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DIASTEREOSELECTIVE SYNTHESIS OF 2,8-DIOXABICYCLO[3.3.1]NONANE DERIVATIVES VIA I$_2$-MEDIATED CASCADE REACTIONS

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Abstract – The highly diastereoselective one-pot synthesis generating a variety of 9,9-dimethyl-2,8-dioxabicyclo[3.3.1]nonane derivatives up to *dr* >19:1 has been established by the reaction of a 2'-methoxylchalcone with isobutyraldehyde via a spontaneous sequential one-pot Michael addition/aldol reaction/demethylative bicyclization in the presence of molecular iodine.

The 2,8-dioxabicyclo[3.3.1]nonanes structural unit is frequently encountered in natural products and is an useful scaffolds with potential applications in antioxidant, immunomodulatory, anti-inflammatory, and, antiviral agents (Figure 1), e.g.,[1] Consequently, developing efficient methods for synthesizing the compounds carrying this functionality have recently received considerable attention and therefore, various methods have been developed.[2-8]

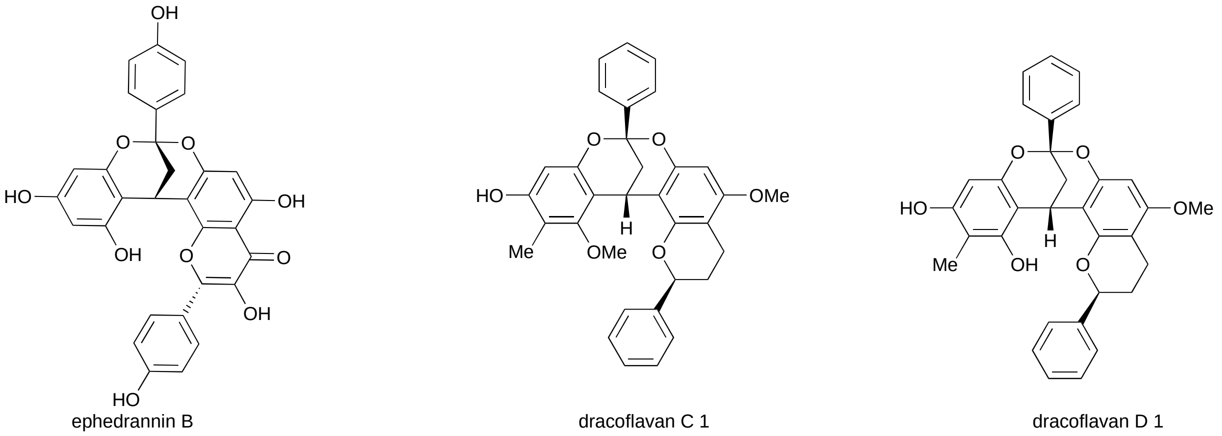
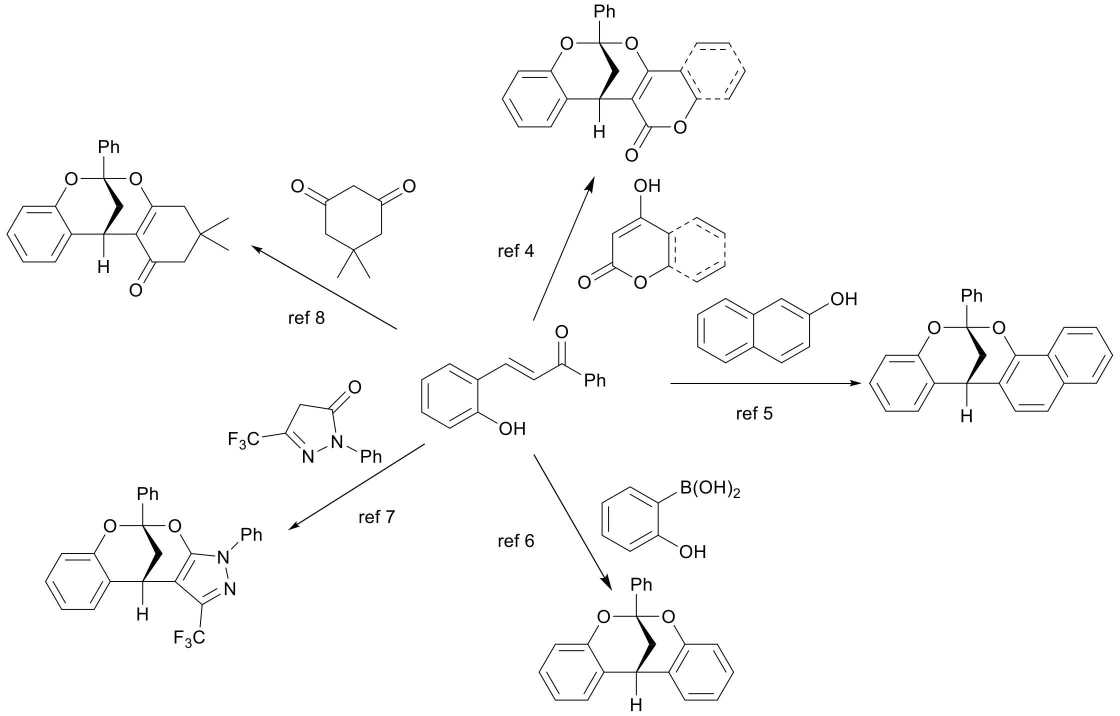


