gem-Disubstituent Effect: Theoretical Basis and Synthetic Applications

Michael E. Jung* and Grazia Piizzi*

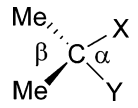
Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095-1569

Received June 2, 2004

Contents

1. Introduction

The *gem*-dialkyl effect is the name given to the acceleration of a cyclization due to the replacement of hydrogen atoms with alkyl groups on the carbons tethering the two reacting centers.[1] This effect has been known and studied for nearly a century, and several hypotheses on its origin have been posited. The first explanation, proposed in 1915 by Thorpe and Ingold,[2] postulated that the mutual repulsion of *gem*-dimethyl groups in an open carbon chain causes an increase in angle β with a simultaneous decrease in angle α:



This compression of the internal angle brings the X and Y groups closer together and thus promotes the cyclization ("Thorpe−Ingold effect").[3] If α is part of a small ring, this effect would also result in ring stabilization. However, this rate enhancement is not limited to the formation of strained rings but also exists in medium and large rings.[4] Therefore, in 1960 Bruice and Pandit suggested an alternative explanation for the enhanced rate of ring closure upon substitution.[5] They attributed the kinetic effect of the *gem*-dialkyl substitution to the increase in the population of reactive rotamers with the two ends properly oriented for the cyclization ("reactive rotamer effect"). In the same year, Allinger and Zalkow described in thermodynamic terms the magnitude and direction of the *gem*-dialkyl effect in the formation of cyclohexanes from hexanes.[6] Two contributions were identified: (i) due to the increased number of *gauche* interactions present in the open chain substrate compared with the cyclized product, the enthalpy favors the ring closure of substituted hexanes; and (ii) because branching reduces the rotation in the open chain more than that in the ring, thus increasing the ΔS, the entropy also favors ring closure. Consequently, the formation of substituted six-membered rings is promoted by a decrease in both $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ terms. Since these pioneering contributions, a multitude of theoretical and experimental investigations have been described in the literature in an attempt to interpret the effect of geminal substitution with dialkyl or other groups (*gem*-disubstituent effect). The goal of this review is to provide a comprehensive overview of both the early and the more recent theories on the topic. Examples of the applicability of this promoting effect for the cyclization of both simple and complex rings continue

10.1021/cr940337h CCC: $53.50
Published on Web 05/11/2005

Michael Jung was born in New Orleans, LA, in 1947. He received his Ph.D. from Columbia University in 1973 working as a synthetic organic chemist with Gilbert Stork and continued his postdoctoral training as a NATO Postdoctoral Fellow in 1973–1974 at the Eidgenössische Technische Hochschule (ETH) in Zürich with Albert Eschenmoser. He has been a professor in the Department of Chemistry and Biochemistry at the University of California, Los Angeles (UCLA), since 1974. He has long had strong interests in the development of useful synthetic methods and the total synthesis of biologically active natural and unnatural products. Thus, the Jung research group develops new synthetic methods to prepare complex natural products and their analogues and carries out structure–activity relationships on pharmaceutically active species. In the past few years, the Jung group has become much more interested in the development of new lead candidates for the treatment of human diseases. Professor Jung has published over 230 articles and is an author on over 13 patents. He has given nearly 450 invited lectures and is a synthetic consultant for more than 15 industrial research sites.

Grazia Piizzi received her laurea in pharmaceutical chemistry from the University "La Sapienza", in Rome, Italy, in 1998. She then moved to the University of California, Los Angeles (UCLA), where she worked on the total synthesis of ouabain under the direction of Prof. Michael E. Jung. In 2004, after receiving her Ph.D. in organic chemistry from UCLA, she moved to the Massachusetts Institute of Technology, where she is currently working with Prof. Mohammad Movassaghi as postdoctoral fellow.

to appear in the literature and will also be presented. The rate enhancement resulting from the replacement of hydrogen atoms on the carbon tethering two reacting centers with alkyl or other substituents has been widely used in organic synthesis, and several of these examples will also be discussed in this review. In addition, the biological implications for the *gem*-disubstitution in the mechanism of enzymatic catalysis and the numerous applications in the design of new pharmaceutical agents will be described.

2. Theoretical Basis

In general, intramolecular reactions occur more rapidly than their intermolecular counterparts owing to their more favorable entropy change on passing to the transition state.[7] When five- and six-membered rings are formed, this entropic contribution produces a favorable ΔG and equilibrium constant. Some intramolecular reactions, however, have smaller equilibrium or rate constants relative to their bimolecular analogues, due to the increased ring strain in the product or in the transition state, respectively. In these cases, the favorable entropy change is offset by an unfavorable enthalpy. However, some changes in the structure of the substrate can reduce the unfavorable ΔH term and increase the equilibrium and the rate constants for cyclization. An important example of such structural changes is the introduction of substituents in the carbon chain undergoing cyclization. At low temperatures, long unsubstituted paraffin chains exist in an *all-anti* (zigzag) and extended conformation, which is unfavorable for cyclization. When the hydrogens of a methylene carbon in the chain are replaced with two methyl groups, the adjacent C−C bond can adopt *gauche* conformations as readily as *anti* conformations, and thus a bend of the main chain, necessary for cyclization, becomes more probable (*gem*-dimethyl effect).[8]

Since the beginning of the last century, alkyl substitution has been recognized as promoting the formation and stability of cyclic compounds. However, several theories and experimental results have been presented to explain the source of the observed increase in the rate and equilibrium constants.

2.1. Thorpe–Ingold Effect[3] (Theory of Valency Deviation)

Historically, the first explanation for the *gem*-dialkyl effect was internal angle reduction. In 1915, Beesley, Ingold, and Thorpe observed a correlation between the changes in the bond angles of the carbons of an open-chain structure with the formation and stability of the corresponding cyclized product.[2] They reported that substitution of the methylene hydrogens with the more sterically demanding alkyl groups produces a compression of the internal angle (θ). As a result, the two reactive units, X and Y, at the end of the system move closer together, and this facilitates the cyclization (Figure 1).[9] Thus, the

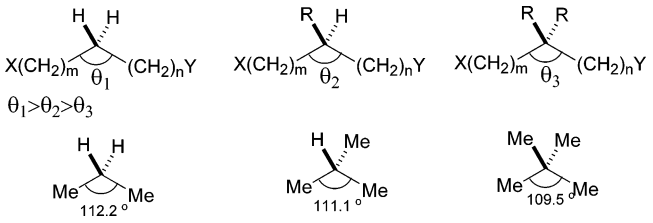


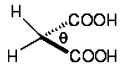
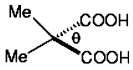
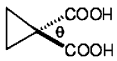
Figure 1. Thorpe−Ingold effect.

C−C−C angle of propane is 112.2°, but it is reduced to 111.1° in isobutane and to 109.5° in neopentane, where methyl groups replace one or both hydrogens at the central carbon.

Table 1. Relative Rates of Ring Closures of Chlorohydrins

compound	relative rate
$HOCH_2CH_2Cl$	1
$HOCH_2CHClCH_3$	5.5
$CH_3CHOHCH_2Cl$	21
$HOCH_2CCl(CH_3)_2$	248
$(CH_3)_2COHCH_2Cl$	252
$(CH_3)_2COHCHClCH_3$	1360
$CH_3CHOHCCl(CH_3)_2$	2040
$(CH_3)_2COHCCl(CH_3)_2$	11,600

Table 2. Effect of *gem*-Dialkyl Substitution on Bond Angle

Compound	Angle (deg)
	110.0
	106.2
	118.4

This first explanation for the increase of the rate of cyclization upon substitution is commonly referred to as the "Thorpe−Ingold effect" or the "theory of valency deviation." One of first demonstrations of this effect can be found in the cyclization of chlorohydrins to form epoxides (Table 1).[10] Table 1 shows that replacement of the C-2 methylene hydrogens of 2-chloroethanol with a *gem*-dimethyl group produces an increase of ~200-fold in the rate of ring closure. A similar rate enhancement is observed when the *gem*-dimethyl group is placed next to the attacking nucleophile. It is noteworthy that the simultaneous replacement of all four hydrogens of 2-chloroethanol with methyl groups results in an increase in the rate of cyclization of $>10^4$. Experimental evidence of the *gem*-disubstitution effect on bond angle was obtained from X-ray measurements on a series of substituted malonic acids (Table 2).[11] The angle θ between the two carboxyl groups is 110° for malonic acid (close to the normal tetrahedral angle), but it decreases to 106.2° for the dimethyl-substituted analogue, due to the Thorpe−Ingold effect. If one examines the reaction between the two carboxyl groups to form a four-membered ring anhydride, then the cyclization of dimethylmalonic acid will be favored over that of the unsubstituted parent. In the case of cyclopropane-1,1-dicarboxylic acid, the observed bond angle θ is 118.4°, due to the decrease in the cyclopropane ring angle. This large angle between substituents on small rings has been used to distinguish between angle and rotamer effects (see section 2.2.3, Scheme 5). In 1984 Engberts et al. described the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides **1a**−**c** for which they observed compression of the bond angle upon *gem*-disubstitution (Scheme 1).[12] The hydrolysis of the sulfonamide **1a**−**c** involves intramolecular nucleophilic catalysis by the carboxylate group, via a four-membered ring intermediate. Thus, the strain associated with the formation of this small ring is

Scheme 1

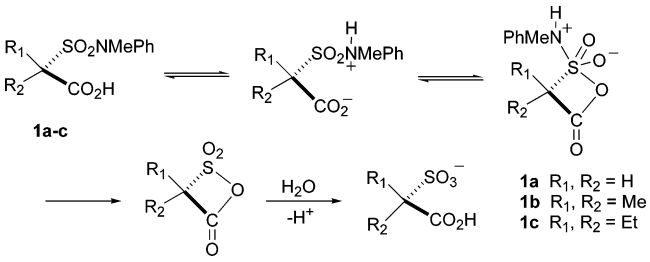
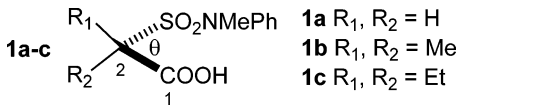


Table 3. Structure and Reactivity for the Intramolecular Carboxyl-Catalyzed Hydrolysis of Sulfonamides 1a−c



compd	S−C_2−C_1 angle θ^a (deg)	S−C_2 length^a (Å)	$k_{rel}{}^b$
1a	110.4	1.794	1
1b	105.0	1.826	44.1
1c	105.3	1.859	242

^{a} Obtained from X-ray data. ^{b} In H_2O at 75 °C (UV method).

expected to be relieved by alkyl substitution at the central carbon and, as a result, the overall rate of hydrolysis should be increased. Table 3 summarizes the relative rate of hydrolysis of the sulfonamides **1a**−**c** along with the bond angles and lengths obtained from the X-ray structures. The reported values of k_{rel} confirm the increase in the rate of hydrolysis upon alkyl substitution. Moreover, comparison of the S−C_2−C_1 bond angle θ and the S−C_2 bond length of the sulfonamide **1a** with those of **1b** or **1c** suggests the reason for the greater reactivity of the substituted compounds. As predicted by the Thorpe−Ingold effect, due to the unfavorable nonbonding interaction between the alkyl substituent and the carboxyl and sulfonamido groups, the internal angle θ decreases while the S−C_2 bond length increases with substitution. As a result, the strain of the four-membered ring intermediate (and of the transition state leading to it) is relieved and the hydrolysis rate increases. However, the case of the sulfonamide **1c** is somewhat surprising. The increase in the rate of hydrolysis with the size of the alkyl substituent (**1b** versus **1c**) is not related to a decrease in the bond angle θ but only to an increase in the S−C_2 length. The authors suggest that in the sulfonamide **1b**, the S−C_2−C_1 angle has reached its minimum (105.0°) due to the steric repulsion between the sulfonamido and carboxyl groups. It is noteworthy at this point to mention a recent example in which the Thorpe−Ingold effect does not increase the stability of small rings but instead destabilizes them. This is the case of the geminal-substituted [1.1.0]bicyclobutanes (Figure 2).[13] The presence of geminal substituents on the bicyclobutane ring systems of **2** and **3** contributes to their decreased stability versus the unsubstituted analogues. Although many factors are operative in this very sterically hindered system, the DFT calculations show that the angle α between the geminal groups increases while the two complementary angles β and γ decrease, thereby moving the endo *tert*-butyl

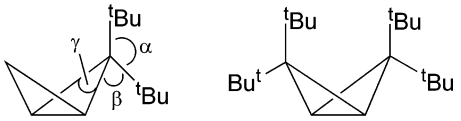


Figure 2. Substituted [1.1.0] bicyclobutanes.

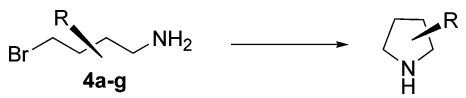
group closer to the endo hydrogen and, partly because of this steric repulsion and the increase in α, moving the exo *tert*-butyl group closer to the bridgehead hydrogens, all of which destabilize the system.

The experimental evidence presented so far implicates the compression of the internal angle (Thorpe−Ingold effect) as the main factor responsible for the effect of *gem*-disubstitution on the stability and formation of small rings. However, because the *gem*-disubstituent effect also extends to five- and six-membered rings, where there is very little or no change in bond angle, several authors have questioned the validity of the Thorpe−Ingold theory.

2.2. *gem*-Disubstituent Effect on the Formation of Medium Rings

In 1961, von Schleyer pointed out that often the change in bond angle observed upon substitution is too small (2−3°) to explain the large rate enhancement during cyclization.[14] For example, during the cyclization of some substituted bromobutylamines, Brown et al. observed an increase in the rate up to 10^4, as shown in Table 4.[15] From their data it is evident that both the position and the size of the *gem*-disubstituent have a profound effect on the rate of ring closure of the 4-bromobutylamines **4a**−**g** to the corresponding pyrrolidines. The introduction of a *gem*-dimethyl group on the carbon bearing the amino group (**4b**) produces a 2-fold increase in the rate of cyclization as compared to the unsubstituted compound (**4a**). Geminal dimethyl substitution at the second carbon (**4c**) results in a rate enhancement of 158, whereas cyclization of the C-3 dimethyl compound (**4g**) occurs at a slower rate, as expected from a substrate where the leaving group occupies a neopentyl position. Finally, the remarkable effect of the size of the substituent in promoting the cyclization can be seen for diethyl-substituted (**4d**), diisopropyl-substituted (**4e**), and diphenyl-substituted (**4f**) compounds. The amplitude of these effects suggests that the source of the rate enhancement cannot be the change in the bond angle upon substitution (negligible for five-membered rings). Instead, the authors propose that alkyl substitution strongly affects the distribution of rotational conformations due to the nonbonded interactions with the chain. Thus, in the case of *gem*-disubstituted compounds, the "coiled" configurations are preferred over the extended parent molecules, and this consequently increases the cyclization probability. Later, other research groups investigated the effect of substitution during the cyclization of medium rings. An analysis of the equilibrium and kinetic constants as well as the thermodynamic parameters of these reactions prompted new hypotheses and interpretations of the *gem*-disubstituent effect.

Table 4. Relative Rate (k_{rel}) of Cyclization of Bromobutylamines 4a−g to the Corresponding Pyrrolidines at 30 °C



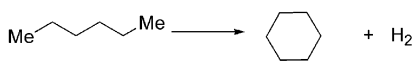
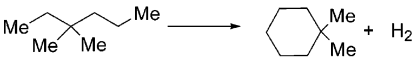
starting amine as hydrobromide		k_{rel}[a]
4-bromobutylamine	**4a**	1.0[b]
4-bromo-1,1-dimethylbutylamine	**4b**	2.19[b]
4-bromo-2,2-dimethylbutylamine	**4c**	158[c]
4-bromo-2,2-diethylbutylamine	**4d**	594[d]
4-bromo-2,2-diisopropylbutylamine	**4e**	9190[e]
4-bromo-2,2-diphenylbutylamine	**4f**	5250[b]
4-bromo-3,3-dimethylbutylamine	**4g**	0.158[b]

[a] The reactions were run in the presence of (b) 0.5 M NaOAc and 0.25 M AcOH, (c) 0.25 M NaOAc and 0.25 M AcOH, (d) 0.5 M HCO_2Na and 1.0 M HCO_2H, and (d) 0.5 M NaOAc and 1.0 M AcOH.

2.2.1. Allinger and Zalkow's Thermodynamic Analysis

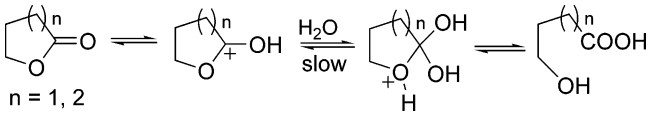
The first quantitative analysis of the thermodynamic factors involved in the *gem*-dimethyl effect was proposed by Allinger and Zalkow in 1960.[6] They studied the effect of dimethyl substitution on a group of ring closure reactions leading to substituted cyclohexane systems. The equilibrium constants and the thermodynamic properties calculated are presented in Table 5.[6] Upon replacement of the methylene hydrogens with methyl groups, the equilibrium constants for the formation of the cyclohexanes are increased by 10^2−10^3. This pronounced effect of alkyl substituents is due to more favorable values of either $\Delta H°$ or $\Delta S°$ or both. The authors point out that in the cyclization of *n*-hexane to cyclohexane, six new *gauche* interactions are formed, whereas the number of new *gauche* interactions compared to those in the starting material differs with the position of the *gem*-dimethyl substitution; that is, the 2,2-dimethyl also has six additional *gauche* interactions in the product (and therefore a similar $\Delta H°$), whereas the 3,3-dimethyl analogue has only four additional *gauche* interactions, because the starting acyclic system has several additional *gauche* interactions and, therefore, a more favorable $\Delta H°$. Another way of stating this is that by using the first reaction as a base, the 2,2-dimethyl case adds two *gauche* interactions in both the open chain and the ring and thus does not affect the $\Delta H°$ but does reduce the entropy in the open chain relative to the ring (positive change in $\Delta S°$), whereas the 3,3-dimethyl case adds four *gauche* interactions in the open chain but only two in the ring and, thus, the $\Delta H°$ is decreased. In addition, the entropy loss upon cyclization is less in the substituted compound because the alkyl substituents restrict the rotation in the open chain form and thus decrease the rotational entropy. Furthermore, in those cases in which cyclization is the rate-determining step of the reaction, the arguments presented here for the $\Delta H°$ and $\Delta S°$ terms can be translated to the kinetic terms $\Delta H^{‡}$ and $\Delta S^{‡}$ and to the rate of cyclization. Similar effects can be found for the hydrolysis of substituted γ-butyrolactones and δ-valerolactones.[16] Because lactonization is the only simple example of a cyclization reaction that is reversible, it is interest-

Table 5. Effect of Dimethyl Substitution on the Equilibrium Constants and Thermodynamic Properties for the Cyclization of Cyclohexanes at 25 °C[a]

Reaction	ΔG^o (kcal mole^{-1})	ΔH^o (kcal mole^{-1})	ΔS^o (cal °K^{-1})	K_{eq}
	7.65	10.53	9.66	2.40×10^{-7}
	5.86	10.45	15.39	4.96×10^{-5}
	5.23	9.35	13.85	1.44×10^{-4}

[a] Calculated from standard thermodynamic data.[6]

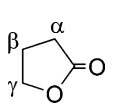
Scheme 2

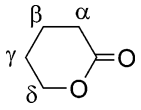


ing to see how alkylation affects the forward and reverse reactions. For both lactones, the mechanism of acid-catalyzed hydrolysis involves the attack of a water molecule on the protonated lactone as the rate-determining step of the reaction (Scheme 2). Thus, alkyl substituents near the reaction center will retard the ring-opening reaction.

The equilibrium and rate constants for the hydrolysis of five- and six-membered ring lactones are reported in Table 6. Clearly, methyl substitution results in a decrease in the equilibrium and rate constants of the hydrolysis of butyrolactones and valerolactones. The large decrease in the equilibrium constants observed upon substitution must be due to two simultaneous factors. First, presumably the increase in the rate of cyclization is the principal factor and is probably due to the effect of the methyl substituents on the ring stabilization. Second, the decrease in the rate opening contributes to this retardation and most likely arises from the steric hindrance in the approach of a water molecule. On a thermodynamic base, the authors ascribe these changes to a favorable enthalpy and entropy of activation, as proposed earlier by Allinger and Zalkow.[6]

Table 6. Effect of Methyl Substituents on the Equilibrium and Rate Constants for the Hydrolysis of γ-Butyrolactones and δ-Valerolactones at 25 °C





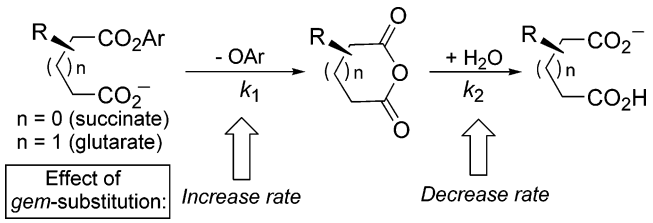
substitution	$K_H^a \times 10^2$	$k_H^a \times 10^2$	k_H^b	k_H^b
none	34.7	2.20	16.3	2.16
α-methyl	2.45			
β-methyl	4.81		0.92	1.92
γ-methyl	7.81	1.58		
δ-methyl			2.64	1.16
α,α-dimethyl	<1			
β,β-dimethyl	<1		0.090	0.734
γ,γ-dimethyl	2.8			
δ,δ-dimethyl			2.31	0.125

[a] Data at 25 °C, L mol^{-1} min^{-1} in 0.025 M hydrochloric acid. [b] Data at 25 °C, L mol^{-1} min^{-1} in 0.020 M hydrochloric acid.

2.2.2. Reactive-Rotamer Hypothesis

The effect of geminal substitution on the ring closure and ring opening of five- and six-membered anhydrides was extensively investigated by Bruice et al.[5,17] The authors studied the intramolecular hydrolysis of a series of monophenyl esters, which occurs through the formation of the intermediate anhydrides (Scheme 3).

Scheme 3



The kinetic effects of α and β geminal substitution on the rate of formation and hydrolysis of succinic and glutaric anhydrides are summarized in Scheme 3. From the study of the relative rate of hydrolysis of several monoesters, the authors concluded that the geminal substitution, in particular at the β position, increased the rates of ring closure (k_1) and decreased the rates of ring opening (k_2).

