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Stereoselective Cascade Double-Annulations Provide Diversely Ring-Fused Tetracyclic Benzopyrones

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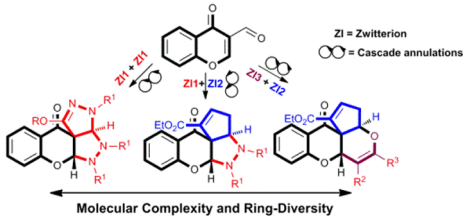
ABSTRACT



A cascade double-annulation strategy employing diverse pairs of zwitterions with 3-formylchromones is presented that provides stereoselective access to complex tetracyclic benzopyrones. Different zwitterions incorporated different rings that include aza-, oxa-, and carbocycles fused to a common benzopyrone scaffold and in the process created three contiguous chiral centers including an all-carbon-quaternary center with high efficiency and excellent stereoselectivity.

Building focused compound collections based on privileged scaffolds of natural product and/or drugs is an important goal in chemical biology[1] and drug discovery[2] research. Chemical transformations that further build up novel ring systems on privileged scaffolds might enrich the scanty supply of new chemical entities and are therefore highly desired.[3] In particular, concise and stereoselective synthetic routes to complex natural product based polycyclic compounds rich in sp^3 character, i.e., decorated with more than one chiral center, remain a formidable challenge in organic syntheses.[4] The benzopyrone or chroman-4-one scaffold is one of the privileged ring systems that exists in the molecular frameworks of numerous natural products that display a range of different biological activities (Figure 1).[5] However, efficient and stereoselective synthetic access to

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(1) (a) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451–453. (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nature Commun.* **2010**, *1*, 1–13.

(2) (a) Connor, C. J. O.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444–4456 and references cited therein. (b) Terstappen, G. C.; Schlupen, C.; Raggiaschi, R.; Gaviraghi, G. *Nat. Rev. Drug Discov.* **2007**, *6*, 891–903. (c) Lehar, J.; Stockwell, B. R.; Giaever, G.; Nislow, C. *Nat. Chem. Biol.* **2008**, *4*, 674–681. (d) Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6699–6702.

(3) (a) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224–3242. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104–109.

(4) (a) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402–13404. (b) Liu, W.; Khedkar, V.; Baskar, B.; Schurmann, M.; Kumar, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900–6905. (c) Lee, D. S.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712. (d) Robbins, D.; Newton, A. F.; Gignoux, C.; Legeay, J. C.; Sinclair, A.; Rejzek, M.; Laxon, C. A.; Yalamanchili, S. K.; Lewis, W.; O'Connell, M. A.; Stockman, R. A. *Chem. Sci.* **2011**, *2*, 2232–2235. (e) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 10800–10826.

(5) (a) Machado, N. F. L.; Marques, M. P. M. *Curr. Bioact. Compd.* **2010**, *6*, 76–89. (b) Sharma, S. K.; Kumar, S.; Chand, K.; Kathuria, A.; Gupta, A.; Jain, R. *Curr. Med. Chem.* **2011**, *18*, 3825–3852. (c) Khadem, S.; Marles, R. J. *Molecules* **2012**, *17*, 191–206.

(6) (a) Liu, Y.; Huang, L. P.; Xie, F. C.; Chen, X. X.; Hu, Y. H. *Org. Biomol. Chem.* **2011**, *9*, 2680–2684. (b) Wittstein, K.; Garcia, A. B.; Schurmann, M.; Kumar, K. *Synlett* **2012**, 227–232. (c) Baskar, B.; Dakas, P. Y.; Kumar, K. *Org. Lett.* **2011**, *13*, 1988–1991. (d) Waldmann, H.; Khedkar, V.; Duckert, H.; Schumann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6869–6872.

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higher order polycyclic benzopyrones remains scarcely reported in the literature.[6]

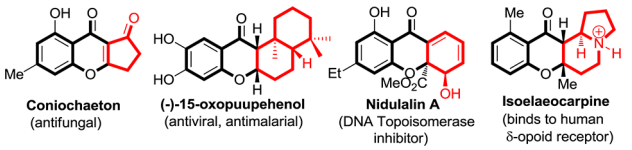


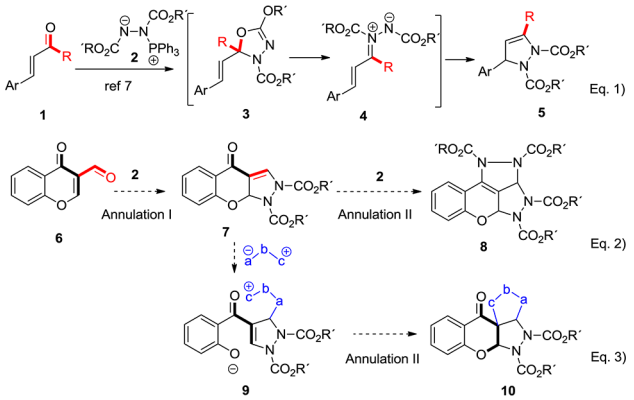
Figure 1. Natural products embodying a common benzoyprone scaffold fused to different ring systems.

