Tetrahedron 87 (2021) 132117

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of (−)-4-desacetoxy-1-oxovindoline: Single atom exchange of an embedded core heteroatom in vindoline

Byron A. Boon, Yi-Yun Yu, Dale L. Boger*

Department of Chemistry and the Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA, 92037, USA

ARTICLE INFO

Article history:
Received 26 February 2021
Received in revised form
21 March 2021
Accepted 23 March 2021
Available online 29 March 2021

Dedication. This article is dedicated to Professor Steve Martin, a good friend and long-time member of the Tetrahedron Board of Editors alongside which I had the pleasure of serving for many years.

Keywords:
Oxadiazole cycloaddition cascade
Vindoline analogue
Vinca alkaloids

ABSTRACT

A concise total synthesis of (−)-4-desacetoxy-1-oxovindoline is disclosed, bearing a single heteroatom exchange in the core structure of the natural product 4-desacetoxyvindoline. Central to the synthesis is powerful oxadiazole intramolecular [4 + 2]/[3 + 2] cycloaddition cascade that formed four C–C bonds, created three new rings, and established five contiguous stereocenters about the new formed central 6-membered ring.

1. Introduction

Vindoline (**1**) and its naturally occurring immediate biosynthetic precursor 4-desacetoxyvindoline (**2**) are found as components of the more complex Vinca alkaloids, constituting the lower half of the structures of vinblastine (**3**) and 4-desacetoxyvinblastine (Fig. 1) [1,2]. Although both **3** and 4-desacetoxyvinblastine exhibit efficacious antitumor activity [3], the former is found in natural sources in amounts at least 10-fold higher. Consequently, vinblastine and the related naturally occurring Vinca alkaloid vincristine (**4**) were explored and introduced into the clinic by Eli Lilly [1]. Today, they are widely used in a variety of curative combination therapies for the treatment of cancer and vinblastine is the second most prescribed small molecule oncology drug. Despite their similarities, differing only in the N1 methyl versus formyl substituent, vinblastine and vincristine display near identical on target tubulin binding affinities [4], but exhibit distinguishable characteristic cellular uptake and efflux rates [5], and different tumor sensitivities [1]. In addition, they display different dose limiting toxicities, where peripheral neuropathy is the dose-limiting side effect of vincristine chemotherapy, whereas reversible myelosuppression is common to vinblastine treatments [6,7]. These observations suggest that the embedded N1-heteroatom and its substituent affect the in vivo disposition of drugs, but do not appear to impact intracellular target engagement and the ensuing functional activity. As a result of this and in an extension of our studies on vinblastine [8], we targeted single heteroatom replacements [9] (O and S) of the N1 center embedded in the core structure of the natural product drugs with the intention of further probing this unique impact. Of the initial candidate replacements to explore, the O1 (**5**) versus N1 substitution was most attractive, providing a cLogP and calculated polar surface area (PSA) that lies precisely halfway between those of vinblastine (N1Me, **3**) and vincristine (N1CHO, **4**).

As a result, we first targeted the total synthesis 4-desacetoxy-1-oxovindoline (**6**) with use of methodology inspired by and first explored with vindoline [10] that in turn was utilized in the total synthesis of vinblastine [11], vincristine and related natural products [12], and subsequently for a series of analogs [13–26]. Key to the approach to vindoline that maps seamlessly onto the analogue **6** was a powerful oxadiazole intramolecular [4 + 2]/[3 + 2] cycloaddition cascade with tethered dienophile-dipolarophile pairs [27,28] (Fig. 1).

* Corresponding author.
E-mail addresses: boger@scripps.edu, bogeradm@scripps.edu (D.L. Boger).

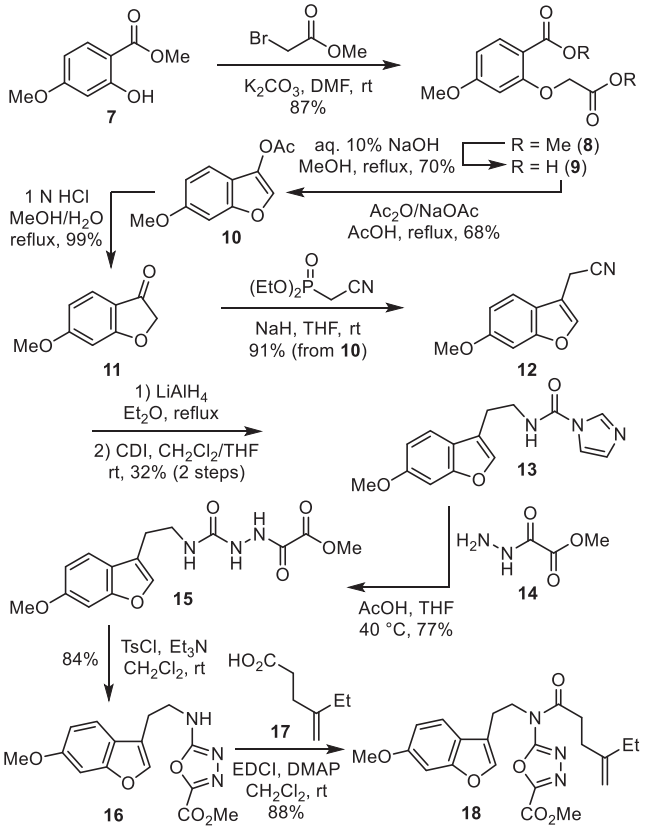
https://doi.org/10.1016/j.tet.2021.132117
0040-4020/

2. Results and discussion

Synthesis of **6** began with the commercial phenol **7** and its use in the preparation of the known, but not commercially available, starting ketone **11** [29] (Scheme 1). Phenol alkylation with methyl 2-bromoacetate in the presence of K_2CO_3 gave diester **8** in excellent yield (87%). In a two-step procedure, hydrolysis of **8** (aq NaOH, MeOH) afforded crude diacid **9**, which underwent an intramolecular cyclization/decarboxylation reaction sequence mediated by Ac_2O/NaOAc in AcOH to provide benzofuran **10**. Completion of the preparation of the benzofuran starting material **11** [29] was accomplished by hydrolysis of **10** under acidic conditions (1 N HCl, MeOH/H_2O, reflux, 99%), which was subsequently converted to the known nitrile **12** [30] in excellent yield (91%, 2 steps from **10**) with use of a Horner–Wadsworth–Emmons reaction (NaH, diethyl cyanomethylphosphonoacetate).

