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Application of the β-Azidonation Reaction to the Synthesis of the Antitumor Alkaloid (+)-Pancratistatin

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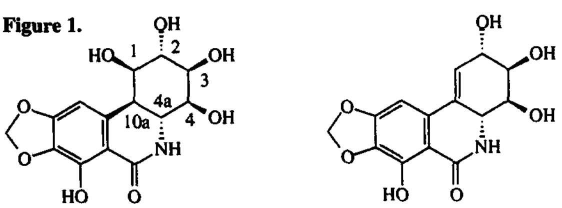
Abstract:- *o*-Vanillin **21** was converted into **24** following literature procedures. Treatment of **24** with *n*-BuLi/THF followed by addition of **25** gave **26**. Dehydration ($POCl_3$/pyridine/DBU), hydrogenation and hydrolysis of **26** gave the ketone **29**. Chirality was introduced by deprotonation of **29** with the lithium salt of (+)-bis(α-methylbenzyl)amine, followed by triisopropylsilyl trifluoromethanesulfonate to give **30** (95%). β-Azidonation of **30** with $(PhIO)_n/TMSN_3$ rapidly produced **31** (95%) as a mixture of *trans*- and *cis*- diastereomers in a 3.5:1 ratio. Reduction with $LiAlH_4$ followed by methyl chloroformate/pyridine gave **32**, which on treatment with $MCPBA/CH_2Cl_2$/imidazole resulted in **33**. Hydrolysis of **33** gave **34**, which when exposed to $KOBu^t$/HMPA at 90 °C resulted in **39**. After conversion of **39** into enone **42**, epoxidation with $NaHCO_3/H_2O_2$/MeOH gave **43**. Reduction of **43** with L-selectride followed by solvolysis with sodium benzoate in water gave **46**, which was immediately acetylated to give **47**. Lactam formation (Tf_2O/DMAP) converted **47** into **48** and the regioisomer **49** (7:1). The mixture of **48** and **49** demethylated to give **50** and the acetate protecting groups removed to give (+)-pancratistatin **1**.

Keywords: alkaloid, pancratistatin, antitumor, β-azidonation, triisopropylsilyl (TIPS) enol ethers, prochiral, desymmetrization.

Introduction

The Amaryllidaceae alkaloids have played in central role in the development of alkaloid chemistry. The elucidation of their structures, and the strategies and methodology developed for their synthesis have been motivated by their diverse and important pharmacological properties.[1] A relatively recent addition to the 100 or so Amaryllidaceae alkaloids is pancratistatin **1** (**Figure 1**). In 1984 Pettit and coworkers reported the structure of pancratistatin **1** isolated from the roots of the Hawaiian Pancratium littorale Jacq.[2] Subsequently, pancratistatine has become a significant target for total synthesis because of its increasing potential as a clinically useful antitumor agent.[3] However, the supply of **1** is limited, and attempts to synthesize **1** from more abundant alkaloids such as narciclasine **2** have to-date not been successful.[4]

Figure 1.



1, Pancratistatin 2, Narciclasine

The first synthesis of (±)-**1** was first reported by Danishefsky.[5] The key strategic elements are shown in **Scheme 1**. The Diels-Alder adduct **3** was converted through several steps into **4**, which was subjected to the Overman allylic imidate rearrangement[6] to give **5**, after osmium tetroxide dihydroxylation, **Scheme 1** Treatment of the lactone **5** with K_2CO_3/MeOH, followed by DCC and hydrogenolysis of the benzyl groups resulted in **1**. The use of the *cis*-fused lactone→*trans*-fused amide transformation provides a highly stereocontrolled synthesis of **1**.

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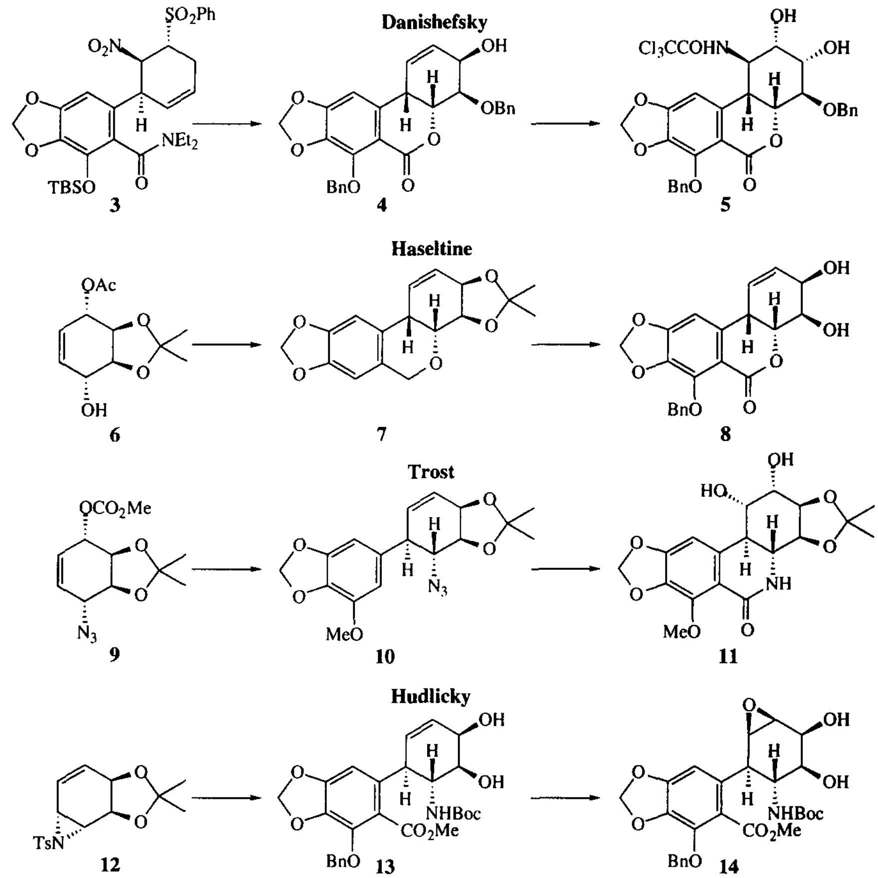
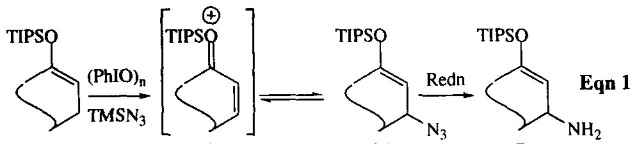
Recently, Haseltine has described an enantioselective synthesis of (+)-**1** that correlates with the advanced intermediate **4** in the Danishefsky synthesis.[7] The enantioselectivity was obtained from the enzymatic desymmetrization of the diacetate precursor to **6**. Subsequent conversion of **6** into **7**, and oxidative transformations of **7** lead to **8**, which on protection , *O*-benzylation, and deprotection provided **4** as a single enantiomer.

