Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 4, pp. 503-506, 1994

0957-4166/94 $6.00+0.00

0957-4166(94)E0062-F

(*N*-Methylphenylsulfoximidoyl)methyllithium: A Versatile Reagent for the Determination of Absolute Configuration of Six-Membered Ring Ketones

Marcelo D. Preite, Manuel González-Sierra,* Juan Zinczuk and Edmundo A. Rúveda.*

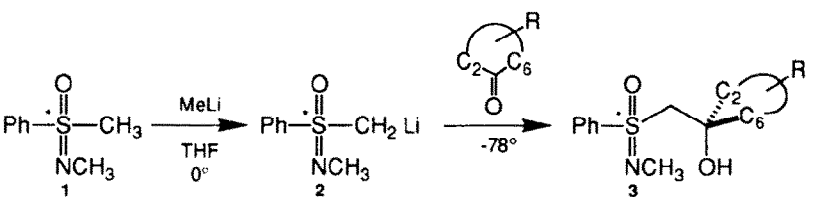
Instituto de Química Orgánica de Síntesis (CONICET-UNR) Facultad de Ciencias Bioquímicas y Farmacéuticas, Casilla de Correo 991, 2000 Rosario, Argentina

Abstract: The diastereotopic chemical shift differences of the ^{1}H and ^{13}C NMR signals of the adducts formed by addition of (*N*-methylphenylsulfoximidoyl)methyllithium (**2**) to cyclic ketones has been studied. The stereodifferentiation of the proton and carbon atoms follow a very regular pattern and the rule that can be drawn provides an alternative and complementary method to earlier procedures for the determination of absolute configuration of six-membered ring ketones.

The determination of absolute configuration has been a matter of major concern in the characterization of naturally occurring compounds and, more recently, in enantioselective organic synthesis.[1] Thus, the development of new methods to aid in these assignments is of great interest.

Sulfoximine derivatives, developed and thoroughly described by Carl R. Johnson, are well known compounds and have been used frequently in organic synthesis.[2] Addition of optically pure (*N*-methylphenylsulfoximidoyl)methyllithium (**2**), to a cyclic prochiral or chiral ketone, for instance, results in the formation of two optically active diastereoisomeric β-hydroxysulfoximines (**3**), which may be separated by chromatography, affording the corresponding active compounds (Scheme 1).

Scheme 1



Recently, we have been involved with the adducts derived from the reaction of optically pure **2** and a racemic six-membered ring ketone, in connection with its resolution,[3] and became aware of the appearance of significant diastereotopic chemical shift differences on the ^{1}H and ^{13}C NMR signals of the diastereoisomeric pair. Such differences resemble those reported in the ^{1}H NMR spectra of the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters of secondary alcohols,[4a] or those in the ^{13}C NMR spectra of (2R,3R)-2,3-butanediol ketals of six-membered ring ketones.[5]

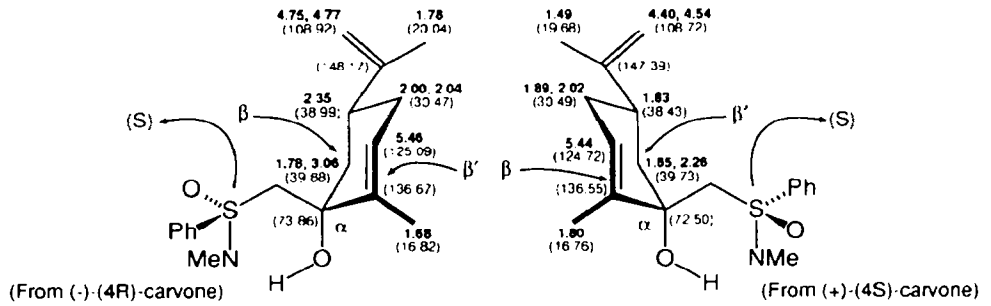
In the hope that such chemical shift differences might be used to determine the absolute configuration of the parent ketones, in analogy to the modified Mosher's[4a] and Lemière's[5] methods, we prepared the adducts[6] of the ketones shown in Table 1, and performed a complete NMR study[7] of each compound for every diastereoisomeric pair, carrying out a separate analysis of the ^{1}H and ^{13}C NMR data.

