Syn-Selective Michael Addition of Nitromethane Derivatives to Enoates Derived from (*R*)-(+)-Glyceraldehyde Acetonide

Jeronimo S. Costa,[†] Ayres G. Dias,[†,‡] Aline L. Anholeto,[†] Mônica D. Monteiro,[†] Vera L. Patrocinio,*[,§] and Paulo R. R. Costa*[,†]

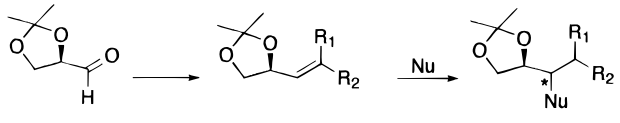
Laboratório de Síntese Orgânica I, Laboratório de Síntese Orgânica III, Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS, Bloco-H, Ilha da cidade Universitária, 21941-590, Rio de Janeiro, RJ, Brazil, and Instituto de Química, Universidade Estadual do Rio de Janeiro

Received April 29, 1996[⊗]

We report the syn-selective Michael addition of a series of substituted primary and secondary nitromethane derivatives **4a**−**g** to chiral enoates (*Z*)-**2a** and (*E*)-**2a** in the presence of TBAF·3H_2O or DBU. Regardless of the base employed, adducts *syn*-**5a**−**g** were obtained in good de (80−100%) from the reactions of **4a**−**g** with (*Z*)-**2a**. However, in the addition to (*E*)-**2a**, the syn-diastereoselectivities depended on the structure of the nucleophile (80−90% de for nitromethane (**4a**), 80% de for phenylnitromethane (**4g**), 50 and 34% de for the primary nitromethane derivatives **4b** and **4d**, and 0 and 6% de for the secondary nitromethane derivatives **4c** and **4f**). A mixture of epimers (2:1/1:1) was obtained at the chiral center bearing the nitro group in **5b** and **5d**−**g**. The syn/anti ratio C-3,C-4 is kinetically controlled, while the epimeric ratio at the CNO_2 chiral center (C-1′) seems to be thermodynamically controlled. Adducts **5a**,**b**,**c**,**g** were transformed into the respective cis-β,γ-disubstituted γ-butyrolactones **6a**, **7**, **9a**, and **9c**. A mechanistic rationale to explain the observed diastereoselectivities is proposed.

Introduction

Different strategies using the Michael addition of nucleophiles to α,β-unsaturated carbonyl compounds have been developed to obtain enantiomerically enriched adducts.[1] In particular, the use of enantiomerically pure Michael acceptors with a chiral center in the γ-position bearing an oxygen has been extensively studied and is a powerful tool in synthesis.[1a−c,2] Compounds such as **2** are among the most studied chiral Michael acceptors of this type, since they can be easily prepared from (*R*)-(+)-glyceraldehyde acetonide (**1**), a chiral building block obtained from inexpensive D-(+)-mannitol[3] (Figure 1). The stereochemical outcome of these reactions depends on the structure of the nucleophile, and both syn-[1b,4,5] and anti-addition[1b,6] have been reported. In some cases, the selectivity has been shown to be dependent on the geometry of the double bond in the Michael acceptor.[7]



***Z*-2a**, R_1 = CO_2Et,R_2 = H; ***E*-2a**,R_1 = H,R_2 = CO_2Et
***E*-2b**, R_1 = H, R_2 = $COCH_2CO_2Et$; ***E*-2c**, R_1 = F, R_2 = CO_2Et
***Z*-2d**, R_1 = COMe, R_2 = H; ***E*-2d**, R_1 = H, R_2 = COMe

Figure 1. Diastereoselective Michael addition to enoates **2** derived from (*R*)-(+)-glyceraldehyde acetonide **1**.

Recently, we described[4] a highly syn-selective Michael addition of nitromethane (**4a**) to both enoates (*Z*)-**2a** and (*E*)-**2a** in the presence of TBAF·3H_2O or DBU. Herein, we disclose the results obtained in the addition of a series of nitromethane derivatives **4b**−**g** to these enoates (Scheme 1).

