ORGANIC LETTERS

2011
Vol. 13, No. 8
1988–1991

Natural Product Biosynthesis Inspired Concise and Stereoselective Synthesis of Benzopyrones and Related Scaffolds

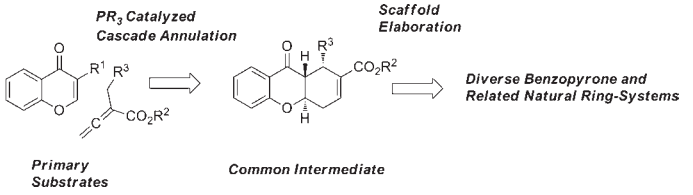
Baburaj Baskar, Pierre-Yves Dakas, and Kamal Kumar*

Max-Planck-Institut für molekulare Physiologie, Otto-Hahn Strasse 11, 44227-Dortmund, Germany

kamal.kumar@mpi-dortmund.mpg.de

Received February 11, 2011

ABSTRACT



A natural product biosynthesis-inspired strategy to explore biologically relevant chemical space is presented. A phosphine-catalyzed cascade and stereoselective annulation provides a common tricyclic benzopyrone intermediate that was efficiently transformed into diverse and related naturally occurring scaffolds.

Biological activity is a unique property for any molecule to possess, a key requisite for various discovery programs in academic and pharmaceutical laboratories, and a crucial function at a molecular level in numerous life-sustaining processes.[1] Recent years have witnessed chemists' endeavors targeting bioactive small molecules shaping up different hypothesis, for instance Diversity Oriented Synthesis[2] and Biology Oriented Synthesis.[3] It would however be enlightening to understand the way nature targets bioactive regions of vast chemical space while creating diverse natural products.[4] Adapting similar strategies in compound library syntheses might enrich them with desired and interesting biological activities. In a prominent biosynthetic strategy, primary metabolites or derivatives would build up the intermediate scaffold, which is later transformed into diverse secondary metabolites, often retaining the molecular framework of the intermediate.[5] For instance, in indole alkaloid biosynthesis,[6] tryptamine is converted into a template structure, Strictosidine, which is further transformed into a variety of monoterpene indole alkaloids (Figure 1A).

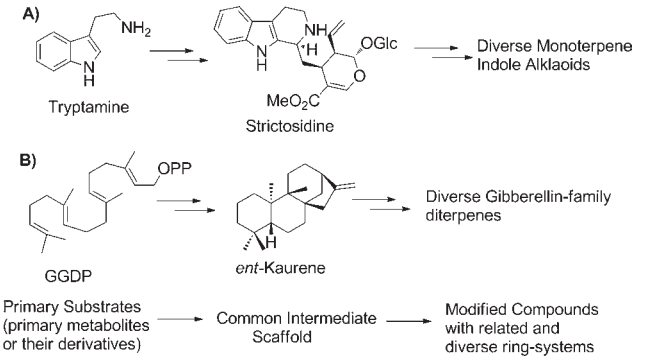


Figure 1. (A and B) Biosynthetic strategies leading to diverse secondary metabolites.

Similarly, in the Gibberellin biosynthesis pathway, geranylgeranyl diphosphate (GGDP) is cyclized to form

(1) (a) Dobson, C. M. *Nature* **2004**, *432*, 824–828. (b) Lipinski, C.; Hopkins, A. *Nature* **2004**, *432*, 855–861.

(2) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 1–13 and references therein.

(3) (a) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, accepted. (b) Wilk, W.; Zimmermann, T. J.; Kaiser, M.; Waldmann, H. *Biol. Chem.* **2010**, *391*, 491–497. (c) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103–1114.

(4) Fischbach, M. A.; Clardy, J. *Nat. Chem. Biol.* **2007**, *3*, 353–355.

(5) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901.

(6) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

10.1021/ol200389p
Published on Web 03/18/2011

ent-kaurene, which undergoes skeletal and functional group transformations to at least 136 products with only a few of them displaying biological activities (Figure 1B).[7]

In a research program targeting concise synthesis of natural product-inspired[8] focused compound collections for chemical biology research, we devised a biosynthesis-inspired synthesis strategy wherein a common intermediate scaffold would be efficiently transformed into diverse naturally occurring ring systems. Here we present an efficient and concise synthesis access to naturally occurring benzopyrone[9] and related scaffolds employing easily accessible primary substrates.

