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PAPER

Exploiting the vicinal disubstituent effect on the diastereoselective synthesis of γ and δ lactones†

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Trifluoroacetic acid catalysed lactonization of vicinal disubstituted γ-hydroxyesters was investigated in different solvents. The reaction kinetics, monitored by NMR spectroscopy, showed that: (i) the *vic*-disubstituent effect is stereoselective since the *anti* diastereoisomer ring closes substantially more rapidly than the *syn* isomer ring; (ii) the *anti-vic* effect is much stronger than the classical Thorpe–Ingold effect (known also as the *gem*-disubstituent effect), instead the *syn* diastereoisomers have rate constants comparable to that of the *gem*-disubstituted ester; (iii) the *vic*-effect can be enhanced by increasing the steric hindrance of one of the two substituents or carrying out the reaction in non-polar solvents. DFT computations of energy barriers ($\Delta G^{\ddagger}$) were in good agreement with the experimental data. The distortion/interaction-activation strain model together with the Winstein–Holness kinetic scheme gave more insights into the origin of the *vic*-effect. An application of this effect consists of the diastereomeric resolution of disubstituted γ and δ lactones, among which are the naturally occurring *Nicotiana t.* lactone, the whisky and cognac oak lactones, and the *Aerangis* lactone. Both *cis* and *trans* diastereoisomers of these lactones were isolated in good yield and with high diastereomeric excess (de >92%). The selectivities of the diastereomeric resolution process, determined by NMR spectroscopy, are reported as well.

Introduction

The rate of intramolecular reactions affording small to medium rings is often accelerated by introducing a geminal disubstituent group (C–CR_2–C) into a linear precursor (Fig. 1a). These different kinetic behaviours, often referred to as *gem*-disubstituent effects, were first studied by Thorpe and Ingold.[1,2] They concluded that, by increasing the R–C–R angle compression β arising from the mutual steric repulsion of the geminal substituents of the precursor, the terminal reactive groups should be brought into a more favourable orientation (decreasing of the α angle) for ring formation, and consequentially to an increase of both reaction rate and equilibrium constant (Fig. 1a).

An impressive example of this effect was found in the comparative rates of lactone formation from various 2-hydroxy phenyl propionic acid derivatives. The placement of a *gem*-dimethyl group accelerated the cyclization rate constant 400 times[3] with respect to the unsubstituted precursor and further substitution (trimethyl lock effect) speeded-up the ring closure by 5 orders of magnitude.[3b,c]

Incidentally, although the *gem*-disubstituent effect is consistently adopted in many fields of organic chemistry includ-

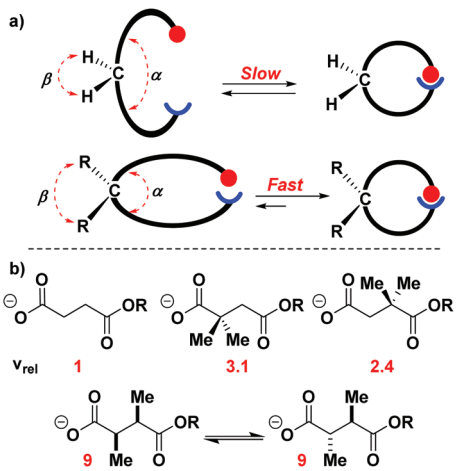

Fig. 1 (a) Explanation by internal angle reduction of the Thorpe–Ingold effect; (b) cyclization rates of succinate derivatives.

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†Electronic supplementary information (ESI) available: Experimental procedures, compound characterization, copies of ^{1}H-NMR and ^{13}C-NMR spectra of all compounds and Cartesian coordinates of all computed structures. See DOI: 10.1039/c8ob02715c

ing metal-catalysed cyclizations,[4] asymmetric catalyses,[5] peptide chemistry[6] and polymerizations,[7] its full comprehension is still largely debated, as shown by the numerous explanations that have been put forward in the last fifty years.[2]

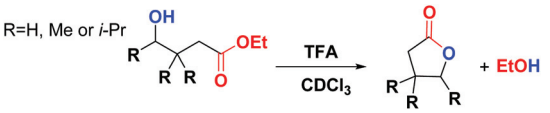
In contrast, and quite surprisingly, the effect produced by two substituents in a vicinal stereochemical relationship (the *vic*-disubstituent effect) has only been marginally considered.[2,8,9]

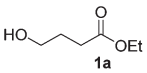
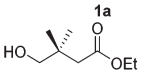
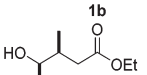
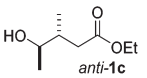
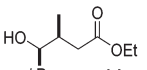
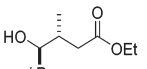
In the seventies Eberson *et al.* investigated the base catalysed cyclization of succinic acid derivatives: the reaction rate of the *vic*-dimethyl substituted succinates was found to be slightly greater than that of the *gem*-dimethyl isomers, but, it was not possible to determine which of the two diastereoisomers underwent faster ring closure, due to the *syn*/*anti* equilibrium (Fig. 1b).[9c]

However, concerning the *vic*-effect, some issues ought to be clarified. More precisely, is the ring closure rate acceleration (i) larger or smaller than that produced by a *gem*-substitution? (ii) Is it depending on the relative stereochemistry of the two vicinal substituents (*syn* or *anti*) of the linear precursor? (iii) How influential is the steric hindrance of the substituents? (iv) Has the solvent any effect on points (i) and (ii)?

