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Enantioselective Synthesis of Protected Nitrocyclohexitols with Five Stereocenters. Total Synthesis of (+)-Pancratistatin

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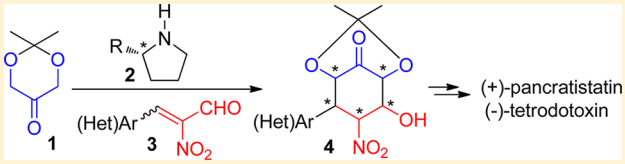
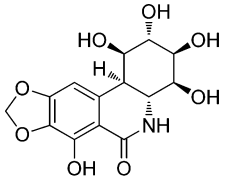
Supporting Information

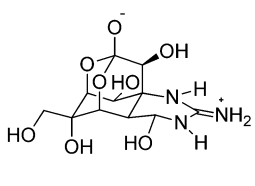
ABSTRACT: 2-Methoxymethylpyrrolidine best performed, among several other proline derivatives, to control the enantioselective [3+3] annulation of β-(hetero)aryl-α-nitro-α,β-enals with commercial 2,2-dimethyl-1,3-dioxan-5-one, a procedure that renders highly oxygenated nitrocyclohexanes endowed with five new stereocenters. Use of this reaction allowed the development of a total synthesis of the antitumoral natural product (+)-pancratistatin; it also converted our previous racemic route to tetrodotoxin into an enantioselective one.



New reactions that can build complex chiral structures from simple achiral fragments in an enantioselective manner are in high demand (especially when the reaction products are recurrent biologically relevant units that cannot be easily accessed through alternative methodologies). A case in point is that of nitrogen-bearing polyhydroxylated cyclohexanes. These structural units are indeed present in numerous pharmacologically significant compounds [in particular, more than 20000 anti-infective, antitumor, immune, anti-inflammatory, peptidomimetic, anti-ulcer, dermatological, and nervous system agents having a cyclohexane ring with (at least) one nitrogen and three oxygens attached have been reported in more than 82000 references to date (≈13000 in the past four years)].[1] Such a large number of compounds endowed with a nitrogenated and heavily oxygenated cyclohexane, along with their relevance, call for the development of appropriate synthetic procedures, so that sufficient quantities of them become available for the complete study of their properties and applications. This is particularly so for natural products present in minute amounts in their sources, a situation that fully applies to the antitumoral isocarbostyril constituents of the plant family Amaryllidaceae,[2] with (+)-pancratistatin as one of the main representatives,[3] and to the sodium channel blocker (−)-tetrodotoxin and its analogues (Figure 1).[4−6] However, despite previous efforts, the enantioselective syntheses of their corresponding chiral nitrogen-bearing polyoxygenated cyclohexane cores usually involve long multistep routes.[7−10]



(+)-Pancratistatin

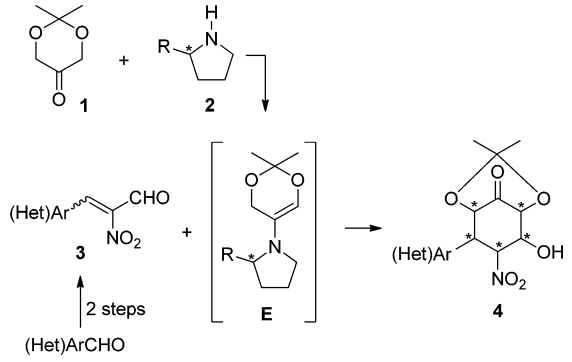


(-)-Tetrodotoxin

Figure 1. Representative examples of pharmacologically relevant natural products endowed with a nitrogen-bearing polyoxygenated cyclohexane core.

In this context, we herein report the enantioselective annulation of β-(hetero)aryl-α-nitro-α,β-enals (**3**) with enamines **E** to form protected nitrocyclohexitols **4**, a process by which five new stereocenters are generated (Scheme 1).

Scheme 1. Convergent Synthesis of Nitrogen-Bearing Polyoxygenated Cyclohexanes 4 by Enantioselective Annulation of Nitroenals 3 with Chiral Enamines E (a three-step procedure from commercially available fragments)



Because **1** and **2**, precursors of **E**, are commercially available and enals **3** are prepared in two steps from commercial aldehydes and 2-nitroethanol, the nitrogen-bearing highly oxygenated cyclohexane derivatives of type **4** can thus be accessed in just three synthetic operations starting form commercial sources. The power of the reaction is demonstrated with the completion of a short total synthesis of (+)-pan-

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cratistatin in which the enantioselective annulation procedure is the main key step. Moreover, the reported annulations of **3a** and **3b** to deliver enantiomerically pure **4a** and **4b** (vide infra), respectively, provide for the asymmetric synthesis of tetrodotoxin and some pancratistatin analogues.

