At that time, the reaction mixture was concentrated under reduced pressure to give a crude product mixture which was further purified by PTLC (20–40% EtOAc/hexanes) to furnish the desired products 24a–I.23b

(6-Bromo-7-methoxy-2-(4-methoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)-(4-methoxyphenyl)-methanone (24a). Following the general procedure for the PtCl4-catalyzed o-QM/[4 + 2] cycloaddition reaction using chalcone 23a, benzyl acetate 15 (0.200 g, 0.482 mmol) furnished the corresponding chroman 24a as a 81:19 (2:4-cis,2-trans) inseparable mixture of diastereomers as a yellow sticky gum (0.013 g, 0.021 mmol, 41%). 1H NMR (300 MHz, CDCl3): δ = −0.07 (s, 9H, major), 0.11 (s, 9H, minor), 3.69 (s, 3H, major), 3.76 (s, 3H, minor), 3.80 (s, 3H, major), 3.82 (s, 3H, minor), 3.83 (s, 3H, major), 3.84 (s, 3H, minor), 4.11 (dd, J = 11.0, 10.0 Hz, major), 4.38 (dd, J = 11.0, 0.9 Hz, major), 5.12 (dd, J = 10.0 Hz, 1H, major), 5.56 (dd, J = 9.1 Hz, 1H, major), 6.49 (s, 1H, major), 6.50 (s, 1H, minor), 6.73 (s, J = 8.7 Hz, 2H, minor), 6.76 (d, J = 8.9 Hz, 2H, major), 6.86 (d, J = 8.7 Hz, 2H, major), 6.91 (d, J = 8.9 Hz, 2H, major), 7.26 (d, J = 8.7 Hz, 2H, major), 7.398 (d, J = 8.7 Hz, 2H, minor), 7.400 (s, 1H, minor), 7.69 (d, J = 0.9 Hz, 1H, major), 7.81 (d, J = 8.9 Hz, 2H, major), 7.835 (d, J = 8.9 Hz, 2H, minor). 13C NMR (75 MHz, CDCl3): δ = −0.4 (major), −0.2 (minor), 31.8 (major), 33.9 (major), 48.2 (minor), 50.7 (major), 55.1 (major), 55.2 (minor), 55.4 (major), 56.2 (minor), 56.3 (major), 56.7 (minor), 76.1 (minor), 80.0 (major), 89.1 (major), 100.7 (major), 100.9 (minor), 102.5 (major), 102.8 (minor), 103.2 (major), 104.0 (major), 113.4 (major), 113.85 (major), 113.90 (minor), 113.95 (major), 114.1 (minor), 114.4 (major), 128.5 (major), 128.8 (minor), 129.4 (major), 129.7 (major), 130.1 (minor), 130.2 (major), 130.8 (major), 131.0 (major), 131.4 (major), 132.5 (minor), 132.8 (major), 135.8 (major), 158.5 (major), 159.7 (major), 163.6 (major), 194.2 (minor), 198.9 (major). IR (UATR): νmax 2959, 2838, 2715, 1665, 1660, 1249, 839 cm−1. LRMS (EI): m/z (rel intensity) 580 (19 [C30H36Br2O6Si]+), 578 (17 [C30H34Br2O6]+), 526 (21), 135 (100). TOF-HRMS: calcd for C30H35Br2O6Si (M + H) 759.1107, found 759.1180; calcd for C31H38Si2Br2O6Si (M + H + Na) 818.1182, found 818.1144.

(6-Bromo-2-(3,4-dimethoxyphenyl)-7-methoxy-4-((trimethylsilyl)ethynyl)chroman-3-yl)-(3-methoxyphenyl)-methanone (24b). Following the general procedure for the PtCl4-catalyzed o-QM/[4 + 2] cycloaddition reaction using chalcone 23b, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chroman 24b as a 81:19 (2:4-cis,2-trans) inseparable mixture of diastereomers as a yellow sticky gum (0.017 g, 0.028 mmol, 50%).Mp (EtOAc/hexanes): 74.5–76.6 °C. 1H NMR (300 MHz, CDCl3): δ = −0.06 (s, 9H, major), 0.11 (s, 9H, minor), 3.768 (s, 3H, major), 3.774 (s, 3H, major), 3.81 (s, 3H, major), 3.83 (s, 3H, minor), 3.84 (s, 3H, minor), 3.856 (s, 3H, minor), 3.862 (s, 3H, minor), 4.14 (dd, J = 11.0, 10.0 Hz, major), 4.39 (dd, J = 11.0, 1.0 Hz, major), 4.11 (dd, J = 9.2 Hz, 1H, major), 6.51 (s, 1H, minor), 6.52 (s, 1H, minor), 6.70 (d, J = 8.2 Hz, 1H, major), 6.79 (d, J = 8.9 Hz, 2H, major), 6.84 (d, J = 1.9 Hz, 1H, major), 6.89 (d, J = 2.0 Hz, 1H, minor), 7.04 (dd, J = 8.3, 2.0 Hz, 1H, minor), 7.41 (s, 1H, major), 7.49 (d, J = 8.3 Hz, 1H, major), 7.70 (d, J = 1.0 Hz, 1H, major), 7.75 (d, J = 8.9 Hz, 2H, major), 7.84 (d, J = 8.9 Hz, 2H, minor). 13C NMR (75 MHz, CDCl3): δ = −5.0 (major), −0.2 (minor), 31.8 (minor), 33.9 (major), 48.1 (minor), 50.6 (major), 55.4 (major), 55.5 (major), 55.7 (major), 55.8 (major), 55.9 (major), 60.8 (major), 60.95 (major), 70.0 (major), 70.1 (major), 70.2 (major), 70.3 (minor), 80.5 (minor), 89.1 (major), 91.4 (major), 100.7 (major), 100.9 (major), 103.1 (minor), 104.0 (major), 104.5 (major), 104.9 (minor), 106.7 (minor), 111.4 (major), 114.0 (minor), 114.3 (major), 130.2 (minor), 130.6 (major), 131.0 (major), 132.7 (major), 132.8 (major), 134.7 (major), 135.1 (major), 135.2 (major), 155.5 (major), 155.8 (major), 163.7 (major), 191.0 (minor), 198.7 (major). IR (UATR): νmax 2959, 2715, 1664, 1596, 1125 cm−1. LRMS (EI): m/z (rel intensity) 641 (19 [C31H35Br2O6Si]+), 639 (20 [C31H34Br2O6]+), 328 (26), 135 (100). TOF-HRMS: calcd for C31H37BrNaO6Si (M + Na+) 661.1228, found 661.1240; calcd for C31H37BrNaO6Si (M + Na+) 663.1213, found 663.1232.
(6-Bromo-2-(3,4-dimethoxyphenyl)-7-methoxy-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl) methanone (24e). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23e, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24e as a

