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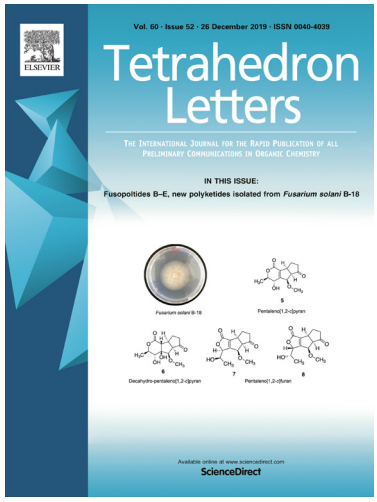

Diastereoselective [3+3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols: efficient assemble of immunosuppressive pentacyclic chromanes

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Diastereoselective [3+3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols: efficient assemble of immunosuppressive pentacyclic chromanes

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ABSTRACT

A base promoted diastereoselective formal [3+3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols towards the synthesis of functionalized pentacyclic indeno[1,2-*b*]chromen-(4b*H*)-ones has been developed. This methodology is appreciated in terms of diastereoselectivity and mild conditions. In addition, the immunosuppressive assay indicates that one of the products has selective inhibition on T-cell proliferation (IC_{50} value of 8.73 μM).

In the past few decades, great progress has been made in the synthesis of biologically active complex molecular structure via cycloaddition reactions. Functionalized chroman complexes represent a privileged structural motif that is found in a broad range of biologically active natural products[1] (e.g., carpanone[2] and (+)-machaeriol[3]) and pharmaceutically active compounds[4], such as (-)-nabilone, which is used as an antiemetic and analgesic agent,[5] CB1 full agonist[6] and GPR40 receptor antagonist[7] (Figure 1). Particularly, the polycyclic chroman cores are recurring structural motifs in natural product comprising (e.g., (-)-siccanin).[1,8] Owing to the importance of chroman framework, the construction of this privileged skeleton and its analogues has attracted considerable attention, and several elegant strategies have been developed.[9] However, most prepared chroman scaffolds are bicyclic and tricyclic chromans.[9,10] In sharp contrast, the development of efficient methods for construction of functionalized polycyclic chromans has received much less attention and still remained challenging. For selected example, the Wu group described the C(sp3)−H bond functionalization of benzo[c]oxepines via C−O bond cleavage/Michael additinon/annulation reaction for the synthesis of multisubstituted chromans.[11] Wang's group achieved the $FeCl_3$-catalyzed cascade reaction of indoles and o-hydroxychalcones for the assembly of indole-bridged polycyclic chromans.[12] The Lin group developed the cascade reaction of azomethine imines and 2-benzalidene-1,3-indanediones to generate the structurally complex polycyclic bridged chroman framework.[13] Schneider reported the Brønsted acid catalyzed intramolecular oxa-Diels-Alder reaction of ortho-quinone methides with dienophiles to construct dihydrochromenochromenes.[14] Recently, a Fe(III)-catalyzed diastereoselective Friedel-Crafts alkylation/

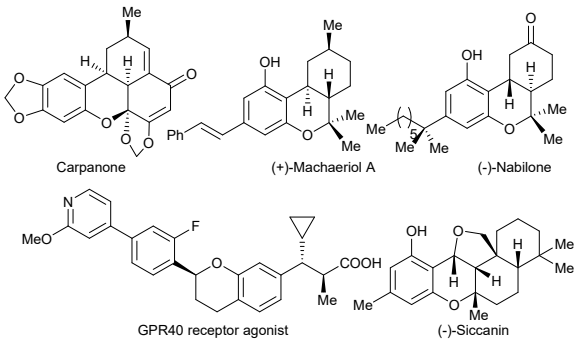


Figure 1. Natural product and pharmaceutical compounds with polycyclic chroman motifs

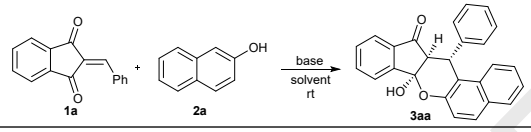
hemiketalization/lactonization cascade has been established for the synthesis of polycyclic bridged 2-chromanol lactones by Kontham.[15] Despite these elegant examples, the development of synthetic method to construct the structurally attractive and biologically important polycyclic chroman framework from readily available starting material is still demanded.

