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Synthesis of a Potential Intermediate for TMC-95A via an Organocatalyzed Aldol Reaction

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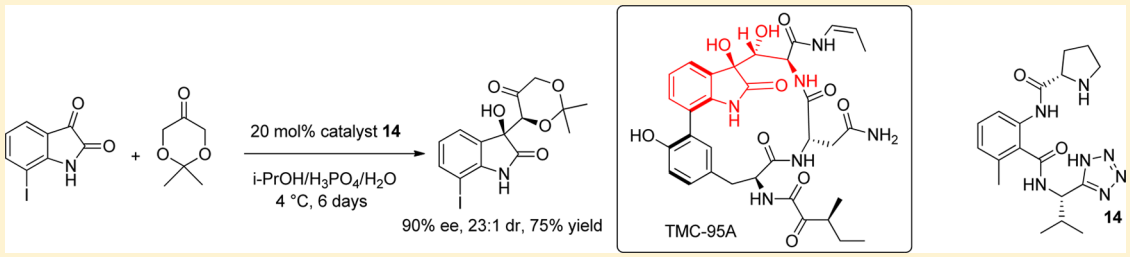
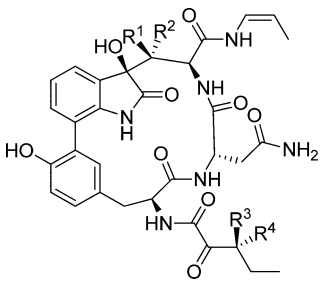
Supporting Information



ABSTRACT: *N*-Prolinylanthranilamide-based pseudopeptide organocatalyst **14** was shown to promote enantioselective direct aldol reaction of 7-iodoisatin and 2,2-dimethyl-1,3-dioxan-5-one with 90% conversion (75% isolated yield), 90% enantioselectivity, and 23:1 diastereoselectivity. To demonstrate the synthetic utility of this chemistry, the racemic aldol reaction product was converted in five steps to a potential intermediate for construction of the natural product TMC-95A.

INTRODUCTION

Given the widespread occurrence in nature of aldol-derived organic compounds, it is not surprising that the development of methods for asymmetric aldol reactions has occupied a prominent place in modern synthetic organic chemistry. In recent years, the emergence of organocatalysts for asymmetric aldol reactions has attracted the attention of numerous researchers.[1] The aldol reaction between isatins and ketones generates 3-substituted 3-hydroxyoxindoles, which are versatile building blocks for many natural products[2] and drug candidates such as TMC-95A-D,[3] convolutamydines,[4] celogentin K,[5] maremycin B,[6] and others. TMC-95A and TMC-95B (Figure 1) represent a new class of powerful reversible proteasome inhibitors,[3a] the total syntheses of which have been reported by several groups.[7] Inoue et al. reported the total synthesis of TMC-95A in 29 steps via intermediate **2**, which was prepared in 13 steps (Scheme 1A).[7c] The efficiency of this synthesis can be improved by securing a shorter route to **2** or similar intermediate, for example, via asymmetric aldol chemistry, recognizing that the protected amine group can be constructed by appropriate manipulation of the carbonyl group of a ketone such as **3** (Scheme 1B).



TMC 95	R^1	R^2	R^3	R^4
A	H	OH	Me	H
B	H	OH	H	Me
C	OH	H	Me	H
D	OH	H	H	Me

Figure 1. Structures of TMC-95A-D.

RESULTS AND DISCUSSION

The *β*-hydroxy carbonyl compound **3** might be secured by aldol reaction of 7-iodoisatin (**4**) and 2,2-dimethyl-1,3-dioxan-5-one (**6**). For the present study, we used this ketone instead of 2-(4-methoxyphenyl)-1,3-dioxan-5-one (required for **2**) since it is commercially available and has a diol protecting group that can be removed using similar conditions. In addition, a PMP acetal would produce an extra stereogenic center from the aldol reaction, further complicating product mixture characterization. This paper describes our efforts to identify a catalyst for highly enantioselective and diastereoselective synthesis of compound **3** and its conversion to intermediate **5**.

We investigated a selection of organocatalysts (Figure 2, Table 1) for the direct asymmetric aldol reaction between 7-iodoisatin and the protected 1,3-dihydroxyacetone. The major product in each case was the desired compound **3**, having two new contiguous stereocenters, one of which is tertiary. To ensure that the correct diastereomer would be produced by the aldol reaction, the relative stereochemistry of this compound was established by X-ray crystal structure determination of racemic material prior to embarking on studies of the asymmetric aldol reaction (see Supporting Information for details and ORTEP plot).

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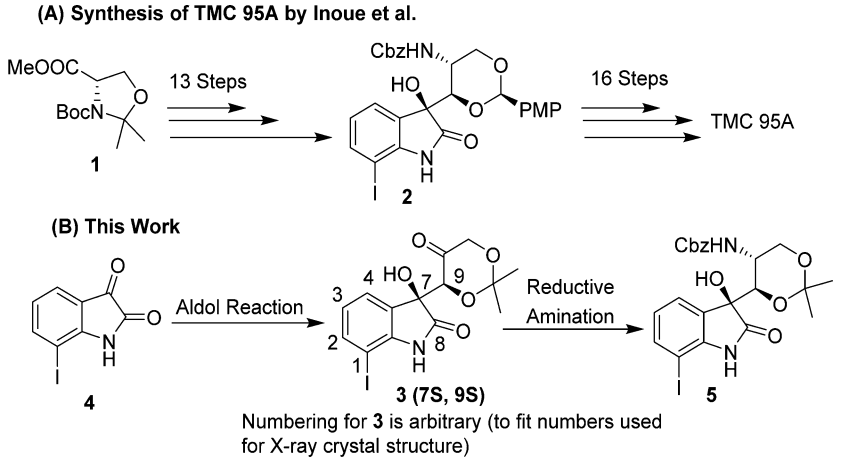
Scheme 1



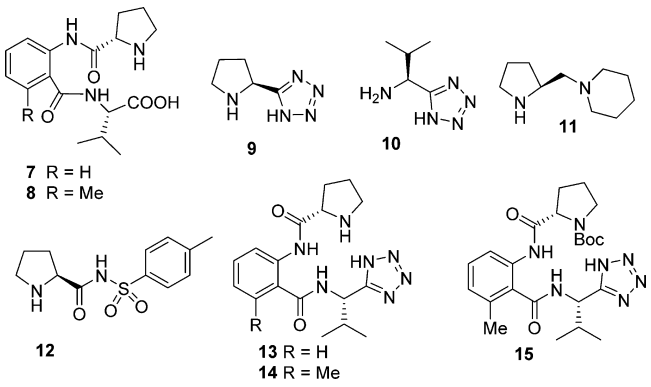


Figure 2. Catalysts investigated for the aldol reaction of 7-iodoisatin (**4**) with 2,2-dimethyl-1,3-dioxan-5-one (**6**).

The CD spectrum of nonracemic **3** showed a negative Cotton effect at around 220−260 nm, which is similar to the CD spectra of oxindole natural products that have the same stereochemistry at the 7-position.[8] In addition, we have shown that catalyst **8** promotes the aldol reaction of acetone with substituted isatins by addition at the *si* face of the isatin carbonyl, as required for **3**.[9a] Asymmetric aldol reactions of isatins and cyclohexanone using nonproline-based organocatalysts have previously been reported,[10] but as far as we are aware, similar reactions with **6** have not been studied.