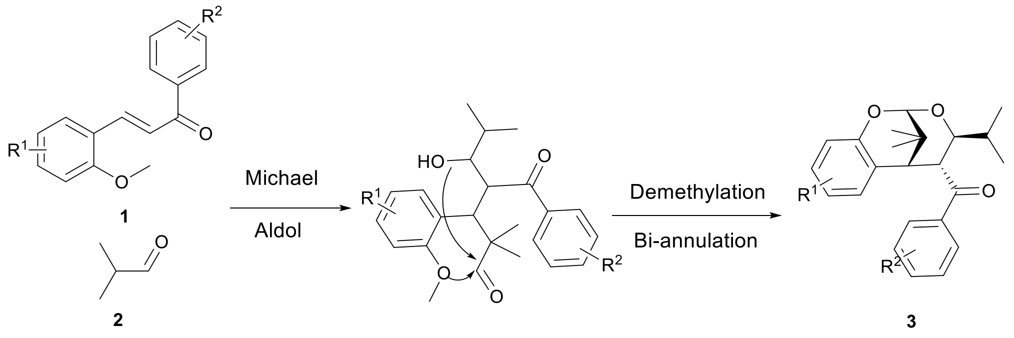
Figure 1. Examples of natural products

Among these, we are interested in the reactions using a 2’-hydroxychalcone as the staring material. As shown, when this was treated with various 1,3-bis-nucleophiles such as 4-hydroxycoumarin,[4] naphthol/ phenol derivatives,[5] 2-hydroxyphenylboronic acid,[6] trifluoromethylpyrazolone,[7] 1,3-diketones,[8] it formed the corresponding compounds having the 2,8-dioxabicyclo[3.3.1]nonane moiety in the product molecule. However, to the best of our knowledge, the synthesis of 2,8-dioxabicyclo[3.3.1]nonanes with two substituents at the bridge ring C9-carbon has rarely been reported (Scheme 1).



Scheme 1. Synthesis of the synthesis of 2,8-dioxabicyclo[3.3.1]nonanes from 2’-hydroxychalcone

Due to greater atom economy, greener, milder reaction conditions and broader substrate compatibility, I_2 is frequently employed in many organic reactions,[9] such as Michael addition and aldol reactions.[10] Given these backgrounds and our interest in the I_2-catalyzed annulation reactions,[11] we reported a new route to 9,9-dimethyl-2,8-dioxabicyclo[3.3.1]nonane derivatives based upon spontaneous Michael/aldol/demethylation/bi-annulation cascade reactions (Scheme 2) by treating 2’-methoxylchalcone 1 with isobutyraldehyde **2** in good diastereoselectivity (Figure 2). In the reaction, we utilized the carbon-carbon double bonds of the chalcones as both the electrophilic and the nucleophilic reaction sites to construct 2,8-dioxabicyclo[3.3.1]nonane structures efficiently.



Scheme 2. Our working hypothesis

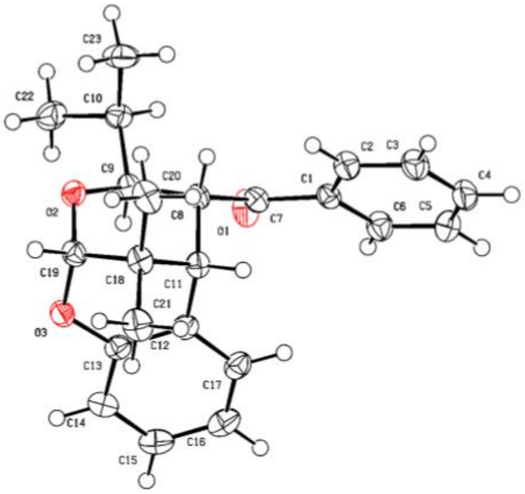
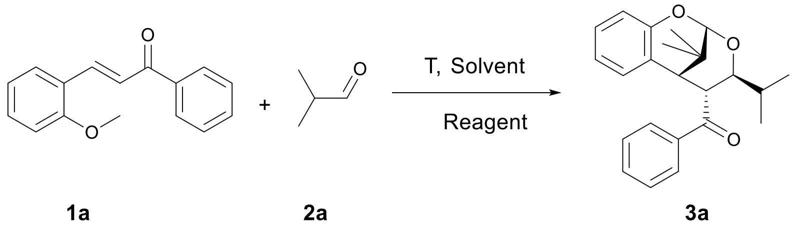


