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Stereoselective Conjugate Addition of Benzyl Phenylsulfonyl Carbanions to Enoates Derived from D-Mannitol

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Received September 30, 2003

The conjugate addition of benzylic phenylsulfonyl carbanions (**2a′**−**d′**) to enoates derived from D-(+)-mannitol (*E*- or *Z*-**1a**−**c**) was studied using THF and THF/HMPA as solvent. Under kinetic conditions (−78 °C), enoate *E*-**1a,b** led to a mixture of *syn*-(*R*,*S*) and *anti*-(*S*,*S*) adducts (55/45), and *syn*-(*R*,*S*) adducts were the main product obtained (∼90/10) from enoate *Z*-**1a**. Under thermodynamic conditions (−78 °C to room temperature) *syn*-(*R*,*S*) adducts were also preferentially formed (∼90/10), despite the geometry at the double bond in the acceptor. Enoate **1c** (*E*/*Z* = 57/43), bearing an additional benzyl group at the α-position, also reacted with carbanions **2′a,b**, under thermodynamic conditions, leading to *syn*-adducts in excellent de (control at the three newly generated stereogenic centers). The adducts were quantitatively transformed into the corresponding *β*-*γ*-disubstituted *γ*-butyrolactones and α,*β*,*γ*-trisubstituted *γ*-butyrolactones. ^{1}H NMR studies (NOE and *J*-coupling) of these lactones allowed us to determine their configuration at the newly generated chiral centers. The reduction of the C−S bond in adducts *syn*-(*R*,*S*) with Na/Hg, followed by treatment of the resulting products in aqueous acid media, led to enantioenriched *β*-benzyl-*γ*-hydroxymethyl-*γ*-butyrolactones. The conformational equilibrium of enoates *E*- and Z-**1b** was evaluated by theoretical calculations (ab initio, MP2/6-31G*), and a mechanistic rationale was proposed to explain the observed stereoselectivities.

Introduction

Conjugate addition is a versatile reaction that allows the formation of new carbon−carbon or carbon−heteroatom bonds from a variety of acceptors and nucleophiles.[1] Enantioenriched adducts can be obtained from prochiral reagents when chiral auxiliaries,[2a−d] chiral nucleophiles,[2e,f] or chiral catalysts[2g−n] are used. Enantiopure acceptors prepared from the chiral pool are also invaluable starting materials to obtain chiral enantioenriched building blocks for synthesis.[3] Enoates such as **1a,b** (Figure 1), easily obtained from D-(+)-mannitol, are among the most studied acceptors of this type.[4] The stereochemical outcome of the conjugate additions to these enoates has been shown to be dependent on the nature of the nucleophile.[5] We previously reported the use of nitromethane derivatives[6a−c] and phenylsulfone derivatives[6d] as nucleophiles in the conjugate addition to **1a**−**c** and **1a,b**, respectively. Whereas *syn*-selectivity was observed for nitromethane derivatives, in the case of allyl and prenyl phenylsulfonyl carbanions, *anti*-adducts predominated under kinetic conditions (−78°), and *syn*-adducts were the main products obtained under thermodynamic conditions (rt).

Benzylic organometallics play an important role in organic synthesis and have been used to prepare com-

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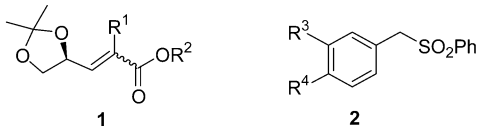
10.1021/jo035427d CCC: $27.50
Published on Web 05/12/2004



for **1** for **2**

a, R^1 = H, R^2 = Et a, R^3 = R^4 = H
b, R^1 = H, R^2 = Me b, R^3 = R^4 = OCH_2O
c, R^1 = CH_2Ph, R^2 = Me c, R^3 = OMe, R^4 = OMe
d, R^3 = OMe, R^4= OBn

