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Efficient *trans*-Selectivity in the Cyclocondensation of (*S*)-2-[2-(*p*-Tolylsulfinyl)phenyl]acetaldehyde with Activated Dienes Catalyzed by $Yb(OTf)_3$

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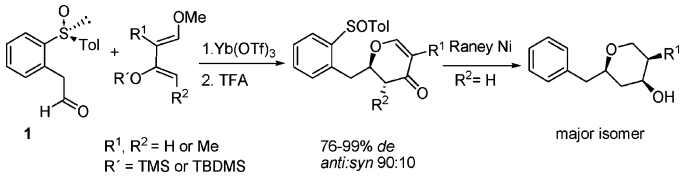
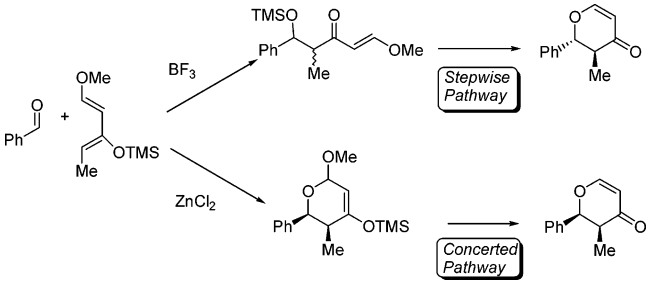


Reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde **1** with Danishefsky's and related dienes took place in the presence of $Yb(OTf)_3$ in a completely stereoselective manner, mediated by a remote sulfinyl group (1,5-asymmetric induction), to afford the corresponding 2,3-dihydro-4*H*-pyran-4-ones. These reactions followed a stepwise mechanism, as was corroborated by isolation of the corresponding intermediates, with a high level of *trans*-selectivity for 4-methyl-substituted dienes. Treatment of the adducts with Raney Ni provided concomitant cleavage of the C−S bond and reduction of the conjugated carbonyl grouping.

Introduction

The hetero Diels−Alder (HDA) reactions of aldehydes with 1-alkoxy-3-(trialkylsilyloxy)-1,3-butadiene (Danishefsky's diene) and related dienes, mediated by Lewis acids, provide one of the most powerful synthetic tools to construct chiral 2,3-dihydro-4-pyranone moieties widely used in the preparation of specific carbohydrates, as well as in the total synthesis of natural products.[1] The stereochemical results obtained in these reactions depend on the nature of the catalyst, which determines their evolution via a concerted or stepwise mechanism (Scheme 1). Thus, Danishefsky et al.[2] reported that the reaction of benzaldehyde with 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene in the presence of BF_3 proceeded in a stepwise pathway, mainly yielding *trans*-2,3-disubstituted dihydropyranones, whereas it followed a concerted mechanism, affording the *cis*-2,3-disubstituted isomers almost exclusively, when catalyzed by $ZnCl_2$. The use of bulkier lanthanides(III) complexes also catalyzes these reactions and significantly increases the *cis*-

SCHEME 1



stereoselectivity.[3] However, the factors determining the mechanism followed by these reactions are not completely clear. In most cases, the isolation of the intermediates is the only possible way to distinguish between the two mechanisms.

The high stereoselectivity of the concerted reactions yielding major *cis*-2,3-disubstituted dihydropyranones (*cis*-selectivity) has been explained by assuming that the *endo* approach was the preferred one. It is additionally favored by the steric interactions between diene and catalyst in a *cis*-arrangement with respect to the aldehydic hydrogen, which destabilizes the *exo* approach mode. The stereoselectivity of the stepwise mechanism is

(1) Reviews: (a) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Heathcock, C. H., Ed., pp 661−706. (b) Waldmann, H. *Synthesis* **1994**, 535. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3558.

(2) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc*. **1985**, *107*, 1246 and references therein.

(3) Bednarski, M. D.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1983**, *105*, 3716.

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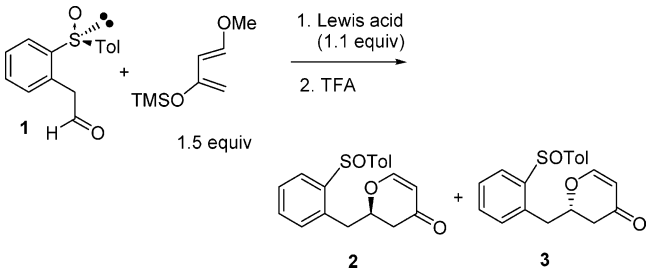
explained on the basis of an extended TS to give *anti*-aldol products (*trans*-selectivity) that evolve into the *trans*-2,3-disubstituted dihydropyranones (Scheme 1). However, the *trans*-selectivity has also been found in concerted processes that occur with aldehydes in the presence of Lewis acids. The resulting chelates exhibit favored *exo* approaches of the dienes in order to avoid the strong steric interactions of the *endo* approaches.[4]

The most widely used asymmetric version of these reactions is that involving chiral catalysts, which provides high levels of *cis*-selectivity.[1c] The low diastereofacial or *endo*-selectivity observed in reactions of enantiomerically pure dienes[5] and the easy racemization of the aldehydes with chiral centers at C-α under the experimental conditions have seriously limited the use of chiral auxiliaries. Although a limited number of examples affording optically pure *trans*-2,3-disubstituted dihydropyranones has been reported,[2,6] the search for efficient methods for preparing these compounds in processes evolving with *trans*-selectivity remains nowadays as an interesting challenge in asymmetric synthesis.

In the course of our research program related to the use of the sulfinyl group to achieve a remote control of the stereoselectivity,[7] we have recently described the significant role of Yb(OTf)$_3$ in the stereochemical control of different nucleophilic addition of hydrides and cyanides to *δ*-ketosulfoxides.[8] The efficiency of this catalyst seems to be due to the formation of stable chelated species with the sulfinyl and carbonyl oxygens, which are highly reactive and show a strong facial discrimination toward the attack of nucleophiles. With the aim of widening the scope of the remote stereoselective functionalization mediated by sulfoxides, we decided to study the hetero Diels−Alder reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde **1** with oxygenated dienes. According to the above-mentioned precedents, **1** could be a substrate liable to evolve with *trans*-selectivity in the reactions catalyzed by Yb(OTf)$_3$ (the *exo* approach would be the preferred one in concerted processes as a result of the formation of the chelated species with the catalyst), which would increase the interest of this study. Their possible evolution through a stepwise mechanism could also take place with *trans*-selectivity. Additionally, this aldehyde should be configurationally stable under the conditions used in these reactions. In this paper, we report the results obtained in the reactions of aldehyde **1** with different Danishefsky-type dienes catalyzed by Yb(OTf)$_3$. They provide a new example evidencing the efficiency of a remote sulfinyl group to control the stereoselectivity of these reactions that evolve with a high *trans*-selectivity through a stepwise mechanism. The results obtained in the reactions of the resulting 2,3-dihydropyranones with Raney nickel are also reported.

