Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue



Cite this: *Org. Biomol. Chem.*, 2014, **12**, 1292

# Investigation of quantitative structure–reactivity relationships in the aliphatic Claisen rearrangement of bis-vinyl ethers reveals a dipolar, dissociative mechanism†

Natasha F. O'Rourke and Jeremy E. Wulff*

Received 6th October 2013,
Accepted 18th December 2013

DOI: 10.1039/c3ob42011f

www.rsc.org/obc

Kinetic investigations of substituent effects in the thermal rearrangement of bis-vinyl ether substrates are reported. Findings indicate that the influence of the various substituent patterns on the rate of rearrangement in these compounds differs from that documented in the literature for the analogous [3,3]-sigmatropic rearrangement of allyl vinyl ethers. In addition, the thermochemical data collected suggests the existence of a dissociative transition state with significant dipolar character. These findings provide a unique contribution to the already extensive body of literature dedicated to mechanistic investigation of the Claisen rearrangement of aliphatic allyl vinyl ethers.

## Introduction

The development of the Claisen rearrangement (and variants thereof) over the past century has unambiguously demonstrated the power and synthetic utility of this deceptively simple transformation.[1–6] While the regio- and stereoselective formation of new carbon–carbon bonds in this manner has been widely accepted to occur through a concerted, albeit asynchronous,[7–10] bond reorganization process *via* a six-membered cyclic transition state,[11,12] many details about the reaction trajectory remain elusive (Fig. 1). Most notably, substituent effects on the rate of Claisen rearrangement have often afforded contradictory interpretations of what the transition-state structure may look like (be it diradical[13–21] or dipolar[21–23] in nature) and theoretical predictions are not always consistent with experimental results.[15,17,24] For these reasons, substituent[17,18,22,25–41] and solvent effects[27,42–44] have been thoroughly investigated over the past three decades in order to elucidate the mechanistic details of the rearrangement and, more specifically, the nature and geometry of the transition-state structure. Although the precise electronic structure of the transition state presumably varies somewhat with changing substitution patterns on the allyl vinyl ether scaffold, there is general consensus as to the highly organized

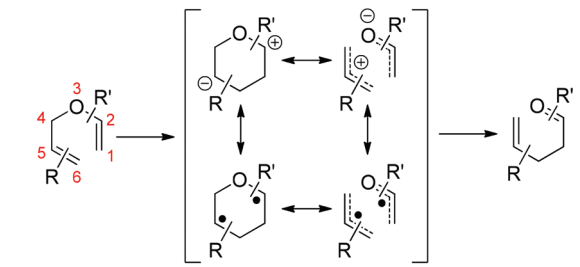



**Fig. 1** Mechanistic options for the aliphatic Claisen rearrangement, and a summary of known substituent effects.

nature of the transition structure itself, consistent with a significant negative $\Delta S^{\ddagger}$ (*vide infra*).

For the past few years, our research group has been interested in the iterative synthesis and synthetic exploitation of oligo-vinyl ethers (Fig. 2).[45–47] As part of this research program, we have had ample opportunity to observe the propensity – or lack thereof – for bis-vinyl ether substrates to undergo Claisen rearrangement. Bis-vinyl ethers are structurally related to the allyl vinyl ethers summarized in Fig. 1 (differing only in the presence of an additional oxygen atom at C-6) but the influence of substitution on their

*Department of Chemistry, University of Victoria, Victoria, BC, Canada, V8W 3V6. E-mail: wulff@uvic.ca*

†Electronic supplementary information (ESI) available: $^{1}$H NMR and $^{13}$C NMR spectra for all new compounds, as well as Eyring and Arrhenius plots used to determine thermodynamic properties. See DOI: 10.1039/c3ob42011f

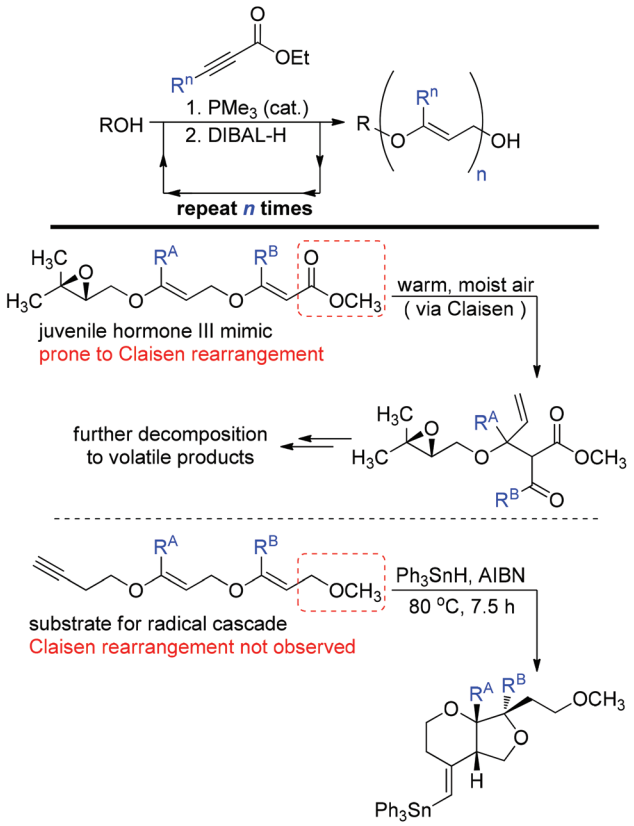



Fig. 2 Iterative synthesis of oligo-vinyl ethers, and synthetic applications.

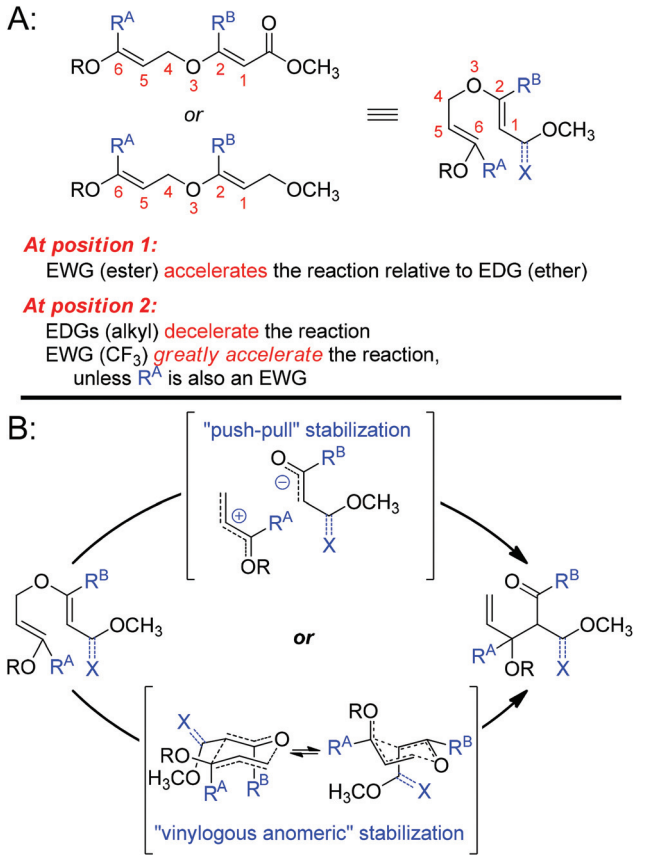



Fig. 3 Reactivity of bis-vinyl ethers toward Claisen rearrangement. A: summary of Claisen rearrangement substituent effects observed from our earlier bis-vinyl ether studies; B: two plausible mechanistic possibilities for the rearrangement.

ability to undergo Claisen rearrangement has not been extensively studied, notwithstanding some significant early contributions by the Curran[22,31,48–50] and Augé[51,52] groups.

In our early studies in this area, we were surprised to find that the substituent effects for our bis-vinyl ethers appeared to differ from those described previously for the analogous allyl vinyl ethers. For instance, in a series of compounds that we prepared as mimics of insect juvenile hormones (Fig. 2), we found that the presence of an electron-withdrawing ester function at the terminus of the bis-vinyl ether system enabled the compounds to undergo a facile Claisen rearrangement at low temperature.[45] This, combined with the ability of the Claisen products to undergo further decomposition (mostly through elimination) to afford volatile byproducts, led us to propose that such compounds might be useful as ecologically degradable insect control agents.[45]

By contrast, compounds in which the electron-withdrawing group was absent were relatively resistant to Claisen rearrangement, such that they could be used as substrates for high-temperature radical cascade reactions.[46,47] The fact that the addition of an electron-withdrawing substituent at C-1 (allyl vinyl ether numbering) resulted in such a dramatic increase in the rate of Claisen rearrangement was surprising, given that previous studies for allyl vinyl ether systems[27,30,32,33,38] had shown that electron *donating* groups at C-1 increased the rate of rearrangement, while electron withdrawing groups actually stabilized the substrates.[25,37]

This early indication that bis-vinyl ethers might undergo Claisen rearrangement through a fundamentally different mechanism than most other allyl vinyl ethers was further supported by a careful study of the stabilities of our variously substituted juvenile hormone mimics (Fig. 3A). As we reported previously,[45] the rate of Claisen rearrangement was greatly enhanced by the addition of an electron-withdrawing $CF_3$ group at C-2 (to such an extent that most such products could not be isolated), but this propensity to undergo rearrangement could be completely mitigated by the installation of a *second* $CF_3$ function at C-6 (to the point where <20% Claisen rearrangement was observed after 14 days of incubation at 37 °C). These data suggested that the rearrangement was promoted by a "push–pull" mechanism (Fig. 3B) where the electron-rich half of the bis-vinyl ether system (C-4 to C-6) acted to stabilize a (partial) positive charge, while the more electron-poor half of the system (C-1 to O-3) acted to stabilize a (partial) negative charge. This description of the reactivity of bis-vinyl ethers is reminiscent of Curran's earlier postulated "vinylogous anomeric" effect to describe the role of the C-6 oxygen,[31,50] but goes further in rationalizing substituent effects at C-1 and C-2.[53]

The implications of this "push–pull" hypothesis for bis-vinyl ethers are significant. First, it suggests the possibility that – if a full charge separation can be supported – bis-vinyl ethers may rearrange through a fully dissociated dipolar mechanism, which is distinct from that observed for other allyl vinyl ethers. Reasoning that such a distinct mechanism would have implications for the thermodynamic properties associated with the rearrangement (particularly the $\Delta S^{\ddagger}$), we undertook to more extensively study the thermally induced Claisen rearrangement of substituted bis-vinyl ethers by variable temperature NMR methods.

## Results and discussion

In designing our substrates for this study, we looked to identify a family of compounds where:

(1) we could systematically vary the electronic properties for at least one of the vinyl ether motifs in the bis-vinyl ether system, in the hopes that subsequent Hammett analysis would shed further light on the mechanism of the reaction;

(2) the substrates would undergo Claisen rearrangement at a temperature that was consistent with study by variable-temperature NMR spectroscopy, in order to measure the $\Delta S^{\ddagger}$ for the rearrangement;

(3) few overlapping signals would be present in the $^1$H NMR spectrum; and

(4) the substrates could be made using our existing iterative protocols, and would be stable enough to isolate and characterize, prior to their use in NMR studies.

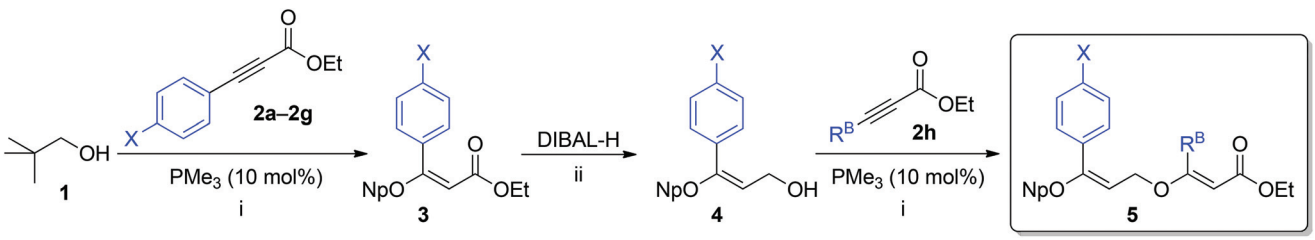
We recognized that an aromatic substituent at either C-2 or C-6 would be ideal for the purpose of systematically varying the electronic properties of the substrates. Since we knew from previous studies[45,46] that aromatic groups were not well-tolerated at $R^B$ (see Fig. 2 and 3 for labelling), we elected to install a series of substituted aromatic rings at $R^A$. Similarly, we chose to focus most of our efforts on bis-vinyl ether systems that were terminated in an ester, since we knew these substrates to rearrange at accessible temperatures. For the alcohol that we used to initiate the iterative synthesis (ROH in Fig. 2), we chose 2,2-dimethylpropanol, since the neopentyl group (Np) has few signals to complicate the NMR spectra, yet contains sufficient mass to render the various synthetic intermediates non-volatile. Compounds **5a–5g** (Table 1) therefore became our primary target for synthesis.

Each of these compounds was accessed efficiently, using the addition/reduction/addition sequence that we developed previously. A broad selection of functional groups (X) on the aryl ring was well-tolerated, allowing us to access substrates incorporating functionality ranging from very electron-rich (*e.g.* *p*-$CH_3O$, entry 1) to very electron-poor (*e.g.* *p*-$CF_3$, entry 8). For most substrates, a methyl group was placed in the $R^B$ position, although we also prepared one compound (**5c**, entry 3) lacking this substituent, for comparative purposes. We also synthesized a deuterated analogue (**5b**-$d_2$, entry 4) with which to carry out kinetic isotope experiments.