(6-Bromo-2-(3,4-dimethoxyphenyl)-7-methoxy-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24i). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23g, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24i as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24g). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23g, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24g as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24h). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23h, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24h as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24f). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23f, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24f as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24d). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23d, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24d as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24c). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23c, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24c as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24b). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23b, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24b as a

(6-Bromo-7-methoxy-2-(3,4,5-trimethoxyphenyl)-4-((trimethylsilyl)ethynyl)chroman-3-yl)(3,4-dimethoxyphenyl)

methanone (24a). Following the general procedure for the PtCl4-

catalyzed α-QM/[4 + 2] cycloaddition reaction using chalcone 23a, benzyl acetate 15 (0.021 g, 0.050 mmol) furnished chromane 24a as a
(major), 60.66 (major), 60.69 (minor), 76.8 (minor), 80.5 (major), 89.1 (major), 91.4 (minor), 100.7 (major), 100.9 (minor), 102.7 (minor), 103.1 (major), 103.9 (major), 104.4 (major), 104.8 (major), 109.6 (major), 110.0 (minor), 110.1 (major), 110.3 (minor), 114.0 (minor), 114.3 (major), 122.1 (minor), 123.4 (major), 129.6 (minor), 131.2 (major), 132.6 (major), 132.86 (minor), 134.6 (major), 138.2 (minor), 148.8 (major), 153.17 (minor), 153.23 (minor), 153.5 (major), 153.6 (major), 155.8 (major), 156.1 (minor), 194.1 (minor), 198.7 (major).

IR (UATR): ν = 2941, 28.8, 2176, 1668, 1582, 1124, 842 cm⁻¹. LRMS (EI): m/z (rel intensity) 700 (17) [C₃₃H₃₇BrO₆Si]+, 698 (13) [C₃₄H₄₃BrO₆Si]+, 388 (22), 195 (100). TOF-HRMS: calc for C₃₄H₄₅BrNO₅Si (M + Na⁺) 718.1872, found 718.1867.

(6-Bromo-7-methoxy-2-((4-methoxyphenyl)-4-(trimethylsilyl)ethynyl)chroman-3-yl)-4-(4-methoxyphenyl)methyl Acetate (25). A solution of the benzyl alcohol and DMAP (0.10 g, 0.20 mmol) in DCM (1.5 mL) was cooled in an ice bath for 10 min before Et₃N (28 µL, 0.20 mmol) and Ac₂O (19 µL, 0.20 mmol) were added successively. The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water (2 mL), and the resulting mixture was extracted with DCM (3 × 2 mL). The combined organic phases were washed with water (3 × 2 mL) and brine (2 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude product, which was isolated by column chromatography on silica (15–30% EtOAc/hexanes) to give the desired product 25 as a white solid (0.075 g, 0.12 mmol, 99%).

1H NMR (300 MHz, CDCl₃): δ = 0.07 (s, 9H), 3.72 (s, 3H), 3.78 (s, 3H), 3.81 (s, 6H), 4.00 (dd, J = 11.0, 10.0 Hz, 1H), 4.09 (dd, J = 11.0, 10.0 Hz, 1H), 4.41 (dd, J = 11.0, 10.0 Hz, 1H), 5.12 (d, J = 1.0 Hz, 1H), 5.93 (d, J = 8.2 Hz, 1H), 5.97 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 0.7 Hz, 1H). 13C NMR (75 MHz, CDCl₃): δ = 15.8, 30.0, 55.9, 56.2, 56.4, 60.9, 80.2, 89.3, 100.8, 103.5, 106.0, 110.0, 111.1, 114.2, 120.0, 130.1, 132.6, 142.9, 149.0, 152.8, 153.6, 155.9, 199.6. IR (UATR): 2925, 2837, 2173, 1686, 1508, 1126 cm⁻¹. LRMS (EI): m/z (rel intensity) 1670 (11) [C₃₃H₃₇BrO₆Si]+, 662 (10) [C₃₃H₃₇BrO₆Si]+, 195 (100).

The reaction mixture was quenched with water (2 mL), and the resulting mixture was extracted with DCM (3 × 2 mL). The combined organic phases were washed with water (3 × 2 mL) and brine (2 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude product, which was used in the next step without further purification.

(6-Bromo-7-methoxy-2-((3,4-dimethoxyphenyl)-4-(trimethylsilyl)ethynyl)chroman-3-yl)-4-(4-methoxyphenyl)methyl Acetate (26). To a solution of chroman TMS acetylide 25 (0.075 g, 0.12 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (TBAF; 0.059 g, 0.18 mmol) at 0 °C, and the reaction mixture was kept at this temperature for 3 h. The reaction mixture was quenched with water (2 mL), and the resulting mixture was extracted with EtOAc (3 × 2 mL). The combined organic phases were washed with water (3 × 2 mL) and brine (2 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude product, which was used in the next step without further purification.

