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Practical Synthesis of (2′*R*)-2′-Deoxy-2′-*C*-methyluridine by Highly Diastereoselective Homogeneous Hydrogenation

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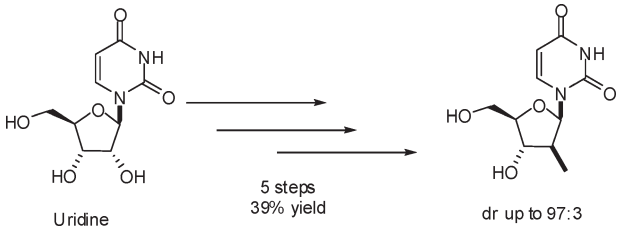

Diastereoselective hydrogenation of 2′-deoxy-2′-*exo*-methyleneuridine was carried out under homogeneous conditions using a low loading of a chiral Rh catalyst. This, coupled with improvements in the synthesis of the substrate, allowed the smooth pilot plant preparation of the title compound on >10 kg scale.

Modified nucleosides continue to hold a central position in the chemotherapy of cancer and viral diseases,[1] and in particular, 2′-modified nucleosides play an important role in research aimed at understanding the detailed molecular basis of RNA function.[2]

In connection with a program in the antiviral area, we needed to prepare multikilo amounts of (2′*R*)-2′-deoxy-2′-*C*-methyluridine (**1**) (Figure 1). Although the latter is a known compound,[3] and its derivatives have been widely incorporated into modified nucleic acids,[4] no practical synthesis of this interesting building block has been reported, and even its physicochemical properties are not fully described. Uridine (**2**), in view of its low cost and ready availability, represents an ideal starting point for a practical synthesis of **1**. Although **1** is formally the result of a simple substitution of the 2′-OH group by a methyl group with inversion of configuration, we deemed that replacement of a suitable leaving group at C-2′ with a methyl organometallic species would be thwarted by the well-known ready participation of the uracil C-2 carbonyl,[5] and we therefore settled on the development of a face-selective hydrogenation of the known 2′-exomethylene derivative **3**. Such hydrogenation has been reported to proceed with modest selectivity using heterogeneous Pd catalysts (e.g., β/α = 3:1 with Pd on $CaCO_3$).[3]

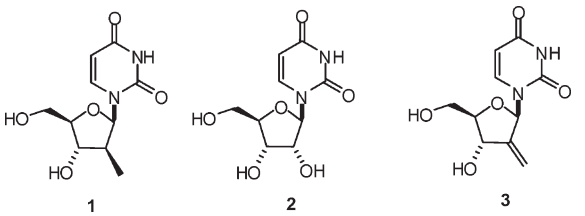

FIGURE 1. Key compounds described in this study.

The selected route is shown in Scheme 1 and is based on the well-established protecting group strategy of Robins.[6] The TIPDS protecting group is ideal for selective protection of the 3′ and 5′ hydroxyl groups in nucleosides and leaves the 2′ hydroxyl largely unprotected. The original conditions, which employ pyridine as solvent, were inconvenient due to the high boiling point of pyridine, its toxicity, and its tendency to inhibit the next (oxidation) step (vide infra), even when present in small amounts. The silylation reaction was therefore carried out in dichloromethane using 4 equiv of imidazole as the base. This protection reaction is not quantitative, and LCMS data indicate the presence of eight impurities, each with intensity >0.2%. While the detailed analysis of the reaction crude is outside the scope of this note, three general observations are important: (1) A large excess of silylating agent must be avoided, because the 2′-position is readily silylated as well. It was found convenient to employ ca. 1.1 equiv. (2) The medium has to be anhydrous. It was found most practical to simply azeotropically dry the solution of uridine and imidazole before addition of the silylating agent. (3) The concentration cannot be increased beyond the one