With all of the desired substrates in hand, we studied their rate of Claisen rearrangement by variable-temperature NMR spectroscopy. Each compound was allowed to rearrange at 4 different temperatures (see Table 2 for temperature ranges; each substrate was measured at 130 °C to provide a direct point of comparison, as well as at 3 other temperatures chosen to provide an analytically feasible data set), in bromobenzene-$d_5$ containing hexamethylbenzene as an internal standard.

Significantly, each of the rearrangements produced a ~1 : 1 ratio of diastereomeric products. While we recognized the

**Table 1** Synthesis of substrates for VT-NMR studies[a]

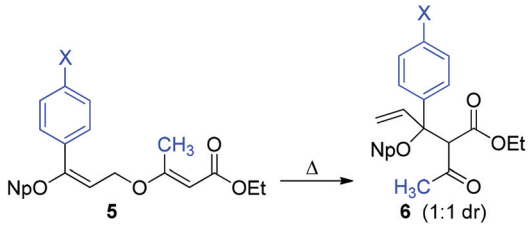



| Entry | X | $R^B$ | 1st addition yield ($E:Z$) | Reduction yield ($E:Z$) | 2nd addition yield ($E:Z$)[b] |
|---|---|---|---|---|---|
| 1 | $CH_3O$ | $CH_3$ | **3a** 94% (15 : 1) | **4a** 97% (18 : 1) | **5a** 99% (9 : 1) |
| 2 | $CH_3$ | $CH_3$ | **3b** 99% (17 : 1) | **4b** 82% (20 : 1) | **5b** 100% (9 : 1) |
| 3 | $CH_3$ | H | **3b** 99% (17 : 1) | **4b** 82% (20 : 1) | **5c** 100% (9 : 1) |
| 4[c] | $CH_3$ | $CH_3$ | **3b** 99% (17 : 1) | **4b**-$d_2$ 75% (14 : 1) | **5b**-$d_2$ 97% (8 : 1) |
| 5 | H | $CH_3$ | **3d**[d] 94% (>20 : 1) | **4d** 98% (>20 : 1) | **5d** 98% (9 : 1) |
| 6 | F | $CH_3$ | **3e** 82% (13 : 1) | **4e** 88% (14 : 1) | **5e** 87% (7 : 1) |
| 7 | Cl | $CH_3$ | **3f** 89% (13 : 1) | **4f** 99% (15 : 1) | **5f** 82% (8 : 1) |
| 8 | $CF_3$ | $CH_3$ | **3g** 78% (>20 : 1) | **4g** 86% (>20 : 1) | **5g** 99% (11 : 1) |

[a] Conditions: (i) $CH_2Cl_2$, 0 to 23 °C, 16 h. (ii) $Et_2O$, −78 to −40 °C, 4 h. [b] For compounds with more than one vinyl ether, the $E:Z$ ratio refers to the ratio of all *E*-product to all other adducts. [c] Compound **5b** was deuterated at the 4-position, by employing $LiAlD_4$ in place of DIBAL-H in the reduction step. [d] The methyl ester was used in place of the ethyl ester for this step.

Table 2 Rate constants, relative rates, and activation parameters for rearrangement of bis-vinyl ethers in bromobenzene-$d_5$




5 6 (1:1 dr)

| Compound | X | $T$ (°C)[a] | $k$ at 130 °C[b] ($\times 10^{-6}$ s$^{-1}$) | $k_{rel}$ | $\Delta G^{\ddagger c,d}$ (kcal mol$^{-1}$) |
|---|---|---|---|---|---|
| **5a** | $CH_3O$ | 100–130 | 783 | 3.3 | 29.5 |
| **5b** | $CH_3$ | 110–140 | 373 | 1.6 | 30.1 |
| **5d** | H | 115–130 | 237 | 1.0 | 30.5 |
| **5e** | F | 115–140 | 212 | 0.9 | 30.6 |
| **5f** | Cl | 120–145 | 114 | 0.5 | 31.1 |
| **5g** | $CF_3$ | 130–145 | 51.0 | 0.2 | 31.7 |

[a] Temperature range of kinetic measurements (±1 °C); a range of 25–30 °C was used, except in cases where this led to problematic decomposition, or where the solvent could not accommodate such a large range. [b] The rate of rearrangement for compounds **5b**, **5c**, **5b**-$d_2$ and **19** was measured multiple times at a fixed temperature (see Table 6); in each case the standard deviation was less than 10%. A maximum error of ±10% is therefore assigned to all rates. [c] $\Delta G^{\ddagger}$ at 130 °C, calculated using the Eyring equation from the observed rate of rearrangement. [d] A maximum error of ±10% in the rate of the reaction corresponds to a maximum error of ±0.1 kcal mol$^{-1}$ in the $\Delta G^{\ddagger}$.

possibility that the rearrangement products, **6**, could be prone to epimerization under the reaction conditions, this observation provided the first suggestion that a dissociative transition state might be involved in the rearrangement.

Analysis of the rate of reaction was complicated somewhat by the fact that *E*,*E*-**5** can undergo partial isomerization to afford mixtures of *E*,*E*; *E*,*Z*; *Z*,*E*; and *Z*,*Z* isomers at these temperatures (though not to an extent that would account for the observed mixture of diastereomeric products[54]), as well as by the fact that the Claisen product **6** can undergo further decomposition. Nonetheless, when these factors were properly accounted for (refer to the Experimental section for details of the NMR analysis), the rates and energies of activation for the rearrangements could be accurately calculated (see Table 2 for values).

As shown in Table 2, the presence of electron-donating groups on the aromatic ring enhanced the rate of rearrangement (relative to phenyl-substituted compound **5d**), while electron-withdrawing groups impeded the reaction. Looking to further quantify the influence of electronics on the rearrangement, the rate data from Table 2 was plotted against a variety of Hammett parameters available from the literature. Our objective in this exercise was to identify which set of parameters provided the best fit to our experimental data. We were particularly interested in comparing the fit for Hammett parameters derived from radical reactions (which therefore report the substituents' ability to stabilize a radical-type transition state) to those parameters derived from polar reactions (and which therefore report the substituents' ability to stabilize a

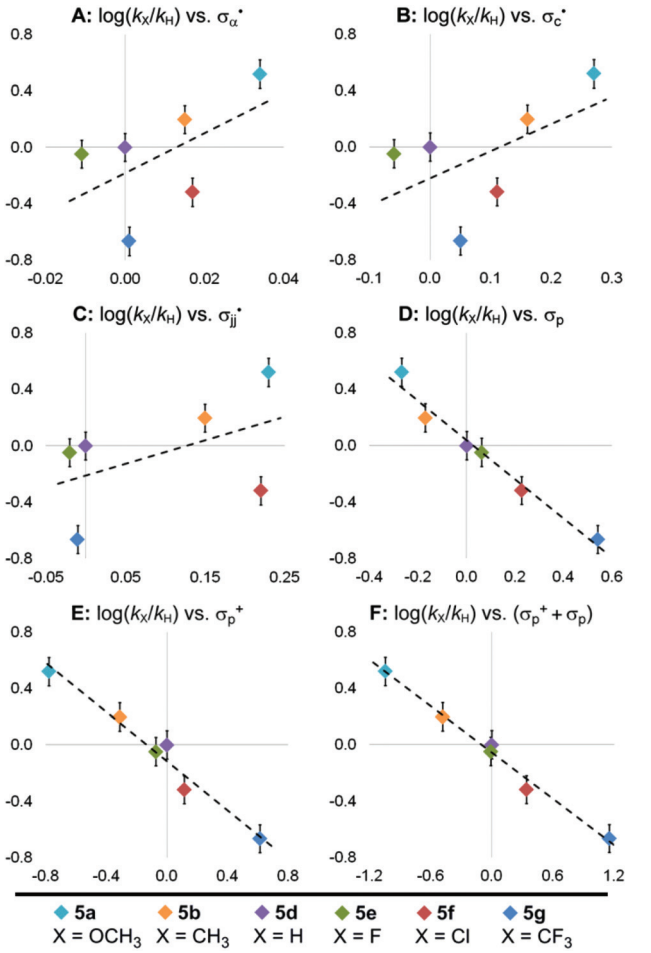



Fig. 4 Hammett plots for the rate of rearrangement of compounds **5**, plotted against different $\sigma$ values (derived from either polar or radical reactions) to probe mechanism.

polar transition state). We hoped to find a large difference between the quality of these fits, which would therefore provide important information about the nature (and relative spin density) of the transition state under study here.

To this end, $\log(k_X/k_H)$ was plotted against: (1) Arnold's $\sigma_\alpha^\bullet$ parameters based on EPR hyperfine coupling of benzyl radicals (Fig. 4A);[55] (2) Creary's $\sigma_C^\bullet$ parameters taken from the rearrangement of methylenecyclopropane systems (Fig. 4B);[56,57] (3) Jiang and Ji's $\sigma_{jj}^\bullet$ parameters measured from the cyclodimerization of trifluorostyrenes (Fig. 4C);[58,59] (4) Hammett's original $\sigma_p$ parameters based on ionization of *para*-substituted benzoic acids (Fig. 4D);[60] and (5) Brown's $\sigma_p^+$ parameters based on solvolysis of substituted *t*-cumyl chlorides (Fig. 4E).[61]

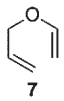
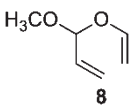
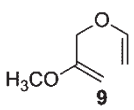
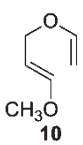
All of the radical-based Hammett parameters provided a very poor correlation ($R^2 < 0.5$) to the data obtained for the rate of rearrangement of bis-vinyl ethers **5** at 130 °C. By contrast, using either set of $\sigma$ values derived from polar reactions ($\sigma_p$ or $\sigma_p^+$) provided an excellent fit to the data ($R^2 = 0.97$ in both cases). Attempts to use dual correlations incorporating both radical- and polar-stabilizing effects, as described by Kim,[62] only worsened the degree of fit. Interestingly, the best fit

($R^2$ = 0.99, Fig. 4F) came from plotting our rate data against the sum of $\sigma_p$ and $\sigma_p^+$. While precedented by the work of both Brown[61] and Kim,[62] we stress that the "blending" of $\sigma$ parameters employed here is strictly empirical, and that the fit in Fig. 4F is not necessarily any more meaningful than that in 4D or 4E. At the same time, this approach may be justified if one considers that the original Hammett values over-emphasize inductive effects at the expense of resonance contributions, while the values calculated by Brown may be said to incorporate resonance effects to a greater degree than might be reasonable in this case.[63] In any event, the data in Fig. 4 clearly argue against the involvement of a diradical-type transition state, and strongly support the existence of a highly polarized transition state.

The measured $\rho$ values are −1.4 for Fig. 4D, and −0.87 for Fig. 4E. These values indicate that a substantial degree of positive charge is associated with the C-6 carbon atom in the transition state, but do not necessarily indicate whether or not the reaction is fully dissociative.[64] In order to more fully probe the degree of organization in the transition state, we sought to examine the change in $\Delta G^{\ddagger}$ with temperature, as a probe for $\Delta S^{\ddagger}$.

A survey of the literature for the aliphatic Claisen rearrangement of simpler allyl vinyl ethers (*e.g.*, **7**–**10**, Table 3) demonstrates that the rearrangement of most such compounds – even those containing an oxygen atom at C-6, like compound **10** – proceeds with a significant negative entropy of activation, indicative of a highly ordered, associative transition state. The experimental indications that bis-vinyl ether esters **5** might rearrange through a dissociated transition state prompted us to consider the $\Delta S^{\ddagger}$ for our system, with the hypothesis that a more dissociative transition state would be revealed by the presence of an atypically positive (*i.e.*, less negative) $\Delta S^{\ddagger}$.[66]

**Table 3** Kinetic data and activation parameters for rearrangements of oxygen-substituted allyl vinyl ethers

| Compound | $k^a$ ($\times 10^{-6}$ s$^{-1}$) | $k_{rel}$ | $\Delta H^{\ddagger}$ (kcal mol$^{-1}$) | $\Delta S^{\ddagger}$ (cal K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|
|  **7** | 0.649[b,c] | 1.0 | 25.4[c] | −15.9[c] |
|  **8** | 62.1[d] | 96 | 22.4[d] | −14.7[d] |
|  **9** | 0.0161[d] | 0.025 | 30.9[d] | −7.0[d] |
|  **10** | 6.12[d] | 9.5 | 24.7[d] | −12.8[d] |

[a] Rate in benzene-$d_6$ at 80 °C. [b] Study performed in di-*n*-butyl ether rather than in benzene. [c] Values taken from ref. 25. [d] Values taken from ref. 22.