The results described herein build on previous work in the area, most importantly, the development of the first general method for the preparation of β-(hetero)aryl-α-nitro-α,β-enals (**3**),[11] and the demonstration of their ability to annulate with enamines **E** derived from achiral secondary amines, such as morpholine or pyrrolidine.[12]

To develop an enantioselective version of the annulation, we selected enal **3a** (1) because the preparation of **3a**, an important step in our synthetic efforts toward tetrodotoxin, has been optimized so that **3a** is quickly obtained from cheap furfural with no chromatography[13] and (2) because **3a** has superior stability compared to those of its aromatic analogues.[11] With **3a** in hand, its enantioselective annulation with enamines **E** formed from dioxanone **1** and a number of chiral pyrrolidines **2** was then tested; the results are listed in Table 1.

Use of D-proline (**2a**) to annulate **1** with **3a** (entry 2) under the conditions previously reported using pyrrolidine (DMF, rt, 0.2 equiv of PPTS)[12] led to **4a** in 7% yield (considerably lower than for the racemic case, 55%, entry 1) and in 37% ee. Just slightly better values were obtained when a 1.5:1 instead of a 1:1 molar ratio of dioxanone to enal was employed (entry 3). The annulation took place likewise using the more convenient acetonitrile as the solvent (entry 4).

Employing the proline benzyl ester **2b** (entry 5), the yield notably increased (50%) and the enantioselectivity decreased (28% ee). This last figure increased to 35 and 51% ee for primary amide **2c** (entry 6) and amine **2d** (entry 7), respectively, but the annulation yield decreased, slightly for the first case (45%) and considerably for the latter (14%).

Use of commercial (*S*)-2-(methoxymethyl)pyrrolidine [(*S*)-**2e**] afforded **4a** in 43−47% yield and 76−81% ee. Crystallization from Et_2O gave the levorotatory enantiomer (−)-**4a** in essentially pure form. Its absolute configuration, shown in the scheme at the top of Table 1, was determined by X-ray analysis of its *p*-bromobenzoate derivative (for details, see the Supporting Information).[14]

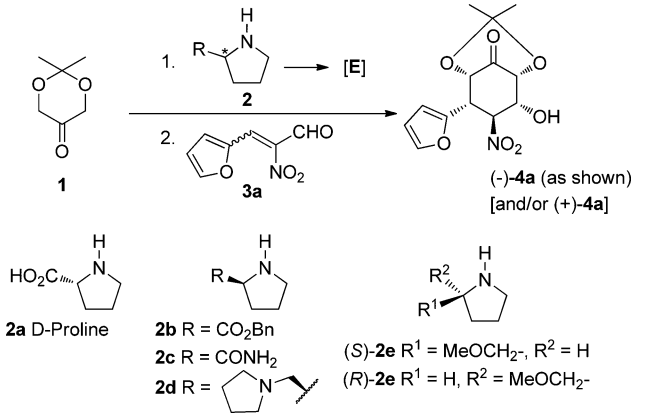
No major changes were observed when CSA and *p*-TsOH were used as additives instead of PPTS. Lower reaction temperatures gave lower yields with no improvements in enantioselection (entries 9−11).

Again, DMF proved to be as good as acetonitrile (42%, 74% ee, entry 12); also, a lower yield was observed for a 1:1 molar ratio of dioxanone to enal (30%, 73% ee, entry 13).

Except for DMSO (49% ee, entry 17), halogenated ($CHCl_3$, entry 14), protic (EtOH, entry 15), and other aprotic (acetone, entry 16) solvents performed similarly in terms of enantioselectivity (70−75% ee) as compared to DMF and acetonitrile. These last two solvents remained better for annulation yields.

With an enantioselective route to protected nitrocyclitols of type **4** available (Scheme 1 and Table 1), we next addressed the preparation of (+)-pancratistatin, which we planned to accomplish from nitroenal **3b** and dioxanone **1**, through the key nitrocyclitol intermediate **4b** and the carbamate derivative **6** (Scheme 2). Ring A of pancratistatin would ultimately come from cheap vanillin, the precursor of nitroenal **3b**; ring C would be assembled in the key enantioselective annulation step, and ring B would be formed by an intramolecular aromatic electrophilic substitution of carbamate **6**.

