Acylphloroglucinols from *Callistemon lanceolatus* DC.

Rattanaburi S., Mahabusarakam W., Phongpaichit S., Carroll A.R.

(2013) Tetrahedron, 69 (30), pp. 6070-6075.

มีบทความอ้างอิงในช่วง 1 ต.ค. 67 – 31 มี.ค. 68 จำนวน 3 บทความ

JOC The Journal of Organic Chemistry

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# Regioselective 1,4-Addition of P(O)−H Species to In Situ-Formed 1-Benzopyrylium Ion from C3-Substituted 2*H*-Chromene Hemiketals to Construct C3-Functionalized C4-Phosphorylated 4*H*-Chromenes

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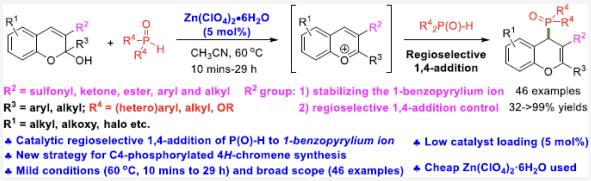
Cite This: *J. Org. Chem.* 2025, 90, 1768−1783 Read Online






ABSTRACT: Herein, we report the first example that P(O)−H species including *H*-phosphonates and *H*-phosphine oxides could participate in a highly regioselective 1,4-addition to in situ generated 1-benzopyrylium ion from C3-substituted 2*H*-chromene hemiketals, which provides a brand-new and effective approach for the synthesis of C4-phosphorylated 4*H*-chromenes with diverse C3-functionality (ketone, ester, sulfonyl, aryl, and alkyl groups). In total, the reaction features the use of inexpensive $Zn(ClO_4)_2 \cdot 6H_2O$ as a catalyst, low catalyst loading (only 5 mol %), mild reaction conditions (60 °C, 10 min to 24 h), and broad substrate scope (46 examples) as well as good to high yields (>90% yield on average). More importantly, mechanistic experiments demonstrated the essential role of the C3-substituent on 2*H*-chromene hemiketals in stabilizing the in situ generated 1-benzopyrylium ion and the regioselective 1,4-addition control.



## INTRODUCTION

Due to the aromaticity of the ten π-electron system, 1-benzopyrylium ion is an intrinsically stable and isolable cationic species, and has been widely utilized as a reactive intermediate in the preparation of 2*H* or 4*H*-chromene derivatives.[1,2] The high electrophilicity at the C4 position makes it prone to undergo 1,4-addition by carbon or heteroatom-based nucleophiles to afford C4-functionalized 4*H*-chromenes.[3] However, attack at the C2-position, namely, 1,2-addition, is also possible, which undoubtedly would produce C2-decorated 2*H*-chromenes.[2c,4,5] Consequently, the development of highly regioselective 1,2- or 1,4-addition to 1-benzopyrylium ion for generation of the corresponding C2-functionalized 2*H*-chromenes or C4-functionalized 4*H*-chromenes is of high significance.

As far as we know, the 1,2- or 1,4-regioselective control has been realized by the substituents on the nucleophile[6] or 1-benzopyrylium ion.[3−5,7] As for the former, only one example was reported by Zhu et al., who found the R group on indole moiety played the key role in determining the products as 2-indolyl-2*H*-chromene or 4-indolyl-4*H*-chromenes in $BF_3 \cdot Et_2O$-mediated nucleophilic substitution reaction between indoles and 2-$CF_3$-3-$CO_2$Et 2*H*-chromene hemiketals (Scheme 1, eqs 1 and 2).[6] On the other hand, 2-unsubstituted 1-benzopyrylium ion tended to undergo 1,2-addition to form C2-functionalized 2*H*-chromenes (eq 3).[2c,4] Especially, these products can be also obtained when 1-benzopyrylium ion derived from 2-aryl- or 2-$CO_2$R-4-aryl-2*H*-chromene hemiketals were employed (eq 4).[5] As regards the preparation of the preparation of 4*H*-chromenes, researchers have found that 3,4-unsubstituted 1-benzopyrylium ion normally prefers a 1,4-addition pattern to furnish C4-functionalized 4*H*-chromenes (eq 5).[3] To enrich the structural diversity of 4*H*-chromenes, people have tried to introduce substituents ($R^2$ group) into 1-benzopyrylium ion at the C3-position,[6,7] which also allows the anticipated 1,4-addition to give C3,4-difunctionalized 4*H*-chromenes (eq 6). However, it is strange that the $R^2$ substituents seem to be limited to electron-withdrawing groups (EWGs) like ester,[6,7a−c,e,f] ketone[7d,g] and sulfonyl units.[7h,i] It is currently unclear whether the EWGs were essential to the regioselective 1,4-addition pathway, or other electron-donating or neutral substituents can be used as well.

