Controlling π-Facial Diastereoselectivity in the 1,3-Dipolar Cycloadditions of Diazomethane to Chiral Pentenoates and Furanones: Enantioselective Stereodivergent Syntheses of Cyclopropane Hydroxy Acids and Didehydro Amino Acids

Marta Martín-Vilà,[†] Neuh Hanafi,[†] José M. Jiménez,[†] Angel Alvarez-Larena,[‡] Joan F. Piniella,[‡] Vicenç Branchadell,[†] Antonio Oliva,[†] and Rosa M. Ortuño*,[†]

Departament de Química and Unitat de Cristal.lografia, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

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The title compounds have been synthesized in both enantiomeric forms and in good overall yields by using D-glyceraldehyde as the single chiral precursor. The efficiency and usefulness of the synthetic routes have been secured by performing controlled manipulations of the functional groups and by highly stereoselective transformations, namely Wittig−Horner condensations and cyclopropanations. Cyclopropane derivatives have been synthesized through 1,3-dipolar cycloaddition of diazomethane to chiral pentenoates or furanones obtained, in turn, from D-glyceraldehyde. *Syn*/*anti* stereochemistry of the cycloadducts has been unequivocally assigned and rationalized. Since π-facial diastereoselectivity involved in these cycloadditions is the opposite for cyclic and open-chain structures, enantiomeric series of products can be derived.

Introduction

The cyclopropane moiety is a structural feature of widespread compounds with interesting biological activities. Among them, 2,3-methano 2-amino acids have been found from natural sources playing important roles in the secondary metabolism of plants.[1] Moreover, saturated 2,3- and 3,4-methano amino acids have been used replacing proteinogenic amino acids in conformationally restricted peptide surrogates with enhanced properties with respect to the normal peptides,[2] and have also been utilized as biological probes in mechanistic studies.[3] In particular, cyclopropane 2,3-didehydro 2-amino acids (DDAAs) have also been found as subunits of natural product structures,[4] but their main interest lies on their usefulness as synthetic precursors to other types of amino acids, obtained by later transformations of the C=C double bond, i.e. reduction, conjugate additions, or cycloadditions.[5]

In turn, cyclopropane hydroxy acid derivatives are also relevant building blocks in the synthesis of several types of products such as amino alcohols and cyclopropyl carbocyclic nucleosides.[6]

The availability of chiral products in both enantiomeric forms is crucial to the study of chirality−activity relationships. Nevertheless, despite the growing discovery of new and efficient methods in asymmetric synthesis, there are still some difficulties in the preparation of enantiomeric series of compounds when the achievement of this goal involves the use of specific chiral precursors or auxiliaries.

Therefore, consideration of this fact and the increasing attention devoted to cyclopropane derivatives by specialists of different fields prompts us to report our results on the enantioselective and stereodivergent synthesis of different kinds of cyclopropyl compounds from a single precursor. Thus, we present in this work the syntheses of conveniently protected 2,3-didehydro-4,5-methano amino acids **1** and *ent*-**1**, a new class of DDAA, and 4-hydroxy-2,3-methano acids **2** and *ent*-**2**, using D-glyceraldehyde acetonide[7] as the only chiral precursor (Chart 1). The success of the synthetic strategy is based on the combination of highly stereoselective cyclopropanation of convenient substrates, stereoselective Wittig−Horner condensations, and controlled manipulation of functional groups.

Among the currently used cyclopropanation methods, we chose the one involving 1,3-dipolar cycloaddition of diazomethane to chiral dipolarophiles followed by photolysis of the pyrazolines produced. We have already employed this protocol in our laboratory to synthesize several 2,3-methano 2-amino acids in a highly efficient and stereoselective manner.[8]

We will show that the control of π-facial diastereoselectivity in the cycloadditions of diazomethane to chiral furanones or to functionally equivalent pentenoates

[†] Departament de Química. E-mail: iqor9@cc.uab.es.
[‡] Unitat de Cristal.lografia. E-mail: angel@salduba.uab.es.

(1) See, for instance: (a) Sakamura, S.; Ichichara, A.; Shiraishi, K.; Sato, H.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636. (b) Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant Physiol.* **1982**, *70*, 195. (c) Mitchell, R. E. *Phytochemistry* **1985**, *24*, 1485. (d) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103.

(2) Burgess, K.; Ho, K.-K.; Moye-Sherman D. *Synlett* **1994**, 575, and references therein.

(3) For reviews on the isolation, synthesis, and biological properties of cyclopropane amino acids, see: (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2234. (b) Alami, A.; Calmes, M.; Daunis, J. Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.

(4) Kotha, S. *Tetrahedron* **1994**, *50*, 3639. See p 3650 and references therein.

(5) (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159. (b) Duthaler, R. A. *Tetrahedron* **1994**, *50*, 1539.

(6) (a) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236. (b) Lee, M. G.; Du, J. F.; Chun, M. W.; Chu, C. K. *J. Org. Chem.* **1997**, *62*, 1991. These authors synthesized enantiomeric nucleosides using D- and L-glyceraldehyde as chiral precursors which, in turn, were obtained from D-mannitol and L-gulono-γ-lactone, respectively.

(7) Mann, J.; Partlett, N. K.; Thomas, A. *J. Chem. Res.* (S) **1987**, 369, and references therein. Although D-glyceraldehyde acetonide is commercially available it can be easily prepared from D-mannitol according to this work.

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Chart 1

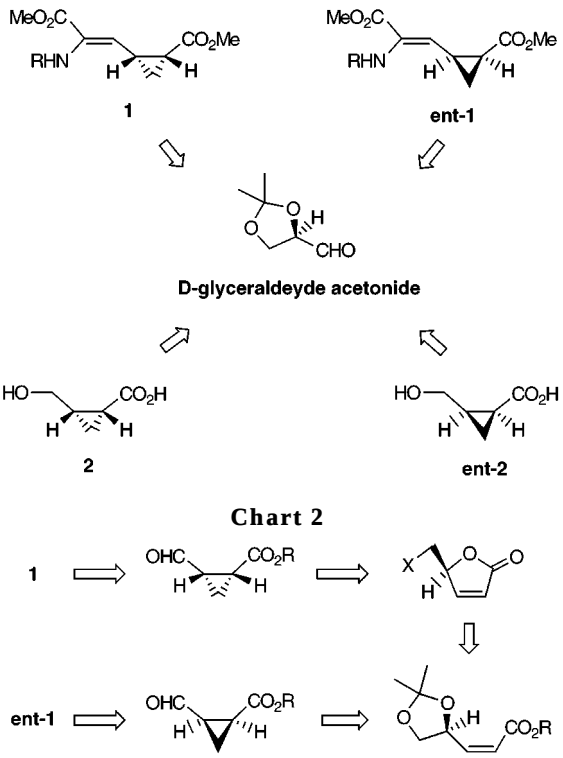


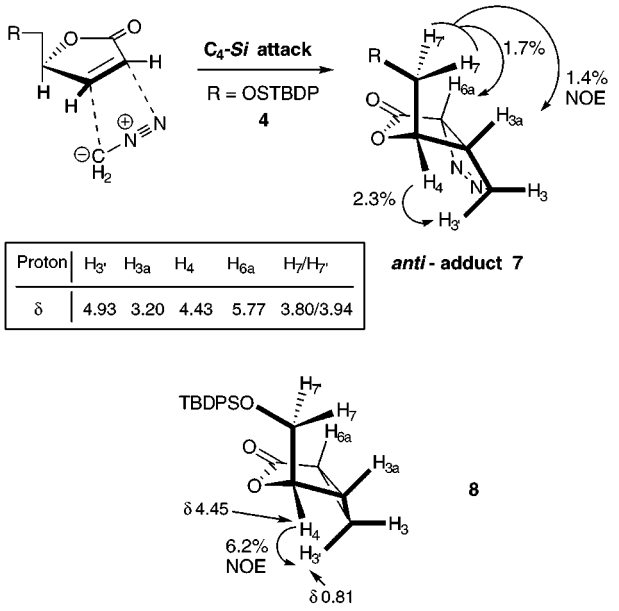
Chart 2

results in excellent de's and provides alternative routes to synthesize enantioselectively the target molecules. Preferential π-facial diastereoselection of diazomethane toward chiral pentenoates has been the subject of contradictory interpretations.[9,10] From our results the stereoselectivity of these cycloadditions has been unambiguously established. A discussion on these features is presented below.

