Synthetic Approach to the ABCD Ring System of Anticancer Agent Fredericamycin A via Claisen Rearrangement and Ring-Closing Metathesis as Key Steps

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Supporting Information

ABSTRACT: A new synthetic strategy to the ABCD ring system of the anticancer agent fredericamycin A (NSC-305263) was realized by the Diels−Alder reaction and olefin metathesis as key steps. The tactics developed here for the construction of the ABCD ring system also involve double Claisen rearrangement followed by a retro-Diels−Alder reaction and ring-closing metathesis. The metathesis approach performs a key role in the construction of A and D rings of the ABCD core unit. More importantly, ABCD fragment synthesis was accomplished without the involvement of protecting groups.

INTRODUCTION

Fredericamycin A 1 (Figure 1), a quinone-based natural product, was first isolated in 1981 from the fermentation broth of the strain Streptomyces griseus (ATCC 49344, FCRC-48).1 It comprises a hexacyclic ring containing a single chiral quaternary center (spiro[4.4]nonene ring system) conjoined with the naphthoquinone and isoquinolone moieties, which are not present in any other natural product.2 The design and synthesis of highly oxygenated polyaromatic fredericamycin A 1 are difficult tasks due to the presence of a dense functionality, and synthesis is important due to its in vitro cytotoxic and in vivo antibiotic antitumor activity.3

Because of its special features of the spirocyclic core (spiro[4.4]nonane ring), fredericamycin A 1 exhibits an interesting biological activity;4 it is highly cytotoxic against murine leukemia KB and Du-145 prostate tumors, and also shows good activity against in vivo tumor models such as P388D1 mouse leukemia, CD8F mammary tumors, B16 melanoma, and L1210 cell lines.5,3b Fredericamycin A also acts as a potent inhibitor against ovarian tumors and also inhibits both topoisomerases I and II.6,3b Furthermore, compound 1 exhibited an irreversible inhibitor of the peptidyl-prolyl cis–trans isomerase (PP1) Pin 1 with a Ki of 0.82 μM and also inhibited the DNA processing enzymes.7,6,3b

In this context, several synthetic routes have been reported in the literature.8 The first successful total synthesis of compound 1 was completed in racemic form by Kelly and co-workers in 1986.9 Afterward, several research groups like Boger et al.,5 Clive et al.,8c Kita et al.,8e Bach et al.,11 and Rama Rao et al.8d reported the total synthesis of fredericamycin.

Limited approaches are available for the synthesis of the spirocyclic indene framework of fredericamycin A 1.10 These includes the rearrangement reactions,11 cycloadditions,12 intermolecular alkyne-chromium carbene complex cyclization,13 metal-mediated 1,2-carbonyl shift,14 radical pathways,15 photochemical approach,16 Diels−Alder reactions (DA),17 and palladium-catalyzed cross-coupling acylation.18 The construction of a spirocyclic ring system is indeed a synthetic challenge. To the best of our knowledge, there are no reports available for the construction of the spirocyclic core with a functionalized BCD ring system of fredericamycin A 1 through double Claisen rearrangement (CR) and ring-closing metathesis (RCM) as key steps. Here, the RCM protocol was identified as a key step to create a spirocyclic core, the A and D ring system of fredericamycin A 1. Several metathesis catalysts are

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now available for ring closure of olefinic precursors. Here, we used G-I and G-II catalysts to realize the metathesis step. The key synthon to fredericamycin A \( \text{1} \), consisting of the ABCD ring system, was assembled by adopting the DA reaction,\(^{19} \) Claisen rearrangement,\(^{20} \) and RCM protocol.\(^{21} \) The key steps in our synthetic strategy involving RCM for CD ring construction, ceric ammonium nitrate (CAN) oxidation, and DA reaction along with the aromatization sequence have been considered to assemble a fully functionalized BCD ring system. Additionally, one-pot Claisen rearrangement (CR) with the retro-Diels–Alder reaction (rDA)\(^{22} \) followed by RCM provides a new entry to the ABCD framework of fredericamycin A \( \text{1} \).

