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Origin of Chiral Induction in Radical Reactions with the Diastereoisomers (5*R*)- and (5*S*)-5-*l*-Menthyloxyfuran-2[5*H*]-one

Siniša Marinković,[†] Cédric Brulé,[†] Norbert Hoffmann,*[,†] Elise Prost,[‡] Jean-Marc Nuzillard,[‡] and Véronique Bulach[§]

Laboratoire des Réactions Sélectives et Applications, UMR (6519) CNRS et Université de Reims Champagne-Ardenne, UFR Sciences, B.P. 1039, F-51687 Reims, Cedex 2, France, Laboratoire d'Isolement, Structure, Transformations et Synthèse de Substances Naturelles, UMR (6013) CNRS et Université de Reims Champagne-Ardenne, UFR Sciences, B.P. 1039, F-51687 Reims, Cedex 2, France, and Laboratoire de Chimie de Coordination Organique (UMR 7513 CNRS) Institut Le Bel, Université Louis Pasteur, 4 rue Blaise Pascal, F-67070 Strasbourg, Cedex, France

norbert.hoffmann@univ-reims.fr

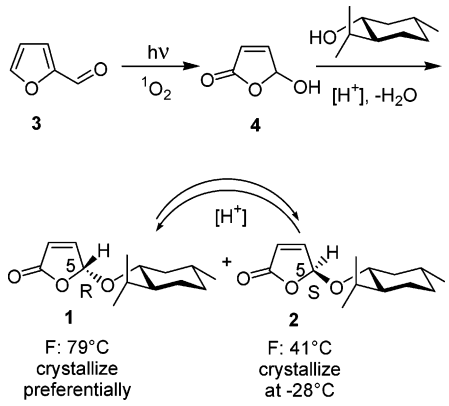
Received September 18, 2003

Acetalization of 5-hydroxyfuran-2[5*H*]-one with *l*-menthol yields (5*R*)- (**1**) and (5*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) in equal amounts. The diastereomer **1** crystallizes preferentially. For the first time, the isolation of pure diastereoisomer **2** is reported. Different diastereoselectivities were observed in the radical tandem reaction of **1** and **2** with *N*,*N*-dimethylaniline. The privileged conformations in solution of the substrates and the products of the radical reaction were then determined, and X-ray crystal structure analyses were carried out on the reaction products. The different stereoselectivities in both cases are explained by different orientations of the menthyloxy substituent.

Introduction

Although catalytic methods[1−3] of chiral induction are actually intensively investigated, stoichiometric methods remain important especially because these strategies reveal to be very flexible (for a review of different chiral auxiliaries, see ref 1). About 25 years ago, the homochiral (5*R*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**1**) (Scheme 1) was synthesized with the aim of application to asymmetric synthesis of chiral insecticides.[4] A large number of functional groups are localized on a minimal number of carbon atoms. Menthyloxyfuran-2[5*H*]-one is also a particular interesting chiral synthon since the two enantiomers are equally well available. The enantiomer **1** possessing the configuration *R* at the chiral acetal center in position 5 is obtained by crystallization when (−)- or *l*-menthol is used as chiral alcohol component while **ent-1** is obtained in the same way when (+)- or *d*-menthol is used.[5,6] The potential of 5-menthyloxyfuran-2[5*H*]-one for a wider application to organic syntheses was recognized sometime later.[7]

SCHEME 1



A large number of ground-state reactions such as Michael reactions,[5,8] cyclopropanations,[9,10] Diels−Alder

[†] Laboratoire des Réactions Sélectives et Applications.
[‡] Laboratoire d'Isolement, Structure, Transformations et Synthèse de Substances Naturelles.
[§] Laboratoire de Chimie de Coordination Organique.

