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Synthesis of a cyclic diaryl ether derivative under solid-phase conditions

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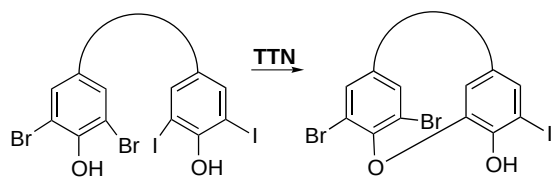
Abstract—The TTN phenolic oxidation, along with the *N*-protective group of the corresponding tripeptide derivatives, was examined to accomplish construction of a cyclic isodityrosine derivative under solid-phase conditions. The desired cyclization was effected under the TTN (thallium(III) trinitrate)/NMP–MeOH conditions to give the corresponding 17-membered ring lactam **12**.

Isodityrosine-related natural products are known not only as components of the plant cell wall but also as bioactive substances isolated from a wide range of natural origins. Based on molecular-based consideration, their prominent activities are apparently arise from the rigid stereochemistry of the peptide chains strongly supported by the diaryl ethers.[1,2] From extensive chemical investigation of these molecules, the assembly of the diaryl ether moieties may be a crucial step in synthesis of the isodityrosine-class natural products. Along with such effective methods as the Ullmann reactions and S_NAr reactions,[3] our phenolic oxidation by employing thallium(III) salts has been recognized as a standard methodology (Scheme 1).[4,5]

However, some problems may be incurred with our methodology: 1) difficulties of construction of diaryl ethers in high yields, owing to easy tendency of phenolic oxidation to polymerization. 2) More than stoichiometric amounts of poisonous thallium(III) salts are usually required for syntheses of the cyclization of halogenated phenols. Accordingly, work-up of the reaction mixture involves troublesome procedures to obtain the oxidation products. The solid-phase synthesis might provide a possible solution to these problems by anchoring molecules to prevent polymerization,[6–8] by washing out excess reagents from the substrate-loaded resin, along with the feasibility of providing libraries for effective screening of leads of new chemotherapeutic agents. Such motivation prompted us to investigate the solid-phase chemistry of the phenolic oxidation.[9]



TTN = thallim trinitrate

Scheme 1.

At the outset, the cyclic isodityrosine derivative **6**, was synthesized as a reference by the usual solution procedure (Scheme 2). Successive peptide-chain elongation was commenced by coupling of dibromo-L-tyrosine methyl ester **1** with the isoleucine derivative **2**, leading to **3**. After deprotection of the Boc group in the N-terminal, further connection with diiodo-L-tyrosine (**4**) provided the tripeptide substrate **5** for the oxidation. Upon treatment of **5** with TTN in THF–MeOH, the desired cyclization effectively proceeded to afford the cyclic diaryl ether **6**[15] in 66% yield. The direction of the cyclization was unambiguously determined by the mass spectrum that exhibited a molecular ion possessing two bromines and one iodine.[10] Since **6** was obtained by the solution procedure, this peptide skeleton would be synthesized on an appropriate resin. Base-labile Fmoc groups are adopted as *N*-protective groups to carry out the repeated peptide elongation on resin. Although

Keywords: isodityrosine; diaryl ether; thallium trinitrate; phenolic oxidation; solid-phase reaction.