During the past decades, due to the 1C,3O-bisnucleophilic reactivity, β-naphthols have emerged as powerful and versatile building blocks in a variety of [3+n] cycloaddition reactions with biselectrophilic compounds for the synthesis of various biologically active heterocycles.[16] On the other hand, since the widely application of immunosuppressive agents in organ transplantation and immunity-associated disorders, the past half century has witnessed the fast progress of this research field, especially, the development of selective immunosuppressive

dr… …yed immunosuppressants,[18] herein, we report the synthesis of pentacyclic chromanes via the formal [3+3] cycloaddition reactions of β-naphthols with 2-arylideneindan-1,3-diones and its promising selective inhibition on T-cell proliferation. Although Wu et al discribed the C(sp3)−H bond functionalization of benzo[c]oxepines via C−O bond cleavage/Michael additinon/annulation reaction of β-naphthols with structurally complex benzo[c]oxepines under harsh conditions,[11] the development of more rapid access to pentacyclic chromans with readily available starting material under mild reaction conditions is still desirable. To the best of our knowledge, there is no report on the synthesis and immunosuppressive activity of pentacyclic chromanes by using β-naphthols and 2-arylideneindan-1,3-diones as the starting material.

The initial study was conducted by using 2-arylideneindan-1,3-dione **1a** and β-naphthol **2a** as model substrates with various bases at room temperature. The results are summarized in Table 1. To our delight, the Friedel-crafts reaction and intramolecular hemiketalization proceeded smoothly and the desired compound **3aa** was obtained in a single diastereoisomer in 13% yield when Na_2CO_3 was used as the base. Then different bases were screened in toluene at room temperature. The organic bases proved to be the effective catalyst in this transformation, and TEA afforded the product in 88% yield. Further investigations on the reaction media were conducted with various solvents by using TEA (20 mol%) as catalyst. Comparable results were observed when acetonitrile or methanol was used (Table 1, entries 7 and 9). However, the ether solvents resulted in drastically decreased yields (Table 1, entries 6 and 8). Chlorinated solvent such as dichloromethane and chloroform is beneficial to the reaction efficiency, and chloroform gave the best results, yielding **3aa** in 98% yield. The products in all the cases retained excellent diastereoselectivities and only one diastereoisomer was observed.

Table 1
Optimization of the reaction conditions.[a]



1a 2a 3aa

Entry	Catalyst	Solvent	Time (h)	Yield %
1	Na2CO3	Toluene	48	13
2	K2CO3	Toluene	48	16
3	TEA	Toluene	48	88
4	DIPEA	Toluene	48	46
5	DBU	Toluene	48	57
6	TEA	THF	48	34
7	TEA	MeCN	48	79
8	TEA	Dioxane	48	40
9	TEA	MeOH	48	79
10	TEA	$CHCl_3$	36	98
11	TEA	DCM	48	93

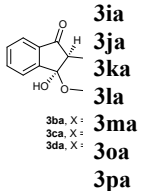
[a] Unless otherwise noted, the reactions were performed with **1a** (0.20 mmol), **2a** (0.24 mmol) and base (0.04 mmol) in 2.0 ml solvent.

[b] Isolated yield of the product, only one diastereoisomer was observed by crude NMR analysis.

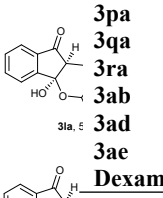
With the optimal conditions established, the substrate scope and limitation of this formal [3+3] cycloaddition reaction with a (Table 1, entry 10) and the results are outlined in Table 2. The reaction proceeded smoothly and delivered the corresponding pentacyclic chroman (±)-3 (**3aa-sa**) in moderate to excellent yield in single diastereoisomer except for **3ta** and **3ua**. Generally, obvious electronic effect has been observed. The substrates with electron-withdrawing substituents on the phenyl ring of 2-arylideneindan-1,3-diones gave higher yields than the electron-neutral and electron-donating ones (**3aa-fa**, **3ja** and **3ka** vs **3ga**, **3ha**, **3la**). 2-arylideneindan-1,3-diones bearing substituents at the ortho and meta position of the phenyl ring were also good substrates for this reaction (**3ia**, **3ja** and **3ka**). Interestingly, substrates with a sterically more bulky group on the phenyl ring of 2-arylideneindan-1,3-diones exerted a negligible effect on the reaction efficiency (**3ja**, **3ka** and **3ma**). Then, naphthyl and heterocyclic substituents were investigated. The electron-donating heterocycles had significant influence on the yields, giving only 47-63% yields (**3qa**, **3ra** and **3sa**). We also tried the pyrrole substituted 2-arylideneindan-1,3-dione. However, no desired product was detected, and the starting material decomposed. When the **1u** was applied, no reaction was observed even at 50 °C, mainly due to the electron donating nature of the isopropyl group. Although the multisubstituted 2-arylideneindan-1,3-diones were compatible in this reaction (**3la** and **3ma**), **3ua** was not obtained mainly because of the poor solubility of **1u**.

