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Convergent Synthesis of Pancratistatin from Piperonal and Xylose

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A synthesis of the antitumour agent pancratistatin is described from piperonal and D-xylose. Piperonal is converted into cinnamyl bromide **11** while methyl 5-iodoribofuranoside **12** is derived from xylose. The allylic bromide and the iodocarbohydrate are combined in a zinc-mediated tandem reaction to afford a highly functionalised 1,7-diene, which is then converted into the corresponding cyclohexene by ring-closing olefin metathesis. Subsequent Overman rearrangement, dihydroxylation and deprotection afford the natural product in a total of 25 steps from the two starting materials. The longest linear sequence is from piperonal and gives rise to pancratistatin in 18 steps and 7.0% overall yield.

Introduction

Pancratistatin was isolated in 1984 from the bulbs of the Hawaiian Amaryllidaceae plant *Hymenocallis littoralis*.[1,2] The structure was elucidated by NMR spectroscopy and X-ray crystallographic analysis and the natural product was shown to possess a highly hydroxylated phenanthridone skeleton with six contiguous stereocentres (Figure 1). Subsequent biological studies revealed that pancratistatin exhibited strong in vitro cancer cell growth inhibitory activity when tested against a panel of human tumour lines.[3] Significant antiviral[4] and antiparasitic[5] activity have also been observed. The detailed mechanism of action is not known, but it has been shown that pancratistatin acts in the mitochondria of the cancerous cells and induces apoptosis.[6] The potent antitumour activity has stimulated efforts to develop pancratistatin into an anticancer drug. Due to the poor solubility of the parent molecule these investigations have employed prodrugs of the natural product containing either a 7-*O*-phosphate or a 3,4-*O*-cyclic phosphate.[7] Many derivatives of pancratistatin have also been prepared and tested for antitumour activity to identify the minimum cytotoxic pharmacophore.[8] The conclusion from these studies has been that the entire phenanthridone skeleton, the *trans* B,C ring junction and the hydroxy groups at position 2, 3, 4, and 7 are necessary to maintain high biological activity.

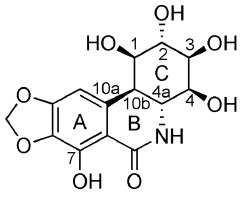

Figure 1. Structure of pancratistatin.

Pancratistatin is only available in small quantities from natural sources. The original isolation in 1984 afforded the natural product in only 0.028% yield from the available material.[1] Although, the target molecule has also been identified in other Amaryllidaceae species[9] the limited supply has been a serious drawback in the development of pancratistatin as an antitumour agent. As a result, a number of total syntheses have been developed starting from either an achiral starting material or a compound from the chiral pool.[10] The first synthesis in 1989 was a racemic synthesis in a total of 26 linear steps from pyrogallol.[11] Since then a total of eight asymmetric syntheses have appeared where six are enantioselective syntheses starting from various cyclohexene or aromatic starting materials while two start from members of the chiral pool – the natural products narciclasine and pinitol.[12] The shortest syntheses from commercial starting materials are based on a whole-cell bio-oxidation of bromobenzene,[12g] a palladium-catalysed desymmetrisation of conduritol A,[12h] and a ring-opening of a cyclic sulfate in pinitol.[12a] In these three cases the natural product is obtained in a total of 13–20 linear steps and 2–7% overall yield.

Over the past decade we have exploited the synthesis of carbocyclic natural products from carbohydrates by the use of a zinc-mediated tandem reaction and ring-closing olefin

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metathesis.[13,14] Methyl ω-iodoglycosides are subjected to zinc metal in the presence of allylic bromides. Under these conditions, the starting glycoside undergoes a reductive fragmentation to furnish an unsaturated aldehyde, which is then allylated in situ. The α,ω-diene thus obtained is subsequently converted into the corresponding carbocycle by ring-closing metathesis. We and others have used the combination of these organometallic reactions to prepare several carbocyclic natural products from carbohydrates including the calystegines,[15] the gabosines,[16] cyclophellitol[17] and 7-deoxypancratistatin.[18]

Herein, we describe an expedient and convergent synthesis of pancratistatin from piperonal and xylose where a zinc-mediated tandem reaction and ring-closing metathesis serve as the key steps.

Results and Discussion

The synthesis employs the same overall strategy as used in our earlier synthesis of the 7-deoxy congener. The amide nitrogen will be installed by an Overman rearrangement from allylic alcohol **B** that in turn will be prepared by ring-closing metathesis from diene **C** (Figure 2). The latter will be assembled by a zinc-mediated tandem reaction between allylating agent **D** and ribofuranoside **E**. The synthesis of **E** from xylose was investigated in our earlier work[18] while the allylating agent has not been described before.

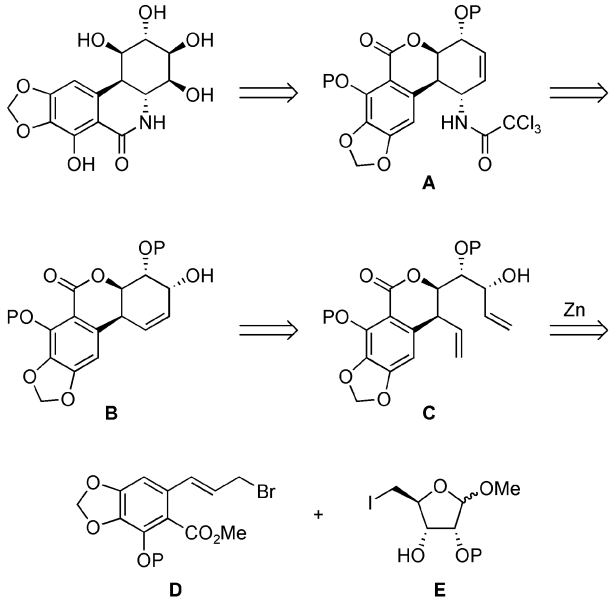
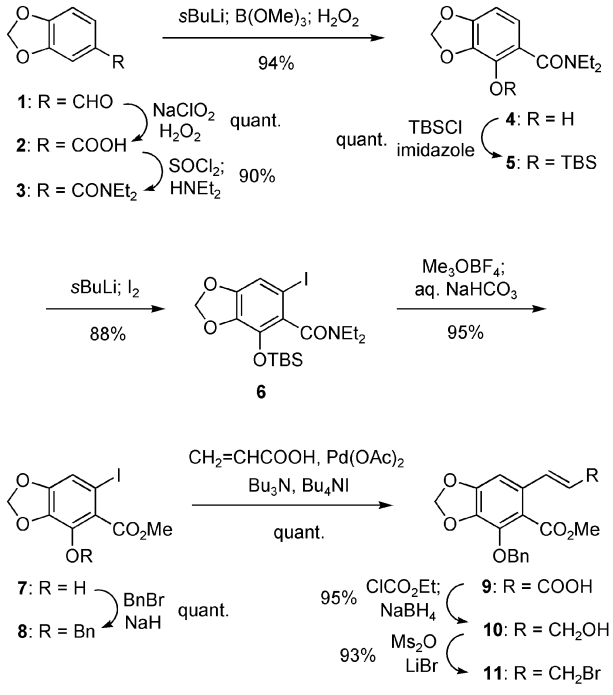


