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Hetero Diels–Alder reaction of olefin with *o*-quinone methides generated using (±)-binolphosphoric acid for the stereoselective synthesis of 2,4-diarylbenzopyrans: application to the formal synthesis of myristinin B/C†

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Hetero Diels–Alder reaction of olefin with *o*-quinone methides (*o*-QMs) generated using (±)-binolphosphoric acid was developed for the stereoselective synthesis of 2,4-diarylbenzopyrans. The method thus developed was utilized in the formal synthesis of myristinin B/C.

Over the years, *o*-quinone methides (*o*-QMs) have emerged as an important class of reactive intermediates in organic synthesis.[1] *o*-QMs are generated under various reaction conditions and are widely utilized as heterodienes in inverse electron demand [4 + 2] cycloaddition reactions. *o*-QMs are highly ephemeral in nature and require *in situ* generation often under harsh conditions like either high temperature[2] or use of strong acidic[3] and basic conditions.[4] The unwanted side reactions like dimerization and decomposition of the *o*-QMs precursors in many cases necessitate use of huge excess of dienophiles. The majority of the methods reported earlier employ a labile protecting group on the phenol and/or a good leaving group at the benzylic position so as to minimize their extreme reactivity in forming *o*-QM in an uncontrolled manner. This leads to added steps in the synthesis. Thus, *a mild method for the generation of o-QMs in a controlled manner at ambient temperature is still highly desirable*. In continuation of our interest in developing concise strategies for the synthesis of flavonoids,[5] herein we disclose a mild and efficient protocol for the synthesis of 2,4-diarylbenzopyrans using *o*-QMs generated using (±)-binolphosphoric acid (BPA) and styrene derivatives. We further demonstrate that the protection on phenol or conversion of benzylic alcohol into a better leaving group is not necessary under the reaction conditions employed. The application of this method in a concise formal synthesis of myristinin B/C is also described.

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The 2,4-diarylbenzopyran skeleton is found in a small group of bioactive flavonoid natural products like myristinins A–F (**1–4**), dininsinone (**5**) and psiguadial C (**6**) and D (**7**) (Fig. 1). Even though synthesis of 2-aryl chroman or flavans has attracted considerable attention from synthetic chemists, there are only scattered reports on the synthesis of 2,4-diarylbenzopyrans.[6]

We envisaged that 2,4-diarylbenzopyrans **8** could be rapidly assembled using hetero Diels–Alder reaction between aryl substituted *o*-quinone methides (*o*-QMs) and styrene derivatives **10** (Scheme 1). Further, we decided to explore the possibility of utilizing the *o*-hydroxy bisbenzylic alcohols **9** without any protection or converting the benzylic hydroxy group to a better leaving group to generate requisite *o*-QMs.

Initial efforts were directed at identifying an appropriate catalyst to effect the [4 + 2] cycloaddition of aryl substituted *o*-QMs and styrenes. Thermolysis of the known[7] alcohol **9a** in the presence of excess equiv. of olefin **10a** resulted in the formation of 2,4-diarylbenzopyran **8a** in moderate yield albeit with excellent diastereoselectivity (Table 1, entry 1). In a quest to generate *o*-QM at ambient temperature, the reactants were subjected to treatment with various Lewis and Brønsted acids with varying efficiency. Use

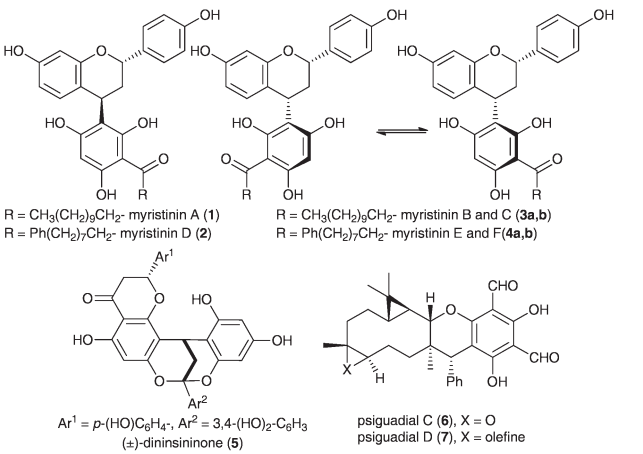
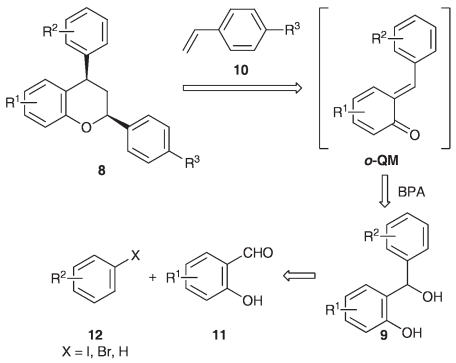


Fig. 1 Natural products bearing an arylbenzopyran moiety.