Table 1. Enantioselective Annulations of Nitroenal 3a with Dioxanone 1 Using Pyrrolidines 2a−e[a]



entry	2	1:3a[b]	solvent, T[c]	yield[d] (%)	% ee,[e] product[f]
1[g]	Pyrr[h]	1:1	DMF, rt	55	(±)-**4a**
2	**2a**	1:1	DMF, rt	7	37, (+)-**4a**
3	**2a**	1.5:1	DMF, rt	8	39, (+)-**4a**
4	**2a**	1.5:1	CH_3CN, rt	5	35, (+)-**4a**
5	**2b**	1.5:1	CH_3CN, rt	50	28, (−)-**4a**
6	**2c**	1.5:1	CH_3CN, rt	45	35, (−)-**4a**
7	**2d**	1.5:1	CH_3CN, rt	14	51, (−)-**4a**
8	(*S*)-**2e**	1.5:1	CH_3CN, rt	43−47	76−81, (−)-**4a** >99%[i]
9	(*R*)-**2e**	1.5:1	CH_3CN, 0 °C	39	77, (+)-**4a**
10	(*R*)-**2e**	1.5:1	CH_3CN, −20 °C	35	75, (+)-**4a**
11	(*R*)-**2e**	1.5:1	CH_3CN, −40 °C	30	75, (+)-**4a**
12	(*R*)-**2e**	1.5:1	DMF, rt	42	74, (+)-**4a**
13	(*R*)-**2e**	1:1	DMF, rt	30	73, (+)-**4a**
14	(*R*)-**2e**	1.5:1	$CHCl_3$, rt	22	75, (+)-**4a**
15	(*R*)-**2e**	1.5:1	EtOH, rt	21	72, (+)-**4a**
16	(*R*)-**2e**	1.5:1	acetone, rt	19	70, (+)-**4a**
17	(*R*)-**2e**	1.5:1	DMSO, rt	33	49, (+)-**4a**

[a]Annulations were performed according to the general procedure reported in the Experimental Section. The structure shown for compound **4a** is that of its levorotatory enantiomer, (−)-**4a**. [b]Molar ratio. [c]Annulation temperature in degrees Celsius. [d]Isolated yield. [e]Determined by chiral HPLC. [f]Major enantiomer of **4a**. [g]Racemic annulation using pyrrolidine (see ref 12). [h]Pyrrolidine. [i]After crystallization.

Transformation of vanillin into 5-methoxypiperonal (three steps, 57% yield)[15] and of this last one into enal **3b** (two steps, 51%)[11] was achieved as previously reported. Annulation of dioxanone **1** with nitroenal **3b** using (*R*)-2-(methoxymethyl)-pyrrolidine [(*R*)-**2e**] gave **4b** in 38% yield and 75% ee (>99% ee after crystallization); its five stereogenic carbons matched the configuration required by the final target at C1, C3, C4, C4a, and C10b.

For the conversion of nitrocyclitol **4b** into **6**, the required methylcarbamate unit at C4a was first installed through reduction of the nitro group to amine and subsequent acylation to **5** (Scheme 3). We then sujected compound **5** to a three-step sequence (steps 3−5, 87% overall yield) to perform the stereoselective reduction of its C2 keto group and to change the protection group pattern so as to make it compatible with the following step, the aromatic electrophilic substitution of **6**.

Treatment of **6** with triflic anhydride and DMAP at 0 °C,[16] followed by acid hydrolysis of the corresponding iminoether