Subsequent reduction of nitrile **12** with $LiAlH_4$, followed by *N*-acylation of the crude free amine with CDI (*N*,*N*-carbonyldiimidazole) gave urea **13** (Scheme 1). Addition of methyl oxalylhydrazide (**14**) [27] in the presence of AcOH in THF furnished the oxadiazole precursor **15** (77%). Upon treatment with tosyl chloride (TsCl) and Et_3N, **15** underwent a dehydrative cyclization to provide oxadiazole **16** in good yield (84%). The key cycloaddition precursor was prepared by *N*-acylation of **16** with carboxylic acid **17** [27] promoted by EDCI, providing **18** in excellent yield (88%).

We turned to [4 + 2]/[3 + 2] cascade cycloaddition reaction of oxadiazole **18** initiated by the inverse electron demand Diels–Alder of the tethered alkene with the activated electron-deficient oxadiazole [31]. Precedent for the anticipated [3 + 2] cycloaddition participation of a tethered benzofuran was disclosed in our original work disclosing the cycloaddition cascade [27] (Fig. 2). Notably, a



Scheme 1. Synthesis of oxadiazole **18**.

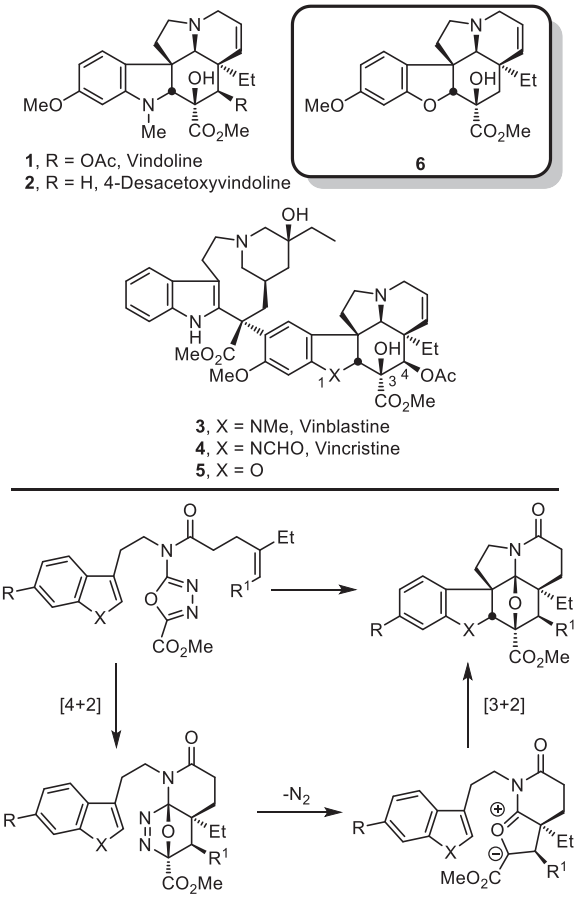


Fig. 1. Structure of natural products, target analogue **6**, and key cycloaddition cascade.

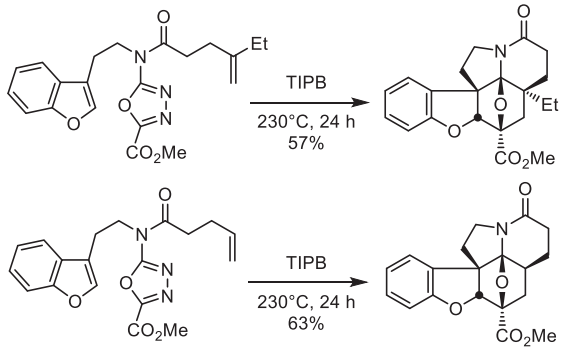
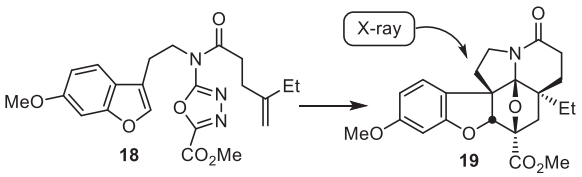


Fig. 2. Precedent for cycloaddition cascade [27].

single diastereomer is formed that results from exclusive endo [3 + 2] cycloaddition of the benzofuran with the uniquely stabilized intermediate 1,3-dipole directed to the face opposite the newly formed lactam, a stereochemical outcome dictated by the benzofuran linking tether.

