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RAPID AND CONVERGENT SYNTHESIS OF A 2,4'-LINKED TRI-OXAZOLE IN AN APPROACH TO POLY-OXAZOLES

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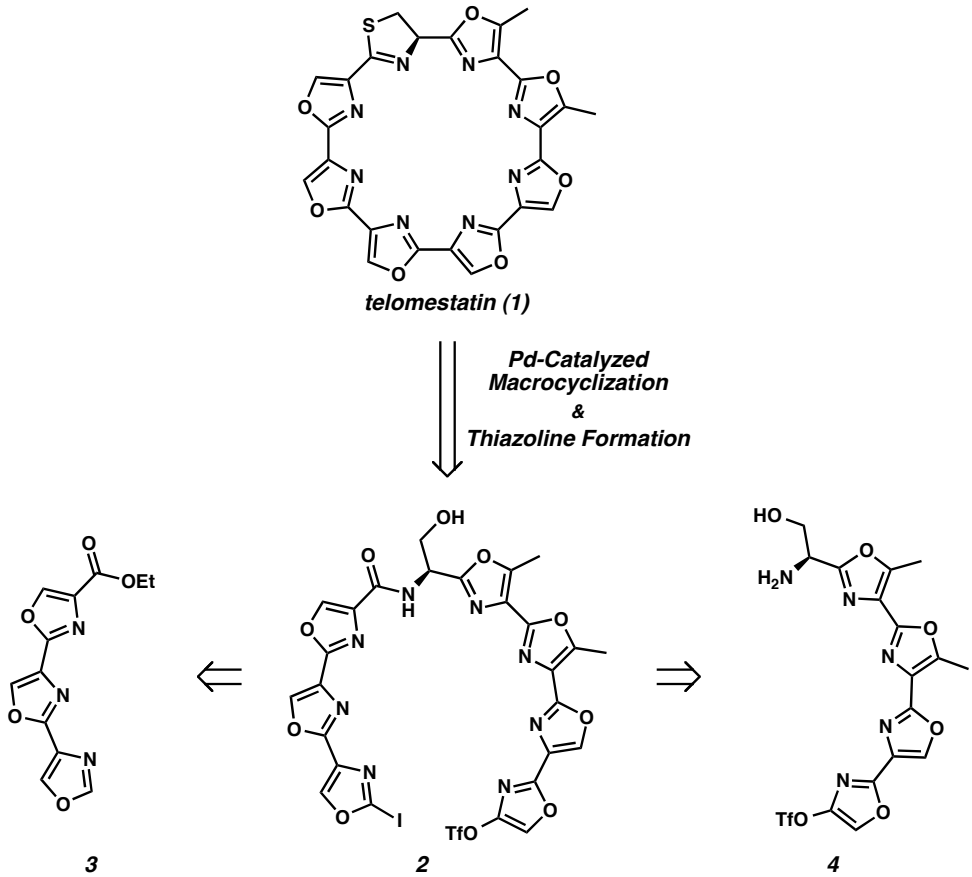
Abstract – A rapid and convergent synthesis of a 2,4'-linked tri-oxazole using a Negishi coupling is described.

Due to the biological importance of polyoxazole-containing compounds, a multitude of synthetic approaches have been described.[1] While preparations of mono- and di-substituted oxazoles are common, reports describing the synthesis of longer oxazole chains are much more scarce.[2,3] We became interested in efficient routes to 2,4'-polyoxazoles during studies on the total synthesis of telomestatin (**1**, Scheme 1), a potent telomerase inhibitor.[4,5,6,7] Herein, we present a rapid and convergent synthesis of a 2,4'-linked tri-oxazole using a Negishi coupling.

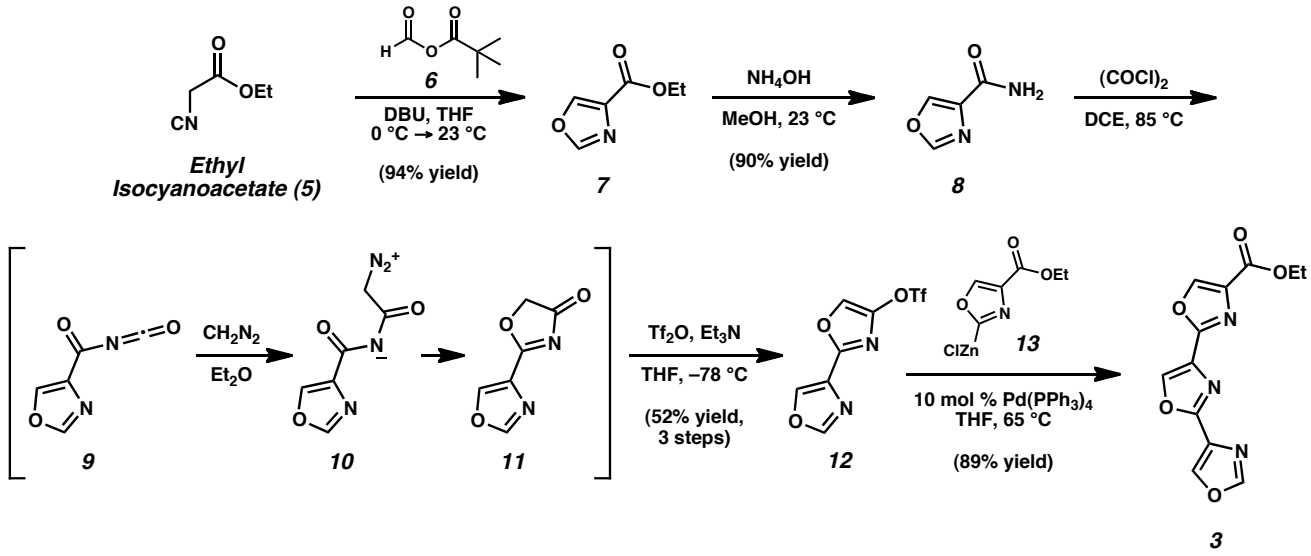
Our retrosynthetic analysis for telomestatin (**1**) is featured in Scheme 1. On the basis of the reported telomestatin (**1**) syntheses,[5] we envisioned a late-stage installation of the sulfur moiety and the thiazoline ring. Additionally, in order to maximize synthetic efficiency, we sought to complete the final aryl–aryl linkage of **2** and induce macrocyclization using a palladium-catalyzed cross-coupling.[8,9] This maneuver would also allow for a high degree of convergency by dividing the molecule into two roughly equal halves. Disconnection across the amide bond in **2** then reveals tri-oxazole fragment **3** and tetrakis-oxazole amino alcohol **4**.

