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Stereocontrolled Synthesis of the Diene and Triene Macrolactones of Oximidines I and II: Organometallic Coupling versus Standard Macrolactonization

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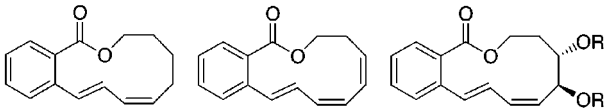
ABSTRACT



1 2 3

Stereocontrolled construction of the 12-membered diene and triene lactones 1, 2, and 3, characteristic of the antitumor agent oximidines I and II, are reported and were based on an intramolecular Castro–Stephens coupling for the construction of a cyclic enyne or dienyne followed by stereoselective reduction of the cyclic alkyne for introduction of the *cis*-olefin of the targets. A comparison of the effectiveness of this protocol is made with standard macrolactonization.

Oximidines I and II (Figure 1) are members of a new family of cytotoxic natural products isolated in 1999 from *Pseudomonas*.[1] These agents exhibit cytotoxicity at ng/mL levels that is selective for *ras* and *src* oncogene transformed cells. The agents effect inhibition of the cell cycle at the G1 phase,[1] and recent studies have identified the cellular target of the oximidines as mammalian vacuolar-type (H^+)-ATPases.[2] The oximidines possess a functionalized and polyunsaturated 12-membered lactone that is relatively immobile as the result of the presence of 10 contiguous sp^2 or *pseudo*-sp^2 atoms.

There has been no synthetic work on the diene and triene oximidine macrocycles,[3] and only recently have reports appeared[4−6] on the total synthesis of the structurally related cytotoxic agents salicylihalamides A and B.[7] We now describe a stereocontrolled entry into the unsaturated lactone ring systems of oximidines I and II that is based on an intramolecular Castro−Stephens coupling reaction[8,9] for macrocycle formation.[10] One of the most significant synthetic challenges in constructing the macrocycle systems of these agents is control of (*E*,*Z*)-diene and (*E*,*Z*,*Z*)-triene stereochemistry. As a straightforward solution to this problem, we have used an alkyne to (*Z*)-alkene transformation as a method for olefin stereocontrol in the transformation of **2** to **1**, where

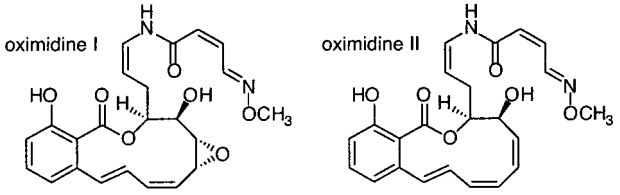


Figure 1. Structures of oximidines I and II.

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(3) For simplified model systems lacking the conjugated diene/triene system, see: Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221−1224.

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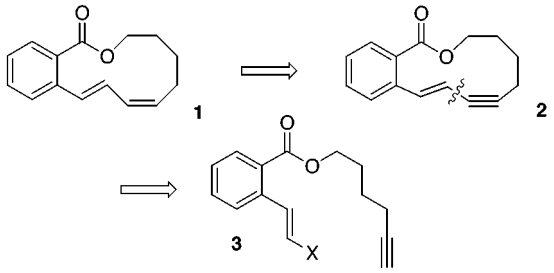
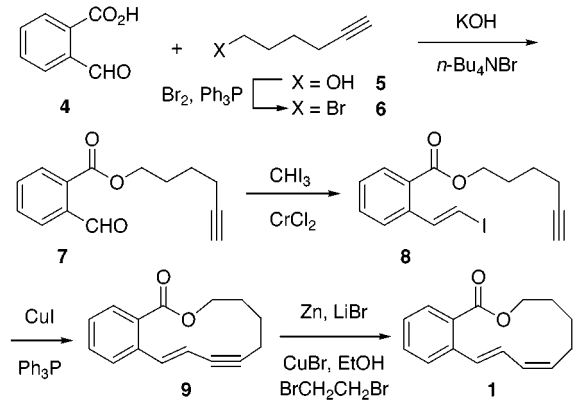
Scheme 1



the cyclic enyne of **2** arises from an intramolecular copper-promoted macrocyclization reaction between the (*E*)-vinyl halide and terminal alkyne of **3** (Scheme 1). Inherent in this plan is the issue of ring strain in the formation of macrocyclic enyne and dienyne systems.

