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A Direct Route to the Pyrrolo[2,1-c][1,4]benzodiazepine Ring System Using Aryl Triflates

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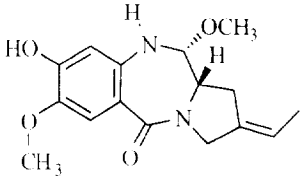
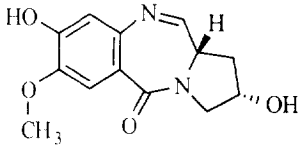
Abstract: The pyrrolo[2,1-c][1,4]benzodiazepine and dibenzo[b,e][1,4]diazepine skeletons were rapidly generated from salicylic acids. The key step in these syntheses was the substitution of an aryl triflate.

The pyrrolo[2,1-c][1,4]benzodiazepines are a novel and growing class of heterocyclic antibiotics.[1] Some members of this class such as tomaymycin (**1**) and neothramycin A (**3**) exhibit potent antitumor activity. The antitumor activity appears to be related to the ability of these compounds to selectively bind to certain DNA sequences.[2] Recently, the synthetic approaches to this class of compounds have been reviewed by Thurston and Bose.[3] All of the synthetic pathways to the pyrrolo[2,1-c][1,4]benzodiazepines which have been reported to date begin with either substituted anthranilic acids or nitro phenols. We recently reported a direct preparation of benzodiazepines using a combination of quinone photochemistry and aryl triflate chemistry.[4]



Tomaymycin (**1**)



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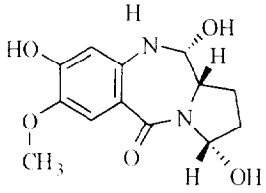
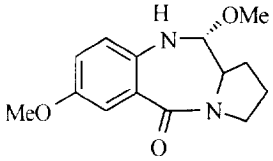


Neothramycin A (**3**)



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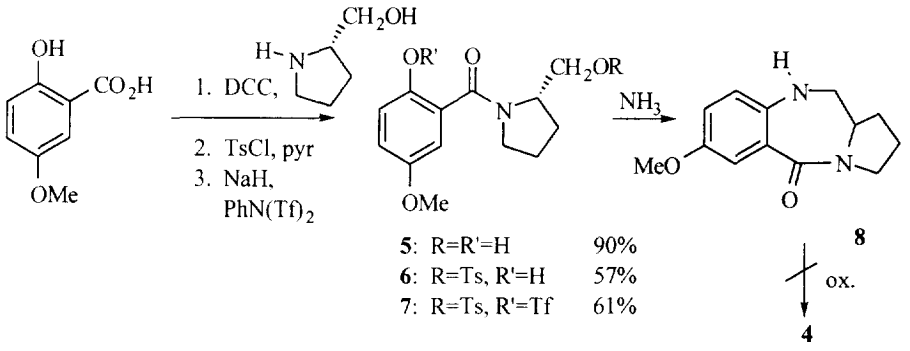
We report herein two direct syntheses of the pyrrolo[2,1-c][1,4]benzodiazepine skeleton featuring both intermolecular and intramolecular reactions of aryl triflates.

Our first synthetic approach began with commercially available 5-methoxy salicylic acid. The amide **5** was formed in 90% isolated yield using dicyclohexyl carbodiimide (DCC), N-hydroxybenzotriazole and (S) - prolinol in THF at 0 °C.[5] Selective reaction of the primary alcohol with tosyl chloride in the presence of excess pyridine in methylene chloride afforded tosylate **6** in 57% yield. The phenol was then converted into the aryl triflate **7** in 61% yield using N-phenyl triflimide and sodium hydride in THF at 0 °C. Reaction of the triflate in aqueous ammonia at 110 °C for 48 hours provided the tricyclic skeleton **8** in 51% isolated yield. We next attempted to oxidize **8** in methanol to generate the carbinolamine moiety.[6] Unfortunately, reaction of amine **8** with various oxidizing agents (ceric ammonium nitrate, DDQ, silver oxide) did not produce the desired compound **4**.

