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Synthetic studies toward citrinadin A: construction of the pentacyclic core

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Abstract

This manuscript describes the preparation of an advanced intermediate toward the total synthesis of citrinadin A featuring a [3+2] cycloaddition employing *in situ* generation of the dipole.

Keywords

Citrinadin; spirooxindole; natural product; synthesis; [3+2] nitrone cycloaddition

1. Introduction

In the early 2000's, Kobayashi and coworkers reported the isolation of two secondary metabolites, citrinadin A and B, from the marine fungus *Penicillium citrinum* N059.[1] Structural determination efforts by Kobayashi revealed that the two congeners possess the same complex spirooxindole-containing pentacyclic core and differ only by an *N,N*-dimethylvaline appendage resident on citrinadin A (cf. **1** and **2**, Figure 1, top).

The interesting structural features of these compounds have led several groups to begin exploring their total syntheses. Recently our efforts and those of the Martin group led to completed syntheses of citrinadin B and A, respectively. These efforts independently led to the conclusion that the structures assigned by Kobayashi were sound in terms of connectivity but required revision at the stereochemical level.[2,3,4,5] As illustrated in Figure 1 (bottom), the reassigned structures of citrinadins A and B differ at the stereogenic centers residing within the pentacyclic core. Herein, we report synthetic efforts toward citrinadin A (**3**) that have now resulted in the stereoselective preparation of its core structure.

2. Results and Discussion

Citrinadin A possesses several synthetically challenging features, including an epoxy ketone side chain and a rare *N,N*-dimethylvaline ester. We envisioned that both of these moieties would be installed at a late stage, a maneuver that was particularly important for the delicate epoxy ketone. Thus, from a retrosynthetic perspective, citrinadin A was seen as arising from

This manuscript is dedicated to Professor Amos B. Smith, III, an inspirational mentor and good friend.

5, wherein an aryl bromide is poised for installation of the epoxy ketone side chain, and a masked alcohol will enable installation of the ester through a Mitsunobu reaction (Scheme 1). Epoxide **5** would be available from pentacycle **6** via reductive cleavage of the isoxazolidine N–O bond and subsequent quinolizidine formation. The isoxazolidine **6** would result from the intermolecular [3+2] cycloaddition of enone **7** and nitrone **8**. The requisite enone is the same as that employed in our previous synthesis of citrinadin B, while the nitrone was expected to arise from known diol **11** (*vide infra*).

During our initial studies towards citrinadin A,[6] we attempted to pre-form the nitrone prior to cycloaddition. Although this approach was successful in our synthesis of citrinadin B, under similar conditions **8** performed poorly. After considerable experimentation we eventually turned to a strategy that employed *in situ* generation of the requisite nitrone.[6] As illustrated retrosynthetically in Scheme 2, delivery of the nitrone would follow from desilylative cyclization of TBS-protected oxime **10** which, in turn, would arise from the known diol **11**.[7]

In the forward sense, known diol **11** was converted to the known lactone **12** using a sequence previously reported by Nakamura and coworkers, which involved exposure to PPTS in refluxing dichloroethane, followed by TBDPS protection (Scheme 3).[7] Subsequent treatment of **12** with DIBAL-H furnished the corresponding lactol **13** as a 1:1 mixture of diastereomers which, upon exposure to hydroxylamine hydrochloride, underwent smooth conversion to oxime **14** as a 1:1 mixture of *E* and *Z* isomers. Converting **14** into a substrate suitable for desilylative cyclization required initial TBS protection of the oxime alcohol and activation of the remaining secondary alcohol through tosylation.

Having prepared racemic nitrone precursor **10** we began to explore its ability to undergo cycloaddition with the previously prepared racemic enone **7**. As alluded to above, attempts to employ the preformed nitrone met with limited success. Thus, we began investigating generation of the ntirone *in situ* and, after an exhaustive screen of fluorine sources, solvents, and ratios of **7** to **10**, we discovered that TBAT in benzene with three equivalents of **10** gave the best overall result (Scheme 4).[6]

We were pleased to learn that unlike the nitrone cycloaddition used en route to citrinadin B, which required 9 days, the reaction of **7** with **10** furnished the desired cycloadduct in just 24 h.[8] Although **15b** was the minor diastereomer, we have demonstrated in preliminary studies that use of enantioenriched **7**,[5] gives a d.r. of 3:2, while use of enantioenriched **7** and enantioenriched **10**, derived from commercially available chiral ethyl-3-hydroxybutyrate, gives a d.r. of 2:1. Fortunately, **15a** and **15b** were separable via flash column chromatography thus, in these early studies, we were able to continue advancing the desired cycloadduct (**15b**) towards citrinadin A.

Towards this end, **15b** was advanced by reaction with trimethylsulfoxonium iodide and sodium hydride (Scheme 5). The derived Corey-Chaykovsky adduct (**16**) was stereoselectively produced in good yield.[9,10] Subsequent exposure of **16** to TMSCl and NaI promoted intramolecular attack of the epoxide by the isoxazolidine nitrogen to furnish an ammonium salt (**17**), which was then reduced with zinc in AcOH to give diol **18** thereby

completing construction of the core ring system.[11] This began setting the stage for eventual incorporation of the angular nitrogen atom. Toward this end, the least hindered alcohol in **18** was activated for displacement by treating with MsCl and Et_3N. Subsequent exposure of the derived mesylate to K_2CO_3 promoted the formation of key intermediate **19**, wherein the ring fusion epoxides stands ready to mediate incorporation of the final nitrogen.