Initial attempts to promote the cascade cycloaddition reaction of **18** under standard reaction conditions in 1,2-dichlorobenzene (DCB) at 180 °C or in 1,3,5-triisopropylbenzene (TIPB) at 180–230 °C did not provide **19** in significant quantities although trace amounts of product were observed at the higher temperatures (Fig. 3). Other high boiling solvents (xylenes, dimethyl sulfoxide (DMSO), *N*-methylpyrrolidine (NMP) and decalin), added



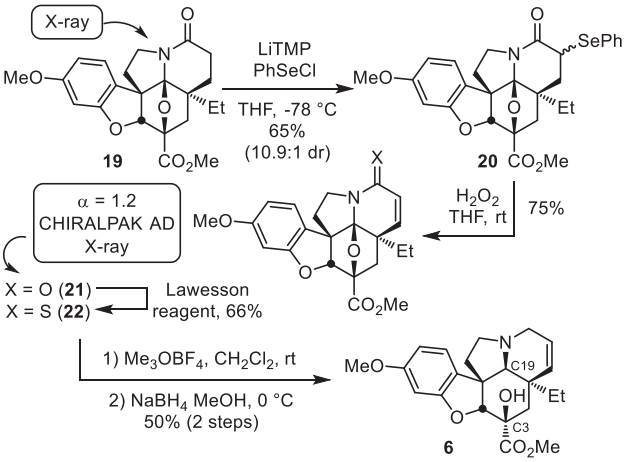
entry[a]	solvent	temperature (°C)	yield (%)
1	DCB	180	0
2	TIPB	230	4
3	Dowtherm A	230	18
4	Dowtherm A	250	27
5	Dowtherm A	reflux	30
6[b]	Therminol 62	330	28
7[b]	Therminol 66	330	36
8[c]	Downtherm A	250	31
9[d]	Downtherm A	250	35
10[e]	Downtherm A	250	40
11[f]	Downtherm A	250	36

[a]Unless indicated otherwise 0.01 mmol scale, 0.5 mM, 24 h. [b]2 h. [c]72 h. [d]0.08 mmol scale. [e]0.12 mmol scale. [f]0.18 mmol scale.

Fig. 3. Cascade cycloaddition optimization.

Lewis acids, and microwave conditions were unsuccessful in facilitating the cycloaddition cascade reaction (not shown). Although the initiating [4 + 2] cycloaddition was observed to proceed uneventfully, providing the product derived from hydrolysis of the intermediate 1,3-dipole upon workup, the ensuing [3 + 2] cycloaddition with the electron-rich benzofuran proved surprisingly slow. To explore higher temperature reaction conditions, the thermal heat transfer fluid Dowtherm A was examined as solvent where promising yields of **19** were observed upon warming at 230 °C (18%). The yield of **19** increased with further elevated temperatures of 250 °C (27%) and reflux (30%, bp Dowtherm A = 257 °C). Solvents such as Therminol 62 and Therminol 66 with even higher boiling points gave similar yields of **19** at higher temperatures and shorter reaction times (330 °C, 2 h), but removal of these solvents proved challenging, precluding their general use. Cycloadduct yields were similar for reactions run for 24 h or 72 h in Dowtherm A and further examination of the reaction gave reliable yields on the scales of 0.01–0.18 mmol (31–40%, 24 h, 250 °C). As highlighted previously, this reaction displays a remarkable diastereoselectivity, generating a single cascade cycloadduct **19** whose structure was unambiguously established with a single-crystal X-ray structure determination [32]. Although the conversion was more modest than we would like, the powerful reaction assembles the full target skeleton, forming four C–C bonds, creating three new rings, and establishing five contiguous and four quaternary stereocenters about the new formed central 6-membered ring.

Completion of the synthesis of **6** required C6–C7 double bond installation and removal of the C8 amide carbonyl (Scheme 2). Phenylselenation of amide **19** was successfully mediated by LiTMP to provide **20** (65%, 10.9:1 dr). A H_2O_2-mediated selenide oxidation and subsequent selenoxide elimination in THF gave α,β-unsaturated amide **21** in good yield (75%). Resolution of **21** was accomplished (α = 1.25) on a semipreparative Daicel CHIRALPAK AD column (2 × 25 cm, 30% *i*PrOH/hexanes, 7 mL/min) to provide (+)-**21** (t_r = 24.1 min), bearing the natural absolute configuration of vindoline, and *ent*-(−)-**21** (t_r = 19.3 min). Both the structure and absolute stereochemistry of natural (+)-**21** and *ent*-(−)-**21** were unambiguously established by single crystal X-ray diffraction [32]. Amide **21** was converted to thioamide **22** with Lawesson reagent (66%). In a two-step one pot sequence, each enantiomer of **22** was *S*-alkylated with Meerwein salt (Me_3OBF_4), and subjected to reductive N,O-ketal cleavage and desulfurization by treatment with



Scheme 2. Completion of the synthesis of (−)-4-desacetoxy-1-oxovindoline (**6**).

$NaBH_4$, removing the C8 functionality, releasing the C3-hydroxyl group and introducing the C19 stereochemistry, to provide (−)-**6** (50%, 2 steps) and its enantiomer.

3. Conclusions

A concise total synthesis of (−)-4-desacetoxy-1-oxovindoline (**6**) is disclosed, bearing a single heteroatom exchange in the core structure of the natural product 4-desacetoxyvindoline (**2**). Central to the synthesis is a powerful oxadiazole intramolecular [4 + 2]/[3 + 2] cycloaddition cascade that formed four C–C bonds, created three new rings, and established five contiguous and four quaternary stereocenters about the new formed central 6-membered ring. Extensions of the studies to the synthesis of 1-oxovindoline and their incorporation into vinblastine analogs are in progress and will be reported in due course.

