Organic LETTERS

Letter

pubs.acs.org/OrgLett

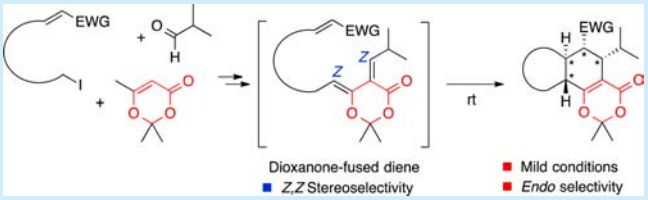
Dioxanone-Fused Dienes Enable Highly *Endo*-Selective Intramolecular Diels–Alder Reactions

Yoshifumi Aoki, Ken Ohmori,* and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8550, Japan

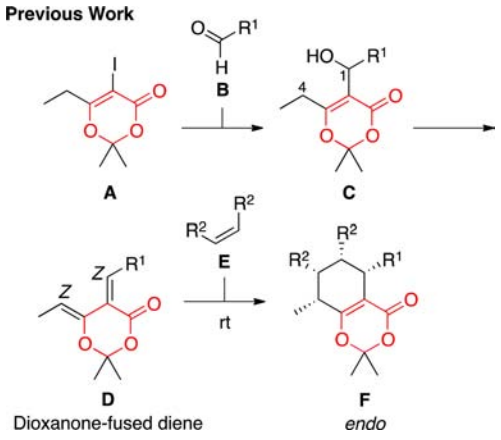
Supporting Information

ABSTRACT: Intramolecular Diels–Alder reactions of dioxanone-fused (*Z*,*Z*)-dienes, available in a stereoselective manner from the corresponding alcohols are described. These dienes exhibited high reactivity and high levels of *endo* selectivity, giving functionalized *trans*-fused bicyclic compounds.



In our recent study on natural product synthesis, we reported an approach to functionalized cyclohexane derivatives via a three-component assembly using dioxinone as a key platform (Scheme 1).[1] The halogen–lithium exchange of iododioxinone

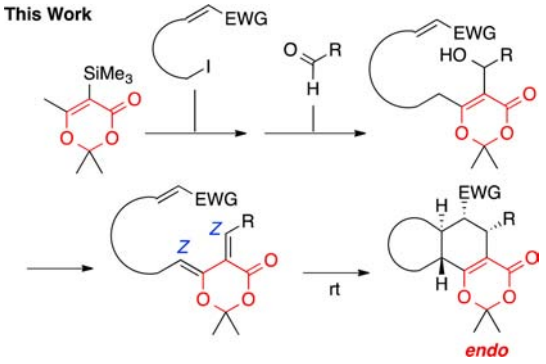
Scheme 1. Diels–Alder Reactions of Dioxanone-Fused Dienes



A followed by the reaction with aldehyde **B** gives alcohol **C**, which undergoes facile 1,4-elimination by treatment with Tf_2O, giving (*Z*,*Z*)-diene **D** with rigorous stereoselectivity. Due to the *s-cis* diene structure enforced by fusion to a dioxanone ring, diene **D** is an excellent Diels–Alder substrate, reacting with various dienophiles **E** at room temperature. Worthy of note is the excellent *endo*-selectivities, giving stereodefined cycloadduct **F** with high synthetic potential by the regenerated dioxinone moiety ready for various transformations.[2]

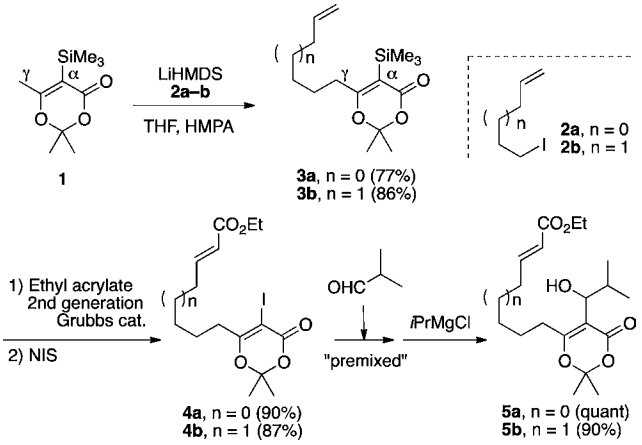
We envisaged that such features would be also useful in the intramolecular Diels–Alder (IMDA) reactions, which are powerful tools for constructing highly functionalized bicycles.[3,4] Herein, we are pleased to report positive results, realizing the expeditious, stereoselective construction of functionalized bicyclic skeletons with high stereoselectivity (Scheme 2).

