Synthesis of (*S*,*S*)-Isodityrosinol in a Fully Differentiated Form via Diels-Alder Methodology

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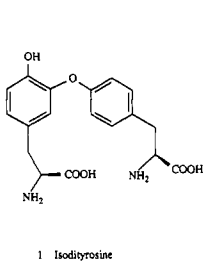
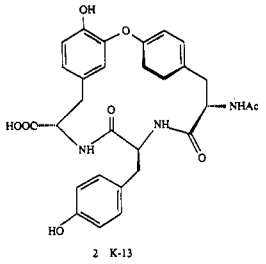
Summary: A Diels-Alder cycloaddition reaction of an aryloxy diene **7** and an acetylenic ketone **8** derived, respectively, from L-tyrosine and D-serine leads to the synthesis of the diaryl ether unit common to isodityrosine, which upon elaboration provides the functionally differentiated (*S*,*S*)-isodityrosinol **15**.

(*S*,*S*)-Isodityrosine (**1**) is a major constituent of several cyclic peptide antibiotics, including K-13,[1] OF4949-I-IV,[2] piperazinomycin,[3] the bouvardins,[4] and related RA-I-VII.[5] Total syntheses of **1** have been effected,[6] and in connection with the total synthesis of the above isodityrosine-containing antibiotics, the preparation of differentially protected isodityrosine derivatives has been reported.[7] The elaboration of the diaryl ether unit in the above studies has been accomplished by the connection of phenolic and/or aryl halide substrates by methods involving the Ullmann reaction,[6,7b,c,f,g,j] a thallium trinitrate procedure,[7a,e,h,i] and arene metal (Mn, Fe, or Ru) carbonyl[8a] or aryl iodonium complexes.[8b]



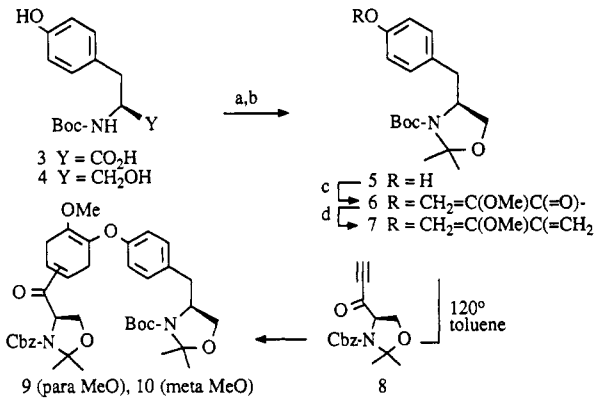
1 Isodityrosine



2 K-13

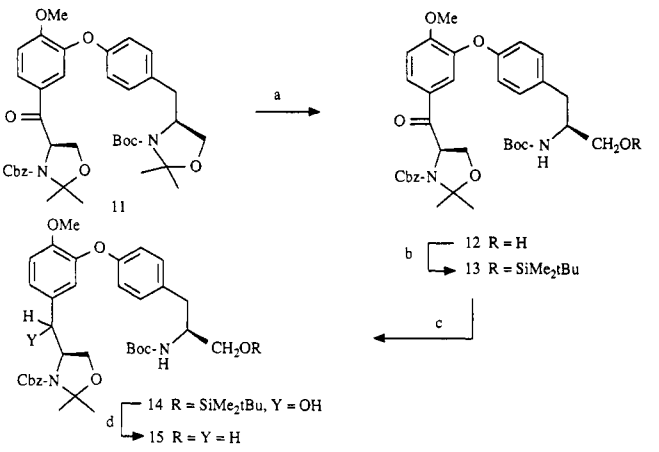
We recently reported[9] application of the Diels-Alder reaction involving an amino acid derived acetylenic ketone dienophile with aryloxy-substituted dienes to furnish, following elimination or oxidation to an aromatic ring, diaryl ether derivatives. This methodology offers a new approach to the synthesis of diaryl ether amino acid derivatives. We have extended the method to a synthesis of a fully differentiated isodityrosinol **15**, a suitably functionalized precursor for the synthesis of isodityrosine peptide antibiotics.

Scheme I[a]



[a] Key: (a) $LiAlH_4$, ether, 82%; (b) 2,2-dimethoxypropane, TsOH, acetone, 87%; (c) 2-methoxyacrylic acid, DCC, DMAP, 82%; (d) Tebbe's reagent, toluene, 64%.

Scheme II[a]



[a] Key: (a) MeOH, TsOH, rt, 68%; (b) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, 100%; (c) $NaBH_4$, MeOH, 93%; (d) (1) thiocarbonyl diimidazole, DMAP, 63%, (2) *n*-Bu_3SnH, AIBN, toluene, 96%, (3) *n*-Bu_4NF, THF, 100%.

N-(*tert*-Butyloxycarbonyl)-L-tyrosine (**3**) was reduced[10] with $LiAlH_4$ to the primary alcohol **4**, which was converted to the oxazolidine derivative **5** by treatment with 2,2-dimethoxypropane and tosic acid in acetone.[11] Acylation of the phenolic hydroxyl with 2-methoxyacrylic acid[12] provided ester **6**. Reaction of **6** with the Tebbe reagent[13] yielded aryloxy diene **7** in 64% yield. A Diels-Alder reaction between diene **7** and the previously reported[9] acetylenic ketone **8** resulted in the formation, in 91% yield, of a nearly equal mixture of regioisomers **9** and **10** which