A suspension of the chroman alkyne and Pd on CaCO₃ (0.051 g, 0.076 g, 0.13 mmol) in toluene (2 mL) at 0 °C was used in the next step without further purification.
General Procedure for the Desilylation Using Cs2CO3 in Methanol. To a solution of ketone chroman TMS acetylde 24 (1.0 equiv) in 1/1 THF/MeOH (20 mL mmol) was added Cs2CO3 (2.0 equiv) at 0 °C, and the reaction mixture was stirred at a temperature between 5 and 9 °C until the starting material was consumed, as indicated by TLC (typically 3–4 h). Water and EtOAc were added, and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc, and the combined organic phases were concentrated under reduced pressure. The residue was washed with water and brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography on silica to give the desilylated product.

(6-Bromo-2-(3,4-dimethoxyphenyl)-4-ethyl-7-methoxy-chroman-3-yl)(3,4-dimethoxyphenyl)methanone (35c). Following the general procedure for the desilylation using Cs2CO3, ketone chroman TMS acetylde 24h (0.321 g, 0.502 mmol) was converted to the corresponding ketone chroman alkyne 28, which was obtained as a yellow sticky gum (0.063 g, 0.11 mmol, 82%). 1H NMR (300 MHz, CDCl3): δ 2.14 (d, J = 2.4 Hz, 1H), 3.07 (d, J = 10.0 Hz, 1H), 4.45 (dd, J = 10.6, 9.9 Hz, 1H), 6.89 (dd, J = 8.2, 1.8 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 8.2, 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 0.7 Hz, 1H). 13C NMR (75 MHz, CDCl3): δ 29.3 (s), 32.3, 50.7, 55.2, 55.3, 56.2, 72.2, 80.3, 82.2, 83.9, 102.6, 102.7, 113.4, 113.45, 113.51, 113.57, 123.4, 127.1, 127.5, 133.1, 133.2 (major), 133.2 (minor), 155.6, 155.7, 158.3. IR (UATR): ν max 3288, 2937, 2836, 1672, 1595, 1262, 1152, 1026 cm−1. LRMS (EI): m/z (rel intensity) 554 (13) [C28H24BrO13]+, 552 (14) [C28H23BrO12]+, 374 (16), 372, (20), 165 (100). TOF-HRMS: calcd for C28H24BrO13(M + Na+) 575.1040, found 575.1036; calcd for C28H24BrO13(M + Na+) 575.1021, found 575.1025.

General Procedure for the Lindlar Hydrogenation and Ally Grignard Addition. A suspension of ketone chroman alkyne (1 equiv) and Pd on CaCO3 (30 mol %) in DCM (30 mL mmol−1) was stirred at room temperature under an H3 atmosphere (300 psi). After the mixture was stirred for 5 h, the palladium catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure to give the crude corresponding ketone alkyne product, which was used in the next step without further purification.

To a solution of the ketone chroman alkyne in 1/2 THF/EtO2 (20 mol mmol−1) was added allylamines magnesium (1.0 M in EtO2) 2.5 equiv) at 0 °C. The mixture was stirred and slowly warmed to 10 °C, at which it was stirred for an additional 18 h. The reaction mixture was quenched with saturated NH4Cl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography on silica (0–30% EtOAc/hexanes) to give the desired diol alcohol product.

1-6-Bromo-7-methoxy-2-(4-methoxyphenyl)-4-vinylchroman-3-yl(1-(4-methoxyphenyl)-1-ethynyl)-2(3H)-one. Following the general procedure for the Lindlar hydrogenation and ally Grignard addition, ketone chroman alkyne 28 (0.070 g, 0.14 mmol) was converted to the corresponding diene alcohol 29, which was obtained as a 2:1 inseparable mixture of diastereomers as a white sticky gum (0.063 g, 0.11 mmol, 82%). 1H NMR (300 MHz, CDCl3): δ 2.32 (s, 1H, minor), 2.40–2.49 (m, 1H, minor), 2.58–2.66 (m, 1H, major), 2.78 (d, J = 7.1 Hz, 1H, major), 3.02 (dd, J = 13.7, 5.5 Hz, 1H, minor), 3.51–3.60 (m, 1H, major), 3.74 (s, 3H, major), 3.81 (s, 3H, major), 3.88 (s, 3H, major), 4.53–4.71 (m, 2H, major), 4.96–5.20 (m, 3H, major), 5.46–5.64 (m, 2H, major), 6.53 (s, 1H, minor), 6.56 (s, 1H, minor), 6.73 (d, J = 8.8 Hz, 2H, major), 6.74 (d, J = 8.9 Hz, 2H, minor), 6.88 (d, J = 9.0 Hz, 2H, minor), 6.89 (d, J = 8.7 Hz, 2H, major), 6.96 (d, J = 9.0 Hz, 2H, major), 6.99 (d, J = 8.7 Hz, 2H, minor), 7.11 (s, 1H, minor), 7.14 (s, 1H, major), 7.39 (d, J = 8.8 Hz, 2H, major), 7.42 (d, J = 8.9 Hz, 2H, major). 13C NMR (75 MHz, CDCl3): δ 37.4, 37.8 (minor), 42.2, (minor), 42.4 (major), 54.0 (major), 55.1 (major), 55.2 (major), 56.1 (major), 74.4 (minor), 74.5 (major), 78.0 (minor), 78.3 (major), 100.7 (minor), 100.8 (major), 102.6 (major), 102.7 (minor), 113.4 (minor), 113.45 (major), 113.51 (minor), 113.6 (major), 113.68 (minor), 113.70 (major), 117.5 (major), 118.0 (minor), 120.0 (major), 120.2 (minor), 126.7 (major), 126.8 (major), 127.2 (major), 127.5 (major), 133.1 (major), 133.2 (major), 133.4 (major), 133.6 (major), 133.69 (major), 133.71 (major), 136.4 (minor), 136.7 (major), 141.8, 142.0 (major), 153.1 (major), 153.3 (minor), 155.17 (minor), 155.22 (major), 158.3 (minor), 158.3 (minor), 158.3 (minor).
Following the general procedure for the Lindlar hydrogenation and allyl Grignard addition, ketone alkyne 35 (0.106 g, 0.198 mmol) was converted to the corresponding diene alcohol 36b, which was obtained as a 1:1 inseparable mixture of diastereomers as a yellow sticky gum (0.113 g, 0.194 mmol, 98%).