4. Experimental section

4.1. General information

All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. All commercial compounds were used as received unless otherwise noted. Lawesson's reagent was purchased from Acros Organics (lot #A0352925) and was recrystallized from toluene prior to use. Dowtherm A was purchased from Fisher Scientific (lot #10200385) and was dried for 2 d over activated 4 Å mol sieves and passed through a column of oven-dried basic alumina prior to use. Basic alumina was purchased from Acros Organics (lot# A0390637) and was oven dried at 150 °C for 2 d prior to use. 4 Å mol sieves (8–12 mesh) were purchased from Acros Organics (lot #A0356556) and were oven dried at 150 °C for 2 d prior to use. Reactions were monitored using MilliporeSigma TLC plates (0.25 mm, 60-F_{254}) and were visualized using short-wave UV light as well as cerium ammonium molybdate stain. Preparative thin-layer chromatography (PTLC) was performed with MilliporeSigma plates (0.5 mm, 60-F_{254}). Column chromatography was performed using SiliCycle silica gel (SiO_2, 40–63 μm) and reagent grade solvents. NMR spectra were recorded on Bruker AVIII 400 (5 mm BBFO probe), Bruker AV NEO 500 (5 mm BBFO Smart Probe), or Bruker AVIII HD 600 spectrometers (either a 5 mm CPDCH CryoProbe or a 5 mm CPQCl CryoProbe). Spectra recordings were calibrated to the solvent signal ($CDCl_3$ δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR, DMSO-d_6 δ = 2.50 for ^{1}H NMR and δ = 39.52

for ^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or b (broadened). Coupling constants (*J*) (H,H) are given in Hz. The single crystal X-ray diffraction studies were carried out on a Bruker SMART APEX II CCD diffractometer equipped with Cu K_α radiation ($\lambda = 1.54178$). IR spectra were recorded with a Nicolet 380 FTIR with an ATR attachment and selected absorptions are reported in cm^{-1}. High resolution mass spectral data was recorded on a Waters LC with a Waters G2-XS detector. Chiral HPLC separations were performed on Shimadzu LC-6AD with a Shimadzu SPD-10A VP UV–Vis detector with a CHIRALPAK AD column (2 × 25 cm). Optical rotations were recorded on a Rudolph Research Analytical Autopol III Automatic Polarimeter. Compound **11** [29], **12** [30] and **17** [27] were prepared by previously established literature procedures and were identical in all respects with reported material.

4.2. Compound 12

Sodium hydride (2.63 g, 73.3 mmol) was suspended in THF (100 mL). Diethyl (cyanomethyl)phosphonate (11.9 mL, 73.3 mmol) was added dropwise over 10 min at 25 °C and the reaction mixture was stirred for 30 min. The solution was cooled to 0 °C, stirred for 30 min, and a solution of **11** [29] (5.95 g, 36.7 mmol) in THF (20 mL) was added dropwise over 10 min at that temperature. The solution was warmed to 25 °C over 1 h and stirred for 15 h. The reaction was quenched with the addition of water and the mixture was extracted with EtOAc (3x). The organic layers were combined, washed with saturated aq NaCl, dried with $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (SiO_2, 20% EtOAc/hexanes) gave 6.22 g (91%) of **12** as a yellow solid identical in all respects with authentic material [30]: ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, $J = 1.3$ Hz, 1H), 7.46 (d, $J = 8.6$ Hz, 1H), 7.06 (d, $J = 2.3$ Hz, 1H), 6.96 (dd, $J = 8.6, 2.2$ Hz, 1H), 3.89 (s, 3H), 3.76 (d, $J = 1.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 156.7, 141.8, 119.6, 119.2, 116.9, 112.5, 110.1, 96.4, 55.9, 13.3; IR (neat) 3108, 2916, 2834, 2202, 1623, 1585, 1442, 1265, 1193, 1224, 1144, 1121, 1018, 932, 807 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{11}H_9NO_2$) 188.0712, found 188.0711.

4.3. Compound 13

$LiAlH_4$ (3.78 g, 99.6 mmol) was suspended in Et_2O (81 mL) at 0 °C and a solution of compound **12** [30] (6.21 g, 33.2 mmol) in Et_2O (186 mL) was added dropwise over 30 min. The solution was warmed at reflux for 3 h before being cooled to 0 °C and quenched with the slow sequential dropwise addition of water (3.8 mL), aq 15% NaOH (3.8 mL) and water (11.3 mL). The solution was warmed to 25 °C and stirred for 1 h. $MgSO_4$ was added until the mixture was free flowing, and stirred for an additional 30 min. The mixture was filtered, the solids were rinsed with Et_2O, and the mixture was concentrated in vacuo to give 4.44 g of crude amine as a red oil that was used without further purification. For the synthesis of **13**, 1,1′-carbonyldiimidazole (5.65 g, 34.8 mmol) was dissolved in THF (23 mL) at 0 °C and a solution of the crude amine (4.44 g, 23.2 mmol) in CH_2Cl_2 (116 mL) was added dropwise over 30 min. The solution was warmed to 25 °C and stirred for 19 h. The reaction mixture was concentrated in vacuo. Column chromatography (SiO_2, 85:11:4 CH_2Cl_2/acetone/MeOH) gave 3.02 g (32% over 2 steps) of **13** as an orange solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.44–7.35 (m, 2H), 7.24 (t, $J = 1.3$ Hz, 1H), 7.03 (s, 1H), 7.01 (d, $J = 2.2$ Hz, 1H), 6.88 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.16 (br s, 1H), 3.85 (s, 3H), 3.74 (q, $J = 6.5$ Hz, 2H), 3.01 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 156.4, 149.1, 141.0, 135.8, 129.6, 121.1, 119.5, 116.9, 116.5, 111.8, 96.3, 55.8, 40.6, 23.8; IR (neat) 3030, 3014, 2998, 2971, 1739, 1420, 1366, 1240, 1217, 1150 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{15}H_{16}N_3O_3$) 286.1192, found 286.1195.