■ RESULTS AND DISCUSSION

Our retrosynthetic approach to the ABCD ring system \( \text{2} \) of fredericamycin A \( \text{1} \) is shown in Scheme 1. The target molecule \( \text{2} \) may be assembled from bis-hydroxy derivative \( \text{3} \) via the RCM and oxidation sequence. Interestingly, the bis-hydroxy derivative \( \text{3} \) could be derived from the aromatized compound \( \text{4} \) through O-allylation and one-pot double Claisen rearrangement (CR) followed by the rDA reaction. The dihydroxy ketone \( \text{4} \) may be generated from \( \text{5} \) via oxidation and DA reactions followed by aromatization. The spiro derivative \( \text{5} \) can be obtained from dimethoxy indanone \( \text{6} \) by C-allylation followed by RCM. Indanone \( \text{6} \) was prepared from the commercially available starting material such as 2,5-dimethoxybenzaldehyde \( \text{7} \) based on the known procedures.\(^{23} \)

Our journey toward the target molecule \( \text{2} \) started with the synthesis of key building block dimethoxy indanone \( \text{6} \).\(^{24} \) In this regard, 2,5-dimethoxybenzaldehyde \( \text{7} \) reacted with malonic acid under Knoevenagel conditions to produce the acid \( \text{8} \) in 88% yield. Next, acid derivative \( \text{8} \) was subjected to hydrogenation with 10% Pd/C and gave the saturated acid \( \text{9} \) in 97% yield. Further, acid-catalyzed cyclization of \( \text{9} \) in the presence of phosphorous pentoxide (\( \text{P}_2\text{O}_5 \)) and methanesulfonic acid (\( \text{MeSO}_3\text{H} \)) produced the dimethoxy indanone derivative \( \text{6} \) (69%).\(^{25} \) Having prepared the known indanone derivative \( \text{6} \), our next target was the spiro[4.4]nonene ring system, which constitutes the CD ring fragment of fredericamycin A. Next, the indanone \( \text{6} \) was subjected to allylation with allyl bromide in the presence of \( \text{NaH} \) to provide the diallyl indanone \( \text{10} \) in excellent yield. Subsequently, the indanone derivative \( \text{10} \) proceeded for RCM via the G-II catalyst to generate the ring-closure product \( \text{5} \) (89%). Here, we observed that spiro ring formation with a quaternary center in the presence of the G-I catalyst is slower and the RCM product has less yield (60–65%). The structure of the RCM product \( \text{5} \) (Scheme 2) has been proven by spectral parameters (\(^1\text{H}, \(^1\text{C} \) NMR, and HRMS data).

Having prepared the tricyclic spiro compound \( \text{5} \), the attention was then directed toward its expansion to the ABCD ring system. The spiro ketone \( \text{5} \) was subjected for CAN oxidation at 0 °C to deliver the quinone derivative \( \text{11} \), which acts as a powerful dienophile in the DA reaction with cyclopentadiene. Thermal cycloaddition of quinone \( \text{11} \) with a freshly cracked cyclopentadiene gave the DA adduct \( \text{12} \) in excellent yield (92%). Armed with the DA adduct \( \text{12} \) in hand,
we focused our efforts to assemble the ABCD core of fredericamycin A 1. In this regard, the Diels−Alder adduct 12 was further treated for aromatization24 with 60−120 mesh silica gel to generate the corresponding annulated hydroquinone-fused norbornadiene 4 in moderate yield (Scheme 3). The aromatized product structure 4 was supported by spectral data (1H, 13C NMR DEPT 135, and HRMS). Next, the hydroquinone 4 was O-allylated under basic conditions using allyl bromide in dry DMF to produce the diallyl compound 13 in 77% yield. To introduce the A ring of the ABCD core of fredericamycin A 1, we utilized a one-pot rDA reaction followed by double CR. To this end, the O-allyl derivative 13 was heated at 180 °C in a sealed tube for 12 h to produce the diallyl hydroquinone 3 in 40% yield (based on the starting material recovered, 11%). Also, several minor products were formed during the rearrangement sequence, and they could not be isolated in pure form (TLC monitoring).