3. Conclusion

In summary, we have prepared a late stage intermediate en route to citrinadin A with an approach that employs an intermolecular [3+2] nitrone cycloaddition. The latter was found to best proceed under conditions wherein the nitrone is produced *in situ* and, although the cycloaddition was performed with racemic substrates, its stereochemical outcome clearly indicates that enantioenriched substrates will selectively deliver material required for preparation of the natural product. These efforts have also illustrated that the derived cycloadduct can be advanced to an intermediate (**19**) that contains all of the functional groups required for conversion to citrinadin A. The aryl bromide will allow for attachment of the epoxyketone, removal of the TBDPS group will set the stage for introduction of the valine ester via a Mitsunobu reaction and opening of the ring-fusion epoxide will provide access to the requisite anti relationship between the methylamine and alcohol substituents. Work towards these ends is underway and will be reported in due course.

4. Experimentals

4.1. General

Unless otherwise noted, all reactions have been carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard vacuum-line techniques. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, methylene chloride, toluene, acetonitrile, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC as follows: tetrahydrofuran, diethyl ether, acetonitrile, and methylene chloride were passed through two packed columns of neutral alumina, while benzene and toluene were passed through a column of alumina and a column of Q5. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor 27 FTIR. 1H and 13C NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 autosampler, or Varian Inova 300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd =

doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra (HRMS) were performed at the Central Instrument Facility by Donald L. Dick of Colorado State University.

4.1.1. Lactol 13—Lactone **12** (3.2 g, 8.7 mmol) in dichloromethane (90 ml) was cooled to −78 °C for the addition of diisobutylaluminum hydride solution (1 M in hexanes, 9.6 ml, 9.6 mmol). This stirred cold for two hours at which time the reaction was quenched at −78 °C with methanol (9 ml) and allowed to warm to room temperature. The resulting reaction solution was vigorously stirred with an added solution of Rochelle's salt (9 g in 100 ml H_2O) for one hour. Following separation of the layers, the aqueous portion was extracted with diethyl ether, and the combined organics were washed with brine, dried (Na_2SO_4), and concentrated to provide lactol **13** as a 1:1 mixture of anomers (3.2 g, 100% yield), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71-7.68 (m, 8H), 7.46-7.36 (m, 12H), 5.30 (br t, 1H), 4.50 (ddd, *J* = 9.7, 6.6, 2.1 Hz, 1H), 4.22 (m, 1H), 3.91 (m, 2H), 3.79 (tt, *J* = 10.9, 4.8 Hz, 1H), 3.31 (dqd, *J* = 11.6, 5.9, 1.9 Hz, 1H), 3.01 (t, *J* = 2.6 Hz, 1H), 2.09 (ddt, *J* = 12.2, 4.4, 2.1 Hz, 1H), 1.98 (ddt, *J* = 12.8, 4.7, 1.7 Hz, 1H), 1.76 (m, 2H), 1.60 (dddd, *J* = 12.9, 11.0, 3.6, 2.0 Hz, 1H), 1.48~1.26 (m, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.08 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.83, 134.60, 134.48, 134.24, 134.13, 129.84, 129.82, 129.70, 129.69, 127.76, 127.74, 127.67, 127.65, 94.39, 92.93, 68.28, 68.16, 65.14, 64.16, 43.30, 42.61, 42.29, 39.51, 27.07, 27.01, 21.51, 21.27, 19.24, 19.19; IR (thin film): 3398 (br, m), 2932 (m), 2858 (m), 1428 (m), 1112 (s), 702 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{30}NaO_3Si$ [M +Na]: 393.1858. Found: 393.1862.

4.1.2 Oxime 14—The lactol **13** (2.8 g, 7.6 mmol) was then taken up in pyridine (15 ml). To this was added anhydrous magnesium sulfate (1.8 g, 15.2 mmol) and hydroxylamine hydrochloride (791 mg, 11.4 mmol). This was allowed to stir at room temperature for 36 hours. To work up, the reaction mixture was filtered through Celite, which was subsequently washed with 1:1 dichloromethane/hexanes and then dichloromethane. The resulting solution was concentrated, azeotroped with hexanes, and subjected to column chromatography (5% →10% →15% →30% →50% ethyl acetate/hexanes) to provide oxime **14** as an oil in a 1:1 mixture of *E/Z* isomers (2.9 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.81 (br s, 1H), 7.71~7.66 (m, 8H), 7.45~7.35 (m, 12H), 7.26 (t, *J* = 6.3 Hz, 1H), 6.67 (t, *J* = 5.5 Hz, 1H), 4.15 (m, 2H), 3.94 (m, 2H), 2.63~2.41 (m, 5H), 2.30 (ddd, *J* = 14.6 Hz, 6.6 Hz, 4.4 Hz, 1H), 1.66- 1.52 (m, 4H), 1.069 (s, 9H), 1.065 (s, 9H), 1.05 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.54, 148.81, 148.64, 136.02, 135.99, 133.48, 133.47, 133.38, 133.33, 130.09, 127.89, 69.73, 69.24, 64.60, 64.52, 45.08, 44.63, 36.70, 32.38, 27.11, 23.78, 19.35; IR (thin film): 3268 (br, m), 2931 (m), 2858 (m), 1428 (m), 1112 (s), 738 (m), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{31}NNaO_3Si$ [M+Na]: 408.1969. Found: 408.1971.

