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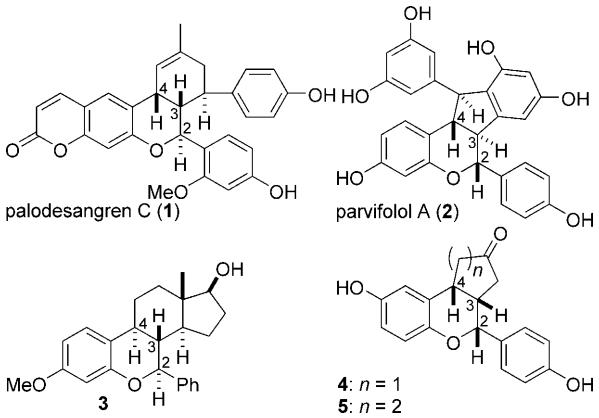
A Convergent General Strategy for the Functionalized 2-Aryl Cycloalkyl-Fused Chromans: Intramolecular Hetero-Diels–Alder Reactions of *ortho*-Quinone Methides

Jumreang Tummatorn,[a] Somsak Ruchirawat,[a, b] and Poonsakdi Ploypradith*[a, b]

Chroman is a core structure of flavonoids, which have been shown to exhibit a wide array of biological activities.[1] Palodesangren C (**1**; Scheme 1), a natural Diels–Alder adduct isolated from *Brosimum rubescens*, showed potent inhibition of the binding of 5α-dihydrotestosterone (DHT) with the androgen receptor.[2] Parvifolol A (**2**; Scheme 1), a natural product isolated from *Gnetum parvifolium*, was evaluated for the inhibitory activity in the Maillard reaction (protein glycation) associated with diabetic complications and aging of the skin.[3] Compound **3** was synthesized and studied as an estradiol analogue.[4] Some tricyclic 2-aryl-3,4-cycloalkyl-fused benzopyrans (**4**, **5**; Scheme 1) were synthesized and investigated for their high affinity to and selectivity for the estrogen receptor β over the α.[5,6]



Scheme 1. Examples of 2-arylcycloalkyl-fused chromans (shown with relative stereochemistry).

Some synthetic methods have been developed for chromans by hetero-Diels–Alder (HDA) reactions.[7] However, despite the presence of the 2-aryl group in some natural products and synthetic compounds, the synthesis of 2-aryl-3,4-cycloalkyl-fused chromans has been relatively unexplored, partly due to the susceptible nature of styrenes to polymerization. To date, the reported syntheses have been largely performed for the 2-alkylcycloalkyl-fused chromans and pyranobenzopyrans.[8] In addition, modifications on the cycloalkyl-fused rings would be difficult because the cycloalkyl or pyranyl moieties are nonfunctionalized. Moreover, different strategies were required for cyclopentyl- and cyclohexyl-fused compounds (**4**, **5**).[6] Thus, developing a general synthetic strategy for the tricyclic core of 2-aryl-3,4-cycloalkyl-fused chromans with defined stereocenters (C2, C3, and C4) and functionalizable moieties on the cycloalkyl ring would be pivotal.

Recently, as part of our research in the use of solid-supported reagents in organic synthesis,[9] our group has reported the successful generation of *o*-QMs and their intermolecular HDA reactions with styrene derivatives under mild conditions mediated by *p*-toluenesulfonic acid (*p*-TsOH) immobilized on silica (PTS-Si) in toluene.[9d] We now envisioned that PTS-Si could be employed to generate *ortho*-quinone methide (*o*-QM), which, upon reacting intramolecularly with the tethered dienophile (i.e., styrenes), could form the tricyclic 2-aryl-3,4-cycloalkyl-fused chroman.

As shown retrosynthetically in Scheme 2, the precursors for the intramolecular HDA reactions would be derived from aldol condensation between the benzaldehyde derivative (**6**) and ketone (X = H; Y = Me) or the acetophenone derivative (**7**) and the aldehyde (X = Me; Y = H). Synthesis of these cycloalkyl-fused chroman systems would be highly convergent and requires a similar strategy to assemble the precursors for the intramolecular *o*-QM/HDA reactions.

