Stereochemical model of [2+2]cycloaddition of chlorosulfonyl isocyanate to chiral vinyl ethers

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A comparison of steady-state NOE coefficients measured for vinyl-substituted isopropyl ethers with conformations generated by a molecular mechanics program allowed a characterization of the most favorable ground state conformations. With high confidence it was possible to assign the lowest energy conformation to one which is characterized by a diastereo-zeroplane consisting of the *s-trans* vinyl group, the stereogenic center and the methyl group (Fig. 3). A stereochemical model of the transition state for [2+2]cycloaddition of chlorosulfonyl isocyanate and vinyl ethers is proposed, based on the lowest energy conformation derived from NOE coefficients, which agrees well with the experimental facts and provides a sound explanation of the direction of asymmetric induction.

Introduction

The [2+2]cycloaddition of chlorosulfonyl isocyanate (CSI) to vinyl ethers is an exothermic reaction. According to the Hammond postulate, the transition states of exothermic reactions resemble the starting materials in energy and geometry. It would therefore be reasonable to use the ground-state conformation of vinyl ethers to reflect the conformation in the transition state. This has been a general way to propose stereochemical models for many reactions involving vinyl ethers. The conformation of vinyl ethers has been studied extensively using a variety of methods.[1–3] Recent calculations on isopropyl vinyl ether published by Denmark *et al.*[2] reported the *synclinal s-cis* conformation **1** as the most stable one whereas the corresponding *s-trans* conformation **2** was found to be about 1 kcal mol^{-1} less favored (Fig. 1). Very recently transition state structures for cycloadditions involving vinyl ethers have been located using *ab initio* calculations by Houk *et al.*[3] In agreement with previous predictions and experimental evidence, the conformational preference of vinyl ethers in the transition state of Diels–Alder and 1,3-dipolar cycloadditions was calculated to be in favor of the *s-trans* conformation **2** by 1.2–6.6 kcal mol^{-1}, in contrast to the ground state which was calculated to favor the *s-cis* conformation **1** by 2.3 kcal mol^{-1}.[3] It is therefore not clear whether an *s-cis* or an *s-trans* conformation is the more appropriate to use for modeling [2+2]cycloadditions of vinyl ethers. In the work presented below, we show that the only model consistent with the experimental results[4–10] is an *s-trans* conformation, which allows a coherent rationalization of all results to date and clear predictions for novel reactions.

Several years ago we initiated a synthetic project aimed at transforming chiral vinyl ethers derived from sugars and from readily available hydroxy acids into 1-oxabicyclic-β-lactams.[4,5] The crucial step of the synthesis involved [2+2]cycloaddition of vinyl ethers and isocyanates. This reaction has been shown to display, in many cases, excellent diastereoselectivity.[4,5] The search for a stereochemical model that could rationalize the results of the [2+2]cycloadditions of isocyanates and vinyl ethers has been a consequence of our studies. In the case of cyclic vinyl ethers (glycals), the isocyanate approaches the sugar molecule exclusively *anti* with respect to the substituent at C-3 (Fig. 2).[4,5] The more or less rigid glycal ring restricts considerations to the steric requirements of substituents next to the double bond and their location above or below the plane of the ring. In the case of dihydropyran **3** derived from an acrolein dimer we observed very low stereoselectivity in [2+2]cycloadditions with tosyl† and trichloroacetyl isocyanates.[6,7] Our explanation for this is that the ground state conformation of **3** is probably a half-chair one with an equatorial position of the acetoxymethyl substituent.[11] Consequently the H-6 proton is located perpendicularly to the diastereo-zeroplane whereas both C-5 and CH_2OAc lie slightly above the plane (torsion angle C2–O–C6–$CH_2OAc \approx 210°$, torsion angle C2–O–C6–C5 ≈ 330°). It is reasonable to assume that the conformation **3**

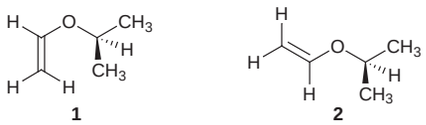


Fig. 1 *Synclinal s-cis* **1** and *s-trans* **2** conformation of isopropyl vinyl ether.[2]

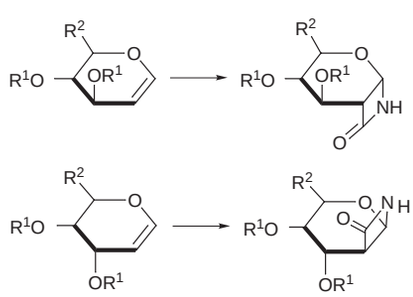
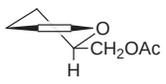


Fig. 2 Stereochemical course of [2+2]cycloaddition of the chlorosulfonyl isocyanate to glycals. In all cases the isocyanate approaches the glycal molecule *anti* with respect to the substituent at C-3 of the pyranoid ring.

† Tosyl = toluene-*p*-sulfonyl.



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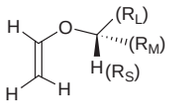

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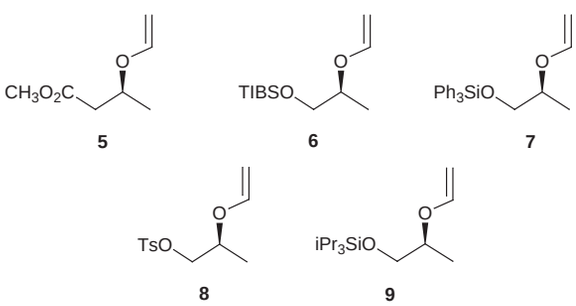
participates in the transition state of [2+2]cycloaddition, thus the low asymmetric induction is understandable.