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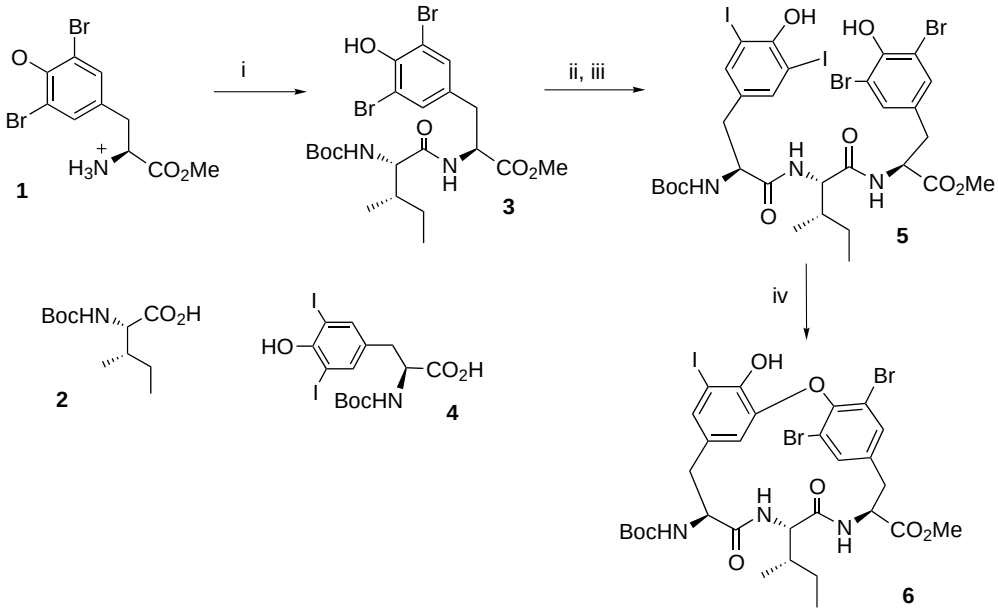
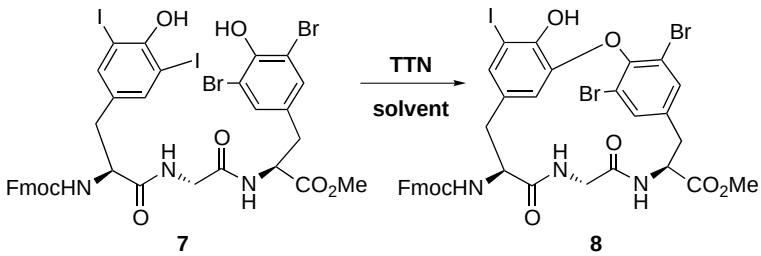


Scheme 2. *Reagents and conditions*: (i) Boc-L-isoleucine (**2**), DCC, HOBt, NMM/THF (63%); (ii) TFA/CH_2Cl_2; (iii) Boc-diiodo-L-tyrosine (**4**), BOP, Et_3N/DMF (84% in two steps); (iv) TTN/THF–MeOH (8:1) (66%).

MeOH is the best solvent for the TTN oxidation, lack of swelling of resin in this solvent would interfere with the smooth solid-phase reaction. Accordingly, combinations of MeOH with CH_2Cl_2, DMF, and NMP, known as effective solvents for resin swelling, were inspected to acquire the expected cyclization of **7** prepared by essentially the same procedure as in the case of **5** (Scheme 3). Upon comparison of the solvent pairs, the NMP–MeOH provided the best results in the conversion of **7** into **8** (entry 3).

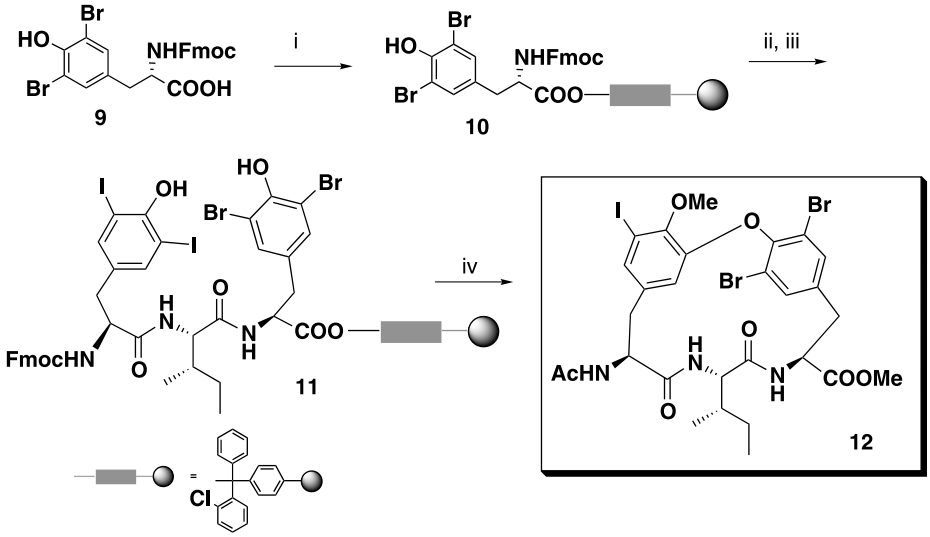
Based on these findings, the solid-phase synthesis of **12** was initiated with loading of Fmoc-dibromo-L-tyrosine (**9**) (0.3 equiv. mol) onto the trityl resin (1 equiv. mol),[12] leading to **10** in 81% yield (Scheme 4). Successive peptide-chain elongation afforded the tripeptide bound to the resin **11**: the loading amount was confirmed to be 65% of the theoretical amount after cleavage of the linkage under AcOH–TFE/CH_2Cl_2 conditions. Consequently, the tripeptide **11** in hand was submitted to the TTN oxidation, followed by switching the *N*-protective group to an acetyl group, reduction,[13] cleaving from the resin, and methylation to give the desired cyclic isodityrosine **12**[15] in 17% yield as the sole oxidation product.[14]

