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Double Diels–Alder Reactions of Linear Conjugated Tetraenes

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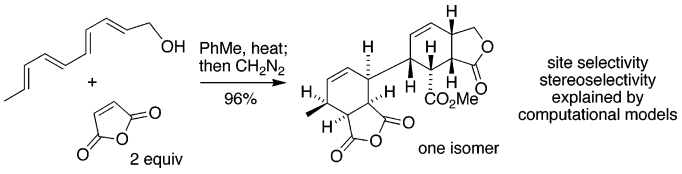


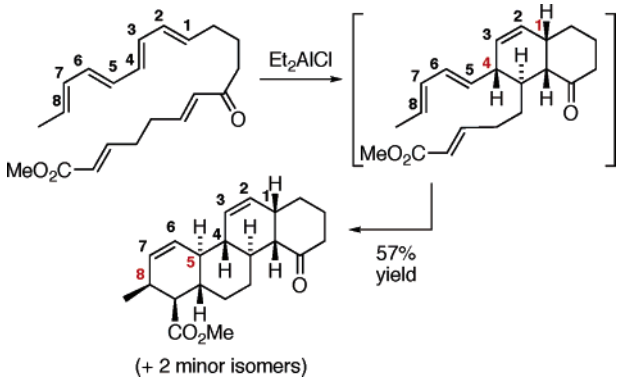
Linear conjugated tetraenes are shown to participate effectively as bis-dienes in sequences involving either two intermolecular Diels–Alder reactions or an intramolecular followed by an intermolecular Diels–Alder reaction. Thus, simple tetraenol **1** is transformed into tetracyclic products **5**, **6**, and **9** in high yielding and highly stereoselective sequences with maleic anhydride involving the formation of three rings, four C–C bonds and one C–O bond, and eight stereocenters. In the latter case, the one-pot reaction protocol is very simple, and furnishes a single diastereoisomeric product in essentially quantitative yield. Linear conjugated tetraenes exhibit complete terminal site selectivity in reactions with dienophiles and computational investigations reveal that two discrete π-conjugative interactions are the origin of this unexpected reactivity. B3LYP/6-31G(d) transition structures also allow an explanation of unexpectedly high π-diastereofacial selectivities witnessed during these transformations, through the identification of preferred C1–C* diene conformations and nonbonded interactions. These new experimental and computational findings encourage the use of linear conjugated polyenes in domino sequences.

Introduction

Sequences of Diels–Alder reactions have been known for many years. Indeed, one of the first examples of the "diene synthesis" reinvestigated by Diels and Alder involved the union of two molecules of cyclopentadiene with a molecule of benzoquinone.[1,2] More recent research[3] involves the development of new efficient strategies for polycycle construction, with a strong emphasis on the regiochemical and stereochemical control of cycloaddition events. Our contributions in this area involve domino *intra*molecular–*intra*molecular Diels–Alder sequences of linear conjugated tetraenes, reactions that are constrained to occur with a particular *site*[4] selectivity (Scheme 1).[5]

In a pioneering study, Kraus developed a very short synthetic entry to the hydrofluorenone skeleton through an *inter*molecular–*intra*molecular Diels–Alder sequence, carried out upon 2-silyloxy-1,3,5,7-tetraene substrates (Scheme 2).[6] The site selectivity obtained in Kraus' study is not surprising considering the electronic bias brought to bear by the 2-silyloxy group.

SCHEME 1. Domino Intramolecular Diels–Alder Sequence on a Linear Conjugated Tetraene



The research described herein aimed to answer this question: Can *electronically unbiased all-E*-1,3,5,7-tetraene substrates participate in selective transformations

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(1) Diels, O.; Alder, K. *Justus Leibigs Ann. Chem.* **1928**, *460*, 98–122.

(2) Original study: (a) Albrecht, W. *Justus Leibigs Ann. Chem.* **1906**, *348*, 31–49. See also: (b) von Euler, H.; Josephsen, K. O. *Chem. Ber.* **1920**, *53*, 822–826. For a fascinating historical account, see: (c) Berson, J. A. *Chemical Creativity: Ideas from the Work of Woodward, Hückel, Meerwein and Others*; Wiley-VCH: Weinheim, Germany, 1999.

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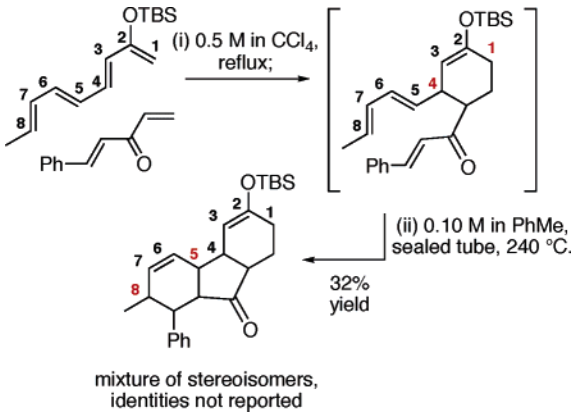
SCHEME 2. Site Selectivity during an *Inter*molecular Cycloaddition of a 2-Silyloxy-1,3,5,7-tetraene by Kraus and Taschner[6]



through the two other possible double cycloaddition modes, namely *intra*molecular–*inter*molecular Diels–Alder and *inter*molecular–*inter*molecular Diels–Alder sequences?

We were confident that an *intra*molecular–*inter*molecular Diels–Alder sequence would be achievable since, in addition to the control of site selectivity exhibited during the first cycloaddition event in Scheme 1, there are many other reports of successful intramolecular

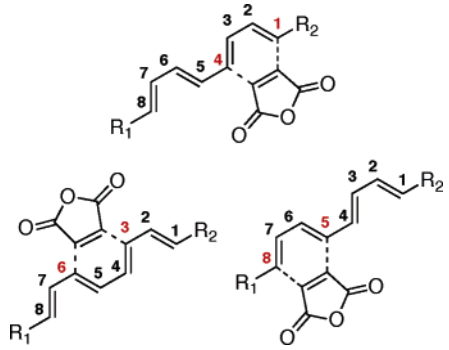


FIGURE 1. The three possible sites of addition of a simple dienophile (maleic anhydride) to an unsymmetrically substituted linear conjugated tetraene.

Diels–Alder (IMDA) reactions on linear conjugated trienes, tetraenes, and higher polyenes.[7] We were less confident regarding the development of *inter*molecular–*inter*molecular Diels–Alder sequences with simple *all-E*-1,3,5,7-tetraene substrates since, in principle, three regioisomeric products can be formed, through dienophile addition across C1–C4, C3–C6, and C5–C8 of the 1,3,5,7-tetraene moiety (Figure 1). Despite the enormous body of experimental and theoretical results relating to the Diels–Alder reaction, the *inter*molecular cycloaddition of dienophiles to linear conjugated tetraenes remains, with the exception of Kraus' study, unexplored.