N-Prolinylanthranilamide pseudopeptides **7** and **8** have been reported by us to be effective organocatalysts for the aldol reactions of isatins and acetone to afford 3-substituted 3-hydroxyoxindoles.[9] Accordingly, these compounds were screened for the aldol reaction shown in Figure 1B. In addition to **7** and **8**, we screened L-proline, L-valine, and other known catalysts, such as tetrazoles **9**[11] and **10**,[12] diamine **11**,[13] and sulfonamide **12**.[14] Initially, we employed the optimized conditions that were developed in our earlier work for **7** and **8**.[9b] Both L-proline and L-valine were ineffective under these conditions (Table 1, entries 1 and 2). Catalyst **8** gave better enantio- and diastereoselectivity than **7** (Table 1, entry 4 vs 3), illustrating the beneficial effect of 6-methyl substitution in the anthranilic acid core as previously observed,[9] but the conversion was still low. By using tetrazoles **9** and **10**, the enantioselectivity was improved compared to **8**, again with low conversion (entries 5 and 6). Also, there was very poor conversion using catalysts **11** and **12** (entries 7 and 8). Proline tetrazole (**9**) has been reported in the literature for aldol reaction of isatins and isobutyraldehyde using isopropyl alcohol as the solvent and H_3PO_4 as an additive.[15] Good conversion and diastereoselectivity were obtained for the present reaction using **9** in isopropyl alcohol and using TFA and water as additives, but the ee was low compared to the reaction in DMSO (entry 9 vs 5). By using 30 mol % H_3PO_4 (relative to 7-iodoisatin) in isopropyl alcohol, maintaining water as previously used the reaction ran to completion in 24 h and gave good ee and dr (entry 10). Catalyst **10** also afforded complete conversion and good ee and dr under these conditions. Increased reaction rate, but poor selectivity was observed for catalyst **11** under these conditions (entry 13), while **12** gave increased rate with good stereoselectivity (entry 14).

The marked improvement observed upon using amino tetrazoles versus the corresponding amino acids (Table 1, entry 10 vs 1 and 11 vs 2) prompted us to replace the carboxyl group of our catalysts with a tetrazole moiety. Catalysts **13** and **14**, being the tetrazole analogues of **7** and **8**, would test the effect of 6-methyl substitution in the anthranilic acid core, while a comparison of **15** with **14** would confirm that the tetrazole unit in the absence of the secondary amine is ineffective (the accepted mechanism requiring formation of an enamine from the latter moiety). By using catalyst **14**, the reaction afforded 90% ee and 23:1 diastereoselectivity at 90% conversion (Table 1, entry 17). The reaction was much slower (5−6 days) compared to proline tetrazole (Table 1, entry 10, reaction completed in 24 h), as well as catalyst **8** (3 days), but the diastereo- and enantioselectivity were much higher. By using catalyst **13**, the enantiomeric excess and diastereoselectivity were both lower compared to catalyst **14**, which again confirms the beneficial effect of introducing the 6-methyl group noted in our earlier work (entry 17 vs 15), the improvement being comparable to that observed with the corresponding carboxylic acid derivatives (compare with entry 4 vs 3). There was no conversion using catalyst **15**, which indicates that the secondary amine is essential for the aldol transformation, as expected (entry 18). The slower reactivity of **13** and **14**, compared to that of simpler amino acid tetrazoles, is likely due to increased steric hindrance at the structural units that are responsible for activity, in particular, the proline amino group. Anthranilamides of this type show an intramolecular hydrogen bonding between the anilide NH and neighboring CO, which was reported by us[9b] and other groups (Figure 3).[16] We previously suggested that this favors a conformation that places the secondary amine

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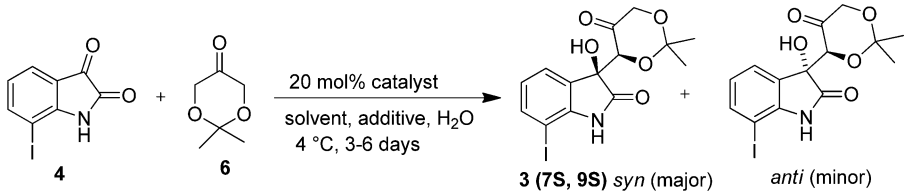
Table 1. Optimization of Organocatalytic Aldol Reaction of 7-Iodoisatin and 2,2-Dimethyl-1,3-dioxan-5-one



entry[a]	catalyst	solvent, additive	conversion (%)[b]	*syn*/*anti*, ee (%)[c]
1	L-pro	DMSO, TFA	<5	ND
2	L-val	DMSO, TFA	<5	ND
3	**7**	DMSO, TFA	18	5:1, 65
4	**8**	DMSO, TFA	25	7:1, 72
5	**9**	DMSO, TFA	20	4:1, 80
6	**10**	DMSO, TFA	20	4:1, 78
7	**11**	DMSO, TFA	<5	ND
8	**12**	DMSO, TFA	<5	ND
9	**9**	*i*-PrOH, TFA	60	15:1, 64
10[d]	**9**	*i*-PrOH, H_3PO_4	100	17:1, 68
11[d]	**10**	*i*-PrOH, H_3PO_4	100	19:1, 69
12[d]	**8**	*i*-PrOH, H_3PO_4	80	17:1, 58
13[d]	**11**	*i*-PrOH, H_3PO_4	70	4:1, 5
14[d]	**12**	*i*-PrOH, H_3PO_4	40	16:1, 63
15[d]	**13**	*i*-PrOH, H_3PO_4	90	19:1, 84
16	**14**	DMSO, TFA	<10	ND
17[d]	**14**	*i*-PrOH, H_3PO_4	90	23:1, 90
18[d]	**15**	*i*-PrOH, H_3PO_4	0	ND

[a]Unless specified otherwise, the concentration of 7-iodoisatin is 0.20 M, and 2,2-dimethyl-1,3-dioxan-5-one/DMSO is 0.8 M, 550 mol % of water, 10 mol % of TFA; the reactions were run at 4 °C. Volume of DMSO = 0.4 mL. Reaction time = 72 h. [b]Percent conversion was determined from the HPLC of the crude reaction mixture. [c]Diastereoselectivity and enantiomeric excess were determined by HPLC using CHIRALPAK AD-H column. [d]Unless specified otherwise, the concentration of 7-iodoisatin is 0.20 M, and 2,2-dimethyl-1,3-dioxan-5-one/isopropyl alcohol is 0.80 M, 550 mol % of water, 30 mol % of H_3PO_4; the reactions were run at 4 °C. Volume of isopropyl alcohol = 0.1 mL. Reaction time = 24−144 h.

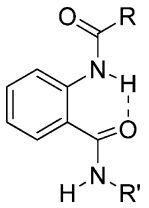


Figure 3. Intramolecular hydrogen bonding for *N*-acylanthranilamides (dashed line).

and carboxylic acid moieties in close proximity, as required for promoting the aldol reaction. Variable-temperature ^{1}H NMR studies with catalyst **14** confirmed the same hydrogen bonding interaction for this compound. A temperature coefficient ($\Delta\delta/\Delta T$) of 2.4 ppb/K for **14** compared to **7** (4.6 ppb/K) indicates that **14** has significantly stronger hydrogen bonding and suggests a greater preference for the "reverse turn" conformation that influences its catalytic competency.

