Regio- and stereocontrolled Diels–Alder reaction tethered by Asp-Thr dipeptide†

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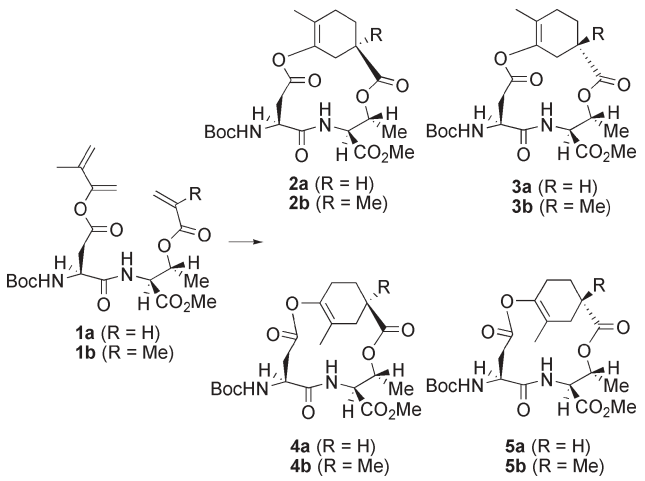
The Asp-Thr tethered Diels–Alder reaction of 1a was accomplished to provide 2a exclusively in a regio- and stereoselective manner.

The Diels–Alder reaction has been a synthetically important method for the formation of a 6-membered ring accompanied by the creation of stereogenic centers. The unique regio- and stereocontrol obtainable from the Diels–Alder reaction has been explored. The intramolecular version of the reaction is especially valuable.[1] A temporary connecting group between diene and dienophile, such as an ether linkage, an ester linkage, an amide linkage,[2–7] or a silicon tether, brings the reaction sites closer and accelerates the reaction often with exclusive regioselectivity and stereoselectivity. We wish to report here a novel approach, illustrated by the dipeptide-tethered[8,9] regio- and stereocontrolled Diels–Alder reaction of **1** (Scheme 1).

We designed a dipeptide of aspartic acid and threonine (Asp-Thr) derivatives as a tether. A carboxylic acid of the former and a hydroxyl group of the latter were employed for the attachment of a dienol and an α,β-unsaturated acid, respectively (Scheme 1). Questions are (1) whether the Diels–Alder reaction can take place; (2) how we can predict regio- and stereoselectivity.‡ Conformational analysis of **1** (Macromodel[10] version 6.0 with MMFF force field) suggested that the reaction sites are close (*ca.* 5 Å) even at the ground state, so that the Diels–Alder reaction should proceed. We have previously reported that MM2 transition state models[11] are useful to predict the stereochemistry of the transannular Diels–Alder reaction of a flexible macrocycle designed for the synthesis of steroids.[12] These models were not, however, able to predict regiochemistry. More precise theoretical transition state (TS) calculations were needed to predict both the regio- and stereoselection to be anticipated by the unprecedented Diels–Alder reaction of **1**. The appropriate TSs of such a flexible and relatively big molecule obtained by density functional theory (DFT) were as follows: (1) various candidates for the TSs were generated by a MM2 TS model method and their energies were obtained by DFT, namely B3LYP/6-31G(d), which is reliable for pericyclic reactions.[13,14] (2) The lower energy conformations (within 30 kJ mol^{-1} from the lowest) were used for the TS search by making a reaction profile based on PM3, and the appropriate structures were optimized using Spartan.§ (3) The respective four lowest energy TSs that would produce regio- and stereoisomers **2a–5a** and **2b–5b** were selected. (4) The four PM3-optimized TSs were fully optimized using B3LYP/6-31G(d) on Gaussian 98[15] to provide **2A–5A** and **2B–5B**, respectively (Fig. 1). Vibration mode analyses were carried out to obtain the zero-point energy (ZPE) and to confirm that the TS structure has only one imaginary normal mode corresponding to the reaction coordinate. (5) The relative energies (including ZPE corrections) of **2A–5A** and **2B–5B**, using various levels of theory were obtained (Table 1): the predicted Boltzmann distribution in the reaction of **1** at 150 °C [**2a** : **3a** : **4a** : **5a** = 63 : 37 : 0 : 0 (entry 5, B3LYP/6-311+G(d,p)); 67 : 33 : 0 : 0 (entry 7, MP2/6-31+G(d,p))] and [**2b** : **3b** : **4b** : **5b** = 36 : 56 : 8 : 0 (entry 5, B3LYP/6-311+G(d,p)); 51 : 47 : 2 : 0 (entry 7, MP2/6-31+G(d,p))]. Formation of regioisomers **4** and **5** is not predicted by either calculation. The energy differences are due to the different orientation of the carbonyl group of the ester, such that **TS2** and **TS3** adopt an s-*cis* conformation whereas **TS4** and **TS5** adopt an s-*trans* conformation. Interestingly, **TS2** and **TS3** seem to have similar enantiotopic conformations at the peptide tether except for the orientation of the amide bond between Asp-Thr. Increasing the basis set sizes indicated that the transition state **2A** is more favorable than **3A** in both DFT and MP2 calculations. On the other hand, the DFT calculation suggested that **3B** is preferred to **2B** whereas the MP2 calculation exhibited no energy difference between them.