Results and Discussion

Preliminary studies, carried out by our group, show that facial diastereoselectivity in the reactions between diazomethane and chiral 3-substituted furanones favors preferential attack to the π-face opposite to the substituent, provinding anti adducts. On the contrary, when chiral 4-alkoxy pentenoates are used, syn adducts are the major stereoisomers produced. These findings allowed us to design stereoselective syntheses of the target molecules. A rationalization of the stereochemical outcome of these cycloadditions follows the description and discussion of the synthetic strategies.

1. Synthesis of Didehydro Amino Acids 1 and *ent*-1. Compounds **1** and *ent*-**1** are retrosynthetically related to enantiomeric aldehydes which provide the absolute configuration of the stereogenic centers (Chart 2). These intermediates were obtained through diastereoselective 1,3-dipolar cycloadditions of diazomethane to a chiral furanone and a chiral pentenoate, respectively, followed by photolysis of the resultant pyrazolines. The furanone was obtained from the pentenoate, the chirality



Proton	$H_{3'}$	H_{3a}	H_4	H_{6a}	$H_7/H_{7'}$
δ	4.93	3.20	4.43	5.77	3.80/3.94

Figure 1. Stereochemical assignments of pyrazoline **7** and cyclopropane **8**, resultant from cycloaddition of diazomethane to furanone **4**.

of the stereogenic centers being the same in both dipolarophiles. In the last step of the synthetic plan, Wittig–Horner condensations of the enantiomeric aldehydes with suitable phosphonates bearing the preformed amino acid moiety lead to the target molecules. Stereoselectivity in the production of *Z*/*E* diastereoisomers was controlled after investigation of the influence that base, temperature, and reaction time exert on the stereochemistry.

Furanone **3** (Scheme 1) was easily obtained from D-glyceraldehyde acetonide through Wittig condensation with (methoxycarbonylmethylidene)triphenylphosphorane, chromatographic separation of *Z*/*E* isomers, and hydrolysis with concomitant lactonization of the (*Z*)-isomer.[7] Reaction of **3** with *tert*-butyldiphenylsilyl chloride in the presence of DMAP provided lactone **4** in 94% yield. This compound was treated with excess ethereal diazomethane to afford quantitatively pyrazoline **7**[11] as a single stereoisomer, as a result of exclusive addition of diazomethane to the C_4-*Si* face of the C=C double bond.

Anti stereochemistry of **7** was assigned by NOE experiments, as stated in Figure 1. Thus, significant enhancement on $H_{3'}$ was observed when H_4 was selectively irradiated. Moreover, presaturation of protons H_7 and $H_{7'}$ produced NOE on H_{3a} and H_{6a} in agreement with the proposed configuration. This configuration was also assigned to the pyrazolines produced from reaction between diazomethane and both (*S*)-5-(hydroxymethyl)-2(5*H*)-furanone[12a] and (*S*)-5-(pivaloyloxymethyl)-2(5*H*)-furanone.[12b] Δ^1-Pyrazoline **7** is a crystalline solid which

(8) (a) Jiménez, J. M.; Rifé, J.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 537. (b) Jiménez, J. M.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 3203. (c) Jiménez, J. M.; Bourdelande, J. L.; Ortuño, R. M. *Tetrahedron* **1997**, *53*, 3777.

(9) Galley, G.; Pätzel, M.; Jones, P. G. *Tetrahedron* **1995**, *51*, 1631.

(10) Baskaran, S.; Vasu, J.; Prasad, R.; Kodukulla, K.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 4515.

(11) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055. Pyrazoline **7** is depicted in this work with anti stereochemistry, but this configuration is not justified. Although we have used polar solvents to determine specific rotation for **7** due to the low solubility of this crystalline compound in carbon tetrachloride, the latter was the solvent used by those authors.

(12) (a) Ortuño, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1987**, *43*, 2199. In this work, pyrazoline from diazomethane and (*S*)-5-(hydroxymethyl)-2(5*H*)-furanone was used as intermediate in the synthesis of (*S*)-5-(hydroxymethyl)-4-methyl-2(5*H*)-furanone (umbelactone), but stereochemistry was not assigned. We have now confirmed anti stereochemistry from NOE enhancements: 1.5% from $H_7/H_{7'}$ to H_{3a} and 3.4% from H_4 to $H_{3'}$. (b) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267.

Scheme 1

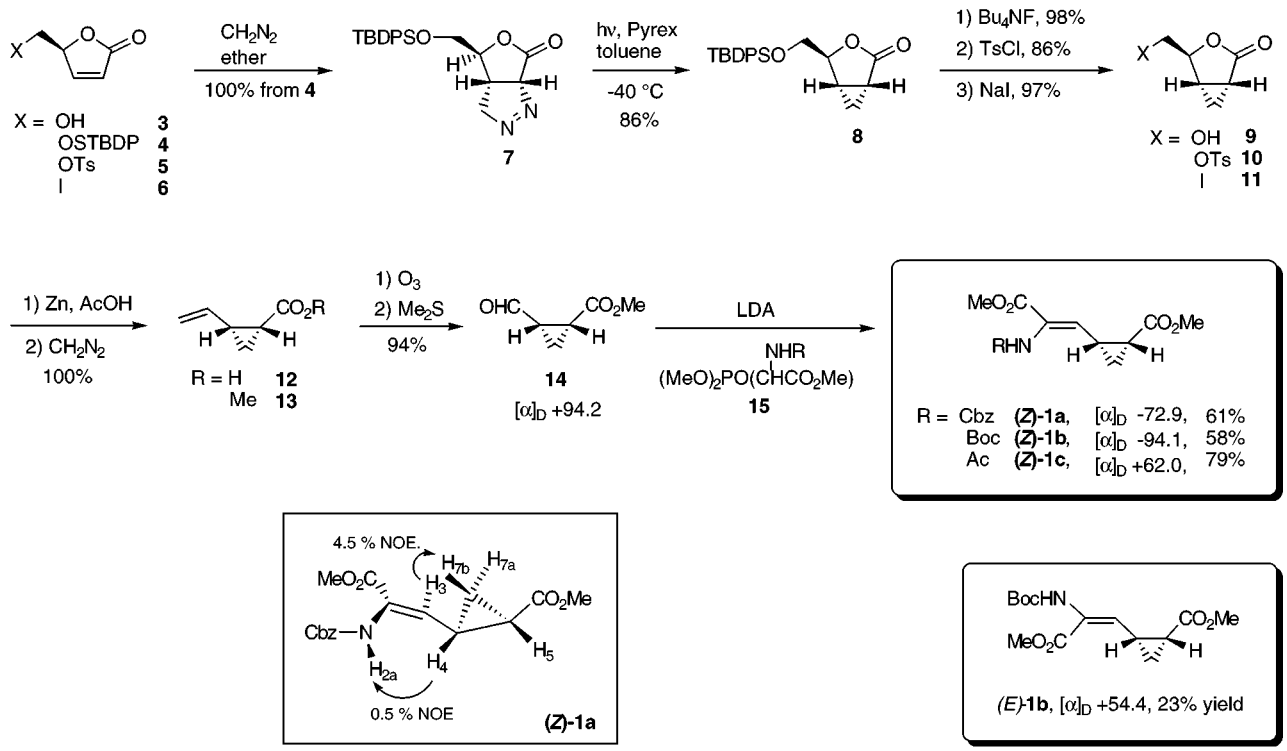


Table 1. Photolysis of Pyrazoline 7 To Afford Cyclopropane 8[a]

entry	solvent[b]	photosensitizer (equiv)	temp (°C)[c]	time	% yield	ref
1	toluene		rt	4 h	58	this work
2	toluene		−40	1 h	86	
3	dichloromethane		rt	3 h	35	
4	dichloromethane		−78	8 h	42	
5	dichloromethane	benzophenone (0.01)	rt	15 min	51	
6	dichloromethane	benzophenone (0.01)	−78	30 min	84	
7	dichloromethane			2 h	12	14
8	benzene−acetonitrile (1:1)	benzophenone (0.1)		4 h	5	14

[a] Irradiations were performed with a 125 W medium-pressure mercury-lamp. [b] 0.02 M solutions were used in all cases. [c] Referred to external temperature.

undergoes tautomerization to a Δ^2-pyrazoline in trace-acid-containing solutions. The observed tautomer is the one in which the C=N bond is not conjugated to carbonyl, as deduced by ^{1}H NMR.

