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Total Synthesis of Bauhinoxepin J: A Biologically Active Dibenzo[*b*,*f*]oxepin Isolated from *Bauhinia purpurea*

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Bauhinoxepin J possessing antimycobacterial, antimalarial, and tumor growth inhibitory activities was efficiently synthesized. The method involves crucial steps, including a coupling reaction of two aromatic moieties to construct the desired carbon framework, chemoselective phenol oxidation of a bisphenol derivative to establish a key cyclization precursor, and construction of a characteristic seven-membered dihydrooxepin ring by internal cyclization to yield the target bauhinoxepin J.

Introduction

In recent years, numerous tricyclic dibenzo[*b*,*f*]oxepins and related compounds have been isolated from the plant belonging to the *Bauhinia* genus, particularly from *Bauhinia saccocalyx* and *Bauhinia purpurea*.[1–4] Several of these structurally unique natural products have been reported to exhibit attractive biological activities such as antimycobacterial,[1,3] antimalarial,[1] antifungal,[1] cytotoxic,[1,2,4] and anti-inflammatory[1] activities. In most cases, however, further biological studies of these natural products are extremely limited, presumably because of the scarcity of samples from natural resources.[1–4] As a consequence, the development of an efficient and reliable method for the synthesis of dibenzo[*b*,*f*]oxepins is desirable and worthwhile from the viewpoint of medicinal chemistry and pharmaceuticals.

Representative examples of naturally occurring dibenzo[*b*,*f*]oxepins are depicted in Figure 1. Bauhinoxepin A (**1**) was isolated from *B. saccocalyx* by Kittakoop and co-workers in 2004.[3] This compound shows antimycobacterial activities with an MIC value of 6.25 μM.[3] Bauhiniastatin 1 (**2**), isolated from *B. purpurea* by Pettit and co-workers in 2006, exhibits significant growth inhibitory activity against several human cancer cell lines with IC_{50} values at micromolar levels.[2] Bulbophyol B (**3**), isolated from *Bulbophyllum kwangtungense* by Wu in 2006, displays growth inhibition against human epithelial carcinoma (HeLa) and human erythomyeloblastoid leukaemia (K562) cell lines in the low micromolar range.[4] Kittakoop and co-workers continued searching for bioactive compounds and consequently discovered eight new dibenzo[*b*,*f*]oxepins including bauhinoxepin J (**4**) from *B. purpurea* in 2007.[1] Although **4** appears to have a relatively simple structure, it exhibits remarkable biological activities including antimycobacterial activity (MIC = 24.4 μM), antimalarial activity (IC_{50} = 5.8 μM), and tumor growth inhibitory activity (KB cells: IC_{50} = 10.5 μM; BC cells: IC_{50} = 12.1 μM).[1]

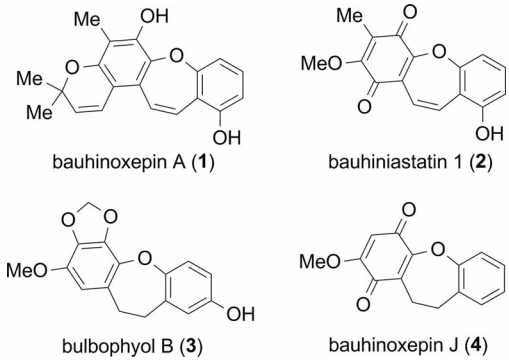

Figure 1. Representative structures of naturally occurring dibenzo[*b*,*f*]oxepins.

To date, the synthesis of naturally occurring dibenzo[*b*,*f*]-oxepins has not been widely reported. In 2008, Yao and co-workers reported the first total synthesis of bulbophyol B (**3**) by using an intramolecular Ullmann-type biaryl ether formation reaction (18% overall yield in 12 steps).[5] In the following year, Kraus and co-workers reported the first total synthesis of bauhinoxepin J (**4**) by employing unique intramolecular radical cyclization of a quinone ring (25% overall yield in 4 steps).[6] More recently, Yoshida and co-workers reported an approach to the dibenzo[*b*,*f*]oxepin core of **4** by using an oxidative dearomatization/cyclization protocol (13% overall yield in 7 steps).[7] In this study, we describe our total synthesis of **4** by using an efficient and convenient process.

