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Synthesis of 2,3-Di- and 2,3,4-Trisubstituted Furans from 1,2-Dioxines Generated by an Enyne-RCM/Diels−Alder Reaction Sequence

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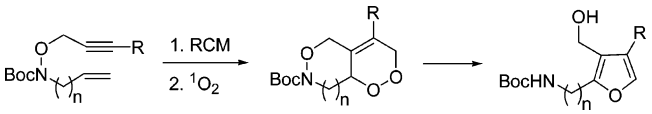


An efficient method for the synthesis of 2,3- and 2,3,4-substituted furans starting from acyclic enynes was developed using an enyne-RCM/Diels−Alder reaction sequence. The reaction conditions for the transformation of 1,2-dioxines having an adjacent 1,2-oxazine ring into furans and the cleavage of N−O bonds are discussed.

Furans are one of the most biologically important heterocyclic compounds and play important roles as a subunit in many natural products. Among them, 2,3-substituted furans such as pinguisone (**1**)[1] and 2,3,4-substituted furans such as petasalbine (**2**)[2] and teubrevin G (**3**)[3] constitute structurally distinctive features (Figure 1). Considerable effort has been directed toward the development of new and efficient methodologies for the synthesis of furans.[4] General methods toward substituted furans employ condensation of acyclic dicarbonyl equivalents or the substitution of existing furan rings. However, these methods have difficulties in stereoselective synthesis of polysubstituted furans and polycyclic furans such as **1** and **2**. The strategy synthesizing the furan ring in the ring-forming step is an attractive method for the synthesis of polycyclic furans. The tandem Diels−Alder cycloaddition/retro Diels−Alder reaction of the oxazoles tethered with an acetylenic dienophile is a well-known methodology.[5] Utilizing alkynes tethered with an alkene instead of an oxazole is an attractive alternative method because the introduction of alkenes is straightforward. The tethered enynes could be cyclized by ring-closing metathesis (RCM) reaction[6] to afford 1,3-dienes that could be further transformed into furans.

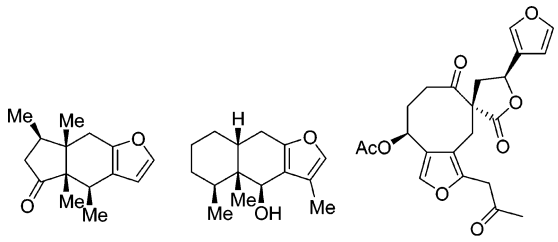
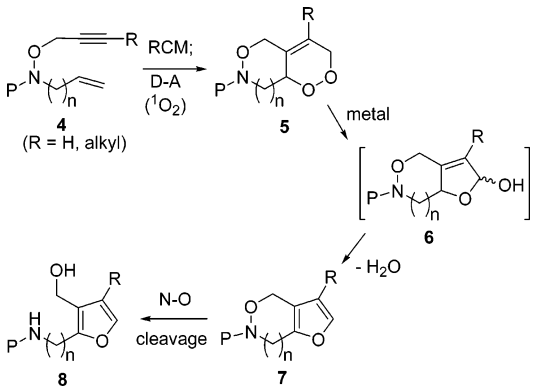


FIGURE 1. Representative polycyclic furans.

SCHEME 1



We have recently reported the synthesis of 1,2-oxazines by RCM reactions of dienes and enynes tethered by an N−O bond.[7] The heterocyclic 1,2-dioxines **5** were generated by Diels−Alder reaction of the enyne-RCM adducts with singlet oxygen (Scheme 1).[8] 1,2-Dioxines are synthetically useful for the introduction of 1,4-dioxygen functionalities.[9] Strong base or transition metal-catalyzed cleavage of the peroxide bond often yields mixtures of 1,4-diols, *cis*-γ-hydroxyenones, and bisepoxides. The unstable *cis*-γ-hydroxyenones undergo facile dehydration to furans and rearrangement to 1,4-diketones. However, the controlled syntheses of furans from 1,2-dioxines are often

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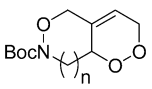
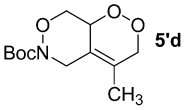
TABLE 1. Synthesis of Furans from 1,2-Dioxines by $FeSO_4$[a]





entry	peroxide	products (% yield)	
1	**5a**	**7a** (-)	**9a** (70)
2	**5b**	**7b** (98)	
3	**5c**	**7c** (88)	
4	**5'd**	**7'd** (26)	**9'd** (30)

[a] Conditions: $FeSO_4 \cdot 7H_2O$, THF−H_2O (1:1), rt.

