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Intramolecular Diels−Alder Reactions Employing Hydroxamate Tethers: The First Examples and Promising Prospects

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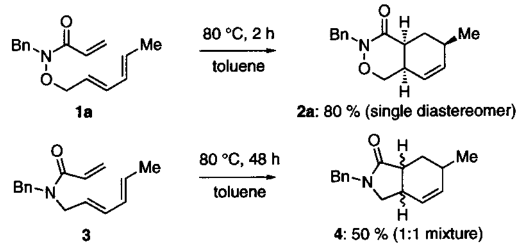
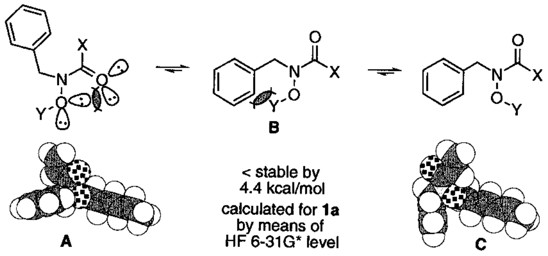
The intramolecular Diels−Alder reaction (IMDA)[1] is a powerful and important tool for the regio- and stereoselective construction of functionalized cyclohexene frameworks. In our efforts to explore promising IMDA systems which fulfill the four criteria, (1) easy connection between diene and dienophile parts by using a tethering group,[2] (2) high reactivity, (3) homogeneous stereochemical consequences, and (4) highly versatile latent functionality of the tethering group itself, we found that hydroxamate-tethered triene **1a** deserved serious consideration in this context: when a solution of **1a** in toluene was heated at 80 °C for 2 h, cycloadduct **2a** was obtained as a single diastereomer (80%) (Scheme 1). The potential of **1a** became quickly apparent when the IMDA of trienic amide **3** was examined, which was not completed even after 48 h at 80 °C and led to **4** as a mixture of two diastereomers (1:1) in 50% yield (Scheme 1).

Scheme 1



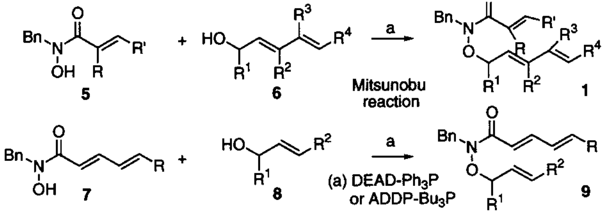
Scheme 2



One of the factors responsible for these contrasting results can be the most stable conformation of *N*-benzylhydroxamates illustrated as C in which the diene and dienophile parts (X and Y) are in close proximity (Scheme 2): Hartree Fock 6-31G* level calculation indicated that the conformer C is more stable than an A-type one by 4.4 kcal/mol in the case of **1a**.[3] Thus, the IMDA of **1a** must be entropically highly favored.

In Scheme 3 is outlined the typical synthesis of two hydroxamate-tethered triene systems (**1** and **9**). Acylation of *N*-benzylhydroxylamine (BHA)[4] with alkenoic or alkadienoic acid chlorides exclusively took place not at the oxygen atom but at the nitrogen atom to furnish **5** or **7**, respectively. Because of enhanced nucleophilicity of the hydroxy group in these hydroxamic acids,[5] Mitsunobu reaction[6] of 2,4-hexadiene-1-ol (**6**) or allylic alcohol (**8**) with **5** or **7** nicely proceeded to afford trienes **1** or **9**, respectively, in high yield [DEAD-Ph$_3$P or 1,1-(azodicarbonyl)dipiperidine (ADDP)-Bu$_3$P,[7] room temperature/2 h].

Scheme 3



One of the significant and amazing consequences of the IMDA of **1** and **9** was exclusive stereochemical results, a cis-fused ring system from **1** or **11** and trans-fused one from **9**. As illustrated in Table 1 and Scheme 4, cis-fused cycloadducts **2** and **13** (or **12**) were obtained as a single isomer with an absolute (**2f**) or illustrated relative configuration[8] in high yield. The reaction of **1c** proceeded so rapidly that it was completed when the introduction of the diene part had finished (THF, rt, 1 h). Although the reaction became more sluggish when both ends of the triene chain bore one substituent (**1e**) or the diene end was geminally substituted (**1g**), the stereochemical homogeneity remained intact. Treating the enone **10**, itself obtained similarly as shown in Scheme 3, with TBSOTf in THF at 0 °C in the presence of Et$_3$N gave the enol silyl ether **11**, which was smoothly converted in situ into the cis-fused cycloadduct **12**, which, on acidic hydrolysis[9] led to **13** in high yield. The enol silyl ethers **11b**−**d** were sufficiently stable to be isolated in quantitative yield; heating to 90−100 °C in toluene led to cycloadducts **12** or **13**, depending on the stability of intermediates **12** to silica gel chromatography.