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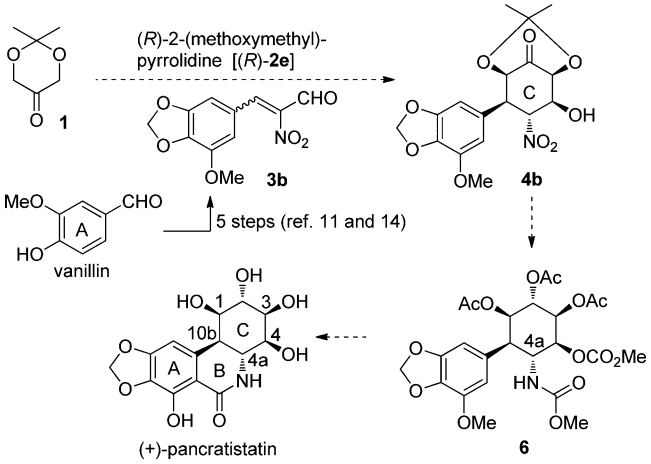
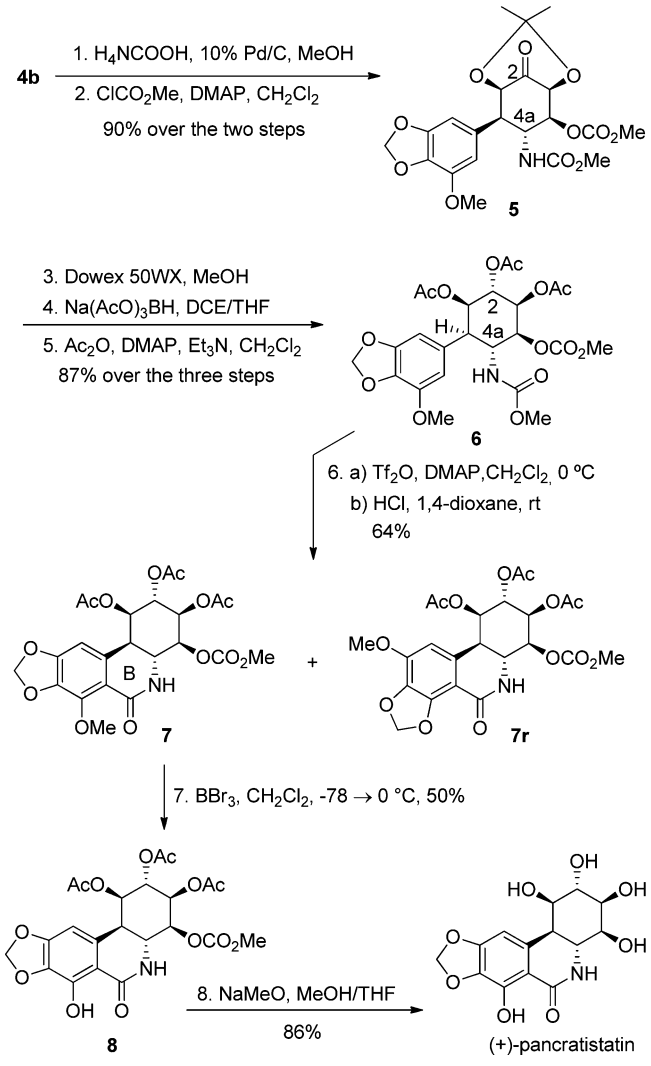
Scheme 2. Synthetic Plan for the Preparation of (+)-Pancratistatin



Scheme 3. Conversion of Nitrocyclitol 4b into (+)-Pancratistatin



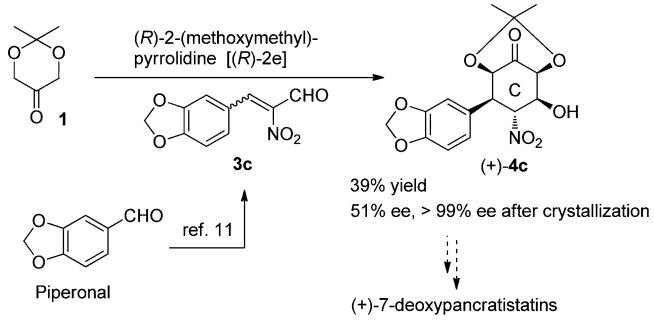
intermediate, gave the desired lactam **7**, together with its regioisomer **7r** in a 9:1 ratio and 64% overall yield. Final cleavage of the aromatic methyl ether and removal of the hydroxyl protecting groups were best achieved through successive treatment with BBr_3 and NaMeO, thus affording (+)-pancratistatin.

Certainly, the enantioselective annulation process that yields protected nitrocyclitols of type **4** described herein offers a way to obtain other compounds apart from pancratistatin in enantiomerically pure form.

This is the case for tetrodotoxin, for which we recently reported a racemic route through (±)-**4a**.[13] An alternative use of (+)-**4a**, now available through enantioselective annulation, would afford (−)-tetrodotoxin.

Furthermore, diverse analogues of pancratistatin could now be obtained in enantiomerically pure form through different nitrocyclitols of type **4** starting from a variety of aromatic aldehydes. In particular, 7-deoxy analogues, e.g., the naturally occurring (+)-7-deoxy-pancratistatin itself, would be accessible from piperonal through nitroenal **3c** and its annulation product, the protected nitrocyclitol intermediate (+)-**4c** (Scheme 4).