Results and discussion

The stereochemical analysis of [2+2]cycloaddition is much more complicated when a vinyl ether is located in an acyclic system. For detailed examination we selected five relatively simple chiral vinyl ethers **5**–**9**. Recently, in order to explain the stereochemical course of the [2+2]cycloaddition of CSI to vinyl ethers derived from readily available polyols,[10] we have applied Denmark's[2] *s-cis* conformation **1** as the conformation of the transition state. The diastereo-zeroplane in this model is supposed to consist of the vinyl group, the stereogenic center and the large (R_L) substituent. Diastereofacial differentiation in such a stereochemical model (**4**) is related to atomic requirements of the methyl group (R_M) *versus* the hydrogen atom (R_S). The isocyanate approaches the double bond from the R_S (H) side. This stereochemical model was used to explain the direction of asymmetric induction of [2+2]cycloaddition of CSI to **7** and **8**. The model **4** looks, however, deficient if one applies it to vinyl ethers of more complicated structure.[8,9] In order to verify the model **4** we decided to look more deeply into [2+2]cycloaddition experimental facts and ^{1}H NMR spectra of vinyl ethers investigated by us.



5 6 7 8 9

Conformational analysis by ^{1}H NMR

Conformational analysis of vinyl ethers **5**–**8** was based on steady-state NOEs and molecular modeling. For each studied compound the analysis was done in the same way, in several steps. The first step involved generation of a set of low-energy conformers (a 10 kcal mol^{-1} energy window was applied) using the molecular modeling program PCMODEL[12] (for details of calculations see Experimental). Then for each conformer from the set, theoretical steady-state NOEs were calculated (scaled using an external relaxation parameter[13]) using the computer program *NOE*.[14] As a measure of fit of calculated to experimental NOEs, root-mean-square deviation factors rms_{NOE} were used (for definition see Experimental). The last step of the analysis was an assessment if the conformation with the lowest rms_{NOE} factor was significantly better fitted to the NOE data than any other low-energy conformer from the set. In this approach computed energies of individual conformers were ignored and all structures from the conformational set were treated as equally probable.

In order to find experimentally the preferred conformation of model vinyl ethers in solution, steady-state NOE measurements were run for compounds **5** and **6** at room temperature in [$^2H_8$]toluene (cycloaddition reactions were performed in toluene at −40 °C). It should be stressed that high reactivity of CSI towards simple vinyl ethers, and towards many functional groups, particularly in polar aprotic solvents, restricts reaction conditions to low temperature and to non polar solvent.[8–10] Table 1 shows steady-state NOEs measured for **5**. Parameters of the low energy conformers and rms_{NOE} factors for vinyl ether **5** are presented in Table 2, entry 1.

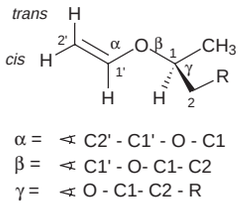


Fig. 3 Numbering of atoms in vinyl ethers **5**–**8** and definitions of torsion angles.

Conformer *(±)ap(−)sc(+)sc*—Klyne–Prelog notation related to *a*, *β* and *γ* torsion angles (Fig. 3)—of **5** has the lowest value of rms_{NOE} = 0.266. On the basis of statistical analysis (at a 10% significance level) of the values of the rms_{NOE} factors, one can state that conformer *(±)ap(−)sc(+)sc* is significantly better fitted to the experimental NOEs than any other conformer from the set except conformers *(±)ap(−)sc(+)ac*, *(±)ap(−)-sc(±)ap* and *(±)ap(−)sc(−)sc* (for details of statistical calculations see Experimental). All these conformers exhibit the *s-trans* type of conformation around the C1′–O bond (torsion angle *a* is around ±180°). Furthermore, all best fitted structures have similar values of torsions around the O–C1 bond (*β*) which oscillate around −75°. It is also clear from Table 2 (entry 1) that the values of torsions around the C1–C2 bond (*γ*) have practically no influence on the rms_{NOE} factors. This means that on the basis of presented steady-state NOE data one can only define a preferred conformation around the C1′–O and O–C1 bonds. Conformations around the C1–C2 and C2–R bonds cannot be defined but they have only a minor influence on the stereochemical course of cycloaddition.

Similar steady-state NOE experiments in [$^2H_8$]toluene at room temperature and calculations were performed for vinyl ether **6** (Table 1 and Table 2, entry 2). Within a 10% significance interval of the lowest rms_{NOE} factor the two conformers *(±)ap(+)sc(−)sc* (rms_{NOE} = 0.522) and *(±)ap(−)sc(−)sc* (rms_{NOE} = 0.591) are present. Both of them have the *s-trans* type of conformation around the C1′–O bond (torsion angle *a*). The conformation around the O–C1 bond (torsion angle *β*) cannot be defined. It should be noted, however, that the relative geometry of C1′ and C2 in both conformers is the same [*(+)sc* and *(−)sc*].

For vinyl ethers **7** and **8** steady-state NOE experiments were performed at room temperature in [^{2}H]chloroform solution. Results for compound **7** are shown in Table 1 and Table 2 (entry 3). As can be seen only *s-trans* conformations are present within the 10 kcal mol^{-1} energy window, because of the steric requirements of the bulky triphenylsilyl group. Although the rotamer *(±)ap(−)sc(+)sc* is the one that fits best, there are several conformers of **7** which fit the NOE data equally well (see Table 2, entry 3), therefore it is not possible to define the conformation around the O–C1 bond (torsion angle *β*).

Results for vinyl ether **8** (Table 1 and Table 2, entry 3) are less clear. The best fitted *(±)ap(−)sc(−)sc* conformer (rms_{NOE} = 0.263) has the same conformation around C1′–O and O–C1 as the best fitted conformers modeled for **5**, but within the calculated 10% significance interval of rms_{NOE}, there are present also two other conformers: *(±)sp(−)sc(−)sc* and *(±)ap(±)ap-(+)sc*. One of them, namely *(±)sp(−)sc(−)sc* (rms_{NOE} = 0.319) is the *s-cis* type conformation around the C1′–O bond. Therefore, on the basis of steady-state NOE data, one can state that in the case of **8** the preferred conformation could also be *(±)ap(−)sc(−)sc* but with lower confidence than that for vinyl ether **5**.

