Allylic Stereocontrol of the Intramolecular Diels–Alder Reaction

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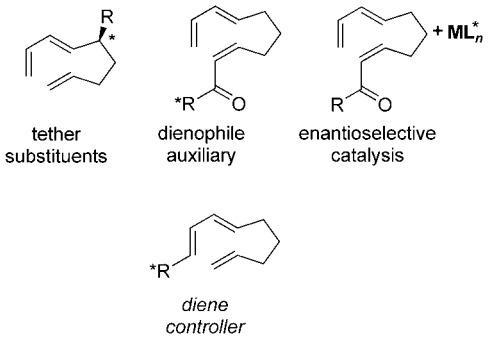
Abstract: The stereochemical outcome of the intramolecular Diels–Alder reaction of ester-linked 1,3,8-nonatrienes can be controlled by substituents about a stereogenic center attached to C1. The scope and limitations of this approach have been investigated, with variation in substrate structure about the allylic stereocenter and the dienophile. The stereochemical outcomes of these reactions are explained by reference to B3LYP/6–31G(d) transition structures. New insights into the conformational preferences of allylic alcohol derivatives are reported, results which allow an explanation of the differing levels of π-diastereofacial selectivity and *cis/trans* (i.e. *endo/exo*) selectivity from the reaction.

Keywords: chiral pool · cycloaddition · density functional calculations · diastereoselectivity · synthetic methods

Introduction

There is continuing interest in the intramolecular Diels–Alder (IMDA) reaction in both the realms of synthesis[1] and biosynthesis.[2] An understanding of the stereochemical preferences of IMDA reactions is pivotal to its successful synthetic application and biosynthetic rationalization. The stereochemical complexity of this reaction stems from the four contiguous stereocenters that are created. The concerted, suprafacial nature of the bond-forming process allows the generation of four stereoisomeric products that are interrelated in *cis/trans* (*exo/endo*)[3] and π-facial senses. In recent times, transition structures (TSs) for certain IMDA reactions have been located by using density functional theory (DFT). With reference to these TS geometries, *cis/trans* and π-facial selectivities of IMDA reactions have been discussed in detail.[4–10] This approach promises to greatly simplify the prediction of IMDA stereoselectivities. Herein we describe a detailed synthetic investigation into a new stereocontrol method for IMDA reactions and the development of theoretical models to rationalize these experimental findings.[11]

Reported methods for obtaining enantiomerically pure products from IMDA reactions (Scheme 1) involve the placement of suitable substituents on the linking chain be-



Scheme 1. The three reported methods for achieving stereocontrol in IMDA reactions and the diene controller approach under scrutiny.

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Supporting information for this article (Cartesian coordinates and energies of B3LYP/6–31G(d) optimized TS geometries, synthetic details, compound characterization, crystallographic data and selected ^{1}H and ^{13}C NMR spectra) is available on the WWW under http://www.chemeurj.org/ or from the author.

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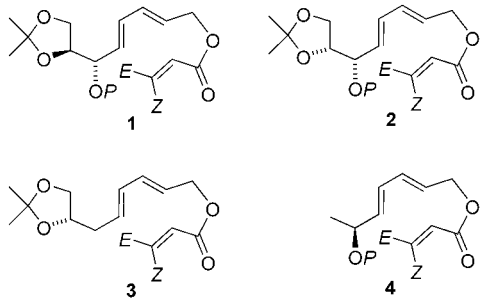
tween the diene and dienophile,[12] by attaching an auxiliary to the dienophile terminus,[13] and through enantioselective cycloaddition of achiral trienes with chiral Lewis acids.[14] We were intrigued by the possibility of controlling the stereochemical outcome of IMDA reactions by constructing chiral substrates with a stereocontrolling element at the terminus of an acyclic diene. Previous reports of IMDA reactions of substrates with diene auxiliaries employ either conformationally restricted chiral semicyclic dienes,[15] or are complicated by the presence of additional tether substituents and dienophile auxiliaries.[16]

Herein, we explore the scope and limitations of the allylic stereocontrol method for IMDA reactions. IMDA reactions of ester-linked 1,3,8-nonatriene[17] **1** are reported, along with cycloaddition reactions of three additional groups of substrates; namely, triene esters **2**–**4** (Scheme 2). Series **2**, diastereomeric with **1**, was prepared to investigate the dependence of stereoselectivity upon the relative configurations at the allylic and homoallylic stereocenters. Chiral trienes **3** and **4** would uncouple the effects of the allylic and homoallylic stereocenters, allowing a more general assessment of the applicability of this approach. To shed light upon stereoselectivities, these reactions are examined computationally by using the hybrid B3LYP functional together with the 6–31G(d) basis set. It is generally accepted that B3LYP/6–31G(d) models give reliable geometries of TSs and activation energies for pericyclic reactions.[4–10,18]



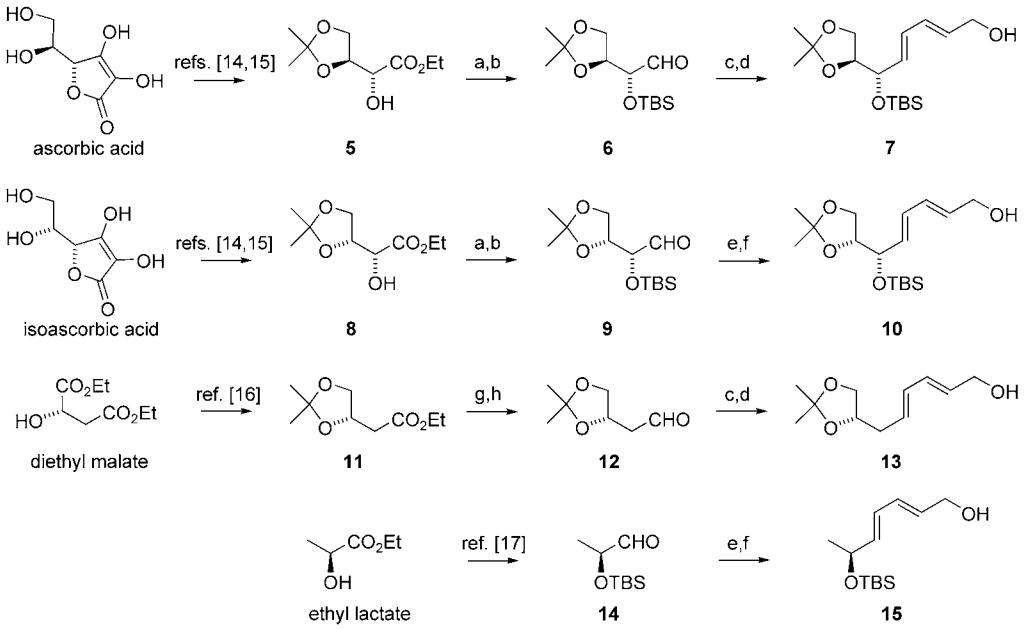
Scheme 2. Chiral trienes under investigation. The effect of the groups *P*, *E*, and *Z* upon IMDA stereoselectivity is examined.

Results

Synthesis of the chiral dienols

Chiral dienols **7**, **10**, **13**, and **15** were prepared from the inexpensive and readily available chiral precursors L-ascorbic acid, D-isoascorbic acid, L-malic acid, and L-lactic acid respectively, as shown in Scheme 3. The syntheses of these dienols follow the same general pathway, involving the chain extension of a chiral ester into the corresponding conjugated diene.

