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Total synthesis of LL-Z1640-2 utilizing a late-stage intramolecular Nozaki–Hiyama–Kishi reaction

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ABSTRACT

A total synthesis of LL-Z1640-2 (**2**), a potent and selective kinase inhibitor, has been completed. The key step of the convergent synthesis utilized a late-stage intramolecular Nozaki–Hiyama–Kishi (NHK) reaction to close the macrocycle at the C6′–C7′ bond.

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Hypothemycin (**1**) and LL-Z1640-2 (also known as C292 and 5-(*Z*)-7-oxozeaenol) (**2**) (Fig. 1) are macrolactones of the resorcylic acid lactone (RAL) class of natural products that have generated substantial interest due to their potent inhibition of selected kinases.[1,2] Both **1** and **2** are produced via the polyketide biosynthetic pathways of several fungal strains and their structures were first reported in 1980 and 1978, respectively.[3,4] Extensive research on these agents and related *cis*-enone RALs (i.e., radicicol A and L-783277) revealed that **2** is a potent inhibitor of TNFα production,[5] MEK,[6] and JNK/p38.[7,8] Furthermore, it has also been recognized that **1** and **2** target selected members of the kinome including Erk2, TAK1, and Kit.[9–11] In 2006, Santi and co-workers showed that the *cis*-enone of **1** acted as a Michael acceptor in the presence of select kinases which contain a conserved cysteine residue (Cys166 in Erk2).[12] This key interaction was further corroborated by X-ray crystal structures of hypothemycin (**1**)[13] and LL-Z1640-2 (**2**)[9] covalently bound within the ATP binding domain of Erk2 through the Cys residue. There are at least 46 kinases that contain a Cys residue in the hinge region suggesting a high promiscuity of these important natural products across the kinome. Given the detailed structural understanding of the binding mechanism, obtaining rationally designed analogues that limit binding, covalent modification, and inhibition to a selected sub-domain of the kinome are conceivable. Achieving this goal requires efficient and expedient synthetic methods that afford both the natural products and the desired analogues. Recently, Winssinger and co-workers have synthesized a RAL library of hypothemycin, LL-Z-1640-2, and L-783277 analogues to investigate the structure–activity relationship of kinase inhibition.[14]

The first total synthesis of LL-Z1640-2 (**2**) was published by Tatsuta et al.[15] in 2001 followed by the Lett and co-worker[16] and Winssinger[17] groups completing total syntheses of **2** and hypothemycin (**1**). Additionally, Marquez and co-workers have detailed a synthesis establishing the framework needed to complete the total synthesis of **2** via a late-stage ring-closing metathesis reaction,[18] while Hearn et al. recently presented a semisynthetic approach to analogues of **1**.[19] Despite the use of different subunits in constructing the carbon framework, all three total syntheses relied upon a macrolactonization to establish the core ring structure.[15–17] Diverging from previous synthetic strategies toward the preparation of LL-Z1640-2 (**2**), we intended to exploit the intramolecular Nozaki–Hiyama–Kishi (NHK) reaction in macrocycle formation at the C6′–C7′ bond.[20,21] Winssinger and co-workers have published several convergent strategies relying on three principle subunits (an aryl selenide, an alkyl iodide (precursor to C1′–C6′), and a *cis*-vinyl bromide (precursor to C7′–C10′)) that can be coupled in different sequences to form the cyclic scaffold of **1** and **2**.[17] We envisioned a synthetic strategy that, like the Winssinger approach, was modular and allowed insertion of related fragments for rapid library expansion and SAR explorations. Our route to **2** depended on an aryl selenide nucleophile for a precedented[17a] sequence of alkylation, oxidation, and elimination to generate the requisite C6–C1′–C2′ *trans*-olefin scaffold (Fig. 1). Subsequent Mitsunobu esterification would provide access to an advanced intermediate poised for macrocyclization with the intramolecular NHK reaction. The success of this strategy would allow modified versions of key intermediates **5**, **6**, and **7** to enter a similar synthetic sequence providing advanced SAR explorations around **2** in a rapid manner.

