JOC Article

Conformational Studies by Dynamic NMR. 98.[1] Stereodynamics of Bond Rotation in β-Hydroxyesters

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The dynamic processes due to restricted intramolecular motions have been observed in a number of variously substituted β-hydroxyesters by variable-temperature NMR spectroscopy. The barriers for three such processes (i.e. Ph−C, *t*-Bu−C, and $C_\alpha-C_\beta$ bond rotation) have been measured.

In a previous paper we had investigated the stereodynamic processes occurring in some representative amino alcohols and their amide precursors.[2] If the amide moieties are replaced by ester groups, compounds **1**−**4** are obtained: *t*-BuPhC(OH)−CHMeCOOR, R = Ph (**1**), *t*-Bu (**2**), Et (**3**), and *i*-PrPhC(OH)−CHMeCOOEt (**4**).

These β-hydroxyesters can be prepared either through a stereoselective aldol condensation of a propionic ester enolate with the appropriate ketone (*tert*-butyl or isopropyl phenyl ketone) or through a nucleophilic transfer of a *tert*-butyl or isopropyl moiety to an α-methyl-substituted β-ketoester. The latter strategy was preferred to avoid the severe steric hindrance involved in the former approach. The highly stereoselective protocol, successfully applied to ketoamides[3] and related systems,[4] was used in the present case. For instance, treatment of the phenyl 2-methyl-3-oxo-3-phenylpropanoate **5** with $TiCl_4$ yields the rigid cyclic chelate intermediate, which offers a high stereofacial discrimination to an attacking carbon nucleophile. Addition of the *t*-BuMgBr·$CeCl_3$ complex results in the stereoselective (de > 97) formation of **1**, as shown in Scheme 1. Likewise, derivatives **2**−**4** were prepared by reacting the appropriate cerium complex with the appropriate propanoate (see the Experimental Section).

As in the case of the amides previously investigated, these esters should display the effects of restricted rotation about the Ph−C and the *t*-Bu−C bonds. Conformers of different stability might also result from restricted rotation about the bond connecting the carbons in the α and β positions, i.e., C(OH)−CHMe. The investigation of these three dynamic processes constitutes the subject of the present work.

Preliminary to this study, however, must be the unambiguous assessment of the stereoconfiguration of these compounds: the presence of two asymmetric carbon centers entails in fact the possible existence of two pairs of diastereoisomers, i.e., the racemic *R*,*R S*,*S* or the racemic *R*,*S S*,*R*. As mentioned, the synthetic procedure employed here is completely stereoselective, so that only one of the two possible diastereoisomers is available.

MM calculations[5] for phenyl 3-hydroxy-2,4,4-trimethyl-3-phenylpentanoate indicate that in both diastereoisomers an intramolecular hydrogen bond occurs between the OH and the C═O moieties, yielding a six-membered ring, as shown in Scheme 2.

In the *R**,*R** diastereoisomer the *tert*-butyl and the methyl groups lie on the same side of this ring (Scheme 2, right) whereas in the *R**,*S** diastereoisomer (Scheme 2, left) they lie on the opposite side: the reverse situation obviously applies to the methine hydrogen. In the case of the *R****,***S** diastereoisomer the MM computed averaged distance between the three methyl hydrogens and the nine *tert*-butyl hydrogens is too large (5.6 Å) to yield a noticeable NOE effect, whereas the distance between the hydrogens of the *tert*-butyl and that of the methine (3.9 Å) is compatible with the detection of a substantial NOE effect. In the case of the *R**,*R** diastereoisomer these distances would obviously follow an opposite trend, thus reversing the expectation for the observable NOE effects.

In Figure 1 a number of NOE experiments (DPFGSE-NOE sequence[6]) are reported for compound **1** at −75 °C. Such a low temperature had to be used to freeze the Ph−C bond rotation on the NMR time scale (see further) to avoid the saturation transfer effects.[7] Saturation of the CH quartet signal (trace b) enhances the *tert*-butyl single line (obviously NOE is also experienced by the OH and CH_3 signals) and, conversely, saturation of the *tert*-butyl

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[1] Part 97: Casarini, D.; Grilli, S.; Lunazzi, L.; Mazzanti A. *J. Org. Chem*. **2004**, *69*, 345.