Scheme 2. IMDA Reactions of Dioxanone-Fused Dienes



Scheme 3 illustrates the preparation of triene precursors **5a** and **5b**. TMS-Dioxinone **1** served as the starting material, allowing selective γ-alkylation via the derived lithium dienolate

Scheme 3. Preparation of Triene Precursors



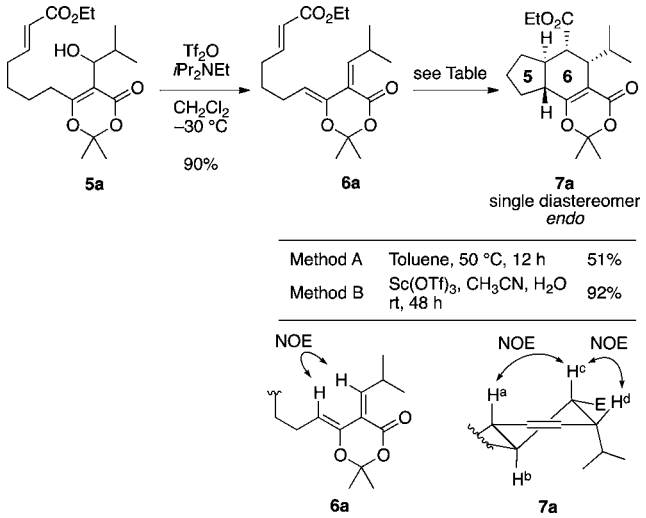
Received: April 21, 2015
Published: May 14, 2015

DOI: 10.1021/acs.orglett.5b01172
Org. Lett. 2015, 17, 2756–2759

(LiHMDS, HMPA, THF, −78 °C, 1 h) followed by a reaction with iodoolefin **2a** (2.0 equiv, −78 °C → rt, 2 h), giving the product **3a** in 77% yield.[5] The presence of the TMS group in **1** was essential, as the reaction of the corresponding non-TMS congener suffered from a competing α-alkylation and/or polyalkylations. Conversion of **3a**, involving the olefin metathesis with ethyl acrylate (3.0 equiv, second Grubbs catalyst, CH_2Cl_2, reflux, 2 h) and iodo-desilylation,[6] gave iododioxinone **4a** in 90% yield. Upon addition of *i*-PrMgCl (2.0 equiv) to a mixture of **4a** and isobutyraldehyde (2.3 equiv) in Et_2O (−30 °C, 10 min), the iodine−magnesium exchange followed by 1,2-addition proceeded to give alcohol **5a** in quantitative yield. Along the same lines, homologue **5b** with a one-carbon longer chain was prepared (Scheme 3).

With the potential diene precursors **5a** and **5b**, generation of the diene was examined. Treatment of **5a** with Tf_2O in the presence of a Hünig base (4.0 equiv, CH_2Cl_2, −30 °C, 20 min) gave triene **6a** in 90% yield. The (*Z*,*Z*)-isomer was exclusively obtained, and the stereochemistry was assigned by diagnostic NOEs (Scheme 4, below left).

Scheme 4. Sulfonylation and IMDA Reaction

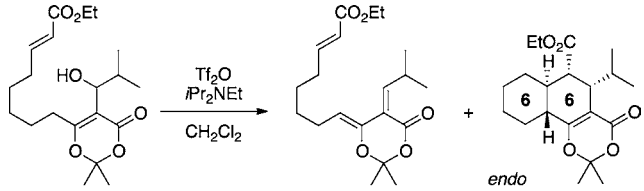


Upon heating (toluene, 50 °C, 12 h), triene **6a** underwent slow cycloaddition, giving the *endo* cycloadduct **7a** in moderate yield (Method A). The stereochemistry of **7a** was assigned by the diagnostic NOE correlations (Scheme 4), indicating an all-*cis* relationship of the hydrogens H^a, H^c, and H^d. Further optimization identified $Sc(OTf)_3$ as an effective catalyst,[7] allowing smooth cycloaddition at room temperature with complete *endo* selectivity (Method B: $Sc(OTf)_3$, CH_3CN, H_2O, rt, 48 h).

