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SYNTHETIC STUDIES TOWARD WELWITINDOLINONE ALKALOIDS. TANDEM ALDOL−MICHAEL REACTION TO FORM THE CARBOCYCLIC CORE OF WELWITINDOLINONES

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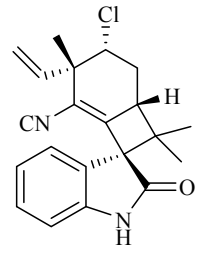
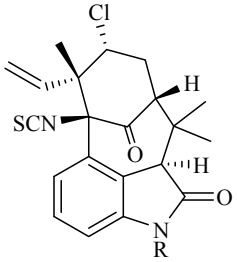
Abstract – A tandem aldol−Michael reaction effectively constructed a bridged ketone, which is the carbocyclic core of the welwitindolinone family.

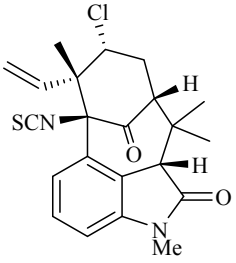
In 1994, Moore and coworkers isolated a series of novel indole alkaloids **1**-**7** from the extracts of blue-green cyanobacteria *Hapalosiphon welwitschii* and *Westiena intracta*.[1] Five years later, oxidized welwitindolinones **8**-**11** were isolated from the epilithic algae *Fischerella muscicola* and *F. major*.[2] Inter alia, *N*-methylwelwitindolinone C isothiocyanate (**7**), which was later dubbed welwistatin, possesses the most relevant biological activity of the entire family (Figure 1).



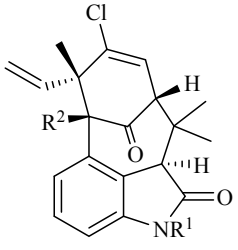
welwitindolinone A isonitrile (**1**)



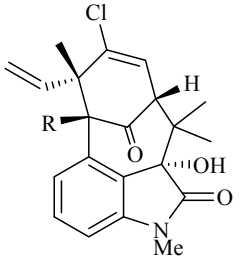
R=H: welwitindolinone B isothiocyanate (**2**)
R=Me: *N*-Me-welwitindolinone B isothiocyanate (**3**)



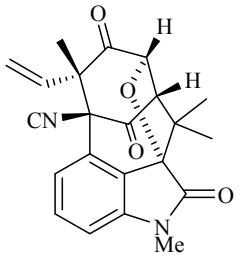
3-*epi*-welwitindolinone B isothiocyanate (**4**)



R^1=H, R^2=NCS: welwitindolinone C isothiocyanate (**5**)
R^1=Me, R^2=NC: *N*-Me-welwitindolinone C isonitrile (**6**)
R^1=Me, R^2=NCS: *N*-Me-welwitindolinone C isothiocyanate (**7**) = welwistatin



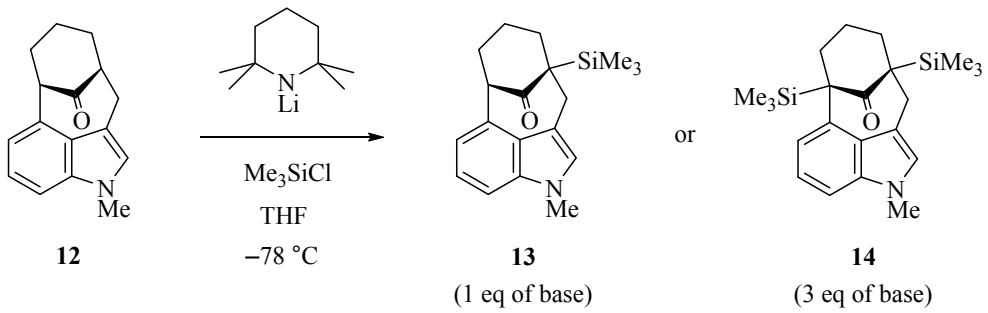
R=NC: 3-OH-*N*-Me-welwitindolinone C isonitrile (**8**)
R=NCS: 3-OH-*N*-Me-welwitindolinone C isothiocyanate (**9**)
R=NHCHO: 3-OH-*N*-Me-welwitindolinone C formamide (**10**)