Prompted by the above questions we decided to study the trifluoro acetic acid (TFA) catalysed lactonization of γ-hydroxyesters **1a–d** in different solvents (Chart 1), either by kinetic measurements or by DFT computations.

Table 1 Kinetics of TFA catalysed ring closure of γ-hydroxyesters **1a–d** in $CDCl_3$ at 303 K, and the relative experimental and computed energy barriers



Hydroxyester	k_r	$\delta\Delta G^{\ddagger}_{r,Exp}$ (kcal mol^{-1})	$\delta\Delta G^{\ddagger}_{r,Comp}$ (kcal mol^{-1})
 **1a**	1.0[a]	0.00	0.00
 **1b**	4.4[a]	−0.88	−1.08
 *syn*-**1c**	5.3	−1.00	−0.93
 *anti*-**1c**	99.4 (18.9)[b]	−2.77 (−1.77)[c]	−2.88 (−1.95)[c]
 *i*-Pr *syn*-**1d**	5.3	−1.00	—[d]
 *i*-Pr *anti*-**1d**	415.0 (78.4)[b]	−3.63 (−2.63)[c]	—[e]

[a] Data ref. 10. [b] Selectivity, $s = k_{anti}/k_{syn}$. [c] $\delta\Delta G^{\ddagger}_{anti-syn} = \Delta G^{\ddagger}_{anti} - \Delta G^{\ddagger}_{syn}$. [d] Not calculated. [e] Computations have been carried out only for the (1*Re*,3*S*,4*R*,g^+,*E*) isomer of *anti*-**1d**.

Results and discussion

Kinetic study

The ring closure reaction rates of hydroxyesters **1a–b** (in $CDCl_3$ at 303 K) have been recently determined by ^{1}H-NMR spectroscopy.[10] In the present work the kinetics of esters **1c–d** were analogously measured (see the ESI† for the preparation of esters). The data were analysed on the basis of a pseudo first-order reaction in the hydroxyester concentration [E], according to the following equation:

$$-d[E]/dt = k_2[E][TFA] = k_{obs}[TFA].$$

The observed reaction rate constants k_{obs} were obtained by linear regression of $\ln([E]/[E]_0)$ *vs.* time (for linear regression plots see the ESI†). In Table 1 are reported the rate constants ($k_r = k_{2,ester}/k_{2,\mathbf{1a}}$) and the Gibbs free energies of activation ($\delta\Delta G^{\ddagger}_{r,Exp} = -0.607 \ln k_r$) relative to the ring closure of the unsubstituted ester, *i.e.* **1a**.

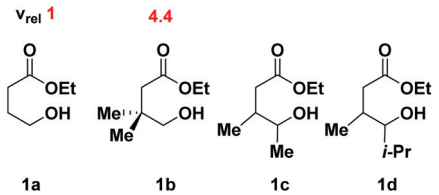


Chart 1 γ-Hydroxyesters examined for the study of the vicinal disubstituent effect.

The inspection of Table 1 shows that the rate constants k_r of the *vic*-disubstituted hydroxyesters **1c–d** are strongly influenced by the relative stereochemistry, being that the *anti* diastereoisomers cyclize always much more rapidly than the *syn* isomers. Evidently, the effect has to be related to the steric hindrance of the substituent, since by replacing the methyl at C(4) carbon with an i-Pr group, the selectivity ($s = k_{obs,anti}/k_{obs,syn}$) dramatically increases from 19 for **1c** up to an astonishing value of roughly $s = 80$ for **1d**.[11] On the other hand, the k_r of the *syn*-diastereoisomers are surprisingly very similar being unaffected by the steric hindrance of the substituent. Finally, the acceleration produced by a *syn* disubstitution is comparable to that of a *gem*-dimethyl group (the difference between the $\delta\Delta G^{\ddagger}_{r,Exp}$ of **1b** and **1c** or **1d** is just of 0.12 kcal mol^{-1}). Alternatively, the *anti-vic* disubstitution induces a much higher reaction rate enhancement; in the case of *anti*-**1d** it reaches the awesome value of 415.

Concerning point (iv), in Table 2 are reported the selectivity *s* of **1c** ($s = k_{obs,anti\text{-}\mathbf{1c}}/k_{obs,syn\text{-}\mathbf{1c}}$) and the corresponding differential energy barriers in different solvents.

The size of *s* changes significantly from aprotic solvents of different polarities to water. First, in water the ring closure of hydroxyesters occurs by specific acid catalysis (SAC), whereas, for aprotic solvents the cyclization goes through a general acid

Table 2 Kinetic data of TFA catalysed ring closure of **1c** at 303 K in different solvents

Solvent	Selectivity ($s = k_{obs,anti\text{-}\mathbf{1c}}/k_{obs,syn\text{-}\mathbf{1c}}$)	$\delta\Delta G^{\ddagger}_{r,Exp}$ (kcal mol^{-1})	ε_r [a]
C_6D_6	26.2	−1.97	2.28
$CDCl_3$	18.9	−1.77	4.81
d_3-MeCN	12.6	−1.52	36.64
D_2O	10.5	−1.41	78.54

[a] Dielectric constant.

catalysis (GAC),[10] thus, it is not surprising that the type of mechanism might have an influence on the extent of the *vic*-effect. Moreover, we observed that in less polar solvents, such as benzene, the *anti-vic*-effect is substantially stronger than in more polar solvents, *e.g.* MeCN. This behaviour is likely due to the strength of the H-bond interactions occurring between the ester (E) and the TFA in the catalytic complex ***CC*** (Fig. 2). In reverse, it is well known that by increasing the solvent's polarity the H-bond becomes weaker. At the most, in an H-bonding disrupting solvent such as DMSO we did not observe any reactivity.

