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Formal total synthesis of (±)-cortistatin A

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Abstract

A second-generation synthesis of the pentacyclic core of the cortistatins, a family of rearranged steroidal alkaloids that have recently attracted much attention, is reported. The improved sequence provides access to significant quantities of this key compound, which enabled a formal total synthesis of (±)-cortistatin A by conversion to the key Nicolaou/Hirama dienone. It is anticipated that this new, robust route to the pentacyclic core will facilitate the total synthesis of a range of natural products in the cortistatin family, as well as the construction of key structural analogs to probe the promising biological activity of these important compounds.

Keywords

cortistatin A; formal total synthesis; cycloisomerization; oxidative dearomatization; angiogenesis

1. Introduction

The cortistatins are a family of rearranged steroidal alkaloids isolated from the Indonesian marine sponge *Corticium simplex* by Kobayashi and co-workers (Figure 1).¹ In addition to possessing an unprecedented pentacyclic skeleton, these compounds exhibit potent antiproliferative activity against human umbilical vein endothelial cells (HUVECs), which are a standard model for antiangiogenic activity.² Cortistatin A (**1**), the most potent member of this family, was found to have an IC₅₀ of 1.8 nM against HUVECs. As a result of their unique structural features and impressive biological activity, these compounds have generated significant interest among the synthetic community.³ This interest has led to one semi-synthesis⁴ and two total syntheses of (+)-cortistatin A,⁵ and one total synthesis of cortistatin J (**3**).⁶ Additionally, one formal total synthesis of (+)-cortistatin A⁷ and a number of synthetic approaches⁸ have been reported.

Although the antiangiogenic activity of the cortistatins suggests the potential for therapeutic applications, a detailed understanding of the mode of action of these compounds is still lacking. Important strides have been made as a result of several structure-activity studies which indicated the importance of the isoquinoline and dimethylamino groups for potent activity.^{6,9} Additionally, a recent high-throughput kinase binding assay identified cortistatin A as a high-affinity ligand for the protein kinases CDK8, CDK11 and ROCK,¹⁰ the latter of which is involved in the regulation of cell proliferation through modulation of Rho GTPases.

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Supplementary data Supplementary data associated with this article can be found in the online version, at

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¹¹ However, the experimentally observed discrepancy between the kinase binding affinity and antiproliferative activity of cortistatin A underscores the need for further work in this area to fully elucidate the details surrounding the biological activity of the cortistatins.¹⁰ Undoubtedly, such advances will hinge upon on the ability of synthetic chemists to supply meaningful quantities of both the naturally occurring cortistatins and strategic synthetic analogs. As a step toward this goal, we report herein a formal total synthesis of (±)-cortistatin A which was enabled by an improved synthesis of the cortistatin pentacyclic core over our previously reported approach. The development of a scalable route to this key intermediate sets the stage for the synthesis of a range of both natural and unnatural cortistatins.

2. Results and discussion

Our initial synthetic efforts toward the cortistatins led to a synthesis of the cortistatin pentacyclic core (**14**), which proceeded in eleven steps and 5.3% overall yield from aldehyde **8** and indanone **6** (Scheme 1).^{8c} As a prerequisite to further synthetic studies, we required access to significant quantities of **14** and sought an improved route to this compound. We had initially chosen to begin with PMB-protected indanone **6** due to the range of mild conditions available for cleavage of the PMB ether.¹² However, we speculated that the potential reactivity of this electron-rich moiety toward the Brønsted and Lewis acids that were employed in several of our synthetic manipulations (*vide infra*) might have contributed to the modest yields of these steps.

To circumvent these obstacles, benzyloxy indanone **7** was employed in a second-generation synthesis. This sequence commenced by treating **7** with KOH in the presence of aldehyde **8** to effect an aldol condensation to provide enone **9** in 76% yield (Scheme 1). Two-stage reduction of this α,β -unsaturated enone, followed by dehydration of the resultant indanol, gave indene **10** in 67% yield over the three steps. We were gratified to find that subjecting **10** to catalytic PtCl₂ at 50 °C promoted enyne cycloisomerization to forge tetracycle **11** in 82% yield, as compared to the 61% yield obtained for cycloisomerization of the PMB analog of **10**.^{8c} Chemoselective reduction of the disubstituted double bond of **11** with diimide, generated *in situ* from TsNHNH₂ and Et₃N, was followed by cleavage of the benzyl ether moiety with Na/naphthalide to give phenol **12** in 77% yield over the two steps. Reprotection as the TES ether and treatment with *m*-CPBA provided epoxide **13**, an intermediate previously prepared from **6**.^{8c} Regioselective opening of the epoxide moiety accompanied by removal of the TES group was achieved by treatment of **13** with *n*-BuLi to provide an intermediate allylic alcohol. This species subsequently underwent oxidative dearomatization¹³ upon slow addition to a solution of PhI(OAc)₂ at -78 °C to provide pentacycle **14** in 57% yield over the two steps. We were pleased to find that this readily scalable sequence provided pentacycle **14** in 9.6% overall yield from aldehyde **8** and benzyloxy indanone **7**, nearly double the yield of the previous sequence that employed PMB-protected indanone **6**.