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10.1021/jo030292x CCC: $27.50
Published on Web 02/06/2004

reactions,[11,12] additions of dipole compounds[13] and radicals,[14−16] tandem or domino reactions,[17] *cis*-hydroxylations,[18] and complexation to metal atoms[19] have been carried out often with complete facial diastereoselectivity. Photochemical [2 + 2] cycloaddition which occurs at the excited state of **1** was significantly less diastereoselective[20,21] since the geometry of the excited state of alkoxyfuranones is significantly different from the ground-state geometry.[22]

(5*R*)-5-*l*-Menthyloxyfuran-2[5*H*]-one (**1**) was easily obtained in dia- and enantiopure form due to the high crystallinity of this menthol derivative. Many similar menthyloxy derivatives have been described in the literature. Menthyloxyfuranone derivatives carrying an additional alkyl substituent[21,23,24] or halogen atoms at the double bond[10,25] have been obtained in enantiopure form. Sulfonyl or sulfinyl substituents in these positions are sometimes necessary to enhance the reactivity.[26] Menthol seems to contribute significantly to the high crystallinity of one diastereomeric acetal. All attempts to replace it by another enantiopure alcohol were not successful.[12,27] In some of these cases, however, the diastereomers could be separated by chromatography.

For the first time, the present publication reports the isolation of (5*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**). Despite numerous applications to asymmetric organic synthesis, only few publications give a deeper insight into the origin of chiral induction of **1** or **ent-1**. One major question which frequently arises deals with the influence of the menthyloxy substituent, and many alternatives are proposed. The following study reveals the influence of the chiral acetal function on one hand and the menthyl moiety on the other hand, on the diastereoselectivity of the tandem addition cyclization reaction of **1** and **2** with tertiary aromatic amines.

Results and Discussion

(5*R*)-5-*l*-Menthyloxyfuran-2[5*H*]-one (**1**) was synthesized in two steps (Scheme 1). Photooxygenation of furfural **3**[28] provided 5-hydroxyfuran-2[5*H*]-one **4** in high yield (91%). The reaction was preferentially carried out in methanol as solvent. During the reaction and when the solvent was evaporated, care was taken to maintain the temperature under 35 °C so that to acetalization with methanol was avoided.[29] Acetalization with (−)-menthol yielded the two diastereomers (5*R*)- (**1**) and (5*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) with a ratio of about 1/1. When the recrystallization from petroleum ether was carried out at about 4 °C or at room temperature, only the (5*R*)-diastereoisomer **1** was isolated.[30] This isomer was mostly applied to organic synthesis. Especially in the case when the crystallization is carried out in the presence of traces of acid, **2** is progressively transformed into **1** as far as the latter crystallizes.[5] In this way, only one stereoisomer of 5-menthyloxyfuran-2[5*H*]-one is obtained. However, when the crystallization was performed from petroleum ether at −28 °C, two forms of crystals were observed. Small needles possessing a melting point of 79 °C were isolated as the major product and correspond to structure **1**. Aside from this isomer, more massive crystals could be picked out in gram scale. These crystals with a melting point of 41 °C possess a size between 2 mm and 2.5 cm and correspond to structure **2**. They have been picked out with tweezers or have been recovered by passing the crystal mixture through a sieve. Some characteristic NMR data are also given in the Supporting Information.

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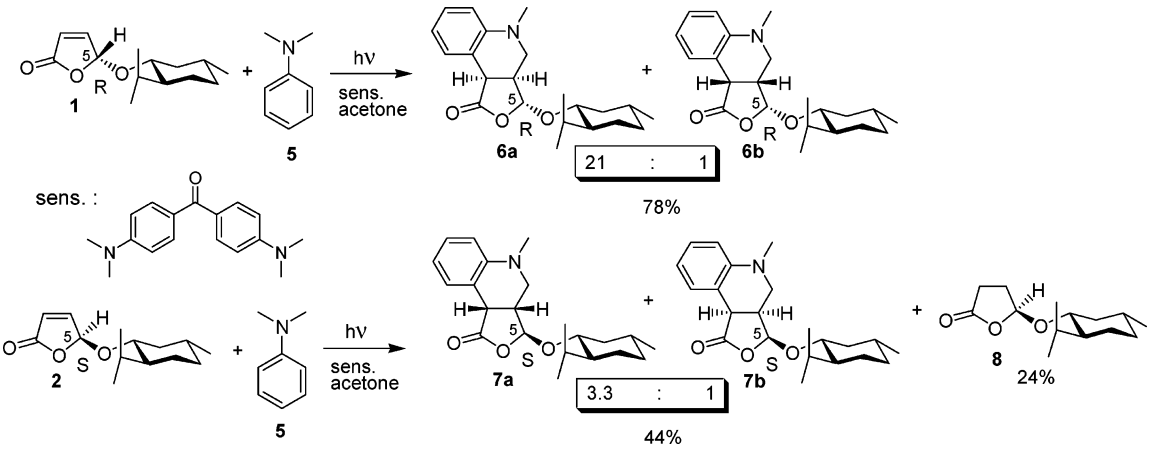
(30) The diastereoismer **ent-1** possessing the *S* configuration at the acetal center can be obtained via the same procedure using *d*-menthol as chiral substrate.