FIGURE 1. Enoates and benzyl phenylsulfone derivatives used in this work: (*) *o*-hydrogen of phenyl ring, (**) more stable conformer, (#) hydrogen of CH_2OAc group.

pounds of pharmaceutical interest. Benzylic lithium and magnesium compounds, especially those bearing alkoxyde groups at the aromatic ring, are difficult to prepare from the corresponding halides, leading to extensive formation of Wurtz-coupling side products.[7a] This problem can be overcome by the use of lithium powder in the presence of a catalytic amount of naphthalene,[7b] lithium−tellurium exchange,[7c] magnesium in the presence of anthracene,[7d] or through fragmentation of sterically hindered zinc alcoholates.[7a] However, the use of these species as nucleophiles in conjugate addition reactions is rare. In this paper, we report the use of benzylic phenylsulfonyl carbanions derived from benzyl phenylsulfones (**2a**−**d**) as synthetic equivalents of benzylic organometallics in stereoselective conjugate addition reactions to enoates **1a**−**c** (Figure 1).[8]

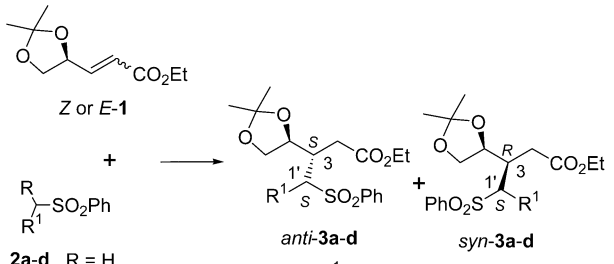
Results

The product distribution obtained in the conjugate addition of phenylsulfonyl carbanions **2′a**−**d**[9] to enoate *E*-**1a** is described in Table 1. When **2′a** was used as nucleophile with *E*-**1a** as acceptor, the product distribution at −78 °C did not depend on the nature of the solvent used (THF or THF/HMPA, entries 1 and 2), and a mixture of *anti*-**3a** and *syn*-**3a** (55/45) was obtained. When the reaction pot was allowed to warm to room temperature before quenching, however, *syn*-**3a** was the main yield (90/10), regardless of the solvent used (entries 3,4). The reaction of other benzyl phenylsulfonyl carbanions (**2′b**−**d**) with *E*-**1a** showed similar reactivities and stereoselectivities. *syn*-Adducts **3b**−**d** (dr ∼90/10) were obtained in condition 3 (entries 6, 8, and 9), while in condition 1 (entries 5 and 7) mixtures of *anti*-**3b**−**c** and *syn*-**3b**−**c** (55/45) were formed.

We investigated if the stereoselectivity could be increased using enoate *Z*-**1a** as acceptor and discovered that it reacted with carbanion **2′a** under conditions 1 and 3, to give exclusively *syn*-**3a** (Table 1, entries 10 and 11). However, the reaction involving **2′b** (entries 12 and 13) was less stereoselective. By chance, the reactions with *Z*-**1a** have similar kinetic and thermodynamic product distributions (compare entries 10 and 12 with entries 11 and 13). During the course of this study, we eventually used enoates *E*- and *Z*-**1b** as acceptors and similar stereoselectivities were obtained.

Enoate **1c** (a mixture of geometric isomers, 57/43) was also used as acceptor in reactions with phenylsulfonyl carbanions **2′a,b** (Table 2). No reaction was observed at −78 °C, but when the mixture was allowed to warm to

TABLE 1. Addition of 2a−d to Enoates *E*- and *Z*-1a[a]