1H NMR (300 MHz, CDCl3): δ 2.50 (m, 1H), 2.59 (1H, minor), 3.55 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.62 (m, 2H), 4.96 (s, 1H, major), 5.27 (m, 2.5H), 5.45–5.69 (2H, 1H), 6.54 (s, 1H, minor), 6.67 (s, 1H, major), 6.58–6.68 (2H, 1H), 6.71 (d, J = 8.4 Hz, 1H, minor), 6.72 (d, J = 8.3 Hz, 1H, major), 6.837 (d, J = 8.5 Hz, 1H, minor), 6.844 (d, J = 8.4 Hz, 1H, major), 6.99–7.04 (1H, major), 7.10 (d, J = 2.0 Hz, 1H, minor), 7.13 (s, 1H, major), 7.18 (s, 1H, minor), 7.28 (s, 1H, major), 7.30–7.32 (m, 1H). 13C NMR (75 MHz, CDCl3): δ 37.7 (major), 37.9 (minor), 42.1 (major), 42.9 (major), 54.0 (minor), 54.1 (major), 55.7 (major), 55.80 (major), 55.83 (minor), 55.9 (major), 56.0 (major), 56.2 (major), 74.4 (minor), 75.1 (major), 78.1 (major), 78.4 (major), 100.6 (minor), 100.9 (major), 102.8 (major), 109.3 (major), 109.4 (major), 109.7 (major), 109.9 (minor), 110.5 (minor), 110.7 (major), 110.8 (major), 113.8 (minor), 113.9 (major), 117.8 (major), 117.9 (major), 118.0 (major), 118.1 (major), 120.1 (major), 120.4 (minor), 129.1 (minor), 129.3 (major), 132.9 (major), 133.1 (major), 133.7 (minor), 133.9 (major), 134.2 (major), 136.9 (major), 137.0 (major), 137.2 (major), 141.9 (major), 142.1 (major), 147.8 (major), 147.9 (minor), 148.0 (major), 148.1 (minor), 148.6 (major), 148.7 (minor), 148.8 (minor), 148.9 (major), 153.3 (major), 153.4 (minor), 153.5 (major). IR (UATR): νmax 3546, 2937, 1607, 1515, 1257, 1144, 1027 cm−1. TOF-HRMS: calcld for C31H33BrNaO (M + Na+) 635.1444, found 635.1437.

**General Procedure for the BF3·Et2O-Mediated Et3SiH Reduction.** A solution of alcohol (1.0 equiv) in DCM (10 mL) was cooled in an ice bath for 5 min. At this time, Et3SiH (1.5 equiv) was added to quench the reaction. The aqueous layer was extracted with DCM, and the combined organic phases were washed with water and brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by PTLC to get the desired product.

6-Bromo-7-methoxy-2-(4-methoxyphenyl)-4-vinylchroman (27). Following the general procedure for the BF3·Et2O-Mediated Et3SiH reduction at 0 °C for 2 h, diene alcohol 29 (0.016 g, 0.029 mmol) furnished the diene 27 as a yellow sticky gum (0.025 mmol, 86%).

**1-(6-Bromo-7-methoxy-2-(4-methoxyphenyl)-4-vinylchroman-3-yl)-1-(3,4-dimethoxyphenyl)but-3-en-1-yl)-4-vinylchroman (27).** Following the general procedure for the BF3·Et2O-Mediated Et3SiH reduction at 0 °C for 2 h, diene alcohol 29 (0.045 g, 0.080 mmol) furnished the diene 27 as a yellow sticky gum (0.086 g, 0.148 mmol) instead of 28. H NMR (300 MHz, CDCl3): δ 1.82–1.93 (m, 1H), 1.95–2.07 (m, 1H), 2.20 (dt, J = 6.8, 1.7 Hz, 1H), 2.70 (dd, J = 10.1, 6.8, 5.6 Hz, 1H), 3.11–3.16 (m, 1H), 3.73 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.62 (dd, J = 17.0, 2.1 Hz, 1H), 4.68 (dd, J = 10.2, 2.1 Hz, 1H), 4.78 (dt, J = 17.0, 1.5 Hz, 1H), 5.17 (dt, J = 10.1, 1.3 Hz, 1H), 5.17–5.30 (m, 2H), 5.98 (dd, J = 17.0, 10.2, 5.5 Hz, 1H), 6.42 (s, 1H), 6.62 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 6.83 (s, 1H), 6.98 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H).