Received: August 22, 2024
Revised: December 25, 2024
Accepted: January 10, 2025
Published: January 24, 2025





https://doi.org/10.1021/acs.joc.4c02113
J. Org. Chem. 2025, 90, 1768−1783

Ethers. *Adv. Synth. Catal.* **2018**, *360*, 2446. (d) Jiang, C.; Chen, Y.; Zhang, H.; Tan, J.-P.; Wang, T. Catalyst-Free Synthesis of α-Functionalized 2*H*-Chromenes in Water: A Tandem Self-Promoted *pseudo*-Substitution and Decarboxylation Process. *Chem.—Asian J.* **2019**, *14*, 2938−2944. (e) Yang, F.; Li, Y.; Floreancig, P. E.; Li, X.; Liu, L. Copper-Catalyzed Oxidative Cross-Dehydrogenative Coupling of 2*H*-Chromenes and Terminal Alkynes. *Org. Biomol. Chem.* **2018**, *16*, 5144.

(5) (a) Wu, Y.-C.; Li, H.-J.; Liu, L.; Demoulin, N.; Liu, Z.; Wang, D.; Chen, Y.-J. Hafnium Triflate as an Efficient Catalyst for Direct Friedel−Crafts Reactions of Chromene Hemiacetals. *Adv. Synth. Catal.* **2011**, *353*, 907. (b) Wu, Y.-C.; Li, H.-J.; Liu, L.; Demoulin, N.; Liu, Z.; Wang, D.; Chen, Y.-J. Facile Synthesis of Spiropyrans from Chromene Hemiacetal Esters and Bifunctional Nucleophiles. *Synlett* **2011**, *11*, 1573−1578. (c) Huang, D.-M.; Li, H.-J.; Wang, Q.; Yan, P.; Wu, Y.-C. Synthesis of 2-(2*H*-Chromenyl)-Oxazoles from 2*H*-Chromene Hemiacetals by Using a Modified Passerini-Type Reaction. *ChemistrySelect* **2018**, *3*, 9658. (d) Wang, D.-Y.; Li, H.-J.; Huang, D.-M.; Wu, Y.-C. Tin(ii)-Catalyzed Dehydrative Cross-Coupling of 2*H*-Chromene Hemiacetals with Ketones. *Org. Biomol. Chem.* **2020**, *18*, 9308. (e) Zheng, S.-L.; Zou, Y.-X.; Wen, Z.; Gu, J.-F.; Gu, L.-H.; Chen, L. $Y(OTf)_3$-Catalyzed Phosphorylation of 2*H*-Chromene Hemiacetals with P(O)−H Compounds to 2-Phosphorylated 2*H*-Chromenes. *Org. Biomol. Chem.* **2021**, *19*, 6812−6816. (f) Zheng, S.-L.; Wen, Z.; Yang, K.-C.; Zeng, Y.; Chen, L.; Deng, C.-F. Copper(ii)-Catalyzed Direct Dehydrative Alkynylation of 2*H*-Chromene Hemiketals with Terminal Alkynes to 2,2-Disubstituted 2-Alkynylated 2*H*-Chromenes. *Org. Biomol. Chem.* **2022**, *20*, 3785−3789. (g) Kikuchi, J.; Kodama, S.; Terada, M. Radical Addition Reaction between Chromenols and Toluene Derivatives Initiated by Brønsted Acid Aatalyst under Light Irradiation. *Org. Front. Chem.* **2021**, *8*, 4153. For an exception, see: (h) Terada, M.; Yamanaka, T.; Toda, Y. Chiral Anion Catalysis in the Enantioselective 1,4-Reduction of the 1-Benzopyrylium Ion as a Reactive Intermediate. *Chem.—Eur. J.* **2013**, *19*, 13658−13662.