TABLE 1. Reaction of 1 and Danishefsky's Diene under Different Conditions



1 **2** **3**

entry	Lewis acid	solvent	temp	additive	time	2:3 ratio
1		CH_2Cl_2	rt		16 h	
2	Yb(OTf)$_3$	THF	rt		16 h	*a*
3	Yb(OTf)$_3$	toluene	rt		7 h	*a*
4	Yb(OTf)$_3$	CH_2Cl_2	rt		16 h	74:26[b]
5	Ti(O*i*-Pr)$_4$	CH_2Cl_2	rt		13 h	
6	BF_3OEt_2	CH_2Cl_2	rt		13 h	46:54[c]
7	In(OTf)$_3$	CH_2Cl_2	rt		13 h	
8	Yb(O*i*-Pr)$_3$	CH_2Cl_2	rt		20 h	*d*
9	Yb(OTf)$_3$	CH_2Cl_2	−40 °C		24 h	86:14[b]
10	Yb(OTf)$_3$	CH_2Cl_2	−78 °C		36 h	90:10[c]
11	Yb(OTf)$_3$	CH_2Cl_2	rt	MS 4Å	3 h	74:26[a]
12	Yb(OTf)$_3$	CH_2Cl_2	0 °C	MS 4Å	20 h	77:33[b]
13	Yb(OTf)$_3$	CH_2Cl_2	−78 °C	MS 4Å	30 h	88:12[c]
14	Yb(OTf)$_3$	CH_3CN	rt		5 min	78:22[b]
15	Yb(OTf)$_3$	CH_3CN	−40 °C		5 min	88:12[c]
16	Yb(OTf)$_3$	EtCN	−78 °C		2 h	90:10[b]
17	Yb(OTf)$_3$	DMF	−40 °C		2 h	

[a] Traces of the adducts were detected. [b] Determined by NMR. [c] Determined by HPLC. [d] Complex reaction mixture.

Results and Discussion

We have used the recently reported (*S*)-2-[2-(*p*-tolylsulfinyl)-phenyl]acetaldehyde **1**[9] as the starting material. We first investigated its reaction with the Danishefsky's diene under different conditions (Table 1). The reaction did not evolve in the absence of Lewis acids (entry 1), but when it was performed in the presence of Yb(OTf)$_3$, the formation of the HDA adducts **2** and **3** could be observed. The composition of the reaction mixture was dependent on the solvent. In toluene or THF only traces of adducts were detected (entries 2 and 3), but complete disappearance of the starting material was observed in CH_2Cl_2 with formation of a 3:1 mixture of adducts **2**:**3** (entry 4). The use of other Lewis acids as catalysts did not improve the reactivity, either by decreasing the stereoselectivity or by precluding the reaction (entries 5−8). The stereoselectivity was substantially improved by lowering the temperature in CH_2Cl_2 (entries 9 and 10), with the best result being obtained at −78 °C. Under these conditions a 90:10 mixture of **2** and **3** was obtained (entry 10). The addition of molecular sieves (4 Å) enhanced the reactivity (shorter reaction times were necessary for the reaction to reach completion) without affecting the stereoselectivity (entries 11−13).[10] The best results were

(4) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.

(5) See ref 1a, p 681.

(6) For reactions with achiral catalysis, see: (a) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Tetrahedron* **1996**, *52*, 2167. For reactions with chiral catalysis, see: (b) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793.

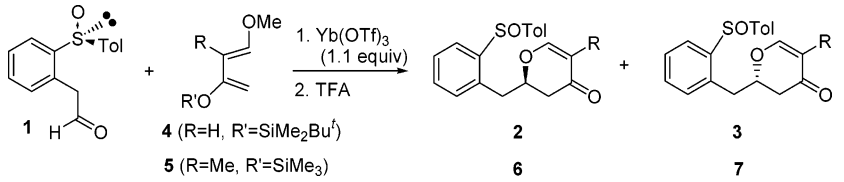
(7) (a) García Ruano, J. L.; Carreño, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736. (b) García Ruano, J. L.; Alemán, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677. (c) García Ruano, J. L.; Alemán, J. *Org. Lett.* **2003**, *5*, 4513. (d) García Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron* **2004**, *60*, 5383. (e) García Ruano, J. L.; Martín-Castro, A. M.; Tato, F.; Cárdenas, D. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1963. (f) García Ruano, J. L.; Martín-Castro, A. M.; Tato, F.; Pastor, C. J. *J. Org. Chem.* **2005**, *70*, 7346.

(8) (a) García Ruano, J. L.; Fernández-Ibáñez, M. A.; Maestro, M. C.; Rodríguez-Fernández, M. M. *J. Org. Chem.* **2005**, *70*, 1796. (b) García Ruano, J. L.; Fernández-Ibáñez, M. A.; Maestro, M. C.; Rodríguez-Fernández, M. M. *Tetrahedron* **2006**, *62*, 1245.

(9) García Ruano, J. L.; Alemán, J.; Aranda, M. T.; Fernández-Ibáñez, M. A.; Rodríguez-Fernández, M. M.; Maestro, M. C.; *Tetrahedron* **2004**, *60*, 10067.

(10) The importance of molecular sieves in Lewis acid promoted Diels−Alder cycloadditions has been reported: Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Pert, S., Jr. *J. Org. Chem.* **1996**, *61*, 671.