Linear conjugated trienes and higher polyenes were regarded as substituted 1,3-dienes by Sauer,[8] and the site selectivity problem associated with such systems was suggested over 50 years ago by Alder.[9] This *site* selectivity issue could conceivably be addressed by substituent effects (cf. Scheme 2) and alkene geometries within the conjugated tetraene precursor[10] or by protection.[11] Nevertheless, we were interested in ascertaining the *inherent* site selectivity in reactions of *all-E*-1,3,5,7-tetraene systems with dienophiles. This paper describes our surprising preliminary experimental findings toward this end, along with the stereochemical issues raised by such reactions, and the development of theoretical models to understand these experimental results.

Results and Discussion

Reactions between tetraenol **1**[12] and maleic anhydride (**2**) were investigated.

(3) Sequences of Diels–Alder reactions. Review: (a) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176. Recent papers: (b) Marchionni, C.; Vogel, P.; Roversi, P. *Tetrahedron Lett.* **1996**, *37*, 4149–4152. (c) Winkler, J. D.; Kim, H. S.; Kim, S.; Penkett, C. S.; Bhattacharya, S. K.; Ando, K.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 2957–2962. (d) Saito, T.; Kimura, H.; Chonan, T.; Soda, T.; Karakasa, T. *Chem. Commun.* **1997**, 1013–1014. (e) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418–4427. (f) Lautens, M.; Fillion, E. J. *Org. Chem.* **1998**, *63*, 647–656. (g) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419. (h) Golobish, T. D.; Burke, J. K.; Kim, A. H.; Chong, S. W.; Probst, E. L.; Carroll, P. J.; Dailey, W. P. *Tetrahedron* **1998**, *54*, 7013–7024. (i) Winkler, J. D.; Kwak, Y.-S. *J. Org. Chem.* **1998**, *63*, 8634–8635. (j) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiminez, J. L.; Palacios, J. C. *Tetrahedron Lett.* **1998**, *39*, 9301–9304. (k) Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573–575. (l) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013–1016. (m) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. J. *Org. Chem.* **1999**, *64*, 3595–3607. (n) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1999**, *64*, 9348–9357. (o) Bushby, N.; Moody, C. J.; Riddick, D. A.; Waldron, I. R. *Chem. Commun.* **1999**, 793–794. (p) Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. *Heterocycles* **1999**, *50*, 653–656. (q) Tsuge, O.; Hatta, T.; Fujiwara, T.; Yokohari, T.; Tsuge, A.; Moriguchi, T. *Heterocycles* **1999**, *50*, 661–666. (r) Marchionni, C.; Meilert, K.; Vogel, P.; Schenk, K. *Synlett* **2000**, 1111–1114. (s) Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363–3380. (t) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120–9124. (u) Marchionni, C.; Vogel, P. *Helv. Chim. Acta* **2001**, *84*, 431–472. (v) Bushby, N.; Moody, C. J.; Riddick, D. A.; Waldron, I. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2183–2193. (w) Schwenter, M.-E.; Schenk, K.; Scopelliti, R.; Vogel, P. *Heterocycles* **2002**, *57*, 1513–1524. (x) Saito, T.; Kobayashi, S.; Ohgaki, M.; Wada, M.; Nagahiro, C. *Tetrahedron Lett.* **2002**, *43*, 2627–2631. (y) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361–7364. (z) Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4135–4137. (aa) Spino, C.; Hill, B.; Dube, P.; Gingras, S. *Can. J. Chem.* **2003**, *81*, 81–108. (ab) Chaplin, J. H.; Edwards, A. J.; Flynn, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1842–1844. (ac) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805–1808.

(4) We use the term *site selectivity* to describe the location of reaction of a dienophile at a conjugated tetraene rather than *regioselectivity*, since the latter term enjoys common usage as a descriptor for the orienation of addition between unsymmetrical dienes and unsymmetrical dienophiles.

(5) (a) Nörret, M.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4074–4076. (b) Turner, C. I.; Williamson, R. M.; Turner, P.; Sherburn, M. S. *Chem. Commun.* **2003**, 1610–1611.

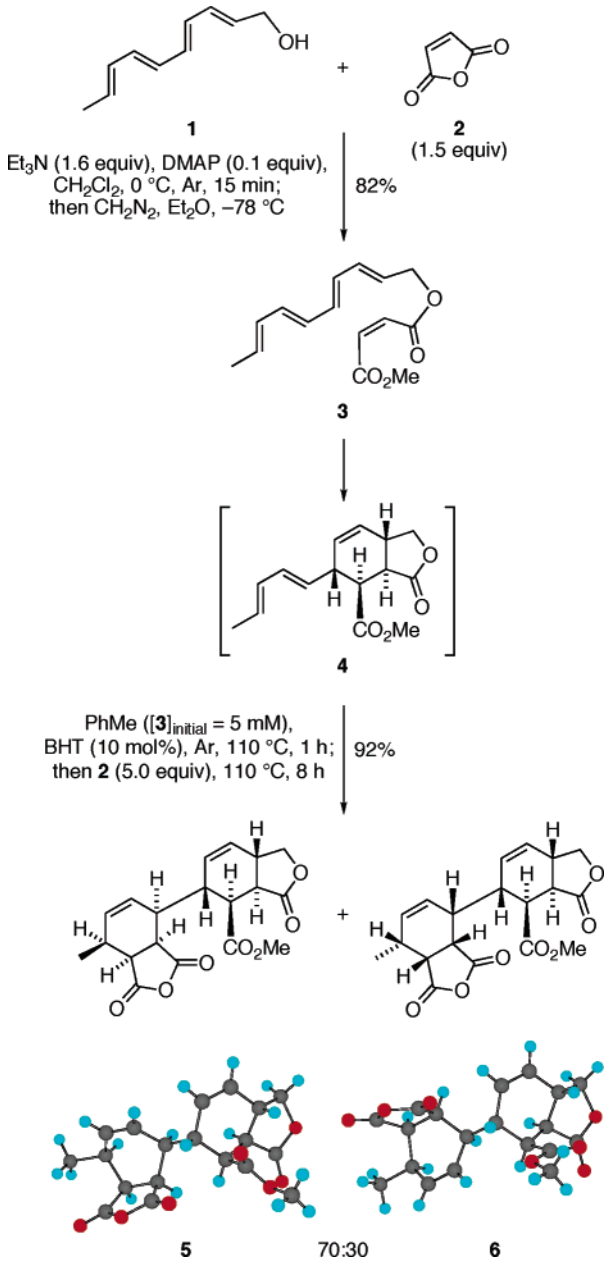
(6) Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974–1977.