Scheme 1



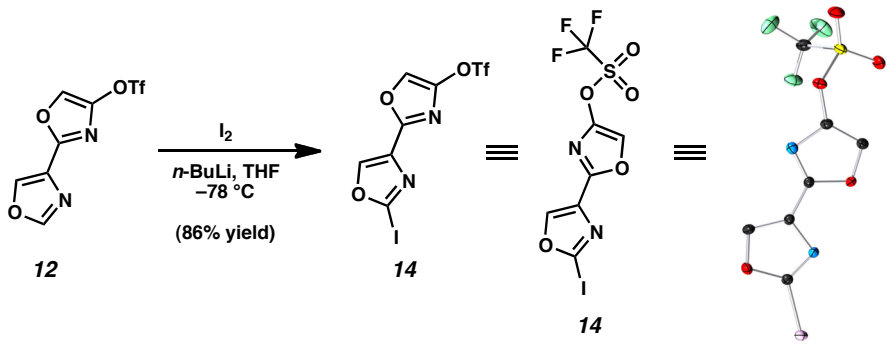
Our synthesis of the left-hand tri-oxazole portion (**3**) of telomestatin (**1**) began with the preparation of known oxazole ester **7**. Exposure of ethyl isocyanoacetate (**5**) to mixed anhydride **6**[10] and DBU led to a high yield of oxazole ester **7**,[11] which was smoothly converted to amide **8** by the action of aqueous ammonia in methanol (Scheme 2). Conversion to bis-oxazole triflate **12** was achieved by means of a three-step sequence, which commenced by heating amide **8** in the presence of oxalyl chloride to give rise to acyl isocyanate **9**.

Scheme 2



Subjection of acyl isocyanate **9** to anhydrous, alcohol-free diazomethane dried over sodium metal[12] led to in situ production of **10**, which rapidly cyclized with loss of nitrogen to form oxazolone **11**.[13] Treatment of this intermediate with Tf_2O and amine base produced bis-oxazole triflate **12** in 52% yield over 3 steps.[14] Further confirmation of the structural identity was achieved by single crystal X-ray diffraction upon conversion to the iodo derivative (**12** → **14**, Scheme 3).[15]

Scheme 3



A wide range of cross-couplings of appropriate mono- and bis-oxazole subunits were investigated to prepare the desired tri-oxazole fragment (**3**), including Stille, Suzuki, and Negishi protocols.[16,17] Ultimately, the Negishi approach proved to be the most robust to accomplish this union.[16] The necessary zinc reagent (**13**) for this reaction could be prepared from **7** via a deprotonation/quenching event with LiHMDS and $ZnCl_2$, furnishing tri-oxazole **3** after successful aryl fusion with bis-oxazole **12**.[18] This approach was also used in a similar fashion to prepare a tetrakis-oxazole.[19]

In conclusion, we have presented an efficient and convergent synthesis of a tri-oxazole fragment. Existing studies to utilize this methodology toward a total synthesis of telomestatin are ongoing in our laboratory.

ACKNOWLEDGEMENTS

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[15] See supporting information; iodobis-oxazole triflate **14** is shown with 50% probability ellipsoids (Note: Only *Molecule A* is depicted). Crystallographic data have been deposited at the CCDC, 12 Union

Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 282586.

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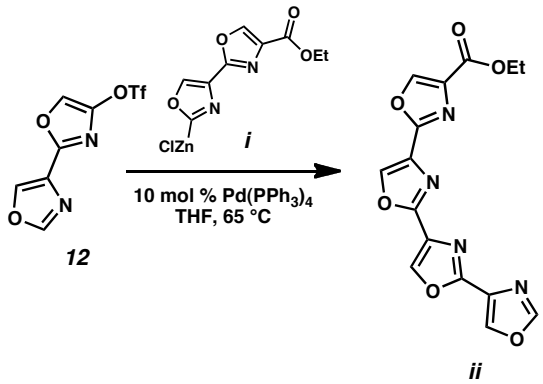
[19] This approach was also successful in producing small quantities of tetrakis-oxazole **ii**, which was prepared from triflate **12** and Negishi reagent **i**. Negishi reagent **i** was made in a two-step process: ethoxycarbonylation of **12**, followed by metalation in a similar fashion as **13**.



12 *ii*