Z or *E*-**1** **2a-d** R = H **2'a-d** R = Li *i*. THF, BuLi, 0°C

anti-**3a-d** *syn*-**3a-d**

a) R^1 = Ph,
b) R^1 = 3,4-methylenedioxyphenyl,
c) R^1 = 3,4-dimethoxyphenyl
d) R^1 = 3-methoxy-4-bezyloxyphenyl

entry	2	%	**1a**	condition[b]	*anti*-**3**	*syn*-**3**
1	**2a**	56	*E*	1	55	45
2	**2a**	53	*E*	2	55	45
3	**2a**	59	*E*	3	10	90
4	**2a**	52	*E*	4	10	90
5	**2b**	55	*E*	1	55	45
6	**2b**	57	*E*	3	10	90
7	**2c**	55	*E*	1	55	45
8	**2c**	57	*E*	3	10	90
9	**2d**	52	*E*	3	15	85
10	**2a**	55	*Z*	1	<5	>95
11	**2a**	53	*Z*	3	<5	>95
12	**2b**	65	*Z*	1	13	87
13	**2b**	63	*Z*	3	13	87

[a] Product distribution was measured by quantitative ^{13}C NMR or ^{13}H NMR. [b] Condition 1: THF, 1 h at −78 °C, NH_4Cl. Condition 2: THF/HMPA, 1 h at −78 °C, NH_4Cl. Condition 3: THF, −78 °C to room temperature, NH_4Cl. Condition 4: THF/HMPA, −78 °C to room temperature, NH_4Cl.

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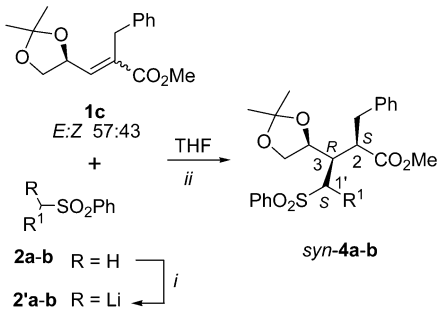
(8) Phenylnitromethane was previously used by our group as synthetic equivalent of benzyl carbanions in conjugate addition to *E*-**1a,b**. However, neither the synthesis of oxygenated phenylnitromethane derivatives nor the conjugate addition of these compounds to *E*-**1a,b** led to satisfactory results.

(9) Benzyl phenylsulphones were prepared as described in Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422.

TABLE 2. Conjugate Addition of Phenylsulfonyl Carbanions 3a,b to α-Substituted Enoate[a]

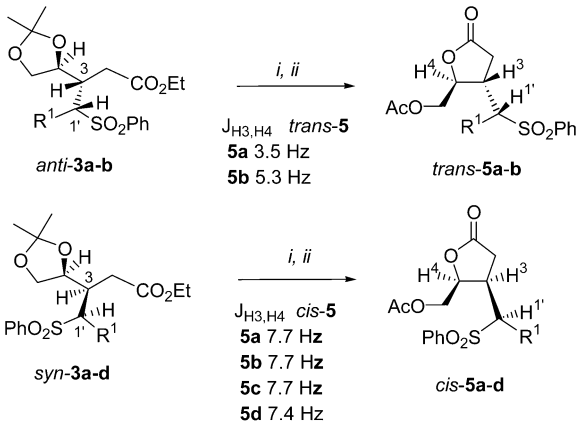


i. THF, BuLi, -78^{0}C or LDA, THF, -78^0 (for **2d**)
ii. -78^{0}C to rt (3h for **2a** and 15h to **2b**)

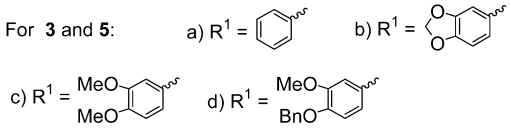
entry	**2**	% *syn*-**4**	de
1	**2a**	40	88
2	**2b**	74	90

[a] The assignment of the stereogenic center in C1′ (*S*) was based on mechanistic considerations but could not be determined by NOE experiments. Product distribution was measured by quantitative ^{13}C NMR or ^{13}H NMR.