4.4. Compound 15

Compound **13** (3.02 g, 10.6 mmol) was dissolved in THF (67 mL) and AcOH (0.67 mL, 11.7 mmol) was added at 25 °C. Compound **14** [27] (1.38 g, 11.7 mmol) was added in one portion, and the solution was warmed at 40 °C for 22 h. The solvent was removed in vacuo. Column chromatography (SiO_2, 80:18:2 CH_2Cl_2/acetone/MeOH) gave 2.73 g (77%) of **15** as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.13 (s, 1H), 7.42–7.31 (m, 2H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.84 (dd, $J = 8.5, 2.3$ Hz, 1H), 5.97 (t, $J = 5.7$ Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.45 (q, $J = 6.6$ Hz, 2H), 2.79 (t, $J = 6.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.1, 157.2, 156.3, 154.9, 141.1, 121.2, 119.6, 117.0, 111.5, 96.1, 55.7, 53.7, 39.6, 24.1; IR (neat) 3320, 3120, 1722, 1634, 1579, 1492, 1254, 1147, 1126 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{15}H_{18}N_3O_6$) 336.1196, found 336.1198.

4.5. Compound 16

Compound **15** (2.71 g, 8.09 mmol) was dissolved in CH_2Cl_2 (81 mL) followed by Et_3N (3.38 mL, 24.3 mmol) and TsCl (2.01 g, 10.5 mmol). The reaction mixture was stirred for 17 h at 25 °C before the solvent was removed in vacuo. Column chromatography (SiO_2, 50:47:3 EtOAc/hexanes/Et_3N) gave 2.17 g (84%) of **16** as a tan solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.02 (d, $J = 2.2$ Hz, 1H), 6.90 (dd, $J = 8.6, 2.2$ Hz, 1H), 5.35 (s, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.79 (q, $J = 6.5$ Hz, 2H), 3.03 (t, $J = 6.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 158.5, 156.6, 154.9, 151.8, 141.4, 120.9, 119.6, 116.3, 111.9, 96.3, 55.9, 53.4, 42.9, 23.8; IR (neat) 3235, 3120, 2958, 1731, 1628, 1439, 1187, 1142, 1055, 1021, 807 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{15}H_{16}N_3O_5$) 318.1090, found 318.1093.

4.6. Compound 18

Compound **16** (3.09 g, 9.75 mmol) was dissolved in CH_2Cl_2 (16 mL) and a solution of **17** [27] (3.12 g, 24.4 mmol) in CH_2Cl_2 (16 mL) was added dropwise over 10 min at 0 °C. EDCI·HCl (5.61 g, 29.2 mmol) and DMAP (2.38 g, 19.5 mmol) were added sequentially, each in a single portion, at 0 °C and the mixture was stirred for 30 min. The solution was allowed to warm to 25 °C and stirred for 24 h. The solvent was removed in vacuo. Column chromatography (SiO_2, 33% EtOAc/hexanes) gave 3.68 g (88%) of **18** as a light yellow solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.5$ Hz, 1H), 7.36 (s, 1H), 6.96 (d, $J = 2.3$ Hz, 1H), 6.88 (dd, $J = 8.6, 2.2$ Hz, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 4.29–4.22 (m, 2H), 4.02 (s, 3H), 3.83 (s, 3H), 3.07–2.97 (m, 4H), 2.40 (t, $J = 7.7$ Hz, 2H), 2.04 (q, $J = 7.4$ Hz, 2H), 1.03 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 162.0, 158.3, 156.5, 154.2, 153.6, 149.5, 141.5, 120.9, 119.8, 115.9, 111.9, 108.6, 96.2, 55.8, 53.8, 46.8, 35.0, 30.9, 29.1, 22.8, 12.4; IR (neat) 2965, 1754, 1707, 1623, 1563, 1493, 1439, 1319, 1284, 1181, 1023, 932, 896 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{22}H_{26}N_3O_6$) 428.1822, found 428.1822.

4.7. Compound 19

Compound **18** (50.0 mg, 0.117 mmol) was dissolved in Dowtherm A (234 mL) and the solution was sparged for 30 min with N_2 with a gas dispersion tube in a 350 mL pressure vessel (Dowtherm A was dried for 2 d over activated 4 Å mol sieves and passed through a small column of oven-dried basic alumina prior to use). The reaction vessel was sealed, and the solution was warmed at 250 °C for 24 h. The reaction mixture was cooled to 25 °C and passed through a small column (SiO_2), and the column was flushed with hexanes (500 mL) to dryness. The cycloadduct was flushed through the column with EtOAc (100 mL) and concentrated in vacuo. PTLC (SiO_2 50% EtOAc/hexanes) gave 17.7 mg (38%, typically

32–40%) of **19** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88–6.82 (m, 1H), 6.47–6.43 (m, 2H), 5.11 (d, J = 1.1 Hz, 1H), 3.96 (d, J = 10.4 Hz, 1H), 3.96 (dd, J = 10.4, 2.4 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.52 (dt, J = 12.9, 10.4 Hz, 1H), 2.45–2.37 (m, 1H), 2.34–2.21 (m, 3H), 2.20 (d, J = 13.0 Hz, 1H), 1.84 (dd, J = 13.0, 1.3 Hz, 1H), 1.79–1.74 (m, 1H), 0.92 (dq, J = 14.8, 7.3 Hz, 1H), 0.63 (t, J = 7.4 Hz, 3H), 0.29 (dq, J = 14.7, 7.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 170.3, 162.4, 161.9, 124.3, 120.1, 107.9, 107.1, 97.1, 94.2, 84.4, 64.5, 55.7, 53.1, 47.1, 43.7, 37.9, 35.1, 29.4, 28.0, 22.4, 9.9; IR (neat) 2958, 1738, 1592, 1394, 1355, 1322, 1217, 1122, 1083, 1056, 864 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{22}H_{26}NO_6$) 400.1760, found 400.1765. The structure and relative stereochemistry of **19** were unambiguously established with a single crystal X-ray crystal structure (CCDC 2064479), see Supporting Information S23–S24.