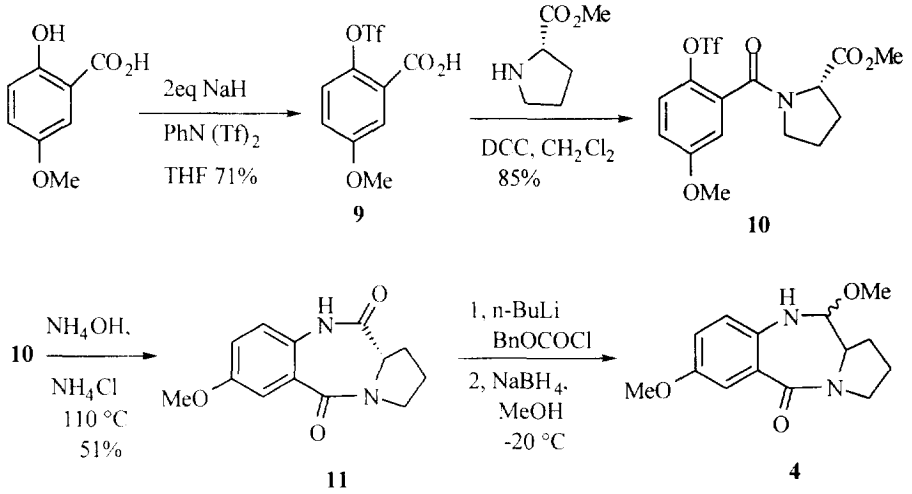


Although the oxidation did not provide our synthetic objective, the cyclization of the aryl triflate proceeded well. We therefore decided to attempt the intramolecular cyclization of an amide triflate. After a number of unsuccessful attempts to generate the precursor **10**, we found that the dianion of 5-methoxy salicylic acid reacted slowly but cleanly in THF with N-phenyl triflimide to generate acid **9** in 71% yield. Reaction of acid **9** with the methyl ester of (S) - proline[7] in the presence of an excess of DCC in methylene chloride at 0 °C furnished amide **10** in 85% isolated yield.

We initially attempted to prepare the primary carboxamide from the ester; however, a much more efficient route soon became clear. Reaction of ester triflate **10** with ammonium hydroxide and ammonium chloride at 110 °C afforded the pyrrolo[2,1-c][1,4]benzodiazepine skeleton in one step in 51% yield. Examination of minor products from this reaction suggests that intermolecular reaction of ammonia with the aryl triflate may precede cyclization to produce lactam **11**. The extent of racemization was studied using a polarimeter. The rotation of lactam **11** was -11.44° (compared to -26.53° for **10**), suggesting that some racemization may have occurred.

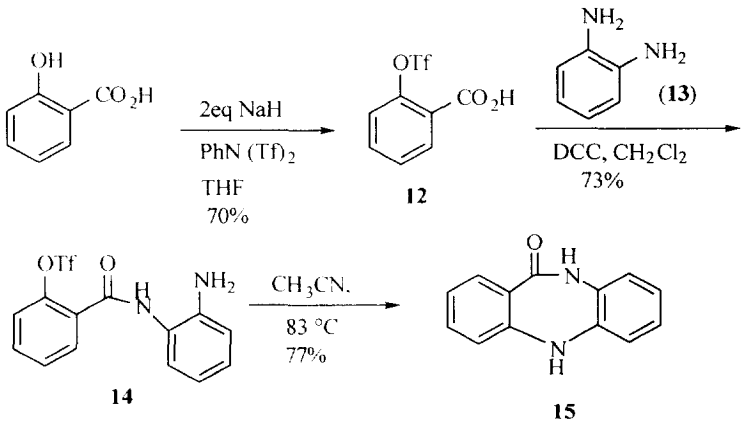
The transformation of the N-aryl lactam into the carbinol amine moiety was accomplished by the method of Thurston and Kaumaga.[8] Compound **11** was reacted with n-

butyllithium followed by benzyl chloroformate to produce an imide. This imide was then reacted with sodium borohydride in methanol at -20 °C to afford compound **4** in 47% yield.