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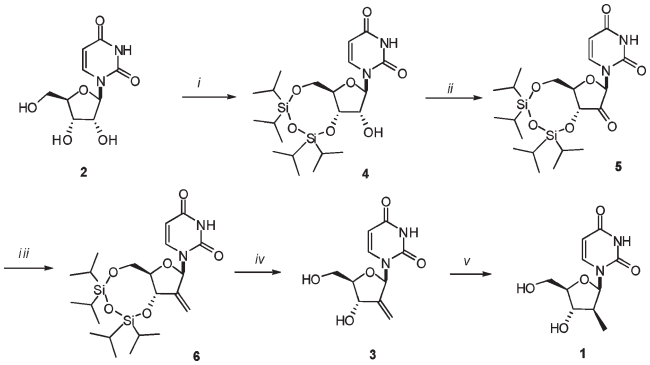
SCHEME 1. Practical Synthesis of 1 from Uridine (2)



Reaction conditions: (i) $TPDSCl_2$, imid, CH_2Cl_2, rt; (ii) TEMPO (0.2 equiv), $PhI(OAc)_2$, CH_2Cl_2, 15 °C; (iii) Ph_3PCH_3Br, *t*-BuOK, THF, 50 °C; (iv) HCl, MeOH, rt; (v) $[Rh(COD)Cl]_2$, MeOH, ligand **10**, 50 bar H_2.

reported here, under batch conditions, without producing substantial amounts of a variety of double condensation products (i.e., compounds containing 1 equiv of TIPDS and 2 equiv of uridine), and the reaction temperature should be kept at or below 20 °C. With these modifications, the reaction gave up to 88% yield (by in situ HPLC assay), a considerable improvement over the 65−70% obtained with the original method. The organic layer was simply washed with water and used for the next step. A sample was chromatographed to yield pure **4**, which was a foam and retained much solvent: an analytical standard of high purity was therefore difficult to produce. The assay yield of the organic solution, under these imperfect conditions, was consistently 85−88.5% on a scale from 100 g up to10 kg.

Although the oxidation of **4** to **5** is known, the oxidizing agents used are either based on extremely toxic Cr(VI)[7] or on hazardous Dess−Martin periodinane.[8] Therefore, we developed a more scalable procedure, which makes use of catalytic TEMPO and stoichiometric oxidant $PhI(OAc)_2$.[9] This reaction was conveniently carried out using the dichloromethane solution from step 1, after a water wash. At the end of the oxidation, simple solvent switch to heptane and cooling produced crystalline **5** in 90−91% yield (76% isolated over two steps) on 100 g scale.[10] The material was >99% pure by HPLC (area %). A few important experimental considerations apply to this reaction as well: (1) The reaction was run at 15 °C with 0.2 equiv of TEMPO. Lower temperatures or lower catalyst loads led to exceedingly long reaction times, whereas higher temperature led to premature catalyst loss. Under the optimized conditions the reaction took 16−24 h. (2) The reaction displayed sigmoidal kinetics. Reasoning that the 2 equiv of AcOH produced in the reaction may catalyze the reaction, AcOH was introduced in stoichiometric amounts from the beginning, dramatically reducing the initiation phase. This result is due to the catalytic effect of acids in promoting the disproportionation of TEMPO to

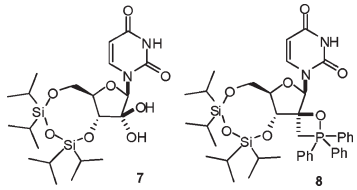


FIGURE 2. Relevant impurities and intermediates.

inactive hydroxylamine and the active oxammonium species, which $PhI(OAc)_2$ is unable to produce.[10] (3) The product displayed a hitherto unreported tendency to form a stable *gem*-diol (**7**, Figure 2), both in solution and in the isolated product if drying was incomplete. This was shown by ^1H and ^{13}C NMR data in the presence of traces of water and by LCMS. In particular, in the ^{13}C NMR spectrum the resonance for the C-2′ carbonyl group at δ 204.7 ($CDCl_3$) decreased upon saturation with D_2O, with the concomitant formation of a new resonance at δ 99.1 (2′-*gem*-diol C).[11] The tendency to form the hydrate was strong even under our reversed-phase HPLC monitoring conditions, and therefore, a special normal-phase method had to be developed (silica gel, EtOH/heptane). However, the distillation prior to crystallization removed the water of hydration, and the product was obtained as a sharp-melting, crystalline white powder.