Each experimentally observed steady-state NOE coefficient is

Table 1 Experimental steady-state NOEs (%) for vinyl ethers **5** and **6** in [$^2H_8$]toluene solution and for vinyl ethers **7** and **8** in [^{2}H]chloroform solution. For numbering of protons see Fig. 3. Estimated precision of experimental NOEs is ±1%. N.d. = not determined

Irradiated proton	Observed proton																			
	1′				2′-*trans*				1				2′-*cis*				Me			
1′					−1.4	−0.7	0.3	−0.8	9.9	5.6	6.4	3.1	4.0	N.d.	6.6	7.4	0.2	0.1	N.d	−0.9
2′-*trans*	−1.8	−0.8	0.3	−1.3					4.1	5.2	2.7	3.4	28.3	N.d.	20.4	22.5	−0.2	1.0	N.d.	−0.5
1	10.8	11.5	10.4	8.0	3.3	6.8	6.6	3.6					−2.4[a]	N.d.	−14.3[a]	−2.8[a]	1.1	N.d.	N.d.	−1.5
2′-*cis*	7.5	N.d.	8.5	7.6	23.2	N.d.	21.8	23.9	−3.8[a]	N.d.	−6.2[a]	−4.5[a]					−1.5	1.6	N.d.	0.2
Me	−0.8	2.3	N.d.	−1.3	−1.1	1.4	N.d.	−2.2	7.8	13.8	N.d.	9.5	1.4	N.d.	N.d.	−4.2				
Vinyl ether	**5**	**6**	**7**	**8**	**5**	**6**	**7**	**8**	**5**	**6**	**7**	**8**	**5**	**6**	**7**	**8**	**5**	**6**	**7**	**8**

[a] Direct saturation due to nonselective irradiation.

Table 2 Parameters of low energy conformers of vinyl ethers **5**–**8** and rms_{NOE} factors. Conformers best fitted to the steady-state NOE data are given in bold. For definitions of torsion angles α, β and γ see Fig. 3

Energy[a]/ kcal mol^{-1}	Torsion angle/°			Type of conformation	rms_{NOE}[b]
	α	β	γ		
Entry 1: vinyl ether **5**					
5.72	5.33	−165.24	58.87	*(±)sp(±)ap(+)sc*	0.414
6.24	−4.94	−75.03	179.08	*(±)sp(−)sc(±)ap*	0.396
6.29	−5.92	−73.92	−61.81	*(±)sp(−)sc(−)sc*	0.390
6.44	5.02	−164.39	175.28	*(±)sp(±)ap(±)ap*	0.412
6.71	−176.76	−167.80	58.28	*(±)ap(±)ap(+)sc*	0.339
7.29	**171.49**	**−79.55**	**68.49**	***(±)ap(−)sc(+)sc***	**0.266**
7.73	**178.09**	**−71.12**	**−174.83**	***(±)ap(−)sc(±)ap***	**0.289**
7.73	−178.09	−166.81	175.46	*(±)ap(±)ap(±)ap*	0.344
7.91	**174.62**	**−68.12**	**−50.92**	***(±)ap(−)sc(−)sc***	**0.290**
8.11	−10.04	−85.63	85.81	*(±)sp(−)sc(+)sc*	0.421
10.45	**178.53**	**−80.75**	**121.95**	***(±)ap(−)sc(+)ac***	**0.272**
11.28	−164.40	4.96	60.88	*(±)ap(±)sp(+)sc*	0.414
14.77	2.03	64.80	172.74	*(±)sp(+)sc(±)ap*	0.508
Entry 2: vinyl ether **6**					
32.43	−7.80	−85.14	66.95	*(±)sp(−)sc(+)sc*	0.759
32.60	−6.45	−72.57	−58.95	*(±)sp(−)sc(−)sc*	0.666
33.32	−3.70	−76.34	117.58	*(±)sp(−)sc(+)ac*	0.701
36.31	**173.51**	**−64.96**	**−51.42**	***(±)ap(−)sc(−)sc***	**0.522**
38.67	14.87	−170.66	−85.66	*(±)sp(±)ap(−)sc*	0.679
39.48	−178.65	63.94	171.30	*(±)ap(+)sc(±)ap*	0.893
40.23	**−176.71**	**72.67**	**−64.65**	***(±)ap(+)sc(−)sc***	**0.591**
Entry 3: vinyl ether **7**					
41.57	**177.13**	**−79.80**	**66.08**	***(±)ap(−)sc(+)sc***	**0.265**
41.61	**173.25**	**−67.28**	**−57.89**	***(±)ap(−)sc(−)sc***	**0.284**
41.62	**−177.93**	**−166.83**	**175.50**	***(±)ap(±)ap(±)sap***	**0.270**
41.72	**178.13**	**−72.50**	**175.70**	***(±)ap(−)sc(±)ap***	**0.277**
41.75	**−179.79**	**−166.74**	**64.43**	***(±)ap(±)ap(+)sc***	**0.271**
41.82	**−177.22**	**168.43**	**−65.22**	***(±)ap(±)ap(−)sc***	**0.273**
42.09	−178.14	72.73	−72.84	*(±)ap(+)sc(−)sc*	0.405
42.18	178.95	65.69	172.83	*(±)ap(+)sc(±)ap*	0.409
42.51	179.70	61.57	51.50	*(±)ap(+)sc(+)sc*	0.408
50.71	−178.66	71.15	142.78	*(±)ap(+)sc(+)ac*	0.403
Entry 4: vinyl ether **8**					
12.85	5.31	−164.87	58.75	*(±)sp(±)ap(+)sc*	0.358
14.11	−179.83	−167.17	57.24	*(±)ap(±)ap(+)sc*	0.332
14.14	−3.78	−76.23	173.37	*(±)sp(−)sc(±)ap*	0.332
14.29	5.50	−163.55	174.96	*(±)sp(±)ap(±)ap*	0.357
14.64	**177.80**	**−72.78**	**−62.18**	***(±)ap(−)sc(−)sc***	**0.263**
15.16	**−7.55**	**−71.62**	**−45.57**	***(±)sp(−)sc(−)sc***	**0.319**
15.19	−177.42	−166.04	173.09	*(±)ap(±)ap(±)ap*	0.333
15.25	**−179.60**	**−165.91**	**62.76**	***(±)ap*(±)ap(+)sc**	**0.326**
15.93	7.82	−162.91	−49.13	*(±)sp(±)ap(−)sc*	0.357
16.27	−2.41	66.92	63.99	*(±)sp(+)sc(+)sc*	0.455
16.29	−173.63	−170.50	−63.18	*(±)ap(±)ap(−)sc*	0.347