Computational study

In our previous article[10] we performed a DFT computational study (model chemistry B3LYP/6-31G(d)/SCRF = SMD,[12–14] Gaussian09 software[15]), which established that the rate determining step (RDS) of the GAC ring closure of γ-hydroxyesters is the conversion of the catalytic complex ***CC*** into the tetrahedral intermediate ***TI1*** through a transition state ***TS1***‡ (Fig. 2, for the complete catalytic cycle see the ESI†). Moreover, we concluded that the different reaction rates are mainly related to enthalpy factors, and were well rationalized in terms of energy strain.

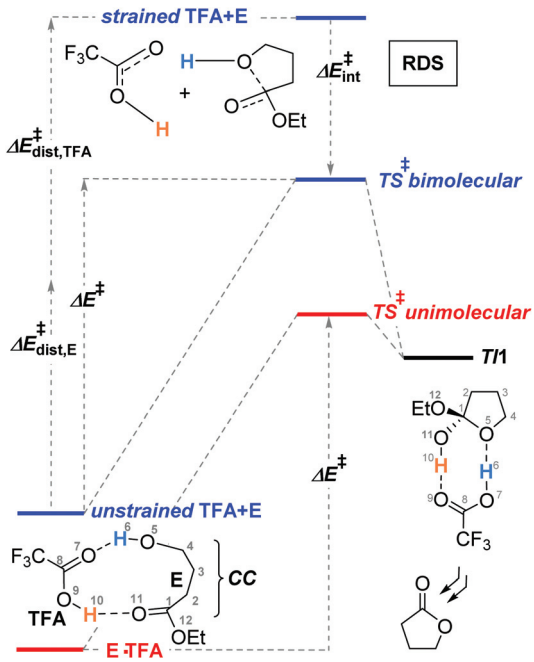


Fig. 2 Rate determining step of the TFA catalysed ring closure of γ-hydroxyester **1a**, and D/I-A decomposition of $\Delta E^{\ddagger}$ for unimolecular reactions.

In the present study we adopted the same model chemistry previously used: each species of the RDS exists as a mixture of different stereoisomers that we classified in relation to the conformational and stereochemical configurations (Fig. ESI3†). For instance, *syn*-(3*R*,4*R*)-***CC*-1c** is distributed into 8 energetically different stereoisomers: (1*Re*,g^+,*E*), (1*Re*,g^+,*Z*), (1*Si*,g^+,*E*), (1*Si* g^+,*Z*), (1*Re*,g^-,*E*), (1*Re*,g^-,*Z*), (1*Si*,g^-,*E*), and (1*Re*,g^-,*Z*).[16] The stereo descriptors g^+/g^- are related to the sign of the torsional angle τ[OC(1)C(2)C(3)], while *E* or *Z* to the angle τ[EtO(12)C(1)O(11)H(10)]. Finally, the 1*Re*/1*Si* face is relative to the CO carbonyl group prochirality: for achiral esters **1a–b** was chosen arbitrarily 1*Re*, whereas for chiral **1c** we arbitrarily analysed all the stereoisomeric subsets of the *syn*-(3*R*,4*R*)-**1c** and the *anti*-(3*S*,4*R*)-**1c** diastereoisomers. For all esters, we found that the *E* conformers of ***CC*** are thermodynamically more stable than the *Z* isomers, for instance the Boltzmann distribution analysis of all stereoisomers of *anti*-(3*S*,3*R*)-***CC*-1c** indicates that (1*Re*,g^-,*E*) and (1*Re*,g^+,*E*) have a molar fraction of x = 49.1% and x = 32.9%, respectively.

For each stereoisomer of the catalytic complex we found the corresponding ***TS1***‡ (checked by IRC analysis, see the ESI†) and ***TI1***, and then each rate constant k was calculated with Eyring's equation. Thus, it was possible to determine the mean rate constant k_w of each stereoisomeric subset by the Winstein–Holness equation ($k_w = \sum x_i\, k_i$).[17] Finally, the ensemble free energy barrier $\Delta G^{\ddagger}_{Comp.}$ was calculated by Eyring's equation. Using this approach, the differential computed Gibbs energy barriers $\delta\Delta G^{\ddagger}_{r,Comp}$ correlated very well with the experimental values $\delta\Delta G^{\ddagger}_{r,Exp}$ (coefficient of determination R^2 = 0.99, Fig. ESI4†).

In Table 3 we report the computed Gibbs energy barriers $\Delta G^{\ddagger}$ of each conformer of esters **1b** and *anti*-**1c**, together with the molar fractions x of the ***CC***, the rate constants k and the weighted rate constants ($x \times k$); remarkably the ratio between the two k_w was very close to the experimental value (20 *vs.* 23).

However, the *anti-vic* disubstituent effect takes its origin by the fact that for the hydroxyester *anti*-**1c** the ***CC*** conformer with the lowest energy barrier, *i.e.* (1*Si*,g^+,*E*), is also the one mostly populated (x = 49.1%). Inversely, even if one of the conformers of the *gem*-dimethyl ester **1b** has in absolute the lowest energy barrier, *i.e.* (1*Re*,g^-,*E*) with $\Delta G^{\ddagger}$ = 11.95 kcal mol^{-1}, its reacting ground state is scarcely populated (x = 0.2%). In addition, the rotamer of *gem*-dimethyl ester **1b** with the highest molar fraction, *i.e.* (1*Re*,g^+,*E*), is associated with a chemical path with a much higher energy barrier ($\Delta G^{\ddagger}$ = 15.22 kcal mol^{-1}).

