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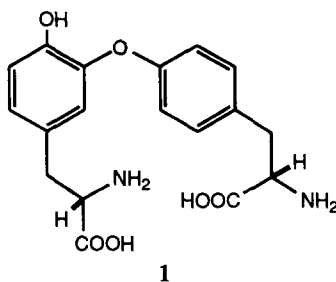
NEW METHOD FOR THE PREPARATION OF *o*-ARYLOXYPHENOLS: PUMMERER-TYPE REARRANGEMENT OF AN *o*-HYDROXYARYL SULFOXIDE

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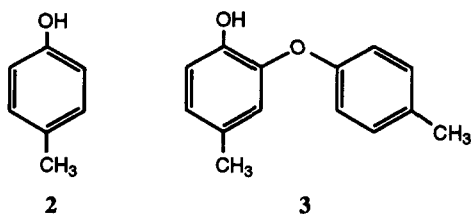
Summary: A facile two-step preparation of *o*-aryloxyphenols is described in which the key step is the intramolecular trapping of an α -keto sulfonium salt prepared by Pummerer rearrangement of a symmetrical *o*-hydroxyaryl sulfoxide to give an orthoquinone mono(monothioacetal).

The isodityrosine class of antibiotics⁴ is a large and diverse group of naturally occurring compounds which all share as a structural feature a unit of isodityrosine 1, a dimeric amino acid formed by oxidation of tyrosine.⁵ Its members show strong biological properties, including antifungal, angiotensin converting enzyme inhibition,



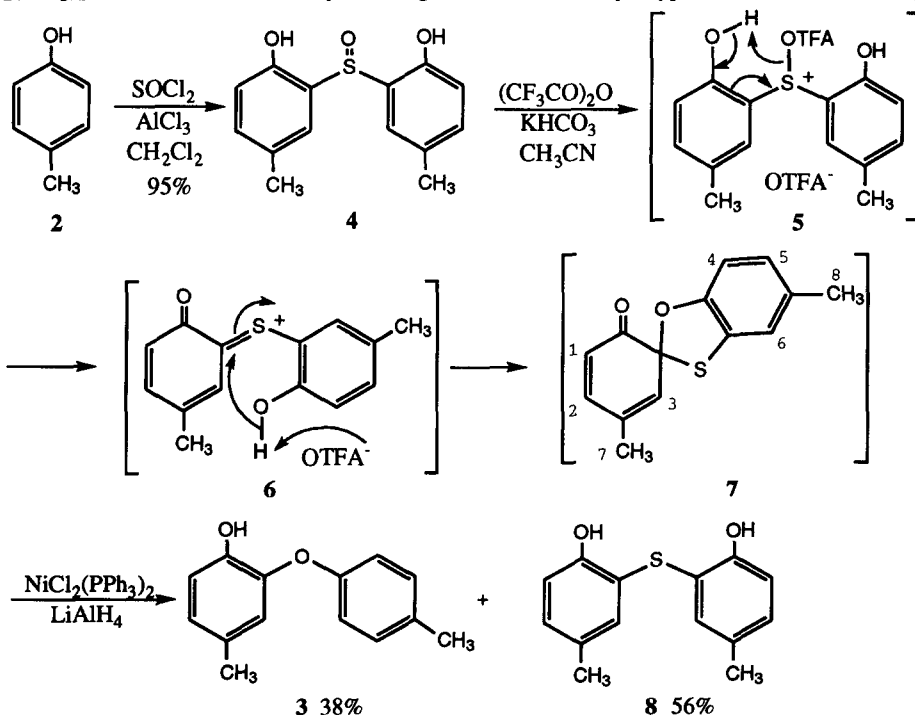
antitumor activity and others.⁴ For some time, we⁶ and others⁴ have been interested in developing a new general approach for the synthesis of isodityrosine and the natural products containing it as a structural unit. We now report a new method for the preparation of *o*-aryloxyphenols by the internal trapping of an α -ketosulfonium salt prepared by an interesting Pummerer-type rearrangement of an *o*-hydroxyaryl sulfoxide.

Of the several methods developed to prepare *o*-aryloxyphenols, three - Ullmann coupling,^{4ak} oxidative coupling of polyhalophenols,^{4bcdi} and substitution of aryl halides^{4efj} - are used most often. Several of these methods are quite good but others suffer from lower yields or the necessity to do significant chemistry after the key coupling reaction. We thought that one might be able to prepare an orthoquinone mono(monothioacetal) from a symmetrical *o*-hydroxyaryl sulfoxide and then reductively remove the sulfur atom to produce the desired *o*-aryloxyphenol. We

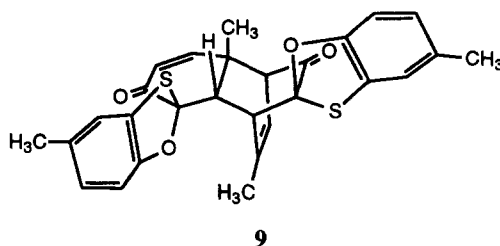


decided to test this principle with *p*-cresol **2** to prepare the *o*-aryloxyphenol **3**.

