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Iterative two-step strategy for C2–C4′ linked poly-oxazole synthesis using Suzuki–Miyaura cross-coupling reaction

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Abstract—An iterative method for the synthesis of C2–C4′ linked poly-oxazoles has been developed. This efficient two-step repetitive process includes TBS–iodine exchange reaction and Suzuki–Miyaura cross-coupling reaction with oxazolylboronate **8**, which allows appending a bis-oxazole moiety per each iteration. The synthesis of bis-, tris-, tetrakis-, pentakis-, and hexakis-oxazoles (**10**, **14**, **22**, **18**, and **24**) was achieved starting from the common intermediate **7** in 1–5 steps.

In the last two decades, various natural products containing C2–C4′ linked poly-oxazole moieties such as telomestatin (**1**),[1,2] and ulapualide A (**2**)[3–5] (Fig. 1) have been isolated and reported to possess a wide variety of biological activities.[6] For the purpose of preparation of these successive C2–C4′ linked poly-oxazole subunits, a large number of iterative methods have been developed,[7] which are classified as the following types: (i) Hantzsch-type synthesis,[5c] (ii) formation and oxidation of oxazolines,[2e,4a,e,8] (iii) cyclodehydration,[9] (iv) Rh(II) catalyzed cycloaddition reaction,[10] (v) Chan-type rearrangement,[11] (vi) cyclization of alkynyl derivatives,[12] (vii) photolysis or pyrolysis of *N*-acylisoxazol-5-ones,[13] (viii) Pummerer rearrangement,[14] (ix) ring enlargement of *N*-acylazirizines,[15] and (x) S_NAr substitution with TosMIC anion.[16]

Meanwhile, Suzuki–Miyaura cross-coupling reaction using boronic acid derivatives has played an important role for biaryl synthesis due to their easy availability, low toxicity, air stability, and wide functional-group tolerance.[17] In the area of oligophenylenes several iterative two-step cross-coupling-activation methodologies including Suzuki–Miyaura reaction were disclosed to prepare functionalized oligophenylenes.[18] In terms of poly-oxazole synthesis, we could find out only one patent relevant to the iterative synthesis including Suzuki–Miyaura cross-coupling using oxazol-2-ylboronic acid.[19] In addition, few examples of the preparation and

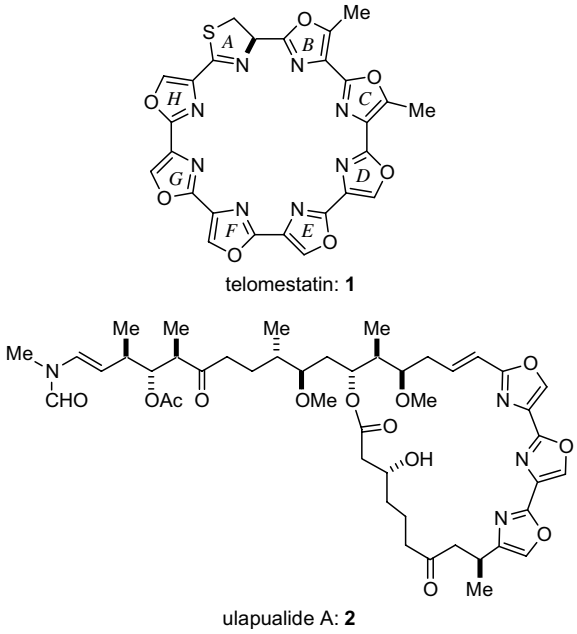

Figure 1. Natural products containing C2–C4′ linked poly-oxazole moiety.

Keywords: Poly-oxazole; Suzuki–Miyaura cross-coupling reaction; Iterative synthesis; Oxazolylboronate; Telomestatin.
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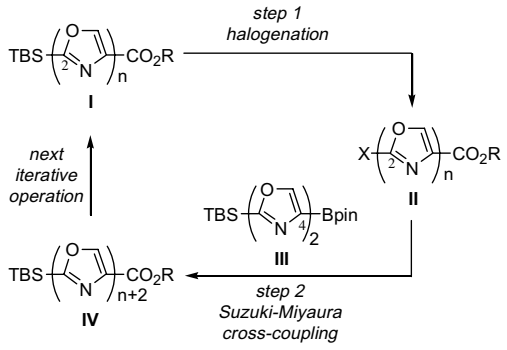
cross-coupling reaction of oxazolylboronates have been reported to date.[20]