13C NMR (75 MHz, CDCl3): δ 39.6, 41.8, 42.1, 46.3, 52.5, 53.3, 56.2, 74.6, 106.6, 102.1, 113.0, 113.8, 115.3, 115.6, 117.2, 126.4, 129.6, 132.4, 134.4, 137.1, 142.9, 155.0, 155.2, 155.8. IR (UATR): νmax 3552, 2932, 2836, 1610, 1121, 2446, 1651 cm−1. TOF-HRMS: calcld for C31H33BrNaO (M + Na+) 575.1434, found 575.1437.
7.1, 5.0 Hz, 1H), 3.06 (1H). Following the general procedure for the BF₃·Et₂O-mediated Et₃SiH reduction at 0 °C for 2 h, diene 36c (0.030 g, 0.049 mmol) furnished the diene 37c as a yellow sticky gum (0.010 g, 0.017 mmol, 34%). 1H NMR (300 MHz, CDCl₃): δ 1.75–1.86 (m, 1H), 1.99–2.12 (m, 1H), 2.18 (br d, J = 7.1 Hz, 1H), 2.69 (dd, 1J = 12.0, 5.2 Hz, 1H, 3.06–3.11 (m, 1H), 3.69 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.63 (dd, 1J = 17.0, 2.0 Hz, 1H), 4.71 (dd, 1J = 10.2, 2.0 Hz, 1H), 4.78 (dt, 1J = 17.0, 1.4 Hz, 1H), 5.20 (dd, 1J = 10.2, 1.3 Hz, 1H), 5.22–5.34 (m, 2H), 6.00 (dd, 1J = 17.0, 10.2 Hz, 1H), 6.29 (d, 1J = 1.9 Hz, 1H), 6.42 (dd, 1J = 8.2, 1.9 Hz, 1H), 6.79 (s, 1H), 6.63 (d, 1J = 8.2 Hz, 1H), 6.85 (s, 1H), 6.95 (d, 1J = 8.2 Hz, 1H), 7.03–7.10 (m, 2H). 13C NMR (75 MHz, CDCl₃): δ 35.9, 41.9, 45.2, 46.6, 55.8, 55.9, 56.1, 56.2, 74.5, 100.6, 102.3, 108.7, 110.7, 112.7, 113.5, 147.3, 148.0, 148.8, 158.3, 155.3, 158.3 Hz, J. Org. Chem. 2017, 82, 2672–2688.

79BrNaO₄ (M + Na⁺) furnishes the diene 37c as a yellow sticky gum (0.010 g, 0.017 mmol). The reaction mixture was stirred at 60 °C for 5 h in the solvent of choice. The residue was purified by PTLC (50/24 DCM/MeOH/hexanes) to give the desired cyclic product.

General Procedure for the Ring-Closing Metathesis. Grubbs II catalyst (10 mol %) or Hoveyda–Grubbs II catalyst (2 mol %) was added to a solution of the corresponding diene (1 equiv) in toluene (100 mL mmol). The mixture was heated at 70 °C for 18 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by PTLC (50/24 DCM/MeOH/hexanes) to give the desired cyclic product.

79BrO₅⁺, 253

For the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol %), diene 37c (0.010 g, 0.017 mmol) was converted to the corresponding tricyclic product 38c, which was obtained as a yellow sticky gum (0.003 g, 0.013 mmol, 80%). 1H NMR (300 MHz, CDCl₃): δ 2.16–2.28 (m, 1H), 2.66–2.87 (m, 2H), 2.35 (dd, 1J = 7.0, 3.1 Hz, 1H), 3.59 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 3.90–3.99 (m, 1H), 5.26 (d, 1J = 4.6 Hz, 1H), 5.97 (dd, 1J = 10.2, 4.5 Hz, 1H), 6.32–6.50 (m, 8H), 7.58 (d, 1J = 7.0 Hz, 1H). 13C NMR (75 MHz, CDCl₃): δ 28.7, 34.9, 39.8, 42.9, 55.6, 57.5, 57.6, 59.5, 59.5, 61.9, 81.9, 101.5, 101.9, 110.7, 112.5, 117.2, 121.4, 127.7, 128.1, 130.2, 131.6, 135.5, 147.3, 148.8, 148.8, 158.3, 155.3, 158.3 Hz, J. Org. Chem. 2017, 82, 2672–2688.

Grubbs II catalyst (5 mol %) and the diene alcohol 31 (0.013 g, 0.025 mmol) was converted to the corresponding tricyclic product 38c, which was obtained as a yellow sticky gum (0.003 g, 0.013 mmol, 80%). The reaction mixture was evaporated under reduced pressure. The residue was purified by PTLC (50/24 DCM/MeOH/hexanes) to give the desired cyclic product.

For the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol %), diene 37c (0.010 g, 0.017 mmol) was converted to the corresponding tricyclic product 38c, which was obtained as a yellow sticky gum (0.003 g, 0.013 mmol, 80%). 1H NMR (300 MHz, CDCl₃): δ 1.81 (br s, 1H), 2.53–2.72 (m, 3H), 3.36 (br d, 1J = 7.7 Hz, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.66 (d, 1J = 10.4 Hz, 1H), 6.03–6.13 (m, 1H), 6.30 (dd, 1J = 10.2, 1.9 Hz, 1H), 6.34 (s, 1H), 6.67 (d, 1J = 8.9 Hz, 2H), 7.00 (d, 1J = 8.7 Hz, 2H), 7.34 (d, 1J = 8.7 Hz, 2H), 7.38 (d, 1J = 8.7 Hz, 2H), 7.45 (s, 1H). 13C NMR (75 MHz, CDCl₃): δ 36.3, 44.0, 48.9, 55.2, 55.3, 56.2, 74.9, 78.8, 101.1, 101.2, 113.2, 114.3, 118.1, 127.0, 127.2, 128.0, 129.4, 129.8, 132.6, 136.1, 154.1, 154.9, 158.8, 160.2 (1H). IR (ATR): ν max 3563, 2932, 2834, 1608, 1513, 1255, 1146, 1027 cm⁻¹. LRMS (EI): m/z (rel intensity) 569 (100) [C₃₀H₂₉BrO₅⁺], 570 (97) [C₂₉H₂₇BrO₅⁺], 571 (97), 572 (32), 573 (38), 283 (45), 121 (85). TOF-HRMS: calc for C₃₀H₂₉BrO₅⁺ (M + Na⁺) 559.1091, found 559.110. TOF-HRMS: calc for C₂₉H₂₇BrO₅⁺ (M + Na⁺) 561.1072, found 561.1074.