Thus, ascorbic and isoascorbic acids were smoothly converted into monoacetonides[19] before oxidative cleavage with potassium carbonate and hydrogen peroxide in water. The resulting potassium carboxylates were treated with ethyl iodide to give α-hydroxy esters **5** and **8**.[20] Regioselective reduction of diethyl malate with borane/dimethyl sul-

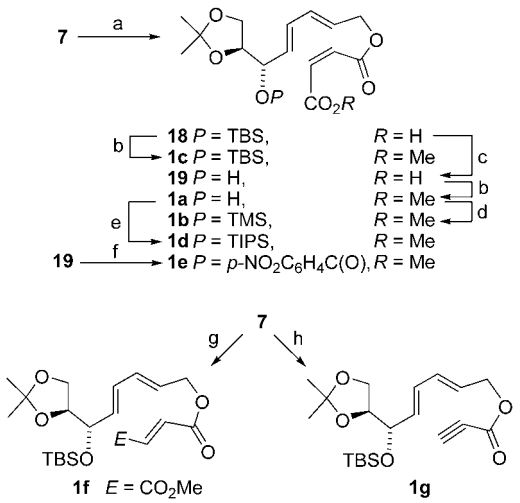


Scheme 3. Synthesis of chiral dienols **7**, **10**, **13**, and **15**: a) TBSCl, imidazole, DMF, RT, ascorbate 68%; isoascorbate 91%. b) DIBALH, CH_2Cl_2, −100°C to −78°C, ascorbate 86%; isoascorbate 58%. c) $Ph_3P{=}CHCH{=}CHCO_2Et$ (**16**), CH_2Cl_2, reflux, then PhSH, AIBN, PhH, reflux; ascorbate 78%; malate 27%. d) DIBALH, CH_2Cl_2, −78°C, ascorbate 74%; malate 93%. e) $LiN(Si(CH_3)_3)_2$, $(CH_3O)_2P(=O)CH_2CH{=}CHCO_2Me$ (**17**), THF, −78°C, isoascorbate 70%; lactate 42%. f) DIBALH, Et_2O, 0°C, isoascorbate 80%; lactate 88%. g) $LiAlH_4$, THF, 0°C, 92%. h) Dess–Martin periodinane, CH_2Cl_2, 78%. TBSCl = *tert*-butyldimethylsilyl chloride, DIBALH = diisopropylaluminum hydride, AIBN = 2,2′-azobisisobutyronitrile.

fide complex, followed by treatment of the resulting diol with 2,2-dimethoxypropane[21] produced acetonide **11** in 70% yield after distillation. Silylation of the α-hydroxy esters followed by reduction with diisobutylaluminum hydride (DIBALH) at low temperature produced aldehydes **6**, **9**, and **14**[22] cleanly. In the ascorbate series, the diene was installed through treatment of aldehyde **6** with stabilized ylide **16**[23] in refluxing dichloromethane. The dienoate ester was thereby produced as a mixture of (*Z*)- and (*E*)-stereoisomers about the newly formed alkene (*Z*:*E* = 79:21), which was equilibrated to the (*E,E*)-diene under radical conditions.[24] In the isoascorbate and lactate series, chain extensions were carried out by Horner–Wadsworth–Emmons reaction with phosphonate **17**.[25] The diene esters were reduced cleanly to the dienols with DIBALH. In the malate series, a two-step reduction–oxidation[26] sequence was necessary for conversion of ester **11** into aldehyde **12**. A Wittig reaction between sensitive aldehyde **12** and stabilized ylide **16** produced the diene ester as a 50:50 mixture of (*Z*)- and (*E*)-stereoisomers in a disappointing 35% yield after chromatography.[27] Following isomerization to the (*E,E*)-diene, DIBALH reduction gave dienol **13** in 93% yield as a colorless oil. Yield optimization of this final sequence was postponed, pending the results of IMDA reactions in this series.

Triene synthesis and IMDA reactions

The ascorbate series: Ascorbic acid derived dienol **7** was converted into precursors for IMDA reaction differing in both the stereocenter oxygen substituent *P* and the nature of the dienophile. Seven triene derivatives were prepared (Scheme 4, **1a–g**).

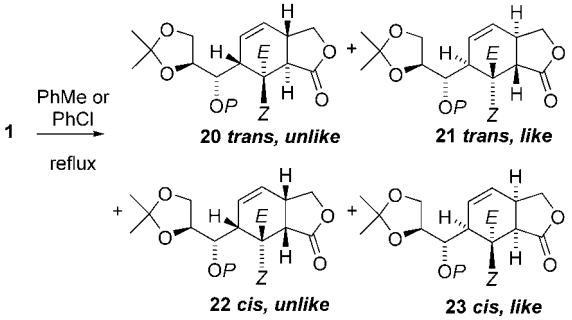


Scheme 4. Synthesis of triene derivatives **1a–g**: a) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, RT, 99%. b) CH_2N_2, Et_2O, **18**→**1c**, 74%; **19**→**1a**, 80%. c) nBu_4NF, THF, RT, 85%. d) TMSOTf, Et_3N, DMAP, CH_2Cl_2, RT, 51%. e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, RT, 91%. f) *p*-$NO_2C_6H_4COCl$, pyridine, DMAP, 25°C, 82%; g) (*E*)-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, RT, 96%. h) $HO_2CC{\equiv}CH$, DCC, DMAP, Et_2O, RT, 65%. DMAP = 4-dimethylaminopyridine, TIPS = triisopropylsilyl, TMS = trimethylsilyl, DCC = *N,N*′-dicyclohexylcarbodiimide.

Reaction of dienol **7** with maleic anhydride furnished a near quantitative yield of carboxylic acid **18**, which was treated with diazomethane to give diester **1c**. Desilylation of diester **1c** gave an unacceptably low yield (26%) of secondary alcohol **1a**. A much better result (85% yield) was, however, obtained by deprotection of acid **18**. The resulting hydroxy acid **19** was converted to methyl ester **1a**, which was used to prepare trimethylsilyl derivative **1b** and triisopropylsilyl derivative **1d** by exposure to the appropriate trialkylsilyl triflate. Reaction of alcohol **1a** with *para*-nitrobenzoyl chloride gave ester **1e**. Fumarate ester **1f** and propynoate ester **1g** were prepared by Steglich esterification of dienol **7** with the requisite carboxylic acid.

Precursors **1a–e** underwent IMDA reactions at high dilution in boiling toluene to produce mixtures of the four possible cycloadducts (Table 1). In all five cases, two of the four adducts were formed in significantly larger amounts than the other two.

Table 1. IMDA reactions of ascorbic acid derived trienes **1a–f**.



Triene substrate **1**	*P/E/Z*	Solvent/ Reaction time[a] [h]	Isolated yield[b] [%]	Adduct ratio[c,d,e] **20**:**21**:**22**:**23**
a	H/H/CO_2Me	PhMe/5	86	56:32:8:4
b	TMS/H/CO_2Me	PhMe/12	67	80:14:4:2
c	TBS/H/CO_2Me	PhMe/15	80	86:9:4:1
d	TIPS/H/CO_2Me	PhMe/18	68	92:7:1:0
e	PNB/H/CO_2Me	PhMe/12	95	49:39:6:6
f	TBS/CO_2Me/H	PhCl/53	62	12:3:82:3

[a] Time required for >95% conversion, as judged by ^{1}H NMR spectroscopy. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. Differences +/−3%. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] The two minor adducts were not fully characterized.