(7) For IMDA reactions on conjugated trienes, tetraenes, and higher polyenes, see: (a) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509–1511. (b) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879–4882. (c) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429–3432. (d) Trost, B. M.; Lautens, M.; Hung, M.-H.; Carmichael, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 7641–7643. (e) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327–4330. (f) Boeckman, R. K., Jr.; Enholm, E. J.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4743–4745. (g) Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903–3906. (h) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541–3544. (i) Takeda, K.; Kobayashi, T.; Saito, K.; Yoshii, E. *J. Org. Chem.* **1988**, *53*, 1092–1095. (j) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951–6954. (k) Hudlicky, T.; Seone, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239–4243. (l) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398–2403. (m) Thomas, E. J. *Acc. Chem. Res.* **1991**, *24*, 229–235. (n) Chen, R.-M.; Weng, W.-W.; Luh, T.-Y. *J. Org. Chem.* **1995**, *60*, 3272–3273. (o) Shealy, Y. F.; Riordan, J. M.; Frye, J. L.; Campbell, S. R. *Tetrahedron* **1996**, *52*, 405–424.

(8) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211–230.

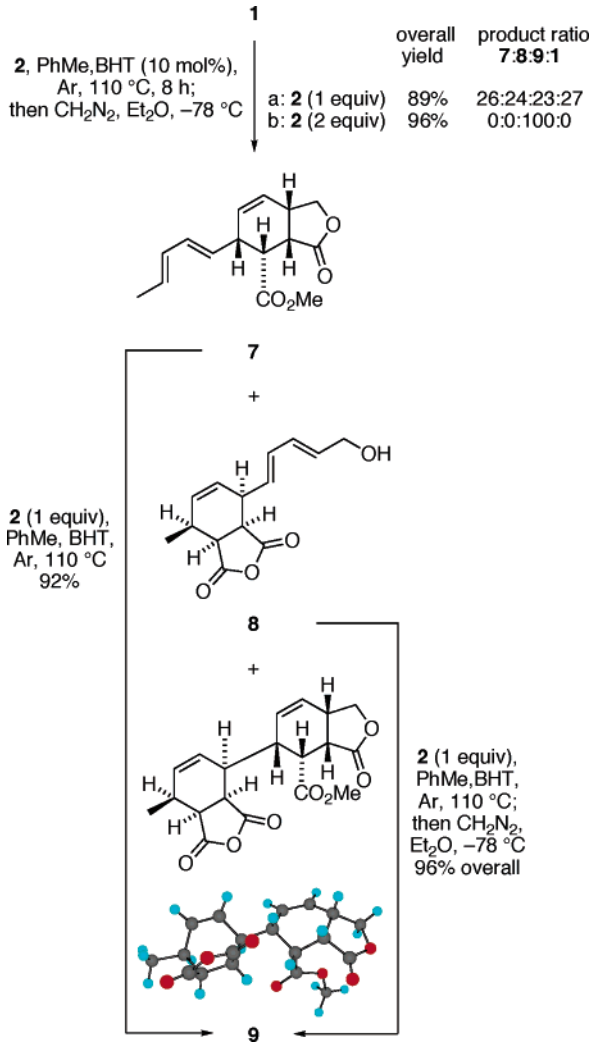
(9) Alder, K.; Schumacher, M. *Fortsch. Chem. Org. Naturst.* **1953**, *10*, 1–118.

SCHEME 3. An *Intra*molecular–*Inter*molecular Cycloaddition Sequence



An *Intra*molecular Diels–Alder–*Inter*molecular Diels–Alder Sequence. Maleate ester **3** was prepared in excellent yield from tetraene alcohol **1** by esterification with maleic anhydride (**2**) followed by low-temperature treatment with diazomethane. Intramolecular Diels–Alder reaction of *Z*-methyl ester **3** was carried out in a dilute solution of toluene at reflux in the presence of a small amount of BHT (Scheme 3). IMDA reaction of **3** proceeded swiftly and cleanly with consumption of starting material complete after 1 h. Analysis of the reaction mixture by ^{1}H NMR and HPLC revealed that *trans*-cycloadduct **4** was formed exclusively. This product could be isolated and characterized at this stage. Alternatively, after completion of the IMDA reaction, the reaction mixture was charged with 5 molar equiv of maleic anhydride. Continued heating at 110 °C for 8 h gave rise to a 70:30 mixture of the double cycloadducts **5** and **6**,

SCHEME 4. An *Inter*molecular–*Inter*molecular Cycloaddition Sequence

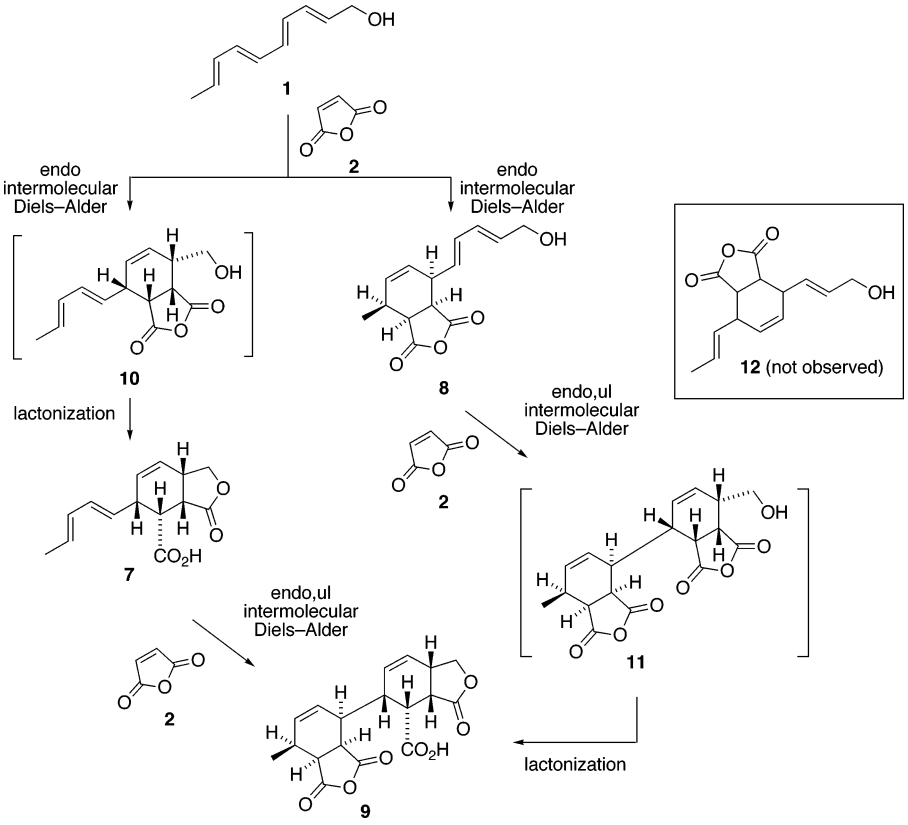


the products of *unlike* (*ul*) and *like* (*lk*) addition,[13] respectively, in high yield. Diastereomeric tetracycles **5** and **6** were isolated in pure form by HPLC. Initially, stereochemical assignments of **5** and **6** were made on the basis of COSY and NOESY experiments. These assignments were later confirmed by single-crystal X-ray analyses.[14]

An *Inter*molecular Diels–Alder–*Inter*molecular Diels–Alder Sequence. The double *inter*molecular Diels–Alder reaction sequence between tetraenol **1** and maleic anhydride (**2**) presents both site selectivity and stereochemical issues. The outcomes of *inter*molecular cycloadditions between **1** and maleic anhydride (**2**) are depicted in Scheme 4.

