Synthetic Methods

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Construction of Chiral Bridged Tricyclic Benzopyrans: Enantioselective Catalytic Diels–Alder Reaction and a One-Pot Reduction/Acid-Catalyzed Stereoselective Cyclization**

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Abstract: *An asymmetric two-step approach to chiral bridged tricyclic benzopyrans, core structures featured in various natural products, is described. In the synthesis, an unprecedented enantioselective catalytic decarboxylative Diels–Alder reaction is developed using readily available coumarin-3-carboxylic acids and aldehydes as reactants under mild reaction conditions. Notably, the decarboxylation-assisted release of the catalyst enables the process to proceed efficiently with high enantio- and diastereoselectivity. Furthermore, a one-pot procedure for either a $LiAlH_4$- or $NaBH_4$-mediated reduction with subsequent acid-catalyzed intramolecular cyclization of the Diels–Alder adducts was identified for the efficient formation of the chiral bridged tricyclic benzopyrans.*

The discovery of powerful simplifying transformations for rapid access to the core structures featured in natural products is a central goal of organic synthesis. The bridged tricyclic benzopyran framework **A** is present in a fascinating array of structurally diverse and biologically intriguing complex natural products such as cannabinoid,[1] oxabicyclononane, murrayamines D and cyclomahanimbine,[2] and kuwanol B (Figure 1),[3] sanggenone R,[4a] mulberrofurans I and S and sorocenol B,[4b] and saustralisin B,[4c] mongolicin C,[4d] and isorubraine, etc.[4e] The construction of the bridged scaffold requires installing two contiguous chiral centers, including one quaternary center. Typically, this substructure is built through acid-catalyzed cyclizations of phenolic alkene precursors.[5] However, asymmetric synthesis of the scaffolds remains elusive. To the best of our knowledge, only a single study was reported by Yao and co-workers describing a binary $Pd(OAc)_2$ and (*S*)-Trip system to catalyze an enantioselective annulation process between 2-hydroxystyrenes and 2-alkynylbenaldehyes or 1-(2-alkynylphenyl)ketones.[6] To streamline substantial advances in this arena, new catalytic asymmetric methodologies using simple substances are more appealing.

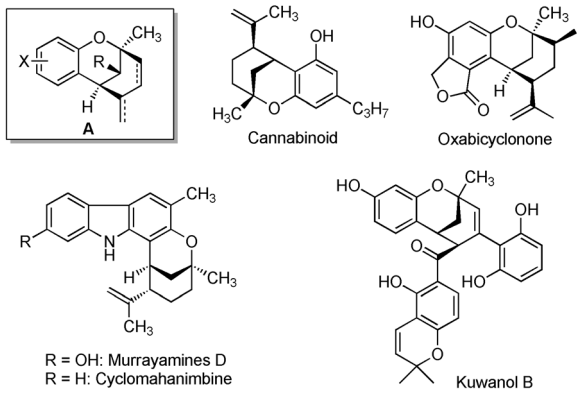

Figure 1. The bridged tricyclic benzopyran core unit **A** found in natural products.

Herein, we report an efficient two-step access to the chiral complex molecular architecture (Scheme 1). A novel catalytic enantioselective Diels–Alder reaction of readily available coumarin-3-carboxylic acids (**2**) with aldehydes (**1**) is designed.[7] The carboxylic moiety not only enhances the reactivitity of coumarins as dienophiles, but also facilitates the release of the amine catalyst.[8] Different from the reported studies in aminocatalytic Diels–Alder reactions where the dienophiles contain a prerequisite α-hydrogen atom, which is essential for the release of the amine catalyst,[9] a novel catalyst release mode by decarboxylation was uncovered. Importantly, the decarboxylation-assisted release of the catalyst enables the Diels–Alder reaction to proceed efficiently (short reaction times and high yields) under mild reaction conditions with high enantio- and diastereoselectivity. Moreover, a new one-pot protocol involving either a $LiAlH_4$- or $NaBH_4$-mediated reduction and subsequent acid-catalyzed intramolecular stereoselective cyclization of the Diels–Alder adducts was identified for the efficient formation of the chiral bridged tricyclic benzopyran **8**. The cyclization involves an interesting phenolic attack of the diene moiety driven by dehydration of the allylic alcohol in **6** (Scheme 1).