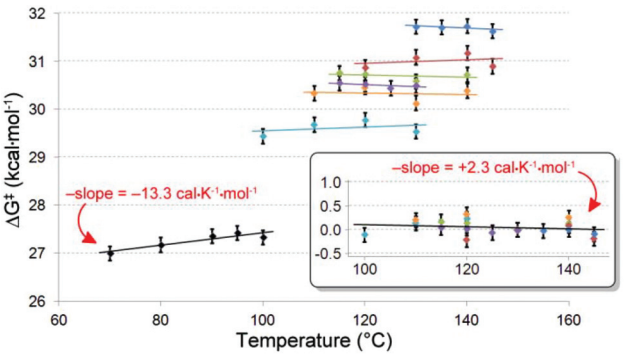



**Fig. 5** Change in $\Delta G^{\ddagger}$ with temperature for bis-vinyl ethers **5** and **13**. Coloured data points correspond to measurements for compounds **5a**–**5g** (see legend in Fig. 4 for details). Black data points correspond to measurements for compound **13**. Inset plot shows the change in $\Delta G^{\ddagger}$ (in units of kcal mol$^{-1}$) for all aryl-substituted compounds, relative to the measured $\Delta G^{\ddagger}$ at 130 °C.[65]

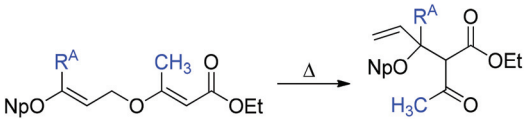
As shown in Fig. 5, for each of the bis-vinyl ether esters examined, the $\Delta G^{\ddagger}$ remains constant, within experimental error. Since the slope of $\Delta G^{\ddagger}$ *vs.* temperature must correspond to $-\Delta S^{\ddagger}$, this indicates that the entropy of activation must be small. Indeed, *each* of the coloured lines in Fig. 5 (corresponding to best fits through the raw data for compounds **5a**–**5g**) has a slope of less than 5 cal K$^{-1}$ mol$^{-1}$ – suggestive of a less negative $\Delta S^{\ddagger}$ than for any of the compounds indicated in Table 3.

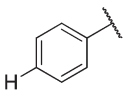
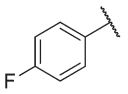
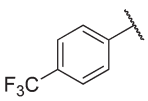
Canonical determination of $\Delta S^{\ddagger}$ by Eyring analysis was somewhat complicated by the fact that for some of our compounds (**5a**, **5b**, and **5f**) overlap of characteristic NMR signals used for kinetic analysis (see Experimental for details) prevented accurate integration. This necessarily led to small uncertainties in the rates, which in turn led to Eyring plots with less than perfect fits ($R^2$ = 0.98 or below; refer to the ESI† for Eyring and Arrhenius plots). Because determination of $\Delta S^{\ddagger}$ by this method requires that one extrapolate far outside of one's data points to obtain the intercept, this led to unsatisfactory errors in the determination of the activation entropy. For each of these three substrates, the calculated *range* for $\Delta S^{\ddagger}$ encompassed 0 cal K$^{-1}$ mol$^{-1}$ (suggesting, at least, that the actual value is small), but the calculated uncertainty (based on the standard error of the intercept) associated with these measurements was larger than 5 cal K$^{-1}$ mol$^{-1}$.

Fortunately, for compounds **5d**, **5e** and **5g**, good-quality data sets could be collected at all temperatures used in the study. For each of these compounds, high-quality Eyring plots ($R^2$ > 0.99) could be obtained, which limited the calculated uncertainty in the measurement of $\Delta S^{\ddagger}$. Data for these compounds are shown in Table 4, and reveal that the rearrangement of each compound is associated with a small *positive*

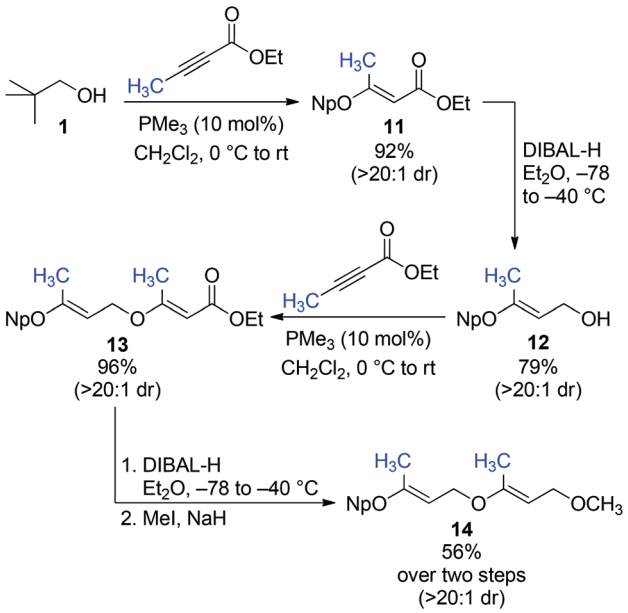
 

Table 4 Entropy of activation, determined by Eyring plot




| Compound | $R^A$ | Product dr | $\Delta S^{\ddagger}$ [a] (cal $K^{-1}$ $mol^{-1}$) |
|---|---|---|---|
| **5d** |  | 1 : 1 | +4.8 ± 3.7 |
| **5e** |  | 1 : 1 | +2.8 ± 4.6 |
| **5g** |  | 1 : 1 | +4.9 ± 3.6 |
| **13** |  | 3 : 1 | −13.5 ± 3.2 |

[a] Calculated uncertainties are based on the standard error of the intercept, as determined by the XLfit statistical analysis package.




Scheme 1 Synthesis of additional substrates for temperature studies.

$\Delta S^{\ddagger}$, in distinct contrast to the larger, negative values reported for the prototypical allyl vinyl ethers in Table 3.

The data for compounds **5d**, **5e** and **5g** in Table 4 are compelling, but necessarily neglect measurements associated with more electron-rich aromatic rings. In order to include these data in our determination of $\Delta S^{\ddagger}$, we devised an alternative method: if one assumes that all of compounds **5a–5g** have approximately the same entropy of activation (*i.e.*, that the differences in rates are entirely due to enthalpic factors associated with electron-withdrawing or -releasing groups), then one can normalize the $\Delta G^{\ddagger}$ data in Fig. 5, by shifting the 130 °C data for each compound to the same, arbitrary, point on the graph. $\Delta G^{\ddagger}$ measurements at other temperatures can then be plotted according to their distance above or below the measured $\Delta G^{\ddagger}$ at 130 °C. All of the data in the resulting plot – included as an inset to Fig. 5 – can then be used to fit a single line, the slope of which (multiplied by −1) corresponds to the consensus $\Delta S^{\ddagger}$ for compounds **5**. In the event, this method provided an activation entropy of +2.3 cal $K^{-1}$ $mol^{-1}$. This is consistent with the values in Table 4, and is arguably a better measure of the true consensus $\Delta S^{\ddagger}$ for compounds **5**, since it is drawn from a greater number of individual measurements.[65]

To the best of our knowledge, this is the least negative $\Delta S^{\ddagger}$ determined for the thermal aliphatic Claisen rearrangement of any allyl vinyl ether substrate, and it provides strong evidence in favour of a dissociative transition state.

The aromatic ring in substrates **5a–5g** was added to allow us to explore the electronic effects of various substituents on the properties of the vinyl ether moiety to which those substituents were conjugated. In order to evaluate the effect that the aromatic function, itself, had on stabilizing the dissociative transition state through the presence of additional conjugation, we repeated the temperature study with alkyl-substituted bis-vinyl ether **13**, prepared as indicated in Scheme 1.

Compound **13** was similarly allowed to rearrange at 5 temperatures in bromobenzene-$d_5$, and the energy of activation was calculated in an identical manner to the experiments described above for substrates **5a–5g**. The results (see Fig. 5 for a comparison of $\Delta G^{\ddagger}$ data from **5** and **13**, and Table 4 for the product ratio and $\Delta S^{\ddagger}$) indicated that alkyl-substituted compound **13** behaves significantly differently than the aryl-substituted analogues **5a–5g**. Instead of producing a 1 : 1 mixture of diastereomers, **13** rearranged to afford a 3 : 1 ratio of products,[67] with a calculated $\Delta S^{\ddagger}$ of approximately −13 cal $K^{-1}$ $mol^{-1}$. This is significantly different than the $\Delta S^{\ddagger}$ measured for compounds **5** (*i.e.*, the two best fit lines shown in black in Fig. 5 reveal significantly different relationships), and is within experimental error of the value reported for compound **10** (see Table 3). These data indicate that the transition state for the rearrangement of **13** is less dissociative than that for compounds **5**.

Alkyl-substituted bis-vinyl ether **13** was found to rearrange considerably faster than **5a–5g**, necessitating the use of a lower temperature range in order to obtain a good-quality data set. The $\Delta G^{\ddagger}$ for **13** is approximately 90% that of phenyl-substituted bis-vinyl ether **5d**, while the relative rate of rearrangement (corrected to 130 °C by extrapolating from the Eyring equation) is approximately 28 times faster.

The lower temperature required for the rearrangement of **13** meant that it was a superior substrate for the measurement of solvent effects, since a greater range of solvents could be

Table 5 Claisen rearrangements of non-aryl substrates, solvent effects and effect of reduction at C-1

| Compound | Solvent ($\varepsilon$) | $T$ (°C)[a] | $k$ at 70 °C ($\times 10^{-6}$ s$^{-1}$) | $k_{rel}$[b] | $\Delta G^{\ddagger}$[c] (kcal mol$^{-1}$) |
|---|---|---|---|---|---|
| **13** | $C_6D_6$ (2.3) | 70 | 20.3 | 0.5 | 27.5 |
| **13** | $C_6D_5Br$ (5.2) | 70–100 | 44.1 | 1.0 | 27.0 |
| **13** | $(CD_2Cl)_2$ (10.4) | 70 | 207 | 4.7 | 25.9 |
| **13** | $CD_3CN$ (37.5) | 70 | 393 | 8.9 | 25.5 |
| **14** | $C_6D_5Br$ (5.2) | 110 | —[d] | —[d] | —[d] |

[a] Temperature range of kinetic measurements (±1 °C). [b] Relative to the rate of compound **13** in $C_6D_5Br$. [c] $\Delta G^{\ddagger}$ at 70 °C, calculated from the observed rate of rearrangement. [d] Attempts to measure the rate of rearrangement of **14** revealed an autocatalytic process that did not display first order kinetics.

employed. We therefore monitored the Claisen rearrangement of **13** in both less polar (benzene-$d_6$) and more polar, aprotic (dichloroethane-$d_4$, acetonitrile-$d_3$) NMR solvents (see Table 5). The results showed a substantial increase in reaction rate with increasing dielectric constant. Attempts to monitor the reaction in methanol-$d_4$ or $D_2O$ were unsuccessful, in that both the rearrangement and subsequent decomposition occurred too rapidly to follow by NMR spectroscopy, even at 30 °C.

By contrast, the aliphatic Claisen rearrangement of less-substituted allyl vinyl ethers is known to be relatively unaffected by changes in solvent polarity; for example, compound **10** experiences only a 3.2-fold increase in the rate of rearrangement at 80 °C, upon moving from benzene to acetonitrile (compared to a 19.4-fold increase for **13**).[22] The fact that the rearrangement of **13** is much more sensitive to solvent effects than is **10**, strongly suggests that **13** rearranges through a more polarized transition state. This would be most consistent with a greater degree of heterolytic cleavage of the O-3–C-4 bond, prior to the formation of the new bond between C-1 and C-6. Thus, while alkyl-substituted bis-vinyl ether **13** evidently rearranges through a more organized transition state than do aryl-substituted bis-vinyl ethers **5** (as evidenced by the more negative $\Delta S^{\ddagger}$), its transition state nonetheless appears to be more fragmented than that experienced by the simpler allyl vinyl ether substrate **10**.

The lower temperature required for the rearrangement of ester **13** (relative to **5**) also provided an opportunity for us to investigate the reaction of the corresponding reduced analogue, **14**. We knew from our previous studies that bis-vinyl ether substrates not containing electron-withdrawing groups at C-1 were relatively resistant to Claisen rearrangement (*e.g.*, see Fig. 2); as a result, the reduced forms of **5a–5g** were not expected to rearrange at accessible temperatures, and so were not pursued. Since **13** rearranged more easily, however, we hoped that the corresponding methyl ether would provide a tractable target for study. We therefore prepared **14** as shown in Scheme 1, and studied its rearrangement by NMR spectroscopy. Gratifyingly, the reaction – although slower than the corresponding transformation for **13** – was found to proceed smoothly at 110 °C in bromobenzene-$d_5$, to give a ~5 : 1 mixture of diastereomeric products. Unfortunately, reproducible measurement of the rate of this reaction was not possible under the conditions of our NMR experiment. The attempted kinetic analysis of the rearrangement of **14** revealed a substantial lack of linearity that was most consistent with an auto-catalytic process. We speculate that the rearrangement product from **14** undergoes decomposition under the conditions of the experiment, and that one of the resulting decomposition products serves to promote the initial rearrangement.[68]

Table 6 Substituent effects at C-2 and C-4

| Compound | $k^a$ ($\times 10^{-6}$ s$^{-1}$) | $k_{rel}$ | Notes |
|---|---|---|---|
| **5b** | 373 ± 8[b] | 1.00 | |
| **5c** | 253 ± 24[c] | 0.68 ± 0.08 | |
| **5b**-$d_2$ | 251 ± 10[b] | 0.67 ± 0.04 | $k_H/k_D$ = 1.48 ± 0.10 |
| **19** | 451 ± 2[c] | 1.21 ± 0.03 | $k_{19}/k_{5c}$ = 1.79 ± 0.20 |

[a] Measured at 130 °C. [b] Standard deviation over 4 measurements. [c] Standard deviation over 3 measurements.