[2] Bartoli, G.; Grilli, S.; Lunazzi, L.; Massaccesi, M.; Mazzanti, A.; Rinaldi, S. *J. Org. Chem*. **2002**, *67*, 2659.

[3] Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett*. **2001**, *42*, 6093.

[4] Bartoli, G.; Bosco, M.; Di Martino, E.; Marcantoni, E.; Sambri, L. *Eur. J. Org. Chem*. **2001**, 2901.

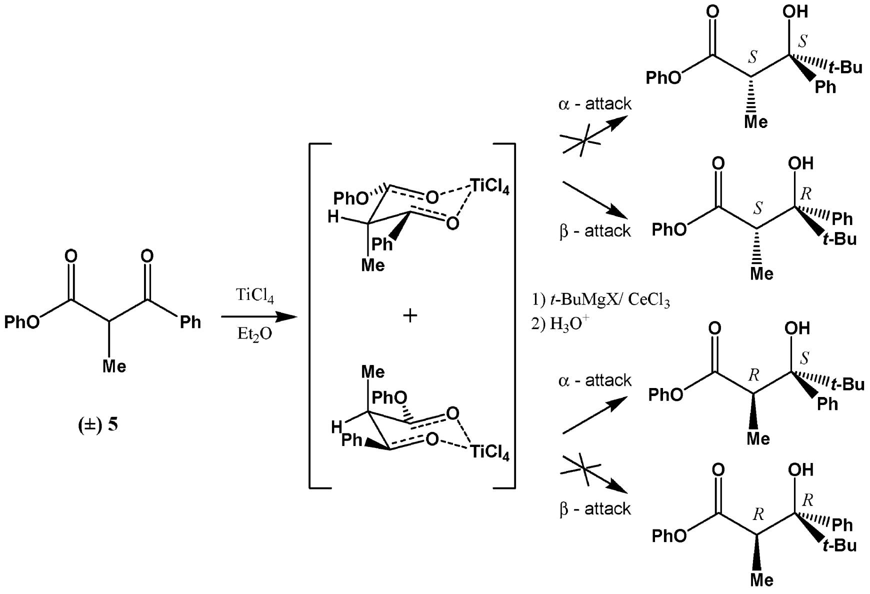
[5] MMX force field as implemented in the computer package PC Model v 7.5, Serena Software, Bloomington, IN. A dielectric constant of 1.5 has been used.

[6] Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc*. **1994**, *116*, 6037. Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc*. **1995**, *117*, 4199. Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson*. **1997**, *125*, 302. Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Reson*. **1999**, *141*, 191.

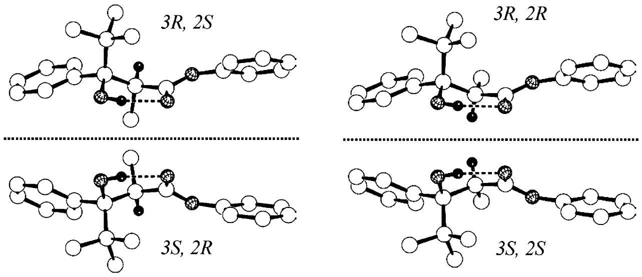
[7] Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; Chapter 5.

10.1021/jo0355754 CCC: $27.50

SCHEME 1



SCHEME 2. Computed Structures of the Possible Stereoisomers of *t*-BuPhC(OH)−CHMeCOOPh[a]



[a] The hydrogen atoms are omitted, except those of the OH and CH moieties (black atoms); the carbon and the oxygen atoms are white and gray, respectively.

single line (trace d) enhances the CH quartet but not the CH_3 doublet signal (consistently, saturation of the latter signal, as in trace c, does not enhance the *tert*-butyl line). All these experiments thus agree in assigning the *R**,*S** structure to compound **1**. This assignment could be confidently transferred to compounds **2** and **3** since they were obtained with the same stereoselective reaction.

The tridimensional energy map of **1**, computed[5] as a function of the *t*-Bu−C and Ph−C rotation angles, suggests that the two motions are not correlated but occur independently of each other: the corresponding barriers are calculated to be 4.6 and 19.8 kcal mol^{-1}, respectively (see the Supporting Information). The same calculations predict a barrier with an intermediate value of 10.0 kcal mol^{-1} for the rotation process about the C_α−C_β bond. Essentially the same values were computed for **2** and **3**. Even allowing for the approximations involved in the MM computational approach of the barriers, their trend should parallel that of the real values. Such a trend might be experimentally determined since the corresponding rotation rates are expected to lie in a range compatible with the NMR lifetime.