With a robust route to pentacycle **14** established, we were poised to explore conditions for its elaboration to the cortistatin natural products. In accord with our general synthetic strategy, **14** is imbued with the diene substitution pattern which directly corresponds to cortistatins K and L (**4** and **5**) and should readily serve as a precursor to these natural products. However, as an intermediate synthetic goal, we chose to target dienone **25**,^{5a,7a} which was previously advanced to (+)-cortistatin A by Nicolaou et al. This effort would thus constitute a formal total synthesis of **1**. To this end, it was necessary to effect a transposition of the C1,C19 diene moiety of trienone **14** to reposition this functionality to C10,C9. The direct oxidative conversion of **14** to **17** (Scheme 2) was attempted with various oxidants such as PdCl₂, DDQ,^{8h} PhI(OAc)₂¹⁴ and CAN in the presence of MeOH, but these

endeavors did not prove fruitful. We next attempted to activate the dienol ether moiety of **14** with a suitable electrophile that could subsequently be removed to generate the diene. The method of Venturello and co-workers (NBS or NCS in MeOH)¹⁵ gave a mixture of halogen and methoxy-containing products, none of which could be readily transformed to diene **17**. Similarly disappointing results were obtained using NIS or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH). However, treatment of **14** with *m*-CPBA at 0 °C led to selective epoxidation of the trisubstituted double bond to yield epoxide **15**, which was subsequently opened with camphor sulfonic acid (CSA) in MeOH to provide tertiary alcohol **16**. After examining a variety of conditions for the dehydration of **16**, we were pleased to find that activation of the hydroxyl group with trifluoroacetic anhydride led to its facile elimination, providing diene **17** in 58% yield over the three-step sequence.

With diene **17** in hand, we next examined conditions for selective hydrogenation of the enone double bond. Although Crabtree's catalyst proved to be chemoselective toward reduction of the enone double bond of **17**, we were disappointed to observe a significant amount of decomposition products in the crude product mixture. We attribute this fact to the lability of the ketal moiety of **17**, which under the Lewis acidic reaction conditions may ionize and lead to decomposition of both the product and the starting material. A survey of heterogeneous catalysts revealed Pt/C, PtO₂ and Rh/Al₂O₃ to be unsuitable for this transformation, leading to mixtures of over-reduced products and decomposition. However, using Rh/C in THF,¹⁶ we were able to obtain a 72% yield of ketone **18**. A slight improvement in yield was realized by employing Wilkinson's catalyst in benzene, which provided a 75% yield of **18**. Further reduction of ketone **18** with LiEt₃BH then delivered alcohol **19** in 56% yield.

Dehydration of **19** was attempted with Martin's sulfurane¹⁷ and the Burgess reagent¹⁸ without success. Although the corresponding thiocarbonate of alcohol **19** could be readily formed, attempted Chugaev elimination led instead to loss of one equivalent of MeOH. Because the ketal moiety seemed to be playing a role in each of these undesired outcomes, it was cleaved with 1% HCl to give α -hydroxy ketone **20**. Unfortunately, dehydration of this compound was also unsuccessful under a variety of conditions (Amberlyst 15,¹⁹ TsOH,²⁰ POCl₃ or TsCl/pyr, TFAA/Et₃N, Martin's sulfurane). Attempted Barton deoxygenation or Chugaev elimination of the corresponding thiocarbonate of **20** also led to decomposition. In an alternative approach, ketone **18** was converted to enol triflate **21** by sequential treatment with LDA and PhNTf₂ in THF at -78 °C. However, attempts to reduce the triflate moiety of this species led to mixtures of products along with significant decomposition. The corresponding dienone (**22**) also fared poorly under reduction conditions.