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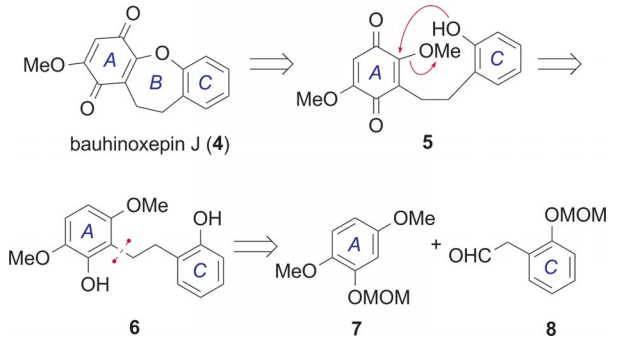
Results and Discussion

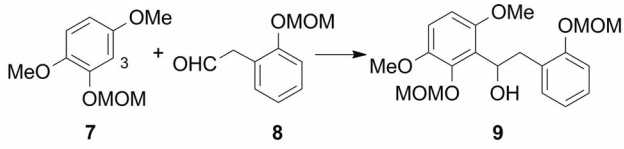
Our retrosynthetic analysis for the synthesis of bauhinoxepin J (**4**) is outlined in Scheme 1. We envisioned that target molecule **4** could be synthesized from phenolic quinone **5** by the formation of a characteristic seven-membered dihydrooxepin (B ring) through an internal nucleophilic addition/elimination sequence. To the best of our knowledge, this type of cyclization to construct the dihydrodibenzo[*b*,*f*]-oxepin skeleton (ABC ring) has not been previously reported; thus, this approach posed a considerable challenge from a synthetic viewpoint. Key cyclization precursor **5** was expected to be accessible through chemoselective phenol oxidation of bisphenol **6** by using a combination of molecular oxygen and salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)].[8] In this quinone formation step, we believed that a more electron-rich phenol moiety (A ring) would be preferentially oxidized to yield **5**.[9] Intermediate **6**, in turn, was to be prepared by a coupling reaction of known trioxybenzene **7**[10] (A ring moiety) with known phenylacetaldehyde **8**[11] (C ring moiety) followed by functional group manipulation and deprotection.



Scheme 1. Retrosynthetic analysis for the synthesis of bauhinoxepin J (**4**).

The synthesis commenced with the coupling reaction of **7**[10] with **8**[11] to construct the requisite carbon framework (**7** + **8** → **9**, Table 1). Site-selective lithiation at the C3 position in **7** was achieved by treatment with *n*BuLi in Et_2O under reflux temperature,[12] and the aryllithium generated in situ was allowed to react with **8** from –78 to –50 °C to give the desired coupling product **9**, albeit in 40% yield (Table 1, Entry 1). When THF was used as the solvent, the yield of product **9** was moderately improved to 56% (Table 1, Entry 2). We assumed these modest yields (40–56%) to be the result of possible enolization of the formyl group in **8** under basic conditions.[13] To overcome this problem, we considered using an organocerium reagent, which is known to have lower basicity and higher nucleophilicity than the corresponding organolithium reagent.[14] To this end, lithiated **7** (prepared under the conditions described in Table 1, Entry 2) was treated with anhydrous cerium chloride in THF at –78 °C to yield the corresponding cerium reagent,[15] which was then allowed to react with **8** at the same temperature to give coupling product **9** in a satisfactory yield (75%; Table 1, Entry 3).

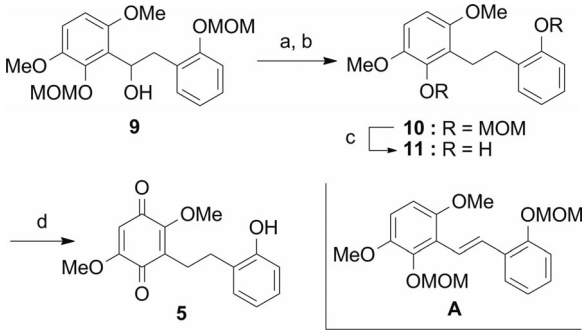
Table 1. Coupling reaction of trioxybenzene **7** and phenylacetaldehyde **8**.