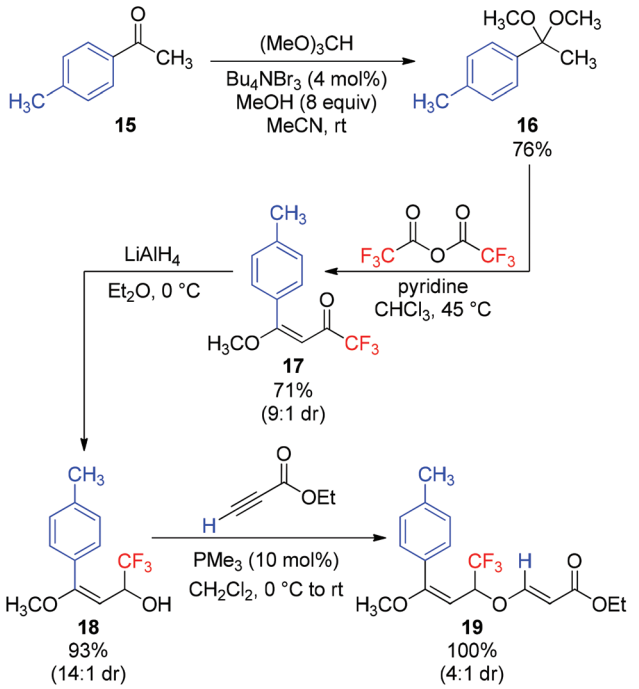
Although a full study of reduced bis-vinyl ethers like **14** is beyond the scope of the current work, these data nonetheless suggest that such compounds rearrange by a distinct mechanism to that of **5** or **13**. Presumably, in the absence of an electron-withdrawing group at C-1, this class of compounds cannot stabilize the C-1–O-3 anion required for the dissociative transition state, and so instead proceeds through a higher-energy associative transition state that is better described by Curran's "vinylogous anomeric" model.

Returning to the aromatic substrates (**5**), we next compared the rate of rearrangement for **5b** (bearing a methyl substituent at the C-2 position) to that for **5c** (which lacks this substituent). Compound **5c** was found to rearrange at a lower rate than **5b** in bromobenzene-$d_5$ (Table 6). This is opposite to the result for prepared films of our juvenile hormone analogues, in which the rate of rearrangement decreased moving from hydrogen, to methyl, to ethyl at the position labeled $R^B$ in Fig. 2. The difference may be due to slight changes to the mechanism of rearrangement for solvated *vs.* adsorbed samples. In any event, the change in rate for **5c** compared to **5b** is relatively small, and is probably more reflective of steric demands than of electronic effects.

More informative was our study of the secondary deuterium isotope effect at C-4. Although **5b** and **5b**-$d_2$ have essentially the same steric properties, the deuterated analogue rearranged considerably slower, resulting in a large secondary isotope effect of 1.48. This is consistent with a large degree of bond-breaking between O-3 and C-4 (and therefore a significant change in hybridization at C-4) early in the reaction pathway. The large $k_H/k_D$ ratio thus provides additional evidence favoring a dissociative transition state.[69]

As an additional mechanistic probe, we were interested in the effect of placing a $CF_3$ substituent at the C-4 position. We reasoned that the presence of an electron-withdrawing group




**Scheme 2** Synthesis of a C-4 analogue.

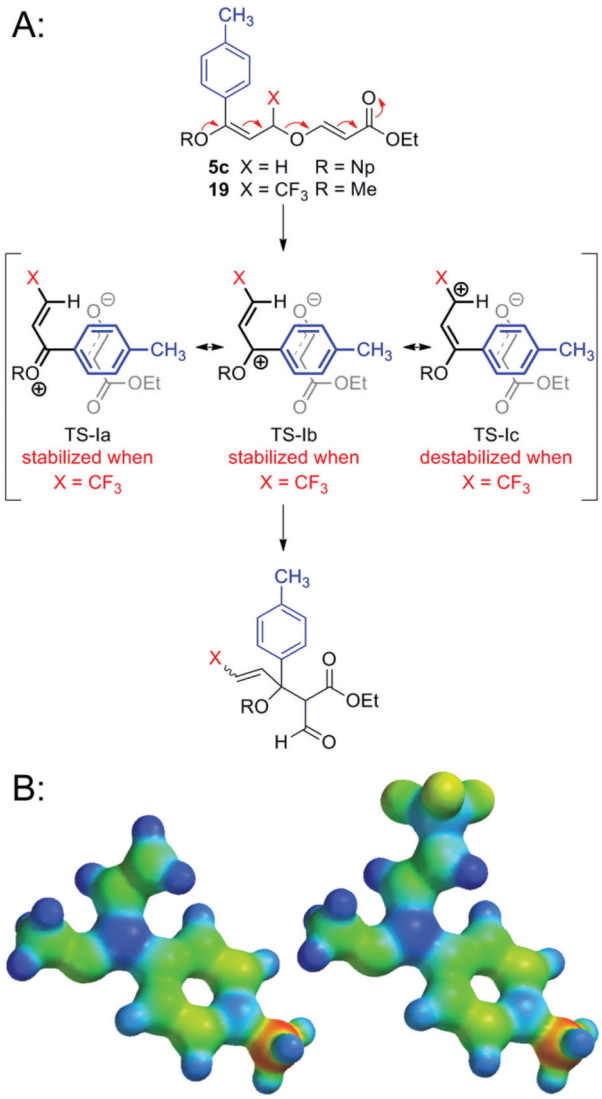


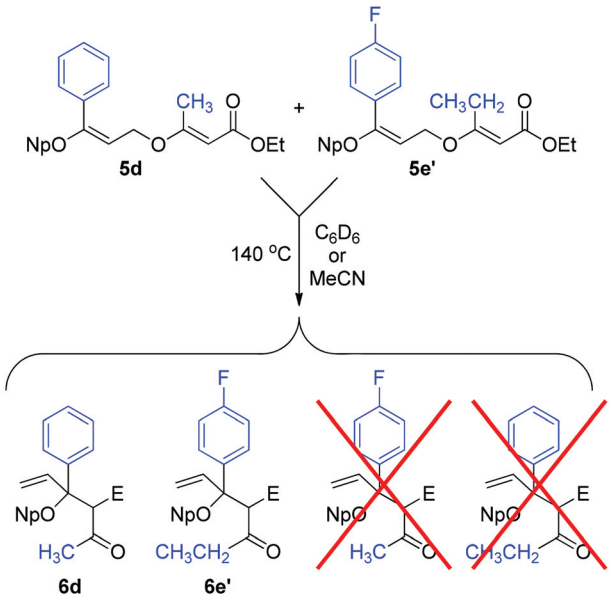

**Fig. 6** Rationale for transition state stabilization by the $CF_3$ substituent. A: Postulated resonance structures for the dissociative transition state. B: Calculated electronic potential maps for the cationic fragments of transition states leading from **5c** and **19**.

at this position might reduce the rate of reaction, by destabilizing the carbocation present on the C-4–C-6 fragment in the dissociative transition state.

We were unable to access the appropriate substrate through a modification of our iterative synthetic protocol, and so instead made use of a route reported by Bonacorso,[70] to access trifluoroketone **17** (Scheme 2). The ketone function was selectively reduced, and the resulting alcohol was added to ethyl propiolate to furnish substrate **19** in good overall yield. The rearrangement of this substrate was monitored under the usual conditions, and was found to proceed nearly twice as fast as the closest analogue, **5c** (see Table 6 for data). This is a larger rate enhancement than for the analogous C4-trifluoromethylated allyl vinyl ether described by Gajewski ($k_{rel}$ = 1.3 compared to allyl vinyl ether).[18]

Although unexpected, the faster rate of rearrangement for **19** relative to **5c** is understandable if one considers that the $CF_3$ group has a significant destabilizing influence on only one of the three resonance structures in the proposed fully-dissociative transition state (TS-Ic, Fig. 6A). For the other two possible resonance structures (both of which are likely to be more significant contributors to the overall electronic structure), the $CF_3$ substituent may actually be *stabilizing*, since it allows for additional substitution at the C-4–C-5 olefin. This analysis was further supported by DFT calculations,[71] which confirmed that most of the positive charge for the cationic fragment postulated to occur in TS-I is located at the carbon (C-6) bearing the aromatic substituent (Fig. 6B). The $CF_3$ substituent at C-4 therefore has little electronic influence, other than to provide additional substitution.

At this stage in our investigation, we had uncovered significant evidence supporting a largely dissociative transition state (TS-I, Fig. 6) for bis-vinyl ethers like **5a–5g** and **19** that contain both an electron-withdrawing C-1 function, as well as additional conjugation at C-6. In order to probe the *extent* of this dissociation, we conducted a crossover experiment (Scheme 3), in which substrates **5d** and **5e′** were allowed to react in solution together, under a variety of conditions. Only the products from individually reacting substrates (**6d** and **6e′**) were observed, in a ~1 : 1 ratio. No crossover products were detected by MS analysis. This indicates that the two fragments depicted in TS-I (Fig. 6) are tightly associated with one another. Although they can presumably react with different trajectories (to form diastereomeric mixtures of products) they are not free to diffuse through solution in either polar or non-polar solvents.




Scheme 3 Crossover experiment.

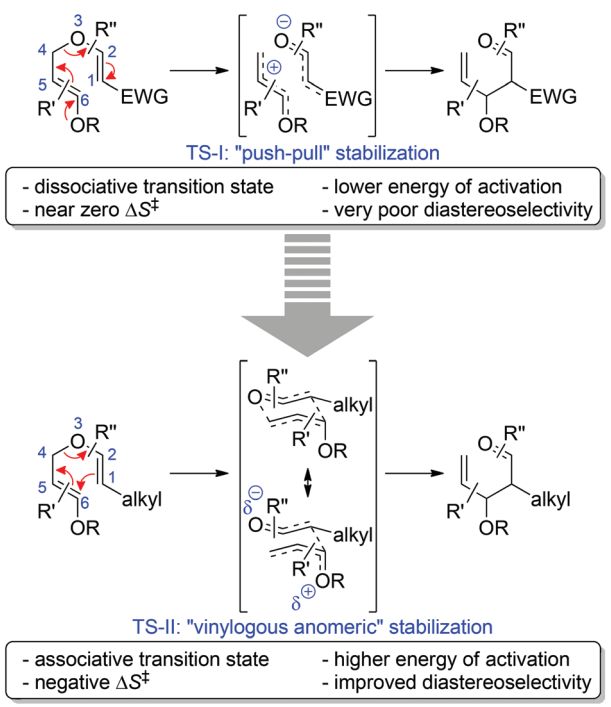
## Conclusion

Several lines of evidence described herein support the mechanistic hypothesis illustrated in Scheme 4. In this hypothesis, we view the aliphatic Claisen rearrangement of bis-vinyl ethers as taking place on a continuum between two mechanistic extremes: TS-I (the "push–pull" mechanism that we have principally focused on here) and TS-II (Curran's "vinylogous anomeric" model).

Bis-vinyl ethers like **5a–5g** and **19**, containing *both* an electron-withdrawing C-1 function *and* additional conjugation at C-6, are best described as rearranging through TS-I. This model explains the complete lack of diastereoselectivity for these reactions, as well as the observed substituent effects, near-zero entropy of activation, and large secondary isotope effect. TS-I is essentially a heterolytic fragmentation pathway, but crossover experiments confirm that the two fragments remain tightly associated, and cannot diffuse through solution. The $\Delta S^{\ddagger}$ measured for compounds **5** is particularly noteworthy; at +2.3 cal $K^{-1}$ $mol^{-1}$, this is the most positive $\Delta S^{\ddagger}$ ever reported for a non-catalyzed aliphatic Claisen rearrangement. We believe that this represents the first conclusive evidence of a fully dissociative transition state in a Claisen rearrangement, though earlier reports have suggested similar mechanistic hypotheses for unusually fast rearrangements.[22,72]

Although compounds lacking electron-withdrawing groups at C-1 (*e.g.*, **10** and **14**) are not the principal focus of this work (since these compounds have already been ably studied by others)[22,40] it appears that the inability for these compounds to stabilize an anion in the C-1–O-3 fragment of the allyl vinyl ether system does not permit these substrates to rearrange through a dissociative transition state; as a result, these compounds must react through a more traditional associative pathway as described earlier by Curran. This would explain the improved diastereoselectivity observed for the rearrangement of **14**, although non-linear effects make it more challenging to assess the thermodynamic properties for this rearrangement.

Substrate **13**, which has the ester substituent at C-1 to stabilize an anion in the transition state, but lacks the aromatic function to assist in additional resonance stabilization for the carbocation fragment in TS-I, might be said to occupy mechanistic space somewhere in the middle of this continuum. This compound rearranged with a substantial negative entropy of activation, but nonetheless afforded a modest diastereoselectivity and showed a large solvent effect – both hallmarks of a more dissociative transition state than experienced by those compounds lacking the C-1 ester function.




Scheme 4 Mechanistic proposal, accounting for differences in reactivity with different C-1 and C-6 substitution.

## Experimental

### General experimental procedures

All reactions were performed in oven- or flame-dried glassware, under a positive pressure of argon, unless otherwise indicated. Organic solutions were concentrated between 35–40 °C by rotary evaporation under vacuum. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (0.20 mm, 60 Å pore-size, 230–400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light followed by staining with potassium permanganate. Flash-column chromatography was performed over silica gel 60 (Caledon, 63–200 μM).

All reagents were used as received from Sigma Aldrich, unless otherwise indicated. Commercial solvents were used as received with the following exceptions. Anhydrous tetrahydrofuran was distilled from sodium/benzophenone prior to use. Dichloromethane was dried by passage through a column of alumina in a commercial solvent purification system (SPS). Triethylamine was distilled over calcium hydride and degassed by freeze–pump–thaw prior to use.