Conditions for the photolysis of pyrazoline **7** were crucial in order to obtain good yields of cyclopropane **8** and to prevent the formation of the olefinic insertion product. Thus, solvent, temperature, and the use of photosensitizers were investigated, results of selected experiments being shown in Table 1. All reactions were performed using 0.02 M solutions contained in a Pyrex reactor by irradiation with a 125 W medium-pressure mercury-lamp. Product remained unaltered when 1,4-dioxane was used as a solvent at −40 °C and at room temperature. The use of ether or benzene−acetonitrile resulted in the exclusive production of byproducts, at room temperature, or low yields of **8** at −40 or −78 °C. Better results were found with toluene or dichloromethane. Thus, irradiation of toluene solutions, at −40 °C for 1 h, afforded 86% of cyclopropane **8** (Table 1, entry 2). Similar results were obtained when benzophenone was added to dichloromethane solutions, reaction being much slower in absence of the photosensitizer as deduced from comparison of entries 3/4 with 5/6 in Table 1. Results could be well reproduced when working in multigram preparative scale using a 400 W lamp. Anti stereochemistry of **8** was confirmed by NOE experiments as shown in Figure 1.

Cyclopropanation of tosyloxy and iodo derivatives **5** and **6**[13] was also attempted, but byproducts were obtained due to elimination of *p*-TsOH or HI, respectively. These results differ from those described by Mann et al.[14] in a work which appeared at the same time as a short communication on our preliminary results.[15] These authors studied the photolysis of several pyrazolines derived from furanones with 5-*O* substituents, such as TBDMS, TBDPS, benzoyl, and tosyl (see Table 1, entries 7 and 8).

Deprotection of the primary alcohol was accomplished by treatment of silyl ether **8** with n-Bu_4NF to afford alcohol **9** as a crystalline solid. Direct conversion of **9** into aldehyde **14** with $Pb(OAc)_4$ in refluxing benzene−methanol[16] gave a low yield (10%) of the desired product along with unreacted starting material **9** and methoxy-furanone derived from **9**. These products could not be

(13) Camps, P.; Cardellach, J.; Font, J.; Ortuño, R. M.; Ponsatí, O. *Tetrahedron* **1982**, *38*, 2359.

(14) Butler, P. I.; Clarke, T.; Dell, C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1503. In this work, aldehyde **14** was synthesized in 20% from furanone **5**, but their physical and spectroscopic data were not described.

(15) Hanafi, H.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 1657.

isolated by flash chromatography, and reaction of the mixture with phosphonate **15a** (R = Cbz)[17] afforded a condensation product in very low yield. Oxidation of **9** with sodium periodate in the presence of 2 N H_2SO_4[18] only led to the recovery of the starting material.

The successful synthetic pathway to gain access to **14** is depicted in Scheme 1. Alcohol **9** was converted into iodide **11** via tosylate intermediate **10** in 83% yield for the two steps. Vinyl acid **12** was quantitatively obtained by reductive β-elimination performed by exposure of iodide **11** to powdered zinc in glacial acetic acid and converted into methyl ester **13** by reaction with diazomethane.

Ozonolysis of vinyl derivative **13** as a dichloromethane solution at −40 °C, followed by treatment with dimethyl sulfide, provided aldehyde **14** in 94% yield which was obtained in 66% overall yield from furanone **4**.[14]

The didehydro amino acid key intermediates **1a**, **1b**, and **1c** were accessible by Wittig−Horner condensation of **14** with phosphonates **15a**−**c**.[17] Several bases, such as LDA, *tert*-BuOK, BuLi, and NaH in THF or CH_2Cl_2, were used to generate the anions derived from the corresponding phosphonates. Condensation reactions were conducted at room temperature, affording the expected products in 61−81% yields. While (*Z*)-isomers were exclusively obtained for **1a** and **1c** (Scheme 1), mixtures of *Z*/*E* stereoisomers **1b** were obtained in 65:35 (BuLi) to 80:20 (the other bases) ratio.

(*Z*)-Stereochemistry was assigned to the exclusive or major products on the basis of differential NOE experiments. For instance, for (*Z*)-**1a**, 0.5% NOE was observed on H_{2a} when H_4,H_5 (chemical shifts for these protons are very close) were irradiated. Furthermore, significant NOE values were found for H_7, but not for H_{2a}, when H_3 was selectively irradiated. In addition, NOE produced between H_3 and H_{7b} suggests a conformation around C_3-C_4 as represented in Scheme 1, in which these protons are close. Similar results were obtained from (*Z*)-**1b** and (*Z*)-**1c**. This high stereoselectivity of phosphonates **15a**−**c** to afford mainly (*Z*)-geometry diastereoisomers in Wittig−Horner reactions had been previously observed in our laboratory in the condensation with D-glyceraldehyde acetonide, independently of the base, solvent, or temperature used.[8a] Recently, Le Corre et al. reported the synthesis of the *trans*-(1*S*,2*S*)-isomer of formyl ester **14**, from (*S*)-glutamic acid. They reported that the condensation of this compound with **15a** afforded a 70:30 mixture of *Z*/*E* stereoisomers in 65% yield[19] which correlates well with our previous finding.

(4*R*,5*R*)-2,3-Didehydro-4,5-methano amino acids (*Z*)-**1** were thus synthesized in highly stereoselective and efficient manner in 38−52% overall yields from chiral furanone **4**.

The synthesis of enantiomeric amino acids *ent*-**1** was undertaken from pentenoates **16**, prepared from D-glyceraldehyde acetonide[7] (Scheme 2). (*Z*)-**16a** resulted to be less reactive than (*E*)-**16a** toward diazomethane but more stereoselective. This behavior is similar to that observed in the Diels−Alder cycloadditions of pentenoates (*Z*)- and (*E*)-**16a** to several dienes.[20a,c] Thus, treatment of (*Z*)-**16a** with ethereal diazomethane at room temperature for 18 h led almost quantitatively to a >95:5 mixture of *syn*/*anti* pyrazolines from which major product **17a** was isolated. Structural analysis by X-ray diffraction of a single crystal confirmed its syn stereochemistry as shown in Figure 2.[21] In turn, (*E*)-**16a** was reacted with diazomethane at room temperature for 2 h to afford a 75:25 mixture of pyrazolines **17a** being the major isomer.

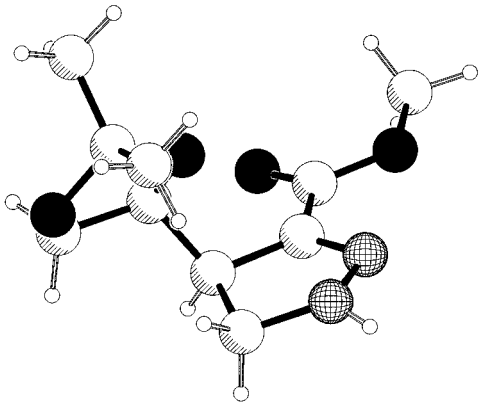
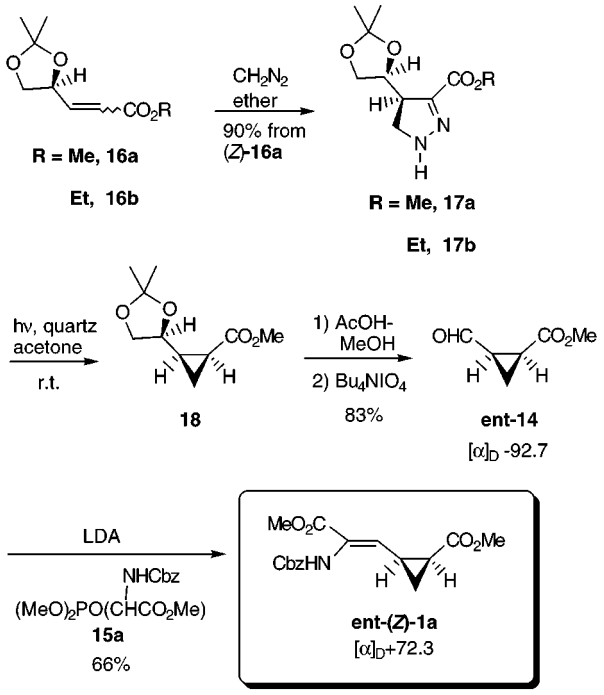


Figure 2. Structure of pyrazoline **17a** as determined by X-ray structural analysis

Scheme 2



In the optimal conditions, acetone solutions of pyrazoline **17a** contained in quartz reactors were irradiated with a 125 W medium-pressure mercury-lamp to give

(16) Hamada, Y.; Iwai, K.; Shiori, T. *Tetrahedron Lett.* **1990**, *31*, 5041.