Figure 2. Retrosynthesis.

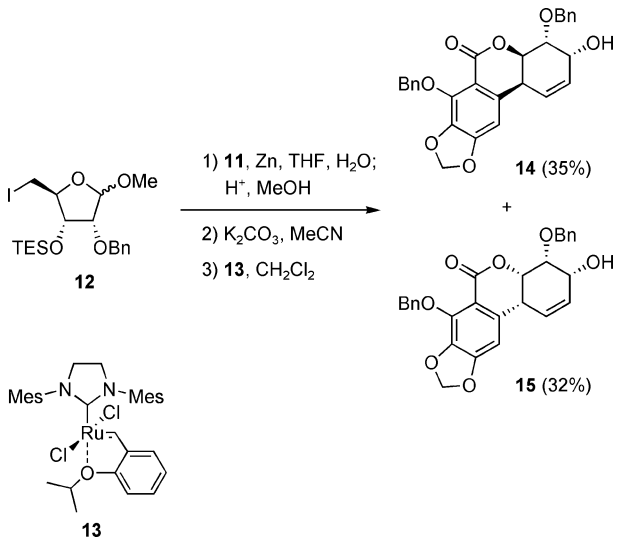
Piperonal (**1**) is a cheap starting material for ring A and is easily oxidized with sodium chlorite – hydrogen peroxide[19] to piperonylic acid (**2**) and further converted into the corresponding diethylamide **3** (Scheme 1). To introduce the hydroxy functionality a directed *ortho* metallation[20] was employed followed by quenching with trimethyl borate and oxidation with hydrogen peroxide.[12g,21] The resulting phenol **4** was TBS protected and then converted into **6**[22] in 74% overall yield from piperonal. Other directing groups were also investigated in the *ortho* metallations, but the corresponding 1,3-dimethylimidazolidine and *N*-cyclohexylimine of piperonal both gave significantly lower yields than the diethyl amide. Treatment of **6** with Meerwein's reagent following Keck's procedure[23] resulted in loss of the silyl group and concomitant transformation into ester **7**.[22] Subsequent benzyl protection furnished benzyl ether **8**. The allylic moiety was introduced by a Heck coupling with acrylic acid followed by reduction to the allylic alcohol **10**. The Heck reaction was carried out under phosphane-free conditions[24] because the presence of triphenylphosphane was found to give only moderate yields. Conversion into the allylic mesylate and substitution with bromide then gave the desired allylating agent **11**. Reagent **11** is crystalline and completely stable at room temperature for many months.



Scheme 1. Synthesis of allylating agent.

The carbohydrate coupling partner **12** was prepared from D-xylose in 7 steps and 42% overall yield following our previously developed protocol.[18] With both the allylating agent and the iodofuranoside in hand the stage was now set to investigate the zinc-mediated tandem reaction. The reaction was carried out in a 3:1 THF/H_2O mixture under sonication at 40 °C. Treatment of furanoside **12** with zinc under these conditions and adding 1.5 equiv. of bromide **11** by syringe pump at the same time gave the coupling product as a 1.1:1 mixture of two diastereomers, which could not be separated by silica gel chromatography (Scheme 2). Contrary to our earlier observations[18] the products were reluctant to lactonise and the crude product was therefore treated with potassium carbonate in acetonitrile to complete the lactonisation. Again, the products could not be separated and consequently the following metathesis reaction was carried out with Hoveyda–Grubbs 2nd generation

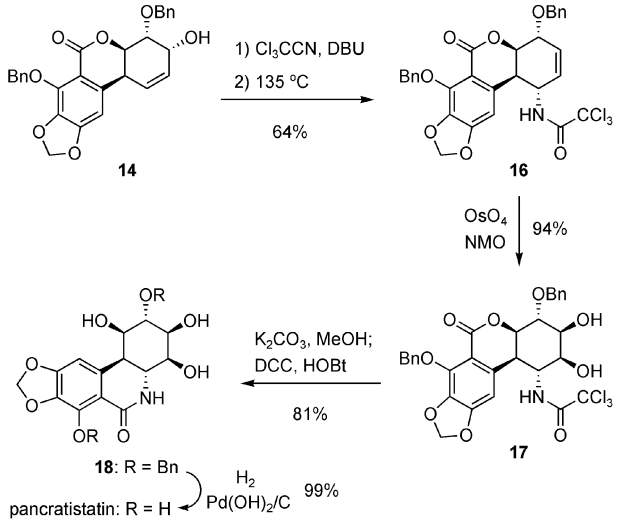
catalyst **13**[25] to give 67% isolated yield of two cyclohexenes which could now be separated. The main diastereomer **14** was obtained in 35% yield from **12** and had the correct stereochemistry for the natural product. The other diastereomer was shown by NMR to be the all *cis*-configured isomer **15**.



Scheme 2. Tandem reaction and metathesis.