[a] Calculated for minimised structures using MM3 force field. [b] For definition see Experimental.

in general averaged through all conformations present in solution. Therefore one should not exclude the possibility that a conformational mixture exists in solution which is better fitted to the experimental data than any single-conformational model. To check this possibility multiple regression analysis was run in the same manner as published recently for a derivative of 2,3-dihydrobenzofuran.[15] For the studied molecules we have found conformational mixtures with lower rms_{NOE} factors than for the best fitted single conformation, but the improvement of the quality of fit was not statistically significant.

In order to place further limits on the conformation of **5**, a series of one-dimensional transient DPFGSE NOE (double-pulsed-field gradient spin echo) experiments[16] was run for the same sample as used for steady-state experiments. The well resolved signal of H-1′ proton at 6.23 ppm was inverted by a selective pulse and the fractional enhancements of the H-1 and H-2′ *cis* signals were observed as a function of mixing time (Fig. 4). Using a calibration distance between H-1′ and H-2′ *cis* of 2.42 Å, a distance between H-1′ and H-1 protons of around 2.4 Å was estimated. This value fits well the proposed *s-trans* model of the vinyl ether and it is not consistent with the *s-cis* conformations postulated by Denmark (Fig. 5). Furthermore, this distance is consistent with the *(±)ap(−)sc* conformation of vinyl ethers **5**–**8** which is the conformation that best fits the steady-state NOE measurements.

Thus, a combination of steady-state and DPFGSE NOE experiments has allowed a characterization of the preferred ground-state conformations. With high confidence we can assign the lowest energy conformation to **10** (Fig. 6) which corresponds to a distorted form of Denmark's *synclinal s-trans* conformation **2** (Fig. 3). This assignment is unambiguous for **5** whereas for **6**–**8** the NOE data, at the very least, do not contradict such an assumption. The diastereo-zeroplane of **10** consists of the *s-trans* vinyl group, the stereogenic center, and the methyl substituent (R_M). The bulkiest methoxycarbonylmethyl (**5**), sulfonyloxymethyl or triphenylsiloxymethyl group is

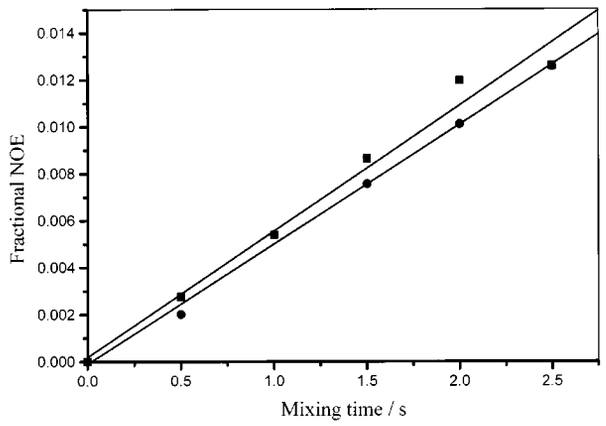


Fig. 4 Fractional NOEs as a function of mixing time in DPFGSE NOE experiments. The signal of the H-1′ proton was inverted by a selective pulse. Circles and squares correspond to the enhancements of H-2′ *cis* (used for calibration of distance) and H-1 resonances respectively.

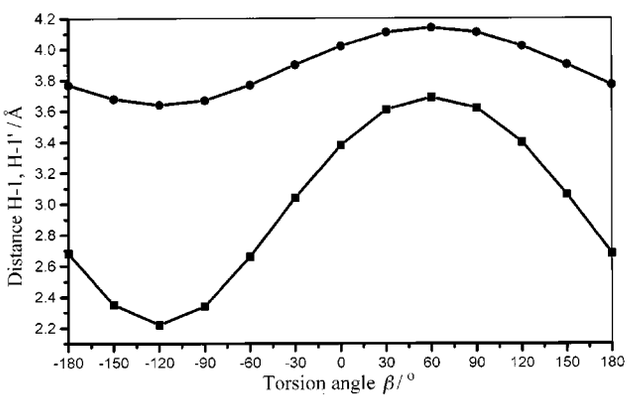


Fig. 5 The distance between H-1 and H-1′ protons in vinyl ethers as a function of torsion angle *β*. Circles and squares correspond to *s-cis* and *s-trans* conformations around the C1′–O bond (torsion angle *α*). For numbering of atoms and definitions of torsion angles see Fig. 3.

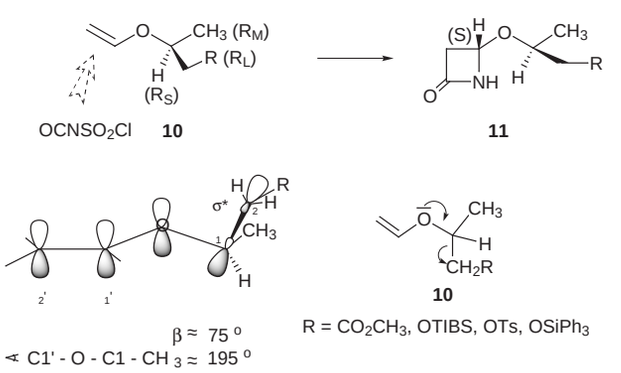


Fig. 6 The conformation of vinyl-substituted isopropyl ethers in the transition state of [2+2]cycloaddition with chlorosulfonyl isocyanate. Illustration of stereoelectronic effects operating in these reactions.

located out of plane, *synclinal* to C-1′ of the vinyl group. The torsion angle *β* C1′–O–C1–C2 ≈ 75°. Consequently the methyl substituent is slightly out of the plane; torsion angle C1′–O–C1–CH_3 ≈ 195°. Diastereofacial differentiation in such a stereochemical model is related to atomic requirements of R_L *versus* the hydrogen atom (R_S) (Fig. 6). The isocyanate approaches the double bond from the R_S (H) side. The stereochemical model which uses conformation **10** predicts the same direction of asymmetric induction as the model based on conformation **4**.