4.1.3 Nitrone precursor 10—To a solution of oxime **14** (2.9 g, 7.6 mmol, azeotroped in toluene) in dichloromethane (75 ml) was added imidazole (1 g, 15.2 mmol). The solution was cooled to 0 °C in an ice bath and tertbutyldimethylsilyl chloride (0.6 g, 4 mmol) was added. The reaction was stirred cold for 45 minutes. Then, another portion of tertbutyldimethylsilyl chloride (0.6 g, 4 mmol) was added and the reaction was allowed to

gradually come to room temperature overnight. The reaction was extracted with a NH_4Cl (50% sat., aq., soln.) and the aqueous was extracted with diethyl ether. The organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (0%→2%→4%→8%→15% ethyl acetate/hexanes) to yield the TBS-protected oxime as an oil with a 1:1 mixture of olefin isomers (3 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73~7.68 (m, 8H), 7.47~7.37 (m, 12H), 7.33 (t, *J* = 6.3 Hz, 1H), 6.85 (t, *J* = 5.4 Hz, 1H), 4.17 (m, 2H), 4.01 (m, 2H), 2.70 (ddd, *J* = 15.6 Hz, 7.1 Hz, 5.5 Hz, 1H), 2.57 (ddd, *J* = 15.7 Hz, 9.9 Hz, 5.1 Hz, 1H), 2.53 (dt, *J* = 14.5 Hz, 6.6 Hz, 1H), 2.5 (d, *J* = 3.0 Hz, 1H), 2.31 (ddd, *J* = 14.5 Hz, 5.9 Hz, 4.3 Hz, 1H), 2.27 (d, J = 3.2 Hz, 1H), 1.61 (m, 5H), 1.093 (d, *J* = 6.0 Hz, 3H), 1.09 (s, 18H), 1.07 (d, *J* = 6.4, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.14 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.31, 152.10, 136.06, 136.01, 133.53, 133.46, 133.38, 133.25, 130.13, 130.11, 127.93, 127.90, 69.99, 69.48, 64.49, 64.31, 44.99, 44.03, 36.52, 32.86, 27.14, 26.23, 26.16, 23.82, 19.39, 19.34, 18.29, 18.23, −5.14, −5.16; IR (thin film): 3452 (br, m), 2931 (s), 2858 (s), 1472 (m), 1112 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{46}NO_3Si_2$ [M+H]: 500.3020. Found: 500.3016.

A solution of the TBS-protected oxime (1.1 g, 3.6 mmol) and pyridine (10 ml) in dichloromethane (30 ml) was cooled to 0 °C in an ice bath. To this was added tosyl chloride (2.7 g, 14.4 mmol). The solution was allowed to gradually warm to room temperature overnight (20 h). The reaction was washed with $CuSO_4$ (10% aq. soln.) and the aqueous layer was extracted with diethyl ether. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by flash chromatography (1%→2%→3% ethyl acetate/hexanes) to provide tosylate **10** (1.3 g, 81% yield) as a 1:1 mixture of *E/Z* olefin isomers, which was either used immediately or temporarily stored as a solution (1 M in benzene, over molecular sieves) in the freezer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55~7.49 (m, 12H), 7.34~7.21 (m, 12H), 7.16 (t, *J* = 6.2 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 4H), 6.70 (t, *J* = 5.2 Hz, 1H), 4.46 (m, 2H), 3.75 (quintet, *J* = 5.7 Hz, 2H), 2.30 (dt, J = 16.0 Hz, 5.4 Hz, 1H), 2.29 (s, 6H), 2.26 (dt, *J* = 16.0 Hz, 5.6 Hz, 1H), 2.13 (dt, *J* = 14.6 Hz, 6.3 Hz, 1H), 2.06 (ddd, *J* = 14.6 Hz, 6.2 Hz, 4.9 Hz, 1H), 1.74 (ddd, *J* = 14.5 Hz, 7.5 Hz, 6.1 Hz, 1H), 1.68 (dd, *J* = 14.0 Hz, 7.2 Hz, 1H), 1.49 (tt, *J* = 14.0 Hz, 5.7 Hz, 2H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.907 (s, 9H), 0.903 (s, 9H), 0.89 (d, *J* = 3.0 Hz, 3H), 0.79 (s, 9H), 0.77 (s, 9H), 0.005 (d, J = 2.5 Hz, 6H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.20, 18.25, 19.35, 19.39, 21.27, 21.47, 21.74, 26.15, 26.22, 27.08, 33.09, 37.22, 44.25, 44.62, 68.30, 68.71, 77.88, 77.96, 127.70, 127.72, 127.81, 127.83, 127.85, 129.81, 129.93, 129.97, 133.64, 133.70, 133.77, 134.81, 134.87, 135.93, 135.95, 135.98, 144.46, 144.49, 152.09, 152.18, - 5.11, −5.15; IR (thin film): 2931 (m), 2858 (m), 1363 (m), 1177 (s), 1111 (m), 919 (m), 703 (m) cm^{-1}; HRMS (ESI) Calcd. for $C_{35}H_{52}NO_5SSi_2$ [M+H]: 654.3105. Found: 654.3113.

4.1.4 Isoxazolidines 15a and 15b—To a solution of the nitrone precursor **10** (118 mg, 0.18 mmol) in benzene (900 μl) was added $MgSO_4$ (43 mg, 0.36 mmol) and the enone **7** (24.5 mg, 0.06 mmol). Lastly, tetrabutylammonium difluorotriphenylsilicate (97 mg, 0.18 mmol) was added in two portions. This stirred at ambient temperature overnight (17 hours). At that time the heterogeneous mixture was diluted with dichloromethane (1 ml) and filtered through a celite plug. The filtrate was directly adsorbed onto silica gel and purified by flash