Scheme 1, Summary of Current Strategies



The Trost[8] synthesis of **1** introduces the chirality by desymmetrization of the symmetrical dicarbonate precursor to **9** with a palladium-catalyzed displacement by azide anion in the presence of a chiral ligand. Subsequent conversion of **9** into **10**, *cis*-dihydroxylation of **10** and formation of the lactam ring gave **11**, which required inversion at C-1 and deprotection to give **1**. Hudlicky[9] has employed the aziridine **12** (derived from dihydroxylation of bromobenzene) which was converted into **13**. The key steps involved subsequent conversion of **13** into the epoxide **14** which on treatment with sodium benzoate in water at 100 °C for six days gave **1** (51%). This crucial reaction offer the best solution to the introduction of the *trans*-1,2-diol functionality. Also, as commented upon by Hudlicky, the epoxide of opposite stereochemistry (**14**, with 1,2-α) should, through diaxial opening, give the same product as **14** (1,2-β). There are also several reported syntheses of the simpler 7-deoxypancratistatin.[10]

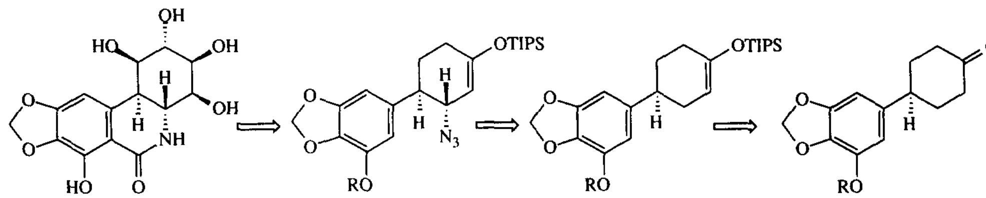
Retrosynthetic Analysis



15 **15a** **16** **17** **Eqn 1**

The strategy that we have developed is based upon the use of the β-azidonation of triisopropylsilyl (TIPS) enol ethers, **Eqn 1**. We have previously shown that treatment of TIPS enol ethers **15** with iodosyl benzene in the presence of trimethylsilyl azide produces the β-azido adduct **16** (>95%) *via* the enonium ion **15a**.[11] Reduction of the azide **16** with lithium aluminum hydride gave the amine **17**. In general, we have found that β-amino TIPS enol ethers and their *N*-acyl or *N*-Ts derivatives are stable compounds, and will only undergo β-elimination to give enones if treated with fluoride anion.[12,13]

Scheme 2, Retrosynthetic Analysis



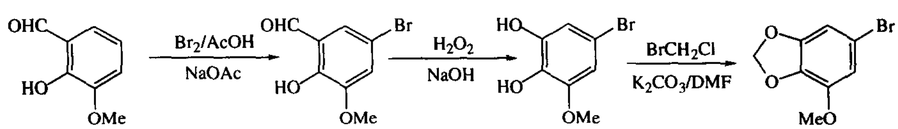
1 **18** **19** **20, prochiral ketone**

Based on the above methodology the retrosynthetic analysis of **1** leads to the key intermediate **18**, which can be derived from **19** using the above β-azidonation reaction, **Scheme 2**.[14] Starting with the prochiral cyclohexanone **20**, formation of the TIPS enol ether using a chiral lithium dialkylamide should provide the requisite product **19** in an enantio-enriched form. Both Koga and Simpkins have reported a number of examples of desymmetrization of prochiral cyclohexanones using C_2-symmetric chiral lithium dialkylamides and trapping of the resulting lithium enolates with either TMSCl(OTf) or TBSCl(OTf) to give the corresponding silyl enol ethers in enantiomeric excesses (ee's) of 50-95%.[15] Simpkins also discovered that conducting the above reactions in the presence of lithium chloride improved the *ee's*, in some cases to as high as 95%.[16]

Synthesis of Prochiral 4-Arylcyclohexanone

Treatment of *o*-vanillin **21** with Br_2/AcOH/AcONa gave **22**,[17] which was subjected to Dakin oxidation conditions to give **23**.[18] *O*-Methylenation of **23** gave the known arylbromide **24**, **Scheme 3**.[19] While there are many methods that could be used for the conversion of **24** and **25** into **29**, the classical sequence of transformation as depicted in **Scheme 4** served to be reliable and readily scaled-up.

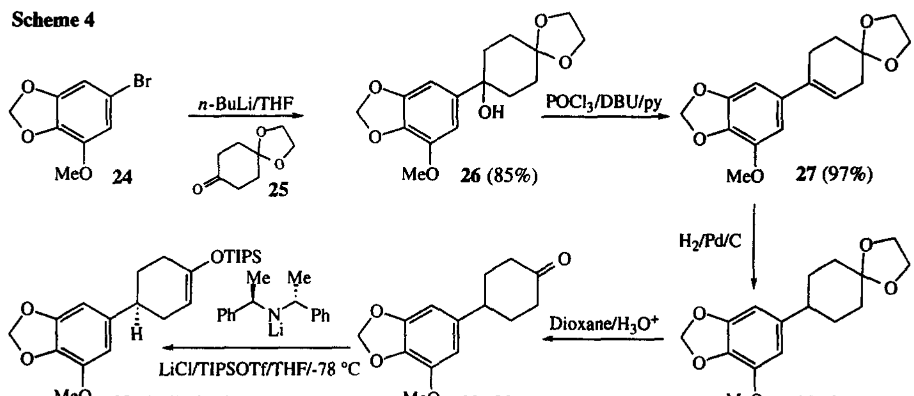
Scheme 3



21, *o*-vanillin **22** (86%) **23** (89%) **24** (85%)

Treatment of **24** with *n*-BuLi in tetrahydrofuran at -78 °C, followed by addition of **25** gave **26**. The tertiary alcohol **26** was dehydrated ($POCl_3$/pyridine/DBU) to give **27** (97%). Hydrogenation of **27** over 10% Pd/C gave **28**, which was hydrolyzed under acidic conditions to the ketone **29**. All attempts to directly deoxygenate **26** to give **28** directly were unsuccessful, and consequently the sequence involving dehydration followed by hydrogenation was necessary. Deprotonation of **29** with the lithium salt of (+)-bis(α-methylbenzyl)amine[20] in the presence of lithium chloride at -78 °C followed by triisopropylsilyl trifluoromethanesulfonate gave **30** (95%), Scheme 4.[21]

Scheme 4

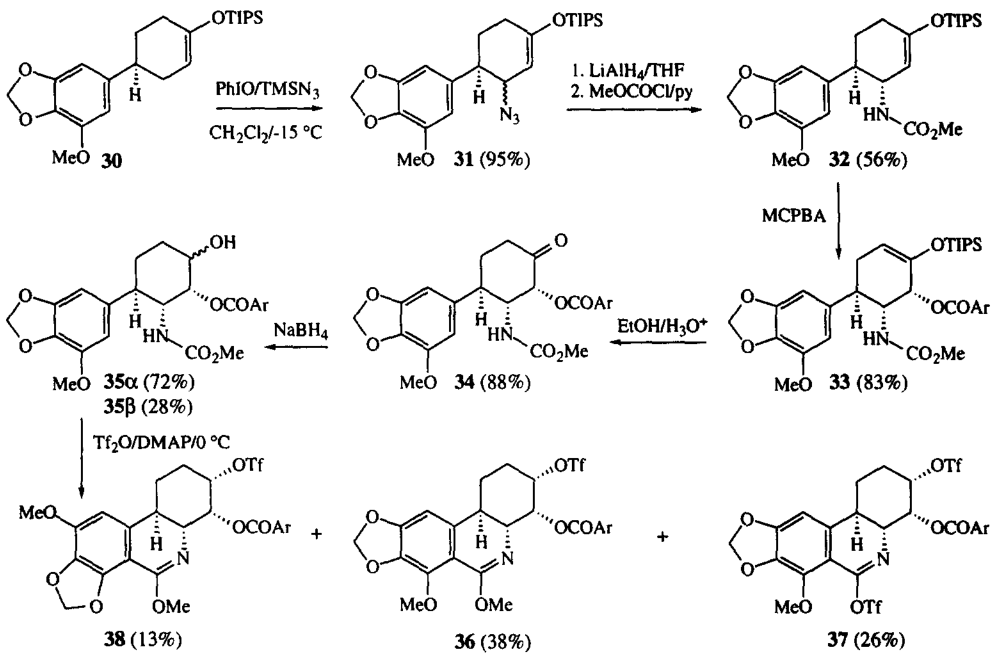


Treatment of **30** with $(PhIO)_n$/$TMSN_3$ in CH_2Cl_2 at -15° C rapidly produced **31** (95%) as a mixture of *trans*- and *cis*- diastereomers in a 3.5:1 ratio, **Scheme 5**. It is important to use $(PhIO)_n$ that has been prepared and stored in a freezer for no more than three months, otherwise the β-azidonation reaction will not work in good yields. The deterioration of iodosylbenzene is caused by disproportionation to iodoxybenzene ($PhIO_2$) which is inactive with respect to the β-azidonation reaction.[22] Exposure of the mixture of *cis*- and *trans*- **31** to $LiBPh_4$/CH_2Cl_2 did not improve the ratio by equilibration *via* the putative enonium ion **15a**, Eqn 1, but led to decomposition and elimination to dienes.[11] The mixture of *cis*- and *trans*-**31** was reduced with lithium aluminum hydride and directly treated with methyl chloroformate/pyridine to give **32**, which after two crystallizations from cyclohexane gave the pure *trans*-isomer of **32**.