N-Me-welwitindolinone D isonitrile (**11**)

Figure 1. Structures of Welwitindolinone Alkaloids

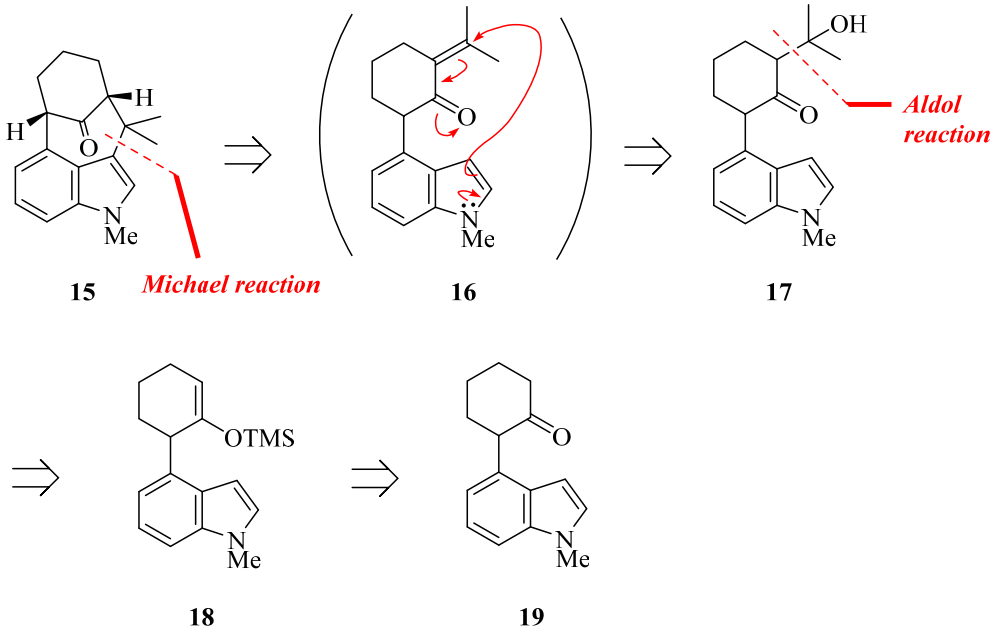
The Moore group showed that welwistatin **7** attenuates the resistance of MCF-7/ADR cells to vinblastine and actinomycin D at doses as low as 1 μM.[3] Additionally, a 36 kb welwitindolinone biosynthetic gene cluster in *H. welwitschii* was recently identified.[4] Except for welwitindolinone A isonitrile (**1**), all welwitindolinones possess a 3,4-disubstituted oxindole with a bicyclo[4.3.1]decane ring system, numerous stereocenters, and many heteroatoms. Since their initial discovery, numerous approaches toward welwitindolinone alkaloids have been published.[5]



12 **13** (1 eq of base) **14** (3 eq of base)

Scheme 1. Silylation of bridged ketone **12**

We have been interested in several chemical reactivities of bridged ketone **12** reported by the Simpkins group.[6] They demonstrated that each bridgehead hydrogen in ketone **12**, which bears the welwistatin skeleton, can be removed with a strong base and the corresponding anion can react with various electrophiles (Scheme 1).