Then, we turned our attention to further investigate the scope and limitation by reacting **1a** with a variety of β-naphthol **2** bearing different substituents. As shown in Table 3, a wide range of β-naphthols underwent the Friedel-crafts reaction and

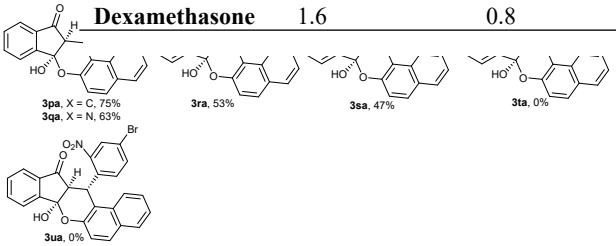
Table 2
Substrat… diones[a,l]



3ba, X =
3ca, X =
3da, X =



3la, 5



3ua, 0%

Table 4
Immunosuppressive effects of the products on murine lymphocyte proliferation induced by ConA or LPS. (IC_{50} in μM)

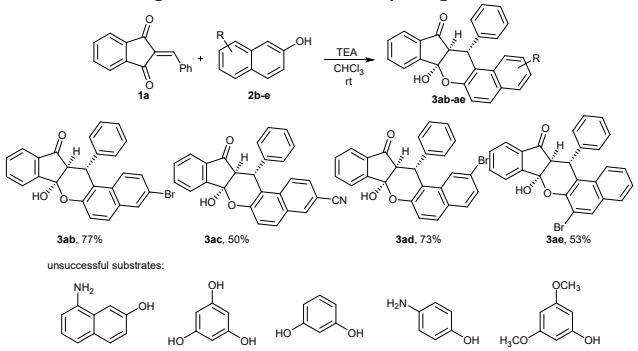
cmpd	ConA-induced T-cell proliferation	LPS-induced B-cell proliferation
3aa	12.7	>100
3ba	18.2	17.7
3ca	11.7	95.7
3ea	15.6	28.8
3fa	13.5	31.4
3ha	11.9	35.1
3ia	18.6	65.8
3ja	11.6	70.8
3ka	17.2	74.9
3la	49.2	42.5
3ma	26.3	>100
3oa	16.9	>100
3pa	15.7	>100
3qa	27.5	29.3
3ra	63.3	27.9
3ab	8.7	73.2
3ad	16.4	47.3
3ae	19.2	57.9
Dexamethasone	1.6	0.8

[a] Unless otherwise noted, the reactions were performed with **1** (0.20 mmol), **2a** (0.24 mmol) and base (0.04 mmol) in 2.0 ml solvent.

[b] Isolated yield of the product, only one diastereoisomer was observed by crude NMR analysis.

Ta

Substrate scope and limitation of β-naphthols[a,b]



[a] Unless otherwise noted, the reactions were performed with **1** (0.20 mmol), **2a** (0.24 mmol) and base (0.04 mmol) in 2.0 ml solvent.

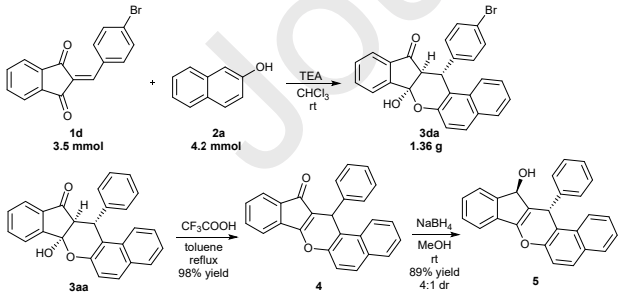
[b] Isolated yield of the product, only one diastereoisomer was observed by crude NMR analysis.

intramolecular hemiketalization process smoothly and yielded corresponding pentacyclic chromans **3ab**−**ae** in 50−77% yields (Table 3). The electron deficient substituent on β-naphthol had detrimental effects on the reaction efficiency, which could be ascribed to the low nucleophilicity caused by the electron-withdrawing cyanogroup (**3ac**). However, the electron-rich 8-aminonaphthalen-2-ol did not undergo any reaction under the standardized condition. Other electron-rich phenols were also applied in this reaction, however, no reaction was observed, perhaps because of the decreased electrophilicity of the phenols.