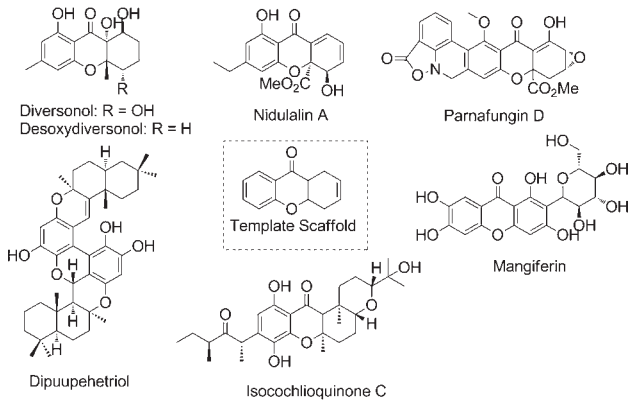
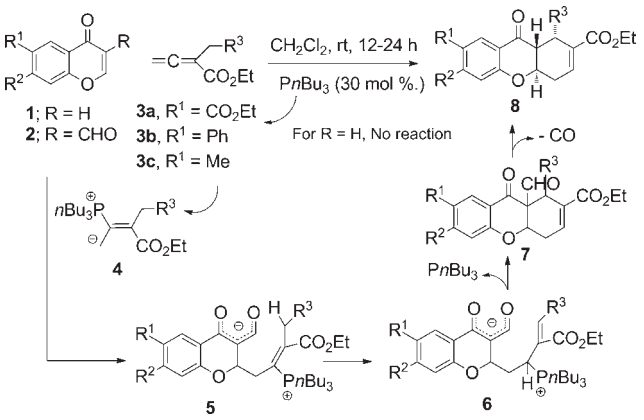


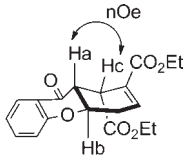
Figure 2. Natural products embodying benzopyrone and related frameworks and the common scaffold to access diverse natural ring systems.

A structural analysis of the natural products embodying diverse benzopyrone[10] scaffolds led us to choose the tricyclic cyclohexene-fused-chromone ring as the common scaffold for further elaboration into natural ring systems (Figure 2). To this end, we explored a phosphine-catalyzed [4 + 2] annulation reaction of the zwitterion (**4**) (generated by addition of phosphine[11] to allene ester **3**) with 4*H*-chromen-4-one **1** (Scheme 1). Recently, Kwon et al. have demonstrated the feasibility of the annulation of **4** with 1,1-dicyanoolefins;[12] however, further scope of this annulation remains unexplored.[13] The reaction of **4** with chromone **1**, to our disappointment, did not yield any desired product even under forcing reaction conditions. We reasoned that vinylogous ester **1** might not be sufficiently electron-deficient to receive a nucleophilic attack of the zwitterion **4** at the C-2 position. Gratifyingly, employing more electron-deficient 3-formylchromone **2**, we observed a cascade reaction sequence of [4 + 2] annulation of the zwitterion **4a** ($R^3 = CO_2Et$) with **2** followed by deformylation to provide the desired scaffold **8a** in excellent yield (Table 1) and with good diastereoselectivity (~8:1).

Differently substituted chromones (**2**) yielded the cascade annulation adducts **8a**–**e** in moderate to very good yields (Table 1) and with high diastereoselectivities (see Supporting Information).

Scheme 1. Phosphine-Catalyzed Cascade Synthesis of Common Benzopyrone Scaffold





Allene ester **3b** also underwent the cascade annulation, smoothly yielding adducts **8f**–**i** supporting a phenyl substitution on cyclohexene ring of the tricyclic benzopyrones in good yields and diastereoselectivities (for spectroscopic

(7) (a) Combs, A. P.; Kapoor, T. M.; Feng, S. B.; Chen, J. K.; DaudeSnow, L. F.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 287–288. (b) Tudzynski, B. *Appl. Microbiol. Biot.* **2005**, *66*, 597–611. (c) Hedden, P.; Phillips, A. L.; Rojas, M. C.; Carrera, E.; Tudzynski, B. *J. Plant Growth Regul.* **2001**, *20*, 319–331.

(8) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224–3242.

(9) Waldmann, H.; Khedkar, V.; Dückert, H.; Schürmann, M.; Oppel, Iris, M.; Kumar, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6869–6872.