For the synthesis of model system **1** (Scheme 2), alkylative

Scheme 2



esterification[11] of phthalaldehydic acid (**4**) with 6-bromo-1-hexyne (**6**) (aqueous KOH, *n*-Bu_4NBr, 80 °C, 18 h, 84%), which was prepared from 5-hexyn-1-ol (**5**) (Br_2, Ph_3P, CH_3CN, 0 °C, 87%),[12] afforded ester **7** (90%). Takai olefination[13] of the aldehyde of **7** (CHI_3, $CrCl_2$, THF, 0 °C, 2 h) afforded vinyl iodide **8** (65%) as an inseparable 4.3:1 *E*/*Z* mixture of stereoisomers. Under traditional Sonogashira coupling protocols, the cyclization partner **8** was transformed to a series of unidentifiable compounds, not including the desired lactone **9**. Using the modified Castro−Stephens coupling conditions of Miura and co-workers[14] (catalytic CuI, Ph_3P, K_2CO_3, DMF, 120 °C), cyclization of **8** afforded cyclic enyne lactone **9** in modest yields (37%), in addition to a small amount of dimeric product (10−15%). Stereoselective reduction of the alkyne of **9** (Zn^0, $BrCH_2CH_2Br$, LiBr, CuBr, EtOH, reflux)[15] afforded the (*E*,*Z*)-diene lactone **1** (71%).

The modest yield for this cyclization may be a consequence of the strained ring system that is formed, as similar yields in the synthesis of strained cycloalkynes are precedented.[10,16] Computer modeling (MMX force field) showed the alkyne sp-sp^3 and sp-sp^2 bonds of **9** to be approximately 25° from linearity (Figure 2). The source of copper (e.g., CuCl vs. CuI) had little effect on the conversion of **8** to **9**, and the phosphine additive had a modest effect, with improvement noted for bisphosphines 1,3-diphenylphosphinopropane (46%) and 1,4-diphenylphosphinobutane (43%). The reaction worked equally well in DMF, DMSO, or *N*-methylpyrrolidinone (NMP) but poorly in xylenes. The use of Cs_2CO_3 in place of K_2CO_3 had no effect.

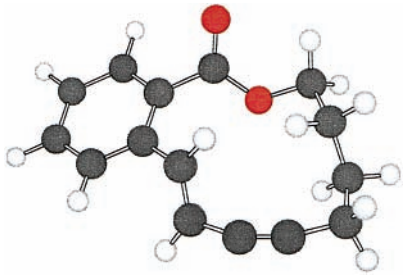


Figure 2. Energy minimized (MMX global minimum) cyclic enyne **9** showing distorted alkyne bonds.

The more elaborate alkyne cyclization partner bearing an additional (*Z*)-alkene was synthesized from 3-butyn-1-ol (**10**) by iodination of the dianion of **10** (94%) to afford **11** (Scheme 3), followed by diimide reduction (2 equiv of $TsNHNH_2$, 3 equiv of NaOAc, 1:1 THF/H_2O, reflux, 4 h, 60%) to *cis*-vinyl iodide **12**. Sonogashira coupling of **12** with trimethylsilylacetylene (0.04 equiv of $Pd(PPh_3)_4$, 0.16 equiv of CuI, Et_2NH, 0 °C) afforded **13** (90%). Conversion of the

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(5) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817−1820.
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(9) The Castro−Stephens and Sonogashira reactions effect sp^2-sp carbon−carbon bond formation. The Castro−Stephens coupling uses stoichiometric copper, whereas the Sonogashira variant uses catalytic palladium and copper: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. Sonogashira, K. Cross-Coupling Reactions to sp Carbon Atoms. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich , F., Stang, P. Eds.; Wiley-VCH: New York, 1998; pp 203−229.
(10) There has been only a single description of the use of either coupling reaction for the synthesis of macrolactones: Yoshimura, F.; Kawata, S.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 8281−8285.
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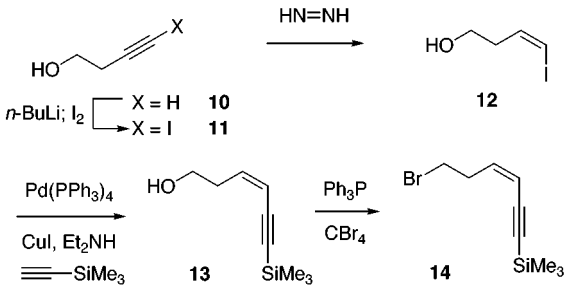
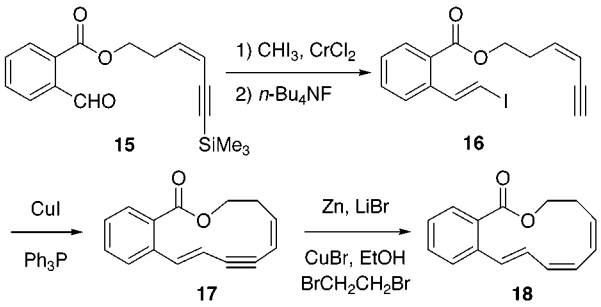
Scheme 3



hydroxyl group of **13** to the corresponding bromide (Ph_3P, CBr_4, −30 °C CH_2Cl_2, 3 h) afforded **14** (91%).