Scheme 4. Enantioselective Synthesis of Protected Nitrocyclitol (+)-4c



In summary, the enantioselective annulation of 2,2-dimethyl-1,3-dioxan-5-one (**1**) with β-(hetero)aryl-α-nitro-α,β-enals (**3a**−**c**) renders highly oxygenated nitrocyclohexanes **4a**−**c**, respectively, endowed with five new stereocenters in enantioenriched form (enantiopure through subsequent crystallization). As enals **3** are available from aldehydes and 2-nitroethanol in two reactions, access to **4** involves three steps from commercially available compounds. These protected nitrocyclitols **4** serve well as advanced key synthetic intermediates for the (+)-pancratistatin and (−)-tetrodotoxin families of natural products.

EXPERIMENTAL SECTION

Enantioselective Annulation of Dioxanone 1 with Nitroenals 3. General Procedure. A mixture of dioxanone **1** (1 or 1.5 equiv), the chiral pyrrolidine **2** (0.8 equiv), and anhydrous Na_2SO_4 in a dry solvent was magnetically stirred under argon at rt for 3 h. A solution of nitroenal **3** (1 equiv) and PPTS (0.2 equiv) in the same dry solvent was added. After 2 h, the reaction mixture was diluted with a 1:4 (v:v) EtOH/H_2O mixture. Solvent removal (rotary evaporator) and chromatography (20% EtOAc/hexane) gave the corresponding protected nitrocyclitol **4**.

Protected Nitrocyclitol 4a. Prepared according to the general procedure from **1** (117 mg, 0.9 mmol), (*R*)-2-(methoxymethyl)-pyrrolidine [(*R*)-**2e**, 59 μL, 0.48 mmol], and **3a** (100 mg, 0.6 mmol) in $CHCl_3$: 22% yield; 78% ee; 7% (first crop, unoptimized) and >99% ee after crystallization from Et_2O; $[\alpha]_D^{20}$ = +181.7 (*c* = 1, $CHCl_3$); white solid; mp 190−199 °C dec (Et_2O/hexane); R_f = 0.44 (silica gel plates, 30% EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J* = 1.8 Hz, 1H), 6.39 (d, *J* = 3.3 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.33 (dd, *J* = 11.6, 9.5 Hz, 1H), 4.55 (dd, *J* = 2.4, ≈1.6 Hz, 1H), 4.51 (dd, *J* ≈ 2.4, ≈1.3 Hz, 1H), 4.21 (ddd, *J* = 10.6, ≈9.5, 1.6 Hz, 1H), 3.52 (dd,

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J = 11.6, 1.3 Hz, 1H), 2.96 (d, J = 10.6 Hz, 1H), 1.58 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.2, 147.3, 143.1, 110.8, 108.9, 99.9, 89.0, 79.1, 77.0, 76.2, 44.3, 28.2, 25.4; LRMS (ESI-TOF) m/z (%) 320.0 [$(M + Na)^+$, 46], 298.1 [$(M + H)^+$, 100], 245.1 (18); HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{13}H_{16}NO_7$ 298.0921, found 298.0921.

Protected Nitrocyclitol 4b. Prepared according to the general procedure from **1** (256 mg, 1.97 mmol), (*R*)-2-(methoxymethyl)-pyrrolidine [(*R*)-**2e**, 195 μL, 1.58 mmol], and **3b** (500 mg, 1.97 mmol) in DMF: 300 mg; 38% yield; 75% ee; 8% (first crop, unoptimized) and >99% ee after crystallization from Et_2O; white solid; mp 167 °C (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = +133.9 (c = 1, $CHCl_3$); R_f = 0.51 (silica gel plates, 30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66 (d, J = 1.5 Hz, 1H), 6.49 (d, J = 1.5 Hz, 1H), 5.97 (dd, J = 1.5, 1.5 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 5.33 (dd, J = 11.7, 9.4 Hz, 1H), 4.56 (dd, $J \approx$ 2.4, ≈2.4 Hz, 1H), 4.39–4.34 (m, 1H), 4.22 (ddd, J = 10.6, 9.4, 2.4 Hz, 1H), 3.88 (s, 3H), 3.11 (dd, J =11.7, 1.1 Hz, 1H), 2.97 (d, J = 10.6 Hz, 1H), 1.64 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 149.2, 143.6, 135.7, 128.0, 108.7, 102.4, 101.7, 99.9, 90.9, 79.2, 78.9, 76.2, 56.6, 50.2, 28.3, 25.3; LRMS (EI) m/z 381.0 [$(M)^+$, 94]; IR ($CHCl_3$) 3496 (OH), 1735 (CO), 1556 (NO_2) cm^{-1}; HRMS [EI, $(M)^+$] m/z calcd for $C_{17}H_{19}NO_9$ 381.1060, found 381.1064.

