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Highly Diastereoselective Type-I IMDA Reaction Forming Medium-Sized Macrolactones

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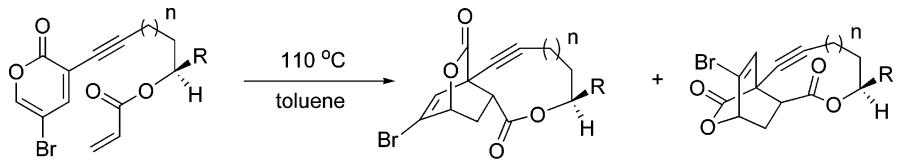
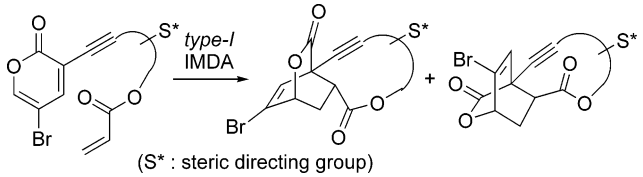
ABSTRACT



Intramolecular Diels−Alder (IMDA) reactions of 2-pyrones containing an alkyne tether occur with remarkably high diastereofacial selectivity to provide medium-sized macrolactones. Because of the strain in the alkyne-tethered macrocyclic system, a single methyl group in the tether provides sufficient conformational bias to generate medium-sized macrocycles with unusually high selectivity.

Intramolecular Diels−Alder (IMDA) reactions have proven to be powerful tools for forming carbocycles, which have been utilized in the synthesis of natural products of varying molecular complexity.[1] One of the most important challenges in these transformations is control of the stereoselectivity between the two diastereotopic faces of the diene (Scheme 1). In contrast to IMDA reactions that form five- or six-membered fused cycles,[2] diastereofacial control for medium- and large-sized rings has presented a formidable task. One apparent obstacle is the large degree of conformational freedom associated with the tethered chain.[3] Unlike its Type-II intramolecular counterpart, Type-I IMDA reactions that form medium-sized macrolactones have remained much unexplored and are often unsatisfactory with respect to both stereoselectivity and yield.[4] For instance, Stork and Naka-

Scheme 1. Diastereofacial Control in IMDA Reactions Containing an Alkyne-Tethered 2-Pyrone System



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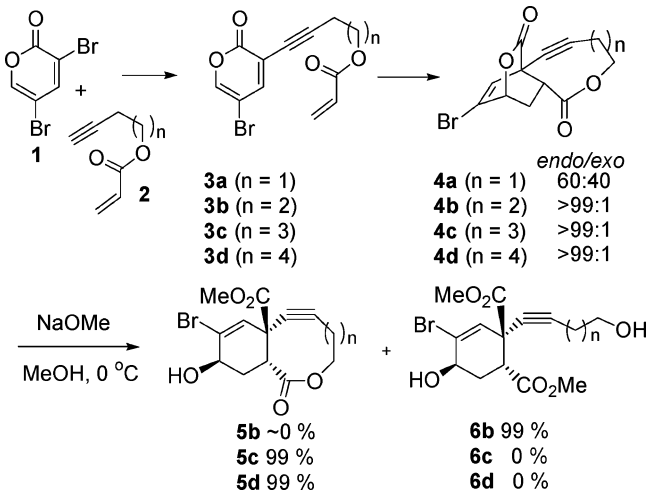
mura reported the use of a Type-I IMDA strategy in their synthesis of cytochalasins F and B, affording the tetracyclic adduct in 35% yield as a 4:1 mixture of *endo*:*exo* products.[5] The total synthesis of pinnatoxin reported by Kishi and coworkers also showcased the adventurous nature of the Type-I IMDA approach, providing a key intermediate in 34% yield, along with two other isomers.[6] We envisioned that introducing an sp^2- and/or sp-hybridized carbon(s) would reduce conformational flexibility and thereby lead to a high level of stereocontrol. In this report, we describe a surprisingly high diastereofacial and *endo*/*exo*-selective Type-I IMDA macrolactonization of alkyne-tethered 2-pyrones bearing a steric directing group (Scheme 1).