The stereochemistry of each the two major cycloadducts from the three silyl ether substrates **1b–d** was elucidated by using 2D NMR experiments. The large coupling constant between the axial hydrogen atoms at the ring junction (^3J = 13.6–13.8 Hz) indicates the less thermodynamically stable *trans*-ring fusion. The *trans* adducts **20** and **21** exhibited a clear conformational preference in solution, which allowed the new and existing stereochemistry to be correlated through NOE measurements.[28] The identities of the alcohol cycloadducts **20a** and **21a** were secured by conversion into

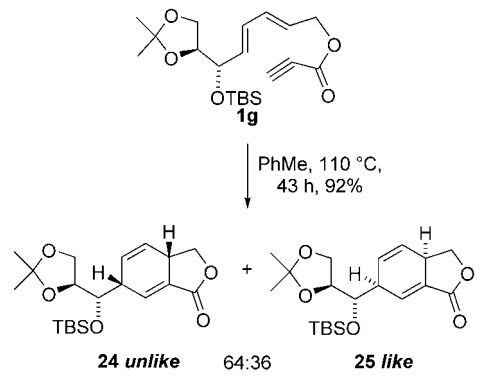
the corresponding TMS derivatives **20b** and **21b**. The major and minor isomers obtained from this silylation reaction were identical in every respect to those produced in the IMDA reaction of TMS ether precursor **1b**. Finally, the identities of cycloadducts **20e** and **21e** were confirmed by esterification of the alcohols **20a** and **21a** with *para*-nitrobenzoyl chloride in the usual manner. Insufficient quantities of the two minor cycloadducts were obtained from these experiments for full characterization.

The stereoselectivities observed for maleate derivatives **1a–e** (Table 1) are intriguing in that the level of π-diastereofacial selectivity varies considerably with group *P*. The alcohol substrate **1a** exhibits only modest *unlike*[29] π-diastereofacial preference between the two *trans*-cycloadducts but this improves considerably after the installation of common silyl protecting groups.[30] A progressive improvement in *unlike* selectivity is observed as the size of the silyl group is increased (cf. **1b**→**1c**→**1d**). The triisopropylsilyl (TIPS) derivative **1d**, the most sterically demanding protecting group examined, instigates a remarkably high level of stereocontrol. Conversely—and unexpectedly—the *para*-nitrobenzoate derivative **1e** exhibits the lowest π-diastereofacial selectivity of the five substrates.

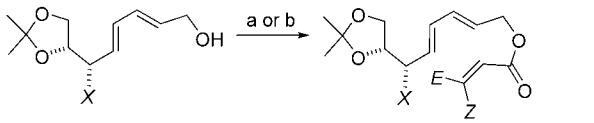
As expected, the fumarate precursor **1f** was significantly less reactive than the corresponding maleate **1c**.[31] The same isolated yields and stereochemical outcomes[28] were obtained when **1f** was heated in toluene or chlorobenzene, although the former required prolonged reaction times for complete conversion. Fumarate **1f** underwent cycloaddition with virtually complete *unlike*-selectivity and high *cis*-selectivity, the latter feature being in stark contrast to previous findings with pentadienyl fumarates, which generally furnish mildly *trans*-selective IMDA reactions.[4,7,10,31,32]

The last precursor derived from ascorbic acid, the alkynic dienophile **1g**, underwent a smooth IMDA reaction at 110 °C (Scheme 5).[31] Lacking questions of *cis/trans*-stereoselectivity, this substrate perhaps best exemplifies the *unlike* π-diastereofacial preference found in this series.[33]

Isoascorbate and malate series: The results obtained thus far raised two important questions. 1) Are the outcomes of these reactions dependent upon the *relative* stereochemistry of this starting material? 2) Is the allylic stereocenter necessary for stereoselectivity? To answer the first question, isoascorbic acid derived dienol **10** was converted into maleate and fumarate derivatives **2a** and **2b** in the same manner as described previously (Scheme 6). To address the second issue, malic acid derived dienol **13** was transformed into corresponding trienes **3x** and **3y**.



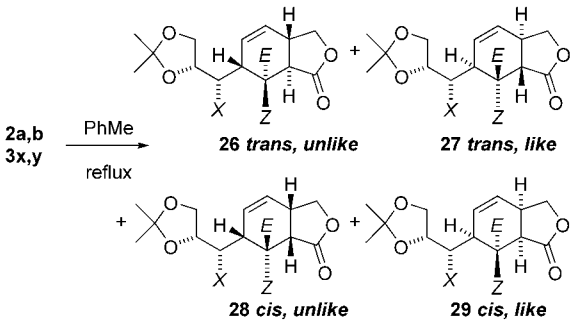
Scheme 5. IMDA reaction of ascorbic acid derived alkynoate **1g**. TBS = *tert*-butyldimethylsilyl.



Scheme 6. Conversion of **10** and **13** into **2a,b** and **3x,y**, respectively: a) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, RT, then CH_2N_2, Et_2O, 0 °C, **10**→**2a**, 74%; **13**→**3x**, 56%. b) (*E*)-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, RT, **10**→**2b**, 78%; **1**→**3y**, 74%.

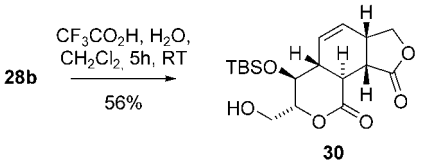
The isoascorbic acid derived precursors underwent IMDA reactions with approximately the same ease as the ascorbic acid series, whereas the malic acid derived precursors cyclized somewhat more rapidly (Table 2). Product stereochemistries in the isoascorbate series were determined in the same manner as the ascorbate compounds. The stereochemical identity of the major product from fumarate precursor **2b** was established by selective acetal deprotection/lactonization to **30** (Scheme 7). In the malic acid products, the ring junction stereochemistry was clearly evident from NMR coupling constants, as discussed previously.

Table 2. IMDA reactions of isoascorbic acid and malic acid derived precursors **2a,b** and **3x,y**.



Triene substrate	*X/E/Z*	Solvent/ Reaction time[a] [h]	Isolated yield[b] [%]	Adduct ratio[c,d,e] **26**:**27**:**28**:**29**
2a	OTBS/H/CO_2Me	PhMe/9.5	86	78:16:4:2
2b	OTBS/CO_2Me/H	PhCl/72	89	9:6:66:19
3x	H/H/CO_2Me	PhMe/3.5	89	41:39:11:9
3y	H/CO_2Me/H	PhCl/43	89	32:33:18:17

[a] Time required for >95% conversion, as judged by ^{1}H NMR spectroscopy. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] The stereochemical identities of the two minor adducts were not elucidated.



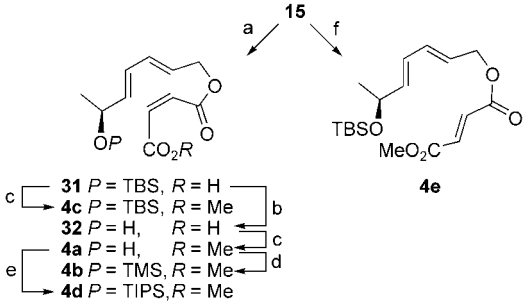
Scheme 7. Acetonide deprotection/lactonization of **28b**.