(6) Pang, W.; Han, J. W.; Zhao, J. W.; Zhu, S. Z. Regioselective Carbon-Carbon Bond Formation in the Reaction of 2-Hydroxy-2-(trifluoromethyl)-2*H*-chromenes with Indoles Promoted by Lewis Acid. *Synthesis* **2011**, *20*, 3364−3370.

(7) (a) Li, X.; Zhao, J.; Wang, Z.; Han, J.; Zhao, J.; Zhu, S. Reactions of 2-(Trifluoromethyl)-2-hydroxy-2*H*-chromenes with Thiophenols Promoted by Lewis Acid. *Tetrahedron* **2012**, *68*, 8011. (b) Zhang, L.; Li, X.; Wang, Z.; Zhao, J.; Wang, J.; Han, J.; Zhu, S. Reactions of 2-(Trifluoromethyl)-2-hydroxy-2*H*-chromenes with Silyl Enol Ethers Promoted by $AlCl_3$. *Tetrahedron* **2013**, *69*, 7975−7980. (c) Rao, L. C.; Kumar, N. S.; Dileepkumar, V.; Murthy, U. S. N.; Meshram, H. M. On Water" Synthesis of Highly Functionalized 4*H*-Chromenes via Carbon−Carbon Bond Formation under Microwave Irradiation and Their Antibacterial Properties. *RSC Adv.* **2015**, *5*, 28958. (d) Rao, L. C.; Kumar, N. S.; Bheeram, V. R.; Hemambika, S.; Mukkamala, S. B. An Efficient ZnO-Nanoparticle-Catalyzed Regio- and Chemoselective Synthesis of Novel Functionalized 4*H*-Chromenes in Aqueous Medium. *ChemistrySelect* **2018**, *3*, 7485. (e) Rao, L. C.; Kumar, N. S.; Meshram, H. M. Microwave Assisted Novel and Regioselective Functionalization of Imidazopyridines with Chromene Acetals and β-Nitrostyrenes. *RSC Adv.* **2015**, *5*, 70949−70957. (f) Vasantha, R.; Lenin, D. V.; Rao, L. C. Water Extract of Lemon (WEL) as a Promoter: Green and Regioselective Synthesis of Alkyl-4-(1H-indol-3 yl)-2-alkyl-4*H*-chromene-3-carboxylates Using 4*H*-chromenes and Indoles. *ChemistrySelect* **2020**, *5*, 14004−14007. (g) Yoshioka, E.; Goto, Y.; Minato, I.; Miyabe, H. Aqueous-Medium Selective Modification of Cysteine and Related Thiols with Tricyclic Oxygen-Heterocycles. *Synthesis* **2017**, *49*, 4887. (h) Kumar, A.; Thadkapally, S.; Menon, R. S. Base-Mediated Cyclocondensation of Salicylaldehydes and 2-Bromoallyl Sulfones for the Synthesis of 3-Sulfonylchromene Derivatives and Their Regioselective Friedel−Crafts Heteroarylation Reactions. *J. Org. Chem.* **2015**, *80*, 11048. (i) Yin, C.-L.; Qin, R. Z.; Qin, H. L. One-Pot Three-Component Synthesis of Indolyl-4*H*-chromene-3-sulfonyl Fluoride: A Class of Important Pharmacophore. *J. Org. Chem.* **2024**, *89*, 3618.