Several experiments were performed in order to improve the ratio between **14** and **15**. In fact, increasing the THF/H_2O ratio to 9:1 did result in a 5:1 ratio of **14** and **15**, but unfortunately the combined yield of the two cyclohexenes was only 22% in this case. Slight improvements in the diastereomeric ratio were also observed when THF was replaced with dioxane or when the allylation was performed in a saturated aqueous ammonium chloride solution, but again the isolated yields were rather low. In other applications of the tandem reaction we have been able to isolate the intermediate aldehyde and use a different metal in the allylation step.[15c,17] Although, the aldehyde from fragmentation of **12** could be isolated, the ensuing allylation with **11** in the presence of indium or tin failed completely. Since it seems impossible to improve the diastereoselectivity without compromising the yield we decided to continue the synthesis with the 35% isolated yield of **14** over the key steps.

Cyclohexene **14** is identical with an intermediate in the first racemic synthesis of pancratistatin.[11] However, we have modified the experimental conditions for some of the final steps in order to improve the yields. First, allylic alcohol **14** is converted into the corresponding imidate with trichloroacetonitrile and DBU which gave a better conversion than with sodium hydride as the base (Scheme 3).[11] The Overman rearrangement has previously been achieved at 100–105 °C for 1.2 h under high vacuum,[11] but in our hands the imidate was completely stable under these conditions. Nevertheless, heating the allylic imidate to 135 °C for 21 h did bring about the rearrangement and afforded amide **16** in good yield. Dihydroxylation of the olefin proceeded slowly, but otherwise uneventfully from the concave side of the ring system to give diol **17**. Deprotection of the trichloroacetamide is achieved with potassium carbonate in refluxing methanol. For the 7-deoxy analogue the free amine reacts immediately with the ester moiety to form the lactam.[18] However, the 7-benzyloxy group seems to hamper the rotation around the C10a–C10b bond[12g] and further activation is necessary for the lactamisation to occur. DCC was used in the first synthesis,[11] but in our hands it was also necessary to add HOBt in order to obtain a good yield of lactam **18**. With our modifications partially protected pancratistatin **18** is prepared from **14** in 49% overall yield over the four steps as compared to 25% yield in the first synthesis.[11] Final debenzylation of **18** by hydrogenolysis proceeded in near quantitative yield to give (+)-pancratistatin with optical rotation and NMR spectroscopic data in agreement with literature values. Nevertheless, it should be noted that carbon 10b at δ = 39.4 ppm has not been assigned previously in the ^{13}C NMR of pancratistatin since it appears under the [D_6]DMSO signal.



Scheme 3. Synthesis of (+)-pancratistatin.

Although pancratistatin and 7-deoxypancratistatin display a range of biological activities we are not aware that they have been tested as glycosidase inhibitors. Since we have previously prepared several carbocyclic natural products that act as glucosidase inhibitors[15a,15c,17] we decided also to test the two pancratistatins. Both were evaluated against baker's yeast α-glucosidase, almond β-glucosidase and almond α-mannosidase.[26] Interestingly, 7-deoxypancratistatin was a moderate inhibitor of β-glucosidase (K_i = 2.8×10^{-5} M) while the parent molecule showed no inhibition of the three enzymes.

Conclusions

In summary, we have developed a convergent synthesis of the antitumour agent pancratistatin from piperonal and D-xylose. The synthesis employs a total of 18 linear steps from piperonal and affords the natural product in 7.0% overall yield. From D-xylose the total number of linear steps is 15 and the overall yield is 7.1%. The number of steps and

overall yields of the target molecule compare favourably with some of the most efficient syntheses of pancratistatin that have been achieved to date.

Experimental Section

General: THF was distilled from Na/benzophenone under N_2, while DMF and CH_2Cl_2 were dried with 3- and 4-Å molecular sieves, respectively. Solvents used for chromatography were of HPLC grade. Zinc dust (8.0 g, 122 mmol) was activated by stirring with 2 M HCl (150 mL) for 10 min, filtered and washed successively with H_2O, MeOH and Et_2O, and dried with a heatgun under high vacuum for 10 min to leave a fine, light grey powder. Sonications were carried out in a sonic bath containing 1% liquid detergent. Thin-layer chromatography was performed on aluminium plates coated with silica gel 60. Visualisation was done by UV or by dipping into a solution of cerium(IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by charring with a heatgun. Flash chromatography was performed with silica gel 60 (35–70 μm). Optical rotations were measured on a Perkin–Elmer 241 polarimeter while IR spectra were recorded with a Bruker Alpha FT-IR spectrometer. NMR spectra were recorded with a Varian Mercury 300 or a Varian Unity Inova 500 instrument. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ = 7.26 ppm)/$CDCl_3$ (δ = 77.0 ppm) or DMSO (δ = 2.50 ppm)/[D_6]DMSO (δ = 39.4 ppm). High-resolution mass spectra were recorded at the Department of Physics and Chemistry, University of Southern Denmark.

Piperonylic Acid (2): A solution of $NaClO_2$ (48.0 g, 0.425 mol) in H_2O (400 mL) was added dropwise over 30 min to a stirred solution of piperonal (45.04 g, 0.300 mol) in MeCN (300 mL) containing NaH_2PO_4 (9.6 g, 0.080 mol) in H_2O (120 mL) and 35% H_2O_2 (30 mL). The temperature was kept below 15 °C by the use of an ice-bath. After the addition the ice-bath was removed and the solution was stirred for another 2 h. More NaH_2PO_4 (2.4 g, 0.020 mol) and 35% H_2O_2 (8.0 mL) were added along with a solution of $NaClO_2$ (12.1 g, 0.134 mol) in H_2O (60 mL). After 1 h additional $NaClO_2$ (4.0 g, 0.044 mol) was added and the mixture was stirred for 2 h before it was quenched with Na_2SO_3 (3.0 g). Then 37% HCl (20 mL) was added and the slurry was filtered. The phases were separated and the aqueous phase was extracted twice with EtOAc (400 mL + 200 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated to give 50.0 g (quantitative) of a white solid. R_f = 0.58 (EtOAc/heptane/AcOH, 1:1:0.02); m.p. 225–227 °C (ref.[27] 229–231 °C). IR (KBr): $\tilde{\nu}$ = 2918, 2560, 1671, 1617, 1452, 1298, 1260, 1113, 1036 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 12.77 (br. s, 1 H), 7.54 (dd, J = 1.7, 8.1 Hz, 1 H), 7.36 (d, J = 1.6 Hz, 1 H), 6.99 (d, J = 8.1 Hz, 1 H), 6.12 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 166.6, 151.1, 147.4, 124.9, 124.6, 108.8, 108.0, 101.9 ppm. $C_8H_6O_4$ (166.1): calcd. C 57.84, H 3.64; found C 57.78, H 3.73.