TABLE 2. Reaction of 1 with Dienes 4 and 5



entry	diene	solvent	temp (°C)	time (h)	additive	isolated yield (%)	products ratio[a]
1	**4**	CH_3CN	−40	2		*b*	
2	**4**	CH_3CN	−40	3	MS 4Å	54	**2**(92):**3**(8)
3	**4**	CH_3CN/CH_2Cl_2	−78	13	MS 4Å	32	**2**(94):**3**(6)
4	**5**	CH_3CN	−40	2	MS 4Å	57	**6**(88):**7**(12)
5	**5**	CH_3CN/CH_2Cl_2	−78	8	MS 4Å	49	**6**(88):**7**(12)

[a] Measured by HPLC. [b] Traces of the product were detected.

obtained by using CH_3CN as the solvent, which strongly increased the reactivity but scarcely affected the stereoselectivity (entries 14 and 15). When the reaction was conducted at −40 °C in this solvent (entry 15), a 88:12 mixture of **2** and **3** was obtained in only 5 min. By lowering the temperature to −78 °C (which required the use of EtCN as the solvent) the diastereoselectivity was only slightly improved (entry 16). The reaction did not work in DMF (entry 17). The major diastereoisomer **2**, which was easily separated from **3** by crystallization, was obtained in 69% isolated yield from the mixture obtained under conditions of entry 15.

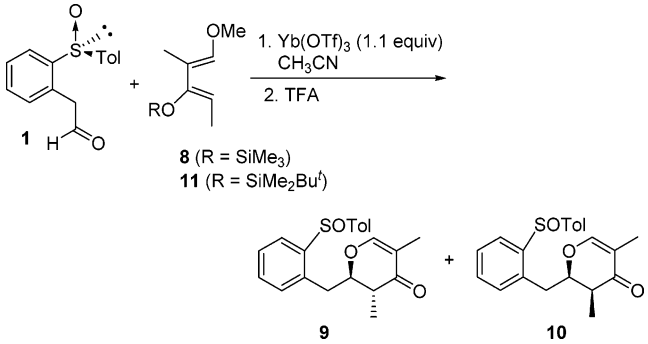
Once we had determined the best conditions for these cyclocondensation reactions, we studied the influence of the size of the silyloxy group at C-3[2,11] as well as that of one methyl group at C-2. The results are summarized in Table 2.

The reaction of aldehyde **1** with 1-methoxy-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**4**) did not work in the conditions indicated in entry 1. In the presence of molecular sieves (4 Å) the reaction required 3 h in acetonitrile at −40 °C to reach completion, affording a 92:8 mixture of compounds **2** and **3** (entry 2, Table 2). This result is indicative of a stereoselectivity slightly higher than that observed with Danishefsky's diene (entry 15, Table 1). However, the increase in the size of the silyloxy group also produced a substantial decrease in both reactivity and yield (compare entry 2, Table 2 and entry 15, Table 1). By lowering the temperature to −78 °C (CH_3CN/CH_2Cl_2 1:1 as the solvent) the stereoselectivity became only slightly higher (88% de), but the yield is much poorer (32%, entry 3). The reactions of **1** with dienes bearing even bulkier sililoxy groups, such as *trans*-1-methoxy-3-(triisopropylsilyloxy)-1,3-butadiene, were unfruitful.

The reaction of **1** with 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**5**) afforded a mixture of **6** and **7**, readily separated by crystallization or chromatography. The stereoselectivity of this reaction at −40 °C (entry 4) in the presence of MS (4 Å) was similar to that observed for Danishefsky's diene (76% de), but the yield was lower (57%). The major component could be isolated in 39% yield after crystallization. In this case, both the stereoselectivity and the yield were only scarcely modified by lowering the temperature to −78 °C (entry 5, Table 2).

Finally, we have checked the influence of a methyl group at C-4 by studying the behavior of the *trans*-1-methoxy-2-methyl-3-(trialkylsilyloxy)-1,3-pentadienes **8** and **11** in their reaction with the aldehyde **1**. These reactions are much more interesting because the resulting adducts had two chiral stereocenters and provide information about the stereoselectivity control at the diene moiety. The results are summarized in Table 3.

TABLE 3. Reaction of 1 with *trans*-1-Methoxy-2-methyl-3-(trialkylsilyloxy)-1,3-pentadienes 8 and 11



entry	diene (equiv)	temp (°C)	time (h)	additive	conversion[a] (yield %)	**9**:**10** ratio[a]
1	**8** (1.5)	20	3		85[b]	73:27
2	**8** (1.5)	0	3.5		80[b]	78:22
3	**8** (1.5)	−40	7		80	90:10
4	**8** (3)	−40	3	MS 4Å	100 (65)	90:10
5[c]	**8** (3)	−78	14	MS 4Å	(63)[d]	90:10
6	**11** (1.5)	−10	6	MS 4Å	97	61:39
7	**11** (1.5)	−40	6	MS 4Å	89	62:38
8	**11** (3)	−40	6	MS 4Å	90	63:37
9	**11** (1.5)	−40	21	MS 4Å	100 (56)	62:38
10[c]	**11** (3)	−78	14	MS 4Å	36	60:40

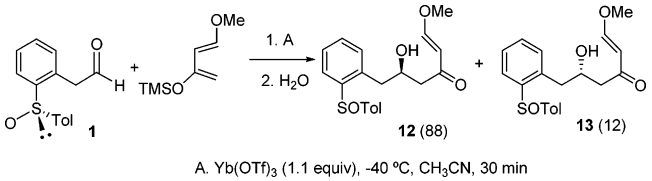
[a] Measured by ^1H NMR. [b] Unreacted starting material could be recovered. [c] A 1:1 mixture of CH_3CN/CH_2Cl_2 was used as the solvent. [d] Incomplete conversion (% conversion not determined).