SCHEME 1. Lactonization of Adducts 3a−d in Acid Medium



i - HCl(20%), MeOH , 93 - 97%;
ii - Ac_2O, Py, DMAP, rt, overnigth, 95 - 98%.



room temperature and kept at this temperature for 3 h, a *syn*-selective conjugate addition took place leading to adducts *syn*-**4a,b** as the main yields, along with a very small amount of a diastereomer whose structure was not determined, which might be removed by chromatography.

Stereochemical Assignments. The configurations of the chiral centers in adducts *anti*-**3a,b** and *syn*-**3a**−**d** (C3 and C1′) were assigned after their transformation into the corresponding lactones *trans*-**5a,b** and *cis*-**5a**−**d**, by reaction in aqueous acid medium, followed by acetylation (Scheme 1). In the course of our studies on *β*,*γ*-disubstituted-*γ*-butyrolactones derived from D-(+)-mannitol, we observed that the *trans*-isomers showed values for $J_{H3,H4}$ (ca. 4−6 Hz) smaller than those of the *cis*-isomers (ca. 7−9 Hz). Moreover, in *cis*-lactones, H3 exhibits an NOE

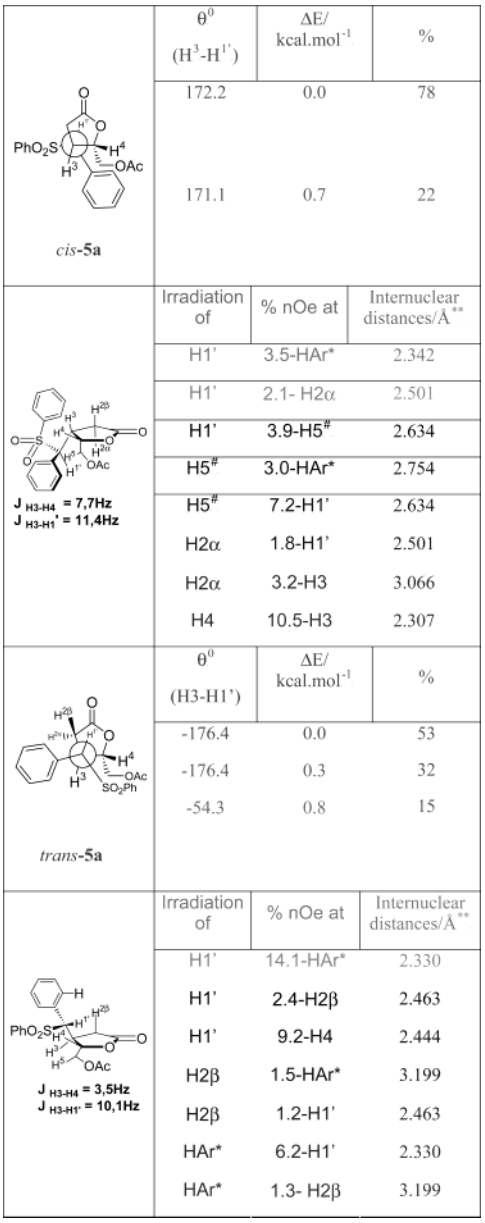


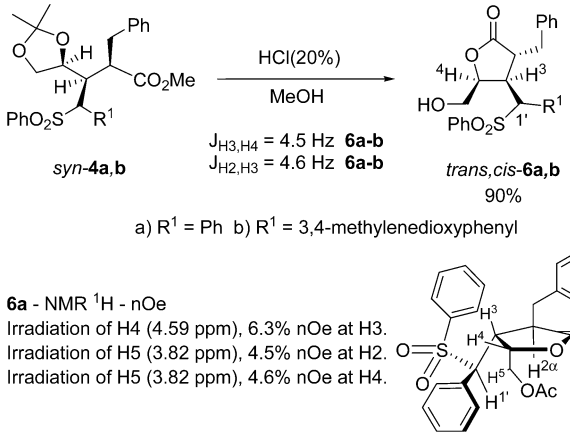
FIGURE 2. MM2* calculation and NOE effects in lactones *cis*-**5a** and *trans*-**5a**.

