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Intramolecular Diels–Alder reactions with substituted Feringa-butenolides: a dramatic increase in reactivity by double activation

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Abstract

A thermal intramolecular *endo*-selective Diels–Alder reaction with a substituted Feringa-butenolide is described. The structure of the main product is determined by single crystal X-ray analysis. By double activation of the dienophile substructure a dramatic increase in reactivity is reported, which leads to a decrease in reaction temperature by more than 100°C.

1. Introduction

Intramolecular Diels–Alder reactions[1] (IMDA reactions) are a powerful tool in natural product synthesis to construct highly substituted polycyclic carbon skeletons. Most IMDA reactions use crotonate type dienophile substructures, whereas methacrylate type[2] dienophiles are rarely used in IMDA reactions (Fig. 1).

a **b**

Figure. 1. Two types of dienophile substructures in IMDA reactions: (a) crotonate type dienophile; (b) methacrylate type dienophile

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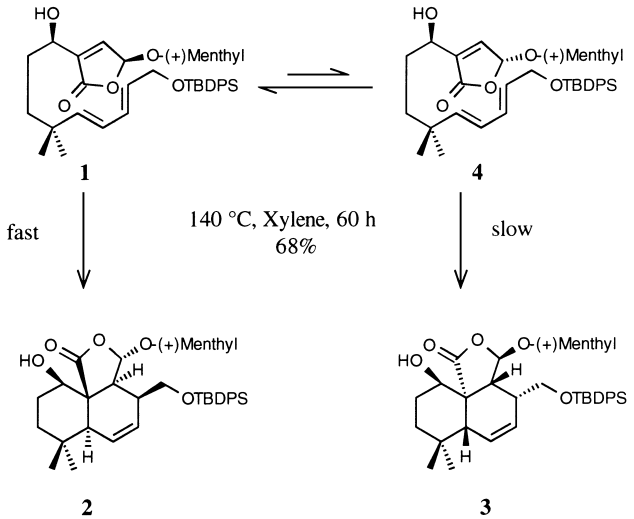
Feringa-butenolides were used as dienophiles in intermolecular Diels–Alder reactions[3] and as dipolarophiles in 1,3-dipolar cycloadditions.[4] In our project towards the total synthesis of mniopetals[5] we described the first IMDA reaction of the substituted Feringa-butenolide **1**, which contains a methacrylate type dienophile substructure.

2. Results and discussion

When the trienolide **1** is heated at 140°C in xylene for 60 h in a silylated flask, the tricyclic adduct **2** is obtained in 68% yield along with **3** in 12% yield (**2**:**3** ca. 5.6:1) and a mixture of unreacted starting material **1** and its epimer **4** (Scheme 1). Silylation of the flask is necessary to reduce epimerization of **1** catalyzed by the glass surface.



Scheme 1. IMDA reaction of **1**

Crystallization of **2** from *n*-pentane gave crystals suitable for X-ray analysis.[6] The corresponding ORTEP-drawing is shown in Fig. 2. The unit cell contains two molecules which differ in the conformations of the menthyl residue and the OTBDMS group. This probably stems from packing effects. Additionally, there is a weak hydrogen bond between the secondary alcohol OH4 and the acetal oxygen O3 (see Fig. 2). The crystallographic data are shown in Table 1.

To prevent complete epimerization of **1** to **4** during the IMDA reaction, we thought that activation of the dienophile by an additional electron withdrawing group should lead to an increased reactivity and therefore to lower reaction temperatures.[7] Therefore, we decided to doubly activate **1** through oxidation[8] to the corresponding ketone **5**. This was best achieved by Dess–Martin periodinane[9] in the presence of 2,6-lutidine as base to neutralize the acetic acid liberated during the oxidation. When we carried out this oxidation at room temperature TLC showed a clean reaction giving **6** in ca. 79–81% yield along with ca. 14% of the corresponding *exo*-product after 16 hours. The expected oxo-trienolide **5** could not be detected. Compound **5** cyclizes spontaneously to give **6**, identical with the product obtained by oxidation of **2** with PDC (Scheme 2).