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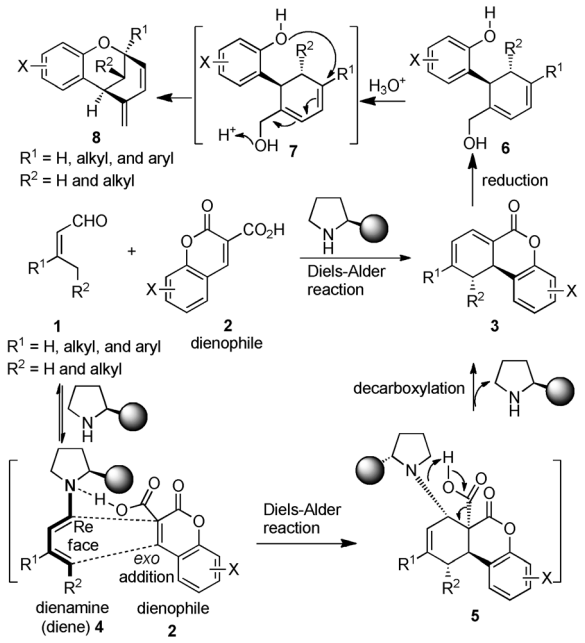
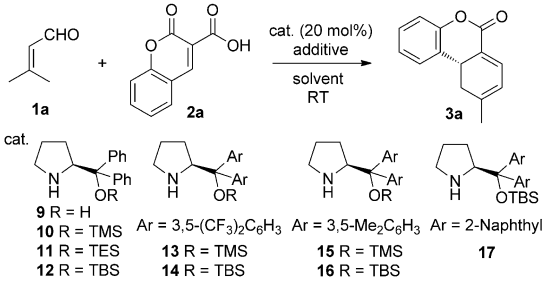


Scheme 1. Proposed two-step approach to the preparation of bridged tricyclic benzopyrans involving a catalytic asymmetric Diels–Alder reaction and a simple reduction/acid-promoted intramolecular cyclization.

Table 1: Optimization of reaction conditions.[a]



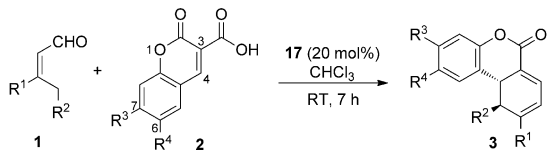
Entry	Cat.	Additive	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**9**	none	DCE	10	81	19
2	**10**	none	DCE	0.5	97	54
3	**11**	none	DCE	0.5	94	74
4	**12**	none	DCE	1	95	81
5	**13**	none	DCE	2/3	92	10
6	**14**	none	DCE	3	87	0
7	**15**	none	DCE	3	94	61
8	**16**	none	DCE	10	85	89
9	**17**	none	DCE	10	96	92
10	**17**	none	toluene	4	94	39
11	**17**	none	TME	4	90	29
12	**17**	none	THF	4	91	40
13	**17**	none	EtOAc	4	85	54
14	**17**	none	CH_3CN	4	81	69
15	**17**	none	DMSO	6	80	76
16	**17**	none	CH_2Cl_2	7	97	88
17	**17**	none	$CHCl_3$	7	95	94
18	**17**	none	MeOH	7	79	87
19	**17**	$PhCO_2H$	$CHCl_3$	10	91	91
20	**17**	AcOH	$CHCl_3$	10	90	90
21	**17**	DIPEA	$CHCl_3$	10	81	86
22	**17**	2,6-lutidine	$CHCl_3$	10	83	91
23[d]	**17**	none	$CHCl_3$	24	89	92

[a] Reaction conditions: unless specified, see Experimental Section. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] 0 °C. TME = *tert*-butyl methyl ether. DIPEA = diisopropylethylamine, DMSO = dimethyl sulfoxide, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