It was anticipated that epoxidation of **32** would proceed by axial addition, and eventually, after a series of intermediate steps, form **33**.[23,24] Indeed, treatment of **32** with MCPBA/CH_2Cl_2/imidazole resulted in **33** in excellent yield. It was difficult to assign the stereochemistry of **33** because of carbamate resonance that caused line broadening of the crucial vicinal proton signals. In order to confirm the structure of **33** and examine some further potentially applicable transformations, albeit with the wrong diastereomer, we hydrolyzed **33** to give **34** (88%). Reduction of **34** with $NaBH_4$/MeOH gave **35α** (72%) and **35β** (28%) (stereochemistry assigned from subsequent X-ray determination of **36**). The major diastereomer **35α** was subjected to modified Bischler-Napieralski reaction conditions (Tf_2O/DMAP)[25] to give the imino ether **36** (38%), **37** (26%), and the incorrect regioisomer **38** (13%). The structure and stereochemistry of **36** was confirmed by X-ray crystallography. Consequently, as suspected, the stereochemistry established at C-4 (pancratistatin numbering) in **33** was incorrect.

Since the *m*-chlorobenzoyl(oxy) substituent in **34** is axial, we expected that epimerization to the more stable equatorial isomer could be readily achieved. Indeed, during the acid catalyzed hydrolysis of **33** into **34** there was observed the formation of the epimerized compound **39** to the extent of 12%. It was eventually found that treatment of **34** with KOBu^t/HMPA at 90 °C resulted in complete conversion into **39**, **Scheme 6**. Having established the correct C-4 stereochemistry, the functionalization of the C-1 and C-2 was now required.

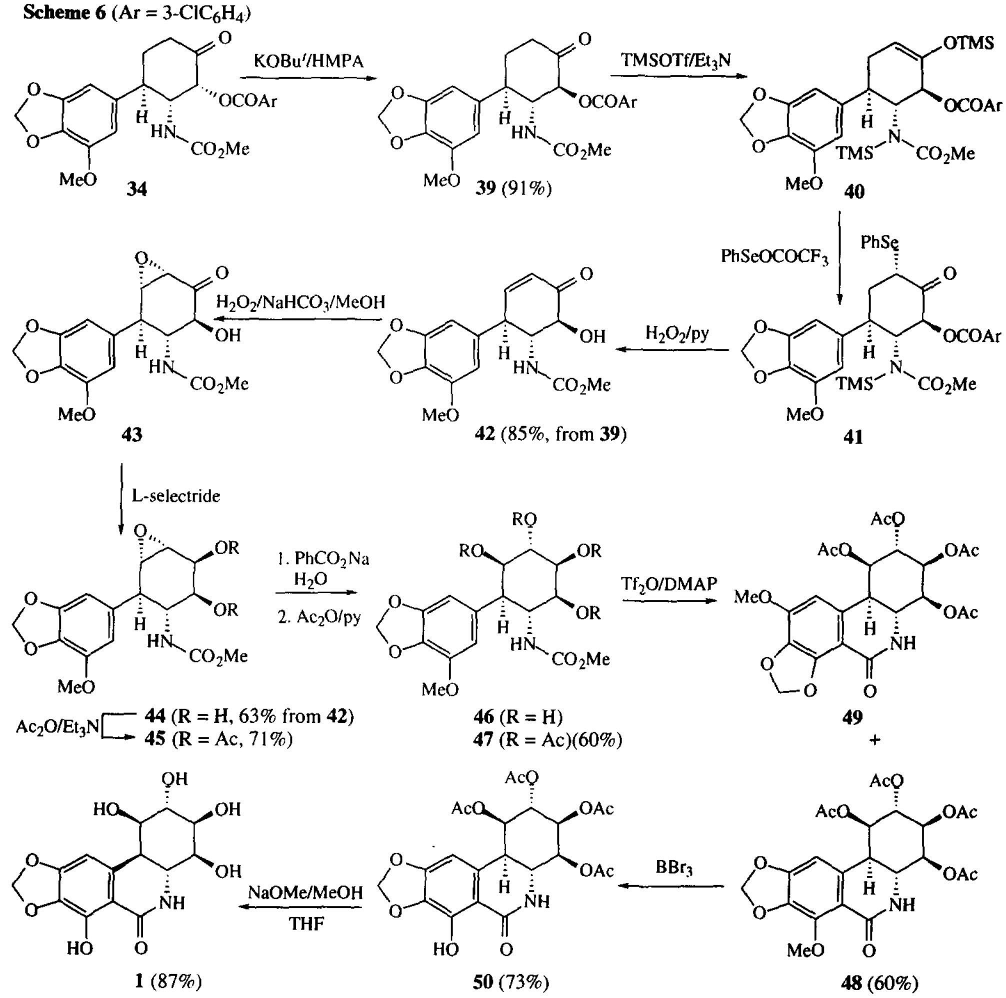
Scheme 5 (Ar = 3-ClC_6H_4)



Despite the numerous methods that have been developed for the conversion of saturated ketones into α,β-unsaturated ketones, it proved to be particularly difficult to transform **39** into **42** in an efficient manner. Eventually, it was found that treatment of **39** with Et_3N/trimethylsilyl trifluoromethanesulfonate at 0 °C gave the bis-trimethylsilyl derivative **40**. When **40** was treated with freshly prepared $PhSeOCOCF_3$ (PhSeCl + $AgOCOCF_3$) it was converted into **41**, which on oxidation with hydrogen peroxide in pyridine/CH_2Cl_2 gave the enone **42** in 85% yield from **39**. While the enone **42** was converted into the epoxide **43** by treatment with H_2O_2/NaOH/MeOH the yield was low (25%) because the product **43** was rapidly destroyed under the strongly alkaline reaction conditions. Whereas, using $NaHCO_3$/H_2O_2/MeOH gave **43** (75%). Reduction of **43** with L-selectride gave **44** (63%) with the required stereochemistry at C-3. The stereochemistry of **44** was unambiguously established by single crystal X-ray analysis of the derived diacetate **45**.

At this stage we were in a position to solvolyze the epoxide **44** under the Hudlicky conditions (cf. 14, Scheme 1). Exposure of **44** to sodium benzoate in water at 100 °C for 4 days gave **46**, which was immediately acetylated to give **47** (60% from **44**). Bischler-Napieralski reaction conditions (Tf_2O/DMAP) converted **47** into **48** and the regioisomer **49** (7:1, cf **35**) which were inseparable at this stage. The mixture of **48** and **49** was treated with boron tribromide/CH_2Cl_2 at -78 ° to 0 °C to give **50** and unreacted **49**, which was now readily separable. The acetate protecting groups were removed by treatment of **50** with NaOMe/MeOH to give (+)-**1** (87%), which was identical to an authentic sample. The synthesis proceeds in 22 steps from commercially available *o*-vanillin in an overall yield of 1.2% (ca. 70% per step).

