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TETRAHEDRON

Synthesis of pyrrolobenzodiazepines via the PIFA oxidation of amines. Synthesis of 8-Deoxy DC-81

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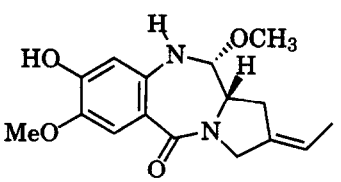
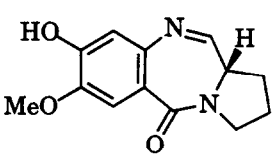
Summary: PIFA can be used to introduce the imine moiety into a precursor to the pyrrolobenzodiazepines in 62% yield. This oxidation completes an efficient four-step synthesis of 8-deoxy DC-81.

The pyrrolo[2,1-c][1,4]benzodiazepine class of natural products contains promising leads for the treatment of disease. Several syntheses and approaches have been reported and are collated in an excellent review by Thurston and Bose.[1] Two members of this class are depicted below. The most valuable drug discovered so far has been tomaymycin (**1**). Both compounds shown below bind DNA in a sequence-selective manner. Currently, these compounds are of interest as potential gene targeted drugs.[2]



Tomaymycin (**1**)



DC-81 (**2**)

In the course of developing novel and direct synthetic pathways to the pyrrolobenzodiazepine skeleton, we reported the synthesis of amine **4** in four steps from 5-methoxysalicylic acid and prolinol (**3**).[3] The key step was the formation of the diazepine subunit by way of an aryl triflate amination. As described in our earlier publication,[3] the resulting amine **4** was subjected to oxidation by a number of reagents, including CAN, DDQ, silver (II) oxide and N-chlorosuccinimide (to form a chloro amine which could undergo dehydrohalogenation).[4] Although we were unable to oxidize the amine to the corresponding imine or alpha-methoxy amine, we did develop an alternative route to the pyrrolobenzodiazepine system using 5-methoxysalicylic acid and the methyl ester of proline. This route has the drawback that the basic reaction conditions required for the cyclization of the ester triflate resulted in some racemization of the product, a bis-lactam.

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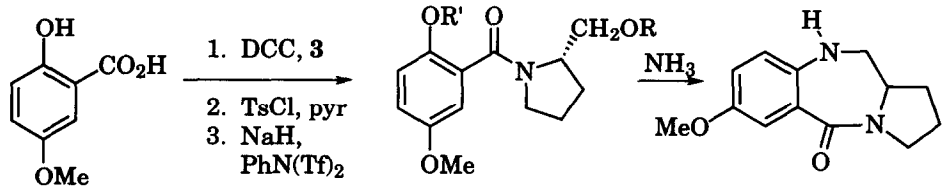
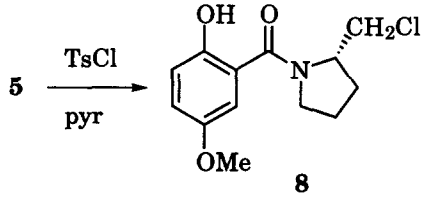


5: R=R'=H
6: R=Ts, R'=H
7: R=Ts, R'=Tf

4

Recently, we decided to apply the elegant chemistry developed by Kita to the oxidation of amine **4**. Kita has discovered a wealth of new chemistry related to bis(trifluoroacetoxy)iodobenzene (PIFA). Of immediate interest to this project, he has shown that phenols can be efficiently oxidized to quinone hemiketals in excellent yields.[5]

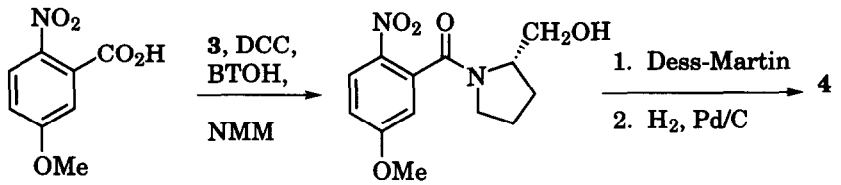
In order to explore the application of this chemistry to the functionalization of benzodiazepines, we needed to generate additional quantities of amine **4**. Despite considerable experimentation, *we have found that the previously-described*[3] *three-step sequence from amide* **5** *to* **4** *does not work*. Repeated attempts to generate the tosylate phenol **6** by treatment with para-toluenesulfonyl chloride and base led to mixtures from which the chloride **8** (49% yield) and a mixture of **6** and the isomeric aryl tosylate (46% yield) were isolated. The authors of this paper did manage to synthesize triflate **7** by first forming the triflate alcohol using n-BuLi followed by N-phenyl triflimide in THF at 0 °C and then making the tosylate using para-toluenesulfonyl chloride and pyridine at 0 °C. Unfortunately, **7** could not be converted to **4** using the reaction conditions described in the earlier paper.[3,6] The authors of this paper have found that treatment of compound **7** with sodium azide in acetonitrile followed by azide reduction (Ph_3P followed by H_2O) provided an amine triflate which failed to cyclize to **4** upon treatment with base.[7]