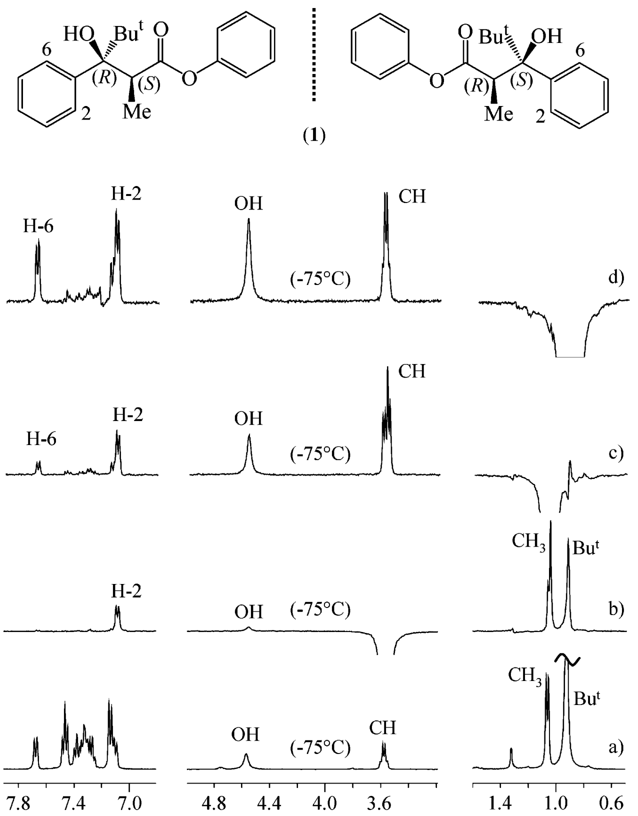


FIGURE 1. ^{1}H NMR spectrum (400 MHz in CD_2Cl_2) of compound **1** at −75 °C (trace a). The NOE experiments were obtained at the same temperature by saturating the CH quartet (trace b); the Me doublet (trace c) and the *tert*-butyl singlet (trace d) are also displayed.

The ^{13}C NMR spectrum of the aromatic region of **3** at −43 °C (Figure 2) actually shows two lines for the ortho (128.1 and 126.6 ppm), two lines for the meta (127.75 and 126.8 ppm), and one line (126.45 ppm) for the para carbons.[8] On raising the temperature the latter line

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[8] Unambiguous assignment of the ortho and meta lines was obtained by means of a gHSQC sequence (see: Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon: Oxford, UK, 1999; Chapter 6) carried out at −43 °C, as reported in the Supporting Information.