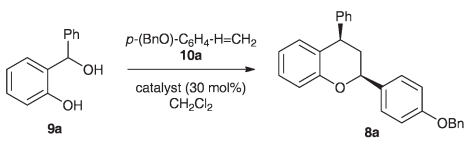
Scheme 1 Retrosynthetic analysis of 2,4-diarylbenzopyrans **8**.

of strong Lewis acid like $BF_3{\cdot}OEt_2$ and milder Lewis acid like $Bi(OTf)_3$ improved the efficiency of the reaction significantly, but the diastereoselectivity was poor (Table 1, entries 2 and 3). Many Brønsted acids like *p*-TSA, (±)-BPA, H_3PO_4, $HClO_4$ and CF_3CO_2H too were tested as catalysts (Table 1, entries 4–8). The best result was obtained with (±)-BPA as the catalyst where the product **8a** was formed in 90% yield and moderate diastereoselectivity (d.r. = 3 : 1) favouring *cis* isomer and hence this was used as the catalyst of choice for studying the scope of the reaction.[8] The most notable feature of this study was that *only slight excess of styrene* (*1.1 equiv.*) *was necessary for efficient Diels-Alder reaction*. *This is in contrast to many literature reported methods*, *where huge excess of dienophile was found to be necessary for suppressing side reactions*.

Table 2 outlines the scope of the (±)-BPA mediated [4 + 2] cycloaddition reaction with various *o*-QM precursors and dienophiles. Reaction of *o*-QM, generated *in situ* from variety of *o*-hydroxy bisbenzylic alcohols **9a–f**, with different styrene derivatives **10** that are electronically rich produced the diarylflavans **8b–h** in good yields and moderate selectivity favouring the *cis* isomer (Table 2, entries 1–7). Alkyl substituted *o*-hydroxy benzylalcohol **9f** was also found to participate in this reaction efficiently furnishing the alkyl chroman **8i** in very good yield (Table 2, entry 8). Most notably, electron deficient enone **10f** served as an excellent dienophile in the reaction with alcohol **9a** furnishing the densely functionalized chroman **8j** in excellent yields and moderate selectivity favouring the *trans*-2,4-diarylisomer as the major product (Table 2, entry 9). *This example is particularly interesting as use of an acyclic enone is uncommon in a [4 + 2] cycloaddition with o-QM*. In continuation of our interest on using vinylogous functional groups in organic synthesis,[9] we also explored the reaction of *trans*-methoxyacrylate (**10g**) as dienophile. Gratifyingly, the reaction was found to be effective leading to chroman acetal **8k–l** in good yields (Table 2, entries 10–11). The relative stereochemistry of the chromans was deduced on the basis of a ^1H-^1H NOESY and NOE spectra. It was further unambiguously ascertained by single crystal X-ray diffraction analysis on the chromans **8b**, **8d**, **8f** and **8j**.[10] Good diastereoselectivity observed under thermal condition is an outcome of a concerted, *endo* approach of the dienophile. On the contrary, the moderate diastereoselectivity observed in the (±)-BPA mediated cycloaddition reaction is consistent with the ionic pathway involving formation of benzylic cation and stepwise reaction. The *cis* isomer is dominant perhaps due to preference of both the bulky substituents to occupy equatorial orientation.