Interestingly, by the joined effect of these molar fractions and rate constants, the lactonization of *anti*-**1c** goes mainly through the (1*Si*,g^-,*E*) stereoisomer (over 98%), whereas for **1b**, among all possible chemical paths, the ring closure occurs predominantly through the conformers with an *E* conformation. Thus, in this case, the advantage of the *anti-vic* effect over the

Table 3 Computed Gibbs energy barriers, molar fractions and rate constants relative to the RDS of lactonization of **1b** and *anti*-**1c**

Ester	Configuration	x^a (%)	$\Delta G^{\ddagger}$ (kcal mol^{-1})	k^b (s^{-1})	$x \times k$ (s^{-1})	$x \times k/k_w$ (%)
1b	(1*Re*,g^+,*E*)	85.2	15.22	66.8	57.0	67.0
	(1*Re*,g^+,*Z*)	5.8	15.98	19.0	1.1	1.3
k_w 85.0 (s^{-1})	(1*Re*,g^-,*E*)	0.2	11.95	1.53×10^4	25.7	30.3
	(1*Re*, g^-,*Z*)	8.8	16.19	13.4	1.18	1.4
anti-**1c** [c]	(1*Re*,g^+,*Z*)	0.2	16.09	16.0	0.04	<0.1
	(1*Re*,g^-,*E*)	32.9	15.17	72.8	24.0	1.4
	(1*Re*,g^-,*Z*)	14.4	15.63	33.9	4.9	0.3
k_w 1647 (s^{-1})	(1*Si*,g^+,*Z*)	0.8	14.40	262.6	2.1	0.1
	(1*Si*,g^-,*E*)	49.1	12.87	3341.7	1640.2	98.0
	(1*Si*,g^-,*Z*)	2.6	14.87	120.2	3.2	0.2

[a] By Boltzmann's distribution of ***CC***. [b] By Eyring's equation. [c] For (3*R*,4*S*)-**1c** we found six out of eight possible chemical paths, and trajectories associated with (g^+,*E*) conformations appear to be forbidden for steric reasons.

classical Thorpe–Ingold effect arises primarily from a more favourable synergy between high population and low energy barriers, in agreement with the stereo population control hypothesis of Cohen and Milstien.[3a] Such explanation is confirmed by the perceived lower efficacy of the *syn-vic* effect of *syn*-**1c**, which can be compared to that of **1b** (Table ESI4†).

Last but not least, if the k_w are calculated taking into account exclusively the enthalpy component of the $\Delta G^{\ddagger}$ the ratio $k_{w,anti\text{-}1c}/k_{w,1b}$ decreases to 6.1 ($\delta\Delta H^{\ddagger}$ = 1.09 kcal mol^{-1}, Table ESI5†), and this result shows that the entropy too plays an important role in the *anti-vic* effect.[18]

However, at this stage, we were more interested to rationalize the relation between the reactivity and substituent effects (either geminal or vicinal) in terms of energy without thermal corrections. To begin with, the Brønsted–Evans–Polany (BEP) plots of compounds **1a–d** showed a rough correlation between the energy barrier $\Delta E^{\ddagger}$ and the reaction energy ΔE_{rxn} (Fig. ESI5†);[19] however, when they were repeated for classes of conformers, *i.e.* (g^+,*E*), (g^-,*E*), (g^+,*Z*) and (g^-,*Z*), the R^2 improved significantly (Fig. 3 for (g^-,*E*) and Fig. ESI6 and ESI8–9† for the other conformational subsets).

This result suggests that, independent of the degree of substitution and of the regio-/stereochemistry of hydroxyester, each class of conformers has its own ring closure activation strain mode (*vide infra*).

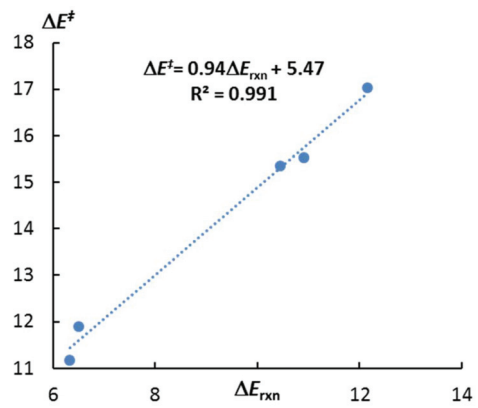


Fig. 3 Correlation between $\Delta E^{\ddagger}$ and ΔE_{rxn} for the (g^-,*E*) conformational subset; the energies are in kcal mol^{-1}.

Thenceforth, in order to gain more insights into the substituent effect, we carried out the analysis of the energy barrier by the distortion/interaction activation strain model (D/I-ASM) of Houk and Bickelhaupt,[20] an approach inspired by the pioneering work of Morokuma and Ziegler on the activation energy decomposition analysis[21] (EDA).

