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Studies on the Synthesis of the Inostamycin Natural Products: A Reductive Aldol/Reductive Claisen Approach to the C_{10}–C_{24} Ketone Fragment

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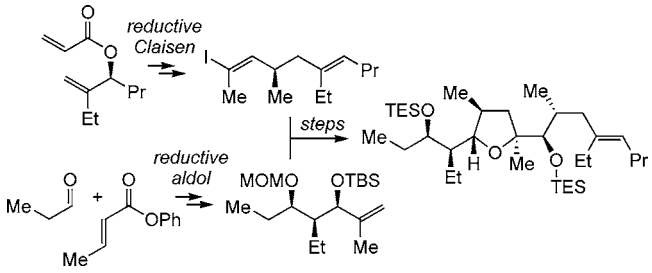
ABSTRACT



An approach to the C_{10}–C_{24} ketone fragment of the inostamycin family of polyether antibiotics is described. The synthetic strategy utilizes an asymmetric Rh-catalyzed reductive aldol reaction and a stereoselective Rh-catalyzed reductive Claisen rearrangement as the key steps in formation of alkene and vinyl iodide synthons, respectively.

In the process of screening for inhibitors of phosphatidyl inositol turnover, Imoto and Umezawa isolated inostamycin A (Figure 1) from the culture broth of a microorganism from

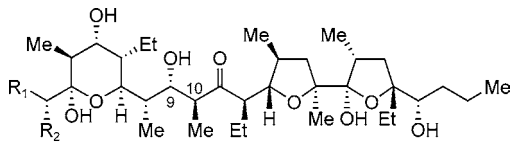


Figure 1. The inostamycin natural products.

the genus *Streptomyces* sp. MH816-AF15.[1] Several years later, Shindo et al. reported the isolation of inostamycins B and C from the culture broths of the same microorganism.[2] The three inostamycins differ only in the functionality occurring at the C_2 position. Inostamycin A elicits a wide range of pharmacological effects, showing inhibitory action toward both phosphatidyl inositol turnover and inositol transferase, while also possessing anti-HIV activity at 0.17 μM concentration, and anticancer activity against RPMI-8826 (GI_{50} = 10 nM), HL-60 (GI_{50} = 25 nM), and CCRF-CEM (GI_{50} = 32 nM) leukemia cell lines and some non-small cell lung carcinoma cell lines.[3] Inostamycins B and C also show activity against Gram-positive bacteria in vitro comparable to that of inostamycin A, and also show cytocidal activity against *src*-NIH-3T3 cells, albeit with less potency than

(1) Imoto, M.; Umezawa, K.; Takahashi, Y.; Naganawa, H.; Iitaka, Y.; Nakamura, H.; Koizumi, Y.; Sasaki, Y.; Hamada, M.; Sawa, T.; Takeuchi, T. *J. Nat. Prod.* **1990**, *53*, 825.

(2) Odai, H.; Shindo, K.; Odagawa, A.; Mochizuki, J.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 939.

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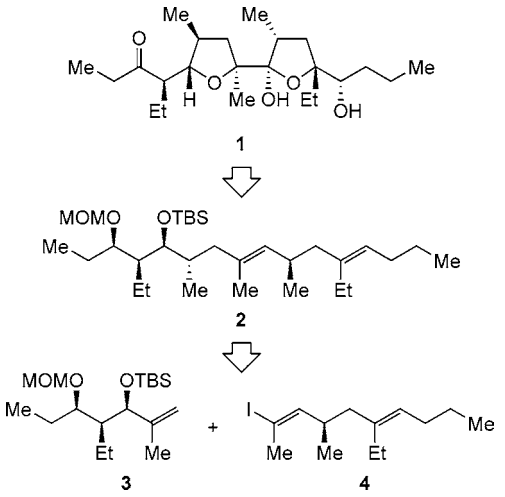
Scheme 1

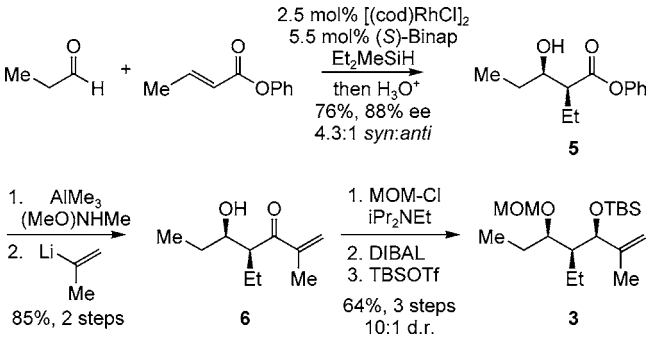


inostamycin A (IC_{50} values of 0.5 versus 0.07 μg/mL for inostamycin A).[2]