4.8. Compound 20

Compound **19** (52.6 mg, 0.132 mmol) and PhSeCl (50.4 mg, 0.263 mmol) were dissolved in THF at −78 °C. In a separate flask, 2,2,6,6-tetramethylpiperidine (0.3 mL, 1.78 mmol) was dissolved in THF (3.7 mL) at 0 °C then *n*-BuLi (0.71 mL, 1.78 mmol, 2.5 M in hexanes) was added dropwise and the solution was stirred for 1 h, before being cooled to −78 °C. The LiTMP solution (0.66 mL, 0.263 mmol) was added dropwise at −78 °C and the mixture was stirred for an additional 30 min before additional LiTMP solution was added (0.33 mL, 0.132 mmol). After 1 h, a third portion of LiTMP was added (0.16 mL, 0.066 mmol) and the solution was stirred for an additional 30 min prior to quench with saturated aq NH_4Cl (3.2 mL). The solution was warmed to 25 °C, diluted with water (4 mL), and the mixture was extracted with EtOAc (3x). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (SiO_2, 33% EtOAc/hexanes) gave 47.8 mg (65%, 10.9:1 dr) of **20** as a clear colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ (major diastereomer) 7.67 (dd, J = 7.5, 1.7 Hz, 2H), 7.31–7.26 (m, 3H), 6.86–6.81 (m, 1H), 6.46–6.41 (m, 2H), 5.10 (s, 1H), 4.05–3.92 (m, 2H), 3.90–3.84 (m, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.55 (dt, J = 12.9, 10.4 Hz, 1H), 2.45 (t, J = 13.3 Hz, 1H), 2.25 (dd, J = 12.8, 7.8 Hz, 1H), 2.11 (d, J = 13.1 Hz, 1H), 1.99 (dd, J = 13.8, 6.2 Hz, 1H), 1.79 (d, J = 13.1 Hz, 1H), 0.88 (dq, J = 14.7, 7.3 Hz, 1H), 0.50 (t, J = 7.4 Hz, 3H), 0.23 (dq, J = 14.7, 7.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (major diastereomer) 169.9, 162.4, 162.0, 135.3, 129.2, 128.9, 128.3, 124.3, 119.8, 107.9, 106.9, 97.1, 94.1, 84.3, 64.4, 60.5, 55.7, 53.0, 47.8, 44.9, 39.6, 37.7, 36.7, 35.2, 22.8, 21.2, 14.3, 9.8; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{28}H_{30}NO_6Se$) 556.1233, found 556.1231.

4.9. Compound (+)-21

Compound **20** (112 mg, 0.202 mmol) was dissolved in THF (20 mL) followed by the addition of aq 30% H_2O_2 (70 μL, 0.809 mmol) and the solution was stirred at 25 °C. After 2 h the reaction was quenched with the addition of saturated aq $Na_2S_2O_3$ (3 mL). The mixture was diluted with water, extracted with CH_2Cl_2 (3x), dried with $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (SiO_2, 33% hexanes/EtOAc) gave 59.9 mg (75%) of **21** as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04–7.00 (m, 1H), 6.50–6.45 (m, 2H), 6.24 (d, J = 9.8 Hz, 1H), 5.97 (d, J = 9.8 Hz, 1H), 5.17 (s, 1H), 4.18 (ddd, J = 11.5, 9.9, 1.3 Hz, 1H), 3.96 (td, J = 11.4, 7.6 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 2.56 (dt, J = 12.8, 10.3 Hz, 1H), 2.42–2.27 (m, 3H), 0.84–0.71 (m, 2H), 0.59 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 163.1, 162.0, 161.5, 148.8, 123.7, 122.3, 118.5, 107.1, 106.7, 96.3, 93.5, 82.8, 64.2, 55.1, 52.6, 47.2, 46.3, 38.9, 34.7, 27.0, 8.6; IR (neat) 3055, 2952, 1743, 1658, 1620, 1498, 1438, 1379, 1268, 1120, 905, 727 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{22}H_{24}NO_6$) 398.1604, found 398.1608. Chiral HPLC (CHIRALPAK AD, 2 × 25 cm, 30% *i*PrOH/Hexanes, 7 mL/min) allowed **21** to be separated into individual enantiomers (t_R [unnatural] = 19.3 min, t_R [natural] = 24.1 min) Fig. 4. For natural (+)-**21**: $[\alpha]_D^{24}$ +153 (*c* 1.0, $CHCl_3$). For unnatural (−)-**21**: $[\alpha]_D^{24}$ − 154 (*c* 1.0, $CHCl_3$). The structure and absolute stereochemistry of each enantiomer of **21** were unambiguously established by X-ray crystallography conducted with colorless crystals obtained from slow vapor diffusion with CH_2Cl_2/pentanes (CCDC 2064480 for natural (+)-**21** and CCDC 2064481 for *ent*-(−)-**21**). For further X-ray crystallography details, see supplementary data pages S25–S28.

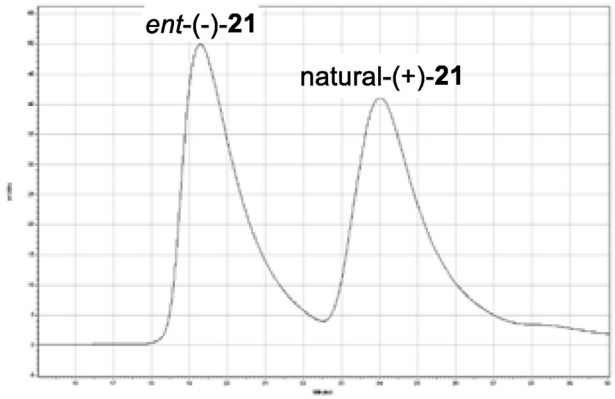


Fig. 4. Chiral HPLC trace of racemic **21**.