Protected Nitrocyclitol 4c. Prepared according to the general procedure from **1** (1.05 g, 8.07 mmol), (*R*)-2-(methoxymethyl)-pyrrolidine [(*R*)-**2e**, 530 μL, 4.30 mmol], and **3c** (1.19 g, 5.38 mmol) in CH_3CN: 39% yield; 51% ee; 13% (first crop, unoptimized) and >99% ee after crystallization from *i*-PrOH; white solid; mp 203 °C (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = +122.6 (c = 1, $CHCl_3$); R_f = 0.36 (silica gel plates, 25% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (d, J = 1.5 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.97 (d, J = 1.4 Hz, 1H), 5.96 (d, J = 1.4 Hz, 1H), 5.33 (dd, J = 11.7, 9.4 Hz, 1H), 4.56 (dd, J = 2.4, 2.4 Hz, 1H), 4.35 (dd, J = 2.4, 1.4 Hz, 1H), 4.22 (br s, 1H), 3.13 (dd, J = 11.7, 1.4 Hz, 1H), 2.95 (br s, 1H), 1.65 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 148.1, 148.1, 127.4, 122.4, 108.6, 108.5, 101.3, 99.9, 91.0, 79.2, 79.0, 76.2, 50.0, 28.4, 25.3; LRMS (CI) m/z (%) 351.0 [$(M)^+$, 35]; IR ($CHCl_3$) 1733 (CO), 1556 (NO_2) cm^{-1}; HRMS [EI, $(M)^+$] m/z calcd for $C_{16}H_{17}NO_8$ 351.0954, found 351.0950.

***p*-Nitrobenzoate of (−)-4a.** DMAP (2 mg, 0.017 mmol), DCC (139 mg, 0.67 mmol), and 4-bromobenzoic acid (47 mg, 0.23 mmol) were successively added to a solution of nitrocyclitol (−)-**4a** (50 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) under Ar. After being stirred for 10 min, the mixture was washed with 0.1 M aqueous HCl (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was dried and the solvent removed. Column chromatography (silica gel, 10% EtOAc/hexane) afforded the *p*-bromobenzoate of (−)-**4a** (63 mg, 78%) as a white solid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.90 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 3.3 Hz, 1H), 6.38 (dd, J_1 = 3.3 Hz, J_2 = 1.9 Hz, 1H), 5.76 (dd, J_1 = 11.6 Hz, J_2 = 10.1 Hz, 1H), 5.49 (dd, J_1 = 10.1 Hz, J_2 = 2.1 Hz, J = 10.1, 2.1 Hz, 1H), 4.88 (dd, $J_1 \approx$ 2.3 Hz, $J_2 \approx$ 2.3 Hz, 1H), 4.56 (dd, $J_1 \approx$ 2.1 Hz, $J_2 \approx$ 2.1 Hz, 1H), 3.65 (dd, J = 11.6, 1.7 Hz, 1H), 1.60 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 204.3, 163.9, 146.9, 143.3, 132.0 (2C), 131.5 (2C), 129.3, 127.1, 110.8, 109.3, 99.7, 85.2, 77.0, 76.9, 76.3, 44.4, 28.3, 25.3.