(∼2%) after irradiation at H4.[6] The same trend was observed for the new lactones, as shown in Scheme 1. Since the configuration at C4 in these lactones is known, the measurement of $J_{H3,H4}$ led to the determination of the absolute configuration at C3.

The configuration at C1′ was also determined by ^{1}H homonuclear *J* coupling and NOE measurements. Since the dihedral angle along C3−C1′ bond affects the NOE involving H1′ as well as the value of $J_{H3,H1'}$, we performed molecular mechanics calculations (MM2*)[10] for *trans*-**5a** and *cis*-**5a** lactones in order to know more about the conformational equilibrium in these compounds. Figure 2 shows the most stable conformers for these lactones, their relative steric energies, and calculated geometries.

(10) *Macro Model*, v. 6.5: Mohamadi F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M., Caulfield, C., Chang, G., Hendrickson, T., Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

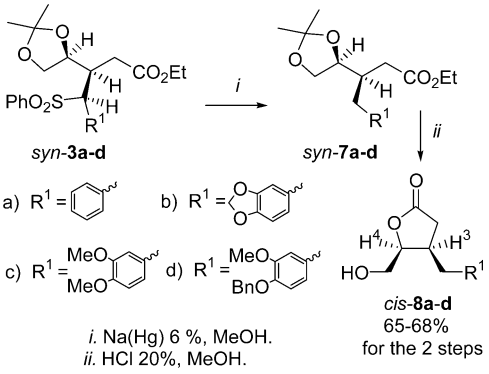
SCHEME 2. Lactonization of Adducts Syn 4a,b in Acid Medium



The examination of the structures obtained reveals that, in all cases, H1′ is over the lactone ring, leaving the bigger R^1 and $PhSO_2$ groups further away from the lactone ring vicinity. The calculated rotation barriers for the most stable conformers of lactones *trans*-**5a** and *cis*-**5a** ranges between 5 and 7 kcal mol^{-1}, and the sharp signals observed in the ^{1}H NMR spectra of such compounds suggest that these conformers are in a fast equilibrium at room temperature.[11] In *cis*-lactone **5a**, the inside position of H1′ was suggested by the observed NOE between this hydrogen and hydrogens H2α and H5. Similarly, the strong NOE observed between H1′ and hydrogens H4 and H2*β* in the NMR of **5a** *trans*-lactone was suggestive of the inside position of that hydrogen in this compound. The calculated dihedral angles $\theta_{H3-C3-C1'-H1'}$ (ca. 171−176°) for lactones *trans*-**5a** and *cis*-**5a** are in accordance with the measured $J_{H3,H1'}$ values (10.1 and 11.4 Hz, Figure 2).[11] For *cis*-**5a**, irradiation of the hydrogens of CH_2OAc group produced a NOE in aromatic (Ph) hydrogen, placing this ring α-oriented in the right side of the molecule (*S*-configuration). The irradiation of H2*β* in lactone *trans*-**5a** (Figure 2) was the most elucidative experiment to determine the configuration at C1′, since NOE enhancements were observed at the aromatic (Ph) group, thus placing this substituent *β*-oriented in the left side of the molecule (*S*-configuration). The NOE measurements on benzyl phenylsulfone **2a** and the heteronucler correlation experiments (HETCOR) on lactone *cis*-**5a** permitted the differentiation of the hydrogen atoms placed at the Ph and the $PhSO_2$ aromatic rings. So did the NOE studies involving lactones *trans*-**5a** and *cis*-**5b,c** and benzyl phenylsulfones **2b,c**.

