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Biomimetic Dehydrogenative Diels-Alder Cycloadditions: Total Syntheses of Brosimones A and B**

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Abstract

Passing (H₂) Gas—Concise syntheses of the natural products brosimones A and B using sequential dehydrogenative Diels-Alder (DHDA) cycloadditions are reported. The syntheses employ either Pt/C-cyclopentene or DDQ to effect dehydrogenation of prenylchalcone substrates in combination with silver nanoparticles (AgNP's) to promote subsequent Diels-Alder cycloadditions.

Keywords

dehydrogenative cycloaddition; Diels-Alder; nanoparticle catalyst; brosimone

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Nature creates an intriguing array of molecular architectures which has attracted extensive investigations on natural product identification, origin, biological activities, and chemical synthesis.^[1] In particular, biosynthetic studies have inspired elegant biomimetic total synthesis of natural products.^[2] Herein, we report biomimetic syntheses of the natural products brosimones A and B featuring multicatalytic,^[3] dehydrogenative Diels-Alder (DHDA) cycloadditions^[4] of 2'-hydroxychalcones.

Prenylflavonoid Diels-Alder natural products,^[5] mainly isolated from the root bark of mulberry trees (*Morus alba*), are biosynthetically derived from electron-rich 2'-hydroxychalcone dienophiles and flavonoid dienes. Pioneering studies by Nomura and coworkers have determined that the requisite diene subunits arise from prenyl groups in nature. In one key experiment,^[6] the natural product artonin I (**1**) was isolated from *Morus alba* cell extract after both prenylated flavone **2** and chalcone **3** were fed to cell culture (Figure 1).

As part of our continuing interest^[7] in the total synthesis of prenylflavonoid Diels-Alder and related natural products,^[8] we have recently reported silica-supported silver nanoparticles (AgNP's)^[9] as a highly efficient catalyst for [4+2] cycloadditions of 2'-hydroxychalcones. Inspired by the aforementioned biosynthesis studies, further investigation was directed to the development of catalysts that enable biomimetic, DHDA cycloadditions employing prenyl groups as diene precursors. In this regard, we envisioned tandem reactions that employ one catalyst system to promote dehydrogenation of prenyl groups to 1,3-substituted dienes^[10] in combination with silica-supported AgNP's to catalyze Diels-Alder cycloadditions of chalcone dienophiles and *in situ*-generated dienes.

Brosimones A (**4**)^[11] and B (**5**)^[12] were both isolated from the plant *Brosimopsis oblongifolia* in Brazil and feature dimeric structures derived from prenyl chalcone **7** (Figure 2). The intriguing biosynthetic relationship and structures of the brosimones, in particular the [3.3]metacyclopheane core^[13] of **4**, underscores the compounds as attractive targets for development of DHDA cycloadditions.

Our initial studies began with model reactions using prenyl chalcone **8**. After screening a number of catalysts and oxidants,^[14] we observed that the desired dehydrogenative cycloaddition was catalyzed by a mixture of platinum on activated carbon (Pt/C)^[15] and silica-supported AgNP's in an ambient air atmosphere (Table 1, entry 1) which afforded cycloadducts *exo*-**9** and *endo*-**10** in 52% combined yield. We also examined hydrogen scavengers for transfer dehydrogenation including cyclopentene^[16] (entry 3) and norbornene^[17] (entry 6). Use of cyclopentene afforded the best yield and mass balance and was chosen as the optimal hydrogen scavenger. Control experiments showed that reactions with cyclopentene did not proceed without Pt/C (entry 4) and were significantly less efficient in the absence of AgNP's (entry 5). The use of AgNP catalyst also promotes enhanced formation of the desired *exo* diastereomer **9** (*cf.* entries 3 and 5), which may be explained by conversion of *endo*-**10** to *exo*-**9** under AgNP-catalyzed conditions.^[14] Use of Lewis acids including BF₃·Et₂O and AgOTf in place of the AgNP's afforded minimal dehydrogenative cycloaddition products.^[14]