Results

In Scheme 1, our optimized results for the Michael addition of **4a**−**g** to (*Z*)-**2a** (*Z*/*E* = 9/1) and (*E*)-**2a** (*Z*/*E* = 1/32) are presented. In the resulting adducts **5a**−**g** a new chiral center is diastereoselectively formed (C-3). In adducts **5b** and **5d**−**g**, an additional chiral center, that bearing the nitro group (C-1′), is also created. The reactions were run with DBU in CH_3CN[9a] or TBAF·3H_2O in THF;[9b,c] the observed *syn*-**5a**−**g**/*anti*-**5a**−**g** ratios (C-

[†] Laboratório de Síntese Orgânica I, Universidade Federal do Rio de Janeiro.
[‡] Universidade Estadual do Rio de Janeiro.
[§] Laboratório de Síntese Orgânica III, Universidade Federal do Rio de Janeiro.
[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) (a) Yamamoto, Y.; Pyne, S. G.; Schinzer, D.; Feringa, B. L.; Jansen J. F. G. A. In *Stereoselective Synthesis;* Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21b. Little, R. D.; Masjedizadeh, M. R. *Org. React*. **1995**, *47*, 315. Cook, C. E.; Allen, D. A.; Miller, D. B.; Whisnant, C. C. *J. Am. Chem. Soc.* **1995**, *117*, 7269. d'Angelo, J.; Cavé, C.; Desmaele, D.; Dumas, F. *Trends Org. Chem*. **1993**, *4*, 555. (b) Leonard, J. *Contemp. Org. Synth*. **1994**, 387. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev*. **1992**, *92*, 771.

(2) Yoshida, S.; Yamanaka, J.; Miyake, T.; Moritani, Y.; Ohmizu, H.; Iwasaki, T. *Tetrahedron Lett*. **1995**, *36*, 7271. Revesz, L.; Briswalter, C.; Heng, R.; Leutwiler, A.; Mueller, R.; Wuethrich, H. *Tetrahedron Lett*. **1994**, *35*, 9693. Smajda, W.; Zahouily, M.; Malacria, M. *Tetrahedron Lett*. **1992**, *38*, 5511.

(3) Leonard, J.; Mohialdin, S.; Swain, P. A. *Synth. Commun*. **1989**, *19*, 3529. Mann, J.; Partlett, N.; Thomaz, A. *J. Chem. Res., Synop*. **1987**, 369. Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.

(4) Patrocinio, V. L.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474.

(5) Nomura, M.; Kanemasa, S. *Tetrahedron Lett*. **1994**, *35*, 143.

(6) Nilsson, K.; Ullenius, C. *Tetrahedron* **1994**, *50*, 13173.

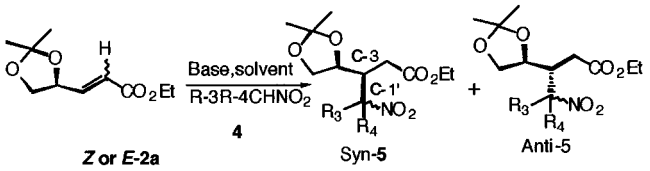
(7) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett*. **1994**, 827. Morikawa, T.; Washio, Y; Harada, S.; Hanai, R.; Kayashita, T.; Nemoto, H.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, *1*, 271.

(8) For recent studies in racemic series on the Michael of nitronates see, *inter alia*: Francke, W.; Schröder, F.; Walter, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *Liebigs Ann*. **1995**, 965. Thomas, A.; Rajappa, S. *Tetrahedron* **1995**, *51*, 10571. Ballini, R.; Marziali, P.; Mozzicafreddo, A *J. Org. Chem*. **1996**, *61*, 3209. Marti, R. E.; Helnzer, J.; Seebach, D. *Liebigs Ann. Chem*. **1995**, *7*, 1193.

(9) (a) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, 51, 4213. Ono, N.; Kamimura A.; Kaji, A. *Synthesis* **1984**, 226. (b) Clark, J. H. *Chem. Rev*. **1980**, 80, 429. (c) The use of old solutions of TBAF·3H_2O in THF can lead to a decrease in the chemical yield.

S0022-3263(96)00788-8 CCC: $14.00

Scheme 1. Syn-Michael Addition of Nitromethane Derivatives 4a−g to Enoates (*Z*)-2a and (*E*)-2a



4 or **5** : **a**, $R_3 = R_4 = H$; **b**, $R_3 = H$, $R_4 = CH_3$; **c**, $R_3 = R_4 = CH_3$; **d**, $R_3 = H$, $R_4 = CH_2CH(OCH_3)_2$; **e**, $R_3 = H$, $R_4 = (CH_2)_2OAc$; **f**, $R_3 = CH_3$, $R_4 = (CH_2)_2CO_2CH_3$; **g**, $R_3 = H$, $R_4 = Ph$