(17) (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53. (b) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis* **1991**, 49.

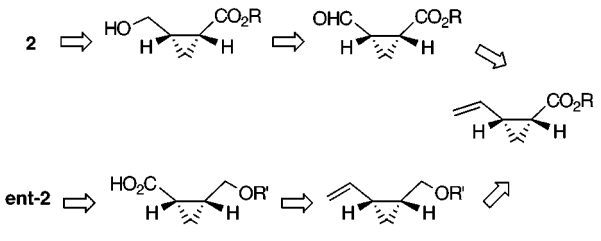
(18) (a) Mulzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63. (b) Krief, A.; Dumont, W.; Pasau. P. Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039.

(19) Le Corre, M.; Hercouet, A.; Bessieres, B. *Tetrahedron: Asymmetry* **1995**, *6*, 683.

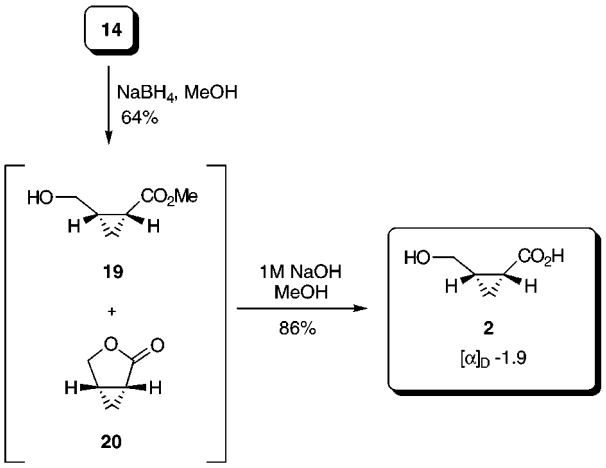
(20) (a) Casas, R.; Parella, T.; Branchadell, V.; Oliva, A.; Ortuño, R. M.; Guingant, A. *Tetrahedron* **1992**, *48*, 2659. (b) Sbai, A.; Branchadell, V.; Oliva, A. *J. Org. Chem.* **1996**, *61*, 621. (c) Sbai, A.; Branchadell, V.; Ortuño, R. M.; Oliva, A. *J. Org. Chem.* **1997**, *62*, 3049.

(21) The atomic coordinates and thermal parameters for structure **17a** are available on request from the Director of the Cambridge Crystallographic Data Centre. Any request should be accompanied by a full literature citation for this paper. Please note that the crystallographic numbering differs from that used in this article.

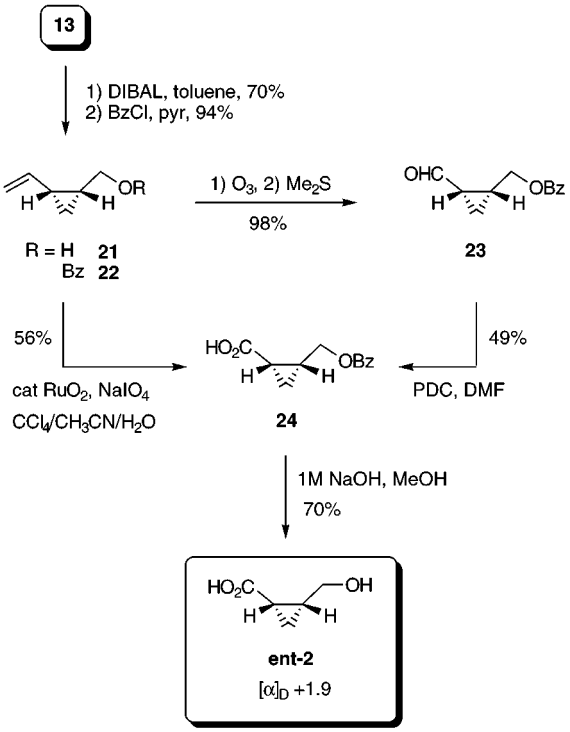
Chart 3



Scheme 3



Scheme 4



cyclopropane **18** with yield ranging from 10% to 80%. Instability of the pyrazoline in solution and the difficulty of Δ^2-pyrazolines to release nitrogen giving the cyclopropane precursor-biradical[22] may account for these erratic results.

Treatment of **18** with a few drops of acetic acid in methanol followed by an oxidative cleavage of the resultant diol with tetrabutylammonium periodate afforded aldehyde *ent*-**14**, in 83% yield for the two steps. Condensation of this compound with phosphonate **15a** in the presence of LDA furnished (4*S*,5*S*)-didehydro-3,4-methano amino acid *ent*-(*Z*)-**1a**, whose specific rotation is in excellent accordance with that found for (*Z*)-**1a**. This result shows the usefulness of this synthetic route starting from pentenoates to obtain enantiomeric products with respect to those resultant from furanones.

2. Synthesis of Hydroxy Acids 2 and *ent*-2. The synthesis of these enantiomeric compounds was achieved through stereodivergent routes from vinyl ester **13** obtained, in turn, from furanone **4** (Scheme 1). In this case, selective manipulation of the functional groups led to reverse the chirality of these molecules, allowing the isolation of both enantiomeric products. Thus, hydroxy acid **2** was obtained from degradation of the vinyl sidechain to a hydroxymethyl group. Alternatively, oxidation of the C=C double bond in **13** to a carboxylic acid and reduction of the ester group to a primary alcohol afforded *ent*-**2** (Chart 3).

The corresponding synthetic routes were carried out as follows. Aldehyde **14** was reduced with methanolic $NaBH_4$ to afford a mixture of hydroxy ester **19** and lactone **20** in 64% yield (Scheme 3). Although these compounds could not be isolated by flash chromatography, their identity was stablished by the spectroscopic data of enriched fractions. Subsequent saponification of the mixture with methanolic 1 M NaOH gave hydroxy acid **2** as a crystalline solid mp 60−61 °C, $[\alpha]_D$ −1.9 (*c* 0.4, $CHCl_3$) in 52% yield from **13** and 37% overall yield from furanone **4**.

The synthesis of *ent*-**2** started with reduction of ester **13** upon treatment with DIBAL followed by benzoylation of the resultant primary alcohol, affording vinyl ester **22** in 65% for the two steps (Scheme 4). The synthesis of acid **24** was undertaken by following two alternative pathways. First, ozonolysis of **22** provided almost quantitatively aldehyde **23** which was oxidized to acid **24** with PDC in DMF, in 49% yield. On the other hand, one-step oxidation of **21** with catalytic RuO_2 and $NaIO_4$ was more efficient and gave compound **24** in 56% yield. Finally, saponification of the benzoyl ester by using 1 M NaOH in methanol furnished hydroxy acid *ent*-**2**, mp 61−62, $[\alpha]_D$ +1.9 (*c* 0.4, $CHCl_3$), in 26% yield from vinyl ester **13** and 18% overall yield from furanone **4**.

In this way, both enantiomeric hydroxy acids **2** and *ent*-**2** were synthesized in satisfactory overall yields from vinyl ester **13** as a common intermediate.

3. π-Facial Diastereoselectivity in the Cycloadditions of Diazomethane to Furanones 3 and 4, and to Pentenoates 16. In a previous publication, we showed and rationalized the opposite facial diastereoselectivity in the Diels−Alder cycloadditions of chiral 5-(hydroxymethyl)-2(5*H*)-furanone **3** and derivatives, with respect to the one showed by its equivalent open-chain hydroxy pentenoate (*Z*)-**16a**.[20a] In the case of alkyl-monosubstituted furanones, the preferential attack of the dienes occurs always on the less hindered C_4-*Si* face, anti to the substituent at the C-5 position, and the same result is obtained for the diazomethane cycloadditions (Figure 1). The case of the pentenoates is complicated by the conformational freedom of the molecules. Diastereoselection favors the C_3-*Re* face, that is, the production of

(22) March J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1992; p 1046 and references therein.