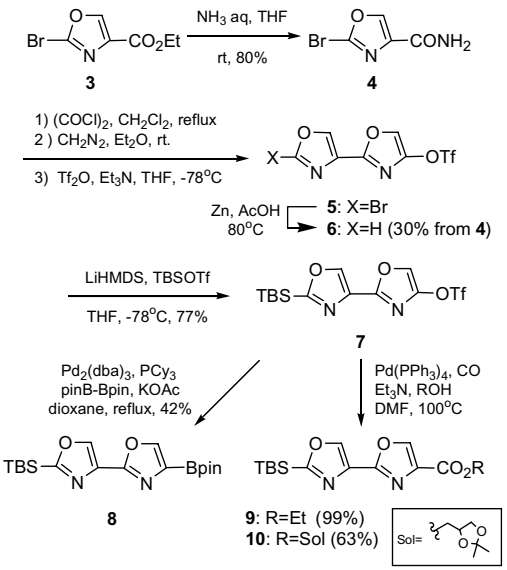
Recently, we initiated the project toward the synthesis of natural products containing poly-oxazole systems such as telomestatin (**1**) and ulapualide (**2**) with an iterative manner including Suzuki–Miyaura cross-coupling reaction of oxazolylboronates and we communicated the first example of the synthesis and cross-coupling reaction of oxazol-4-ylboronates.[21] In this literature, we wish to describe our efficient and repetitive two-step poly-oxazole synthesis using oxazol-4-ylboronates to be able to access natural products including C2–C4′ linked poly-oxazole system based on our preliminary results.[22]

Our strategy for poly-oxazole synthesis is outlined in Scheme 1. We envisaged that our repetitive procedure would involve halogenation at C2 position in 2-TBS-oxazole **I**, followed by Suzuki–Miyaura cross-coupling reaction of the resulting 2-halooxazole **II** with oxazol-4-ylboronate **III** to afford the corresponding poly-oxazole **IV** incorporating an additional bis-oxazole ring. The resulting 2-TBS-polyoxazole **IV** will serve as a precursor for the next iterative operation.[23] Since this procedure will allow appending a bis-oxazole moiety per each iterative cycle, we expected to obtain both odd- and even-numbered poly-oxazoles starting from mono-oxazole **I** ($n = 1$) and bis-oxazole **I** ($n = 2$), respectively.

As shown in Scheme 2, we initially pursued the synthesis of oxazolylboronate **8** (=**III**) and bis-oxazole **9** [=**I** ($n = 2$)]. Our synthesis commenced with exposure of the known 2-bromooxazole **3**[24] to aqueous ammonia in THF at ambient temperature for 24 h to give an 80% yield of the corresponding carboxamide **4**. Taking advantage of Sheehan–Smith's method,[25] **4** was then converted to bis-oxazole **6** in moderate yield (30%) over 4 steps involving (1) acylisocyanate formation with oxalyl dichloride, (2) diazomethane induced oxazolone formation, (3) triflation with triflic anhydride,[25b,26] and (4) removal of bromine atom at C2′ position in the resulting bromide **5**[27] by use of zinc powder in acetic acid. Careful treatment of **6** with 1.1 equiv of lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C, followed by addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at the same temperature produced 2′-TBS-oxazole **7** as a common precursor for **8** and **9** in 77% yield.[28] The desired oxazol-4-ylboronate **8** (=**III**) was obtained in 42% yield by borylation of **7** under Ishiyama–Miyaura condition [2.5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 15 mol % PCy_3, 2 equiv of bis(pinacolato)diboron (pinB-Bpin) and 3 equiv of KOAc in refluxing dioxane].[28,29] On the other hand, carboethoxylation[30] of triflate **7** was carried out by treatment with 5 mol % $Pd(PPh_3)_4$ in the presence of large excess of ethanol and 2 equiv of triethylamine under carbon monoxide in DMF at 100 °C to give the expected bis-oxazole **9** in 99% yield.