2.2.2.1. *gem*-Dialkyl Effect on the Rate of Anhydride Formation (k_1). The effect of substitution on k_1 can be explained by the decrease in unprofitable rotamer distribution in the ground state. A schematic representation of the Bruice "reactive-rotamer effect" is given in Figures 3 and 4.[9]

Figure 3 presents the Newman projections for the cyclization of generic (a) unsubstituted and (b) substituted open chains. In both cases, for the cyclization to occur, the reactive units X and Y must approach each other, and this requires rotation about the central C−C bonds. In the case of an unsubstituted carbon chain (a), the rotation converts the most stable (and therefore more highly populated) *anti* conformation into the *gauche* conformation (reactive rotamer). When the methylene hydrogens are replaced with one or two substituents, the energy of the "*gauche*"

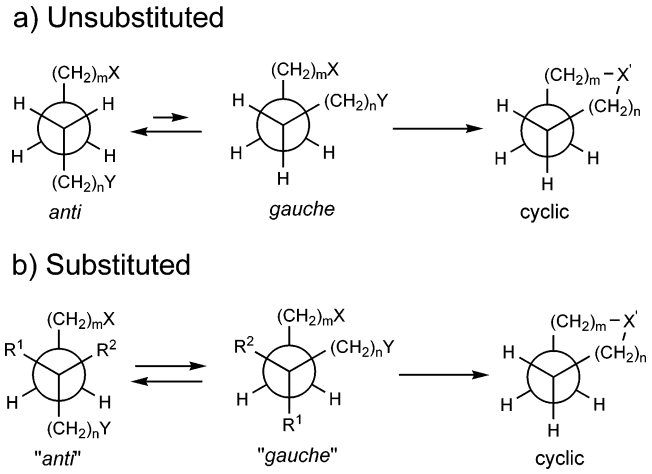


Figure 3. Reactive-rotamer effect on cyclization.

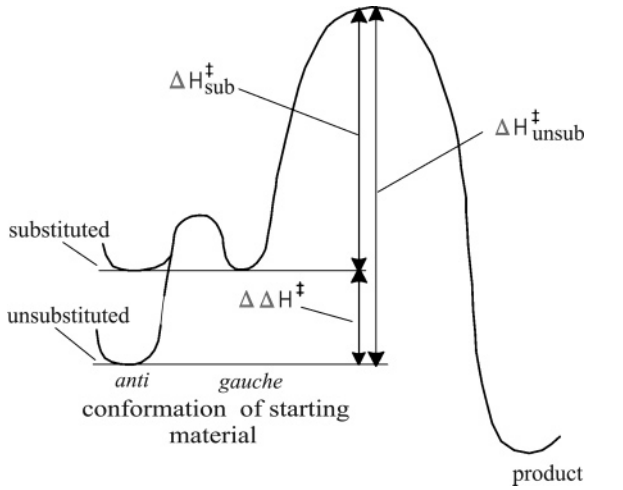


Figure 4. Reactive-rotamer effect and energy diagram for cyclization (assuming the transition states enthalpies for the substituted and unsubstituted reactions are the same).

rotamer, required for cyclization, equals the energy of the corresponding "*anti*" rotamer. As a result, the cyclization of the substituted compound (Bruice's monophenyl esters) is facilitated by a higher population of the reactive rotamer. These effects are also elucidated in Figure 4. In terms of energy, substitution results in an increase in the energy of the ground state so that the activation energy for the cyclization of the substituted compound ($\Delta H^{\ddagger}_{sub}$) is lower than that of the unsubstituted ($\Delta H^{\ddagger}_{unsub}$). In addition, during the hydrolysis of the monophenyl esters, Bruice et al. observed that increasing the steric bulk of the substituent produces rate acceleration due to the greater statistical proximity of the carboxyl and ester groups.[18] The effect of large geminal groups was also observed on the dissociation constants of several substituted glutaric acids.[19] Geminal substitution decreased the population of extended rotamers, favoring the carboxyl orientation that is effective for intramolecular hydrogen bonding. As a result, as the carboxyl groups of the dicarboxylic acid are brought into close proximity, the value of the first dissociation constant increases while that of the second constant decreases (due to the stronger hydrogen bonding between the carboxylate and the second acid hydrogen).

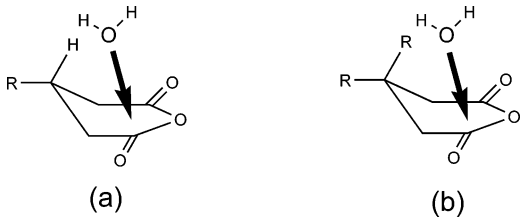
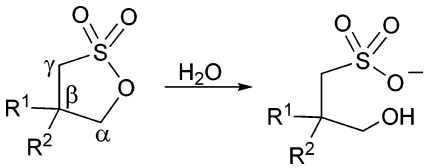


Figure 5. Nucleophilic attack on substituted anhydrides.

Table 7. Rate of Hydrolysis of Substituted Sultones and Related Compounds



entry	R^1	R^2	T (°C)	rel rate	ref
	(a) Cyclic Sulfonates				
1	H	H	40	1	20
2	Me	H	40	0.21	20
3	Me	Me	40	0.0035	20
	(b) Acyclic Sulfonates				
4	$PrOSO_2Ph$		60	1	21
5	iBuOSO$_2$Ph		60	0.32	21
6	*neo*PenOSO$_2$Ph		60	0.15	21

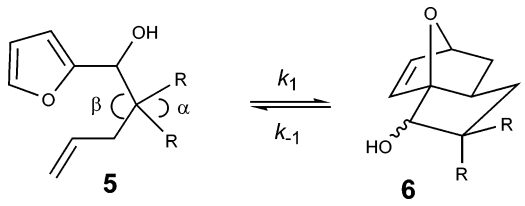
2.2.2.2. *gem*-Dialkyl Effect on the Rate of Anhydride Hydrolysis (k_2). The decrease in the rate of anhydride hydrolysis (k_2) upon substitution, observed by Bruice et al., can be explained by considering the steric hindrance to the approach of the nucleophile (water or hydroxide) to the anhydride carbonyl group (Figure 5).[5a,17a] This conclusion is supported by the fact that only one β substituent does not produce a change in the rate of hydrolysis as compared to the unsubstituted anhydride. This substituent can be accommodated easily in a pseudoequatorial position in the half-chair conformation of the anhydride and, thus, it would not hinder the nucleophilic attack (Figure 5a). Conversely, in the case of β *gem*-disubstitution, one of the groups is forced into the axial position, where it slows the nucleophilic attack and, thus, the anhydride hydrolysis (Figure 5b).

A similar effect has also been observed for the hydrolysis of β substituted five-membered ring sultones (Table 7).[20,21] The introduction of one methyl group at the β position (entry 2) of the parent sultone produces a 5-fold retardation of the rate of hydrolysis, whereas the second group (entry 3) causes an additional 60-fold decrease. However, in the open-chain sulfonates (entries 4−6), the decrease in the rate of ring opening is clearly more limited, as in the case of anhydride hydrolysis, where the significant retardation of the sultone ring-opening reaction upon geminal substitution can be explained by the increase of steric hindrance of the attack of the nucleophile.

2.2.3. Reactive-Rotamer or Thorpe–Ingold Effect?

The two hypotheses on the origin of the *gem*-dialkyl effect presented so far are still an object of debate in the scientific community. Nevertheless, their validity has been directly tested independently by two re-

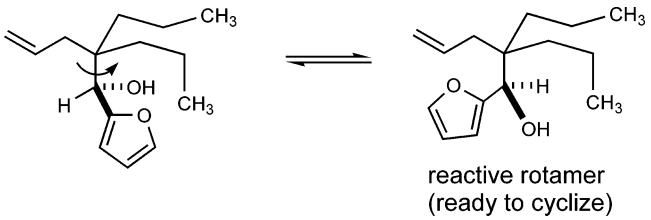
Table 8. Substituent Effects on the Rates and Equilibria of Intramolecular Diels–Alder Reactions



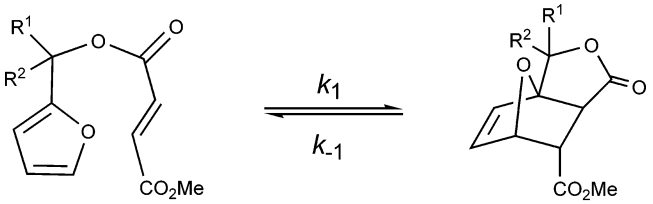
entry	R	$k_1 \times 10^6$ s^{-1}	rel rate	K_{eq}	$t_{1/2}$ (h)	% yield
1	–H		no reaction			
2	–Me			<0.05		<5
3	$-CH_2(CH_2)_3CH_2-$	1.46	1	0.9	131	47
4	$-CH_2CH_2CH_3$	2.73	1.8	1.4	71	58
5	$-S(CH_2)_3S-$	5.95	4.1	3.2	32	76
6	$-SCH_2CH_3$	6.94	4.8	5.7	28	85
7	$-OCH_2CH_3$	14.3	9.8	4.7	13	82

search groups. In both cases, the model reaction used to study the source of the *gem*-dialkyl effect was an intramolecular Diels–Alder cycloaddition with furan as the diene. The first research group, Sternbach et al., studied the effect of substituents on the alkyl chain connecting the furan and the dienophile (Table 8).[22] The rates and equilibria of the intramolecular Diels–Alder reaction of substituted precursors (**5**) are summarized in Table 8, along with the yields of the mixture of the cycloadducts **6**. The first and most striking effect can be seen by comparing entries 1, 2, and 4. The unsubstituted precursor (entry 1) gave no reaction, and the *gem*-dimethyl case (entry 2) afforded only a trace of the final product. However, the dipropyl case (entry 4) gave a 58% yield of the desired mixture. Moreover, when the cyclic substitution (entries 3 and 5) is compared with the acyclic cases (entries 4 and 6), the latter cyclize more rapidly and with higher efficiency. Finally, substituents carrying a heteroatom (entries 5–7) facilitate the intramolecular Diels–Alder more than the analogues with only carbon atoms. To explain the origin of these effects, the authors examined the X-ray structure of one of the Diels–Alder precursors (entry 5). In the solid state, both of the angles α and β (Table 8) were found to be larger than the tetrahedral value. These findings obviously rule out the Thorpe–Ingold effect, which would predict a compression of the angle β as a consequence of the *gem*-disubstitution. Instead, the major factor responsible for the rate and efficiency enhancement described in Table 8 is related to the change in energy of the ground state of the Diels–Alder precursors (**5**), which produces an increase in the population of the rotamer required for cyclization (reactive rotamer in Scheme 4).

Scheme 4



Scheme 5



7a	$R^1 = R^2 = H$	**8a**
7b	$R^1 = H\ R^2 = Me$	**8b**
7c	$R^1 = R^2 = (CH_2)_2$	**8c**
7d	$R^1 = R^2 = (CH_2)_3$	**8d**
7e	$R^1 = R^2 = Me$	**8e**

In addition, when sulfur is the atom directly attached to the tethering chain (Table 8, entries 5 and 6), the increased bond length of the C–S bond and the reduced van der Waals radius for sulfur, as compared to the carbon analogue, help to minimize the eclipsing interactions required for the rotation shown in Scheme 4.

New experimental evidence supporting the "reactive-rotamer" hypothesis and disproving the Thorpe–Ingold effect came from the studies of Jung et al. on the intramolecular Diels–Alder cycloaddition of 2-furfuryl methyl fumarates (Scheme 5).[23] The authors designed a system that would allow these two possible sources of the *gem*-dialkyl effect to be in opposition. When a small-membered ring is used as the dialkyl substituent (**7c** and **7d**), a direct comparison of the reactive-rotamer and Thorpe–Ingold effects becomes possible (Figure 6). If the former is

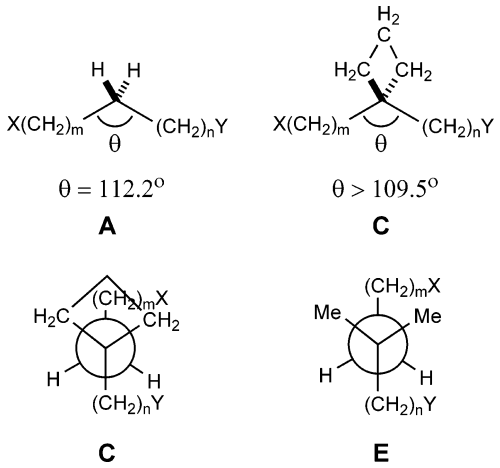


Figure 6. Effect of small ring on reactive-rotamer and Thorpe–Ingold effects.

dominant, then compound **C** (ex. **7c**) should cyclize as quickly as the dimethyl analogue **E** (ex. **7e**), but if the Thorpe–Ingold effect is more important, then the cyclization of compound **C** should be slower due to the enlargement of the angle θ imposed by the ring strain.

The results of the intramolecular Diels–Alder cycloaddition of the precursors **7a–e** are summarized in Table 9.[23c] It is clear that *gem*-dialkyl substitution on the tethering chain produced an enhancement of the rate of cyclization. However, from a comparison of the rate constants of the cyclobutyl system **7d** with

Table 9. Kinetic Parameters for the Intramolecular Diels–Alder of the Furfuryl Fumarates 7a–e at 298 K in CD_3CN

compd	k_{298} (s^{-1})	k_{rel}	E_{act} (kcal/mol)	$\Delta H^{\ddagger}_{298}$ (kcal/mol)	$\Delta S^{\ddagger}_{298}$ (cal/mol·deg)	$\Delta G^{\ddagger}_{298}$ (kcal/mol)
7a	1.94×10^{-7}	1	20.5	19.8	−22.7	26.6
7b	1.62×10^{-6}	8.35	19.1	18.4	−23.2	25.3
7c	2.03×10^{-6}	10.5	17.9	17.3	−26.6	25.2
7d	4.03×10^{-5}	208	16.9	16.3	−23.9	23.4
7e	4.12×10^{-4}	2123	15.5	14.9	−24.0	22.1

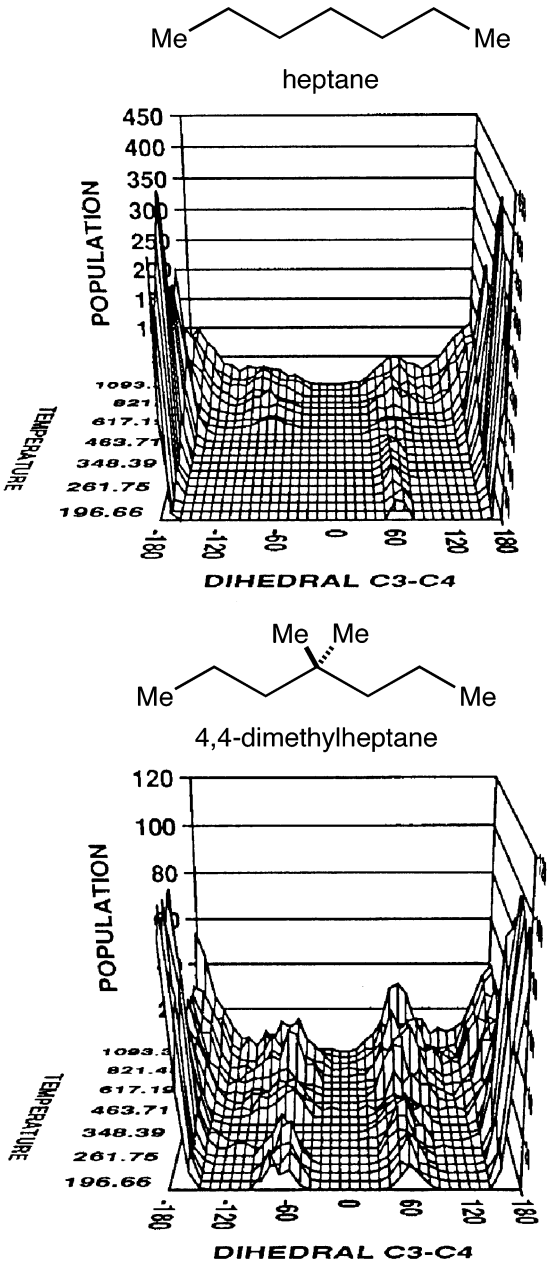


Figure 7. Map of populated rotational conformers of *n*-heptane (top) and 4,4-dimethylheptane (bottom).

the dihydro (**7a**) and monomethyl (**7b**) compounds, it is possible to estimate the relative importance of the rotamer and angle compression effects. Even with an angle θ between the reacting units larger than those of **7a** and **7b**, the cyclobutyl-substituted precursor **7d** cyclized much more quickly than both **7a** and **7b**. Therefore, at least for the cyclization of five-membered rings, the *gem*-dialkyl effect cannot be explained using the Thorpe–Ingold theory. Other factors, such as the change in the population of the reactive rotamer, should be considered. In addition, from an inspection of the kinetic activation parameters in Table 9, the authors concluded that the decrease in the free energy of activation ($\Delta G^{\ddagger}$) observed upon *gem*-dialkyl substitution is nearly entirely due to the lowering of the enthalpy factor ($\Delta H^{\ddagger}$) and not to differences in the entropy of activation ($\Delta S^{\ddagger}$). Subsequent molecular mechanics (SIBFA)/continuum reaction field calculations indicated the source of the observed decrease in $\Delta H^{\ddagger}$.[24] The presence of methyl or *gem*-dimethyl substitution on the diene–dienophile linker produces a change in the van der Waals forces resulting in the stabilization of the folded conformers (required for cyclization) over the extended conformation of the Diels–Alder precursor.

Using the Anneal–Conformer program, Wilson et al. analyzed the conformations of highly flexible systems and found that the introduction of a *gem*-dimethyl group at C-4 in heptane results in a significant increase in the population of the *gauche* conformations around the C3–C4 bond (Figure 7).[25] In agreement with Bruice's reactive-rotamer hypothesis and subsequent experimental evidence, even at low temperatures, 4,4-dimethylheptane shows an increase in the population of the folded (*gauche*) conformer as compared to the unsubstituted compound.

2.2.4. Facilitated Transition Hypothesis

In 1994, Dolata et al., used the WIZARD conformational search program to study the source of the *gem*-dialkyl effect observed by Jung[23] and Sternbach[22] in intramolecular Diels–Alder cycloadditions.[26] Using the WIZARD technique, the ground-state and transition-state conformations were calculated and the concentrations of the reactive rotamers were determined using a Boltzmann distribution. When the rate of cyclization was plotted versus the percentage of reactive rotamers, the expected linear relationship was not observed. Thus, the authors concluded that the reactive-rotamer effect was not the major contributor to rate enhancement described for Diels–Alder cycloadditions. Instead, they proposed that the observed rate enhancement is due to an overall reduction of the $\Delta H^{\ddagger}$ of the reaction and not to the relative concentrations of the reactive rotamers. Dialkyl substitution decreases the rotational barrier between the ground-state conformations and the transition state, and this results in a "facilitated transition" between the reactive rotamer and the products of cyclization ("Facilitated Transition" hypothesis).

2.2.5. Stereopopulation Control

One of the most common points of disagreement with the reactive-rotamer hypothesis is based on the evidence that, for some systems, the rate enhancement upon *gem*-disubstitution goes up to 10^{11}. Thus, it would seem unlikely that this effect could arise solely from a decrease in unprofitable rotamer distribution. The X-ray structure of the alcohol **9**, which is structurally related to the acid **10**, suggests that although the conformation around the C5–C7 bond is the one favorable for the acid to cyclize, the

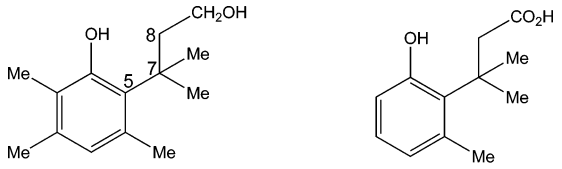
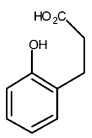
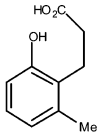
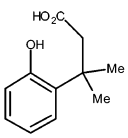
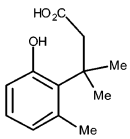


Figure 8. Substituted hydrocoumarinic alcohol (**9**) and acid (**10**).

Table 10. Rate and Equilibrium Constants for the Lactonization of Substituted Hydrocoumarinic Acids at 30 °C in 20% Aqueous Dioxane

	 **11**	 **12**	 **13**	 **10**
$k_{H_3O^+}$ ($mole^{-1}$ s^{-1})	5.9 x 10^{-6}	5.9 x 10^{-6}	2.6 x 10^{-2}	3.0 x 10^{5}
k_{rel}	1	1	4400	5.1 x 10^{10}
K_{eq}	0.0373	0.621	25.67	>99

conformation around the C7−C8 bond is not and would require a rotation of ~120° (Figure 8).[27]

To explain these differences, Cohen and Milstien determined the rate and equilibrium constants for the lactonization of several substituted hydrocoumarinic acids (Table 10).[28] Analysis of the kinetic data shows that although a methyl group alone on the aromatic ring (**12**) produces no change in the rate of cyclization as compared to the parent acid (**11**), the addition of a *gem*-dimethyl group on the carbon chain (**10**) results in an impressive rate enhancement (>10^{10}). Thus, the authors speculated that the unique interlocking ("trimethyl lock") of the three methyl groups (*gem*-dimethyl on the chain and the methyl on the aromatic ring) produces a "severe conformational restriction of the side chain, which narrows the distribution of conformations by eliminating nonproductive isomers." Consequently, they proposed the "stereopopulation control" hypothesis as a model to explain the restriction in rotational freedom experienced by a substrate during an enzymatic reaction and the resulting rate enhancement.