The reaction between aldehyde **1** and diene **8** at room temperature in the absence of MS 4 Å afforded a 73:27 mixture of only two compounds **9** and **10**, epimers at C-3, the *trans*-isomer **9** being the major one (entry 1). After 3 h the conversion was not complete, and the signals attributed to the enolic form of aldehyde **1** could be detected in ^1H NMR spectrum of the crude reaction.[12] At lower temperatures, the stereoselectivity increased, but the conversion remained incomplete even at larger reaction times (compare entries 2 and 3). Complete conversion was achieved in the presence of molecular sieves (4 Å) by using 3 equiv of the diene (entry 4) with formation of a 90:10

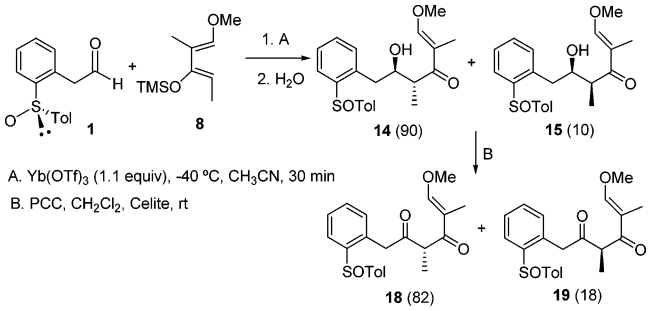
(11) Danishefsky, S. J.; Chao, K.-H.; Schulte, G. *J. Org. Chem.* **1985**, *50*, 4650.

(12) Unreacted aldehyde **1** can be recovered by column chromatography.

SCHEME 2



SCHEME 3

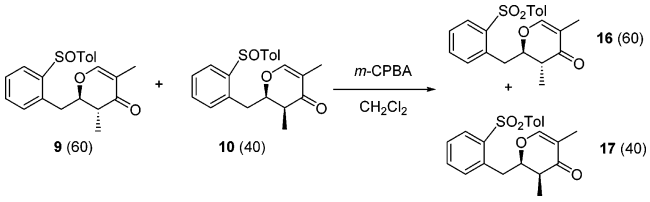


mixture of **9** and **10**, with the *trans*-**9** isomer being obtained as the major product. The stereoselectivity did not improve at −78 °C (entry 5). Surprisingly, an increase of the size of the trialkylsilyloxy group, as it was the case of diene **11**, caused a decrease in the stereoselectivity, thus yielding a ca. 60:40 mixture of compounds *trans*-**9** and *cis*-**10** in all the studied conditions (entries 6−10). These mixtures could be separated by flash column chromatography. Under conditions of entry 4, optically pure major *trans*-isomer **9** was obtained in a 51% yield.

In summary, these results indicate that any increase in the size of the silyloxy group has a scarce influence on the stereoselectivity control in reactions from 1,3-disubstituted dienes (**4** and Danishefsky's diene), but it is large and negative for 1,2,3,4-tetrasubstituted ones (**8** and **11**). By comparison of the results obtained from Danishefsky's diene and **5**, it can be stated that the presence of the methyl group at C-2 does not affect significantly the stereoselectivity. Finally, the reactivity is strongly dependent on the solvent (larger in CH_3CN than in CH_2Cl_2). All of these facts are not easily compatible with a concerted mechanism. Therefore, the formation of the *trans* isomers as the major ones in these reactions suggested that they are stepwise processes involving Mukaiyama's aldol condensation followed by intramolecular cyclization of the resulting intermediate. To confirm this hypothesis, we investigated the reaction between aldehyde **1** and Danishefsky's diene (1.5 equiv) in the presence of $Yb(OTf)_3$ treating the resulting mixture with water instead of TFA (Scheme 2). Under these conditions a mixture of β-hydroxyketones **12** and **13** was isolated in the same proportion that **2** and **3** were obtained when the mixture was treated with TFA (Table 1, entry 15). These compounds were those resulting from Mukaiyama's reaction of the silylenolether moiety of Danishefsky's diene to the carbonyl group of **1** activated by the Lewis acid. When the mixture **12** + **13** was treated with TFA, the formation of the mixture **2** + **3** (in identical proportion to that of the starting products) was observed. This fact strongly supports that **12** and **13** are the intermediates in the reactions shown in Table 1.

Under similar conditions, reaction of **1** with **8** also provided a mixture of hydroxyketones **14** and **15** (Scheme 3) in proportions identical to that observed for adducts **9** and **10**, thus suggesting that reactions shown in Table 3 also evolve in a two-step sequence, **14** and **15** acting as the intermediates.

SCHEME 4



The absolute configuration of compound **2** was unequivocally determined as [(S)*S*,2*R*] by X-ray diffraction studies.[13] As compound **3** is epimer of **2** at the only chiral center created in the reaction of **1** with Danishefsky's diene, we have assigned [(S)*S*,2*S*] configuration to compound **3**. Therefore, the absolute configuration of compounds **12** [(S)*S*,2*R*] and **13** [(S)*S*,2*S*], intermediates in the formation of **2** and **3**, can also be unequivocally established.

The configurations of adducts **6** and **7**, obtained in the reactions of **1** with the diene **5**, were assigned by assuming the same facial preference in the attack of **5** and Danishefsky's diene to the carbonyl group at **1**. This assumption is supported by the NMR spectra of the major isomers **2** and **6**, which show a similar pattern of signals for the benzylic ABX system and are completely different to that of the minor isomers **3** and **7**.

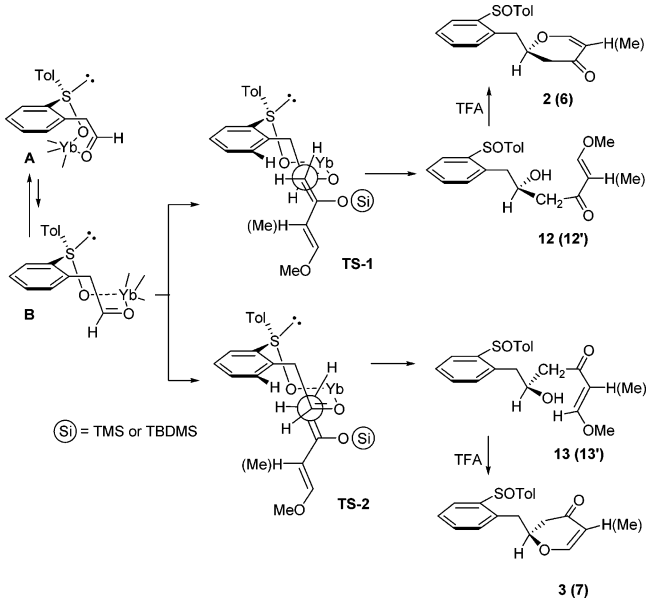
The absolute configuration of compound **9** was unequivocally assigned as [(S)*S*,2*R*,3*R*] by X-ray analysis.[13] It allowed the assignment of the configuration of **14** (Scheme 3), which is presumably its precursor. Bearing in mind that two chiral centers are created in these reactions, the configuration of the minor epimer **10** could be [(S)*S*,2*R*,3*S*], [(S)*S*,2*S*,3*R*], or [(S)*S*,2*S*,3*S*], the former ones differing from **9** in only one of the two new chiral centers and the third one differing in both of them. To exclude the last possibility we performed the reaction in a 60:40 mixture of **9** and **10** with *m*-CPBA, which gave a 60:40 mixture of two nonenantiomeric sulfones, **16** and **17**, with different ^1H NMR spectra (Scheme 4).