The rigorous stereoselectivity was also the case for the one-carbon homologue **5b** (Scheme 5). Upon treatment of alcohol **5b** with Tf_2O (Hünig base, 4.0 equiv, CH_2Cl_2, −30 °C, 10 min), (*Z*,*Z*)-triene **6b** was obtained in 85% yield. Surprisingly, a small amount of different product was obtained, which proved to be the cycloadduct **7b**[8] in 11% yield, suggesting the high reactivity of **6b** in the IMDA reaction. Indeed, after sulfonylation, warming to rt enabled the IMDA reaction to proceed, giving **7b** in 90% yield.

The facile and exclusive formation of the *endo* cycloadducts **7a** and **7b** is notable, which stands in sharp contrast to the reactions of simpler trienes, such as **I** and **II**, requiring high

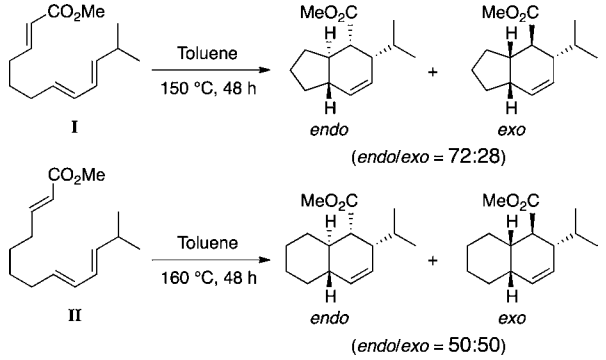
Scheme 5. Reaction of Alcohol 5b



conditions	6b	7b
−30 °C, 10 min	85%	11%
−30 °C → rt, 12 h	–	90%

temperatures and resulting in poor stereoselectivities (Scheme 6).[9,10] Thus, the dioxanone fused to the diene moiety poses a significant influence on the reactivity and the reaction course.

Scheme 6. Previous Examples



What is the role of the dioxanone moiety? The high reactivity is attributed to the *s-cis* diene structure enforced by fusion to a dioxanone ring. On the other hand, the high *endo* selectivity calls for other arguments.

Although *endo* selectivities have been traditionally attributed to the secondary orbital interaction, recent arguments invoked other effects, e.g. steric effects, electrostatic forces, etc.[11] Indeed, a computational study[12] on the reaction of **6b** suggested that the decisive factor is the steric repulsion, although the secondary orbital interactions are operative (*vide infra*).

In the transition structure $\mathbf{TS}_{exo}$ going to the *exo* cycloadduct, the tethering chain and one of the oxygen atoms in the dioxanone ring are repulsive. By contrast, transition structure $\mathbf{TS}_{endo}$, 3.22 kcal/mol lower than $\mathbf{TS}_{exo}$, is free from such repulsion (Figure 1).[13]

To gain further insight, NBO analysis[14] was conducted on $\mathbf{TS}_{endo}$ for evaluating the donor/acceptor interactions. Two stabilizing interactions were suggested in $\mathbf{TS}_{endo}$ (Figure 2). We found that the π electrons of the C=C bond of the diene moiety are delocalized into the antibonding orbital of the C=O bond of the dienophile moiety, providing stabilization of 0.76 kcal/mol. This represents the secondary orbital interaction, which is relatively small when accounting for the rigorous selectivity.

Indeed, the NBO analysis suggested an additional stabilizing effect by a C−H/n interaction in $\mathbf{TS}_{endo}$. The carbonyl oxygen is placed in close proximity to the methyl group (2.15 Å), suggesting the lone pair of the carbonyl group is delocalized to the antibonding orbital of the carbon−hydrogen bond.

