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Total Synthesis of (±)-Sorocenol B Employing Nanoparticle Catalysis

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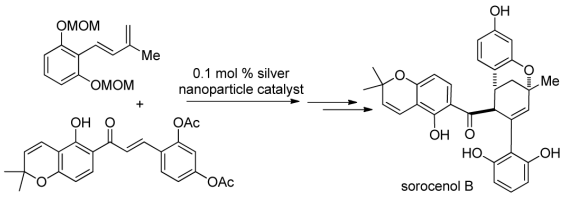
Abstract



The total synthesis of (±)-sorocenol B has been accomplished featuring key steps including silver nanoparticle (AgNP)-catalyzed Diels-Alder cycloaddition and late-stage Pd(II)-catalyzed oxidative cyclization. The synthetic natural product exhibited low micromolar cytotoxic activity against a number of human cancer cell lines.

Nanoparticle catalysis has emerged as a rapidly growing, multidisciplinary research area leading to increasing applications in organic synthesis.[1] The development of nanoparticle-mediated methodologies to access complex molecules, especially natural products, is particularly attractive but has been achieved with limited success thus far.[2] Herein, we report the first synthesis of the natural product sorocenol B in racemic form employing silver nanoparticle (AgNP)-catalyzed Diels-Alder cycloadditions of 2′-hydroxychalcones.[3]

Sorocenol B (**1**) was isolated from the root bark of *Sorocea bonplandii* with an overall yield of 3 milligrams per kilogram of dried bark.[4] Due to the sparse distribution of its natural plant source, there has been no further report on this natural product since its first isolation in 1995.[5] Structurally, compound **1** is characterized by an intriguing bicyclo[3.3.1] core which is postulated to be biosynthetically derived from oxidative cyclization of 2′-hydroxychalcone-derived Diels-Alder cycloadduct **2** (Scheme 1).[4] Natural products containing similar bicyclic core structures include mulberrofuran I (**3**),[6] australisin B (**4**),[7] and mongolicin C (**5**)[8] which are structurally related to chalcomoracin (**6**)[9] and mulberrofuran C (**7**),[10] respectively.

In our retrosynthetic analysis (Scheme 2), (±)-**1** may be derived from MOM acetal precursor **8** which may be prepared through biomimetic, late-stage oxidative cyclization of cycloadducts **9** and/or **10**. We envisioned that the synthesis of **9**/**10** could be achieved employing AgNP-catalyzed Diels-Alder cycloaddition[3] between 2′-hydroxychalcone **11** and

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Supporting Information Available Expertimental procedures and characterization data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

diene **12** which should be derived from commercially available chromene **13** and resorcinol (**14**), respectively.

The synthesis of the acetylated chalcone **11** commenced with Claisen-Schmidt condensation between chromene **13** and benzaldehyde **15** which smoothly generated chalcone **16** in 96% yield (Scheme 3). The use of NaH as a base in THF represents an improved protocol for chalcone formation which generally affords higher yields in shorter reaction times compared to conventional KOH/MeOH conditions.[11] MOM hydrolysis of **16** using 3 M aqueous HCl in refluxing methanol, followed by acetylation, provided chalcone **11** in 79% yield (two steps).[12]

The requisite diene **12** was prepared in four steps from resorcinol (**14**). Protection of **14** with MOMCl and NaH in DMF afforded MOM ether **17** in 91% yield. Regioselective formylation of **15** was carried out employing *n*BuLi in the presence of TMEDA followed by quenching the resulting aryl lithium intermediate with DMF which provided benzaldehyde **18** in 83% yield.[13] Sequential base-catalyzed aldol condensation between **18** and acetone (92% yield)[14] and Wittig olefination of the resulting α,β-unsaturated ketone **19** (79% yield) afforded the desired diene **12**.

With both chalcone **11** and diene **12** in hand, we investigated the key Diels-Alder cycloaddition utilizing silica-supported silver nanoparticles (AgNP's), a highly efficient and user-friendly catalyst recently developed in our laboratory.[3a] With 0.1 mol % catalyst loading at mild reaction temperature, **11** and **12** reacted cleanly in air to afford the desired cycloadducts in 90% combined yield with a 2:1 ratio of separable *endo*/*exo* diastereomers (**20** and **21**, Scheme 4). Notably, the *endo*-cycloadduct **20** was chromatographically inseparable from chalcone **11**, therefore complete conversion of the starting material **11** was necessary for smooth access to the cycloadducts. In comparison, the uncatalyzed, thermal Diels-Alder cycloaddition of **11** and **12** did not proceed to completion to afford cycloadducts **20**/**21** (53% combined NMR yield, 1:2 ratio) even in the presence of large excess (11 equiv relative to **11**) of diene **12**.[15]