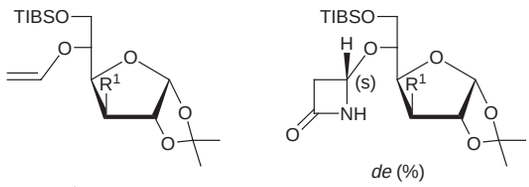
The conformation **10** requires, however, a reasonable explanation which would provide grounds for the *synclinal* position of the bulkiest substituent at the chirality center. This effect apparently is caused by interaction of the conjugated π electrons of the double bond and the lone pair of electrons of the oxygen atom, from one side, and the antibonding σ*-orbital of the C1–C2 (R_L) bond from the other side (Fig. 6). It seems justified to predict a lower energy σ*-orbital for the C–C bond bearing an electronegative group or atom, such as methoxycarbonyl in **5** or the tosylated or silylated oxygen atom in **6**, **7** and **8**, than for the C1–CH_3 bond. One can assume that introduction of the electronegative substituent to one of the terminal carbon atoms of the isopropyl fragment of isopropyl vinyl ether causes the shift of that carbon to the *synclinal* position with regard to the C–1′ carbon atom of the vinyl, and this is followed by the switch of the double bond from the *s-cis* to the *s-trans* conformation due to steric interaction between these two substituents. We are not able to verify theoretically the postulated stereoelectronic effect operating in the substituted isopropyl fragment of vinyl isopropyl ethers. Similar stereoelectronic attractions however have been postulated and verified theoretically and experimentally to explain the anomeric effect,[17] the Cieplak model[18] of nucleophilic addition to cyclohexanone and the Felkin model[19] of addition to the carbonyl group. The latter predicts the location of a heteroatom rather than a carbon atom (low-lying σ*-orbital), perpendicularly to the carbonyl double bond.[19] The stereochemical model of the ground-state of vinyl ethers derived from NOE measurements (Fig. 6) suits well the experimental facts, which do not indicate any charge transfer interaction but strongly suggest some kind of stereoelectronic effect that helps to fix the conformation of the transition state. This is particularly striking if one compares ethers **8** and **9** which have triphenylsiloxy and triisopropylsiloxy groups, respectively, but both afford a similar magnitude of asymmetric induction.[10]

For asymmetric [2+2]cycloaddition of CSI to 1,2-*O*-isopropylidene-5-*O*-vinyl-α-D-glucofuranoses **12**–**16** leading to β-lactams **17**–**21** which depended on substitution and configuration at the C-3 carbon atom, we previously proposed the model **22** which postulated an interaction between the nucleophilic olefin and the electrophilic arylsulfonyl substituent, and an *s-trans* conformation of the vinyl ether. The direction of asymmetric induction in the CSI addition to **12**–**16** could be explained using model **4**. In order to rationalize the results, however, the terminal sulfonyloxymethyl group had to be located *synclinal* to C–1′ of the vinyl (lower lying σ*-orbital of the C-6–sulfonyloxymethyl bond than that of C-4–furanoid ring oxygen), whereas the bulky furanoid substituent lay in the diastereo-zeroplane. The evident relationship between the value of asymmetric induction and the size of the substituent at C-3 indicates that the attack of isocyanate occurs from the side occupied by the R^1 substituent. Examination of the rotation around the C-4, C-5 bond in the model **22** shows that the R^1 substituent is turned in the *re* side of the olefin. Consequently, size diminution of the R^1 substituent opens up access of the isocyanate to the *re* side of the double bond and increases predominance of the (4′-*S*) diastereoisomer.

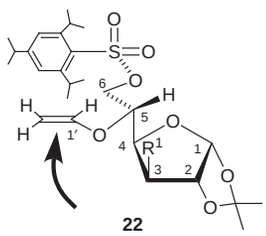
The interaction between the double bond and the phenyl ring has been postulated to explain high asymmetric induction in a variety of reactions taking place on the double bond.[20] More careful examination of such stereoelectronic effects, however, showed that their existence as a sole factor that determines the direction and magnitude of stereoselectivity can be questionable.[21]

To get evidence supporting the model **22** we synthesized three vinyl ethers **23**–**25** having *p*-chloro-, *p*-methyl- and *p*-methoxyphenylsulfonyl groups at the C-6 atom.

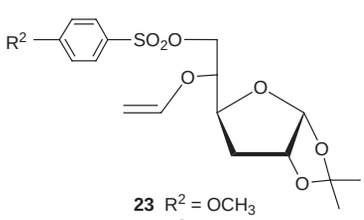
[2+2]Cycloaddition of CSI to vinyl ethers **23**–**25** was performed according to the general procedure; the chlorosulfonyl group was removed from the nitrogen atom of the adduct by sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al) reduction.[22] The corresponding (4′*S*)-azetidin-2′-ones **26**–**28** were obtained with 75, 80, and 80% *de*, respectively. Face-



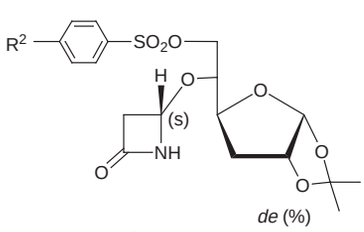
12	R^1 = OBzh		*de* (%)
13	R^1 = OCH_2SCH_3	**17**	8
14	R^1 = OBn	**18**	38
15	R^1 = OCH_3	**19**	64
16	R^1 = H	**20**	92
		21	95