Attention was next turned towards applying the developed method for the synthesis of myristinin B/C (**2**). Myristinins A–F (**1–4**) were isolated independently from *Myristica cinnamomea*,[11] *Knema elegans*[12] and *Horsfieldia amygdaline*.[13] These were the first atropisomeric flavonoids isolated from nature. Further, they were found to be anti-inflammatory, antifungal and also exhibited biochemical activity, both as a potent DNA-damaging agent and DNA polymerase *β* inhibitor. Hecht *et al.* reported the first and the only total synthesis of myristinin A (**1**) and B/C (**3a**/**b**) involving a fairly lengthy strategy.[12,6b] It was envisaged that the synthesis of myristinins B/C can be achieved by the regioselective Friedel–Crafts reaction of the trimethoxy aryl ring in arylchroman **8f** or **8g** with lauroyl chloride. However, all our attempts using a variety of conditions met with failure. Similarly, regioselective directed *ortho* lithiation of flavan **8f**, **g** or lithium halogen exchange on **8h** followed by trapping of the aryllithium intermediate with lauroyl

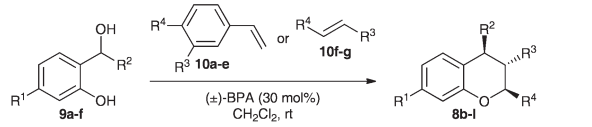
Table 1 Optimization of the [4 + 2] cycloaddition of styrene **10a** and *o*-QM generated from alcohol **9a**



Entry	Catalyst	Styrene equiv.	Temp. (°C)	Time (h)	Yield (%)[a]	d.r.[b] *cis* : *trans*
1	—	5	110	24	53	⩾19 : 1
2	$BF_3{\cdot}OEt_2$	1.1	0–rt	1	66	1 : 1
3	$Bi(OTf)_3$	1.1	rt	4	86	1 : 1
4	*p*-TSA	1.1	rt	2.5	60	3 : 1
5	**(±)-BPA**	**1.1**	**rt**	**20**	**90**	**3 : 1**
6	$HClO_4$	1.1	0–rt	3	n.d.[c]	—
7	H_3PO_4	1.1	0–rt	3	n.d.[c]	—
8	CF_3CO_2H	1.1	0–rt	4	60	1 : 1

[a] Isolated yield. [b] In all the cases, d.r. was determined on the crude reaction mixtures by ^1H-NMR on a 400 MHz instrument. [c] Not detected.

Table 2 Scope of the [4 + 2] cycloaddition reaction of *o*-QM, generated from alcohols **9** using (±)-BPA with various dienophiles **10**



9a: R^1 = H, R^2 = Ph
9b: R^1 = H, R^2 = 4-OMe-C_6H_4
9c: R^1 = H, R^2 = 2,4,6-$(OMe)_3$-C_6H_2
9d: R^1 = OMe, R^2 = 2,4,6-$(OMe)_3$-C_6H_2
9e: R^1 = OMe, R^2 = 3-iodo-2,4,6-$(OMe)_3$-C_6H
9f: R^1 = H, R^2 = *n*-Bu

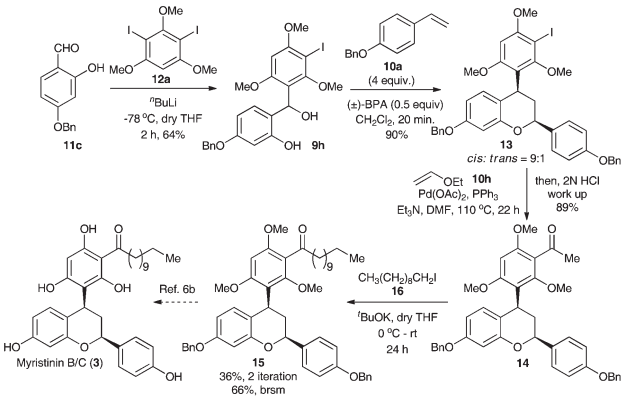
10a: R^3 = H, R^4 = OBn
10b: R^3 = R^4 = H
10c: R^3 = H, R^4 = Me
10d: R^3-R^4 = -OCH_2O-
10e: R^3 = H, R^4 = OMe
10f: R^3 = 4-(MeO)-C_6H_4-CO-, R^4 = 2,4,6-$(MeO)_3$-C_6H_2
10g: R^3 = CO_2Me, R^4 = OMe

Entry	Alcohol	Dienophile[c]	Product	Time (h)	Yield (%)[a]	d.r.[b] *cis* : *trans*
1	**9a**	**10b**	**8b**	24	62	3 : 1
2	**9a**	**10c**	**8c**	22	61	2 : 1
3	**9a**	**10d**	**8d**	22	79	3 : 1
4	**9b**	**10a**	**8e**	23	94	3 : 1
5	**9c**	**10e**	**8f**	24	90	3 : 1
6	**9d**	**10e**	**8g**	22	80	3 : 1
7	**9e**	**10e**	**8h**	2[d]	66	5 : 1
8	**9f**	**10a**	**8i**	22	74	3 : 1
9	**9a**	**10f**	**8j**	10	90	1 : 2
10	**9a**	**10g**	**8k**	12	68	2 : 1
11	**9c**	**10g**	**8l**	3.5	73	8 : 1