In conclusion, the TTN oxidation of *ortho*,*ortho*-dihalogenated phenols was demonstrated under the solid-phase conditions to develop safe and effective methodology for production of isodityrosine-class bioactive molecules, as well as to aim at production of a screening library of isodityrosine congeners. Optimization of the reaction conditions is in progress.



entries	solvent	yields of the oxidation (%)
1	DMF - MeOH (10 : 1)	19
2	CH_2Cl_2 - MeOH (10 : 1)	33
3	NMP - MeOH (10 : 1)	49

Scheme 3.



Scheme 4. *Reagents and conditions*: (i) *i*-Pr_2NEt/CH_2Cl_2, 81%; (ii) 30% piperidine/DMF; Fmoc-L-isoleucine, HATU, *i*-Pr_2NEt/DMF; (iii) 30% piperidine/DMF; Fmoc-diiodo-L-tyrosine, HATU, *i*-Pr_2NEt/DMF, 65% from **10** after acid hydrolysis (AcOH–TFE/CH_2Cl_2); (iv) (a) TTN/NMP–MEOH (10:1), (b) 30% piperidine, (c) Ac_2O, *i*-Pr_2NEt, (d) $NaBH_4$, (e) 10% AcOH, (f) $TMSCHN_2$, 17% from **11**.

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10. In general, the ether linkage is constructed at the halogen substituent possessing a lower oxidation potential (ex. iodo group in **5**). However, it is possible that stereochemical strain interferes with this selection. For instance (Ref. 11), a substrate for K-13, L-tyr-L-tyr-L-tyr involving a Cl–I pair, provided a considerable amount of the product cyclized by the undesired direction. Accordingly, the structure of the oxidation product should be carefully inspected by means of mass spectrometry.
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12. The 2-chlorotritylchloride resin was purchased from Novabiochem: loading, 1.3 mmol/g; polymer matrix, copolymer of styrene–1% DVB, 100–200 mesh.
13. This step was required to eliminate the remaining oxidant.
14. Upon using the Wang resin, (4-bromomethyl)-phenoxymethyl polystylene, the tripeptide was obtained in lower yield than in the case of the trityl resin, probably owing to the acidic phenol group of the tyrosine residue that might take part in the loading reaction. Although **12** accompanied no unexpected oxidation products, cleavage of the substrate from the resin under the acidic TTN reactions, might result in the low yield.
15. Selected data of the cyclic products. Compound **6**: IR (film) 1660 cm^{-1}; δ_H ($CDCl_3$) 0.89 (6H, complex), 1.08 (1H, m), 1.26 (1H, m), 1.49 (9H, s), 1.76 (1H, m), 2.52 (1H, t, $J=13$ Hz), 2.71 (1H, dd, $J=3.2$, 14.2 Hz), 3.30 (1H, dd, $J=6.1$, 14.2 Hz), 3.41 (1H, dd, $J=4.1$, 13.2 Hz), 3.85 (3H, s), 4.33 (1H, m), 4.41 (1H, dd, $J=4.3$, 9.6 Hz), 4.93 (1H, ddd, $J=4.1$, 8.4, 12.8 Hz), 5.26 (1H, d, $J=7.1$ Hz), 5.74 (1H, d, $J=1.7$ Hz), 6.00 (2H, complex), 6.11 (1H, s), 7.07 (1H, d, $J=1.7$ Hz), 7.30 (1H, d, $J=1.9$ Hz), 7.63 (1H, d, $J=1.9$ Hz). FAB-MAS. Found: m/z 853.9951. Calcd for $C_{30}H_{37}O_8N_3{}^{79}Br^{81}BrI$, 885.9975 (M+H). Compound **12**: IR (film) 1742, 1638 cm^{-1}; δ_H ($CDCl_3$) 0.89 (6H, complex), 2.01 (3H, d, $J=4.3$ Hz), 3.86 (3H, s), 4.91 (1H, m), 5.72 (1H, d, $J=2.2$ Hz), 7.08 (1H, d, $J=2.2$ Hz), 7.29 (1H, d, $J=1.6$ Hz), 7.61 (1H, d, $J=1.6$ Hz). FAB-MAS. Found: m/z 809.9732. Calcd for $C_{28}H_{33}O_7N_3{}^{79}Br^{81}BrI$, 809.9712 (M+H).