After obtaining good ee with 7-iodoisatin, catalyst **14** was screened for reactions of other isatins (Figure 4). By using 7-chloroisatin, there was a drop in ee and dr. Substitution did not appear to adversely impact reactivity. The aldol reactions of 5-bromo-, 6-bromo-, and 4-bromoisatin afforded good yield, dr, and ee. We do not have a rational explanation for the observed variations in diastereoselectivity using these different substrates.

Concurrent with our studies on the aldol reaction, we investigated methods for the further conversion of **3** to the TMC-95A intermediate **5**, using racemic material for a more expedient evaluation of our strategy. The most direct approach

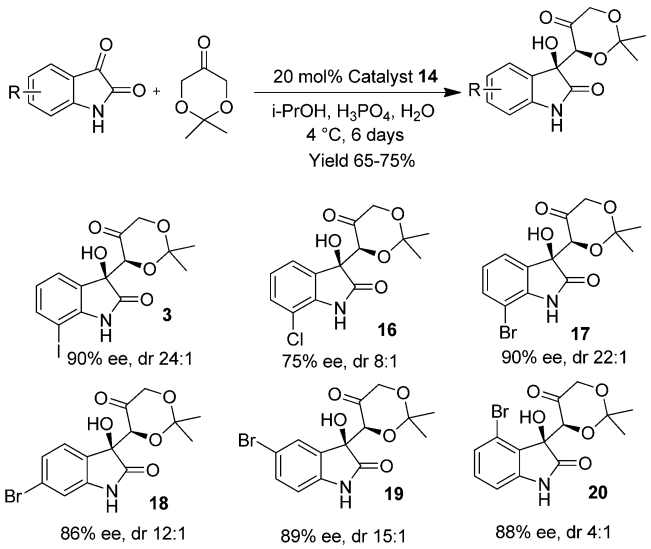


Figure 4. Products from aldol reactions of substituted isatins and 2,2-dimethyl-1,3-dioxan-5-one.

would be a stereocontrolled reductive amination of **3**. In order to test the feasibility of enlisting the tertiary 7-hydroxyl as a directing group for this type of transformation, we carried out model studies on reduction of the carbonyl group of **3** using different reagents. Hydroxyl-directed reduction using $NaBH(OAc)_3$/AcOH at −10 °C, as developed by Evans,[17] afforded the *anti*-1,3-diol **22** with excellent selectivity. In contrast, the

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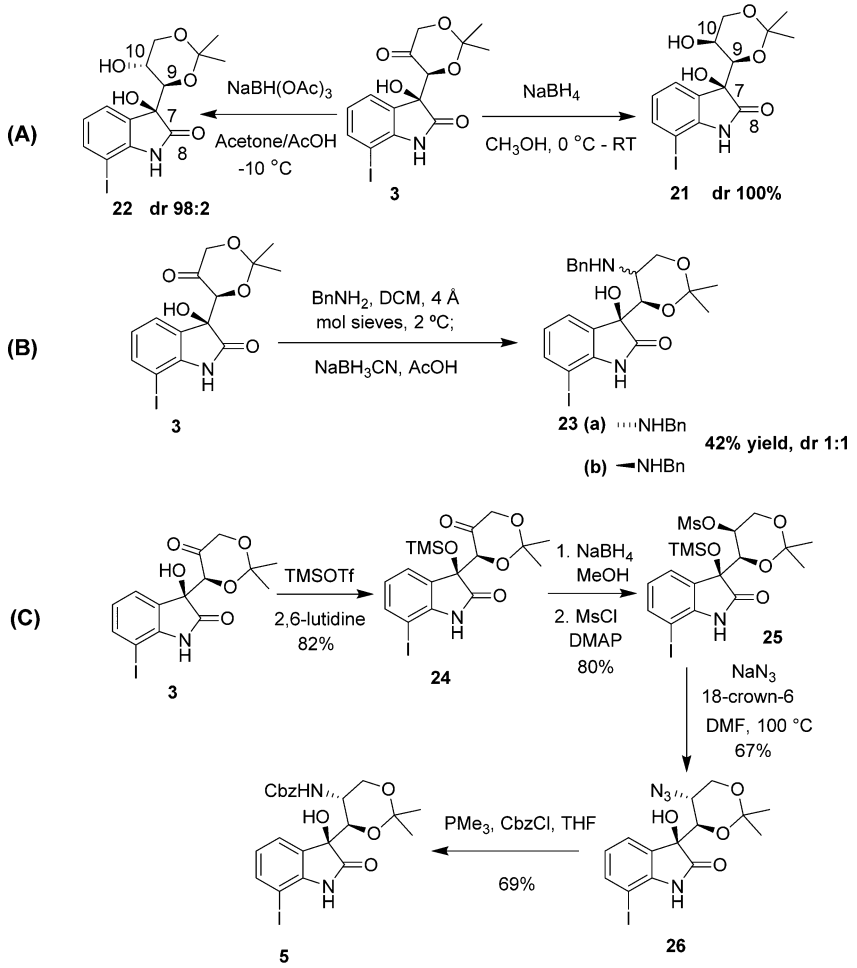
Scheme 2. (A) Model Study on Reduction of 3, (B) Optimized Conditions for Reductive Amination, and (C) Stereocontrolled Route to Intermediate 5



syn-1,3-diol **21** was obtained by steric approach control using $NaBH_4$/MeOH (Scheme 2). The small coupling constant (J = 1.6 Hz) between H9 and H10 (numbering as for **3**, Scheme 1) for **21** confirms their *syn* (axial/equatorial) relationship, compared to the greater diaxial coupling for **22** (J = 9.2 Hz).

This result prompted us to examine the possibility of a hydroxy-directed reductive amination[18] to produce intermediate **23a** (NHBn replacing NHCbz of **5**). Attempted direct reductive amination using benzylamine combined with $NaBH(OAc)_3$ afforded alcohol **22** instead of the amine, indicating that ketone reduction outpaces imine formation/reduction. Various methods for reduction of the preformed imine,[18a] oxime, oximino benzyl ether,[18b] or oximino benzoyl ester also did not afford the desired product. We were eventually able to prepare intermediate **23**, but as an equimolar mixture of epimers (a) and (b) in 42% yield by reaction of **3** with benzylamine/AcOH in DCM in the presence of molecular sieves, followed by in situ treatment of the resulting imine with $NaBH_3CN$ at 2 °C. While the formation of this equimolar mixture is somewhat disappointing, it does suggest some hydroxyl participation during the reduction (which would result in **23a**), given the observation that steric approach control during reduction of **3** gives a single diastereomer analogous to **23b**. Unfortunately, the desired isomer **23a** could not be obtained pure from the mixture of epimers. In view of the technical difficulties and poor stereocontrol encountered with the reductive amination of **3**, we elected to use a somewhat longer but more reliable sequence for the synthesis of **5**.[19]

The alcohol **3** reacted smoothly with TMSOTf to afford **24** in greater than 80% yield. Borohydride reduction of the carbonyl group followed by conversion of the resulting secondary alcohol to mesylate **25** proceeded in good yield (preparation of the mesylate without prior tertiary hydroxyl protection was problematic). The mesylate underwent S_N2 reaction with an azide ion to furnish **26** by using NaN_3/18-crown-6 in DMF at 100 °C, which proceeded with concomitant removal of the TMS group. After screening a variety of reaction conditions, azide **26** was successfully converted to the Cbz-protected amine **5** in 69% yield in one step using PMe_3/CbzCl.