$^1$H chemical shifts are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent ($CDCl_3$: $\delta$ 7.26; $CD_3C(O)CD_3$: 2.05; $C_6D_6$: 7.16). Likewise, $^{13}$C chemical shifts are referenced to the carbon resonances of the solvent ($CDCl_3$: $\delta$ 77.22; $CD_3C(O)CD_3$: 29.85; $C_6D_6$: 128.06). Accurate masses were obtained using an orbitrap MS. Infrared spectra were collected using an FT-IR spectrometer.

### Synthesis of aryl-alkynoates (2a–g)

Aryl alkynoates were accessed from commercially available *para*-substituted aryl iodides following the general procedures described below for the Sonogashira coupling to trimethylsilylacetylene, followed by TBAF deprotection to the aryl acetylide and final acylation in the presence of ethyl or methyl chloroformate.

### General procedure for the Sonogashira coupling[73]

To a two-neck round bottom flask containing bis-(triphenylphosphine)palladium(II) dichloride (0.02 mmol), copper(I) iodide (0.04 mmol) and 1.8 mL of dry, degassed triethylamine, kept under an atmosphere of argon, was added the appropriate aryl iodide (1.00 mmol) followed by trimethylsilylacetylene (1.20 mmol). The reaction mixture was stirred at 60 °C for 5 h before being partitioned between ethyl acetate and water (1 : 1, 25 mL). The aqueous and organic phases were separated and the aqueous layer extracted twice with ethyl acetate. The combined organic extracts were washed with a saturated solution of NaCl (aq.), dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo*, and purified by flash column chromatography on silica gel to afford the corresponding, known alkynylsilanes, with spectral data that were in good agreement with the literature.

### General procedure for the TBAF deprotection of alkynylsilanes

Tetrabutylammonium fluoride (1.10 mmol) was added dropwise to a solution of trimethyl(arylethynyl)silane (1.00 mmol) in anhydrous tetrahydrofuran (2.4 mL) at 0 °C. After 20 min the reaction was quenched with a saturated solution of $NH_4Cl$ (aq.) and extracted three times with diethyl ether. The organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and then purified by flash column chromatography to afford the volatile phenyl acetylene derivatives used in the subsequent acylation step with ethyl or methyl chloroformate.

### General procedure for acylation of aryl alkynes[74]

*n*-BuLi (1.05 mmol, 2.5 M in hexanes) was added dropwise to a stirred solution of ethynylarene (1.00 mmol) in 1 mL of dry tetrahydrofuran at −78 °C. The mixture was reacted at −78 °C for 1.5 h followed by addition of ethyl chloroformate (1.20 mmol) and subsequently warmed to ambient temperature overnight (19 h). The reaction was quenched with a saturated solution of $NH_4Cl$ (aq.) and extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography on silica gel to afford known compounds **2a–g**.

### General procedure for conjugate addition

The alkyne (**2a–g**, ethyl propiolate or ethyl-2-butynoate, 1.00 mmol) was added dropwise to a stirred solution of alcohol (**1**, **4a–g**, **12** or **18**, 1.00 mmol) and trimethylphosphine (1.0 M in THF, 0.10 mmol) in dry dichloromethane (10 mL) at 0 °C and then warmed to room temperature overnight (18 h). The solvent was removed under vacuum, and the residue was re-suspended in diethyl ether (~5 mL). The resulting suspension was filtered through a thin layer of basic alumina, the filtrate was concentrated *in vacuo* and purified by flash column chromatography using silica gel pretreated with 1% triethylamine to afford the conjugate addition product **3a–g**, **5a–g**, **11**, **13** or **19** as clear colourless to yellow oils.

### General procedure for DIBAL-H reduction

Diisobutylaluminum hydride (1.0 M in hexanes, 2.20 mmol) was added dropwise to a stirred solution of ester (**3a–g**, **11** or **13**, 1.00 mmol) in diethyl ether[75] (15 mL) at −78 °C. After 1 h the reaction flask was moved to a −40 °C bath for an additional 2 h. The reaction mixture was poured into a vigorously stirred mixture of Rochelle's salt (0.5 M, 100 mL), diethyl ether (100 mL) and glycerol (0.2 mL mmol$^{-1}$ DIBAL-H). Vigorous stirring was maintained until the phases became clear, at which point the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography using silica gel pretreated with 1% triethylamine to afford alcohols **4a–g**, **12** and **13′** as clear colourless to yellow oils.

### Procedure for methylation of 13′

Following our procedure reported earlier,[46] iodomethane (3.00 mmol) was added dropwise *via* syringe to a stirred mixture of alcohol **13′** (1.00 mmol) in dry tetrahydrofuran (3.5 mL) at 0 °C. Sodium hydride (60% w/w in mineral oil, 3.00 mmol) was added in one portion to the reaction mixture and the resulting slurry was warmed to ambient temperature overnight (~18 h). The reaction was quenched with saturated $NH_4Cl$ (aq.) and 10% KOH (aq.) and extracted twice with diethyl ether. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and

purified by flash column chromatography using silica gel pretreated with 1% triethylamine to afford methyl ether **14** as a clear, colourless oil.

### Procedure for preparation of 1,1,1-trifluoro-4-methoxy-4-(4-methylphenyl)-3-buten-2-one (17)[70]

To a stirred solution of 4-methylacetophenone dimethylacetal **16**[76] (1.00 mmol) and pyridine (2.00 mmol) in chloroform (1.0 mL) at 0 °C was added trifluoroacetic anhydride (2.00 mmol) dropwise. The resulting reaction mixture was warmed to ambient temperature and then heated at 45 °C overnight (16 h). The reaction mixture was cooled and then quenched by addition of 0.1 M HCl (~2 mL). The aqueous and organic phases were separated. The organic layer was washed with 0.1 M HCl (2 × 2.5 mL), then water (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification was achieved by filtration through a plug of basic alumina to afford **17** as a bright yellow solid.

### Synthesis of 1,1,1-trifluoro-4-methoxy-4-(4-methylphenyl)-3-buten-2-ol (18)

Lithium aluminum hydride (1.50 mmol) was added in one portion to a stirred solution of **17** (1.00 mmol) in dry diethyl ether (20 mL) at 0 °C. After 20 min the reaction was quenched with 10% KOH (aq.) and then extracted with diethyl ether (2 × 15 mL). The combined organic extracts were washed with a saturated solution of NaCl (aq.), dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by flash column chromatography using silica gel pretreated with 1% triethylamine to afford **18** as a clear, colourless oil.

### General procedure for kinetic measurements

A solution of bis-vinyl ether (0.01 mmol) in the specified solvent (0.5 mL) spiked with an internal standard (0.005 M hexamethylbenzene or 0.010 M 1,4-dioxane for $R^A$ = aryl or alkyl, respectively) was added to a 5 mm NMR tube and the progress of the reaction monitored by $^1$H NMR spectroscopy over time at 500 MHz in an instrument pre-equilibrated to the temperature indicated (±1 °C). Plots of $[A]_t/[A]_o$ *vs.* $t$ were obtained for **5** or **13**, where $[A]_t$ is the integral for the observed protons in the starting bis-vinyl ether (the average of the ∑(vinyl ether olefins)) normalized to the internal standard, and $[A]_o$ is the sum of the normalized integrals for the starting bis-vinyl ether and rearrangement product (using the ∑(*alpha*-protons) for both diastereomers produced). By-products produced in the reaction (*i.e.* elimination products) were also accounted for in the calculation of $[A]_o$, based on normalized signals for the terminal olefin. First-order rate constants, $k$, were obtained by fitting the data to equation $[A]_t = [A]_o e^{-kt} + B$ using linear least squares analysis.[77] The activation energy was calculated directly from $k$ using the Eyring equation, $\Delta G^{\ddagger} = RT[\ln(k_B/h) - \ln(k/T)]$. Eyring and Arrhenius parameters were also generated from the resulting $k$ values, and associated error in thermodynamic properties determined on the basis of error associated with the slope and intercept for the data set were obtained using the XLfit statistical analysis package.

**Ethyl 3-(4-methoxyphenyl)propiolate (2a).**[78] Clear, colorless oil (943 mg, 91% yield); $R_f$ = 0.53 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 9.1 Hz, 2H), 6.88 (d, $J$ = 9.1 Hz, 2H), 4.29 (q, $J$ = 7.2 Hz, 2H), 3.84 (s, 3H), 1.35 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.7 (C), 154.6 (C), 135.1 (CH), 114.5 (CH), 111.6 (C), 87.1 (C), 80.4 (C), 62.1 ($CH_2$), 55.6 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 3-(4-methylphenyl)propiolate (2b).**[78] Clear, yellow oil (2.30 g, 95% yield); $R_f$ = 0.57 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 8.2 Hz, 2H), 7.17 (d, $J$ = 7.9 Hz, 2H), 4.29 (q, $J$ = 7.1 Hz, 2H), 2.37 (s, 3H), 1.35 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 154.4 (C), 141.5 (C), 133.2 (CH), 129.5 (CH), 116.7 (C), 86.8 (C), 80.6 (C), 62.2 ($CH_2$), 21.9 ($CH_3$), 14.3 ($CH_3$).

**Ethyl 3-(4-fluorophenyl)propiolate (2e).**[78] Orange solid (1.42 g, 96% yield); $R_f$ = 0.52 (hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.59 (dd, $J$ = 9.1, 5.3 Hz, 2H), 7.07 (t, $J$ = 8.6 Hz, 2H), 4.30 (q, $J$ = 7.1 Hz, 2H), 1.35 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.1 (d, $J_{C-F}$ = 254.0 Hz, CF), 154.2 (C), 135.4 (d, $J_{C-F}$ = 8.8 Hz, CH), 116.3 (d, $J_{C-F}$ = 22.2 Hz, CH), 116.0 (d, $J_{C-F}$ = 3.3 Hz, C), 85.2 (C), 80.8 (C), 62.4 ($CH_2$), 14.3 ($CH_3$).

**Ethyl 3-(4-chlorophenyl)propiolate (2f).**[78] Orange solid (1.74 g, 80% yield); $R_f$ = 0.59 (hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.51 (d, $J$ = 8.5 Hz, 2H), 7.36 (d, $J$ = 8.5 Hz, 2H), 4.31 (q, $J$ = 7.1 Hz, 2H), 1.36 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 153.9 (C), 137.1 (C), 134.2 (CH), 129.1 (CH), 118.2 (C), 84.7 (C), 81.6 (C), 62.3 ($CH_2$), 14.2 ($CH_3$).

**Ethyl 3-(4-(trifluoromethyl)phenyl)propiolate (2g).**[79] Brown-orange oil (295 mg, 84% yield); $R_f$ = 0.61 (10 : 4 : 1 hexanes–dichloromethane–diethyl ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 8.5 Hz, 2H), 7.64 (d, $J$ = 8.5 Hz, 2H), 4.32 (q, $J$ = 7.1 Hz, 2H), 1.37 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 153.8 (C), 133.3 (CH), 132.6 (C), 125.7 (q, $J_{C-F}$ = 3.7 Hz, CH), 123.7 (C), 123.4 (q, $J_{C-F}$ = 272.7 Hz, $CF_3$), 84.0 (C), 82.5 (C), 62.6 ($CH_2$), 14.3 ($CH_3$).

**Ethyl 3-(4-methoxyphenyl)-3-(neopentyloxy)acrylate (3a).** Clear, pale yellow oil (465 mg, 94% yield, 15 : 1 $E$ : $Z$); $R_f$ = 0.52 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.58 (d, $J$ = 9.1 Hz, 2H, major), 7.45 (d, $J$ = 9.1 Hz, 2H, minor), 7.00 (d, $J$ = 8.8 Hz, 2H, major), 6.92 (d, $J$ = 9.1 Hz, 2H, minor), 5.44 (s, 1H, major), 5.19 (s, 1H, minor), 4.12 (q, $J$ = 7.1 Hz, 2H, major), 3.98 (q, $J$ = 7.1 Hz, 2H, minor), 3.86 (s, 3H, major), 3.84 (s, 3H, minor), 3.69 (s, 2H, major), 3.65 (s, 2H, minor), 1.25 (t, $J$ = 7.0 Hz, 3H, major), 1.13 (t, $J$ = 7.0 Hz, 3H, minor), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 168.6 (C), 165.4 (C), 162.4 (C), 129.8 (CH), 128.7 (C), 114.8 (CH), 98.5 (CH), 83.2 ($CH_2$), 59.8 ($CH_2$), 55.8 ($CH_3$), 33.3 (C), 26.8 ($CH_3$), 14.8 ($CH_3$); IR (neat, $cm^{-1}$) 2957 (m), 2904 (w), 2870 (w), 2839 (w), 1716 (s), 1606 (s), 1512 (s), 1253 (s), 1156 (s), 1098 (s), 1032 (m), 836 (m), 666 (w); HRMS (ESI) calcd for $C_{17}H_{24}O_4 + Na^+$ 315.1567, found 315.1564.