The Wittig reaction has been reported to occur in 51−92% yield using a base like the dimsyl anion in DMSO or sodium *tert*-butoxide in ether/benzene.[12] On a large scale, a major problem is, of course, the removal of the triphenylphosphine oxide (TPPO) formed in the reaction on a stoichiometric basis. We also found that traces of TPPO inhibited our hydrogenation step (vide infra) and a specification for TPPO content in **3** had to be set at ≤1 mol %. Our preferred conditions for the reaction made use of *tert*-amylate as base (a 25% w/w solution in toluene) and toluene as the sole solvent. We found that the [2 + 2] cycloaddition took place immediately at rt (as shown by disappearance of starting material in the HPLC) to yield an intermediate that was readily detected by HPLC and gave the characteristic NMR pattern of an oxaphosphetane (**8**, ^{13}P: δ −66.6). This required prolonged warming to yield **6** (5 h at 35 °C). This phenomenon is unusual but precedented in related systems described by Robins.[12b] The yield in solution, determined by HPLC assay, was 85−90%. Removal of TPPO entailed a solvent switch to heptane, from which the bulk of TPPO crystallizes, and filtration of the supernatant through a silica gel pad. The ensuing heptane solution contained **3** in 79−85% yield on a 0.1−10 kg scale. The TPPO content at this stage was 5−8 mol %, which we knew could be substantially reduced (to below 1%) in the next step. It was possible to isolate the product, if desired, by crystallization from MeOH/water, but on plant scale it was found much more convenient to take this heptane solution directly into the deprotection step. Desilylation with fluoride presented workup problems because of the aqueous solubility of **3**. It was found most practical to carry out the deprotection using

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(10) The yield for the two steps averaged 74% on a 10 kg scale. The reaction was inhibited by base, including imidazole, and promoted by water and AcOH. In spite of the thorough attempts to identify all variables in this reaction, on scale the reaction displayed a variable reaction time, and up to 48 h and addition of more reagent were employed in one case.
(11) Upon saturation of the solvent with D_2O, **7** constituted 40% of the **7** + **5** mixture in $CDCl_3$, 51% in CD_3CN, and 68% in THF-d_8.
(12) (a) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Clarke-Katzenburg, R. H.; Cheng, Y.-C.; Prusoff, W. H.; Mancini, W. R.; Birnbaum, G. I.; Gabe, E. J.; Giziewicz, J. *J. Med. Chem.* **1991**, *34*, 2607. (b) Samano, V.; Robins, M. J. *Synthesis* **1991**, 283.

TABLE 1. Selected Screen Results (eq 1)

entry	metal used (4 mol %)	ligand (4 mol %)	% de (HPLC)
1	$[Rh(nbd)_2]BF_4$	**10**	98.1
2	$[RuCl_2(p\text{-cymene})]_2$	**11**	96.6
3	[Rh (COD)]BF_4	dipf, **12**	91.2
4	$[Rh(nbd)_2]BF_4$	*ent*-**10**	78.7
5	$[Rh(nbd)_2]BF_4$	dppf	64.0
6	$[Rh(nbd)_2]BF_4$	**13**	84.8

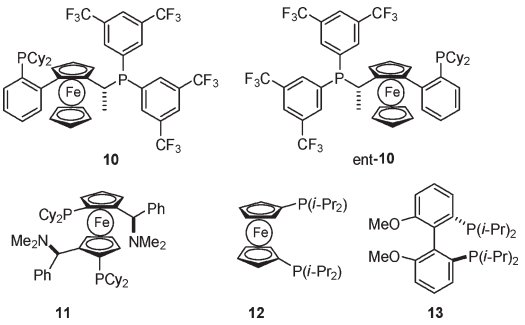
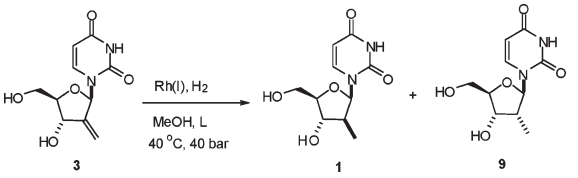


FIGURE 3. Representative ligands screened.