Scheme 1

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† Electronic supplementary information (ESI) available: Cartesian coordinates of optimized structures **2A–5A** and **2B–5B**, energies of single point calculations, zero-point energy corrections and magnitudes of imaginary frequencies. Experimental details, spectral data of **1a**, **1b**, **2a**, **2b** and **3b**, and structure determination of **2a**. See http://dx.doi.org/10.1039/b509156j

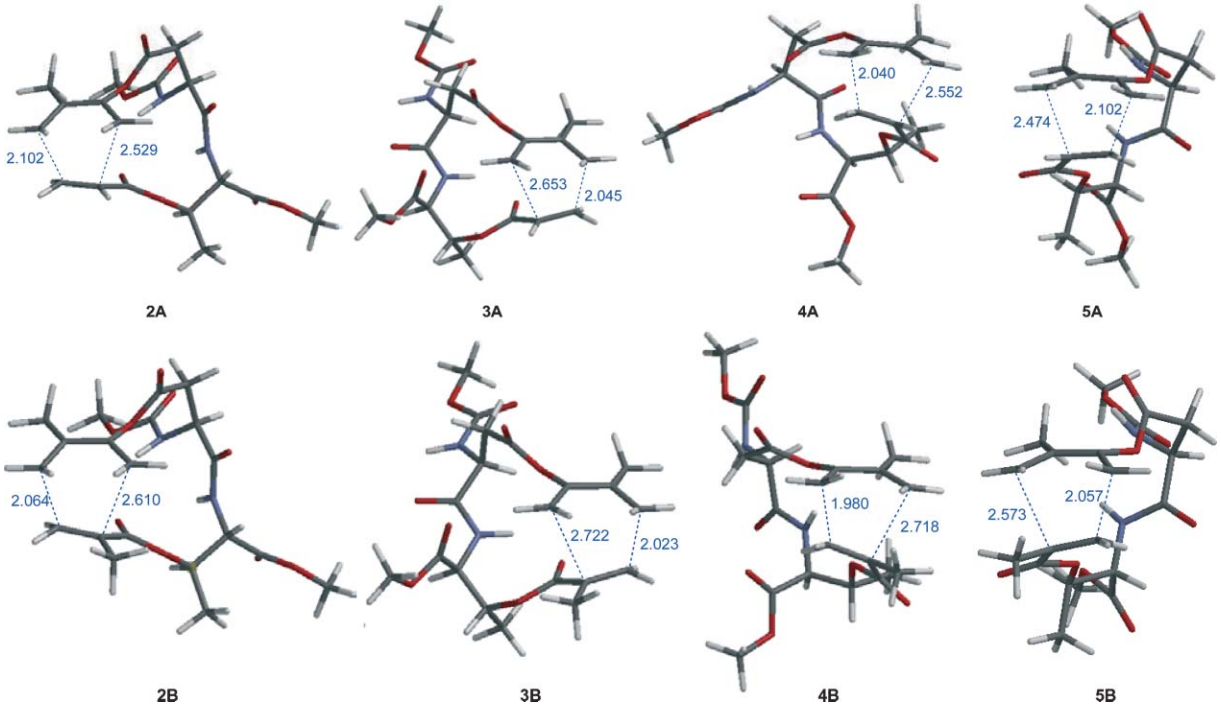

Fig. 1 B3LYP/6-31G(d) optimized TS structures. All calculations were carried out, for simplicity, on a methylcarbamate derivative instead of the *t*-butoxycarbamate. TSs **2A–5A** lead to **2a–5a** and TSs **2B–5B** lead to **2b–5b**.

Amidation of protected aspartic acid **6** with threonine methyl ester **7**, followed by removal of a benzyl group, provided dipeptide **8** (Scheme 2). Enol ester formation of **8** with 2-methyl-1-buten-3-yne (**9**) was carried out, using $RuCl_2(PPh_3)$(*p*-cymene) as a catalyst,[16] in toluene at 80 °C for 24 h. Enol ester **10** was obtained in 77% yield with 93% regioselectivity.¶ Removal of a TES group (cat. camphorsulfonic acid/methanol/rt) and acylation of the resulting alcohol with acryloyl chloride or methacryloyl chloride (CH_2Cl_2/*i*-Pr_2EtN/0 °C) afforded **1a** and **1b** in 80% and 61% yields, respectively.