For the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol %), diene 37c (0.010 g, 0.017 mmol) was converted to the corresponding tricyclic product 38c, which was obtained as a brown oil (0.018 g, 0.034 mmol, 29%), and the corresponding tricyclic product 32, which was obtained as a brown oil (0.030 g, 0.057 mmol, 48%).
furnished the corresponding tricyclic product 33 as a yellow sticky gum (0.010 g, 0.020 mmol, 58%). 1H NMR (300 MHz, CDCl3): δ 2.18–2.29 (m, 1H), 2.41 (dd, J = 10.9, 3.2 Hz, 1H), 2.58–2.75 (m, 1H), 2.95 (dd, J = 7.0, 3.2 Hz, 1H), 3.46 (br d, J = 10.9 Hz, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 4.48 (d, J = 10.9 Hz, 1H), 6.07 (dd, J = 9.8, 4.3, 2.5 Hz, 1H), 6.29–6.36 (m, 1H), 6.36 (s, 1H), 6.77 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 1.0 Hz, 1H). 13C NMR (75 MHz, CDCl3): δ 31.9, 33.1, 36.8, 41.9, 55.2, 55.4, 56.1, 81.1, 101.1, 101.7, 113.3, 114.3, 118.1, 127.7, 129.6, 129.8, 130.0, 130.7, 133.9, 154.5, 154.8, 158.4, 160.1. IR (UATR): νmax 2931, 2862, 1614, 1513, 1487, 1462, 1406 cm–1. TOF-HRMS: calcd for C28H27NO4 (M + NH4)1+ 529.0972, found 529.0977; calcd for C29H29BrNO4 (M + Na+) 531.0969, found 531.0967.

(6a,6b,7β,10aβ)-2-Bromo-3-methoxy-6,7-bis(4-methoxyphenyl)-6a,7,8,10a-tetrahydro-6h-benzoc[chromene-7-ol (39a and 40a). Following the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol%), diene alcohol (0.007 g, 0.019 mmol) was converted to the corresponding tricyclic product 39b, which was obtained as a yellow oil (0.013 g, 0.024 mmol, 23%), and the corresponding tricyclic product 40b, which was obtained as a yellow oil (0.028 g, 0.052 mmol, 59%). (6a,6b,7β,10aα)-2-Bromo-3-methoxy-6,7-bis(4-methoxyphenyl)-6a,7,8,10a-tetrahydro-6h-benzoc[chromene-7-ol (39b). 1H NMR (300 MHz, CDCl3): δ 1.82 (br s, 1H), 2.59–2.74 (m, 3H), 3.42 (br d, J = 10.5 Hz, 1H), 3.75 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 4.69 (d, J = 10.5 Hz, 1H), 6.10 (dd, J = 9.9, 6.5, 3.3 Hz, 1H), 6.28–6.35 (m, 1H), 6.35 (s, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.96–7.05 (m, 4H), 7.38 (d, J = 8.6 Hz, 2H), 7.46 (s, J = 10.9 Hz, 1H), 7.50 (s, J = 10.9 Hz, 1H), 7.77 (s, J = 10.9 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 8.56 (d, J = 8.6 Hz, 2H), 8.64 (d, J = 8.7 Hz, 2H), 7.39 (s, 1H). 13C NMR (75 MHz, CDCl3): δ 24.9, 39.9, 40.4, 42.3, 55.19, 55.21, 56.2, 77.03, 100.9, 102.3, 163.1, 112.3, 119.1, 125.6, 127.5, 129.4, 130.2, 131.1, 132.7, 135.1, 154.9, 155.0, 156.9, 159.4. IR (UATR): νmax 2931, 2862, 1614, 1513, 1477 cm–1. LRMS (EI): m/z (rel intensity) 508 (44) [C30H28Br2O4]1+, 506 (37) [C29H29Br2O4]1+, 253 (100), 121 (91). TOF-HRMS: calcd for C29H29BrNO4 (M + Na+) 579.0985, found 579.0972; calcd for C30H31BrNO4 (M + Na+) 581.1091, found 581.1082.

2-Bromo-6-(3,4-dimethoxyphenyl)-3-methoxy-7-(3-methoxyphenyl)-6a,7,8,10a-tetrahydro-6h-benzoc[chromene-7-ol (39b and 40b). Following the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol%), diene alcohol (0.007 g, 0.019 mmol) was converted to the corresponding tricyclic product 39b, which was obtained as a yellow oil (0.013 g, 0.024 mmol, 23%), and the corresponding tricyclic product 40b, which was obtained as a yellow oil (0.028 g, 0.052 mmol, 59%). (6a,6b,7β,10aα)-2-Bromo-3-methoxy-6,7-bis(4-methoxyphenyl)-6a,7,8,10a-tetrahydro-6h-benzoc[chromene-7-ol (40b). 1H NMR (300 MHz, CDCl3): δ 2.18–2.29 (m, 2H), 2.42 (t, J = 10.1 Hz, 1H), 2.67–2.78 (m, 1H), 3.60 (br s, 3H), 3.68 (s, 3H), 3.68–3.74 (m, 1H), 3.75 (s, 3H), 3.76–3.84 (m, 1H), 6.15 (d, J = 10.1 Hz, 1H), 6.20–6.28 (m, 1H), 6.39–6.49 (m, 7H), 6.60 (br d, J = 8.0 Hz, 1H), 7.46 (d, J = 0.8 Hz, 1H). 13C NMR (75 MHz, CDCl3): δ 34.0, 43.3, 52.8, 55.2, 55.5, 56.3, 72.5, 80.2, 102.7, 102.9, 108.8, 110.4, 113.1, 117.6, 123.9, 125.0, 126.2, 127.5, 128.0, 134.8, 136.7, 147.5, 148.1, 154.8, 155.0. IR (UATR): νmax 3032, 2933, 1608, 1514, 1244 cm–1. LRMS (EI): m/z (rel intensity) 554 (30) [C30H28Br2O4]1+, 552 (27) [C30H28BrNO4]1+, 165 (100). TOF-HRMS: calcd for C30H29BrNaO4 (M + Na+) 575.1040, found 575.1040; calcd for C30H29BrNaO4 (M + Na+) 577.1021, found 577.1021.