DOI: 10.1021/acs.orglett.5b01172
Org. Lett. 2015, 17, 2756−2759

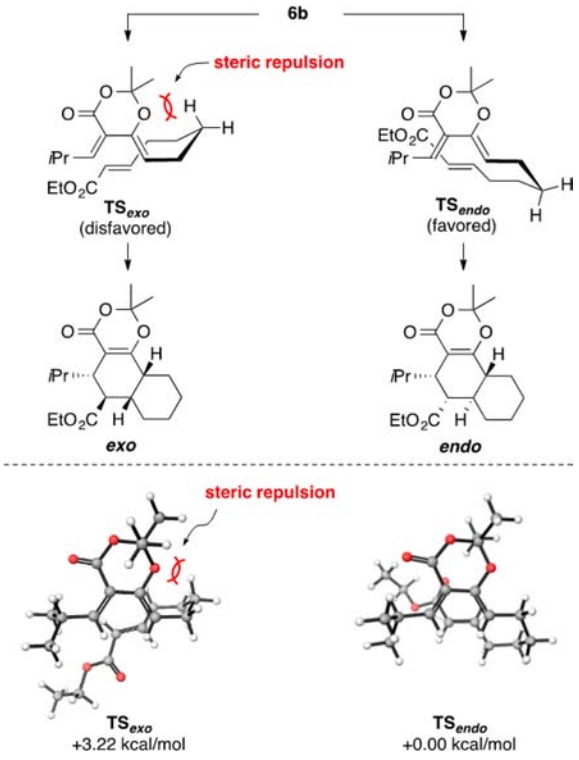


Figure 1. TS$_{exo}$ and TS$_{endo}$.

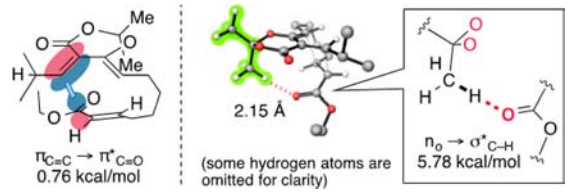
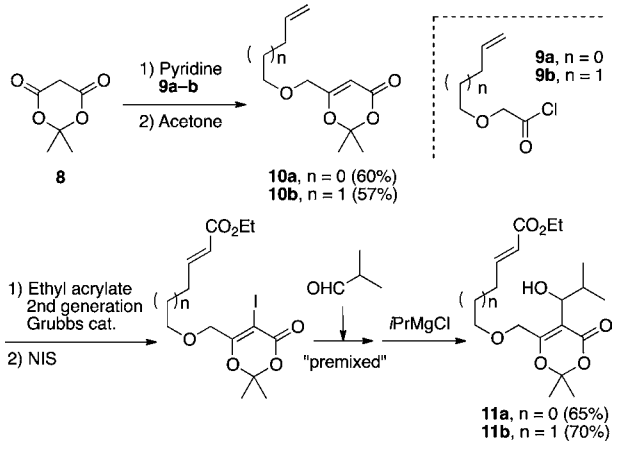


Figure 2. NBO analysis on TS$_{endo}$.

Thus, the high *endo* selectivity could be attributed to the following factors: (1) destabilization of **TS**$_{exo}$ by steric repulsion, and (2) stabilization of **TS**$_{endo}$ by a weak secondary orbital interaction and by a C−H/n interaction.

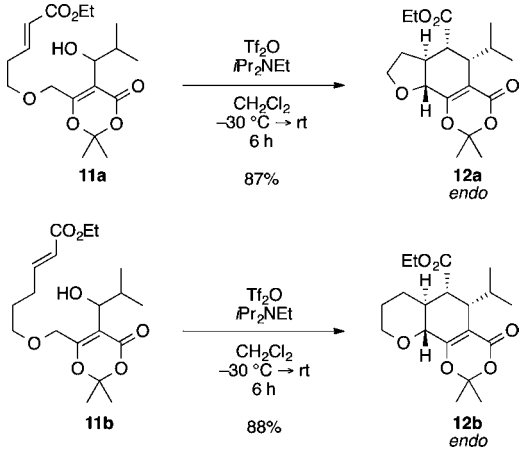
We next examined the reactions of the oxygen-tethered trienes, for which the precursors **11a** and **11b** were prepared (Scheme 7). Meldrum's acid (**8**) was combined with acid chloride **9a** (pyridine, CH_2Cl_2, 0 °C → rt, 20 min), and heating of the resulting product in the presence of acetone (toluene, reflux, 2 h) afforded dioxinone **10a** in 60% yield in two steps. The following manipulation to the triene precursor **11a** was conducted in a similar way as mentioned above. The protocol was also applied to the synthesis of **11b**.[15]

Scheme 7. Preparation of Alcohols 11a and 11b



Upon treatment of alcohol **11a** with Tf_2O (*i*-Pr_2NEt, CH_2Cl_2, −30 °C, 20 min, then rt, 6 h), hydrobenzofuran **12a**[8] was obtained in 87% yield. The NOE correlations confirmed the stereochemistry as indicated (Scheme 8).

Scheme 8. Reactions of Oxygen-Tethered Trienes



Notably, the reactivity is much higher for the oxygen-tethered triene, generated from alcohol **11a**, as it underwent the IMDA reaction without resorting to any catalyst. This stands in contrast to the corresponding carbon-tethered triene **6a** that required Lewis acid catalysis (*vide supra*). This enhanced reactivity is due to the electron donation from the oxygen lone pair, raising the HOMO level of the diene. Under the same conditions, the reaction of alcohol **11b** with a longer chain also gave the *endo* cycloadduct **12b**[8] as the sole product in 88% yield.