4.10. Compound (+)-22

Compound **21** (30.0 mg, 0.0755 mmol) was dissolved in toluene (15 mL) and Lawesson's reagent (33.6 mg, 0.0803 mmol) was added in a single portion. The solution was warmed at 100 °C for 45 min. The reaction was concentrated in vacuo. PTLC (SiO_2, 50% EtOAc/hexanes) gave 20.7 mg (66%) of **22** as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09–6.98 (m, 1H), 6.51–6.44 (m, 2H), 6.43 (d, J = 9.5 Hz, 1H), 5.91 (d, J = 9.5 Hz, 1H), 5.18 (d, J = 1.1 Hz, 1H), 4.48 (ddd, J = 13.4, 9.7, 1.2 Hz, 1H), 4.16 (ddd, J = 13.4, 11.4, 7.6 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.61 (ddd, J = 12.8, 11.3, 9.6 Hz, 1H), 2.42–2.29 (m, 3H), 0.80 (dq, J = 15.1, 7.7 Hz, 1H), 0.71 (dq, J = 14.1, 7.1 Hz, 1H), 0.53 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.2, 169.4, 162.6, 162.2, 140.8, 129.9, 124.3, 118.7, 107.7, 104.8, 96.9, 94.2, 83.5, 65.3, 55.7, 53.2, 53.1, 48.2, 45.9, 34.9, 27.5, 9.1; IR (neat) 2955, 2923, 1738, 1673, 1622, 1594, 1499, 1261, 1123, 1033, 907, 801 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{22}H_{24}NO_5S$) 414.1375, found 414.1384; For natural (+)-**22**: $[\alpha]_D^{26}$ +383 (*c* 0.5, $CHCl_3$). For unnatural (−)-**22**: $[\alpha]_D^{24}$ − 390 (*c* 0.5, $CHCl_3$).

4.11. (−)-4-Desacetoxy-1-oxovindoline [(−)-6]

Compound **22** (19.1 mg, 0.0462 mmol) and Me_3OBF_4 (20.5 mg, 0.139 mmol) were dissolved in CH_2Cl_2 (9.4 mL) and the solution was stirred at 25 °C for 1 h. CH_2Cl_2 was removed by passing a stream of N_2 over the reaction mixture, MeOH (9.4 mL) was added, and the solution was cooled to 0 °C. $NaBH_4$ (17.5 mg, 0.462 mmol) was added and the solution was stirred for 30 min. The reaction was quenched with the addition of saturated aq $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3x), dried with $MgSO_4$, filtered and concentrated in vacuo. PTLC (SiO_2, 50% EtOAc/hexanes) gave 8.9 mg (50%) of **6** as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (s, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.45 (dd, J = 8.3, 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.70 (ddd, J = 9.9, 5.4, 1.7 Hz, 1H), 5.48 (ddd, J = 9.9, 2.7, 1.4 Hz, 1H), 4.86 (d, J = 1.7 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.40–3.33 (m, 2H), 2.78 (dt, J = 15.7, 2.2 Hz, 1H), 2.55–2.46 (m, 2H),

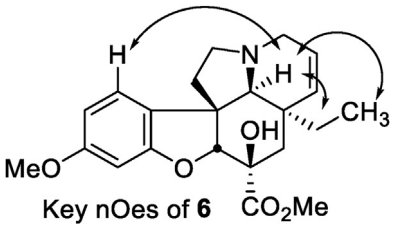


Fig. 5. Diagnostic nOes.

2.43–2.30 (m, 2H), 2.07 (dd, $J = 14.9, 1.8$ Hz, 1H), 1.82 (d, $J = 15.0$ Hz, 1H), 1.02 (dq, $J = 14.7, 7.4$ Hz, 1H), 0.78 (dq, $J = 14.3, 7.3$ Hz, 1H), 0.61 (t, $J = 7.4$ Hz, 3H) (see Fig. 5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 161.3, 160.0, 136.4, 123.3, 123.2, 121.5, 107.7, 96.1, 93.5, 76.5, 68.1, 55.6, 53..0, 52.6, 51.6, 51.0, 41.1, 37.4, 37.3, 34.3, 8.0; IR (neat) 2923, 2852, 1716, 1541, 1499, 1379, 1268, 1151, 913, 826 cm^{-1}; HRMS (ESI-TOF): calcd $[M+H]^+$ ($C_{22}H_{28}NO_5$) 386.1967, found 386.1962; For natural (−)-**6** $[\alpha]_D^{25}$ − 32 (*c* 0.07, $CHCl_3$).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are especially grateful to the National Institutes of Health for financial support of the studies (CA042056, DLB). We thank Porina Va, Justin Sears and Youqian Deng for preliminary studies and Dr. Milan Gembicky of the UCSD Crystallography Lab for the X-ray structure determinations disclosed herein.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132117.