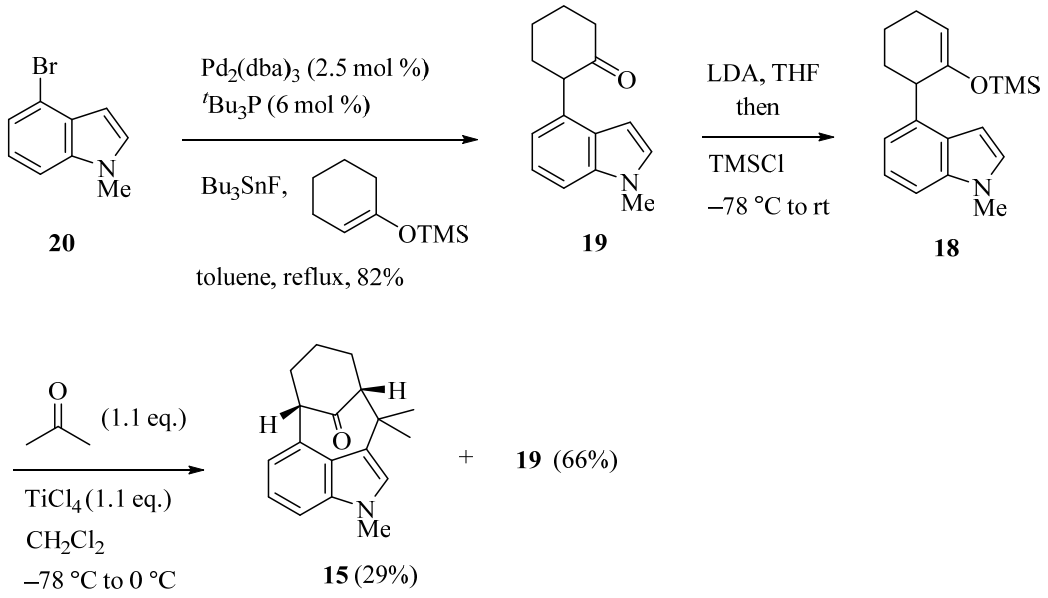
15 **16** **17** **18** **19**

Scheme 2. Retrosynthetic analysis of tetracyclic compound **15**

We considered that bridged ketone **15** might have a similar reactivity as **12** and could be transformed into welwistatin **7** through functional group manipulation. Accordingly, **15** was adopted as our immediate

target molecule. Herein we report an efficient synthesis of **15** employing a tandem aldol−Michael reaction.

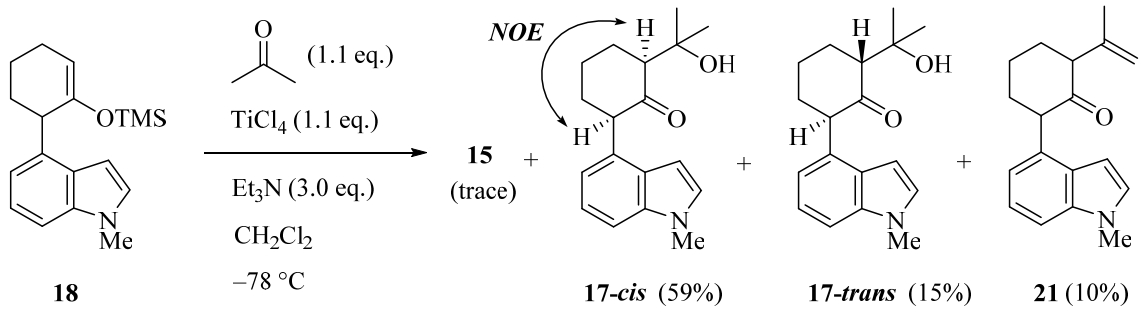
Scheme 2 shows the retrosynthesis of bridged ketone **15.** It was anticipated that bridged ketone **15** could be derived from intermediate **16** through an intramolecular Michael reaction at C-3 of the indole ring. Intermediate **17**, which is a potential precursor of intermediate **16**, could be fashioned from silyl enol ether **18** and acetone through a Mukaiyama cross aldol reaction. Finally, intermediate **18** could be formed by trapping the corresponding kinetic enolate, generated from ketone **19**, with chlorotrimethylsilane.



Scheme 3. Cross aldol reaction of silyl enol ether **18**

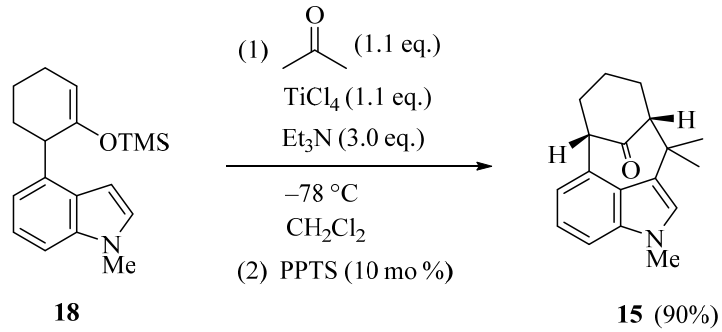
Our approach began with the synthesis of indolylcyclohexanone **19** (Scheme 3). Using Rawal's protocol,[7] palladium-catalyzed coupling of (cyclohex-1-en-1-yloxy)trimethylsilane with 4-bromoindole **20**[8] provided ketone **19**[9] in 82% yield. After conversion of **19** to silyl enol ether **18** under kinetically controlled reaction conditions, a crucial intermolecular cross aldol reaction was performed.[10] Although expected aldol product **17** was not isolated, cyclization product **15** was obtained in 29% yield along with ketone **19** (66%). The spectroscopic properties of synthetic **15** are identical to the previous report.[11] It is unclear at present whether the cyclization reaction proceeded via a Michael reaction[12] or an attack on the generated tertiary carbocation at the β-position of the carbonyl group in **17**.