To confirm the absolute configuration of **10**, we performed the oxidation with PCC of the 90:10 mixture of **14** and **15**, obtained under the conditions shown at the Scheme 3. The reaction afforded a mixture of two 1,3-diketosulfoxides **18** and **19** (Scheme 3), which indicates that they (as well as their precursors **14** and **15**) differ in the configuration at the methinic carbon. The proportion of **18** and **19** (82:12) is very similar but not identical to that of the starting **14** and **15** (90:10), which is not unexpected on the basis of the high acidity of the methinic proton flanked by two carbonyl groups in **18** and **19**.

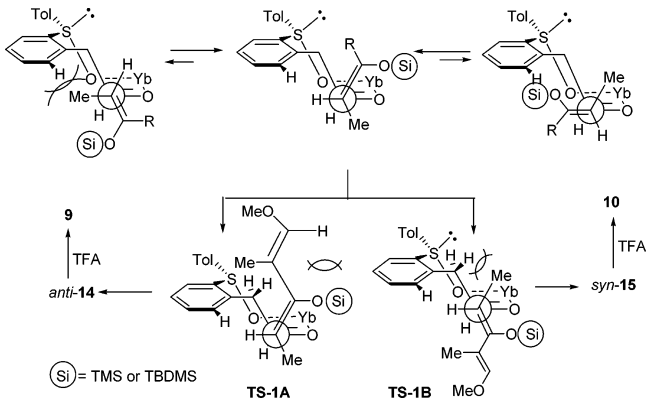
Once it has been established that these reactions take place following a two-step process, their stereochemical results must be explained as a consequence of an intermolecular approach of the silylenolether moiety of the dienes to the less hindered face of the carbonyl. Concerning the π-facial selectivity at the electrophile, it is very high with Danishefsky's diene as well as with **5** (up to 80% de), it increases with the size of the trialkylsilyloxy group for **4** (up to 88% de) and is complete with **8** and **11** (>98% de). Concerning the facial selectivity at the nucleophile (only possible for **8** and **11**), it is also very high for **8** (80% de) but significantly decreases for **11** (ca. 20% de). This behavior can be explained by assuming that chelated

(13) Crystallographic data of structures **2** and **9** have been deposited with the Cambridge Crystallographic Data Center, deposition no. CCDC 601082 (**2**) and deposition no. 601083 (**9**). The coordinates can be obtained on request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

SCHEME 5



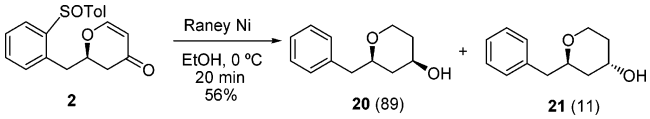
SCHEME 6



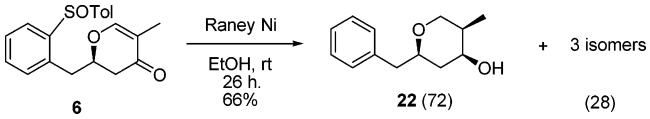
species formed from **1** and $Yb(OTf)_3$ act as the electrophile in Mukaiyama's reaction. Two chelated species, **A** and **B**, could be formed, the latter one being the most stable due to steric reasons. The favored approach of the nucleophile will take place to the less hindered pro-*R* face of the aldehyde in its **B** chelated conformation (**TS-1**), yielding intermediate **12** or **12′** that evolves into **2** or **6** by reaction with TFA (Scheme 5). The approach of the nucleophile to the pro-*S* face (**TS-2**), which gives **13** and **13′**, would be highly hindered, and it is only possible for dienes, such as **4**, **5**, and Danishefsky's diene, with no substituents at C-4. The selectivity must be slightly higher as the size of the silyloxy group becomes larger (compound **4**) and is scarcely modified by the presence of a methyl group at C-2 (compound **5**), as can be deduced from Scheme 5.

Reactions of aldehyde **1** with dienes **8** and **11**, which bear a methyl group at C-4, take place with a complete control of the configuration at the hydroxylic carbon (**TS-2** at Scheme 5 would be strongly hindered). The formation of a mixture of epimers is the result of the approach to the less hindered face of the electrophile from both faces of the nucleophile. The strong preference for the *trans*-isomer can be explained assuming that only those approaches exhibiting antiperiplanar arrangement between the hydrogen at nucleophile and the C═O bond at electrophile are possible. The other two conformations would be strongly destabilized by steric interactions of the carbons in

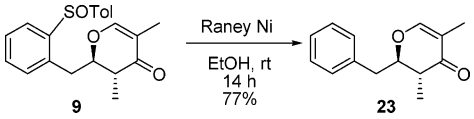
SCHEME 7



SCHEME 8



SCHEME 9



antiperiplanar arrangement with respect to the arylsulfinyl group (Scheme 6). **TS-1A** and **TS-1B** are the transition states fulfilling these requirements. They differ in the face of the nucleophile which is being attacked by the electrophile and afford compounds *anti*-**14** and *syn*-**15** respectively, that finally will be transformed with TFA into **9** and **10**. The fact that the *anti*-**14** isomer is obtained as the major one suggests the greater stability of **TS-1A** with respect to **TS-1B**. Although it is not obvious from Scheme 6, it could be explained by assuming that the steric interactions between the CH_2 at the chelated species and the methyl group (tetrahedral) are higher than those with the alkenyl group (trigonal).