References

[1] The alkaloids, in: A. Brossi, M. Suffness (Eds.) 37, Academic, San Diego, 1990.
[2] N. Neuss, A.J. Barnes Jr., L.L. Huckstep, Experientia 31 (1975) 18.
[3] C.J. Barnett, G.J. Cullinan, K. Gerzon, B.C. Hoying, W.E. Jones, W.M. Newlon, G.A. Poore, R.L. Robison, M.J. Sweeney, G.C. Todd, R.W. Dyke, R.L. Nelson, R. L, J. Med. Chem. 21 (1978) 88.
[4] S. Lobert, B. Vulevic, J.J. Correia, Biochemistry 35 (1996) 6806.
[5] (a) P.W. Gout, L.L. Wijcik, C.T. Beer, Eur. J. Canc. 14 (1965) 1167;
(b) P.J. Ferguson, J.R. Phillips, M. Selner, C.E. Cass, Canc. Res. 44 (1984) 3307.
[6] E.K. Rowinsky, R.C. Donehower, Pharmacol. Ther. 52 (1991) 35.
[7] C.E.M. Gidding, S.J. Kellie, W.A. Kamps, S.S.N. de Graaf, Crit. Rev. Oncol. Hematol. 29 (1999) 267.
[8] J.E. Sears, D.L. Boger, Acc. Chem. Res. 48 (2015) 653.
[9] D.L. Boger, J. Org. Chem. 82 (2017) 11961.
[10] (a) Y. Choi, H. Ishikawa, J. Velcicky, G.I. Elliott, M.M. Miller, D.L. Boger, Org. Lett. 7 (2005) 4539;
(b) H. Ishikawa, G.I. Elliott, J. Velcicky, Y. Choi, D.L. Boger, J. Am. Chem. Soc. 128 (2006) 10596.
[11] H. Ishikawa, D.A. Colby, D.L. Boger, J. Am. Chem. Soc. 130 (2008) 420.
[12] H. Ishikawa, D.A. Colby, S. Seto, P. Va, A. Tam, H. Kakei, T.J. Rayl, I. Hwang, D.L. Boger, J. Am. Chem. Soc. 131 (2009) 4904.
[13] A. Tam, H. Gotoh, W.M. Robertson, D.L. Boger, Bioorg. Med. Chem. Lett 20 (2010) 6408.
[14] (a) Y. Sasaki, D. Kato, D. L Boger, J. Am. Chem. Soc. 132 (2010) 13533;
(b) D. Kato, Y. Sasaki, D.L. Boger, J. Am. Chem. Soc. 132 (2010) 3685.
[15] P. Va, E.L. Campbell, W.M. Robertson, D.L. Boger, J. Am. Chem. Soc. 132 (2010) 8489.
[16] H. Gotoh, K.K. Duncan, W.M. Robertson, D.L. Boger, ACS Med. Chem. Lett. 2 (2011) 948.
[17] (a) E.K. Leggans, T.J. Barker, K. K Duncan, D.L. Boger, Org. Lett. 14 (2012) 1428;
(b) T.J. Barker, D.L. Boger, J. Am. Chem. Soc. 134 (2012) 13588.
[18] T.J. Barker, K.K. Duncan, K. Otrubova, D.L. Boger, ACS Med. Chem. Lett. 4 (2013) 985.
[19] K.D. Schleicher, Y. Sasaki, A. Tam, D. Kato, K.K. Duncan, D.L. Boger, J. Med. Chem. 56 (2013) 483.
[20] E.K. Leggans, K.K. Duncan, T.J. Barker, K.D. Schleicher, D.L. Boger, J. Med. Chem. 56 (2013) 628.
[21] E.L. Campbell, C.K. Skepper, K. Sankar, K.K. Duncan, D.L. Boger, Org. Lett. 15 (2013) 5306.
[22] O. Allemann, M. Brutsch, J.C. Lukesh, D.M. Brody, D.L. Boger, J. Am. Chem. Soc. 138 (2016) 8376.
[23] D.W. Carney, J.C. Lukesh, D.M. Brody, M.M. Brütsch, D.L. Boger, Proc. Natl. Acad. Sci. U.S.A. 113 (2016) 9691.
[24] S. Yang, K. Sankar, C.K. Skepper, T.J. Barker, J.C. Lukesh III, D.M. Brody, M.M. Brutsch, D.L. Boger, Chem. Sci. 8 (2017) 1560.
[25] J.C. Lukesh III, D.W. Carney, H. Dong, R.M. Cross, V. Shukla, K.K. Duncan, S. Yang, D.M. Brody, M.M. Brutsch, A. Radakovic, D.L. Boger, J. Med. Chem. 60 (2017) 7591.
[26] (a) H. Gotoh, J.E. Sears, A. Eschenmoser, D.L. Boger, J. Am. Chem. Soc. 134 (2012) 13240;
(b) B.A. Boon, D.L. Boger, J. Am. Chem. Soc. 141 (2019) 14349.
[27] (a) G.I. Elliott, J.R. Fuchs, B.S.J. Blagg, H. Ishikawa, H. Tao, Z.Q. Yuan, D.L. Boger, J. Am. Chem. Soc. 128 (2006) 10589;
(b) G.D. Wilkie, G.I. Elliott, B.S.J. Blagg, S.E. Wolkenberg, D.R. Soenen, M.M. Miller, S. Pollack, D.L. Boger, J. Am. Chem. Soc. 124 (2002) 11292.
[28] J.E. Sears, D.L. Boger, Acc. Chem. Res. 49 (2016) 241.
[29] (a) A.M. Venkatesan, O. Dos Santos, J. Ellingboe, D.A. Evrard, B.L. Harrison, D.L. Smith, R. Scerni, G.A. Hornby, L.E. Schechter, T.H. Andree, Bioorg. Med. Chem. Lett 20 (2010) 824;
(b) D.T. Connor, W.A. Cetenko, M.D. Mullican, R.J. Sorenson, P.C. Unangst, R.J. Weikert, R.L. Adolphson, J.A. Kennedy, D.O. Thueson, J. Med. Chem. 35 (1992) 958;
(c) J. Brewer, W. Davidson, J. Elix, R. Leppik, Aust. J. Chem. 24 (1971) 1883.
[30] J. Chan, J. Elix, B. Ferguson, Aust. J. Chem. 28 (1975) 1097.
[31] J. Zhang, V. Shukla, D.L. Boger, J. Org. Chem. 84 (2019) 9397.
[32] The structure and relative stereochemistry of **19** were unambiguously established with a single crystal X-ray structure determination (CCDC 2064479). The structure and relative and absolute stereochemistry of (+)-**21** (CCDC 2064480) and *ent*-(−)-**21** (CCDC 2064481) were unambiguously established with single crystal X-ray structure determinations. Crystallographic data for the structures are provided in the supplementary data and have been deposited with the Cambridge Crystallographic Data Centre. Copies can be obtained from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0) 1223–336033 or e-mail: deposit@ccdc.cam.ac.uk).