Here, we present *cascade double-annulations* as stereoselective complexity generating transformations wherein diverse pairs of zwitterions add in tandem to a common substrate, 3-formylchromones to generate highly complex tetracyclic benzopyrones decorated with two new rings and three contiguous chiral centers including an all-carbon-quaternary center.

We envisioned that a general synthetic access that keeps the chroman-4-one scaffold intact and provides diverse ring systems fused to this core structure would provide far greater structural diversity in the focused compound collection. The reported annulation of chalcones (**1**) with Huisgeńs zwitterion **2** leading to pyrazolines (eq 1, Scheme 1)[7] raised our curiosity for a possible cascade double-annulation sequence to access complex benzopyrones. We wondered how the expected adduct **7** arising from a reaction of 3-formylchromone **6** and **2** would react, if at all, to another nucleophilic zwitterion (eq 2 and 3). Unlike the reaction of **2** with chalcone **1** (eq 1) that consumes the ketone moiety in **5**, adduct **7** still keeps an α,β-unsaturated ketone for a further annulation. A second zwitterion, for instance **2** might undergo sequential annulation as depicted in eq 1 to yield tetracyclic benzopyrone **8** (eq 2, Scheme 1). However, a plausible S_N2' addition of another zwitterion might lead to an intermediate phenoxide **9** that cyclizes to yield novel and complex tetracyclic benzopyrone **10** (eq 3). We anticipated that the latter cascade annulation might exploit different zwitterions[8] as annulations partners and thus building differently ring-fused and complex tetracyclic benzopyrones (eq 3, Scheme 1).

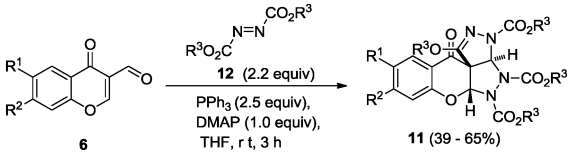
In order to ascertain the annulation potential of the Huisgeń's zwitterion **2** on 3-formylchromone, an equimolar THF solution of 3-formylchromone (**6a**) and triphenylphosphine was treated with diisopropyl diazodicarboxylate (DIAD) for 3 h at room temperature. Though the reaction afforded the expected monoannulation adduct **7** in 26% yield, to our surprise, bis-adduct **11a** was also formed in about 27% yield along with unreacted 3-formylchromone (~40%). The structure and stereochemistry of the tetracyclic adduct **11a** was established by 2D-NMR analysis and was

Scheme 1. Design of Cascade Annulation Strategy Providing Diversely Ring-Fused and Complex Benzopyrones



further unambiguously confirmed by single-crystal X-ray analysis (Supporting Information).[9] Increasing the amount of DIAD and the phosphine (2.2 and 2.5 equiv, respectively) enhanced the yield of **11a** more than 2-fold (entry 1 in Table 1). Differently substituted 3-formylchromones and diazodicarboxylates (**12**) were employed in this cascade double-annulation reaction that yielded benzopyrones **11a**–**j** in moderate to very good yields (Scheme 2 and Table 1). Excellent stereoselectivity (>99% de) was observed in this novel cascade double-annulation that generates three contiguous chiral centers with one of them an all-carbon quaternary center.

Scheme 2. Cascade Double Annulation of 3-Formylchromones with Two Huisgen Zwitterions



Isolation of the monoannulation adduct **7a** suggested the possibility of trapping this intermediate with another zwitterion to afford diversely ring-fused and complex benzopyrones. That implies the use of similar reaction conditions that leads to intermediate **7**. To incorporate a carbocycle along with a heterocycle in the tetracyclic benzopyrones, we resorted to [3 + 2] annulation reaction of allene ester (**13**) derived zwitterion **15**[8d] with intermediate **7** (Scheme 4a). In the presence of phosphine, substrates **6**, **12**, and **13** can undergo many possible and reported reactions.[10] However, treating a mixture of phosphine and chromones

(7) Nair, V.; Mathew, S. C.; Biju, A. T.; Suresh, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2070–2073.

(8) (a) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530. (b) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. *Chem.—Asian J* **2008**, *3*, 810–820. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (d) Ye, L. W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152.

(9) (a) While this work was in progress, Papafilippou et al. reported a reaction of **2** with **6** leading to chromeno[2,3-*e*]tetrazepines (ref 9b). In our hands and under reported conditions, we did not observe formation of tetrazepines. (b) Papafilippou, A.; Terzidis, M. A.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. *Tetrahedron Lett.* **2011**, *52*, 1306–1309.