■ CONCLUSIONS

In summary, the aldol reaction of 7-iodoisatin with 2,2-dimethyl-1,3-dioxan-5-one catalyzed by the *N*-prolinylanthranilamide-based pseudopeptide **14** afforded the aldol product **3** in high yield and excellent stereoselectivity. While we were able to synthesize intermediate **23** (NHBn instead of NHCbz) by reductive amination of **3** in a one-pot, two-step operation, this reaction suffered from poor stereoselectivity and low yield. Compound **3** was more efficiently converted to the potential TMC-95A intermediate **5** over five steps in 25% overall yield. We are confident that an identical asymmetric aldol strategy can be used to secure compound **2**, which is a known

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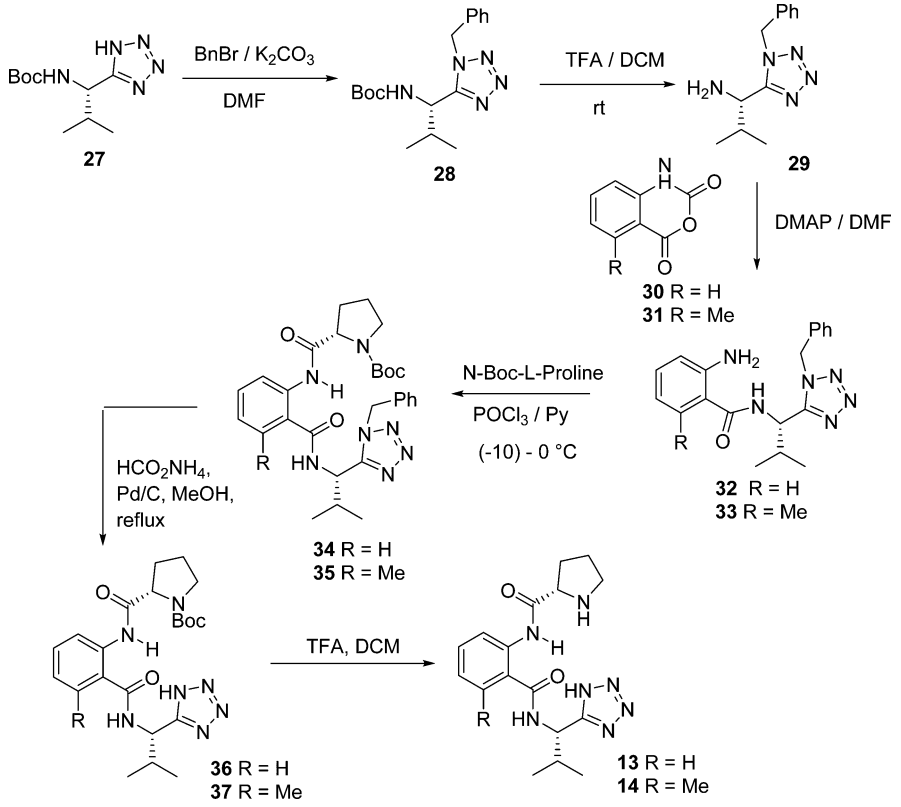
Scheme 3



intermediate for TMC-95A synthesis and differs from **5** only in the nature of its 1,3-diol protection.

EXPERIMENTAL SECTION

General Methods. All reactions were performed with anhydrous solvents in oven-dried and argon-charged glassware unless otherwise stated. All solvents were freshly distilled before use. Analytical thin layer chromatography was carried out using glass bedded silica gel 60 F 254, 0.25 mm thickness. Flash chromatography was carried out on silica gel 60 Å (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer (operating frequency refers to ^{1}H) and are internally referenced to residual solvent signals. High-resolution mass spectra were recorded using a magnetic sector mass analyzer.

For the synthesis of catalysts **13** and **14** (Scheme 3), experimental details are given for the synthesis of **14**, and characterization data only are listed for compounds leading to **13**, the procedures being identical.

*(S)-tert-Butyl (1-(1-Benzyl-1H-tetrazol-5-yl)-2-methylpropyl)-carbamate (**28**).* To a stirred solution of (*S*)-*tert*-butyl (2-methyl-1-(1*H*-tetrazol-5-yl)propyl)carbamate (**27**)[20] (400 mg, 1.65 mmol) in dry DMF (6 mL) was added potassium carbonate (343 mg, 2.5 mmol) followed by benzyl bromide (0.4 mL, 3.3 mmol). The reaction mixture was stirred at rt for 24 h and monitored by TLC. After completion of the reaction, the mixture was quenched with water and the product was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuum. Flash chromatography (hexanes/ethyl acetate = 1:1) afforded **28** as a white solid (377 mg, 69%). (Note: the regiochemistry of benzylation is uncertain, but this is inconsequential as the benzyl group is removed later. The ^{1}H NMR spectrum is complicated by the presence of Boc rotamers): $[\alpha]_D^{23}$ = −8.8 (*c* = 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (5H, m), 5.75, 5.58 (2H, ABq, *J* = 18 Hz, $\Delta\upsilon$ = 31 Hz), 5.02 (1H, m), 4.66 (1H, m), 2.15 (1H, m), 1.41 and 1.38 (each s, 9H total, rotamers), 0.93, 0.87, 0.85, and 0.47 (6H total, each d, *J* = 6.8 ppm, rotamers, diastereotopic Me groups); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.2, 166.7, 158.4, 156.0, 148.8, 144.8, 141.8, 136.2, 135.8, 134.0, 133.3, 130.7, 130.3, 129.4, 129.3, 128.5, 128.4, 128.3, 127.3, 121.2, 120.6, 120.3, 114.1, 113.9, 113.8, 108.9, 57.1, 51.6, 49.4, 32.6, 31.9, 22.4, 20.3, 19.3, 18.9, 17.9; HRMS (EI) calcd for $C_{17}H_{26}N_5O_2$ $[M + H]^+$ 332.2067, found 332.2082.

*(S)-1-(1-Benzyl-1H-tetrazol-5-yl)-2-methylpropan-1-amine (**29**).* To a stirred solution of **28** (350 mg, 1.05 mmol) in DCM (5 mL) was added trifluoroacetic acid (0.3 mL), and stirring was continued for 72 h. After completion of the reaction, the excess solvent was removed by rotary evaporation. The residue was dissolved in ethyl acetate and washed with $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated to afford **29** as a yellow oil (182 mg, 75%): $[\alpha]_D^{23}$ = −6.2 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (5H), 5.65 (2H, d, *J* = 1.2 Hz), 3.97(1H, d, *J* = 4.8 Hz), 2.06 (1H), 1.67 (2H, s), 0.84 (6H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 170.1, 133.6, 129.4, 129.2, 129.1, 129.05, 128.4, 56.8, 54.2, 34.1, 19.2, 18.0; HRMS (EI) calcd for $C_{12}H_{17}N_5$ $[M + H]^+$ 232.1562, found 232.1562.