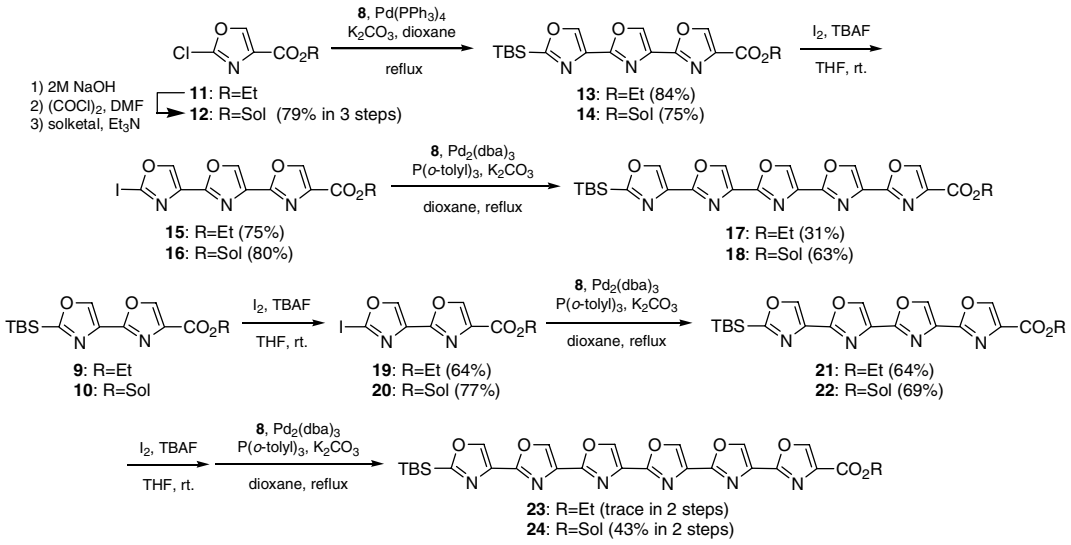


Scheme 1. Our iterative method for poly-oxazole synthesis.



Scheme 2. Synthesis of oxazolylboronate **8** and bis-oxazoles (**9** and **10**).

Succeeded in the synthesis of **8** and **9**, we turned our attention to the establishment of the new iterative methodology for poly-oxazole synthesis as depicted in Scheme 3. At first, we investigated the synthesis of the odd-numbered poly-oxazoles starting from the known mono-oxazole **11**.[24] In our previous paper,[21] we reported Suzuki–Miyaura coupling of oxazol-4-ylboronates with various aryl halides under normal reaction condition [$Pd(PPh_3)_4$, K_2CO_3] provided the corresponding oxazole derivatives in high yield. Upon this condition, the reaction between **8** and **11** proceeded smoothly to furnish the desired tris-oxazole **13** in 84% yield. Then, the second iterative cycle to obtain pentakis-oxazole was executed as follows. The expected TBS–iodine exchange reaction of **13** was carried out in the presence of TBAF (tetra-*n*-butylammonium fluoride) and iodine, resulting in the formation of the corresponding iodide **15** in 75% yield. The key cross-coupling reaction of **15** with **8** was best achieved under improved reaction condition [$Pd_2(dba)_3{\cdot}CHCl_3$, P(*o*-tolyl)$_3$, K_2CO_3] to furnish pentakis-oxazole **17** in 31% yield. Next, the synthesis of the even-numbered poly-oxazoles was examined in the same fashion. Starting from bis-oxazole **9**, the first iterative cycle was performed by TBS–iodine exchange reaction (64%), followed by Suzuki–Miyaura cross-coupling reaction of the resulting bis-

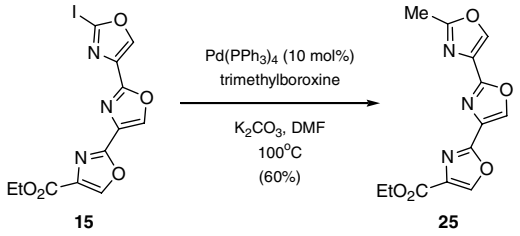


Scheme 3. Synthesis of bis-, tris-, tetrakis-, pentakis-, and hexakis-oxazoles.

oxazole **19** with **8** to provide tetrakis-oxazole **21** in 64% yield. To append the further bis-oxazole moiety, the second iterative cycle was repeated from **21**, however, only trace amount of hexakis-oxazole **23** was obtained.

