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Synthesis of Strained 1,3-Diene Macrocycles via Copper-Mediated Castro–Stephens Coupling/Alkyne Reduction Tandem Reactions

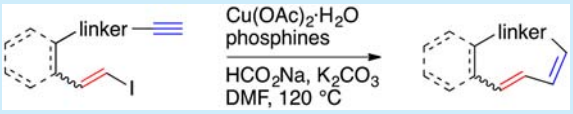
Wei Li,[†] Christopher M. Schneider,[‡] and Gunda I. Georg*[,†]

[†]Department of Chemistry, Department of Medicinal Chemistry, and the Institute for Therapeutics Discovery and Development, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414, United States

[‡]Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

Supporting Information

ABSTRACT: A copper-mediated macrocyclization involving the reaction of a vinyl iodide and a terminal alkyne followed by an in situ reduction of the enyne intermediate is reported. The reaction generates a conjugated *Z*-double bond within a strained medium-size lactone, lactam, or ether macrocycle. A variety of macrocyclic compounds bearing different ring sizes and functionalities were synthesized. A complementary stepwise procedure was also developed for less strained ring systems.



Highly functionalized macrocycles are prevalent structural features in natural products and are present in more than 100 marketed drugs.[1] We are particularly interested in macrocycles possessing conjugated *E*,*Z*-polyene units within the ring since this motif is present in a number of natural products with diverse and potent bioactivities such as latrunculin A, oximidine II, lactimidomycin, and radicicol (Figure 1).[2]

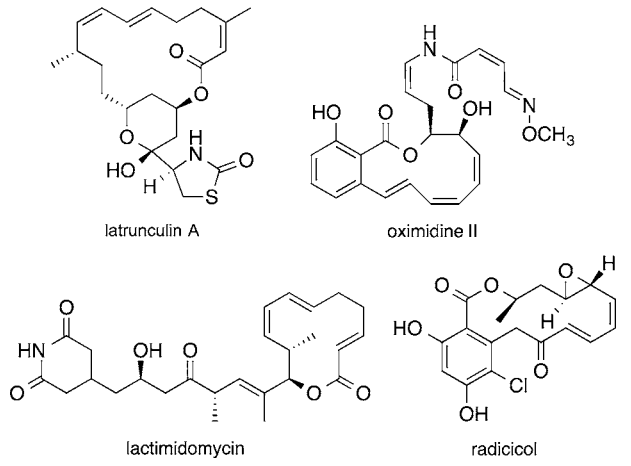
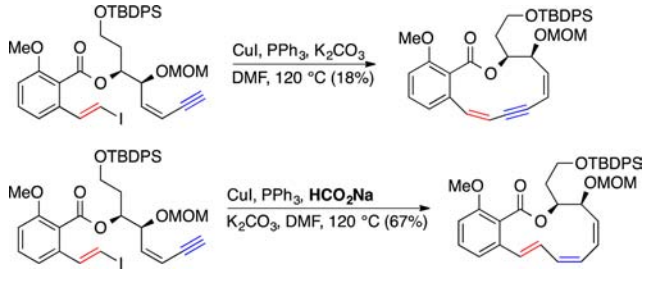


Figure 1. Selected examples of polyunsaturated macrocyclic natural products.

Most reported total syntheses of these natural products rely on variants of ring-closing metathesis (RCM) reactions,[3] which exhibited low efficiency for highly strained ring systems such as oximidine II[3c] and could potentially generate *E*/*Z* isomers and ring contraction products.[3f,4] A palladium-catalyzed Suzuki cross-coupling reaction was also employed for the synthesis of oximidine II,[5] but the yield for the macrocyclization was similar to those achieved with RCM reactions. A sequential RCM/intramolecular palladium-catalyzed cross-coupling reaction between an alkenyl iodide and a siloxane also provided access to an oximidine-like macrocyclic structure and related analogues in good yields.[6] For the synthesis of lactimidomycin, the *E*,*Z*-configuration of the 1,3-diene was established using a RCM reaction; however, a silyl directing group was needed for regio- and stereocontrol.[3f] Despite these successful total syntheses, methods to prepare conjugated polyene macrocycles are underexplored, and new efficient methods that are tolerant of diverse functional groups would be important to further explore these types of structures for biomedical applications.