**Ethyl 3-(neopentyloxy)-3-*p*-tolylacrylate (3b).** Clear, yellow oil (915 mg, 99% yield, 17 : 1 $E$ : $Z$); $R_f$ = 0.63 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.51 (d, $J$ = 8.2 Hz, 2H), 7.27 (d, $J$ = 7.9 Hz, 2H), 5.45 (s, 1H), 4.13 (q, $J$ = 7.1 Hz, 2H), 3.67 (s, 2H), 2.37 (s, 3H), 1.25 (t, $J$ = 7.2 Hz, 3H),

1.02 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 168.7 (C), 165.3 (C), 141.3 (C), 133.7 (C), 130.1 (CH), 128.2 (CH), 99.4 (CH), 83.1 ($CH_2$), 59.8 ($CH_2$), 33.3 (C), 26.8 ($CH_3$), 21.3 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 3030 (w), 2957 (s), 2870 (s), 1713 (s), 1621 (s), 1273 (s), 1154 (s), 1097 (s), 1040 (s), 820 (s), 727 (w); HRMS (ESI) calcd for $C_{17}H_{24}O_3$ + $Na^+$ 299.1618, found 299.1615.

**Methyl 3-(neopentyloxy)-3-phenylacrylate (3d).** Clear, pale yellow oil (437 mg, 94% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.42 (hexanes–ethyl acetate, 9 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.64–7.59 (m, 2H), 7.49–7.44 (m, 3H), 5.50 (s, 1H), 3.67 (s, 2H), 3.66 (s, 3H), 1.02 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 168.7 (C), 165.6 (C), 136.4 (C), 131.1 (CH), 129.5 (CH), 128.2 (CH), 99.7 (CH), 83.1 ($CH_2$), 51.0 ($CH_3$), 33.3 (C), 26.7 ($CH_3$); IR (neat, cm$^{-1}$) 3056 (w), 2955 (s), 2870 (m), 1722 (s), 1622 (s), 1275 (s), 1156 (s), 1099 (s), 1015 (m), 777 (m), 699 (m); HRMS (ESI) calcd for $C_{15}H_{20}O_3$ + $Na^+$ 271.1305, found 271.1305.

**Ethyl 3-(4-fluorophenyl)-3-(neopentyloxy)acrylate (3e).** Clear, orange oil (1.71 g, 82% yield, 13 : 1 *E* : *Z*); $R_f$ = 0.72 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.69 (dd, *J* = 9.1, 5.3 Hz, 2H), 7.22 (t, *J* = 8.9 Hz, 2H), 5.49 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 167.2 (C), 165.2 (C), 164.7 (d, $J_{C-F}$ = 248.6 Hz, CF), 132.9 (d, $J_{C-F}$ = 3.3 Hz, C), 130.5 (d, $J_{C-F}$ = 8.3 Hz, CH), 116.4 (d, $J_{C-F}$ = 22.1 Hz, CH), 100.0 (CH), 83.3 ($CH_2$), 60.0 ($CH_2$), 33.3 (C), 26.8 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2958 (s), 2871 (m), 1716 (s), 1621 (s), 1508 (s), 1261 (m), 1157 (s), 1097 (m), 1040 (w), 842 (m); HRMS (ESI) calcd for $C_{16}H_{21}FO_3$ + $Na^+$ 303.1367, found 303.1366.

**Ethyl 3-(4-chlorophenyl)-3-(neopentyloxy)acrylate (3f).** Clear, orange oil (936 mg, 89% yield, 13 : 1 *E* : *Z*); $R_f$ = 0.65 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.66 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 5.54 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 166.8 (C), 165.1 (C), 136.5 (C), 135.3 (C), 129.8 (CH), 129.7 (CH), 100.5 (CH), 83.4 ($CH_2$), 60.1 ($CH_2$), 33.3 (C), 26.8 ($CH_3$), 14.7 ($CH_3$); IR (neat, cm$^{-1}$) 2957 (s), 2870 (m), 1716 (s), 1621 (s), 1489 (s), 1260 (s), 1161 (s), 1092 (s), 836 (s); HRMS (ESI) calcd for $C_{16}H_{21}ClO_3$ + $Na^+$ 319.1071, found 319.1070.

**Ethyl 3-(4-(trifluoromethyl)phenyl)-3-(neopentyloxy)acrylate (3g).** Clear, orange oil (658 mg, 78% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.50 (hexanes–diethyl ether, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.88 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 5.65 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 166.1 (C), 165.1 (C), 140.5 (C), 132.0 (q, $J_{C-F}$ = 32.4 Hz, C), 128.9 (CH), 126.4 (q, $J_{C-F}$ = 3.7 Hz, CH), 125.1 (q, $J_{C-F}$ = 271.1 Hz, $CF_3$), 101.8 (CH), 83.5 ($CH_2$), 60.2 ($CH_2$), 33.3 (C), 26.7 ($CH_3$), 14.7 ($CH_3$); IR (neat, cm$^{-1}$) 2960 (m), 2904 (w), 2872 (w), 1717 (s), 1616 (s), 1324 (s), 1169 (s), 1130 (s), 1067 (s), 848 (w), 666 (w); HRMS (ESI) calcd for $C_{17}H_{21}F_3O_3$ + $Na^+$ 353.1335, found 353.1336.

**3-(4-Methoxyphenyl)-3-(neopentyloxy)prop-2-en-1-ol (4a).** Clear, colourless oil (339 mg, 97% yield, 18 : 1 *E* : *Z*); $R_f$ = 0.22 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.41 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.38 (t, *J* = 6.7 Hz, 1H), 4.33 (dd, *J* = 6.6, 5.7 Hz, 2H), 3.81 (s, 3H), 3.52 (t, *J* = 5.6 Hz, 1H), 3.28 (s, 2H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 160.7 (C), 155.2 (C), 129.3 (C), 128.3 (CH), 114.6 (CH), 113.6 (CH), 81.6 ($CH_2$), 57.3 ($CH_2$), 55.6 ($CH_3$), 33.0 (C), 26.9 ($CH_3$); IR (neat, cm$^{-1}$) 3367 (br, m), 2955 (s), 2901 (m), 2868 (m), 2825 (w), 1655 (w), 1608 (s), 1510 (s), 1249 (s), 1173 (s), 1033 (s), 967 (w), 837 (m); HRMS (ESI) calcd for $C_{15}H_{22}O_3$ + $Na^+$ 273.1461, found 273.1462.

**3-(Neopentyloxy)-3-*p*-tolylprop-2-en-1-ol (4b).** Clear, colourless oil (389 mg, 82% yield, 20 : 1 *E* : *Z*); $R_f$ = 0.33 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.37 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.44 (t, *J* = 6.6 Hz, 1H), 4.34 (d, *J* = 6.7 Hz, 2H), 3.56 (br s, 1H), 3.28 (s, 2H), 2.33 (s, 3H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 155.4 (C), 138.7 (C), 134.2 (C), 129.9 (CH), 126.9 (CH), 114.6 (CH), 81.6 ($CH_2$), 57.3 ($CH_2$), 33.0 (C), 26.9 ($CH_3$), 21.2 ($CH_3$); IR (neat, cm$^{-1}$) 3325 (br, s), 3027 (w), 2955 (s), 2868 (s), 1652 (s), 1511 (s), 1057 (s), 1019 (s), 968 (s), 825 (s), 803 (w), 770 (w), 722 (w); HRMS (ESI) calcd for $C_{15}H_{22}O_2$ + $Na^+$ 257.1512, found 257.1513.

**3-(Neopentyloxy)-3-*p*-tolylprop-2-en-1,1-dideuterio-1-ol (4b-*d*$_2$).** Clear, pale yellow oil (116 mg, 75% yield, 14 : 1 *E* : *Z*); $R_f$ = 0.30 (hexanes–dichloromethane–diethyl ether, 5 : 5 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.37 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.43 (s, 1H), 3.51 (br s, 1H), 3.28 (s, 2H), 2.33 (s, 3H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 155.6 (C), 138.7 (C), 134.2 (C), 129.9 (CH), 126.9 (CH), 114.4 (CH), 81.6 ($CH_2$), 33.0 (C), 27.0 ($CH_3$), 21.2 ($CH_3$); IR (neat, cm$^{-1}$) 3344 (br, s), 3027 (w), 2955 (s), 2918 (m), 2968 (m), 1651 (m), 1510 (m), 1316 (m), 1062 (m), 1019 (w), 823 (m); HRMS (ESI) calcd for $C_{15}H_{20}D_2O_2$ + $Na^+$ 259.1637, found 259.1636.

**3-(Neopentyloxy)-3-phenylprop-2-en-1-ol (4d).** Clear, colorless oil (334 mg, 98% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.60 (hexanes–ethyl acetate, 2 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.51–7.46 (m, 2H), 7.41–7.31 (m, 3H), 5.50 (t, *J* = 6.7 Hz, 1H), 4.36 (dd, *J* = 6.7, 5.6 Hz, 2H), 3.60 (t, *J* = 5.6 Hz, 1H), 3.29 (s, 2H), 1.02 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 155.3 (C), 137.0 (C), 129.3 (CH), 129.0 (CH), 126.9 (CH), 115.4 (CH), 81.6 ($CH_2$), 57.3 ($CH_2$), 33.0 (C), 26.9 ($CH_3$); IR (neat, cm$^{-1}$) 3338 (m, br), 3059 (w), 2956 (s), 2899 (s), 2868 (s), 1652 (m), 1363 (m), 1057 (s), 1028 (s), 755 (m), 698 (m); HRMS (ESI) calcd for $C_{14}H_{20}O_2$ + $Na^+$ 243.1355, found 243.1355.

**3-(4-Fluorophenyl)-3-(neopentyloxy)prop-2-en-1-ol (4e).** Clear, orange-yellow oil (319 mg, 88% yield, 14 : 1 *E* : *Z*); $R_f$ = 0.21 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.52 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.14 (t, *J* = 8.9 Hz, 2H), 5.48 (t, *J* = 6.6 Hz, 1H), 4.35 (dd, *J* = 6.4, 5.6 Hz, 2H), 3.63 (t, *J* = 5.6 Hz, 1H), 3.29 (s, 2H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 163.5 (d, $J_{C-F}$ = 245.4 Hz, CF), 154.3 (C), 133.4 (d, $J_{C-F}$ = 3.3 Hz, C), 128.9 (d, $J_{C-F}$ = 8.5 Hz, CH), 116.1 (d, $J_{C-F}$ = 21.4 Hz, CH), 115.4 (CH), 81.7 ($CH_2$), 57.3 ($CH_2$), 33.0 (C), 26.9 ($CH_3$); IR (neat, cm$^{-1}$) 3335 (br, s), 3048 (w), 2956 (s), 2904 (s), 2869 (s), 1652 (s), 1604 (s), 1507 (s), 1055 (s), 842 (s); HRMS (ESI) calcd for $C_{14}H_{19}FO_2$ + $Na^+$ 261.1261, found 261.1260.

**3-(4-Chlorophenyl)-3-(neopentyloxy)prop-2-en-1-ol (4f).** Clear, yellow oil (409 mg, 99% yield, 15 : 1 *E* : *Z*); $R_f$ = 0.31 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.51 (d, $J$ = 8.8 Hz, 2H), 7.41 (d, $J$ = 8.8 Hz, 2H), 5.56 (t, $J$ = 6.7 Hz, 1H), 4.35 (dd, $J$ = 6.4, 5.6 Hz, 2H), 3.65 (t, $J$ = 5.6 Hz, 1H), 3.30 (s, 2H), 1.02 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 154.1 (C), 135.8 (C), 134.2 (C), 129.4 (CH), 128.4 (CH), 116.2 (CH), 81.8 ($CH_2$), 57.2 ($CH_2$), 33.0 (C), 26.9 ($CH_3$); IR (neat, cm$^{-1}$) 3325 (br, m), 2956 (s), 2868 (m), 1652 (m), 1488 (s), 1092 (s), 1054 (s), 1014 (s), 966 (m), 836 (m), 789 (w); HRMS (ESI) calcd for $C_{14}H_{19}ClO_2$ + $Na^+$ 277.0966, found 277.0965.

**3-(Neopentyloxy)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (4g).** Clear, pale yellow oil (214 mg, 86% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.24 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.72 (s, 4H), 5.71 (t, $J$ = 6.6 Hz, 1H), 4.39 (dd, $J$ = 6.4, 5.6 Hz, 2H), 3.73 (t, $J$ = 5.7 Hz, 1H), 3.32 (s, 2H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 153.7 (C), 140.9 (C), 130.2 (q, $J_{C-F}$ = 32.4 Hz, C), 127.3 (CH), 126.2 (q, $J_{C-F}$ = 4.1 Hz, CH), 125.3 (q, $J_{C-F}$ = 271.2 Hz, $CF_3$), 118.1 (CH), 82.0 ($CH_2$), 57.3 ($CH_2$), 33.0 (C), 26.9 ($CH_3$); IR (neat, cm$^{-1}$) 3325 (br, m), 2959 (m), 2906 (m), 2871 (m), 1651 (w), 1618 (w), 1327 (s), 1128 (s), 1069 (s), 967 (w), 852 (m); LRMS (ESI) calcd for 2($C_{15}H_{19}F_3O_2$) + $K^+$ 615.23, found 615.33.