(8) (a) Aridoss, G.; Zhou, B.; Hermanson, D. L.; Bleeker, N. P.; Xing, C.-G. Structure−Activity Relationship (SAR) Study of Ethyl 2-Amino-6-(3,5-dimethoxyphenyl)-4-(2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (CXL017) and the Potential of the Lead against Multidrug Resistance in Cancer Treatment. *J. Med. Chem.* **2012**, *55*, 5566. (b) Das, S. G.; Hermanson, D. L.; Bleeker, N.; Lowman, X.; Li, Y.-F.; Kelekar, A.; Xing, C.-G. Ethyl 2-Amino-6-(3,5-dimethoxyphenyl)-4-(2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (CXL017): A Novel Scaffold That Resensitizes Multidrug Resistant Leukemia Cells to Chemotherapy. *ACS Chem. Biol.* **2013**, *8*, 327. (c) Pinto, S. O.; Pontes, O.; Baltazar, F.; Costa, M. In vivo Efficacy Studies of Chromene-based Compounds in Triple-Negative Breast Cancer—A Systematic Review. *Eur. J. Pharmacol.* **2020**, *887*, No. 173452. (d) Raj, V.; Lee, J. 2*H*/4*H*-Chromenes—A Versatile Biologically Attractive Scaffold. *Front. Chem.* **2020**, *8*, 623.

(9) (a) Joulain, D.; Tabacchi, R. Two Volatile β-chromenes from *Wisteria Sinensis* Flowers. *Pyhtochemistry* **1994**, *37*, 1769. (b) Demyttenaere, J.; Syngel, K. V.; Markusse, A. P.; Vervisch, S.; Debenedetti, S.; Kimpe, N. D. Synthesis of 6-Methoxy-4H-1-benzopyran-7-ol, a Character Donating Component of the Fragrance of *Wisteria Sinensis*. *Tetrahedron* **2002**, *58*, 2163−2166. (c) Nakashima, K.-I.; Abe, N.; Kamiya, F.; Ito, T.; Oyama, M.; Iinuma, M. Novel Flavonoids in Dragon's Blood of *Daemonorops draco*. *Helv. Chim. Acta* **2009**, *92*, 1999. (d) Hufford, C. D.; Oguntimein, B. O.; Baker, J. K. New Flavonoid and Coumarin Derivatives of Uvaria Afzelii. *J. Org. Chem.* **1981**, *46*, 3073. (e) Rattanaburi, S.; Mahabusarakam, W.; Phongpaichit, S.; Carroll, A. R. Acylphloroglucinols from *Callistemon lanceolatus* DC. *Tetrahedron* **2013**, *69*, 6070. (f) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Zhao, J.; Grundy, C. C.; Xu, L.; Lamothe, S.; Gourdeau, H.; Denis, R.; Tseng, B.; Kasibhatla, S.; Cai, S.-X. Discovery of 4-Aryl-4*H*-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-Based High-Throughput Screening Assay. 3. Structure−Activity Relationships of Fused Rings at the 7,8-Positions. *J. Med. Chem.* **2007**, *50*, 2858−2864. (g) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. Discovery of 4-Aryl-4*H*-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-based High-Throughput Screening Assay. 1. Structure−Activity Relationships of the 4-Aryl Group. *J. Med. Chem.* **2004**, *47*, 6299. (h) Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W. F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. Aminocyanopyridine Inhibitors of Mitogen Activated Protein Kinase-activated Protein Kinase 2 (MK-2). *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587. (i) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Grundy, C. C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Arrardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. Discovery of 4-Aryl-4*H*-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-based High-throughput Screening Assay. 2. Structure−activity Relationships of the 7- and 5-, 6-, 8-Positions. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745.

(10) (a) Gross, H.; Costisella, B.; Keitel, I.; Sonnenschein, H.; Kunath, A. *a*-Substituierte Phosphonate 66. Zur Reaktion Von Benzopyrylium-bzw. Furylchloriden Mit Trivalenten Phosphorverbindungen. *Phosphorus, Sulfur, and Silicon and the Related Elements* **1993**, *84*, 129. (b) Abaev, V.; Karsanov, I. V.; Urtaeva, Z. K.; Blinokhvatov, A. F.; Bumber, O. Preparation and Properties of (4*H*-Pyran-4-yl)diphenylphosphine Oxides. *Zh. Obshch. Khim.* **1990**, *60*, 1012. (c) Ali, T. E.; Assiri, M. A.; EI-Shaaer, H. M.; Hassan, M. M.; Fouda, A. M.; Hassanin, N. M. Reaction of 2-Imino-2*H*-chromene-3-carboxamide with Some Phosphorus Esters: Synthesis of Some Novel Chromenes Containing Phosphorus Heterocycles and Phosphonate Groups and Their Antioxidant and Cytotoxicity Properties. *Synth. Commun.* **2019**, *49*, 2983−2994. (d) Tajti, Á.; Szabó, K. E.; Popovics-Tóh, N.; Iskanderrov, J.; Perdih, F.; Laszlo, H.,