***N,N*-Diethyl-1,3-benzodioxole-5-carboxamide (3):** Piperonylic acid (74.5 g, 0.446 mol) was suspended in $SOCl_2$ (325 mL, 4.46 mol) and the mixture was heated to reflux for 1.5 h. The solution was cooled to room temperature and excess $SOCl_2$ removed under reduced pressure. CH_2Cl_2 (350 mL) was added to the residue and the flask was placed in an ice-bath followed by dropwise addition of diethylamine (185.2 mL, 1.78 mol). The mixture was stirred under Ar overnight and then washed with 2 M HCl (3 × 1 L). The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 3:7 → 1:1) to yield 88.6 g (90%) of **3**. R_f = 0.25 (EtOAc/heptane, 1:1); m.p. 65–66 °C (ref.[28] 62–65 °C). IR (KBr): $\tilde{\nu}$ = 2983, 2944, 2903, 1610, 1465, 1438, 1291, 1241, 1036 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.88–6.78 (m, 3 H), 5.97 (s, 2 H), 3.37 (br. s, 4 H), 1.16 (br. s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 148.2, 147.4, 130.9, 120.4, 108.1, 107.3, 101.2, 43.2, 40.1, 13.8 ppm. $C_{12}H_{15}NO_3$ (221.3): calcd. C 65.14, H 6.83, N 6.33; found C 65.50, H 6.77, N 6.28.

***N,N*-Diethyl-4-hydroxy-1,3-benzodioxole-5-carboxamide (4):** Amide **3** (40.0 g, 0.181 mol) was dissolved in THF (500 mL) followed by addition of dry TMEDA (30.0 mL, 0.199 mol). The mixture was cooled to –78 °C and *s*BuLi (140 mL, 1.42 M in cyclohexane, 0.199 mol) was added dropwise over 2 h with the temperature not exceeding –72 °C. The deep red solution was stirred for 1 h at –78 °C after which time dry $B(OMe)_3$ (24.3 mL, 0.217 mol) was added and the solution was warmed to 0 °C in an ice-bath. Then acetic acid (16.8 mL, 0.293 mol) was added followed by slow addition of 35% H_2O_2 (42 mL, 0.488 mol). The solution was stirred overnight at ambient temperature and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (600 mL) and washed with 10% aqueous $Na_2S_2O_3$ (1 L). The aqueous phase was filtered through a pad of Celite and extracted with additional CH_2Cl_2 (2 × 400 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by dry column vacuum chromatography[29] (EtOAc/heptane, 1:4 → 1:3) to yield 40.5 g (94%) of phenol **4**. R_f = 0.30 (EtOAc/heptane, 1:1); m.p. 59–60.5 °C. IR (KBr): $\tilde{\nu}$ = 2983, 2657, 1639, 1583, 1503, 1457, 1075, 1033, 801 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.06 (s, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 6.40 (d, J = 8.3 Hz, 1 H), 6.01 (s, 2 H), 3.51 (q, J = 7.1 Hz, 4 H), 1.26 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 150.7, 143.6, 135.2, 121.6, 114.2, 101.9, 99.6, 42.3, 13.3 ppm. $C_{12}H_{15}NO_4$ (237.3): calcd. C 60.75, H 6.37, N 5.90; found C 60.87, H 6.31, N 5.89. MS: m/z = 260.1 [M + Na]$^+$.

***N,N*-Diethyl-4-(*tert*-butyldimethylsilyloxy)-1,3-benzodioxole-5-carboxamide (5):** Phenol **4** (10.0 g, 42.2 mmol) was dissolved in CH_2Cl_2 (210 mL) under Ar and imidazole (5.74 g, 84.3 mmol) was added followed by TBSCl (7.04 g, 46.7 mmol). The mixture was stirred at room temperature overnight and filtered through a pad of Celite, which was washed with CH_2Cl_2 (30 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (250 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The yellow oil was purified by dry column vacuum chromatography[29] (EtOAc/heptane, 1:19 → 1:1) to yield 14.8 g (quantitative) of an oil, which solidified on standing. R_f = 0.47 (EtOAc/heptane, 1:1); m.p. 65 °C. IR (KBr): $\tilde{\nu}$ = 2928, 2856, 1638, 1617, 1479, 1280, 1249, 1073, 1035, 865, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.68 (d, J = 8.0 Hz, 1 H), 6.50 (d, J = 8.0 Hz, 1 H), 5.97–5.88 (m, 2 H), 3.51 (m, 2 H), 3.34–3.03 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.01 (t, J = 7.1 Hz, 3 H), 0.94 (s, 9 H), 0.21 (s, 3 H), 0.18 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 148.9, 136.8, 135.3, 125.5, 120.7, 102.5, 100.9, 42.9, 39.3, 25.6, 18.2, 14.0, 13.2, –4.5 ppm. $C_{18}H_{29}NO_4Si$ (351.5): calcd. C 61.50, H 8.32, N 3.98; found C 61.69, H 8.20, N 4.11. HRMS: calcd. for $C_{36}H_{58}N_2O_8Si_2Na$ [2M + Na]$^+$ m/z 725.3629; found m/z 725.3617.