(1*R*,5*S*,6*S*,7*R*,8*R*)-8-(7-Methoxy-1,3-benzodioxol-5-yl)-7-[(methoxycarbonyl)amino]-3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]non-6-yl Methyl Carbonate (5). A suspension of **4b** (500 mg, 1.20 mmol), 10% Pd/C (639 mg), and ammonium formate (342 mg, 5.43 mmol) in dry methanol (12 mL) was stirred under H_2 at rt. After completion of the reduction (as monitored by TLC), the catalyst was filtered off and washed with methanol and EtOAc. The combined washings and the filtrate were evaporated in vacuo. The resultant amine was dissolved in dry CH_2Cl_2 (12 mL) and treated with DMAP (606 mg, 4.96 mmol) and methyl chloroformate (372 μL, 4.72 mmol). After being stirred for 2 h at rt, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (12 mL) and extracted with CH_2Cl_2 (3 × 12 mL). Chromatography (30% EtOAc/hexane) gave **5** (487 mg, 90%) as a white foam: R_f = 0.42 (50% EtOAc/hexane); mp 119–123 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +129.2 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60 (s, 1H), 6.56 (m, 1H), 5.96 (s, 2H), 4.92 (br s, 1H), 4.69 (br s, 1H), 4.69–4.60 (m, 2H), 4.34–4.26 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.55 (br s, 3H), 3.05 (br s, 1H), 1.63 (s, 3H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.4, 156.2, 154.8, 148.9, 143.4, 134.9, 130.7, 108.5, 102.8, 101.5, 99.3, 79.7, 79.0, 77.6, 56.5, 55.2, 52.2, 51.1, 49.9, 28.3, 25.3; LRMS (CI) m/z (%) 468.0 [$(M + H)^+$, 18], 392.0 (100), 334.0 (75), 317.0 (94), 259.0 (55); HRMS [CI, $(M + H)^+$] m/z calcd for $C_{21}H_{26}NO_{11}$ 468.15059, found 468.15031.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*S*)-4-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)-5-(methoxycarbonyl)amino-6-(methoxycarbonyloxy)cyclohexane-1,2,3-triyl Triacetate (6). A mixture of **5** (150 mg, 0.32 mmol) and Dowex 50WX (687 mg) in MeOH (9.7 mL) was stirred for 2 days at 60 °C. After filtration, the solvent was evaporated in vacuo and the residue dissolved in a dry DCE/THF mixture (1:1, 9.7 mL) under argon. $NaBH(AcO)_3$ (342 mg, 1.62 mmol) was added and the mixture stirred at rt for 2 h. After the reaction had been quenched with 30% aqueous hydrogen peroxide (30%, 600 μL) and the solvent had been evaporated, the crude was dissolved in dry CH_2Cl_2 (9.7 mL) and treated with Et_3N (1.2 mL), Ac_2O (0.6 mL), and DMAP (8 mg, 0.065 mmol). After being stirred for 4 h at rt, the mixture was treated with a saturated aqueous solution of $NaHCO_3$ (9.7 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Chromatography (50% EtOAc/hexane) gave **6** (156 mg, 87%) as a white solid: R_f = 0.40 (60% EtOAc/hexane); mp 118–122 °C (Et_2O); $[\alpha]_D^{20}$ = −124.1 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (s, 2H), 5.95 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 5.45 (dd, $J \approx$ 2.6, ≈2.6 Hz, 1H), 5.14 (dd, $J \approx$ 2.9, ≈2.9 Hz, 1H), 5.09 (d, J = 9.2 Hz, 1H), 5.03 (br s, 1H), 4.64 (ddd, J = 10.7, 9.2, 7.9 Hz, 1H), 4.48 (br s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.56 (br s, 3H), 3.38–3.26 (m, 1H), 2.19 (s, 3H), 2.17 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 168.7, 168.2, 156.4, 155.3, 148.9, 143.3, 134.6, 130.1, 108.5, 102.8, 101.4, 74.8, 71.9, 68.4, 68.0, 56.7, 55.2, 52.2, 48.2, 47.0, 20.8, 20.8, 20.7; LRMS (ESI-TOF) m/z (%) 578.1 [$(M + Na)^+$, 76], 556.2 [$(M + H)^+$, 100], 360.1 (38); HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{24}H_{30}NO_{14}$ 556.1666, found 556.1661.