TABLE 2. Reductive Cleavage of the Peroxide Bonds[a]

entry	peroxide	products (% yield)	
1	**5a**	**10a** (84)	
2	**5b**	**10b** (78)	**7b** (15)
3	**5c**	**10c** (79)	**7c** (13)
4	**5'd**	**10'd** (89)	

[a] Conditions: Zn−AcOH, CH_2Cl_2, rt.

complicated and highly dependent on the substrate structures and reaction conditions. Herein we report optimized reaction conditions for the transformation of 1,2-dioxines **5** into furans **7** and a general synthetic approach to 2,3- and 2,3,4-substituted furans **7** and **8**, respectively, from acyclic enynes **4**.

Results and Discussion

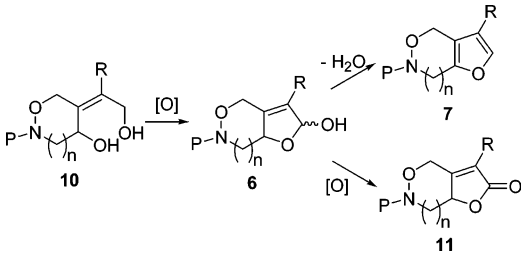
Direct Conversions of 1,2-Dioxines to Furans. 1,2-Dioxines (**5a**−**c** and **5′d**) were synthesized starting from the corresponding acyclic enynes according to the published procedure ((1) enyne-RCM; (2) Diels−Alder reaction with singlet oxygen).[8] Attempts at directly converting peroxides **5** to furans **7** using strong bases such as *t*-BuOK and $LiN(SiMe_3)_2$ were unsuccessful. Next, ring-opening reactions catalyzed by $FeSO_4$ were examined (Table 1).[10] 1,2-Dioxines **5b**,**c** having seven- and eight-membered adjacent rings, respectively, were transformed into the corresponding furans **7b**,**c** in high yields (Table 1, entries 2 and 3). However, 1,2-dioxines having a six-membered ring produced mainly lactol compounds **9a** and **9′d** instead of the corresponding furans (Table 1, entries 1 and 4).

TABLE 3. Oxidation of the Allylic Diols[a]

entry	diol	products, % yields	
1	**10a**		
	condition	**7a**	**11a**
	A	–	61
	B	41	39
	C	80	5
	D	41	15
	E	64	–
2	**10b**		
	condition	**7b**	**11b**
	A	27	54
	B	71	23
	C	75	–
	D	54	–
	E	77	–
3	**10c**		
	condition	**7c**	**11c**
	A	8	68
	B	92	–
	C	68	–
	D	–	–
	E	87	–
4	**10'd**		
	condition	**7'd**	**11'd**
	A	–	85
	B	31	44
	C	–	80
	D	10	32
	E	83	–

[a] Conditions: (**A**) NMO (2.0 equiv), TPAP (0.08 equiv), 4 Å MS, 10% CH_3CN in CH_2Cl_2, 25 °C; (**B**) PCC (1.5 equiv), 4 Å MS, CH_2Cl_2, 25 °C; (**C**) IBX, EtOAc, 80 °C; (**D**) IBX, DMSO, 50 °C; (**E**) Pyr/SO_3, DMSO, Et_3N, CH_2Cl_2, 25 °C.

