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To be cited as: *Chem. Eur. J.* 10.1002/chem.202003805

Link to VoR: https://doi.org/10.1002/chem.202003805

WILEY-VCH

10.1002/chem.202003805

RESEARCH ARTICLE

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Design of Functional Chromene-type Kobayashi Precursor: Gram-scale Total Synthesis of Natural Xanthones *via* Highly Regioselective Aryne Annulation

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Abstract: 2,2-Dimethyl-2*H*-chromene motif is widely found in many bioactive molecules, and is a privileged structure in pharmaceutical area. We have developed a concise and regioselective approach to chromenes and chromanes *via* an aryne-based synthetic strategy. A practical, gram-scale synthetic route to chromene-type aryne precursor was explored. Subsequently, cyclization under mild conditions afforded tetracyclic xanthone skeletons with excellent regioselectivity. Our approach provides a concise strategy for the gram-scale synthesis of chromene-type xanthones such as 6-deoxyisojacareubin, cylindroxanthone D, staudtiixanthone D, brasilixanthone A and cudracuspixanthone O.

Introduction

2,2-Dimethyl-2*H*-chromene motif is widely found in natural products[1] as bioactive fragments, such as 6-deoxyisojacareubin (anti-tumor),[2] inophyllum B (anti-HIV),[3] deguelin (ubiquinone oxidoreductase)[4] and pongapinone A (anti-inflammatory)[5] (Figure 1). Due to their promising biological activities, the development of practical synthetic methodologies to chromene fragments has attracted considerable interest.[6] A number of elegant methods have been developed to produce chromene-based compounds including the thermal rearrangement of aryl propargyl ethers,[6c] condensation of phenols with α,β-unsaturated carbonyls[6d-e] and transition metal-catalyzed cyclization approaches.[6f-h] However, the majority of the existing methods either starts with pre-functionalized phenols, which are not easily accessible, or requires multi-step syntheses to form the chromene core. Furthermore, judicious control of product regioselectivity is still of great challenge.[7] Therefore, effective and selective strategies to the construction of polycyclic chromenes from readily accessible starting materials remain to be explored.

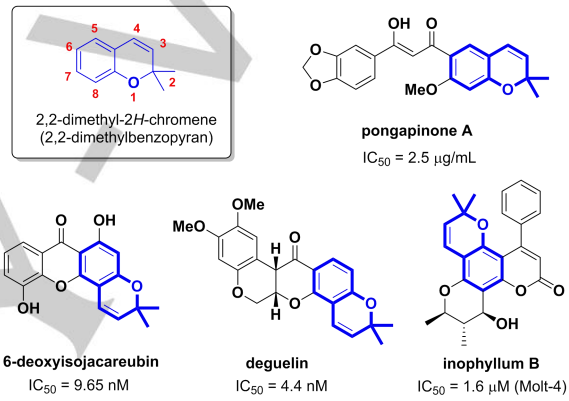
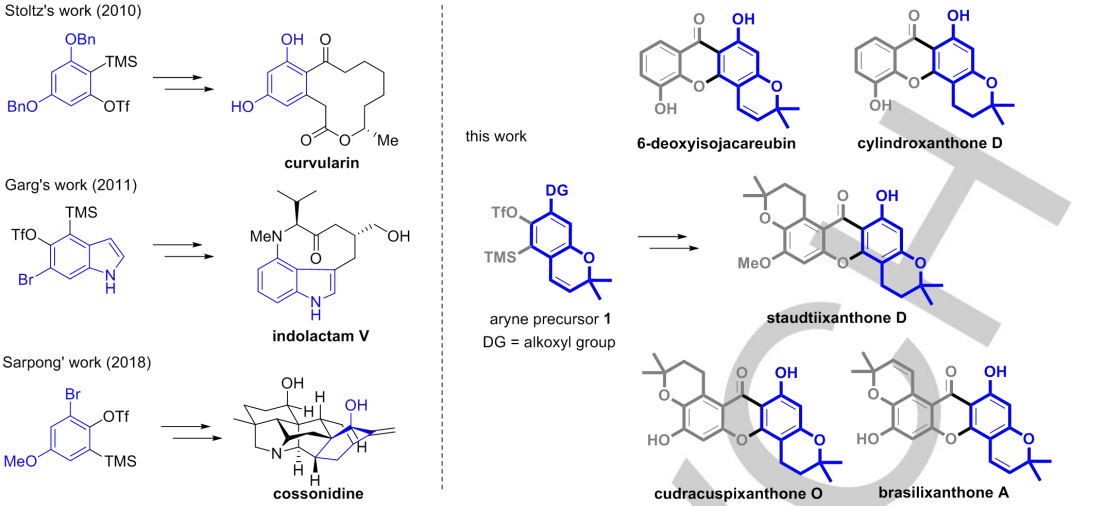


Figure 1. Representative natural chromene.