SCHEME 2



These observations suggest that the formation of crystal germs at low temperature is faster for the isomer **1** than for **2**. The crystal growth, however, seems to be faster for **2** than for **1**. The crystals of **1** are stable at room temperature while those of **2** are less stable. After ~2 months, we observed small needles growing slowly on the surface of these crystals even when they were stored at 4 °C. **2** is transformed slowly into **1**, which indicates that the metastability of crystalline **2** is rather low. Nevertheless, they were sufficiently stable to perform studies with this menthyloxyfuranone isomer. Such crystalline-induced dynamic resolution are well-known, and some of them have even been applied at industry scale.[3,31−34] It should be mentioned that the crystallization must be carried out in absence of any trace of acid. Otherwise, only crystals of **1** are recovered even at low temperature. Apparently, the acid-catalyzed epimerization of **2** is too fast to permit its crystallization.

When diastereoselective reactions with (5*R*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**1**) are studied, the question frequently arises what is the contribution of the menthyl group to chiral induction. Having the two stereoisomers (*R*)- (**1**) and (*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) in hand, we decided to determine the part of chirality induced by the acetal and that one induced by the menthyl moiety. According to the concept of double induction,[35] these two elements could constitute a matched and a mismatched pair in the isomers **1** and **2**.[36]

SCHEME 3. Mechanism of the Tandem Addition−Cyclization Reaction and the Competing Partial Reduction of 1 or 2

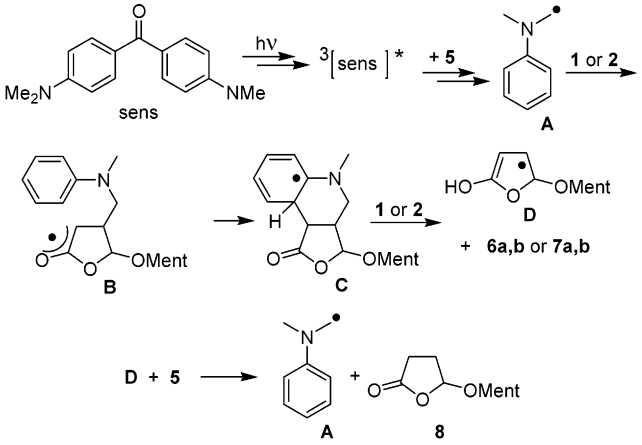
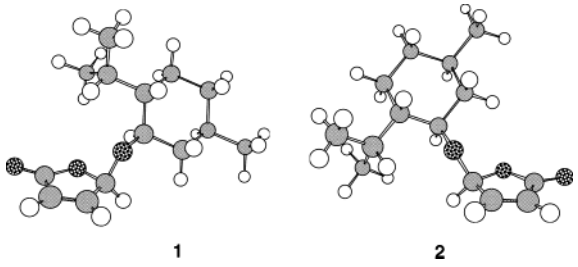


CHART 1. Privileged Conformations Obtained by NOESY Measurements and Modelization



To examine this hypothesis, we have chosen the diastereoselective radical tandem addition cyclization reaction with *N*,*N*-dimethylaniline **5**. As we have recently reported in the case of **1**, this reaction could be efficiently carried out under the conditions of photochemical induced electron transfer using electron-donor-substituted aro-

(31) These crystalline-induced dynamic resolutions are also named asymmetric transformation of second order or second kind while the corresponding reactions in solution are called asymmetric transformation of first order or first kind.

