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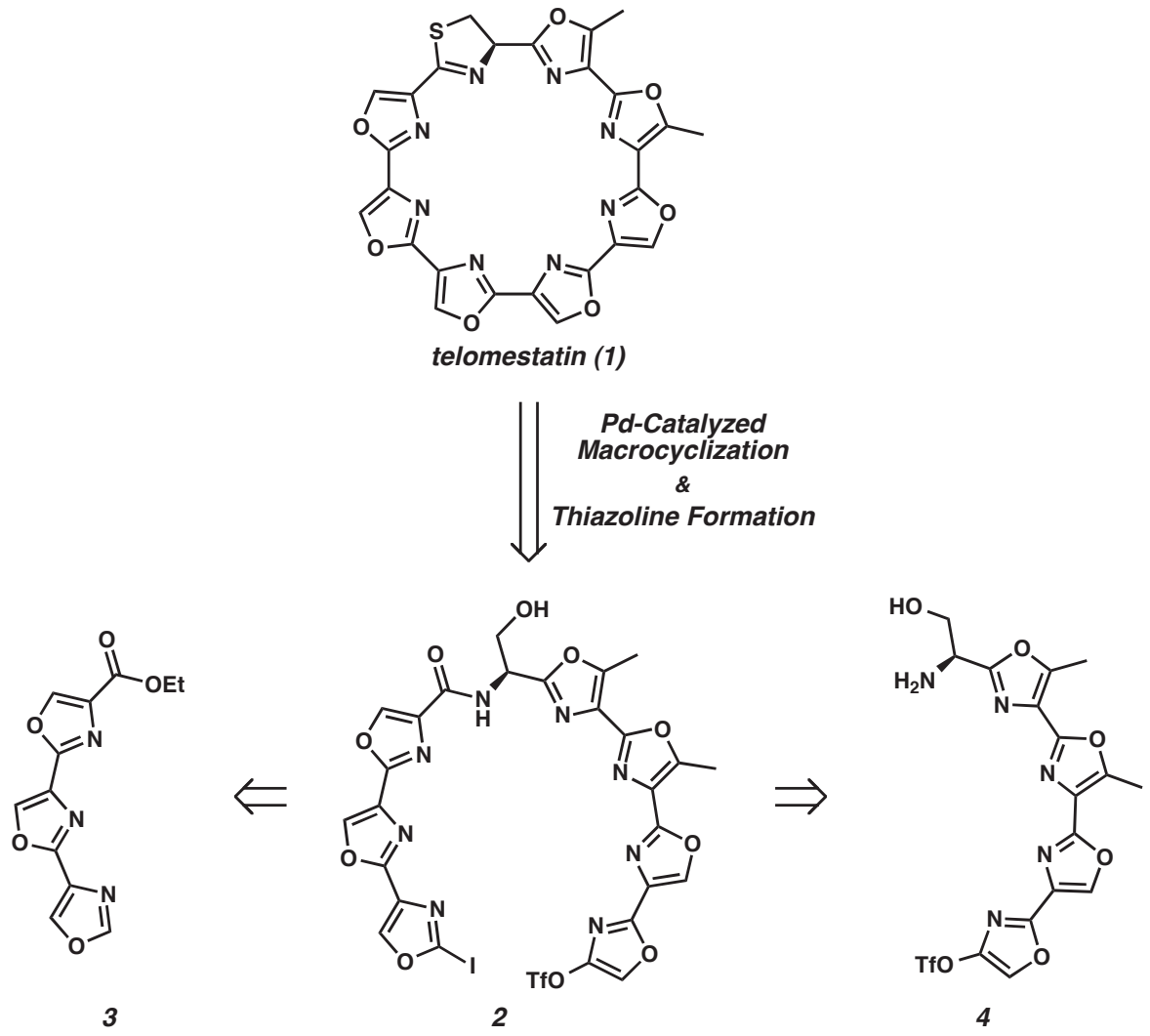
Abstract – A rapid and convergent synthesis of a 2,4'-linked tri-oxazole using a Negishi coupling is described.

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.[4-7] Herein, we present a rapid and convergent synthesis of a 2,4'-linked tri-oxazole using a Negishi coupling.