chromatography (0%→2.5%→5%→→20% ethyl acetate/hexanes) to provide two isoxazolidine diastereomers (39 mg total, 84% yield, **15a:15b** = dr 7:3), the desired isoxazolidine **15b** (12 mg) and the undesired diastereomer **15a** (27 mg), both as white foams. *Isoxazolidine* **15a**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.70 (m, *J* = 1.5 Hz, 4H), 7.57 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.44-7.27 (m, 10H), 7.23 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.9 Hz, 1H), 5.42 (m, 2H), 3.98 (br s, 1H), 3.79 (br m, 1H), 3.42 (br m, 2H), 2.90 (s, 2H), 2.44 (br m, 1H), 2.02 (d, *J* = 14.4 Hz, 1H), 1.91 (d, *J* = 14.4 Hz, 1H), 1.55 (m, 1H), 1.25 (m, 1H), 1.13 (m, 12H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.35, 19.24, 19.99, 20.62, 22.44, 27.10, 32.31, 38.16, 39.59, 43.70, 44.96, 48.24, 48.67, 55.01, 61.28, 65.67, 77.36, 93.73, 102.10, 123.49, 125.97, 126.57, 127.20, 127.78, 128.65, 129.80, 129.86, 133.98, 134.02, 134.40, 136.01, 136.06, 137.78, 141.04, 180.54, 213.66; IR (thin film): 2930 (s), 1751 (s), 1718 (s), 1450 (m), 1104 (s), 733 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{44}H_{49}BrN_2O_4Si$ [M+H+2]: 779.2723. Found: 779.2707. *Isoxazolidine* **15b**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72-7.67 (m, 4H), 7.46-7.39 (m, 6H), 7.37 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.33-7.29 (m, 2H), 7.26-7.22 (m, 3H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.71 (t, *J* = 7.8 Hz, 1H), 5.40 (d, *J* = 3.4 Hz, 2H, 4.03 (br m, 1H), 3.93 (br m, 1H), 3.37 (m, 2H), 3.29 (d, *J* = 18.9 Hz, 1H), 2.53 (d, *J* = 18.9 Hz, 1H), 2.26 (br m, 1H), 1.88 (br s, 2H), 1.68 (d, *J* = 14.2 Hz, 1H), 1.31 (t, *J* = 12.7 Hz, 1H), 1.23 (s, 3H), 1.19 (d, *J* = 5.7 Hz, 3H), 1.14 (s, 9H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.00, 178.69, 141.09, 137.59, 135.97, 135.92, 135.19, 134.59, 134.00, 133.80, 130.02, 129.90, 128.64, 127.88, 127.82, 127.28, 126.84, 123.46, 122.43, 102.48, 93.00, 66.02, 60.98, 54.39, 49.61, 49.56, 45.10, 43.08, 42.08, 39.62, 32.07, 27.08, 20.84, 19.93, 19.76, 19.43; IR (thin film): 3278 (br w), 2963 (m), 1748 (s), 1722 (s), 1450 (m), 1125 (s), 1068 (s), 729 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{44}H_{49}BrN_2O_4Si$ [M+H+2]: 779.2723. Found: 779.2703.

4.1.5 Spiroepoxide 16—To a solution of trimethylsulfoxonium iodide (145.3 mg, 0.66 mmol) in DMSO (2.2 ml) was added NaH (60% in mineral oil, 26.4 mg, 0.66 mmol). After stirring at room temperature for 4 hours, the resulting homogenous solution was added a solution of the ketone **15b**(170 mg, 0.22 mmol) in THF (4.4 ml) cooled to 0 °C in an ice bath to produce an opaque white solution. This was stirred at ambient temperature for 36 h, cooled to 0 °C, and quenched with saturated $NaHCO_3$ solution. The mixture was diluted with H_2O and the aqueous layer was extracted with ethyl acetate. The combined organic portions were washed with brine solution, dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (4%→8%→12%→30% ethyl acetate/hexanes) to provide the desired product **16** as a white foam (140 mg, 80% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72 (m, 4H), 7.42 (m, 6H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.30 (m, 3H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.21 (m, 2H), 6.87 (t, *J* = 7.8 Hz, 1H), 5.35 (s, 2H), 3.96 (s, 1H), 3.34~3.24 (m, 4H) 3.05 (s, 1H), 2.55 (d, *J* = 14.6 Hz, 1H), 2.43 (br s, 1H), 2.20 (d, *J* = 14.6 Hz, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.62 (m, 1H), 1.28~1.09 (m: 9H;3H;3H;1H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.69, 141.14, 137.82, 136.56, 136.00, 134.11, 134.00, 129.87, 128.60, 127.78, 127.14, 126.68, 124.07, 122.57, 102.19, 91.85, 77.36, 65.72, 65.57, 59.19, 56.05, 55.21, 50.44, 49.64, 44.88, 39.55, 38.26, 36.92, 36.21, 34.81, 34.66, 32.45, 31.72, 29.20, 27.12, 27.06, 25.42, 23.48, 22.79, 21.00, 20.85, 19.32, 18.91, 14.26, 11.57; IR (thin film): 2930 (s), 1723 (s), 1450 (s), 1105 (s), 734 (s), 703 (s) cm^{-1}; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_4Si$ [M+H+2]: 793.2880. Found: 793.2870.

4.1.6 Ammonium Salt 17—To a solution of the epoxide **16** (30 mg, 0.04 mmol) in acetonitrile/tetrahydrofuran (3:1, 0.6 ml) cooled to 0 °C in an ice bath was added NaI (30 mg, 0.2 mmol) and TMSCl (12.5 ml, 0.1 mmol). The clear solution became yellow and a precipitate formed. After stirring for 4 hours, the reaction was diluted with Et_2O and washed with saturated $Na_2S_2O_3$ solution. (Note: DO NOT wash with brine solution.) The aqueous layer was extracted with ethyl acetate. The combined organic extracts were concentrated *in vacuo* and purified by flash chromatography (20% → 40%→60%→ 80%→100% ethyl acetate/hexanes → 5% methanol/dichloromethane) to provide the desired product **17** as a clear glass (26 mg, 70% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.66 (m, *J* = 1.6 Hz, 4H), 7.54 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.50-7.40 (m, 6H), 7.31 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.28 (m, 1H), 7.22 (m, 1H), 7.13 (m, 2H), 6.89 (dd, *J* = 8.2, 7.6 Hz, 1H), 5.31 (s, 2H), 5.16 (d, *J* = 11.9 Hz, 1H), 4.10 (d, *J* = 11.9 Hz, 1H), 4.01 (m, 2H), 3.82 (m, 1H), 2.99 (q, *J* = 13.3 Hz, 2H), 2.81 (dd, *J* = 12.4, 8.0 Hz, 1H), 2.49~2.41 (m, 2H), 2.21 (m, 1H), 2.15 (dt, *J* = 15.6, 5.4 Hz, 1H), 1.84 (dd, *J* = 15.1, 4.6 Hz, 1H), 1.24 (d, 3H), 1.07 (s, 9H), 1.04 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.83, 180.27, 140.10, 137.40, 135.83, 134.43, 132.87, 132.76, 130.50, 130.48, 128.71, 128.24, 128.21, 127.40, 127.22, 126.40, 123.95, 108.64, 102.07, 98.63, 86.22, 77.36, 75.58, 68.75, 65.64, 64.58, 61.68, 51.33, 46.51, 45.11, 36.22, 35.10, 29.86, 26.95, 26.35, 26.28, 20.70, 19.15, 13.36; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_4Si$ [M+H+2]: 793.2874. Found: 793.2861.