To accelerate the aldol reaction, different parameters (e.g., substrate concentrations, Lewis acids, and additives) were carefully screened.[13] When the aldol reaction was conducted in the presence of 3.0 equivalent of Et_3N, expected aldol product **17** was produced in 74% yield as a 4:1 mixture of diastereoisomers along with dehydrated product **21** (10%). The exact role of Et_3N is unclear. The relative stereochemistry of the major aldol product **17-*cis*** was determined by a NOE experiment (Scheme 4).



Scheme 4. Cross aldol reaction of silyl enol ether **18** in the presence of Et_3N

Based on the above results, we planned a tandem aldol−Michael reaction using silyl enol ether **18**. To our delight, when the crude aldol product, obtained from **18** with acetone, was subjected to an acidic treatment with pyridinium *p*-toluenesulfonate, desired product **15** was isolated in 90% yield (Scheme 5). It is worth noting that the reaction described above provided **15** in excellent reproducibility in a high yield without depending upon a reaction scale.



Scheme 5. Tandem aldol–cyclization reaction of silyl enol ether **18**

In conclusion, we synthesized bridged ketone **15**, which is the carbocyclic core of the welwitindolinone family, by a tandem aldol−Michael reaction as the key step in an overall yield of 66% starting from 4-bromoindole **20**. Because the previous preparation of bridged ketone **15** requires more steps and has an overall yield of less than 10%,[11] the present methodology should provide a useful knowledge regarding welwitindolinone synthesis.

EXPERIMENTAL

Unless otherwise noted, all reactions were performed in an oven-dried glassware, sealed with rubber septum under an atmosphere of argon. Anhydrous CH_2Cl_2 was purchased from Kanto Chemical Co., Inc. Et_3N and TMSCl were distilled from CaH_2 prior to use. Acetone was distilled from $KMnO_4$. Toluene was distilled from P_2O_5. $TiCl_4$ was distilled prior to use. Unless otherwise mentioned, materials were obtained

from commercial suppliers and used without further purification. Flash column chromatography was carried out using Cica 60 N (spherical / 40-50 μm) silica gel. Compounds were visualized using an ultraviolet lamp (254 nm) and / or by staining with *p*-anisaldehyde (in EtOH) or ammonium molybdate (in 10% H_2SO_4). IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 400 MR (400 MHz) spectrometer with $CHCl_3$ and C_6H_6 as an internal standard. ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometer with $CDCl_3$ as an internal standard. Mass spectra were recorded on Jeol JMS-AX 700 spectrometer.

2-(1-Methyl-1*H*-indol-4-yl)cyclohexan-1-one (19).[9] To a mixture of (cyclohex-1-en-1-yloxy)trimethylsilane (1.62 g, 9.51 mmol), **20** (998 mg, 4.75 mmol), tris(dibenzylidenacetone)dipalladium(0) (109 mg, 0.119 mmol), and Bu_3SnF (2.94 g, 9.51 mmol) was added a solution of *t*-Bu_3P (69.0 μL, 0.284 mmol) in toluene (20 mL) at rt. The resulting mixture was heated under reflux for 24 h. After cooling to rt, the mixture was diluted with EtOAc, washed twice with 1N aqueous NaOH solution, brine, dried over Na_2SO_4, and concentrated to afford a crude product. The crude product was purified by flash column chromatography on silica gel with hexane-EtOAc (4:1 v/v) to produce **19** (885 mg, 82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 6.8 Hz), 7.23 (1H, dd, *J* = 6.8 and 6.4 Hz), 7.05 (1H, d, *J* = 3.2 Hz), 6.97 (1H, dd, *J* = 6.4 and 1.4 Hz), 6.33 (1H, d, *J* = 3.2 Hz), 4.00 (1H, dd, *J* = 6.4 and 5.6 Hz), 3.79 (1H, s), 2.64–2.51 (2H, m), 2.42–2.28 (2H, m), 2.26–2.15 (1H, m), 2.13–2.04 (1H, m) and 1.97–1.84 (2H, m)