We pursued an alternative approach to this structural motif via a two-step ene–yene macrocyclization[7]/alkyne reduction sequence en route to the total synthesis of oximidine II (Scheme 1). Initial attempts were disappointing. The highly strained cyclic dienyne intermediate was obtained in very low yield, and the double bond underwent *E*–*Z* isomerization to release ring strain.[8] Further investigations revealed that the ene–yne coupling reaction performed in the presence of the

Scheme 1. Ene–Yne Coupling/Reduction Approach in the Total Synthesis of Oximidine II



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reducing reagent sodium formate allowed the in situ reduction of the dienyne to afford the desired triene macrocycle in a single step.[9] The 67% yield compared favorably to the 40–50% yields reported for the ring-closing steps in the two previous total syntheses.[3c,5] Encouraged by this success, we decided to explore this coupling/reduction tandem transformation as a general method for the construction of conjugated polyunsaturated macrocycles.

For optimization studies, we initially examined the coupling/reduction tandem reaction with vinyl iodide **1a** (Table 1) under conditions similar to those reported for the

Table 1. Optimization of the Reaction Conditions[a]

entry	temp (°C)	solvent	ligand	yield[b] (%)	ratio (**2a**/**3a**)[c]
1	120	DMF	PPh_3	34	20:1
2	100	DMF	PPh_3	0	N/A
3	140	DMF	PPh_3	19	6:1
4	120	DMSO	PPh_3	31	20:1
5	120	toluene	PPh_3	0	N/A
6	120	dioxane	PPh_3	0	N/A
7	120	DMF	P^tBu_3	49	20:1
8	120	DMF	$P(OEt)_3$	53	18:1
9[d]	120	DMF	PPh_3	64	90:1
10	120	DMF	dppe	73	11:1
11	120	DMF	*rac*-BINAP	72	25:1
12	120	DMF	(*R*)-phanephos	71	44:1
13[e]	120	DMF	(*R*)-phanephos	73	44:1
14[f]	120	DMF	(*R*)-phanephos	N/A	28:1
15	120	DMF	L-proline	30	4:1
16	120	DMF	DMEDA	39	20:1

[a]Reaction conditions unless otherwise specified: **1a** (0.005 M), $Cu(OAc)_2$ (0.33 equiv), ligand (P/Cu = 3), HCO_2Na (4 equiv), K_2CO_3 (1.5 equiv) under N_2 for 2 h. [b]Isolated yield. [c]Calculated from ^1H NMR. [d]$Cu(OAc)_2$ (1 equiv) and PPh_3 (1 equiv) were used. [e]$Cu(OAc)_2$ (0.2 equiv) and phanephos (0.3 equiv) were used. [f]$Cu(OAc)_2$ (0.1 equiv), phanephos (0.15 equiv) and reaction time (4 h); 70% conversion. Dppe = 1,2-bis(diphenylphosphinoethane; BINAP = bis(diphenyl-phosphino)-1,1′-binaphthalene; phanephos = 4,12-bis(diphenylphosphino)[2.2]paracyclophane; DMEDA = *N*,*N*′-dimethylethylenediamine.

total synthesis of oximidine II (HCO_2Na (4 equiv), K_2CO_3, (1.5 equiv), $Cu(OAc)_2$ (0.33 equiv), and PPh_3 (1 equiv) at 120 °C in DMF for 2 h). We employed $Cu(OAc)_2$ as the metal source instead of the previously reported CuI because we observed better reproducibility of the reaction on large scale with $Cu(OAc)_2$.[10] When these conditions were employed, vinyl iodide **1a** furnished the expected 12-membered *E*,*Z*-diene lactone **2a** in a modest 34% yield along with the undesired acylic product **3a** (entry 1). At 100 °C (Table 1, entry 2), no conversion was observed, while at 140 °C (Table 1, entry 3) both yield and selectivity decreased. The reaction performed best at 120 °C (entries 1 and 4). Next, DMF was identified as the optimal solvent (entries 4—6). Less polar solvents (entries 5 and 6) were inefficient. Using other monodentate phosphorus ligands (entries 7 and 8) slightly improved the yields. Stoichiometric amounts of $Cu(OAc)_2$ and 3 equiv of PPh_3 facilitated the reaction significantly (entry 9). Finally, we were pleased to find that high yields of over 70% could be achieved with bidentate ligands under catalytic conditions (HCO_2Na (4 equiv), K_2CO_3, (1.5 equiv), $Cu(OAc)_2$ (0.33 equiv), and bidentate ligand (0.5 equiv) at 120 °C in DMF for 2 h, entries 10—12). Among them, phanephos afforded the best selectivity for diene **2a**, and the efficiency was not diminished under lower catalyst loading (0.2 equiv of $Cu(OAc)_2$ 0.3 equiv of phanephos, entry 13). Further lowering the catalyst loading (0.1 equiv of $Cu(OAc)_2$ 0.15 equiv of phanephos, entry 14) resulted in incomplete reaction (70% conversion) even after 4 h. *N*- or *O*-ligands exhibited inferior reactivities (entries 15 and 16).