2.2.6. Relief of Ground-State Strain

Some authors have argued that the stereopopulation control proposed by Cohen et al.[28] can account for a maximum rate enhancement of 10^4, leaving a rate factor of 10^7 that requires a different explanation. Thus, the dramatic rate acceleration observed for the cyclization of substituted hydrocoumarinic acids (Table 10) is attributed to a large relief of ground-state strain in these compounds.[29] The steric repulsions present in the ground state, due to the aryl methyl group and the alkyl substituents on the side chain, were confirmed by experimental and theoretical evidence. Loudon et al. observed a secondary deuterium isotope effect (k_H/k_D = 1.09) when they replaced the side-chain methyls with deuterated methyls.[29a] In addition, Wilcox et al. used a force-field model to calculate the difference in strain energy between the lactonization of **11** and that of **14** (Figure 9).[29b] The energy difference was found to be 10.3 kcal/mol, equivalent to approximately a 10^7 difference in rate, which is in close agreement with the experimental observation. This led to the conclusion that conventional relief of steric compression (enthalpy factor), rather than conformational locking (entropic factor), was the dominant factor favoring the lactonization of substituted hydrocoumarinic acids.

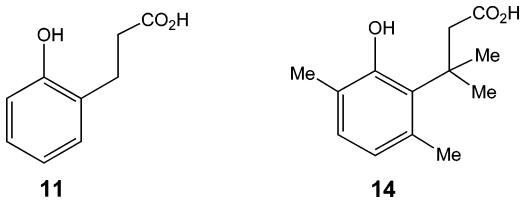
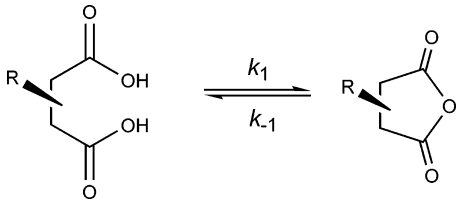


Figure 9. Hydrocoumarinic acids.

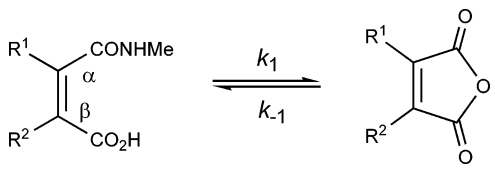
Table 11. Rate and Equilibrium Constants for the Formation of Succinic Anhydrides at 60 °C in Aqueous Solution



succinic acid	k_1	K_{eq}
unsubstituted	9×10^{-6}	7×10^{-6}
methyl	5.9×10^{-5}	4.2×10^{-5}
2,2-dimethyl	1.1×10^{-4}	1.0×10^{-4}
tetramethyl	0.018	0.17

The relief of steric strain in the product has been recognized as favoring the cyclization of several other substituted substrates. For example, Eberson[30] and Kirby[31] investigated the effect of substitution on the rate of formation of the anhydrides from the analogous succinic and maleamic acids, respectively. The rate and equilibrium constants for the formation of succinic anhydrides are summarized in Table 11.[30] Substitution clearly results in an increase of the rate of cyclization and causes a shift of the equilibrium to the anhydride side. These effects are attributed to a favorable enthalpy factor due to the relief of severe nonbonded interactions present in the open chain but minimized in the cyclic product. Kirby et al. obtained similar results for the hydrolysis of substituted maleamic acids to form the corresponding anhydride (Table 12).[31] Even though the data summarized in Table 12 do not involve geminal substitution, they help to confirm the relief of steric strain as a major driving force because there is no question of a change in the rotational freedom. A close examination of the rates of cyclization of the maleamic acids shows that the introduction of two methyl groups (entry 4) produces a large rate enhancement that derives exclusively from a decrease in the enthalpy of activation. As expected, the rate of cyclization of the monoalkylmaleamic acids increases with the size of the substituent (entries 5−7). In addition, the angles α and β of the monomethyl case (entry 3) are much larger than the standard 120°,

Table 12. Thermodynamic Parameters and Bond Angles for the Formation of Maleic Anhydrides at 39 °C



entry	R^1	R^2	rel k_1	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})	α^a (deg)	β^a
1	H	H	1	24.6	2.9		
2	H	Me	31.2	22.8	2.1		
3	Me	H	30.0			126.8	131.7
4	Me	Me	1.5×10^4	14.8[a]	−8[a]	121.0	121.7[b]
5	H	Et	32.8				
6	H	*i*Pr	44.5				
7	H	*t*Bu	68.0	22.5	2.7		
8	$-(CH_2)_4-$		540	20.5	2.4		
9	$-(CH_2)_3-$		4.2×10^{-5}	33.9	10.6	127.7	131.5
10	$-(CH_2)_2-$		4.2×10^{-6}			132.1	133.4[c]

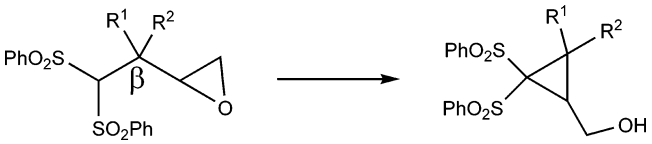
[a] Data given for the *N*-propylmaleamic acid. [b] Angles are for the diisopropyl case. [c] Angles are for the diacid.

probably due to the nonbonded repulsion between the carboxyl and the amide groups. When an alkyl group replaces both olefinic hydrogens, the change in bond angle is limited (entry 4) unless the substituents are linked together in a five- or four-membered ring (entries 9 and 10). In these last two cases, the reacting groups are pulled apart as compared to the unsubstituted maleamic acid, leading to a dramatic fall in the efficiency of cyclization. In conclusion, the accumulation of the four planar substituents on the central double bond of maleamic acids produces a significant steric compression, which is relieved in the cyclic product and the transition state leading to it.

Theoretical calculations of the steric effects in the S_N2 ring closure of bromoalkylamines also prompted DeTar and Luthra to conclude that earlier studies had overestimated the entropic effects (e.g., stereopopulation control).[32] Thus, they proposed that the striking *gem*-dialkyl effect they and others had observed[15] for the cyclization of bromoalkylamines is mostly enthalpic in origin. As was the case for the cyclization of hexanes to cyclohexanes discussed earlier, the authors attribute the rate enhancement seen upon substitution to the decrease in the number of new *gauche* interactions in going from the acyclic to the cyclic compounds.

More recent examples of the *gem*-dialkyl effect, such as for the cyclization of aromatic sultones,[33] have been explained in terms of reduced ground-state strain and van der Waals repulsion in the transition state. During the rearrangement of γ-epoxy bissulfones to the corresponding cyclopropanes, dialkyl substitution at the β-carbon results in an increase of the reaction rate, which can also be explained by the decrease in the enthalpy of activation due to the relief of nonbonding interactions (Scheme 6).[34]

Scheme 6



2.3. *gem*-Dialkyl Effect on the Formation of Large Rings

One of the first examples of the *gem*-dimethyl effect on the cyclization of large rings was observed by Björnstad and Borgen during the synthesis of 16- and 18-membered cycloalkynes.[35] The presence of the *gem*-dimethyl group causes a bend on the carbon chain, therefore allowing the two reaction centers to approach each other. In the unsubstituted case, no cyclized product was obtained. Later, Galli et al. carried out the quantitative determination of the *gem*-dimethyl effect on the rate of formation of medium- and large-membered ring lactones from the corresponding potassium ω-bromoalkanoates (Table 13).[36] From the data, it is immediately clear that the *gem*-dimethyl effect decreases as the size of the lactones being formed increases. The rate enhancement is still appreciable for $n = 10$ but it reverses for $n = 11$. This result suggests that the *gem*-dimethyl effect may be caused by the interplay of more than one factor, depending on the size of the ring. In the case of six-membered ring lactones, the increase in the reaction rate can be easily explained by the contribution of a favorable $\Delta H°$ and $\Delta S°$, as proposed by Allinger and Zalkow.[6] However, in the case of larger rings, for which the rotational freedom is similar to that of the open-chain form, the entropic contribution to the *gem*-dialkyl effect becomes less important. Similarly, the enthalpic factor is expected to be negligible when a large, strainless ring is formed. In conclusion, the origin of the modest rate enhancement observed during the formation of large-membered rings is complex and probably relies on several factors.

Table 13. *gem*-Dimethyl Effect on the Rate of Lactonization of Potassium ω-Bromoalkanoate in Aqueous Solution at 50 °C

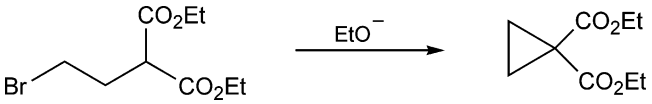
ω-bromo acid	n^a	k_{rel}
5-bromopentanoic acid	6	1.0
$Br(CH_2)_2C(CH_3)_2CH_2CO_2H$	6	38.5
8-bromooctanoic acid	9	1.0
$Br(CH_2)_5C(CH_3)_2CH_2CO_2H$	9	6.62
9-bromononanoic acid	10	1.0
$Br(CH_2)_6C(CH_3)_2CH_2CO_2H$	10	1.13
10-bromodecanoic acid	11	1.0
$Br(CH_2)_7C(CH_3)_2CH_2CO_2H$	11	0.61
15-bromopentadecanoic acid	16	1.0
$Br(CH_2)_6C(CH_3)_2(CH_2)_7CO_2H$	16	1.22

[a] Ring size of the product.

2.4. *gem*-Dialkyl and -Dialkoxycarbonyl Effect on the Strain Energy and Stability of Small Rings

In recent years, new evidence of the *gem*-disubstituent effect on the formation of small rings has been described in the literature. Interestingly, in several cases the increase of the rate of cyclization has not been explained by the Thorpe−Ingold theory (angle compression).[2] For example, Rüchardt et al. first attributed the high rate of ring closure of *gem*-

Scheme 7



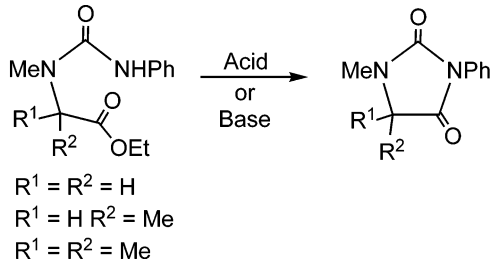
dialkoxycarbonyl cyclopropanes to the ring stabilization, which arises from the conjugative interaction between the electron-withdrawing substituent and the ring (Scheme 7).[37] However, they noted that the stabilization energy of these small rings upon *gem*-dialkoxycarbonyl substitution was <8 kJ mol^{-1}. Thus, the authors reasoned that the observed rate enhancement must come from the decrease of the nonbonding interactions and rotational entropy, as proposed by Allinger and Zalkow for the case of *gem*-dimethyl substitution on medium rings.[6]

The *gem*-dimethyl substitution was also found to lower the strain energy of cyclopropanes, cyclobutanes, epoxides, and dimethyldioxirane (DMDO) by 6−10 kcal/mol relative to their unsubstituted analogues.[38] Bach and Dmitrenko associated the unusual thermodynamic stability of these systems with the strength of the bond between the CH_3 and the carbon of the ring.

2.5. Change of the Rate-Determining Step Induced by the *gem*-Dialkyl Effect

In 1989, Kirby et al. described an interesting example of the consequences of *gem*-dimethyl substitution. Their study involved the *gem*-dialkyl effect on the base- and acid-catalyzed cyclizations of three hydantoate esters (Scheme 8).[39a] They observed that

Scheme 8



at low pH, the introduction of one and two methyl groups increased the cyclization rate by 30- and 1100-fold, respectively. However, under base-catalyzed conditions, the introduction of one methyl produced a rate enhancement of 13-fold, whereas the second methyl reduced the reaction rate by a factor of 6 as compared to the unsubstituted case (Figure 10).

These results suggest a change in the mechanism of the base-catalyzed cyclization for the most substituted substrates. In particular, the authors proposed that the rate-determining step of the cyclization changes from the formation (k_2) to the breakdown (k_3) of the tetrahedral intermediate **T** (Scheme 9).[39b−d]

For the most substituted esters, the steric hindrance of the *gem*-dialkyl group slows the proton transfer to the ethoxide leaving group during the rate-determining step (Figure 11). Consequently, the expected rate enhancement due to the geminal substitution is reduced.

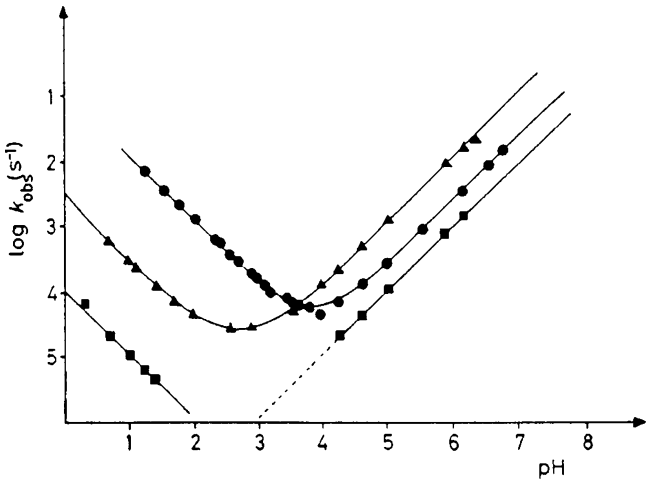
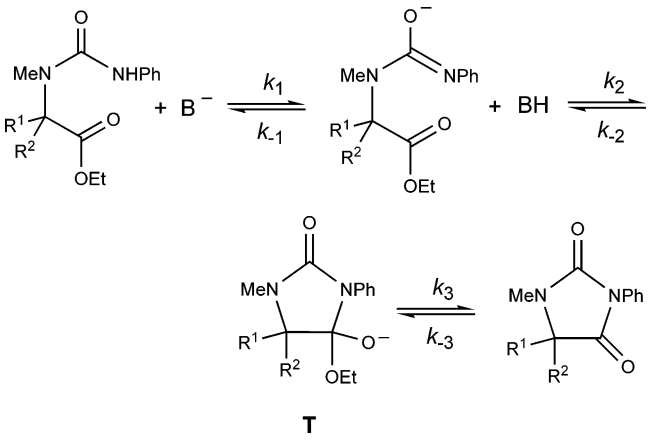
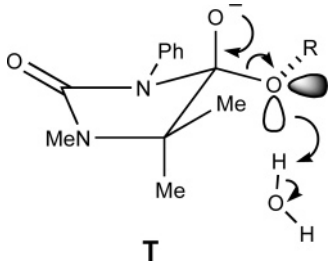


Figure 10. pH profile of the *gem*-dialkyl effect on the rate of cyclization of hydantoate esters: (■) $R^1 = R^2 = H$; (▲) $R^1 = H$, $R^2 = Me$; (●) $R^1 = R^2 = Me$.

Scheme 9



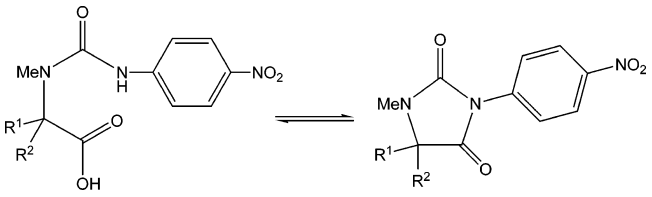
The change of the rate-determining step for the base-catalyzed cyclization of hydantoate esters upon substitution has been confirmed by the presence of the required kinetic isotope effect. Additional evidence came from the study of the cyclization of the corresponding acids **15** (Scheme 10). The replacement of the ethyl group (hydantoate esters, Scheme 9) with a hydrogen (hydantoic acids, Scheme 10) is expected to facilitate the approach of the general acid (Figure 11) and thereby increase the rate of the cyclization. The hydantoic acid **15c** cyclized 15 times more rapidly than the monomethyl-substituted analogue **15b**, thus confirming that, as predicted, a "normal" *gem*-dimethyl effect is operative.



T

Figure 11. Decomposition of the tetrahedral intermediate **T**.

Scheme 10



15a $R^1 = R^2 = H$
15b $R^1 = H$ $R^2 = Me$
15c $R^1 = R^2 = Me$

3. Synthetic Applications

The *gem*-disubstituent effect has been widely used in synthetic organic chemistry to improve the efficiency, and thus the yields, of various cyclizations. One of the first examples of such synthetic applications involves the acyloin and dinitrile condensations of substituted polymethylene compounds (Figure 12).[40] The author explains that with substitution of

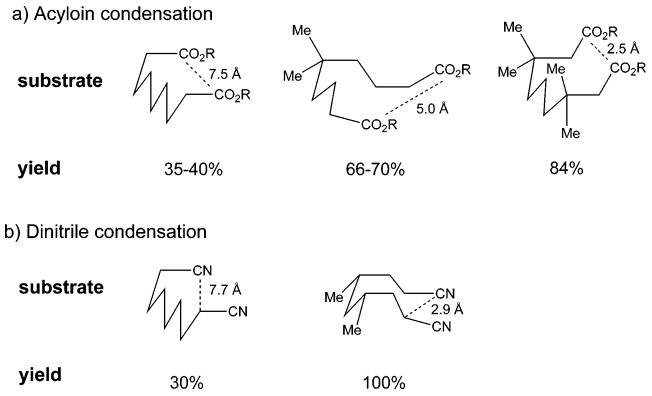
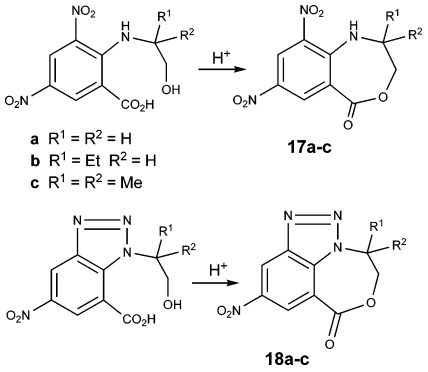


Figure 12. Conformational effects of methyl substituents on the yields of the (a) acyloin and (b) dinitrile condensations.

a methyl group, the possibility of a bent chain conformation increases and that the yields of the cyclization can be roughly related to the distances between the reactive groups in a reasonable conformation, made possible by the methyl or dimethyl substitution. Similarly, Newman et al. described the use of substituted diols for the selective formation of ketals of 5α-androstane-3,17-dione (**16**; Table 14).[41] They observed that use of 2,2-dialkyl-1,3-propanediols increased the stability and decreased the hydrolysis rates of the corresponding ketals. In particular, higher yields of the 3-ketal 17-one derivative of **16** could be obtained by using 2,2-dimethyl- or 2,2-diethyl-1,3-propanediols than by using ethylene glycol or 1,3-propanediol.

Another early example of the effect of mono- and dialkyl substitution on the rate of cyclization was observed during the synthesis of the oxazepinone derivatives **17** and **18** (Table 15).[42] Whereas the compounds with only one alkyl (R) group (**17b** and **18b**) cyclized only slightly more quickly than the unsubstituted ones, the *gem*-disubstituted substrates **17c** and **18c** cyclized 24 and 140 000 times more quickly than their parent compounds, respectively.

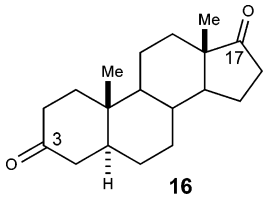
Table 15. Relative Rates of Formation of Substituted Oxazepinones 17a−c and 18a−c at 45 °C



compd	rel rate	compd	rel rate
17a	1.0	**18a**	0.52
17b	3.7	**18b**	0.63
17c	24.0	**18c**	73000

Since these early contributions, a large variety of reactions have benefited from the effect of substitution in promoting selective ring formation and increasing the concentration of cyclic material at equilibrium. Thus, the *gem*-disubstituent effect has been used in several types of synthetic transformations to improve the yield and selectivity of the cyclizations.

Table 14. Equilibrium Constants for the Formation of 5α-Androstane-3,17-dione Ketals and Relative Rates of Hydrolysis

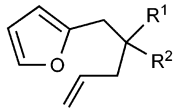
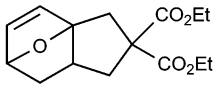
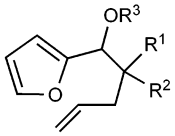
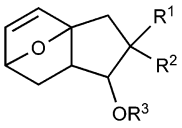
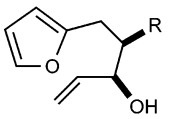
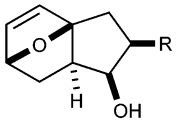
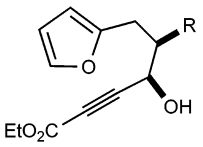
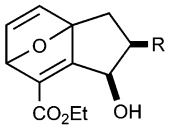
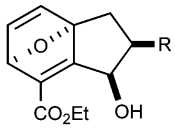
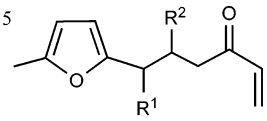
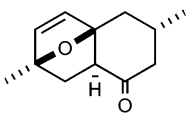
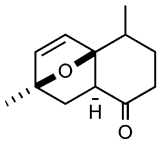


16

	equilibrium constants		rel hydrolysis rate			
glycol	K_3[a]	K_{17}[b]	3-ketal	17-ketal	3-ketal-17-one	17-ketal-3-one
1,3-propanediol	0.03		1.00	1.00	1.00	1.00
2,2-dimethyl-1,3-propanediol	0.45	0.004	0.10	0.17	0.09	0.11
2,2-diethyl-1,3-propanediol	0.57	0.002	0.05	0.06	0.03	0.04

[a] K_3 = equilibrium constant for ketalization of C3 carbonyl. [b] K_{17} = equilibrium constant for ketalization of C17 carbonyl.