Comparing to other conventional methodologies, aryne-based synthetic approaches have many advantages in constructing ring-fused systems.[8,9] In particular, for the formation of multiple bonds in one-step, the presence of aryne can greatly improve the efficiency for the production of complex polycyclic skeletons. In previously reported total synthesis of natural products with arynes, nevertheless, the *in situ* generation of aryne from precursors generally involves harsh reaction conditions such as the use of organolithium/Grignard reagent/KNH_2/$NaNH_2$. Alternatively, Kobayashi precursors have become the method of choice in the past 20 years owing to the mild reaction conditions of arynes.[8] However, due to the complicated synthetic steps of functionalized Kobayashi precursors, its application in the construction of functional molecules is limited. In addition, regioselective control remains a challenge for nonsymmetric arynes. Few examples exist, including those reported by Stoltz,[10] Garg[11] and Sarpong[12] groups, using multifunctional Kobayashi precursors for the total synthesis of polycyclic natural products.



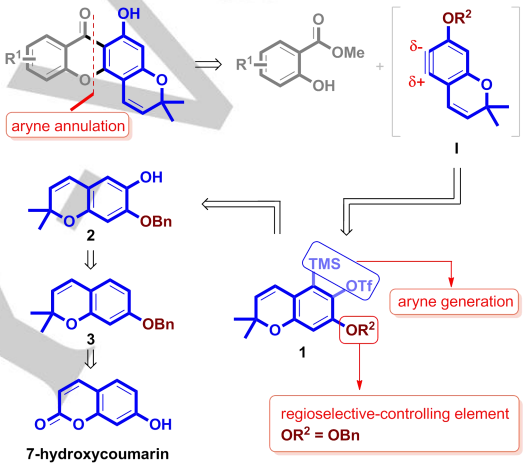
Scheme 1. Total synthesis of natural products based on multifunctional arynes with regioselectivity-controlling element.

Considering the outstanding biological properties of chromene, herein we design a novel synthetic route to Kobayashi precursor containing a 2,2-dimethyl-2*H*-chromene moiety, which is further used as a core building block to accomplish the total synthesis of a series of natural xanthones in gram-scale including 6-deoxyisojacareubin,[13] cylindroxanthone D,[14] staudtiixanthone D,[15,16] brasilixanthone A,[17] and cudracuspixanthone O.[18] Specially, alkoxyl group is introduced to the precursor structure to direct regioselectivity, enabling functional transformations of the product.

Results and Discussion

As shown in Scheme 2, a retrosynthetic analysis identifies precursor **1** as our first target material. Firstly, strategic removal of trimethylsilyl and trifluoromethanesulfonyl groups gives rise to phenol **2**, which can be prepared by oxidation of the corresponding aldehyde. Removal of the formyl group affords ether **3**, which can be traced back to the commercially available chemical 7-hydroxycoumarin. The introduction of benzyloxy group to precursor **1** guides the formyl group to the correct position, which serves as a regioselectivity-controlling element in the subsequent aryne-based reactions.[19]