4.1.7 Diol 18—To a solution of this ammonium salt **17**(8 mg, 0.009 mmol) in tetrahydrofuran/acetic acid (180 μl / 240 μl) was added activated zinc powder (4 mg, ~0.05 mmol). The reaction mixture was vigorously stirred under nitrogen for 18 h at ambient temperature, after which time the solvent had evaporated. The solvent mixture tetrahydrofuran/acetic acid (180 μl / 240 μl) was added again, and the reaction was stirred in a sealed flask for 2 more days. This was filtered through a pad of Celite, rinsed with dichloromethane, and concentrated *in vacuo*. The resulting yellowish oil was dissolved in dichloromethane, washed with $NaHCO_3$ (sat. aq. soln.) and the aqueous portion extracted with ethyl acetate/dichloromethane. The combined organic layers were concentrated and purified by flash chromatography (basic Al_2O_3, 0%→1%→2% methanol/dichloromethane) to provide the desired product **18** as a clear oil (5 mg, 71% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.65 (m, 4H), 7.48 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.39 (m, 6H), 7.32 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.28 (m, 2H), 7.21 (m, 3H), 6.93 (dd, *J* = 8.1, 7.5 Hz, 1H), 5.36 (s, 2H), 4.90 (d, *J* = 2.7 Hz, 1H), 4.31 (b s, 1H), 3.92 (tt, *J* = 11.0, 4.5 Hz, 1H), 3.23 (d, *J* = 10.2 Hz, 1H), 2.98 (m, 1H), 2.75 (tt, *J* = 11.1, 2.8 Hz, 1H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.22 (d, *J* = 10.2 Hz, 1H), 2.02 (d, *J* = 14.4 Hz, 1H), 1.82 (ddt, *J* = 12.2, 4.5, 2.4 Hz, 1H), 1.74 (td, *J* = 11.7, 4.7 Hz, 1H), 1.63~1.57 (m, 2H), 1.45 (dd, *J* = 13.0, 3.4 Hz, 1H), 1.32 (m, 1H), 1.22 (s, 3H), 1.05 (s, 9H), 0.87 (s, 3H), 0.75 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.31, 140.15, 137.31, 136.57, 135.89, 135.84, 134.76, 134.54, 133.70, 129.74, 129.72, 128.66, 127.71, 127.68, 127.27, 126.87, 126.59, 124.01, 102.23, 82.93, 81.97, 77.36, 66.16, 61.05, 56.35, 55.56, 52.49, 46.38, 46.06, 45.22, 43.74, 41.96, 36.13, 29.86, 27.19, 27.14, 21.68, 19.27, 11.79; IR (thin film): 3390 (br), 3069 (w), 2959, 2929, 2856, 1686 (s), 1450, 1359, 1106, 1064, 734, 701 cm^{-1}; HRMS (ESI) Calcd. for $C_{45}H_{53}BrN_2O_4Si$ [M+H+2]: 795.3036. Found: 795.3028.

4.1.8 Ring-fusion epoxide 19—To a solution of the diol **18** (116 mg, 0.141 mmol) in dichloromethane (3.0 mL) at room temperature was added MsCl (32.5 μL, 0.423 mmol), dropwise, and let stir for 5 minutes. To the resulting clear yellow solution was added triethylamine (0.2 mL, 1.41 mmol), dropwise, to give a dark orange, clear solution that was allowed to stir for 2 h, after which equal ammounts of MsCl and triethylamine were again and allowed to stir for 3 h. Methanol (3.0 mL) was added, followed by K_2CO_3 (0.083 g, 0.60 mmol), to give a cloudy orange reaction mixture. After 16 h, the reaction was quenches with $NaHCO_3$ (sat. aq. soln., 10 mL), extracted with dichloromethane/ethyl acetate, with combined organics washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was dry loaded on silica and purified via flash column chromatography (5 → 10 → 20 → 30 → 50% ethyl acetate/hexanes + 1% triethylamine ea.) to furnish the desired epoxide as on off-white foam (83.0 mg, 76% yield) and recovered starting material (29 mg). *Note:* To ensure reproducible ^{1}H NMR data, product was taken up in 10% methanol/dichloromethane, passed through a plug of basic alumina with 10% methanol/dichloromethane as eluent and concentrated *in vacuo*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (ddd, J = 8.1, 4.2, 1.5 Hz, 4H), 7.45 ~ 7.40 (m, 2H), 7.40 ~ 7.35 (m, 4H), 7.31 (dd, J = 8.2, 1.1 Hz, 1H), 7.25 (d, J = 6.6 Hz, 1H), 7.23 ~ 7.14 (m, 5H), 7.08 (dd, J = 7.6, 1.2 Hz, 1H), 6.84 (t, J = 7.8 Hz, 1H), 5.31 (s, 2H), 3.90 (tt, J = 10.4, 4.4 Hz, 1H), 3.16 ~ 3.06 (m, 2H), 3.02 (dq, J = 7.3, 3.9, 3.5 Hz, 1H), 2.60 (d, J = 14.6 Hz, 1H), 2.58 ~ 2.52 (m, 1H), 2.19 (d, J = 14.6 Hz, 1H), 1.92 ~ 1.77 (m, 3H), 1.69 (ddd, J = 12.2, 10.5, 4.5 Hz, 1H), 1.64 ~ 1.57 (m, 1H), 1.33 (dt, J = 12.7, 10.6 Hz, 1H), 1.06 (s, 9H), 1.01 (s, 3H), 0.94 (s, 3H), 0.71 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.47, 140.70, 138.06, 137.99, 135.87, 135.82, 134.61, 134.46, 134.41, 134.12, 129.76, 129.73, 129.16, 128.41, 128.38, 128.35, 127.71, 127.68, 127.66, 127.07, 126.98, 125.43, 125.27, 122.51, 101.86, 70.14, 65.93, 65.55, 59.07, 52.47, 49.54, 47.93, 44.97, 44.66, 43.10, 42.15, 40.82, 31.89, 31.66, 27.11, 25.95, 21.60, 20.34, 19.23, 11.44. IR (thin film): 3069 (w), 2931, 2856, 2247 (w), 1724, 1461, 1333, 1109 (s), 1070, 732, 702, 511 cm^{-1}; HRMS (ESI) Calcd. for $C_{45}H_{52}BrN_2O_3Si$ [M+H+2]: 777.2931. Found: 777.2910.