Synthetic elaboration of the aryl selenide **7** is accomplished starting from commercially available 2,4-dimethoxy-6-methylbenzoic acid via known methods (2-(trimethylsilyl)ethyl (TMSE) protection and selenation).[17a] Alkene **8** was derived in two-steps from 2-deoxyribose utilizing an established procedure.[22] Further elaboration of **8** involved ozonolysis followed by immediate reduction of aldehyde **9** with $NaBH_4$ to afford the latent primary alcohol **10**, which was ultimately converted to alkyl iodide **6** using Appel conditions (I_2, PPh_3, imid.) (Scheme 1). Synthesis of both the bromo and the iodo versions of the *Z*-vinyl halide subunit began from the same silyl protected *R*-homoallylic alcohol **12**.[23] Olefin

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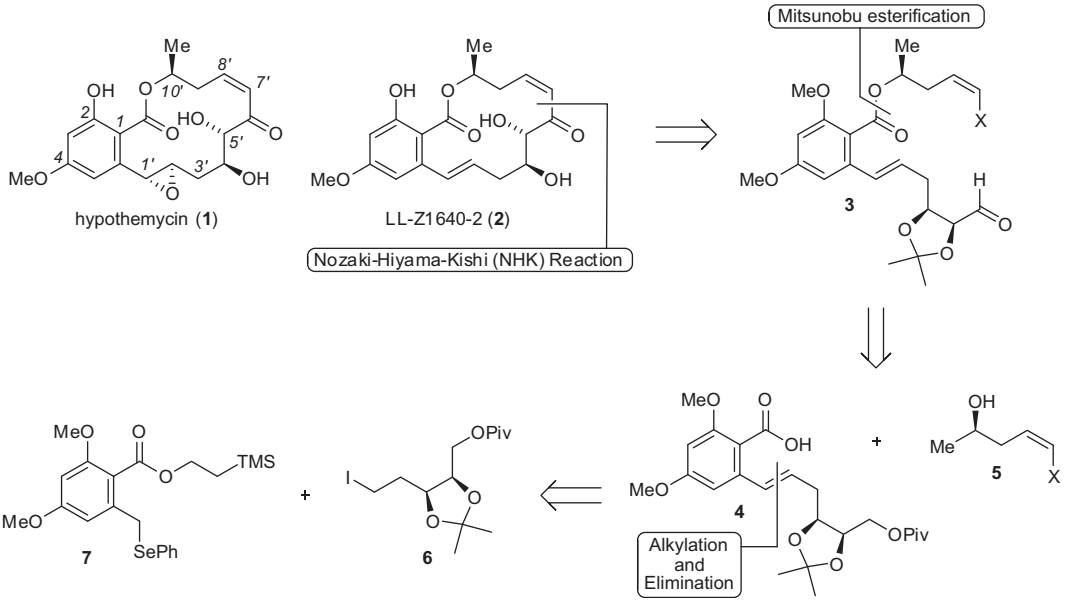
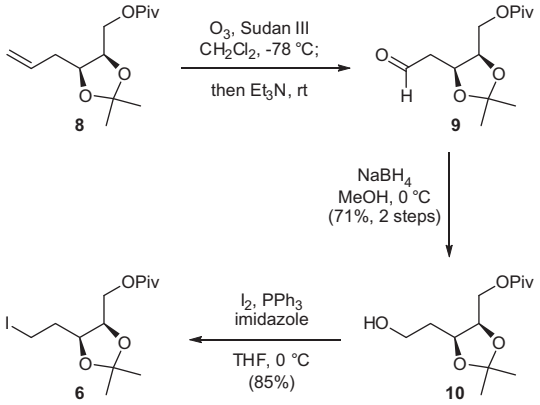
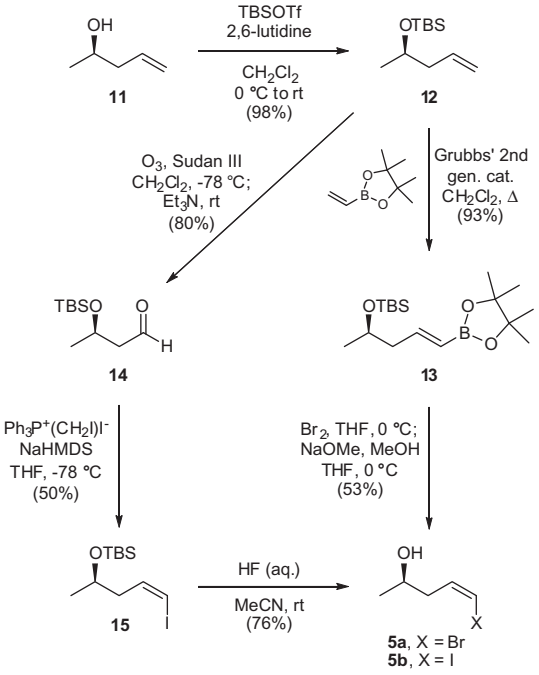


Figure 1. Structures of hypothemycin (**1**) and LL-Z1640-2 (**2**) with retrosynthetic analysis.