The cyclic (*E*,*Z*,*Z*)-triene system of oximidine II was constructed from bromide **14** (Scheme 4) as above to afford

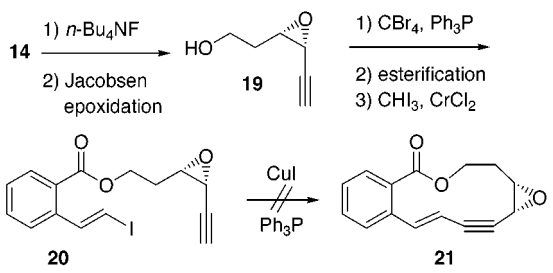
Scheme 4



ester **15** (60%). Takai olefination (78%) followed by removal of the silyl group (96%) afforded **16** as a 4:1 ratio of stereoisomers. The enyne ester of **16** underwent cyclization onto the vinyl iodide to afford the macrocyclic dienyne **17** in modest yield (35%), again the yield being a consequence of ring strain (alkyne nonlinearity ca. 24°). Semireduction of the alkyne of **17** afforded (*E*,*Z*,*Z*)-triene lactone **18** (64%).

For the epoxide-bearing lactone of oximidine I, the propargylic epoxide **19** was synthesized from **14** using a Jacobsen epoxidation (Scheme 5).[17] Transformation of the

Scheme 5

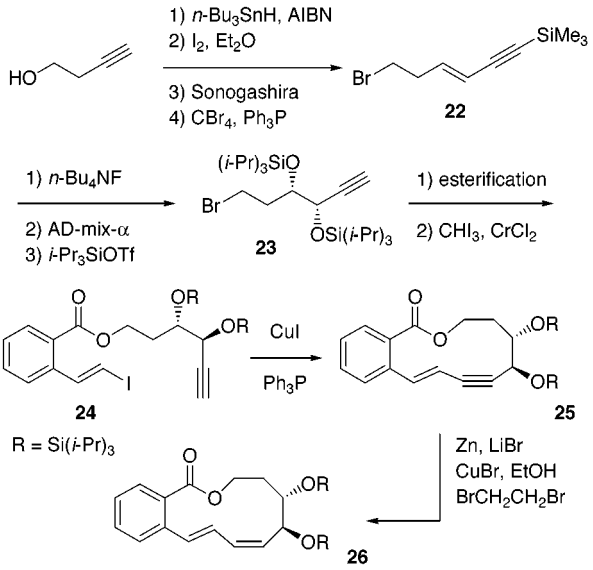


primary alcohol of **19** to the bromide, esterification of phthalaldehydic acid, and Takai olefination afforded **20**.

Intramolecular Castro−Stephens coupling of **20** under a variety of reaction conditions failed to provide the unsaturated macrolactone **21**. This is not surprising given the potential sensitivity of propargylic and allylic epoxides, and so it appeared that this factor led to the failure of this particular cyclization.

As a *syn*-1,2-diol could potentially serve as a precursor to the oximidine I *cis*-epoxide, this option was implemented in the synthesis of macrolactone **26** (Scheme 6). Enyne **22**

Scheme 6



was synthesized from 3-butyn-1-ol by hydrostannylation (*n*-Bu_3SnH, AIBN, 90 °C, 16 h, 80%) and iodination (83%) to afford the *trans*-vinyl iodide,[18] which was coupled with trimethylsilylacetylene (0.04 equiv of $Pd(PPh_3)_4$, 0.16 equiv of CuI, Et_2NH, THF, 0 °C, 1.5 h, 95%). Conversion of the alcohol to the bromide (CBr_4, Ph_3P, CH_2Cl_2, −30 °C, 82%) afforded **22**. Sharpless asymmetric dihydroxylation[19] of **22** afforded the *syn*-1,2-diol, which was protected as the bis-silyl ether **23** (*i*-Pr_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 92%). Esterification of phthalaldehydic acid (63%) and Takai olefination (72%) provided **24**. The Castro−Stephens cyclization of **24** proceeded in 15% yield for the formation of enyne **25**, likely because of ring strain and the presence of a potentially reactive propargylic ether. Reduction of the alkyne of **25** afforded the (*E*,*Z*)-diene lactone **26** (76%).