https://doi.org/10.1021/acs.joc.4c02113
*J. Org. Chem.* 2025, 90, 1768−1783

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Article

# Formation of 2*H*- and 4*H*-chromene Rings in Intramolecular Rauhut−Currier Reaction, Catalyzed by Lithium Selenolates

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Cite This: *ACS Omega* 2025, 10, 3652−3664

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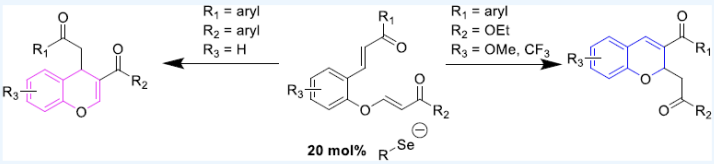


**ABSTRACT:** In this paper, we present the first example of using a catalytic amount of a nucleophilic seleno-organic catalyst in a tandem seleno-Michael/Michael reaction, leading to the formation of 2*H*/4*H*-chromenes. Chromenes represent a highly significant group of oxygen-containing heterocycles commonly found as structural scaffolds in a diverse range of fields such as medicinal chemistry, pharmaceutical agents, drug candidates, synthetic chemistry, and materials chemistry. Various preparation methods have been developed, utilizing different substrates in conjunction with metal catalysts, organocatalysts, Brønsted acids, bases, or Lewis acids. The synthetic utility of lithium selenolates has been demonstrated as efficient nucleophilic catalysts in the Rauhut−Currier cyclization of chalcone derivatives. This methodology allows for the synthesis of 2*H*- and 4*H*-chromenes depending on the substituents directly connected to the carbonyl group. The investigation focuses on the impact of various substituents in the aromatic fragment as well as conditions and selenolates. The scope of different starting materials was also considered.

## INTRODUCTION

Chromenes represent a highly significant group of oxygen-containing heterocycles that are commonly found as structural scaffolds in a diverse range of natural compounds,[1−9] pharmaceutical agents,[10] and drug candidates.[11,12] Compounds with a chromene motif in their structures exhibit a multitude of diverse properties such as antibacterial/antimicrobial,[13] antiviral, antitumor, anticancer, anti-inflammatory, antitubercular, diuretic, antifungicidal, antidiabetic, anticoagulant, antianaphylactic, *anti*-HIV, and antioxidant activities. Compounds from this group also have photochromic properties[14−17] used in materials chemistry (Figure 1).

This ubiquity of chromene fragments stimulated the development of various methods for synthesizing such compounds. The 2*H*-chromene ring is constructed mainly in three types of transformations: Brønsted and Lewis acid/base catalysis,[18−24] enantioselective organocatalysis,[25−27] and (transition)-metal[28−32] catalysis. The first approach is important because transition-metal-free methods prevent contamination of bioactive/pharmaceutical compounds with potentially toxic metals. This is also the preferred choice for economic aspects (transition metals, especially noble metals, are expensive). Therefore, metal-free methods for the synthesis of 2*H*-chromenes are of interest and have already received attention. Organocatalysis is one of the emerging fields of catalysis and plays an important role in the asymmetric synthesis of 2*H*-chromenes. Metal catalysis plays an important role in chemical transformations that are difficult or impossible to perform using conventional methods. This type of catalysts has been successfully used in the synthesis of 2*H*-chromenes.[33]