With a model reaction established, DHDA cycloaddition/dimerization of **11** using the optimized Pt/C-AgNP conditions with cyclopentene as H₂ scavenger afforded the cycloadducts *exo*-**12** and *endo*-**13** (1.2:1) in 64 % yield.^[14] Transfer hydrogenolysis of *exo*-**12** was accomplished employing 1,4-cyclohexadiene as hydrogen donor to afford brosimone B (**5**) with the trisubstituted olefin remaining intact (Scheme 1).^[18] Use of ammonium formate^[19] as additive was found to further accelerate the hydrogenolysis. Spectral data for synthetic brosimone B were in agreement with those reported by Messina

and coworkers for the natural product.^[12] Methylation of **5** afforded protected derivative **14**, the structure of which was determined by X-ray crystal structure analysis.^[20]

We next studied dehydrogenative cycloaddition of *exo*-**12** to access brosimone A (**4**) (Scheme 2). Treatment of *exo*-**12** with catalytic Pt/C and AgNP's in combination with cyclopentene as H₂ scavenger did not lead to substantial formation of desired cycloadducts even at temperatures up to 130 °C. After screening a series of reaction parameters, we found that in the presence of excess 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)^[4f, 21] and AgNP's as catalyst, *exo*-**12** was converted to the cycloadduct *exo-endo*-**15**^[22] in 17% yield using chlorobenzene as solvent at 90 °C. In addition, DDQ adduct **16** was isolated in 34% yield, which further supported the intermediacy of diene **17**.^[23] In a similar fashion, treatment of prenylchalcone **11** with DDQ in the absence of AgNP's afforded DHDA adduct **18** in 55% yield and 5:1 d.r., with no *exo*-**12** or *endo*-**13** observed (Scheme 3, major *endo* diastereomer shown). The structure and stereochemistry of **18** were confirmed by X-ray crystallography.^[20]

Further experiments revealed that increasing the reaction temperature (130 °C) for DHDA of *exo*-**12** in the presence of AgNP's predominantly afforded *exo-exo*-cycloadduct **19** in 62% yield (Scheme 2). Replacement of AgNP's with Lewis acids led to inferior results. Substantial decomposition occurred with BF₃·Et₂O, Cu(OTf)₂,^[24] or In(OTf)₃^[25] as Lewis acids; a 7% yield of **19** was obtained using AgOTf (20 mol%) as catalyst. Cycloadduct **19** was not observed in a control experiment with silica gel at 130 °C demonstrating the utility of AgNP's to access brosimone A derivative **19**.^[14] Further studies showed that DDQ adduct **16** could be converted to *exo-exo*-**19** in 84% yield under AgNP-catalyzed conditions, which suggested tandem retro-Diels-Alder/Diels-Alder processes^[8a] consistent with temperature-dependent stereoselectivity affording *exo-endo*-**15** (kinetically favored product) and *exo-exo*-**19** (thermodynamically favored product). Moreover, *exo-endo*-**15** was converted exclusively to *exo-exo*-**19** under AgNP-promoted conditions at 130 °C. A control experiment without AgNP's also showed trace conversion of **15** to **19** reinforcing the fact that AgNP's may facilitate tandem retro-Diels-Alder/Diels-Alder processes.

Final hydrogenolysis of *exo-exo*-**19** afforded brosimone A (**4**) in 91% yield (Scheme 4). Methylation of **4** afforded hexamethylether **20** which allowed unambiguous structure and stereochemical assignments for synthetic brosimone A (**4**) based on X-ray crystallography.^[20] The X-ray structure of **20** revealed a C₂-symmetric *syn*-[3,3]metacyclopentane^[26] structure with slightly distorted aromatic rings^[13] ($\phi_{C_a-C_b-C_c-C_d}=6.4^\circ$).

Our previous studies provided strong evidence for an electron transfer mechanism for AgNP-catalyzed Diels-Alder cycloadditions.^[9a] A simplified computational model of AgNP-catalyzed cycloadditions was constructed using corresponding diene of substrate **14** which was found to have similar reactivity to hexabenzylether **12** (Scheme 5).^[14] Density functional theory was used to predict the energetics of cycloaddition by different mechanisms. The lowest barriers were observed for a process that involved one electron substrate oxidation, deprotonation of the phenol, and complexation of the resultant radical with Ag(I) on the surface of the AgNP's.^[27] Figure 3 shows the energetics of stepwise intramolecular cycloadditions^[28] to yield observed cycloadducts. Our predicted reaction energetics and calculated transition states^[14] support the observation that the *exo-endo-syn* stereoisomer (*cf.* *exo-endo*-**15**, Scheme 2) is the kinetic product which may be converted to the more thermodynamically stable *exo-exo-syn* diastereomer (*cf.* *exo-exo*-**19**, Scheme 2) through cycloreversion. Pathways to *exo-exo-anti* and *exo-endo-anti* products (Scheme 5), which were not observed experimentally lie at higher energy.^[14]