Table 16. Substituent Effects on Intramolecular Diels−Alder Cycloaddition with the Diene Furan

Entry	Substrate	R	Conditions	Product	Result	Reference
1		$R^1 = R^2 = CO_2Et$	C_6H_6/5d/80 °C		40% conv.	43
2						
		a $R^1 = R^2 = H$			NR	44
		b $R^1 = R^2 = Me$			NR	
		c $R^1,R^2 = S(CH_2)_3S$	C_6H_6/3d/80 °C		63%	
		d $R^1 = R^2 = OEt$	C_6H_6/1d/80 °C		61%	
		e $R^1,R^2 = CH_2(CH_2)_3CH_2$	C_6D_6/11d/80 °C[a]		47%	45
	a $R^1 = R^2 = H$					
		f $R^1 = R^2 = Pr$	C_6D_6/6d/80 °C[a]		58%	
		g $R^1 = R^2 = SEt$	C_6D_6/56h/80 °C[a]		85%	
	b $R^1 = H$ $R^2 = Me$					
		R^3 = Bn				
		h $R^1 = R^2 = H$			NR	46
		i $R^1,R^2 = S(CH_2)_3S$	C_6H_6/28d/80 °C		62%	
	c $R^1 = Me$ $R^2 = H$	**R^3 = Me**				
		j $R^1 = R^2 = H$			NR	
		k $R^1,R^2 = S(CH_2)_3S$	C_6H_6/2d/80 °C		100%	
3		**a** R = H	C_6H_6/2d/80 °C		NR	47
		b R = *t*Bu	C_6H_6/2d/80 °C		70%[b]	
4		**a** R = H	C_6H_6/80 °C		$t_{1/2}$ = 100h	47, 48
		b R = *t*Bu	C_6H_6/80 °C		$t_{1/2}$ = 26 min	
5		**a** $R^1 = R^2 = H$	CH_2Cl_2/Fluorosil/Δ		NR	49
		b $R^1 = H$ $R^2 = Me$	CH_2Cl_2/Fluorosil/12h, r.t.		SM: Adduct 0 : 100	
		c $R^1 = Me$ $R^2 = H$	CH_2Cl_2/Fluorosil/12h, r.t.		SM: Adduct 14 : 86	

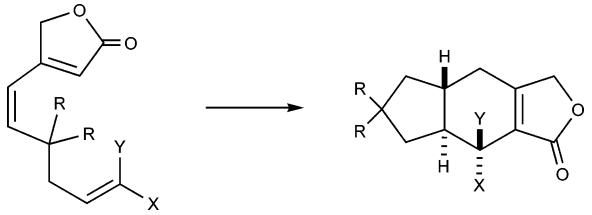
[a] Reactions were carried out in a sealed NMR tube. [b] Twenty percent of starting material was also recovered.

3.1. Pericyclic Reactions

3.1.1. Diels–Alder Cycloadditions

The intramolecular Diels−Alder reaction (IMDA) is one of the most useful carbon−carbon bond-forming reactions in organic synthesis. In particular, the IMDA with furan as the diene has been extensively used for the total synthesis of several natural products. Several research groups investigated the effect of substitution on the alkyl chain bridging the diene and the dienophile, and the results are summarized in Table 16. In 1978, Parker et al. reported an example of IMDA with a furan having *gem*-dialkoxycarbonyl substituents on the tethering chain (entry 1).[43] Despite the lack of an activated dienophile, this substrate underwent cycloaddition to give

Table 17. Substituent Effects on Intramolecular Diels–Alder Cycloaddition of Several Trienes



entry	R	X	Y	$t_{1/2}$[a] (min)	k_{rel}
1	H	CO_2Me	CO_2Me	870	1
2	Me	CO_2Me	CO_2Me	222	3.9
3	H	CO_2Me	H	3780	0.2
4	Me	CO_2Me	H	702	1.2
5	H	CO_2tBu	CN	372	2.3
6	Me	CO_2Me	CN	84	10.3

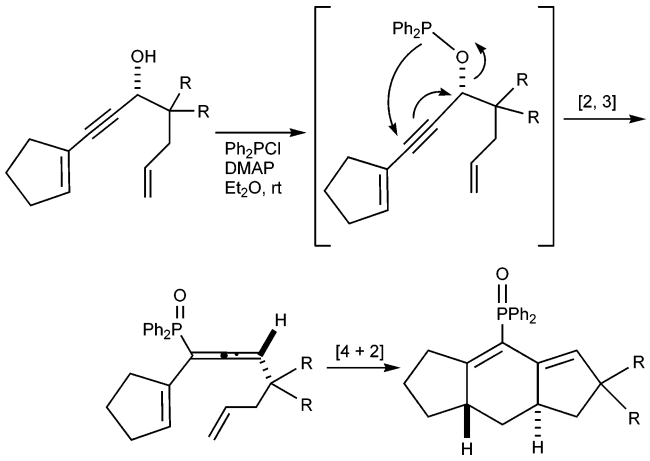
[a] Determined by NMR in toluene-d_8 at 110 °C.

a modest yield of the desired product. A few years later, Sternbach et al. carried out extensive studies on the effect of remote substituents on the furan IMDA (entry 2).[44–46] Except for the dimethyl-substituted case (entry 2b), every other *gem*-disubstituent on the C2 was extremely important for the cyclization. Clearly, the substrates containing cyclic and acyclic thioketal (*gem*-dithioalkoxy) substituents (entries 2c, 2g, 2i, and 2k) underwent cyclization at a faster rate and in good yields, whereas the unsubstituted cases failed to react (entries 2a, 2h, and 2j). The rigidity caused by the dithiane ring and the S–C–S bond angle plays a major role in the success of the furan IMDA of these substrates. By anchoring a *tert*-butyl group on the connecting chain, De Clercq et al. obtained a good yield in one case (entry 3b) and a rate enhancement of 240 for the IMDA with furan in another case (entry 4b) when compared to the unsubstituted cases.[47,48] A significant reaction rate enhancement was also observed for the IMDA of the furan derivatives of entries 5b and 5c.[49] These results are noteworthy because refluxing the unsubstituted substrate (entry 5a) in CH_2Cl_2/fluorosil gave no cyclization product.

The *gem*-disubstituent effect has also been observed in the IMDA involving dienes other than furan.

In 1982, Boeckman et al. described the effect of substitution in the connecting chain on the rate of intramolecular [4+2] cycloaddition of several trienes (Table 17).[50] As expected, the introduction of methyl groups in these systems produced a rate enhancement of ring closure between 3.9 and 6 as compared to the parent case (entries 1, 3, and 5 versus entries 2, 4, and 6). Similar results were observed during the [4+2] cycloaddition of some allenyl phosphine oxides (Table 18).[51] In this study, several propargylic alcohols were treated with chlorodiphenylphosphine to afford the phosphinite ester intermediates, which spontaneously underwent [2,3] sigmatropic rearrangement to give the allenyl phosphine oxides. The rate of the subsequent intramolecular [4+2] was shown to be affected by the presence of *gem*-dialkyl groups on the bridging alkyl chain. However, the size of the alkyl substituent proved to have a minor effect

Table 18. *gem*-Dialkyl Effect on the Intramolecular Diels–Alder Cycloaddition of Allenyl Phosphine Oxides



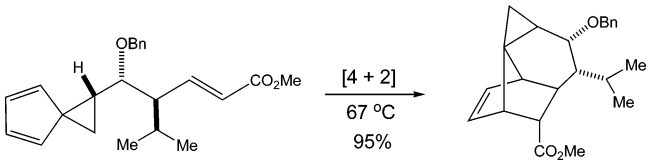
entry	R	$t_{1/2}$[a] (min)	k_{rel}	yield (%)
1	H	656	1	69
2	Me	143	4.6	71
3	Et	30.9	21.2	70
4	Pr	23.6	27.8	63

[a] Determined by NMR in $CDCl_3$ at 25 °C.

on the rate of cycloaddition (entry 2 versus entries 3 and 4).

Another example of the beneficial effect of substituents on reactivity was observed during the intramolecular Diels–Alder approach to some tricyclic sesquiterpenes (Scheme 11).[52]

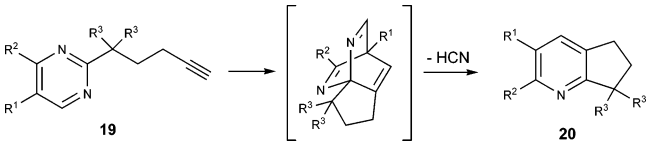
Scheme 11



The cyclization of triene took place at 67 °C to give the desired bridged tetracyclic compound in 95% yield. However, the parent system lacking both the isopropyl and alkoxy groups failed to undergo cycloaddition even at 195 °C.

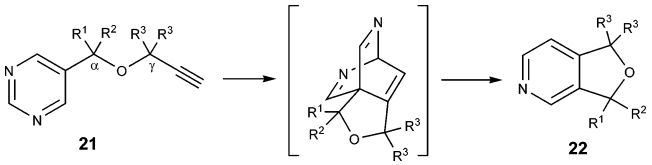
Some inverse electron demand Diels–Alder reactions involving heterodienes such as pyrimidines[53] and triazines[54] have also been studied due to their

Table 19. *gem*-Disubstituent Effect on the Intramolecular Diels–Alder Cycloaddition of 2-(Alkynyl)pyrimidines



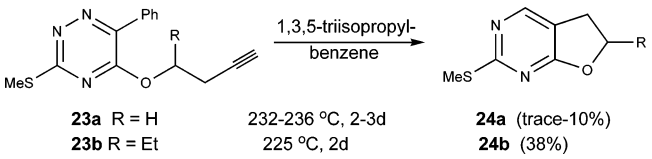
entry	R^1	R^2	R^3	reaction conditions	yield (%)
1	H	H	H	210 °C, 2 h	63
2	H	H	CN	130 °C, 24 h	92
3	NO_2	H	H	210 °C, 0.5 h	58
4	NO_2	H	CN	130 °C, 6 h	96
5	Ph	H	H	210 °C, 3 h	65
6	Ph	H	CN	140 °C, 15 h	100

Table 20. *gem*-Disubstituent Effect on the Intramolecular Diels–Alder Cycloaddition of 5-Propynyloxymethylpyrimidines in Nitrobenzene at 140 °C



entry	R^1	R^2	R^3	k_{rel}	$t_{1/2}$ (h)	yield (%)
1	H	H	H	1	2.80	90
2	Me	H	H	1.9	1.50	84
3	Ph	H	H	1.6	1.75	81
4	Me	Me	H	10.0	0.28	68
5	$-(CH_2)_4-$		H	17.3	0.16	81
6	H	H	Me	3.3	0.83	70

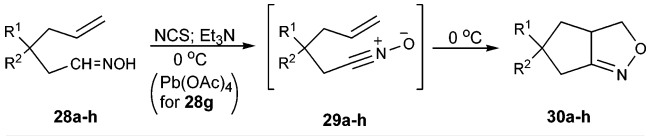
Scheme 12



synthetic utility. For example, van der Plas described the effect of *gem*-dicyano substitution on the intramolecular [4+2] cyclization of 2-(alkynyl)pyrimidines **19** (Table 19).[53a] The formation of the *gem*-disubstituted products **20** (entries 2, 4, and 6) occurred at lower temperatures and in higher yields than the parent bicyclic pyridines (entries 1, 3, and 5). Furthermore, introduction of one or two substituents at the α or γ position of the 5-propynyloxymethylpyrimidines **21** produced an increase in the rate of the Diels–Alder cycloaddition (Table 20).[53b] As expected, the increase of the rate of formation of 1,3-dihydrofuro[3,4-*c*]pyridines **22** as compared to the parent system was more pronounced for the *gem*-disubstituted compounds (entry 1 versus entries 4–6). These results can be explained by the shorter distance between the reacting centers in the substituted cases, due to the reactive-rotamer effect, resulting in favorable enthalpic and entropic driving forces for the cyclizations.

The intramolecular Diels–Alder of 1,2,4-triazines has also shown to be accelerated by the presence of an alkyl group in the side chain (Scheme 12).[54] The introduction of an ethyl group (**23b**) presumably facilitates the orientation of the side chain into a conformation that promotes the cycloaddition. As a result, the desired 2,3-dihydrofuro[2,3-*d*]pyrimidine **24b** is formed in higher yield than the unsubstituted substrate (**24a**).

Table 21. *gem*-Disubstituent Effect on the Intramolecular Dipolar Cycloaddition of Nitrile Oxides 29a–h



nitrile oxide	R^1	R^2	$t_{1/2}$ (min)	k_{rel}
29a	H	H	990	1.0
29b	Me	H	624	1.6
29c	Me	Me	910	1.1
29d	$(CH_2)_4$		338	2.9
29e	Ph	H	248	4.0
29f	CO_2Me	CO_2Me	46	21.5
29g	CO_2Me	H	173	5.7
29h	$S(CH_2)_3S$		<4	>247

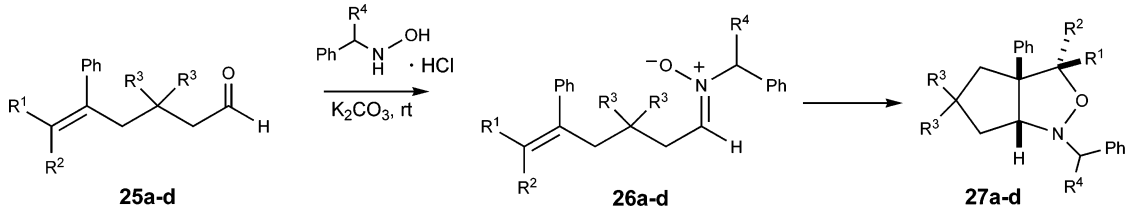
3.1.2. Dipolar Cycloadditions

Other pericyclic reactions beside the Diels–Alder cycloaddition have been used extensively in organic synthesis to construct the polycyclic systems found in many natural products. Several studies have been carried out to understand the structural requirements of the substrate which promote the cycloaddition. One of these structural variations involves the introduction of *gem*-disubstituents in the chain connecting the reacting centers. For example, the intramolecular nitrone cycloaddition of **26** (formed from the aldehydes **25**) to give desired adducts **27** required different reaction conditions depending on the substitution pattern (Scheme 13).[55]

The cycloaddition of the unsubstituted nitrone (**26a**) required high temperature, whereas the reaction of the *gem*-dicarboalkoxy (**26b** and **26c**) and dithioalkoxy (**26d**) nitrones was carried out at lower temperatures to give comparable yields of the corresponding cycloadducts.

The beneficial effect of a variety of substituents was also observed by Jung et al. during the intramolecular dipolar cycloaddition of the nitrile oxides **29a–h** (Table 21).[56] The nitrile oxides were prepared from the aldoximes **28** under standard conditions and reacted in situ to give the desired bicyclic adducts **30a–h**. The rate of cyclization varied greatly depending upon the substitution present on the tethering chain. The *gem*-dimethyl nitrile oxide (**29c**) cyclized more slowly than the monomethyl case, probably

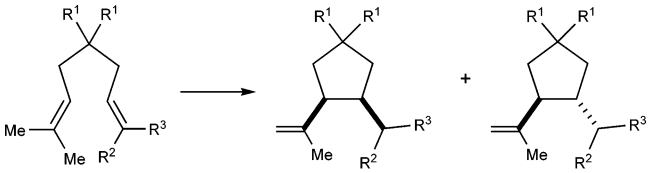
Scheme 13



a $R^1 = CO_2Et$ $R^2 = H$ $R^3 = R^4 = H$
b $R^1 = H$ $R^2 = R^3 = CO_2Et$ $R^4 = H$
c $R^1 = H$ $R^2 = R^3 = CO_2Et$ $R^4 = Me$
d $R^1 = H$ $R^2, R^3 = S(CH_2)_3S$ $R^4 = Me$

toluene reflux, 9h: **27a** 77% (from aldehyde)
benzene r.t., 12h: **27b** 75% (from aldehyde)
benzene r.t., 12h: **27c** 83% (from aldehyde)
benzene reflux, 2h: **27d** 78% (from aldehyde)

Table 22. *gem*-Disubstituent Effect on the Intramolecular Ene Reaction of 1,6-Dienes 31a−d



31 **32** **33**

diene	R^1	R^2	R^3	conditions[a]	combined yield (%)	product **32** (%)	product **33** (%)	$t_{1/2}$ (min)
31a	H	CO_2Me	H	253 °C, 40 h	80	76	24	207
31b	Me	CO_2Me	H	222 °C, 35 h	85	72	28	64
31c	H	CO_2Me	CO_2Me	255 °C, 5 h	70	13	87	912
31d	Me	CO_2Me	CO_2Me	117 °C, 65 h	80	20	80	241

[a] Reactions were carried out in sealed ampules without solvent.

because of the steric interaction between the methyl group and the angular hydrogen in the transition state for the cyclization.[56] However, the *gem*-dicarboalkoxy case (**29f**) cyclized >20 times more rapidly than the parent unsubstituted nitrile oxide (**29a**). The greatest rate enhancement was observed for the thioketal **29h**, which reacted >200 times more rapidly than the unsubstituted compound. Both of these substrates, **29f** and **29h**, which showed a significant *gem*-disubstitution effect, have high synthetic utility because they can be easily prepared by sequential alkylation and used in organic synthesis.

3.1.3. Ene Reactions

Ene reactions have been widely used in organic synthesis for constructing the carbon skeleton of several natural products. For this reason, several research groups studied the effect of substituents on the enophile and on the connecting chain. In 1986, Sarkar et al. reported the effect of geminal substitution on the intramolecular ene reaction of 1,6-dienes (Table 22).[57] From a comparison of the dienes **31a** versus **31b** and the dienes **31c** versus **31d** it is clear that the geminal substitution has an effect on the rate of cyclization but little influence on the ratio of the two diastereomeric products (**32** and **33**). The rate enhancement observed is probably due to the increase of the population of the cisoid conformers required for cyclization. Narasaka et al. have also investigated the effect of substitution on the rate of the asymmetric intramolecular ene reaction catalyzed by a chiral titanium alkoxide (Scheme 14).[58]

The parent oxazolidinone **34a** underwent a very slow ene reaction with a large amount of starting material recovered after 20 days at 0 °C. The desired ene product **35a** was isolated in low yield along with the hydrolyzed hetero-Diels−Alder adduct **36a**. When the methylene hydrogens on the connecting chain were replaced with a *gem*-dimethyl group (**34b**), the cyclization was completed in only 4 days at 0 °C to give the ene (**35b**) and the Diels−Alder (**36b**) products in comparable yields. A higher yield of the desired compound **35b** was obtained when the solvent used was 1,1,2-trichloro-1,2,2-trifluoroethane. Interestingly, the ene reaction of the thioketal derivative **34c** proceeded much more quickly than that in the *gem*-dimethyl case and was complete in 2 days at 0 °C in 1,3,5-trimethylbenzene.

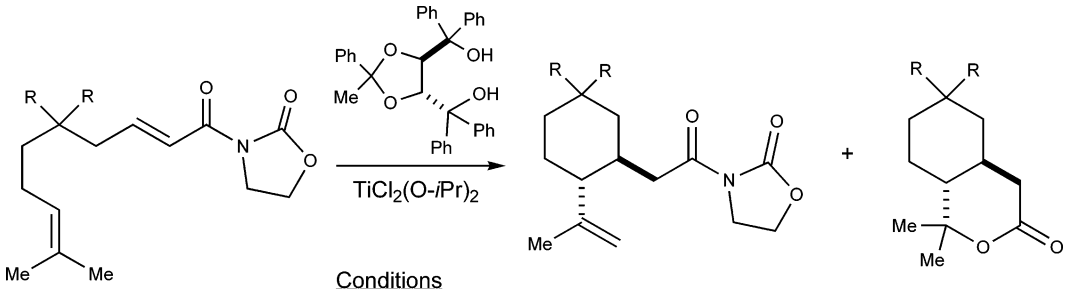
3.1.4. Claisen Rearrangements

β-Allenic esters **38** are useful intermediates in organic synthesis. They can be readily prepared from the corresponding prop-2-ynyl alcohols (**37**) by a thermal, acid-catalyzed Claisen rearrangement, as described by Crandall et al. (Scheme 15).[59] Clearly, the presence of a *gem*-dialkyl group favors the Claisen rearrangements, resulting in higher yield of the desired allenic esters (**38b** and **38c**) and shorter reaction times. Similarly, the rates of thermal, Claisen-like cyclization of some aryl propargyl ethers (**39**) were affected by the presence of substituents (Table 23).[60] As expected, the monomethylated chromenes (**40b** and **40e**) were formed ~10 times more rapdily than their unsubstituted counterparts (**40a** and **40d**). However, geminal dimethyl substitution gave a much larger (>1000) rate enhancement (**40c** and **40f**) as a result of the more favorable orientation of the ethynyl group for cyclization.

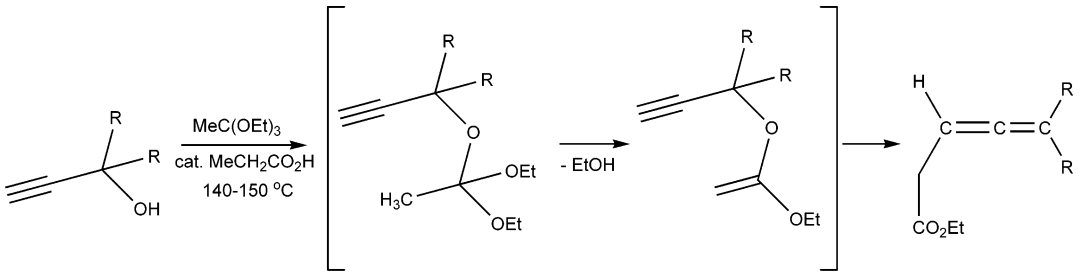
3.2. Radical Cyclizations

During the past two decades, the synthetic utility of radical reactions has been rediscovered. One of the reasons for the high interest is the high tolerability

Scheme 14

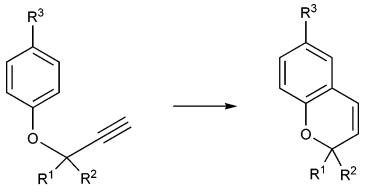


Scheme 15



		Reaction Time	
37a	R = H	5h	**38a** (34%)
37b	R = Me	1.5h	**38b** (54%)
37c	R = -$(CH_2)_5$-	1h	**38c** (51%)

Table 23. *gem*-Dimethyl Effect on the Thermal Cyclization of Propargyl Ethers 39a–f in *o*-Dichlorobenzene



39 **40**

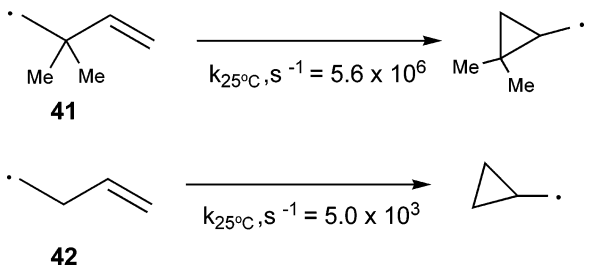
propargyl ether	R^1	R^2	R^3	k_{rel}[a]	yield (%)
39a	H	H	NO_2	1	46
39b	H	Me	NO_2	9.1	84
39c	Me	Me	NO_2	1400	75
39d	H	H	CN	1	
39e	H	Me	CN	10	99
39f	Me	Me	CN	1000	100

[a] Data were extrapolated to 161.6 °C.