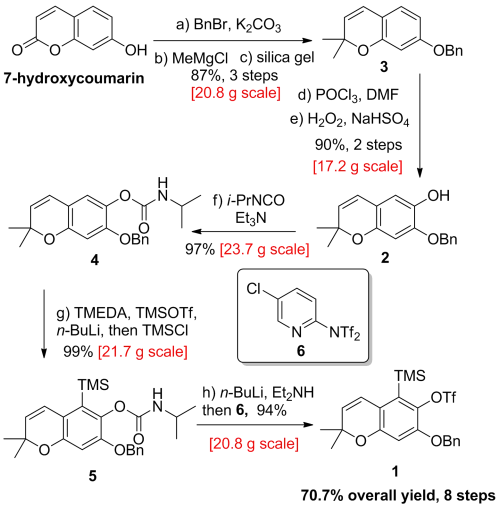
The synthesis began with a scalable preparation of silyl aryl triflate **1** (Scheme 3). After benzylation of 7-hydroxycoumarin, the dimethylpyran ring was constructed with MeMgCl, followed by an acid-catalyzed cyclization. According to Erhardt's method,[20] benzyl ether **3** was obtained in 87% yield over 3 steps with mildly acidic silica gel as cyclization reagent. Treating compound **3** with $POCl_3$/DMF produced the corresponding aldehyde, and a following Dakin oxidation furnished the desired phenol **2** in 90% overall yield. Phenol **2** was allowed to react with isopropyl isocyanate producing carbamate **4** in 97% yield. Silylation of carbamate **4** was accomplished by a one-pot method developed by Snieckus and Hoppe.[21] First, compound



Scheme 2. Retrosynthetic analysis of related chromene and triflate **1**.

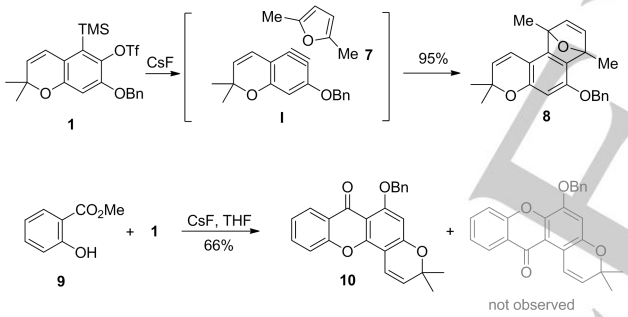
4 underwent an *N*-silylation; then, treatment with *n*-BuLi produced aryl lithium species, which was quenched by chlorotrimethylsilane (TMSCl) to give silylcarbamate **5** in 99% yield. We determined that methyl *tert*-butyl ether was a better solvent than the commonly used diethyl ether. Exposure of carbamate **5** to *n*-BuLi and Et_2NH in THF furnished intermediate *o*-silylphenol lithium, which was then triflated with Comins' reagent (**6**). Silyltriflate **1** was obtained as a white solid in 94% yield. Through this approach, more than 20 grams of silyltriflate **1** was prepared in more than 70% overall yield from readily accessible 7-hydroxycoumarin. It is worth mentioning that silyltriflate **1** was found stable and can be stored at room temperature for 6 months in the air with no obvious deterioration (Figure. 2). This route provides a rapid and scalable access to storable triflate **1**, which can serve as a building block in the subsequent synthesis of natural products in sufficient quantity.

Figure 2. Physical state comparison of silyltriflate **1**.



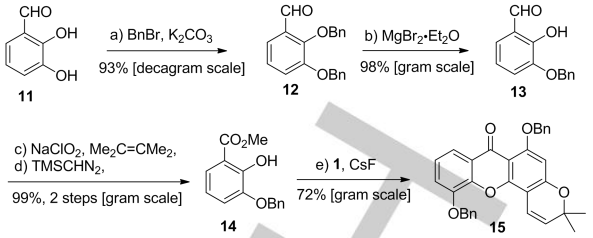
Scheme 3. 20 g-scale synthesis of silyltriflate **1**.

Trapping experiments of aryne **I** (from precursor **1**, Scheme 4) were carried out by Diels-Alder reaction with 2,5-dimethylfuran (**7**) to give product **8** in 95% yield. This confirms that aryne **I** was successfully generated *in situ* (Schemes 2 and 4). We then examined the feasibility to construct xanthones from aryne **I**. To our delight, precursor **1** and methyl salicylate (**9**) could undergo cyclization smoothly under mild conditions reported by Larock group.[22] Xanthone **10** was obtained in 66% yield with no regio-isomer observed, indicating the excellent regioselectivity control effect of the benzyloxy group.