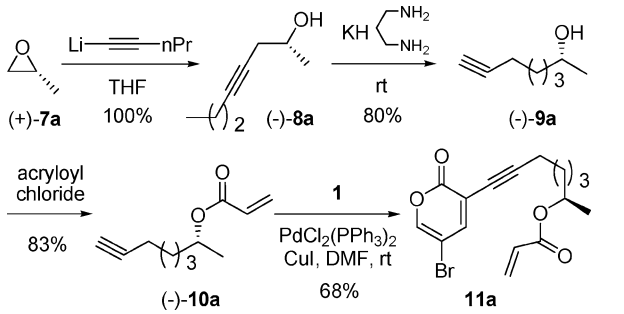
As a part of our ongoing research program on 3,5-dibromo-2-pyrone **1**,[7] we recently reported that **1** undergoes regio- and chemoselective Sonogashira coupling reactions at C3, to provide **3a**−**3d** in good to excellent yields (Scheme 2).[7a]

Scheme 2. IMDA−Macrolactonization of 2-Pyrones



The resulting coupling products were also shown to undergo IMDA reactions, with high *exo/endo* selectivity, to afford macrocycles **4a**−**4d** with a carbon skeleton reminiscent of the cyclohexane-based macrocyclic musks.[7a,8] During our continued study on the selective ring opening of the bicyclic lactone unit with methoxide, we observed that the selectivity depends on the size of macrolactone. In the cases of 10- and 11-membered macrocycles **4c** and **4d**, the more strained [2,2,2]-bicyclic lactone opening was achieved in an exclusive fashion to produce only **5c** and **5d**, respectively. However, for the nine-membered-ring homolog, the opening of the macrolactone became competitive to give **6b**, implicating substantial ring strain in the alkyne-tethered macrocycle (Scheme 2). For more selective lactone ring opening, we prepared several analogues of **4** bearing an alkyl group adjacent to the macrocyclic ester oxygen. A representative synthetic procedure for these series is outlined in Scheme 3 for (*R*)-**11a**. Opening

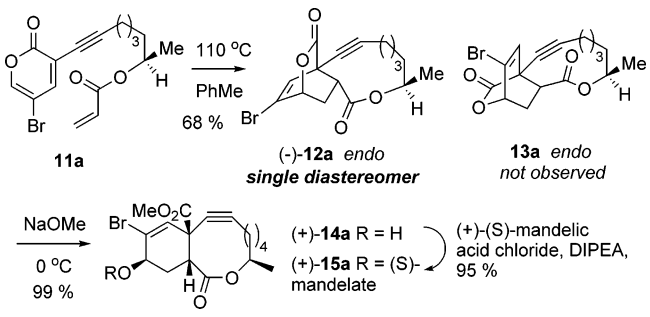
Scheme 3. Synthesis of **11a**



of (*R*)-propylene oxide **7a** with pentyne anion, followed by isomerization of the triple bond,[9] delivered (−)-**9a** in 80% overall yield with greater than 98% ee. Acylation of the resulting secondary alcohol provided (−)-**10a**. Their enantiomeric purity was confirmed by chiral HPLC analysis. Subsequent chemo- and regioselective Pd-catalyzed Sonogashira coupling reactions with 3,5-dibromo-2-pyrone led to (*R*)-**11a**, which was directly subjected to the IMDA cycloaddition reaction because of the instability of **11a**.

To our surprise, heating **11a** at reflux in toluene provided a single 11-membered macrolactone, (−)-**12a**, in 68% yield (95% based on 72% conversion, Scheme 4). Examination

Scheme 4. Highly Diastereoselective IMDA Cycloaddition of **11a**



of the NMR spectra of crude **12a** as well as purified **12a**, indicated that no other diastereomers were produced. To eliminate the possibility that any two of the other possible

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diastereomers (*endo*/*exo* as well as facial diastereomers) might have overlapping signals, we conducted a derivatization study and chiral HPLC analysis as follows. Conversion of (+)-**14a** to its corresponding (*S*)-mandelate ester (+)-**15a** was carried out as shown in Scheme 4. Spectroscopic analysis was consistent with the presence of a single diastereomer.[10] Additionally, chiral HPLC analysis [chiralcel OJ, hexane/isopropyl alcohol (97:3), 1 mL/min] of the crude reaction mixture revealed no other diastereomers (or enantiomers) present in the IMDA cycloaddition product. Fortuitously, bicyclic lactone (−)-**12a** was recrystallized to form a single crystal from Et_2O/hexane, and the relative and absolute stereochemistry of the three new stereocenters in (−)-**12a** was unambiguously established (Figure 1).[11]