In order to construct the bicyclo[3,3,1] framework of (±)-**1**, the next step entailed unmasking the acetyl-protected phenols of **20**/**21** followed by treatment with oxidants to accomplish oxidative cyclization, a process involving formal allylic C-H bond activation.[16] After exploring a number of unproductive oxidative conditions (*e.g.* DDQ,[17] CAN,[18] and $Pd(OAc)_2$/1,4-benzoquinone[19]), we found that substrate **9**, prepared from *endo* diastereomer **20**, reacted employing Stoltz's conditions for oxidative Wacker cyclization (catalytic $Pd(OAc)_2$/pyridine in toluene under an oxygen atmosphere)[20] providing the desired bicyclic product **8** and its C-4 epimer **22** (2:1 ratio) in 50% combined yield (Scheme 5a). The relative stereochemistry of both **8** and **22** were unambiguously determined by key NOE signals (Scheme 6, *e.g.* H-4 and H-26 for **8**, H-4 and H-6 for **22**). Interestingly, deacylation of the *exo* diastereomer **21** to **10** followed by Pd-catalyzed oxidative cyclization did not afford the cyclized product (Scheme 5b).

The distinctive reactivities of **9** and **10** may be rationalized by the proposed mechanism for the Pd(II)-mediated oxidative cyclization.[20] As shown in Scheme 5a, complexation of the Pd(II) catalyst with the unprotected phenol of **9** followed by intramolecular alkene insertion should generate intermediate **24**. Subsequent *syn*-β-hydride elimination of **24** provides the desired bicyclo [3.3.1] product **8**. In the case of **10**, *syn*-β-hydride elimination is not feasible due to stereochemical restrictions. In addition, the presence of pyridine may lead to the formation of the minor product **22** through epimerization at the C-4 stereocenter of β,γ-unsaturated ketone **8**.

Finally, MOM hydrolysis of **8** using aqueous HCl in refluxing MeOH completed the total synthesis of natural product (±)-**1** in 74% yield without epimerization at the C-4 position. The relative stereochemistry of synthetic (±)-**1** was confirmed by NOE analysis (Scheme 7, key signal: H-4 and H-26). Spectroscopic data for synthetic (±)-**1** were identical to those reported in the original isolation paper.[4]

In preliminary studies, the biological activity of synthetic (±)-**1** was evaluated in the National Cancer Institute (NCI) 60 human cancer cell screen.[15] Single-dose assays at 10^{-5} M showed that (±)-**1** exhibited antitumor activity with a mean cell growth of 26% of control. Subsequent full-dose response assays of (±)-**1** exhibited low micromolar-level cytotoxic activities (mean GI_{50} values of 3.3 μM) and moderate selectivity. Tumor cell lines that are most sensitive to (±)-**1** include prostate cancer PC-3 (GI_{50} = 1.1 μM), melanoma LOX IMVI (GI_{50} = 1.4 μM), leukemia MOLT-4 (GI_{50} = 1.4 μM), and colon cancer HCC-2998 (GI_{50} = 1.4 μM).