Scheme 1. Synthesis of alkyl iodide subunit **6**.

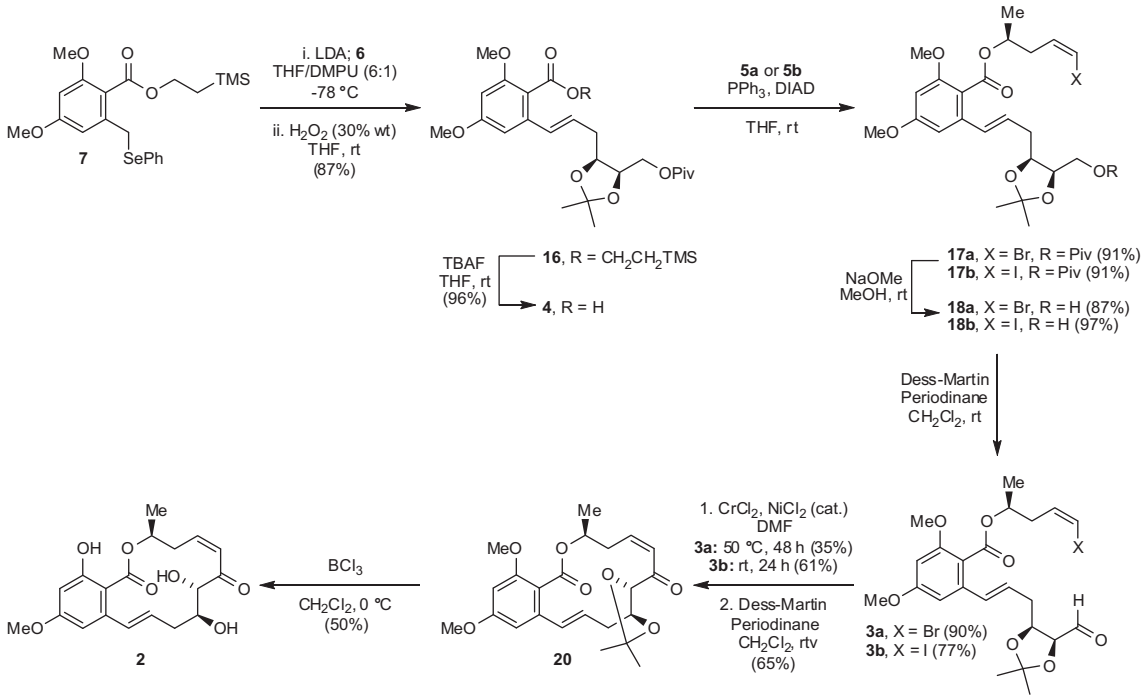


Scheme 2. Synthesis of *Z*-vinyl halides **5a** and **5b**.

cross-metathesis with vinyl boronic acid resulted in the desired *E*-vinyl boronate ester **13** in high yield (Scheme 2).[24] Using conditions developed by Brown et al.,[25] **13** was subjected to Br_2 resulting in the formation of a dibromide species *in situ*. Treatment with NaOMe/MeOH induced elimination and concomitant TBS deprotection providing *Z*-vinyl bromide **5a**. Preparation of *Z*-vinyl iodide **5b**[26] required an alternate synthetic approach as vinyl boronic esters subjected to I_2 under equivalent conditions result in retention of configuration yielding the undesired *E*-vinyl iodide.[25c,25d] As such, ozonolysis of **12** and subsequent Wittig olefination of the formed aldehyde **14** using phosphonium methyl iodide provided *Z*-vinyl iodide **15**, which upon silyl deprotection with HF gave **5b** in good yield.