The major diastereomer obtained from intramolecular cycloadditions of isoascorbic acid derived substrates **2a** and **2b** (Table 2) correlates with those obtained in the ascorbic acid series **1c** and **2f** (Table 1). Thus, a (*Z*)-dienophile precursor (i.e. **2a** or **1c**) gives the *trans, unlike* adduct, whereas the (*E*)-dienophile precusor (i.e. **2b** or **1f**) gives the *cis, unlike* adduct. The adduct ratios are similar but not identical, indicating a contribution to the overall stereochemical outcome by the configuration at the homoallylic site. No π-diastereofacial selectivity was witnessed in cyclization of either maleate **3x** or fumarate **3y**, however, indicating that a lone homoallylic stereocenter is insufficient to invoke stereoselection. It is noteworthy that the (*E*)-dienophile precursor **3x** undergoes a *trans*-selective IMDA reaction, a result which is consistent with previous findings[4,7,10,31,32] but in contrast to those of the other three fumarate precursors in the present study.

Lactate series: In the research described so far, it has been demonstrated that stereogenic elements at the diene terminus can induce high levels of stereoselectivity upon IMDA reactions. Ascorbate- and isoascorbate-derived systems **1** and **2** are complicated by the presence of two stereocenters and an acetal functional group. Would precursors lacking these structural features also give rise to stereoselective IMDA reactions? To answer this question and, furthermore, to minimize the assumptions made in the computational modeling of this reaction, we elected to carry out a synthetic study on dienol **15**. Thus, lactic acid derived dienol **15** was converted into the four maleate esters **4a–d**, and the fumarate ester **4e** using similar procedures to those described previously (Scheme 8).

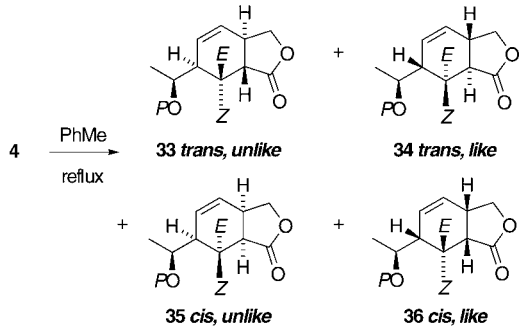
The five triene precursors underwent IMDA reactions in refluxing toluene (Table 3) over slightly shorter reaction times than those of the corresponding ascorbic and isoascorbic acid derived precursors (Table 1 and Table 2). Furthermore, mixtures of the four possible cycloadducts were produced in all cases.

The four cycloadducts obtained from the IMDA reaction of the maleate TBS ether **4c** were separated by HPLC. The ring junction geometry of cycloadducts **33c** and **34c** was evident from the large *trans*-diaxial coupling constants (^3J = 13.5 Hz) between the ring junction hydrogen atoms. On the basis of 2D NMR experiments it was possible only to elucidate the relative stereochemistry at the four new stereocenters; the lack of conformational preference about the C1′–C5 bond precluded the correlation of new with existing stereochemistry in this set of cycloadducts. Thus, five single-crystal X-ray analyses were carried out on derivatives to



Scheme 8. Conversion of dienol **15** into maleate esters **4a–d**: a) maleic anhydride, Et_3N, DMAP, CH_2Cl_2, RT, 75%. b) nBu$_4$NF, THF, RT, 44%. c) CH_2N_2, Et_2O, 0°C, **31**→**4c**; 87%, **31**–**4a**, 44%. d) TMSOTf, Et_3N, DMAP, CH_2Cl_2, RT, 88%. e) TIPSOTf, Et_3N, CH_2Cl_2, RT, 78%. f) (*E*)-$HO_2CCH{=}CHCO_2Me$, DCC, DMAP, Et_2O, RT, 89%.

Table 3. IMDA reactions of lactic acid derived trienes **4a–e**.



Triene substrate **4**	*P/E/Z*	Solvent/ Reaction time[a] [h]	Isolated yield[b] [%]	Adduct ratio[c,d] **33**:**34**:**35**:**36**
a	H/H/CO_2Me	PhMe/4.5	88	41:36:5:18[e]
b	TMS/H/CO_2Me	PhMe/6.5	83	56:30:6:8
c	TBS/H/CO_2Me	PhMe/7.25	96	61:27:5:7
d	TIPS/H/CO_2Me	PhMe/8.25	85	63:26:5:6
e	TBS/CO_2Me/H	PhCl/43	73	8:28:40:24

[a] Time required for >95% conversion, as judged by ^{1}H NMR spectroscopy. [b] Combined isolated yield for the four adducts after chromatography. [c] Determined from ^{1}H NMR spectra and HPLC analyses of crude reaction mixtures. Differences +/−3%. [d] Kinetic product ratios are reported: control experiments confirmed that all cycloadducts were stable to the reaction conditions. [e] Tricyclic *bis*-lactones **37** and **38** were isolated instead of *cis*-adducts **35a** and **36a** in this series. See main text for an explanation.

confirm the stereochemical identities of all 20 cycloadducts in the lactate series.[28]

The main features of the lactate series can be summarized as follows. The (*Z*)-dienophile precursors **4a–d**, once again, undergo strongly *trans*-selective IMDA reactions. The alcohol substrate **4a** exhibits a very small π-diastereofacial selectivity during cycloaddition. The corresponding silyl ethers undergo more stereoslective IMDA reactions, with higher levels of π-diastereofacial selectivity being obtained with larger silyl groups. Nevertheless, the highest level of π-facial selectivity delivered by a lactate-derived precursor (**4d**, *unlike*:*like* = 68:32) is considerably lower than that witnessed in the ascorbate series (**1d**, *unlike*:*like* = 93:7). The (*E*)-dienophile precursor **4e** undergoes a reaction with considerably

lower stereoselectivity than the corresponding ascorbate and isoascorbate trienes, **1f** and **2b**, respectively. Once again, however, the *cis,unlike* diastereomer is the major adduct.

Whilst the stereoselectivity of IMDA reactions of precursors **1**–**4** varies considerably, the following generalizations can be made:

1) Maleate esters of dienols **7**, **10**, **13**, and **15** undergo *trans*-selective IMDA reactions, whereas the corresponding fumarate esters are generally *cis*-selective. The exception is fumarate **3y**, which undergoes a *trans*-selective IMDA reaction. These selectivities are more pronounced the larger the substituents attached to the allylic stereocenter.
2) Chiral allylic alcohols (**1a** and **4a**) give poor to moderate levels of π-diastereofacial selectivity in IMDA reactions. Silyl ether derivatives of these allylic alcohol precursors give moderate to high levels of π-facial stereoselectivity, with an increase in the size of the silyl protecting group leading to an increase in stereoselection. An allylic benzoyloxy derivative gave essentially no π-facial discrimination in these reactions.
3) An increase in the size of the alkyl group leads to an increase in π-facial stereoselectivity (compare results of substrates **1** and **2** with those of **4**).
4) The two diastereomeric dienols **7** and **10** gave similar but non-identical stereoisomer ratios, a result which demonstrates that the allylic stereocenter controls the outcome of these reactions to a large extent.
5) An allylic stereocenter appears to be necessary for π-facial stereoselectivity, since substrates carrying an allylic methylene and homoallylic stereocenter (**3x**,**y**) gave no stereocontrol.