We next applied this coupling/reduction tandem reaction to the synthesis of a diverse set of substrates (Table 2). We found that 11- to 13-membered rings **2a**, **2b**, and **2d** with an *E*,*Z*-1,3-diene moiety were obtained in good yields (Table 2, entries 1, 2, and 4). A more strained 10-membered homologue **2c** was also accessible, albeit only in 26% yield (entry 3). The alkyne reduction step was clearly driven by the release of ring strain from the enyne intermediate, which in case of the 13-membered ring analogue (entry 4) was observed after 2 h but converted to **2d** after 22–24 h. 14-Membered (entry 5) or larger rings formed the enyne but were not reduced to produce dienes even after prolonged reaction time. A phenylvinyl iodide with an ether linkage (entry 7) worked equally as the ester linkages. An unprotected phenol and a secondary amide (entries 8 and 9) were not well tolerated. In contrast, a protected amide (entry 10) provided the desired lactam **2j** in 79% yield. Both vinyl iodide and terminal alkyne coupling partners can be aromatic or aliphatic (entries 11 and 12). Vinyl iodide double-bond isomerization was observed for substrate **1l** (entry 12A and Scheme 2), which furnished an inseparable mixture (11:1) of **2l** and enyne **4**. When dppe was used as the ligand, **2l** was obtained in 82% as the sole product (entry 12 B). *Z*,*Z*-Diene macrocycles were difficult to access with this method since the *Z*-enyne intermediate is much less strained than its *E*-counterpart, and thus, the alkyne reduction did not take place (entry 13). When the ring system was strained enough to afford the desired diene product **2n** in 30% yield (entry 14), significant amounts of the dimer **5** (34%) were formed concomitantly (Scheme 2). In the majority of the above examples, the undesired deiodinated product **3** was negligible. For those substrates that produced a significant quantity of compound **3**, the use of stoichiometric amounts of copper and ligand could completely suppress the side reaction (entries 4 and 6).

Ring systems that were not strained enough to trigger the in situ alkyne reduction afforded macrocyclic enynes. This transformation is worth noting, since the intramolecular ene–yne C–C couplings (Sonogashira or Castro–Stephens) have not been widely applied to macrocyclizations,[8,11] and most of them employed phenyl iodide substrates. In addition, the desired diene macrocycles could be obtained from the enynes through a sequential reduction step (Scheme 3). Thus, the iodides were subjected to the ene–yne coupling conditions in the absence of HCO_2Na, and the crude enyne was then treated with in situ formed Cu–H.[12] The 14-membered macrocycle **2e** and 17-membered macrocycle **2p** were synthesized using these conditions. Double-bond isomerization as seen in Pd-catalyzed transhydrogenation[13] of enynes was not detected herein.