The increase in the size of the silyloxy group (as it is the case for diene **11** with respect to **8**) leads to a substantial decrease in the stereoselectivity, which means that the stability differences between **TS-1A** and **TS-1B** are smaller. From Scheme 6, it could be inferred that interactions $H/OSiR_3$ in **TS-1A** could distort the planarity of the dienic system thus increasing its steric interactions with the benzylic protons of the aldehyde. This effect must be more important for **11** ($OSiMe_2Bu^t$), and therefore the relative stabilities of its corresponding **TS-1A** and **TS-1B** should be more alike, which accounts for the observed decrease in stereoselectivity.

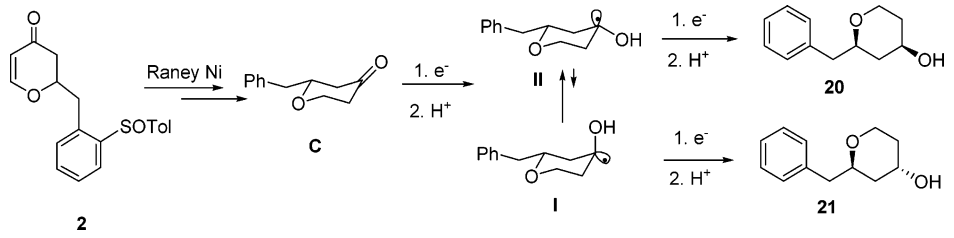
The reaction of **2** with Raney Ni (EtOH) for 20 min at 0 °C afforded a 89:11 mixture of alcohols **20** and **21** in 56% yield (Scheme 7), which evidenced that hydrogenolysis of the C−S bond and reduction of the olefinic and carbonylic double bonds took place simultaneously under these conditions. The separation of the mixture by flash column chromatography gave the major stereoisomer **20** in 40% isolated yield. The configurational assignment of compounds **20** and **21** was unequivocally established by NMR (see Supporting Information).

To the best of our knowledge, this is the first reported complete reduction of the conjugated carbonyl system of these dihydropyranones with Raney Ni. As the mechanism of these reductions presumably involves free radicals, the use of Raney Ni could be complementary to other reducing agents, such as Pd/H_2 or $NaBH_3CN/BF_3$, usually employed for this type of reductions.[14]

The reaction of **6** with Raney Ni (EtOH) also provokes the C−S cleavage and the total reduction of the conjugated system. However, its reactivity is much lower, requiring 26 h at room

(14) (a) Hauser, F. M.; Hu, X. *Org. Lett.* **2002**, *4*, 977. (b) Zhang, S.; Zhen, J.; Reith, M. E. A.; Dutta, A. K. *Bioorg. Med. Chem.* **2004**, *12*, 6301.

SCHEME 10



temperature to complete the reduction, providing a mixture of the four possible stereoisomers (Scheme 8) in 66% combined yield. This mixture could not be separated. Only the structure of the major alcohol **22** could be established from the NMR spectrum of the reaction mixture (see Supporting Information).

Finally, the reaction of **9** with Raney Ni only produced the hydrogenolysis of the C−S bond in good yield without affecting the dihydropyranone moiety (Scheme 9).

The results obtained in the reduction of **2** with Raney Ni could be explained by assuming the formation of 4-tetrahydropyranone **C** as the intermediate that resulted from the reduction of the C═C bond and the hydrogenolysis of the C−S bond. Compound **C** reacted with the Raney Ni according to a set mechanism (Scheme 10) affording a mixture of the two possible alcohols. The higher stability of the intermediate **II** with the OH group in equatorial arrangement would account for the formation of the isomer **20** as the major one. Starting from **6** a mixture of two diastereoisomeric 2-benzyl-5-methyl 4-pyranones would be formed in the first step, whose further reduction would provide the four possible alcohols.

Conclusions

In summary, we have demonstrated that the asymmetric HDA reactions of aldehyde **1** with 1,3-dioxygenated dienes catalized by $Yb(OTf)_3$ proceeds in a highly stereoselective way controlled by a remote sulfinyl group (1,5-asymmetric induction). The reactions occur following a stepwise mechanism (the intermediates could be isolated) with a high level of *trans*-selectivity for 4-methyl-substituted dienes. The reduction of the resulting sulfinyl dihydropyranones with Raney Ni provided 4-hydroxyoxanes with concomitant cleavage of the C−S bond and reduction of the conjugated carbonyl grouping.

Experimental Section

Hetero Diels−Alder Reaction. General Procedure. A solution of aldehyde **1** (0.39 mmol) and $Yb(OTf)_3$ (0.46 mmol) in CH_3CN (3.4 mL) was stirred for 30 min at room temperature under argon atmosphere (in the presence of MS 4 Å if so indicated). Then, the solution was cooled to the temperature shown in each case, and the corresponding diene (0.59 mmol) was added via syringe. The resulting solution was stirred at the same temperature for the indicated time, TFA (0.2 mL) was added, and the mixture stirred at room temperature for 2 h. Saturated aqueous Na_2CO_3 solution (1 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using the eluent indicated in each case.

[2*R*,(S)*S*]-2-[2-(*p*-Tolylsulfinyl)benzyl]-2,3-dihydro-4*H*-pyran-4-one (2) was obtained as a 88:12 mixture of **2** and **3**, following the general procedure from Danishefsky's diene, at −40 °C for 5 min. The crude mixture was purified by flash chromatography (ethyl acetate−hexane, 1:1). Combined yield 87%. Recrystallization (ethyl acetate−hexane) affords pure **2** (69%) as a white solid. The de was determined by HPLC (Chiralcel OD, *i*-PrOH−hexane, 10:90, 1.0 mL/min, [2*R*,(S)*S*]-**2** t_R = 58.3, [2*S*,(S)*S*]-**3** t_R = 81.2). $[\alpha]^{20}_D$ −84.5 (*c* 0.5, $CHCl_3$). Mp: 150−152 °C. IR (film): 3054, 2923, 2360, 1677 and 1593. ^{1}H NMR: 7.93 (m, 1H), 7.50−7.41 (m, 4H), 7.29−7.23 (m, 4H), 5.36 (dd, *J* 6.0 and 0.9 Hz, 1H), 4.39 (m, 1H), 3.27 (dd, *J* 14.5 and 8.1 Hz, 1H), 3.07 (dd, *J* 14.5 and 5.0 Hz, 1H), 2.48 (dd, *J* 16.6 and 12.2 Hz, 1H), 2.40 (ddd, *J* 16.6, 4.5 and 0.9 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR: 191.5, 162.6, 143.7, 141.9, 141.3, 134.6, 131.4, 131.2, 130.1, 128.3, 126.0, 125.9, 107.2, 78.8, 41.4, 36.1, 21.3. MS (FAB$^+$) *m*/*z*: 327 (100) [M + 1], 154 (18), 91 (7). HRMS [M + 1]: calcd for $C_{19}H_{19}O_3S$ 327.1054, found 327.1044. Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56; S, 9.82. Found: C, 69.53; H, 5.67; S, 9.48.