In summary, we have developed biomimetic, dehydrogenative Diels-Alder cycloadditions which have enabled concise syntheses of the natural product brosimone B and the [3.3]metacyclophane natural product brosimone A. The syntheses employ Pt/C-cyclopentene or DDQ to effect dehydrogenation of prenylchalcones in combination with silver nanoparticles to promote subsequent Diels-Alder cycloaddition. Experiments confirmed the formation of a kinetic *exo-endo* diastereomer of a protected form of brosimone A which could be converted to a thermodynamic *exo-exo* isomer using AgNP's at higher temperature. Density functional theory was used to predict the energetics of AgNP-catalyzed cycloadditions; the lowest barriers were observed for a process involving one electron oxidation, phenol deprotonation, and complexation of the resultant radical with Ag(I) on the surface of the AgNP. Further applications of dehydrogenative Diels-Alder cycloadditions and reaction development using silver nanoparticles are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Proposed biosynthesis of artonin I (**1**).

Figure 2.
Biomimetic synthetic design for brosimones A and B.

Figure 3.
B3LYP/LANL2DZ energetics of AgNP-catalyzed cycloadditions.

Scheme 1.

Synthesis of brosimone B. a) Pt/C (10 mol%), AgNP (0.2 mol%), cyclopentene, DCE, 110 °C, 48 h, 64%, *endo*-**13**: *exo*-**12** = 1: 1.2; b) Pd/C (40 mol%), HCO₂NH₄ (2 equiv), 1,4-cyclohexadiene, acetone, 40 °C, 24 h, 85%; c) K₂CO₃, Me₂SO₄, acetone, 40 °C, 4 h, 15%.

Scheme 2.

Dehydrogenative cycloadditions to access cycloadducts *exo-endo-15*, *16*, and *exo-exo-19*. a) DDQ (1.6 equiv), AgNP (0.3 mol%), PhCl, 90 °C, 48 h, *exo-endo-15*, 17%, *16*, 34%; b) DDQ (1.5 equiv), AgNP (0.3 mol%), PhCl, 130 °C, 72 h, 62%, d.r. > 20: 1; c) AgNP (0.3 mol%), PhCl, 130 °C, 48 h, 95%; d) AgNP (0.4 mol%), PhCl, 130 °C, 48 h, 84%.

Scheme 3.

DDQ-derived cycloadduct formation. a) DDQ (2.1 equiv), DCE, 90 °C, 24 h, 55%, d.r. = 5:1.

Scheme 4.

Synthesis of brosimone A. a) Pd/C (60 mol%), HCO₂NH₄ (2 equiv), HCO₂H, 1,4-cyclohexadiene, acetone, 40 °C, 24 h, 91%; b) K₂CO₃, MeI, acetone, 40 °C, 12 h, 13%.

Scheme 5.

Model reactions for calculations. a) DDQ (1.5 equiv), AgNP (0.2 mol%), PhCl, 130 °C, 72 h, 72%; b) DDQ (1.5 equiv), AgNP (0.2 mol%), PhCl, 90 °C, 48 h, 15%; c) AgNP (0.2 mol %), PhCl, 130 °C, 48 h, 94%.

Table 1Initial methodology development employing a model prenylchalcone.^[a]

entry	hydrogen scavenger	conv. ^[b]	<i>endo</i> - 10 / <i>exo</i> - 9 ^[b]
1	air (1 atm.)	88% (52%) ^[c]	52:48
2 ^[d]	O ₂ (1 atm.)	79% (60%) ^[c]	57:43
3	cyclopentene (9 equiv)	66% (61%) ^[c]	42:58
4 ^[e]	cyclopentene (9 equiv)	<10%	-
5 ^[f]	cyclopentene (9 equiv)	38% (8%) ^[c]	72:28
6	norbornene (10 equiv)	76% (44%) ^[c]	50:50
7	none	40% (18%) ^[c]	55:45

^[a] See Supporting Information for experimental details.^[b] Based on ¹H NMR integration.^[c] Isolated yield shown in parentheses.^[d] 5 mol% Pt/C, 0.1 mol% AgNP.^[e] In the absence of Pt/C.^[f] In the absence of AgNP's.