The formation of unexpected hydroquinone derivative 3 can be explained on the basis of initially formed quinone intermediate 3A from compound 13 (via Claisen/Retro), which undergoes rapid transformation to hydroquinone 3 due to the presence of the active −CH2 group adjacent to the spiro

Figure 2. Suggested mechanism for hydroquinone 3 formation.
system, which acts as a hydrogen source and is further involved in the aromatization process (Figure 2). The highly conjugated quinone 3A participated in the generation of carbocation intermediate 3C via vinlogous enol 3B. Later on, the formed carbocation 3C further rearranged to 3D, and elimination of proton followed to produce 3E. Finally, the quinone intermediate 3A was involved in the virtual disproportionation to give the major product 3 along with the oxidized product 3F. The by-product 3F was confirmed by its mass spectral (HRMS) data (Supporting Information).

To install the A ring by the RCM strategy, compound 3 was reacted with the Grubbs (G-I) catalyst to generate the tetracyclic compound (RCM product) 14. The RCM product 14 was fully established with spectral parameters such as IR, 1H NMR, and 13C NMR and further supported by HRMS data (Scheme 3). To complete the target compound, the ABCD ring analogue of fredericamycin A 1, the RCM product 14 was subjected to SeO₂ oxidation in dioxane for 2 h at 70 °C, followed by column chromatography. The structure of compound 1 was supported with 1H, 13C NMR, and mass spectroscopic data (Scheme 3).

### CONCLUSIONS

To conclude, we have established a useful synthetic strategy to assemble the ABCD ring system of antitumor agent fredericamycin A starting with commercially available 2,5-dimethoxybenzaldehyde 7 through the CR and two-fold RCM sequence. The metathesis sequence provided an opportunity for the construction of A and D rings of the ABCD framework of fredericamycin A. So far, there are no reports available in the literature for the construction of the ABCD core of fredericamycin A. Here, a tacit combination of RCM, one-pot rDA reaction, and double CR has been used to provide access to the target molecule. Moreover, construction of the ABCD ring system of fredericamycin A 1 was successfully established with protecting-group-free synthesis.

### EXPERIMENTAL SECTION

#### General Experimental Details.

All of the essential reagents, chemicals, and required solvents were used as such directly obtained from commercial suppliers. Thin-layer chromatography (TLC) plates were made on 10 × 5 glass plates layered with commercial grade Acme silica gel (GF-254 × chromatography (TLC) plates were made on 10 × 200 mesh glass). The by-product 3F was removed from the reaction mixture by column chromatography using 40% ethyl acetate in pet ether as the eluent system. Dimethylformamide (DMF) and CH₂Cl₂ were distilled over a CaH₂, and EtOAc was dried with anhydrous K₂CO₃. Dimethylformamide (DMF) and CH₂Cl₂ were distilled over a CaH₂, and EtOAc was dried with anhydrous K₂CO₃.

All IR spectra were recorded with a Nicolet Impact-400 FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra (1H, 13C, and DEPT 135) were recorded on 400 and 500 MHz spectrometers (Bruker) with a CDCl₃ solvent, and chemical shifts (δ ppm) are reported relative to the internal standard such as TMS. The J values (coupling constants) are given in hertz. Mass spectra (HRMS) were recorded under positive ion electrospray ionization (ESI, Q-ToF) mode.

**Synthesis of (E)-3-(2,5-Dimethoxyphenyl)acrylic Acid (8)**

To stir a solution of unsaturated acid 8 (5.24 mmol) in dry EtOAc (50 mL), Pd/C (250 mg, 10% palladium on carbon) was added, and then the reaction mixture was stirred at room temperature for 5 h under hydrogen gas (balloon pressure). Progress of the reaction was monitored by TLC, and the crude mixture was passed through a Celite pad and washed with ethyl acetate (3 times, 20 mL). The filtrate was evaporated at reduced pressure, and the crude product was recrystallized from EtOAc/hexane to furnish the saturated derivative 9 as a colorless crystalline solid.