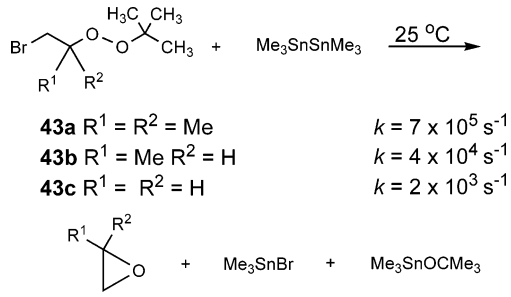
of radical processes toward a large variety of functional groups. In addition, radical cyclizations allow the formation of strained rings, such as cyclopropanes and cyclobutanes, which are difficult to access by other routes. The change in hybridization accompanying the formation of small rings relieves steric compression between *gem* substituents. Consequently, substituted radicals undergo cyclization more readily than the parent species.[61] For example, the rearrangement of 2,2-dimethyl-3-butenyl radical (**41**, Scheme 16) occurred 3 orders of magnitude more quickly than that of its unsubstituted parent, 3-butenyl radical (**42**).[62]

Similarly, the homolytic ring closure of β-peroxyalkyl radicals to form oxiranes is accelerated by the presence of one or two methyl groups (**43a**–**c**, Scheme 17).[63]

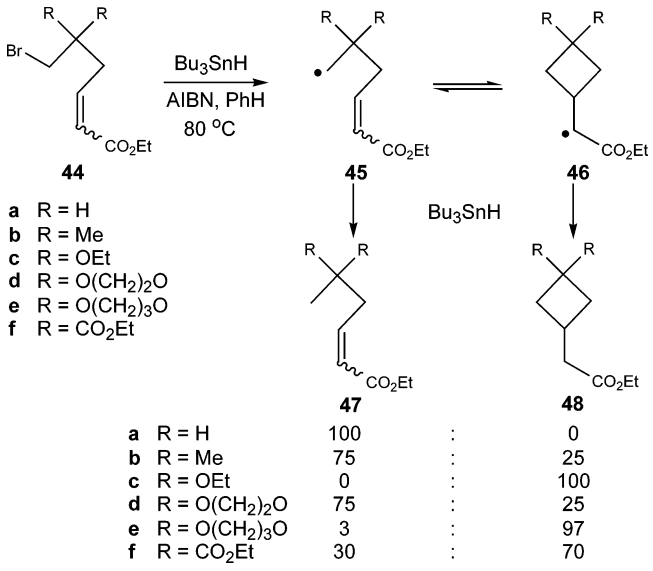
Scheme 16



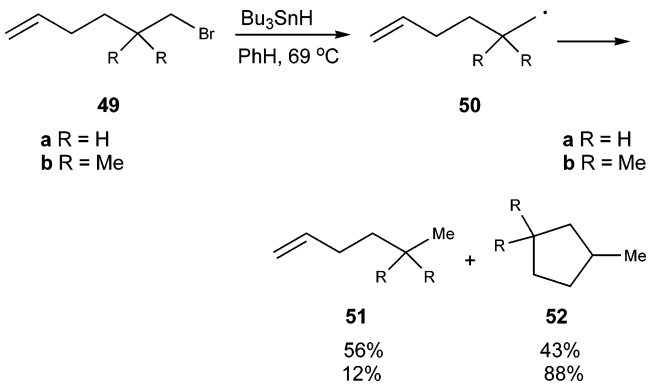
Scheme 17



Scheme 18



Scheme 19



Scheme 20

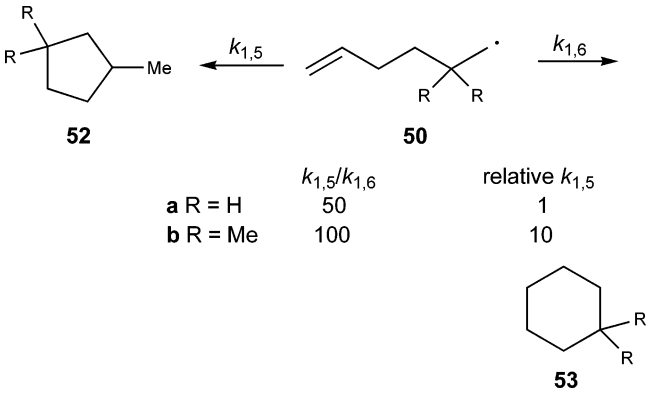
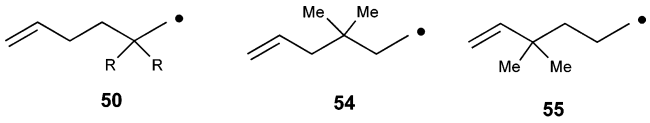


Table 24. Kinetic Data for 1,5-Ring Closure of Substituted Hexenyl Radicals in Benzene at 25 °C



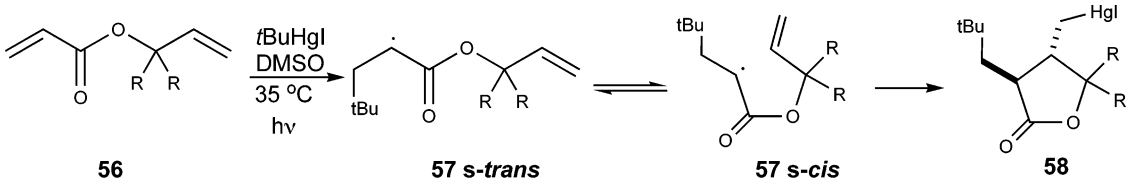
radical	k_{rel}	radical	k_{rel}
50a	1	**54**	21.86
50b	15.1	**55**	13.71

The synthesis of cyclobutanes could also be accomplished via cyclization of the cyclobutylcarbinyl radical **45** (Scheme 18).[64] However, due to the strain of the forming ring, this cyclization is a reversible process, so that further reduction of radicals **45a** and **45b** produces only the acyclic product **47a** or a mixture of acyclic and cyclic products **47b** and **48b**, respectively. Surprisingly, the *gem*-dialkoxy-substituted radical (**45c**) afforded, after only 1 h, the cyclic product **48c** exclusively, and no simple reduced compound (**47c**) was detected. Furthermore, a remarkable ring-size effect was observed for the ketal derivatives **45d** and **45e**. The smaller angle in the dioxolane ring (**45d**) likely increases the angle between the radical-bearing carbon and the electrophilic double bond, thus decreasing the likelihood of cyclization. The *gem*-dicarboalkoxy effect is operative in this radical cyclization (**45f**) as it was in the previously described dipolar cycloaddition.[56a] Computational studies have shown that in all cases investigated experimentally, the *gem*-disubstitution causes a 2−5 kcal/mol decrease in the activation energy for the cyclization.[64d] Consequently, the energy required to convert the *anti* to the *syn* conformer necessary for cyclization is overcome by the *gem*-disubstituent effect, which causes the *syn* conformer to be the global minimum. Radical cyclizations are also extremely useful for the synthesis of five- and six-membered ring systems. One of the earlier reports on the cyclization of hex-5-enyl radicals (**50**) demonstrated that a *gem*-dimethyl group (**50b**) enhances the rate of ring closure, which leads to the cyclopentane **52b** as the major product (Scheme 19).[65]

The regioselectivity of ring closure of hex-5-enyl radicals has been extensively investigated by Beckwith et al.,[66] According to Baldwin's rules, both hex-5-enyl radicals **50a** and **50b** should prefer 1,5-*exo*-cyclization over 1,6-*endo*-cyclization due to the necessity for maximum orbital overlap in the transition state.[67] However, comparison of the kinetic parameters at 80 °C showed that the cyclization of the 2,2-dimethylhex-5-enyl radical (**50b**) is both more rapid and more regioselective than that of the parent radical (**50a**) (Scheme 20).[66a,68] These results suggest that the nonbonded interactions in the transition state, responsible for the observed regioselectivity, are more severe in the *gem*-disubstituted case than for the parent compound.

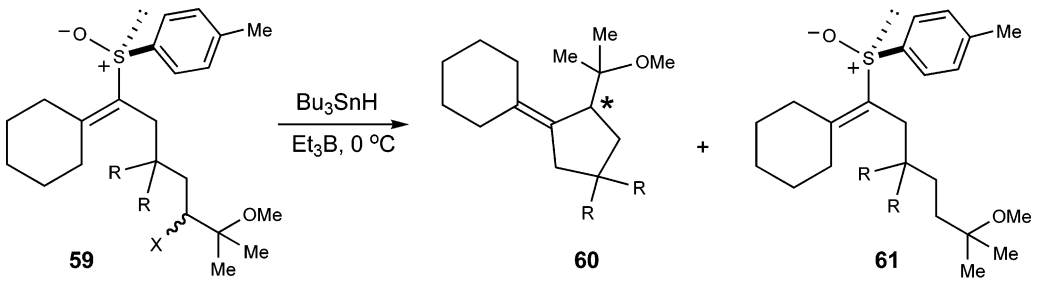
In a later study the same authors investigated the effect of the position of the *gem*-dimethyl group on the rate of 1,5-cyclization of several hex-5-enyl radi-

Scheme 21



	reaction time	yield
a R = H	slow[70]	~10%
b R = Me	0.2h	65%

Scheme 22



a R = H	X = Br	--	90%
b R = CO_2Et	X = PhSe	77% (88% *ee*, *S*)	--

cals (Table 24).[66b] As expected, all three *gem*-dimethyl-substituted radicals (**50b**, **54**, and **55**) underwent 1,5-ring closure more quickly than the unsubstituted radical **50a**. However, the rate enhancement for the 3,3-dimethyl case (**54**) is the highest due to the greater number of *gauche* interactions between the dimethyl group and the substituents at C2 and C4. Whereas the compound with a dimethyl group at C3 (**54**) has two such interactions, radicals **50b** and **55** have only one *gauche* interaction with the substituent at C3. As a result, the rates of cyclization of **50b** and **55** are comparable and lower than that of **54**. Several theoretical studies using MM2 force-field calculation of the strain energies of the transition structures showed good agreement with the experimental results discussed above.[66c,d]

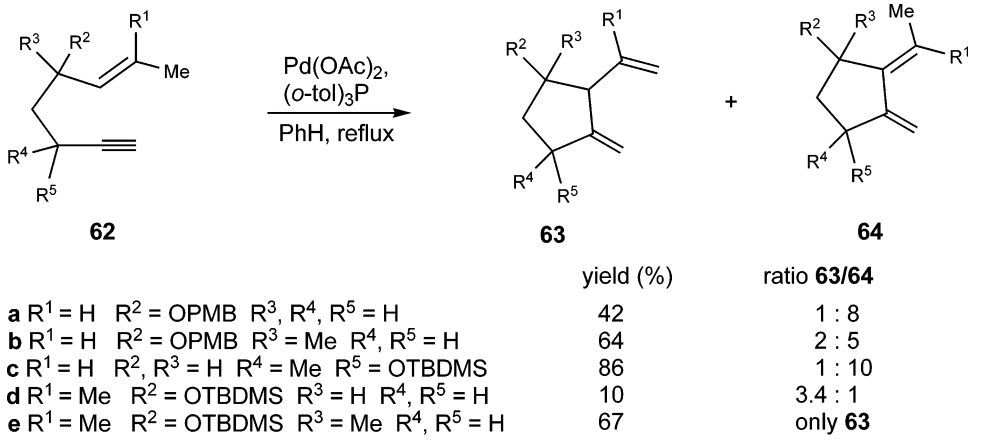
A dramatic *gem*-dimethyl effect has also been observed during the photochemically promoted 5-*exo*-cyclization of ester radicals leading to lactones (Scheme 21).[69] Whereas the photolysis of *t*BuHgI with allyl acrylate **56a** gave the final lactone **58a** in only 10% yield, the cyclization of the *gem*-dimethyl-substituted acrylate **56b** was faster and afforded a higher yield of the cyclized product (**58b**). This difference in reactivity can be rationalized by considering that *gem*-dimethyl substitution would reduce the energy of the s-*trans* to s-*cis* interconversion of the radical **57**, which is necessary for the cyclization to occur.

Similar results were reported by Malacria et al. for the asymmetric intramolecular radical cyclization of enantiopure sulfoxides (Scheme 22).[71] In the absence of the *gem*-dicarboalkoxy group (**59a**), no cyclization product (**60a**) was observed, but only the reduced product (**61a**) was isolated in good yield. As expected, the introduction of the *gem*-disubstituent group on the tether promoted the cyclization and afforded only the desired compound (**60b**).

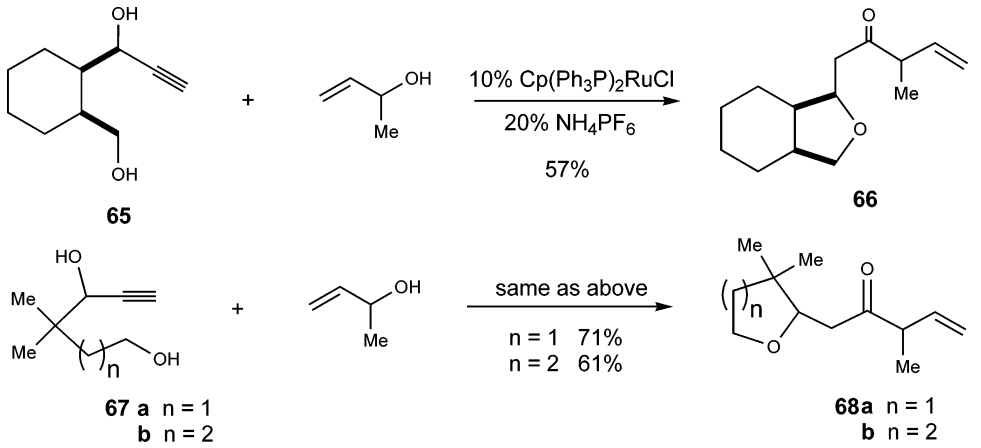
3.3. Transition-Metal-Catalyzed Cyclizations

Annulations using transition-metal-catalyzed reactions represent an important and an ever-evolving

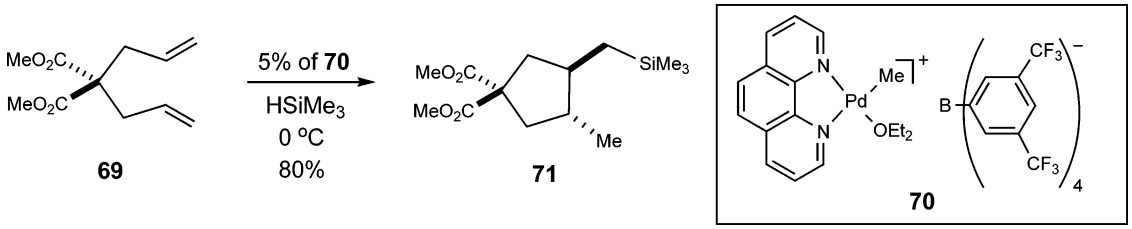
Scheme 23



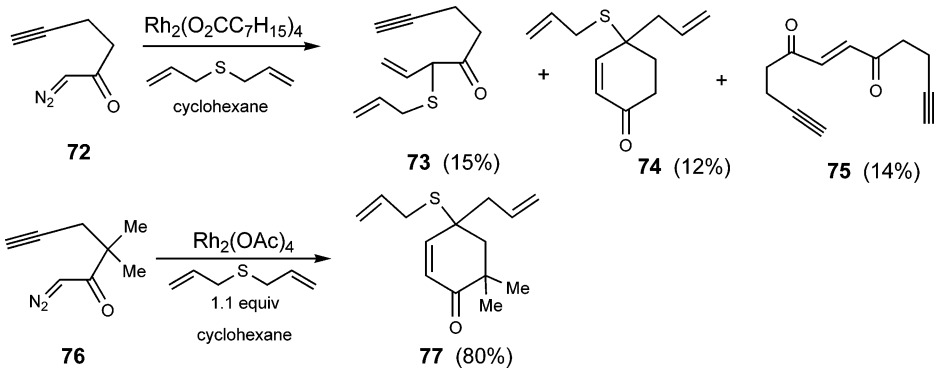
Scheme 24



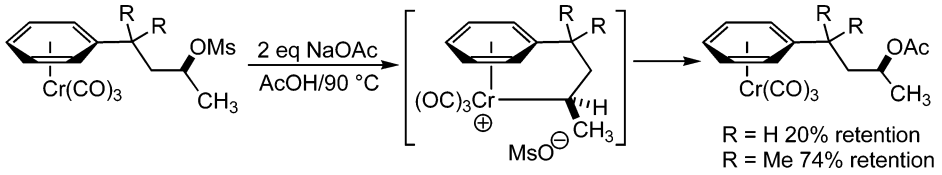
Scheme 25



Scheme 26



Scheme 27



tool for the synthetic chemist. Most of these transformations involve the intramolecular reaction of dienes or enynes with transition metals such as palladium, ruthenium, or rhodium. In one of the pioneering contributions to this research area, Trost et al. explored the effect of the tether substitution on the outcome of palladium-catalyzed cycloisomerization of 1,6-enynes **62** (Scheme 23).[72] Clearly, the introduction of a methyl group next to the olefin (**62b** and **62e**) or next to the triple bond (**62c**) promoted the cyclization and improved the yield of the cyclized products (**63** and **64**). Even though not required, the *gem*-dimethyl group was also found to facilitate the ruthenium-catalyzed tandem cyclization−addition of propargyl alcohols such as **65** and **67** (Scheme 24).[73] Several 4,4-dicarbomethoxy-substituted dienes, such as **69**, underwent facile cyclization/hydrosilylation to give the corresponding carbocycle (**71**) in good yield (Scheme 25).[74] The authors reported that "the protocol required *gem*-bis(carbomethoxy) or related groups at the 4,4′-position of the diene for greatest efficiency".

The importance of the *gem*-dimethyl group in promoting cyclization has also been observed during the rhodium-induced alkyne insertion/rearrangement of diazoketones **72** and **76** (Scheme 26).[75] Whereas the reaction of the unsubstituted diazoketone **72** in the presence of diallyl sulfide gave low yield of the desired cyclized product (**74**) along with uncyclized products (**73** and the dimer **75**), the *gem*-dimethyl-substituted derivative (**76**) afforded only the desired enone (**77**) in high yield.

Other examples of transition-metal-catalyzed cyclizations that benefit from *gem*-disubstitution can be found in the recent literature.[76] For example, Merlic[76a] showed that the presence of a *gem*-dimethyl group allowed better participation of the chromium unit in the solvolysis of the secondary mesylate, resulting in net retention via double inversion in contrast to the unsubstituted case, which gave mainly direct inversion without the participation of the chromacyclic cation (Scheme 27).

3.4. Ring-Closing Metathesis

In the past two decades, ring-closing metathesis (RCM) of acyclic dienes has become a powerful reaction for the synthesis of medium- and large-membered rings. Currently, several protocols and catalysts are available that display good tolerance toward functional groups commonly used in organic synthesis. As a result, RCM is now largely used in the synthesis of natural products containing functionalized cyclic olefins. In one of the earliest reports on the use of the Schrock catalyst (**78**, Figure 13),[77]

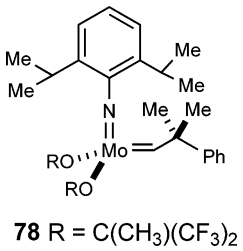
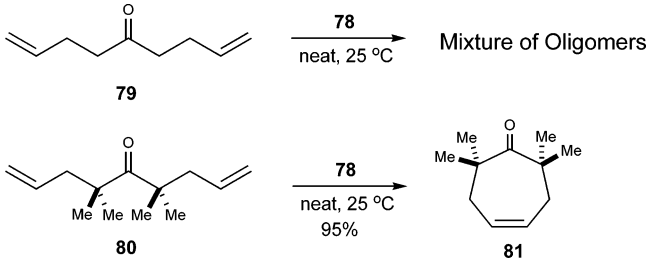


Figure 13. Schrock's molybdenum alkylidene catalyst.

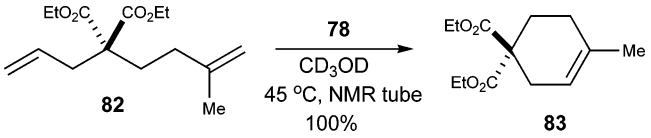
Forbes et al. investigated the effect of the presence of two *gem*-dimethyl groups on the RCM of several dienes (Scheme 28).[78]

Attempted cyclization of the unsubstituted diene **79** gave only a complex mixture of oligomers. However, upon introduction of two *gem*-dimethyl groups, the RCM on the resulting diene (**80**) afforded the desired cycloheptenone **81** in excellent yield. MM2

Scheme 28



Scheme 29



calculations revealed that the cyclized product **81** is significantly more stable (>10 kcal/mol) than any conformations of the dimer expected from a single metathesis on the starting diene **80**. On the other hand, in the case of the unmethylated ketone **79**, the dimer was found to be more stable than the cyclic ketone by 3 kcal/mol, as confirmed by the experimental results. Similar results were obtained by Grubbs et al. during the RCM of several *gem*-dicarboalkoxy-substituted dienes (**82**) using the same molybdenum catalyst (**78**) (Scheme 29).[79]

The higher reactivity of the dienes with the *gem*-diester on the backbone is attributed by the authors to the ease of adopting a conformation favorable for the cyclization.