Thus, a solution of tetraenol **1** and 1 molar equiv of maleic anhydride (**2**) in toluene was heated at 110 °C for 12 h (Scheme 4). The reaction mixture was then cooled to −78 °C and treated with an ethereal solution of diazomethane. Analysis of the reaction mixture by ^{1}H NMR and HPLC revealed a statistical distribution (26:24:23:27) of three new products and unreacted starting material. Isolation of pure samples of all products was achieved with HPLC. Identification of all three products and their associated stereochemistries was

SCHEME 5. Proposed Mechanism for the *Inter*molecular–*Inter*molecular Diels–Alder Sequence



achieved through NMR experiments. The structure of tetracycle **9** was confirmed by single-crystal X-ray analysis.[15]

The statistical product mixture of **7**, **8**, **9**, and starting material **1** further indicates that a molecule of maleic anhydride reacts with *mono*-adducts **7** and **8** to give rise to the same carboxylic acid, which upon reaction with diazomethane yields ester **9**. That this is indeed the case was demonstrated by the following reactions. To separate solutions of *mono*-adducts **7** and **8** in toluene was added a single molar equivalent of maleic anhydride and the resulting two solutions were heated for 8 h. After this time the crude reaction mixture from **8** was cooled to −78 °C and subjected to ethereal diazomethane. Analysis of the reaction mixtures by HPLC and NMR confirmed that a single bis-adduct **9** was formed in both reactions. Furthermore, heating a solution of tetraenol **1** with 2 equiv of maleic anhydride in toluene at 110 °C for 12 h, followed by treatment of the crude reaction mixture with ethereal diazomethane, delivered a single double cycloadduct, **9**, in essentially quantitative yield. A mechanism accounting for these findings is depicted in Scheme 5.

Thus, formation of *mono*-adducts **7** and **8** in equal amount demonstrates that the two terminal diene moieties of tetraenol **1** exhibit the same reactivity toward cycloaddition with maleic anhydride. The first Diels–Alder reaction does exhibit some degree of site selectivity insofar as the "dead end" cycloadduct **12**—arising from addition of maleic anhydride to the "internal" diene moiety of tetraenol **1** (cf. docking mode depicted in the center of Figure 1)—is not formed. That the internal diene adduct **12** was neither isolated nor observed is intriguing.

The exclusive formation of the single diastereomeric double cycloadduct **9** indicates that two different *inter*molecular Diels–Alder reactions (i.e. **7** → **9** and **8** → **9**) are proceeding with complete *ul* π-diastereofacial selectivity to give *the same diastereomeric product.* Whereas *endo*-selectivity is expected for these intermolecular cycloadditions, the origin of π-facial selectivity is unclear. A similar situation exists with the intramolecular/intermolecular double Diels–Alder sequence (Scheme 3), with the *exo*/*endo* selectivities of the cycloadditions being predictable and explainable but not the π-facial selectivity. Computational investigations were carried out to understand the origins of site selectivity and π-diastereofacial selectivity from these reactions.

Computational Studies

Site Selectivity. Although, on purely statistical grounds, addition to a terminal butadiene residue of a linear conjugated tetraene should occur twice as rapidly as addition to the internal butadiene, this factor alone cannot account for the observed overwhelming preference for the former mode in the reaction between tetraenol **1** and maleic anhydride. Simple frontier MO arguments[16] fail to account for the site selectivity either; indeed, inspection of the Hartree–Fock HOMO coefficients of 2,4,6,8-decatetraene **13** actually incorrectly predicts a slight preference for internal addition. To gain insight into the origins of the experimentally observed site selectivity, gas-phase Density Functional Theory (DFT) calculations were carried out to locate and analyze the transition structures (TSs) for the Diels–Alder reactions between maleic anhydride and 2,4,6,8-decatetraene **13**, the latter acting as an acceptable model for the experimentally used tetraenol **1**. All calculations were carried

out with the Gaussian 03 program,[17] using the hybrid B3LYP functional[18] in conjunction with the 6-31G(d) basis set (B3LYP/6-31G(d)),[19] a combination that is known to give acceptable relative energies and geometries for pericyclic reactions.[20−24]

The two fully optimized B3LYP/6-31G(d) Diels−Alder *endo* TSs, **terminal-TS** and **internal-TS**, corresponding respectively to maleic anhydride addition to terminal and internal butadiene residues of **13**, were located and fully characterized by vibrational frequency analysis. These TSs are depicted in Figure 2.

The **terminal-TS** is strongly preferred over the **internal-TS** by 12.9 kJ/mol, amounting to approximately 99% terminal addition by maleic anhydride at 110 °C.[25]

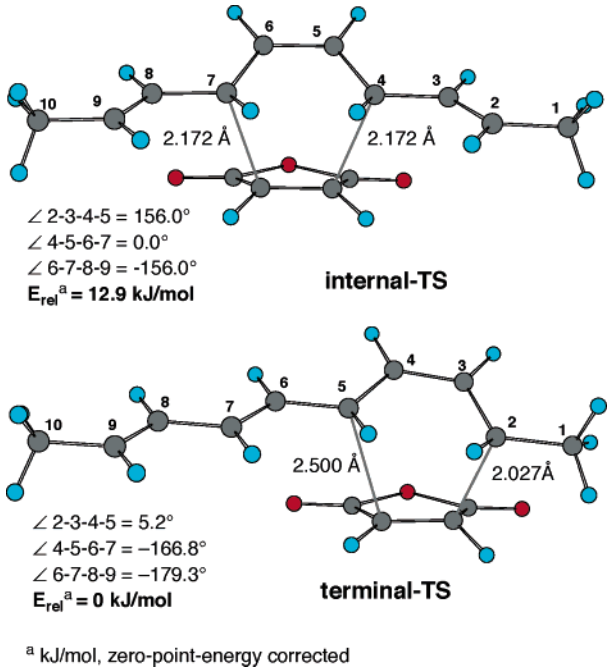


FIGURE 2. Fully optimized B3LYP/6-31G(d) *endo*-transition structures for the Diels−Alder cycloaddition of maleic anhydride to 2,4,6,8-decatetraene.