*(S)-2-Amino-N-(1-(1-benzyl-1H-tetrazol-5-yl)-2-methylpropyl)-6-methylbenzamide (**33**).* To a stirred solution of 6-methylisatoic anhydride (**31**) (400 mg, 2.25 mmol) in dry DMF (8 mL) were added DMAP (275 mg, 2.25 mmol) and **29** (520 mg, 2.25 mmol). The reaction mixture was stirred for 24 h at 100 °C, with progress being monitored by TLC using 50% ethyl acetate in hexanes. The reaction mixture was cooled to rt, then poured into ice water, and the product was extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (hexanes/ethyl acetate = 1:2) afforded **33** (420 mg, 52%): $[\alpha]_D^{23}$ = −28.3 (*c* = 0.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (1H, t, *J* = 8 Hz), 7.37 (5H), 7.07 (1H, d, *J* = 8 Hz), 6.93 (1H, d, *J* = 8 Hz), 6.12−5.82 (3H), 4.97 (1H, s), 2.62 (3H, s), 2.29 (1H, m), 1.05 (3H, d, *J* = 6 Hz), 0.56 (3H, d, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.3, 155.9, 153.4, 143.5, 136.0, 134.3, 129.4, 129.2, 128.3, 127.2, 122.4, 51.5, 51.1, 32.2, 22.8, 19.2; HRMS (EI) calcd for $C_{20}H_{24}N_6O$ $[M]^+$ 364.2012, found 364.2015.

*(S)-tert-Butyl 2-((2-(((S)-1-(1-Benzyl-1H-tetrazol-5-yl)-2-methylpropyl)carbamoyl)-3-methylphenyl)carbamoyl)pyrrolidine-1-carboxylate (**35**).* To a stirred solution of *N*-Boc-L-proline (71 mg,

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0.32 mmol) in pyridine (2 mL) under argon was added dropwise phosphorus oxychloride (0.2 mL, 2.0 mmol), maintaining the temperature at −10 °C. The reaction mixture was stirred for 1 h at −10 °C, followed by addition of a solution of **33** (116.5 mg, 0.32 mmol) in pyridine (1 mL). Stirring was continued for 8 h at −10 to −5 °C, then the mixture was added to ice-cooled 1 M aq HCl solution, and the product was extracted with ethyl acetate (3 × 10 mL). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate = 1:1) afforded **35** as pale yellow gum (114 mg, 62%): $[\alpha]_D^{23}$ = −45.6 (*c* = 0.08, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm, rotamers) 7.69−7.84 (1H, m), 7.49−7.21 (6H, m), 7.05 (1H, d, *J* = 7.6 Hz), 6.0−5.78 (2H, m), 5.38−5.01 (1H, m), 4.45−4.22 (1H, m), 3.41 (2H, m), 2.40−1.81 (5H), 1.81−1.59 (3H), 1.40 (9H), 1.01, 0.45 (6H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 177.1, 175.9, 170.5, 162.2, 160.5, 158.7, 139.9, 139.4, 138.6, 138.0, 133.8, 133.6, 133.2, 132.9, 132.7, 132.4, 132.0, 130.9, 130.6, 125.4, 124.7, 84.2, 65.3, 65.1, 64.8, 60.7, 56.2, 55.1, 36.7, 35.5, 35.0, 34.2, 33.9, 31.5, 28.2, 28.0, 27.4, 22.8, 22.6, 22.4, 22.1; HRMS (EI) calcd for $C_{30}H_{39}N_7O_4$ $[M]^+$ 561.3064, found 561.3069.

*(S)-tert-Butyl-2-((3-methyl-2-(((S)-2-methyl-1-(1H-tetrazol-5-yl)-propyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (**37**).* To a 10 mL three-neck reaction flask equipped with nitrogen inlet and outlet and reflux condenser was added 10 mL of dry methanol followed by ammonium formate (1.1 g, 18 mmol). The solution was degassed by passing N_2 for 10 min, followed by addition of 50 mg of 10% Pd/C. After 5 min, amide **35** (100 mg, 0.18 mmol) in 1 mL of dry methanol was added, and the resulting mixture was stirred for 4 h at reflux temperature. The reaction progress was monitored by TLC using 80% ethyl acetate in hexanes. After completion of the reaction, the mixture was filtered through Celite and concentrated. Flash chromatography using 10% methanol in DCM to afforded **37** as a gum (60 mg, 71%): $[\alpha]_D^{23}$ = −59.2 (*c* = 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm, rotamers) 7.77, 7.72 (1H, d, *J* = 8.0 Hz), 7.29 (1H, t, *J* = 8.0 Hz), 7.08 (1H, d, *J* = 8.0 Hz), 5.35 (1H, m), 4.61, 4.20 (1H, m), 3.21 (2H, m), 2.40 (3H, s), 2.31−1.46 (5H), 1.41 (9H), 1.01 (6H). ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 173.5, 169.7, 161.1, 154.8, 135.3, 134.5, 130.7, 129.1, 126.7, 121.4, 80.2, 61.1, 60.8, 59.7, 52.0, 31.7, 31.2, 30.7, 30.4, 29.9, 29.3, 27.6, 27.4, 24.1, 23.4, 18.7, 18.6, 17.7, 17.5; HRMS (EI) calcd for $C_{23}H_{33}N_7O_4$ $[M]^+$ 471.2594, found 471.2562.

*(S)-N-(3-Methyl-2-(((S)-2-methyl-1-(1H-tetrazol-5-yl)propyl)-carbamoyl)phenyl)pyrrolidine-2-carboxamide (**14**).* To a stirred solution of **37** (50 mg, 0.13 mmol) in 2 mL of dichloromethane was added 0.05 mL of TFA at room temperature. The reaction mixture was stirred for 72 h and then concentrated in vacuo. To remove acidic impurity, the product was dissolved in ice-cooled $NaHCO_3$ solution and extracted with ethyl acetate (2 × 2 mL). The aqueous layer was acidified with 1 M aq HCl and extracted with 1-butanol (3 × 2 mL). The 1-butanol layer was collected, dried over Na_2SO_4, and concentrated in vacuo to afford **14** (yield 20 mg, 51%): $[\alpha]_D^{23}$ = −91.2 (*c* = 0.015, 5% TFA in CH_3OH); mp 139−142 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 7.68 (1H, d, *J* = 8.0 Hz), 7.30 (1H, t, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 5.29 (1H, m), 4.70 (1H, m), 3.42−3.20 (2H, m), 2.40−2.20 (5H), 2.13−1.81 (3H), 0.99 (3H, d, *J* = 6.4 Hz), 0.95 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 168.9, 168.1, 158.9, 135.1, 135.09, 131.6, 128.9, 126.4, 120.3, 60.7, 52.4, 46.6, 31.1, 30.9, 28.5, 24.0, 20.4, 19.5, 18.4; HRMS (ESI) calcd for $C_{18}H_{26}N_3O_2$ $[M + H]^+$ 372.2142, found 372.2142.

*(S)-2-Amino-N-(1-(1-benzyl-1H-tetrazol-5-yl)-2-methylpropyl)-benzamide (**32**).* Compound **32** was prepared as described for compound **33**, via ring opening of isatoic anhydride (**30**) by valine *N*-benzyltetrazole (**29**): yield = 56%; $[\alpha]_D^{23}$ = −23.3 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (5H), 7.14 (1H, m), 6.93 (1H, d, *J* = 8.8 Hz), 6.61, 6.51 (2H, t, *J* = 8.8 Hz), 5.75 (2H), 5.45 (2H, br s), 5.41, 5.15 (1H, m), 2.35 (1H, m), 0.98, 0.41 (6H). The product was used in the next step without further characterization.