22



23 R^2 = OCH_3
24 R^2 = CH_3
25 R^2 = Cl



		de (%)
26	R^2 = OCH_3	75
27	R^2 = CH_3	80
28	R^2 = Cl	80

discriminations of CSI addition to vinyl ethers **23**–**25** do not differ significantly and they are lower than that found for ether **14**. These results therefore exclude our postulated complexation of the nucleophilic olefin by the electrophilic aromatic ring as an important element that helps to decide the direction and magnitude of asymmetric induction.[9] It is obvious that if such interaction occurs, it should be stronger for more accessible and more electrophilic tosyl (**24**) or *p*-chlorobenzenesulfonyl (**25**) substituents than for the triisopropylbenzenesulfonyl (TIBS) group (**16**). NOE experiments performed for compounds **23**–**25** showed no observable through-space interactions between aromatic and olefin protons. It should be mentioned that we have undertaken steady-state NOE measurements for compound **16**. However, due to overlapping of signals in the ^{1}H NMR spectrum, selective irradiation of all protons was not possible. Because of lack of information we could not obtain a consistent picture of conformational behavior.

The model **10** corresponds well to the model **22** in which we postulated interaction between the nucleophilic olefin and electrophilic aryl substituents in order to explain the *synclinal* conformation of the C-1 vinyl carbon atom and the sulfonyloxymethyl group. The ground-state conformation **10** shown in Fig. 6 predicts such *synclinal* arrangement but without any requirement for a charge-transfer interaction. The model **10** predicts that the substituent located out of the diastereozeroplane will be the one having a low-lying σ*-orbital of the C–C bond (*i.e.* the arylsulfonyloxymethyl substituent), whereas the magnitude of stereodifferentiation depends on the size of the substituents, R_L *versus* R_S.

In conclusion, we have shown that the conformation **10** shown in Fig. 6, which can be rationalized on stereoelectronic grounds, is able to explain a large number of experimental results on [2+2]cycloaddition reactions of chlorosulfonyl isocyanate to chiral vinyl ethers.

Experimental

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were obtained with a FT-IR-1600 Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded with Bruker AM 500 and Varian INOVA 500 spectrometers. Chemical shifts are given in ppm and *J* values in Hz. Column chromatography was performed on Merck Kiesel gel (230–400 mesh).

(*S*)-Methyl 2-vinyloxybutyrate 5

The title compound was prepared according to the literature procedure.[9] (Found: C, 57.9; H, 8.3; $C_7H_{12}O_3$ requires C, 58.33; H, 8.33%); $[\alpha]_D$ +96 (*c* 1.2, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1643 (vinyl) and 1690 (CO); δ_H(200 MHz; C_6D_6) 1.17 (3H, d, *J* 6.2, CH_3), 2.25 (1H, dd, *J* 6.0 and 15.6, H-2a), 2.67 (1H, dd, *J* 7.0 and 15.6, H-2b), 3.44 (3H, s, COMe), 4.13 (1H, dd, *J* 1.5 and 6.6, H-2′ *cis*), 4.39 (1H, m, H-1), 4.53 (1H, dd, *J* 1.5 and 14.2, H-2′ *trans*), 6.35 (1H, dd, *J* 6.6 and 14.2, H-1′).

Compounds **6**–**9** were prepared from methyl (*S*)-lactate by protection of the hydroxy group as the mixed acetate, followed by reduction with lithium aluminum hydride, respective standard sulfonylation or silylation, and TMS-triflate-catalysed elimination of ethanol (**Method A**).[10]

5-*O*-Vinyl ethers **23**–**25** were prepared from 3-deoxy-1,2-*O*-isopropylidene-α-D-ribohexofuranose in two steps by standard sulfonylation of the primary hydroxy group, followed by mercury acetate-catalysed transetherification (**Method B**).[9]

General procedure for the preparation of the chiral vinyl ethers

Method A. To a solution of the mixed acetal (7.0 mmol) in CH_2Cl_2 (7 cm^3), triethylamine (1.46 cm^3, 10.5 mmol) was added at room temperature under argon. The mixture was then cooled to 0 °C and TMSOTf (1.76 cm^3, 9.1 mmol) was added dropwise, followed by further stirring for 2 h at 0 °C. The mixture was treated with 10% NaOH (10 cm^3) and diluted with hexane (100 cm^3). After evaporation of the solvent, column chromatography of the residue afforded the respective enol ether as a colorless oil with yields from 70 to 85%.

(S)-1-Triisopropylbenzenesulfonyloxy-2-vinyloxypropane **6**. (Found: C, 65.1; H, 8.8; S, 8.9; $C_{20}H_{32}O_4S$ requires C, 65.22; H, 8.69; S, 8.69%); $[\alpha]_D$ +7.6 (*c* 0.5, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1638 (vinyl); δ_H(200 MHz; C_6D_6) 0.97 (3H, d, *J* 6.2, CH_3), 2.78 (1H, septet, *p*-C*H*$(CH_3)_2$), 3.88 (1H, m, H-1), 3.96–4.05 (3H, m, H-2a, H-2b and H-2′ *cis*), 4.30 (1H, dd, *J* 1.7 and 14.2, H-2′ *trans*), 4.67 (2H, septet, 2 × *o*-C*H*$(CH_3)_2$), 6.25 (1H, dd, *J* 6.6 and 14.1, H-1′).

(S)-1-Tosyloxy-2-vinyloxypropane **7**. (Found: C, 56.3; H, 6.1; S, 12.3; $C_{12}H_{16}O_4S$ requires C, 56.25; H, 6.25; S, 12.5%); $[\alpha]_D$ +12.3 (*c* 1.0, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1632 (vinyl); δ_H(C_6D_6) 0.77 (3H, d, *J* 6.3, CH_3), 1.80 (3H, s, Ts), 3.65 (1H, m, H-1), 3.80 (2H, m, H-2a and H-2b), 3.88 (1H, dd, *J* 1.7 and 6.6, H-2′ *cis*), 4.20 (1H, dd, *J* 1.7 and 14.2, H-2′ *trans*), 5.98 (1H, dd, *J* 6.6 and 14.2, H-1′).