***N,N*-Diethyl-4-(*tert*-butyldimethylsilyloxy)-6-iodo-1,3-benzodioxole-5-carboxamide (6):** Amide **5** (10.0 g, 2.85 mmol) was dissolved in THF (140 mL) under Ar and TMEDA (4.5 mL, 2.99 mmol) was added. The solution was cooled to –78 °C and *s*BuLi (23.5 mL, 1.33 M in cyclohexane, 31.3 mmol) was added dropwise over 15 min with the temperature not exceeding –74 °C. The mixture was stirred for 2 h at –78 °C at which point it had become yellow. Then I_2 (8.67 g in 34 mL of THF, 34.1 mmol) was added dropwise with the

temperature not exceeding –70 °C and the cooling bath was removed. The solution was warmed to room temperature and then poured into H_2O (200 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 1:6) to yield 12.0 g (88%). R_f = 0.47 (EtOAc/heptane, 3:7); m.p. 66–67 °C. IR (KBr): $\tilde{\nu}$ = 2932, 2860, 1624, 1465, 1410, 1287, 1266, 1094, 1037, 874, 841 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (s, 1 H), 5.95 (d, J = 1.4 Hz, 1 H), 5.92 (d, J = 1.4 Hz, 1 H), 3.92–3.78 (m, 1 H), 3.25–3.08 (m, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.11 (t, J = 7.2 Hz, 3 H), 0.93 (s, 9 H), 0.22 (s, 3 H), 0.18 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 149.3, 137.5, 135.9, 130.5, 112.5, 101.4, 82.2, 43.0, 39.3, 25.5, 18.2, 13.8, 12.6, –4.2, –4.7 ppm. $C_{18}H_{28}INO_4Si$ (477.4): calcd. C 45.28, H 5.91, N 2.93; found C 45.46, H 5.87, N 2.84. MS: m/z = 977.2 [2M + Na]$^+$. NMR spectroscopic data are in accordance with literature values.[22]

Methyl 4-Hydroxy-6-iodo-1,3-benzodioxole-5-carboxylate (7): Amide **6** (12.30 g, 25.8 mmol) was dissolved in CH_3CN (129 mL) under N_2 and Na_2HPO_4 (5.49 g, 38.7 mmol) and Me_3OBF_4 (11.44 g, 77.3 mmol) were added. The suspension was stirred for 3.5 h followed by slow addition of saturated aqueous $NaHCO_3$ (161 mL) from an addition funnel under vigorous stirring. Additional solid $NaHCO_3$ (10.82 g, 128.8 mmol) was added and the slurry was stirred at ambient temperature for 15 h, and then poured into H_2O (500 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and passed through a short column of silica to yield 7.867 g (95%) of the ester. R_f = 0.30 (EtOAc/heptane, 3:7); m.p. 159–160 °C (ref.[23a] 155–157 °C). IR (KBr): $\tilde{\nu}$ = 3006, 2947, 1666, 1503, 1490, 1340, 1301, 1194, 1081, 1036, 986 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.00 (s, 1 H), 7.19 (s, 1 H), 6.07 (s, 2 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 152.6, 146.8, 135.6, 115.4, 112.4, 102.9, 84.6, 51.9 ppm. $C_9H_7IO_5$ (322.1): calcd. C 33.56, H 2.19; found C 33.43, H 2.13. HRMS: calcd. for $C_9H_7IO_5Na$ [M + Na]$^+$ m/z 344.9230; found m/z 344.9232. NMR spectroscopic data are in accordance with literature values.[23]

Methyl 4-Hydroxy-6-iodo-1,3-benzodioxole-5-carboxylate (8): Phenol **7** (19.0 g, 59.0 mmol) was dissolved in DMF (500 mL) under Ar and cooled to 0 °C. NaH (4.0 g, 55–65% in mineral oil, 88.5 mmol) was added in small portions and the suspension was stirred for 20 min followed by addition of BnBr (14.0 mL, 118 mmol). The mixture was stirred at ambient temperature overnight, quenched with H_2O and poured into Et_2O (500 mL). The solution was washed with H_2O (4 × 1 L) and the combined aqueous layers were extracted with Et_2O (2 × 500 mL). The combined organic phases were concentrated and co-concentrated with toluene. The residue was purified by dry column vacuum chromatography[29] (EtOAc/heptane, 1:9) to yield 24.3 g (quantitative). R_f = 0.42 (EtOAc/heptane, 3:7); m.p. 106–107 °C. IR (KBr): $\tilde{\nu}$ = 3029, 2948, 2912, 1727, 1617, 1466, 1374, 1346, 1271, 1134, 1088, 1037 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 6.96 (s, 1 H), 5.97 (s, 2 H), 5.24 (s, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 150.7, 139.9, 137.4, 136.4, 128.4, 128.2, 127.9, 127.8, 113.4, 101.9, 81.0, 74.3, 52.7 ppm. $C_{16}H_{13}IO_5$ (412.2): calcd. C 46.62, H 3.18; found C 46.48, H 3.11. MS: m/z = 434.9 [M + Na]$^+$.

Methyl (*E*)-4-Benzyloxy-6-(2-carboxyvinyl)-1,3-benzodioxole-5-carboxylate (9): Iodide **8** (1.00 g, 2.43 mmol) was dissolved in DMF (10 mL) under Ar and the mixture degassed by sonication. Bu_3N (2.9 mL, 12.1 mmol), acrylic acid (0.50 mL 7.28 mmol), Bu_4NI (0.896 g, 2.43 mmol) and $Pd(OAc)_2$ (11.0 mg, 49 μmol, 2 mol-%) were added, successively. The solution was heated to 100 °C for 2.5 h and then poured into 1 M HCl (100 mL) and EtOAc (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane/AcOH, 1:1:0.01) to yield 0.861 g (quantitative) of a white solid. R_f = 0.21 (EtOAc/heptane/AcOH, 1:1:0.01); m.p. 185–187 °C. IR (KBr): $\tilde{\nu}$ = 3300–2700, 2675, 1731, 1680, 1628, 1602, 1480, 1430, 1381, 1290, 1265, 1217, 1088, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 15.8 Hz, 1 H), 7.43–7.29 (m, 5 H), 6.86 (s, 1 H), 6.26 (d, J = 15.7 Hz, 1 H), 6.04 (s, 2 H), 5.25 (s, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 166.7, 150.5, 142.9, 139.4, 138.7, 136.4, 128.3, 128.1, 127.8, 127.0, 123.7, 118.4, 102.0, 100.7, 74.2, 52.6 ppm. $C_{19}H_{16}O_7$ (356.3): calcd. C 64.04, H 4.53; found C 63.83, H 4.62. HRMS: calcd. for $C_{19}H_{17}O_7$ [M + H]$^+$ m/z 357.0974; found m/z 357.0980.