When the data collected for the diastereoisomeric pairs, are fitted to the idealized conformation model (exemplified by the β-hydroxysulfoximines derived from (+)- and (-)-carvone and (+)-(S)-**2**), shown in Figure 1, a very consistent relationship between the chemical shift values and the absolute configuration is found. The basic concept for the model is essentially the same as Mosher proposed[4b] in which the $-NCH_3$ group takes the place of the $-CF_3$ group of the MTPA.

The relation found for the ^{1}H chemical shifts can be expressed by the following rule: a shielding for the β′ hydrogens places such atoms in the same side of the plane as the sulfoximine phenyl group. On the other hand, a deshielding for the β hydrogens places these atoms in the opposite side. The effect follows the same trend for hydrogens in the γ and δ positions but rapidly decreases with distance to the sulfoximine moiety.

In the case of the ^{13}C NMR data, the rule states: a downfield shift for the β′ carbon (same side of the plane as the phenyl group), and an upfield shift for the β carbon (opposite side of the plane as the phenyl group) (Figure 1). The changes also affect the carbons further away from the α-C but they seemed to be dependent on the six-membered ring conformation. Table 1 shows the ^{1}H δ values and ^{13}C chemical shifts of the most significant hydrogen and carbon atoms in the compounds studied.

Figure 1



Bold numbers refer to ^{1}H δ, in ppm (numbers in parentheses refer to ^{13}C chemical shifts, in ppm)

The fitting on the model and the use of this simple rule, allow the assignment of the absolute configuration of the newly formed chiral center and, by extension, that of all the other centers present in the parent ketone. At this point, one must pay attention to the diastereofacial preference of the lithium reagent addition. Fortunately, we found this reaction to be highly sterically demanding, adding mainly from the less hindered face of the ketone.

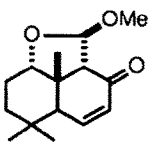
In conclusion, the method we propose is comparable to that of Lemière,[5] but the diastereoisomeric chemical shift differences observed are larger than those currently reported (up to 6 ppm in ^{13}C). In addition, it can be applied to cyclohexenones and cyclohexanones which exist mainly in boat or twist conformations, as those depicted in Table 1, for which Lemière's method does not apply. Besides, the rule can also be used for ^{1}H NMR, and works exactly as Mosher's method,[4a] and the diastereoisomeric chemical shift differences observed are also substantially larger (up to 1.24 ppm).

Table 1

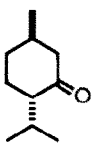
Substrate§	Reagent 2	^{13}C chemical shifts		^{1}H chemical shifts	
		β	β′	β	β′
(-)-**4**	S	129.83	67.81	6.69	1.63
(+)-**4**	S	61.85	129.97	2.88	5.56
(-)-**5**	R	46.30	51.24	1.25, 2.71	0.94
(-)-**5**	S	50.67	47.61	0.98	0.82, 2.23
(-)-**6**	S	39.68	136.67	1.78, 3.06	1.68*
(+)-**6**	S	136.55	39.73	1.80*	1.65, 2.26
(+)-**7**	S	44.47	53.79	2.26	0.85*
(-)-**7**	S	52.98	48.14	1.09*	1.03, 1.99
(+)-**8**	S	48.88	131.24	1.32, 2.36	1.27, 2.36*
(+)-**8**	R	130.60	49.87	1.47, 2.51*	1.30, 1.87
(+)-**9**	S	43.80	47.85	1.47, 2.45	2.00
(-)-**9**	S	45.09	46.97	2.99	1.34
(-)-**10**	S	30.68	124.44	1.94, 2.61	5.11
(-)-**10**	R	123.21	31.93	5.73	1.86, 2.14
(+)-**11**	S	28.90	52.06	2.20, 2.70	1.84
(+)-**11**	R	50.01	32.22	2.71	1.65, 1.92

§ Figure 2 shows the structures of one of the enantiomers of the ketones used in this study.
* Correspond to a γ or γ′ atom.