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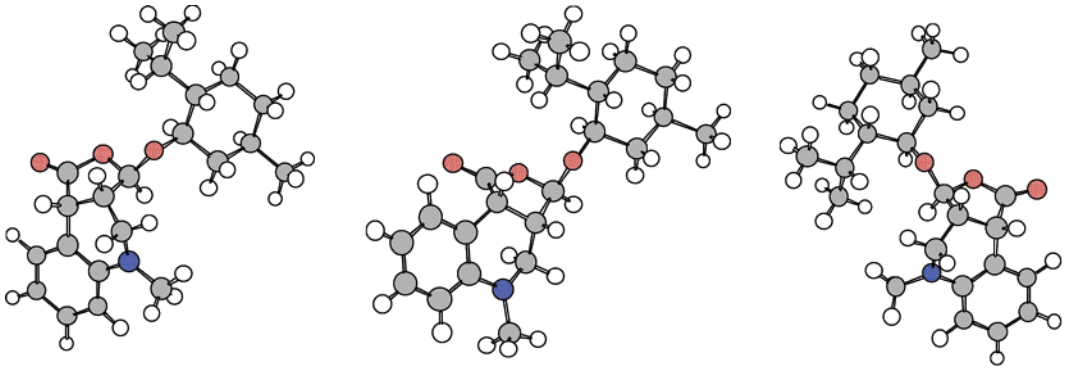
(36) It should be noted that the concept of double induction was mainly developed for cases where chiral information is localized on the two reaction partners. Nevertheless, the concept should be applicable for cases where the two elements of chiral induction are located only on one substrate as far as the two corresponding diastereomers are investigated. For corresponding examples, see: Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.

CHART 2. Privileged Conformations Obtained by NOESY Measurements and Modelization



matic ketones (e.g., Michler's ketone) as sensitizer (Scheme 2).[16,37] When the reaction was performed with (*R*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**1**), the tetrahydroquinoline derivatives **6a**,**b** were isolated with a diastereomeric ratio of 21/1 (91% de). X-ray structure analysis of the major compound **6a** indicated that the radical attack of the intermediately formed α-aminoalkyl radicals **A** (Scheme 3) added preferentially anti with respect to the menthyloxy substituent.[37] The resulting electrophilic oxoallyl **B** radical then added rapidly with the electron rich aromatic ring. The resulting intermediate **C** underwent rearomatization to yield the final products **6a,b**. This oxidation step was accompanied with the partial reduction of **1** which lead to the formation of **8**. We completely suppressed this side reaction by adding ketones such as acetone to the reaction mixture (for mechanistic details see ref 16). Now, we have carried out the reaction with (*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) under the same conditions. Once again, the radical attack occurred preferentially anti with respect to the menthyloxy substituent. However, the major tetrahydroquinoline derivative **7a** was only obtained in a ratio of about 3:1 (53% de) with the isomer **7b** resulting from the opposite radical attack. Furthermore, the yield of tetrahydroquinolines was lower and the side product **8** resulting from the partial reduction of **2** was also obtained (compare Scheme 3).

To explain these results, we have carried out a conformational analysis of both diastereoisomers **1** and **2** by NMR. Using the quantitative NOESY technique, we were able to determine interatomic distances around the acetal function. On the basis of these values, a modeling of **1** and **2** was carried out using MM3 calculations and Monte Carlo type of conformational analysis. One thousand starting geometries with randomly drawn diedral angles were submitted to geometry optimization. The preferential conformations are shown in Chart 1. In both cases, one face of the flat furanone ring is sterically hindered by the chiral acetal function. Nevertheless, the olefinic moiety remains free for attack of a reaction partner in the *β*-position. The main difference between the two diastereoisomers results from the orientation of the menthyl moiety. In the case of **1**, the isopropyl substituent reaches into the encumbered face, while in the preferential conformation of **2**, only a CH_2 group of the menthyl ring is placed in the hindered face. The methyl group in position 5 is directed in a concave manner and does not have a significant influence on the stereoselection.