These experimental results clearly demonstrate that the presence of an allylic stereocenter can indeed give rise to high levels of stereoselectivity in IMDA reactions. Inspection of molecular models and literature searches gave no clear reasons for the observed experimental stereoselectivities. The C* substituents would be expected to adopt an approximately staggered arrangement with respect to the developing C1–C9 bond,[34,35] with allylic alkyl, silyloxy, and hydrogen substituents distributed among the *inside* (*in*), *anti* (*an*), and *outside* (*ou*) positions in TSs, as depicted by **41** (Figure 1). The facial selectivity is determined by the positional preferences of the C* substituents for the *in*, *an*, and *ou* sites in the TS. What are these preferences? This question was answered from model computational studies.

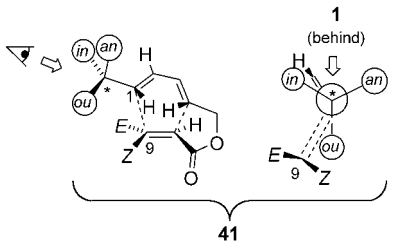
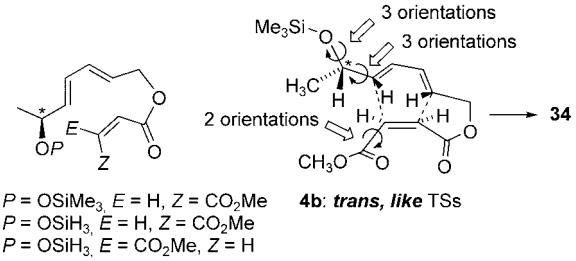


Figure 1. A representation of one of the *trans*-TSs. The Newman projection formula on the right depicts a view along the C*–C1 bond of the structure on the left.

Computational Results

B3LYP/6–31G(d) density functional theory calculations were conducted on maleate and fumarate IMDA precursors **4b**, **4f** and **4g** (Scheme 9).[36] A preliminary account of this work has appeared, describing a model which was based only on the computed *trans* IMDA TSs of the *Z* ester, $OSiH_3$ structure **4f**.[5] The computational modeling of these reactions is complicated by the large number of possible reactive orientations of each precursor. Thus, in addition to the three conformations about the C*–C1 bond, three conformations about the allylic C*–O bond and s-*cis*/s-*trans* orientations of the C9–CO_2CH_3 bond are feasible (Scheme 9). In principle, therefore, a total of 72 diastereomeric TSs can be envisioned *for each IMDA precursor*, with 18 diastereomeric TSs leading to each of the four cycloadducts, **33**–**36** (see Table 3 for these structures). It was impractical to calculate all 72 TSs at this level of theory for each IMDA precusor and, consequently, relaxed potential energy scans were carried out on model TSs to locate the lowest energy conformation about the allylic C*–O bond. Although we are confident that we have located the lowest energy conformation in each case we cannot guarantee it to be the case.[37] IMDA TSs for **4f** in which the ester adopts the s-*cis* conformation were found to be slightly (2.5–6.0 kJ mol^{-1}) lower in energy than the corresponding s-*trans* TSs. In all other respects, the two sets of TSs, one with s-*cis* and the other with s-*trans* ester conformations showed very similar trends, particularly with respect to facial selectivity; hence discussion here will be limited to the s-*cis* TSs.



Scheme 9. Structures of the three precursors under scrutiny by DFT and the 18 possible diastereomeric TSs for the *trans, like* IMDA cycloaddition mode of **4b**.

These considerations led to a more manageable three TSs leading to each of the four diastereomeric adducts. These three TSs, corresponding to three low-energy conformations about the C*–C1 bond (see Figure 1), were located for each of the four cycloaddition modes (*cis/trans*; *like/unlike* combinations) and their relative energies (including zero-point en-

ergies) were used to construct a predicted Boltzmann distribution of stereoisomeric cycloadducts. The structures and relative energies of 12 diastereomeric TSs for the IMDA reaction of C*-OSiH_3 *Z*-dienophile precursor **4f** are depicted in Figure 2.

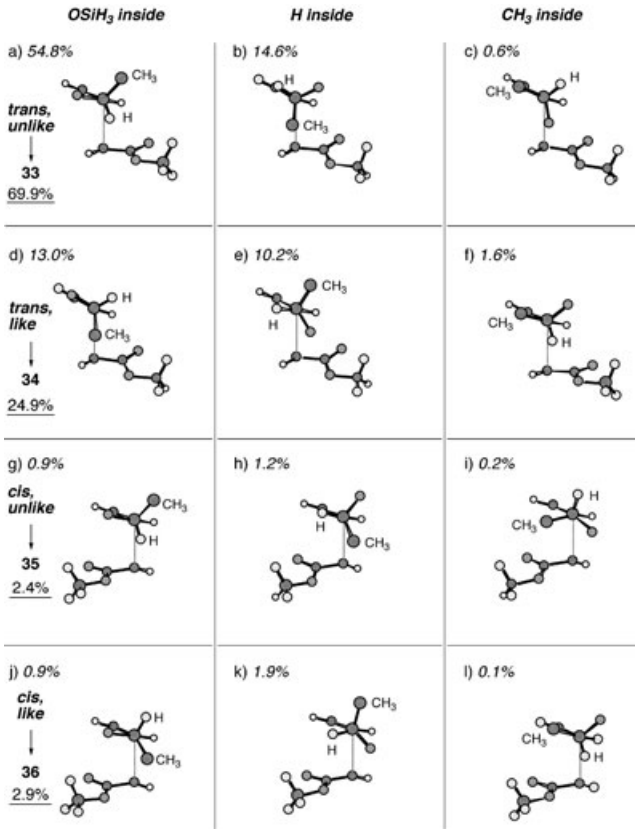


Figure 2. TSs and calculated Boltzmann populations (italic for individual TSs, the underlined number is the total for each diastereomeric adduct) at 383 K for the IMDA reaction of **4f**. The twelve TSs are viewed down the C1–C* axis and the developing C1−C9 bond is depicted as a vertical gray line. C*-H and C*-CH_3 are labeled throughout and some atoms are omitted for clarity. Structures a)–c) lead to the *trans, unlike* adduct **33f**; d)–f) lead to *trans, like* adduct **34f**; g)–i) lead to *cis, unlike* adduct **35f**; and j)–l) lead to the *cis, like* adduct **36f**. Structures on the left have the -$OSiMe_3$ group *inside*, those in the center column have the -H *inside*, and those on the right have the -CH_3 *inside*. To facilitate comparisons between TSs, dienophile approach from below is depicted throughout, hence the configuration at the allylic stereocenter is inverted in the *unlike* TSs.

For both C*-OSiH_3 triene **4f** and C*-OSiMe_3 triene **4b**, theory correctly predicts the major–minor product sequence: the predicted Boltzmann populations of IMDA adducts from the reaction of **4b** at 383 K in the gas phase (**33b**:**34b**:**35b**:**36b** = 81.9:15.3:1.2:1.6[28]) compares favorably with the experimentally determined ratio in refluxing toluene (Table 3, entry 2; **33b**:**34b**:**35b**:**36b** = 56:30:6:8). Considering the complexity and multiplicity of TSs examined and the omission of solvent effects in the calculations—which are expected to be small, considering the low polarity of the toluene or chlorobenzene solvents used in the experiments—the close correlation between theory and experiment is remarkable, providing compelling evidence in support of the reliability of our theoretical model.