Essentially, in this model $\Delta E^{\ddagger}$ is decomposed as a sum of two contributions: $\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int}$. The distortion or strain energy $\Delta E^{\ddagger}_{dist}$ takes into account all structural deformations needed to transform the reagents, from their lowest energy conformations, into the structures adopted in the transition state. Instead, the interaction energy $\Delta E^{\ddagger}_{int}$ is more related to the electronic reorganization of the reagents needed to give the product. This activation energy barrier decomposition, originally conceived for bimolecular reactions, was ingeniously extended by Bickelhaupt to unimolecular reactions through the formal splitting of the reactant into two fragments.[22] Since our RDS is a unimolecular reaction, we followed that procedure by breaking the ***CC*** into the ester and TFA fragments (Fig. 2). Therefore, the total distortion energy is:

$$\Delta E^{\ddagger}_{dist} = \Delta E^{\ddagger}_{dist,E} + \Delta E^{\ddagger}_{dist,TFA}$$

where, $\Delta E^{\ddagger}_{dist,E} = E^{TS1}_{E} - E^{CC}_{E}$ and $\Delta E^{\ddagger}_{dist,TFA} = E^{TS1}_{TFA} - E^{CC}_{TFA}$.

In Fig. 4 we show the correlation of $\Delta E^{\ddagger}$ with the ester distortion energy $\Delta E^{\ddagger}_{dist,E}$ and with the TFA deformation energy $\Delta E^{\ddagger}_{dist,TFA}$ for the (g^-,*E*) subset of esters. We were particularly interested in this subset because it contains two of the most reactive conformers, *i.e.* (1*Re*,g^-,*E*)-**1b** ($\Delta E^{\ddagger}$ = 11.17 kcal mol^{-1}) and (1*Re*,3*R*,4*R*,g^-,*E*)-**1c** ($\Delta E^{\ddagger}$ = 11.90 kcal mol^{-1}).

It appears that $\Delta E^{\ddagger}$ is well correlated with the ester deformation energy $\Delta E^{\ddagger}_{dist,E}$ ($R^2 > 0.98$), while the energy spent to distort the TFA seems to have less influence on the different reaction rates. Indeed, the percent difference of $\Delta E^{\ddagger}_{dist,TFA}$ of the slowest ester, *i.e.* **1a**, with the fastest one, *i.e.* **1b**, is much lower than that of $\Delta E^{\ddagger}_{dist,E}$, 3% and 12%, respectively. Since the interaction energy $\Delta E^{\ddagger}_{int}$, similarly to the $\Delta E^{\ddagger}_{dist,TFA}$, is poorly correlated with the $\Delta E^{\ddagger}$, we can conclude that the GAC ring

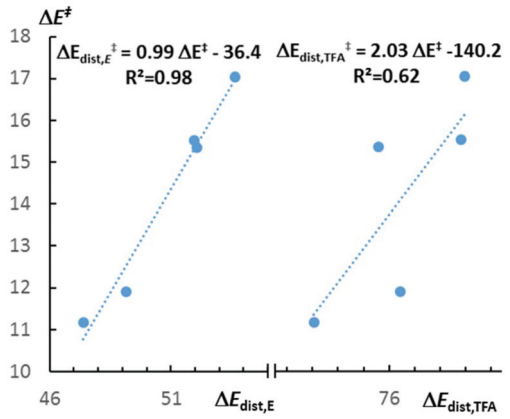


Fig. 4 Correlation between $\Delta E^{\ddagger}$ and distortion energies involved in the lactonization of (g^{-},*E*)-**1a–c** subset of conformers; the energies are in kcal mol^{-1}.

closure of γ-hydroxyesters is primarily an ester strain controlled process. The lactonization of the other conformational families of hydroxyesters showed analogous trends (see the ESI†).

We reckon that the ester distortion energy $\Delta E^{\ddagger}_{\mathrm{dist,E}}$ is mainly employed to bring the nucleophilic hydroxyl group closer to the electrophilic C=O through a complex scissoring movement during the transition state formation. To better illustrate this point in Fig. 5 we show both ***CC*** and ***TS*1**‡ ester fragments of the most reactive conformers of the (g^{-},*E*) subset together with some geometrical parameters (we omitted the ***TI*1** ester fragments representation, since the RDS goes through a late transition state). Certainly, this type of conformation somehow determines a different variation of the ring strain exerted by the substituents during the ***TS*1**‡ formation. However, even

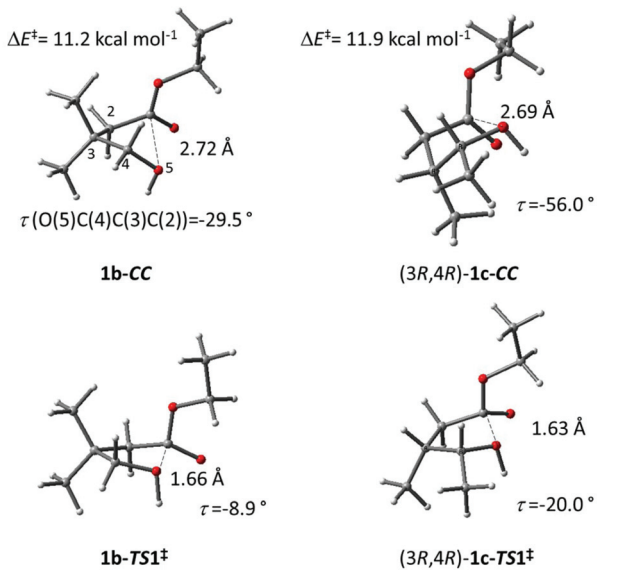


Fig. 5 Selected catalytic complex and transition state ester fragments of the (g^{-},*E*) subset.

inside of each conformational subset, the substituent effect cannot be related in a simple way to changes of individual geometrical parameters.[23] For instance, although (1*Re*,g^{-},*E*)-**1b** and (1*Re*,3*R*,4*R*,g^{-},*E*)-**1c** have energy barriers very similar, the differential dihedral angles $\Delta\tau$ ($\Delta\tau = \tau\ \boldsymbol{CC} - \tau\ \boldsymbol{TS1}^{\ddagger}$) are quite different, whereas the differential nucleophile–electrophile distance of 1.06 Å is more or less the same for all esters of this conformational subset. Reasonably, the molecular rearrangement of the ester from the unstrained state in the ***CC*** to the strained state in the ***TS*1**‡ is the result of several distortions, which overall cooperates with the scissoring process.