To check whether these steric effects are really the main cause of the stereoselectivity, we have performed the same kind of structural analysis on the main products **6a** and **7a** of the tandem addition cyclization reaction (Scheme 2). The results are shown in Chart 2. In **6a** as well as in **7a** the orientations of the menthyl substituent in the privileged conformations are almost identical with those ones of the in the privileged conformations of the corresponding substrates **1** and **2**. In the case **6a**, two conformations of almost equal energy were found from modeling which was guided by the atom distances obtained from NOESY measurements. The differences result from the orientation of the CH_2 group of the tetrahydroquinoline moiety. In structure **6a**, it is turned anti with respect to the acetal function while in structure **6a′** it is turned in a syn position. As a consequence, the tetrahydrofuranone possesses different envelope conformations. However, these differences have no significant influence on the orientation of the mentyl subsituent.

X-ray structure analysis of compounds **6a** (see ref 37) and **7a** could be carried out, and we wondered whether the orientations of the menthyl substituent in the crystal resembled those ones in solution. The results of these analysis are shown in the supporting material. The scalar properties of the diastereoisomers are mainly determined by the relative configuration near the chiral centers of the acetal function of the furanone moieties and the C1′ of the mentyl substituent. The characteristic parameters: distances H5−H1′, H5−H6′eq and H5−H7′ and the torsion angle of H5−C5−C1′−H1′ are given in the Supporting Information. There are very similar orientations of the menthyloxy substituent of **1** in solution and the corresponding products **6a** (or **6a′**) in solution and in the crystal. The same observation is made for **2** and **7a** in solution and the crystal. However, significant differences in the orientation of the menthyloxy substituent are observed for structures resulting from the diastereomer **1** and structures resulting from **2**. Due to the similarity of conformations in the substrates and the corresponding products, we suppose that very similar conformers should exist in the transition state of the addition of the α-aminoalkyl radical **A** to **1** or **2** (Scheme 3) leading to the intermediate **B**. A modification of the

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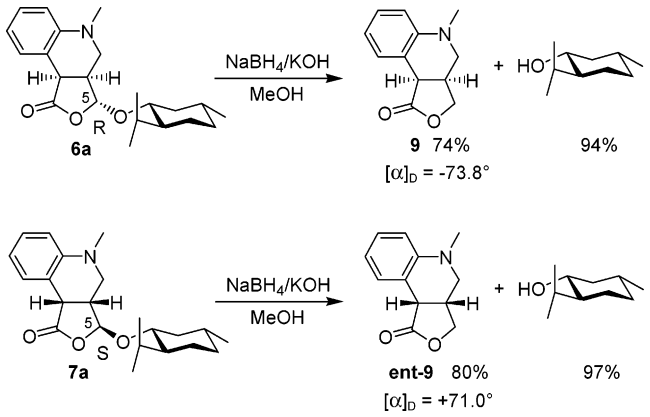
SCHEME 4



stereoselectivity by an eventual reversibility of this step should be negligible since intermediate **B** reacts rapidly via intramolecular addition of the electrophilic oxoallyl radical to the electron- rich aniline moiety.[38,39] The difference of stereoselectivity in the radical tandem addition cyclization reaction of *N*,*N*-dimethylaniline **5** with the diastereoisomers **1** and **2** of menthyloxyfuran-2[5*H*]-one may be explained essentially by the steric hindrance in two different conformations. In this context, the observed stereoselectivity do not fit with the assumptions made for the Curtin−Hammett principle.[33,40]

As mentioned above, the chirality is induced by two elements, the acetal center and the menthyl substituent. In the context of double induction,[35] these two elements constitute a matched pair in the case of **1** and a mismatched pair in the case of **2**. The dominant factor is the acetal function since the attack of the α-aminoalkyl radical occurs preferentially anti with respect to the menthyloxy substituent. A minor part of the chirality is induced by the menthyl moiety. If we consider that the observed stereoselectivity results from the sum of both effects according to the concept of double induction, about 70% of the chiral induction results from the acetal and 30% from the menthyl moiety (based on the corresponding $\Delta\Delta G^{\ddagger}$ values which are obtained according to refs 33, 35, 40).

