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Model studies on construction of the oxabicyclic [3.3.1] core of the mulberry Diels–Alder adducts morusalbanol A and 441772-64-1

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ABSTRACT

Preparation of the oxabicyclic [3.3.1] cores of morusalbanol A and 441772-64-1 was achieved via the intramolecular cyclization of *cis–trans* (*endo*) mulberry Diels–Alder adducts. The latter were derived from a hydrogen bond-assisted regioselective Diels–Alder reaction between a chalcone dienophile and a dehydroprenyl diene. Results from these studies provide important insights into the syntheses of morusalbanol A and related mulberry Diels–Alder adducts.

Introduction

Morusalbanol A is a mulberry Diels–Alder adduct isolated from the bark of *Morus alba*, which exhibits interesting neuroprotective activity.[1] The structure of morusalbanol A is characterized by an oxabicyclic [3.3.1] core which is derived from the intramolecular cyclization of a *cis–trans* (*endo*) mulberry Diels–Alder adduct. Morusalbanol A shows evidence of atropisomerism due to the rotational hindrance of the D/E-rings about the C5-C15 and C4-C8-C9 bonds (Fig. 1).[1] Additional examples of other natural products in this class are cathayanon E,[2] wittiorumin F,[3] and 441772-64-1 (CAS Registry Number) (Fig. 1).[4]

In continuation of our interest in the syntheses of mulberry Diels–Alder adducts, we wanted to develop a viable procedure for the synthesis of morusalbanol A and 441772-64-1. Nonetheless, an important issue needed to be addressed during the planning of the synthesis of these compounds: the formation of the requisite *cis–trans* (*endo*) Diels–Alder precursor. Our approach hinged on the hydrogen bond-assisted regioselective Diels–Alder reaction between chalcone dienophile **I** and dehydroprenyl diene **II** (Scheme 1), which would result in the formation of *cis-trans* (*endo*) and *trans–trans* (*exo*) Diels–Alder adducts in one step. Adducts having the *cis–trans* stereochemistry on the cyclohexene ring would be derived from an *endo* transition state, while the *trans–trans* stereochemistry would be obtained from the *exo* transition state. The feasibility of such a [4+2] cycloaddition reaction has recently been demonstrated by Porco and co-workers,[5,6] Rizzacasa and co-workers,[7,8] and our group.[9] It was envisaged that the *ortho* and *para* hydroxyl groups on the aryl ring of diene **II** could be selectively protected due to their relative positions to the carbonyl group. Subsequent intramolecular cyclization of the *cis–trans* (*endo*) adducts **III** and **IV** would then produce morusalbanol A and 441772-64-1, respectively.

Results and discussion

Prior to embarking on the total synthesis of morusalbanol A and 441772-64-1, we examined the [4+2] cycloaddition reaction using model dienes **1a**,**b** and dienophiles **2a**,**b** (Table 1). We anticipated that deprotection of the *para* hydroxyl group would enable *cis–trans* (*endo*) Diels–Alder adduct **3a** to undergo intramolecular cyclization to produce the oxabicyclic [3.3.1] skeleton found in 441772-64-1, while the *para* methyl ether protected, *cis–trans* (*endo*) Diels–Alder adduct **3b** would undergo bond rotation and