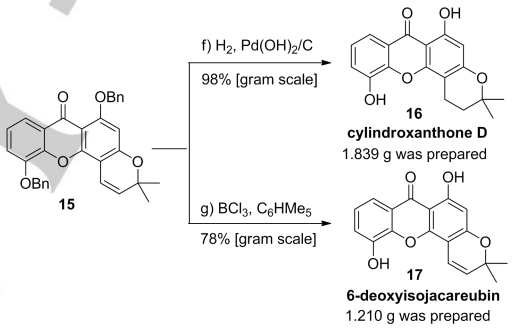
Scheme 4. Generation and trapping of chromene-type aryne **I**.

Next, we attempted the total synthesis of cylindroxanthone D (**16**) and 6-deoxyisojacareubin (**17**) in gram-scale (Scheme 6). As shown in Scheme 5, dibenzylation of the commercially available starting material 2,3-dihydroxybenzaldehyde (**11**) with benzyl bromide (BnBr) gave rise to aldehyde **12** in 93% yield. Selective debenzylation of compound **12** using $MgBr_2{\cdot}Et_2O$ afforded salicylaldehyde **13** in 98% yield. Subsequently, Pinnick oxidation and methylation conditions efficiently accomplished the gram-scale synthesis of salicylate **14** in 99% yield over 2 steps. Cyclization of salicylate **14** with precursor **1** gave xanthone **15** in 72% yield.



Scheme 5. Gram-scale synthesis of xanthone **15**.

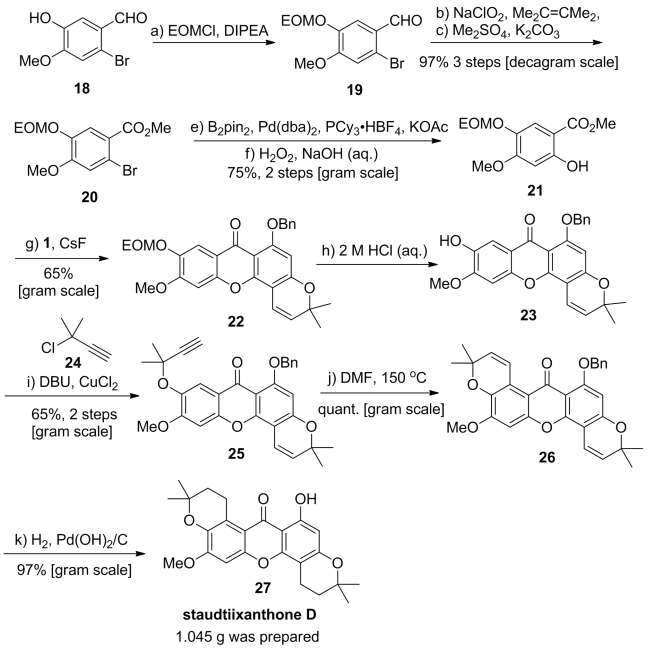
With xanthone **15** in hand, we turned our attention to the removal of benzyl groups through different approaches (Scheme 6). Unfortunately, using the typical condition [$Pd(OH)_2/C$, H_2 (1 atm.), MeOH] did not lead to hydrogenation of **15** after 48 hours. No improvement was observed with EtOAc or EtOH as solvent. To our surprise, treatment of **15** with $Pd(OH)_2/C$ in THF under a balloon pressure of H_2 afforded cylindroxanthone D (**16**) in 98% yield. A plausible explanation is that the solubility of the product is poor in solvents such as MeOH. On the other hand, treatment of **15** with BCl_3 mildly removed the two benzyl groups[23] in one step, producing 6-deoxyisojacareubin (**17**) in 78% yield. Using our precursor developed, the natural xanthones **16** and **17** were synthesized in grams.



Scheme 6. Gram-scale total synthesis of cylindroxanthone D and 6-deoxyisojacareubin.