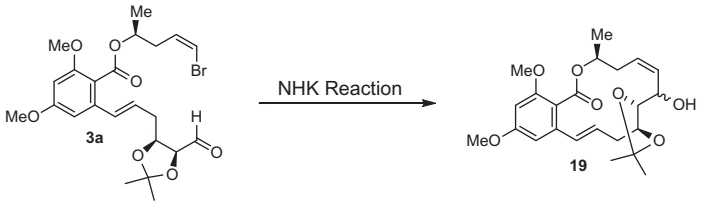
Treatment of aryl selenide **7** with LDA followed by addition of alkyl iodide **6** produced a mixture of alkylation products, which upon stirring with H_2O_2 afforded *trans*-olefin product **16** exclusively in high yield (Scheme 3). Removal of the TMSE group with TBAF furnished the key carboxylic acid intermediate **4** in excellent yield. The carbon skeleton is completed via Mitsunobu esterification with either vinyl bromide **5a** or vinyl iodide **5b** (yield was unaffected by the halogen). Pivalate deprotection and Dess–Martin oxidation occurred in a straightforward manner giving aldehydes **3a** and **3b** in 90% and 77% yield, respectively.

Initial explorations into the intramolecular NHK reaction to obtain the desired macrocycle **19** utilized vinyl bromide **3a** under various conditions (Table 1). Modifications to solvent system, equivalents of $CrCl_2$, reaction temperature, and reaction time were all unsuccessful in improving the low yields. During the course of the reaction, the starting material was rapidly consumed in agreement with the literature that oxidative addition of Ni to the substrate can be fast.[20] While the formation of a Cr–O bond is the thermodynamic driving force, the formation of product was slow, which is a common occurrence with the intramolecular NHK reaction.[21] The diminished yields might be attributed to decomposition of the organochromium intermediates despite the tolerance of numerous functional groups to the reaction conditions. Attempts



Scheme 3. Completion of the synthesis of LL-Z1640-2 (**2**).

Table 1
Conditions and results of NHK reaction with **3a**



Entry	$CrCl_2$ (equiv)	$NiCl_2$ (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	5	10	DMF	rt	24	15
2	5	10	DMF	50	24	26
3	10	5	DMF	50	48	35
4	10	5	DMF	50	72	34
5	10	5	DMF/4-^{t}BuPy (3:1)	50	48	30
6	10	5	DMSO	50	48	No product
7	10	5	DMSO/4-^{t}BuPy (3:1)	50	48	5
8	10	5	DMSO/DMF (20:1)	50	48	No product
9	10	5	THF/DMF (2:1)	50	48	19
10	10	5	THF/DMF/4-^{t}BuPy (6:3:1)	50	48	12
11	10	5	DME/DMF (6:1)	50	48	10

at further optimization through prolonged reaction times (>48 h) and specialized workup (aq sodium serinate[21d]) were unsuccessful. Based on this study, the best reaction conditions (entry 3, Table 1) provided the desired macrolactone in a modest 35% yield.

Further efforts at optimizing the yield prompted a halogen switch to vinyl iodide **3b**, which was subjected to the best vinyl bromide reaction conditions ($CrCl_2$ (10 equiv), $NiCl_2$ (5 mol %), DMF). Gratifyingly, the yield of the intramolecular NHK increased to an acceptable 61% with reduced reaction temperature (room temperature) and time (24 h). Exposure to longer reaction times and increased temperatures were ineffective at increasing the yield. The macrocyclization appears to have proceeded in a stereoselective fashion since macrocycle **19** was isolated as a single diastereomer. Previous examples of the intramolecular NHK reaction have demonstrated that proximal stereocenters and variation of the protecting groups can affect stereochemical outcome.[21] However, we did not investigate this aspect as the subsequent oxidation of the newly formed allylic alcohol renders the diastereoselectivity inconsequential to the synthesis. The ensuing penultimate Dess–Martin oxidation of the allylic alcohol afforded *cis*-enone **20** without incident. Selective deprotection of the *ortho* methoxy group with simultaneous removal of the acetonide was elicited by subjecting **20** to BCl_3 as previously reported to complete the total synthesis of LL-Z1640-2 (**2**).[17a]

In summary, this study has demonstrated the utility of an intramolecular Nozaki–Hiyama–Kishi reaction in establishing the macrolactone during the total synthesis of the naturally occurring macrolide LL-Z1640-2 (**2**). The resulting synthetic sequence provides a convergent strategy allowing for rapid exploration of novel analogues of this important natural product.

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Supplementary data

Supplementary data (experimental procedures and characterization data along with NMR spectra are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.092.

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