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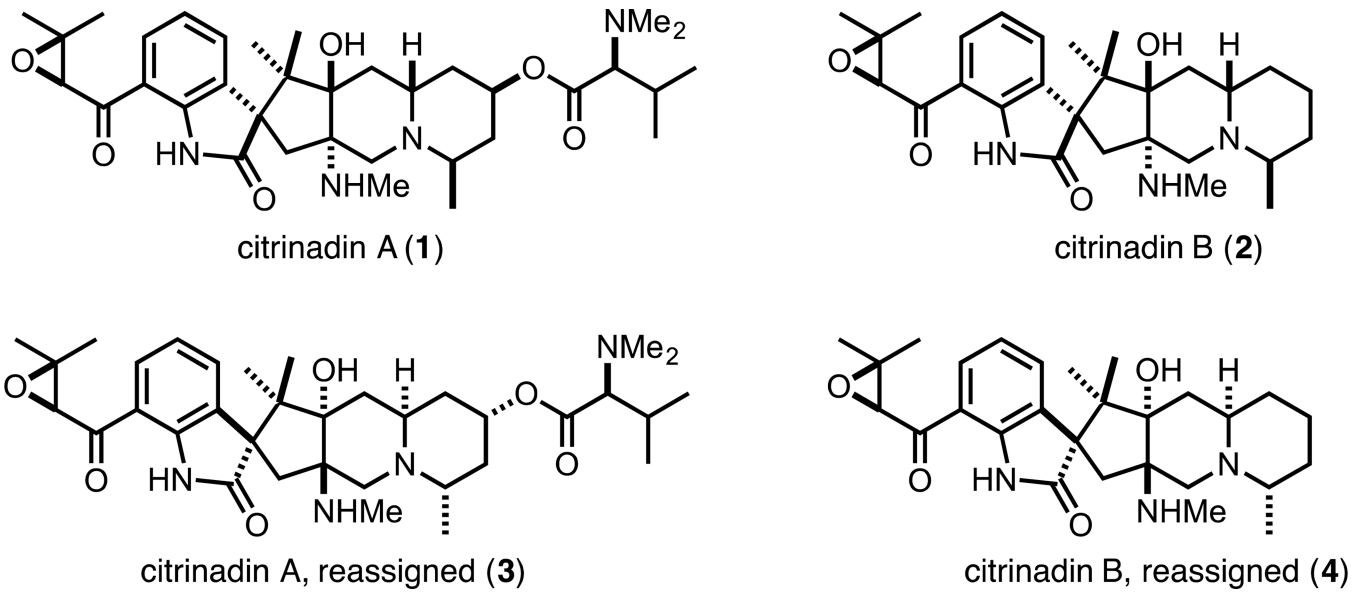
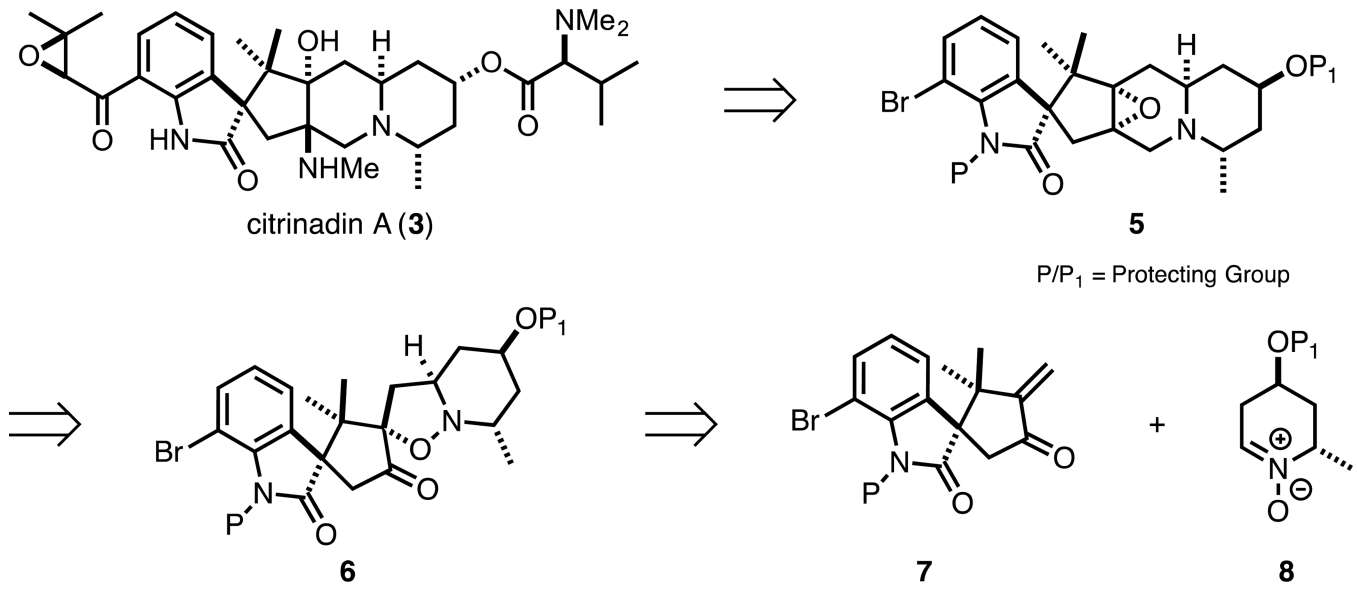
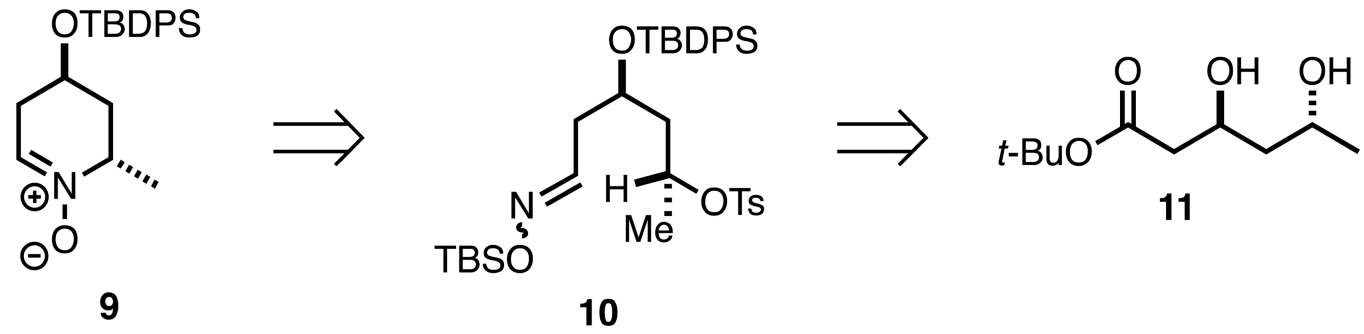