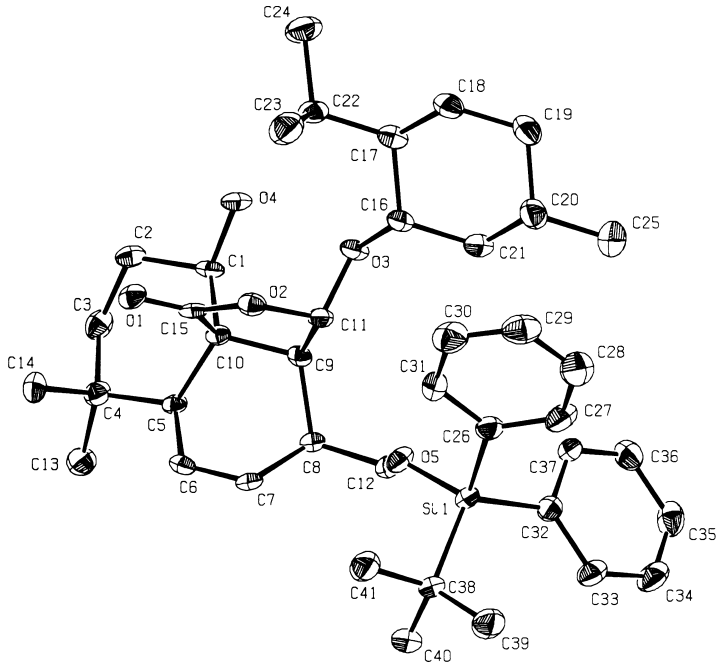
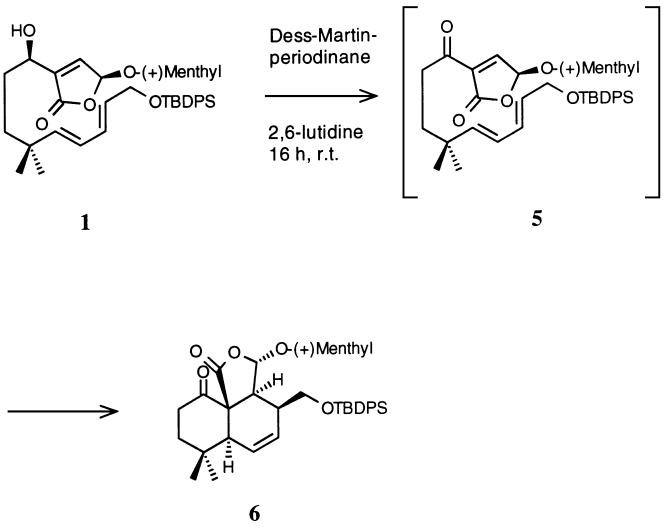


Figure. 2. ORTEP-drawing of **2**

Table 1
Selected crystallographic data for **2**

	2
chem formula	$C_{41}H_{58}O_5Si$
fw	658.95
cryst system	monoclinic
space group / No.	P 2_1 / 4
a (pm)	1414.76(3)
b (pm)	1106.82(2)
c (pm)	2476.61(5)
β (deg)	95.607(1)
V (10^6 pm^3)	3859.5(1)
Z	4
ρ_{calcd} (g cm^{-3})	1.134
F_{000}	1432
Θ range (deg / *h,k,l*)	1.59 to 25.09 / ±16, ±13, ±29
no. of rflns collcd	26635
no. of indep rflns (all data / $I_o>2\sigma(I_o)$	13626 / 11395
no. of params refined	1309
R1 ($I_o>2\sigma(I_o)$ / all data)	0.0572 / 0.0750
wR2 ($I_o>2\sigma(I_o)$ / all data)	0.0895 / 0.0934
GOF	1.113



Scheme 2. IMDA reaction with a double activated Feringa-butenolide

Thus, double activation leads to a dramatic increase in reactivity which results in decrease of reaction temperature by more than 120°C and a decrease in reaction time. The method described here is a simple means to accelerate IMDA reactions with methacrylate-type dienophile substructures which are very sluggish under usual reaction conditions or contain thermally labile groups.

3. Experimental

Compound **1** (79.7 mg, 0.121 mmol) and 2,6-lutidine (113 μl, 0.968 mmol, 8 equiv.) are dissolved in dried CH_2Cl_2 (11 ml) under nitrogen at room temperature. A solution of Dess–Martin reagent in CH_2Cl_2 (0.363 mmol, 0.85 ml) is added dropwise and the reaction mixture is stirred overnight. The reaction is quenched by diluting with diethyl ether and adding saturated $Na_2S_2O_3$ solution. The phases are separated and the aqueous layer is extracted with ether. The combined organic extracts are dried with $MgSO_4$ and the product is purified by flash chromatography (*n*-pentane:diethyl ether, 15:1 (v/v)). Yield: 62.9 mg (79%). ^{1}H NMR ($CDCl_3$, 360 MHz, δ relative to TMS): 7.66 (m, 4H), 7.42 (m, 6H), 6.06 (m, 1H), 5.98 (dt, 9.1 Hz, 3.2 Hz, 1H), 5.30 (d, 2.6 Hz, 1H), 3.90 (m, 2H), 3.50 (dd, 5.8 Hz, 1.9 Hz, 1H), 3.35 (m, 2H), 2.42–2.31 (m, 2H), 2.19 (m, 1H), 2.02 (br. s, 1H), 1.96 (m, 1H), 1.87 (br. d, 12.3 Hz, 1H), 1.70 (m, 1H), 1.59 (s, 3H), 1.41 (s, 3H), 1.09 (s, 9H), 1.02 (s, 3H), 0.81 (d, 7.2 Hz, 3H), 0.80 (d, 6.5 Hz, 3H), 0.64 (d, 7.2 Hz, 3H), 1.3–0.7 (m, 4H). ^{13}C NMR ($CDCl_3$, 90 MHz, δ relative to $CDCl_3$): 203.8, 173.0, 135.6, 135.5, 133.4, 133.3, 131.8, 129.8, 129.7, 127.8, 76.4, 66.6, 63.4, 52.2, 47.5, 46.0, 39.9, 39.2, 39.0, 35.8, 34.3, 33.2, 32.3, 31.3, 29.7, 26.9, 25.1, 23.0, 22.2, 22.0, 20.8, 19.3, 15.5.