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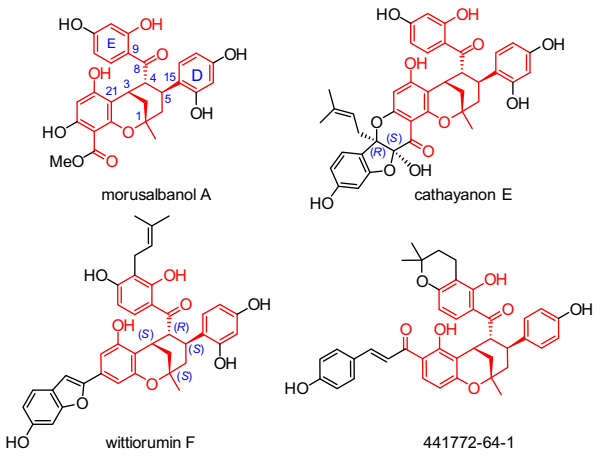
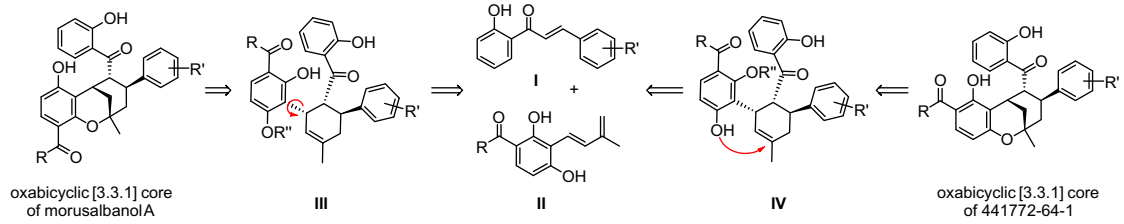


Figure 1. Morusalbanol A and related mulberry Diels–Alder adducts.

subsequent cyclization to produce the oxabicyclic [3.3.1] skeleton found in morusalbanol A.

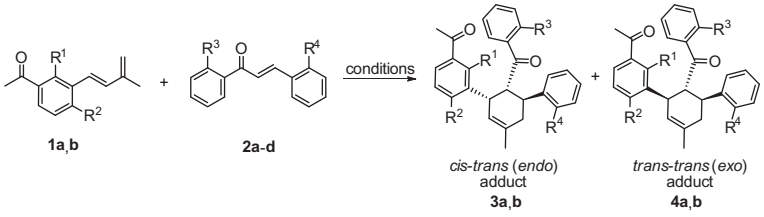
The preparation of diene **1a** is outlined in Scheme 2. Regioselective iodination of commercially available 2′,4′-dihydroxyacetophenone **5** with I_2/KIO_3 in EtOH/H_2O utilizing the method of Yu[10] gave iodobenzene **6** in high yields. Selective protection of the *para* OH group in **6** with an ethoxymethoxy (EOM) group, followed by methylation of the remaining *ortho* OH group with dimethyl sulfate gave iodide **7**. Heck coupling of **7** with 2-methylbut-3-en-2-ol and subsequent dehydration using AcCl/pyridine provided the desired diene **1a** in 81% yield (two steps).[11] The synthesis of diene **1b** from iodide **6** was achieved by selective methyl ether protection of the *para* OH group which smoothly gave acetophenone **7a** in 85% yield (Scheme 2). Subsequent Heck coupling and dehydration of **7a** gave diene **1b** in 77% yield (two steps). The required chalcone dienophiles **2a–d** were prepared from the corresponding acetophenones and benzaldehydes via the Claisen–Schmidt condensation (see ESI).

The thermal Diels–Alder reaction of diene **1a** with chalcone dienophile **2a** in toluene at 150 °C for 24 h afforded an inseparable mixture of *cis–trans* (*endo*) and *trans–trans* (*exo*) adducts **3a** and **4a** in a 3:2 ratio and 55% yield (Table 1, entry 1). The same reaction between diene **1b** and dienophile **2b** also gave the desired cycloadducts in 49% yield as an inseparable 1:1 mixture of *endo*/*exo* diastereomers (**3b** and **4b**, Table 1, entry 2). Following Rizzacasa and co-workers' report of the substantial rate enhancement for the Diels–Alder reaction for a hydrogen-bonded *ortho* OH substituent on a chalcone dienophile,[8] we also examined the thermal Diels–Alder reaction of diene **1a** with dienophiles **2c** and **2d**, both of which lacked an *ortho* OH substituent. As expected, all attempts to perform the thermal Diels–Alder reaction between diene **1a** and dienophiles **2c** or **2d** failed to yield the desired products (Table 1, entries 3 and 4). In each case, the dienophile was recovered, although the diene decomposed. This clearly indicated that the presence of an *ortho* OH substituent on the dienophile was essential for the Diels–Alder reactivity.