2 M aqueous HCl in MeOH at 35−40 °C for 7 h. Solvent switch in vacuo to acetonitrile and cooling yielded white crystals of **3** in 84−87% isolated yield over two steps. The material was >99.5% pure by HPLC assay. It is important to carry out the crystallization slowly and to determine the content of the cleaved disilanol in the product. A specification of 0.5 mol % had to be set on this impurity because it poisoned the homogeneous catalyst used in the final step.[13]

With a practical four-step, two-isolation synthesis of **3** in hand, we were ready to attempt the unprecedented face-selective hydrogenation of **3** (eq 1).[14] A 96-plate screen was carried out using three metal salts: Rh(I), Ru(II), and Ir(I) in different alcoholic solvents using a battery of 43 phosphorus ligands, both achiral and chiral. The s/c ratio was set at 25 with *T* at 40 °C and the hydrogen pressure at 40 bar. Whereas Ir(I) catalysts were essentially inert under these conditions, excellent turnover was obtained with several Rh(I) and Ru(II) salts (Table 1 and Figure 3).



(1)

The most diastereoselective achiral ligand was dipf (**12**), in conjunction with Rh(I) sources. However, chiral ligand **10** gave the best de in this preliminary screen, and this was a "matched" effect, as evidenced by the lower de obtained for *ent*-**10** (Table 1, entry 4).[15] Experiments 1−3 were repeated as individual runs at a more acceptable s/c ratio of 100, and the Ru(II) catalysts proved more sluggish than the Rh(I). For all these reasons, it was decided to optimize and scale the reaction in entry 1.

(13) ^{1}H NMR is quite sufficient to determine the level of silanol-related contaminants, given the high intensity of the isopropyl peaks.

(14) In preliminary tests, hydrogenation of **6** was sluggish and less diastereoselective.

(15) A full description of the screening results can be found in the Supporting Information.

The optimized hydrogenation was carried out with an s/c ratio of 800 in degassed MeOH at 40 bar and 40 °C over 12−16 h. On a 6−7 kg scale, upon increasing the concentration to 25% w/v, the de dropped slightly from 97 to 98% in the lab to 93−95% in a 50 L stainless steel autoclave. After removal of the catalyst by pad filtration, isolation of the final product could be carried out, with some losses, by recrystallization from THF−acetone (71%) with 96.4% purity and 94.02% de. In conclusion, we have described the first practical diastereoselective and chromatography-free synthesis of **1**, and we have scaled the protocol to produce tens of kilograms of this important intermediate. Our protocol should facilitate the application of this modified uridine analogue to biological studies and drug design.

Experimental Section

1-((6a*R*,8*R*,9a*R*)-2,2,4,4-Tetraisopropyl-9-oxotetrahydro-6*H*-furo-[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1*H*,3*H*)-dione (5). In a 2 L four-necked flask equipped with temperature probe, addition funnel, overhead stirrer, and distillation head was charged uridine (100.1 g, 0.410 mol), followed by imidazole (111.4 g, 1.110 mol) and anhydrous dichloromethane (1.0 L); the solution was stirred and distilled at atmospheric pressure to a volume of 750 mL (KF water analysis indicated <0.05%). TIPDS dichloride (141.9 g, 0.450 mol) was added dropwise as a solution in CH_2Cl_2 (200 mL) over 40 min while being cooled to 10−15 °C (internal temperature), and then the mixture was stirred at this temperature for 3 h. Water was added (1 L), and the two-phase mixture was separated. The organic layer was diluted to 1.4 L, assayed by HPLC (content: 169 g of **4**), and used directly for the oxidation reaction as follows: in a 2 L four-necked flask equipped with temperature probe, addition funnel, overhead stirrer, and nitrogen inlet was introduced the solution of **4**, which was then cooled to 15 °C and then treated with bis(acetoxy)iodobenzene (145 g, 0.451 mol), acetic acid (20.8 g, 0.347 mol), and with medium stirring, a solution of TEMPO (10.8 g, 0.069 mol, 0.2 equiv) in DCM (40 mL) over 10 min. The mixture was stirred at 13−18 °C until the starting material was consumed, typically 18−24 h. After the reaction was complete, aqueous sodium thiosulfate was added (1 N, 850 mL) with stirring for 10 min. The phases were separated, and the organic phase was washed with water (1 L). The organic phase was concentrated to 550 mL, and then heptane (700 mL) was added, and the mixture was distilled at reduced pressure (internal T < 50 °C) until no more dichloromethane was left; the residue was cooled in ice and stirred for 3 h. The copious precipitate was filtered and washed with cold heptane (2 × 200 mL). The cake was dried in vacuo at 45 °C for 14 h to yield **5** as a white powder (152 g, 76.5% from uridine). Mp: 187.0 °C dec. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (br s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 5.76 (dd, J = 8.0 Hz, J' = 1.5 Hz, 1H), 5.05 (d, J = 9.2 Hz, 1H), 5.00 (s, 1H), 4.20−4.10 (m, 2H), 3.94 (m, 1H), 1.20−0.90 (m, 28H). HRMS: calcd for $C_{21}H_{36}N_2O_7Si_2$ $[M + H]^+$ 485.2134, found 485.2131. HRMS for **7**: calcd for $C_{21}H_{38}N_2O_8Si_2$ $[M + H]^+$ 503.2239, found 503.2242.