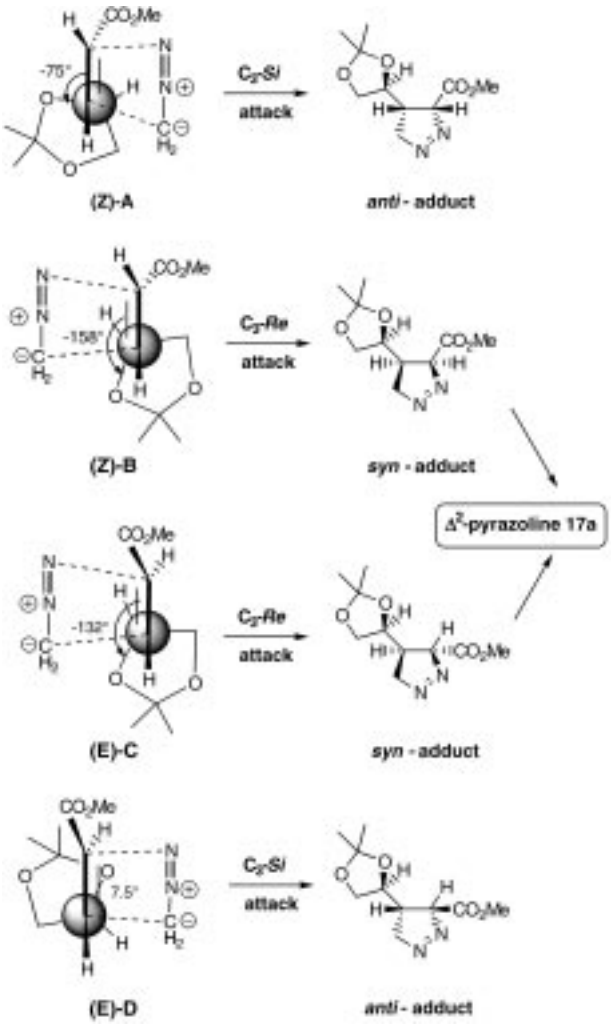


Figure 3. Stereochemical features in the production of syn/anti adducts from diazomethane and active conformers for pentenoates (*Z*)-**16a** [(***Z***)-**A**, (***Z***)-**B**] and (***E***)-**16a** [(***E***)-**C**, (***E***)-**D**], determined at the BLYP/6-31G* level of calculation.

syn-adducts either in uncatalyzed[20a,b] or catalyzed Diels–Alder reactions.[20c]

The facial diastereoselectivity in the 1,3-dipolar cycloadditions of (*E*)-**16a**/**b** to several dipoles has previously been reported. Whereas azomethyne ylides,[23a,b] nitrones,[23a,c] and nitrile oxides[23a,d] gave predominantly anti adducts, syn isomers were found with nitrilimines,[23e] silyl nitronates,[23f] and diazo compounds other than diazomethane.[9] Pätzel et al. assigned syn stereochemistry to the adduct **17b**, obtained from diazomethane and pentenoate (*E*)-**16b**, by comparison with other studied dipolarophiles.[9] Later, Trivedi et al.[10] reported anti stereochemistry to be predominant in the cycloadditions of this dipole to both (*Z*)- and (*E*)-**16b**, and they rationalized this stereoselectivity, in the case of the (*Z*)-pentenoate, by preferential C_3-*Si* attack to a conformer like (*Z*)-**A** in Figure 3.

In our work, X-ray analysis of pyrazoline **17a** confirms unequivocally syn stereochemistry such as depicted in Figure 2. Moreover, the preferential production of syn adducts can be rationalized by considering the active conformations for (*Z*)- and (*E*)-**16** as shown in Figure 3.

In a previous study, we calculated conformational enthalpies for (*Z*)- and (*E*)-**16a** by the AM1 method.[20a] The position of the ester group with respect to the C–C double bond was fixed to be *s-cis* and the rotation around the C_3-C_4 bond was considered. In the case of (*Z*) isomer, the only energy minimum corresponded to (*Z*)-**B**, in which the $C_2-C_3-C_4-O$ dihedral angle is −153°. When the structure is optimized at the BLYP/6-31G* level of calculation, the value obtained for the dihedral angle is −158°.

In the Diels–Alder reactions of (*Z*)-**16a** with butadiene[20a] and cyclopentadiene[20c] the conformation of the enoate was maintained in the transition state corresponding to the most favorable syn isomer. In the transition state leading to the anti cycloadduct the conformation of the enoate was (*Z*)-**A**. At the BLYP/6-31G* level of calculation, the geometry optimization of such conformer by keeping the $C_2-C_3-C_4-O$ dihedral angle frozen leads to a structure 4.3 kcal/mol higher in energy than (*Z*)-**B**. Contributing factors accounting for such a large energy difference would include (*Z*)-**A** suffering from destabilizing interaction between H_3 and H_5 as well as dipole–dipole interactions which are relieved in (*Z*)-**B**. Thus, the major stereoisomer, i.e. syn adduct, results from the attack of diazomethane to the less hindered C_3-*Re* face in (*Z*)-**B** with the allylic hydrogen pointing to the incoming diazomethane.

This facial diastereoselection is the opposite to that accounting for the only observed anti stereoisomers produced by C_4-*Si* attack to chiral 5-alkyl or 5-heteroalkyl-2(5*H*)-furanones, as described above. On the contrary, C_3-*Si* attack to conformer (*Z*)-**A** leads to minor anti adduct. Thus, in the 1,3-dipolar cycloadditions of diazomethane to the (*Z*) and (*E*) pentenoates **16**, as well as in their Diels–Alder cycloadditions,[20] the antiperiplanar attack with respect to the C–O bond (conformation (*Z*)-**A**) is not the most favorable one to account for the isomer ratio. For (*E*)-pentenoate **16a**, two energy minima are observed in the rotation around the C_3-C_4 bond: (*E*)-**C** and (*E*)-**D**. The energy difference between these conformations is only 0.1 kcal/mol at the BLYP/6-31G* level. Conformation (*E*)-**C** is equivalent to (*Z*)-**B**, while the thermodynamically most stable (*E*)-**D** shows a $C_2-C_3-C_4-O$ dihedral angle of 7.5°. Again, C_3-*Re* attack provides major syn stereoisomer, from (*E*)-**C**. In turn, minor anti adduct results from C_3-*Si* attack to (*E*)-**D**.

It is noteworthy that the same compound **17a** is obtained from both pentenoates, (*Z*)- and (*E*)-**16**, since the obtained Δ^1-pyrazolines must tautomerize rapidly to the thermodynamically most stable Δ^2-pyrazoline.

Concluding Remarks

In conclusion, as a result of the present work, the stereochemical outcome of the cycloadditions of diazomethane to 5-(alkoxymethyl)-2(5*H*)-furanones and the functionally equivalent γ-alkoxy pentenoates has been unequivocally established both by direct stereochemical analysis and by chemical correlation. Moreover, a rationalization of the predominant diastereoselection has been realized through computation of the energies and geometries of the active conformers.

(23) (a) Annunziata, R., Benaglia, M.; Cinquini, M.; Raimondi, L. *Tetrahedron* **1993**, *49*, 8629. (b) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005. (c) Busqué, F.; de March, P.; Figueredo, M., Font, J.; Monsalvatje, M.; Virgili, A.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 8578. (d) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (e) Grubert, L.; Galley, G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1137. (f) Galley, G.; Jones, P. G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2073.

The opposite π-facial diastereoselectivity in the cycloadditions to these chiral furanones and pentenoates was revealed to be useful in the synthesis of enantiomeric series of products, starting from D-glyceraldehyde as the only source of chirality.

The cyclopropyl intermediates synthesized are small molecules densely functionalized. Thus, selective transformation of functional groups allows design of stereodivergent and efficient routes for the enantioselective synthesis of hydroxy acids.

Both types of target molecules synthesized, namely 2,3-didehydro-4,5-methano-2-amino acids and 3-hydroxy-2,3-methano acids, are useful chiral building blocks for the synthesis of a variety of enantiomerically pure cyclopropane derivatives. Active investigation in this field is being carried out in our laboratory.

Experimental Section

Flash column chromatography was carried out on silica gel (240−400 mesh). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (ot) being reported. Electron impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given on the δ scale.