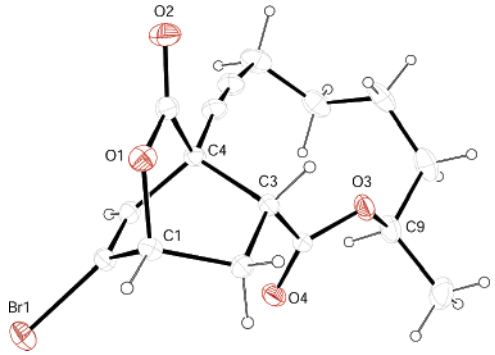
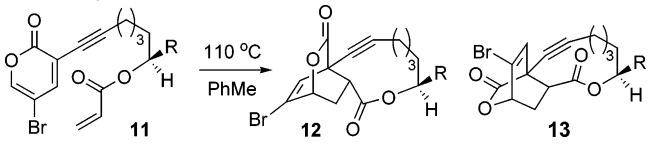


Figure 1. X-ray diffraction data for (−)-**12a**.

Interestingly, when the methyl group in the tether was replaced with the bulkier isopropyl or *tert*-butyl group, the observed diastereofacial selectivity decreased (Table 1). We

Table 1. Effect of Directing Group on Diastereofacial Selectivity



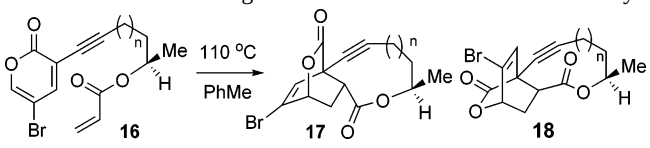
entry	10	time (h)	12 *endo*/*exo*	13[a] *endo*/*exo*	yield[b] (%)
1	**11b** (R = *i*-Pr)	14	88 (100:0)	12 (100:0)	64
2	**11c** (R = *t*-Bu)[c]	14	80 (100:0)	20 (100:0)	61

[a] Minor diastereomers decomposed upon separation with HPLC. [b] Isolated yields. [c] A racemate was used.

envisioned that the bulkier substituent would exert an increased level of steric repulsion, diminishing the energy difference between two corresponding transition states (leading to **12** and **13**, respectively).

We then set out to examine the ring size effect on the diastereofacial selectivity (Table 2). Unlike **11a** and **16d**

Table 2. Effect of Ring Size on the Diastereofacial Selectivity[a]



entry	16	time (h)	17 *endo*/*exo*	18 *endo*/*exo*	yield (%)
1	**16a** ($n = 1$)	16	100 (100:0)	0	57
2	**16b** ($n = 5$)	16	78 (77:23)	22 (50:50)	58

[a] Stereochemistry of the major diastereomer was deduced from the analogy to (−)-**12a**.

(forming 11- and 9-membered macrocycles, respectively), **16b** showed some stereochemical leakage during the cycloaddition into the 13-membered lactone (entry 2). Moreover, each of **17b** and **18b** was attained as a mixture of *endo*/*exo* isomers (77/23 and 50/50, respectively) and the diastereoselectivity (ratio of **17b**/**18b**) decreased to 78:22. In general the observed diastereofacial selectivity was higher for the smaller macrocycles.

In conclusion, we have demonstrated that alkyne-tethered 2-pyrones undergo highly diastereoselective intramolecular Diels−Alder cycloaddition reactions to provide 9- to 11-membered macrolactones fused a bicyclolactone, representing a rare case of stereocontrolled macrocycle forming Type-I Diels−Alder reactions. Further studies of asymmetric Type-I IMDA reactions of other diene systems are currently underway in our laboratory.

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

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(10) Determination of the relative stereochemistry according to the method of Trost was not successful because of the relatively small chemical shift difference between the (*R*) and (*S*) mandelates of (+)-**14a**. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687.

(11) $[\alpha]^{25}_D = -54$ (*c* 1.00, $CHCl_3$). The mother liquor, after concentration, contained only (−)-**12a** having the same sense and magnitude of optical rotation.