The configuration at C2 and C3 in adducts *syn*-**4a,b** was also determined after their transformation into lactones *trans,cis*-**6a,b** (Scheme 2). It is worth noting that the coupling constant between H3 and H4 is smaller (∼4 Hz) than that observed for lactones *cis*-**5a**−**d** (∼7 Hz), which are not substituted in C2. This change is probably due to additional conformational constraints imposed by the presence of the benzyl group at C2. The *cis*-relationship between the hydrogen H3 and H4 atoms was confirmed by the strong NOE observed at H3 after irradiation at H4. The NOE enhancement at H2 after irradiation of H5 suggests the *R* configuration for C2. Noe experiments failed to confirm the stereochemistry at C1′. Since the *S*-configuration at C1′ in adducts *syn*-**3a**−**d** did not depend on the geometry of the double bound in **1a,b** acceptors or on reaction conditions, we proposed the same configuration at this stereogenic center for the *syn*-**4a,b** products, basing ourselves in mechanistic considerations.

SCHEME 3. Reduction of C−S Bond in Adducts Syn-3a-d



Cleavage of C−S Bond in Adducts. The C−S bond in compounds *syn*-**3a**−**d** was cleaved under reductive conditions (Na/Hg).[12] Reactions to these compounds in aqueous acid led to the corresponding lactones *cis*-**8a**−**d** (Scheme 3). The measured $J_{H3,H4}$ for these lactones and the NOE effects observed between H3 and H4 validated the proposed configuration at the new stereogenic centers in C3, generated at the conjugated addition step.

Discussion

It seems clear that in conditions 3 and 4 the product distribution is under thermodynamic control, since the *anti*-adducts formed in the reactions of **2′a**−**d** with *E*-**1a** at −78 °C were transformed into *syn*-adducts by raising the temperature at which the reaction was quenched (−78 °C to room temperature), thus suggesting that a conjugate/retroconjugate addition process is in operation. The product distribution at room temperature strongly favors adducts *syn*-**3a**−**d**; the equilibrium being reached after 3 h, irrespective of the solvent used (THF or THF−HMPA).

The reaction of **2′a** with *E*-**1a** at −78 °C (conditions 1 and 2) was reinvestigated in order to determine if the stereoselectivity is kinetically controlled or some equilibration occurs, even at this temperature. The product distribution was measured from 10 s to 1 h (the time used in Table 1), in the presence and absence of HMPA, and the enoate was completely consumed after 5 min. Since the *syn*-**3a**/*anti*-**3a** ratio did not change with time, we assume that at −78 °C the product distribution is kinetically controlled, regardless of the presence of HMPA, disclosing the occurrence of a chelated transition state.

To propose a mechanistic rationale for the observed kinetic stereoselectivities, the conformational equilibrium of enoates *Z*-**1b** and *E*-**1b** was investigated using ab initio calculations (MP2/6-31G*).[13] These calculations furnished

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(12) Anderson, M. B.; Ranasinghe, M. G.; Palmer, J. T.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3125.