[a] Dr. J. Tummatorn, Prof. Dr. S. Ruchirawat, Dr. P. Ploypradith
Laboratory of Medicinal Chemistry, Chulabhorn Research Institute
Vipavadee-Rangsit Highway, Bangkok 10210 (Thailand)
Fax: (+662) 574-2027
E-mail: poonsakdi@cri.or.th

[b] Prof. Dr. S. Ruchirawat, Dr. P. Ploypradith
Program in Chemical Biology, Chulabhorn Graduate Institute
Vipavadee-Rangsit Highway, Bangkok 10210 (Thailand)

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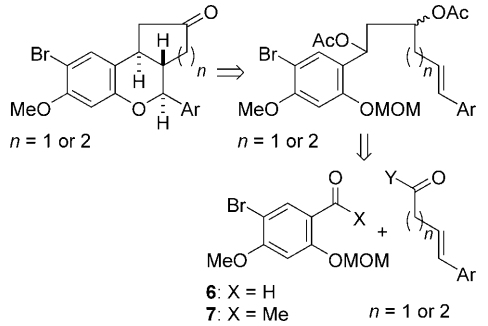
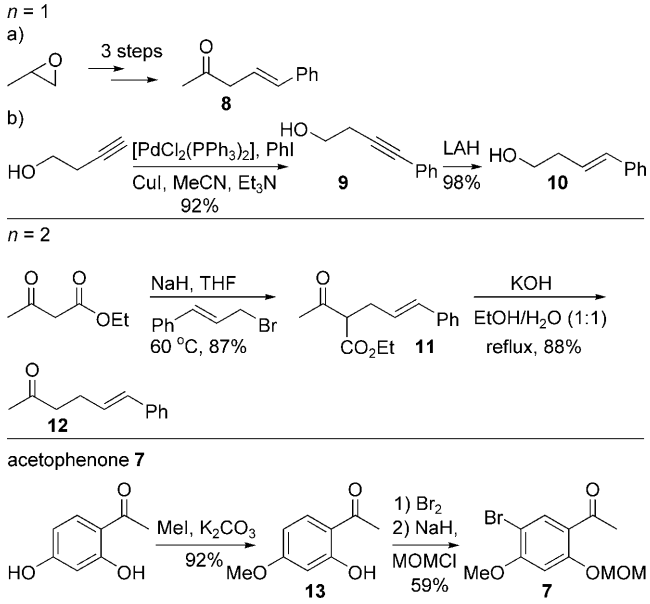


Scheme 2. Retrosynthetic analysis for the cycloalkyl-fused chromans. MOM = methoxymethyl.

Our efforts then focused on 1) the syntheses of styrene-containing fragments of different chain length, 2) the aldol condensation, and 3) the *o*-QM/HDA reactions.

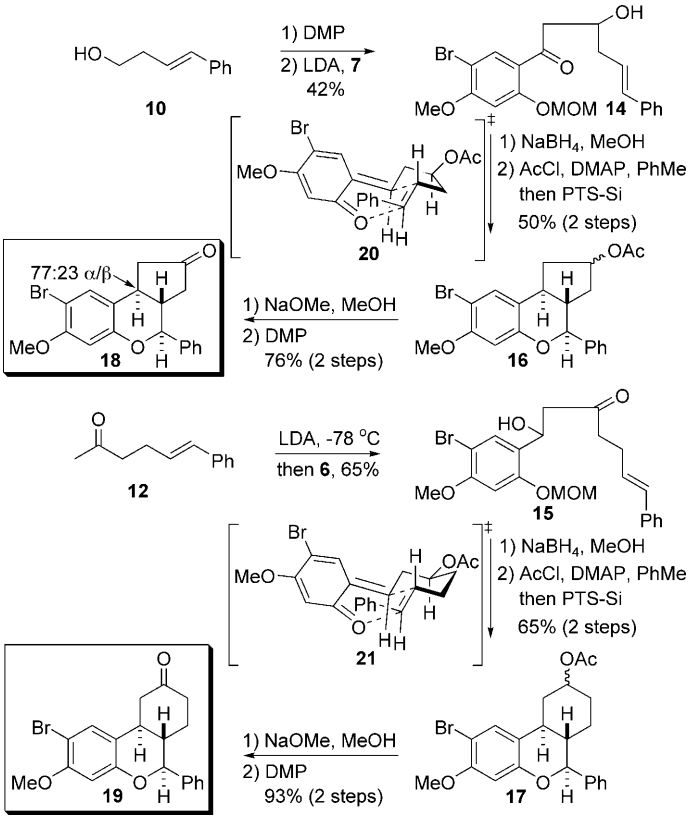
As depicted in Scheme 3, the requisite styrene-containing fragments could be easily prepared. For $n=1$, we first anticipated that ketone **8**[10] could be used in the aldol condensation with benzaldehyde **6**. However, regioselective generation of kinetic enolate of **8** by lithium diisopropylamide (LDA) was difficult. The presence of the styrene moiety rendered the α-methylene protons more acidic and deprotonation of these protons became competitive with that of the α-methyl protons. Thus, an alternative pair for aldol condensation was considered and the target styrene-containing fragment would contain the aldehyde group rather than the ketone. Such a fragment could be synthesized starting from the Sonogashira coupling between iodobenzene and but-3-yn-1-ol, which gave the product **9** in 92% yield. The *trans*-styrene moiety was installed by LAH reduction of the alkyne, giving **10** in 98% yield.