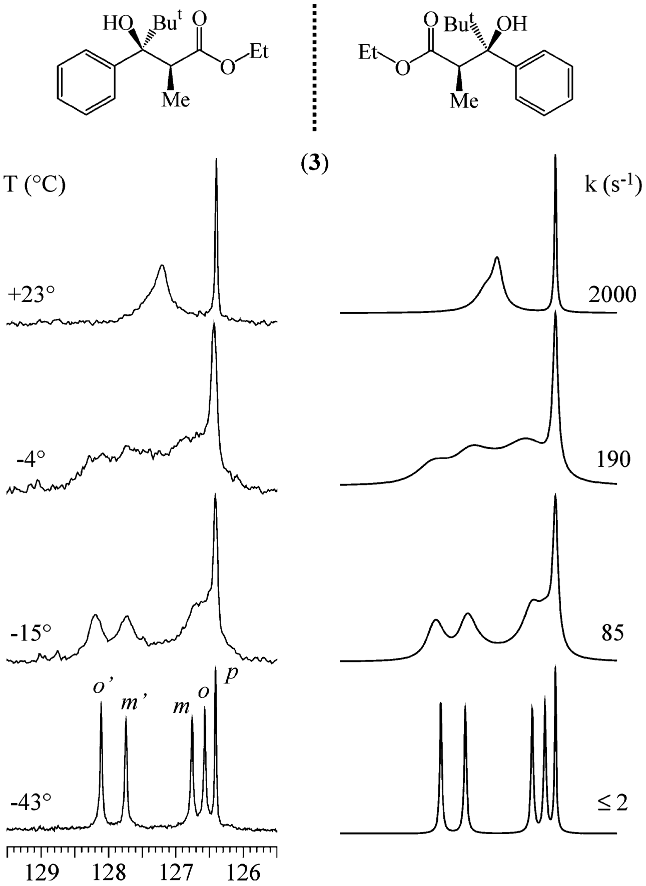

FIGURE 2. Temperature dependence (left) of the aromatic ^{13}C NMR signals (100.6 MHz in CD_2Cl_2) of compound **3**. On the right the spectra simulated with the rate constants indicated are reported.

TABLE 1. Barriers ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Dynamic Processes Measured in 1−4

compd	Ph−C rotation[a]	*t*-Bu−C rotation[a]	$C_{\alpha}-C_{\beta}$ rotation[b]
1 (R = Ph)	12.8	6.8	8.7
2 (R = *t*-Bu)	13.0	7.1	9.0
3 (R = Et)	12.8	7.1	9.1
4	11.3		7.7

[a] Estimated error ±0.15 kcal mol^{-1}. [b] Estimated error ±0.25 kcal mol^{-1}.

remains sharp whereas the others broaden and coalesce, eventually yielding one line for the ortho and one line for the meta carbons. At ambient temperature, however, these two lines are still too broad to be resolved and only at +60 °C (in tetrachloroehtylene) do they become distinguishable. Computer line shape simulations (Figure 2, right) provided the rate constants for the rotation about the Ph−C bond at various temperatures: from these values the corresponding barrier was obtained ($\Delta G^{\ddagger} = 12.8 \pm 0.15$ kcal mol^{-1}, as in Table 1). As is often observed in conformational processes[9] the free energy of activation is independent of temperature within the experimental errors, thus suggesting a negligible $\Delta S^{\ddagger}$ value.

The relatively high barriers observed for the phenyl−C bond rotation in **1−3** are most likely due to the steric effect exerted by the bulky *tert*-butyl substituent. This could be proved by substituting the *tert*-butyl with an isopropyl group, as in *i*-PrPhC(OH)−CHMeCOOEt, **4**.

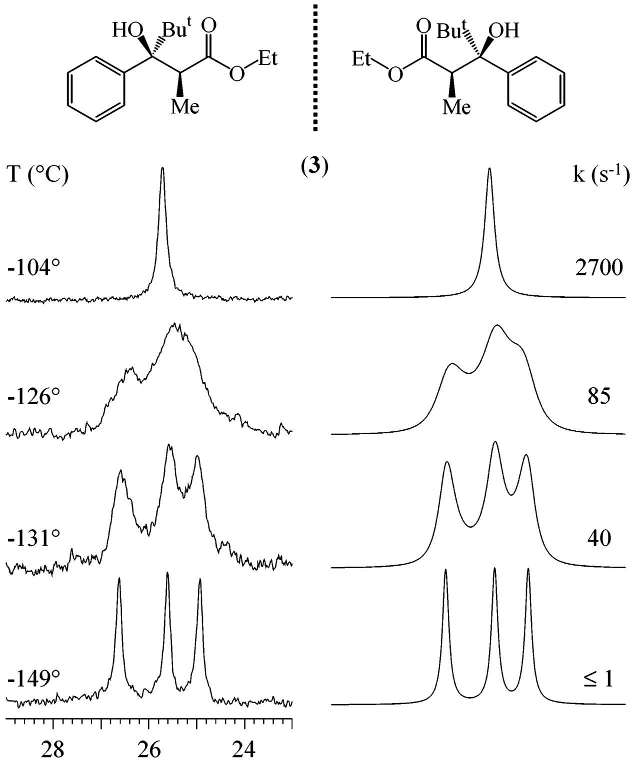

FIGURE 3. ^{13}C NMR spectrum (100.6 MHz in CHF_2Cl) of the *tert*-butyl methyl group of **3** as function of temperature (left). On the right the simulated spectra are reported.