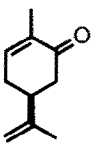
Figure 2



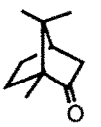
(–)-**4**



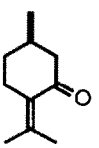
(–)-**5**



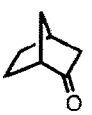
(+)-**6**



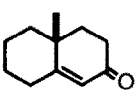
(+)-**7**



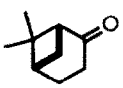
(+)-**8**



(–)-**9**



(–)-**10**



(+)-**11**

Finally, using the known reactivity of the β-hydroxysulfoximine adducts, the parent ketone can be easily recovered by mild heating. Alternatively, tertiary, optically active alcohols can be generated by reductive cleavage of the C-S bond.[2b]

Acknowledgment- This work was supported by CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and UNR (Universidad Nacional de Rosario). M. D. P. thanks CONICET for a fellowship.

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6 - A typical experiment:

a) (*S*)-S-β-hydroxysulfoximine from (-)-(*R*)-carvone (**6**): A solution of methyllithium in ether (0.74 mmol, 1.7 M), was added to a solution of (+)-(*S*)-N,S-dimethyl-S-phenylsulfoximine [(+)-**1**] (126 mg, 0.74 mmol) and triphenylmethane (5 mg, used as an indicator) in dry tetrahydrofuran (10 mL) at 0° C, under nitrogen. After stirring at room temperature for 15 min, the orange solution was cooled to -78° C (yellow solution), and (-)-(*R*)-carvone (100 mg, 0.67 mmol), dissolved in anhydrous tetrahydrofuran (5 mL), was added over 5 min. The mixture was allowed to stir until TLC showed no starting material remained (15 min). The cold mixture was poured into saturated aqueous ammonium chloride solution and extracted twice with ether. The combined organic extracts were dried over magnesium sulfate, filtered, and evaporated *in vacuo*, to afford 252 mg of crude product as a yellow oil. This was purified by flash chromatography and recrystallised from ether to yield the desired product, as a white crystalline solid (136 mg, 64%): mp: 105° (dec.) (from ether). Found: H: 7.90%, C: 67.67%, N: 4.58%, S: 10.32% (Calculated for $C_{18}H_{25}O_2NS$: H: 7.89%, C: 67.68%, N: 4.38%, S: 10.04%).

b) (*S*)-S-β-hydroxysulfoximine from (+) (*S*)-carvone (**6**): The addition of the lithium salt of (+)-**1** (142 mg, 0.84 mmol) to (+)-(*S*)-carvone (115 mg, 0.77 mmol) at -78°C, afforded 281 mg of crude product as a yellowish oil, which was purified by flash chromatography and recrystallised from ether to yield the desired β-hydroxysulfoximine, as a white crystalline solid (176 mg, 72%): mp: 55° (dec.) (from ether). Found: H: 8.12%, C: 67.92%, N: 4.72%, S: 10.32% (Calculated for $C_{18}H_{25}O_2NS$: H: 7.89%, C: 67.68%, N: 4.38%, S: 10.04%).

With substrates **5**, **8**, **10** and **11** the reaction was performed with (±)-**1** and with (+)-**1** in order to determine the ^1H and ^{13}C NMR data of both diastereoisomeric β-hydroxysulfoximines.

7 - The ^1H and ^{13}C NMR experiments (in ~1.25% and ~10% solution, respectively, in $CDCl_3$), were measured at 200.13 and 50.33 MHz, respectively, on a Bruker ACE-200 spectrometer. The complete assignment of the signals was achieved by a combination of 1D, 2D (HH and CH COSY), and NOE difference experiments using standard Bruker software.

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(*Received in USA* 27 *December* 1993; *accepted* 17 *February* 1994)