To demonstrate an application in asymmetric synthesis, the major isomers **6a** and **7a** were transformed into the corresponding enantiomeric tetrahydroquinolines **9** and **ent-9** (Scheme 4). The chiral auxiliary is removed via $NaBH_4$ reduction. The opposite optical rotatory power of the products gave further support for the configurations of **6a** and **7a**.

Conclusion

In summary, the (5*R*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**1**) diastereoisomer (or (5*S*)-5-*d*-menthyloxyfuran-2[5*H*]-one (**ent-1**)) can easily be isolated in pure form by crystallization as described in the literature. By applying particular crystallization conditions, we have also isolated the diastereomer (5*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) in pure form. In contrast to the expectation that chiral induction only occurs by the acetal center, we observed significantly different diastereoselectivities in the radical reactions of **1** or **2** with the amine **5**. A conformational analysis of the substrates **1** and **2** as well as of the major products **6a** and **7a** of the radical reaction indicated that the diastereoselectivity of the investigated reaction can be explained by the privileged conformations of **1** and **2** in which the facial hindrance is significantly different. Concerning two elements of chiral induction, it is concluded that the acetal function contribute mainly to the chiral induction (∼70%) while the menthyl moiety contributes to a minor degree (∼30%).

Experimental Section

(5*R*)-5-*l*-Menthyloxyfuran-2[5*H*]-one (1) and (5*S*)-5-*l*-Menthyloxyfuran-2[5*H*]-one (2). A solution of 5-hydroxyfuran-2[5*H*]-one (**4**) (110 g), (−)-menthol (17 2 g), and catalytic amounts of *p*-toluenesulfonic acid in toluene (1 L) were heated under reflux with a Dean−Stark apparatus until water separation ceased (after about 10 h). The reaction solution was washed with a saturated solution of $NaHCO_3$ and water. The organic phase was separated and dried with $MgSO_4$. After evaporation of the toluene, the residue was crystallized from petroleum ether (500 mL) at −28 °C. The crystals were washed with a small amount of cooled petroleum ether. The large crystals of **2** were picked out with tweezers. Smaller crystals of **2** were separated by passing the crystal mixture through a sieve. The needle formed crystals were recrystallized from petroleum ether. Yield of **2**: 14.2 g (5%). Yield of **1**: 107.1 g (41%). Further fractions of **1** were recovered by the ordinary crystallization process at 4 °C.

1: mp 79 °C; $[\alpha]^{24}_{D} = -135.4$, $[\alpha]^{24}_{578} = -140.5$, $[\alpha]^{24}_{546} = -159.1$, $[\alpha]^{24}_{436} = -269.8$, $[\alpha]^{24}_{365} = -428.5$ ($c = 0.948$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, $J = 1.1, 5.7$ Hz, 1H), 6.21 (dd, $J = 1.1, 5.7$ Hz, 1H), 6.09 (t, $J = 1.1$ Hz, 1H), 3.66 (dt, $J = 4.5, 10.5$ Hz, 1H), 2.16 (m, 1H), 2.12 (dsep, $J = 2.5, 7.0$ Hz, 1H), 1.67 (m, 2H), 1.41 (m, 1H), 1.26 (ddt, $J = 13.2, 10.5, 2.5$ Hz, 1H), 0.99 (m, 1H), 0.96 (m, 1H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 3H), 0.83 (m, 1H), 0.80 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.8, 150.9, 124.8, 100.4, 79.1, 47.7, 40.3, 34.1, 31.4, 25.3, 23.1, 22.2, 20.8, 15.7$. Anal. Calcd for $C_{14}H_{22}O_3$ (238.3): C, 70.59; H, 9.24. Found: C, 70.33; H, 9.59.