Figure 2. X-Ray structure of 3a

Initially, we investigated the reaction between 2-methoxychalcone **1a** and isobutyraldehyde **2a** as model substrates in sealed tube under the conditions shown in Table 1. Delightedly, the expected product **3a** was obtained in 24% yield as the single diastereoisomer with concurrent demethylation of 2'-methoxy group when toluene was used as the solvent at 80 ºC (Table 1, entry 1). Its stereochemistry was determined unambiguously as shown by X-ray crystal structure analysis (Figure 2). The product **3a** was obtained in 38% yield when $ClCH_2CH_2Cl$ was used as solvent in place of toluene (Table 1, entry 2). Although the reaction in other solvents, including THF, MeCN, DMF, and DMSO, did not yield the expected product (Table 1, entries 3-6), we were pleased to find that when the reaction was carried out in the absence of a solvent, the product **3a** was obtained in 65% yield (Table 1, entry 8). Inorganic salts containing iodine atom, such as sodium iodide, copper (I) iodide and ammonium iodide, did not catalyze the reaction (Table 1, entries 8-10). In addition, the loading amount of the catalyst was also explored. When the amount of I_2 was decreased to 80 mol%, some **1a** remained unreacted, and a decrease in yield was observed (Table 1, entry 11). The investigation of the effect of the temperature showed that the reaction gave the best results at 70 ℃ (Table 1, entries 12-14).

Table 1. Optimization of the reaction conditions



Entry	Solvent	Reagent	T [℃]	Time(h)	Yield (%)[a]
1[b]	toluene	I_2	80	12	24
2[b]	DCE	I_2	80	12	38
3[b]	THF	I_2	80	12	0
4[b]	MeCN	I_2	80	12	0
5[b]	DMF	I_2	80	12	0
6[b]	DMSO	I_2	80	12	0
7[c]		I_2	80	12	65
8[c]		KI	80	12	0
9[c]		NH_4I	80	12	0
10[c]		CuI	80	12	0
11[d]		I_2	80	12	22

12 [c]	I_2	90	12	59
13 [c]	I_2	70	12	76
14 [c]	I_2	60	12	54

[a] Isolated yields are provided.

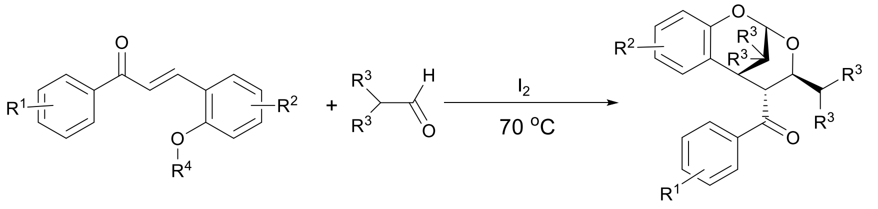
[b] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 mmol), iodine (0.51 mmol), and in solvent (3.0 mL)

[c] Reaction conditions: **1a** (0.5 mmol), **2a** (3.0 mL), reagent (0.51 mmol).

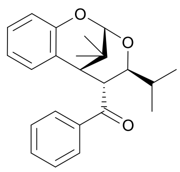
[d] Reaction condition: **1a** (0.5 mmol), **2a** (3.0 mmol), iodine (0.41 mmol).

With the optimized reaction conditions in hand, we then investigated the substrate scope and generality of this protocol, and the results are summarized in Table 2. Generally, the cascade reaction had a wide applicability and all the cases could afford the expected products **3a-q** in 42-77% yields. Initially, we examined the effect of R^1 substituents and the results revealed that the positions of the substituents had little effect on the yields (**3c** vs **3g** and **3d** vs **3f**) and the substrates with electron-withdrawing group delivered higher yields than the ones with electron-donating groups (**3b** vs **3e**). Then, the reactivity of substituents (R^2) of chalcones **1** was also investigated, and the target products were obtained in moderate yields (**3o** and **3p**). It is noteworthy that the products **3e** and **3k** in which selective *ortho*-demethylation occurs with keeping the other methoxy group(s) unchanged. Finally, different aldehydes were examined. 2-Ethylbutanal (**2**, R^3 = Et) underwent the desired transformation to give products **3q** in 56% yield. The yield dropped sharply with the increase of the bulkiness (**3a** vs **3q**). Linear aldehydes such as butyraldehyde and the aldehydes with an aromatic group at α position such as 2-phenylpropanal failed to generate the desired products. When the R^4 substituent on the **1** was altered (Table 2, entry 18), a moderate yield (65%) was obtained for product **3a**. The naphthyl- and thiophene-substituted *ortho*-methoxy chalcones **2m** and **2n** were also proved to be suitable reaction partners for this reaction, giving **3m** and **3n** in 50% and 42% yields. Only one diastereoisomer was obtained for all cases, although the products contained four stereocenters, two of which were quaternary carbon centers.