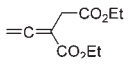
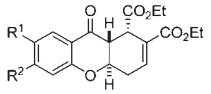
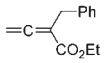
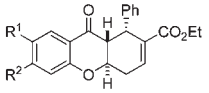
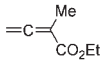
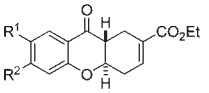
(10) (a) Kesarkar, S.; Bhandage, A.; Deshmukh, S.; Shevkar, K.; Abhyankar, M. *J. Pharm. Res.* **2009**, *2*, 1148–54. (b) Overy, D.; Calati, K.; Kahn, J. N.; Hsu, M. J.; Martin, J.; Collado, J.; Roemer, T.; Harris, G.; Parish, C. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1224–1227. (c) Phuwapraisirisan, P.; Udomchotphruet, S.; Surapinit, S.; Tip-Pyang, S. *Nat. Prod. Res.* **2006**, *20*, 1332–1337. (d) Phuwapraisirisan, P.; Sawang, K.; Siripong, P.; Tip-Pyang, S. *Tetrahedron Lett.* **2007**, *48*, 5193–5195. (e) Pritchard, R. G.; Sheldrake, H. M.; Taylor, I. Z.; Wallace, T. W. *Tetrahedron Lett.* **2008**, *49*, 4156–4159. (f) Parish, C. A.; Smith, S. K.; Calati, K.; Zink, D.; Wilson, K.; Roemer, T.; Jiang, B.; Xu, D. M.; Bills, G.; Platas, G.; Pelaez, F.; Diez, M. T.; Tsou, N.; McKeown, A. E.; Ball, R. G.; Powles, M. A.; Yeung, L.; Liberator, P.; Harris, G. *J. Am. Chem. Soc.* **2008**, *130*, 7060–7066. (g) Sato, S.; Suga, Y.; Yoshimura, T.; Nakagawa, R.; Tsuji, T.; Umemura, K.; Andoh, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2653–2656. (h) Horak, R. M.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 363–367.

(11) (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544. (b) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Cat.* **2004**, *346*, 1035–1050.

(12) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632–12633.

(13) (a) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550–2551. (b) Guo, H. C.; Xu, Q. H.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318–6319. (c) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289–4291. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235.

Table 1. Phosphine Catalyzed Cascade Synthesis of Tricyclic Benzopyrones **8**

allene ester	annulation product, yield[a]
 **3a**	 **8a-d**
	8a; $R^1 = R^2 = H$; 83%
	8b; $R^1 = Me$, $R^2 = H$; 79%
	8c; $R^1 = Cl$, $R^2 = H$; 65%
	8d; $R^1 = Cl$, $R^2 = Me$; 60%
	8e; $R^1 = Br$, $R^2 = H$; 47%
 **3b**	 **8e-g**
	8f; $R^1 = R^2 = H$; 85%
	8g; $R^1 = Me$, $R^2 = H$; 80%
	8h; $R^1 = Cl$, $R^2 = Me$; 78%
	8i; $R^1 = Br$, $R^2 = H$, 55%
 **3c**	 **8h-k**
	8j; $R^1 = R^2 = H$; 67%
	8k; $R^1 = Me$, $R^2 = H$; 63%
	8l; $R^1 = Cl$, $R^2 = H$; 61%
	8m; $R^1 = Br$, $R^2 = H$; 60%

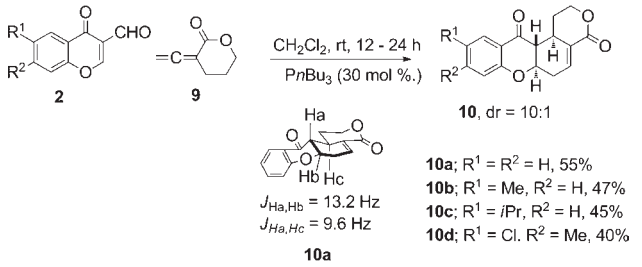
[a] Isolated yields.

details of representative molecules, see Supporting Information).[14]

When allene **3c** was employed in this cascade annulation with **2**, benzopyrones **8j**–**8m** were obtained as single diastereoisomers in very good yields (Table 1). Overall, the cascade annulation of zwitterions **4** with 3-formylchromones provided an efficient and concise route to the desired common scaffolds embodying up to three stereogenic centers.