Methyl (*E*)-4-Benzyloxy-6-(3-hydroxyprop-1-enyl)-1,3-benzodioxole-5-carboxylate (10): Carboxylic acid **9** (9.369 g, 26.3 mmol) was dissolved in THF (98 mL) under Ar and cooled to –6 °C, where Et_3N (4.8 mL, 34.2 mmol) was added. Ethyl chloroformate (3.0 mL, 31.6 mmol) was added dropwise and the suspension was stirred for 2 h at –5 to –2 °C. The mixture was filtered and the filter cake washed with THF (120 mL). To the filtrate was added H_2O (16 mL) and the solution was cooled to 0 °C followed by dropwise addition of $NaBH_4$ (34.2 mL, 2 M in triglyme, 68.4 mmol) with the temperature not exceeding 1 °C. The reaction was stirred for 2.5 h at 0 °C and then quenched with 1 M HCl (55 mL). The THF was removed in vacuo and the residue poured into 1 M HCl (95 mL) and extracted twice with toluene (400 and 200 mL). The combined organic phases were washed with H_2O (4 × 500 mL) and concentrated in vacuo to yield 8.579 g (95%) of the allyl alcohol. R_f = 0.20 (EtOAc/heptane, 1:1); m.p. 88 °C. IR (KBr): $\tilde{\nu}$ = 3400–3100, 3008, 2896, 2850, 1727, 1611, 1483, 1472, 1428, 1375, 1292, 1247, 1142, 1079, 1031 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 6.74 (s, 1 H), 6.51 (dt, J = 1.5, 15.6 Hz, 1 H), 6.19 (dt, J = 5.6, 15.7 Hz, 1 H), 5.97 (s, 2 H), 5.23 (s, 2 H), 4.25 (dd, J = 1.1, 5.6 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 150.3, 139.2, 136.8, 136.2, 130.5, 129.9, 128.3, 128.1, 127.8, 127.0, 120.8, 101.6, 100.2, 74.1, 63.5, 52.4 ppm. $C_{19}H_{18}O_6$ (342.4): calcd. C 66.66, H 5.30; found C 66.29, H 5.21. HRMS: calcd. for $C_{19}H_{19}O_6$ [M + H]$^+$ m/z 343.1182; found m/z 343.1163.

Methyl (*E*)-4-Benzyloxy-6-(3-bromoprop-1-enyl)-1,3-benzodioxole-5-carboxylate (11): Allyl alcohol **10** (2.716 g, 7.93 mmol) was dissolved in THF (30 mL) under Ar followed by addition of Et_3N (1.8 mL, 12.9 mmol) and LiBr (2.02 g, 23.3 mmol). The solution was cooled to –40 °C and Ms_2O (2.08 g, 11.9 mmol) was added. The suspension was warmed to room temperature over 4 h (the cooling bath was removed after 1 h at –10 °C). The reaction was quenched with 4.8% HBr (50 mL) and extracted with EtOAc (50 mL + 3 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 1:3) to yield 2.973 g (93%) of a white solid (unstable on dry SiO_2). R_f = 0.58 (EtOAc/heptane, 1:1); m.p. 69.5–71 °C. IR (KBr): $\tilde{\nu}$ = 3026, 2968, 2894, 1722, 1607, 1497, 1477, 1380, 1290, 1259, 1195, 1146, 1095, 1030 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 6.76 (s, 1 H), 6.56 (d, J = 15.4 Hz, 1 H), 6.24 (dt, J = 7.8, 15.4 Hz, 1 H), 5.98 (s, 2 H), 5.24 (s, 2 H), 4.09 (dd, J = 0.9, 7.8 Hz, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 150.4, 139.3, 136.8, 136.7, 130.4, 128.9, 128.4, 128.1, 127.8, 126.8, 121.2,

101.7, 100.3, 74.1, 52.4, 33.0 ppm. $C_{19}H_{17}BrO_5$ (405.3): calcd. C 56.31, H 4.23; found C 56.10, H 4.13. HRMS: calcd. for $C_{19}H_{18}BrO_5$ $[M + H]^+$ *m*/*z* 405.0338; found *m*/*z* 405.0362.

(3*R*,4*R*,4a*R*,11b*S*)-4,7-Dibenzyloxy-3-hydroxy-3,4,4a,11b-tetrahydro-6*H*-[1,3]benzodioxolo[5,6-*c*]chromen-6-one (14): Iodide **12**[18] (1.0036 g, 2.10 mmol) was dissolved in THF (30 mL) under Ar in a 100 mL conical flask and water (10 mL) was added. After addition of activated Zn (1.371 g, 21.0 mmol) the suspension was sonicated at 40–45 °C, while the allylating reagent **11** (1.271 g, 3.14 mmol) in THF (10 mL) was added by syringe pump over 5 h. After the addition the mixture was sonicated for another 2 h and then filtered through a pad of Celite, which was washed with EtOAc (3 × 20 mL). To the filtrate was added 12% aqueous NH_4Cl (50 mL) and the phases were separated. The aqueous phase was extracted with more EtOAc (3 × 20 mL) and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in MeOH (50 mL) and stirred with Amberlite IR-120(H^+) (15 mL) overnight. The resin was filtered off and rinsed with acetone. The filtrate was concentrated in vacuo and co-concentrated with toluene (2 × 10 mL). The residue was dissolved in anhydrous CH_3CN (25 mL), K_2CO_3 (1.037 g, 7.50 mmol) was added and the suspension was refluxed under Ar for 1.5 h. The mixture cooled to room temperature, diluted with CH_2Cl_2 (30 mL), poured into 12% aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (25 mL), degassed by sonication under Ar and Hoveyda-Grubbs' 2nd generation catalyst (37.7 mg, 60.2 μmol) was added. The solution was refluxed for 1.5 h under Ar after which it was concentrated in vacuo and purified by flash chromatography (EtOAc/heptane, 2:3 → 3:2) to yield 345 mg (35%) of the desired diastereomer **14** and 318 mg (32%) of the undesired **15** as white foams.