To understand whether the modest yields for the intramolecular Castro−Stephens coupling reactions were a specific limitation of the synthetic protocol or were the result of features inherent in the target molecules, we examined the complementary bond forming process of macrolactonization.

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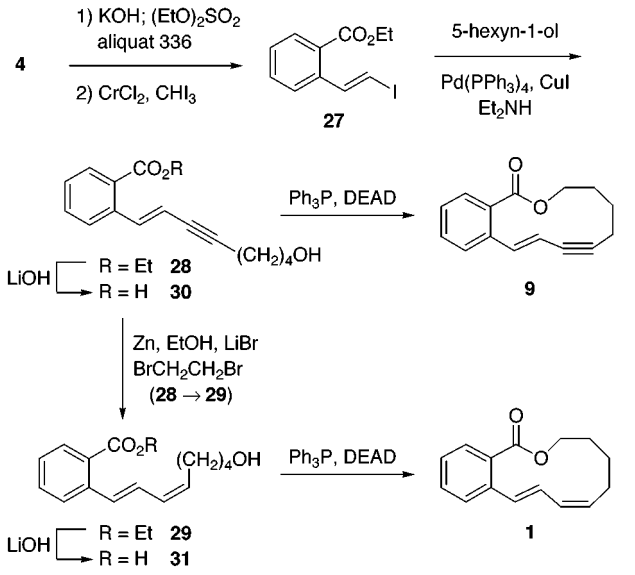
We were especially interested in understanding the role that bond strain played in the formation of cyclic enyne systems, and so we undertook a comparative study of macrolactonization to form cyclic enyne **9** versus cyclic (*E*,*Z*)-diene **1** (Scheme 7). The cyclization substrates chosen for study were

Scheme 7



synthesized by Sonogashira coupling of the vinyl iodide of **27** (prepared from phthalaldehydic acid by alkylative esterification and Takai olefination) with 5-hexyn-1-ol to afford **28** (76%). Semireduction of the alkyne of **28** afforded the (*E*,*Z*)-dienol **29** (88%). Saponification of the methyl esters of **28** and **29** (LiOH, 4:1 MeOH/H_2O, 16 h, 25 °C) afforded the corresponding carboxylic acids **30** (95%) and **31** (94%), respectively.

The most effective method for performing macrolactonization in these systems was the Mitsunobu protocol.[20] Under standard cyclization conditions (1.7 equiv of Ph_3P, 1.4 equiv of $EtO_2CN{=}NCO_2Et$, benzene, 0.004 M, 24 h, 25 °C), enyne substrate **30** afforded **9** in 26% yield plus 12% dimer. Diene substrate **31** afforded **1** in 23% yield with 5% dimer under similar conditions (1.7 equiv of Ph_3P, 1.4 equiv of $EtO_2CN{=}NCO_2Et$, benzene, 0.004 M, 18 h). Yields were not increased upon extended exposure of **30** and **31** to the reaction conditions. Protocols that rely on nucleophilic acyl substitution such as that of Yamaguchi[21] were ineffective at providing any of the cyclized products. These results clarify two important aspects of the present work. There was no significant difference in the gross rate of macrolactonization of **30** versus **31** or in isolated yield of enyne **9** compared with diene **1**, so it does not appear that the strained cyclic alkyne of **9** is the sole limiting factor of the cyclization yields. Rather, this seems to be an inherent feature of the unsaturated macrocyclic systems. In addition, using the standard synthetic strategy of macrolactonization, the yields of cyclization products were significantly lower than with the organometallic-based coupling protocol described above, indicating the suitability of the more complex protocol for the synthesis of these ring systems.

This report is the first description of the synthesis of the unsaturated diene and triene macrolactone ring systems of oximidines I and II. The Castro−Stephens macrocyclization reaction was achieved in modest yields, presumably because of the strain present in the macrocyclic enyne and dienyne ring systems. Several factors contribute to this being a valuable synthetic strategy, including the simplicity of the approach, the degree of stereocontrol achieved in the formation of the conjugated stereogenic double bonds, and the convergent nature of the macrocyclization process.

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Supporting Information Available: Procedure for intramolecular Castro−Stephens coupling reactions and spectral characterization of cyclization precursors **8**, **16**, **20**, and **24**, cycloalkyne products **9**, **17**, and **25**, and products **1**, **18**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016744E

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