Scheme 30

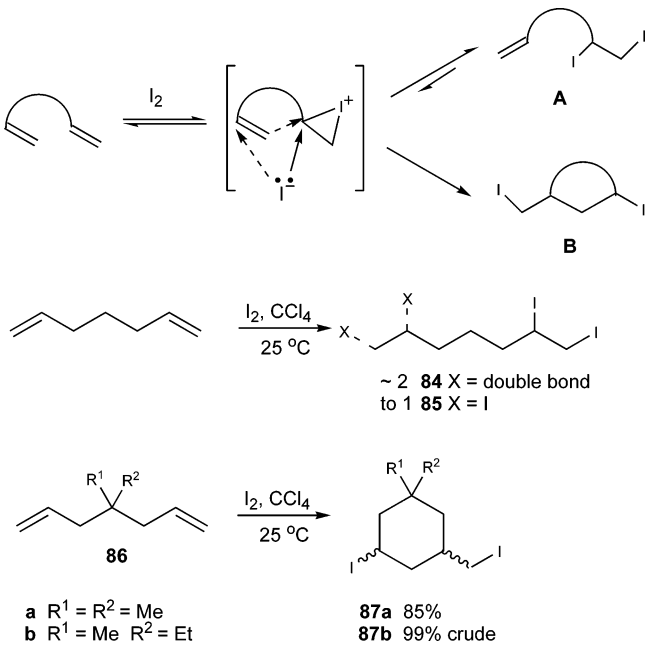
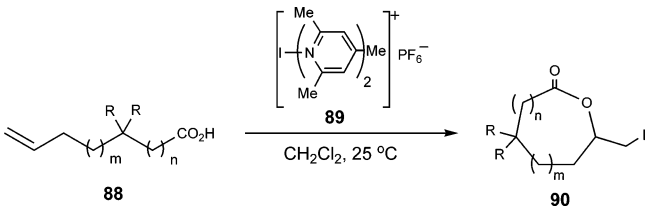


Table 25. Iodolactonization of ω-Alkenoic Acids Using Bis(*sym*-collidine)iodine(I) Hexafluorophosphate 89



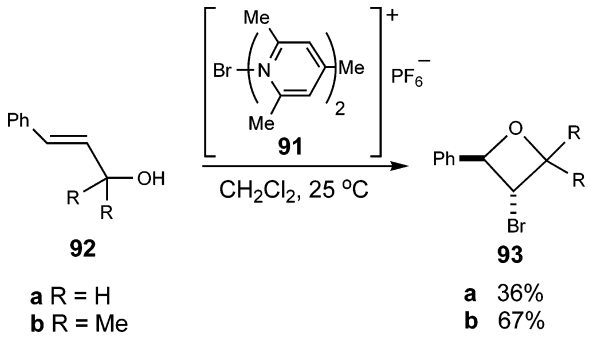
	alkenoic acids					
entry	m	n	R	reaction time (h)	ring size	yield (%)
a	2	0	H	18	7	76
b	2	0	Me	1	7	57
c	1	1	Me	2	7	70
d	0	2	Me	1	7	81
e	3	0	H	4	8	5
f	3	0	Me	2	8	23
g	2	1	Me	17	8	41
h	1	2	Me	5	8, 9	43
i	3	1	Me	5	9	19
j	5	1	Me	14	11, 12	27

3.5. Electrophilic Cyclizations

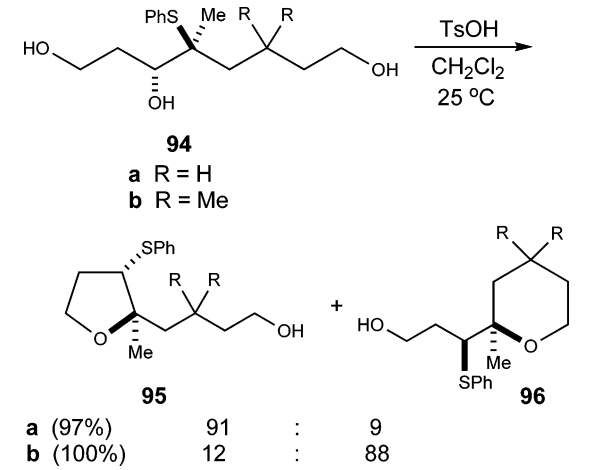
The *gem*-disubstituent effect has also been successfully applied to the cyclization catalyzed by electrophiles such as halides and protic acids. As a result, functionalized lactones, oxetanes, and cyclic ethers can be prepared in high yield and efficiency by introducing a *gem*-disubstituent on the cyclizing chain. For example, treatment of a diene with iodine can yield the iodine addition product (**A**) or the cyclized compound (**B**) depending on the structure of the starting material (Scheme 30).[80] When 1,6-heptadiene reacted with 1 equiv of iodine, a mixture of the mono- and bis-adducts **84** and **85** was observed. However, introduction of dialkyl substituents into the 4-position of the diene (**86a** and **86b**) completely changes the reaction pathway toward cyclization to give **87a**,**b**.

Several medium-size lactones (**90**) have been prepared via iodolactonization of ω-alkenoic acids (**88**)

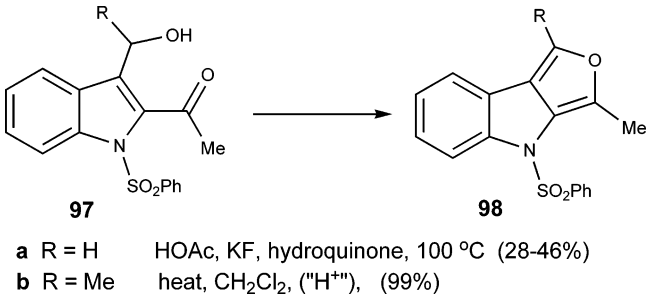
Scheme 31



Scheme 32



Scheme 33



using bis(*sym*-collidine)iodine(I) hexafluorophosphate (**89**) (Table 25).[81] Comparison of the rates of cyclization of 6-heptenoic acid **88a** and the 2,2-, 3,3-, and 4,4-dimethyl analogues **88b**−**d** indicates a positive *gem*-dimethyl effect, although the yields of the substituted product can be either lower or higher depending on the case. The eight-membered cases (**88e** versus the substituted analogues **88f**,**g**) indicate higher yields of cyclization, although the reaction times varied, so the *gem*-dimethyl effect is less clear-cut (although the comparison of **88e** versus **88f** is clear). When the ring size becomes nine-membered or higher (**88i**,**j**), the geminal substitution favors the formation of the lactones, because no reaction was observed with the corresponding unsubstituted acids.[81a] The reagent **91**, identical to **89** but containing bromine in place of iodine, promotes the formation of oxetane systems via a rare 4-*endo*-*trig* cyclization (Scheme 31).[82]

Thus, for the electrophilic cyclization of the allylic alcohols **92**, the presence of a *gem*-dimethyl group is beneficial. Similar results were obtained for the iodoetherification of both allylic and homoallylic alcohols using iodonium(I) bis-*sym*-collidine perchlorate.[83]

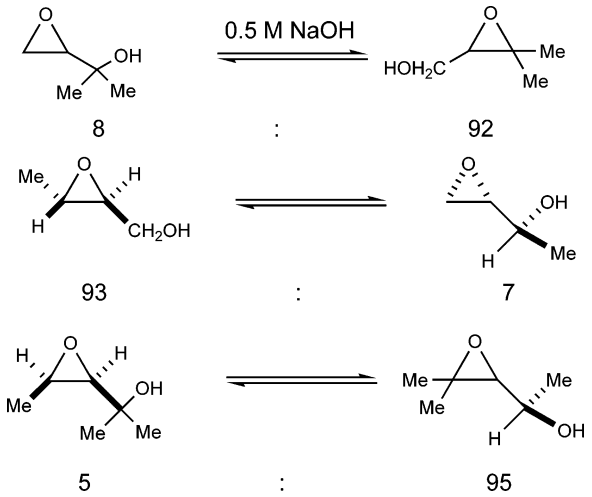
The *gem*-disubstituent effect has also been reported for the synthesis of tetrahydrofurans (THF) and tetrahydropyrans (THP) (Scheme 32).[84] The introduction of a *gem*-dimethyl group on the reacting sulfide (**94**) causes a switch in regioselectivity to form the more substituted ring preferentially. The unsubstituted case (**94a**) afforded mainly the THF product (**95a**), whereas the *gem*-dimethyl case (**94b**) gave mostly the THP compound (**96b**), with the more substituted ring.

Another example of electrophilic cyclization promoted by substitution in the tethering chain involves the formation of 4*H*-furo[3,4-*b*]indoles (**98**) (Scheme 33).[85] The presence of a methyl group in the open-chain substrate (**97b**) favors the cyclization to afford the desired 4*H*-furo[3,4-*b*]indole (**98b**) in high yield.

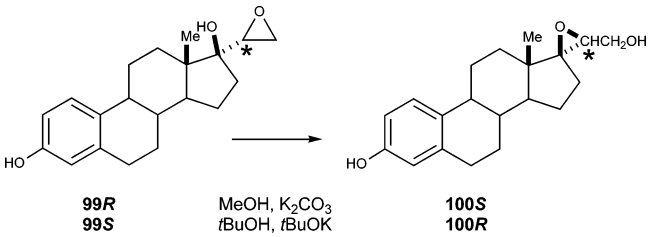
3.6. Other Cyclizations

Other examples of synthetic applications of the *gem*-dialkyl effect include the Payne rearrangement, the electrochemical-induced spirocyclization of alkanoic acids, and the photochemical oxa-di-π-

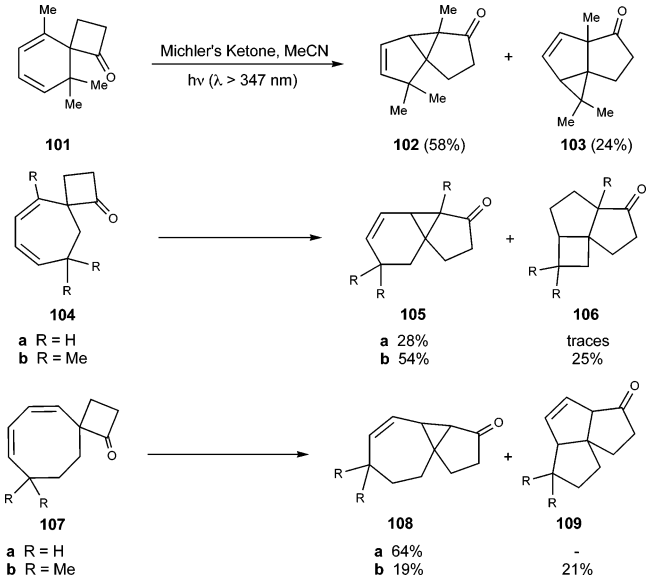
Scheme 34



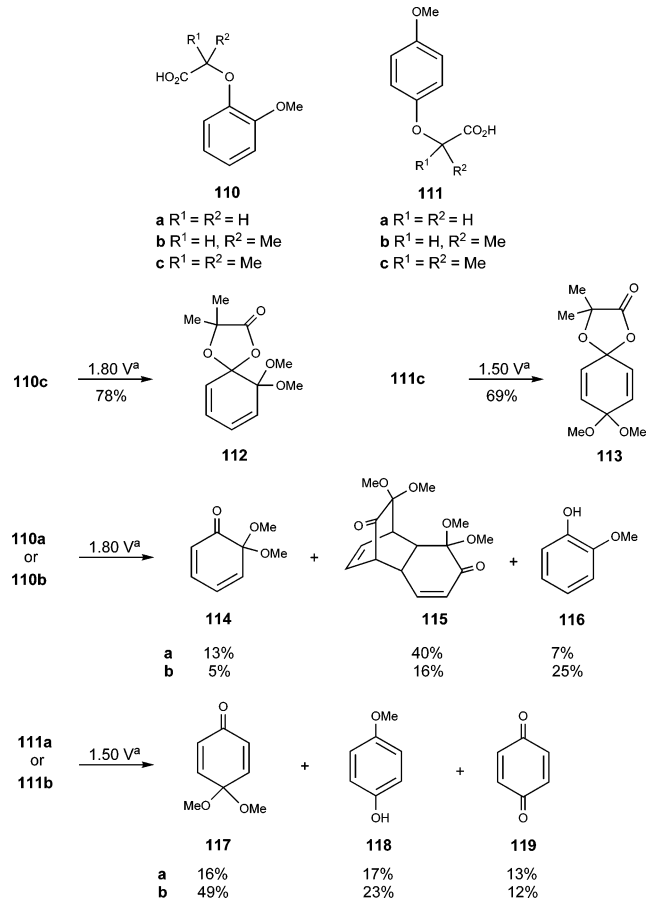
Scheme 35



Scheme 36

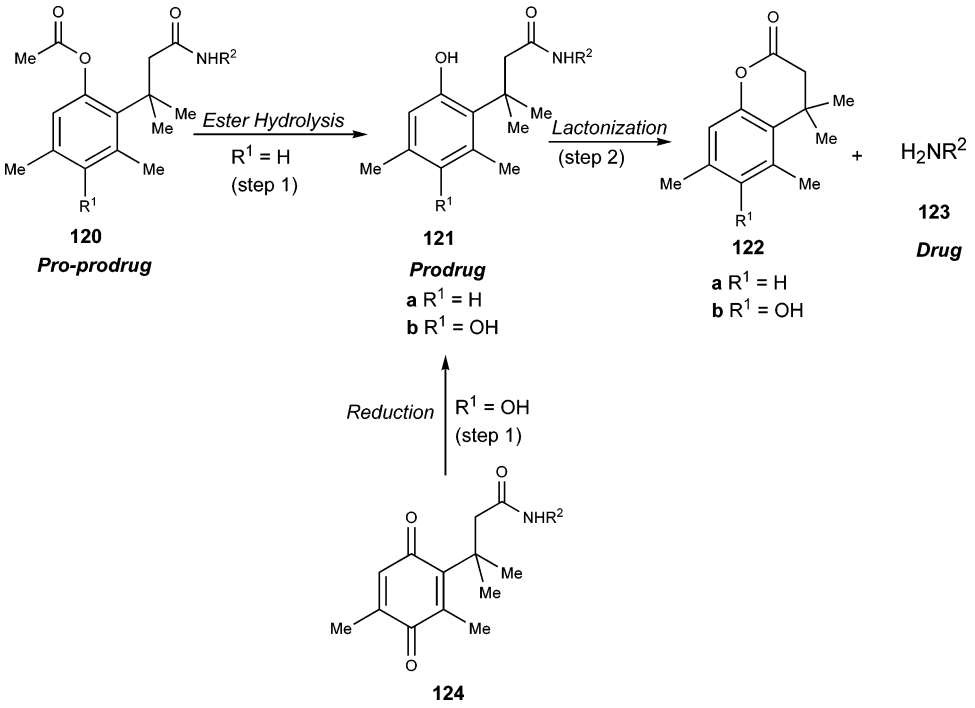


Scheme 37



[a] Platinum-coated titanium anode; MeCN/MeOH (9:1), 2,6-Lutidine, $LiClO_4$

Scheme 38



methane rearrangement. In 1962 Payne reported that during a series of epoxide migrations (Payne rearrangement), the more highly substituted epoxides were the most stable at equilibrium (Scheme 34).[86] The increase in the equilibrium constant is probably due to the decrease in angle strain upon *gem*-disubstitution as shown in Scheme 34. As a result, the more substituted and more stable epoxide is present at equilibrium. Similar examples of Payne rearrangement have been reported in the literature.[87] Norpregnatriene derivatives **99*R*** and **99*S***, when subjected to the Payne conditions, gave the rearranged and more substituted epoxides **100*S*** and **100*R***, respectively (Scheme 35).[87a]

Another interesting manifestation of the *gem*-dialkyl effect appears in the photochemical oxa-di-π-methane rearrangement of substituted cyclobutanones (**101**, **104**, and **107**) (Scheme 36).[88] The presence of a *gem*-dimethyl group clearly changes the product distribution. Only the substituted substrates (**101**, **104b**, and **107b**) afforded the products of vinylogous ring closure (**103**, **106b**, and **109b**). Conversely, the unsubstituted cyclobutanones (**104a** and **107a**) gave only products of a rearrangement involving just a single double bond (**105a** and **108a**).

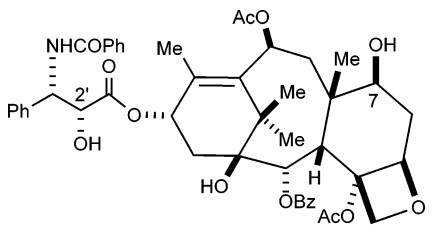
Even electrochemically induced cyclizations have been shown to be affected by geminal substitution (Scheme 37).[89] α-Dimethylated carboxylic acids (**110c** and **111c**) undergo anodic oxidation to yield the spiroannulated products (**112** and **113**) in high yield. However, unsubstituted or monomethylated carboxylic acids (**110a**,**b**, **111a**, and **111b**) do not undergo any spirolactonization but yield only products resulting from competing nucleophilic trapping of the radical cation intermediate by the solvent (**114**−**119**).

4. Biochemical and Pharmaceutical Implications

The source of the large rate acceleration observed in enzymatic reactions can be found in the events accompanying the formation of the enzyme−substrate complex (ES), before the bond-breaking and bond-forming processes begin.[90] These events may involve several conformational changes of the substrate to maximize the interaction with the enzyme active site ("lock and key" model). As a result, the reacting groups on the substrate reach the correct orientation with their counterparts on the active site, and this decreases the stabilization of the ground state and the energy of the transition state or relieves the strain upon formation of the intermediates or products. Several authors recognized the similarities between a monomolecular enzymatic process and an intramolecular reaction.[5b,7] The enhancement of the rate of an intramolecular reaction can be achieved by arranging the reacting groups on the substrate in the same steric configuration as in the transition state. This steric compression can sometimes be obtained by introducing a *gem*-disubstituent in the chain connecting the reacting centers. As a result, the source of the kinetic effect of the geminal substitution, discussed so far, is similar to that involved in enzymatic catalysis.

4.1. "Trimethyl Lock Effect"

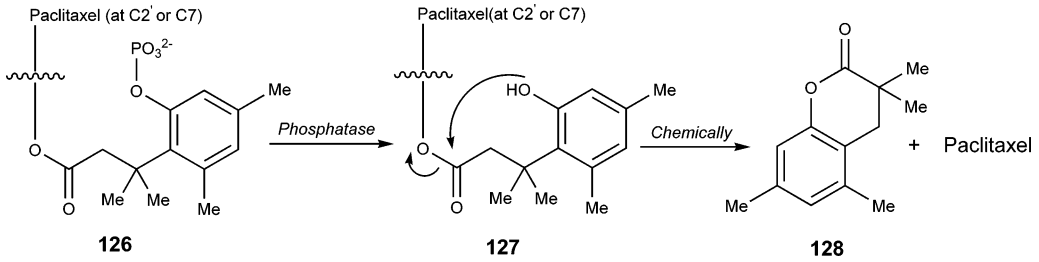
The conformational restriction imposed by the presence of three methyl groups on the hydrocoumarinic acids results in a rate enhancement for the



125

Figure 14. Paclitaxel.

Scheme 39



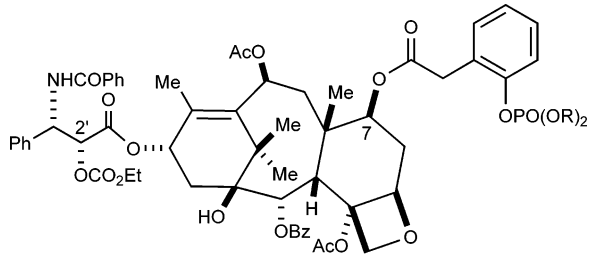
cyclization on the order of 10^{11} as reported by some authors[28,29] (see sections 2.2.5 and 2.2.6) and of 10^5 as found by others.[91] This structural feature has been used to prepare chemical entities (prodrugs), which upon cyclization can release a biologically active molecule (drug).[92] For example, Borchardt et al. reported the use of the 3-(2′-acetoxy-4′,6′-dimethyl)-phenyl-3,3-dimethylpropionamide derivative (**120**) as an esterase-sensitive pro-prodrug for amines (**123**) (Scheme 38).[93] Upon acetate hydrolysis by an esterase (the so-called "enzymic trigger"), the amide **120** is converted to the highly chemically reactive hydroxyamide **121a**. Alternatively, a similar reactive prodrug, **121b**, can be formed by reduction of the analogous quinone propionamide **124**. Due to the presence of the trimethyl lock, the prodrug **121** can then rapidly cyclize to give the lactone **122** and release the biologically active amine **123**.

Another remarkable example of the pharmaceutical applications of the trimethyl lock involves the preparation of prodrugs of Taxol. Taxol is the trade name for paclitaxel (**125**), a natural diterpene currently approved by the U.S. FDA as a potent anticancer agent (Figure 14).[94] Despite its exceptional biological activity, paclitaxel displays poor solubility in water, a major problem for intravenous administration. One approach to solve this solubility problem has been proposed by Ueda et al.[95] A prodrug of paclitaxel is prepared by introducing a water-soluble substituent, which can then be cleaved in vivo by enzymes to regenerate the parent drug ("prodrug approach", Scheme 39).

The introduction of a highly methylated hydroxyphenylpropionic acid at C2′ or C7 of paclitaxel (**126**) guarantees water solubility. After hydrolysis by a phosphatase, the hydroxypropionate ester **127**, with the assistance of the trimethyl lock, can readily undergo lactonization to release the active drug, paclitaxel. Interestingly, in the absence of the trimethyl lock group, the resulting 2′-ethylcarbonate derivative of paclitaxel (**129**) was still hydrolyzed by the phosphatase, but the subsequent lactonization was too slow to generate the parent paclitaxel-2′-ethylcarbonate (Figure 15).[95b] As a result, the paclitaxel prodrug **129** did not show appreciable in vivo antitumor activity. The trimethyl lock has also been applied as the pro-prodrug strategy for Ganciclovir (**130**), the current drug of choice for the treatment of cytomegalovirus retinitis (Figure 16).[96]

Due to the low oral bioavailability of Ganciclovir, a prodrug approach in which a masked water-soluble group (acetate trigger) can be revealed in vivo by the action of an enzyme (esterase) is of definite clinical utility. Thus, after absorption and enzymatic hydrolysis, the pro-prodrug derivative **131** will liberate the hydrophilic phenolic group, which will then rapidly cyclize to release the active drug (**130**). As a result, the trimethyl lock derivative of Ganciclovir (**131**) displayed an oral bioavailability 4-fold greater than that of the parent drug (**130**).