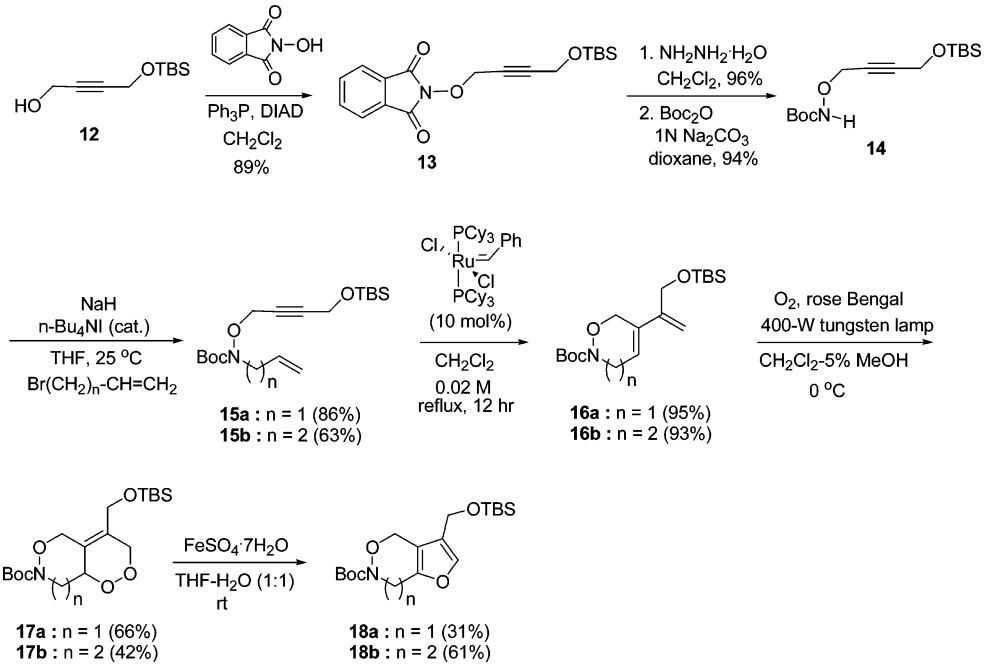
SCHEME 2



Two-Step Conversions of 1,2-Dioxines to Furans. Since the direct syntheses of furans **7a** and **7′d** from the

(10) (a) Herz, W.; Ligon, R. C.; Turner, J. A.; Blount, J. F. *J. Org. Chem.* **1977**, *42*, 1885. (b) Herz, W.; Turner, J. A. *J. Org. Chem.* **1977**, *42*, 1900.

SCHEME 3



corresponding 1,2-oxazines were unsuccessful, we examined a two-step sequence (reductive cleavage of the O−O bond and subsequent oxidative dehydration). The peroxides were treated with Zn−AcOH in dichloromethane at room temperature to yield the allylic diols in good yields (Table 2).[11] Occasionally, furans (**7b** and **7c**) were also formed as minor products under the reaction conditions (Table 2, entries 2 and 3).

Oxidations of the diols (**10a**−**c** and **10′d**) were investigated under several different conditions, and the results using five representative conditions ((**A**) NMO (2.0 equiv), TPAP (0.08 equiv), 4 Å MS, 10% CH_3CN in CH_2Cl_2, 25 °C; (**B**) PCC (1.5 equiv), 4 Å MS, CH_2Cl_2, 25 °C; (**C**) IBX, EtOAc, 80 °C; (**D**) IBX, DMSO, 50 °C; (**E**) Pyr/SO_3, DMSO, Et_3N, CH_2Cl_2, 25 °C) were summarized in Table 3. We expected the less-hindered primary allylic alcohol to be oxidized first under these conditions to give the lactol **6** (Scheme 2). The intermediate lactol **6** could either be oxidized further to lactone **11** or undergo dehydration to give furan **7** depending on the oxidation conditions and the stabilities of the lactols.

When the diols (**10a**−**c** and **10′d**) were oxidized under conditions **A** (TPAP/NMO), the α,β-unsaturated γ-butyrolactones (**11a**−**c** and **11′d**) were obtained as major products (Table 3). In the cases of diols having adjacent six-membered rings (**10a** and **10′d**), the corresponding lactones (**11a** and **11′d**) were formed exclusively (Table 3, entries 1 and 4). Under conditions **B** (PCC), on the other hand, the product ratios of the furans (**7a**−**c** and **7′d**) increased. In the case of diol **10c**, which has an adjacent eight-membered ring, we observed a complete reversal of the product ratio: the lactone **11c** was the predominant product formed under conditions **A**, but only the furan **7c** was formed under conditions **B** (Table 3, entry 3). Oxidations with IBX under refluxing ethyl acetate (conditions **C**) worked well for the formation of 2,3-disubstituted furans **7a**−**c** (Table 3, entries 1−3). However, these conditions failed to yield the 2,3,4-trisubstituted furan **7′d** (Table 3, entry 4). The IBX oxidations in DMSO (conditions **D**) were not suitable for the synthesis of either furans or lactones. Among several oxidation conditions examined, the modified Swern oxidation conditions (conditions **E**, Pyr/SO_3, DMSO) were the most effective for the conversion of diols into furans. Only furans were obtained for the tested diols, and the yields were uniformly good.

Synthesis of 2,3,4-Trisubstituted Furans from Enynes. With the optimized conditions for the conversion of 1,2-dioxines to furans in hand, we then applied the enyne-RCM/Diels−Alder reaction sequence for the synthesis of 2,3,4-trisubstituted furans. The relatively stable and easily cleavable N−O tether was adopted for the synthesis. Monoprotected 2-butyne-1,4-diol (**12**)[12] was coupled with *N*-hydroxyphthalimide under Mitsunobu conditions to give **13** (Scheme 3). Compound **13** was treated with hydrazine, and the crude hydroxylamine was protected with Boc group to produce **14** in good yield. Alkylations with allyl bromide and 4-bromo-1-butene furnished **15a** and **15b**, respectively. Ring-closing metathesis with first-generation Grubbs' catalyst under refluxing dichloromethane yielded **16a** (95%) and **16b** (93%) in high yields. Cycloaddition reactions of dienes with singlet oxygen were conducted in CH_2Cl_2−5% MeOH solutions to obtain the 1,2-dioxines **17a** (66%) and **17b** (42%). While the $FeSO_4$-catalyzed conversion of **17b** to **18b** was fairly good (61%), the yield for the direct synthesis of **18a** from **17a** was not good (31%).