This finding is in good agreement with the experimental finding of exclusive terminal addition. Parenthetically, we also calculated the same two fully optimized TSs using the HF/6-31G(d) and MP2/6-31G(d) theoretical models. The former Hartree−Fock (HF) model does not take electron correlation into account, while the latter, Moller−Plesset (MP) model includes an electron correlation correction truncated at second order.[19a] Both HF and MP2 models predict preferential terminal addition, *but with significantly reduced selectivity compared to the B3LYP prediction*. Thus, the HF and MP2 energetic preferences

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for terminal addition (and percentage terminal site selectivity[25] at 110 °C) are only 5.0 (89%) and 3.3 kJ/mol (83%), respectively.

Inspection of the geometries of **terminal-TS** and **internal-TS** depicted in Figure 2 suggests a two-part explanation for the observed site selectivity. First, while the **internal-TS** is synchronous, possessing C_s symmetry, the **terminal-TS** is strongly asynchronous with the lengths of the two forming bonds differing by 0.47 Å. The longer of these two forming bonds is associated with the carbon atom C5 of the diene reaction center which bears the butadienyl substituent, whereas the shorter forming bond is associated with the carbon atom C2 of the diene reaction center which bears a methyl group. Moreover, the forming bond at C5 in **terminal-TS** is 0.33 Å longer, and less developed, than the forming bonds in **internal-TS**, suggesting, using the arguments of Dewar et al.,[26] that the butadienyl substituent in **terminal-TS** is better able to stabilize that TS, by conjugative interactions, than one of the vinyl substituents in **internal-TS**. It is reasonable to expect that the butadienyl substituent should be a stronger conjugating group to the diene reaction center than a single vinyl substituent by dint of the fact that both HOMO-LUMO energy gaps involving the butadienyl substituent and the diene reaction center[27] are narrower than the corresponding HOMO-LUMO gaps between a vinyl substituent and the diene reaction center, thereby producing stronger stabilizing two-orbital two-electron interactions in **terminal-TS**, compared to **internal-TS**. It is also noteworthy from the TS geometries shown in Figure 2 that both vinyl substituents in **internal-TS** are twisted 11° more out of conjugation with the diene reaction center (the relevant torsion angle is 156°) than is the butadiene substituent in **terminal-TS** (the relevant torsional angle is 167°). This feature will further reduce the conjugating power of the vinyl groups in **internal-TS** relative to the butadiene substituent in **terminal-TS**. Second, although there are two conjugating groups in **internal-TS** compared to one in **terminal-TS**, the butadiene substituent in the latter TS retains its resonance energy which, of course, is absent in the vinyl substituents in **internal-TS**.

Summarizing, it is proposed that the site selectivity observed in the Diels–Alder reaction could be due to the combined resonance energy of butadiene and the conjugative interaction between the butadienyl substituent and the diene reaction center in **terminal-TS** being stronger than the combined conjugative interactions of the two vinyl groups in **internal-TS**. The plausibility of this idea was strengthened by the findings from the following computational experiment in which all conjugative interactions between the substituent and the diene reaction center, and within the butadienyl substituent, were minimized by setting torsional angles between pairs of conjugating double bonds equal to 90° in the **internal-TS** and **terminal-TS**. The two maximally π-conjugative decoupled TSs are depicted in boxes in Figure 3 as **internal-TS-90-*a*-90-*b*** and **terminal-TS-90-*a*-90-*b***. Note that in the latter structure the resonance energy of the butadienyl substituent has been switched off, as has the conjugation between this substituent and the diene reaction center.

Two computational procedures were followed: in the first procedure, termed *single-point*, the π-decoupled TSs were simply generated from the fully optimized structures, **internal-TS** and **terminal-TS**, by 90° rigid rotation about the appropriate single bonds. Single-point energy calculations were then carried out on these unoptimized quasi-TSs. In the second procedure, termed *relaxed*, the energies of the various π-decoupled structures were obtained from the optimized (relaxed) geometries of the aforementioned quasi-TSs, subject only to the constraint that the predetermined orthogonality between pairs of double bonds is maintained throughout the geometry optimization. These optimized TSs and the results of these calculations are depicted graphically in Figure 3.

Turning first to the single-point calculations, we see that the fully π-decoupled **terminal-TS-90-*a*-90-*b*** is about 15 kJ/mol less stable than the fully π-decoupled **internal-TS-90-*a*-90-*b*** and this is due largely to the fact that **terminal-TS-90-*a*-90-*b*** retains its strong bond-forming asynchronicity, even though the deletion of π-conjugative interactions between the substituent and diene should lead to a more synchronous TS. Indeed, geometry optimization of **terminal-TS-90-*a*-90-*b*** does produce a nearly synchronous TS (Figure 3), which is now only 3.7 kJ/mol higher in energy than relaxed **internal-TS-90-*a*-90-*b***. From the data shown in Figure 3, the single-point resonance energy of butadiene and the π-conjugation energy between this substituent and the diene reaction center are 37.2 and 42.6 kJ/mol, respectively, and are nearly equal in strength. The combined π-conjugation energy from these two sources of 79.8 kJ/mol in **terminal-TS** is significantly larger, by about 28 kJ/mol, than the total π-conjugation energy of 52 kJ/mol between both vinyl groups and the diene reaction center in **internal-TS**. A similar conclusion is drawn from the relaxed calculations, with the total π-conjugation energy of 66.4 kJ/mol in **terminal-TS** being 16.7 kJ/mol greater than that in **internal-TS**. The single-point π-conjugation energy between the butadienyl substituent and the reaction center (42.6 kJ/mol) is larger, by 9.2 kJ/mol, than the corresponding relaxed value and this substantiates what was said earlier, namely the butadienyl substituent-reaction center π-conjugative interaction energy in-