Compound **11** can be synthesized from commercially available 5-methoxy salicylic acid in only three steps. Our route should be very flexible with regard to substituents at C-6 and C-8 (pyrrolo[2,1-c][1,4]benzodiazepine numbering). We are presently evaluating a more effective procedure for the conversion of amide **11** into compound **4**.

In the course of working out the conditions for the synthesis of **11**, we prepared triflate **12** from salicylic acid. Condensation of triflate **12** with 1,2-diaminobenzene and DCC afforded a 73% yield of amide **14**. Cyclization of amide **14** into lactam **15** was smoothly effected by boiling amide **14** in anhydrous acetonitrile for 24 hours. Compound **15** was produced in 77% yield. The preparation of compound **15** under mild reaction conditions is likely attributable to the fact that this reaction involved an intramolecular triflate displacement. Dibenzepin, a related dibenzo[b,e][1,4]diazepine, exhibits antidepressant activity.[9]



Because of its directness and the mild reaction conditions required, our route could make available dibenzo[b,e][1,4]diazepines with novel substitution patterns.

Inter- and intramolecular reactions of aryl triflates provide direct and flexible pathways to benzodiazepines and dibenzazepines. Substitution reactions of aryl triflates proceed much more efficiently than those of the corresponding halides.[10] The synthesis of more highly functionalized analogs of **4** and **15** is in progress. The biological evaluation of compounds **4**, **8** and **15** will be reported in due course.

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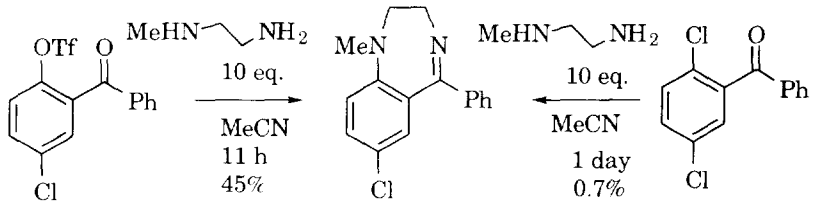
References

1. Remers, W. In *Antitumor Antibiotics*; Wiley and Sons: New York, 1988; pp 28-92. Hurley, L. H.; Needham-VanDevanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 230.
2. Dervan, P. B. *Science* **1986**, 232, 464.
3. Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, 94, 433-465.
4. Kraus, G. A.; Maeda, H. *Tetrahedron Lett.* **1994**, 35, 9189.
5. (S) - prolinol: Enders, D.; Eichenauer, H. *Chemische. Berichte* **1979**, *112*, 2933. For the use of DCC and N-hydroxybenzotriazole for amide formation, see Windridge, G. C.; Jorgensen, E. C. , *J. Am. Chem. Soc.* **1971**, **93**, 6318.
6. Several methods are available for the conversion of cyclic secondary amines into imines or the related carbinolamines. A compilation of these methods can be found in Houben-Weil Methoden der Org. Chemie, volume E14b, (Georg Thieme Verlag, New York, 1990), p. 226.
7. Matoba, K.; Yonamoto, H.; Fukui, M.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 3918-3925.
8. Thurston, D. E.; Kaumaga, T. P. *Tetrahedron Lett.* **1984**, *25*, 2649-2652.
9. Egli, A.; Michaelis, W. R. *Analytical Profiles of Drug Substances*, volume 9, Florey, K.., ed. (Academic Press, New York, 1980), pp181-206.
10. The following example[4] illustrates the advantage of triflates over halides. In the experiment with dichlorobenzophenone, the remainder of the material after one day was the starting reagent.



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