Diastereomeric resolution

As a final point, we show a practical application of the *vic*-disubstituent effect consisting of the diastereoselective synthesis of some of the most important naturally occurring cyclic esters such as the *Nicotiana tabacum* lactone, *i.e.* **2c**,[24] the whisky and cognac oak lactones, **2e** and **2f** respectively,[25] and the *Aerangis* lactone,[26] *i.e.* **2g**, and in addition the valero lactones **2h–i** (Fig. 6).

Interest on these compounds goes beyond the typical natural products' synthesis, since they possess unique olfac-

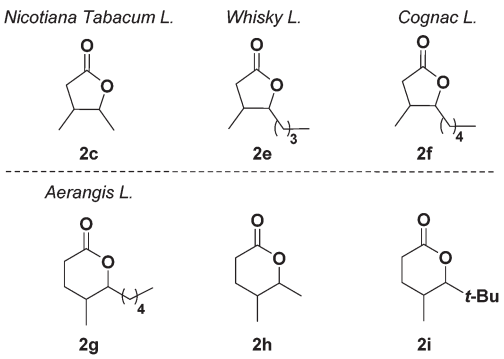
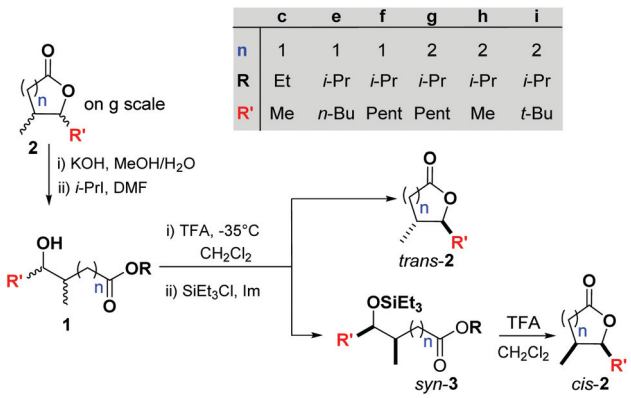


Fig. 6 Lactones subjected to the resolution based on the vicinal disubstituent effect.



Scheme 1 Diastereomeric resolution of γ- and δ-*vic*-disubstituted lactones.

Table 4 Diastereomeric excesses and yields of the kinetic resolution of *vic*-disubstituted γ and δ lactones carried out at −35 °C, together with the selectivity measured at 303 K

					Trans		*Cis*	
Ester	*n*	R′	R	Selectivity[a] ($s = k_{anti}/k_{syn}$)	Yield[b] (%)	De[c] (%)	Yield[d] (%)	De[c] (%)
1c	1	Me	Et	17.8 (42)[e]	80	94	69	99
1d	1	i-Pr	Et	78.4 (>250)[e]	—[f]	—	—	—
1e	1	*n*-Bu	i-Pr	21.7 (50)[e]	78	98	70	99
1f	1	*n*-Pent	i-Pr	—[g]	75	96	72	98
1g	2	*n*-Pent	i-Pr	—[g]	79	94	70	98
1h	2	Me	i-Pr	16.2 (34)[e]	83	92	70	98
1i	2	*t*-Bu	i-Pr	142 (>250)[e]	90[h]	92[h]	83[h]	98[h]

[a] The selectivity was determined at 303 K. [b] Yields are based upon isolated products relative to *anti*-**1**. [c] By ^{1}H-NMR. [d] Yields are based upon isolated products relative to *syn*-**1**, over three steps: (i) *O*-silylation, (ii) protective group cleavage and (iii) ring closure. [e] Selectivity calculated at 238 K. [f] No resolution has been carried out. [g] No kinetics have been carried out. [h] The resolution was accomplished without *O*-silylation.

tory properties. Indeed, these γ and δ lactones are key-ingredients of the flavours & fragrances industry. Moreover, the odour's perception of chiral odorant molecules often depends on the absolute stereochemical configuration,[27] however, it is not uncommon to find fragrances in which the odour threshold difference between the enantiomers is almost negligible, while for the diastereoisomers it is much more pronounced. For instance, the two diastereoisomers of *Aerangis* lactone **2g** have very different odour thresholds, and the perfume of the *cis* diastereoisomer is much more intense than the *trans* isomer.[27b] However, even if many asymmetric syntheses of these lactones have been reported,[26,27a,b,28] they are still produced at the industrial scale as racemic mixtures of the two diastereoisomers; this is likely due to the relatively low commercial value of these fragrances/flavours, which is still economically unfeasible with the actual costs of most of the stereoselective synthetic methodologies. Besides, chromatographic separations on a large scale are impractical as well.[29] Thus, a very cheap and efficient method for the resolution of diastereomeric mixtures of these lactones would be a highly desirable goal.

First, with the ethyl hydroxyester **1c** (*syn*/*anti* ≈ 1 : 1) in our hands, we tested the TFA catalysed diastereoselective ring closure in CH_2Cl_2 on a preparative scale (Scheme 1). In order to improve the diastereomeric excess of lactone *trans*-**2c** and of the unconsumed *syn*-**1c**, the reaction was carried out at −35 °C.