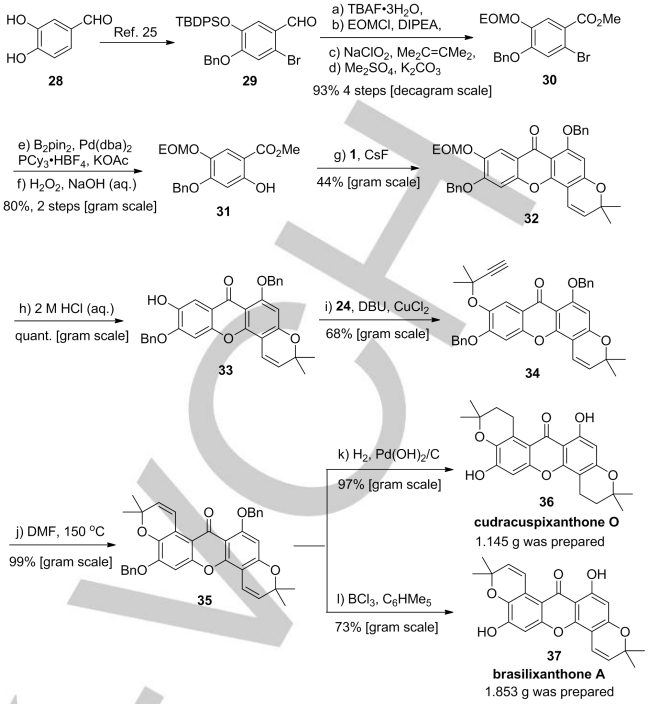
Pentacyclic xanthone with both chromene and chromane fragment is the skeleton of many bioactive compounds.[18,24] As a consequence, we then turned to construct these highly substituted xanthones. Commercially available 5-bromoisovanillin (**18**) was used as a starting material to accomplish the total synthesis of staudtiixanthone D (**27**). As illustrated in Scheme 7, treatment of phenol **18** with ethoxymethyl chloride (EOMCl) in the presence of *N*,*N*-diisopropylethylamin (DIPEA) afforded EOM ether **19**, which was oxidized with $NaClO_2$ and then methylated with Me_2SO_4 to give methyl benzoate **20** in 97% yield over 3 steps. Subsequently, Pd-catalyzed boronation and oxidation gave methyl salicylate **21** in 75% yield over 2 steps. In the presence of CsF, salicylate **22** was cyclized with aryne **I** (from precursor **1**) to give tetracyclic xanthone **23** in 65% yield. An acidic hydrolysis that removes the EOM group followed by a reaction with 3-chloro-3-methyl-1-butyne (**24**) in the presence of $CuCl_2$ and DBU resulted in the formation of propargylic ether **25** in 65% overall yield. Heating of **25** in DMF induced tandem Claisen rearrangement/cyclization, producing pentacyclic xanthone **26** in quantitative yield. Treatment of compound **26** with $Pd(OH)_2/C$ in THF under a

balloon pressure of H_2 accomplished the gram-scale preparation of Staudtiixanthone D (**27**) in 97% yield.



Scheme 7. Gram-scale total synthesis of Staudtiixanthone D.

This route can also be applied as a model for the total synthesis of cudracuspixanthone O (**36**) and brasilixanthone A (**37**). As shown in Scheme 8, aldehyde **29** was prepared from 3,4-dihydroxybenzaldehyde (**28**) according to the reported procedure.[25] Treatment of compound **29** with tetrabutylammonium fluoride (TBAF) gave the corresponding phenol, which was then protected to form EOM ether. Pinnick oxidation of this EOM ether followed by methylation furnished methyl bromobenzoate **30** in 93% overall yield. Subsequently, Miyaura borylation and oxidation led to salicylate **31** in 80% yield over 2 steps, which underwent aryne-based ring-forming reaction with precursor **1** to give the xanthone **32** in 44% yield (for details, see supporting information). Tetracyclic xanthone **32** was treated with aq. HCl to give phenol **33** in quantitative yield. Propargylation employing the same reaction conditions as used above afforded chromene **35** in 67% yield over 2 steps. Using similar debenzylation methods, 1.145 g of cudracuspixanthone O (**36**) and 1.853 g of brasilixanthone A (**37**) were obtained in 97% and 73% yield, respectively.



Scheme 8. Gram-scale total synthesis of cudracuspixanthone O and brasilixanthone A.

Conclusion

In summary, we have developed a practical synthetic route to chromene-type aryne precursors, with chromene fragments turned into shelf-stable synthetic building blocks in more than 70% overall yield over 8 steps in a scale of 20 grams. Furthermore, a novel synthetic strategy for constructing highly substituted chromenes and chromanes with high efficiency and excellent regioselectivity has been disclosed *via* aryne annulation. This led to the gram-scale total synthesis of natural products 6-deoxyisojacareubin, cylindroxanthone D, staudtiixanthone D, brasilixanthone A and cudracuspixanthone O.