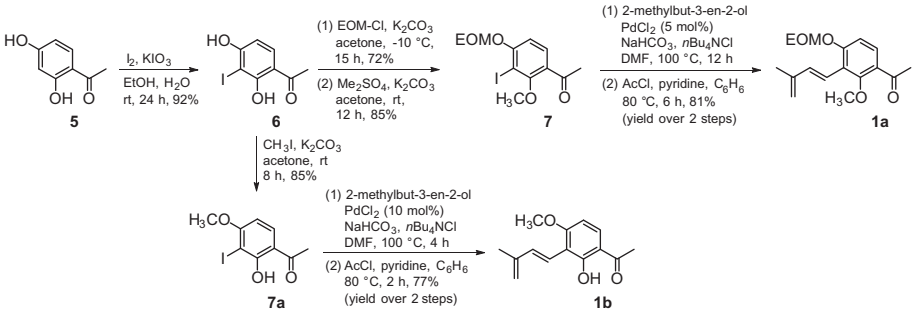
Scheme 1. Retrosynthetic analysis for morusalbanol A and 441772-64-1.

Table 1
Development of initial methodology employing a model diene and dienophile

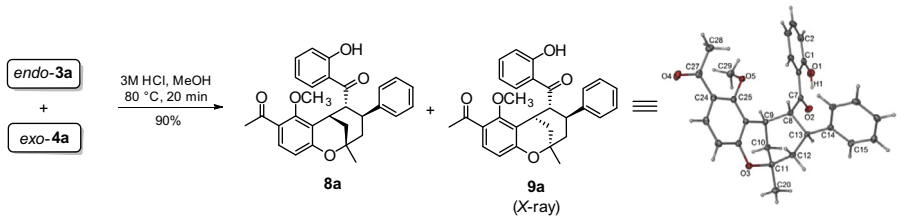


Entry		Diene			Dienophile		Conditions[a]	Yield[b]	*endo*/*exo*[c]
		R^1	R^2		R^3	R^4			
1	**1a**	OCH_3	OEOM	**2a**	OH	H	Thermal	55%	3/2
2	**1b**	OH	OCH_3	**2b**	OH	OEOM	Thermal	49%	1/1
3	**1a**	OCH_3	OEOM	**2c**	H	H	Thermal	—	—
4	**1a**	OCH_3	OEOM	**2d**	OCH_3	H	Thermal	—	—
5	**1a**	OCH_3	OEOM	**2a**	OH	H	AgOTf	38%	0/1
6	**1a**	OCH_3	OEOM	**2a**	OH	H	$AgBF_4$	20%	0/1

[a] Thermal reaction conditions: toluene (2 mL/mmol), 150 °C, 24 h, pressure tube. Catalytic conditions: CH_2Cl_2 (4 mL/mmol), rt, 1 h. Molar ratio of diene/dienophile/catalyst = 1.1/1/0.3.
[b] Isolated yield.
[c] *endo*/*exo* ratios based on ^1H NMR.



Scheme 2. Synthesis of model dienes **1a** and **1b**.



Scheme 3. Acid catalyzed intramolecular cyclization of *endo*-**3a** and *exo*-**4a**.

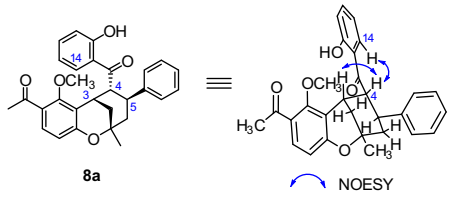


Figure 2. Key NOESY correlations leading to relative stereochemistry assignment of **8a**, the oxabicyclic [3.3.1] core of 441772-64-1.