In summary, a concise total synthesis of (±)-sorocenol B has been accomplished employing a silver nanoparticle (AgNP)-catalyzed Diels-Alder cycloaddition. A late-stage Pd(II)-catalyzed oxidative cyclization of the derived *endo* cycloadduct has been used to access the bicyclo[3.3.1] framework of sorocenol B. Further studies on the applications of metal nanoparticle catalysts in complex molecule synthesis are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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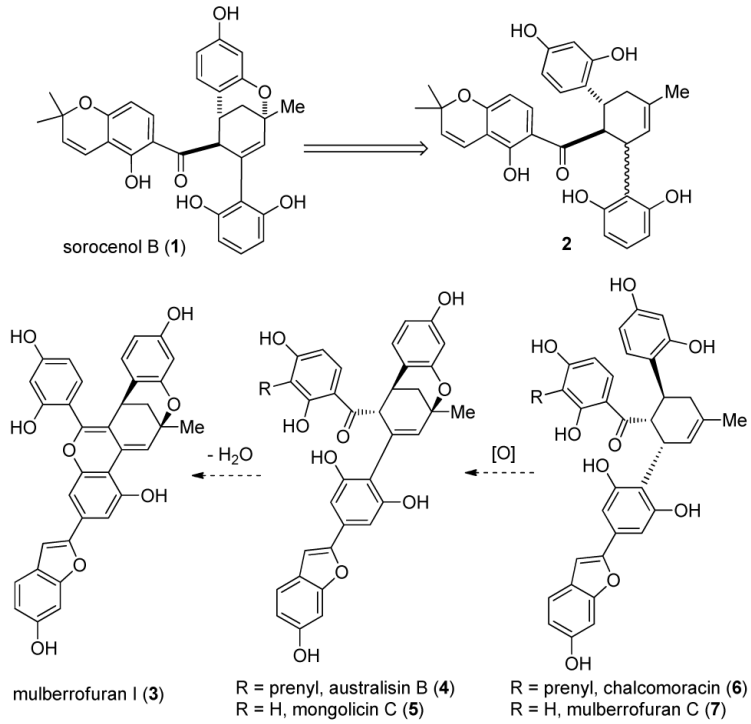
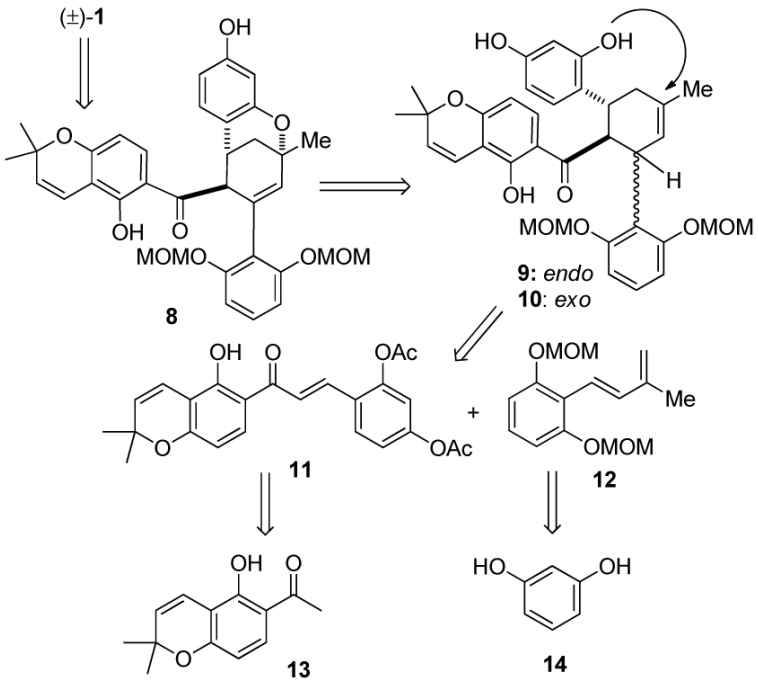
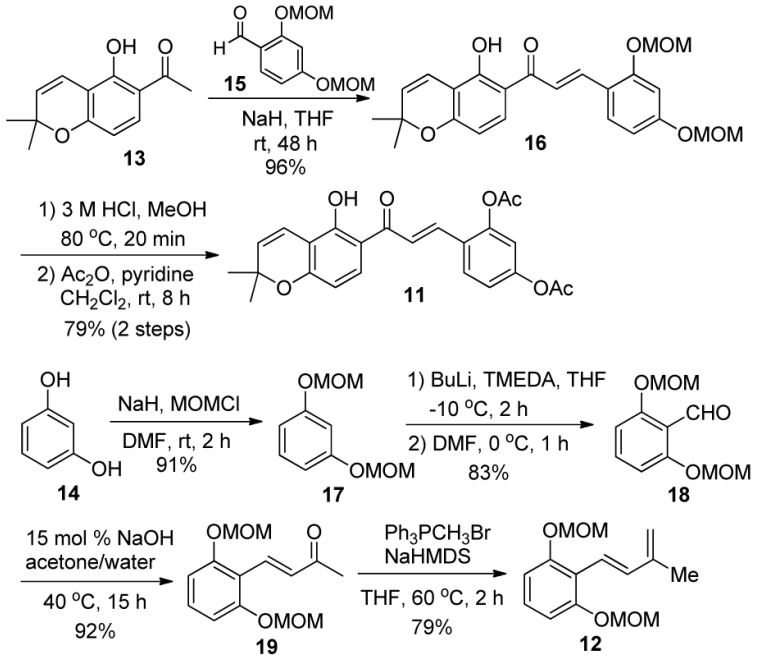


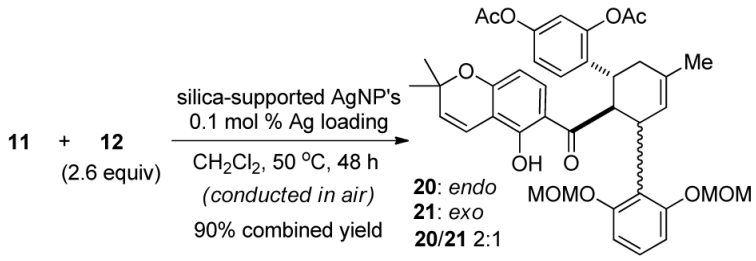
Scheme 1.
Biosynthesis of Sorocenol B and Related Natural Products