**Synthesis of 3-(2,5-Dimethoxyphenyl)propanoic Acid (9)**

To stir a solution of CH₃SO₃H (10.0 mL, 153 mmol), 1H NMR (400 MHz, CDCl₃): δ = 8.07 (d, J = 16.2 Hz, 1H), 7.07 (d, J = 3.04 Hz, 1H), 6.95 (d, J = 3.0 Hz, 1H), 6.93−6.85 (m, 1H), 6.52 (d, J = 16.1 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃): δ = 173.1, 153.5, 153.1, 142.3, 123.6, 118.0, 117.8, 113.5, 112.5, 56.1, 55.8 ppm.

**Synthesis of 4,7-Dimethoxy-2,3-dihydro-1H-inden-1-one (6)**

To stir a solution of CH₃SO₃H (10.0 mL, 153 mmol), anhydrous P₂O₅ (2.00 g, 13.7 mmol) was added, and the resulting mixture was stirred at 70 °C for 1 h, and slowly, the temperature was increased to 110−115 °C for 3 h. Upon completion, the reaction mixture was allowed to cool, and then cold water was poured. Acidification with HCl (pH 5) led to the formation of crude acid 8 as a yellow precipitate. Afterward, crude (E)-3-(2,5-dimethoxyphenyl)acrylic acid was recrystallized from EtOAc/hexane and yielded the pure cinnamic acid 8 as yellow crystalline needles.

Yield: 88% (5.5 g); mp: 145−147 °C; 1H NMR (400 MHz, CDCl₃): δ = 8.07 (d, J = 16.2 Hz, 1H), 7.07 (d, J = 3.04 Hz, 1H), 6.95 (d, J = 3.0 Hz, 1H), 6.93−6.85 (m, 1H), 6.52 (d, J = 16.1 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃): δ = 173.1, 153.5, 153.1, 142.3, 123.6, 118.0, 117.8, 113.5, 112.5, 56.1, 55.8 ppm.

**Synthesis of 4,7-Dimethoxy-2,3-dihydro-1H-inden-1-one (6)**

Yield: 97% (4.85 g); mp: 67−69 °C; 1H NMR (400 MHz, CDCl₃): δ = 6.77−6.70 (m, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 2.91 (d, J = 7.6 Hz, 2H), 2.65 (d, J = 7.6 Hz, 2H); 13C NMR (100 MHz, CDCl₃): δ = 179.7, 153.5, 151.8, 129.8, 116.4, 111.8, 111.2, 55.8, 55.8, 34.1, 26.1 ppm.

**4,7-Dimethoxy-2,3-dihydro-1H-inden-1-one (6)**

Yield: 69% (507 mg); mp: 127−129 °C (lit. 123−125 °C); 1H NMR (500 MHz, CDCl₃): δ = 6.96 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.97−2.95 (m, 2H), 2.65−2.63 (m, 2H) ppm; 13C NMR (125 MHz, CDCl₃): δ = 205.1, 151.8, 150.5, 146.1, 126.4, 116.6, 56.1, 55.9, 36.8, 22.3 ppm.
2,2-Diallyl-4,7-dimethoxy-2,3-dihydro-1H-inden-1-one (10). To a stirred solution of NaH (2.87 g, 6 equiv.) in THF, dimethoxy indanone (6 g, 20.81 mmol) in 50 mL of THF was added at 0 °C under a N2 atmosphere. Further, the reaction mixture was kept under stirring at rt for 10 min. Later on, allyl bromide (10 mL, 124.8 mmol) was added, and then the reaction mixture was allowed to stir at rt for 6 h. Progress of the reaction was monitored based on TLC, and the reaction mixture was quenched with saturated NH4Cl solution (15 mL) and extracted with EtOAc. The organic layers were washed with brine, dried over anhydrous Na2SO4, and evaporated in vacuo. The reaction mixture was purified by column chromatography using 100–200 mesh silica gel with 10% EtOAc/pet ether as the solvent system to afford the diallylated compound 10 obtained as a colorless crystalline solid.