The observed stereochemical consequences strongly suggest the existence of an endo-transition state as shown below (TS$_1$: endo-boat) in which two oxygen atoms in the O−N−C=O unit can avoid electrostatic repulsion as mentioned above for the

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[1] For reviews of IMDA, see: (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.4, pp 513−550. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; pp 269−331. (d) Padwa, A.; Schoffstall, A. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1990; Vol. 2, pp 1−89.

[2] References to other temporary heteroatom tether strategies for intramolecular Diels−Alder reactions are provided in Supporting Information.

[3] Ab initio molecular orbital calculations were performed with the GAUSSIAN 94/98 program package at the HF 6-31G* level: for details, see Supporting Information.

[4] A substituent on the nitrogen atom turned out to be crucial: for instance *N*-CH$_3$, no substituent, or *N*-benzoyl resulted in low yield and poor selectivity, decomposition, or deacylation and decomposition, respectively.

[5] Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778−1785.

[6] (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679−680. (b) Grochowski, E.; Jurczak, J. *Synthesis* **1976**, 682−684.

[7] Only in the case of sterically nondemanding secondary allylic alcohols, an S$_N$2′-type pathway competitively took place: it turned out that the super Mitsunobu conditions [Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642] worked much better in such cases in which, fortunately, the S$_N$2 and S$_N$2′ products could be separated by SiO$_2$ column chromatography.

[8] All products gave satisfactory spectroscopic data (NMR, IR, and MS). The stereochemistry of all the cycloadducts was determined by NOESY measurement and the evaluation of J_{H-H} values: see Supporting Information.

[9] The stereochemistry of cycloadducts **12** was determined on the basis of spectroscopic data at the stage of **13** because the enol silyl ether group of **12** is somewhat unstable and a mixture of **12** and **13** was usually obtained.

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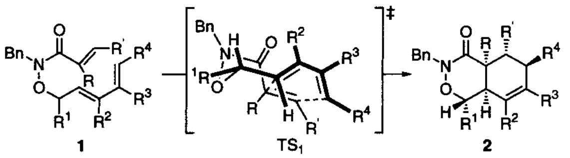
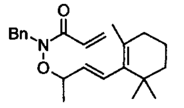
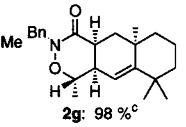
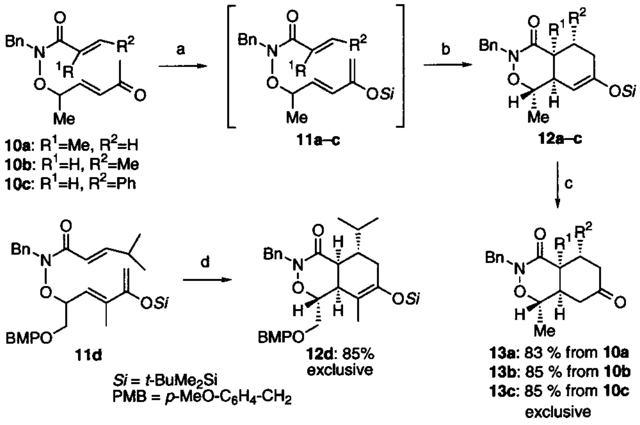
Table 1. Results of Hydroxamate-Tethered IMDA of **1a**−**1g**



	conditions	yield[a]
1b: R,R^4=Me; R',R^{1-3}= H	90 °C, 10 h, PhMe	**2b**: 83 %
1c: R=Me; R',$R^{1,3,4}$=H; R^2=SPh	rt, 1 h, THF	**2c**: 80 %
1d: R,R^2=Me; R',$R^{1,4}$=H; R^3=SPh	90 °C, 17 h, PhMe	**2d**: 97 %
1e: R,R^{1-3}=H; R',R^4=Me	90 °C, 20 h, PhMe[b]	**2e**: 44 %
1f : R,R^2=Me; R',$R^{3,4}$=H R^1=$TBSOCH_2$ (α)	90 °C, 17 h, PhMe	**2f**: 80 %
1g: 	110 °C, 10 h, PhMe (50% conv)	 **2g**: 98 %[c]

[a] For isolated product by CC (SiO_2). [b] SiO_2 was required as a promoter to achieve 100% conv. [c] Based on reacted **1g**.