The Diels–Alder reaction of **1a** was accomplished in toluene at 150 °C for 24 h in the presence of $NaHCO_3$ to provide **2a** in 75% yield, as a single diastereomer. Addition of $NaHCO_3$ is essential to avoid removal of a BOC group. No epimerization of the α-positions of the dipeptide moiety was detected. On the other hand, the reaction of **1b** under the same reaction conditions for 36 h afforded a 50 : 50 mixture of stereoisomers **2b** and **3b** in 80% combined yield. It should be noted that the unprecedented peptide-tethered macrocyclic Diels–Alder reaction has proceeded. The regioselectivity is in good agreement with the ratios predicted by the theoretical models. The stereoselectivity is, however, not completely identical with the predicted ratios obtained with DFT and MP2 calculations but the latter exhibited a better correlation, a preferred product **2a** in the reaction of **1a** and non-selectivity of **2b** and **3b** in the reaction of **1b**.[17]‖

Basic hydrolysis of **2a**, followed by acidification afforded 3-oxo-4-methylcyclohexanecarboxylic acid whose absolute configuration was determined to be (1*R*,4*R*) on the basis of the observation of a positive Cotton effect (292 nm) in its CD spectrum.[18]

We have demonstrated that the novel peptide-tethered Diels–Alder reaction proceeds with high stereo- and regiocontrol. Although high level theoretical calculations can predict the regioselectivity but do not exactly match the stereochemistry with the experimental results at the moment, this model could support designing other tethers for the synthesis of various cyclic peptido mimetic compounds.

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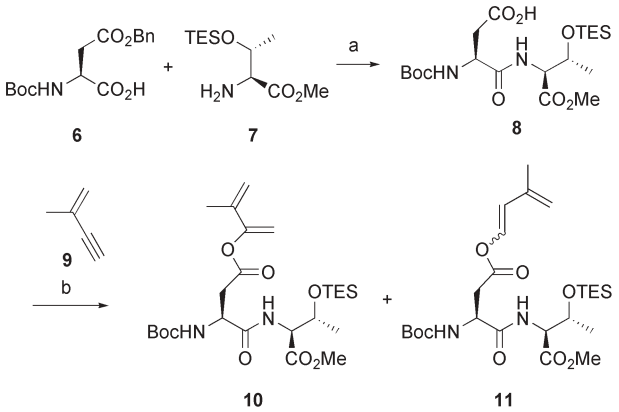
Table 1 Transition state calculation of the Asp-Thr tethered Diels–Alder reaction of **1a** and **1b**

		(R = H) Energy difference/kJ mol^{-1}				(R = Me) Energy difference/kJ mol^{-1}			
Entry	Basis set	**2A**	**3A**	**4A**	**5A**	**2B**	**3B**	**4B**	**5B**
1	B3LYP/6-31G(d)//PM3	0.0	6.0	34.8	38.7	−2.1	0.0	33.2	37.0
2	B3LYP/6-31G(d)//B3LYP/6-31G(d)	0.0	−0.1	21.0	31.9	3.0	0.0	11.3	38.0
3	B3LYP/6-31+G(d,p)//B3LYP/6-31G(d)	0.0	1.3	21.6	28.4	2.0	0.0	8.3	33.5
4	B3LYP/6-311G(d,p)//B3LYP/6-31G(d)	0.0	1.7	20.6	31.3	1.5	0.0	9.1	35.4
5	B3LYP/6-311+G(d,p)//B3LYP/6-31G(d)	0.0	1.8	21.5	28.3	1.5	0.0	7.0	32.6
6	MP2/6-31G(d,p)//B3LYP/6-31G(d)	0.0	2.0	27.3	29.4	−0.1	0.0	9.5	31.0
7	MP2/6-31+G(d,p)//B3LYP/6-31G(d)	0.0	2.6	28.9	26.5	−0.3	0.0	10.7	28.4



Scheme 2 Reagents and reaction conditions (a) (i) EDCI, HOBt, NEt_3, DMF, rt (97%); (ii) H_2, $Pd(OH)_2$, K_2CO_3, ethyl acetate, rt (90%). (b) 3 mol% $RuCl_2(PPh_3)$(*p*-cymene), toluene, 80 °C (77%).

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Notes and references

‡ Intermolecular Diels–Alder reaction of the corresponding system gave a 1 : 1 mixture of the regioisomers.
§ Spartan ′02 (version 1.0.1), Wavefunction, Inc., Irvine, CA 92612, USA
¶ The reaction using a reported catalyst, $RuCl_2(PMe_3)$(*p*-cymene), provided a 33 : 67 mixture of **10** and **11** in 89% yield. Presumably, steric repulsion of a ligand may cause this high regioselectivity.
‖ The better performance of MP2 might arise from better inclusion of dispersion energy arising from differing transannular interactions.

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