Scheme 3. Synthesis of styrene-containing fragments **12**, **14**, and acetophenone derivative **7**. LAH = lithium aluminum hydride.

For $n=2$, alkylation of ethyl acetoacetate with cinnamyl bromide using NaH as base gave **11** in 87% yield, which was subjected to saponification/decarboxylation conditions with KOH to provide **12** in 88% yield. The benzaldehyde **6** could be readily prepared.[9d] The acetophenone **7** was prepared in three steps from 2,4-dihydroxyacetophenone via **13**.

With both fragments of each cycloalkyl-fused chromans in hand, the aldol condensations of respective pairs were studied (Scheme 4). Alcohol **10** was oxidized to the aldehyde using Dess–Martin periodinane (DMP). The crude aldehyde was used directly in the aldol condensation with the enolate of acetophenone **7**, giving **14** in 42% yield. For $n=2$, aldol condensation of the methyl ketone **12** with benzaldehyde **6** gave **15** in 65% yield.

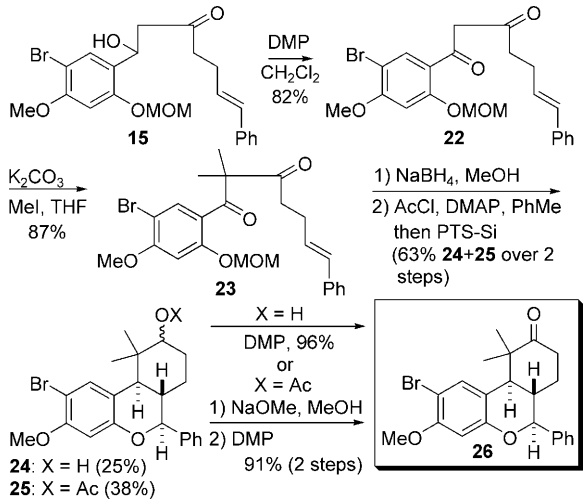


Scheme 4. Aldol condensation/reduction/acetylation/*o*-QM/HDA reactions and proposed *exo* transition states, providing the chromans as racemates (shown with relative stereochemistry). DMAP = 4-dimethylaminopyridine.

After some experimentation,[11] it was found that borohydride reduction of the ketone followed by a one-pot acetylation and PTS-Si-mediated *o*-QM/HDA reaction sequence in toluene occurred smoothly for both substrates, providing the products **16** and **17** in 50 and 65% yields over two steps, respectively. Subsequent base-mediated cleavage of the acetates followed by DMP oxidation furnished the ketones **18** and **19** in 76 and 93% yields over two steps, respectively. Compound **19** was obtained as a single isomer, suggesting that the *o*-QM/HDA reaction occurred with high stereose-

lectivity. Compound **18**, on the other hand, was obtained as a 77:23 (H_α/H_β) mixture of C4-epimers. The C3–C4 *trans* relationship in the major product of **18** and in compound **19** suggested the *exo* transition states **20** and **21**.[8]

Our new method also allowed easy access to other modifications on the cyclohexyl ring. The β-hydroxy ketone **15** was oxidized by DMP to the 1,3-diketone **22** in 82% yield, which underwent bis-methylation to give the product **23** in 87% yield (Scheme 5). Subsequent borohydride reduction

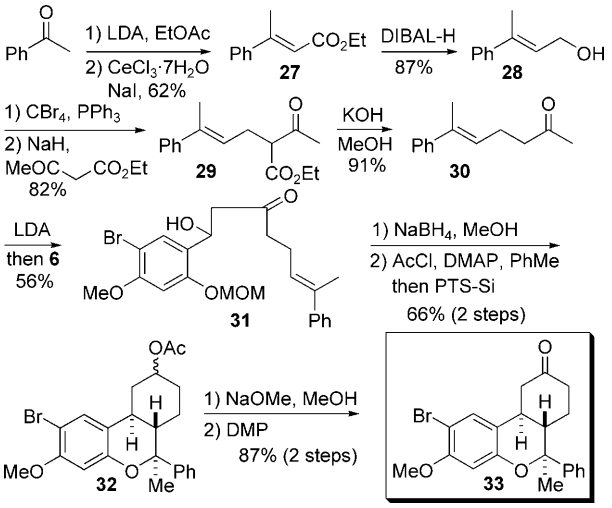


Scheme 5. Synthesis of modified cyclohexyl-fused chroman.