entry	2a	4	base[a]/solv.	5 (%)[b]	syn/anti-5 d.e.[c](%)	epimeric ratio at c1′
1	*ZorE*	4a	TBAF/THF	71	90	—
2	*Z*	4a	DBU/CH_3CN	70	80	—
3	*Z*	4b	DBU/CH_3CN	70	90	1.5/1
4	*Z*	4b	TBAF/THF	75	90	1.4/1
5	*E*	4b	DBU/CH_3CN	65	50	1.5/1
6	*E*	4b	TBAF/THF	65	50	1.4/1
7	*Z*	4c	DBU/CH_3CN	70	94	—
8	*Z*	4c	TBAF/THF	80	94	—
9	*E*[d]	4c	DBU/CH_3CN	68	0	—
10	*Z*	4d	TBAF/THF	77	94	1.3/1
11	*E*	4d	TBAF/THF	70	34	1.1/1
12	*Z*	4e	TBAF/THF	63	92	1.1/1
13	*Z*	4f	TBAF/THF	80	100	1.4/1
14	*E*	4f	DBU/CH_3CN	70	6	1.1/1
15	*Z*	4g	TBAF/THF	62	80	2.0/1
16	*E*	4g	TBAF/THF	60	80	2.0/1
17	*Z*	4g	DBU/CH_3CN	67	80	2.0/1
18	*E*	4g	DBU/CH_3CN	65	80	2.0/1

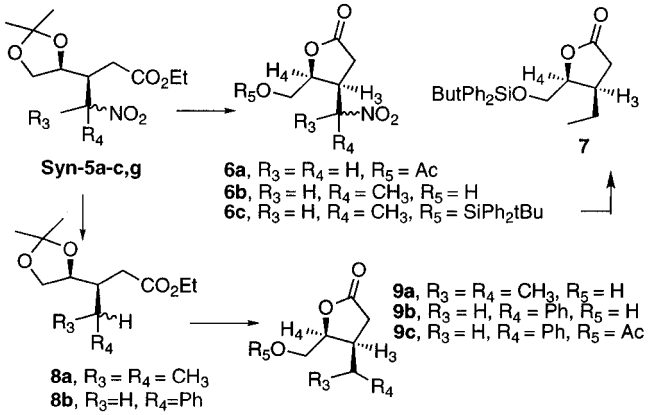
[a] Other bases such as TMAF/DMSO and KF/Al_2O/THF were used, and similar de and yields were observed. [b] After purification by flash chromatography. [c] Measured by quantitative ^{13}C NMR and/or HPLC. [d] Methyl ester was used.

3) and the epimeric ratios at the CNO_2 (C-1′) center in the products were shown to be independent of the base employed.

The additions of nitromethane (**4a**) and phenylnitromethane (**4g**) led, respectively, to **5a** and **5g** in a good syn/anti ratio (de at C-3 = 80−90% and 80%), regardless of the stereochemistry of the double bond in **2a** (entries 1, 2, and 15−18, Scheme 1). A mixture of epimers at C-1′ was observed for adduct **5g** (2/1 ratio). On the other hand, when **4b**−**f** were used, the syn/anti ratio (de at C-3) depended on the stereochemistry of **2a**. High de (90−100%) were observed in the reactions of these nitro derivatives with (*Z*)-**2a** (entries 3, 4, 7, 8, 10, 12, and 13, Scheme 1), in contrast with the results obtained when (*E*)-**2a** was used as acceptor. In these latter cases, the addition of primary nitromethane derivatives **4b** and **4d** led to the corresponding adducts **5b** and **5d** in moderate de (50% and 34%, respectively, entries 5, 6, and 11, Scheme 1), while adducts **5c** and **5f** were obtained in very low de from the addition of secondary nitromethane derivatives **4c** and **4f** (0% and 6%, entries 9 and 14, Scheme 1). The adducts **4b** and **4d**−**f** were obtained as mixtures of epimers at C-1′.

The syn stereochemistry of **5b** was unambiguously determined by chemical correlations with the known lactone **7** (cyclization, silylation, and denitration, Scheme 2). Compounds **5a**, **5c**, and **5g** were transformed into lactones **6a**, **9a**, and **9c**, respectively, in order to establish the syn-stereochemistry (Scheme 2). Hydrolysis of the ketal group in **5a** with 20% HCl in MeOH, was followed *in situ* by selective lactonization[10] of the resulting diol. Acetylation of the crude product obtained led to the nitro

Scheme 2. Confirmation of Syn-Stereochemistry in Adducts 5a,b,c,g



5a → **6a**; **8b** → **9b**, HCl 20%,CH_3OH; Ac_2O, $HClO_4$, 80%
8a → **9a**, HCl 20%,CH_3OH, 90%. **5b** → **6b**, HCl 20%,CH_3OH; TBDPSiCl, DMF, imidazole, 90%. **6b** → **7**; **5c** → **8a**; **5g** → **8b**, Bu_3SnH, AIBN, Tol., ref., 40%, 65%, 60%

γ-butyrolactone derivative **6a**. As previously reported,[4] the cis-relationship between H-3 and H-4 in lactone **6a**, and thus the syn-stereochemistry in adduct **5a**, was determined by the coupling constant ($J_{H-3,H-4} = 7.5$ Hz) and confirmed by irradiation at H-4 (δ 4.95), which led to an enhancement of 3% in intensity of H-3 (δ 3.59). With **5c** and **5g**, however, the C−NO_2 bond was first cleaved with Bu_3SnH,[12] leading to compounds **8a** and **8b**, respectively. Reaction of **8a** with 20% HCl in MeOH selectively furnished the *cis*-γ-butyrolactone **9a** ($J_{H-3,H-4} = 7.3$ Hz), while treatment **8b** under the same conditions, followed by acetylation of the resulting intermediate **9b**, furnished the corresponding *cis*-lactone **9c** ($J_{H-3,H-4} = 7.2$ Hz).