8

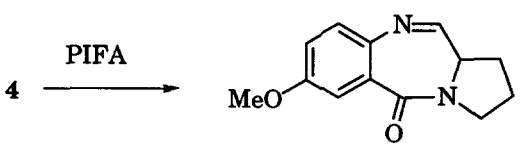
We ultimately identified a workable synthesis of **4** from 5-methoxy-2-nitro benzoic acid (**9**) by adapting chemistry originally reported by Thurston and coworkers.[8] This route involved formation of amide **10** in 94% yield with **3**, DCC, N-hydroxybenzotriazole (BTOH) and N-methylmorpholine (NMM). Dess-Martin oxidation of the resulting alcohol in 83% yield and reductive cyclization afforded **4** in 77% yield.[9] Amine **4** could be prepared

in gram quantities by this route. Its NMR spectrum differed significantly from the NMR reported in the thesis. Moreover, R_f values on thin layer chromatography were dramatically different, with the authentic amine synthesized by standard reactions shown below being much more polar.



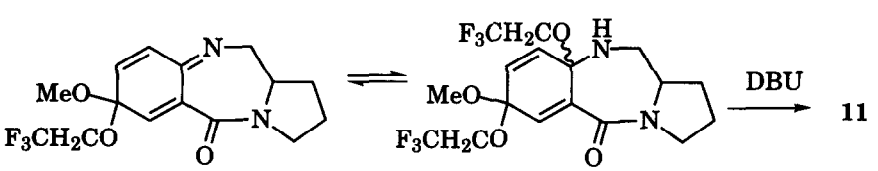
9 10

With gram quantities of amine **4** in hand, the Kita oxidation was evaluated using PIFA. The desired imine **11** was produced in 62% isolated yield when the reaction was conducted in 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol with potassium carbonate followed by basic workup. No product was obtained in acetonitrile or nitromethane. The workup conditions proved to be critical for best yields. Non-aqueous basic workup provided the highest yields.



11

Compounds produced when the workup was omitted were tentatively assigned structures **12** and **13** based on its NMR spectrum. A related imine ketal produced by iodobenzene diacetate oxidation was recently reported by White and coworkers.[10] The compounds were unstable and could rapidly be converted in quantitative yield into compound **11** using DBU.



12 13

The direct preparation of 8-deoxy DC-81 (**11**) has been achieved in four steps from commercially available starting materials. This pathway represents a direct and reproducible avenue for the synthesis of this class of compounds. Since structure-activity studies have

shown that methyl and hydroxyl substituents at C-8 can be interchanged with little effect on biological activity, we anticipate that **11** will have activity comparable to that of DC-81.[11] The PIFA oxidation represents an useful protocol for introducing the imine moiety into the pyrrolobenzodiazepine system.

Acknowledgement. We thank Professor Yasuyuki Kita for helpful discussions. We thank the Goho Life Sciences Foundation for travel support for GK.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

(2*S*)-*N*-(5-Methoxy-2-nitobenzoyl)pyrrolidinemethanol (10). To a suspension of 5-methoxy-2-nitrobenzoic acid (197 mg, 1 mmol) in dry methylene chloride (10 mL) cooled to 0°C were added 4-methylmorpholine (0.22 mL, 2 mmol), DCC (216 mg, 1.05 mmol) and N-hydroxybenzotriazole (135 mg, 1 mmol) followed by (S)-(+)-2-pyrrolidinemethanol (101 mg, 1 mmol). The resulting mixture was stirred for 12 h at rt then filtered, washed with water and brine and dried over magnesium sulfate. The solvent was then removed in vacuo to give a crude residue, which was purified by sgc (EA) to give **10** (263 mg, 94%) as a light-yellow oil. ^{1}H NMR($CDCl_3$) δ 1.69-1.89 (m, 3H), 2.09-2.18 (m, 1H), 3.14-3.18 (m, 2H), 3.76-3.85 (m, 2H), 3.89 (s, 3H), 4.32-4.37 (m, 1H), 4.44 (br s, 1H) 6.83 (d, J = 2.7 Hz, 1H), 6.96 (dd, J = 9.3, 2.7 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 24.4, 28.5, 49.7, 56.4, 61.6, 112.8, 114.9, 127.5, 136.0, 137.5, 164.7. IR (neat) cm^{-1} 3392, 1621, 1588, 1516. HRMS m/z $(M - H_2O)^+$: 262.0947, calcd for $C_{13}H_{14}N_2O_4$: 262.0954.