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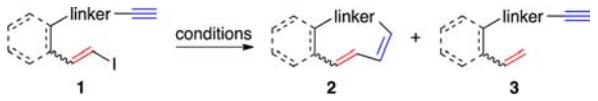
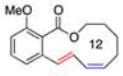
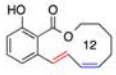
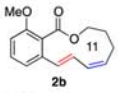
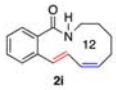
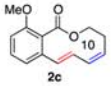
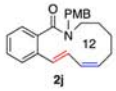
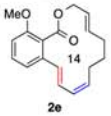
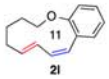
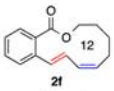
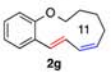
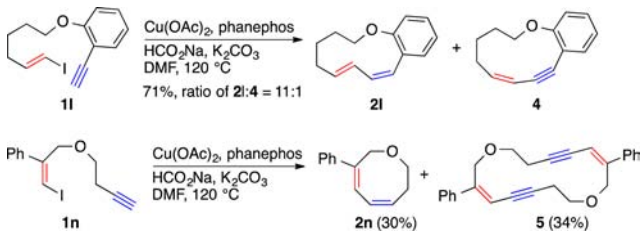
Table 2. Reaction Scope



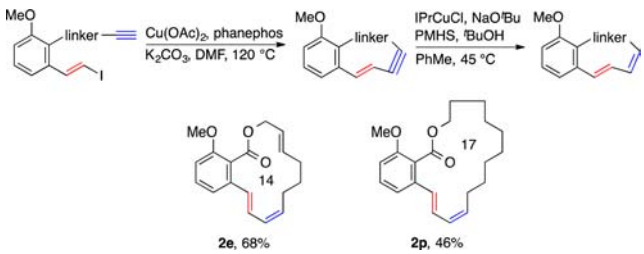
entry	product	conditions[a]	yield (%)[b]	ratio (2:3)[c]	entry	product	conditions[a]	yield (%)[b]	ratio (2:3)[c]
1	 2a	A, 2 h	73	44:1	8	 2h	C, 3 h	12	**2h** only
2	 2b	A, 2 h B, 2.5 h	62 68	59:1 36:1	9	 2i	A, 2h	0[g]	N/A
3	 2c	D, 2 h	26	**2c** only	10	 2j	A, 3.5 h	79	**2j** only
4	 2d	B, 24 h C, 22 h	72 53	12:1 **2d** only	11	 2k	A[e], 3 h B, 3 h	62 70	**2k** only **2k** only
5	 2e	A, 24 h	0[f]	N/A	12	 2l	A, 4 h D, 4 h	71[h] 82	**2l** only
6	 2f	A, 2 h C, 2 h	60 60	5.6:1 **2f** only	13	 2m	A, 3 h	0[f]	N/A
7	 2g	A[d], 6 h	62	**2g** only	14	 2n	A, 5 h	30[i]	N/A

[a]Reaction conditions unless otherwise specified: **1** (0.005 M), HCO_2Na (4 equiv), K_2CO_3 (1.5 equiv) under N_2; (A) $Cu(OAc)_2$ (0.2 equiv), phanephos (0.3 equiv); (B) $Cu(OAc)_2$ (0.33 equiv), BINAP (0.5 equiv); (C) $Cu(OAc)_2$ (1 equiv), PPh_3 (3 equiv); (D) $Cu(OAc)_2$ (0.33 equiv), dppe (0.5 equiv). Reaction times were not fully optimized. [b]Isolated yield. [c]Calculated from ^1H NMR. [d]$Cu(OAc)_2$ (0.1 equiv), phanephos (0.15 equiv) were used. [e]$Cu(OAc)_2$ (0.33 equiv), phanephos (0.33 equiv) were used. [f]Only enyne was isolated. [g]Decomposed. [h]Combined yield of inseparable mixture of diene **2l** and enyne **4** (ratio 11:1). [i]34% of dimerized product **5** was also isolated.

Scheme 2. Reactions of Substrates 1l and 1n



Scheme 3. Stepwise Coupling/Reduction Synthesis of 14- and 17-Membered Macrocycles



In summary, a tandem reaction involving an intramolecular Castro–Stephens coupling and in situ alkyne semireduction has been developed for the construction of macrocycles containing conjugated *E,Z*-diene units. The reaction is ring-strain dependent and particularly efficient for 11–13-membered rings. The synthesis of larger and thus less strained macrocycles can be realized through a complementary stepwise sequence. This methodology has been previously used in the total synthesis of the natural product oximidine II, and very recently, we have completed a concise formal total synthesis of lactimidomycin employing the improved conditions that we have discussed in this report.[14] Further investigations on applications in natural product synthesis are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental section, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01892.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: georg@umn.edu.

Notes

The authors declare no competing financial interest.

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