After that most of the hydroxyester *anti*-**1c** converted into the lactone *trans*-**2c**,[30] the reaction was quenched with imidazole and the unreacted isomer *syn*-**1c** was quantitatively *O*-silylated with $SiEt_3Cl$ affording the silyl ether **3**. Then, the latter was easily separated from the very polar lactone, *i.e.* *trans*-**2c**, by a column chromatography technique, or alternatively the two products could be separated by bulb-to-bulb distillation. Finally, the silyl ether **3** was quantitatively transformed into the lactone *cis*-**2c** by treatment with an excess of TFA in CH_2Cl_2. By adopting this procedure both *trans* and *cis* isomers of *Nicotiana tabacum* lactone were isolated with a high diastereomeric excess, de = 94% and 99%, respectively (Table 4).

For the resolution of lactones **2e–i** we found more convenient to work with the isopropyl hydroxyl esters, *i.e.* **1e–i**, since the latter are less reactive than the corresponding ethyl esters, which instead undergo cyclization too easily.[24] Thus, lactones **2e–i** (see the ESI† for the preparation of these substrates) were opened with KOH in MeOH to give the potassium carboxylate salt, which was then transformed into the isopropyl esters **2e–i** with i-PrI in DMF (Scheme 1).[31] The afforded esters were subjected directly to kinetic resolution without any purification; in Table 4 we report the selectivity (for the kinetic study of **2e** and **2g–i** see the ESI†), and both yield and diastereomeric excess of *cis* and *trans* lactones.

Table 4 shows that the des are in all cases very high (at worst de = 92%), and even when the resolution was applied to the synthesis of the less strained δ lactones (**2g–2i**) the results were still very satisfactory. The best des have been achieved for the *cis* lactones, since most of the hydroxyester mixtures were unbalanced in favour of the *syn*-isomer. Particularly significant is the case of **1i**, indeed, even by starting from a mixture of hydroxyester highly unreached of the *syn* diastereoisomer (*syn*-**1i**/*anti*-**1i**, 78 : 22 by ^{1}H-NMR) was still possible to isolate *trans*-**2i** with a good de of 92%.

Not surprisingly, the selectivity improved by increasing the steric hindrance of one of the two substituents, and emblematic is the case of **2h** and **2i**: by changing a methyl with a *t*-butyl group the selectivity improved by almost one order of magnitude, s = 16 and 142, respectively. Noteworthily, the hydroxyester *syn*-**1i** ring closes so slowly with respect to the *anti*-**1i** that the resolution was accomplished without the need for the *O*-silylating step. Indeed, in this case the unconsumed *syn* hydroxyester, *i.e.* *syn*-**1i**, and the *trans*-lactone, *i.e.* *trans*-**2i**, were directly separated by column chromatography.

Conclusion

To sum up, we found that the GAC lactonization rate of *vic*-disubstituted γ and δ-hydroxyesters is strongly influenced by the relative stereochemistry: the *syn-vic* effect is comparable to the classical *gem* disubstituent effect, whereas the *anti-vic* effect

overwhelms the latter by one order of magnitude at the worst. The rate acceleration can be amplified simply by increasing the steric hindrance of one of the two substituents: for instance, in the case of **1d** the rate is enhanced by a factor of almost two orders of magnitude relative to the ring closure of the *gem*-dimethyl hydroxyl ester. Computations suggest that the observed rate accelerations may be attributed, primarily, to a synergy between the population and the conformer reactivity, which for the *anti* diastereoisomers is much more favourable with respect to the *syn* or the *gem* isomers. These conclusions are in agreement with the stereo population hypothesis of Cohen and Milstien, and even though, entropic effects cannot be neglected. Moreover, we found a strong correlation between the ester strain energy and the activation barrier.

Clearly, the *vic*-effect opens a new paradigm in the field of generalized substituent effect, since it offers the possibility of controlling the ring closure rate through the relative stereochemistry of the substituents; and this is the real novelty with respect to the classical Thorpe–Ingold effect. We reckon that, as the *gem* disubstituent effect has undoubtedly played an important role for over 100 years in several fields of organic chemistry, the *vicinal* effect should provide further benefits. In this regard, the reported highly efficient diastereomeric resolution of the very important *Quercus* flavours and *Aerangis* l. fragrance is a preliminary example of the potentiality of the *vic*-disubstituent effect. Computational studies and further applications are ongoing in our laboratory and will be the subject of upcoming reports.

Experimental

General procedure for the diastereomeric resolution of lactones

Ring opening of lactones to give hydroxyesters. To an ice cooled and well stirred solution of lactone **2** (17.0 mmol) in MeOH (30 mL) was added a solution of KOH (19.0 mmol) in H_2O (3 mL). The heterogeneous mixture was stirred for 5 hours at room temperature and then concentrated under vacuum to give a viscous oil. The latter was treated with Et_2O (4 × 10 mL) and concentrated under reduced pressure. This procedure was repeated at least 4 times in such a way to eliminate all traces of H_2O and MeOH. The crude material was left under high vacuum for 6 hours. Then, to a solution of the crude mixture in anhydrous DMF (45 mL) was added 2-iodopropane (5.8 g, 34 mmol). After 14 hours, the reaction mixture was diluted with brine (sat., 70 mL) and then extracted with Et_2O (5 × 40 mL). The combined organic phase was washed with brine (sat., 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding hydroxyester **1**,[32] which was of sufficient purity[33] for the next step.