Scheme 6 (Ar = 3-ClC_6H_4)



Experimental

5-Bromo-3-methoxysalicylaldehyde 22. To a solution of **21** (73.7 g, 0.48 mol) and sodium acetate (60 g, 0.73 mol) in acetic acid (1.8 L) was added bromine (25 mL, 0.48 mol) in acetic acid (20 mL). The resultant yellow solution was stirred at room temperature for 30 min. Acetic acid was evaporated *in vacuo*, and the residue was partitioned between CH_2Cl_2 (1 L) and H_2O (1 L). The organic phase was washed with H_2O (2 x 1 L), dried ($MgSO_4$) and evaporated *in vacuo* to leave a brown solid. Recrystallization from acetic acid/H_2O gave **22** (96.2 g, 0.416 mol, 86%) as yellow needles, R_f 0.53 (CH_2Cl_2/hexanes 4:1); Mp 122-124 °C (lit[17] 128-129 °C); IR (Nujol) 1651, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.00 (1H, s), 9.84 (1H, s), 7.29 (1H, d, J = 2.1 Hz), 7.16 (1H, d, J = 2.0 Hz), 3.91 (3H, s); HRMS (CI) calcd for $C_8H_8BrO_3$ (MH^+) 230.9657, found 230.9646.

3,4-Dihydroxy-5-methoxybromobenzene 23. To a solution of **22** (20 g, 86.6 mmol) in 2% NaOH (425 mL) at room temperature was added a solution of 30% H_2O_2 (54 g, 476 mmol) in H_2O (510 mL). The mixture turned a deep purple color and was left to stir for 30 min; 2M HCl (50 mL) was added and the solution lightened to a pale pink color. The aqueous solution was extracted with CH_2Cl_2 (4 x 250 mL). The combined extracts were washed with saturated aqueous Na_2SO_3 (2 x 500 mL), and dried (Na_2SO_4). Evaporation *in vacuo* gave crude **23** (16.8 g, 77 mmol, 89%) as a white solid, R_f 0.28 (hexanes/EtOAc 7:3); Mp 72-74 °C (lit[18] 74-76 °C); IR (Nujol) 3478, 1621, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (1H, d, J = 2.2 Hz), 6.61 (1H, d, J = 2.1 Hz), 5.35 (2H, bs), 3.86 (3H, s); HRMS (CI) calcd for $C_7H_8BrO_3$ (MH^+) 218.9657, found 218.9662.

3,4-Methylenedioxy-5-methoxybromobenzene 24. To a mixture of **23** (20 g, 90.9 mmol) in DMF (230 mL) and K_2CO_3 (18.9 g, 136 mmol) was added bromochloromethane (6.6 mL, 100 mmol). The mixture was warmed to 80 °C for 2 h during which time it turned a dirty green color. A further portion of bromochloromethane (6.6 mL, 100 mmol) was added and heating continued for 1 h. The solution was allowed to cool, diluted with H_2O (230 mL) and extracted with Et_2O (3 x 250 mL). The combined ethereal layers were washed with brine (200 ml) and dried ($MgSO_4$). Evaporation *in vacuo* yielded crude product, which was purified by chromatography over silica gel eluting with hexanes/Et_2O (9:1). Recrystallization from Et_2O/hexanes gave **24** (17.67 g, 76.5 mmol, 85%) as white crystals, R_f 0.66 (hexanes/Et_2O 4:1); Mp 80-81 °C (lit[19] 78-79 °C); IR (Nujol) 1626, 1495, 1455, 1422 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (2H, m), 5.97 (2H, s), 3.88 (3H, s); HRMS (CI) calcd for $C_8H_8BrO_3$ (MH^+) 230.9657, found 230.9650.

6-(Cyclohex-1-ol-4-ethyleneketal)-4-methoxy-1,3-benzodioxole 26. To a solution of **24** (2.4 g, 10 mmol) in THF (40 mL) at -78 °C was added *n*-BuLi (2.5M in hexanes) (4.4 mL, 11 mmol). The mixture turned yellow and was stirred at -78 °C for 3 h before the addition of a solution of **25** (2.0 g, 12 mmol) in THF (10 mL). The resulting solution was allowed to warm slowly to room temperature over 2 h. Saturated aqueous NH_4Cl (60 mL) and Et_2O (160 mL) were added. The ethereal layer was washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with hexanes/EtOAc (1:1) to give **26** (2.62 g, 8.5 mmol, 85%) as a white solid, R_f 0.29 (EtOAc/hexanes 3:2); Mp 140-143 °C; IR ($CHCl_3$) 3484, 1634, 1514, 1455 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 6.74 (1H, d, *J* = 1.8 Hz), 6.70 (1H, d, *J* = 1.5 Hz), 5.95 (2H, s), 3.98 (4H, m), 3.91 (3H, s), 2.09 (4H, m), 1.73 (4H, m), 1.56 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 143.7, 143.1, 133.8, 108.3, 104.2, 101.3, 99.1, 72.3, 64.2, 64.1, 56.5, 36.6, 30.7; HRMS (CI) calcd for $C_{16}H_{20}O_6$ (M^+) 308.1260, found 308.1270. Used directly in the next step.

6-(Cyclohex-1-ene-4-ethyleneketal)-4-methoxy-1,3-benzodioxole 27. To a solution of **26** (600 mg, 2.0 mmol) in pyridine (12 mL) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.6 mL, 4.0 mmol) followed by $POCl_3$ (0.36 mL, 4 mmol) dropwise. The resultant orange solution was stirred at room temperature for 1 h, and at 80 °C for 30 min during which time the orange color darkened. The solution was recooled to 0 °C, and diluted carefully with EtOAc (60 mL) and H_2O (60 mL). The organic phase was washed with H_2O and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with hexanes/EtOAc (4:1) to give **27** (0.56 g, 1.93 mmol, 97%) as a pale yellow gum, R_f 0.26 (EtOAc/hexanes 1:4); IR ($CHCl_3$) 1624, 1509, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, d, *J* = 1.2 Hz), 6.55 (1H, d, *J* = 1.1 Hz), 5.93 (2H, s), 5.86 (1H, m), 4.01 (4H, s), 3.88 (3H, s), 2.59 (2H, m), 2.43 (2H, bs), 1.89 (2H, t, *J* = 6.5 Hz); HRMS (CI) calcd for $C_{16}H_{19}O_5$ (MH^+) 291.1232, found 291.1231.

6-(Cyclohex-4-ethyleneketal)-4-methoxy-1,3-benzodioxole 28. A suspension of Pd (10% on activated charcoal) (5 mg, 2 mol%) in a solution of **27** (150 mg, 0.5 mmol) in methanol (6 mL) was stirred under an atmosphere of hydrogen for 90 min. The mixture was filtered through a short pad of celite and evaporated *in vacuo*. Recrystallization of the crude product from methanol furnished **28** (127 mg, 0.43 mmol, 87%) as white crystals, R_f 0.39 (EtOAc/hexanes 1:4); Mp 84-86 °C; IR ($CHCl_3$) 1634, 1515, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (1H, d, *J* = 1.3 Hz), 6.39 (1H, d, *J* = 1.2 Hz), 5.92 (2H, s), 3.98 (4H, s), 3.89 (3H, s), 2.48 (1H, m), 1.86-1.59 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 143.1, 141.2, 133.0, 108.1, 105.8, 100.9, 100.6, 64.0, 56.2, 43.2, 34.8, 31.5; HRMS (CI) calcd for $C_{16}H_{21}O_5$ (MH^+) 293.1389, found 293.1385.

6-(Cyclohex-4-one)-4-methoxy-1,3-benzodioxole 29. To a stirred solution of **28** (0.29 g, 1.0 mmol) in dioxane (3 mL) was added H_2SO_4:H_2O (1:1) (1.5 mL). The resultant solution was left to stir at room temperature for 40 min. H_2O (6 mL) was added and the emulsion extracted with CH_2Cl_2 (3 x 6 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with pentane/EtOAc (4:1) to give **29** (221 mg, 0.89 mmol, 89%) as a white solid, R_f 0.22 (hexanes/EtOAc 4:1); Mp 73-75 °C; IR (Nujol) 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, d, *J* = 1.3 Hz), 6.40 (1H, d, *J* = 1.3 Hz), 5.94 (2H, s), 3.91 (3H, s), 2.93 (1H, m), 2.48 (4H, m), 2.19 (2H, m), 1.90 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 148.8, 143.3, 139.5, 133.5, 105.1, 101.1, 100.5, 56.5, 42.7, 41.1, 34.0; HRMS (CI) calcd for $C_{14}H_{17}O_4$ (MH^+) 249.1127, found 249.1133.