**Ethyl 3-(3-(4-methoxyphenyl)-3-(neopentyloxy)allyloxy)but-2-enoate (5a).** Clear, colourless oil (73.0 mg, 99% yield, 9 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.44 (d, $J$ = 8.8 Hz, 2H), 6.96 (d, $J$ = 8.8 Hz, 2H), 5.36 (t, $J$ = 7.0 Hz, 1H), 5.20 (s, 1H), 4.64 (d, $J$ = 7.0 Hz, 2H), 4.07 (q, $J$ = 7.1 Hz, 2H), 3.83 (s, 3H), 3.34 (s, 2H), 2.27 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.4 (C), 168.1 (C), 161.2 (C), 158.9 (C), 128.8 (CH), 128.4 (C), 114.8 (CH), 106.3 (CH), 92.0 (CH), 81.6 ($CH_2$), 63.8 ($CH_2$), 59.5 ($CH_2$), 55.6 ($CH_3$), 33.0 (C), 26.9 ($CH_3$), 19.2 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2956 (s), 2901 (m), 2869 (w), 2838 (w), 1711 (s), 1621 (s), 1511 (s), 1250 (s), 1141 (s), 1055 (s), 838 (m), 818 (m); HRMS (ESI) calcd for $C_{21}H_{30}O_5$ + $Na^+$ 385.1985, found 385.1984.

**Ethyl 3-(3-(neopentyloxy)-3-*p*-tolylallyloxy)but-2-enoate (5b).** Clear, colourless oil (56.8 mg, 100% yield, 9 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.40 (d, $J$ = 8.2 Hz, 2H), 7.22 (d, $J$ = 7.9 Hz, 2H), 5.41 (t, $J$ = 6.9 Hz, 1H), 5.20 (s, 1H), 4.66 (d, $J$ = 7.0 Hz, 2H), 4.08 (q, $J$ = 7.1 Hz, 2H), 3.34 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.3 (C), 168.1 (C), 159.0 (C), 139.6 (C), 133.3 (C), 130.0 (CH), 127.4 (CH), 107.2 (CH), 92.1 (CH), 81.6 ($CH_2$), 63.8 ($CH_2$), 59.5 ($CH_2$), 33.1 (C), 26.9 ($CH_3$), 21.2 ($CH_3$), 19.2 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2956 (m), 2898 (m), 2869 (m), 1712 (s), 1621 (s), 1274 (m), 1142 (s), 1056 (s), 825 (m); HRMS (ESI) calcd for $C_{21}H_{30}O_4$ + $Na^+$ 369.2036, found 369.2034.

**Ethyl 3-(1,1-dideuterio-3-(neopentyloxy)-3-*p*-tolylallyloxy)but-2-enoate (5b-*d*$_2$).** Clear, pale yellow oil (36.9 mg, 97% yield, 8 : 1 *E* : *Z*); $^1$H NMR (500 MHz, $(CD_3)_2CO$) $\delta$ 7.39 (d, $J$ = 8.5 Hz, 2H), 7.22 (d, $J$ = 7.9 Hz, 2H), 5.41 (s, 1H), 5.20 (s, 1H), 4.07 (q, $J$ = 7.1 Hz, 2H), 3.35 (s, 2H), 2.35 (s, 3H), 2.26 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (125 MHz, $(CD_3)_2CO$) $\delta$ 172.4 (C), 168.1 (C), 159.1 (C), 139.6 (C), 133.3 (C), 130.1 (CH), 127.4 (CH), 107.1 (CH), 92.1 (CH), 81.6 ($CH_2$), 59.5 ($CH_2$), 33.1 (C), 26.9 ($CH_3$), 21.2 ($CH_3$), 19.2 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2956 (m), 2869 (m), 1712 (s), 1621 (s), 1279 (m), 1144 (s), 1069 (s), 824 (m); HRMS (ESI) calcd for 2($C_{21}H_{28}D_2O_4$) + $Na^+$ 719.4431, found 719.4432.

**Ethyl 3-(3-(neopentyloxy)-3-*p*-tolylallyloxy)acrylate (5c).** Clear, pale yellow oil (60.2 mg, 100% yield, 9 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.65 (d, $J$ = 12.6 Hz, 1H), 7.40 (d, $J$ = 8.2 Hz, 2H), 7.23 (d, $J$ = 7.9 Hz, 2H), 5.43 (t, $J$ = 7.3 Hz, 1H), 5.31 (d, $J$ = 12.6 Hz, 1H), 4.72 (d, $J$ = 7.3 Hz, 2H), 4.10 (q, $J$ = 7.1 Hz, 2H), 3.34 (s, 2H), 2.35 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 167.7 (C), 163.0 (CH), 159.8 (C), 139.7 (C), 133.1 (C), 130.1 (CH), 127.5 (CH), 106.9 (CH), 97.5 (CH), 81.7 ($CH_2$), 66.4 ($CH_2$), 59.9 ($CH_2$), 33.0 (C), 26.9 ($CH_3$), 21.2 ($CH_3$), 14.7 ($CH_3$); IR (neat, cm$^{-1}$) 2957 (m), 2869 (m), 1712 (s), 1639 (m), 1623 (s), 1130 (s), 1056 (s), 827 (m), 666 (m); HRMS (ESI) calcd for $C_{20}H_{28}O_4$ + $Na^+$ 355.1880, found 355.1880.

**Ethyl 3-(3-(neopentyloxy)-3-phenylallyloxy)but-2-enoate (5d).** Clear, colorless oil (40.2 mg, 98% yield, 9 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.54–7.49 (m, 2H), 7.46–7.37 (m, 3H), 5.48 (t, $J$ = 7.0 Hz, 1H), 5.21 (s, 1H), 4.68 (d, $J$ = 7.0 Hz, 2H), 4.07 (q, $J$ = 7.1 Hz, 2H), 3.36 (s, 2H), 2.27 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.3 (C), 168.1 (C), 158.9 (C), 136.1 (C), 129.7 (CH), 129.4 (CH), 127.4 (CH), 108.1 (CH), 92.1 (CH), 81.7 ($CH_2$), 63.8 ($CH_2$), 59.5 ($CH_2$), 33.1 (C), 26.9 ($CH_3$), 19.1 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2957 (s), 2905 (m), 2869 (m), 1712 (s), 1621 (s), 1273 (s), 1141 (s), 1056 (s), 818 (m), 767 (m), 699 (m); HRMS (ESI) calcd for $C_{20}H_{28}O_4$ + $Na^+$ 355.1880, found 355.1878.

**Ethyl 3-(3-(4-fluorophenyl)-3-(neopentyloxy)allyloxy)but-2-enoate (5e).** Clear, pale yellow oil (65.5 mg, 87% yield, 7 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.56 (dd, $J$ = 8.9, 5.4 Hz, 2H), 7.18 (t, $J$ = 8.8 Hz, 2H), 5.47 (t, $J$ = 7.0 Hz, 1H), 5.20 (s, 1H), 4.66 (d, $J$ = 6.7 Hz, 2H), 4.08 (q, $J$ = 7.1 Hz, 2H), 3.35 (s, 2H), 2.27 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.9 (C), 168.1 (C), 163.9 (d, $J_{C-F}$ = 245.4 Hz, CF), 157.9 (C), 132.5 (d, $J_{C-F}$ = 3.2 Hz, C), 129.5 (d, $J_{C-F}$ = 8.6 Hz, CH), 116.3 (d, $J_{C-F}$ = 22.1 Hz, CH), 108.2 (CH), 92.2 (CH), 81.8 ($CH_2$), 63.7 ($CH_2$), 59.5 ($CH_2$), 33.1 (C), 26.9 ($CH_3$), 19.1 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2958 (m), 2905 (w), 2871 (w), 1711 (s), 1622 (s), 1507 (m), 1271 (m), 1229 (m), 1141 (s), 1053 (s), 953 (w), 843 (m), 818 (m); HRMS (ESI) calcd for $C_{20}H_{27}FO_4$ + $Na^+$ 373.1786, found 373.1783.

**Ethyl 3-(3-(4-fluorophenyl)-3-(neopentyloxy)allyloxy)pent-2-enoate (5e′).** Clear, yellow oil (55.4 mg, 88% yield, 6 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.57 (dd, $J$ = 8.9, 5.4 Hz, 2H), 7.19 (t, $J$ = 8.9 Hz, 2H), 5.49 (t, $J$ = 6.9 Hz, 1H), 5.14 (s, 1H), 4.66 (d, $J$ = 7.0 Hz, 2H), 4.08 (q, $J$ = 7.0 Hz, 2H), 3.36 (s, 2H), 2.75 (q, $J$ = 7.4 Hz, 2H), 1.22 (t, $J$ = 7.2 Hz, 3H), 1.09 (t, $J$ = 7.5 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 177.1 (C), 167.8 (C), 163.9 (d, $J_{C-F}$ = 246.5 Hz, CF), 158.0 (C), 132.6 (d, $J_{C-F}$ = 3.3 Hz, C), 129.5 (d, $J_{C-F}$ = 8.0 Hz, CH), 116.3 (d, $J_{C-F}$ = 22.0 Hz, CH), 108.2 (CH), 91.3 (CH), 81.9 ($CH_2$), 63.7 ($CH_2$), 59.6 ($CH_2$), 33.1 (C), 26.9 ($CH_3$), 26.1 ($CH_2$), 14.8 ($CH_3$), 12.3 ($CH_3$); IR (neat, cm$^{-1}$) 2971 (m), 2958 (m), 2904 (w), 2870 (w),

1712 (s), 1620 (s), 1508 (s), 1377 (m), 1228 (m), 1141 (s), 1053 (s), 843 (m), 822 (m); HRMS (ESI) calcd for $2(C_{21}H_{29}FO_4) + Na^+$ 751.3992, found 751.3991.

**Ethyl 3-(3-(4-chlorophenyl)-3-(neopentyloxy)allyloxy)but-2-enoate (5f).** Clear, pale yellow oil (120 mg, 82% yield, 8 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.53 (d, $J$ = 8.8 Hz, 2H), 7.44 (d, $J$ = 8.8 Hz, 2H), 5.54 (t, $J$ = 7.0 Hz, 1H), 5.20 (s, 1H), 4.67 (d, $J$ = 7.0 Hz, 2H), 4.08 (q, $J$ = 7.1 Hz, 2H), 3.36 (s, 2H), 2.27 (s, 3H), 1.22 (t, $J$ = 7.0 Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.2 (C), 168.0 (C), 157.6 (C), 135.0 (C), 134.9 (C), 129.6 (CH), 128.9 (CH), 109.0 (CH), 92.2 (CH), 81.9 ($CH_2$), 63.6 ($CH_2$), 59.5 ($CH_2$), 33.0 (C), 26.8 ($CH_3$), 19.1 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2957 (m), 2869 (w), 1711 (s), 1621 (s), 1272 (m), 1142 (s), 1054 (s), 839 (w), 818 (w); HRMS (ESI) calcd for $C_{20}H_{27}ClO_4 + Na^+$ 389.1490, found 389.1486.

**Ethyl 3-(3-(neopentyloxy)-3-(4-(trifluoromethyl)phenyl)-allyloxy)but-2-enoate (5g).** Clear, colourless oil (86.9 mg, 99% yield, 11 : 1 *E* : *Z*); $^1$H NMR (500 MHz, $(CD_3)_2CO$) $\delta$ 7.76 (s, 4H), 5.69 (t, $J$ = 6.8 Hz, 1H), 5.21 (s, 1H), 4.71 (d, $J$ = 7.2 Hz, 2H), 4.08 (q, $J$ = 7.2 Hz, 2H), 3.39 (s, 2H), 2.28 (s, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H), 1.05 (s, 9H); $^{13}$C NMR (125 MHz, $(CD_3)_2CO$) $\delta$ 172.2 (C), 168.0 (C), 157.2 (C), 140.1 (C), 130.9 (q, $J_{C-F}$ = 32.4 Hz, C), 127.9 (CH), 126.4 (q, $J_{C-F}$ = 3.8 Hz, CH), 125.2 (q, $J_{C-F}$ = 271.3 Hz, $CF_3$), 110.8 (CH), 92.3 (CH), 82.0 ($CH_2$), 63.6 ($CH_2$), 59.6 ($CH_2$), 33.1 (C), 26.8 ($CH_3$), 19.1 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2959 (s), 2866 (m), 1713 (s), 1622 (s), 1326 (s), 1273 (m), 1141 (s), 1068 (s), 1017 (m), 852 (w), 819 (w); HRMS (ESI) calcd for $C_{20}H_{25}F_3O_4 + Na^+$ 409.1597, found 409.1600.

**Ethyl 3-(neopentyloxy)but-2-enoate (11).** Clear, colorless oil (1.88 g, 92% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.56 (hexanes–ethyl ether, 9 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 5.02 (s, 1H), 4.06 (q, $J$ = 7.0 Hz, 2H), 3.48 (s, 2H), 2.27 (s, 3H), 1.20 (t, $J$ = 7.0 Hz, 3H), 0.99 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.8 (C), 168.1 (C), 91.8 (CH), 78.5 ($CH_2$), 59.5 ($CH_2$), 31.9 (C), 26.7 ($CH_3$), 18.9 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2959 (m), 2871 (w), 1713 (s), 1623 (s), 1281 (m), 1139 (s), 1056 (s), 817 (w); HRMS (ESI) calcd for $C_{11}H_{20}O_3 + H^+$ 201.1485, found 201.1486.

**3-(Neopentyloxy)but-2-en-1-ol (12).** Clear, colorless oil (257 mg, 79% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.32 (hexanes–ethyl ether, 1 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 4.65 (t, $J$ = 7.3 Hz, 1H), 4.04 (dd, $J$ = 7.3, 5.6 Hz, 2H), 3.29 (s, 2H), 3.19 (t, $J$ = 5.6 Hz, 1H), 1.80 (s, 3H), 0.95 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 156.5 (C), 98.5 (CH), 77.1 ($CH_2$), 59.0 ($CH_2$), 31.9 (C), 26.9 ($CH_3$), 16.3 ($CH_3$); IR (neat, cm$^{-1}$) 3330 (br, s), 2956 (s), 2902 (s), 2870 (s), 1661 (s), 1245 (s), 1080 (s), 986 (s), 841 (w), 792 (m); HRMS (ESI) calcd for $C_9H_{18}O_2 + Na^+$ 181.1199, found 181.1201.