*(S)-tert-Butyl-2-((2-(((S)-1-(1-benzyl-1H-tetrazol-5-yl)-2-methyl-propyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (**34**):* Yield 55%; $[\alpha]_D^{23}$ = −39.6 (*c* = 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm, rotamer) 9.18, 8.92 (1H), 8.56, 8.41 (1H), 7.77 (1H, m), 7.45−7.31 (6H), 7.19 (1H), 5.95 (2H, m), 5.22, 4.98 (1H), 4.20 (1H), 3.42 (2H), 2.55−1.70 (5H), 1.40 (9H), 1.20, 1.02 (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.3, 175.6, 172.5, 169.4, 166.2, 156.1, 155.9, 154.5, 154.2, 140.2, 139.6, 134.3, 133.7, 133.2, 129.4, 129.3, 128.8, 128.5, 127.7, 123.0, 120.8, 118.0, 80.9, 80.4, 80.2, 62.8, 59.1, 57.1, 51.8, 51.5, 49.6, 46.9, 46.5, 33.2, 31.7, 31.6, 31.0, 29., 28.5, 24.6, 23.9, 23.8, 21.1, 19.7, 19.3, 18.9, 18.6. The product was used in the next step without further characterization.

*(S)-tert-Butyl-2-((2-(((S)-2-methyl-1-(1H-tetrazol-5-yl)propyl)-carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (**36**):* Yield 71%; $[\alpha]_D^{23}$ = −48.9 (*c* = 0.04, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm, rotamers) 8.29 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.46 (1H, t, *J* = 8.0 Hz), 7.18 (1H, t, *J* = 8.0 Hz), 5.22 (1H, m), 3.90 (1H, m), 2.99 (2H, m), 2.41−2.10 (2H, m), 1.99−1.60 (12H), 1.15−0.80 (6H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 175.5, 172.8, 169.7, 157.5, 154.7, 138.5, 132.5, 128.2, 123.4, 121.1, 120.9, 120.5, 80.6, 80.2, 80.0, 62.6, 62.1, 59.3, 58.9, 51.5, 51.4, 46.3, 31.4, 31.1, 30.6, 30.3, 29.8, 27.6, 27.4, 24.0, 23.9, 23.4, 18.7, 18.5; HRMS (ESI) calcd for $C_{22}H_{32}N_7O_4$ $[M + H]^+$ 458.2516, found 458.2512.

*(S)-N-(2-(((S)-2-Methyl-1-(1H-tetrazol-5-yl)propyl)carbamoyl)-phenyl)pyrrolidine-2-carboxamide (**13**):* Yield 55%; mp 149−151 °C; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 8.09 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.50 (1H, t, *J* = 8.0 Hz), 7.24 (1H, t, *J* = 8.0 Hz), 5.21 (1H, m), 4.50 (1H, m), 3.40 (2H, m), 2.58−2.38 (2H), 2.20−1.98 (3H), 1.10 (3H, d, *J* = 6.0 Hz), 0.95 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 170.7, 168.0, 159.1, 137.9, 133.1, 129.4, 125.9, 125.4, 123.8, 62.0, 52.4, 47.3, 47.2, 32.7, 30.5, 25.0, 19.6, 19.3; HRMS (ESI) calcd for $C_{17}H_{24}N_7O_2$ $[M + H]^+$ 358.1991, found 358.1971.

General Aldol Reaction Procedure and Product Characterization. To a 3 mL reaction vial was taken up 20 mol % of catalyst in 0.1 mL of isopropyl alcohol followed by 550 mol % of water and 30 mol % of H_3PO_4 added to it (mol % is relative to 7-iodoisatin). The reaction mixture was stirred for 10 min at 4 °C after which time 2,2-dimethyl-1,3-dioxan-5-one (0.8 mmol) was added. The reaction mixture was stirred for another 10 min at 4 °C followed by addition of 7-iodoisatin (0.2 mmol) and then stirred for 24 h to 6 days (monitored by TLC) at 4 °C. After completion of the reaction, the mixture was quenched with water and extracted into ethyl acetate, dried over Na_2SO_4, concentrated in vacuo, and separated by flash chromatography using 1:1 ethyl acetate/hexanes. Specific rotations of aldol products were not determined because they were not obtained optically pure.

*(S)-3-((S)-2,2-Dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxy-7-iodo-indolin-2-one (**3**):* Isolated yield 75%; mp 198−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.38 (1H, s), 7.53 (1H, dd, *J* = 8.0, 1.2 Hz), 7.35 (1H, dd, *J* = 8.0, 1.2 Hz), 6.69 (1H, t, *J* = 8.0 Hz), 6.40 (1H, s), 4.62 (1H, d, *J* = 1.6 Hz), 4.03 (1H, dd, *J* = 17.6, 1.6 Hz), 3.90 (1H, d, *J* = 17.6 Hz), 1.43 (3H, s), 1.40 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 207.0, 176.5, 146.8, 139.0, 130.5, 125.8, 124.2, 102.7, 101.3, 78.9, 75.5, 75.3, 67.0, 24.8, 23.7; HRMS (EI) calcd for $C_{14}H_{14}INO_5$ $[M]^+$ 402.9917, found 402.9918.

*(S)-7-Chloro-3-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxyindolin-2-one (**16**):* Yield 74%; mp 169−170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.77 (1H, s), 7.273 (2H), 6.89 (1H), 6.41(1H), 4.64 (1H, d, *J* = 1.6 Hz), 4.40 (1H, dd, *J* = 18.0, 1.6 Hz), 3.90 (1H, d, *J* = 18.0 Hz), 1.42 (3H, s), 1.40 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 207.0, 176.7, 141.5, 131.2, 130.1, 124.9, 123.5, 114.3, 101.3, 78.7, 75.0, 67.0, 24.7, 23.7; HRMS (EI) calcd for $C_{14}H_{14}ClNO_5$ $[M]^+$ 311.0516, found 311.0513.

*(S)-7-Bromo-3-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxyindolin-2-one (**17**):* Yield 70%; mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (1H, br s), 7.38 (1H, d, *J* = 8.0 Hz), 7.23 (1H, d, *J* = 8.0 Hz), 6.85 (1H, t, *J* = 8.0 Hz), 4.48 (1H, d, *J* = 1.2 Hz), 4.22 (1H, dd, *J* = 18, 1.2 Hz), 3.98 (1H, d, *J* = 18 Hz), 1.32 (3H, s), 1.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.9, 175.2, 141.9, 133.3, 129.4, 124.6, 124.5, 123.4, 101.8, 101.7, 75.7, 75.3, 67.0,

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66.9, 24.0, 23.6, 23.5, 23.4; HRMS (EI) calcd for $C_{14}H_{14}BrNO_5$ $[M]^+$ 355.0055, found 355.0046.

*(S)-6-Bromo-3-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxyindolin-2-one (**18**):* Yield 72%; mp 184−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.49 (1H, s), 7.27 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 8.0, 1.6 Hz), 6.89 (1H, d, J = 1.6 Hz), 6.37 (1H, s), 4.64 (1H, 1.2 Hz), 4.02 (1H, dd, J = 16.0, 1.6 Hz), 3.90 (1H, d, J = 16.0 Hz), 1.45 (3H, s), 1.41 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 205.0, 176.3, 143.1, 132.8, 131.7, 129.1, 113.6, 112.1, 101.4, 78.6, 74.3, 67.0, 24.6, 23.8; HRMS (EI) calcd for $C_{14}H_{14}BrNO_5$ $[M]^+$ 355.0055, found 355.0047.