Interestingly, the use of silver catalysts (AgOTf and $AgBF_4$) for the Diels–Alder reaction between diene **1a** and dienophile **2a** promoted the selective formation of *exo*-**4a**, albeit in low yields (Table 1, entries 5 and 6). The use of other Lewis acids such as $AlBr_3$, $FeCl_3$, $Ga(OTf)_3$, $TiCl_4$, and $BF_3{\cdot}Et_2O$ did not give any of the desired product. In these cases, both the diene and dienophile decomposed.

Cyclization to form the desired oxabicyclic ring was achieved by heating a solution of *endo*-**3a** and *exo*-**4a** in 3 M aqueous HCl in MeOH for 20 min. Deprotection of the EOM group and subsequent intramolecular cyclization occurred to give the desired oxabicyclic [3.3.1] compounds in 90% combined yield as a 3:2 mixture of separable diastereomers (**8a** and **9a**, Scheme 3). Diastereomer **8a** represents the core skeleton of the natural product 441772-64-1.

The stereochemistry of each of the oxabicyclic diastereomers was confirmed by ^1H NMR and NOESY experiments. The diastereomer **8a**, which was derived from *endo*-**3a** showed a large coupling constant (J = 11.6 Hz) from the splitting between H4 and H5. This clearly indicated the *trans*-diaxial arrangement of H4 and H5 in diastereomer **8a**. The small coupling constant (J = 3.0 Hz) between H3 and H4 implied a *cis*-orientation with H3 being in an equatorial position. NOESY correlations between the aromatic protons H14 and H4 on the cyclohexane ring and between H3 and H4 also indicated a *cis* arrangement (Fig. 2).

The structure and stereochemistry of diastereomer **9a** were confirmed by single crystal X-ray crystallography.[12] The formation of oxabicyclo[3.3.1] **9a** from its *trans–trans* Diels–Alder precursor *exo*-**4a** was rather surprising. Natural products containing similar oxabicyclic core structures including morusalbanol A, wittiorumin F, and cathayanon E were all exclusively derived from their *cis–trans* (*endo*) Diels–Alder precursors.[1–3] Yu and co-workers hypothesized that the *trans–trans* (*exo*) Diels–Alder adducts did not meet the spatial requirement to form an oxabicyclic compound.[2,3] They demonstrated that the treatment of a *cis–trans* (*endo*) Diels–Alder adduct, chalcomoracin in 5% triflic acid/MeOH afforded a mixture of oxabicyclic and ketalized products (wittiorumin F and mulberrofuran F, Fig. 3).[3] However, subjecting the *trans–trans* (*exo*) Diels–Alder adduct, mulberrofuran J (not shown) to similar reaction conditions, did not yield any oxabicyclic or ketalized product.[3]

Next, we examined the intramolecular cyclization of *endo*-**3b** and *exo*-**4b** (Scheme 4). When a solution of *endo*-**3b** and *exo*-**4b** in 3M aqueous HCl in MeOH was heated for 20 min, a new oxabicyclic compound **10** was obtained in 92% yield (based on *endo*-**3b**) along with the recovery of *exo*-**4b** (EOM group was cleaved).