While we were planning further elaboration of the common scaffold into higher order tetracyclic benzopyrones,[10d,h] we realized that employing an exocyclic allene ester in the cascade annulation-deformylation reaction sequence with **2** could provide a straightforward synthesis of tetracyclic benzopyrones. The exocyclic allenic lactone **9** was thus synthesized by Wittig olefination of the ketene with corresponding phosphorus ylide (see Supporting Information) and employed in the cascade annulation reaction (Scheme 2). Pleasingly, the reaction went smoothly providing efficient, direct, and diastereoselective (dr ≅ 10:1) access to tetracyclic benzopyrones **10a**–**d**. To the best of our knowledge, this is the first report of employing allenic lactone in a phosphine catalyzed annulation reaction.

Scheme 2. Cascade Synthesis of Tetracyclic Benzopyrones



Efficient and stereoselective synthesis of the stereodecorated common scaffold set the stage for their further transformations into naturally occurring benzopyrone and related scaffolds (Figure 2). It is notable that this strategy offers great synthetic challenges and calls for developments in devising stereoselective and high yielding skeletal-transformations of multifunctionalized small molecules. We chose xanthone ring systems as the first target modification of common scaffold **8** (Scheme 3). Xanthone ring systems are ubiquitous molecular architectures in a variety of naturally occurring and synthetic compounds possessing diverse and important biological activities.[15] Therefore, there has been a continued interest in the development of efficient synthetic methods for functionalized xanthone rings.[16]

Treating **8** with 2 equiv of DDQ under microwave heating conditions at 220 °C for 10 min in 1,2-dichlorobenzene provided the desired xanthones **11a**–**c** in excellent yields.[17] The same method also yielded tetracylic xanthones **12a**–**b** in very high yields employing benzoyprones **10a** and **10c**, respectively (Scheme 3).

The stereodecoration on the common scaffold should be passed on to higher order ring systems to achieve more three-dimensional diversity and to incorporate further complexity in the resulting molecules. To this end, we targeted stereoselective epoxidation of the olefin present in the substrates **8**. We reasoned that the π-facial selectivity in the epoxidations would be influenced by the spatially arranged functional groups in **8** and could provide benzopyrone epoxides supporting up to five stereogenic centers. Such complex electrophiles would be interesting

(14) (a) Lee, Y. G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K. Y. *J. Org. Chem.* **1991**, *56*, 2058–2066. (b) Hintz, S.; Mattay, J.; van Eldik, R.; Fu, W. F. *Eur. J. Org. Chem.* **1998**, 1583–1596.

(15) (a) Pinto, M. M. M.; Sousa, M. E.; Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517–2538. (b) Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, *12*, 2447–2479. (c) Palmer, B. D.; Henare, K.; Woon, S. T.; Sutherland, R.; Reddy, C.; Wang, L. C. S.; Kieda, C.; Ching, L. M. *J. Med. Chem.* **2007**, *50*, 3757–3764.

(16) Zhao, L. Z.; Xie, F. C.; Cheng, G.; Hu, Y. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 6520–6523 and references therein.

(17) All our attempts to partially dehydrogenate **8** leading to cyclohexadiene ring structure that exist in Nidulalin A failed and provided only the xanthone ring; however a similar framework **16b** was obtained during reducitve olefination of common scaffold (Scheme 3).

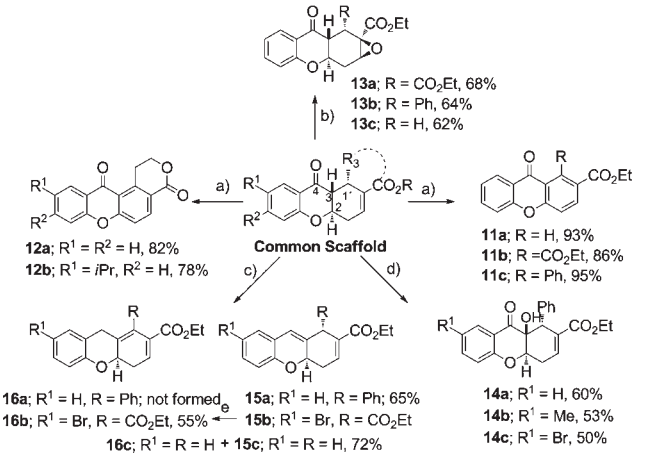
candidates in chemical biology investigations.[18] While *m*CPBA failed to convert the substrate **8a** into the epoxide, treatment of **8a** with freshly prepared trifluoroperacetic acid (see Supporting Information) at 0 °C provided the epoxide **13a** in 68% isolated yield as major product (dr = 9:1). Employing **8f** supporting a phenyl substitution provided **13b** with even better diastereoselectivity (> 30:1). On the contrary, **8j** lacking any functional group on C1′ (Scheme 3) provided 1:0.65 mixture of two inseparable epoxides **13c**, indicating the steric steering of epoxidations favoring *anti*-epoxide formation.[19]