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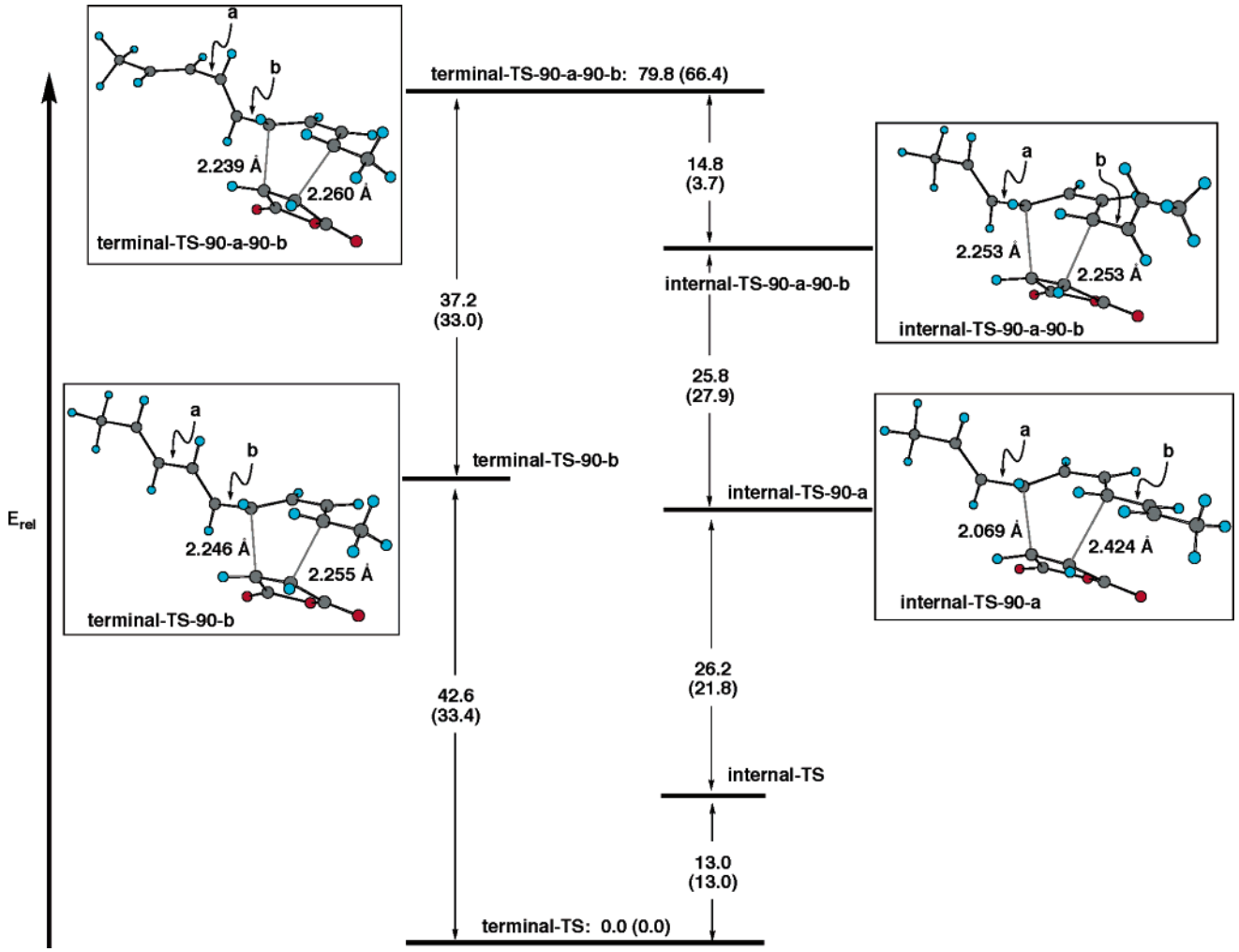

FIGURE 3. Geometries and single-point relative energies (relaxed energies in parentheses) of π-conjugative decoupled *endo*-transition structures for the Diels–Alder cycloaddition of maleic anhydride to 2,4,6,8-decatetraene. Relaxed TSs are depicted.

creases with increasing forming bond length at C5 in the **terminal-TSs** (cf. 2.500 Å in **terminal-TS**, Figure 2, and 2.246 Å in **terminal-TS-90-*b***). The corresponding difference between the relaxed and single-point π-conjugative interaction energies in **internal-TS** of 4.4 kJ/mol (=26.2−21.8, Figure 3) is much smaller than that in **terminal-TS** because the forming bond lengths in **internal-TS** are only marginally longer than those in **internal-TS-90-*a***.

Similar conclusions followed from HF/6-31G(d) and MP2/6-31G(d) calculations, although the degree of π-conjugative interactions, of the type discussed above, is smaller with these models.[28] It is known that DFT overemphasizes π-electron delocalization,[29−32] although the qualitative conclusions drawn from our study are expected to hold true.

In summary, the results from both computational methods strongly point to increased π-conjugation effects involving the butadienyl substituent in **terminal-TS**, compared to the two vinyl substituents in **internal-TS**, as the origin of terminal site selectivity observed in the reaction of tetraenol **1** and maleic anhydride. Interestingly, both the resonance energy of butadiene and the magnitude of the π-conjugative interaction between this substituent and the diene reaction center in **terminal-TS** play equally important roles in realizing the site selectivity.

***π*-Diastereofacial Selectivity.** Two intermolecular Diels–Alder reactions (**7** → **9** and **8** → **9**; Scheme 5) exhibited complete *ul* π-diastereofacial selectivity, and another (**4** → **5** + **6**; Scheme 3) exhibited moderate *ul* π-diastereofacial selectivity. Inspection of molecular models and literature searches gave no clear reasons for the observed experimental stereoselectivities, so a detailed computational investigation into one of these three reactions (**4** → **5** + **6**) was conducted. While no specific

(28) The relaxed π-conjugative interaction energies (kJ/mol) from the HF/6-31G(d) (MP2/6-31G(d) in parentheses) calculations are the following. (1) **terminal-TS**: butadiene resonance energy = 25.4 (26.7) and π-conjugative interaction energy between the butadienyl substituent and the diene reaction center = 24.4 (29.1). **internal-TS**: total π-conjugative interactions between both vinyl substituents and the diene reaction center = 43.5 (48.1).

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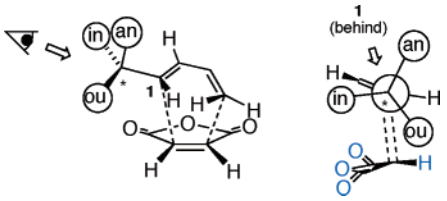

FIGURE 4. Schematic representations of one of the second cycloaddition TSs. The Newman projection formula on the right depicts a view along the C*–C1 bond of the structure on the left.

efforts were directed toward the computational modeling of the other two reactions, the general conclusions obtained by this study are applicable to these related systems.

In the TSs for cycloaddition, the C* substituents would be expected to adopt an approximately staggered arrangement with respect to the developing adjacent covalent bond,[33] with the allylic substituents taking up the *inside* (*in*), *anti* (*an*), or *outside* (*ou*) positions (Figure 4). Thus, maleic anhydride approaches the diene face opposite to the *anti* substituent. For ease of visual comparison, TSs with opposite facial selectivities will be depicted. (i.e. maleic anhydride is shown approaching the same face of the diene throughout but opposite configurations of C* are shown for *like* and *unlike* approaches.)