Minor diastereoisomer **3** was not isolated. It was characterized from a 52:48 mixture of **2** and **3**. ^{1}H NMR (representative parameters): 5.39 (dd, *J* 6.0 and 1.1 Hz, 1H), 3.26−3.18 (m, 2H), 2.60−2.44 (m, 2H). ^{13}C NMR: 191.1, 162.5, 143.8, 142.0, 141.4, 134.8, 131.5, 131.3, 130.2, 128.4, 126.5, 126.0, 107.3, 78.8, 41.5, 36.3, 21.3. HRMS (ES$^+$) [M + 1]: calcd for $C_{19}H_{19}O_3S$ 327.1049, found 327.1057.

[2*R*,(S)*S*]-5-Methyl-2-[2-(*p*-tolylsulfinyl)benzyl]-2,3-dihydro-4*H*-pyran-4-one (6) was obtained as a 88:12 mixture of **6** and **7**, following the general procedure in the presence of MS 4 Å from diene **5** at −40 °C for 2 h. The crude mixture was purified by flash chromatography (ethyl acetate−hexane, 1:1). Combined yield 57%. Recrystallization (ethyl acetate−hexane) afforded diastereomerically pure **6** (39%) as a white solid. The de was determined by HPLC (Chiralcel OD, *i*-PrOH−hexane, 10:90, 1.0 mL/min, [2*R*,(S)*S*]-**6** t_R = 47.9, [2*S*,(S)*S*]-**7** t_R = 66.9). $[\alpha]^{20}_D$ −92.1 (*c* 0.9, $CHCl_3$). Mp: 148−150 °C. IR (film): 3008, 1657, 1616 and 1154. ^{1}H NMR: 7.93 (m, 1H, Ar), 7.50−7.43 (m, 4H, Ar), 7.29−7.16 (m, 4H), 4.35 (m, 1H), 3.26 (dd, *J* 14.4 and 7.8 Hz, 1H), 3.01 (dd, *J* 14.5 and 5.0 Hz, 1H), 2.53−2.36 (m, 2H), 2.36 (s, 3H), 1.64 (s, 3H). ^{13}C NMR: 192.1, 159.0, 143.8, 141.9, 141.4, 134.8, 131.3, 131.2, 130.1, 128.3, 125.9 (2C), 113.9, 78.6, 41.2, 36.3, 21.3, 10.3. MS (FAB$^+$) *m*/*z*: 341 (100) [M + 1], 139 (23), 14 (91). HRMS [M + 1]: calcd for $C_{20}H_{21}O_3S$ 341.1211, found 341.1217. Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.44; H, 5.95; S, 9.38.

Minor diastereoisomer **7** was not isolated. It was characterized from a 82:12 mixture of **6** and **7**. ^{1}H NMR (200 MHz) (representative parameters): 3.22−3.15 (m, 2H), 2.60−2.41 (m, 2H). HRMS (ES$^+$) [M + 1]: calcd for $C_{20}H_{21}O_3S$ 341.1205, found 341.1214.

[2*R*,3*R*,(S)*S*]-3,5-Dimethyl-2-[2-(*p*-tolylsulfinyl)benzyl]-2,3-dihydro-4*H*-pyran-4-one (9) was obtained as a 90:10 mixture of **9** and **10** (combined yield 65%), following the general procedure in the presence of MS 4 Å from diene **8** at −40 °C for 3 h. Compound **9** was isolated diastereomerically pure (51%) as a white solid by flash column chromatography (ethyl acetate−hexane, 1:2). $[\alpha]^{20}_D$ −81.0 (*c* 1.5, $CHCl_3$). Mp: 130−132 °C. IR (film): 2997, 2927, 1666, 1595 and 1171. ^{1}H NMR: 7.88 (m, 1H), 7.48−7.37 (m, 4H), 7.31−7.09 (m, 4H), 4.12 (m, 1H), 3.17 (dd, *J* 14.6 and 8.0 Hz, 1H), 3.08 (dd, *J* 13.9 and 3.6 Hz, 1H), 2.50−2.38 (m, 1H), 2.34 (s, 3H), 1.63 (s, 3H), 1.17 (d, *J* 7.3 Hz, 3H). ^{13}C NMR: 194.8, 157.8, 144.0, 141.7, 141.6, 135.7, 131.2, 130.1, 128.2, 126.0, 125.8 (2C), 112.7, 83.5, 44.0, 34.6, 21.4, 11.8, 10.6. MS (FAB$^+$) *m*/*z*: 355 (100)

[M + 1], 139 (39), 91 (96). HRMS [M + 1]: calcd for $C_{21}H_{23}O_3S$ 355.1362, found 355.1350.

Minor diastereoisomer **10** was not isolated. It was characterized from a 58:42 mixture of **9** and **10**. ^{1}H NMR (representative parameters): 3.16−3.04 (m, 1H), 2.76 (dd, *J* 14.7 and 3.8 Hz, 1H), 2.27 (s, 3H), 1.55 (d, *J* 1.1 Hz, 3H), 1.05 (d, *J* 7.3 Hz, 3H). ^{13}C NMR: 196.7, 158.5, 143.7, 142.0, 141.5, 135.5, 131.1, 130.0, 129.7, 126.1, 126.0 (2C), 112.4, 81.4, 43.4, 32.4, 21.3, 11.4, 9.7. HRMS (ES^+) [M + 1]: calcd for $C_{21}H_{23}O_3S$ 355.1362, found 355.1357.

Reaction with Raney Nickel. General Procedure. An excess of activated Raney nickel was added, at the temperature shown for each case, to a solution of the corresponding pyranone (0.22 mmol) in absolute EtOH (2 mL). The reaction mixture was stirred for the indicated time, prior its filtration through Celite. The solvent was removed under vacuum, and the residue was purified by flash column chromatography with the specified eluent.