(-)-(1*S*)-6-[4-Triisopropylsilyl(oxy)-cyclohex-3-ene]-4-methoxy-1,3-benzodioxole 30. To a stirred solution of (+)-bis(α-methylbenzyl)amine (8.64 g, 33 mmol) in THF (240 mL) at -78 °C was added *n*-BuLi (13.2 mL, 33 mmol, 2.5 M in hexane). The yellow solution was allowed to warm to room temperature, recooled to -78 °C, and dry LiCl (0.47 g, 11 mmol) in THF (120 mL) was added followed by a solution of **2** (5.46 g, 22 mmol) in THF (24 mL). The resultant red solution was stirred at -78 °C for 1 h, and triisopropylsilyl trifluoromethanesulfonate (30 mL, 110 mmol) was added. The red color dissipated, and the solution was allowed to warm slowly to room temperature over 2 h before quenching with saturated aqueous NH_4Cl (500 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford a pale yellow oil. The crude product was chromatographed over silica gel eluting with hexanes/Et_2O (9:1) to give **30** (8.40 g, 20.8 mmol, 95%) as a colorless oil, R_f 0.71 (hexanes/Et_2O 9:1); $[\alpha]_D^{23}$ (c = 0.95, $CHCl_3$) -24 ; IR (neat) 1668, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (1H, d, J = 1.32 Hz), 6.40 (1H, d, J = 1.3 Hz), 5.92 (2H, s), 5.92 (1H, m), 3.90 (3H, s), 2.65 (1H, m), 2.29-2.08 (4H, m), 1.92-1.76 (2H, m), 1.18 (3H, m), 1.10 (18H, d, J = 5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 148.7, 143.3, 141.6, 133.2, 106.2, 102.6, 101.1, 100.8, 56.5, 40.2, 32.3, 30.5, 30.2, 18.0, 12.6; HRMS (CI) calcd for $C_{23}H_{37}O_4Si$ (MH^+) 405.2461, found 405.2458.

(1*S*,2*RS*)-6-[2-Azido-4-triisopropylsilyl(oxy)cyclohex-3-ene]-4-methoxy-1,3-benzo dioxole 31. To a stirred solution of **30** (6.19 g, 15.3 mmol) in CH_2Cl_2 (100 mL) at -15 °C was added iodosobenzene (4.38 g, 20 mmol) followed by trimethylsilylazide (5.3 ml, 39.8 mmol). The suspension was left to stir at -15 °C for 15 min, and filtered through a short pad of celite. Evaporation *in vacuo* gave **31** as a brown oil (6.46 g, 14.5 mmol, 95%) in a ratio of 3.5:1 (*trans*:*cis*), R_f 0.40 (hexanes/EtOAc 9:1); IR ($CHCl_3$) 2094, 1652, 1627 cm^{-1}; HRMS (C^+) calcd for $C_{23}H_{36}N_3O_4Si$ (MH^+) 446.2475, found 446.2471. Used immediately in the next step.

(+)-(1*S*,2*R*)-6-[2-Methylcarbamoyl-4-triisopropylsilyl(oxy)cyclohex-3-ene]-4-methoxy -1,3-benzodioxole 32. To a stirred solution of crude **31** (6.46 g, 14.5 mmol) in Et_2O (80 mL) at 0 °C was slowly added $LiAlH_4$ (0.55 g, 14.5 mmol). The resultant suspension was stirred at 0 °C for 30 min, and then at room temperature for a further 2 h. The suspension was recooled to 0 °C, and saturated aqueous NH_4Cl (40 mL) was slowly added with stirring over 30 min. The mixture was filtered through a short pad of celite and rinsed with MeOH/EtOAc 1:20 (100 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to give a crude mixture of amines as a brown oil. A solution of the amines and pyridine (3.05 mL, 37.7 mmol) in CH_2Cl_2 (80 mL) was added *via* cannular to a stirred solution of methyl chloroformate (2.7 mL, 34.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resulting solution was stirred at 0 °C for 90 min, saturated aqueous $NaHCO_3$ (100 mL) was added, and the organic phase was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and evaporated *in vacuo* . Filtration through silica gel eluting with EtOAc/hexanes (1:4), followed by evaporation *in vacuo* gave a yellow solid. Two recrystallizations from cyclohexane gave **32** (3.42 g, 7.2 mmol, 49%) as white crystals. Chromatography of the mother liquors over silica gel eluting with hexanes/EtOAc (9:1) gave a further batch of **32** (0.48 g, 1.0 mmol, 7%), R_f 0.35 (hexanes/Et_2O 4:1); Mp 119-120 °C; $[\alpha]_D^{23}$ (c = 1.02, $CHCl_3$) + 56; IR ($CHCl_3$) 3281, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (1H, d, J = 1.3 Hz), 6.39 (1H, bs), 5.93 (2H, s), 4.88 (1H, bs), 4.47 (1H, bs), 3.89 (3H, s), 3.56 (3H, s), 2.47 (1H, m), 2.24 (1H, m), 2.06 (1H, dt, J = 4.3, 17.2 Hz), 1.89 (2H, m), 1.17 (3H, m), 1.08 (18H, d, J = 6.1 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 156.1, 153.9, 143.1, 137.4, 133.5, 106.7, 105.2, 101.2, 101.0, 60.1, 56.3, 52.0, 51.6, 46.5, 29.2, 17.7, 12.3; HRMS (CI) calcd for $C_{25}H_{40}NO_6Si$ (MH^+) 478.2625, found 478.2609.

(+)-(1*S*,2*R*,3*R*)-6-{2-Methylcarbamoyl-3-[3-chlorobenzoyl(oxy)]-4-triisopropylsilyl (oxy)cyclohex-4-ene}-4-methoxy-1,3-benzodioxole 33. To a stirred solution of **32** (2.25 g, 4.7 mmol) in CH_2Cl_2 (22 mL) at 0 °C was added a solution of *m*-chloroperoxybenzoic acid (1.14 g, 6.6 mmol) in CH_2Cl_2 (44 mL). The solution was stirred at 0 °C for 15 min, imidazole (0.7 g, 10.3 mmol) was added, and the solution was warmed to room temperature and stirred for a further 40 min. Saturated aqueous $NaHCO_3$ (40 mL) was added, and the organic phase was washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated to a white foam. The crude product was chromatographed over silica gel eluting with hexanes/EtOAc (7:3) to give **33** (2.47 g, 3.9 mmol, 83%) as a white foam, R_f 0.37 (hexanes/EtOAc 7:3); Mp 90-91 °C; $[\alpha]_D^{23}$ (c = 1.04, $CHCl_3$) +85; IR ($CHCl_3$) 3393, 1716, 1633, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.95 (1H, d, J = 7.7 Hz), 7.60 (1H, d, J = 7.8 Hz), 6.43 (1H, bs), 5.95 (2H, s), 5.38 (1H, s), 4.64-4.34 (2H, m), 3.89 (3H, s), 3.50 (4H, m), 2.73 (1H, bs), 1.87 (2H, m), 1.20 (3H, m), 1.18 (18H, d, J = 8.4 Hz); HRMS (CI) calcd for $C_{32}H_{42}ClNO_8Si$ (MH^+) 632.2446, found 632.2441. Hydrolyzed ketone **34** (0.26 g, 0.55 mmol, 12%) was also isolated.