Yield: 96% (5.4 g); mp: 96–98 °C; IR (neat, cm−1): 3071, 2928, 2840, 1707, 1596, 1496, 1265, 1070; 1H NMR (500 MHz, CDCl3): δ = 6.94 (d, J = 8.7 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 5.64–5.56 (m, 2H), 5.03 (dd, J = 17.0 Hz, 1.7 Hz, 2H), 4.96–4.93 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.84 (s, 2H), 2.38 (d, J = 13.6, 6.5 Hz, 2H), 2.25 (dd, J = 13.6, 8.2 Hz, 2H) ppm; 13C NMR (125 MHz, CDCl3): δ = 208.0, 151.6, 150.3, 143.3, 133.5, 125.8, 118.5, 116.8, 109.4, 56.0, 55.8, 52.2, 41.9, 32.3 ppm; HRMS (ESI, Q-TOF): m/z calc for C18H16NaO3 [M + Na]+: 303.0995, found 303.1001.

4′,7′-Dimethylspiro[cyclopentane-1,2′-inden]-3-en-1′(3′H)-one (5). A solution of 10 (5.8 g, 21.3 mmol) in dry CH2Cl2 (100 mL) was degassed with nitrogen for 0.5 h, then the G-II catalyst (5 mol %) was added, and the resulting reaction mixture was allowed to stir at rt for 1 h until the completion of reaction (TLC). Later on, the solvent was evaporated by recrystallization from EtOAc/pet ether to afford the desired DA product 12 as a yellow crystalline solid in quantitative yield.

Yield: 92% (240 mg); mp: 127–129 °C; IR (neat, cm−1): 3413, 2924, 1737, 1644, 1020; 1H NMR (400 MHz, CDCl3): δ = 8.55 (s, 1H), 6.88 (dd, J = 5.21, 3.08 Hz, 1H), 6.74 (dd, J = 5.04, 3.12 Hz, 1H), 5.71 (s, 2H), 4.65 (bs, 1H), 4.40 (s, 1H), 4.10 (s, 1H), 2.97 (s, 2H), 2.86 (t, J = 15.0 Hz, 2H), 2.38–2.30 (m, 3H), 2.22 (d, J = 7.0 Hz, 1H) ppm; 13C NMR (125 MHz, CDCl3): δ = 212.9, 149.0, 145.0, 143.8, 141.2, 140.4, 138.0, 136.5, 128.8, 121.0, 69.5, 56.4, 47.0, 46.0, 45.6, 45.5, 42.2 ppm; HRMS (ESI, Q-TOF): m/z calc for C24H24NaO3 [M + Na]+: 319.0731, found: 319.0731.

Synthesis of Aromatized Compound (4). The Diels–Alder [4 + 2] product 12 (500 mg, 1.78 mmol) in CH2Cl2 (20 mL) and silica gel (60-mesh, 5.0 g) was added. The reaction mixture was allowed to stir at rt for 6 h with silica gel to promote its adsorption onto the surface of silica gel. Later on, the mixture was allowed to stand on the silica gel column overnight. After column chromatography (10% EtOAc/PE), the desired aromatized hydroquinone derivative 4 was obtained as a pure colorless solid.

Yield: 66% (330 mg); mp: 218–220 °C; IR (neat, cm−1): 3413, 2924, 1737, 1644, 1020; 1H NMR (400 MHz, CDCl3): δ = 8.55 (s, 1H), 6.88 (dd, J = 5.21, 3.08 Hz, 1H), 6.74 (dd, J = 5.04, 3.12 Hz, 1H), 5.71 (s, 2H), 4.65 (bs, 1H), 4.40 (s, 1H), 4.10 (s, 1H), 2.97 (s, 2H), 2.86 (t, J = 15.0 Hz, 2H), 2.38–2.30 (m, 3H), 2.22 (d, J = 7.0 Hz, 1H) ppm; 13C NMR (125 MHz, CDCl3): δ = 212.9, 149.0, 145.0, 143.8, 141.2, 140.4, 138.0, 136.5, 128.8, 121.0, 69.5, 56.4, 47.0, 46.0, 45.6, 45.5, 42.2 ppm; HRMS (ESI, Q-TOF): m/z calc for C24H22NaO3 [M + Na]+: 303.0992, found 303.0995.