(+)-1,2,3-Tri-*O*-acetyl-7-*O*-methyl-4-*O*-methoxycarbonylpancratistatin (7). Trifluoromethanesulfonic anhydride (77 μL, 0.46 mmol) was added to a solution of **6** (50 mg, 0.090 mmol) and DMAP (33 mg, 0.27 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C under argon. After being stirred for 4.5 h at rt, the solution was treated with a saturated aqueous solution of Na_2CO_3 (6 mL) and extracted (EtOAc, 3 × 6 mL). The combined organic extracts were dried; the solvent was evaporated in vacuo, and the crude residue was dissolved in 1,4-dioxane (6 mL) and treated with 2 M HCl (0.6 mL). After being stirred for 17 h, the mixture was neutralized with a saturated aqueous solution of $NaHCO_3$ (6 mL) and extracted (EtOAc, 3 × 6 mL). Chromatography (60% EtOAc/hexane) afforded an inseparable 9:1 mixture of **7** and **7r** (30 mg, 64%): R_f = 0.35 (80% EtOAc/hexane). **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.30 (s, 1H), 6.04 (s, 1H), 5.99 (s, 1H), 5.94 (s, 1H), 5.53–5.52 (m, 2H), 5.25 (dd, $J \approx$ 2.5, ≈2.5 Hz, 1H), 4.97 (dd, J = 10.8, 3.2 Hz, 1H), 4.22 (dd, J = 12.8, 10.8 Hz, 1H), 4.08 (s, 3H), 3.85 (s, 3H), 3.38 (br d, J = 12.8 Hz, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 169.1, 168.2, 163.1, 154.5, 152.4, 145.4, 137.5, 133.0, 115.7, 101.8, 98.9, 75.6, 67.6, 66.5, 66.4, 60.8, 55.5, 47.6, 40.2, 20.7, 20.6, 20.6; LRMS (ESI-TOF) m/z (%) 646.1 [$(M + Na)^+$, 40], 524.1 [$(M + H)^+$, 100]; HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{23}H_{26}NO_{13}$ 524.1404, found 524.1399.

(+)-1,2,3-Tri-*O*-acetyl-4-*O*-methoxycarbonylpancratistatin (8). Boron tribromide (1 M in CH_2Cl_2, 234 μL, 0.234 mmol) was added to a solution of **7** and **7r** (9:1 ratio, 41 mg, 0.078 mmol) in dry CH_2Cl_2 (1.5 mL) under argon at −78 °C. After 45 min at 0 °C, the mixture was treated with an aqueous solution of NH_4OH (1.5 mL), stirred for 20 min, and extracted with CH_2Cl_2 (3 × 2.5 mL). Chromatography (45% EtOAc/hexane) gave **8** (20 mg, 50%) as a white solid: R_f = 0.30 (50% EtOAc/hexane); mp 220–229 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = +50 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.36 (s, 1H), 6.38 (s, 1H), 6.18 (d, J = 1.0 Hz, 1H), 6.04 (s, 2H),

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5.57−5.51 (m, 2H), 5.25 (dd, $J \approx 2.9$, ≈2.9 Hz, 1H), 5.00 (dd, J = 10.8, 3.4 Hz, 1H), 4.31 (dd, J = 13.2, 10.8 Hz, 1H), 3.85 (s, 3H), 3.43 (br d, J = 13.2 Hz, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.5, 169.1, 168.1, 154.4, 153.2, 146.7, 133.4, 131.4, 107.3, 102.4, 96.5, 75.4, 67.5, 66.6, 66.1, 55.6, 48.3, 39.1, 20.7, 20.6, 20.6; LRMS (ESI-TOF) m/z (%) 532.1 [$(M + Na)^+$, 52], 510.1 [$(M + H)^+$, 100], 307.0 (18); HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{22}H_{24}NO_{13}$ 510.1248, found 510.1242.

(+)-Pancratistatin. A solution of **8** (18 mg, 0.035 mmol) in THF (4 mL) with NaMeO (0.5 M in MeOH, 0.7 mL) was stirred for 20 min at rt. The mixture was neutralized with AcOH, and the volatiles were removed in vacuo. Chromatography (20% $MeOH/CHCl_3$) gave (+)-pancratistatin (10 mg, 86%) as a white solid: R_f = 0.80 (25% $MeOH/CHCl_3$); $[\alpha]_D^{20}$ = +46 (c = 1, DMSO); ^{1}H NMR (DMSO, 300 MHz) δ 13.40 (s, 1H), 7.49 (s, 1H), 6.47 (s, 1H), 6.04 (s, 1H), 6.02 (s, 1H), 5.34 (d, J = 3.8 Hz, 1H), 5.07 (m, 2H), 4.81 (d, J = 7.5 Hz, 1H), 4.27 (s, 1H), 3.95 (s, 1H), 3.84 (s, 1H), 3.77−3.62 (m, 2H), 2.96 (d, J = 12.4 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz) 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, 28.9.

■ ASSOCIATED CONTENT

Supporting Information

X-ray data and copies of NMR spectra for the *p*-bromobenzoate of (−)-**4a**, copies of NMR spectra and HPLC chromatograms for **4a−c**, and copies of NMR spectra for **5−8** and (−)-pancratistatin. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

After this published asap on December 3, 2012, reference 7b was added and it reposted on December 10, 2012.