Entry	Conditions	Yield [%][a]
1	**7** (2 equiv.), *n*BuLi (2 equiv.), Et_2O, reflux, 2 h; at –78 °C, add **8** (1 equiv.), –78 to –50 °C, 2 h	40
2	**7** (2 equiv.), *n*BuLi (2 equiv.), THF, 40 °C, 2 h; at –78 °C, add **8** (1 equiv.), –78 °C, 1 h	56
3	**7** (2 equiv.), *n*BuLi (2 equiv.), THF, 40 °C, 2 h; $CeCl_3$ (2 equiv.), –78 °C, 1 h, add **8** (1 equiv.), –78 °C, 1 h	75

[a] Isolated yield.

We then performed the synthesis of phenolic quinone **5**, a precursor of the key cyclization reaction (Scheme 2). Removal of the hydroxy group in **9** was efficiently achieved by trifluoroacetylation (TFAA, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min) followed by hydrogenolysis of the resulting trifluoroacetate [H_2 (balloon), 10% Pd/C, EtOAc, r.t., 24 h],[8a] thus affording deoxygenated product **10** in 77% overall yield. By applying the conventional Barton–McCombie procedure[16] to this deoxygenation process, a lower yield of **10** was observed (33%, 2 steps) and stilbene-type byproduct **A** was obtained as the major product (44%), which was probably generated through unfavorable elimination of the intermediate methyl xanthate during the course of the reactions.



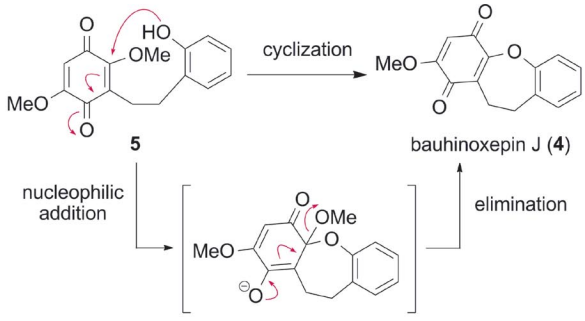
Scheme 2. Synthesis of phenolic quinone **5**. Reagents and conditions: (a) TFAA, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min; (b) H_2 (balloon), 10% Pd/C, EtOAc, r.t., 24 h, 77% (2 steps); (c) 3 M HCl, MeOH, r.t., 12 h, 94%; (d) salcomine, air, MeCN, r.t., 30 min, 89%. TFAA = trifluoroacetic anhydride, DMAP = 4-(dimethylamino)-pyridine, salcomine = *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II).

Continuing the synthesis, deprotection of the two MOM groups in **10** under acidic conditions (3 M HCl, MeOH, r.t., 12 h) gave liberated bisphenol **11** in 94% yield. The subsequent crucial chemoselective quinone formation reaction was successfully achieved by exposure of **11** to air (atmospheric oxygen) in the presence of salcomine (0.5 equiv.) in MeCN at room temperature for 30 min, which resulted in

the clean formation of desired quinone **5** in high yield (89%). In this reaction, the use of oxygen gas instead of air under the same conditions resulted in nonselective and excessive phenol oxidation to give the undesired bisquinone.