1-Methyl-4-(2-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)-1*H*-indole (18). To a solution of diisopropylamine (0.270 mL, 1.93 mmol) in THF (5.0 mL) was added dropwise BuLi (1.10 mL 1.63 M in hexane 1.79 mmol) at −78 °C. After 15 min, ketone **19** (206 mg, 0.906 mmol) in THF (3.0 mL) was added at −78 °C. After stirring for 30 min, TMSCl (0.350 mmol, 2.76 mmol) was added at −78 °C. The mixture was stirred at the same temperature for 15 min, and allowed to warm to rt over a period of 1 h. To the mixture was added a saturated aqueous $NaHCO_3$ solution at 0 °C, and the resulting mixture was extracted three times with hexane–EtOAc (1:1 v/v). The combined organic layers were washed with brine, dried over K_2CO_3 and evaporated to afford a crude product. The crude product was purified by flash column chromatography on silica gel with hexane–EtOAc (20:1 v/v) to lead to **18** (240 mg, 89%) as a pale yellow oil. IR (neat) 1662 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.33–7.26 (2H, m), 6.96 (1H, ddd, *J* = 7.6, 1.2 and 0.8 Hz), 6.68 (1H, dd, *J* = 2.8 and 0.8 Hz), 6.57 (1H, d, *J* = 3.2 Hz), 5.26 (1H, ddd, *J* = 4.0, 1.2 and 0.8 Hz), 4.09 (1H, dd, *J* = 5.6 and 5.2 Hz), 2.93 (3H, s), 2.24–2.04 (4H, m), 1.73–1.63 (1H, m), 1.47–1.39 (1H, m) and 0.07 (9H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 151.8, 137.5, 136.6, 128.2, 127.9, 121.6, 119.3, 107.7, 105.5, 99.7, 44.2, 32.1, 31.6, 24.7, 20.0 and 0.49; LRMS *m/z* 299 $(M)^+$; HRMS calcd for $C_{18}H_{25}ONSi$ $(M)^+$ 299.1705, found 299.1704.

(6*S,10*R**)-2,11,11-Trimethyl-6,7,8,9,10,11-hexahydro-2*H*-6,10-methanocyclonona[*cd*]indol-12-one (15).**[11] To a mixture of **18** (240 mg, 0.801 mmol) and acetone (65.0 μL, 0.882 mmol) in CH_2Cl_2 (8.0 mL) was added titanium tetrachloride (97.0 μL, 0.885 mmol) at −78 °C. After stirring for 15 min, the mixture was allowed to warm to 0 °C. To the mixture was added a saturated aqueous $NaHCO_3$ solution at 0 °C. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to yield a crude product. The crude product was purified by flash column chromatography on silica gel with hexane–EtOAc (3:1 v/v) to give rise to **15** (62.1 mg, 29%) as a dark red oil and **19** (120 mg, 66%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (2H, m), 6.94 (1H, s), 6.85–6.83 (1H, m), 4.06 (1H, dd, *J* = 2.8 and 2.4 Hz), 3.75 (3H, s), 2.59 (1H, d, *J* = 7.2 Hz), 2.31–2.18 (2H, m), 1.97–1.83 (2H, m), 1.55 (3H, s), 1.46–1.34 (1H, m), 1.26–1.18 (1H, m) and 1.14 (3H, s).