The same configuration as for **1** was assigned to this compound since the same stereoselective reaction had been employed for the synthesis (it should be noted, however, that the configuration of **4** must be indicated as *R**,*R** owing to the change in the priority of the substituents). Due to the smaller steric effect of the isopropyl with respect to the *tert*-butyl substituent, the rotation barrier of the phenyl group in **4** (11.3 ± 0.15 kcal mol^{-1}) was found to be about 1.5 kcal mol^{-1} lower than that of the corresponding derivative **3** (Table 1).

The predictions of the MM calculations reported above and the values measured in the analogous amides[2] agree in indicating that the *tert*-butyl rotation barrier should be significantly smaller than that involving the phenyl group: the ^{13}C spectra were therefore investigated in CHF_2Cl to attain the much lower temperatures required for detecting this second dynamic process. As shown in Figure 3, for instance, only below −130 °C could three anisochronous lines be observed for three methyl carbons of the *tert*-butyl group of **3**.

The rate constants obtained by line shape simulation (Figure 3, right) yield a barrier for the *tert*-butyl rotation

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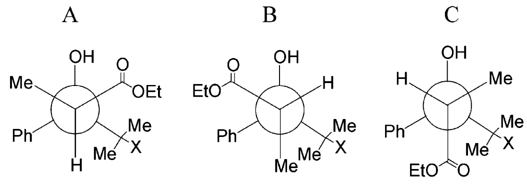
(9) Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484. Bernardi, F., Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron*, **1977**, *33*, 1337. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031. Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1992**, *114*, 6521. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4923.

SCHEME 3 [a]



3 (X=Me)	(E = 0)	(E = 3.7)	(E = 9.0)
4 (X=H)	(E = 0)	(E = 4.2)	(E = 7.1)

[a] The computed[5] relative energies (E) are in kcal mol^{-1}.

equal to 7.1 ± 0.15 kcal mol^{-1}, a smaller value than that found for the phenyl group, as anticipated by calculations. Essentially the same values, as imagined, were found for the analogous compounds **1** and **2** (Table 1).

As mentioned, the third dynamic process that might be detected in this type of molecule is the restricted rotation about the $C_\alpha-C_\beta$ bond. Such a process gives rise to three rotamers, shown in Scheme 3 for the case of derivatives **3** and **4**. The two synclinal rotamers (A and B of Scheme 3) are stabilized by the possibility of hydrogen bonding between the OH and the CO moieties: they are thus expected to be more stable than the third one (antiperiplanar, C) where the H-bonding cannot take place. MM calculations[5] also indicate that A is much more stable[10] than B since the latter experiences a more crowded situation, due to the fact that the methyl group lies between the phenyl and the *tert*-butyl (**3**) or the isopropyl (**4**) substituent. The dynamic process thus corresponds to the exchange between two synclinal rotamers (A and B) with different population; the antiperiplanar rotamer C, on the other hand, is so much less stable that it is expected not to be populated at all.

In the case of derivative **3** we observed indeed that a number of ^{13}C signals (notably those of the CO, CH_α, and C_α-bonded methyl carbons) broadened below ambient temperature and, after having reached a maximum width, sharpened again when the temperature was further lowered, the effect being most evident for the CH_α carbon signal (see the Supporting Information). Such behavior is typical for an exchange process between two very biased species:[11−13] In the present case the population of rotamer B was so low that we could not even observe the corresponding spectrum. On the basis of the signal-to-noise ratio, measured at about −130 °C in a CHF_2Cl solution,[14] it was possible to infer that the population must be lower than 4%.[15] The maximum incremental line-width broadening ($\Delta\omega$), measured at 100.6 MHz for the exchanging CH_α line of **3**, is 26 Hz at −82 °C in CHF_2Cl. The appropriate formula ($k = 2\pi\Delta\omega$)[12] provides the rate constant (k =163 s^{-1}) for the interconversion of the major into the minor conformer. This value corresponds to a barrier ($\Delta G^\ddagger = 9.1 \pm 0.25$ kcal mol^{-1}, Table 1) compatible with the range expected for rotation processes involving sp^3-sp^3 carbon bonds in similarly hindered compounds.[16]