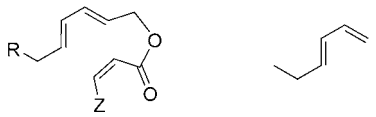
For the (*E*)-dienophile series, the predicted IMDA adduct ratio from the reaction of $OSiH_3$ substrate **4g** is **33**:**34**:**35**:**36** = 25:20:50:5 at 405 K in the gas phase. Experimentally, in refluxing chlorobenzene solution (405 K), the ratio of products for the -OTBS substrate **4e** is 8:28:40:24. Thus, theory correctly predicts: 1) a less stereoselective IMDA reaction for a fumarate ester than the corresponding maleate ester; 2) the identity of the major product, the *cis, unlike* diastereoisomer, 3) the *cis/trans*-selectivity of the reaction, and 4) in a qualitative manner, the π-diastereofacial selectivity within the *cis*-adduct manifold. There is a discrepancy between theory and experiment, however, in the π-diastereofacial selectivity of the *trans*-adducts (exptl: *unlike*:*like* = 22:78; theory *unlike*:*like* = 57:43) Nevertheless, once again, overall there is a very good correlation between experiment and theory. Extensive CPU times were necessary to carry out these calculations and it was not feasible to carry out a similar computational analysis on TBS fumarate precursor **4e**.

The very good correlation between theory and experiment once again demonstrates the validity of the computational model.

Discussion

Following a brief discussion of general features of the TSs located, the computational results will be interpreted to answer the following three questions: 1) What is the origin of the *unlike* π-diastereofacial selectivities of these reactions? 2) Why does the magnitude of π-diastereofacial selectivity change with different RO- substituents? 3) Why do fumarates **1f**, **2b** and **4e** undergo IMDA reactions with anomalously high *cis*-selectivities?

TS geometries and relative energies: For all three trienes examined computationally, the lowest energy IMDA TSs have *unlike* stereochemistry and exhibit a conformation in which the C*-silyloxy group adopts the *inside* position, the C*-methyl group is in the *anti* position, and the C9-CO_2Me group adopts the *exo* orientation. The preferences of the methyl and silyloxy groups for the *anti* and the *inside* positions, respectively, in the lowest energy TSs are a consequence of their respective innate tendencies to adopt these positions in both the transition state and the ground state, irrespective of the presence of the other substituent (vide infra). This conclusion is borne out by the calculations on model IMDA precursors **42** and **43** (Scheme 10), each of which contains only one of these substituents. As shown in Table 4, the most favorable *trans* IMDA TS for **42** is **42a**, with a methyl group in the *anti* position, and that for **43** is **43a**, with a silyloxy group in the *inside* position. The same

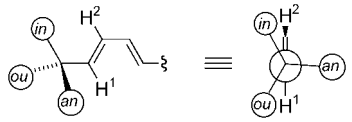


42: R = CH_3, Z = CO_2Me
43: R = $OSiH_3$, Z = CO_2Me
44: R = CH_3, Z = H
45: R = $OSiH_3$, Z = H

46

Scheme 10. Model IMDA precursors employed to investigate the innate conformational preferences of allylic silyloxy and allylic methyl groups.

Table 4. B3LYP/6–31G(d) relative energies [kJ mol^{-1}].[a]



Entry	Structure	*in*	*an*	*ou*	E_{rel}
1	**42a**[b]	H	CH_3	H	0.0 (0.0)
2	**42b**[b]	H	H	CH_3	5.4 (5.5)
3	**42c**[b]	CH_3	H	H	2.3 (2.0)
4	**43a**[b]	$OSiH_3$	H	H	0.0 (0.0)
5	**43b**[b]	H	$OSiH_3$	H	5.9 (6.8)
6	**43c**[b]	H	H	$OSiH_3$	12.6 (12.7)
7	**44a**	H	CH_3	H	0.0 (0.0)
8	**44b**	H	H	CH_3	4.5 (3.9)
9	**44c**	CH_3	H	H	4.3 (4.1)
10	**45a**	$OSiH_3$	H	H	0.0 (0.0)
11	**45b**	H	$OSiH_3$	H	2.2 (3.15)
12	**45c**	H	H	$OSiH_3$	2.1 (1.75)

[a] Relative energies corrected for zero point energy in parentheses. All TSs have *trans*-stereochemistry. Similar results were found for the *cis*-TSs. [b] s-*trans* ester conformation.

trend is found for **44** and **45** in which the C9-ester substituent is absent, thereby demonstrating that the presence of this group is not required for inducing the conformational preferences of the methyl and silyloxy groups in these systems, although its presence does strengthen the preference of the silyloxy group for the *inside* position.

For all TSs located, the forming *internal* (C4–C8) bond is considerably shorter than the developing *peripheral* (C1–C9) bond, giving rise to significant bond-forming asynchronicity (i.e. a difference between the two forming bond lengths). This is exemplified in Figure 3 with the most stable TSs for each of the three series of precursors, **4f**, **4b** and **4g**. The two 9-*Z*-CO_2Me TSs, ***trans, unlike*-4fTS-(a)** and ***trans, unlike*-4bTS-(a)** have large bond-forming asynchronicities of 0.75 and 0.77 Å, respectively, whereas the 9-*E*-CO_2Me TS ***cis, unlike*-4gTS-(g)** exhibits slightly lower levels of bond-forming asynchronicity of 0.56 Å. Similar bond-forming asynchronicities and trends are found in the other TSs. These geometric features are consistent with findings on related systems.[4,7,10] Inspection of the profiles of the 36 IMDA TSs located for trienes **4b, 4f** and **4g** (Figure 2, and Figures S1 and S2[28] in the Supporting Information) reveals that the allylic substituents show little staggering about the forming *peripheral* bond (r_2) that is normally characteristic of additions to allylic systems.[34,35] Indeed, the C1–C* con-

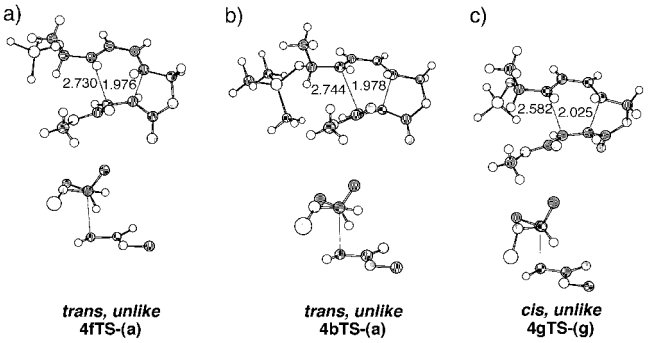


Figure 3. Most stable TSs for each of the three series of precursors. a) ***trans, unlike*-4fTS-(a)** (Figure 5a); b) ***trans, unlike*-4bTS-(a)** (see Figure S1a[28] in the Supporting Information); c) ***cis, unlike*-4gTS-(g)** (see Figure S2g[28] in the Supporting Information). Top: front views (forming bond lengths in Å). Bottom: Newman projections down the O–C* bond. Most H atoms and C3–C8 have been omitted for clarity.

formations in these TSs are essentially the same as those for isolated allylic ethers, with one substituent eclipsing the double bond.[38] This is hardly a surprising finding, given the highly extended length of the developing *peripheral* bond[4,7,10] (the forming *peripheral* bond length reaches a peak at 2.943 Å for $SiMe_3$-substituted TS **4bTS-(d)**, see Figure S1d[28] in the Supporting Information) and the consequent near planarity of the C1 carbon of the diene in these TSs (the sum of the bond angles about this centre is generally greater than 358°).