(1) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455.
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(5) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762.
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(7) K-13 total syntheses: (a) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379. (b) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (c) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498. (d) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000. OF4949 total syntheses: (e) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. (f) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227. (g) Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 5061. Piperazinomycin total synthesis: (h) Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. Bouvardin total synthesis: (i) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957. (j) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427.
(8) (a) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363. (b) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017, 2021.
(9) Olsen, R. K.; Feng, X. *Tetrahedron Lett.* **1991**, *32*, 5721.
(10) For reduction of *O*-methyl-L-tyrosine ethyl ester with $LiAlH_4$, see: Rinaldi, P. L.; Wilk, M. *J. Org. Chem.* **1983**, *48*, 2141.
(11) Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
(12) Ogata, N.; Nozakura, S.; Murashashi, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2987. The reported ester was hydrolyzed in 2 N NaOH to the free acid.
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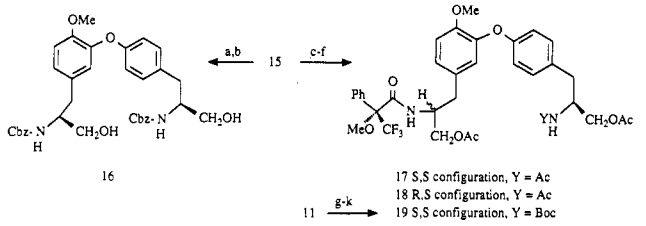
Scheme III[a]



[a] Key: (a) TFA, CH_2Cl_2; (b) Cbz-Cl, $NaHCO_3$, THF, 32%; (c) TFA, CH_2Cl_2; (d) Ac_2O, DMAP, CH_2Cl_2, 50%; (e) HBr, AcOH; (f) Mosher's acid, Et_3N, HOBt, EDCI; (g) (1) $NaBH_4$, MeOH, (2) Barton deoxygenation; (h) MeOH, TsOH; (i) H_2, $Pd(OH)_2$; (j) Mosher's acid, Et_3N, HOBt, EDCI; (k) Ac_2O, DMAP, CH_2Cl_2.

were readily separated by flash chromatography on silica gel (46% yield of desired isomer **9**, 45% yield of isomer **10**).

Regioisomer **9** was oxidized[9] with DDQ in high yield to the diaryl ether **11**. The regiochemical assignment for compound **11** was made by comparison of the ^1H NMR low-field aromatic region with spectra of known[9] regioisomers that have a phenyl group in place of the tyrosine moiety, which clearly differentiates the two regioisomers.

We have observed a fortuitous selective methanolysis of one of the oxazolidine rings in **11** to give **12** in a yield of 68%.[14] That the *N*-(Cbz)oxazolidine ring remained intact was evident from the ^1H NMR spectrum wherein the (Cbz)methylene hydrogens occurred as two AB quartets due to rotamers about the Cbz–*N*-carbamate bond,[15] as they also appear in the spectrum of **11**, and the hydrogen α to the ketone as two pairs of doublets, the doubling again due to rotamers. In contrast, the tyrosine methylene hydrogens occur as a doublet in **12** rather than an ABX pattern as observed in the precursor **11**.

Protection of the alcohol in **12** as the *tert*-butyldimethylsilyl (TBDMS) ether[16] provided **13**, which upon reduction of the ketone with $NaBH_4$ furnished benzylic alcohol **14** in 93% overall yield. Deoxygenation of the secondary alcohol in **14** via Barton's procedure[17] and removal of the TBDMS ether gave in good yield the differentiated isodityrosinol **15**.

Isodityrosinol **15** was converted to the known[6] *N,N'*-bis(Cbz)isodityrosinol **16** by treatment with trifluoroacetic acid followed by acylation of the unprotected amino function with Cbz-Cl (Scheme III). The ^1H NMR spectrum of **16** was superimposable with an authentic spectrum kindly provided by Professor Jung.[6b]

The optical purity of **15** was probed by conversion to Mosher's amide **17** by the sequence of reactions given in Scheme III. The epimer **18**, differing in configuration from **17** at the one α center, was prepared via the above methodology by use of the antipodal form of acetylenic ketone **8** in the Diels–Alder cycloaddition. ^1H NMR analysis of an admixture of **17** and **18** established the clean resolution of the diastereotopic *O*-methyl peaks of the Mosher's amide and that, within the limits of the NMR experiment, none of epimer **18** was detected in a sample of **17** prepared from **15**. The Mosher's amide **19** (Y = Boc) also was prepared by N-acylation with Mosher's acid of the one free amino group in the corresponding mono-*N*-(Boc)diamino diol,[18] followed by acetylation with acetic anhydride. Consistent with the above results, **19** only had a single peak in the NMR spectrum for the *O*-methyl group of the Mosher's amide.

In summary, the Diels–Alder approach to diaryl ether amino acid derivatives has proved to be applicable for the synthesis of a functionally differentiated (*S,S*)-isodityrosinol **15**. The oxidation of the primary alcohol to the carboxylic acid stage in isodityrosine derivatives is precedented;[6b,19] thus, isodityrosinol **15** should prove to be a useful precursor for the synthesis of isodityrosine-derived peptide antibiotics.

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Supplementary Material Available: Experimental procedures and compound characterization data for all compounds (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Without the ketone function, the selectivity is much less and resulted in the formation, in only 33%, of an inseparable 4:1 mixture of monooxazolidines, in which the (Cbz)oxazolidine ring was again cleaved more slowly.

(15) The rotamers of these oxazolidine carbamates slowly interconvert, and NMR spectra often have been measured at 60 °C to obtain simplified spectra; e.g., see: Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772. Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395.

(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(17) Barton, D. H.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(18) This amino diol was prepared from compound **11** by Barton deoxygenation of the corresponding alcohol, hydrolysis of both oxazolidine rings (TsOH, MeOH) under conditions that leave the Boc group in place, and removal of the Cbz group (H_2, $Pd(OH)_2$).

(19) We have oxidized **15** to the corresponding mono acid in a yield of 78% by treatment with $NaIO_4/RuCl_3$ using the procedure of; Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.