(11a*S*)-7-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2.1-c][1,4]benzodiazepin-5-one (4).

A solution of **10** (168 mg, 0.6 mmol) in methylene chloride (3 mL) was added to a stirred solution of Dess-Martin reagent (280 mg, 0.66 mmol) in methylene chloride (5 mL). After 30 min the reaction mixture was diluted with ether (10 mL), quenched with 20% aqueous sodium thiosulfate (3 mL) and saturated aqueous sodium bicarbonate (5 mL) and stirred for 10 more min. Aqueous phase was separated, extracted with ether (10 mL), combined organic fractions washed with water and brine and dried over magnesium sulfate. Evaporation of the solvent followed by sgc (H:EA, 1:2) afforded the aldehyde (138 mg, 83%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) for major rotamer δ 1.83-1.97 (m, 2H), 2.03-2.22 (m, 2H), 3.19 - 3.33 (m, 2H), 4.63 (td, J = 3.4, 1.7 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.99 (dd, J = 9.3, 2.7 Hz, 1H), 8.18 (d, J = 9.3 Hz, 1H), 9.74 (d, J = 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.5, 48.6, 56.3, 64.9, 113.2, 115.0, 127.4, 135.3, 137.7, 164.3, 164.6,

199.3. IR (neat) cm^{-1} 1731, 1638, 1588, 1516. HRMS m/z $(M - CHO)^+$: 249.0878, calcd for $C_{12}H_{13}N_2O_4$ 249.0875.

The nitroaldehyde (112 mg, 4 mmol) was dissolved in MeOH (5 mL) and hydrogenated over 10% Pd/C catalyst (10 mg). After 2 h an additional equal portion of the catalyst was added and hydrogenation continued for 3 more h (or until the required volume of hydrogen was consumed). The catalyst was filtered, MeOH removed in vacuo and resulting amine recrystallized from ethanol to give pure **4** (71 mg, 77%) as pale yellow plates (mp 237 °C). (**4**) ^1H NMR ($CDCl_3$) δ 1.64-1.75 (m, 1H), 1.82-2.00 (m, 2H), 2.14-2.25 (m, 1H) 3.26 (dd, J = 12.0, 9.6 Hz, 1H), 3.52 (dd, J = 12.0, 2.5 Hz, 1H), 3.77 (s, 3H), 3.65-3.90 (m, 4 H), 6.56 (d, J = 9.0 Hz, 1H), 6.84 (dd, J = 9.0, 3.0 Hz, 1H), 7.49 (d, J = 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 23.0, 30.5, 48.0, 54.1, 55.8, 57.0, 114.4, 120.3, 120.7, 121.4, 139.8, 152.6, 167.0. IR (neat) cm^{-1} 3320, 1593, 1573. $[\alpha]_D^{24}$ =3.67 (c 1.25, $CHCl_3$). Anal calcd for $C_{13}H_{16}N_2O_2$, C, 67.22; H, 6.94; N, 12.06, found : C, 67.23; H, 7.21; N, 11.97.

(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2.1-c][1,4]benzodiazepin-5-one (11). To a stirred solution of amine **4** (50 mg, 0.22 mmol) in 2,2,2-trifluoroethanol (5 mL), containing potassium carbonate (104 mg, 0.87 mmol) under Ar was added a solution of (bis[trifluoroacetoxy]iodo)benzene (93 mg, 0.22 mmol) in CF_3CH_2OH (3 mL) dropwise over 30 min. The resulting mixture was stirred for an additional 2 h, then solvent removed in vacuo, the residue was dissolved in 5 mL THF and stirred for 20 min. Removal of solvent followed by sgc (EA) gave the imine **11** (31 mg, 62%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.02-2.09 (m, 2H), 2.27-2.34 (m, 2H), 3.51-3.60 (m, 1H), 3.69-3.75 (m, 1H), 3.78-3.84 (m, 1H), 3.87 (s, 3H), 7.07 (dd, J = 9.0, 3.0 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 3.0 Hz, 1H), 7.67 (d, J = 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 24.2, 29.7, 46.8, 53.6, 55.7, 112.6, 119.5, 128.8, 129.0, 139.7, 157.9, 162.5, 164.7. IR (neat) cm^{-1} 1627, 1604, 1450, 1436. HRMS m/z $(M-H)^+$: 229.0979, calcd for $C_{13}H_{13}N_2O_2$: 229.0977. $[\alpha]_D^{24}$ =8.21 (c 1.25, $CHCl_3$).