Firstly we focused on the proposed catalytic asymmetric Diels–Alder reaction (Table 1). A model reaction between 3-methyl-2-butenal (**1a**) and coumarin-3-carboxylic acid (**2a**) in the presence of the chiral amine **9** in 1,2-dichloroethane (DCE) at room temperature was carried out. To our delight, the process took place regioselectively to give the desired product **3a** in 81% yield, but with poor enantioselectivity (entry 1). The catalyst was facilely released by the designed decarboxylation and a quick process (10 h) was observed. Encouraged by the outcomes, we screened other chiral amine promoters (Table 1). It was found that the catalyst played significant roles in governing reaction efficiency and enantioselectivity. The TMS catalyst **10**[10] was more efficient for promoting the Diels–Alder reaction by affording 97% yield of **3a** within just 30 minutes with a 54% *ee* (entry 2). More bulky diarylprolinol silyl catalysts (e.g., **11** and **12**; entries 3 and 4) further enhanced the enantioselectivity of the product formed. Nonetheless, we were surprised to find that *ee* values of **3a** decreased dramatically when the more hindered catalysts **13** and **14**, bearing CF_3 groups on the aromatic ring, were employed (entries 5 and 6). We speculated that the decrease in the *ee* values might be attributed to the strong electron-withdrawing properties of the CF_3 groups. The assumption was verified by the studies of the catalysts **15** and **16**, wherein the CF_3 moiety was replaced by a methyl group (entries 7 and 8). Among the catalysts probed, **17** proved to be the best. In this case, 96% yield of **3a** with 92% *ee* was achieved within 10 hours (entry 9). In addition to the catalysts, solvents were also critical to the enantioselectivity of the reaction. In general, nonpolar solvents such as toluene, TME, and THF led to low *ee* values (entries 10–12), whereas slightly improved ones were observed with polar solvents such as EtOAc, CH_3CN, DMSO, and MeOH (entries 13–15 and 18). The chlorinated solvents CH_2Cl_2 and $CHCl_3$ were a good choice for the reaction (entries 16 and 17). Acidic or basic additives were detrimental (entries 19–22). Finally, no benefit was gained when the reaction was conducted at a decreased temperature (entry 23).

With the optimized reaction conditions in hand for this **17**-catalyzed Diels–Alder reaction, we probed the reaction scope (Table 2). The results reveal that the process can be applied to both substrates with a broad generality. Uniformly high yields (81–95%) and high *ee* values (90–94%) are obtained for all cases studied. Investigation of the scope by probing **2** indicates that the electronic effect is very limited. The aromatic ring bearing electron-neutral (entries 1 and 9), electron-donating (entries 2–4, 8, and 13), and electron-withdrawing (entries 5–7, 10–12, and 14–19) groups with different substitution patterns are well tolerated and lead to the structurally diverse compounds **3**. With respect to **1**, significant structural variations were explored. It appears that

Table 2: Scope of the **17**-catalyzed Diels–Alder reactions.[a]



Entry	R^1, R^2	R^3, R^4	**3**	Yield [%][b]	*ee* [%][c]
1	Me, H	H, H	**3a**	95	94
2	Me, H	Me, H	**3b**	97	92
3	Me, H	H, Me	**3c**	93	90
4	Me, H	MeO, H	**3d**	89	94
5	Me, H	Br, H	**3e**	97	90
6	Me, H	H, Br	**3f**	94	93
7	Me, H	H, NO_2	**3g**	92	91
8	H, H	MeO, H	**3h**	85	92
9	Ph, H	H, H	**3i**	91	94
10	Ph, H	Br, H	**3j**	89	92
11	3-MeC_6H_4, H	Br, H	**3k**	93	92
12	4-MeC_6H_4, H	Br, H	**3l**	91	90
13	4-FC_6H_4, H	Me, H	**3m**	87	92
14	3-BrC_6H_4, H	Br, H	**3n**	83	92
15	3,4-$Cl_2C_6H_3$, H	Br, H	**3o**	88	94
16[d]	H, Me	Br, H	**3p**	81	90
17[e]	H, Me	H, NO_2	**3q**	91	92
18[f]	H, Et	H, NO_2	**3r**	89	90
19[g]	H, Pr	H, NO_2	**3s**	90	94