The syn-stereochemistry for adducts **5d**−**f** was assigned through comparison of their ^{13}C NMR spectra with those of *syn*-**5a**−**c**,**g**. Specifically the syn-diastereomer in all cases showed greater shielding of the C-1′ asymmetric carbon (CNO_2) and less shielding of the carbon C-3.

Discussion

In order to obtain information on the nature of the stereochemical control in these Michael additions, the nitromethane derivatives **4a**, **4b**, and **4g** were allowed to react with enoates (*Z*)-**2a** and (*E*)-**2a** in the presence of TABAF·$3H_2O$ in THF or DBU in CH_3CN, and the product distribution was analyzed after 10%, 50%, and 80% of enoate conversion. It was observed that the syn/anti ratio at C-3 in the resulting adducts **5a**, **5b**, and **5g**, as well as the epimeric ratio at the CNO_2 (C-1′) chiral center in adducts **5b** and **5g**, was constant, regardless the reaction time and the base employed. Due to the acidity of the hydrogen atoms on the carbon bearing the nitro group, it seems reasonable to assume that formation of these chiral centers is thermodynamically controlled, particularly in light of the report that for aldol addition reactions involving nitronates the stereogenic center bearing the nitro group is easily epimerizable.[13] In

(10) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Jones, M. F. *J. Chem. Soc., Chem. Commun.* **1993**, 23.

(11) (a) Ziegler, F. E.; Tung, J. S. *J. Org. Chem.* **1991**, *56*, 6530 and references cited therein. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365 and references cited therein.

(12) Ono, N.; Miyake, H.; Kati, A. *J. Org. Chem.* **1984**, *49*, 4997.

(13) Whener, V.; Jägger, V. *Angew Chem., Int. Ed. Engl.* **1990**, *29*, 1169. Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261.

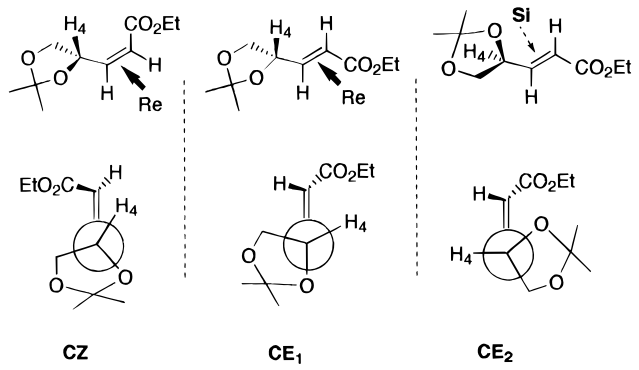


Figure 2. Most stable conformers for enoates (*Z*)-**2a** and (*E*)-**2a** (molecular mechanics, AM1).

contrast, the constant syn/anti ratios seemed to indicate that the chirality at the newly generated center C-3 is kinetically controlled, although the possibility of a rapid equilibration through a retro-Michael−Michael reaction could not, a priori, be completely excluded. Unambiguous evidence favoring kinetic control, though, was obtained when pure *syn*-**5c** and pure *anti*-**5c**, purified by flash chromatography, were allowed to react with TBAF·$3H_2O$ and $CH_3CHCH_3NO_2$ in THF or DBU and $CH_3CHCH_3NO_2$ in CH_3CN. In all cases, *syn*-**5c** and *anti*-**5c** were recovered diastereomerically pure, showing that product equilibration does not occur under the reaction conditions. Thus, since the syn/anti ratio is kinetically controlled, the product distribution shown in Scheme 1 must be due to the difference in energy of the transition states leading to the syn- and anti-adducts.