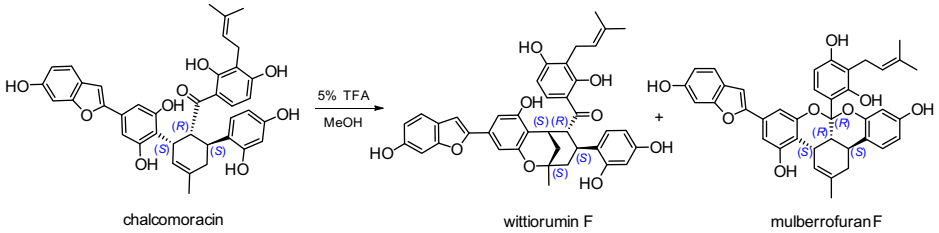
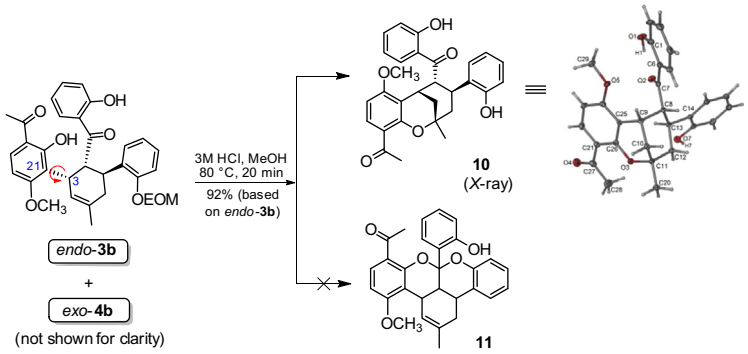


Figure 3. Semisynthesis of wittiorumin F and mulberrofuran F from chalcomoracin C.[3]



Scheme 4. Formation of diastereomer **10**, the oxabicyclic [3.3.1] core of morusalbanol A.

Following Yu and co-workers' observations regarding the semisynthesis of wittiorumin F and mulberrofuran F (Fig. 3), we thought that, due to the *para* methyl ether protecting group, *endo*-**3b** and *exo*-**4b** might undergo intramolecular cyclization to produce a ketalized compound rather than the desired oxabicyclic compound. However, the ^{1}H NMR spectrum of compound **10** was found to be similar to that of **8a** and the ^{13}C NMR spectrum of compound **10** did not appear to correspond to ketalized compound **11**. Instead, the ^{13}C NMR spectrum showed signals for an oxygenated sp^{3} quaternary carbon (δ_c 76.1 ppm) and two carbonyls (δ_c 199.9 and 206.0 ppm). The relative configuration of **10** was determined by HMBC and NOESY correlations. Single-crystal X-ray structure determination confirmed the assignment as compound **10**.[12] Interestingly, subjecting the recovered *exo*-**4b** (without the EOM group) to similar reaction conditions did not yield any product.

The formation of **10** from *endo*-**3b** was unusual. Natural products containing similar cyclohexenyl core structures including kuwanon I,[13] mulberrofuran J,[14] and dorsterone[15] showed restricted rotation about the C3–C21 bond (as shown in Scheme 4) due to the unsymmetrical nature of the aryl ring. Most of the signals in the ^{1}H NMR spectrum of these natural products were either broadened or doubled at room temperature as a result of atropisomerism due to the high rotation barrier. However, in the case of *endo*-**3b**, the barrier for rotation about the C3–C21 bond was negligible, allowing a 180° rotation followed by intramolecular cyclization to form the respective oxabicyclic [3.3.1] core of morusalbanol A.

Conclusion

In conclusion, model studies described in this Letter represent a useful approach toward the synthesis of the oxabicyclic [3.3.1] core system found in morusalbanol A and related mulberry Diels–Alder adducts. In particular, the required *cis–trans* (*endo*) Diels–Alder precursors of morusalbanol A and 441772-64-1 were obtained via the thermal cycloaddition reaction which was proven to be dependent on the presence of a hydrogen-bonded *ortho* OH substituent on the chalcone dienophile. Acid catalyzed intramolecular cyclization of a *cis–trans* (*endo*) Diels–Alder adduct (*endo*-**3a**) afforded the desired oxabicyclic [3.3.1] core of 441772-64-1 in a stereocontrolled manner. Additionally, rotation about the C3–C21 bond of a *para* methyl ether protected, *cis–trans* (*endo*) Diels–Alder adduct (*endo*-**3b**) was observed during acid catalyzed intramolecular cyclization to form the respective oxabicyclic [3.3.1] core of morusalbanol A. Together, the results from this studies provide important insights into the syntheses of morusalbanol A and related mulberry Diels–Alder adducts. Efforts toward the total synthesis of these natural products are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.042.

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