An analogous behavior was observed in the spectra of compounds **1** and **2,** where the population of the minor rotamer was, again, too low to be detected. The corresponding interconversion barriers were found equal to that of **3** within experimental error (Table 1). This is quite understandable since the substituents R of the −COOR moiety (i.e. R = Ph, *t*-Bu, Et in **1**, **2, 3**, respectively) are too far away to significantly affect this rotation process. The interconversion barriers measured in **1**−**3** are intermediate between those due to the Ph−C and *t*-Bu−C bond rotation, in agreement with the trend previously predicted by MM calculations.[5]

In the case of **4** the maximum line-width broadening, due to the restricted $C_\alpha-C_\beta$ bond rotation, occurred at a lower temperature (−103° C) and was much larger than that in the corresponding lines of **1**−**3**, thus suggesting a lower interconversion barrier and a greater proportion of the minor conformer.[17] At −140 °C we could detect, as a consequence, a number of ^{13}C signals due to the minor conformer **4B** of Scheme 3 in a 9% proportion: as an example, the temperature dependence of the lines of the two methine carbons are reported in Figure 4. The knowledge of the chemical shift separation and of the relative population[18] allowed a total line shape analysis to be carried out. The value for the interconversion barrier obtained in this way (7.7 kcal mol^{-1}) agrees with that derived[17] from the formula that makes use of the maximum line-width broadening.

The $C_\alpha-C_\beta$ rotation barrier measured in **4** is at least 1 kcal mol^{-1} lower than those of **1**−**3** (Table 1). This reflects the lower steric hindrance experienced by the rotational transition state when the isopropyl has replaced the *tert*-butyl substituent, an effect analogous to that observed for the phenyl−C bond rotation process mentioned above.

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[10] MM calculations yielded very similar results also for the analogous derivatives **1** and **2**. In fact the conformation shown in Scheme 2 for the ground state of the *R**,*S** diastereoisomer of **1** corresponds to that of a synclinal rotamer.

[11] (a) Anet, F. A. L.; Basus, V. J. *J. Magn. Reson.* **1978**, *32*, 339. (b) Okazawa, N.; Sorensen, T. S. *Can. J. Chem.* **1978**, *56*, 2737.

[12] Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, UK, 1982; p 84.

[13] Anet, F. A. L.; Yavari, I.; Ferguson, I. J.; Katritzky, A. R.; Moreno-Mañas, M.; Robinson, M. I. T. *Chem. Commun.* **1976**, 399. Cerioni, G.; Piras, P.; Marongiu, G.; Macciantelli, D.; Lunazzi, L. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1449. Lunazzi, L.; Placucci, G.; Chatgilialoglu, C.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 819. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839. Lunazzi, L.; Placucci, G.; Macciantelli, D. *Tetrahedron* **1991**, *47*, 6427. Lunazzi, L.; Mazzanti, A.; Casarini, D.; De Lucchi, O.; Fabris, F. *J. Org. Chem* **2000**, *65*, 883. Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2000**, *65*, 3563.

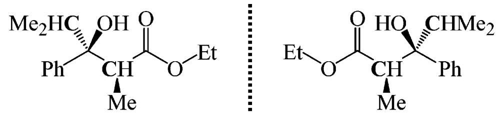
[14] At such a temperature the interconversion rate is slow on the NMR time scale, so that the lines of the two exchanging species are expected to be equally sharp. For this reason the failure of observing the signal of the minor conformer can only be due to an exceedingly low population.

[15] The line broadening effect was not significantly detectable in any of the signals of the ^1H NMR spectrum, owing to the much smaller chemical shift difference between the proton signals of the A and B rotamers of Scheme 3. Most likely the minor signals were obscured by the major ones at low temperature, so that we could not take advantage of the greater sensitivity of ^1H NMR for identifying the spectrum of the minor conformer.

[16] (a) Anderson, J. E. In *The Chemistry of Alkanes and Cycloalkanes*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1992, Chapter 3.II.D. (b) Nagawa, Y.; Yamagaki. T.; Nakanishi, H.; Nakagawa, M.; Tezuka, T. *Tetrahedron Lett.* **1998**, *39*, 1393.

[17] For instance, the maximum incremental width for the line of the isopropyl methine carbon (identified by the gHSQC sequence) is 76 Hz at −103 °C (see Figure 4), corresponding to a 477 s^{-1} rate constant,[12] hence to a $\Delta G^\ddagger$ value of 7.7 kcal mol^{-1}.