Next, we investigated the key intramolecular ether cyclization of **5** under several conditions (**5** → **4**, Table 2). Initial screening to achieve cyclization was carried out by using some standard bases such as $NaN(SiMe_3)_2$, NaH, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dilute solutions (5 mM) of appropriate solvents (Table 2, Entries 1–3). Among them, DBU proved to be superior from the viewpoint of reaction cleanliness (Table 2, Entry 3) although the yield of **4** was not satisfactory (28%). In the case of $NaN(SiMe_3)_2$ and NaH (Table 2, Entries 1 and 2), the reaction was not clean, and the yield of **4** was lower (23 and 18%, respectively). After repeated attempts, we found that the addition of 4 Å molecular sieves (MS, as a methanol scavenger) was effective for this cyclization (Table 2, Entry 4), which gave a higher yield of **4** (35%). To further improve the yield, solvent effects and concentration effects were next examined under the conditions optimized in Table 2, Entry 4. The use of THF, toluene, or 1,2-dichloroethene (DCE) all resulted in lower yields of **4** (0–21%; Table 2, Entries 5–7). Eventually, the best result was obtained when cyclization was performed in a highly dilute solution (0.5 mM) of CH_2Cl_2 with DBU (4 equiv.) under reflux conditions (Table 2, Entry 8), giving rise to **4** in 64% yield. The spectroscopic properties (IR, ^1H and ^{13}C NMR, and HRMS) of synthetic sample **4** were identical to those of natural **4**.[1]

Table 2. Intramolecular ether cyclization of phenolic quinone **5** leading to bauhinoxepin J (**4**).



Entry	Conditions	Yield [%][a]
1	$NaN(SiMe_3)_2$ (1.5 equiv.), THF (5 mM), –78 °C to r.t., 20 h	23
2	NaH (1.5 equiv.), THF (5 mM), r.t., 4 h	18
3	DBU (4 equiv.), CH_2Cl_2 (5 mM), r.t., 10 h	28
4	DBU (4 equiv.), 4Å MS, CH_2Cl_2 (5 mM), reflux, 8 h	35
5	DBU (4 equiv.), 4Å MS, THF (5 mM), reflux, 8 h	0
6	DBU (4 equiv.), 4Å MS, toluene (5 mM), reflux, 3 h	17
7	DBU (4 equiv.), 4Å MS, DCE (5 mM), reflux, 36 h	21
8	DBU (4 equiv.), CH_2Cl_2 (0.5 mM), reflux, 24 h	64

[a] Isolated yield.

Conclusions

We have accomplished the total synthesis of bauhinoxepin J (**4**) in 31% overall yield in 6 steps from the starting materials trioxybenzene **7** and phenylacetaldehyde **8**. The key steps of the synthesis involve the coupling reaction of aromatic moieties **7** and **8** to construct the requisite carbon framework **9** (**7** + **8** → **9**, Table 1), strategic salcomine oxidation of bisphenolic compound **11** to yield cyclization precursor **5** (**11** → **5**, Scheme 2), and formation of the seven-membered dihydrooxepin ring (B ring) by ring closure of phenolic quinone **5** to complete the projected synthesis (**5** → **4**, Table 2). Compared to other reported methods,[5–7] the main advantages of the present synthesis are the higher yields and milder conditions. On the basis of this study, we are currently synthesizing additional analogues of **4** [e.g., possessing substituent group(s) on the benzene ring moiety] with the aim of exploring its structure–activity relationship. In addition, further investigations to identify the action mechanism of **4** by using the synthetic sample are in progress in our laboratories.

Experimental Section

1-[3,6-Dimethoxy-2-(methoxymethoxy)phenyl]-2-[2-(methoxymethoxy)phenyl]ethanol (9): A solution of *n*BuLi (1.60 M in hexane, 1.30 mL, 2.2 mmol) was added dropwise to a stirred solution of 1,4-dimethoxy-2-(methoxymethoxy)benzene (**7**;[10] 422 mg, 2.2 mmol) in dry THF (12 mL) at 0 °C under an atmosphere of argon, and the mixture was heated at 40 °C for 2 h. After cooling, the resulting solution was slowly added to a stirred suspension of anhydrous $CeCl_3$ (600 mg, 2.4 mmol) [prepared by heating $CeCl_3 \cdot 7H_2O$ (finely ground powder, 911 mg, 2.4 mmol) at 140 °C for 2 h under reduced pressure] in dry THF (12 mL) at –78 °C under an atmosphere of argon. After 1 h, a solution of 2-[2-(methoxymethoxy)phenyl]acetaldehyde (**8**)[11] in dry THF (22 mL) was added slowly to the organocerium reagent prepared in situ above at –78 °C, and stirring was further continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) at –78 °C, and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc, 2:1) to give **9** (315 mg, 75%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.09 (dd, J = 6.1, 13.4 Hz, 1 H), 3.39 (dd, J = 8.3, 13.7 Hz, 1 H), 3.48 (s, 3 H), 3.57 (s, 3 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.91 (br. d, J = 10.2 Hz, 1 H), 4.97 (d, J = 5.4 Hz, 1 H), 5.10 (d, J = 5.4 Hz, 1 H), 5.14 (d, J = 6.3 Hz, 1 H), 5.17 (d, J = 6.8 Hz, 1 H), 5.42–5.48 (m, 1 H), 6.57 (d, J = 9.3 Hz, 1 H), 6.75 (d, J = 9.3 Hz, 1 H), 6.85–6.89 (m, 1 H), 7.05–7.14 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.9,