The trimethyl lock group can also be found in prodrugs containing high molecular weight poly(ethylene glycol) (PEG) chains. PEG-conjugated prodrugs accumulate in cancer tissues, where they can selectively deliver the anticancer agent. Such a promising strategy has been developed by Greenwald et al. to prepare PEG−daunorubicin prodrugs (**132**) (Scheme 40).[97] The introduction of a high molecular weight PEG into the trimethyl lock system results in a neutral and highly water-soluble polymeric prodrug capable of passive tumor targeting. Interestingly, the pro-prodrug derivative of daunorubicin (**132**) was found to be more effective than the parent drug in inhibiting the growth of ovarian adenocarcinoma (SKOV3). In addition, the pharmacokinetic properties of the PEG prodrugs developed by Greenwald can be tuned by properly choosing the spacer group, the trigger/linker bond, and the degree of steric hindrance on the aromatic ring. As a result, the rate of formation of the prodrug (**133**) in vivo can be adjusted to different types of drugs in addition to antitumor agents.



129

R = H, Na

Figure 15. 7-(*o*-Phosphonoxyphenylacetyl)paclitaxel-2′-ethylcarbonate.

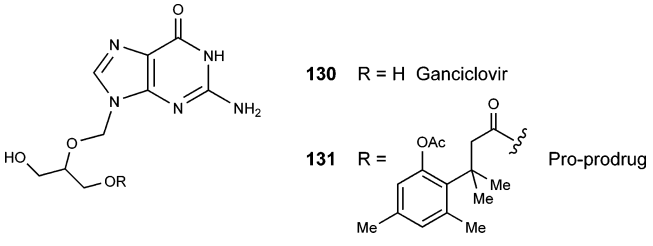
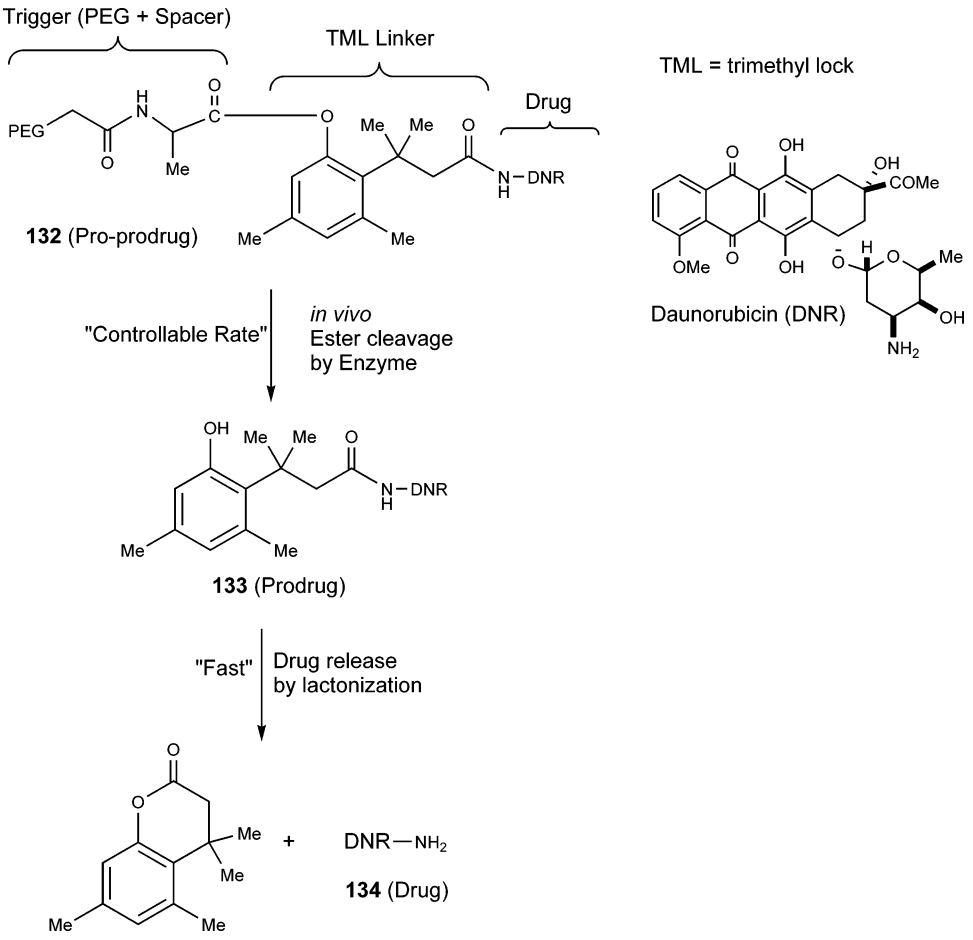


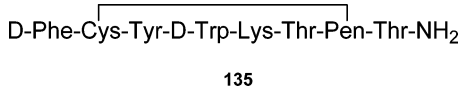
Figure 16. Ganciclovir and its pro-prodrug **131**.

Scheme 40



4.2. *gem*-Dialkyl Substitution in Drug Design

The introduction of geminal disubstituents can be used to improve the pharmacokinetic properties of a drug, as described for the trimethyl lock, or to increase its biological activity. For example, the *gem*-dimethyl group of penicillamine (the dimethyl analogue of cysteine) on the cyclic peptide **135** reduces the dihedral angle of the disulfide bond and the 20-membered ring via a transannular *gem*-dimethyl effect (Figure 17).[98]



135

Figure 17. Somatostatin analogue **135**.

Interestingly, although quite different from somatostatin in sequence and ring size, the conformationally restricted peptide **135** is one of the most potent selective analogues of somatostatin for the μ-opiate receptor. Similarly, *gem*-dialkyl substitution has been used in the design of selective in vivo antagonists of other biologically active peptides. Several potent antagonists of vasopressin and oxytocin were found by converting linear peptides into conformationally restricted molecules via *gem*-dialkyl (dimethyl, diethyl) and cyclopentamethylene substitutions on the β-carbon of the cysteine or the β-mercaptopropionic acid residue at position 1 of the parent peptides.[99] It is speculated that the β,β-dialkyl substitutions modify the interactions of such active cyclic peptides with the receptor in a manner that preserves affinity but eliminates the ability to activate. This same type of effect seems to be the source of the increased biological activity upon geminal substitution of the inhibitors of two classes of enzymes: phospholipase A_2 (PLA_2) and pancreatic carboxypeptidases A and B (CPA and CPB). PLA_2 is a ubiquitous set of enzymes that plays a central role in several important physiological and pathological events such as septic shock, rheumatoid arthritis, and inflammation. The suicide-inhibitory bifunctionally linked substrates (SIBLINKS) comprise a promising class of PLA_2 inhibitors with an interesting mechanism of action (Scheme 41).[100] Upon enzymatic hydrolysis of the ester bond of SIBLINKS **136**−**140**, the resulting carboxylates (**141**−**145**) cyclize to form the corresponding anhydrides (**146**−**150**). If cyclization is faster than diffusion, the anhydride will be formed in the vicinity of the enzyme (PLA_2) active site. As a result, the target enzyme will be acylated and thus inhibited. The biological properties of SIBLINKS **136**−**140** are summarized in Table 26.[100b] Introduction of geminal methyl groups on either the γ carbon (**137**) or the β carbon (**138**) of the glutaryl chain reduces the rate of enzymatic hydrolysis by 1400- and 77500-fold, respectively. Due to the spatial requirements of the multiple methyl groups on the substrate, the PLA_2 is unable to undergo a conformational

Scheme 41

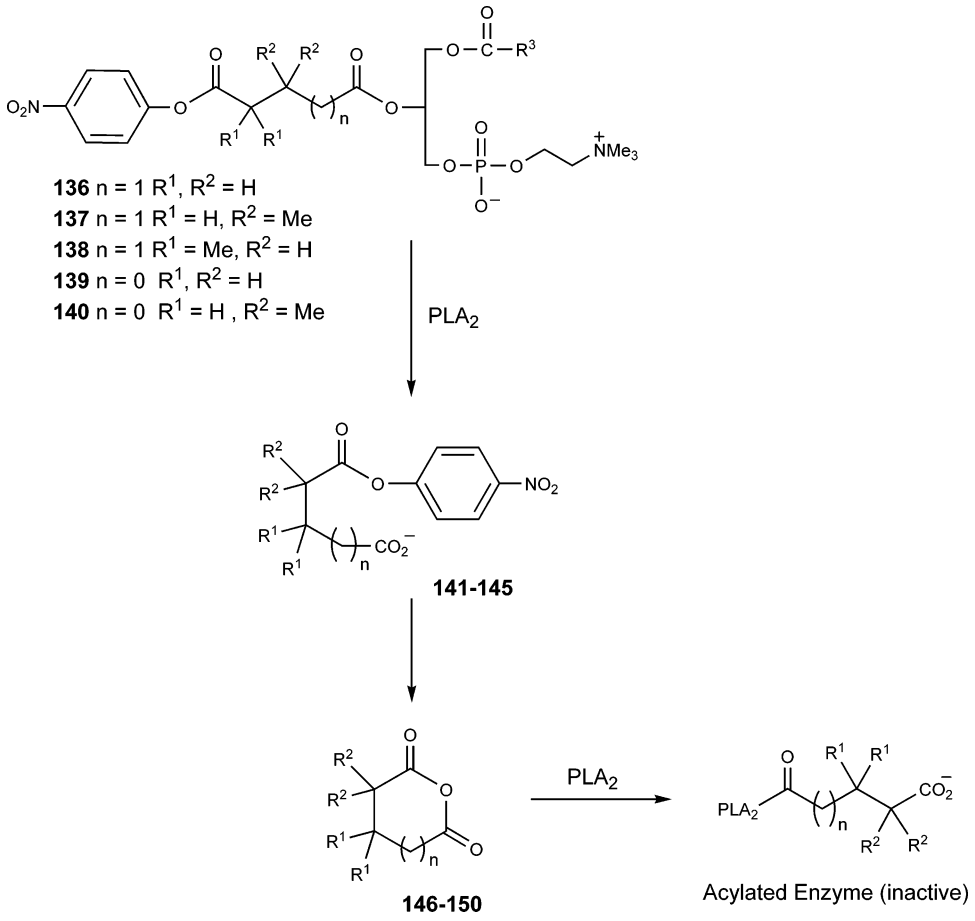
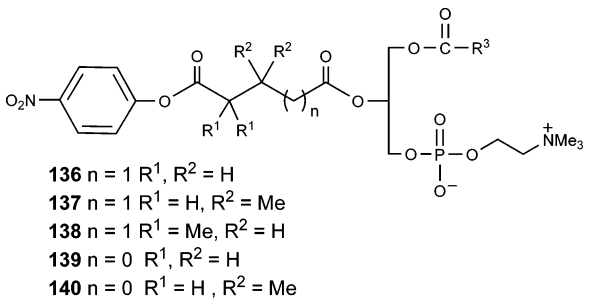


Table 26. Rate of *N. naja naja* Phospholipase A_2-Catalyzed Hydrolysis of Various SIBLINKS, Their Residual Activity,[a] and Partition Ratio (*P*)[b]

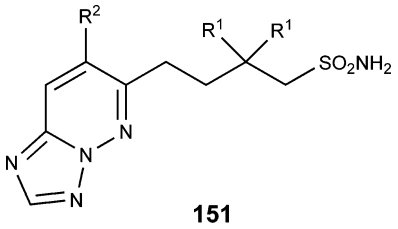


SIBLINK	R^3 chain length	rate (μmol min^{-1} mg^{-1})	rel rate^{-1}	resid act. (%)	*P* (mol/mol)
glutarate					
136a	8	40		100	
136b	10	155	1	100	
dimethylglutarate					
137a	8	0.11		15	52
137b	10	0.11	1400	10	19
137c	12	0.14		18	32
137d	14	0.13			46
137e	16	0.15		15	45
137f	18	0.11			58
138	10	0.002	77500	25	9
succinate					
139a	10	0.6	1925	10	35
139b	16	1.9		8	60
dimethylsuccinate					
140	10	0.005	31000	25	11

[a] Amount of residual enzyme activity remaining after preincubation. [b] Number of moles of SIBLINKS hydrolyzed per mole of enzyme inactivated.

Table 27. Inhibition of Carboxypeptidases A and B (CPA and CPB) by Succinic Acid Derivatives

	inhibition constant (K_i, mM)	
derivative	CPB	CPA
succinic acid	28 ± 4	4 ± 0.8
2,2-dimethyl	0.028 ± 0.002	0.0017 ± 0.0002
2-ethyl-2-methyl (*R*,*S*)	0.0045 ± 0.0004	0.00011 ± 0.00001



151

a $R^1 = R^2 = H$
b $R^1 = Me$ $R^2 = H$
c $R^1 = Et$ $R^2 = H$
d $R^1 = -(CH_2)_4-$ $R^2 = H$
e $R^1 = Et$ $R^2 = Me$

Figure 18. Orally active antiasthmatic bronchodilators.

change required for its catalytic activity. Comparing the values of the partition ratio (*P*) of the SIBLINKS, it is clear that the inhibition efficiency increases (lower *P*) with the methyl substitution on the linker. However, because the differences in the hydrolysis rates do not account quantitatively for the difference in the *P* values, it seems unlikely that the increase in efficiency of the SIBLINKS inhibitors upon substitution can arise from the *gem*-dimethyl effect on the rate of cyclization. Most likely, the methyl groups on either the carboxylates (**141**−**145**) or the anhydrides (**146**−**150**) cause stronger interactions with the active site, resulting in a greater probability for enzyme acylation.

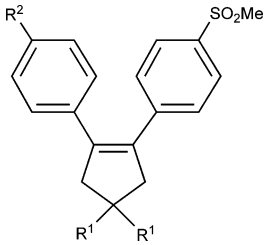
gem-Dialkylsuccinic acids have also been shown to be highly potent inhibitors of both carboxypeptidase A (CPA) and B (CPB) (Table 27).[101] The 2,2-dimethyl- and the 2-methyl-2-ethylsuccinic acids showed an affinity for these enzymes much higher than that of the unsubstituted acid. The authors speculated that there might be a hydrophobic cavity in the native enzymes, CPA and CPB. Thus, the extra methyl groups (cenophilic[102] substituents) could promote better interactions of the inhibitors in this cavity.

In 1997 Miyake et al. developed a new class of orally active antiasthmatic bronchodilators (**151**) (Figure 18).[103] Although the unsubstituted compound **151a** showed only modest antiasthmatic activity, introduction of dimethyl (**151b**), diethyl (**151c**), and tetramethylene (**151d**) groups at the 2-position of the sulfamoylpropyloxy group increased the inhibitory activity. Among all of the derivatives tested, the trialkyl-substituted derivative **151e** proved to be an excellent antiasthmatic bronchodilator.

Nonsteroidal antiinflammatory drugs (NSAIDS) reduce the pain and the swelling associated with inflammation by inhibiting the conversion of arachidonic acid to prostaglandins by the enzymes cyclooxygenase I (COX-1) and II (COX-2).[104] During structure−activity relationship (SAR) study on the parent COX-2 inhibitor **152a**, new analogues with improved COX-1 and COX-2 activities were found (Table 28).[105] The substituents at C4 of the cyclopentene ring are oriented above and below the plane of the double bond and thus they allow one to test the spatial requirements of the active site of the enzyme. Clearly, the introduction of the *gem*-dimethyl group (**152b** and **152c**) caused an increase in both the COX-1 and COX-2 activities, as compared to the unsubstituted compound (**152a**). However, the selectivity was significantly reduced. In addition, replacement of the methyl group with an ethyl (**152d**) resulted in a significant loss on both enzymatic activities, suggesting that the enzyme domain interacting with this region is sensitive to steric bulk.

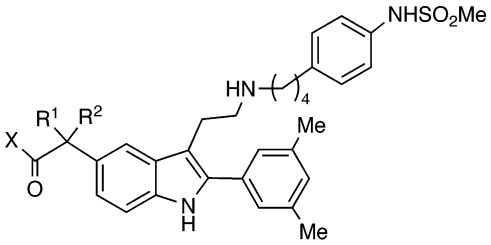
A more recent example of the use of geminal substitution in drug design involves the synthesis of potent inhibitors of the release of the luteinizing hormone (LH) (**153**; Table 29).[106] When a *gem*-dimethyl group was introduced as a spacer between the indole and the carbonyl, the resulting inhibitor showed significantly improved potency (**153a** and **153d** versus **153b**,**c** and **153e**,**f**, respectively).

Table 28. Activity of 4,4-Disubstituted Cyclopentene Cyclooxygenase Inhibitors



			IC$_{50}$ (μM)		
inhibitor	R^1	R^2	COX-1	COX-2	selectivity
152a	H	F	>100	0.026	>3800
152b	Me	F	18.3	0.015	1200
152c	Me	Cl	1.6	0.007	230
152d	Et	F	>100	65	>1.5

Table 29. Inhibition of LH Release by Indole-5-acetates/Acetamides 153



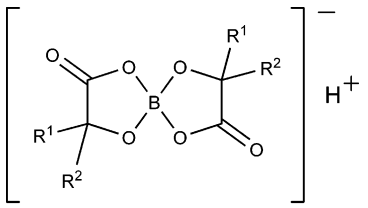
153

compd	R^1	R^2	X	LH release (IC$_{50}$, nM)
153a	H	H	EtO	2000
153b	Me	H	EtO	610
153c	Me	Me	EtO	150
153d	H	H	Et_2N	130
153e	Me	H	Et_2N	130
153f	Me	Me	Et_2N	42

5. Miscellaneous

5.1. *gem*-Disubstituent Effect on the Formation and Stability of Inorganic and Organometallic Complexes

Geminal substitution has also been found to favor the formation and to increase the stability of several types of complexes. For example, substituted α-hydroxycarboxylic acids form strong complexes with boric acid (**154**; Figure 19).[107]



154

Figure 19. General structure of 1:2-boro-α-hydroxy carboxylate complexes.

Interestingly, the electrophoretic mobility of such complexes is very dependent on the degree of substitution at the α-carbon of the carboxylic acids (**155**; Table 30). Comparison of the values of the mobilities of substituted acids (glycolic, mandelic, benzylic, etc.) with that of their unsubstituted counterparts showed a progressive increase upon introduction of substituents. Clearly, for acids more densely substituted on their α-carbon, the *gem*-disubstituent effect is driving the equilibria to favor the five-membered cyclic boric acid complexes, which display higher electrophoretic mobility.

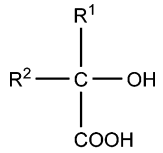
The *gem*-dialkyl effect is also operating in complexes containing strained rings. For example, Green et al. investigated the effect of *gem*-dialkyl groups and other bulky substituents on the stability of azaplatinacyclobutane rings (**158**; Scheme 42).[108] The several azaplatinacyclobutanes **158** were formed quickly and reversibly by treating a solution of the η^2-alkene complex **156** with an amine as in Scheme 41. As expected, the formation of cyclic complexes is aided by bulky groups in Am, R, and maybe Y.

Other organometallic complexes benefit from the introduction of *gem*-dialkyl groups. 1,4,8,11-Tetrathiocyclotetradecane (**159a**) and its derivatives (**160a** and **161a**) have been prepared and the effect of *gem*-dimethyl groups on the formation of the nickel(II) chelates (**159b**, **160b**, and **161b**) evaluated (Figure 20).[109]

The authors found that the Ni(II) affinity for these ligands steadily increases upon geminal substitution in nitromethane solution. Thus, they speculated that the *gem*-dimethyl substituents change the conformational preference of the macrocyclic backbone, favoring the conformations in which the sulfur atoms are preorganized for metal ion chelation.

In 1996, Crans et al. reported the effect of substitution on the ligand geometry for four- and five-coordinate oxovanadium(V) complexes (**162** and **163**; Figure 21).[110] They observed that as methyl groups replace the hydrogen atoms on the ethylene glycol unit, the stability of complex **162** increases over the isomeric form **163**. This effect is probably due to the decrease of the energy difference between the most stable *anti* conformation of the ethylene ligand and the *syn* form present in **162** upon geminal substitution.

Table 30. Mobilities of α-Hydroxy Acids in Electrolytes Containing Boric Acid



155

entry	α-hydroxy acid	R^1	R^2	$\Delta M_N \times 100$ value[a]
1	glycolic	H	H	4
2	L-lactic	H	Me	16
3	D-glyceric	H	CH_2OH	19
4	L-malic	H	CH_2COOH	17
5	α-hydroxyvaleric	H	Pr	21
6	L-mandelic	H	C_6H_5	18
7	DL-α-hydroxybutyric	H	Et	26
8	DL-α-hydroxyisovaleric	H	*i*Pr	32
9	D-tartaric	H	CH(OH)COOH	31
10	citric	CH_2COOH	CH_2COOH	38
11	benzylic	C_6H_5	C_6H_5	30
12	D-tartronic	H	COOH	11
13	α-hydroxyisobutyric	Me	Me	46
14	(−)-heliotric	*i*Pr	CH(Me)OMe	48
15	α-hydroxy-α-methyl-butyric	Me	Et	51

[a] $\Delta M_N \times 100$ values represent differences observed in relative mobilities ($M_N \times 100$ values) before and after addition of boric acid to the electrolyte. Acids were detected after paper electrophoresis in each electrolyte at 20−25 V cm^{-1} and 20 °C for 40 min−1 h.

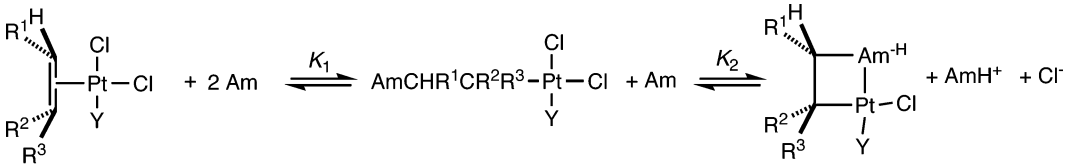
5.2. Reverse *gem*-Disubstituent Effect

The effect of replacing the methylene hydrogens of a chain with alkyl or other groups is usually beneficial for both the rate and efficiency of cyclization, as discussed thus far. However, in some cases lower yields of the substituted cyclic compound have been reported (negative or reverse *gem*-disubstituent effect). For example, during the oxidative coupling of nona-1,8-diyne, the yield of the cyclization of the 5,5-dimethyl derivative (**164b**) was much lower than that of the unsubstituted diyne (**164a)** (Scheme 43).[111]

Similar results were obtained during the cyclization of doubly *gem*-dimethyl-substituted diesters, dinitriles, and diketenes (Table 31).[112] Clearly, the yield of seven- and eight-membered ring unsubstituted ketones is higher than that of the *gem*-dimethyl case. The observed reverse *gem*-dimethyl effect is probably due to the geometrical restrictions that the dimethyl group imposes on the conformation necessary for the cyclization.