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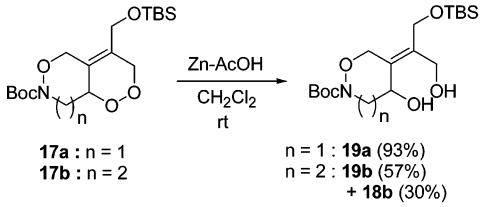
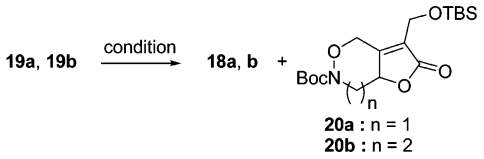
SCHEME 4



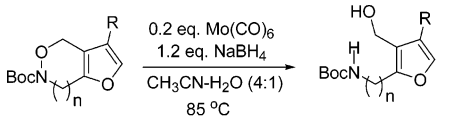


condition	18a	20a	18b	20b
NMO, TPAP	-	80%	-	60%
PCC	37%	33%	58%	-
IBX, EtOAc	70%	-	43%	-
Pyr/SO_3-DMSO	78%	-	96%	-

The two-step synthesis of the furans was then examined. Treatments of **17a** and **17b** with Zn−AcOH followed by oxidations with Pyr/SO_3−DMSO (conditions **E**) afforded furans **18a** and **18b** in good yields (Scheme 4). Oxidations with NMO-TPAP (conditions **A**) afforded lactones **20a** and **20b** only in 80 and 60% yields, respectively. The furan **18b** was again obtained in 30% yield in the reductive cleavage of **17b**. The overall yields for the two-step conversions ((1) Zn−AcOH; (2) Pyr/SO_3, DMSO, Et_3N) of 1,2-dioxines (**17a** and **17b)** to furans (**18a** and **18b**) were 73 and 85%, respectively.

Finally, cleavage of the N−O bond was examined with typical reducing agents. Hydrogenation conditions, activated zinc,[13] and samarium iodide[14] failed to cleave the N−O bond. Therefore, we turned our attention to the $Mo(CO)_6$-catalyzed reaction.[15] Treatments of **7a**−**c**, **18a**, and **18b** with 0.2 equiv of $Mo(CO)_6$ in the presence of $NaBH_4$ (1.2 equiv) under refluxing acetonitrile solutions

SCHEME 5



	n	R	21
7a :	1	H	**21a** (98%)
7b :	2	H	**21b** (87%)
7c :	3	H	**21c** (67%)
18a :	1	CH_2OTBS	**21d** (98%)
18b :	2	CH_2OTBS	**21e** (65%)

afforded **21a**−**e** in high yields (Scheme 5). Overall, furans with functionalizable substituents at 2,3- and 2,3,4-positions were synthesized.

Conclusion

In conclusion, the 1,2-dioxines having an adjacent 1,2-oxazine ring were transformed into the corresponding furans. For 1,2-dioxines having an adjacent seven- or eight-membered ring, Fe(II)-catalyzed direct synthesis of furans was favored. For 1,2-dioxines having an adjacent six-membered ring, however, the two-step sequence (reductive cleavage of O−O bonds; oxidation of the diols) was suitable. The modified Swern oxidation conditions (Pyr/SO_3, DMSO, Et_3N) proved to be the best conditions for the synthesis of furans. The NMO/TPAP conditions, however, afforded mainly α,β-unsaturated γ-butyrolactones. The overall four-step strategy (RCM of enynes, Diels−Alder reaction with singlet oxygen, reduction of the O−O bond, and oxidation of diols) from acyclic enyne percursors to furans was applied for the synthesis of 2,3,4-trisubstituted furans. Synthetic applications of the present approach for the synthesis of biologically active 2,3-di- and 2,3,4-trisubstituted furans are under investigation.

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Supporting Information Available: Experimental details and spectroscopic data for **7a**−**c**, **7′d**, **9a**, **9′d**, **10a**−**c**, **10′d**, **11a**−**c**, **11′d**, **13**, **14**, **15a**,**b**, **16a**,**b**, **17a**,**b**, **18a**,**b**, **19a**,**b**, **20a**,**b**, and **21a**−**e** and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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