(+)-(1*S*,2*R*,3*R*)-6-{2-Methylcarbamoyl-3-[3-chlorobenzoyl(oxy)]-cyclohex-4-one}-4-methoxy-1,3-benzodioxole 34. A stirred solution of **33** (2.06 g, 3.2 mmol) in EtOH (90 mL) and 0.2 M HCl (30 mL) was heated to 90 °C for 1 h. After cooling the solution to room temperature, water (50 mL) was added, the emulsion neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (2x100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to give a colorless oil. The crude product was chromatographed over silica gel eluting with hexanes/EtOAc (2:3) to give **34** (1.33 g, 2.8 mmol, 88%) as a white foam, R_f 0.38 (hexanes/EtOAc 1:1); Mp 90-92 °C; $[\alpha]_D^{23}$ (c = 1.03, $CHCl_3$) +92; IR ($CHCl_3$) 3438, 1727, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, t, J = 2.0 Hz), 7.95 (1H, d, J = 8.0 Hz), 7.60 (1h, dd, J = 7.8, 2.0 Hz), 7.44 (1H, t, J = 7.9 Hz), 6.54 (2H, bs), 5.97 (2H, s), 5.43 (1H, bs), 4.83 (1H, d, J = 8.0 Hz), 4.53 (1H, bs), 3.93 (3H, s), 3.62 (3H, s), 3.25 (1H, bs), 2.73 (1H, m), 2.59 (1H, m), 2.24 (1H, m), 2.03 (1H, bs); HRMS (CI^+) calcd for $C_{23}H_{22}ClNO_8$ (MH^+) 476.1112, found 476.1091. Epimerized ketone **39** (0.21 g, 0.4 mmol, 12%) was also isolated.

(+)-(1*S*,2*R*,3*R*,4*S*)-6-{2-Methylcarbamoyl-3-[3-chlorobenzoyl(oxy)-4-hydroxy]-cyclo hexyl}-4-methoxy-1,3-benzodioxole 35α. To a stirred solution of **34** (250 mg, 0.53 mmol) in MeOH (20 ml) at 0 °C was added $NaBH_4$ (20 mg, 0.53 mmol) in four portions over 2 h. The mixture effervesced and was left to stir for a further 15 min at 0 °C. Saturated aqueous NH_4Cl (20 ml) was added, and the resultant emulsion extracted with EtOAc (3 x 20 ml). The combined organic phases washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture of alcohols was purified by chromatography over silica gel eluting with hexanes/EtOAc (3:2) to give **35α** (182 mg, 0.38 mmol, 72%) as a white foam, R_f 0.3 (hexanes/EtOAc 1:1); Mp 94-96 °C; $[\alpha]_D^{23}$ (c = 1.25, $CHCl_3$) +113; IR ($CHCl_3$) 3595, 3442, 1724, 1635, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.97 (1H, d, J = 7.7 Hz), 7.58 (1H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.9 Hz), 6.41 (1H, s), 6.37 (1H, s), 5.93 (2H, s), 5.79 (1H, s), 4.57 (1H, d, J = 8.3 Hz), 4.09 (2H, m), 3.89

(3H, s), 3.51 (3H, s), 2.76 (1H, m), 2.42 (1H, bs), 2.03 - 1.80 (3H, m), 1.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 156.1, 149.1, 143.6, 136.0, 134.6, 134.1, 133.4, 131.6, 129.9, 129.7, 127.9, 106.7, 101.4, 75.6, 70.2, 56.6, 54.2, 52.2, 43.9, 31.5, 28.4; HRMS (CI) calcd for $C_{23}H_{25}ClNO_8$ (MH^+) 478.1269, found 478.1272. Epimeric alcohol **35β** (72 mg, 0.15 mmol, 28%) was also isolated.

(3*S*,4*R*,4a*R*,10b*R*)-1,3,4a,5,10b-hexahydro-3-trifluoromethylsulfonyl(oxy)-4-chloro benzoyl(oxy)-1,3-dioxolo-4,6-dimethoxy[4,5-j]phenanthridine 36. To a stirred solution of **35α** (222 mg, 0.46 mmol) and DMAP (169 mg, 1.4 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added trifluoromethanesulfonic anhydride (0.39 mL, 2.3 mmol). The resultant white gel suspension was stirred at 0 °C for 2 h, and at room temperature for 1h. Saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (15 mL) were added, and the aqueous phase was extracted with EtOAc (10 mL). The combined extracts washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed over silica gel eluting with hexanes/EtOAc (4:1) followed by recrystallization from CH_2Cl_2/hexanes to give **36** (103 mg, 0.175 mmol, 38%) as white crystals, R_f 0.8 (hexanes/EtOAc 1:1); IR ($CHCl_3$) 1735, 1642, 1484, 1417 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, t, J = 1.6 Hz), 7.95 (1H, dt, J = 7.9, 1.3 Hz), 7.55 (1H, dt, J = 7.7, 1.7 Hz), 7.39 (1H, t, J = 7.9 Hz), 6.55 (1H, s), 6.17 (1H, s), 6.02 (1H, d, J = 1.2 Hz), 5.98 (1H, d, J = 1.4 Hz), 5.06 (1H, m), 3.92 (3H, s), 3.62 (3H, s), 3.27 (1H, dd, J = 13.8, 2.4 Hz), 2.75 (1H, m), 2.53 (1H, m), 2.34 (2H, m), 1.51 (1H, m); HRMS (CI) calcd for $C_{24}H_{22}ClF_3NO_9S$ (MH^+) 592.0656, found 592.0660. Regioisomeric **38** (35 mg, 0.06 mmol, 13%) and di-triflate **37** (85 mg, 0.12 mmol, 26%) were also isolated.

(-)-(1*S*,2*R*,3*S*)-6-{2-Methylcarbamoyl-3-[3-chlorobenzoyl(oxy)]-cyclohex-4-one}-4-methoxy-1,3-benzodioxole 39. To a solution of **34** (1.33 g, 2.8 mmol) in dry HMPA (17 mL) was added *t*-BuOK (1.0 M in THF) (56 μmol, 50 μl). The mixture was heated to 90 °C for 4 h, cooled to room temperature, poured into water (100 mL), and extracted with Et_2O (2 x 75 mL). The combined extracts were washed with water (30 mL), brine, and dried (Na_2SO_4). Evaporation *in vacuo* followed by chromatography over silica gel eluting with hexanes/EtOAc (3:2) gave **39** (1.21 g, 2.5 mmol, 91%) as a white solid, R_f 0.63 (hexanes/EtOAc 1:1); Mp 149-151 °C; $[\alpha]_D^{23}$ (c = 1.03, $CHCl_3$) -23; IR ($CHCl_3$) 3433, 1728, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, t, J = 1.7 Hz), 7.94 (1H, dt, J = 7.5, 1.2 Hz), 7.51 (1H, dt, J = 8.3, 1.7 Hz), 7.36 (1H, t, J = 7.8 Hz), 6.38 (2H, s), 5.93 (2H, s), 5.56 (1H, d, J = 9.5 Hz), 4.70 (1H, d, J = 9.2 Hz), 4.17 (1H, q, J = 9.4 Hz), 3.86 (3H, s), 3.47 (3H, bs), 3.22 (1H, bs), 2.64 (2H, m), 2.20 (1H, m), 1.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 164.7, 156.2, 149.1, 143.7, 134.6, 134.4, 130.9, 130.0, 129.8, 128.1, 106.7, 101.5, 101.4, 79.9, 77.2, 58.2, 56.6, 52.3, 47.6, 39.3, 31.3; HRMS (CI) calcd for $C_{23}H_{22}ClNO_8$ 475.1034, found 475.1027.

(+)-(1*R*2*R*,3*S*)-6-{2-Methylcarbamoyl-3-[3-hydroxy-cyclohex-5-ene-4-one}-4-methoxy-1,3-benzodioxole 42. To a stirred solution of **39** (197 mg, 0.414 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added Et_3N (0.58 mL, 4.14 mmol) and trimethylsilyl trifluoromethanesulfonate (0.37 mL, 2.07 mmol). The solution was stirred at 0 °C for 30 min, then at room temperature for 90 min. Saturated aqueous $NaHCO_3$ (6 mL) was added and stirring continued for a further 5 min. The resulting emulsion was partitioned between 10%

aqueous $NaHCO_3$ (100 mL) and Et_2O (100 mL). The ethereal layer was washed with water and brine, dried (Na_2SO_4) and concentrated to give **40** as a clear colorless oil.