At that moment, we realized that as the number of poly-oxazoles increased, the yield of the cross-coupling reaction decreased. Since this serious problem was attributed to the low solubility of the longer poly-oxazoles in organic solvents, we decided to modify the ester part of the poly-oxazoles. After several investigations, we found out that the corresponding solketal esters showed relatively better solubility. Using solketal esters (**12** and **10**) as starting materials, the iterative process was again investigated.[31] For the odd-numbered poly-oxazoles, the synthesis commenced from solketal ester **12**, prepared from **11** via a three-step sequence [(a) 2 M NaOH, THF, rt. (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt. (c) Sol-ketal, Et_3N, CH_2Cl_2, 79% in 3 steps]. Suzuki–Miyaura cross-coupling reaction of mono-oxazole **12** with **8** provided tris-oxazole **14** in 75% yield. Next, the second iterative process was performed, giving rise to iodide **16** (80%), then pentakis-oxazole **18** in better yield (63%). Since pentakis-oxazole **18** is an equivalent to the *DEFGH*-ring part in telomestatin (**1**), it is regarded as an important synthetic intermediate for the synthesis of **1**. The preparation of the even-numbered poly-oxazoles was initiated from bis-oxazole **10**, which was prepared by carboalkoxylation of **7** in 63% (Scheme 2). Compound **10** was treated with iodine in the presence of TBAF to produce the corresponding iodide **20** in 77% yield. Suzuki–Miyaura coupling reaction of **20** with **8** gave rise to tetrakis-oxazole **22** in 69% yield. The second iterative cycle from **22** through the same manner provided hexakis-oxazole **24** in improved yield (43%) over 2 steps.

Pattenden disclosed the convergent synthesis of tris-oxazole **25** through an iterative step-wise oxazoline formation–oxidation sequence and they achieved the



Scheme 4. Methylation of tris-oxazole **15**.

synthesis of a diastereomer of ulapualide A (**2**) from **25**.[4e,f] As shown in Scheme 4, we demonstrated the preparation of Pattenden's key intermediate **25** from tris-oxazole **15**. To install methyl group at C2″ position in **15**, subjection of **15** to Gray's condition [$Pd(PPh_3)_4$, trimethylboroxine][32] produced a 60% yield of tris-oxazole **25**. The spectroscopic properties (^1H and ^{13}C NMR) of the synthetic tris-oxazole **25** were compatible with those in the literature.[4e]

In summary, we have succeeded in the development of the two-step iterative method for C2–C4′ linked poly-oxazole synthesis including TBS–iodine exchange reaction and Suzuki–Miyaura cross-coupling reaction. Our developed process allows to extend a bis-oxazole moiety per each iteration. Taking advantage of this method, bis-, tris-, tetrakis- pentakis-, and hexakis-oxazoles were synthesized in 1, 2, 3, 4, and 5 steps, respectively, from the common intermediate bis-oxazole **7**. Applying this method, the total synthesis of natural products including poly-oxazole moiety is currently in progress, which will be discussed in due course.