The second group of chromenes, 4*H*-chromenes, can be synthesized by three distinct types of transformations: formation of a dihydropyrane ring ([2 + 4] cycloaddition reactions[34−37] and tandem Michael/cyclization/dehydration[38−40]), postsynthetic nucleophilic modifications of 2*H*-chromenes (nucleophilic addition to 1-benzopyrylium ions[41−45] and 2-iminochromenes[46−48]), and other types of reactions including ring closure metathesis,[49] Rauhut−Currier-type cyclization,[50] and reactions that involve combinations of various tandem reactions.[51,52] Cycloadditions include several reactions catalyzed by Lewis and Brønsted acids, Brønsted bases, transition-metal complexes, organocatalysts, and NHC catalysts. This type of transformation also includes an enantioselective approach. A second convenient ring construction methodology is the Michael/cyclization/dehydration method in which a nucleophile attaches to a 2-hydroxychalcone or 2-hydroxystyrene derivative, under the influence of a Lewis or Brønsted acid. In the final stage, the ring

Received: September 19, 2024
Revised: December 19, 2024
Accepted: December 20, 2024
Published: January 22, 2025





https://doi.org/10.1021/acsomega.4c08613
*ACS Omega* 2025, 10, 3652−3664

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support from the Polish National Science Centre (Grant no. 2017/27/B/ST5/01248) is gratefully acknowledged. The research was carried out with the equipment purchased thanks to the financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08). The research has been supported by a grant from the Faculty of Chemistry under the Strategic Programme Excellence Initiative at Jagiellonian University. The study was carried out using the research infrastructure co-funded by the European Union in the framework of the Smart Growth Operational Program, Measure 4.2; Grant no. POIR.04.02.00−00-D001/20, "ATOMIN 2.0—ATOMic scale science for the INnovative economy".

## ■ REFERENCES


(1) Park, B. H.; Lee, H. J.; Lee, Y. R. Total Synthesis of Chiricanine A, Arahypin-1, trans-Arachidin-2, trans-Arachidin-3, and Arahypin-5 from Peanut Seeds. *J. Nat. Prod.* **2011**, *74* (4), 644−649.

(2) Scopton, A.; Kelly, T. R. Synthesis of azacridone A. *Org. Lett.* **2004**, *6* (21), 3869−3871.

(3) Palmer, C. J.; Josephs, J. L. Synthesis of the Calophyllum coumarins. Part 2. *J. Chem. Soc., Perkin Trans.* **1995**, *1* (24), 3135−3152.

(4) Ribeiro, A. B.; Abdelnur, P. V.; Garcia, C. F.; Belini, A.; Severino, V. G. P.; da Silva, M. F.; Fernandes, J. B.; Vieira, P. C.; de Carvalho, S. A.; de Souza, A. A.; Machado, M. A.; Machado, M. A. Chemical Characterization of Citrus sinensis Grafted on C. limonia and the Effect of Some Isolated Compounds on the Growth of Xylella fastidiosa. *J. Agric. Food Chem.* **2008**, *56* (17), 7815−7822.

(5) Sansom, C. E.; Larsen, L.; Perry, N. B.; Berridge, M. V.; Chia, E. W.; Harper, J. L.; Webb, V. L. An Antiproliferative Bis-prenylated Quinone from the New Zealand Brown Alga Perithalia capillaris. *J. Nat. Prod.* **2007**, *70* (12), 2042−2044.

(6) Chansakaow, S.; Ishikawa, T.; Seki, H.; Sekine, K.; Okada, M.; Chaichantipyuth, C. Identification of deoxymiroestrol as the actual rejuvenating principle of "Kwao Keur", Pueraria mirifica. The known miroestrol may be an artifact. *J. Nat. Prod.* **2000**, *63* (2), 173−175.

(7) Rattanaburi, S.; Mahabusarakam, W.; Phongpaichit, S.; Carroll, A. R. Acylphloroglucinols from Callistemon lanceolatus DC. *Tetrahedron* **2013**, *69* (30), 6070−6075.

(8) Nakashima, K.-I.; Abe, N.; Kamiya, F.; Ito, T.; Oyama, M.; Iinuma, M. Novel Flavonoids in Dragon's Blood of Daemonorops draco. *Helv. Chim. Acta* **2009**, *92* (10), 1999−2008.

(9) Demyttenaere, J.; Van Syngel, K.; Peter Markusse, A.; Vervisch, S.; Debenedetti, S.; De Kimpe, N. Synthesis of 6-methoxy-4H-1-benzopyran-7-ol, a character donating component of the fragrance of Wisteria sinensis. *Tetrahedron* **2002**, *58* (11), 2163−2166.