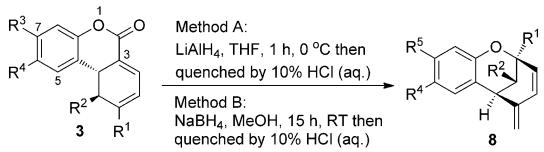
[a] Reaction conditions: unless specified otherwise, see the Experimental Section. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] 15 h, 15:1 d.r. (determined by ^{1}H NMR of crude reaction mixture). [e] 15 h, 14:1 d.r. [f] 15 h, 21:1 d.r. [g] 15 h, 13:1 d.r.

in addition to **1a** (entries 1–7), linear aldehydes (entries 8 and 16–19) and branched β, β′-disubstituted aldehydes (entries 9–15) can serve as effective dienes in the Diels–Alder reactions. In the case of linear enals (entries 16–19), two new stereogenetic centers are formed with high enantio- and diastereoselectivity.

The absolute configuration of **3l** was determined by X-ray crystallographic analysis (see Figure S1 in the Supporting Information).[11] The relative stereochemistry of **3q**, having a *trans* geometry, was determined by an NOE experiment (see Figure S2). The proposed configuration in **5** originates from *Re*-face attack of the dienamine **4** by **2** in an *exo* manner (Scheme 1). This attack occurs because the *Si* face is blocked by the bulky side chain of the catalyst and the interaction between the nitrogen atom of the catalyst and the carboxylic acid moiety in **2** dictates an *exo* addition of the dienophile.[9f] Furthermore, the steric hindrance between the bulky side chain of the catalyst and the lactone moiety in **5** leads to the *cis* configuration of the catalyst and the carboxylic acid. This geometry enables the facile decarboxylation to release the catalyst and the products **3** with the observed configuration. In addition, the carboxylic acid enhances the reactivity of the coumarins **3** as dienophiles. Indeed, without it, no desired Diels–Alder adduct was observed between coumarin and **1a** under identical reaction conditions. In a control study, the carboxylic acid was masked as an ethyl ester, and the Diels–Alder reaction with **1a** in the presence of 100 mol% of **17** occurred, but afforded a catalyst entrapped product in 53% yield based on ^{1}H NMR analysis. However, the product was decomposed on silica gel during purification to give the coumarin-3-carboxylate ethyl ester starting material through a retro-Diels–Alder process.

With **3** in hand, we investigated their transformation into the bridged tricyclic benzopyrans **8** (Scheme 1). As mentioned above, acid-triggered cyclization of phenols with alkenes has been studied in the synthesis of the scaffold.[5] Inspired by the studies, we conceived a possibility of a new cyclization between a phenol and a diene in the presence of an acid (Scheme 1). The required precursor diol **6a** could be obtained by the reduction of the corresponding lactone **3a** (Table 3, entry 1). Surprisingly, after the reduction by $LiAlH_4$,

Table 3: Formation of **8** by one-pot reduction/acid-catalyzed cyclization of **3**.[a]



Entry	R^1, R^2, R^3, R^4, R^5	**3**	**8**	Method	Yield [%][b]	d.r. [%][c]
1	Me, H, H, H, H, H	**3a**	**8a**	A	86	>20:1
2	Me, H, Me, H, Me	**3b**	**8b**	A	91	>20:1
3	Me, H, H, Me, H	**3c**	**8c**	A	93	>20:1
4	Me, H, MeO, H, MeO	**3d**	**8d**	A	87	>20:1[d]
5	Me, H, H, Br, H	**3f**	**8e**	A	85	5.5:1
6	H, H, MeO, H, MeO	**3h**	**8f**	A	84	>20:1
7	Ph, H, Br, H, H	**3j**	**8g**	A	89	>20:1
8	3-MeC_6H_4, H, Br, H, H	**3k**	**8h**	A	87	>20:1
9	H, Me, Br, H, H	**3p**	**8i**	A	83	12:1
10	H, Me, Br, H, Br	**3p**	**8j**	B	75	>20:1