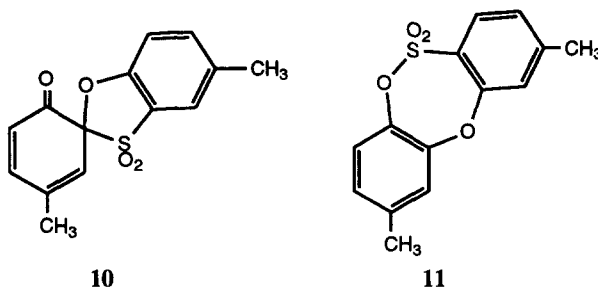
Treatment of **2** with thionyl chloride and anhydrous aluminum trichloride in dichloromethane afforded the known sulfoxide **4** in 95% yield.⁷ Addition of trifluoroacetic anhydride to a mixture of **4** and KHCO_3 in CD_3CN in an NMR tube cooled to -30°C allowed the observation of the disappearance of **4** and the appearance of peaks corresponding to the desired orthoquinone mono(monothioether) **7** [^1H NMR (360 MHz, CD_3CN , -30°C): δ 7.45 (s, 1H, H_6), 7.43 (d, 1H, $J = 8.9$ Hz, H_5), 7.33 (d, 1H, $J = 8.9$ Hz, H_4), 7.06 (dd, 1H, $J = 10.0, 3.0$ Hz, H_2), 6.34 (d, 1H, $J = 10.0$ Hz, H_1), 6.08 (d, 1H, $J = 3.0$ Hz, H_3), 2.35 (s, 3H, H_8), 1.51 (s, 3H, H_7)]. Presumably this compound is formed via internal trapping of the α -ketosulfonium salt **6** (prepared by a Pummerer-type rearrangement of **5**) by the phenolic hydroxyl with loss of two equivalents of trifluoroacetic acid. Reduction of this presumed intermediate was difficult and never proceeded cleanly. The best results were obtained using the desulfurization reagent⁸ prepared from $\text{NiCl}_2(\text{PPh}_3)_2$ and lithium aluminum hydride to give the desired *o*-aryloxyphenol **3** in 38% isolated yield along



with 56% of the symmetric diaryl sulfide **8**. Thus even though the yield of the desulfurization is not high, we are able to form the desired *o*-aryloxyphenol **3** in two steps from *p*-cresol **2** in 36% isolated yield. Other conditions, e.g., Raney nickel and hydrogen, also produced **3** but again in modest yield (~25-30%),⁹ while other reducing agents gave unsatisfactory results. When the reaction mixture containing **7** was heated at 70°C for 10 min after the addition of trifluoroacetic anhydride, the dimeric Diels-Alder product **9** was isolated in 72% yield after flash chromatography. Its structure was determined by x-ray crystallography. This compound is the only adduct formed of the 32 stereo- and regiochemical isomers possible and results from complete double stereodifferentiation with both molecules approaching each other from the oxygen face of the monothioether. This direction of approach is in agreement with literature precedent^{10,11} - namely both diene and dienophile approach each other on the side of the oxygen atoms and anti to the sulfur atoms.



Other ways of converting the mono(monothioether) **7** into the desired *o*-aryloxyphenol **3** were also studied. Oxidation with MCPBA followed by normal workup gave the sulfone **10** in 58% isolated yield. If a basic workup was used, the unusual cyclic sulfonate **11** was isolated instead, but in only 21% isolated yield. Reduction of these, and other similarly prepared intermediates, failed to produce the desired phenol **3** in reasonable yield.



Thus the best method of forming **3** from **4** in our hands is still the one-step preparation via **7** which proceeds in 38% yield. Extension of this method to protected tyrosine derivatives and isodityrosine is currently underway in our laboratory.

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References and Notes

- 1) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.
- 2) Visiting Scholar under the VSNA program sponsored by Rhône-Poulenc.
- 3) To whom questions about the x-ray structure determination should be addressed.
- 4) Many naturally occurring compounds containing this subunit are known, e.g., piperazinomycin, bouvardin and deoxybouvardin, K-13, OF4949-I-IV, RA-I-VII, vancomycin, teicoplanin, and ristocetin. For references to their isolation, structure determination, and synthesis, see: a) Boger, D. L.; Zhou, J. *J. Am. Chem. Soc.* **1993**, *115*, 11426. b) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912. c) Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. d) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379. e) Rama Rao, A. V.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1992**, *33*, 4799. f) Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 5649. g) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 2304 and references in all of the above. For recent approaches to isodityrosine, *o*-aryloxyphenols and 2,6-bis(aryloxy)phenols related to vancomycin, see: h) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017. i) Suzuki, Y.; Hishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 4053. j) Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V.; Khare, V. B. *Tetrahedron Lett.* **1993**, *34*, 1661. k) Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425.
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