Insight into the facial selectivity arising from the *endo* Diels–Alder reaction between maleic anhydride and **4** (Scheme 3) was provided by locating and comparing the TSs for all stereochemical modes of reaction with use of the B3LYP/6-31G(d) theoretical model (gas phase). We[23,34] and others[20] have shown that gas-phase calculations at this level of theory provide predicted stereoselectivities for Diels–Alder reactions that correlate very well with experimental results for reactions carried out in solvents of low polarity such as toluene—the solvent used in the present experimental study. Furthermore, we find consistently good correlations in experimental and calculated stereoisomer ratio, *even though energy differences between stereoisomers are frequently small* (*<4 kJ/mol*).[23,34] The geometries of all possible *endo* Diels–Alder TSs between maleic anhydride and **4** were fully optimized, with no constraints, and were characterized by carrying out harmonic frequency calculations. The TSs are depicted in Figure 5, together with their relative electronic energies (E_{rel}; zero-point energy corrected) and their relative Gibbs free energies (G_{rel}) at 383 K. The percentage population of TSs at 383 K were calculated from the latter quantities. The first thing to note from the data in Figure 5 is that the ratio of *ul*:*lk* products at 383 K is predicted to be 82:18, which is in very good agreement with the experimental finding of 70:30 (Scheme 3), thereby demonstrating the reliability of the level of theory.

It is useful, first of all, to consider the relative preferences of simple alkyl groups for the *an*, *in*, and *ou* dispositions in the TSs for *endo* addition of maleic anhydride to 1-ethylbutadiene and 1-isopropylbutadiene and these findings are presented in Figure 6, parts a and b, respectively. Again, all TSs were fully optimized at the B3LYP/6-31G(d) level. Considering the reaction involving 1-ethylbutadiene, it is seen that the methyl group eschews the nearly eclipsing *in* position preferring, instead, the less sterically congested staggered *an* and *ou* positions. This is also the case in the ground state conformations of 1-ethylbutadiene and 1-butene where the methyl group again favors the staggered conformation over the conformation in which the methyl and adjacent double bond are eclipsed. The slight 0.57 kJ/mol energetic preference of the **Me-*an*** TS over the **Me-*ou*** TS (Figure 6a) is likely due to the presence of the *endo* maleic anhydride causing some steric congestion in the **Me-*ou*** TS. The relative stabilities of the Diels–Alder TSs involving 1-isopropylbutadiene are readily predicted from the results for the reaction involving 1-ethylbutadiene. Thus, the **H-*in*** TS is the most stable because neither methyl substituent occupies the *in* position, whereas the **H-*an*** TS is the least stable because the methyl substituents occupy both the *in* and *ou* positions.

Turning to the Diels–Alder reaction of **4**, only two TSs for each mode of π-diastereofacial addition could be

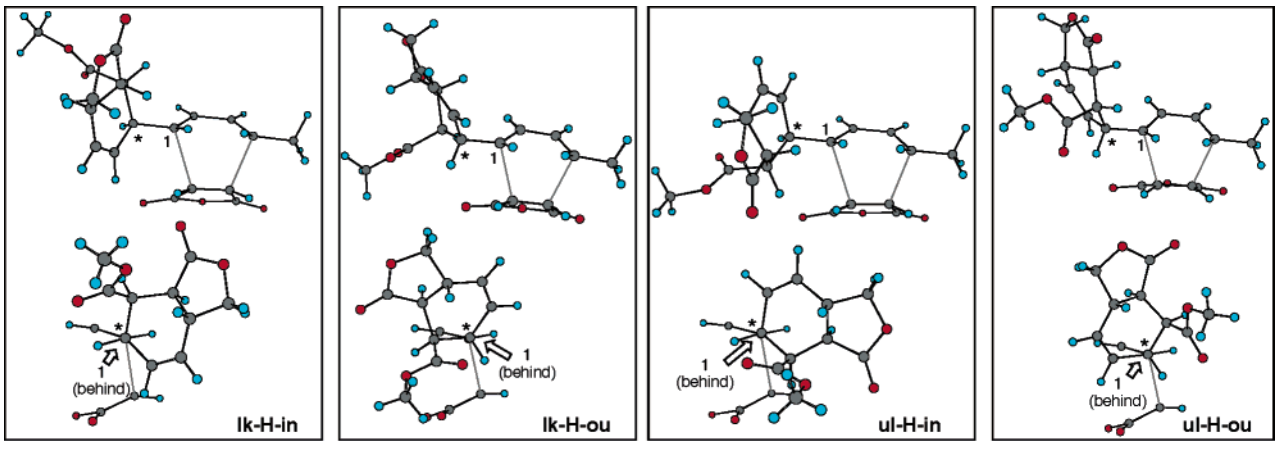

FIGURE 5. Fully optimized B3LYP/6-31G(d) TSs for the conversion **4** → **5** + **6**. The lower structures depict views along the C*–C1 bond of the structure on the top. Rear parts of the lower structures are removed for clarity.

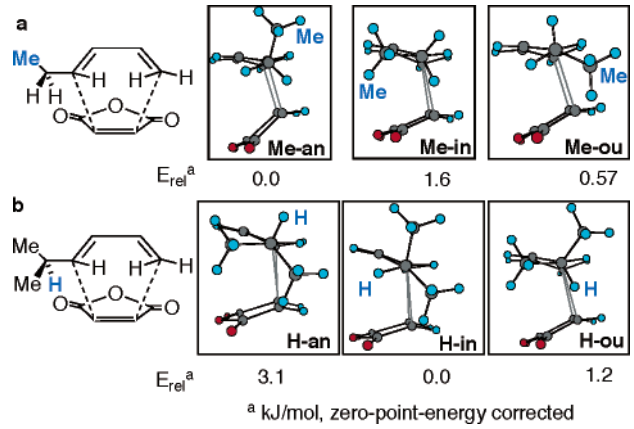

FIGURE 6. Fully optimized B3LYP/6-31G(d) TSs for cycloadditions of maleic anhydride to (a) 1-ethylbutadiene and (b) 1-isopropylbutadiene.

located. A full conformational search about the C*−C1 bond was conducted to locate each TS, which was fully optimized at the B3LYP/6-31G(d) level. Notwithstanding repeated efforts, the two TSs ***lk*-H-*an*** and ***ul*-H-*an*** appear either not to exist or are associated with a very small rotational barrier about the C*−C1 bond. Inspection of molecular models corresponding to the ***lk*-H-*an*** and ***ul*-H-*an*** conformations reveals the presence of very short H····X distances, 1.5−1.6 Å, between the pseudoequatorial $(MeO_2C)C-H$ hydrogen atom of the cyclohexane ring of the C1 substituent and the C2−H hydrogen of the diene in ***ul*-H-*an***, and with a carbonyl oxygen atom of the approaching maleic anhydride in ***lk*-H-*an***. It is this severe steric congestion that is probably responsible for the possible nonexistence of ***lk*-H-*an*** or ***ul*-H-*an*** TSs on the potential energy surface.