Model B3LYP/6–31G(d) calculations on 1-ethyl-s-*cis*-butadiene (**46**), in which the diene moiety is constrained to coplanarity, show that the staggered conformation of the C-Me group is 2.7 kJ mol^{-1} more stable than the conformation with C-Me eclipsing the C=C double bond (Table 4; entry 7 versus entry 8). This energy difference is similar in magnitude to the energetic preference of the *anti* conformation over the *inside* conformation in the TSs for both **42** and **44**, thereby revealing the reactant-like geometry around C1 in these IMDA TSs.

Our model for the favored TS for IMDA reactions, in which the silyloxy group adopts the *inside* position and the alkyl group the *anti* position, is reminiscent of that proposed for both *intermolecular* 1,3-dipolar cycloadditions of nitrile oxides to chiral allylic ethers,[35,39] and Craig's silylacetal tethered IMDA reactions.[40]

Origin of *unlike* π-diastereofacial selectivities: In the preliminary study we suggested that the *inside* preference for the -$OSiR_3$ group might arise from an attractive electrostatic interaction between the oxygen atom and the hydrogen atom at C2.[5] Other workers have suggested that this conformational preference is due to the small lone pair size of the silyl ether oxygen atom.[38] The considerably lower π-facial selectivities observed experimentally in IMDA reactions of alcohol substrates **1a** and **4a** and the *p*-nitrobenzoate ester **1e** versus the corresponding silyl ethers (Table 1 and Table 3) are consistent with our electrostatic argument, but not with the oxygen lone pair size proposal. To shed

light on this issue, the excess charge on the allylic oxygen atom was calculated for model systems using natural population analysis (NPA) using the natural bond orbital scheme of Weinhold et al.[41] The results are as follows (in units of electron charge): $MeOSiMe_3$ −0.890; $MeOSiH_3$ −0.845; MeOH −0.740; MeOMe −0.558; methyl-*p*-nitrobenzoate (alkoxy oxygen) −0.540. Thus, the charge on the oxygen atom is significantly higher for silyl alkyl ethers than for alcohols, dialkyl ethers, or *p*-nitrobenzoate esters, which supports our electrostatic argument. Further evidence for the effect being electrostatic in nature was obtained by examining the preferred conformations of allylic alcohol derivatives. The energy differences between the conformation in which the alkene π bond and the C−O bond are roughly in-plane and the out-of-plane conformation, for allyl alcohol and pertinent derivatives are listed in Table 5. As the electron density about the oxygen atom increases, so does the preference for the in-plane conformation. Indeed, the in-plane conformation is preferred only with the $-OSiMe_3$ and $-O^-$ groups, all others preferring the out-of-plane conformation.[42] This trend is consistent with the aforementioned increased electrostatic stabilization of the in-plane conformer.

Increased stabilization of the -OR *inside* conformation in IMDA reactions should lead to even higher levels of facial stereocontrol than those witnessed in Tables 1—3. This might be achieved by using the alkoxide anion group $-O^-$ (see Table 5). Attempts to examine the IMDA reactions of metal alkoxides derived from alcohol **4a** were thwarted by the instability of the ester groups in the presence of the alkoxide. Investigations with more robust tethers are continuing.

Magnitude of π-diastereofacial selectivities: Theory predicts an IMDA reaction for the maleate $SiMe_3$ substrate which is considerably more π-diastereofacially selective than that of the SiH_3 substrate (*unlike:like* = 5.9:1 ($SiMe_3$); 2.8:1 (SiH_3)). This result is in qualitative agreement with the experimental findings, which demonstrate that the larger the silyl protecting group, the higher the π-diastereofacial selectivity. The origin of this increase in selectivity with increasing size of the SiR_3 group is apparent from inspection of the relative energies, E_{rel}, of the *like* and *unlike trans*-TSs for the IMDA reactions of **4f** and **4b**, presented in Table 6. These data reveal that the major difference in the E_{rel} values for the two systems is between the *like* TSs with H occupying the *inside* position: ***trans, like*-4fTS-(e)** and ***trans, like*-4bTS-(e)** (see Figure 4). The E_{rel} value increases significantly, from 5.4 kJ mol^{-1}, for ***trans, like*-4fTS-(e)**, to 10.2 kJ mol^{-1} for ***trans, like*-4bTS-(e)**. This increase has the consequence of bolstering the importance of the ***trans, unlike*-4bTS-(a)**.

The cause of the destabilization of ***trans, like*-4bTS-(e)** can be understood by examining the differences between the $SiMe_3$ and SiH_3 TSs (Figure 4). IMDA TSs (e) for the SiH_3 and $SiMe_3$ substrates are remarkably similar, with one notable exception: the Si-O-C*-C1 dihedral angle is significantly larger in the $SiMe_3$ TS (−130°), compared to that in the SiH_3 TS (−109°). This difference is probably due to adverse steric interactions between the TMS group and the methyl group of the CO_2Me group in ***trans, like*-4bTS-(e)**. This increased twist about the O−C* bond brings a TMS methyl group into fairly close proximity with C*−H (2.55 Å; see Figure 4); apparently little relief of strain is achieved by the aforementioned twisting mode, consistent with the higher E_{rel} value for ***trans, like*-4bTS-(e)**, compared to ***trans, like*-4fTS-(e)**. This destabilization of TS(e) would be enhanced by the presence of larger silyl substituents (i.e.

Table 5. Conformational preferences of allylic alcohol derivatives.[a,b]

in-plane C–O/C=C conformer | out-of-plane C–O/C=C conformer

R	ΔE [kJ mol^{-1}]
-O*p*NB	3.0
-OMe	0.36
$-OSiH_3$	0.57
$-OSiMe_3$	−2.0
$-O^-$	−5.1

[a] All geometries were optimized fully. [b] A positive value for ΔE means that the out-of-plane conformation is preferred.

Table 6. Relative energies, E_{rel} [kJ mol^{-1}], of *trans, unlike* and *trans, like* TSs for the IMDA reactions of **4b** and **4f**.

	E_{rel} ***trans*-4bTS**	E_{rel} ***trans*-4fTS**
unlike, OSi *in*	0.0	0.0
unlike, H *in*	6.4	4.2
unlike, CH_3 *in*	18.0	14.6
like, OSi *in*	6.3	4.6
like, H *in*	10.2	5.4
like, CH_3 *in*	11.0	11.3

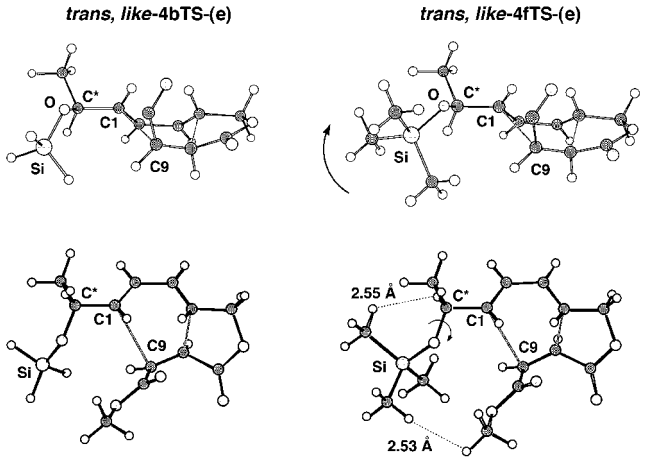


Figure 4. Representations of TSs (e) for the SiH_3 (left hand side) and $SiMe_3$-containing (*Z*)-ester substrate **4**. Top: views down O−C* bond; bottom: front views. Arrows show the direction of rotation about O-Si-C*-C1.