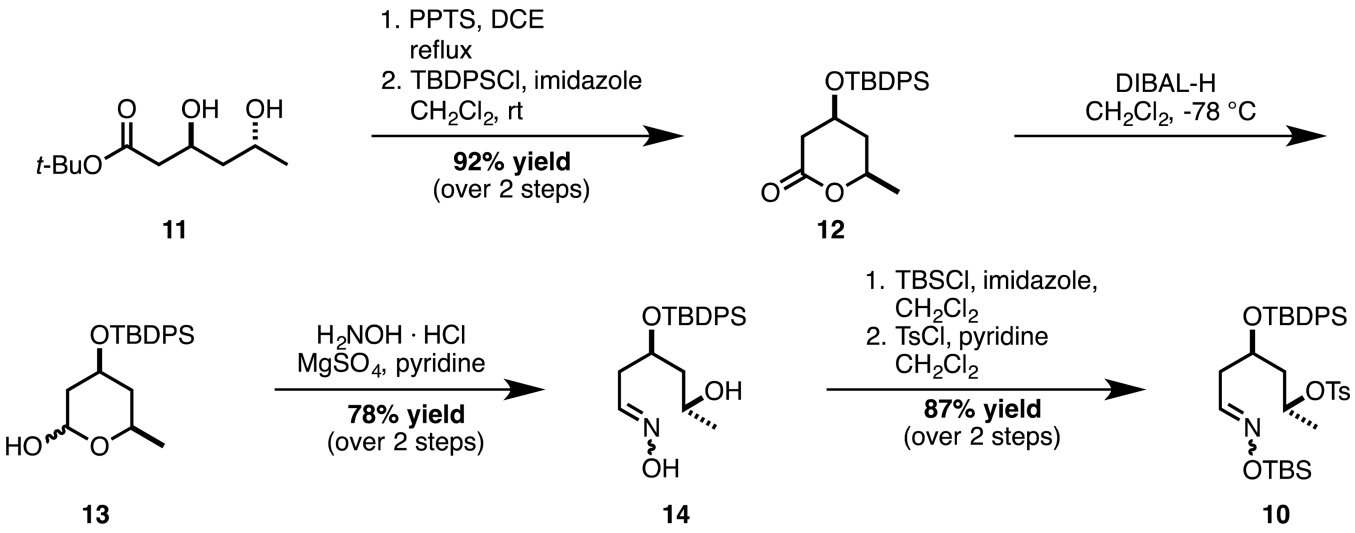
Figure 1.
The Citrinadins



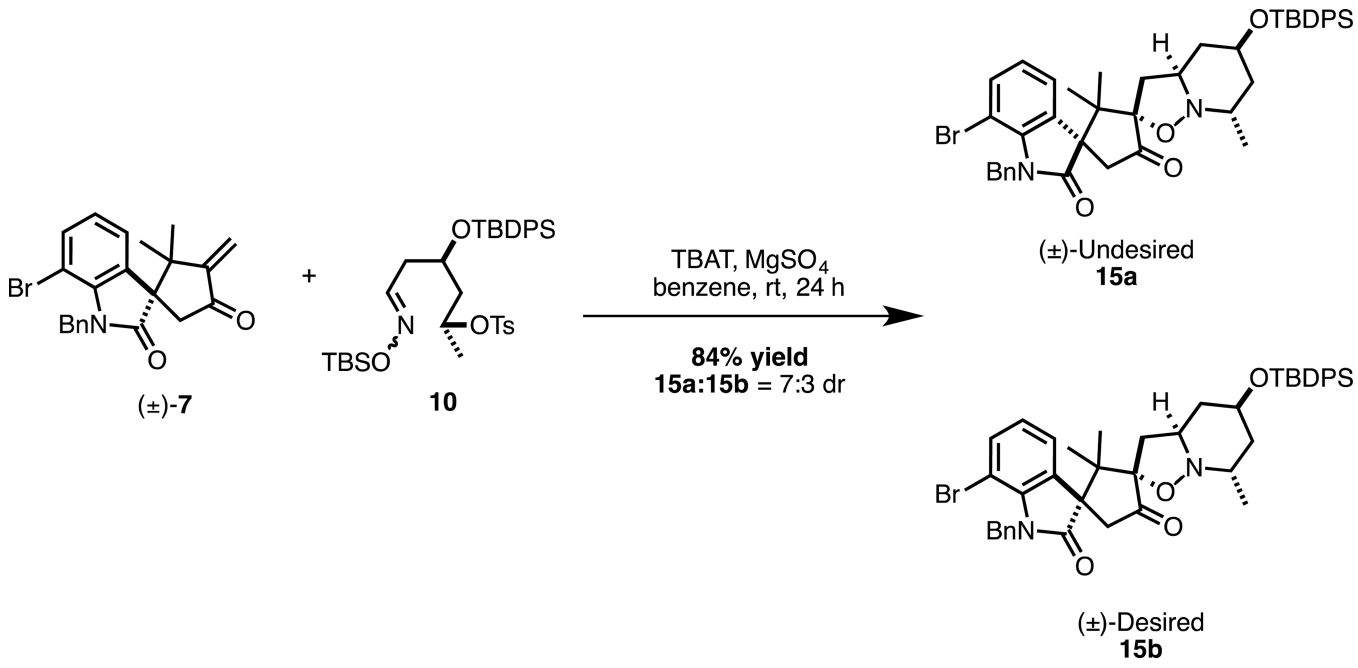
Scheme 1.
Retrosynthetic Analysis of citrinadin A



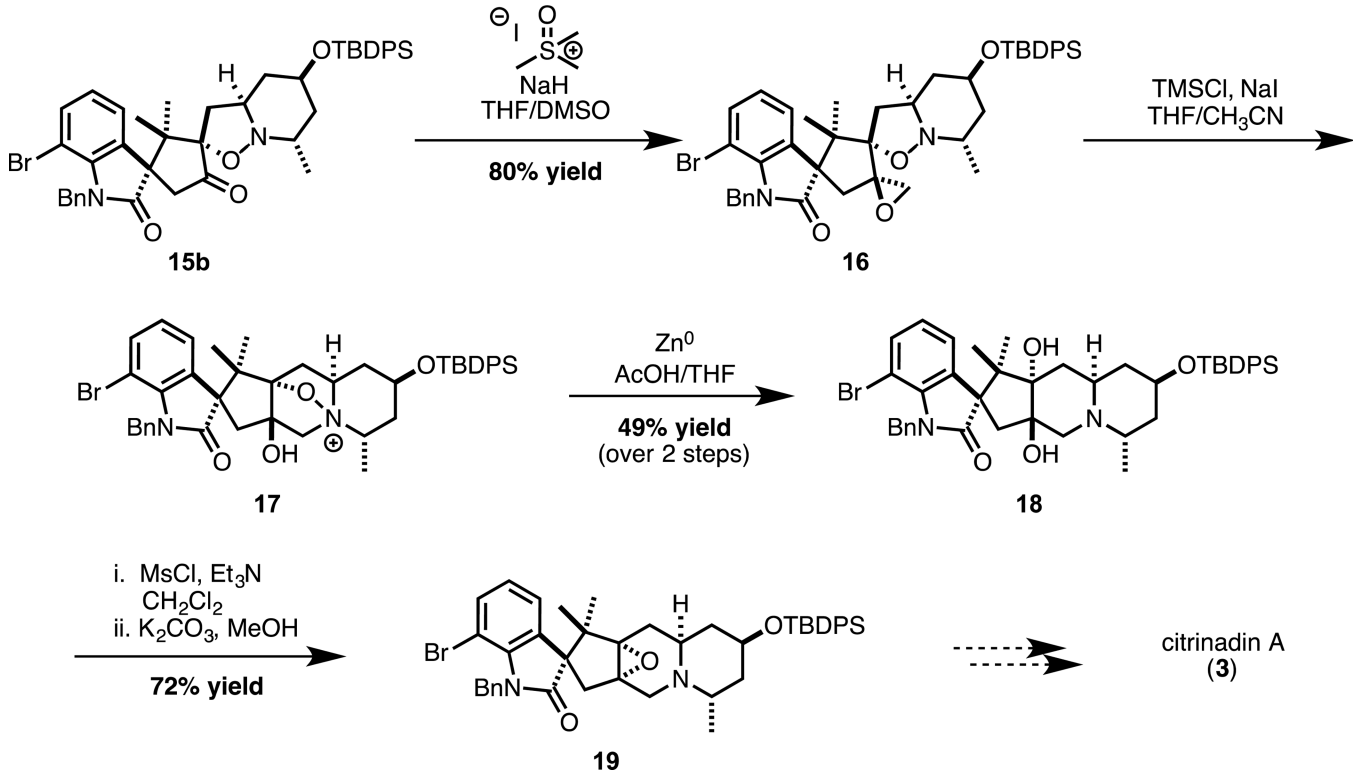
Scheme 2.
Retrosynthesis of Nitrone **9**



Scheme 3.
Synthesis of the Nitrone Precursor



Scheme 4.
[3+2] Nitrone Cycloaddition



Scheme 5.
Completion of the Core Ring System