and one-pot acetylation/*o*-QM/HDA reactions provided a mixture of tricyclic alcohol **24** and acetate **25** in 63% combined yields over 2 steps. Treatment of the acetate with NaOMe followed by DMP oxidation gave the ketone **26** as a single isomer in 91% yield over 2 steps. The alcohol **24** was also oxidized to the ketone by DMP in 96% yield.

In addition, modification at C2 as a quaternary center was performed. Aldol condensation between ethyl acetate and acetophenone using LDA followed by $CeCl_3$–NaI-mediated dehydration[12] gave the α,β-unsaturated ester **27** in 62% yield (Scheme 6). Subsequent DIBAL-H reduction furnished the alcohol **28** in 87% yield, which was converted to the cinnamyl bromide by using CBr_4 and PPh_3. Alkylation of the bromide with ethyl acetoacetate, saponification/decarboxylation, and aldol condensation gave ketone **31** via **29** and **30**. Reduction and one-pot acetylation/*o*-QM/HDA reactions provided the tricyclic chroman acetate **32** in 66% yield over 2 steps. Cleavage of the acetate followed by DMP oxidation gave ketone **33** in 87% yield over 2 steps as a single isomer with the C2-methyl group *syn* to the C4-H.

In summary, we have developed a highly efficient and general strategy for the synthesis of cycloalkyl-fused chroman systems by the PTS-Si-mediated *o*-QM/HDA reactions, which proceeded in 50–66% yields in combination with the preceding reduction and acetylation. The generality of this strategy was demonstrated to provide the cyclopentyl- and



Scheme 6. Synthesis of C2-modified cyclohexyl-fused chroman. DIBAL-H = diisobutylaluminum hydride.

cyclohexyl-fused chroman systems. The use of PTS-Si in toluene was critical to suppress styrene polymerization. In addition, all stereocenters at C2, C3, and C4 were installed with good to excellent stereocontrol in a single step. The approach is flexible for a number of modifications and the key steps are compatible with the modified substrates to provide structurally diverse analogues. In addition, the presence of bromine and a methoxy group on the aromatic ring allowed further modifications, such as those required for installing the coumarin moiety in palodesangren C. Applications of this strategy to synthesize other natural products will be reported in due course.

Experimental Section

General procedure for HDA reactions of o-QMs: $NaBH_4$ (1.1 equiv) was added to a solution of precursor compounds (**14**, **15**, **23**, **31**) (1 equiv) in MeOH (1 mL mmol^{-1}) at room temperature and then the resulting mixture was stirred for 30 min. After removal of the solvent, H_2O was added to the residue and it was extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under a vacuum to give a crude alcohol product. This crude product was dissolved in toluene (1 mL mmol^{-1}), followed by the addition of DMAP (2.5 equiv), and the reaction mixture was stirred until completely dissolved. Acetyl chloride (2.5 equiv) was added dropwise to this solution and then the reaction was stirred vigorously overnight. PTS-Si (1.2 equiv) was added to this mixture at room temperature. The reaction mixture was monitored by TLC analysis. After completion, the resulting mixture was filtered and the solid was washed with EtOAc. The combined organic layers were evaporated and the residue was purified by flash chromatography on silica to yield 2-arylcycloalkyl-fused chroman acetates (**16**, **17**, **25**, **32**) and 2-arylcycloalkyl-fused chromanol (**24**).

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Keywords: chromans · cycloaddition · cyclization · quinone methides · stereoselective reactions

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[10] See the Supporting Information for details.
[11] Direct conversion of the alcohol in compounds **14** and **15** to the acetates for the subsequent *o*-QM/HDA reaction was not successful because of the competing retro-aldol reaction and dehydration among others. Subjecting **15** directly for the *o*-QM/HDA reaction gave **19** in low yield (20%). Treating the 1,3-diol from the borohydride reduction with PTS-Si in toluene or *p*-TsOH in methanol (ref. [8a–d]) gave no desired tricyclic alcohol.
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