(10) Fabian, C. J.; Kimler, B. F.; Zalles, C. M.; Phillips, T. A.; Metheny, T.; Petroff, B. K.; Havighurst, T. C.; Kim, K. M.; Bailey, H. H.; Heckman-Stoddard, B. M. Clinical trial of acolbifene in premenopausal women at high risk for breast cancer. *Cancer Prev. Res.* **2015**, *8* (12), 1146−1155.

(11) Andersson, H.; Demaegdt, H.; Johnsson, A.; Vauquelin, G.; Lindeberg, G.; Hallberg, M.; Erdélyi, M.; Karlén, A.; Hallberg, A. Potent macrocyclic inhibitors of insulin-regulated aminopeptidase (IRAP) by olefin ring-closing metathesis. *J. Med. Chem.* **2011**, *54* (11), 3779−3792.

(12) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. Discovery of 4-Aryl-4H-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-Based High Throughput Screening Assay. 4. Structure−Activity Relationships of N-Alkyl Substituted Pyrrole Fused at the 7,8-Positions. *J. Med. Chem.* **2008**, *51* (3), 417−423.

(13) Ávila, H. P.; Smânia, E. d. F. A.; Monache, F. D.; Smânia, A., Jr. Structure−activity relationship of antibacterial chalcones. *Bioorg. Med. Chem.* **2008**, *16* (22), 9790−9794.

(14) Kumar, P.; Kumar, P.; Venkataramani, S.; Ramasastry, S. S. V. Pd-Catalyzed Formal [3 + 3] Heteroannulation of Allylic gem-Diacetates: Synthesis of Chromene-Based Natural Products and Exploration of Photochromic Properties. *ACS Catal.* **2022**, *12* (2), 963−970.

(15) Yang, Z.; Zhao, J.; Liang, C.; Jiang, H. Materials and Device Design for Epidermal UV Sensors with Real-Time, Skin-Color Specific, and Naked-Eye Quasi-Quantitative Monitoring Capabilities. *Adv. Mater. Technol.* **2023**, *8* (7), 1−10.

(16) Gentili, P. L.; Giubila, M. S.; Germani, R.; Romani, A.; Nicoziani, A.; Spalletti, A.; Heron, B. M. Optical Communication among Oscillatory Reactions and Photo-Excitable Systems: UV and Visible Radiation Can Synchronize Artificial Neuron Models. *Angew. Chem., Int. Ed.* **2017**, *56* (26), 7535−7540.

(17) Zhao, W.; Carreira, E. M. A smart photochromophore through synergistic coupling of photochromic subunits. *J. Am. Chem. Soc.* **2002**, *124* (8), 1582−1583.

(18) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. Synthesis of 3,4-Disubstituted 2H-Benzopyrans through C−C Bond Formation via Electrophilic Cyclization. *J. Org. Chem.* **2007**, *72* (4), 1347−1353.

(19) Shi, M.; Dai, L.-Z.; Shi, Y.-L.; Zhao, G.-L. Potassium Carbonate-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters: an Effective Way to Synthesize Functionalized 2H-Chromenes. *Adv. Synth. Catal.* **2006**, *348* (7−8), 967−972.

(20) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. Unexpected Tandem Ylide Annulation Reaction for Controllable Synthesis of 2H-Chromenes and 4H-Chromenes. *Org. Lett.* **2006**, *8* (17), 3853−3856.

(21) Yoshioka, E.; Kohtani, S.; Miyabe, H. A Multicomponent Coupling Reaction Induced by Insertion of Arynes into the C = O Bond of Formamide. *Angew. Chem., Int. Ed.* **2011**, *50* (29), 6638−6642.

(22) Raju, B. C.; Saidachary, G.; Kumar, J. A.; Sridhar, B. Facile Synthesis of Substituted Ethyl 2-(Chloromethyl)-2-hydroxy-2H-1-benzopyran-3-carboxylates. *Helv. Chim. Acta* **2011**, *94* (2), 248−253.