[a] Reaction conditions: unless specified otherwise, see the Experimental Section. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC using a chiral stationary phase with 91% *ee* (see the Supporting Information for HPLC conditions).

the chiral bridged tricyclic benzopyran **8a** was obtained directly after workup with 10% HCl aqueous solution without requiring an additional acid treatment. Moreover, the unexpected one-pot procedure proceeded smoothly in 86% yield and with excellent diastereoselectivity (>20:1 d.r.). We also extended the protocol to other substrates (entries 2–9). In general, high yields (83–93%) and good to excellent d.r. values (5.5:1–>20:1) were achieved with the representative structurally diverse molecules **3**. Furthermore, the enantioselectivity was largely maintained in the two-step transformations, as demonstrated in the case of **8d** with 91% *ee* (entry 4). The absolute configuration was confirmed by X-ray crystallographic analysis of a single crystal of **8e** (see Figure S3).[12] It is noteworthy that unexpectedly, the debromination concurred with substrates bearing the bromo atom at position 7 (e.g., R^3, entries 7–9), while a Br at the 6-position is not affected (entry 5). The use of the milder $NaBH_4$ could overcome this problem (entry 10). Moreover, the synthetic utility of the reaction products is also demonstrated by photo-

oxidation of **3a** to give the conjugated 6*H*-dibenzo[*b*,*d*]pyran-6-one product in 83% yield in the presence of air (O_2) and the photosensitizer rose bengal [see Eq. (S1)]. The structure is widely featured in numerous natural products such as fasciculiferol,[13] alternariol,[14] and autumnariol and autumnariniol.[15] Furthermore, the the Diels–Alder product **3q** can also be oxidized by *m*CPBA to produce an epoxide [see Eq. (S2)].

In conclusion, we have developed a two-step route for the assembly of chiral bridged tricyclic benzopyrans, a core unit featured in a number of natural products. A novel amine-catalyzed decarboxylative enantioselective Diels–Alder reaction between aldehydes and readily available coumarin-3-carboxylic acids, as dienophiles, has been implemented to construct the chiral precursors. The decarboxylation facilitates the release of the catalyst and achieves high reaction efficiency in terms of reaction time, yield and enantio- and diastereoselectivity. The Diels–Alder adducts are smoothly transformed into the targets by a novel but unexpected one-pot protocol using a $LiAlH_4$- or $NaBH_4$-mediated reduction and subsequent acid-catalyzed stereoselective cyclization. We anticipate that the two new synthetic strategies hold great potential in the exploration of novel organic transformations. The application of the chiral bridged tricyclic benzopyran core in the synthesis of natural products and biologically relevant molecules is also under investigation.

Experimental Section

General procedure for the Diels–Alder reactions: **1** (0.1 mmol) was added to a mixture of coumarin-3-carboxylic acid **2** (0.12 mmol) and the catalyst **17** (9.4 mg, 0.02 mmol) in 0.2 mL of $CHCl_3$. The reaction was stirred at room temperature until **1** was consumed completely (7 h). The mixture was placed on a silica gel column directly and hexane and ethyl acetate (20:1) to give the pure product **3**. The purified compound was used for characterization and chiral HPLC analysis.

General procedure for the reduction-cyclization. Method A: A solution of **3** (0.30 mmol) in 0.5 mL of THF was injected into the mixture of $LiAlH_4$ (23 mg, 0.60 mmol) in 5 mL of THF at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and then quenched with 10% HCl solution. The mixture was stirred until the reduced product was consumed completely as monitored by TLC. The product was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with sodium sulfate and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography, eluting with hexane and ethyl acetate (40:1) to give the pure product **8**. The purified compound was used for characterization.

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