TIPS), which would result in a higher selectivity for the *trans, unlike* adduct **33**.

Anomalous fumarate *cis*-stereoselectivities: In the maleate series, for both SiH_3 (Figure 2) and $SiMe_3$ (see Figure S1[28] in the Supporting Information) substrates, TSs leading to the *trans*-fused bicyclic products are considerably more stable than those leading to the *cis*-fused adducts. These results are consistent with the experimental findings, and are in agreement with computational and synthetic investigations of smaller achiral pentadienyl maleate substrates.[4]

In the case of fumarate systems, TSs leading to *trans*- and *cis*-fused adducts are generally quite similar in energy, with a slight *trans* IMDA selectivity generally witnessed in the laboratory with small achiral substrates.[4,7,10,31,32] In stark contrast, substrates **1f**, **2b**, and **4e** undergo IMDA reactions with anomalously high (up to 85:15) *cis*-selectivities. The origin of this unprecedented preference for the *cis*-cycloadduct can be traced, once again, to preferred inside location of the C*-$OSiR_3$ substituent (Figure 5). In the fumarate *trans*-TSs, the *E*-CO_2Me group must reside directly beneath the *inside* silyloxy group, which necessitates a destabilizing *gauche* conformation between the SiH_3 and C*-CH_3 groups about the C*–O bond (highlighted in the dashed box in Figure 5). In the corresponding *cis*-TS, the *E*-CO_2Me group is located in the *exo* position, hence the *inside* silyl group is free to adopt a lower energy conformation about the C*–O bond in which it avoids the C*-methyl group (note the positioning of the SiH_3 group in the *endo* region in ***cis, unlike*-TS-(g)**). The destabilization of ***trans, unlike*-4gTS-(a)**, relative to ***cis, unlike*-4gTS-(g)**, will be amplified by the presence of larger silyl groups, which will result in a higher selectivity for the *cis*-fused adduct.

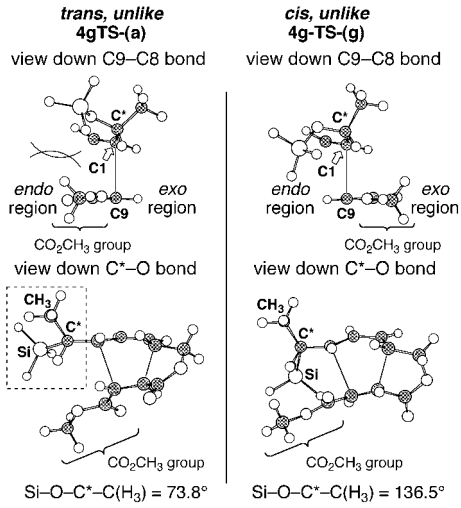


Figure 5. The two most stable (-$OSiH_3$ *inside*, -CH_3 *anti*) fumarate TSs leading to the *trans, unlike* (left) and *cis, unlike* (right) adducts. TS (g) is energetically favored over TS (a). Top: views down the C9–C8 axis (C3–C8 are omitted for clarity); bottom: views down the C*–O bond. The *gauche* interaction between the SiH_3 and CH_3 groups is highlighted in the dashed box. This conformation is brought about by the steric (and possibly electronic) destabilization in the *endo* region in TS (a) indicated in the top left depiction.

Closing Remarks

The synthetic scope and limitations of the IMDA allylic stereocontrol method have been investigated with respect to allylic substituents and dienophile geometry, and a theoretical model has been devised to explain these findings. The computational results offer unprecedented insights into the subtle stereocontrolling influences at play in these synthetically important reactions, and point the way forward for future investigations into additions to chiral allylic systems. The *unlike* π-diastereofacial selectivity observed in these reactions comes about through the preference for a reactive conformation about the bond connecting the diene and the stereocenter in which the silyloxy group adopts an *inside* orientation, as summarized in Figure 6. The dienophile

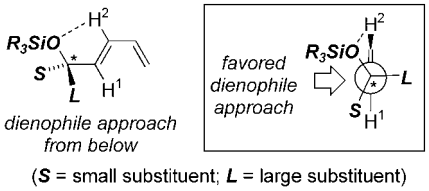
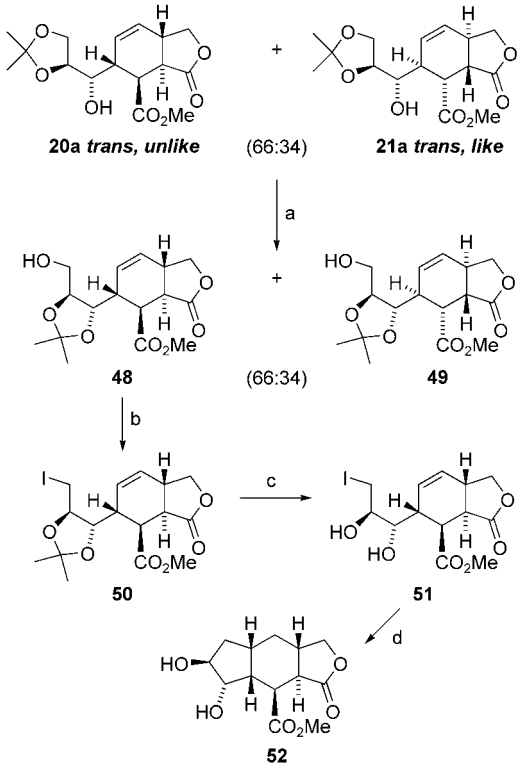


Figure 6. Theoretical model for π-diastereofacial selectivity in addition reactions to chiral allylic silyloxy systems.

reacts at the more accessible π-face of the diene; in the absence of overriding electronic effects, this will be on the side of the diene in which the smaller substituent resides. This model, which also explains the outcomes of *inter*molecular Diels–Alder reactions of acyclic chiral dienols and derivatives,[29b,c] is being further explored and tested.

A particularly important finding from both experimental and computational studies is the requirement for the C*-oxygen atom to be electron rich, thereby strengthening its preference for the inside position by stabilizing electrostatic interactions with the diene C2-H group. Thus, the silyloxy group is much superior to hydroxy, alkoxy, and ester groups in its stereocontrolling ability.

The enantiomerically pure cycloadducts formed in these reactions are rich in functionality, which invites further transformation into structures common with natural products. For example, the mixture of ascorbic acid derived secondary alcohols **20a** and **21a** underwent smooth transacetalization[43] to a separable mixture of primary alcohols **48** and **49** (Scheme 11). The major diastereoisomer was converted to the primary iodide[44] and the acetal group was removed. The resulting diol underwent radical cyclization with tris(trimethylsilyl)silane[45] to give tricycle **52**, with the expected *cis*-indane geometry.[46] The tricylic framework of **52** is found naturally in marasmane sesquiterpenes.[47]



Scheme 11. Synthesis of **52**: a) Amberlyst resin, Me_2CO, RT, 21 h, 96%; b) imidazole (1.9 equiv), Ph_3P (1.6 equiv), I_2 (1.5 equiv), $CHCl_3$, RT, 20 h, 67%; c) Amberlyst resin, MeOH:H_2O (5:1), reflux, 18 h, 82%; d) $(Me_3Si)_3SiH$ (1.1 equiv), AIBN, PhH, reflux, 45 min, 64%.

Acknowledgements

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