55.7, 55.8, 56.3, 57.7, 68.2, 94.5, 99.2, 106.2, 111.2, 113.8, 121.4, 126.3, 127.3, 128.1, 131.1, 144.2, 146.6, 152.0, 155.7 ppm. IR (neat): $\tilde{\nu}$ = 3540, 2993, 2938, 2905, 2835, 1589, 1489, 1257, 1234, 1152, 1074, 1003, 757 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{26}O_7$ $[M]^+$ 378.1679; found 378.1682.

3-(2-Hydroxyphenethyl)-2,5-dimethoxycyclohexa-2,5-diene-1,4-dione (5): Salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)] (22.6 mg, 70 μmol) was added to a stirred solution of **10** (38.1 mg. 0.14 mmol) in dry CH_3CN (15 mL) at room temperature. The suspension was stirred under atmospheric air for 30 min at room temperature. The reaction mixture was diluted with water (20 mL), and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (20 mL), then dried with Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc, 2:1) to give **5** (35.6 mg, 89%) as an orange powder. Recrystallization (hexane/CH_2Cl_2, 1:1) afforded orange prisms. M.p. 166–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61–2.70 (m, 4 H), 3.84 (s, 3 H), 4.00 (s, 3 H), 5.71 (s, 1 H), 5.93 (s, 1 H), 6.76–6.81 (m, 2 H), 7.03–7.08 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 29.3, 56.5, 61.5, 105.6, 115.8, 120.3, 126.7, 127.8, 1285, 130.1, 154.3, 156.0, 158.8, 183.1, 183.3 ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3016, 2943, 2850, 1650, 1599, 1456, 1345, 1325, 1213, 1172, 1051, 845, 754 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{16}O_5$ $[M]^+$ 288.0998; found 288.0994.

2-Methoxy-10,11-dihydrodibenzo[*b*,*f*]oxepine-1,4-dione [Bauhinoxepin J (4)]: A solution of **5** (18.5 mg, 64 μmol) in dry CH_2Cl_2 (128 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (38.4 μL, 0.26 mmol) and 4 Å molecular sieves (170 mg) was heated at reflux for 24 h under an atmosphere of argon. After cooling, the reaction was quenched with 1 M HCl (30 mL), and then diluted with $CHCl_3$ (30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), then dried with Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc, 3:1) to give **4** (10.5 mg, 64%) as a pale yellow oil. The ^{1}H and ^{13}C NMR and IR spectra and MS data (see below) are identical to those of natural bauhinoxepin J. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72–2.75 (m, 2 H), 3.07–3.10 (m, 2 H), 3.84 (s, 3 H), 5.97 (s, 1 H), 7.13–7.17 (m, 2 H), 7.23–7.28 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 30.2, 56.9, 106.0, 121.4, 124.5, 126.4, 128.6, 130.5, 134.4, 153.1, 156.7, 159.8, 181.9, 182.9 ppm. IR (neat): $\tilde{\nu}$ = 2933, 1660, 1604, 1581, 1489, 1455, 1356, 1255, 1227, 1191, 1099, 768 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{12}O_4$ $[M]^+$ 256.0736; found 256.0743.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **10** and **11** along with copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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