In summary, the intramolecular Diels−Alder reactions of dioxanone-fused dienes proceeded with high *endo* selectivity under mild conditions, giving *trans*-fused bicyclic products. The regenerated dioxinone moiety provides additional opportunities for further elaboration. Further work is in progress on the synthesis of natural products.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedure, characterization data, and NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01172.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kohmori@chem.titech.ac.jp.
*E-mail: ksuzuki@chem.titech.ac.jp.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b01172
Org. Lett. 2015, 17, 2756−2759

■ ACKNOWLEDGMENTS

This work was supported by the Grant-in-Aid for Specially Promoted Research (No. 23000006) from JSPS.

■ REFERENCES

(1) Aoki, Y.; Mochizuki, Y.; Yoshinari, T.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2011**, *40*, 1192−1194.
(2) For a review, see: (a) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022−3034. For selected recent examples, see: (b) Fuse, S.; Nakamura, K.; Mifune, Y.; Narubayashi, H.; Hijikuro, I.; Nojima, S.; Tanaka, H.; Takahashi, T. *Synlett* **2014**, *25*, 2806−2813. (c) Fuse, S.; Yoshida, H.; Oosumi, K.; Takahashi, T. *Eur. J. Org. Chem.* **2014**, 4854−4860. (d) Xiao, Q.; Young, K.; Zakarian, A. *Org. Lett.* **2013**, *15*, 3314−3317. (e) George, N. S.; Anderson, K. E.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2013**, 7604−7610. (f) Rentsch, A.; Kalesse, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11381−11384. (g) Yadav, J. S.; Dhara, S.; Hossain, S. S.; Mohapatra, D. K. *J. Org. Chem.* **2012**, *77*, 9628−9633. (h) Chen, J.; Chen, J.; Xie, Y.; Zhang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1024−1027. (i) Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5892−5895.
(3) For recent reviews of IMDA reactions in natural product synthesis, see: (a) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992. (b) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.
(4) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; Wiley-VCH: Weinheim, Germany, 1988.
(5) The selective γ-alkylation is usually unfruitful. For recent examples, see: (a) Haddad, N.; Rukhman, I.; Abramovich, Z. *J. Org. Chem.* **1997**, *62*, 7629−7636. (b) Graalfs, H.; Fröhlich, R.; Wolff, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 1057−1073. (c) Winkler, J. D.; McLaughlin, E. C. *Org. Lett.* **2005**, *7*, 227−229. (d) Skepper, C. K.; Dalisay, D. S.; Molinski, T. F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2029−2032.
(6) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650.
(7) We screened solvents (toluene, CH_2Cl_2, MeOH, CH_3CN, H_2O) and Lewis acids [$La(OTf)_3$, $Lu(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$, $Sc(OTf)_3$] in the intermolecular Diels−Alder reaction of dioxanone-fused diene with dimethyl fumarate. For details, see Supporting Information.
(8) The stereochemistry was determined by NOE correlations; see Supporting Information.
(9) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267−4268.
(10) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825−4829.
(11) For recent discussions on the secondary orbital interactions, see: (a) Fernández, I.; Bickelhaupt, F. M. *J. Comput. Chem.* **2014**, *35*, 371−376. (b) Wannere, C. S.; Paul, A.; Herges, R.; Houk, K. N.; Schaefer, H. F., III; Schleyer, P. v. R. *J. Comput. Chem.* **2007**, *28*, 344−361. (c) García, J. I.; Mayoral, J. A.; Salvatella, L. *Eur. J. Org. Chem.* **2005**, 85−90. (d) García, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658−664.
(12) Geometrical optimizations (minima and transition states) were all carried out at the B3LYP functional and the 6-31G(d) basis set. The vibrational frequencies were computed to characterize the optimized geometries and to evaluate its zero-point vibrational energy and thermal corrections at 298 K.
(13) For previous rationales for the *endo* cycloadduct, see: (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930. (b) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710−712. (c) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327−4330. (d) Boeckman, R. K.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421−3423. (e) Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560−566. (f) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289−6291.
(14) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211−7218.
(15) For the details, see Supporting Information.

DOI: 10.1021/acs.orglett.5b01172
Org. Lett. 2015, 17, 2756−2759