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References

1. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p. 513, and references cited therein.
2. Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085–5088. Brasca, M. G.; Broughton, H. B.; Craig, S.; Ley, S. V.; Somovilla, A. A.; Toogood, P. L. *Tetrahedron Lett.* **1988**, *29*, 1853–1856. Boeckman, R. K.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789–1792.
3. De Jong, J. C.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1247–1262. De Jong, J. C.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1990**, *31*, 3047–3050. De Jong, J. C.; Feringa, B. L. *J. Org. Chem.* **1988**, *53*, 1125–1127.
4. Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607–624. Keller, E.; de Lange, B.; Rispens, M. T.; Feringa, B. L. *Tetrahedron* **1993**, *49*, 8899–8910.
5. Jauch, J. *Synlett* **1999**, 1325–1327.
6. X-Ray crystallography: crystal data and details of the structure determination are presented in Table 1. Suitable single crystals for the X-ray diffraction study were grown by slow evaporation of a *n*-pentane solution of **2**. A clear colorless needle (0.65×0.10×0.05 mm) was stored under perfluorinated ether, transferred in a Lindemann capillary, fixed and sealed. Preliminary examination and data collection were carried out on a Kappa CCD area detector diffraction system (Nonius; Mach3) equipped with a rotating anode and graphite monochromated MoKα radiation (Nonius; Fr951). The unit cell parameters were obtained by full-matrix least-squares refinements of 99137 reflections. Data collection was performed at 123 K (exposure time: 60 s per frame; 8 sets, φ and Ω-scans, Δφ/ΔΩ: 1°; dx: 40.0 mm). A total number of 138016 reflections were collected. Raw data were corrected for Lorentz, polarization, and decay effects and were scaled with the program Denzo-SMN. After merging (R_{int} = 0.0612) a sum of 13626 independent reflections remained and were used for all calculations. All 'heavy atoms' of the asymmetric unit were refined anisotropically. All hydrogen atoms were located in the difference Fourier map and refined with individual isotropic temperature parameters. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$ with SHELXL-97 weighting scheme and stopped at shift/err <0.001. The correct enantiomer is fixed by the synthetic route and confirmed by Flack's parameter $x=0.10$ (9). Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from *International Tables for Crystallography*. All calculations were performed on a DEC 3000 AXP workstation and an Intel Pentium II PC, with the Strux-V system, including the programs Platon, Sir92, and SHELXL-97.
7. Harkin, S. A.; Jones, R. H.; Tapolczay, D. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 489–497. Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 499–505. Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 507–518. Sauter, R.; Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 519–523. Merifield, E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1990**, 464–466. Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Chem. Commun.* **1990**, 467–469.
8. For IMDA reactions with trienes, which cyclize spontaneously at room temperature upon oxidation of an allylic alcohol to the vinyl ketone, see: Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992–3993. Gras, J. L.; Bertrand, M. *Tetrahedron Lett.* **1979**, *20*, 7301–7304. Vig, O. P.; Trehan, I. R.; Kumar, R. *J. Chem. Ind.* **1977**, *15B*, 319–322. Vig, O. P.; Trehan, I. R.; Malik, N.; Kumar, R. *J. Chem. Ind.* **1978**, *16B*, 449–451. For a related reaction, see: Oppolzer, W.; Snowdon, R. L. *Tetrahedron Lett.* **1976**, *17*, 4187–4190.
9. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. Boeckman, R. J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 7, pp. 4982–4987, and references cited therein. Speicher, A.; Bomm, V.; Eicher, T. *J. Prakt. Chemie* **1996**, *338*, 588–590.