Intermediate **4** can be isolated by silica gel chromatography (methanol−dichloromethane 2:98) as a foam and characterized. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.04 (br s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 5.74, (s, 1H), 5.70 (d, J = 8.1 Hz, 1H), 4.30−4.17 (m, 4H), 3.99 (dd, J = 13.1 Hz, J' = 2.1 Hz, 1H), 3.68 (br s, 1H), 1.20−0.95 (m, 28H). HRMS: calcd for $C_{21}H_{39}N_2O_7Si_2$ $[M + H]^+$ 487.2296, found 487.2322.

1-((2*R*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-3-methylenetetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (3). In a 3 L three-necked round-bottom flask equipped with temperature probe, overhead stirrer, and addition funnel was suspended methyltriphenylphosphonium bromide (147 g, 0.412 mol) in anhydrous toluene (1.0 L). To this suspension was added

potassium *tert*-amylate (25% w/w in toluene, 209 g, 0.412 mol) over 20 min at rt (slight exotherm). A solution of **5** (100 g, 0.206 mol) in anhydrous THF (250 mL) was added over 25 min at rt (slight exotherm). The mixture was then heated to 35 °C for 5 h and cooled in ice, and acetic acid (8.7, 0.144 mol) was added in one lot as a quench. Water (620 mL) was added and the brown organic layer separated. The water wash was repeated, and then the organic layer was distilled under reduced pressure to 300 mL ($T < 35-40$ °C). Upon cooling, the solution was seeded with triphenylphosphine oxide, and the mixture was stirred for 2−3 h with ice cooling until a suspension formed. Then heptane (800 mL) was added dropwise over 2 h, and the suspension was stirred for a further 3 h under ice cooling. Filtration was followed by washing the TPPO with heptane (100 mL). The filtrate was treated with ethyl acetate (400 mL), and the solution was filtered through a silica pad (200 g), washing the pad with a mixture of ethyl acetate (800 mL) and heptane (1.7 L). The filtrate was concentrated in vacuo to 300 mL ($T < 45$ °C). Methanol (350 mL) was added, and the solution was again evaporated to 300 mL. After the procedure was repeated once more, the methanol solution was assayed by HPLC and found to contain 84.7 g (85%) of **6**. The product could be isolated by crystallization from MeOH/water (2/1 v/v). Mp: 130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (br s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 6.52 (d, $J = 1.5$ Hz, 1H), 5.71 (dd, $J = 8.0$ Hz, $J' = 1.8$ Hz, 1H), 5.55 (d, $J = 1.5$ Hz, 1H), 5.46 (d, $J = 1.5$ Hz, 1H), 4.82 (m, 1H), 4.15 (dd, $J = 13.2$ Hz, $J' = 2.2$ Hz, 1H), 4.05 (dd, $J = 13.2$, $J' = 2.7$ Hz, 1H), 3.70 (m, 1H), 1.25−0.90 (m, 28H). HRMS: calcd for $C_{22}H_{38}N_2O_6Si_2$ $[M + H]^+$ 483.2341, found 483.2346.