(10) (a) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023–2025. (b) Nair, V.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213–2216.

(**6**) with DIAD followed by addition of allene ester provided the tetracyclic benzopyrones (**14**) in appreciable yields. The cascade double annulation was completely diastereoselective and favored the γ-addition of zwitterion **15**, thus providing adducts **14** as single diastereoisomers (Scheme 3 and Table 1).

Scheme 3. Cascade Double Annulation of 3-Formylchromones with Two Huisgen Zwitterions

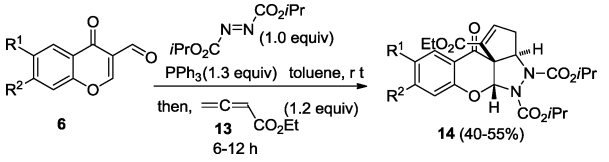


Table 1. Cascade Synthesis of Diversely Ring-Fused Tetracyclic Benzopyrones (**11**, **14**, **26**, and **27**)

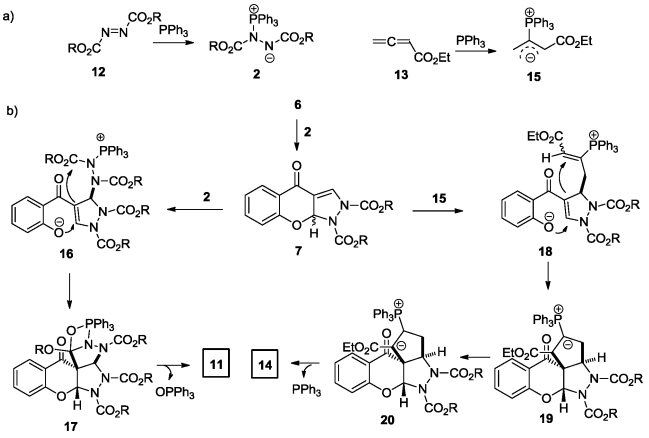
entry	product	R^1	R^2	R^3	yield[a] (%)
1	**11a**	H	H	iPr	65[b]
2	**11b**	Cl	Me	iPr	41[b]
3	**11c**	Br	H	Et	54[b]
4	**11d**	Cl	Me	Et	44[b]
5	**11e**	Me	H	iPr	43[b]
6	**11f**	H	H	Bn	53[b]
7	**11g**	Cl	H	iPr	39[b]
8	**11h**	iPr	H	iPr	51[b]
9	**11i**	H	H	Et	44[b]
10	**11j**	Me	H	Et	52[b]
11	**14a**	iPr	H	iPr	42[c]
12	**14b**	H	H	iPr	48[c]
13	**14c**	Me	H	iPr	46[c]
14	**14d**	Cl	H	iPr	55[c]
15	**14e**	Cl	Me	iPr	40[c]
16	**26a/27a**	H	Me	CO_2Me	21/29[d]
17	**26b/27b**	OMe	H	CO_2Me	40/23
18	**26c/27c**	H	H	CO_2Me	32/42
19	**26d/27d**	H	iPr	CO_2Me	32/38
20	**26e/27e**	H	iPr	H	20/20

[a] Isolated yields. [b] Isolated yields after HPLC purification. [c] 10−15% of **11** was formed and easily separable by column chromatography. [d] 10% each of corresponding **6** and **23** were isolated.

Stereoselectivity in the cascade double-annulations as depicted in Schemes 2 and 3 is plausibly dictated by steric factors along with the preferred *cis*-ring fusions in the ensuing adducts to avoid ring strain. Thus, S_N2' addition of the second zwitterion (**15** or **2**) to the common intermediate **7** is followed by a conjugated addition of the phenoxide (**16** or **18**, Scheme 4b) that happens from the least hindered face (*anti*- to addition of zwitterion **2** or **15**) providing intermediates **17** or **19**. Elimination of phosphine oxide in **17** provided the adducts **11**. The intermediate **19** undergoes a 1,2-H shift leading to **20** before the phosphine leaves the catalytic cycle to yield the adduct **14** (Scheme 4b).