Computational Details. Theoretical calculations have been done at the density functional level using the gradient corrected functionals of Becke[24] and Lee, Yang, and Parr[25] (BLYP) for exchange and correlation, respectively, and the 6-31G* basis set.[26] All calculations have been done using the Gaussian-94 program.[27]

(1*R*,5*S*,6*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-7-oxa-2,3-diazabicyclo[3.3.0]hexan-2-en-8-one (7). Excess ethereal diazomethane was distilled onto an ice-cooled and stirred solution of furanone **4** (10 g, 28.4 mmol) in 25 mL of THF. The resultant mixture was light-protected and stirred at room temperature for 18 h. Then excess diazomethane was destroyed, and solvents were removed to afford quantitatively 11.1 g of pyrazoline **7** as a white solid. Crystals, mp 105−106 °C (from ether−pentane), $[\alpha]_D$ −182 (*c* 1.2, $CHCl_3$) and −212 (*c* 1.7, acetone) [lit.[11] mp 105−106 °C (from ether−pentane), $[\alpha]_D$ −215 (*c* 1.2, CCl_4)]. Spectroscopic data are in good agreement with those described for structure **7** in ref 11.

(1*R*,4*S*,5*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-3-oxabicyclo[3.1.0]hexan-2-one (8). A stirred solution of pyrazoline **7** (10.5 g, 26.5 mmol) in anhydrous toluene (500 mL), contained in a Pyrex reactor under argon atmosphere, cooled at −78°, was irradiated with a 400 W medium-pressure lamp for 2.5 h. Solvent was removed to afford a yellowish solid that was crystallized to afford pure **8** (23.6 g, 86%). Crystals, mp 110−111.5 °C (from CH_2Cl_2−pentane); $[\alpha]_D$ −163.1 (*c* 3.2, $CHCl_3$); IR (KBr) 1771 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 0.82 (m, 1H), 1.01 (s, 9H), 1.21 (m, 1H), 2.08−2.20 (complex absorption, 2H), 3.70 (dd, J = 10.9, 8.0 Hz, 1H), 3.82 (dd, J = 10.9, 7.3, 1H), 4.35 (t, J = 3.6 Hz, 1H), 7.4 (m, 5H), 7.65 (m, 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 11.3, 17.6, 19.1, 19.7, 26.6, 65.1, 80.2, 127.7, 129.8, 132.8, 135.5, 175.9. Anal. Calcd for $C_{22}H_{26}O_3Si$: C, 72.09; H, 7.15. Found: C, 72.11; H, 7.13.

(1*R*,4*S*,5*S*)-4-(Hydroxymethyl)-3-oxabicyclo[3.1.0]hexan-2-one (9). A mixture of compound **8** (8.0 g, 21.8 mmol) and n-Bu_4NF (32.7 mL of a 1.0 M solution in THF, 32.7 mmol) in THF (20 mL) was stirred at room temperature for 10 min. Then the solvent was removed, and the residue was flash chromatographed (hexanes−EtOAc, 1:1) to afford 2.7 g (98% yield) of alcohol **9** as a white solid. Crystals, mp 54−55.5 °C (from CH_2Cl_2−hexane); $[\alpha]_D$ +63.4 (*c* 1.4, $CHCl_3$); IR (KBr) 3445−3409 (broad), 1730 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) 0.85 (m, 1H), 1.21 (m, 1H), 2.11 (m, 2H), 3.01 (broad s, 1H), 3.67 (dd, J = 17.0, 12.1 Hz, 1H), 3.82 (dd, J = 14.6, 12.1, 1H), 4.25 (t, J = 3.6 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 11.5, 17.6, 19.4, 29.6, 64.5, 81.2, 176.4. Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.23; H, 6.19.

(1*R*,4*S*,5*S*)-4-(Iodomethyl)-3-oxabicyclo[3.1.0]hexan-2-one (11). Tosyl chloride (0.6 g, 3.1 mmol) was added in small portions to an ice-cooled and stirred solution of alcohol **9** (0.2 g, 1.6 mmol) and freshly distilled pyridine (0.25 mL, 3.1 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed successively with 1% HCl and water. The organic phase was dried ($MgSO_4$), and solvent was removed at reduced pressure. The residue was flash chromatographed (hexanes−EtOAc, 3:2) to give known tosylate **10**[14] as a white solid (0.4 g, 86% yield). A mixture of compound **10** (0.3 g, 0.9 mmol) and NaI (2.1 g, 13.9 mmol) in dry acetone (15 mL) was heated to reflux for 2 h. Solution was evaporated to dryness, and the residue was poured into EtOAc (20 mL) and water (10 mL). The layers were separated, and the organic phase was washed with 5% aq $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc, the combined organic phases were dried ($MgSO_4$), and solvents were removed at reduced pressure giving iodide **11** which was purified by flash chromatography (hexanes−EtOAc, 4:1) to afford pure **11** as a white solid (0.2 g, 97% yield). Crystals, mp 68−70 °C (from hexanes−EtOAc); $[\alpha]_D$ +86.1 (*c* 1.8, $CHCl_3$); IR (KBr) 1770 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 0.9 (m, 1H), 1.27 (m, 1H), 2.10−2.24 (complex absorption, 2H), 3.21 (dd, J = 10.9, 3.6 Hz, 1H), 3.54 (dd, J = 10.9, 7.3 Hz, 1H), 4.31 (dd, J = 8.3, 4.3 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 8.0, 12.0, 18.0, 23.2, 78.4, 174.8. MS, *m*/*z* (%) 238 (M-1, 25), 111 (90), 97 (100), 55 (20), 41 (45). Anal. Calcd for $C_6H_7O_2I$: C, 30.28; H, 2.96. Found: C, 30.22; H, 2.95.

(1*R*,2*R*)-1-(Methoxycarbonyl)-2-vinylcyclopropane (13). A mixture of iodide **11** (175 mg, 0.7 mmol), powdered Zn (252 mg, 4.5 mmol), and two drops of glacial AcOH in ether (12 mL) was heated to reflux for 1 h. Then the mixture was filtered through Celite, and solvent was removed. The residue was flash chromatographed (hexanes−EtOAc, 1:1) to afford quantitatively 80 mg of acid **12** as a yellowish and highly volatile oil, IR (film) 3200−2945 (broad), 1696, 1644 cm^{-1}. This acid was treated with diazomethane in the usual way to furnish quantitatively ester **13** as a extremely volatile liquid, which was identified by its spectroscopic data. IR (film) 1729, 1645 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.2 (m, 2H), 1.9 (m, 2H), 3.64 (s, 3H), 5.08 (dd, J = 10.2, 2.9 Hz, 1H), 5.22 (dd, J = 17.5, 2.9 Hz, 1H), 5.75 (m, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 14.2, 20.7, 24.8, 51.6, 116.2, 135.3, 172.4; MS, *m*/*z* (%) 126 (M, 10), 95 (26), 67 (100), 55 (17), 41 (49).

(1*R*,2*S*)-2-Formyl-1-(methoxycarbonyl)cyclopropane 14. Ozone was bubbled through a stirred solution of vinyl ester **13** (180 mg, 1.4 mmol) in CH_2Cl_2 at −40 °C for 10 min, and then three drops of Me_2S were added. After stirring for 3 h at room temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with five portions of water. The combined aqueous phases were extracted twice with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), and solvent was removed at reduced pressure to afford aldehyde **14**[14] as a highly volatile liquid (174 mg, 94% yield); $[\alpha]_D$ +94.2 (*c* 2.8, $CHCl_3$); IR (film) 1736 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.2 (m, 1H), 1.5 (m, 1H), 2.0 (m, 2H), 3.68 (s, 3H), 9.3 (d, J = 6.5 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 12.4, 21.1, 22.2, 52.3, 170.4, 175.5; MS, *m*/*z* (%) 128 (M, 1), 100 (100), 97 (80), 96 (36), 69 (84), 68 (72), 55 (72), 41 (95).

(24) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
(25) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. A* **1988**, *37*, 785.
(26) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision B.3; Gaussian Inc.: Pittsburgh, PA, 1995.

General Procedure for Wittig−Horner Condensations. A typical experiment was run as follows for the obtention of **1b**. Methyl 2-(*tert*-butoxycarbonylamino)-2-(dimethoxyphosphonyl)acetate[17] (705 mg, 2.4 mmol) in THF (5 mL) was added to a solution of LDA, prepared from diisopropylamine (364 μL, 2.5 mmol) and n-BuLi (1.63 mL of a 1.6 M solution in hexane, 2.5 mmol), in anhydrous THF (5 mL) at −78 °C, under nitrogen atmosphere. After stirring for 40 min, aldehyde **14** (254 mg, 2.0 mmol) was added, and the mixture was allowed to reach room temperature and then stirred for 5 h. The solution was evaporated to dryness, and the residue was flash chromatographed (hexanes−EtOAc, increasing polarity) to afford (*E*)-**1b** and (*Z*)-**1b**. Yield, physical constants, and spectroscopic data for **1a**−**c** and *ent*-**1a** are described below.