To a suspension of silver trifluoroacetate (137 mg, 0.621 mmol) in CH_2Cl_2 (4 mL) was added phenylselenenyl chloride (111 mg, 0.58 mmol). After stirring rapidly for 15 min a bright yellow suspension formed. A solution of **40** in CH_2Cl_2 (12 mL) was added and the resultant suspension stirred for 10 min, filtered through a short pad of celite and evaporated *in vacuo* to give a deep yellow oil. The oil was dissolved in THF (16 mL) and stirred with 2M HCl (0.8 mL) at room temperature for 2 h. The solution was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give **41** as a yellow oil.

The oil was dissolved in CH_2Cl_2 (15 mL), and pyridine (0.33 mL, 4.14 mmol) added, followed by 10% H_2O_2 (0.47 mL, 4.14 mmol). The resulting emulsion was stirred rapidly for 10 min, and then partitioned between EtOAc (150 mL) and water (150 mL). The organic phase was washed with saturated aqueous Na_2SO_3, 0.5M HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to a pale yellow solid. Chromatography over silica gel eluting with hexanes/EtOAc (3:2) followed by recrystallization from Et_2O gave **42** (166 mg, 0.35 mmol, 85%) as white crystals, R_f 0.20 (hexanes/EtOAc 1:1); Mp 198-199 °C; $[\alpha]_D^{23}$ (c = 1.08, $CHCl_3$) +161; IR ($CHCl_3$) 3420, 1733, 1700, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.96 (1H, d, J = 7.9 Hz), 7.54 (1H, dd, J = 7.4, 1.8 Hz), 7.38 (1H, t, J = 7.9 Hz), 6.90 (1H, dd, J = 10.2, 2.0 Hz), 6.39 (1H, d, J = 1.3 Hz), 6.36 (1H, d, J = 1.2 Hz), 6.24 (1H, dd, J = 10.2, 2.5 Hz), 5.97 (2H, s), 5.83 (1H, bd, J = 11.2 Hz), 5.02 (1H, bd, J = 9 Hz), 4.30 (1H, q, J = 10.6 Hz), 4.01 (1H, bs), 3.88 (3H, s), 3.48 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 165.0, 156.3, 151.6, 149.4, 143.9, 135.0, 134.7, 133.5, 133.4, 131.0, 130.1, 129.9, 128.3, 128.0, 107.8, 102.4, 101.8, 77.0, 58.0, 56.8, 52.4, 48.7; HRMS (CI) calcd for $C_{23}H_{20}ClNO_8$ (MH^+) 474.0956, found 474.0955.

(1*R*,2*R*,3*S*,5*S*,6*S*)-6-{2-Methylcarbamoyl-3-[3-hydroxy-5,6-oxido]-cyclo hex-4-one}-4-methoxy-1,3-benzodioxole 43. A solution of 10% $NaHCO_3$ (0.6 mL, 0.7 mmol) in MeOH (6 mL) and water (3 mL) was added to a stirred solution of **42** (83 mg, 0.175 mmol) and 10% H_2O_2 (0.3 mL) in THF (3 mL). The resultant suspension was stirred at room temperature for 90 min. Saturated aqueous NH_4Cl (20 mL) was added and the mixture extracted with EtOAc (2x30 mL). The combined extracts were washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give **43** as an off-white solid. Used immediately in the next step.

(+)-(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-6-{2-Methylcarbamoyl-3-[3,4-dihydroxy-5,6-oxido]-cyclo hexyl}-4-methoxy-1,3-benzodioxole 44. To a stirred solution of **43** in THF (2 mL) at -78 °C was added L-selectride (1.0 M in THF) (0.29 mL, 0.29 mmol). The mixture was stirred at -78 °C for 15 min, and saturated aqueous NH_4Cl (3 mL) was added. The mixture allowed to warm to room temperature and stirred for a further 2 h. The organic phase was diluted with EtOAc (10 mL), washed with brine, dried (Na_2SO_4), and concentrated to give an off-white solid. The crude product was purified by chromatography over silica gel eluting with EtOAc to give **44** (40 mg, 0.11 mmol, 63%) as a white solid, R_f 0.36 (EtOAc); Mp 136-137 °C; $[\alpha]_D^{23}$ (c = 0.6, $CHCl_3$) +33; IR ($CHCl_3$) 3432, 1719, 1636, 1513, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (1H, s), 6.44 (1H, s), 5.94 (2H, m), 5.58 (1H, bd, J = 9.1 Hz), 4.87 (1H, d, J = 8.1 Hz), 4.30 (2H, m), 3.91 (3H, m), 3.68 (3H, s), 3.55 (3H, m); HRMS (CI) calcd for $C_{16}H_{19}NO_8$ (MH^+) 354.1190, found 354.1189.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-6-{2-Methylcarbamoyl-3-[3,4-diacetoxy-5,6-oxido]-cyclo hexyl}-4-methoxy-1,3-benzodioxole 45. To a stirred solution of **44** (4 mg, 11.3 μmol) and triethylamine (80 μL, 0.57 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added acetic anhydride (21 μL, 0.23 mmol). The resultant solution was stirred at room temperature for 90 min, and the mixture was poured into saturated aqueous $NaHCO_3$ (2 mL) and EtOAc (5 mL). The aqueous phase was extracted with EtOAc (3 mL), the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed over silica gel eluting with EtOAc/hexanes (3:2) followed by recrystallization from CH_2Cl_2/hexanes to give **45** (3.5 mg, 8 μmol, 71%) as white crystals, R_f 0.6 (EtOAc/hexanes 4:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.46 (1H, d, J = 1.2 Hz), 6.41 (1H, d, J = 1.1 Hz), 5.95 (2H, s), 5.78 (1H, t, J = 3.0 Hz), 5.13 (1H, dd, J = 11.5, 3.5 Hz), 4.43 (1H, bm), 4.20 (1H, bm), 3.67 (3H, s), 3.50 (3H, s), 3.36 (1H, d, J = 9.9 Hz), 1.96 (3H, s), 1.22 (3H, s); HRMS (CI) calcd for $C_{20}H_{24}NO_{10}$ (MH^+) 438.1400, found 438.1389.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-6-{2-Methylcarbamoyl-3-[3,4,5,6-tetrahydroxy]-cyclohexyl}-4-methoxy-1,3-benzodioxole 46, and (+)-(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-6-{2-Methylcarbamoyl-3-[3,4,5,6-tetraacetoxy]-cyclohexyl}-4-methoxy-1,3-benzo dioxole 47. A suspension of **44** (70 mg, 0.2 mmol) in water (8.5 mL) containing sodium benzoate (6.5 mg, 40 μmol) was heated at 100 °C for 4 days. After cooling, water was removed *in vacuo* to furnish the crude **46** as a brown solid. Crude **46** was dissolved in pyridine (2 mL) and acetic anhydride (2 mL) and stirred at room temperature for 20 h. The volatile components of the reaction mixture were removed *in vacuo*, and the residue chromatographed over silica gel eluting with hexanes/EtOAc (1:1) to give **47** (66.5 mg, 0.12 mmol, 60%) as a white solid, R_f 0.22 (hexanes/EtOAc 2:3); Mp 92-94 °C; $[\alpha]_D^{23}$ (c = 0.89, $CHCl_3$) +11; IR ($CHCl_3$) 3431, 1746, 1637, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (2H, m), 5.94 (2H, m), 5.34 (1H, t, J = 2.4 Hz), 5.21 (1H, dd, J = 10.6, 3.5 Hz), 5.10 (1H, t, J = 2.8 Hz), 5.01 (1H, bs), 4.70 (1H, q, J = 10.8 Hz), 4.40 (1H, d, J = 10.1 Hz), 3.87 (3H, s), 3.53 (1H, s), 3.20 (1H, dd, J = 12.3, 1.9 Hz), 2.17 (3H, s), 2.17 (3H, s), 2.01 (3H, s), 1.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.3, 168.7, 168.2, 156.6, 148.7, 143.3, 134.5, 130.2, 130.0, 128.3, 108.2, 102.9, 101.4, 72.0, 70.9, 68.6, 68.0, 56.5, 52.2, 47.9, 47.3, 20.8, 20.6; HRMS (CI) calcd for $C_{24}H_{29}NO_{13}$ (MH^+) 540.1717, found 540.1709.