14: R_f = 0.24 (EtOAc/heptane, 1:1). $[\alpha]_D^{23}$ = –113.6 (*c* = 1.07, $CHCl_3$) [ref.[12f] $[\alpha]_D^{25}$ = –74.3 (*c* = 0.14, $CHCl_3$)]. IR (KBr): $\tilde{\nu}$ = 3600–3170, 3026, 2913, 1718, 1610, 1472, 1369 1262, 1184, 1118, 1046, 933, 733, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.27 (m, 10 H), 6.50 (s, 1 H), 6.04 (d, *J* = 1.1 Hz, 1 H), 5.99 (d, *J* = 1.1 Hz, 1 H), 5.76–5.71 (m, 1 H), 5.48–5.44 (m, 1 H), 5.34 (d, *J* = 11.4 Hz, 1 H), 5.29 (d, *J* = 11.3 Hz, 1 H), 4.76–4.69 (m, 3 H), 4.56–4.51 (m, 1 H), 4.15–4.09 (m, 1 H), 3.57–3.53 (m, 1 H), 2.45 (d, *J* = 11.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 153.3, 143.9, 138.9, 138.0, 137.2, 136.7, 129.8, 128.7, 128.3, 128.0, 125.8, 111.5, 102.5, 102.0, 74.8, 74.5, 74.1, 73.9, 64.7, 35.4 ppm. HRMS: calcd. for $C_{28}H_{24}O_7Na$ $[M + Na]^+$ *m*/*z* 495.1415; found *m*/*z* 495.1414. ^1H NMR spectroscopic data are in accordance with literature values.[11,12f]

15: R_f = 0.08 (EtOAc/heptane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.24 (m, 10 H), 6.46 (s, 1 H), 6.08–6.01 (m, 1 H), 6.01 (d, *J* = 1.2 Hz, 1 H), 5.97 (d, *J* = 1.2 Hz, 1 H), 5.44 (d, *J* = 9.9 Hz, 1 H), 5.29 (s, 2 H), 4.89 (d, *J* = 12.0 Hz, 1 H), 4.86–4.83 (m, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.39 (m, 1 H), 3.66 (dd, *J* = 1.6, 5.2 Hz, 1 H), 3.36 (br. s, 1 H), 2.99 (d, *J* = 10.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 153.3, 143.8, 138.0, 137.9, 137.7, 136.7, 129.5, 128.4, 128.2, 127.9, 127.8, 127.7, 124.8, 111.3, 102.0, 101.9, 75.6, 74.3, 74.1, 69.9, 63.2, 40.0 ppm. HRMS: calcd. for $C_{28}H_{24}O_7Na$ $[M + Na]^+$ *m*/*z* 495.1415; found *m*/*z* 495.1409.

(1*S*,4*R*,4a*R*,11b*R*)-4,7-Dibenzyloxy-1-(2,2,2-trichloroacetylamino)-1,4,4a,11b-tetrahydro-6*H*-[1,3]benzodioxolo[5,6-*c*]chromen-6-one (16): Alcohol **14** (0.2912 g, 0.616 mmol) was dissolved in anhydrous CH_2Cl_2 (5.0 mL) under Ar and cooled to –42 °C, where Cl_3CCN (0.31 mL, 3.09 mmol) was added followed by dropwise addition of DBU (0.15 mL, 1.00 mmol). The solution was warmed to –20 °C over 1 h where it was quenched with 12% aqueous NH_4Cl (30 mL). After separating the phases, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 1:4) to yield 0.3729 g (98%) of a white foam. The imidate (0.2563 g, 0.416 mmol) was heated neat to 135 °C in an oil bath under high vacuum (≈ 0.1 Torr) for 21 h. The residue was purified by flash chromatography (EtOAc/heptane, 1:4) to yield 166.9 mg (65%) of a white solid (64% over two steps). R_f = 0.46 (EtOAc/heptane, 1:1). Decomposes > 145 °C (ref.[11] m.p. 186–187 °C). $[\alpha]_D^{21}$ = –30.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3307, 3031, 2909, 2872, 1701, 1615, 1478, 1305, 1264, 1246, 1088, 1053, 818 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.28 (m, 10 H), 6.80 (d, *J* = 9.2 Hz, 1 H), 6.44 (s, 1 H), 6.03 (m, 1 H), 6.00 (d, *J* = 1.4 Hz, 1 H), 5.93 (d, *J* = 1.3 Hz, 1 H), 5.88 (dd, *J* = 1.6, 10.2 Hz, 1 H), 5.38 (d, *J* = 11.4 Hz, 1 H), 5.32 (d, *J* = 11.3 Hz, 1 H), 4.69–4.64 (m, 2 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.48–4.42 (m, 1 H), 4.10–4.06 (m, 1 H), 3.04 (dd, *J* = 2.4, 9.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 160.8, 152.8, 144.6, 138.5, 137.9, 137.2, 136.7, 130.8, 128.6, 128.3, 128.1, 128.0, 127.8, 126.5, 111.1, 103.2, 102.1, 92.3, 75.4, 74.5, 72.2, 70.7, 50.2, 38.9 ppm. HRMS: calcd. for $C_{30}H_{24}Cl_3NO_7Na$ $[M + Na]^+$ *m*/*z* 638.0511; found *m*/*z* 638.0486. ^1H NMR spectroscopic data are in accordance with literature values.[11]

(1*R*,2*S*,3*S*,4*R*,4a*R*,11b*R*)-4,7-Dibenzyloxy-2,3-dihydroxy-1-(2,2,2-trichloroacetylamino)-1,2,3,4,4a,11b-hexahydro-6*H*-[1,3]benzodioxolo[5,6-*c*]chromen-6-one (17): Alkene **16** (163.3 mg, 0.265 mmol) was dissolved in THF (2.65 mL), and NMO (68.0 mg, 0.581 mmol), H_2O (0.2 mL) and OsO_4 (18.4 mg, 72.4 μmol) were added. The solution was stirred in a closed vial for 123 h at room temperature and then poured into 10% aqueous Na_2SO_3 (20 mL) and EtOAc (5 mL). The phases were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 49:1 → 24:1) to yield a white solid (161.7 mg, 94%). R_f = 0.10 (EtOAc/heptane, 1:1); m.p. 201–202 °C (ref.[11] 202–206 °C). $[\alpha]_D^{21}$ = +30.0 (*c* = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3600–3150, 3025, 2923, 1713, 1701, 1610, 1472, 1374, 1297, 1256, 1092 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + 2 drops of CD_3OD): δ = 7.48–7.24 (m, 10 H), 6.43 (s, 1 H), 5.96 (d, *J* = 1.1 Hz, 1 H), 5.85 (d, *J* = 1.0 Hz, 1 H), 5.32 (d, *J* = 11.4 Hz, 1 H), 5.26 (d, *J* = 11.4 Hz, 1 H), 4.64 (d, *J* = 11.7 Hz, 1 H), 4.59–4.55 (m, 2 H), 4.25–4.22 (m, 1 H), 4.14 (dd, *J* = 3.1, 10.7 Hz, 1 H), 4.02 (t, *J* = 2.7 Hz, 1 H), 3.97 (t, *J* = 11.1 Hz, 1 H), 3.34 (dd, *J* = 2.7, 11.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + 2 drops of CD_3OD): δ = 162.7, 161.0, 152.9, 143.9, 138.2, 137.0, 136.8, 136.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 110.7, 104.2, 102.0, 92.5, 76.3, 75.8, 74.4, 72.7, 70.7, 69.1, 52.0, 39.5 ppm. HRMS: calcd. for $C_{30}H_{26}Cl_3NO_9Na$ $[M + Na]^+$ *m*/*z* 672.0565; found *m*/*z* 672.0540. ^1H NMR spectroscopic data are in accordance with literature values.[11]