[18] Since the line shape simulation was carried out between −93 and −117 °C, the population of the minor rotamer in this range was estimated by means of the Boltzmann equation (15% and 12%, respectively), on the reasonable assumption that the value of $\Delta G°$ (0.61 kcal mol^{-1} at −140 °C) is essentially independent of temperature.



(4)

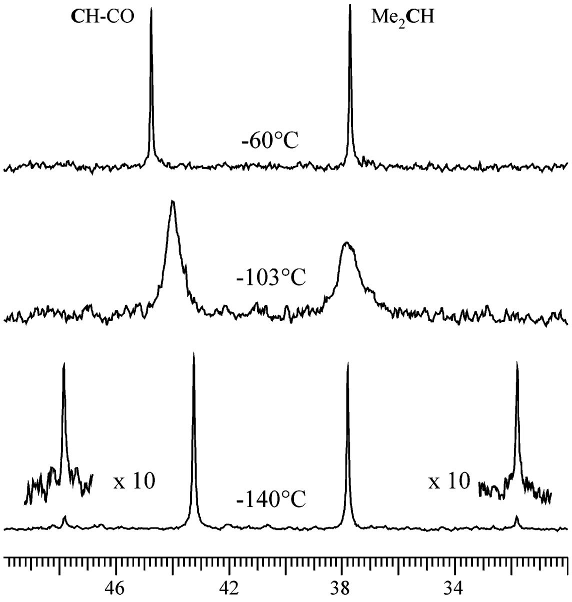


FIGURE 4. Temperature dependence of the ^{13}C NMR (100.6 MHz) methine carbon signals of **4** in CHF_2Cl. At −140 °C the lines of the minor rotamer (about 9%) become visible, as shown in the 10-fold enhanced scale.

Experimental Section

Materials: (2*R,3*S**)-Phenyl 3-Hydroxy-2,4,4-trimethyl-3-phenylpentanoate (1).** To a solution of phenyl 2-methyl-3-oxo-3-phenylpropanoate (1 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (1.5 mmol, 1 M solution in CH_2Cl_2) at −30 °C under an argon atmosphere. After 30 min the reaction was cooled at −78 °C, and a large excess of *t*-BuMgBr−$CeCl_3$ complex (6 mmol) in Et_2O was added. The reaction was stirred at this temperature for 1 h, and then quenched with aqueous HCl (1 M). The usual workup gave a crude product, which was purified by chromatography separation on a silica gel column (petroleum ether/Et_2O 9/1). Yield =48%, de >97; sticky solid; ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) δ 0.98 (s, 9H, *t*-Bu), 1.09 (d, 3H, Me, $J = 7.1$ Hz), 3.58 (q, 1H, CH, $J = 7.1$ Hz), 4.29 (s, 1H, OH), 7.15 (d, 2H, Ph, $J = 8.1$ Hz), 7.20−7.39 (m, 4H, Ph), 7.40−7.48 (m, 2H, Ph), note, very broad signal under the other aromatic signals (2H, Ph); ^{13}C NMR (100.3 MHz, CD_2Cl_2, 25°C) δ 16.7 (Me), 27.5 (3Me), 40.9 (C_q), 42.4 (CH), 82.2 (C_q), 122.1 (2CH), 127.11 (CH), 127.06 (CH), 127.8 (broad signal, 4CH), 130.4 (2CH), 143.2 (C_q), 151.1 (C_q), 178.0 (CO). Anal. Calcd for $C_{20}H_{24}O_3$: C,76.89; H, 7.74. Found: C,76.93; H, 7.78.

(2*R,3*S**)-*tert*-Butyl 3-Hydroxy-2,4,4-trimethyl-3-phenyl-pentanoate (2). 2** was prepared by reaction of *tert*-butyl 2-methyl-3-oxo-3-phenyl propanoate with *t*-BuMgBr−$CeCl_3$ complex under the same conditions adopted for compound **1**. Yield 68%, de >97; sticky solid; ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) δ 0.86 (d, 3H, Me, $J = 7.0$ Hz), 0.87 (s, 9H, *t*-Bu), 1.48 (s, 9H, *t*-Bu), 3.15 (q, 1H, CH, $J = 7.0$), 4.82 (s, 1H, OH), 7.18 (m, 1H, Ph), 7.24−7.29 (m, 4H, Ph), 7.37 (br s, 2H, Ph); ^{13}C NMR (100.3 MHz, CD_2Cl_2, 25 °C) δ 16.7 (Me), 27.5 (3 Me), 28.4 (3 Me), 40.8 (C_q), 42.8 (CH), 81.8 (C_q), 82.5 (C_q), 126.7 (CH), 127.6 (broad signal, 2CH), 127.9 (broad signal, 2CH), 144.0 (C_q), 179.1 (CO). Anal. Calcd for $C_{28}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.90; H, 9.69.