**Ethyl 3-(3-(neopentyloxy)but-2-enyloxy)but-2-enoate (13).** Clear, colourless oil (82.0 mg, 96% yield containing 10% Claisen rearrangement product, >20 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 5.08 (s, 1H), 4.72 (t, $J$ = 7.6 Hz, 1H), 4.40 (d, $J$ = 7.6 Hz, 2H), 4.08 (q, $J$ = 7.1 Hz, 2H), 3.38 (s, 2H), 2.25 (s, 3H), 1.88 (s, 3H), 1.23 (t, $J$ = 7.2 Hz, 3H), 0.99 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 172.6 (C), 168.1 (C), 160.0 (C), 92.3 (CH), 91.9 (CH), 77.5 ($CH_2$), 66.2 ($CH_2$), 59.4 ($CH_2$), 32.0 (C), 26.9 ($CH_3$), 19.2 ($CH_3$), 16.6 ($CH_3$), 14.8 ($CH_3$); IR (neat, cm$^{-1}$) 2957 (s), 2904 (m), 2870 (m), 1712 (s), 1664 (m), 1619 (s), 1390 (m), 1272 (m), 1212 (m), 1132 (s), 1035 (s), 939 (w), 815 (w); HRMS (ESI) calcd for $C_{15}H_{26}O_4 + Na^+$ 293.1723, found 293.1719.

**3-(3-(Neopentyloxy)but-2-enyloxy)but-2-en-1-ol (13′).** Clear, yellow oil (146 mg, 80% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.36 (hexanes–ethyl acetate, 2 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 4.71 (t, $J$ = 7.8 Hz, 1H), 4.66 (t, $J$ = 7.2 Hz, 1H), 4.18 (d, $J$ = 7.6 Hz, 2H), 4.05 (dd, $J$ = 7.5, 5.4 Hz, 2H), 3.34 (s, 2H), 3.19 (t, $J$ = 5.6 Hz, 1H), 1.83 (s, 3H), 1.77 (s, 3H), 0.96 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 158.5 (C), 156.2 (C), 98.6 (CH), 93.6 (CH), 77.3 ($CH_2$), 64.2 ($CH_2$), 59.0 ($CH_2$), 32.0 (C), 26.9 ($CH_3$), 16.6 ($CH_3$); IR (neat, cm$^{-1}$) 3419 (br, m), 2956 (s), 2869 (s), 1661 (s), 1479 (m), 1204 (s), 1079 (s), 936 (m), 900 (m), 783 (w); HRMS (ESI) calcd for $C_{13}H_{24}O_3 + Na^+$ 251.1618, found 251.1618.

**1-Methoxy-3-(3-(neopentyloxy)but-2-enyloxy)but-2-ene (14).** Clear, colourless oil (64.9 mg, 70% yield, >20 : 1 *E* : *Z*); $R_f$ = 0.54 (hexanes–ethyl acetate, 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 4.67 (t, $J$ = 7.2 Hz, 1H), 4.62 (t, $J$ = 7.2 Hz, 1H), 4.21 (d, $J$ = 7.3 Hz, 2H), 3.88 (d, $J$ = 7.3 Hz, 2H), 3.34 (s, 2H), 3.21 (s, 3H), 1.83 (s, 3H), 1.78 (s, 3H), 0.96 (s, 9H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 158.6 (C), 157.8 (C), 94.9 (CH), 93.5 (CH), 77.3 ($CH_2$), 69.2 ($CH_2$), 64.4 ($CH_2$), 56.9 ($CH_3$), 32.0 (C), 26.9 ($CH_3$), 16.8 ($CH_3$), 16.6 ($CH_3$); IR (neat, cm$^{-1}$) 2956 (s), 2923 (s), 2892 (s), 2869 (s), 2813 (w), 1661 (s), 1479 (m), 1389 (s), 1207 (s), 1070 (s), 1048 (s), 946 (w), 901 (w), 782 (w); HRMS (ESI) calcd for $C_{14}H_{26}O_3 + Na^+$ 265.1774, found 265.1774.

**1,1,1-Trifluoro-4-methoxy-4-(4-methylphenyl)-3-buten-2-one (17).**[80] Yellow solid (500 mg, 71% yield, 9 : 1 *E* : *Z*); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.68 (d, $J$ = 8.2 Hz, 2H, minor), 7.43 (d, $J$ = 8.2 Hz, 2H, major), 7.34 (d, $J$ = 7.9 Hz, 2H, minor), 7.24 (d, $J$ = 8.2 Hz, 2H, major), 6.20 (s, 1H, minor), 5.97 (s, 1H, major), 4.09 (s, 3H, minor), 4.04 (s, 3H, major), 2.41 (s, 3H, minor), 2.38 (s, 3H, major); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 179.6 (C), 177.6 (q, $J_{C-F}$ = 32.8 Hz, C), 144.0 (C), 132.2 (C), 130.4 (CH, minor), 130.0 (CH, major), 129.4 (CH, major), 129.3 (CH, minor), 117.9 (q, $J_{C-F}$ = 292.6 Hz, $CF_3$), 95.7 (CH, minor), 92.3 (CH, major), 63.3 ($CH_3$, minor), 58.3 ($CH_3$, major), 21.5 ($CH_3$).

**1,1,1-Trifluoro-4-methoxy-4-*p*-tolylbut-3-en-2-ol (18).** Clear, colourless oil (130 mg, 93% yield, 14 : 1 *E* : *Z*); $R_f$ = 0.15 (hexanes–dichloromethane–diethyl ether, 10 : 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.40 (d, $J$ = 8.2 Hz, 2H, minor), 7.34 (d, $J$ = 8.2 Hz, 2H, major), 7.24 (d, $J$ = 7.9 Hz, 2H, major), 7.11 (d, $J$ = 7.9 Hz, 2H, minor), 5.12 (d, $J$ = 6.2 Hz, 1H), 4.88 (d, $J$ = 10.2 Hz, 1H), 4.51–4.38 (m, 1H), 3.72 (s, 3H, major), 3.54 (s, 3H, minor), 2.36 (s, 3H, major, minor); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 163.7 (C), 140.0 (C), 133.2 (C), 129.7 (CH), 129.4 (CH), 126.6 (q, $J_{C-F}$ = 281.2 Hz, $CF_3$), 94.1 (q, $J_{C-F}$ = 2.2 Hz, CH), 69.2 (q, $J_{C-F}$ = 31.6 Hz, CH), 55.8 ($CH_3$), 21.3 ($CH_3$); IR (neat, cm$^{-1}$) 3391 (br, s), 3009 (w), 2942 (m), 2839 (w), 1652 (s), 1355 (s), 1270 (s), 1171 (s), 1128 (s), 1106 (s), 1038 (s), 977 (w), 857 (m), 827 (m), 743 (m), 695 (s), 668 (w); LRMS (ESI) calcd for $C_{12}H_{13}F_3O_2 + H^+$ 247.09, found 247.07.

**Ethyl 3-(1,1,1-trifluoro-4-methoxy-4-*p*-tolylbut-3-en-3-yloxy)-acrylate (19).** Clear, pale yellow oil (69.7 mg, 100% yield, 4 : 1

E : Z); $R_f$ = 0.35 (hexanes–dichloromethane–ethyl ether, 10 : 4 : 1); $^1$H NMR (300 MHz, $(CD_3)_2CO$) $\delta$ 7.38 (d, $J$ = 12.0 Hz, 1H), 7.34–7.35 (m, 4H), 5.16 (d, $J$ = 12.3 Hz, 1H), 5.02 (dq, $J$ = 10.2, 6.0 Hz, 1H), 4.98 (d, $J$ = 10.2 Hz, 1H), 4.08 (qd, $J$ = 7.1, 0.7 Hz, 2H), 3.81 (s, 3H), 2.39 (s, 3H), 1.21 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $(CD_3)_2CO$) $\delta$ 167.3 (C), 167.0 (C), 160.2 (CH), 140.7 (C), 132.4 (C), 130.2 (CH), 129.5 (CH), 124.9 (q, $J_{C-F}$ = 279.0 Hz, $CF_3$), 100.8 (CH), 89.9 (CH), 78.6 (q, $J_{C-F}$ = 32.4 Hz, CH), 60.2 ($CH_2$), 56.5 ($CH_3$), 21.3 ($CH_3$), 14.6 ($CH_3$); IR (neat, cm$^{-1}$) 3031 (w), 2982 (m), 2941 (m), 2841 (w), 1714 (s), 1645 (s), 1370 (m), 1322 (m), 1274 (s), 1179 (s), 1128 (s), 1043 (m), 1022 (m), 947 (m), 887 (w), 827 (m), 696 (m); HRMS (ESI) calcd for $C_{17}H_{19}F_3O_4$ + $Na^+$ 367.1128, found 367.1124.

**Representative Claisen product from 13**

Clear, colourless oil (1.00 : 1.74 dr[81]); $R_f$ = 0.35 (hexanes-dichloromethane-ethyl ether, 10 : 4 : 1); $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 6.13 (dd, $J$ = 17.6, 10.8 Hz, 1H, major), 5.91 (dd, $J$ = 17.9, 10.8 Hz, 1H, minor), 5.15 (dd, $J$ = 17.6, 1.5 Hz, 1H, major), 5.15 (dd, $J$ = 17.9, 1.3 Hz, 1H, minor), 5.11 (dd, $J$ = 10.1, 1.3 Hz, 1H, major), 5.09 (dd, $J$ = 10.8, 1.2 Hz, 1H, minor), 3.91 (m, 2H major, 2H minor), 3.82 (s, 1H, minor), 3.77 (s, 1H, major), 2.89 (d, $J$ = 10.2 Hz, 1H, major), 2.86 (d, $J$ = 10.8 Hz, 1H, major), 2.86 (d, $J$ = 10.8 Hz, 1H, minor), 2.83 (d, $J$ = 11.1 Hz, 1H, minor), 2.17 (s, 3H, minor), 2.11 (s, 3H, major), 1.56 (s, 3H, minor), 1.47 (s, 3H, major), 0.92 (t, $J$ = 7.1 Hz, 3H, major), 0.92 (t, $J$ = 7.1 Hz, 3H, minor), 0.89 (s, 9H, major), 0.86 (s, 9H, minor); $^{13}$C NMR (75 MHz, $C_6D_6$) $\delta$ 201.3 (C, minor), 200.6 (C, major), 167.5 (C, major), 167.4 (C, minor), 140.9 (CH, minor), 140.5 (CH, major), 117.0 ($CH_2$, minor), 116.6 ($CH_2$, major), 78.4 (C, minor), 77.9 (C, major), 72.0 ($CH_2$, minor), 71.9 ($CH_2$, major), 68.7 (CH, major), 68.1 (CH, minor), 60.8 ($CH_2$, major), 60.7 ($CH_2$, minor), 32.4 ($CH_3$, minor), 31.9 (C, major), 31.7 (C, minor), 31.5 ($CH_3$, major), 27.0 ($CH_3$), 19.9 ($CH_3$, major), 18.2 ($CH_3$, minor), 14.1 ($CH_3$); IR (neat, cm$^{-1}$) 2975 (m), 2955 (s), 2903 (m), 2869 (m), 1733 (s), 1716 (s), 1143 (s), 1071 (s), 927 (w); LRMS (ESI) calcd for $C_{15}H_{26}O_4$ + $Na^+$ 293.17, found 292.87.

## Acknowledgements

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada for operating funds, and for a fellowship to N.F.O. We are also grateful to the Canada Research Chairs program (CRC) and the Michael Smith Foundation for Health Research (MSFHR) for salary support to J.W., and to the University of Victoria for additional operating funds. Finally, we thank Dr Ori Granot and the UVic Genome BC Proteomics Centre for mass spectrometry support and Dr Christopher Barr for assistance with NMR experiments.

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65 The standard error for the slope of the line in the inset to Fig. 5 is 2.4 cal $K^{-1}$ $mol^{-1}$. Thus, the true $\Delta S^{\ddagger}$ may be said to lie between approximately 0 and 5 cal $K^{-1}$ $mol^{-1}$.
66 The presence of *gem*-dialkyl substituents at position 4 can also lead to a reduced $\Delta S^{\ddagger}$, by providing a higher degree of organization in the ground state. See ref. 18.
67 We are hesitant to ascribe too much meaning to the diastereomeric ratio observed in the rearrangement product, given that **6** and related structures could presumably undergo epimerization or diastereoselective decomposition under the reaction conditions. Nonetheless, for the substrates studied here, the diastereoselectivity of the product (when measured directly in the reaction mixture) appears to track with other measures of transition-state organization.
68 The diastereoselectivity of the rearrangement of **14** also appears to change over time, which lends additional support to the hypothesis that more than one mechanism is operative for this substrate.
69 An increase in $sp^2$ character at C-4 in the transition state (relative to the ground state) would be expected to contribute to a large secondary kinetic isotope effect, of the same sign and approximate size as that observed here. However, estimation of the maximum extent of this effect is difficult to predict, since the precise electronic role of the C-6 alkoxy substituent is not perfectly understood. It is possible that hyperconjugative effects owing to the presence of the C-6 alkoxy group lead to an inflated kinetic isotope effect.
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