Procedure A: achievement of *trans*-lactones with high de. To a mixture of *syn*/*anti* hydroxyester **1** (23.4 mmol) in CH_2Cl_2 (60 mL) at – 35 °C was added a precooled solution of TFA (0.01 ÷ 0.1 eq.) in CH_2Cl_2 (2 mL) under a N_2 atmosphere. After the conversion of most of *anti*-**1** hydroxyester (checked by ^{1}H-NMR),[30] the reaction mixture was quenched with imidazole (2.0 eq.) and left to reach r.t., then the solvent was removed under reduced pressure to give a crude material, which was left for at least 15 min under high vacuum.[34] To a solution of the crude material in CH_2Cl_2 (30 mL) were added Et_3SiCl (1.1 eq. with respect to *anti*-**1**) and a catalytic amount of DMAP. After 12 hours, the reaction mixture was concentrated under reduced pressure and subjected to the column chromatography purification procedure using a gradient eluent (SiO_2, *n*-hexane/AcOt, 95 : 5 → 6 : 4) affording in order of elution the silyl derivative **3** and then *trans*-**2**; the latter was distilled with a bulb to bulb apparatus. Alternatively, the organic phase was diluted with CH_2Cl_2 (30 mL), washed with HCl (0.2 M, 2 × 30 mL) and brine (sat., 1 × 30 mL), dried over Na_2SO_4 and concentrated under vacuum. Finally, the lactone was isolated by distillation with a bulb to bulb apparatus.

Trans-4,5-dimethyldihydrofuran-2(3*H*)-one (*trans*-2c). Yield = 80% (0.94 g as a colourless liquid); b.p. 70–80 °C, 0.5 mmHg; purity 99% by GC (t_R = 6.58 min); de 94% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (tt, J = 7.1, 5.5, 3H), 2.76–2.57 (m, 1H), 2.27–2.08 (m, 2H), 1.41 (d, J = 6.2, 3H), 1.15 (d, J = 6.2, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.4, 83.5, 38.3, 37.4, 19.2, 16.9. GC-MS: m/z (%) 114 $[M]^+$ (10), 99 (20), 70 (60), 55 (50), 42 (100).[24]

Procedure B: achievement of *cis*-lactones with high de. This procedure is similar to that of procedure A; however a higher amount of TFA (0.15 eq.) was used, and the conversion of **1** into **2** was pushed over 50% (checked by ^{1}H-NMR),[29] and the *O*-silylation was carried out under the same conditions described for procedure A.

(*syn*)-Ethyl 3-methyl-4-((triethylsilyl)oxy)pentanoate (3c). Yield 78% (2.8 g as a colorless liquid); purity 98% by GC (t_R = 18.91 min); de 99% by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (q, J = 7.1, 2H), 3.81 (qd, J = 6.3, 3.5, 1H), 2.59–2.46 (m, 1H), 2.14–2.00 (m, 2H), 1.27 (t, J = 7.2, 3H), 1.09 (d, J = 6.3, 3H), 1.04–0.86 (m, 15H), 0.60 (td, J = 8.3, 7.7, 7H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.7, 70.8, 60.1, 37.5, 37.4, 20.0, 14.7, 14.3, 6.9, 5.2. GC-MS: m/z (%) 273 $[M - 1]^+$ (1), 259 (2), 245 (100); HRMS (quadrupole) calcd for $C_{12}H_{25}O_3Si^+$ $[M - Et]^+$ 245.1573, found 245.1572.

General procedure for the cleavage of *O*-silyl protective group

To a solution of **3** (1.0 mmol) in CH_2Cl_2 (5 mL) was added TFA (100 μL). After complete conversion of **3** into *cis*-**2**, checked by TLC, the reaction mixture was diluted with Et_2O (15 mL) and washed with a solution of $NaHCO_3$ (sat., 1 × 30 mL) and brine (sat., 1 × 20 mL). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the crude material was subjected to the bulb to bulb distillation apparatus affording *cis*-**2**.

***cis*-4,5-Dimethyldihydrofuran-2(3*H*)-one (*cis*-2c).** Yield = 89% (1.0 g as a colourless liquid); b.p. 73–81 °C, 0.5 mmHg; purity 98% by GC (t_R = 7.34 min); de 99% by ^{1}H-NMR; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.65 (m, 1H), 2.75–2.52 (m, 2H), 2.21 (dd, J = 16.6, 5.1, 1H), 1.29 (d, J = 6.5, 3H), 1.03 (d, J = 6.9, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 176.8, 79.7, 37.0, 33.5, 15.5,

14.0. MS: *m*/*z* (%) 114 $[M]^+$ (10), 99 (20), 70 (60), 55 (50), 42 (100).[24]

Kinetics. The reaction progress was monitored by measuring a series of ^{1}H-NMR (500 MHz) spectra recorded as pseudo 2D of a sample of hydroxyesters in $CDCl_3$ at 303 K allowing a fixed time delay between successive spectra. A pulse width of 30° and a relaxation delay of 2 s were used in order to avoid errors due to the relaxation. An exponential filter was applied to FID for optimization of the signal-to-noise ratio. Baseline correction was applied to spectra before integration. The bias and slope of integrals were carefully adjusted. The sample was prepared by adding directly, with a gastight Hamilton syringe, a solution of TFA in CH_2Cl_2 (20 ÷ 60 μL, 10^{-2} M) to a solution of hydroxyester (typically ≈8–10 mg each) in $CDCl_3$ (500.0 μL) into a NMR tube.

Conflicts of interest

There are no conflicts to declare.

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