Interestingly, while optimizing the epoxidation reaction conditions, we observed that using catalytic *t*BuOK, *t*BuOOH led to selective α-hydroxylation of **8f** yielding **14a** in good yield (Scheme 3). We assume that an epoxide of the enol is initially formed from the least hindered face, that is, *anti* to phenyl-group substitution which opens up to generate α-hydroxyl group.[20] **8g** and **8i** also provided the corresponding α-hydroxylated benzopyrones **14b** and **14c** in moderate yields. Considering the occurrence of α-hydroxylated benzopyrone scaffolds in many natural products (Figure 2), this methodology looks very promising and its further potential in general organic synthesis is being investigated.

In yet another ring elaboration of the common scaffold, **8** was transformed in a one-pot strategy into the dihydroxanthene framework (**15**) supporting the same stereodecoration as in the common scaffold. Various natural products, for instance, dipuuphetriol contain dihydroxanthene ring systems (Figure 2), and an efficient access to suitably functionalized dihydroxanthenes is very desirable. Thus, tricyclic benzopyrone **8f** was reduced to a secondary alcohol using $NaBH_4$ and treatment of the crude reaction product with methane sulfonic acid provided the desired **15a** in good overall yield (Scheme 3). When **8e** supporting an ester group was employed in this ring-transformation, we realized that initially formed **15b** isomerizes to doubly conjugated xanthene **16b** during column chromatography over silica gel.[17] In the case of **8i**, however, both isomeric products **15c** and **16c** were found to exist as an inseparable mixture (Scheme 3).

In summary, we have explored a natural product biosynthesis inspired strategy to access biologically relevant chemical space.[21] In this planning, a phosphine catalyzed cascade annulation reaction was developed to provide a stereochemically decorated common scaffold which was successfully elaborated into diverse natural product based benzopyrone and related ring systems. While this strategy brings new synthetic challenges to transform a stereofunctionalized common intermediate scaffold into diverse natural ring systems, the hope is that compound collections with structural features of natural products will yield interesting and useful small molecules for drug discovery and in particular chemical biology research.

Scheme 3. Elaboration of Common Scaffold into Diverse Natural Ring-Systems[a]



[a] Reaction conditions: a) **8** or **10** (1.0 equiv.), DDQ (2.0 equiv), 1,2-dichlorobenzene, microwave heating (125 w, 220 °C, 10 min.); b) **8** (1.0 equiv), UHP (1.2 equiv) in CH_2Cl_2, TFAA (1.0 equiv), 0 °C, 30 min.; c) **8** (1.0 equiv), $NaBH_4$ (1.5 equiv), MeOH, 10 h, $MeSO_3H$ (~ 20 mol %), benzene, reflux, 12 h; d) **8** (1.0 equiv), KO*t*Bu (0.6 equiv), *t*BuOOH (2.0 equiv), THF, 0 °C, 5 h; e) over silica gel (2−5 h).

Acknowledgment. This research work was supported by Max Planck Gesellschaft. We are grateful to Prof. Dr. H. Waldmann (Max Planck Institute of Molecular Physiology, Dortmund) for his constant support and encouragement.

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.

(18) (a) Greenbaum, D.; Medzihradszky, K. F.; Burlingame, A.; Bogyo, M. *Chem. Biol.* **2000**, *7*, 569–581. (b) Drahl, C.; Cravatt, B. F.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5788–5809.

(19) (a) Mckittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895–4898. (b) Fehr, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2407–2409.

(20) (a) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143–151. (b) Tietze, L., F.; Spiegl, D., A.; Stecker, F.; Major, J.; Raith, C.; Grosse, C. *Chem.—Eur. J.* **2008**, *14*, 8956–8963. (c) Rubottom, G. M.; Vazquez, M. A.; Pelegrin, D. R. *Tetrahedron Lett.* **1974**, 4319–4322.

(21) (a) Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 696–696. (b) Renner, S.; van Otterlo, W. A. L.; Seoane, M. D.; Mocklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. I.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 585–592.