(2*R*,4*R*)-2-Benzyltetrahydro-2*H*-pyran-4-ol (20) was obtained as a 89:11 mixture of diastereoisomers **20** and **21**, by treatment of the pyranone **2** with Raney nickel for 5 min at 0 °C, following the general procedure. The residue was purified (combined yield 56%), and the major compound **20** was isolated diastereomerically pure (40%) as a colorless oil, by flash chromatography (ethyl acetate−hexane, 1:1). $[\alpha]^{20}_D$ +15.0 (*c* 1.6, $CHCl_3$). IR (film): 3406, 2922, 2865 and 1069. ^{1}H NMR: 7.24−7.12 (m, 5H), 3.94 (ddd, *J* 11.9, 4.7 and 1.7 Hz, 1H), 3.65 (tt, *J* 10.9 and 4.5 Hz, 1H), 3.41 (dtd, *J* 11.1, 6.4 and 1.9 Hz, 1H), 3.29 (dt, *J* 12.4 and 2.1 Hz, 1H), 2.87 (dd, *J* 13.6 and 6.6 Hz, 1H), 2.62 (dd, *J* 13.7 and 7.0 Hz, 1H), 1.89−1.83 (m, 1H), 1.82−1.76 (m, 1H), 1.50−1.36 (m, OH + 1H), 1.21−1.09 (m, 1H). ^{13}C NMR: 138.2, 129.4, 128.3, 126.3, 77.4, 68.2, 66.0, 42.6, 41.0, 35.6. MS (FAB^+) *m*/*z*: 193 (47) [M + 1], 154 (100), 91 (46). HRMS [M + 1]: calcd for $C_{12}H_{17}O_2$ 193.1228, found 193.1222.

Minor diastereoisomer **21** was characterized from the above mixture. ^{1}H NMR: 7.23−7.12 (m, 5H), 4.15 (m, 1H), 3.95−3.86 (m, 1H), 3.78 (dt, *J* 11.8 and 2.3 Hz, 1H), 3.75−3.68 (m, 1H), 2.80 (dd, *J* 13.8 and 7.0 Hz, 1H), 2.57 (dd, *J* 13.7 and 6.3 Hz, 1H), 1.78 (m, 1H), 1.62−1.44 (m, 3H). ^{13}C NMR: 138.4, 129.4, 128.2, 126.2, 72.5, 64.2, 62.5, 42.7, 38.4, 33.0. MS (EI^+) *m*/*z*: 192 (0.8) [M^+], 174 (3), 101 (100), 91 (45). HRMS (GC-MS-EI^+) [M^+]: calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1164; [M − 18]: calcd for $C_{12}H_{14}O$ 174.1045, found 174.1052.

Compound **22** was obtained, following the general procedure, as the major diastereoisomer (proportion 72%) from the mixture obtained by treatment of the pyranone **6** with Raney nickel for 26 h at room temperature. It was characterized from the above mixture, previously purified by flash column chromatography (ethyl acetate−hexane, 1:1). Combined yield: 66%. IR (film): 3395, 2901, 2845 and 1100. ^{1}H NMR (500 MHz): 7.22−7.12 (m, 5H), 3.79 (dt, *J* 11.3 and 5.0 Hz, 1H), 3.72 (dd, *J* 11.5 and 1.6 Hz, 1H), 3.42 (dd, *J* 11.5 and 2.2 Hz, 1H), 3.42 (dtd, *J* 13.2, 6.6 and 2.2 Hz, 1H), 2.87 (dd, *J* 13.7 and 6.3 Hz, 1H), 2.64 (dd, *J* 13.7 and 6.6 Hz, 1H), 1.87−1.78 (m, 1H), 1.56 (dddd, *J* 12.6, 4.7, 2.2 and 0.9 Hz, 1H, 1.36 (c, *J* 12.6 Hz, 1H), 0.97 (d, *J* 6.9 Hz, 3H). ^{13}C NMR: 138.2, 129.4, 128.3, 126.3, 77.5, 71.5, 70.0, 42.5, 35.1, 35.0, 9.7. MS (FAB^+) *m*/*z*: 207 (22) [M + 1], 205 (37), 91 (100). HRMS [M − 1]: calcd for $C_{13}H_{17}O_2$ 205.1228, found 205.1230.

(2*R*,3*R*)-2-Benzyl-3,5-dimethyl-2,3-dihydro-4*H*-pyran-4-one (23) was obtained by treatment of the pyranone **9** with Raney nickel for 14 h at room temperature, following the general procedure. The residue was purified by flash chromatography (ethyl acetate−hexane, 1:1) to afford pure **23** (77%) as a colorless oil. $[\alpha]^{20}_D$ +87.0 (*c* 1.2, $CHCl_3$). IR (film): 2928, 1667, 1627, 1171. ^{1}H NMR: 7.27−7.16 (m, 5H), 7.09 (s, 1H), 4.19 (ddd, *J* 11.5, 7.8 and 3.8 Hz, 1H), 3.05 (dd, *J* 14.5 and 3.7 Hz, 1H), 2.87 (dd, *J* 14.5 and 7.8 Hz, 1H), 2.33 (dc, *J* 11.4 and 7.0 Hz, 1H), 1.57 (d, *J* 0.9 Hz, 3H), 1.14 (d, *J* 6.9 Hz, 3H). ^{13}C NMR: 195.2, 158.3, 136.7, 129.7, 128.4, 126.7, 112.5, 84.2, 43.0, 38.6, 11.4, 10.7. MS (FAB^+) *m*/*z*: 217 (92) [M + 1], 216 (13), 91 (96). HRMS [M + 1]: calcd for $C_{14}H_{17}O_2$ 217.1228; found 217.1226. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.89; H, 7.83.

Acknowledgment. This investigation has enjoyed the support of the CICYT (Grant BQU2003-04012). M.A.F.-I. is indebted to the Comunidad Autónoma de Madrid for a predoctoral fellowship.

Supporting Information Available: Experimental data of compounds **12**−**19**. NMR spectra of all compounds. ORTEP diagram and CIF files for compounds **2** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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