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*R*)-1,2,3,4-Tetraacetoxy-1,3,4a,5,10b-hexahydro-1,3-dioxolo-4-methoxy[4,5-j]phenanthridin-6-(2H)-one 48. To a stirred solution of **47** (55 mg, 0.1 mmol) and 4-*N,N*-dimethylaminopyridine (37 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added trifluoromethanesulfonic anhydride (90 μL. 0.51 mmol). The resultant yellow gel suspension was warmed to 5 °C and stirred for 24 h. Saturated aqueous $NaHCO_3$ (4 mL) and EtOAc (6 mL) were added. The aqueous phase was extracted with EtOAc (6 mL), and the combined extracts washed with 0.5 M HCl (2 mL), brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was taken up in dioxane (6 mL), 2 M HCl (0.6 mL) was added and the solution stirred at room temperature for 20 h. The reaction mixture was partitioned between saturated aqueous

$NaHCO_3$ (6 mL) and EtOAc (6 mL). The aqueous phase was extracted with EtOAc (6 mL), the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The crude product was chromatographed over silica gel eluting with EtOAc to give an inseparable mixture of isomers **48 and 49** (34.5 mg, 68 μmol, 68%, 7:1) of which **48** was the major compound (86%, by nmr), R_f 0.10 (hexanes/EtOAc 1:9); IR ($CHCl_3$) 3408, 1754, 1667 cm^{-1}; ^1H NMR (major isomer) (300 MHz, $CDCl_3$) δ 6.30 (1H, s), 6.01 (2H, m), 5.93 (1H, s), 5.52 (1H, t, J = 2.6 Hz), 5.44 (1H, t, J = 6.2 Hz), 5.21 (1H, t, J = 2.9 Hz), 5.13 (1H, dd, J = 10.8, 3.4 Hz), 4.18 (1H, t, J = 11.7 Hz), 4.07 (3H, s), 3.37 (1H, dd, J = 12.7, 2.5 Hz), 2.16 (3H, s), 2.07 (6H, s), 2.03 (3H, s); HRMS (CI^+) calcd for $C_{24}H_{29}NO_{13}$ (MH^+) 508.1455, found 508.1449.

(+)-(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*R*)-1,2,3,4-Tetraacetoxy-1,3,4a,5,10b-hexahydro-1,3-dioxolo-4-hydroxy[4,5-j]phenanthridin-6-(2H)-one 50. To a stirred solution of **48/49** (34.5 mg, 68 μmol) in CH_2Cl_2 (4 mL) at -78 °C was added BBr_3 (60 μL, 61 μmol, 1.0 M in CH_2Cl_2). The cloudy solution was allowed to warm slowly to 0 °C for 90 min, and 10% NH_4OH (4 mL)was added dropwise. A yellow emulsion formed, and was stirred at 0 °C for 15 min. The mixture was poured into EtOAc (15 mL), and the aqueous phase was extracted with EtOAc (10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with hexanes/EtOAc (1:1) to give **50** (24.5 mg, 49 μmol, 73%) as a white solid, R_f 0.22 (hexanes/EtOAc 2:3); Mp 245 °C (dec).; $[\alpha]_D^{23}$ (c = 1.23, $CHCl_3$) +29; IR ($CHCl_3$) 3400, 1756, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.39 (1H, s, 6.18 (1H, s), 6.04 (2H, s), 5.90 (1H, bs), 5.55 (1H, bs), 5.46 (1H, t, J = 2.9 Hz), 5.21 (1H, t, J = 2.8 Hz), 5.17 (1H, dd, J = 10.8, 3.4 Hz), 4.28 (1H, dd, J = 13.1, 10.8 Hz), 3.43 (1H, dd, J = 13.2, 1.9 Hz), 2.16 (3H, s), 2.08 (6H, s), 2.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 169.8, 169.5, 169.0, 168.2, 153.2, 146.8, 133.5, 131.6, 107.3, 102.4, 96.6, 71.7, 67.6, 66.8, 66.2, 48.2, 39.3, 29.7, 20.8, 20.7, 20.6; HRMS (CI) calcd for $C_{22}H_{23}NO_{12}$ (MH^+) 494.1299, found 494.1298.

(+)-Pancratistatin 1. To a solution of **50** (24.5 mg, 49 μmol) in THF (4.5 mL) was added NaOMe (0.5 M in MeOH, 1.0 mL, 0.49 mmol). The mixture was stirred at room temperature for 18 h. Saturated aqueous NH_4Cl (4.5 mL) was added, and the aqueous phase extracted with EtOAc (20 x 15 mL). The crude product was adsorbed directly on to silica gel and eluted with EtOAc/MeOH 9:1) to give **1** (13.8 mg, 42.4 μmol, 87%) as a white solid, R_f 0.14 (EtOAc/MeOH 9:1); Mp 233 °C (dec).; $[\alpha]_D^{23}$ (c = 1.08 DMSO-d_6) +38 (lit values of +40.9, +48 and +44 see refs 9, 2 and 8 respectively).; IR (DMSO-d_6) 3447 and 1667 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 13.05 (1H, s), 7.53 (1H, s), 6.47 (1H, s), 6.02 and 6.04 (2H, two singlets), 5.37 (1H, d, J = 4.0 Hz), 5.10 (2H, m), 4.84 (1H, d, J = 7.5 Hz), 4.27 (1H, m), 3.96 (1H, m), 3.84 (1H, bs), 3.70 (2H, m), 2.95 (1H, d, J = 11.2 Hz).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 152.5, 145.8, 136.1, 132.1, 107.9, 102.2, 98.1, 73.7, 70.6, 70.4, 68.9, 50.9, 29.4.; HRMS (CI) calcd for $C_{14}H_{16}NO_8$ (MH^+) 326.0876, found 326.0860.

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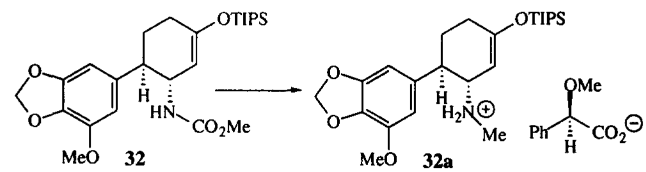

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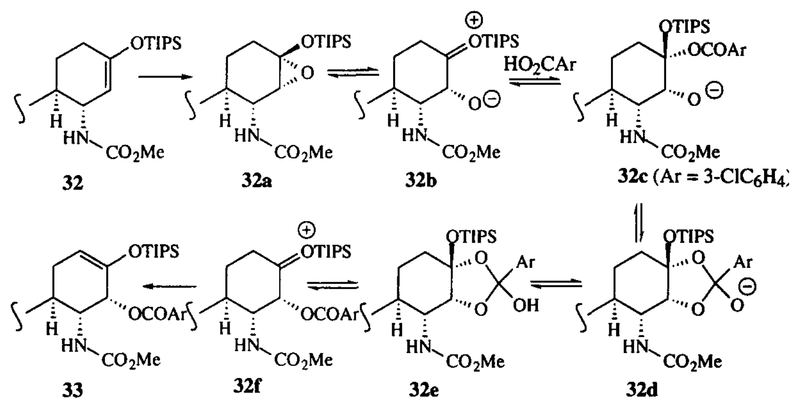
(24) The mechanism for the formation of **33** involves initial epoxide **32a**, which can reversibly open to give **32b**. Interception of **32b** by *m*-chlorobenzoate leads to **32c**, which through the *ortho* ester **32d** can transfer the benzoate resulting in **32f**. Proton loss from **32f** gives **33**.



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