Dimethyl (*Z*)-(4*R*,5*R*)-2-(Benzyloxycarbonylamino)-4,5-methano-2-hexenedioate (*Z*)-1a. Yield: 143 mg (61%). Dense oil, ot 190 °C (0.01 Torr); $[\alpha]_D$ −72.9 (*c* 3.6, $CHCl_3$); IR (film) 3325 (broad), 1721, 1651 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.2 (m, 1H), 1.4 (m, 1H), 2.10 (m, 2H), 3.68 (s, 3H), 3.72 (s, 3H), 5.12 (s, 2H), 6.29 (broad s, 1H), 6.7 (d, J = 10.3 Hz, 1H), 7.47 (m, 5H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 15.81, 20.44, 21.86, 51.95, 52.39, 67.36, 126.20, 128.14, 128.47, 134.75, 135.90, 154.19, 164.72, 172.04; MS, *m*/*z* (%) 334 (M+1, 1), 225 (14), 166 (17), 139 (63), 107 (55), 91 (100), 79 (92), 51 (33). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.18; H, 5.72; N, 4.13.

Dimethyl (*Z*)-(4*S*,5*S*)-2-(Benzyloxycarbonylamino)-4,5-methano-2-hexenedioate *ent*-(*Z*)-1a. Yield: 294 mg (66%). $[\alpha]_D$ +72.3 (*c* 3.2, $CHCl_3$). Spectroscopic and analytical data are in good agreement with those described above for (*Z*)-**1a**.

Dimethyl (*Z*)-(4*R*,5*R*)-2-(*tert*-Butoxycarbonylamino)-4,5-methano-2-hexenedioate (*Z*)-1b. Yield: 340 mg (58%). Crystals, mp 76−78 °C (from EtOAc−pentane); $[\alpha]_D$ −94.1 (*c* 3.0, $CHCl_3$); IR (KBr) 3400−3100 (broad), 1730, 1664 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 0.79 (m, 1H), 1.40 (s, 9H), 1.30 (m, 2H), 2.10 (m, 1H), 3.60 (s, 3H), 3.80 (s, 3H), 6.21 (broad s, 1H), 6.55 (d, J = 8.8 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 19.0, 20.4, 22.0, 28.1, 52.4, 52.5, 80.2, 126.7, 128.1, 156.0, 164.5, 172.0; MS, *m*/*z* (%) 300 (M+1, 2), 255 (28), 139 (63), 107 (55), 91 (100), 79 (92), 53 (30). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.23; H, 7.10; N, 4.72.

Dimethyl (*E*)-(4*R*,5*R*)-2-(*tert*-Butoxycarbonylamino)-4,5-methano-2-hexenedioate (*E*)-1. Yield: 131 mg (23%). Crystals, mp 62−64 °C (from EtOAc−pentane); $[\alpha]_D$ +54.4 (*c* 1.2, $CHCl_3$); IR (KBr) 3400−3100 (broad), 1725, 1667 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.31 (m, 1H), 1.40 (s, 9H), 1.96 (m, 2H), 2.95 (m, 1H), 3.60 (s, 3H), 3.80 (s, 3H), 6.48 (broad s, 1H), 6.52 (d, J = 3.6 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 19.0, 20.2, 22.0, 28.1, 52.6, 52.5, 81.1, 125.9, 127.9, 156.1, 164.0, 172.1. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.09; H, 7.13; N, 4.77

Dimethyl (*Z*)-(4*R*,5*R*)-2-(Acetylamino)-4,5-methano-2-hexenedioate (*Z*)-1c. Yield: 264 mg (79%). Crystals, mp 82−84 °C (from EtOAc−pentane); $[\alpha]_D$ +62.0 (*c* 2.6, $CHCl_3$); IR (KBr) 3500−3000 (broad), 1730, 1678 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.30 (m, 1H), 1.40 (s, 9H), 2.09 (m, 2H), 2.90 (m, 1H), 3.60 (s, 3H), 3.80 (s, 3H), 6.51 (broad s, 1H), 6.55 (d, J = 8.8 Hz, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 19.1, 20.2, 21.6, 23.5, 52.18, 52.9, 125.3, 130.0, 164.6, 169.9, 172.02; MS, *m*/*z* (%) 242 (M+1, 2), 164 (21), 136 (60), 107 (55), 91 (100), 79 (92), 51 (33). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.67; H, 6.32; N, 5.83.

(4*R*,4′*S*)-4-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3-(methoxycarbonyl)-4,5-dihydro-1*H*-pyrazole (17a). From (*Z*)-**16a**: Excess ethereal diazomethane (ca. 15 equiv) was distilled onto a solution of pentenoate (*Z*)-**16a** (3 g, 16 mmol) in ether (5 mL). The mixture was light-protected and stirred at room temperature for 18 h. Excess reagent and solvent were removed, and the solid residue was washed with ether−hexane to afford pure isomer **17a** (3.3 g, 90% yield); crystals, mp 144−146 °C (from ethyl acetate−pentane); $[\alpha]_D$ +24.8 (*c* 1.4, $CHCl_3$); IR (KBr) 3402 (broad), 1707 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.2 (s, 3H), 1.3 (s, 3H), 3.28 (m, 1H), 3.58 (m, 2H), 3.67 (s, 3H), 3.72 (dd, J = 10.2, 7.3 Hz, 1H), 3.95 (dd, J = 8.8, 6.6 Hz, 1H), 4.25 (dd, J = 12.4, 6.6 Hz, 1H), 6.4 (br s, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 24.9, 26.1, 46.5, 50.9, 51.6, 68.1, 73.7, 108.7, 140.2, 162.9. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.67; H, 7.12; N, 12.30.

Methyl (1*S*,2*R*,4′*S*)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)cyclopropanecarboxylate (18). A stirred solution of pyrazoline **17a** (100 mg, 0.4 mmol) in freshly distilled acetone (40 mL) contained in a quartz reactor was irradiated with a 125 W medium-pressure lamp under argon atmosphere. The reaction was monitored by GC until total consumption of the starting material. Then solvent was removed to afford a bright red oil that was flash chromatographed (mixtures of hexanes−EtOAc) affording 69 mg of a yellowish oil identified as **18** by its specroscopic data but contaminated by unidentified byproducts. Since it decomposed under distillation conditions, this product was used in subsequent transformations without further purification. IR (film) 1739 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.19 (dd, J = 7.3, 5.1 Hz, 1H), 1.30 (s, 3H), 1.28 (m, 1H), 1.41 (s, 3H), 1.50 (dd, J = 9.5, 5.1 Hz, 1H), 1.62 (m, 1H), 3.60 (s, 3H), 3.70 (m, 1H), 3.90 (dd, J = 9.5, 5.1 Hz, 1H), 4.10 (m, 1H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 14.1, 2.5, 24.8, 26.4, 28.7, 52.7, 69.3, 75.5, 109.0, 172.0.

(1*S*,2*R*)-2-Formyl-1-(methoxycarbonyl)cyclopropane (*ent*-14). A solution of compound **18** (143 mg, 0.7 mmol) and 3 drops of 90% AcOH in MeOH (5 mL) was stirred at room temperature for 6 h and then evaporated to dryness. The residue was washed with methanol and dried under vacuo. The obtained crude diol was poured into THF (10 mL), and n-Bu_4IO_4 (340 mg, 0.8 mmol) was added to the ice-cooled resultant solution. The mixture was stirred for 2 h, the solvent was removed, and the residue was poured into ether. The precipitated solid was filtered, and the filtrate was evaporated to dryness to afford 75 mg (83% yield) of an oil identified as *ent*-**14** by their spectrocopic data which agree with those described above for **14**. $[\alpha]_D$ −92.7 (*c* 3.0, $CHCl_3$).