Acknowledgements

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28. *Spectral data for* **7**: Mp 50.0–51.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40 (6H, s), 1.00 (9H, s), 7.75 (1H, s), 8.43 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.4 (2 carbons), 16.8, 26.1 (3 carbons), 118.6 (q, $^1J_{CF}$ = 319.4 Hz), 126.2, 129.7, 142.2, 145.7, 153.8, 172.0; HIEIMS *m*/*z* calcd for $C_{13}H_{17}F_3N_2O_5SSi$ (M^+), 398.0580; found, 398.0578. *Spectral data for* **8**: Mp 140.5–141.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.39 (6H, s), 0.99 (9H, s), 1.36 (12H, s), 8.07 (1H, s), 8.50 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.36 (2 carbons), 16.8, 24.8 (4 carbons), 26.2 (3 carbons), 84.4 (2 carbons), 130.5, 141.4, 147.8, 156.6, 171.0; HIEIMS *m*/*z* calcd for $C_{18}H_{29}BN_2O_4Si$ (M^+), 376.1990; found, 376.1995.
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31. *Spectral data for bis-oxazole* **10**: Mp 91.0–92.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40 (6H, s), 1.00 (9H, s), 1.38 (3H, s), 1.45 (3H, s), 3.85 (1H, dd, J = 5.7, 8.6 Hz), 4.14 (1H, dd, J = 6.3, 8.6 Hz), 4.38 (1H, dd, J = 5.8, 11.2 Hz), 4.42 (1H, dd, J = 4.7, 11.2 Hz), 4.46 (1H, m), 8.31 (1H, s), 8.52 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.38 (2 carbons), 16.8, 25.4, 26.1 (3 carbons), 26.8, 65.4, 66.4, 73.5, 110.0, 129.8, 133.9, 142.2, 143.8, 156.5, 160.8, 171.6; HIFABMS *m*/*z* calcd for $C_{19}H_{29}N_2O_6Si$ ($[M+H]^+$), 409.1795; found, 409.1798. *Tris-oxazole* **14**: Mp 122–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.41 (6H, s), 1.00 (9H, s), 1.39 (3H, s), 1.46 (3H, s), 3.85 (1H, dd, J = 5.7, 8.6 Hz), 4.15 (1H, dd, J = 6.2, 8.6 Hz), 4.38 (1H, dd, J = 5.9, 11.2 Hz), 4.43 (1H, dd, J = 4.6, 11.2 Hz), 4.46 (1H, m), 8.34 (1H, s), 8.43 (1H, s), 8.53 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.38 (2 carbons), 16.8, 25.4, 26.1 (3 carbons), 26.8, 65.5, 66.4, 73.5, 110.0, 129.8, 130.7, 134.1, 139.3, 142.1, 144.0, 155.7, 156.8, 160.6, 171.7; HIFABMS *m*/*z* calcd for $C_{22}H_{30}N_3O_7Si$ ($[M+H]^+$), 476.1853; found, 476.1843. *Tetrakis-oxazole* **22**: Mp 199–200 °C; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 0.42 (6H, s), 1.01 (9H, s), 1.39 (3H, s), 1.46 (3H, s), 3.85 (1H, dd, $J = 5.7$, 8.6 Hz), 4.15 (1H, dd, $J = 6.3$, 8.6 Hz), 4.39 (1H, dd, $J = 5.8$, 11.2 Hz), 4.43 (1H, dd, $J = 4.7$, 11.2 Hz), 4.46 (1H, m), 8.34 (1H, s), 8.44 (1H, s), 8.45 (1H, s), 8.55 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.37 (2 carbons), 16.8, 25.4, 26.1 (3 carbons), 26.8, 65.5, 66.4, 73.5, 110.0, 129.8, 130.7, 130.9, 134.1, 139.2, 139.5, 142.1, 144.1, 155.5, 156.1, 156.9, 160.6, 171.7; HIFABMS *m/z* calcd for $C_{25}H_{31}N_4O_8Si$ ($[M+H]^+$), 543.1911; found, 543.1917. *Pentakis-oxazole* **18**: Mp 271–272 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.41 (6H, s), 1.01 (9H, s), 1.39 (3H, s), 1.46 (3H, s), 3.86 (1H, dd, $J = 5.7$, 8.6 Hz), 4.15 (1H, dd, $J = 6.3$, 8.6 Hz), 3.39 (1H, dd, $J = 5.8$, 11.2 Hz), 4.44 (1H, dd, $J = 4.6$, 11.2 Hz), 4.47 (1H, m), 8.36 (1H, s), 8.46 (2H, s), 8.46 (1H, s), 8.55 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.37 (2 carbons), 16.8, 25.4, 26.1 (3 carbons), 26.8, 65.5, 66.4, 73.5, 110.0, 129.8, 130.7, 130.9, 130.9, 134.1, 139.3, 139.4,139.6, 142.1, 144.1, 155.5, 155.9, 156.1, 156.9, 160.6, 171.7; HIFABMS *m/z* calcd for $C_{28}H_{32}N_5O_9Si$ ($[M+H]^+$), 610.1969; found, 610.1973. *Hexakis-oxazole* **24**: Mp > 300 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.42 (6H, s), 1.01 (9H, s), 1.39 (3H, s), 1.46 (3H, s), 3.85 (1H, dd, $J = 5.7$, 8.6 Hz), 4.15 (1H, dd, $J = 6.3$, 8.6 Hz), 4.39 (1H, dd, $J = 5.9$, 11.2 Hz), 4.43 (1H, dd, $J = 4.7$, 11.2 Hz), 4.46 (1H, m), 8.35 (1H, s), 8.45 (1H, s), 8.45 (1H, s), 8.46 (1H, s), 8.47 (1H, s), 8.55 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −6.36 (2 carbons), 16.8, 25.4, 26.1 (3 carbons), 26.8, 65.5, 66.4, 73.5, 110.0, 129.8, 130.7, 131.0, 131.0, 131.01, 134.2, 139.3, 139.5, 139.5, 139.6, 142.1, 144.1, 155.5, 155.9, 156.0, 156.2, 157.0, 160.6, 171.8; HIFABMS *m/z* calcd for $C_{31}H_{33}N_6O_{10}Si$ ($[M+H]^+$), 677.2028; found, 677.2044.

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