(2*S,6*R**)-2-(2-Hydroxypropan-2-yl)-6-(1-methyl-1*H*-indol-4-yl)cyclohexan-1-one (17-*cis*).** To a mixture of **18** (198 mg, 0.661 mmol) and acetone (54.0 μL, 0.733 mmol) in CH_2Cl_2 (6.6 mL) was added titanium tetrachloride (81.0 μL, 0.739 mmol) at −78 °C. After stirring for 15 min, to the mixture was adeed Et_3N (0.280 mL, 2.01 mmol) at −78 °C and stirred for 1 h. The mixture was allowed to warm to 0 °C. To the mixture was added a saturated aqueous $NaHCO_3$ solution at 0 °C. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to afford a crude product. The crude product was purified by flash column chromatography on silica gel with hexane–EtOAc (2:1 v/v) to furnish **12** (1.2 mg, trace) as a dark red oil, **17-*cis*** (112 mg, 59%) as a colorless oil, **17-*trans*** (28.2 mg, 15%) as a colorless oil and **21** (17.3 mg, 10%) as a brown oil. Data for **17-*cis***: IR (neat) 3510 and 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.21 (2H, m), 7.05 (1H, d, *J* = 3.2 Hz), 6.93 (1H, dd, *J* = 7.2 and 0.8 Hz), 6.26 (1H, dd, *J* = 3.2 and 0.8 Hz), 4.01 (1H, dd, *J* = 13.2 and 5.6 Hz), 3.79 (3H, s), 2.71 (1H, ddd, *J* = 13.2, 5.6 and 1.2 Hz), 2.45–2.25 (3H, m), 2.18–2.10 (1H, m), 2.02–1.90 (1H, m), 1.85–1.74 (1H, m) and 1.28 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 136.7, 130.5, 128.8, 127.8, 121.7, 118.5, 108.6, 99.2, 71.6, 60.4, 56.4, 34.9, 33.1, 30.9, 28.8, 25.9 and 25.9; LRMS *m/z* 285 $(M)^+$; HRMS calcd for $C_{18}H_{23}O_2N$ $(M)^+$ 285.1729, found 285.1732. Data for **17-*trans***: IR (neat) 3502 and 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (2H, m), 7.14 (1H, d, *J* = 6.8 Hz), 7.04 (1H, d, *J* = 3.2 Hz), 6.49 (1H, d, *J* = 3.2 Hz), 4.14 (1H, dd, *J* = 5.2 and 4.4 Hz), 3.79 (3H, s), 2.73–2.66 (1H, m), 2.51 (1H, dd, *J* = 12.4 and 5.2 Hz), 2.26–2.11 (3H, m), 1.96–1.76 (2H, m) and 1.12 (6H, s).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 136.9, 130.1, 128.9, 128.0, 121.7, 117.0, 108.6, 100.2, 71.4, 56.3, 55.0, 33.1, 30.1, 29.5, 28.9, 26.3 and 21.9; LRMS *m/z* 285 $(M)^+$; HRMS calcd for $C_{18}H_{23}O_2N$ $(M)^+$ 285.1729, found 285.1730. Data for **21**: IR (neat) 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (0.33H, d, *J* = 2.8 Hz) and 6.28 (1H, d, *J* = 2.8 Hz); LRMS *m/z* 267 $(M)^+$; HRMS calcd for

$C_{18}H_{21}ON$ $(M)^+$ 267.1623, found 267.1623.

Ketone 15 (Tandem aldol−Michael reaction). To a mixture of **18** (50.9 mg, 0.170 mmol) and acetone (14.0 μL, 0.190 mmol) in CH_2Cl_2 (1.7 mL) was added titanium tetrachloride (21.0 μL, 0.192 mmol) at −78 °C. After 15 min, Et_3N (72.0 μL, 0.517 mmol) was added at −78 °C and the stirring of the resulting reaction mixture was continued for 1 h at −78 °C. The mixture was allowed to warm to 0 °C over a period of 30 min. To the mixture were added water and a saturated aqueous $NaHCO_3$ solution at 0 °C. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to afford a crude product. The crude product was added to a benzene solution (5.7 mL) of PPTS (4.3 mg, 17.0 μmol), and the mixture was heated under reflux for 18 h. After cooling to rt, to the reaction mixture was added a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to afford a crude product. The crude product was purified by flash column chromatography on silica gel with hexane–EtOAc (3:1 v/v) to provide **15** (40.8 mg, 90%) as a dark red oil.

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