2-Bromo-6,7-bis(3,4-dimethoxyphenyl)-3-methoxy-6,7-bis(4-methoxyphenyl)-6a,7,8,10a-tetrahydro-6h-benzoc[chromene-7-ol (39c and 40c). Following the general procedure for the ring-closing metathesis using Grubbs II as catalyst (10 mol%), diene alcohol (0.007 g, 0.019 mmol) was converted to the corresponding tricyclic product 39c, which was obtained as a yellow oil (0.008 g, 0.016 mmol, 34%), and the corresponding tricyclic product 40c, which was obtained as a yellow sticky gum (0.006 g, 0.115 mmol, 60%).
1H), 3.48 (d, J = 9.8 Hz, 1H), 5.95–6.03 (m, 1H), 6.02 (dd, J = 2.0 Hz, 1H), 6.11 (dd, J = 8.2, 2.0 Hz, 1H), 6.38–6.49 (m, 4H), 6.49–6.60 (br m, 2H), 7.47 (d, J = 0.8 Hz, 1H). ^1C NMR (75 MHz, CDCl3): δ 33.9, 43.3, 52.8, 55.3, 55.4, 55.8, 55.9, 56.3, 72.4, 81.5, 102.7, 102.8, 108.9, 110.2, 110.3, 110.7, 117.7, 119.1, 123.9, 125.0, 126.2, 127.6, 135.2, 136.8, 147.4, 147.9, 147.95, 148.0, 145.8, 150.5. IR (UATR): v_max = 2932, 2853, 1607, 1443, 1264, 1159, 1050 cm⁻¹. LRMS (EI): m/z (rel intensity) 538 (28) [C₃₀H₂₉BrO₅]⁺, 536 (25) [C₃₀H₂₈BrO₄]⁻, 283 (100), 151 (37). TOF-HRMS: calculated for C₃₀H₂₉BrNaO (M + Na⁺) 559.1091, found 559.1103; calculated for C₃₀H₂₉BrNaO (M + Na⁺) 561.1075, found 561.1092.

Bromo-7-[3,4-dimethoxyphenyl]-3-methoxy-6-(4-methoxyphenyl)-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene (42b). Following the general procedure for the BF₃·EtO-mediated EtSiH reduction at −20 °C for 24 h, tricyclic alcohol 40b (0.023 g, 0.041 mmol) furnished the corresponding tricyclic product 41b (0.004 g, 0.007 mmol, 18%) and the corresponding tricyclic product 42b as a white solid (0.006 g, 0.012 mmol, 27%). Mp (EtOAc/hexanes): 221.5–223.0 °C. ^1H NMR (300 MHz, CDCl3); δ 2.16–2.29 (br m, 2H), 2.40–2.54 (br m, 2H), 2.92–3.00 (br m, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.80–3.86 (br m, 1H), 4.88 (d, J = 10.2 Hz, 1H), 5.77–5.85 (m, 1H), 5.85–5.93 (m, 1H), 6.18 (dd, J = 8.3, 1.6 Hz, 1H), 6.22 (d, J = 1.6 Hz, 1H), 6.40 (s, 1H), 6.42 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.40 (s, 1H). ^1C NMR (75 MHz, CDCl3); δ 25.0, 40.0, 40.7, 42.5, 52.5, 55.5, 56.0, 72.2, 71.1, 100.9, 102.3, 110.1, 113.2, 118.9, 119.0, 125.5, 129.5, 130.2, 131.2, 132.7, 135.8, 146.5, 148.2, 155.0, 155.1, 159.4. IR (UATR): v_max = 2908, 2835, 1515, 1248, 1158 cm⁻¹. LRMS (EI): m/z (rel intensity) 538 (26) [C₃₀H₂₈BrO₄]⁺, 536 (31) [C₃₀H₂₉BrO₅]⁻, 283 (100). TOF-HRMS: calculated for C₃₀H₂₉BrNaO (M + Na⁺) 559.1091, found 559.1096; calculated for C₃₀H₂₉BrNaO (M + Na⁺) 561.1075, found 561.1075.