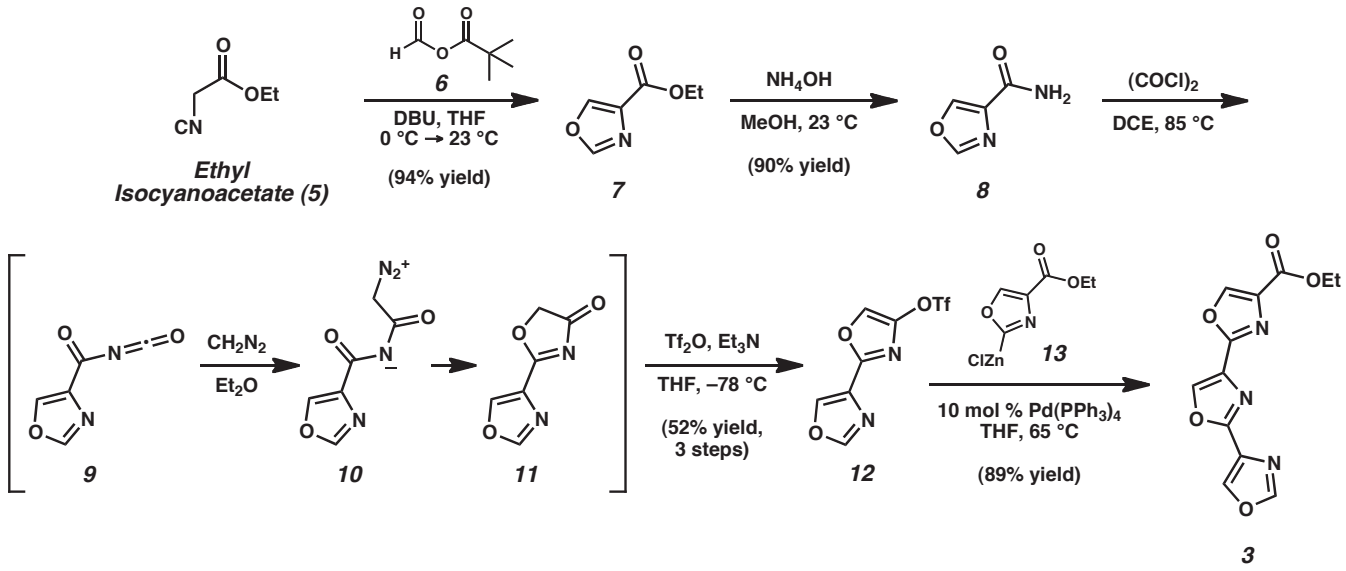
Our retrosynthetic analysis for telomestatin (**1**) is featured Scheme 1. On the basis of the reported telomestatin (**1**) syntheses,[5] we envisioned a late-stage installation of the sulfur moiety and the thiazoline ring. Additionally, in order to maximize synthetic efficiency, we sought to complete 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**.

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.



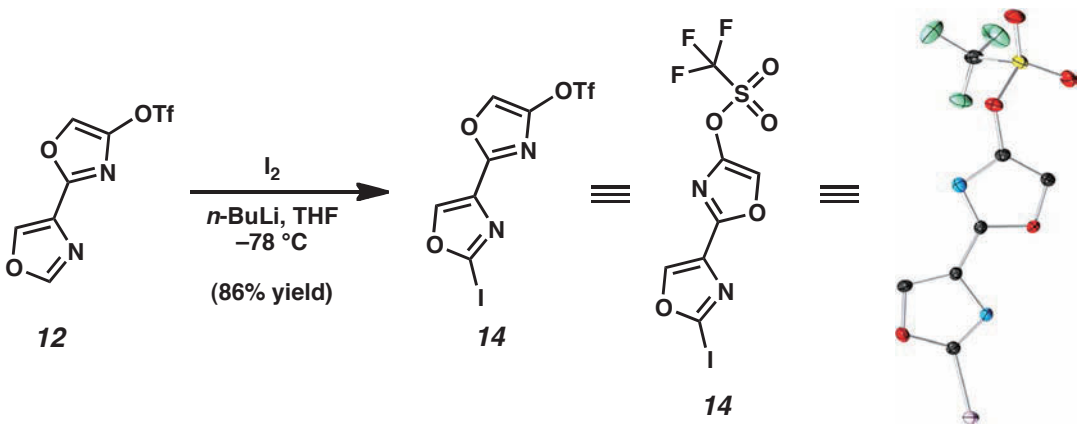
Scheme 1

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. 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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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**.