The diastereoselectivities in the addition of methylcopper[6,14] and fluoride[15a] to enoates having a chiral center in the γ-position bearing an oxygen were previously explained by transition-state energies derived from theoretical calculations (*ab initio* and MM2, respectively). In particular, for the reactions involving enoates (*Z*)- and (*E*)-**2a**, different explanations depending on the nucleophile used have been advanced to account for the syn or anti diastereoselectivities of the addition.[1b,4] A modified Felkin−Anh model has been suggested to rationalize the syn-addition observed in the absence of chelation between the nucleophile and **2a**.[1b,4] More recently, transition states for the addition of tin-centered radicals[7b] and Diels−Alder cycloadditions[15b] to **2a** were calculated using a semiempirical method (AM1). In our calculations (AM1), conformer **CZ** (Figure 2) was determined to be the most stable for enoate (*Z*)-**2a** (>99% of contribution), while for enoate (*E*)-**2a** conformers $\mathbf{CE_1}$ and $\mathbf{CE_2}$ were found to be almost isoenergetic.[16]

In attempting to rationalize our results, we have assumed the involvement of conformer **CZ** in the transition state leading from enoate (*Z*)-**2a** to adducts *syn*-**5a**−**g**. Since our nitronate anions were generated in the absence of metallic cations, cyclic transition states can

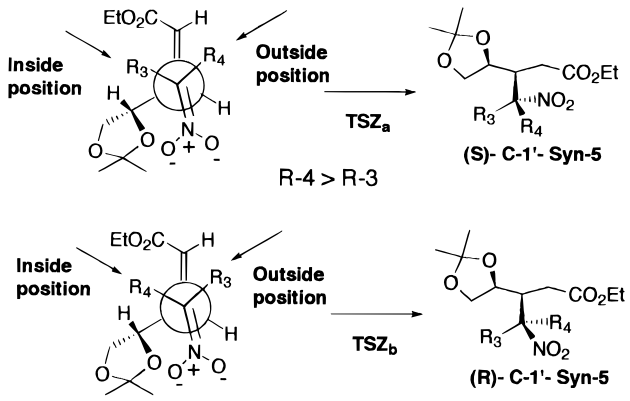


Figure 3. Synclinal approach of nitronates to the *Re* face of (*Z*)-**2a** (conformer CZ), leading to *syn*-**5**.

be discarded and an anti-periplanar approach of these anions to the less hindered *Re*-face of conformer **CZ** might be expected.[18] However, in this approach, a destabilizing electronic interaction between the oxygen atom at the stereogenic center and the polar nitronate group in the incoming nucleophile would occur. For this reason, we propose a synclinal approach (Figure 3), in which this interaction would be minimized. According to this hypothesis, two transition states can be proposed for the reactions of the prochiral nitronates derived from **4b** and **4d**−**g** with (*Z*)-**2a**, namely **TSZa** and **TSZb** (Figure 3).

Considering the addition of primary nitronates derived from **4b**,**d**−**e**,**g**, $\mathbf{TSZ_a}$ would be favored over $\mathbf{TSZ_b}$, since the more bulky group (R_4) of the incoming nucleophile assumes the less hindered outside position. This transition state would lead to adducts *syn*-**5b**, *syn*-**5d-e**, and *syn*-**5g** with the *S* stereochemistry at the CNO_2 stereogenic center as indicated, but due to fast equilibration, this stereochemical information is lost. The transition state for the addition of secondary nitromethane derivatives **4c** and **4f** is more crowed since in these cases an alkyl group is always in the more sterically hindered inside position. However, these steric interactions are minimized due to the synclinal approach. For the addition of **4f**, the epimeric ratio at the CNO_2 center is kinetically controlled (no H atom is available for epimerization). The low π-facial discrimination with the corresponding nitronate (epimeric ratio at CNO_2 center in adduct **5f** = 1.4:1.0, entry 13, Scheme 1) shows that the methyl and the methylene groups are almost sterically equivalent in this reaction.

Our mechanistic interpretation for the reactions involving enoate (*E*)-**2a** is shown in Figure 4. Conformers $\mathbf{CE_1}$ and $\mathbf{CE_2}$ are isoenergetics;[15a,17] while the first would give syn-adducts by attack of the nitronate on the *Re*-face, the second, with a sterically less hindered *Si*-face, would give anti-adducts. A synclinal approach of the nitronates to conformers $\mathbf{CE_1}$ and $\mathbf{CE_2}$ seems likely; two possible transition states originate from each conformer

(14) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524.

(15) (a) Bernardi, A.; Capelli, A. M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 21. (b) Casas, R.; Parella, T.; Branchadell, V.; Oliva, A.; Ortuño, R. M. *Tetrahedron* **1992**, *48*, 2659.

(16) It has been demonstrated by VT-^{1}H NMR that for *E*-enoates bearing an alkoxy group at the stereogenic center the main conformer has H-3 (at the olefinic β-carbon) and H-4 (at the stereogenic center) in an antiperiplanar relationship: Gung, B. W.; Melnick, J. P.; Wolf, M. A.; King, A. *J. Org. Chem.* **1995**, *60*, 1947 and references cited therein. The *s-cis*/*s-trans* conformational preferences of the ester group in enoates has been studied by supersonic jet spectroscopy, NOE, and X-ray analyses: Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068.