Because of our inability to cleanly dehydrate alcohols **19** or **20**, or to reduce triflates **21** or **22**, we returned to enone **17**. We were pleased to find that Luche reduction of **17** led to a single allylic alcohol diastereomer. It should be noted that although the relative configuration of this species has not been determined, it is ultimately inconsequential. The intermediate alcohol was treated with (Boc)₂O and DMAP to provide Boc carbonate **23** in 69% yield over the two steps (Scheme 4). After some experimentation, we were pleased to find that treatment of **23** with Pd(dppf)Cl₂ and ammonium formate and heating to 60 °C provided dienol ether **24**. Although the exact mechanistic details have not been fully elucidated at this stage, we propose that this transformation proceeds via an initial oxidative addition of an *in situ* generated Pd(0) species to the allylic carbonate moiety of **23** to generate a Pd(II)-allyl complex.²¹ Subsequent β -alkoxide elimination²² yields **24** and a free Pd(II) complex, which undergoes reduction by formate to regenerate the active catalyst. Compound **24** readily underwent selective hydrogenation of the disubstituted double bond on treatment with Wilkinson's catalyst to deliver an intermediate enol ether, which upon hydrolysis gave dienone **25** in 77% yield over the three-step sequence. Spectral data for **25**

were in full accord with that previously reported,^{5a,7a} thus completing the formal total synthesis of (±)-cortistatin A (**1**).

3. Conclusions

In summary, we have developed a second-generation synthesis of the pentacyclic core of the cortistatins (**14**) which proceeds in nearly double the yield of our first-generation effort. With access to significant quantities of this intermediate, the formal total synthesis of (±)-cortistatin A (**1**) was completed in eight subsequent steps. Current efforts are directed at utilizing **14** to complete the total syntheses of cortistatins A, K and L and to prepare unnatural analogs for further biological studies.

4. Experimental

General

Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Dichloromethane (CH₂Cl₂) and benzene were distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Half-saturated aq. solutions refer to a freshly prepared 1:1 v/v mixture of the corresponding saturated aq. solution and deionized water. Reaction temperatures above 23 °C refer to oil bath or heating block temperatures, which were controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde stain. SiliCycle Silia-P silica gel (particle size 40–63 μm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on Bruker DRX-500 and AV-600 MHz spectrometers with ¹³C operating frequencies of 125 and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ¹H NMR and δ = 77.0 for ¹³C NMR). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm⁻¹). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a VG Prospec Micromass spectrometer (for EI) or a ThermoFisher Scientific LTQ Orbitrap XL (for ESI).

Ketal 17

To a suspension of pentacycle **14** (87.9 mg, 0.20 mmol) and NaHCO₃ (83.5 mg, 0.99 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C was added *m*-CPBA (~75%, 114 mg, 0.50 mmol). The resulting mixture was stirred at 0 °C for 10 h and then poured onto half-saturated aq. Na₂SO₃ (15 mL) and extracted with Et₂O (3 × 15 mL). The combined organic layers were washed (2 × 15 mL saturated aq. NaHCO₃, 15 mL brine), dried (MgSO₄) and concentrated to give 90.4 mg of crude epoxide **15** as a white powder, which was used without further purification. *R*_f 0.20 (4:1 hexanes/EtOAc). To a solution of crude epoxide **15** (90.4 mg) in CH₂Cl₂ (2.5 mL) and MeOH (2.5 mL) at 0 °C was added camphor sulfonic acid (1.0 mg, 4 mol). The resulting mixture was stirred at 0 °C for 3 h and then poured onto half-saturated aq. NaHCO₃ (15 mL) and extracted with Et₂O (3 × 15 mL). The combined organic layers were washed (15 mL brine), dried (MgSO₄) and concentrated to give 92.7 mg of crude alcohol **16** as a white powder, which was used without further purification. *R*_f 0.30 (4:1 hexanes/EtOAc). A solution of crude alcohol **16** (92.7 mg) and DMAP (4.7 mg, 0.04 mmol) in 1,2-