*(S)-5-Bromo-3-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxyindolin-2-one (**19**):* Yield 75%; mp 191−193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.48 (1H), 7.33 (2H), 6.71 (1H, d, J = 8.0 Hz), 6.41 (1H, s), 4.64 (1H, s), 4.10 (1H, dd, J = 17.6, 1.6 Hz), 3.90 (1H, d, J = 17.6 Hz), 1.45 (3H, s), 1.41 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 207.0, 176.8, 145.5, 128.7, 128.1, 124.7, 122.9, 112.9, 101.3, 78.7, 74.1, 67.0, 24.7, 23.8; HRMS (EI) calcd for $C_{14}H_{14}BrNO_5$ $[M]^+$ 355.0055, found 355.0027.

*(S)-4-Bromo-3-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxyindolin-2-one (**20**):* Yield 75%; mp 190−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.60 (1H, s), 7.12 (2H), 6.76 (1H, d, J = 8.0 Hz), 6.07 (1H, s), 4.99 (1H, s), 4.49 (1H, J = 22.0, 1.6 Hz), 4.40 (1H, d, J = 22.0 Hz), 1.26 (3H, s), 1.17 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 206.3, 178.5, 145.8, 132.3, 127.9, 126.5, 119.1, 100.8, 100.5, 79.5, 74.9, 68.0, 25.9, 23.3; HRMS (EI) calcd for $C_{14}H_{14}BrNO_5$ $[M]^+$ 355.0055, found 355.0035.

Methods for Conversions Shown in Scheme 2. *(S/R)-3-Hydroxy-3-((4R/S,5S/R)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-7-iodoindolin-2-one (rac-**21**).* To a stirred solution of racemic **3** (200 mg, 0.49 mmol; produced by aldol reaction of **4** with **6** in the presence of pyrrolidine as catalyst) in dry methanol (5 mL) was added $NaBH_4$ (9.26 mg, 0.25 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then brought to 4 °C and stirred for another 1 h. After completion of the reaction, excess methanol was removed in vacuo. The reaction mixture was quenched with water and extracted with ethyl acetate, dried over Na_2SO_4, and concentrated to afford *rac*-**21** (178 mg, 75%): mp 198−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.51 (1H, s), 7.52 (1H, dd, J = 8.0, 1.2 Hz), 7.33 (1H, dd, J = 8.0, 1.2 Hz), 6.78 (1H, t, J = 8.0 Hz), 6.41 (1H, s), 4.92 (1H, d, J = 1.6 Hz), 4.27 (1H, d, J = 1.6 Hz), 3.90 (1H, dt, J = 12.8, 1.6 Hz), 3.68 (1H, app. p, J = 1.6 Hz), 3.52 (1H, dd, J = 12.8, 1.6 Hz), 1.20 (3H, s), 1.12 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 179.5, 146.0, 138.5, 133.9, 124.7, 124.4, 99.0, 78.3, 75.9, 75.4, 66.0, 63.2, 29.7, 19.2; HRMS (EI) calcd for $C_{14}H_{17}INO_5$ $[M + H]^+$ 406.0151, found 406.0142.

*(S/R)-3-Hydroxy-3-((4R/S,5R/S)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)-7-iodoindolin-2-one (rac-**22**).* To a stirred solution of racemic **3** (100 mg, 0.25 mmol) in dry acetone was added $NaBH(OAc)_3$ at −15 °C. The reaction mixture was stirred for 2 h at −15 °C. After completion of the reaction, excess acetone was removed in vacuo. The reaction mixture was quenched with water and extracted with ethyl acetate; the organic extract was dried over Na_2SO_4 and concentrated to afford *rac*-**22** as a gum (200 mg, 84%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.07 (1H, s), 7.52 (1H, dd, J = 7.6, 0.8 Hz), 7.30 (1H), 6.73 (1H, t, J = 7.2 Hz), 6.15 (1H, br s), 4.82 (1H, br s), 3.95 (1H, d, J = 6.0 Hz), 3.47−3.39 (2H), 3.17(1H), 1.33 (3H, s), 1.22 (3H, s). The splitting patterns are not clear, so we also ran the NMR in $CDCl_3$: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.06 1H, 7.50 (1H, dd, J = 8.0, 1.2 Hz), 7.28 (1H, dd, J = 8.0, 1.2 Hz), 6.70 (1H, t, J = 8.0 Hz), 3.93 (1H, d, J = 9.2 Hz), 3.43 (1H, ABX, J_{AB} = 11.2, J_{AX} = 5.6 Hz, $\Delta\nu$ = 25.2 Hz), 3.36 (1H, ABX, J_{AB} = 11.2, J_{BX} = 9.2 Hz, $\Delta\nu$ = 25.2 Hz), 3.15 (1H, ddd, J = 9.2, 9.2, 5.6 Hz), 1.30 (3H), 1.20 (3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 177.4, 146.5, 138.6, 131.7, 125.5, 124.0, 98.9, 77.6, 77.0, 75.2, 64.5, 65.7, 29.0, 19.8; HRMS (EI) calcd for $C_{14}H_{17}INO_5$ $[M + H]^+$ 406.0151, found 406.0132.

*(3S/R)-3-((4R/S,5R/S)-5-(Benzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-7-iodoindolin-2-one (rac-**23a**) and (S/R)-3-((4R/S,5S/R)-5-(Benzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-7-iodoindolin-2-one (rac-**23b**).* To a stirred solution of racemic **3** (100 mg, 0.25 mmol) in dry DCM at 2 °C were added benzylamine (0.035 mL, 0.3 mmol) and 4 Å molecular sieves. The mixture was stirred for 24 h, followed by addition of $NaBH_3CN$ (48 mg, 0.75 mmol), and stirring was continued for 48 h at 2 °C. After completion of the reaction, the mixture was concentrated and purified by preparative TLC using 1:1 ethyl acetate and hexanes to afford the mixture of diastereomers *rac*-**23a**/**b** (52 mg, 42%): ^{1}H NMR of 1:1 mixture (400 MHz, $CDCl_3$) δ (ppm) 7.67 (1H), 7.42 (1H), 7.38−7.26 (5H), 6.89 (1H), 6.40 (1H), 5.04 (2H), 4.77−4.27 (3H), 3.80−3.58 (3H), 1.52, 1.35 (6H). Only compound *rac*-**23b** was obtained pure using preparative TLC after three solvent elutions: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (1H, dd, J = 8.0, 1.2 Hz), 7.26−7.14 (6H), 6.33 (1H, t, J = 8.0 Hz), 5.52 (1H, br s), 5.02 (1H, d, J = 16 Hz), 4.51 (1H, d, J = 3.6 Hz), 4.11 (1H, d, J = 16 Hz), 3.85 (1H, dd, J = 13.6, 8.8 Hz), 3.82 (1H, dd, J = 13.6, 8.0 Hz), 3.55 (1H, dd, J = 6.8, 3.6 Hz), 1.27 (3H, s), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.7, 146.7, 139.1, 135.1, 130.6, 128.9, 127.8, 121.1, 118.5, 98.6, 88.0, 82.2, 69.2, 57.9, 51.8, 44.3, 27.9, 19.8; HRMS (ESI) calcd for $C_{21}H_{23}IN_2NaO_4$ $[M + Na]^+$ 517.0600, found 517.0595.