While no synthetic endeavors toward the inostamycin family of compounds have been reported, close structural relatives ferensimycin B and lysocellin have been synthesized by Evans[4] and Yonemitsu and Horita,[5] respectively. In their report on ferensimycin B, Evans and co-workers utilized an aldol coupling strategy as the final step to form the C9−C10 bond between the ethyl ketone and aldehyde fragments with the desired *anti*-aldol product being favored. An analogous aldol coupling strategy was employed by Yonemitsu and Horita in their total synthesis of lysocellin. In our approach to the inostamycin family of natural products, we intended to make a similar aldol disconnection rendering a C_1-C_9 aldehyde and a $C_{10}-C_{24}$ ketone as subtargets in the total synthesis. The structural complexity and functionality inherent in these fragments provided an excellent opportunity to explore the synthetic utility of both reductive aldol[6] and reductive Claisen[7] methodologies developed in our lab. In this paper, we describe our approach to the $C_{10}-C_{24}$ ketone fragment of the inostamycins, which we envisioned arising from the oxidative transformation of diene **2** obtained from tandem hydroboration/B-alkyl Suzuki coupling of alkene **3** and vinyl iodide **4** (Scheme 1).

The synthesis of ketone **1** began with the Rh-catalyzed asymmetric reductive aldol reaction between propionaldehyde and phenyl crotonate, which provided β-hydroxy ester **5** in 76% yield and with 4.3:1 diastereoselectivity and 88% enantioselectivity (Scheme 2).[6] The phenyl ester was then

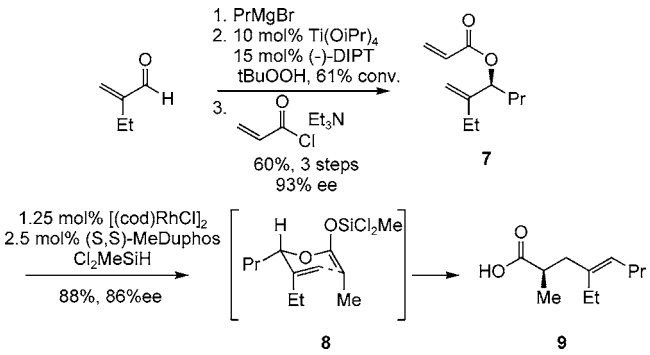
Scheme 2



converted to the derived Weinreb amide and subsequently treated with 2-lithiopropene to form α,β-unsaturated ketone **6**.[8] Protection of the free alcohol as a methoxymethyl ether followed by chelation controlled reduction of the ketone[9] (10:1 diastereoselectivity) and protection of the resulting free alcohol as TBS−ether furnished protected allylic ether **3**.

Our plan for the synthesis of vinyl iodide **4** involved the application of the reductive Claisen rearrangement to install the correctly configured C_{18} stereocenter.[7] While our previous studies found that this reaction proceeded with a high degree of diastereoselectivity, no investigations into the level of chirality transfer in the rearrangement process have been carried out. To test the feasibility of this strategy in the context of the inostamycin synthesis, we prepared allylic acrylate **7**. This was accomplished by Grignard addition to 2-ethylacrolein followed by Sharpless kinetic resolution[10] and esterification with acryloyl chloride (Scheme 3). Treatment

Scheme 3



of compound **7** with $[Rh(cod)Cl]_2$ in the presence of Cl_2-MeSiH and (*S,S*)-Me-DuPhos led to the formation of **9** in 88% yield and with 86% ee.[11] Thus the reductive Claisen,

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(4) Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613.

(5) (a) Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 531. (b) Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 551.

(6) (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (b) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (c) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurriset, P.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309. (d) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, *9*, 1459.

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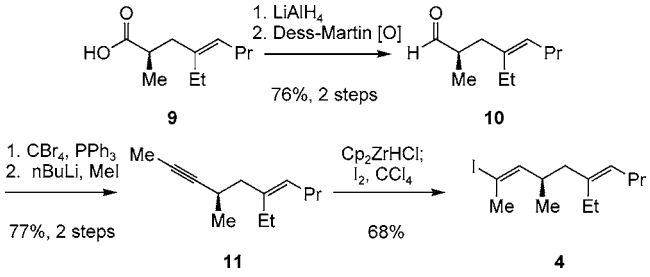
(9) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235.

in this instance, occurred with 92% chirality transfer, a level consistent with previously reported levels of diastereoselectivity in the reductive Claisen rearrangement.[7] Presumably, the reaction proceeds through the intermediacy of an (*E*)-silyl ketene acetal as is generated from allylic acrylates upon reduction with Rh/Duphos and Cl_2MeSiH.[12] Subsequent rearrangement via a six-membered chair transition state such as **8** is consistent with the observed stereochemical outcome of the reaction (Scheme 3). At this point, it is not clear whether the small amount of erosion in enantiomeric purity arises from a competing boat transition structure in the Claisen rearrangement or from imperfect *E*/*Z* selectivity in reduction of the acrylate to the silylketene acetal.