(17) Our calculations (AM1) show C_Z-**2a** as the most important conformation of enoate (*Z*)-**2a** (99%) while for enoate (*E*)-**2a** conformers C_{E1}-**2a** and C_{E2}-**2a** are isoenergetic. These data are in complete agreement with previous studies.[15b] The calculation of transition states for the addition of nitronates to these conformers is under investigation. Amorim, M. B.; Filho, U. F.; Lima, P. G.; Costa, P. R. R. Unpublished results.

(18) The anti-periplanar approximation has been proposed to explain the stereoselectivity in other Michael addition and aldol addition where a metal is not available for coordination. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B. See also ref 1c.

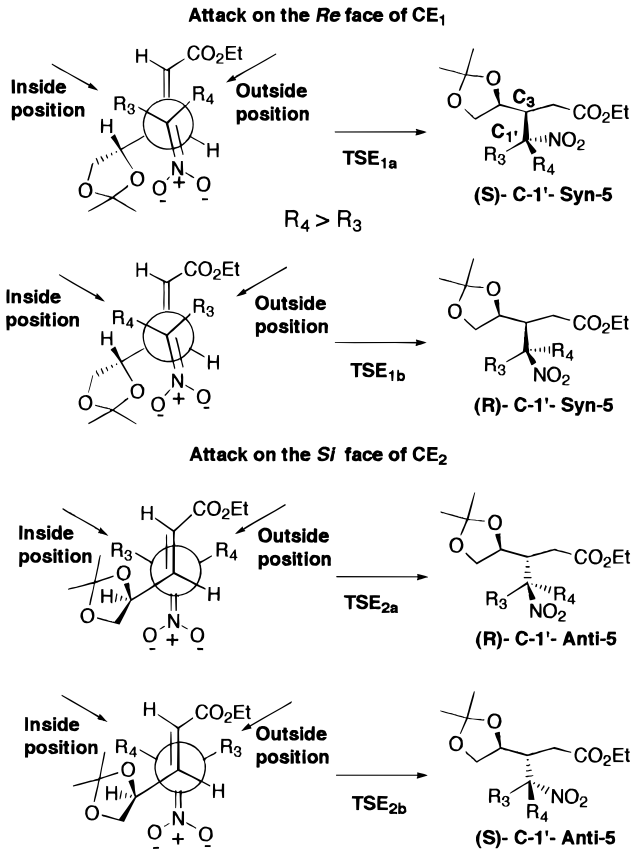


Figure 4. Synclinal approach of nitronates to (*E*)-**2a**. *Re* face of conformer CE_1 and *Si* face of conformer CE_2.

when prochiral nitronates were used as nucleophiles, named **TSE$_{1a}$** and **TSE$_{1b}$** (from **CE$_1$**) and **TSE$_{2a}$** and **TSE$_{2b}$** (from **CE$_2$**).

The very low diastereoselectivity observed in the additions of secondary nitromethane derivatives **4c** and **4f** (0 and 6%, entries 9 and 14, Scheme 1) clearly indicates that in these cases the transition states **TSE$_{1a}$**, **TSE$_{1b}$**, **TSE$_{2a}$**, and **TSE$_{2b}$** are almost equivalent in energy. In these transition states there is a strong destabilizing interaction between an alkyl group in the outside position and the carbethoxy group of the enoate. This strong interaction, maximized in the synclinal approach, would seem to be responsible for bringing the transition states to the same energy level. To explain the higher diastereoselectivities obtained in the addition of the primary nitronates derived from nitroethane (**4b**) (50% de, entries 5 and 6, Scheme 1) and phenylnitromethane (**4g**) (80% de, entries 16 and 18, Scheme 1), we assume to avoid the highly destabilizing steric interactions between R_4 (ethyl or phenyl) and the carbethoxy group, presents in **TSE$_{1a}$** and **TSE$_{2a}$**, the addition of **4b** and **4g** to **CE$_1$** and **CE$_2$** occurs through **TSE$_{1b}$** and **TSE$_{2b}$**, respectively. The degree of steric hindrance of the inside position in conformers **CE$_1$** and **CE$_2$** also needs to be considered to explain the difference in de for **4b** and **4g**. In **CE$_1$**, H-4 is at 60° with respect to the enoate plane, while in **CE$_2$** this angle is 90°. Thus, H-4 is closer to the position of nucleophilic attack in **CE$_2$** and, as a consequence, the inside position is more sterically hindered in this conformer. Once a phenyl group is larger than an ethyl group, **TSE$_{2b}$** is of higher energy for **4g** than for **4b**, explaining the the better syn-diastereoselection observed for **4g**.