[a] Isolated yield. [b] In all the cases, d.r. was determined on the crude reaction mixtures by ^{1}H-NMR on a 400 MHz instrument. [c] 1.1 equiv. of dienophile was used. [d] 50 mol% of BPA and 2 equiv. of dienophile.

chloride too did not furnish the required 1,4-diaryl benzopyran derivative. Hence, an alternate strategy for the formal synthesis of myristinin B/C was envisaged.

Towards this end, selective monolithiation of diiodide **12a**[14] followed by its addition to aldehyde **11c**[15] furnished the *o*-QM precursor, the iodoalcohol **9h**. (±)-BPA catalyzed [4 + 2] cycloaddition reaction of the iodoalcohol **9h** with the olefin **10a** furnished the iodoflavan **13** in excellent yield and good diastereoselectivity favouring *cis* isomer (Scheme 2). Instability of the iodide **13** necessitated the use of excess of dienophile **10a** (4 equiv.) and BPA (0.5 equiv.) in this case. The iodoflavan **13** when subjected to reaction with ethyl vinyl ether (**10h**) under standard Heck reaction conditions, followed by hydrolytic work up procured the ketone **14** in excellent yield. Alkylation reaction of the ketone **14** was attempted using a variety of bases and was found to be particularly challenging, perhaps due to steric hindrance. Finally, generation of the enolate of the ketone **14** using *t*-BuOK as the base and its alkylation with *n*-decyl iodide (**16**) furnished the ketone **15** in moderate yield. Recovered starting ketone was re-subjected to alkylation and after two iterations, the product was obtained in 36% yield [66%, based on recovered starting material (brsm)]. The spectral data of this ketone was found to be in agreement with that reported by Hecht and co-workers. Since they have already transformed the ketone **15** into myristinin B/C by global deprotection using BBr_3 in one step, the present synthesis of the ketone **15** constitutes the formal synthesis of myristinin B/C (**2**). The overall reaction sequence involves just 4 steps from known intermediate with an overall yield of 34%. The brevity of the approach is eminently suitable for the synthesis of library of this biologically important natural product family.



Scheme 2 Formal synthesis of myristinin B/C.

Conclusions

In conclusion, a (±)-BPA catalyzed, mild and efficient protocol for the synthesis of 2,4-diaryl substituted flavans involving [4 + 2] cycloaddition reaction of *o*-QM generated from *o*-hydroxy arylmethyl phenols and styrene derivatives was developed. We have demonstrated that electron deficient enones can participate in cycloaddition with *o*-QM. The method was employed in a concise formal synthesis of atropisomeric myristinin B/C. The method can be potentially extended to the synthesis of other members of this family in a divergent manner. Efforts in this direction are underway in our laboratory and will be reported in due course.

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Notes and references

1 (*a*) D. A. Bolon, *J. Org. Chem.*, 1970, **35**, 3666. Reviews on o-QMs: (*b*) R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367; (*c*) N. J. Willis and C. D. Bray, *Chem.–Eur. J.*, 2012, **18**, 9160.

2 (*a*) R. M. Adlington, J. E. Baldwin, G. J. Pritchard, A. J. Williams and D. J. Watkin, *Org. Lett.*, 1999, **1**, 1937; (*b*) R. Rodriguez, R. M. Adlington, J. E. Moses, A. Cowley and J. E. Baldwin, *Org. Lett.*, 2004, **6**, 3617.

3 (*a*) K. Chiba, T. Hirano, Y. Kitano and M. Tada, *Chem. Commun.*, 1999, 691; (*b*) T. Inoue, S. Inoue and K. Sato, *Chem. Lett.*, 1990, 55; (*c*) T. Inoue, S. Inoue and K. Sato, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1647; (*d*) H. Miyazaki, Y. Honda, K. Honda and S. Inoue, *Tetrahedron Lett.*, 2000, **41**, 2643; (*e*) J.

D. Chambers, J. Crawford, H. W. R. Williams, C. Dufresne, J. Scheigetz, M. A. Bernstein and C. K. Lau, *Can. J. Chem.*, 1992, **70**, 1717.