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Following the general procedure for the Lindlar hydrogenation and allyl Grignard addition (while using methallyl Grignard instead), ketone alkyne 28 (0.170 g, 0.335 mmol) was converted to the corresponding diene alcohol 44, which was obtained as a 1:1 inseparable mixture of diastereomers as a white sticky gum (0.142 g, 0.251 mmol, 75%).$^1$H NMR (300 MHz, CDCl₃): δ 1.31 (s, 3H), 2.54 (s, 1H minor), 2.56 (s, 1H major), 2.58–2.71 (m, 2H), 2.75–2.83 (m, 1H minor), 2.88–2.96 (m, 1H major), 3.46 (d, J = 8.3 Hz, 1H minor), 3.73 (3H), 3.76 (3H minor), 3.80 (s, 6H major), 3.86 (s, 3H minor), 3.87 (3H, major), 4.48–4.59 (m, 2H minor), 4.64–4.73 (m, 2H), 4.78–4.88 (m, 2H), 5.02–5.21 (m, 1H), 5.25 (s, 1H), 5.68 (s, 1H minor), 6.50 (s, 1H major), 6.71 (d, J = 8.8 Hz, 2H major), 6.78 (d, J = 8.7 Hz, 2H minor), 6.83 (d, J = 8.8 Hz, 2H major), 6.87 (d, J = 8.8 Hz, 2H major), 6.93 (d, J = 8.8 Hz, 2H minor), 7.06 (d, J = 8.8 Hz, minor), 7.18 (s, 1H minor), 7.18 (s, 1H major). 13C NMR (75 MHz, CDCl₃): δ 23.0, 28.3, 37.3, 37.8, 42.1, 55.2, 55.4, 56.1, 81.1, 101.0, 101.6, 113.3, 114.3, 118.6, 121.9, 129.7, 130.0, 132.3, 134.0, 154.0, 154.4, 154.7, 158.4, 161.0. IR (UATR): νmax 3070, 1610, 1511, 1217, 1158 cm–1. LRMS (EI): m/z (rel intensity) 522 (31) [C₂₉H₂₉BrO₄⁺], 520 (27) [C₂₉H₂₉BRO₃⁺], 253 (100), 121 (58). TOF-HRMS: calculated for C₂₉H₂₉BRO₃ (M + H⁺) 521.1306, found 521.1313; calculated for C₂₉H₂₉BRo₃ (M + H⁺) 523.1306, found 523.1313.

Following the general procedure for the BF₃·OEt₂-mediated Et₃SiH reduction at 0°C for 1.5 h, tricyclic alcohol 46 (0.060 g, 0.110 mmol) furnished the corresponding tricyclic product 47 (0.07 g, 0.039 mmol, 35%) and the corresponding tricyclic alcohol 48 (white sticky gum (0.013 g, 0.024 mmol, 22%)). 1H NMR (300 MHz, CDCl₃): δ 1.20 (d, J = 2.2 Hz, 1H), 1.73 (br s, 3H), 2.06 (br d, J = 18.2 Hz, 1H), 2.37 (br d, J = 18.2 Hz, 1H), 2.83 (dd, J = 11.7, 4.3 Hz, 1H), 3.75–3.80 (m, 1H), 3.80 (s, 3H), 3.88 (s, 3H), 5.28 (d, J = 4.3 Hz, 1H), 6.03 (br s, 1H), 6.44 (s, 1H), 6.68–6.77 (m, 4H), 6.99 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 0.8 Hz, 1H). 13C NMR (75 MHz, CDCl₃): δ 23.7, 28.3, 37.3, 37.8, 42.1, 55.2, 55.4, 56.1, 81.1, 101.0, 101.6, 113.3, 114.3, 118.6, 121.9, 129.7, 130.0, 132.3, 134.0, 154.0, 154.4, 154.7, 158.4, 161.0. IR (UATR): νmax 2907, 2835, 1610, 1511, 1217, 1158 cm–1. LRMS (EI): m/z (rel intensity) 522 (31) [C₂₉H₂₉BrO₄⁺], 520 (27) [C₂₉H₂₉BRo₃⁺], 253 (100), 121 (58). TOF-HRMS: calculated for C₂₉H₂₉BRO₃ (M + H⁺) 521.1322, found 521.1313; calculated for C₂₉H₂₉BRo₃ (M + H⁺) 523.1306, found 523.1313.

### Associated Content

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03086.

$^1$H and $^13$C NMR spectra for all new compounds, NOE results of compounds 27, 30–34, and 48 and discussion of the assignment of stereochemistry (PDF)

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#### Notes

The authors declare no competing financial interest.

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#### References

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(17) An aldol reaction between benzaldehyde and a styrene ketone similar to 11 but without the Ar group was successful, giving the corresponding product in 65% yield. See ref 16b for more details.


(31) Various conditions using different Lewis acids and hydride sources were investigated for different reaction times and temperatures including the amounts of the Lewis acids and the hydride sources. It is critical to optimize the reaction conditions for each substrate.


(33) The relative stereochemistry of the hydroxy group at C7 of both 31 and 32 was established on the basis of the NOE experiments. For 31, NOE enhancement (2%) was observed between the $\beta$-proton at position 6a and the tertiary hydroxy proton. For 32, no such enhancement could be detected. Thus, compound 31 was assigned as the 7$\beta$-OH and 32 as the 7$\alpha$-OH diastereomer, respectively. While the use of NOE for this particular spectroscopic purpose has not been reported for tertiary alcohols, there have been examples where NOE or 2D-NOESY was employed to establish the regiochemistry of the oxindole: Pavlovskaya, T. L.; Yaremenko, F. G.; Lipson, V. V.; Shishkina, S. V.; Shishkin, O. V.; Musatov, V. I.; Karpenko, A. S. *Beilstein J. Org. Chem.* 2014, 10, 117–126. NOE or 2D-NOESY was also employed to establish the regiochemistry of the hydrazine on the pyrimidine ring: Hutchinson, D. J.; Hanton, L. R.; Moratti, S. C. *Dalton Trans.* 2014, 43, 8205–8218. In both cases, the protons on the heteroatom (N) were irradiated and showed the positive NOE values with the adjacent aromatic protons. In our case, the tertiary hydroxy proton of 31 appears as a sharp singlet and does not interchange with deuterium appreciably. Thus, it is possible to irradiate this tertiary hydroxy proton specifically to observe any enhancement this may cause on other protons. See the Supporting Information for more details.

(34) The stereochemical assignment of all intermediates and final products followed that of 27–34.

(35) For compounds 43 and 48, the relative stereochemistry was also established on the basis of the NOE enhancements (or the lack thereof) and the coupling constants ($J$ values) of the protons on the adjacent carbons. The presence of the hydroxy group was confirmed by mass spectrometry.