O-Allylated Derivative (13). In a suspension of NaH (660 mg, 27.55 mmol) in dry DMF (2 mL), the aromatized derivative 4 (1.1 g, 3.9 mmol) in 15 mL of anhydrous DMF and allyl bromide (1.7 mL, 19.6 mmol) were added at 0 °C in N2 and stirred for 0.5 h at room temperature. On completion of the reaction (based on TLC), the resulting mixture was quenched by aqueous NH4Cl and extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous Na2SO4. Column chromatography by 8% EtOAc/PE gave the desired diallylated product 13 obtained with a pale yellow liquid.

Yield: 77% (1.08 g); IR (neat, cm−1): 3055, 1701, 1609, 1023; 1H NMR (500 MHz, CDCl3): δ = 6.82–6.81 (m, 1H), 6.74–6.73 (m, 1H), 6.12–6.01 (m, 2H), 5.68 (s, 2H), 5.38–5.33 (m, 2H), 5.26 (d, J = 10.4 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 4.62–4.60 (m, 2H), 4.54–4.51 (m, 1H), 4.46–4.43 (m, 1H), 4.17 (bs, 2H), 3.00 (q, J = 17.3 Hz, 2H), 2.87–2.82 (m, 2H), 2.31–2.25 (m, 3H), 2.18 (d, J = 7.0 Hz, 1H) ppm; 13C NMR (125 MHz, CDCl3): δ = 207.2, 151.4, 146.4, 146.3, 142.7, 143.9, 143.8, 141.3 (d), 134.5 (d), 133.9 (d), 128.8 (d), 127.2, 118.0, 117.8 (d), 117.9, 75.4, 74.8, 68.3, 56.3, 48.3, 46.9, 45.7, 45.6, 42.3 ppm; HRMS (ESI, Q-TOF): m/z calc for C24H24NaO3 [M + Na]+: 338.1618, found 338.1613.
5′,6′-Diallyl-4′,7′-dihydroxySpirocyclopentane-1,2′-inden]-3-en-1′(3′H)-one (3). Compound 13 (440 mg, 1.22 mmol) in 1,2-dichlorobenzene (4 mL) in a sealed tube was degassed with N₂ gas for 5 min with stirring. Then the solution was kept at 180 °C for 12 h. After the completion of the reaction, the crude product was directly loaded on a 100–200 mesh silica gel, and the column was eluted with pet ether (200 mL) until 1,2-dichlorobenzene was removed. Further, 2–3% ethyl acetate/petroleum ether elution furnished the dRA derivative 3 as a dark brown liquid along with the starting material in 11% yield.

Yield: 40% (145 mg); IR (neat, cm⁻¹): 3412, 2926, 1678, 1046; ¹H NMR (400 MHz, CDCl₃): δ = 8.81 (s, 1H), 5.98–5.89 (m, 2H), 5.72 (s, 2H), 5.15–4.93 (m, 4H), 4.8 (s, 1H), 3.47 (dt, J = 5.6, 2.0 Hz, 2H), 3.44 (dt, J = 5.4, 1.6 Hz, 2H), 3.0 (s, 2H), 2.8 (d, J = 14.8 Hz, 2H), 2.37 (d, J = 14.4 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 213.0, 149.6, 144.1, 135.9 (d), 135.2, 135.1, 135.0 (d), 128.8 (d), 124.6, 120.3 (d), 116.7 (t), 115.3, 132.2, 131.7, 15.0 Hz, 2H), 2.37 (d, J = 14.4 Hz, 2H) ppm; ¹H NMR (400 MHz, CDCl₃): δ = 8.74 (s, 1H), 5.95

Notes
The authors declare no competing financial interest.

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