Method B. A solution of 5-hydroxy precursor (1 mmol) and mercuric(II) acetate (0.025 mmol) in butyl vinyl ether (15 cm^3) was refluxed for 5 h. The solution was cooled, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel using

hexane–ethyl acetate 12:1 (v/v) as eluent to give **23**–**25** in yields from 50 to 60%.

3-Deoxy-1,2-O-isopropylidene-6-O-p-methoxyphenylsulfonyl-5-O-vinyl-α-D-ribohexofuranose ***23***. $[\alpha]_D$ −1.1 (*c* 1.1, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1638 (vinyl); δ_H(500 MHz; $CDCl_3$) 1.77 (1H, ddd, *J* 4.6, 10.5 and 13.4, H-3a), 2.14 (1H, dd, *J* 4.6 and 13.4, H-3b), 3.88 (3H, s, OMe), 4.00–4.25 (5H, m, H-2′a, 4, 5, 6a and 6b), 4.30 (1H, dd, *J* 1.9 and 13.9, H-2′ *trans*), 4.70 (1H, t, *J* 3.6, H-2), 5.75 (1H, d, *J* 3.6, H-1), 6.25 (1H, dd, *J* 6.4 and 13.9, H-1′); [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 385.0955. $C_{17}H_{21}O_8S$ requires 385.0957].

3-Deoxy-1,2-O-isopropylidene-6-O-tosyl-5-O-vinyl-α-D-ribohexofuranose ***24***. $[\alpha]_D$ −1.3 (*c* 0.2 CH_2Cl_2); ν_{max}(film)/cm^{-1} 1637 (vinyl); δ_H(500 MHz; $CDCl_3$) 1.82 (1H, ddd, *J* 4.7, 10.4 and 13.5, H-3a), 2.14 (1H, dd, *J* 4.7 and 13.5, H-3b), 2.44 (3H, s, Ts), 4.01 (1H, dd, *J* 1.9 and 6.3, H-2′ *cis*), 4.04–4.25 (4H, m, H-4, 5, 6a and 6b), 4.30 (1H, dd, *J* 1.9 and 13.9, H-2′ *trans*), 4.70 (1H, t, *J* 3.6, H-2), 5.75 (1H, d, *J* 3.6, H-1), 6.27 (1H, dd, *J* 6.4 and 13.5, H-1′); [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 396.10044. $C_{17}H_{21}O_7S$ requires 369.10079].

6-O-p-Chlorophenylsulfonyl-3-deoxy-1,2-O-isopropylidene-5-O-vinyl-α-D-ribohexofuranose ***25***. $[\alpha]_D$ −2.7 (*c* 0.9, CH_2Cl_2); ν_{max}(film)/cm^{-1} 1643 (vinyl); δ_H(500 MHz; $CDCl_3$) 1.74 (1H, ddd, *J* 2.7, 9.7 and 16.1, H-3a), 2.14 (1H, dd, *J* 2.7 and 16.1, H-3b), 4.01 (1H, dd, *J* 2.0 and 6.5, H-2′ *cis*), 4.06–4.25 (4H, m, H-4, 5, 6a and 6b), 4.30 (1H, dd, *J* 2.0 and 14.0, H-2′ *trans*), 4.70 (1H, t, *J* 3.6 and 4.2, H-2), 5.75 (1H, d, *J* 3.6, H-1), 6.27 (1H, dd, *J* 6.5 and 14.0, H-1′); [Found: HRMS (LSIMS) *m*/*z* $(M + Na)^+$, 427.0591. $C_{17}H_{21}O_7ClSNa$ requires 427.0594].

[2+2]Cycloaddition of chlorosulfonyl isocyanate to vinyl ethers **23**–**25** was performed according to the procedure described earlier[9] to afford **26**–**28** with yield 50–60%.

(4′S)-5-O-(2′-Oxoazetidin-4′-yl)-3-deoxy-6-O-p-methoxyphenylsulfonyl-1,2-O-isopropylidene-α-D-ribohexofuranose ***26***. ν_{max}($CHCl_3$)/cm^{-1} 1777 (CO); δ_H(500 MHz; $CDCl_3$) *major product* 1.80 (1H, ddd, *J* 4.8, 10.7 and 13.3, H-3a), 1.95 (1H, dd, *J* 4.5 and 13.3, H-3b), 2.78 (1H, ddd, *J* 0.6, 1.4 and 15.2, H-3′a), 3.09 (1H, ddd, *J* 2.7, 4.0 and 15.2, H-3′b), 3.89 (3H, s, OCH_3), 3.97 (1H, dd, *J* 7.5 and 10.8, H-6a), 4.05–4.20 (3H, m, H-4, 5 and 6b), 4.72 (1H, t, H-2), 5.14 (1H, dd, *J* 1.3 and 4.0, H-4′), 5.75 (1H, d, *J* 3.6, H-1); *minor product* 5.16 (1H, dd, *J* 1.3 and 4.0, H-4′). [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 428.10096. $C_{18}H_{21}NO_9S$ requires 428.10152].