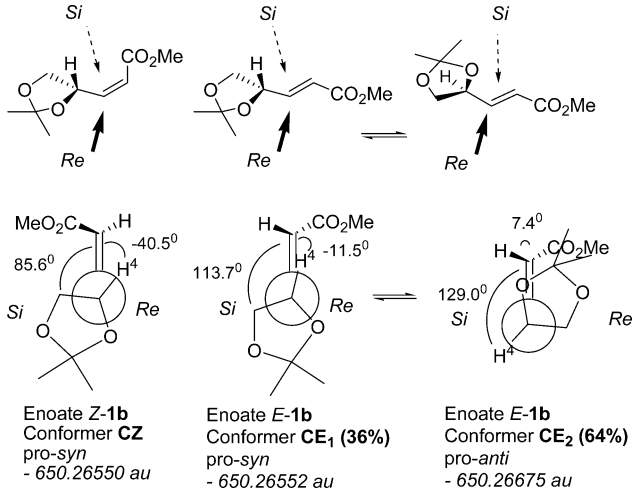


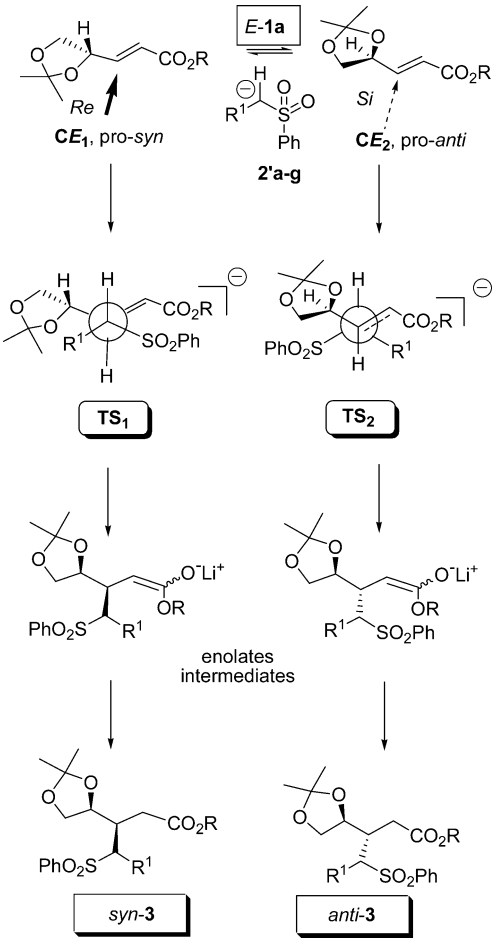
FIGURE 3. Main conformers for enoates *E*- and *Z*-**1b** calculated by molecular modeling.

two minima of energy for enoate *E*-**1b**, $\mathbf{CE_1}$ and $\mathbf{CE_2}$ (36/64, Figure 3), whereas only a minimum of energy was obtained for enoate *Z*-**1b**, **CZ** (Figure 3).[14]

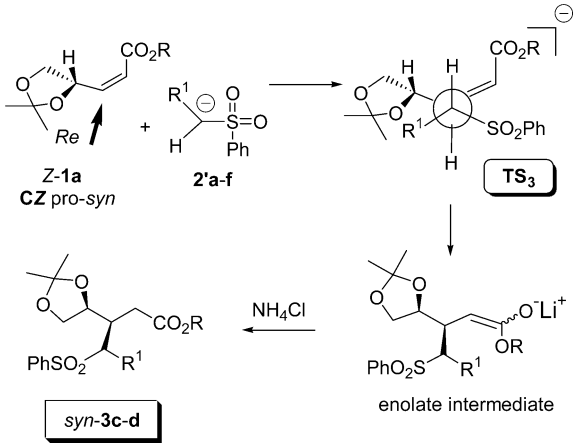
The chelation between the nucleophile (Li atom) and the enoate (oxygen atoms of the acetal or ester group) might affect the conformational equilibrium of the enoate, but because this possibility had been ruled out (the product distribution is identical in the presence or absence of HMPA), we accept that conformer **CZ** (enoate *Z*-**1**) and conformers $\mathbf{CE_1}$ and $\mathbf{CE_2}$ (enoate *E*-**1**) are involved in the transition states leading to the conjugate addition adducts. Taking into account only steric hindrance, it is reasonable to expect that the nucleophiles will attack enoate *Z*-**1** preferentially through the *re* face of conformer **CZ**, yielding *syn*-adducts. On the other hand, the two conformers of enoate *E*-**1** have opposite prochiralities, i.e., whereas the *si* face of $\mathbf{CE_2}$ is the most available (pro-*anti*), the *re* face is the less hindered one (pro-*syn*) in $\mathbf{CE_1}$.