dichloroethane (3.0 mL) and Et₃N (1.5 mL) was treated with trifluoroacetic anhydride (0.13 mL, 0.94 mmol). After being stirred for 1 h at rt, the resulting mixture was heated to 60 °C for 4 h. After cooling to rt, the reaction mixture was poured onto half-saturated aq. NaHCO₃ (15 mL) and extracted with Et₂O (3 × 15 mL). The combined organic layers were washed (15 mL brine), dried (MgSO₄) and concentrated. Flash chromatography (9:1 hexanes/EtOAc + 1% Et₃N) give 54.0 mg (0.11 mmol, 58% over 3 steps) of ketal **17** as a pale yellow oil. **R_f** 0.57 (4:1 hexanes/EtOAc); **¹H NMR** (600 MHz, CDCl₃) δ 6.65 (d, *J* = 10.3 Hz, 1H), 6.39 (s, 1H), 6.10 (d, *J* = 10.3 Hz, 1H), 5.58 (dd, *J* = 5.2, 2.6 Hz, 1H), 3.76 (t, *J* = 8.6 Hz, 1H), 3.54 (s, 3H), 3.19 (s, 3H), 2.38-2.27 (m, 2H), 2.19-2.12 (m, 2H), 2.04-1.95 (m, 2H), 1.90 (td, *J* = 10.6, 8.1 Hz, 1H), 1.83 (ddd, *J* = 16.9, 11.3, 5.4 Hz, 1H), 1.76-1.64 (m, 2H), 1.58-1.50 (m, 1H), 0.88 (s, 9H), 0.77 (s, 3H), 0.028 (s, 3H), 0.025 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 193.1, 147.9, 139.2, 134.6, 128.8, 126.6, 125.7, 97.5, 83.9, 81.5, 78.1, 52.5, 50.0, 46.2, 43.4, 39.7, 39.5, 30.7, 30.4, 25.8, 19.3, 18.0, 13.4, -4.4, -4.8; **IR** (film) $\nu_{\max}$ 2955, 2857, 1709, 1471, 1463, 1387, 1361, 1250, 1177, 1145, 1111, 1046, 991, 837, 776, 738, 666 cm⁻¹; **HRMS** (EI+) calcd for [C₂₇H₄₀O₅Si]⁺: *m/z* 472.2645, found 472.2656.

Boc carbonate **23**

A solution of ketal **17** (10.8 mg, 23 μmol) in MeOH (0.70 mL) and CH₂Cl₂ (0.30 mL) at 0 °C was treated with CeCl₃•7H₂O (34.1 mg, 92 μmol). After 15 min, a solution of NaBH₄ (0.9 mg, 24 μmol) in MeOH (0.20 mL) was added. The resulting solution was stirred at 0 °C for 40 min and then diluted with EtOAc (15 mL). The organic layer was washed (5 mL saturated aq. NaHCO₃, 5 mL brine), dried (MgSO₄) and concentrated to give 9.2 mg (19 μmol, 85%) of the crude allylic alcohol as a white powder, which was used without further purification. **R_f** 0.36 (4:1 hexanes/EtOAc); **¹H NMR** (600 MHz, CDCl₃) δ 6.46 (s, 1H), 5.71 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.58 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.51 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 3.75 (t, *J* = 8.5 Hz, 1H), 3.51 (s, 3H), 3.14 (s, 3H), 2.81 (d, *J* = 11.2 Hz, 1H), 2.27-2.20 (m, 1H), 2.16-2.09 (m, 2H), 2.08-2.02 (m, 1H), 2.02-1.94 (m, 2H), 1.78-1.62 (m, 4H), 1.57-1.49 (m, 1H), 0.88 (s, 9H), 0.76 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 140.0, 134.9, 133.2, 128.3, 126.2, 124.3, 97.4, 82.6, 81.6, 78.4, 72.0, 52.0, 48.4, 46.3, 43.4, 39.5, 30.7, 30.6, 25.8, 19.3, 18.0, 13.5, -4.4, -4.8. A solution of the crude allylic alcohol (7.4 mg, 16 μmol), 4-dimethylaminopyridine (0.4 mg, 3.3 μmol) and di-*tert*-butyl dicarbonate (17.1 mg, 78 μmol) in 1,2-dichloroethane (0.60 mL) was heated at 40 °C. After 17 h, an additional 17.1 mg (78 μmol) of di-*tert*-butyl dicarbonate was added and heating was continued for an additional 20 h. After cooling to rt, the reaction mixture was diluted with EtOAc, filtered through SiO₂ and concentrated to give 11.7 mg of a yellow oil. Flash chromatography (20:1 hexanes/EtOAc + 1% Et₃N) gave 7.2 mg (14 μmol, 81%) of Boc carbonate **23** as a colorless oil. **R_f** 0.52 (4:1 hexanes/EtOAc); **¹H NMR** (600 MHz, CDCl₃) δ 6.44 (s, 1H), 5.70 (ddd, *J* = 10.2, 2.1, 0.7 Hz, 1H), 5.66 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.52 (dd, *J* = 5.3, 2.5 Hz, 1H), 5.39 (t, *J* = 2.1 Hz, 1H), 3.75 (t, *J* = 8.6 Hz, 1H), 3.40 (s, 3H), 3.15 (s, 3H), 2.27-2.20 (m, 1H), 2.19-2.09 (m, 3H), 2.03-1.94 (m, 2H), 1.80-1.62 (m, 4H), 1.57-1.50 (m, 1H), 1.47 (s, 9H), 0.88 (s, 9H), 0.76 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 152.8, 140.0, 134.4, 130.5, 128.7, 126.4, 124.6, 97.8, 82.8, 82.5, 81.6, 78.7, 76.0, 50.7, 49.0, 46.2, 43.4, 39.7, 39.5, 30.7, 30.5, 27.9, 25.8, 19.3, 18.1, 13.5, -4.4, -4.8; **IR** (film) $\nu_{\max}$ 2955, 2930, 2857, 1811, 1738, 1461, 1370, 1279, 1256, 1177, 1161, 863, 837, 776, 665 cm⁻¹; **HRMS** (ESI+) calcd for [C₃₂H₅₀NaO₇Si]⁺ (*M*+Na)⁺: *m/z* 597.3224, found 597.3219.