Also, Nichols et al. observed that during the iodocyclization of cyclic alkenols (**167**), derivatives with-

Scheme 42

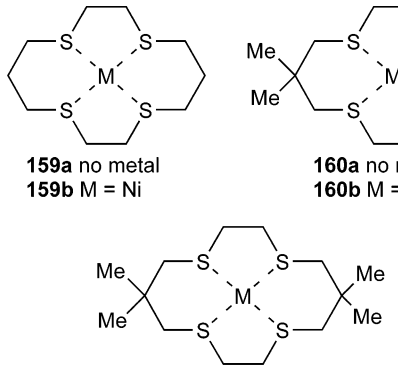


156 **157** **158**

Am = amine Am^{-H} = amine less one proton Y = 4-Mepyr, $NHMe_2$, PPh_3, pyr, $SOMe_2$

a $R^1 = R^2 = R^3 = H$
b $R^1 = Me\ R^2 = R^3 = H$
c $R^1 = Et\ R^2 = R^3 = H$
d $R^1 = R^2 = Me\ R^3 = H$
e $R^1 = R^3 = Me\ R^2 = H$

out additional methyl groups on the backbone cyclized preferentially to the *gem*-disubstituted compounds (Table 32).[113] In the case of five- and six-membered ring alkenols, the introduction of the *gem*-dimethyl group (**167c** and **167f**) results in a decrease in the yield of the cyclized products (**168c** and **168f**). Competition experiments were carried out to estimate the rate differences. When an equimolar mixture of alcohol **167f** and alcohol **167d** or **167e** was treated under the same reaction conditions and monitored by NMR spectroscopy, a greater amount of product was produced from the less substituted alcohol, confirming that the latter had reacted more quickly. The reasons for this pattern of reactivity are unclear but may have to do with the rate of attack of primary and secondary versus tertiary alcohols on the presumed iodonium ion intermediate.

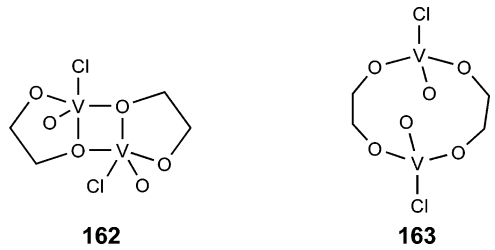


159a no metal
159b M = Ni

160a no metal
160b M = Ni

161a no metal
161b M = Ni

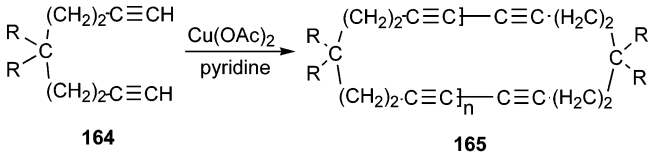
Figure 20. Macrocyclic tetrathioethers.



162 **163**

Figure 21. Oxovanadium(V) complexes.

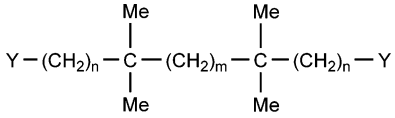
Scheme 43



164
a R = H
b R = Me

165
a R = H ~100%
b R = Me 52%

Table 31. *gem*-Dimethyl Effect on the Cyclization of Diesters, Dinitriles, and Diketenes[a]



166

entry	Y	*m*	*n*	ring size of mono- and diketone	yield[b] (%) monoketone	yield[b] (%) diketone
1	COOR	2	1	7, 14	30 (47)	0 (0)
2	COOR	3	1	8, 16	0 (15)	0 (11)
3	COOR	2	2	9, 18	30 (0)	7 (25)
4	COOR	3	2	10, 20	0.4 (0)	27 (12)
5	COOR	2	3	11, 22	13 (0.5)	15 (23)
6	COOR	3	3	12, 24	8 (0.5)	10 (16)
7	CN	2	1	7, 14	tr[c] (96)	0 (0)
8	CN	2	2	9, 18	2.4 (2.8)	18 (62)
9	CN	3	2	10, 20	0 (0.4)	20 (70)
10	COCl	2	1	7, 14	0 (33)	8 (10)
11	COCl	3	1	8, 16	0 (0)	10 (31)

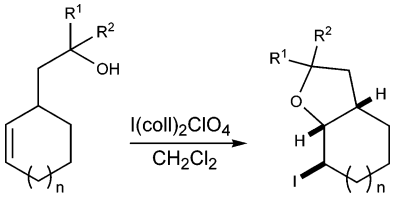
[a] Cyclizations were carried out in xylene in the presence of a solution of potassium *tert*-butoxide in *tert*-butyl alcohol. [b] Yields of the corresponding unsubstituted compound are in parentheses. [c] Traces.

5.3. *vic*-Disubstituent Effect

It is interesting to consider if the presence of vicinal alkyl groups in the chain undergoing cyclization might have the same kinetic effect (*vic*-dialkyl effect) as the *gem*-dialkyl substitution. One of the earliest examples that allows for the comparison of the two effects involves the formation of the anhydrides from the hemiesters of various succinic acids (see section 2.2.2 and Figure 22).[1b,5,17] In this case, the rate of cyclization of the *vic*-dimethyl substituted succinate is slightly greater than that for the *gem*-dimethyl-substituted compound.

A more recent example of vicinal dialkyl effect has been reported by Jung et al. for the electrophilic cyclization of substituted homoallylic alcohols (**169**) to prepare oxetanes (**170**; Table 33).[56b,114] Whereas the *vic*-disubstituted substrates (**169a** and **169c**) afforded predominately the desired oxetanes (**170a**

Table 32. Reverse and Normal *gem*-Dimethyl Effect on the Iodocyclization of Alkenols 167



167 168

alkenol	n	R^1	R^2	yield (%)
167a	0	H	H	33
167b	0	Me	H	40
167c	0	Me	Me	20
167d	1	H	H	67
167e	1	Me	H	42
167f	1	Me	Me	42
167g	2	H	H	40
167h	2	Me	H	80
167i	2	Me	Me	54

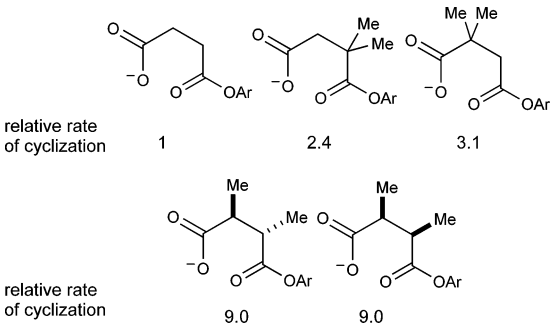
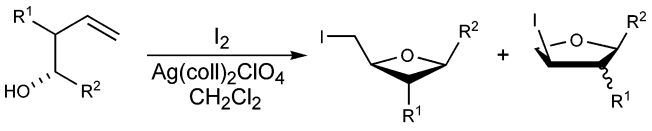


Figure 22. Effect of geminal versus vicinal substitution.

Table 33. Iodoetherification of Homoallylic Alcohols with Silver(I) Bis-*sym*-collidine Perchlorate and Iodine



169 170 171

alcohol	R^1	R^2	yield (%)	yield (%)
a	CH=CH_2	Ar	52−77	traces
b	H	CH_2OTBS	8	24
c	CH=CH_2	CH_2OTBS	62	11

and **170c**), the cyclization of **169b**, which lacks the vicinal substituents, gave mainly the tetrahydrofuran derivative **171b**.

6. Conclusions

The theoretical basis and both synthetic and biochemical applications of the *gem*-disubstituent effect have been presented. Several theories to explain the source of this rate-enhancing effect have been described with their differences and similarities. Most authors agree that the origin of the *gem*-disubstituent effect may vary somewhat depending on the system being analyzed. However, there is little doubt that the beneficial effect of the introduction of a geminal group can be found in many cyclizations. Nearly a hundred years after its first report, the use of geminal substitution is still an important tool for synthetic chemists to increase the rate of formation and the yield of various cyclizations.

7. Acknowledgments

We thank the National Institutes of Health and the National Science Foundation for generous support.

8. References

(1) For reviews, see: (a) Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum Press: New York, 1976; Vol. 1, pp 43−75. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(2) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. (c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *120*, 1117.
(3) Often this term and the "*gem*-dialkyl effect" are used interchangeably, but more correctly the "Thorpe−Ingold effect" refers specifically to the angle change upon substitution, whereas the "*gem*-dialkyl effect" refers to the overall acceleration.
(4) Galli, C.; Giovanelli, G.; Illuminati, G.; Mandolini, L. *J. Org. Chem.* **1979**, *44*, 1258.
(5) (a) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858. (b) Bruice, T. C.; Pandit, U. K. *Proc. Natl. Acad. Sci. U.S.A.* **1960**, *46*, 402.
(6) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.
(7) Page, M. J.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678.
(8) (a) Dale, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 1000. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1965; Chapter 4, pp 189−199.
(9) Jung, M. E. *Synlett* **1990**, 186.
(10) Nilsson, H.; Smith, L. *Z. Phys. Chem.* **1933**, *166A*, 136.
(11) (a) Kirby, A. J.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1753. (b) Derissen, J. L. *Acta Crystallogr.* **1970**, *B26*, 901.
(12) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1984**, *106*, 139.
(13) Saettel, N. J.; Wiest, O. *J. Org. Chem.* **2003**, *68*, 4549.
(14) von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1961**, *83*, 1368.
(15) Brown, R. F.; Van Gulick, N. M. *J. Org. Chem.* **1956**, *21*, 1046.
(16) Wheeler, O. H.; Granell de Rodriguez, E. E. *J. Org. Chem.* **1964**, *29*, 1227.
(17) (a) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1965**, *87*, 4838. (b) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10790.
(18) (a) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1965**, *87*, 4846. (b) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1968**, *90*, 3808.
(19) Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1965**, *87*, 4851.
(20) Bordwell, F. G.; Osborne, E. C.; Chapman, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 2698.
(21) Laughton, P. M.; Robertson, R. E. *Can. J. Chem.* **1955**, *33*, 1207.
(22) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1985**, *26*, 591.
(23) (a) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429. (b) Jung, M. E. *Synlett* **1990**, 186. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.
(24) Giessner-Prettre, C.; Hückel, S.; Maddaluno, J.; Jung, M. E. *J. Org. Chem.* **1997**, *62*, 1439.
(25) (a) Wilson, S. R.; Guarnieri, F.; *Tetrahedron Lett.* **1991**, *32*, 3604. (b) Guarnieri, F.; Cui, W.; Wilson, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1542. (c) Wilson, S. R.; Cui, W.; Moskowitz, J. W.; Schmidt, K. E. *J. Comput. Chem.* **1991**, *12*, 342.
(26) (a) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319. (b) Parrill, A. L.; Dolata, D. P. *J. Mol. Struct.* **1996**, *370*, 187.
(27) Karle, J. M.; Karle, I. L. *J. Am. Chem. Soc.* **1972**, *94*, 9182.
(28) (a) Milstien, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1143. (b) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. (c) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9175.
(29) (a) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275. (b) Winans, R. E.; Wilcox, C. F. *J. Am. Chem. Soc.* **1976**, *98*, 4281.
(30) Eberson, L.; Welinder, H. *J. Am. Chem. Soc.* **1971**, *93*, 5821.
(31) (a) Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1206. (b) Kirby, A. J.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1753.
(32) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505.
(33) Wagenaar, A.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1988**, *53*, 768.

(34) Benedetti, F.; Berti, F., Fabrissin, S.; Gianferrara, T.; Risaliti, A. *J. Org. Chem.* **1991**, *56*, 3530.
(35) Björnstad, S. L.; Borgen, G. *Acta Chem. Scand.* **1975**, *29*, 13.
(36) Galli, C.; Giovannelli, G.; Illuminati, G.; Mandolini, L. *J. Org. Chem.* **1979**, *44*, 1258.
(37) Verevkin, S. P.; Kümmerlin, M.; Beckhaus, H. D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* **1998**, *579*, 9.
(38) (a) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 2588. (b) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 3884.
(39) (a) Blagoeva, I. B.; Tashev, D. T.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1157. (b) Koedjikov, A. H.; Blagoeva, I. B.; Pojarlieff, I. G.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2479. (c) Atay, E.; Blagoeva, I. B.; Kirby, A. J.; Pojarlieff, I. G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2289. (d) Blagoeva, I. B.; Kirby, A. J.; Kochiyashki, I. I.; Koedjikov, A. H.; Pojarlieff, I. G.; Toteva, M. M. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1953.
(40) Dale, J. *J. Chem. Soc.* **1963**, 93.
(41) (a) Newman, M. S.; Harper, R. J., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 6350. (b) Smith, S. W.; Newman, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 1249. (c) Smith, S. W.; Newman, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 1253.
(42) Turk, J.; Haney, W. M.; Heid, G.; Barlow, R. E.; Clapp, L. B. *J. Heterocycl. Chem.* **1971**, 149.
(43) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, *19*, 1689.
(44) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853.
(45) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1985**, *26*, 591.
(46) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, *23*, 303.
(47) Cauwberghs, S.; De Clercq, P. J. *Tetrahedron Lett.* **1988**, *29*, 2493.
(48) De Corte, F.; Nuyttens, F.; Cauwberghs, S.; De Clercq, P. *Tetrahedron Lett.* **1993**, *34*, 1831.
(49) Rogers, C.; Keay, B. A. *Tetrahedron Lett.* **1989**, *30*, 1349.
(50) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.
(51) (a) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1. (b) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278.
(52) (a) Antczak, K.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1985**, *63*, 993. (b) Gallacher, G.; Ng, A. S.; Attah-Poku, S. K.; Antczak, K.; Alward, S. J.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 1709. (c) Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
(53) (a) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5151. (b) Frissen, A. E.; Marcelis, A. T. M.; Buurman, D. G.; Pollmann, C. A. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5611. (c) Stolle, W. A. W.; Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *J. Org. Chem.* **1992**, *57*, 3000.
(54) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287.
(55) (a) Baldwin, S. W.; Wilson, J. D.; Aubé, J. *J. Org. Chem.* **1985**, *50*, 4432. (b) Aubé, J. Ph.D. Thesis, Duke University, 1984.
(56) (a) Jung, M. E.; Vu, B. T. *Tetrahedron Lett.* **1996**, *37*, 451. (b) Jung, M. E. *Synlett* **1999**, 843.
(57) (a) Ghosh, S. K.; Sarkar, T. K. *Tetrahedron Lett.* **1986**, *27*, 525. (b) Sarkar, T. K.; Ghosh, S. K.; Subba Rao, P. S. V.; Satapathi, T. K. *Tetrahedron Lett.* **1990**, *31*, 3461.
(58) Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609.
(59) Crandall, J. K.; Tindell, G. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1411.
(60) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841.
(61) Beckwith, A. L. J.; Ingold, K. U. Free-radical rearrangements. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4, pp 161−310.
(62) Newcomb, M.; Glenn, A. G.; Williams, W. G. *J. Org. Chem.* **1989**, *54*, 2675.
(63) Bloodworth, A. J.; Davies, A. G.; Griffin, I. M.; Muggleton, B.; Roberts, B. P. *J. Am. Chem. Soc.* **1974**, *96*, 7599.
(64) (a) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719. (b) Jung, M. E.; Kiankarimi. *J. Org. Chem.* **1995**, *60*, 7013. (c) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1997**, *38*, 6521. (c) Jung, M. E.; Kiankarimi. *J. Org. Chem.* **1998**, *63*, 2968. (d) Jung, M. E.; Marquez, R.; Houk, K. N. *Tetrahedron Lett.* **1999**, *40*, 2661. (e) Jung, M. E. *Synlett* **1999**, 843.
(65) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2778.
(66) (a) Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535. (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.
(67) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(68) Della, E. W.; Smith, P. A. *Tetrahedron Lett.* **2001**, *42*, 481.
(69) (a) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831. (b) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2066.
(70) The cyclization of ester radicals derived from allyl acrylate (**57**) and allyl acetate is known to be very slow. See: ref 69a; and Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.
(71) Delouvrié, B.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11305.
(72) (a) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491.
(73) Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476.
(74) Widenhoefer, R. A.; DeCarli, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3805.
(75) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1992**, *33*, 169.
(76) (a) Merlic, C. A.; Miller, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 3805. (b) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (c) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. (d) Trost, B. M.; Gelling, O. J. *Tetrahedron Lett.* **1993**, *34*, 8233.
(77) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
(78) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W., Jr.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978.
(79) (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *117*, 77310. (b) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904.
(80) Günther, H. J.; Jäger, V. *Tetrahedron Lett.* **1977**, *29*, 2539.
(81) (a) Simonot, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 4527. (b) Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4.
(82) Homsi, F.; Rousseau, G. *J. Org. Chem.* **1999**, *64*, 81.
(83) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.
(84) (a) McIntyre, S.; Sansbury, F. H.; Warren, S. *Tetrahedron Lett.* **1991**, *32*, 5409. (b) McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457.
(85) Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem.* **1992**, *57*, 5878.
(86) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.
(87) (a) Gill, J. C.; Lockey, P. M.; Marples, B. A.; Traynor, J. R. *J. Med. Chem.* **1986**, *29*, 1537. (b) Bell, T. W.; Ciaccio, J. A. *Tetrahedron Lett.* **1988**, *29*, 865.
(88) Lyle, T. A.; Mereyala, H. B.; Pascual, A.; Frei, B. *Helv. Chim. Acta* **1984**, *67*, 774.
(89) Deffieux, D.; Fabre, I.; Courseille, C.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 4458.
(90) (a) Bruice, T. C. Proximity effects and enzyme catalysis. In *The Enzymes*, 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1970; Vol. 2, Chapter 4, pp 217−279. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.
(91) Caswell, M.; Schmir, G. L. *J. Am. Chem. Soc.* **1980**, *102*, 4815.
(92) For recent reviews, see: (a) Shan, D.; Nicholaou, M. G.; Borchardt, R. T.; Wang, B. *J. Pharm. Sci.* **1997**, *86*, 765. (b) Testa, B.; Mayer, J. M. *Drug Metab. Rev.* **1998**, *30*, 787. (c) Wang, W.; Jiang, J.; Ballard, C. E.; Wang, B. *Curr. Pharm. Des.* **1999**, *5*, 265.
(93) Amsberry, K. L.; Gerstenberger, A. E.; Borchardt, R. T. *Pharm. Res.* **1991**, *8*, 455.
(94) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
(95) (a) Ueda, Y.; Mikkilineni, A. B.; Knipe, J. O.; Rose, W. C.; Casazza, A. M.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1761. (b) Ueda, Y.; Matiskella, J. D.; Mikkilineni, A. B.; Farina, V.; Knipe, J. O.; Rose, W. C.; Casazza, A. M.; Vyas, D. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 247. (c) Vyas, D. M.; Ueda, Y.; Wong, H.; Mastiskella, J. D.; Hauck, S.; Mikkilineni, A. B.; Farina, V.; Rose, W. C.; Casazza, A. M. *ACS Symp. Ser.* **1995**, *No. 583* (Taxane Anticancer Agents), 124−127. (d) Mamber, S. W.; Mikkilineni, A. B.; Pack, E. J.; Rosser, M. P.; Wong, H.; Ueda, Y.; Forenza, S. *J. Pharm. Exp. Ther.* **1995**, *274*, 877.
(96) Dillon, M. P.; Cai, H.; Maag, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1653.
(97) Greenwald, R. B.; Choe, Y. H.; Conover, C. D.; Shum, K.; Wu, D.; Royzen, M. *J. Med. Chem.* **2000**, *43*, 475.
(98) Pelton, J. T.; Cody, W. L.; Hruby, V. J.; Gulya, K.; Hirning, L. D.; Yamamura, H. I.; Burks, T. F. *Peptides: Structure and Function*; Proceedings of the Ninth American Peptide Symposium; Deber, C. M., Hruby, V. J., Kopple, K. D., Eds.; Pierce Chemical: Rockford, IL, 1985; pp 623−626.
(99) Manning, M. Substance P. *Proceedings of the International Symposium Held in Dublin, April 27−29, 1983*; Skrabanek, P., Powell, D., Eds.; Boole Press: Dublin, Ireland, 1983; pp 14−15.
(100) (a) Washburn, W. N.; Dennis, E. A. *J. Am. Chem. Soc.* **1990**, *112*, 2042. (b) Washburn, W. N.; Dennis, E. A. *J. Biol. Chem.* **1991**, *266*, 5042.
(101) Asante-Appiah, E.; Seetharaman, J.; Sicheri, F.; Yang, D. S.-C.; Chan, W. W.-C. *Biochemistry* **1997**, *36*, 8710.
(102) From Greek, meaning empty-loving.
(103) Kuwahara, M.; Kawano, Y.; Kajino, M.; Ashida, Y.; Miyake, A. *Chem. Pharm. Bull.* **1997**, *45*, 1447.
(104) Vane, J. R. *Nat. [New Biol.]* **1971**, *231*, 232.

(105) Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1994**, *37*, 3878.
(106) Ashton, W. T.; Sisco, R. M.; Yang, Y. T.; Lo, J.-L.; Yudkovitz, J. B.; Cheng, K.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1723.
(107) Frahn, J. L. *J. Chromatogr.* **1984**, *314*, 167.
(108) Green, M.; Sarhan, K. K.; Al-Najjar, I. M. *Organometallics* **1984**, *3*, 520.
(109) Desper, J. M.; Gellman, S. H.; Wolf, R. E.; Cooper, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 8663.
(110) Kempf, J. Y.; Maigret, B.; Crans, D. C. *Inorg. Chem.* **1996**, *35*, 6485.
(111) Borgen, G.; Dale, J. *Acta Chem. Scand.* **1972**, *26*, 159.
(112) Borgen, G.; Dale, J. *Acta Chem. Scand.* **1972**, *26*, 952.
(113) Nichols, C. J.; Parks, J. J. *J. Undergrad. Chem. Res.* **2002**, *1*, 27.
(114) (a) Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1996**, *37*, 7667. (b) Nichols, C. J. Ph.D. Thesis, UCLA, 1997.

CR940337H