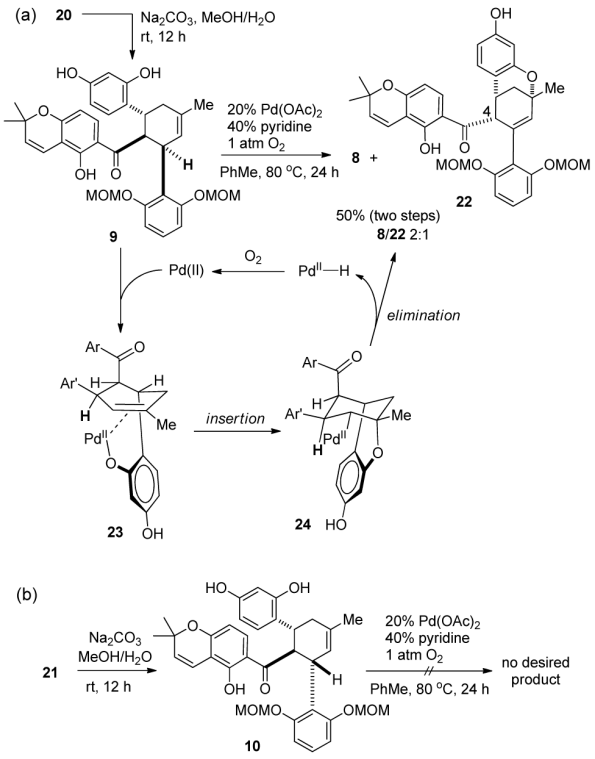
Scheme 2.
Retrosynthetic Analysis for Sorocenol B



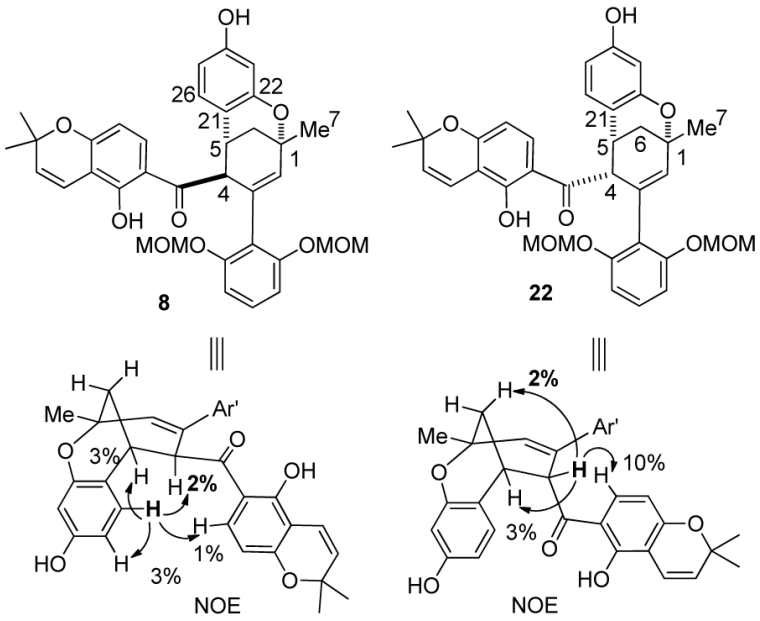
Scheme 3.
Syntheses of Chalcone **11** and Diene **12**



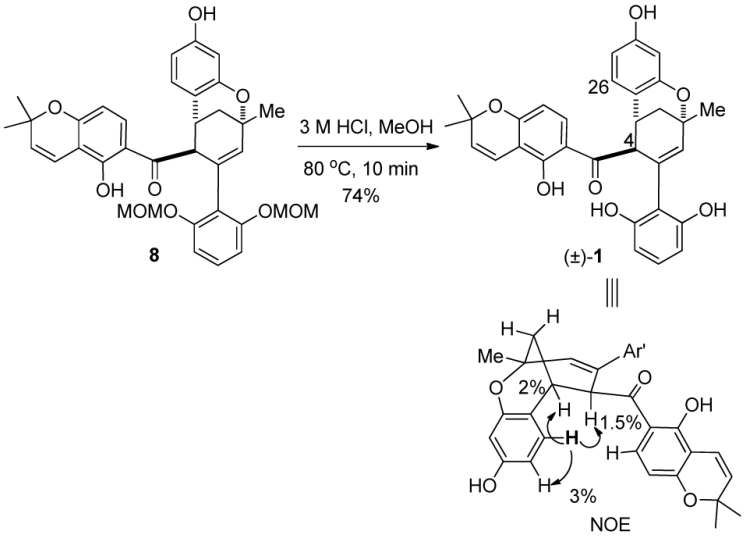
Scheme 4.
AgNP-Catalyzed Diels-Alder Cycloaddition of **11** and **12**



Scheme 5.
Pd(II)-Catalyzed Oxidative Cyclization



Scheme 6.
Key NOE's Leading to Relative Stereochemistry Assignments of **8** and **22**



Scheme 7.
Synthesis of (±)-Sorocenol B