2: mp 41 °C; $[\alpha]^{24}_{D} = -19.6$, $[\alpha]^{25}_{578} = -20.2$, $[\alpha]^{25}_{546} = -22.9$, $[\alpha]^{25}_{436} = -35.6$, $[\alpha]^{25}_{365} = -41.1$ ($c = 0.950$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, $J = 1.0, 5.7$ Hz, 1H), 6.18 (dd, $J = 1.0, 5.7$ Hz, 1H), 5.94 (s, 1H), 3.50 (dt, $J = 4.4, 10.5$ Hz, 1H), 2.23 (m, 1H), 2.10 (dsep, $J = 2.5, 7.0$ Hz, 1H), 1.63 (m, 2H), 1.38 (m, 1H), 1.27 (ddt, $J = 13.3, 10.5, 2.5$ Hz, 1H), 1.04 (dd, $J = 10.5, 12.2$ Hz, 1H), 0.98 (m, 1H), 0.90 (d, $J = 7$ Hz, 6H), 0.82 (m, 1H), 0.79 (d, $J = 7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 150.3, 124.6, 104.5, 82.9, 48.0, 42.4, 34.0, 31.5, 25.6, 23.1, 22.1, 20.8, 16.2; IR (KBr) $\nu = 3496, 3088, 2955, 2924, 2867, 1795, 1752, 1456, 1134, 1011, 899$ cm^{-1}; MS (EI) m/z 239 [$M^+ + 1$] (40), 221 (6), 153 (21), 139 (100), 123 (38), 109 (19). Anal. Calcd for $C_{14}H_{22}O_3$ (238.3): C, 70.59; H, 9.24. Found: C, 70.27; H, 9.63.

Tetrahydroquinoline Derivatives (6a,b). These products were obtained as previously described.[16]

Tetrahydroquinoline Derivatives (7a,b). A solution of (5*S*)-5-*l*-menthyloxyfuran-2[5*H*]-one (**2**) (420 mg), *N*,*N*-dimethylaniline, 4,4′-bis(dimethylamino)benzophenone (40 mg), and acetone (2 mL) in acetonitrile (30 mL) was placed in Pyrex tubes (1.7 cm diameter). After being degassed with argon, the

(38) For a discussion of chiral induction in multistep reactions, see: (a) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. (b) Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567.

(39) For the contribution of polar effects in radical reactions, see: (a) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340. (b) Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401. (c) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. (c) Roberts, B. *Chem. Soc. Rev.* **1999**, *28*, 25.

(40) Nasipuri, D. *Stereochemistry of Organic Compounds*; J. Wiley & Sons: New York, 1991.

solution was irradiated for 8 h in a Rayonet apparatus The solvent was evaporated, and the residue was subjected to flash chromatography (ethyl acetate/petroleum ether). A fraction of 180 mg of pure **7a** was isolated. Another fraction of 98 mg contained **7a** and **7b** in ratio of 1/2. (Yield of **7a**,**b**: 44%). The diastereoselectivity was also determined from unseparated mixture. Yield of **8**: 100 mg (24%). **7a**: mp 147 °C; $[\alpha]^{24}_{D} = +91.3$, $[\alpha]^{25}_{578} = +94.1$, $[\alpha]^{25}_{546} = +104.3$, $[\alpha]^{25}_{436} = +138.1$, $[\alpha]^{25}_{365} = +29.2$ ($c = 1.012$, CH_2Cl_2).

Tetrahydroquinoline Derivatives (9 and ent-9). Preparation and characterization are given in the Supporting Information.

Crystal Structure Characterization of 7a. The crystal structure of **6a** has already been reported.[37] Data for **7a** are given in the Supporting Information and deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-212034 (excluding structure factors).

Acknowledgment. S.M. thanks the Ministère de la Recherche for a doctoral fellowship. We are particularly grateful to Etienne Derat (UMR 6519, Modélisation et Réactivité Chimique) for his help with format transformations of graphical files. This work was funded by the CNRS and the Deutsche Forschungsgemeinschaft in the context of a French German bilateral research project.

Supporting Information Available: General methods of the Experimental Section; synthesis of **4**; parts of the ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** and a table with characteristic chemical shifts; spectroscopic data of **7a**,**b** and **8**; X-ray experimental data for compound **7a**; a Table with characteristic structural parameters obtained from NMR data or X-ray structure analysis from **1**, **2**, **6a**, and **7a**; ^{1}H and ^{13}C NMR spectra of compound **8**; ORTEP representations of X-ray structures of **7a** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030292X