13: (mixture of isomers) ^1H NMR ($CDCl_3$) δ 1.60-1.89 (m, 3H), 2.21-2.37 (m, 1H), 3.18-3.25 (m, 1H), 3.41 and 3.46 (s, 3H), 3.47-4.33 (m, 8H), 4.93 and 5.05 (br d, 1H), 4.96 and 5.37 (d, J = 2 Hz, 1 H), 5.83-5.89 (m, 1H), 5.95-5.99 (m, 1H). MS m/z (CI) 431 (M+1), 331.

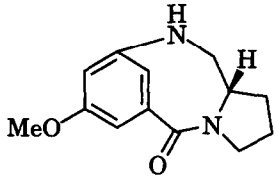
(2S)-N-(5-Methoxy-2-hydroxybenzoyl)-2-(chloromethyl)pyrrolidine (8).

To a stirred solution of dihydroxyamide **5** (251 mg, 1.00 mmol) in dry methylene chloride (5 mL) under Ar at 0 °C was added pyridine (1 mL) followed by para-toluenesulfonyl chloride (200 mg, 1.05 mmol). The resulting mixture was allowed to warm to rt overnight and then was diluted with methylene chloride (20 mL). The organic layer was washed with 1M aqueous sulfuric acid (2 x 10 mL), water, and brine and dried over magnesium sulfate. Evaporation of the solvent followed by sgc (H:EA 4:1) provided compound **8** (131 mg, 49%) as a clear oil. Further elution with change of the solvent system

to H:EA 1:1 gave a mixture of tosylates (186 mg, 46%). ^{1}H NMR ($CDCl_3$) δ 1.70-1.80 (m, 1 H), 2.01-2.22 (m, 3H), 3.65-3.86 (m, 3H), 3.76 (s, 3H), 3.94-3.99 (m, 1H), 4.55-4.63 (m, 1H), 6.89-6.97 (m, 3H) 10.07 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.6, 28.1, 45.8, 52.3, 56.1, 58.3, 113.5, 117.4, 118.5, 119.4, 151.4, 153.8, 170.7. IR (neat) cm^{-1} 3154, 1581, 1449. MS m/z (EI) 269 (M^+, ^{35}Cl, 55%) 271 (M^+, ^{37}Cl, 18%). HRMS m/z (M^+, ^{35}Cl): 269.08145, calcd for $C_{13}H_{16}NO_3{}^{35}Cl$: 269.08187.

References

1. Thurston, D. E.; Bose, D. S. *Chem. Rev.*, **1994**, *94*, 433.
2. Thurston, D. E. "Molecular Aspects of Anticancer Drug-DNA Interactions", Neidle, S.; Waring, M. J. Eds. The Macmillan Press Ltd, 1993, vol. 1, 54-88.
3. Kraus, G. A.; Liu, P. *Tetrahedron Lett*, **1995**, *36*, 7595.
4. Kamal, A.; Howard, P. W.; Reddy, B. S. N.; Reddy, B. S. P.; Thurston, D. E. *Tetrahedron*, **1997**, *53*, 3223. Kamal, A.; Rao, N. V. *J. Chem. Soc. Chem. Comm*, **1996**, 385.
5. Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem*, **1987**, *52*, 3927. Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem*, **1991**, *56*, 435.
6. Liu, P. Masters thesis, Iowa State University, **1995**.
7. The attempted cyclization of the amine triflate provided a product tentatively assigned the unusual structure **14** based on the structural data listed below.



14

14: ^{1}H NMR ($CDCl_3$) δ 1.40-1.47 (m, 1H), 1.83-2.04 (m, 3H) 3.41-3.58 (m, 2 H), 3.78-3.88 (m, 1H), 3.79 (s, 3 H), 4.01-4.06 (m, 2H), 6.93-6.94 (m, 2H), 7.04-7.05 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 31.6, 51.0, 56.1, 58.1, 63.0, 112.5, 112.8, 118.2, 119.0, 151.1, 155.6, 169.6. MS m/z (EI) 232, 217. HRMS m/z (M^+): 232.12123. calcd for $C_{13}H_{16}N_2O_2$: 232.12118.

8. Thurston, D. E.; Langley, D. R. *J. Org. Chem*, **1986**, *51*, 705.
9. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*, **1991**, *113*, 7277. Dess, D. B.; Martin, J. C. *J. Org. Chem*, **1983**, *48*, 4155. Ireland, R. E.; Liu, L. *J. Org. Chem*, **1993**, *58*, 2899.
10. White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc*, **1994**, *116*, 1831.
11. Thurston, D. E.; Hurley, L. H. *Drugs of the Future*, **1983**, *8*, 957.