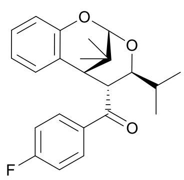
Table 2. Synthesis of various 2,8-dioxabicyclo[3.3.1]nonane derivatives[a,b]



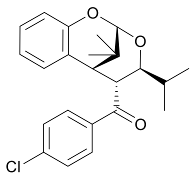
1 **2** **3**



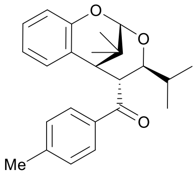
3a: 76%; Dr>19:1



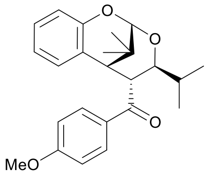
3b: 77%; Dr>19:1



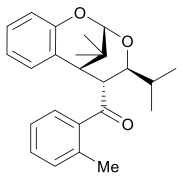
3c: 72%; Dr>19:1



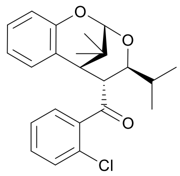
3d: 61%; Dr>19:1



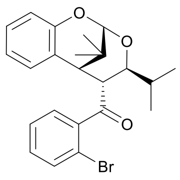
3e: 53%; Dr>19:1



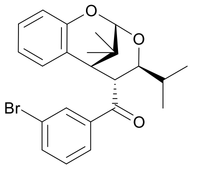
3f: 60%; Dr>19:1



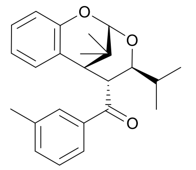
3g: 66%; Dr>19:1



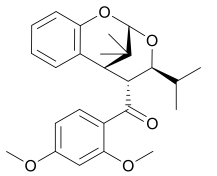
3h: 60%; Dr>19:1



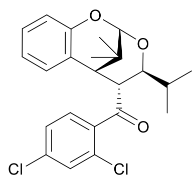
3i: 64%; Dr>19:1



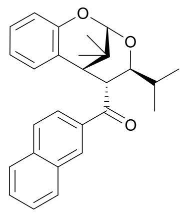
3j: 59%; Dr>19:1



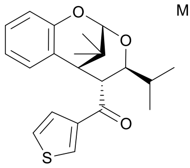
3k: 43%; Dr>19:1



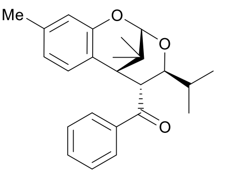
3l: 67%; Dr>19:1



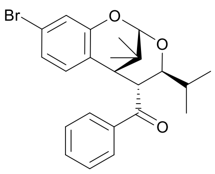
3m: 50%; Dr>19:1



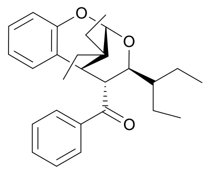
3n: 42%; Dr>19:1



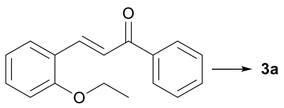
3o: 58%; Dr>19:1



3p:62%; Dr>19:1



3q:56%; Dr>19:1



3a: 65%; Dr>19:1

[a] Isolated yields are provided.

[b] Reaction conditions: 1a (0.5 mmol), 2a (3.0 mL), I_2 (0.51 mmol).

Several reactions were performed to obtain detailed mechanistic information on the process. When a free radical scavenger,[13] TEMPO, was added at the beginning of the reaction, product **3a** could not be detected. When iodine was replaced by NBS,[14] product **3a** was obtained in 56% yield. These indicate that the reaction may carry out via a radical mechanism. When 1.2 equivalent of pyridine was added at the beginning of the reaction, product **3a** could not be detected. The reaction mechanism is being studied in our laboratory.

In summary, we have developed an efficient I_2-mediated diastereoselective synthesis of a series of 9,9-dimethyl-2,8-dioxabicyclo[3.3.1]nonane derivatives by a single step cascading Michael addition/aldol reaction/demethylation/bicyclization between 2'-methoxylchalcone and isobutyraldehyde.

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SUPPORTING INFORMATION

Supplementary data (synthesis of 2,8-dioxabicyclo[3.3.1] nonanes, ^{1}H and ^{13}C NMR, etc.) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/28009/106/12

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12. CCDC 2269026 (**3a**) contains the supplementary crystallo-graphic data for this paper. These data can be obtained free charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
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