(4′S)-5-O-(2′-Oxoazetidin-4′-yl)-3-deoxy-1,2-O-isopropylidene-6-O-tosyl-α-D-ribohexofuranose ***27***. ν_{max}($CHCl_3$)/cm^{-1} 1777 (CO); δ_H(500 MHz; $CDCl_3$) *major product* 1.80 (1H, ddd, *J* 4.7, 10.7 and 13.2, H-3a), 1.95 (1H, dd, *J* 4.5 and 13.2, H-3b), 2.46 (3H, s, Ts), 2.78 (1H, ddd, *J* 0.6, 1.4 and 15.2, H-3′a), 3.08 (1H, ddd, *J* 2.6, 4.0 and 15.2, H-3′b), 3.96 (1H, dd, *J* 7.5 and 11.3, H-6a), 4.07–4.20 (3H, m, H-4, 5 and 6b), 4.72 (1H, t, H-2), 5.12 (1H, dd, *J* 1.4 and 4.0, H-4′), 5.74 (1H, d, *J* 3.6, H-1); *minor product* 5.15 (1H, dd, *J* 1.3 and 4.0, H-4′). [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 412.1068. $C_{18}H_{22}NO_8S$ requires 412.1066].

(4′S)-5-O-(2′-Oxoazetidin-4′-yl)-6-O-(p-chlorophenylsulfonyl)-3-deoxy-1,2-O-isopropylidene-α-D-ribohexofuranose ***28***. ν_{max}($CHCl_3$)/cm^{-1} 1778 (CO); δ_H(500 MHz; $CDCl_3$) *major product* 1.80 (1H, ddd, *J* 4.7, 10.8 and 13.2, H-3a), 1.97 (1H, dd, *J* 4.4 and 13.2, H-3b), 2.81 (1H, ddd, *J* 0.6, 1.4 and 15.2, H-3′a), 3.10 (1H, ddd, *J* 2.7, 4.0 and 15.2, H-3′b), 3.95–4.17 (4H, m, H-4, 5, 6b and 6b), 4.73 (1H, t, H-2), 5.14 (1H, dd, *J* 1.4 and 4.0, H-4′), 5.75 (1H, d, *J* 3.6, H-1); *minor product* 5.17 (1H, dd, *J* 1.4 and 4.0, H-4′). [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 432.0520. $C_{17}H_{19}NO_8SCl$ requires 432.0519].

Calculation of low energy conformations

The program PCMODEL[12] was used to calculate low energy conformations, using the force field MM3. It was done by global optimization of the structure by multiple, near random rotations about rotatable bonds using a Monte Carlo–Metropolis approach to simulated annealing. Conformations obtained in this way were analyzed using the program MMX-COMP[23] to produce a conformational set within about 10 kcal mol^{-1} of the minimum energy conformer. This program orders the calculated conformations in order of energy, and then clusters together conformations within a preset range of dihedral angles (30° of each other). It does it by setting the lowest energy conformer as a representative of the first cluster. The second lowest energy structure is added to the cluster if none of its dihedral angles differs by more than 30° from the first structure; if it does differ in at least one angle, it is taken as a representative of a second cluster. Each new structure is added in the same way.

Steady-state NOE experiments

Steady-state NOEs were performed at room temperature on four samples: **5**, **6** (*ca.* 10 mg/0.7 ml [$^2H_8$]toluene) and **7**, **8** (*ca.* 10 mg/0.7 [^{2}H]chloroform on a Varian INOVA 500 spectrometer using a routine program for multiplet irradiation. The samples were degassed to minimize external relaxation. The longest ^{1}H T_1 times determined for the samples were used for setting up the total irradiation time necessary to produce steady-state NOEs. The experimental conditions used were: 15 s total irradiation, 2 s acquisition, 5000 Hz spectral width, digital resolution 1 Hz. NOE intensities were calibrated by using a reference signal that was unaffected by the irradiation, and the same phase parameters and integration limits were used for reference and irradiated spectra. The estimated precision of the experimental NOE values is ±1% of NOE.

Calculations of the theoretical steady-state NOEs

The theoretical steady-state NOEs were calculated using the computer program *NOE*[14] which is available on request from the authors. A best fit value for the external relaxation parameter (which corresponds to the effective distance of the relaxation sink) was equal to 2.0, 2.3, 1.9 and 1.9 Å for the samples of **5**–**8** respectively. The program *NOE* is based on steady-state equations for multi-spin NOEs in the presence of external relaxation.[13] As a measure of the goodness of fit of calculated to observed NOEs, we used rms_{NOE} factors, defined below in a manner similar to its use in crystallography.

$$rms_{NOE} = \sqrt{\frac{\sum_{i=1}^{N} (NOE_i^{cal} - NOE_i^{exp})^2}{\sum_{i=1}^{N} (NOE_i^{exp})^2}}$$

Statistical calculations

The determination of the best conformational model in solution (either single conformer or conformational mixture) on the basis of experimental and calculated steady-state NOE data cannot be made with absolute confidence. This is due to imperfections of NOE measurements, possible errors in geometry of generated low energy conformers and simplifications used in calculations of theoretical NOEs. Therefore it is necessary to test if the difference between 'a best-fit conformational model' (a model with the lowest rms_{NOE} factor) and the other models is *statistically significant*. For each single conformer a residual sum of squares of the difference between calculated and observed NOEs was calculated. Then for the best fitted conformer, 10% significance intervals for residual sum of squares and for rms_{NOE} were calculated assuming a χ^2 distribution with the appropriate number of degrees of freedom equal to the number of NOEs measured minus one (the external relaxation parameter). In such an approach problems related to multiple comparison (*i.e.* simultaneous comparisons between a large number of possible solutions) were ignored.

The lowest rms_{NOE} factors are equal to 0.266 [conformer *(±)ap(−)sc(+)sc*] for **5**, 0.522 [conformer *(±)ap(−)sc(−)sc*] for **6**, 0.265 [conformer *(±)ap(−)sc(+)sc*] for **7** and 0.263 [conformer *(±)ap(−)sc(−)sc*] for **8**. Ten percent significance intervals for these rms_{NOE} factors are (0.194, 0.335), (0.373, 0.655), (0.181, 0.339) and (0.192, 0.330) respectively.

DPFGSE NOE measurements

DPFGSE NOE (double-pulsed-field gradient spin echo) experiments were run using the pulse sequence published by Stott and co-workers[16] using a shaped 180° selective soft-pulse generated using a standard Varian program for five mixing times: 500, 1000, 1500, 2000 and 2500 ms.

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