Scheme 4[a]

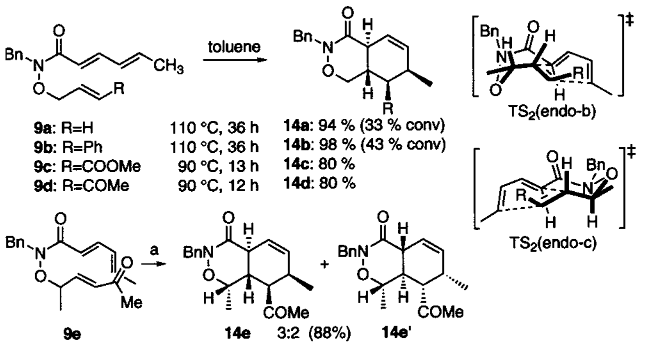


[a] (a) TBSOTf/Et_3N/THF; (b) THF/rt, 1 h for **11a** and PhMe/90 °C, 17 h for **11b,c**; (c) HCl/THF; (d0 PhMe/100 °C, 12 h.

conformation C typical for hydroxamates. It should be pointed out that the configuration of **2f** and **12d** or **13** was perfectly controlled (>99% de) by the stereocenter in the tether. The configuration and functional group assembly in adduct **12d** could make it useful building block for the synthesis of the biologically interesting marine metabolites eunicellin[10] or eleuthrobin.[11]

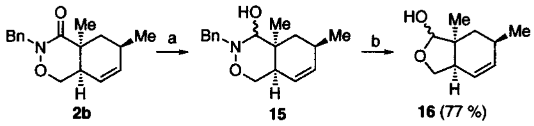
On the other hand trienes **9a**−**e** in which the diene and dienophile parts were interchanged exclusively afforded the trans-fused cycloadducts **14a**−**e** in good yield with the relative configuration[8] as shown: in order for the IMDA of **9** to be completed, the R group in **9** must be electron-withdrawing (**9c**,**d**,**e**) (Scheme 5), otherwise the reaction resulted in low conversion under the given reaction conditions (**9a**,**b**). Although asymmetric induction relying on a stereocenter in the tether (**9e**) turned out to be unsatisfactory [**14e** and **14e′** (3:2)], these diastereisomers were obtained in high yield and could be separated by simple silica gel column chromatography. The origin of the trans-selectivity and low diastereoselectivity observed in **14** can be rationalized by assuming that the reaction involves an endo-boat transition state [TS_2 (endo-b)] and a chair transition state [TS_2 (endo-c)] with a small energy difference between them. The coplanarity of the hydroxamate carbonyl group and the neighboring diene might not be achieved in this case which, therefore, probably make this IMDA system a normal electron demand type. Indeed the IMDA of **9 c**−**e** paralleled in their rates those of **1**.

Scheme 5[a]



[a] Toluene/90 °C, 12 h.

Scheme 6[a]



[a] (a) $LiAlH_4$, (b) Zn/Cu(OAc)$_2$ACOH/H_2O.

The latent functionality of the tethering group seems to be versatile. One simple example is as follows: treating **2b** with lithium aluminum hydride in THF at −78 °C to ambient temperature, afforded the stable hemiaminal intermediate **15**, which, on reductive N−O bond cleavage (Zn, Cu(OAc)$_2$/ AcOH−H_2O),[12] gave **16** in 77% overall yield (Scheme 6).

In conclusion, we have established the promising new hydroxamate-tethered IMDA. A number of permutations of dienes and dienophiles were demonstrated with highly selective and predictable stereochemical consequences. In addition, the ready availability of hydroxamate-tethered triene chains, the proximity of the reaction centers realized by the characteristic conformation of hydroxamates, and the versatile latent functionality will make the "temporary hydroxamate connection" highly attractive. Application of this strategy to complex natural product synthesis is currently in progress.

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Supporting Information Available: Synthetic procedures for **1**, **2**, and **9**−**16**, their spectroscopic data, and copies of ^1H- and ^{13}C NMR spectra for **2** and **12**−**14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010083Z

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(10) For recent total syntheses of eunicellin diterpenoids, see: MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392.

(11) For recent total syntheses of eleutherobin, see: (a) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. LK.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674−8680. (b) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789−792.

(12) For reductive N−O bond cleavage, see: Dondoni, A.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2551−2555.