Intriguingly, the preferred disposition of the C1 groups with respect to the diene—**H-*in*** vs **H-*ou***—is reversed in the two different modes of π-diastereofacial addition. Whereas for the favored *ul* mode of facial addition the ***ul*-H-*ou*** TS is substantially more stable than the ***ul*-H-*in*** TS, by 11.3 kJ/mol, the reverse holds for the less favored *lk* addition, with ***lk*-H-*in*** being more stable than ***ul*-H-*ou***, by about the same amount, 11.6 kJ/mol. On the basis of the foregoing observations, two questions must be answered: (1) What is the origin of the preferred *ul* facial selectivity, and (2) why is **H-*ou*** the preferred TS for *ul* addition, whereas **H-*in*** is the preferred TS for *lk* addition?

Salient geometrical properties of the four TSs are displayed in Figure 7. The first thing to note is that there is a modest degree of asynchronicity in the TSs, with the longer forming bond being associated with the diene carbon atom attached to the more bulky alkyl substituent and, presumably, it is the size of this group that is responsible for the predicted asynchronicity. Indeed, we see that the longer forming bond achieves its maximum length of 2.388 Å in ***ul*-H-*in*** and it is in this TS that there is a particularly short H····H contact of 2.19 Å between the diene substituent and the maleic anhydride molecule. Overall, the forming bonds have comparable lengths in all four TSs and so the origin of the facial selectivity must lie elsewhere.

Inspection of H····H contacts immediately reveals the reason both ***ul*-H-*in*** and ***lk*-H-*ou*** are much less stable than their respective conformers, ***ul*-H-*ou*** and ***lk*-H-*in***; in each of the former pair of TSs, but *not* in the latter pair, there is a fairly short H····H contact amounting to 2.19 and 2.10 Å in ***ul*-H-*in*** and ***lk*-H-*ou***, respectively, and in each TS, it involves the pseudoequatorial $(MeO_2C)C-H$ hydrogen atom of the cyclohexene ring. The strain resulting from these short contacts must be significant because it causes a buttressing 1,3 interaction between the pseudoaxial CO_2Me group and the axial C−H ring junction hydrogen, viz., the carbonyl C····H separation is about 2.66 Å in both TSs. In contrast, this carbonyl C····H distance is about 0.17 Å longer for ***ul*-H-*ou*** and ***lk*-H-*in***, where any adverse steric interactions between the pseudoequatorial $(MeO_2C)C-H$ hydrogen atom of the cyclohexene ring and the diene and maleic anhydride entities are absent. In summary, it is the

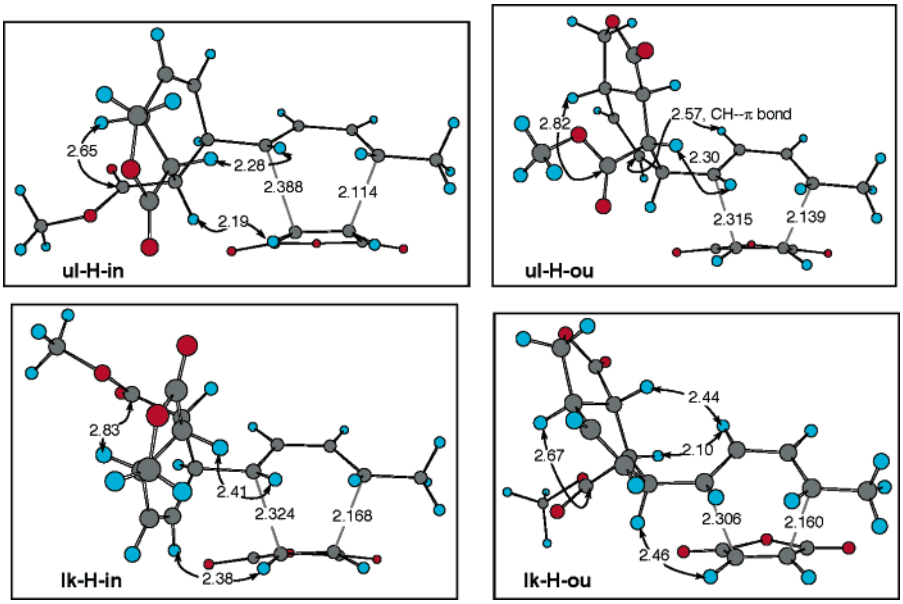

FIGURE 7. Fully optimized B3LYP/6-31G(d) TSs for the conversion **4** → **5** + **6** including close contacts.

presence of short H····H contacts of ca. 2.2 Å, involving the pseudoequatorial (MeO_2C)C–*H* hydrogen of the cyclohexene ring, which are responsible for ***ul*-H-*in*** and ***lk*-H-*ou*** being significantly higher in energy than ***ul*-H-*ou*** and ***lk*-H-*in***.

The lowest energy TS, namely ***ul*-H-*ou***, is moderately more stable than ***lk*-H-*in***, by 4.3 kJ/mol, and the origin of this difference is less obvious. A search for H····H contacts lying within the range 2.3–2.4 Å between the C1 substituent and the diene plus maleic anhydride, however, revealed the presence of two such contacts in ***lk*-H-*in*** but only one in ***ul*-H-*ou*** (Figure 7). Moreover, the C2–H hydrogen atom of the diene is 2.57 Å above the cyclohexene double bond and makes an angle of 105.6° with that double bond, thereby raising the possibility of the presence of a weak stabilizing electrostatic C(sp^2)–H····C=C π-interaction.[35] This kind of configuration is absent in ***lk*-H-*in***.

Conclusions

Linear conjugated tetraenes participate in high-yielding and highly stereoselective double Diels–Alder reaction sequences, providing an expedient entry into highly functionalized polycyclic structures. Furthermore, these processes proceed with complete site selectivity for the terminal butadiene moiety. Computational findings strongly point to increased π-conjugation effects involving the butadienyl substituent in the TS leading to terminal addition products, compared to the two vinyl substituents in the internal TS, as the origin of this terminal site selectivity. The π-diastereofacial selectivities observed in these reactions are explained by TS conformational and steric effects. Thus, up to four new C–C bonds and one new C–O bond and eight new stereocenters can be generated in a "one-pot" process, which represents a remarkable increase in structural complexity. Taken in combination with the results obtained in earlier studies (Schemes 1 and 2), it is apparent that the applicability of linear conjugated tetraenes as building blocks for double DA reaction sequences is very general indeed.

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Supporting Information Available: Synthetic procedures and characterization details, ^1H and ^{13}C NMR spectra, and the Cartesian coordinates of B3LYP/6-31+G(d) optimized TS geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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