A mechanistic rationale to explain the results of the conjugated addition to *E*-**1** is presented in Scheme 4. Since the kinetic stereoselection in the additions of **2′a**−**d** at −78 °C was not affected by the presence of HMPA, it appears that stereoselectivities are achieved through a nonchelated approach between the nucleophiles and conformers $\mathbf{CE_1}$ and $\mathbf{CE_2}$. The configuration at C1′ in the *anti*-adducts (*anti*-**3a**−**d**) can be explained by the transition state $\mathbf{TS_2}$, where the phenylsulfonyl carbanions attack the *si* face of the *E*-enoate (conformer $\mathbf{CE_2}$) in an *anti-periplanar* approach. On the other hand, the configuration at C1′ in the *syn*-adducts (*syn*-**3a**−**d**) can be explained by the transition state $\mathbf{TS_1}$. In this case, a *synclinal* approach was proposed for the attachment of phenylsulfonyl carbanions to the *E*-enoate (conformer $\mathbf{CE_1}$), in order to avoid electrostatic interactions between the oxygen at the stereogenic center and the negatively charged incoming nucleophile. In both transition states,

SCHEME 4. Mechanistic Rationale for the Addition of Phenylsulfonyl Carbanions to Enoate *E*-1a



SCHEME 5. Mechanistic Rationale for the Addition of Benzyl Phenylsulfonyl Carbanions to Enoate *Z*-1a



the benzylic hydrogen was placed in the more hindered position.

The stereoselective formation of *syn*-**3a,b** in the conjugated addition of **2′a,b** to *Z*-**1a** under kinetic conditions can be explained by the intervention of $\mathbf{TS_3}$ (Scheme 5). As a result of the electrostatic repulsion between the incoming nucleophile and the oxygen atom at the chiral center of the acceptor, a synclinal approach of the

(13) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1982**, *56*, 2257.

(14) Because in enoates *E*-**1a** and *E*-**1b**, as well as in enoates *Z*-**1a** and *Z*-**1b**, the $J_{H3,4}$ are identical and they react with phenylsuphonyl carbanions with the same stereoselectivity, one can accept that the conformational equilibrium around C3−C4 bond is little affected by the nature of the ester moiety.

phenylsulfonyl carbanions to conformer $\mathbf{CZ_a}$ was proposed. This places the bulky phenyl groups at the least sterically hindered position available and explains the configuration at C1′ in the adducts.

Last, the *syn*-**3**/*anti*-**3** ratio obtained in the reactions with *E*-**1** under kinetic conditions was 45/55, whereas the contribution of conformers $\mathbf{CE_1}$ (pro-*syn*) and $\mathbf{CE_2}$ (pro-*anti*), calculated by ab initio, was 36/64. To explain these results, we must accept that in these cases the nucleophile attacks $\mathbf{CE_1}$ faster.[15]

Finally, the reactions involving enoate **1c** as acceptor occurred only at room temperature, and in this case the product distribution is thermodynamically controlled.

Conclusions

Benzylic phenylsulfonyl carbanions were used as synthetic equivalents of oxygenated benzylic organometallics in stereoselective conjugate addition to chiral enoates derived from D-mannitol. The resulting *syn*-adducts could be transformed into the corresponding β,γ- and α,β,γ-substituted γ-butyrolactones, which are valuable intermediates for organic synthesis.

Acknowledgment. The authors thank CNPq, CAPES, FAPERJ, and PRONEX for financial support; CNPq for fellowships to P.R.R.C., A.R.G.F., and K.P.P.; CAPES for a fellowship to A.G.D. and G.V.M.deA.V.; E. Migues and M.C.H.P. Lima for NMR and MS spectra; and Federal University of Pernambuco for microanalysis. The authors also thank Prof. Warner B. Koover (IQ-UFRJ) for helpful discussions.

Supporting Information Available: General experimental methods, ^{1}H and ^{13}C NMR spectra, materials, theoretical calculations, and NOE measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035427D

(15) The *syn*/*anti* ratio depends of the nucleophile; for example, allyl and prenyl sulphonyl carbanions attack almost exclusively $\mathbf{CE_2}$,[6d] leading to *anti* adducts, while benzylamine and nitronates attack preferentially $\mathbf{CE_1}$, leading to *syn* adducts.[5b] The reasons for these different preferences are being studied in our laboratory.