To evaluate the synthetic potential of the reaction, a gram-scale synthesis of **3da** was carried out. As shown in Scheme 1, 3.5 mmol of **1d** reacted smoothly with 4.2 mmol of **2a** under the optimized reaction conditions, delivering the corresponding product **3da** in 85% yield (1.36 g). In addition, some chemical transformations were conducted to decorate the product. By treatment of **3aa** with trifluoroacetic, the dehydrated elimination occurred, affording the α,β-unsaturated ketone **4** in 98% yield, which could be further reduced to alcohol **5** by $NaBH_4$ in single diastereoisomers in 71% yield.

The relative configuration of the product (±)-**3da** was unambiguously determined by X-ray crystallographic analysis (CCDC 1962616) (Figure 2). Consequently, all of the other pentacyclic chromans can be assigned to have the same relative configurations by analogy.

Having synthesized a variety of chroman-fused derivatives, we performed preliminary studies of their immunosuppressive



Scheme 1. Gram scale experiment and chemical transformation of the product

activities on Con A induced T-cell proliferation and LPS induced B-cell proliferation *in vitro*, following the established protocol in our previous work. Splenocyte cells were treated with 72 h with the compounds in Table 4 at various concentrations up to 100 μM, and cell viability was determined by CCK-8 assay. All the tested

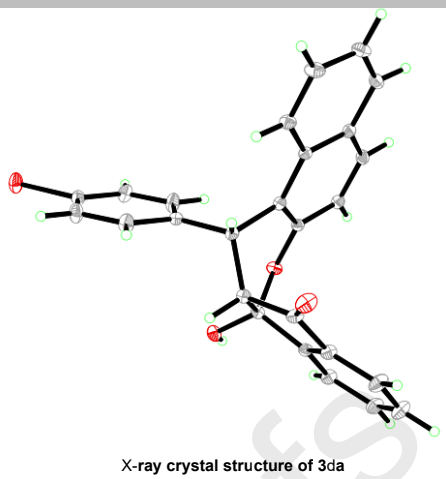


Figure 2. X-ray crystal structure of **3da**

compounds exhibited impressive inhibitive activity against ConA-induced T-cell proliferation. Particularly, compound **3ab** exhibited promising selective inhibition against the T-cell proliferation with IC_{50} value 8.7 μM.

Conclusions

In summary, a diastereoselective formal [3+3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols has been developed for the first time, affording a library of functionalized pentacyclic indeno[1,2-b]chromen-(4b*H*)-ones in good to excellent yields. Member **3ab** of this library showed selective inhibition against ConA-induced T-cell proliferation with IC_{50} value 8.7 μM. This synthetic methodology and the discovery of this type of selective immunosuppressants provide new possibilities to explore novel immunosuppressants by inhibiting T cell proliferation.

Acknowledgments

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Diastereoselective [3+3] cycloaddition reaction of 2-arylideneindan-1,3-diones with β-naphthols: efficient assemble of immunosuppressive pentacyclic chromanes

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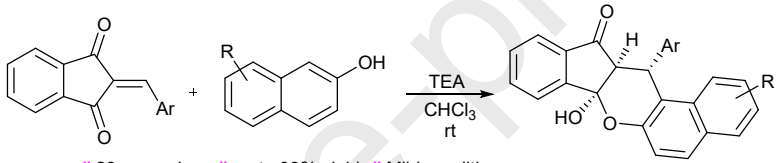
Na Li, Liang Tu, Guiguang Cheng, Houling Sa, Zhenghui Li, Tao Feng, Yongsheng Zheng* and Jikai Liu*



23 examples # up to 99% yield # Mild conditions
Selective inhibition against the T-cell proliferation with IC_{50} value 8.7 μ M

Graphical Abstract

Highlights

- Formal [3+2] cycloadddition of 2-arylideneindan-1,3-diones with β-naphthols.
- Highly efficient, mild approach for the construction of pentacyclic chromanes.
- Broad substrates scope and easily derivation.
- Successful demonstration of gram scale synthesis.
- Promising immunosuppressive activity.