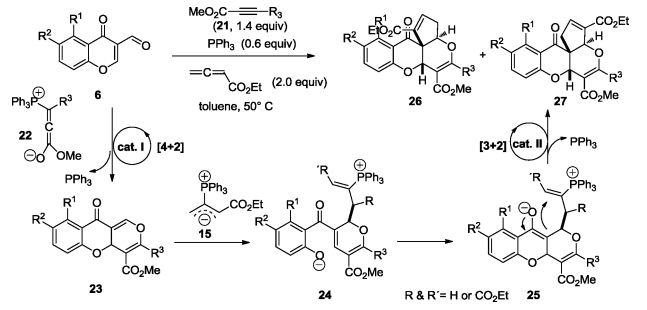
Successful double-annulations with two zwitterions encouraged us to explore zwitterions that could incorporate

Scheme 4. Proposed Mechanism of the Cascade Double Annulations



further diverse rings to the chorman-4-one scaffold. In particular, annulations that are catalyzed by phosphines could provide a dual-catalytic access to novel benzopyrones. To this end, [4 + 2] annulation of zwitterion **22** (generated by addition of phosphine to acetylene carboxylates **21**) with chromones **6** was employed as the first catalytic annulation[6d] followed by catalytic [3 + 2] annulation of zwitterion **15** with the resulting intermediate **23**. Gratifyingly, the cascade annulations worked nicely *albeit* with slightly higher loading of phosphine catalyst (0.6 equiv) and under a constant flow of argon to yield a 1:1 mixture of γ- and α-regioisomeric adducts **26** and **27**, respectively (Scheme 5 and Table 1).[11] Interestingly, these double-annulations too were completely stereoselective. This cascade reaction sequence represents one of the few known cases of stereoselective dual organocatalysis.[12]

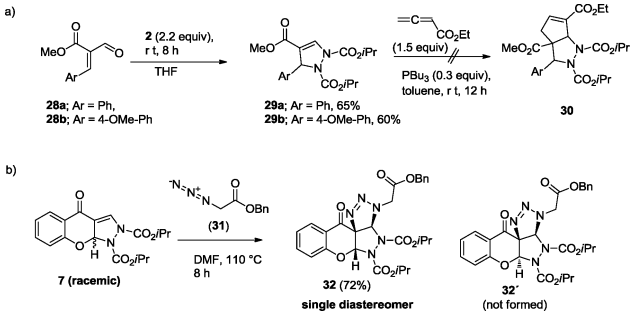
Scheme 5. Dual-Catalyzed Cascade Synthesis of Tetracyclic Benzopyrones



(11) CCDC886337 (**11a**) and CCDC886338 (**26c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) (a) Cai, L. C.; Zhang, B.; Wu, G. P.; Song, H. B.; He, Z. J. *Chem. Commun.* **2011**, *47*, 1045–1047. (b) Rueping, M.; Antonchick, A. R.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903–6906. (c) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5703–5705.

Scheme 6. (a) Attempted Cascade Double Annulation of Olefin **28** with **2** and of Adduct **29a** with Allene-Derived Zwitterion and (b) Annulation of Intermediate **7** with an Azide



To ascertain the proposed role of S_N2' addition of second zwitterion to the intermediate **7** in driving the cascade annulations and determining the stereoselectivity in tetracyclic benzopyrones, we designed some control experiments. In the first case, 2-formyl-3-arylacrylates (**28**), which resemble 3-formylchromone in terms of functional group placement and in principle can undergo double annulation reaction, were treated with 2.2 equiv of Huisgen's zwitterion **2**. However, the reaction yielded only monoannulation adducts **29**.[13] In a separate reaction with allene-derived zwitterion **15**, adduct **29a** did not provide the desired annulation adduct **30** (Scheme 6a). This result manifests the inability of zwitterions **2** and **15** to undergo either conjugated addition or a concerted cycloaddition with **29**.[8a,b] In the second experiment, the intermediate **7** (racemic) was treated with 2-azidobenzyl acetate (**31**). Azides do undergo concerted [3 + 2] cycloaddition reactions with olefins.[14] For this to be the case with the intermediate **7**, the reaction with **31** would yield two diastereoisomers. However, the reaction cleanly yielded the tetracyclic benzopyrone **32** as single diastereoisomer, thus favoring the proposed S_N2' addition of the zwitterion to the intermediate **7**, followed by a cascade annulation as proposed in Scheme 4.

In summary, we have disclosed a novel cascade double-annulation approach as complexity generating transformations around privileged chromone scaffold. Different rings that include aza-, oxa-, and carbocycles were efficiently incorporated to the common benzopyrone scaffold by different zwitterions, thus adding great structural diversity to a small sized compound collection. Overall, two tandem annulations transformed the relatively flat substrates (**6**) into highly sp^3-enriched new chemical entities, with high efficiency and excellent stereoselectivity. Easily accessible substrates and milder reaction conditions make the reactions amenable to compound collection synthesis. With all possiblities to employ various zwitterionic and nonzwitterionic annulation partners, we anticipate that the double-annulation strategy would provide easy and efficient access toward unprecedented and complex benzopyrones that may find applications in various life science disciplines.

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Supporting Information Available. Details of all experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) Basavaiah, D.; Roy, S. *Org. Lett.* **2008**, *10*, 1819–1821.

(14) (a) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354–1355. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526–6529. (c) Muchalski, H.; Hong, K. B.; Johnston, J. N. *Beilstein J Org Chem* **2010**, *6*, 1206–1210.