(23) Liu, F.; Evans, T.; Das, B. C. Synthesis of 2-substituted 2H-chromenes using potassium vinyltrifluoroborates. *Tetrahedron Lett.* **2008**, *49* (10), 1578−1581.

(24) Ferreira, V.; de C da Silva, F.; Jorqueira, A.; Gouvêa, R.; de Souza, M.; Howie, R.; Wardell, J.; Wardell, S. One-Pot Synthesis of 2H-Chromene Derivatives from ortho-Naphthoquinones. *Synlett* **2007**, *2007*, 3123−3126.

(25) Moquist, P. N.; Kodama, T.; Schaus, S. E. Enantioselective Addition of Boronates to Chromene Acetals Catalyzed by a Chiral Brønsted Acid/Lewis Acid System. *Angew. Chem., Int. Ed.* **2010**, *49* (39), 7096−7100.

(26) Xie, J.-W.; Fan, L.-P.; Su, H.; Li, X.-S.; Xu, D.-C. Efficient kinetic resolution of racemic 3-nitro-2H-chromene derivatives catalyzed by Takemoto's organocatalyst. *Org. Biomol. Chem.* **2010**, *8* (9), 2117−2122.

(27) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. Catalytic Enantioselective Domino Oxa-Michael/Aldol Condensations: Asymmetric Synthesis of Benzopyran Derivatives. *Chem.—Eur. J.* **2007**, *13* (2), 574−581.

Angewandte Chemie International Edition / Volume 64, Issue 9 / e202420671

Research Article

# Visible-Light Photocatalyzed Skeletal Rearrangement Enables the Synthesis of Highly Functionalized Xanthenes with Antitumor Activity



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In memory of professor Lixin Dai

First published: 23 December 2024
https://doi.org/10.1002/anie.202420671

## Graphical Abstract

This study presents the first example of a photocatalyzed intramolecular skeletal rearrangement strategy for constructing the xanthene scaffold. This approach has been successfully applied to synthesize highly functionalized xanthenes and to revise the structures of myrtucomvalones E and F. Furthermore, biological studies reveal that a xanthene demonstrates significant antiosteosarcoma activity both in vitro and in vivo.

Back

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14d F. Shaheen, M. Ahmad, N. S. Khan, S. S. Hussain, S. Anjum, B. Tashkhodjaev, K. Turguniv, M. N. Sultankhodzhaev, M. I. Choudhary, A.-U. Rahman, *Eur. J. Org. Chem.* 2006, **2006**, 2371;

CAS | Web of Science® | Google Scholar

14e A. Hiranrat, W. Mahabusarakam, *Tetrahedron* 2008, **64**, 11193–11197;

CAS | Web of Science® | Google Scholar

14f A. R. Carroll, J. Lamb, R. Moni, G. P. Guymer, P. I. Forster, R. J. Quinn, *J. Nat. Prod.* 2008, **71**, 1564–1568;

CAS | PubMed | Web of Science® | Google Scholar

14g S. Rattanaburi, W. Mahabusarakam, S. Phongpaichit, A. R. Carroll, *Tetrahedron* 2013, **69**, 6070–6075;

CAS | Web of Science® | Google Scholar

14h N. Tanaka, Y. Jia, K. Niwa, K. Imabayashi, Y. Tatano, H. Yagi, Y. Kashiwada, *Tetrahedron* 2018, **74**, 117–123;

CAS | Web of Science® | Google Scholar

14i X.-J. Qin, H. Liu, P.-P. Li, W. Ni, L. He, A. Khan, X.-J. Hao, H.-Y. Liu, *Bioorg. Chem.* 2021, **107**, 104519;

CAS | PubMed | Web of Science® | Google Scholar

14j Q.-H. Mo, M.-Q. Yan, X.-L. Zhou, Q. Luo, X. S. Huang, C.-Q. Liang, *Phytochemistry* 2021, **190**, 112890.

CAS | PubMed | Google Scholar

15 T. Shibata, A. Kabumoto, T. Shiragami, O. Ishitani, C. Pac, S. Yanagida, *J. Phys. Chem.* 1990, **94**, 2068–2076.