Finally, the high de obtained in the addition of **4a** shows that for this unhindered nucleophile **TSE$_1$** is highly favored over **TSE$_2$**.

Conclusions

The work described in this paper shows that it is possible to add substituted nitromethane derivatives (primary and secondary nitroalkanes, nitro ketals, and nitro esters) to chiral enoates **2a** in good chemical yields and with high syn selectivity. The easy removal of the nitro group in adducts **5** by reduction of the C−N bond and the possibility of functional group interconversions involving the nitro group,[19] leading to alkyl and functionalized alkyl groups, respectively, makes this methodology complementary to other conjugate addition methods.

Finally, this work provides a synthesis of *cis*-3,4-disubstituted γ-butyrolactones, which are difficult to prepare by other methodologies,[11a] but present in several classes of natural products.[11b] The total synthesis of some naturally occurring lactones of this type using the present methodology is under investigation in our laboratories.

Experimental Section

Materials. All conjugate additions were performed under N_2 atmosphere. THF was distilled from sodium benzophenone under N_2 and DMF from CaH_2. Acetonitrile was dried over 4 Å molecular sieves, TBAF·3H_2O (solid), nitroethane, 2-nitropropane, TBDMS-Cl, TBDPS-Cl, AIBN, Bu_3SnH, and imidazole are commercially available and were used directly. The enoates (*Z*)-**2a** and (*E*)-**2a** as well as the nitro compounds **4d** and **4g** were prepared according to literature procedures.[20,21] The nitro compound **4e** was prepared from 3-nitropropanal[21] by reduction with $NaBH_4$, under standard conditions, followed by acetylation of the alcohol obtained. The nitro compound **4f** was prepared in quantitative yield by conjugate addition of nitroethane to methyl acrylate in the presence of KF supported on Al_2O_3/THF. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Gemini-200 (200 MHz) Varian Instruments in $CDCl_3$ unless specified otherwise. The coupling constants (*J*) are in hertz (Hz). The analyses by HPLC were performed on a Shimadzu LC-A10 chromatograph using a Shimadzu column C_{18} (25 cm × 1.6 i.d. × 5 mm). High-resolution mass spectra were recorded on a Micromass MM_{12} F and a VG AutoSpec spectrometer. IR spectra were recorded on a Perkin-Elmer Model 783 spectrophotometer, and optical rotations were measured on a Perkin-Elmer Model 243-B polarimeter. All melting points are uncorrected and were determined on a Thomas Hoover apparatus.

Preparation of 5b−g, Typical Procedure: Nitroadduct 5b, Using TBAF·3H_2O as Base. To a stirred solution of (*Z*)-**2a** (3.0g, 15 mmol) and $EtNO_2$ (1.13g, 1.5 mmol) in THF (15 mL) was added TBAF·3H_2O (0.39 g, 1.5 mmol) at rt. The resulting yellow solution was stirred for an additional 4 h and poured into H_2O (50 mL), followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Hex/AcOEt 9/1), yielding 3.1 g (75% of pale yellow oil of **5b** as a mixture of syn/anti diasteromers (95/5) and epimeric at the nitro stereocenter, in the syn-isomer 1.4:1.0).

5b, Using DBU as Base. A solution of $EtNO_2$ (0.21 g, 2.75 mmol) and (*Z*)-**2a** (0.5 g, 2.5 mmol) in acetonitrile (10 mL) was mixed with DBU (1,8-diazabicyclo[5.4.0.]undec-7-ene) (0.38 g, 2.5 mmol). The resulting orange solution was kept at room

(19) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. Seebach, D.; Colvin, E.; Lehr, F.; Weller, T. *Chimia* **1979**, 33, 1.
(20) Kornblum, N. *Org. React.* **1962**, *12*, 101.
(21) Öhr, R.; Schwab,W; Ehrler, R.; Jäger, V. *Synthesis* **1986**, 535.