(1*R*,2*S*,3*S*,4*R*,4a*R*,11b*R*)-2,7-Dibenzyloxy-1,3,4-trihydroxy-1,3,4,4a,5,11b-hexahydro-2*H*-[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (18): Lactone **17** (112.2 mg, 0.172 mmol) and K_2CO_3 (239 mg, 1.73 mmol) were suspended in anhydrous 5:2 MeOH/CH_2Cl_2 (7.0 mL) and the mixture was heated to reflux under Ar overnight. The suspension was cooled to room temperature and carefully neutralised with Amberlite IR-120 (H^+). The resin was filtered off, washed with 1:1 MeOH/CH_2Cl_2 and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (8.0 mL), HOBt (55.5 mg, 0.411 mmol) was added and the solution was cooled to –5 °C under Ar. DCC (43.2 mg, 0.209 mmol) was then added and

the mixture was stirred for 5 min before the cooling bath was removed and the reaction was warmed to room temperature over 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 → 24:1) to afford 71.0 mg (81%) of a solid. R_f = 0.40 (CH_2Cl_2/MeOH, 19:1); m.p. 93–94 °C (ref.[11] 98–100 °C). $[\alpha]_D^{21}$ = +52.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3500–3200, 2904, 1644, 1612, 1475, 1453, 1366, 1335, 1285, 1218, 1069, 1030, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.54–7.23 (m, 10 H), 6.66 (s, 1 H), 5.95 (d, *J* = 1.5 Hz, 1 H), 5.94 (d, *J* = 1.5 Hz, 1 H), 5.27 (d, *J* = 11.2 Hz, 1 H), 5.23 (d, *J* = 11.3 Hz, 1 H), 4.98 (br. s, 1 H), 4.64 (d, *J* = 11.8 Hz, 1 H), 4.59 (d, *J* = 11.8 Hz, 1 H), 4.45 (br. s, 1 H), 4.25 (br. s, 1 H), 4.05 (t, *J* = 3.0 Hz, 1 H), 4.01–3.97 (m, 2 H), 3.82 (dd, *J* = 10.1, 13.0 Hz, 1 H), 3.10 (d, *J* = 13.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 152.0, 143.1, 137.6, 137.5, 136.9, 136.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.5, 116.2, 101.7, 101.1, 76.7, 74.9, 72.4, 71.4, 71.0, 67.6, 49.9, 41.5 ppm. HRMS: calcd. for $C_{28}H_{27}NNaO_8$ $[M + Na]^+$ *m/z* 528.1630; found *m/z* 528.1621. ^1H NMR spectroscopic data are in accordance with literature values.[11]

Pancratistatin: Dibenzyl ether **18** (34.2 mg, 67.7 μmol) was dissolved in EtOAc (2.0 mL) and $Pd(OH)_2$/C (104 mg) was added. The suspension was degassed and stirred while H_2 was bubbled through for 2 h (1.0 mL of EtOAc was added after 1.5 h). The mixture was stirred under an H_2 atmosphere for an additional 2 h and then filtered through a small plug of Celite, which was rinsed with 40% MeOH in CH_2Cl_2. The solvent was removed in vacuo to afford 22.0 mg (99%) of a white solid. R_f = 0.24 (CH_2Cl_2/MeOH, 9:1). Decomposes above 250 °C. $[\alpha]_D^{21}$ = +37 (*c* = 1.0, DMSO) [ref.[2a] $[\alpha]_D^{34}$ = +48 (*c* = 1.0, DMSO), ref.[12e] $[\alpha]_D^{23}$ = +38 (*c* = 1.08, DMSO), ref.[12g] $[\alpha]_D^{26}$ = +40.9 (*c* = 1.0, DMSO), ref.[12h] $[\alpha]_D^{25}$ = +44.0 (*c* = 1.0, DMSO)]. IR (neat): $\tilde{\nu}$ = 3348, 2926, 1671, 1615, 1597, 1462, 1416, 1347, 1296, 1228, 1082, 1065, 1036, 876 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 13.06 (s, 1 H), 7.50 (s, 1 H), 6.49 (s, 1 H), 6.06 (s, 1 H), 6.04 (s, 1 H), 5.36 (d, *J* = 4.0 Hz, 1 H), 5.08 (d, *J* = 5.8 Hz, 1 H), 5.05 (d, *J* = 6.1 Hz, 1 H), 4.83 (d, *J* = 7.5 Hz, 1 H), 4.28 (m, 1 H), 3.97 (m, 1 H), 3.85 (m, 1 H), 3.74–3.67 (m, 2 H), 2.97 (br. d, *J* = 11.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 169.4, 152.0, 145.3, 135.6, 131.6, 107.4, 101.7, 97.6, 73.2, 70.1, 69.9, 68.4, 50.4, 39.5 (assigned by HSQC) ppm. HRMS: calcd. for $C_{14}H_{16}NO_8$ $[M + H]^+$ *m/z* 326.0870; found *m/z* 326.0864. NMR spectroscopic data are in accordance with literature values.[11,12c]

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra for compounds **2**–**11**, **14**–**18** and pancratistatin.

Acknowledgments

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