However, it was advantageous to carry out the deprotection directly on the crude product: the MeOH solution obtained above, in a three-necked flask equipped with overhead stirrer, temperature probe, and condenser, was treated with aqueous HCl (2M, 98.2 g, 1.09 equiv) and heated to 40 °C for 7 h. After being cooled to 10 °C, the solution was evaporated at reduced pressure ($T < 15$ °C) to a volume of 300 mL, acetonitrile (400 mL) was added, and the solution was concentrated to 270 mL in vacuo ($T < 15$ °C) and then cooled and stirred for 3 h at 0 °C, while the product slowly crystallized. The precipitate was filtered off and then slurried in methyl *tert*-butyl ether (300 mL) at 40 °C for 2 h (to remove residual disilanol). The mixture was allowed to cool and then filtered. The solid was dried in vacuo at 45 °C over 14 h. Yield: 42.2 g (85%). Mp: 173.5 °C dec. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 11.38 (exch s, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 1.8$ Hz, 1H), 5.68−5.61 (m, 2H), 5.39 (d, $J = 2.2$ Hz, 1H), 5.26 (d, $J = 2.2$ Hz, 1 H), 4.96 (exch s, 1H), 4.47 (exch s, 1H), 3.67−3.57 (m, 3H). ^{13}C NMR (DMSO-d_6) δ 161.7, 149.4, 148.5, 140.2, 110.6, 101.0, 83.4, 82.2, 68.5, 59.2. HRMS: calcd for $C_{10}H_{12}N_2O_5$ $[M + K]^+$ 279.0378, found 279.0374.

1-((2*R*,3*S*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-3-methyl tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (1). A degassed solution of **3** (6.00 g, 25.0 mmol) in MeOH (16 mL) was placed in a 50 mL autoclave, which was purged with argon. $[Rh(nbd)_2]BF_4$ (11.7 mg, 0.0312 mmol) and ligand **10** (32.3 mg, 0.0343 mmol) were added as a solution in dry, degassed MeOH (16 mL) from a Schlenk tube. The autoclave was purged again with three cycles of argon and then three times with 10 bar of hydrogen. The mixture was stirred and heated at 40 °C under 40 bar hydrogen for 16−18 h. The reaction was allowed to cool down and then filtered through a small pad of silica. The filtrate was evaporated to dryness and recrystallized from hot acetone/THF (ca. 20:1, total 20−25 mL), then dried at 40 °C overnight. Yield: 4.3 g (71%). Mp: 138−141 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.30 (exch. s, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 6.08 (d, $J = 7.7$ Hz, 1H), 5.60 (d, $J = 8.1$ Hz, 1H), 5.37 (exch br d, 1H), 5.14 (exch br t, 1 H), 3.73−3.59 (m, 4H), 2.40 (m, 1H), 0.81 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 161.7, 149.2, 139.7, 99.6, 84.0, 83.4, 70.9, 57.5, 43.2, 9.8. HRMS: calcd for $C_{10}H_{15}N_2O_5$ $[M + H]^+$ 243.0975, found 243.0973.

The material still contains 2−3 mol % of the epimer **9**, which can be separated by silica gel chromatography (ethyl acetate/heptane) and characterized: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.32 (exch. s, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 5.81 (d, $J = 9.1$ Hz, 1H), 5.68 (d, $J = 8.1$ Hz, 1H), 5.22 (exch br d, 1H), 5.05 (exch br t, 1 H), 4.05 (m, 1H), 3.85 (m, 1H), 3.56 (m, 2H), 2.22 (m, 1H), 0.92 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 161.6, 149.5, 139.1, 100.7, 86.9, 85.7, 71.2, 60.4, 40.8, 7.2. HRMS: calcd for $C_{10}H_{15}N_2O_5$ $[M + H]^+$ 243.0975, found 243.0969.

Supporting Information Available: Full description of the 96-plate catalyst screen, compound characterization data, and copies of spectra supporting the structural assignments. This material is available free of charge via the Internet at http://pubs.acs.org.