The γ,δ-unsaturated carboxylic acid **9** obtained from the reductive Claisen rearrangement was then converted to aldehyde **10** via a reduction/oxidation sequence and thereafter converted to alkyne **11** by the Corey−Fuchs reaction (Scheme 4).[13] Analysis of the enantiomeric purity at this stage

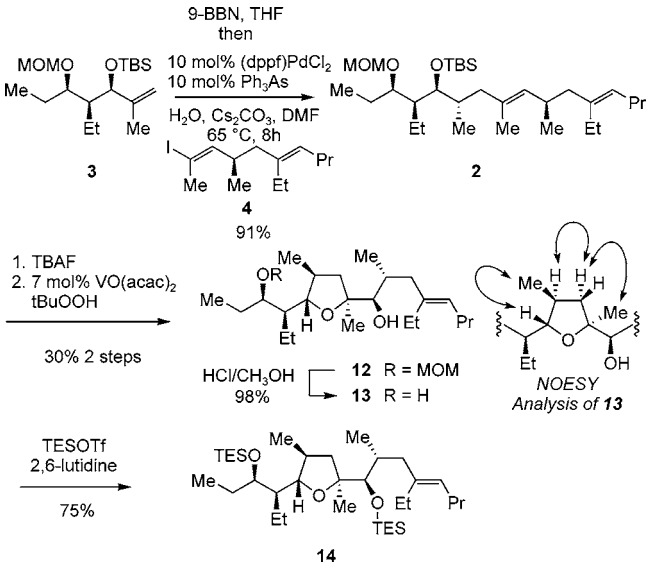
Scheme 4



indicates that the allylic stereocenter was not racemized during the reaction sequence. Hydrozirconation of the methyl alkyne with Schwartz' reagent and iodinolysis of the vinyl zirconium intermediate with iodine provided vinyl iodide **4**.[14]

The union of subunits **3** and **4** was accomplished by carrying out a stereoselective hydroboration[15] of alkene **3** with 9-BBN and effecting a Suzuki−Miyaura coupling of the intermediate alkyl borane with vinyl iodide **4** to provide diene **2** in a 91% yield for the tandem process (Scheme 5).[16] Initial exploratory studies of the oxidative cyclization were conducted. In the event, deprotection of the TBS−ether **2** was then followed by a bis-homoallylic alcohol directed vanadium-catalyzed epoxidation.[17] As expected based on Evans' studies in the ferensimycin synthesis, the intermediate epoxide underwent cyclization to provide trisubstituted furan

Scheme 5



12 with a 6:1 diastereomer ratio. Fortuitously, subsequent epoxidation of bishomoallylic alcohol **12** was sufficiently slow, relative to the oxidation of starting material **2**, that the monooxidation adduct could be isolated. This allowed for protecting group manipulation in preparation for oxidation of the remaining alkene.[18] Under acidic conditions, the MOM protecting group was removed to give **13** and at this stage the relative stereoinduction in the epoxidation/cyclization sequence was determined by NOESY analysis. Subsequently, both free alcohols were then protected as TES−ethers, providing **14**. With the $C_{10}-C_{24}$ carbon framework constructed, and easily removable alcohol protecting groups in place, current efforts are being directed toward developing the oxidation strategy for the $C_{20}-C_{21}$ alkene and conversion to **1**.

In summary, we have described an expeditious and convergent route that constructs the requisite carbon skeleton of the $C_{10}-C_{24}$ ketone fragment of the inostamycin natural products. This pathway involves the use of two Rh-catalyzed methodologies developed in our lab and showcases their utility in the rapid construction of a complex structural subunit of an important natural product. Further studies on the synthesis of the inostamycin family of natural products will be reported in due course.

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Supporting Information Available: Characterization data, spectra, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Evans has shown that oxidation of the $C_{20}-C_{21}$ alkene is a delicate task, and great care must be taken to avoid irreversible formation of a bicyclic ketal (see ref 4).