(2*R,3*S**)-Ethyl 3-Hydroxy-2,4,4-trimethyl-3-phenyl-pentanoate (3). 3** was prepared by reaction of ethyl 2-methyl-3-oxo-3-phenylpropanoate with *t*-BuMgBr−$CeCl_3$ complex under the same conditions adopted for compound **1**. Yield 46%, de >97; sticky solid; ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) δ 0.85 (s, 9H, *t*-Bu), 0.87 (d, 3H, Me, $J = 6.6$ Hz), 1.31 (t, 3H, Me, $J = 7.2$ Hz), 3.28 (q, 1H, CH, $J = 6.6$ Hz), 4.19 (AB system, 2H, CH_2, J_{AB}= 14.0 Hz, $J = 7.2$ Hz), 4.52 (s, 1H, OH), 7.18−7.22 (m, 1H, Ph), 7.28 (t, 2H, Ph, $J = 7.9$ Hz), 7.40 (very broad signal, 2H, Ph); ^{13}C NMR (100.3 MHz, CD_2Cl_2, 25 °C) δ 14.5 (Me), 16.4 (Me), 27.3 (3Me), 40.7 (C_q), 61.9 (CH_2), 81.9 (C_q), 126.9 (CH), 127.7 (broad signal, 4CH), 143.6 (C_q), 179.5 (CO). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.18.

(2*R,3*R**)-Ethyl 3-Hydroxy-2,4-dimethyl-3-phenyl-pentanoate (4). 4** was prepared from the reaction of ethyl 2-methyl-3-oxo-3-pheny propanoate with *i*-PrMgBr−$CeCl_3$ complex under the same conditions adopted for compound **1**. Yield 45%, de >97; oil; ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C) δ 0.74 (d, 3H, Me, $J = 6.7$ Hz), 0.83 (d, 3H, Me, $J = 6.7$ Hz), 0.96 (d, 3H, Me, $J = 7.1$ Hz), 1.25 (t, 3H, Me, $J = 7.2$ Hz), 1.98 (eptet,1H, **CH**Me_2, $J = 6.6$ Hz), 3.23 (q, 1H, CH, $J = 7.1$ Hz), 3.94 (br s, 1H, OH), 4.17 (AB system, 2H, CH_2, J_{AB}= 10.8 Hz, $J = 7.2$ Hz), 7.19−7.22 (m, 1H, Ph), 7.31 (m, 2H, Ph), 7.35 (very broad signal, 2H, Ph); ^{13}C NMR (100.3 MHz, CD_2Cl_2, 25 °C) δ 13.8 (Me), 14.7 (Me), 17.8 (Me), 18.6 (Me), 38.4 (**CH**Me_2), 45.9 (**CH**−CO), 61.7 (CH_2), 80.0 (C_q), 127.2 (4CH), 128.2 (CH), 141.7 (C_q), 178.1 (CO). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.95; H, 8.83.

NMR Measurements. The samples for the ^{13}C NMR low-temperature measurements were prepared by connecting the NMR tubes containing the compound and some C_6D_6 to a vacuum line for the purpose of locking and condensing the gaseous CHF_2Cl under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out with use of a PC version of the DNMR-6 program.[19] When the simulations could be carried out at various temperatures the error on the $\Delta G^{\ddagger}$ values is about ±0.15 kcal mol^{-1} (see Table 1), as previously discussed.[20] In the cases where essentially only the maximum line broadening could be observed at a single temperature the uncertainty is about 50% larger.

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Supporting Information Available: MM conformational parameters for **1**, **3**, and **4**, energy map for **1**, temperature dependence of the ^{13}C NMR signal of the CH_{α} carbon of **3**, and gHSQC spectrum of **3** at −43 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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