Dienone **25**

A solution of Pd(dppf)Cl₂•CH₂Cl₂ (0.6 mg, 0.7 μmol) in DMF (0.20 mL) was added to a suspension of carbonate **23** (1.8 mg, 3.1 μmol) and ammonium formate (ca. 2 mg, 32 μmol) in THF (0.40 mL). The resulting mixture was stirred at rt for 30 min to give an orange solution and then heated to 60 °C for 2.5 h. After cooling to rt, the reaction mixture was diluted with

Et₂O (12 mL) and washed (2 × 5 mL water, 5 mL brine), dried (MgSO₄) and concentrated. The crude material was directly purified by passage through a short plug of SiO₂, eluting with 4:1 hexanes/EtOAc, to give dienol ether **24** as a yellow oil. **R_f** 0.67 (4:1 hexanes/EtOAc). A mixture of the above dienol ether and Rh(PPh₃)₃Cl (ca. 0.2 mg, 0.2 μmol) in benzene (0.50 mL) was placed in a Parr bomb and set under 100 psi of H₂. After being stirred for 11 h, the reaction mixture was diluted with 2:1 hexanes/EtOAc, filtered through SiO₂ and concentrated to give the crude enol ether as a light brown oil. This material was directly dissolved in THF (0.50 mL), cooled to 0 °C and treated with 1% HCl (3 drops). The resulting solution was stirred for 3.5 h, during which time the cooling bath was allowed to gradually expire. The reaction mixture was then diluted with EtOAc, filtered through SiO₂ and concentrated. Flash chromatography (4:1 hexanes/EtOAc) gave 1.0 mg (2.4 μmol, 77% over 3 steps) of dienone **25** as a colorless film. **R_f** 0.28 (4:1 hexanes/EtOAc); **¹H NMR** (600 MHz, CDCl₃) δ 6.93 (s, 1H), 5.87 (dd, *J* = 5.2, 2.8 Hz, 1H), 3.77 (t, *J* = 8.6 Hz, 1H), 2.61–2.53 (m, 1H), 2.38–2.29 (m, 1H), 2.28–2.18 (m, 3H), 2.14 (dd, *J* = 11.5, 8.2 Hz, 1H), 2.08–1.94 (m, 5H), 1.79–1.66 (m, 5H), 1.61–1.49 (m, 1H), 0.88 (s, 9H), 0.76 (s, 3H), 0.033 (s, 3H), 0.031 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 198.6, 140.8, 139.8, 132.3, 132.0, 82.5, 81.5, 81.0, 46.2, 43.3, 40.4, 40.1, 39.4, 33.4, 30.7, 30.4, 25.8, 19.5, 19.1, 18.0, 13.7, –4.4, –4.8; **IR** (film) *v*_{max} 2925, 2853, 1674, 1625, 1581, 1462, 1249, 1196, 1102, 1022, 841, 777, 665 cm^{–1}; **HRMS** (ESI+) calcd for [C₂₅H₃₉O₃Si]⁺ (M+H)⁺: *m/z* 415.2668, found 415.2680.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig 1.
Selected members of the cortistatin family

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.