Acknowledgements

We are grateful for financial support from the Shanghai Pujiang Program (18PJD010), the Natural Science Foundation of Shanghai (19ZR1412300), and the Fundamental Research Funds for the Central Universities (222201814019).

Keywords: arynes • chromene • xanthone • total synthesis • natural products

[1] (a) G. P. Ellis, I. M. Lockhart, The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones; Ellis, G. P., Ed.; Wiley-VCH: New York, **2009**; Vol. 31, pp. 1−1196. (b) R. Pratap, V. J. Ram, *Chem. Rev.* **2014**, *114*, 10476-10526. (c) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939-9953.

[2] M. Dai, X. Yuan, Z.-J. Zhu, L. Shan, R.-H. Liu, Q.-Y. Sun, W.-D. Zhang, *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 314-320.

[3] A. D. Patil, A. J. Freyer, D. S. Eggleston, R. C. Haltiwanger, M. F. Bean, P. B. Taylor, M. J. Caranfa, A. L. Breen, H. R. Bartus, *J. Med. Chem.* **1993**, *36*, 4131-4138.

[4] (a) C. Gerhäuser, S. K. Lee, J. W. Kosmeder, R. M. Moriarty, E. Hamel, R. G. Mehta, R. C. Moon, J. M. Pezzuto, *Cancer Res.* **1997**, *57*, 3429-3435. (b) N. Fang, J. E. Casida, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3380-3384. (c) N. Fang, J. E. Casida, *J. Nat. Prod.* **1999**, *62*, 205-210.

[5] I. Kitagawa, R. Zhang, K. Hori, K. Tsuchiya, H. Shibuya, *Chem. Pharm. Bull.* **1992**, *40*, 2041-2043.

[6] For reviews, see: (a) A. Lévai, T. Tímár, P. Sebok, T. Eszenyi, *HeteroCycles* **2000**, *53*, 1193-1203. (b) N. Majumdar, N. D. Paul, S. Mandal, B. de Bruin and W. D. Wulff, *ACS Catal.* **2015**, *5*, 2329-2366. For selected examples, see: (c) M. Harfenist, E. Thom, *J. Org. Chem.* **1972**, *37*, 841-848. (d) G. Sartori, G. Casiraghi, L. Bolzoni, G. Casnati, *J. Org. Chem.* **1979**, *44*, 803-805. (e) J. T. North, D. R. Kronenthal, A. J. Pullockaran, S. D. Real, H. Y. Chen, *J. Org. Chem.* **1995**, *60*, 3397-3400. (f) I. N. Lykakis, C. Efe, C. Gryparis, M. Stratakis, *Eur. J. Org. Chem.* **2011**, 2334–2338. (g) L. Calmus, A. Corbu, J. Cossy, *Adv. Synth. Catal.* **2015**, *357*, 1381-1386. (h) H. Zeng, J. Ju, R. Hua, *Tetrahedron Lett.* **2011**, *52*, 3926-3928.

[7] For selected examples, see: (a) V. M. Lau, W. C. Pfalzgraff, T. E. Markland, M. W. Kanan, *J. Am. Chem. Soc.* **2017**, *139*, 4035-4041. (b) E-S. Kim, H. Jang, S-Y. Chang, S.-H. Baek, O-N. Bae, H. Kim, *J. Nat. Prod.* **2018**, *81*, 2647-2653. (c) Y. R. Lee, X. Li, J. H. Kim, *J. Org. Chem.* **2008**, *73*, 4313-4316. (d) S. Zheng, X. Li, H. Tan, C. Yu, J. Zhang, Z. Shen, *Eur. J. Org. Chem.* **2013**, 1356-1366.

[8] For reviews of methodologies, see: (a) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.*, **2012**, *41*, 3140-3152. (b) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, **2013**, *11*, 191-218.

[9] For reviews of total synthesis, see: (a) C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.*, **2012**, *51*, 3766-3778. (b) P. M. Tadross, B. M. Stoltz, *Chem. Rev.*, **2012**, *112*, 3550-3577. (c) H. Takikawa, A. Nishii, T. Sakai, K. Suzuki, *Chem. Soc. Rev.*, **2018**, *47*, 8030-8056.