4 (*a*) S. E. Rokita, Y. Jianhong, P. Pande and W. A. Greenberg, *J. Org. Chem.*, 1997, **62**, 3010; (*b*) P. Pande, J. Shearer, Y. Jianhong, W. A. Greenberg and S. E. Rokita, *J. Am. Chem. Soc.*, 1999, **121**, 6773; (*c*) C. Selenski and T. R. R. Pettus, *J. Org. Chem.*, 2004, **69**, 9196; (*d*) R. M. Jones, C. Selenski and T. R. R. Pettus, *J. Org. Chem.*, 2002, **67**, 6911; (*e*) R. M. Jones, R. W. Van De Water, C. C. Lindsey, C. Hoarau, T. Ung and T. R. R. Pettus, *J. Org. Chem.*, 2001, **66**, 3435; (*f*) R. W. Van De Water, D. J. Magdziak, J. N. Chau and T. R. R. Pettus, *J. Am. Chem. Soc.*, 2000, **122**, 6502; (*g*) C. Selenski, L. H. Mejorado and T. R. R. Pettus, *Synlett*, 2004, 1101.

5 S. J. Gharpure, A. M. Sathiyanarayanan and P. Jonnalagadda, *Tetrahedron Lett.*, 2008, **49**, 2974.

6 (*a*) C. Selenski and T. R. R. Pettus, *Tetrahedron*, 2006, **62**, 5298; (*b*) D. J. Maloney, S. Chen and S. M. Hecht, *Org. Lett.*, 2006, **8**, 1925; (*c*) K. Li, K. Vanka, W. H. Thompson and J. A. Tunge, *Org. Lett.*, 2006, **8**, 4711; (*d*) R. C. Oslund, N. Cermak, C. L. M. J. Verlinde and M. H. Gelb, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5415; (*e*) P. Batsomboon, W. Phakhodee, S. Ruchirawat and P. Ploypradith, *J. Org. Chem.*, 2009, **74**, 4009; (*f*) S. Radomkit, P. Sarnpitak, J. Tummatorn, P. Batsomboon, S. Ruchirawat and P. Ploypradith, *Tetrahedron*, 2011, **67**, 3904; (*g*) Y. Chen and M. G. Steinmetz, *Org. Lett.*, 2005, **7**, 3729; (*h*) V. Kumbaraci, D. Ergunes, M. Midilli, S. Begen and N. Talinli, *J. Heterocycl. Chem.*, 2009, **46**, 226.

7 Y. Chiang, A. J. Kresge and Y. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 717.

8 Racemic mixture of benzopyran **8a** was obtained using (*R*)-BPA as the catalyst.

9 (*a*) S. J. Gharpure and S. R. B. Reddy, *Org. Lett.*, 2009, **11**, 2519; (*b*) S. J. Gharpure, M. K. Shukla and U. Vijayasree, *Org. Lett.*, 2009, **11**, 5466; (*c*) S. J. Gharpure and S. K. Porwal, *Tetrahedron*, 2011, **67**, 1216; (*d*) S. J. Gharpure and V. Prasath, *J. Chem. Sci.*, 2011, **123**, 943; (*e*) S. J. Gharpure, P. Niranjana and S. K. Porwal, *Org. Lett.*, 2012, **14**, 5476.

10 CCDC 932658 (**8b**), CCDC 932655 (**8d**), CCDC 932656 (**8f**), CCDC 932657 (**8j**) and CCDC 932659 (**9h**) contain the supplementary crystallographic data for this paper.

11 S. Sawadjoon, P. Kittakoop, K. Kirtikara, V. Vichai, M. Tanticharoen and Y. Thebtaranonth, *J. Org. Chem.*, 2002, **67**, 5470.

12 D. J. Maloney, J.-Z. Deng, S. R. Starck, Z. Gao and S. M. Hecht, *J. Am. Chem. Soc.*, 2005, **127**, 4140.

13 A. Miyake, H. Yamamoto, Y. Takebavashi, H. Imai and K. Honda, *J. Pharma. Expet. Therp.*, 1992, 1302.

14 K. Orito, T. Hatakeyama and H. Suginome, *Synthesis*, 1995, 1273.

15 W. L. Mendelson, M. Holmes and J. Dougherty, *Synth. Commun.*, 1996, **26**, 593.