(1*R*,2*S*)-1-Carboxy-2-(hydroxymethyl)cyclopropane (2). $NaBH_4$ (182 mg, 4.8 mmol) was added to an ice-cooled solution of aldehyde **14** (475 mg, 3.7 mmol) in MeOH (5 mL), and the mixture was stirred for 1 h. Solvent was removed, and the residue was poured into saturated aqueous NH_4Cl (2 mL). The resultant solution was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), and solvent was removed. The residue was flash chromatographed (hexanes−ether, 1:1) affording a 1:1 mixture of hydroxy ester **19** and lactone **20** (300 mg, 64% yield) which were identified from enriched fractions. **(1*R*,2*S*)-2-(Hydroxymethyl)-1-(methoxycarbonyl)cyclopropane (19)**: IR (film) 3444, 1722 cm^{-1}; 400-MHz ^1H NMR (MeOH-d_4) 0.99 (m, 1H), 1.14 (m, 1H), 1.60 (m, 1H), 1.85 (ddd, J = 8.4, 7.9, 5.5, 1H), 3.62 (dd, J = 11.6, 8.5 Hz, 1H), 3.71 (s, 3H), 3.83 (dd, J = 11.6, 6.1 Hz, 1H); 100-MHz ^{13}C NMR (MeOH-d_4) 12.1, 18.1, 24.1, 52.1, 71.1, 174.7. GC-MS, *m*/*z* (%) 113.1 (M, 1), 98.1 (36), 87.1 (77), 74.1 (67), 68.1 (22), 55.1 (100), 41.1 (40). **(1*R*,5*S*)-3-Oxabicyclo[3.1.0]hexan-2-one (20)**: IR (film) 1771 cm^{-1}; 400-MHz ^1H NMR (MeOH-d_4) 0.85 (m, 1H), 1.34 (m, 1H), 2.10 (m, 1H), 2.36 (m, 1H), 4.27 (d, J = 9.2 Hz, 1H), 4,39 (dd, J = 9.2, 4.9 Hz, 1H); 100-MHz ^{13}C NMR (MeOH-d_4) 12.7, 18.5, 30.5, 60.6, 177.9; GC-MS, *m*/*z* (%) 281.1 (M, 1), 98.1 (75), 70.1 (36), 68.1 (59), 42.1 (100), 41.1 (46).

A solution of the mixture **19**/**20** (150 mg) in 1 M methanolic NaOH (6 mL) was stirred at room-temperature overnight and then neutralized with 5% HCl and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), and solvent was removed to afford a yellowish oil that was crystallized to afford pure **2** (115 mg, 86% yield). Crystals, 60−61 °C (from EtOAc−pentane); $[\alpha]_D$ −1.9 and $[\alpha]_{365}$ −2.7 (*c* 0.4, $CHCl_3$); IR (KBr) 3343−3339 (broad), 1623 cm^{-1}; MS, *m*/*z* 116 (M, 1), 99 (20), 73 (100), 70 (39), 60 (40), 55 (97), 44 (73), 43 957); 400-MHz ^1H NMR (acetone-d_6) 0.89 (m, 1H), 1.08 (dt, J = 8.8, 4.4 Hz, 1H), 1.27 (broad s, 1H), 1.56 (m, 1H), 1.73 (m, 1H), 3.6, (dd, J = 11.7, 7.3 Hz, 1H), 3.77 (dd, J = 11.7, 5.8 Hz, 1H); 100-MHz ^{13}C NMR (acetone-d_6) 10.8, 16.5, 23.1, 59.0, 173.4; MS, *m*/*z* (%) 116 (M, 9), 99 (28), 73 (58), 71 (68), 57 (100). Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.48; H, 7.00.

(1*R*,2*R*)-1-(Benzoyloxymethyl)-2-vinylcyclopropane (22). A 1.0 M dichloromethane solution of DIBAL (2.0 mL, 2.0 mmol)

was added via syringe to a stirred solution of vinyl ester **13** (100 mg, 0.8 mmol) in dry CH_2Cl_2 (5 mL) cooled at −78 °C, under nitrogen atmosphere. After stirring for 30 min, water (5 mL) was added dropwise, and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), and solvent was removed. The residue was chromatographed on silica gel to afford 55 mg (70% yield) of alcohol **21** as a yellowish liquid. Freshly distilled benzoyl chloride (0.2 mL, 1.8 mmol) was added to a stirred an ice-cooled solution of **21** (150 mg, 1.5 mmol) and anhydrous pyridine (0.7 mL, 9.2 mmol) in dry CH_2Cl_2 (5 mL), under nitrogen atmosphere. After stirring for 15 min, water (5 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic phases were washed successively with 5% HCl and 10% Na_2CO_3 and dried ($MgSO_4$). Solvent was removed, and the residue was chromatographed on silica gel (hexane−CH_2Cl_2, 6:1) to afford pure **22** (290 mg, 94% yield) as a colorless oil, ot 75−80 °C (0.05 Torr); $[\alpha]_D$ +1.5 (*c* 1.3, $CHCl_3$); IR (film) 1721, 1637 cm^{-1}; MS, *m*/*z* 105 (100), 81 (54), 77 (41), 51 (26), 41 (19); 250-MHz ^1H NMR ($CDCl_3$) 0.54 (dd, *J* = 11.0, 5.8 Hz, 1H), 0.98 (m, 1H), 1.45 (m, 1H), 1.67 (m, 1H), 4.09 (dd, *J* = 11.7, 8.0 1H), 4.38 (dd, *J* = 11.7, 4.4 Hz, 1H), 5.03 (m, 2H), 5.6 (m, 1H), 7.4 (dd, *J* = 8.0, 7.3, 2H), 7.50 (m, 1H), 8.00 (m, 2H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 14.3, 16.8, 19.6, 65.3, 115.6, 128.3, 129.5, 130.4, 132.7, 136.2, 166.6. Anal. Calcd for $C_{12}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.14; H, 6.99.

(1*S*,2*R*)-1-Carboxy-2-(benzoyloxymethyl)cyclopropane (24). Method 1. Catalytic $RuO_2 \times n\ H_2O$ (30 mg) and $NaIO_4$ (2.1 g, 9.8 mmol) were added to a solution of vinyl compound **22** (360 mg, 1.8 mmol) in a 2:2:3 mixture of CCl_4/CH_3CN/H_2O (7 mL). After stirring for 30 min at room temperature, ether (10 mL) was added and the mixture was stirred for 5 min. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and the resultant aqueous phases were acidified with 10% HCl and extracted with ether. All the combined organic phases were dried ($MgSO_4$), and solvent was removed to afford a residue which was washed with pentane and dried under vacuo to afford acid **24** as a solid (220 mg, 56% yield). **Method 2, through aldehyde 23.** Vinyl compound **22** (110 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C underwent ozonolysis following the same procedure than that described above for the preparation of **14**, affording aldehyde **23** (110 mg, 98% yield) as a liquid which was identified by its spectroscopic data and used in the next step without further purification. Aldehyde **23** (110 mg, 0.5 mmol) and pyridinium dichromate (467 mg, 1.1 mmol) in anhydrous DMF (10 mL) were stirred at room temperature for 48 h. The mixture was filtered, and the filtrate was evaporated to dryness under vacuo. The residue was poured into CH_2Cl_2 and washed with saturated aqueous Na_2CO_3. The organic phase was subsequently acidified with 10% HCl and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), and solvent was removed to afford 57 mg (49% yield) of acid **24**. Crystals, mp 85−87 °C; $[\alpha]_D$ +1.7 (*c* 0.8, $CHCl_3$); IR (KBr) 3058, 2960, 1728 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.19 (t, *J* = 7.3 Hz, 2H), 1.81 (m, 2H), 4.25 (m, 1H), 4.70 (m, 1H), 7.35 (m, 2H), 7.48 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 2H); 62.5-MHz ^{13}C NMR ($CDCl_3$) 13.0, 17.4, 20.5, 63.1, 128.3, 129.5, 132.8, 166.4, 178.1. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.40; H, 5.57.

(1*S*,2*R*)-1-Carboxy-2-(hydroxymethyl)cyclopropane (*ent*-2). Compound **24** (220 mg, 1 mmol) in methanolic 1 M NaOH (10 mL) was stirred at room temperature for 2 days. Then the mixture was subsequently neutralized with 5% HCl and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), and solvent was removed to afford a yellow oil that became a white solid after crystallization. The solid was recrystallized to afford pure *ent*-**2** (82 mg, 70% yield). Crystals, mp 61−62 °C (from EtOAc−pentane); $[\alpha]_D$ +1.9 and $[\alpha]_{365}$ +2.6 (*c* 0.4, $CHCl_3$). Spectroscopic and analytical data are in good agreement with those described above for **2**.

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Supporting Information Available: An ORTEP drawing, as well as the atomic coordinates and thermal parameters for structure **17a** (6 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.

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