*(S/R)-3-((S/R)-2,2-Dimethyl-5-oxo-1,3-dioxan-4-yl)-7-iodo-3-((trimethylsilyl)oxy)indolin-2-one (rac-**24**).* To a stirred solution of racemic **3** (300 mg, 0.74) in dry DCM (10 mL) at −15 °C was added 2,6-lutidine (0.86 mL, 7.4 mmol). The mixture was stirred for 10 min, then cooled to −15 °C, followed by addition of trimethylsilyl trifluoromethanesulfonate (0.67 mL, 3.7 mmol). The reaction was stirred at −15 °C for 4 h and monitored by TLC (1:1, ethyl acetate/hexanes) and then was quenched by addition of cold $NaHCO_3$ solution at −15 °C. The mixture was extracted with DCM, washed with cold 5% citric acid solution, and concentrated to afford *rac*-**24** (288 mg, 82%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.67 (1H, s), 7.72 (1H, dd, J = 8.0, 1.2 Hz), 7.53 (1H, dd, J = 8.0, 0.8 Hz), 6.66 (1H, t, J = 8.0 Hz), 5.85 (1H, s), 4.75(1H, d, J = 1.2 Hz), 4.13 (1H, d, J = 17.6 Hz), 4.02 (1H, d, J = 17.6 Hz), 1.57 (3H, s), 1.55 (3H, s), 0.01 (9H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 168.1, 158.9, 135.1, 135.1, 131.6, 128.9, 126.4, 120.3, 119.0, 118.4, 60.7, 52.4, 46.6, 46.2, 31.1, 31.0, 24.3, 24.0, 20.1, 19.5, 18.4; HRMS (ESI) calcd for $C_{17}H_{22}INO_5Si$ $[M + H]^+$ 476.0390, found 476.0382.

*(4R/S,5S/R)-4-((S/R)-7-Iodo-2-oxo-3-((trimethylsilyl)oxy)indolin-3-yl)-2,2-dimethyl-1,3-dioxan-5-yl methanesulfonate (rac-**25**).* Reduction of the ketone of racemic **24** with $NaBH_4$ was accomplished as described for the synthesis of **21** (yield 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.67 (1H, s), 7.63 (1H, dd, J = 8.0, 1.2 Hz), 7.30 (1H, dd, J = 8.0, 0.8 Hz), 6.88 (1H, t, J = 8.0 Hz), 4.84 (1H, s), 4.23 (1H, d, J = 1.2 Hz), 4.1−3.9 (3H), 1.33 (3H), 1.21 (3H), 0.001(9H). Owing to its instability, the crude product was used in the next step without further purification or characterization. To a stirred solution of the alcohol (180 mg, mmol) in CH_2Cl_2 (8 mL) at 0 °C was added DMAP (463 mg, 3.8 mmol). After 10 min, the reaction mixture was cooled to −15 °C and methanesulfonyl chloride (0.15 mL, 1.9 mmol) was added dropwise. After 4 h, the reaction mixture was warmed to rt and stirred for 11 h. The reaction mixture was poured into ice−water and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography (hexanes/ethyl acetate, 2:1) afforded *rac*-**25** (168 mg, 80%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.68 (1H, s), 7.73 (1H, dd, J = 8.0, 1.2 Hz), 7.54 (1H, dd, J = 8.0, 1.2 Hz), 6.93 (1H, t, J = 8.0 Hz), 5.68 (1H, s), 4.64 (1H, d, J = 1.6 Hz), 4.55 (1H, d, J = 1.6 Hz), 4.30, 4.01 (2H, ABq, J = 18.0 Hz), 2.98 (3H, s), 1.49 (3H, s), 1.43 (3H, s), 0.008 (9H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 173.5, 144.0, 137.2, 128.9, 124.6, 122.3, 97.8, 77.1, 73.7, 73.5, 69.3, 61.5, 36.2, 27.4, 17.4, 0.00; HRMS (ESI) calcd for $C_{18}H_{26}INO_7SSiNa$ $[M + Na]^+$ 578.0136, found 578.0138.

*(S/R)-3-((4R/S,5R/S)-5-Azido-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-7-iodoindolin-2-one (rac-**26**).* To a stirred solution of *rac*-**25** (130 mg, 0.24 mmol) in DMF (3 mL) were added 18-crown-6 (124 mg, 0.48 mmol) and NaN_3 (156 mg, 2.4 mmol). The reaction mixture was stirred under argon for 96 h at 100 °C, and progress was monitored by TLC (ethyl acetate/hexanes, 1:2). After completion of the reaction, the mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed with water (3 ×

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20 mL) to remove DMF. The organic layer was dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (hexanes/ethyl acetate, 2:1) of the crude residue afforded *rac*-**26** (69 mg, 67%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.30 (1H, s), 7.55 (1H, dd, J = 8.0, 1.2 Hz), 7.35 (1H, dd, J = 8.0, 1.2 Hz), 6.78 (1H, t, J = 8.0 Hz), 4.09 (1H, m), 3.96 (1H, d, J = 8.0 Hz), 3.77 (1H, dd, J = 12.0, 4.0 Hz), 3.50 (1H, dd, J = 12.0, 5.6 Hz), 1.13 (3H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 177.5, 138.8, 132.6, 124.4, 124.3, 110.2, 100.0, 76.3, 75.6, 75.5, 62.6, 56.3, 27.0, 21.3; HRMS (ESI) calcd for $C_{14}H_{15}IN_4NaO_4$ $[M + Na]^+$ 453.0036, found 453.0020.

*Benzyl ((4R/S,5R/S)-4-((S/R)-3-Hydroxy-7-iodo-2-oxoindolin-3-yl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (rac-**5**).* To a stirred solution of *rac*-**26** (40 mg, 0.09 mmol) in dry THF at 0 °C was added PMe_3 (1.0 M in THF 0.15 mL, 0.13 mmol). The reaction mixture was stirred at 0 °C for 4 h, followed by addition of CbzCl (25 μL), and stirring was continued for 3 h at 0 °C. The reaction mixture was poured into ice-cooled water and extracted with ethyl acetate, and the organic layer was dried over Na_2SO_4 and concentrated. The product was purified by preparative TLC (ethyl acetate/hexanes, 2:3) to afford *rac*-**5** (35 mg, 69%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.07 (1H, br s), 7.51 (1H), 7.29 (5H), 6.98 (1H), 6.73 (1H), 6.15 (1H), 4.95 (2H, ABq, J = 8.0 Hz, $\Delta\nu$ = 16.2 Hz), 4.13 (1H, d, J = 8.0 Hz), 3.54−3.09 (3H), 1.30 (3H, s), 1.22 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 176.9, 154.1, 144.4, 138.5, 133.2, 130.0, 129.8, 128.6, 125.1, 124.3, 79.6, 74.7, 73.1, 58.3, 52.4, 46.8, 26.1, 23.2; HRMS (ESI) calcd for $C_{22}H_{24}IN_2O_6$ $[M + H]^+$ 539.0679, found 539.0674.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, X-ray data, HPLC data, and CD data for compound **3**. 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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