[10] (a) H. Yoshida, T. Morishita, J. Ohshita, *Chem. Lett.*, **2010**, *39*, 508-509. (b) P. M. Tadross, S. C. Virgil, B. M. Stoltz, *Org. Lett.*, **2010**, *12*, 1612-1614.

[11] S. M. Bronner, A. E. Goetz, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 3832-3835.

[12] K. G. M. Kou, J. J. Pflueger, T. Kiho, L. C. Morrill, E. L. Fisher, K. Clagg, T. P. Lebold, J. K. Kisunzu, R. Sarpong, *J. Am. Chem. Soc.* **2018**, *140*, 8105-8109.

[13] P. J. Owen, F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1018-1021.

[14] E. R. Sukandar, S. Kaennakam, K. Rassamee, P. Siripong, S. Fatmawati, T. Ersam, S. Tip-pyang, *Fitoterapia* **2018**, *130*, 112-117.

[15] (a) J. Ngoupayo, T. K. Tabopda, M. S. Ali, *Bioorg. Med. Chem.* **2009**, *17*, 5688-5695. (b) M. C. Kapingu, J. J. Magadula, *Nat. Prod. Commun.* **2008**, *3*, 1501-1504.

[16] Wang et al claimed that the structural identification of natural staudtiixanthone D is incorrect. For details, see: P. Zhou, A. Hou, Y. Wang, *Chin. J. Org. Chem.* **2018**, *38*, 156-161. The spectrum of our synthesized staudtiixanthone D is consistent with the Wang's work.

[17] V. L. L. Marques, F. M. D. Oliveira, L. M. Conserva, R. G. L. Brito, G. M. S.P. Guilhon, *Phytochemistry* **2000**, *55*, 815-818.

[18] Y. H. Jo, S. B. Kim, J. H. Ahn, A. Turk, E.-B. Kwon, M.-O. Kim, B. Y. Hwang, M. K. Lee, *Bioorg. Chem.* **2019**, *92*, 103234.

[19] Many reported examples have mentioned the similar regioselectivity, for selected examples, see ref. 10-12. For precursor **1**, the possible origin of regioselectivity is that the benzyloxy group at C7 polarizes the triple bond of benzyne and shields adjacent atoms, making the position of nucleophilic attack more favored to C5 rather than C6. For more explanations of related regioselectivities, see: J. M. Medina, J. L. Mackey, N. K. Garg, and K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798-15805 and references therein.

[20] N. Malik, Z. Zhang, P. Erhardt, *J. Nat. Prod.* **2015**, *78*, 2940-2947.

[21] M. Kauch, V. Snieckus, D. Hoppe, *J. Org. Chem.* **2005**, *70*, 7149-7158.

[22] (a) J. Zhao and R. C. Larock, *Org. Lett.* **2005**, *7*, 4273-4275. (b) J. Zhao and R. C. Larock, *J. Org. Chem.* **2007**, *72*, 583-588.

[23] K. Okano, K.-i. Okuyama, T. Fukuyama, H. Tokuyama, *Synlett* **2008**, 1977-1980.

[24] Y. H. Jo, S. B. Kim, Q. Liu, B. Y. Hwang, M. K. Lee, *Arch. Pharm. Chem. Life Sci.* **2017**, *350*, e1600263.

[25] S. Madapa, S. Gadhiya, T. Kurtzman, I. L. Alberts, S. Ramsey, M. Reith, W. W. Harding, *Eur. J. Med. Chem.* **2017**, *125*, 255-268.

10.1002/chem.202003805

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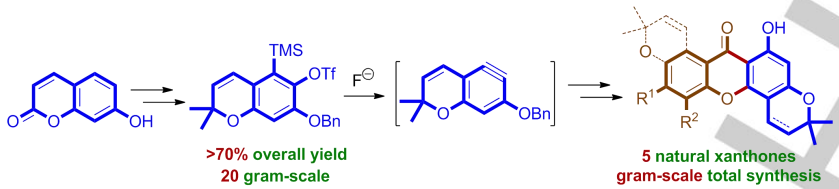

A practical, 20 gram-scale synthetic route to chromene-type aryne precursor was successfully designed and realized. With this key block, total synthesis of 5 natural xanthones (6-deoxyisojacareubin, cylindroxanthone D, staudtiixanthone D, brasilixanthone A, and cudracuspixanthone O) has been accomplished on gram scale.