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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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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 E², wittiorumin F³, 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 dehvdroprenyl diene II (Scheme 1), which would result in the formation

* Corresponding author. E-mail address: cheechinfei@um.edu.my (C.F. Chee). 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 cistrans (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

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.

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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 I₂/KIO₃ in EtOH/H₂O utilizing the method of Yu¹⁰ 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% vield 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 |
|-------|----|------------------|------------------|----|------------------|----------------|-------------------------|--------------------|-----------------------|
| | | \mathbb{R}^1 | R ² | | R ³ | R ⁴ | | | |
| 1 | 1a | OCH ₃ | OEOM | 2a | ОН | Н | Thermal | 55% | 3/2 |
| 2 | 1b | OH | OCH ₃ | 2b | OH | OEOM | Thermal | 49% | 1/1 |
| 3 | 1a | OCH ₃ | OEOM | 2c | Н | Н | Thermal | _ | - |
| 4 | 1a | OCH ₃ | OEOM | 2d | OCH ₃ | Н | Thermal | _ | - |
| 5 | 1a | OCH ₃ | OEOM | 2a | OH | Н | AgOTf | 38% | 0/1 |
| 6 | 1a | OCH ₃ | OEOM | 2a | OH | Н | AgBF ₄ | 20% | 0/1 |

^a Thermal reaction conditions: toluene (2 mL/mmol), 150 °C, 24 h, pressure tube. Catalytic conditions: CH₂Cl₂ (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 AgBF₄) 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 AlBr₃, FeCl₃, Ga(OTf)₃, TiCl₄, and BF₃·Et₂O 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 ¹H NMR spectrum of compound **10** was found to be similar to that of **8a** and the ¹³C NMR spectrum of compound **10** did not appear to correspond to ketalized compound **11**. Instead, the ¹³C NMR spectrum showed signals for an oxygenated sp³ 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 dorsterone¹⁵ 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 ¹H 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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