temperature for 4 h and then poured into 20 mL of water. The mixture was acidified with HCl (10%) until pH 2 and extracted with AcOEt (3 × 30 mL). The combined organic phases were washed with 30 mL of H_2O, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. A viscous residue was obtained and purified as above. Compound **5b** (0.48g, 70%, pale yellow oil) as a mixture of syn/anti diastereomers (95/5) and epimeric at nitro stereocenter (in the syn-isomer 1.5/1.0) was obtained: ^{1}H NMR δ 1.29 (t, J = 7.5, 3H), 1.30 (t, J = 7.5, 3H), 1.36 (s, 6H), 1.42 (s, 3H), 1.45 (s, 3H), 1.57 (d, J = 7.5, 3H), 1.64 (d, J = 7.5, 3H), 2.17−2.41 (m, 2H), 2.41−2.60 (m, 2H), 2.65−2.84 (m, 1H), 2.88−3.04 (m, 1H), 3.57−3.82 (m, 2H), 3.97−4.27 (m, 8H), 4.85−5.01 (m, 2H); ^{13}C NMR δ 13.9, 14.3, 16.0, 25.0, 25.1, 26.1, 26.2, 31.3, 31.5, 41.8, 42.5, 60.9, 67.3, 75.4, 75.5, 82.1, 82.3, 109.3, 170.9, 171.2; MS (70 eV) m/z 260 (M^+ − Me, 35), 169 (47), 141 (64), 127 (45), 101 (100), 95 (89); HRMS (70 eV) m/z for $C_{11}H_{18}NO_6$ (M^+ − Me), calcd 260.113 413, found 260.113 019.

Lactonization of 5b, 8a, and 8b to 6b, 9a, and 9b, Respectively. Typical Procedure: (3*S*,4*S*)-3-Isopropyl-4-(hydroxymethyl)butan-4-olide (9a). To a stirred solution of **8a** (97:3, 0.2 g, 0.82 mmol) in MeOH (4 mL) was added HCl (10%, 1.1 mL) at rt. After 1 h, the solvent was evaporated and the residue filtered through a short pad of silica gel topped with a layer of solid $NaHCO_3$ and anhydrous sodium sulfate (hexane/EtOAc 1:1), providing **9a** (0.11 g, 90%, cis/trans 97/3) as a white solid: $[\alpha]^{25}_D$ = +23 (1.0, MeOH); mp = 118 °C; ^{1}H NMR δ 0.96 (d, J = 4.2, 3H), 0.99 (d, J = 4.1, 3H), 1.70−1.98 (m, 1H), 2.20−2.65 (m, 3H), 3.75−4.05 (m, 1H, OH, exchange with D_2O; 2H), 4.59 (ddd, J = 7.3, 4.3, 3.0); ^{13}C NMR δ 21.0, 21.6, 27.6, 33.3, 45.8, 61.0, 82.4, 177.9; MS (70 eV) m/z 127 (M^+ − 31, 100), 81 (35), 55 (44).

Denitration of 5c, 5g, and 6c to 8a, 8b, and 7, Respectively. Typical Procedure: Ethyl (3*S*,4*S*)-Isopropyl-4,5-*O*-isopropylidenepentanoate (8a). A mixture of **5c** (syn/anti, 97:3, 0.18 g, 0.62 mmol), Bu_3SnH (0.23 g, 0.80 mmol), and AIBN (0.33 g, 0.20 mmol) in benzene (1.5 mL) was heated at 80 °C for 90 min. The reaction mixture was subjected to column chromatography (silica gel, hexane/AcOEt 96/4) to give 0.09 g (yield 64%) of **8a** as a colorless oil (syn/anti = 97:3): $[\alpha]^{25}_D$ = +11 (1.0; $CHCl_3$); ^{1}H NMR δ 0.90 (d, J = 6.0, 3H), 0.93 (d, J = 6.0, 3H), 1.26 (t, J = 7.0, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.81−2.00 (m, 1H), 2.15−2.27 (m, 3 H), 3.57 (dd, J = 8.0, 8.0, 1H), 3.95 (dd, J = 8.0, 6.0, 1H), 4.13 (q, J = 7.0, 2H), 4.05−4.20 (m, 1H); ^{13}C NMR δ 14.0, 18.5, 20.2, 25.2, 26.3, 28.3, 31.6, 43.0, 60.3, 66.8, 76.5, 108.1, 173.3; MS (70 eV) m/z 229 (M^+ − Me, 100), 141 (87), 101 (74), 72 (45).

Acknowledgment. We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Apoio ao Pessoal de Ensino Superior (CAPES) for financial support and for fellowships for all authors. Fundação Universitária José Bonifácio (FUJB, Rio de Janeiro) and Universidade Federal do Rio de Janeiro (UFRJ) are thanked for for financial support. The help of Prof. Antonio J. R. Silva, Francisco Santos, Eduardo Miguez, Cristina Holanda (NPPN-UFRJ), and Leonardo C. M. Coutada (Far-Manguinhos) with the NMR and mass spectra is appreciated. We also thank MSc Ubiracir F. L. Filho (NPPN-UFRJ) and Prof. Warner B. Koover (IQ-UFRJ) for helpful discussions.

Supporting Information Available: Copies of both the ^{1}H and ^{13}C NMR spectra of **5b**−**g**, **6a**−**c**, **8a,b**, and **9a**−**c** and the ^{1}H NMR spectra of *syn*-**5c** (methyl ester) and *anti*-**5c** (methyl ester (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960788X