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Article

Absolute Configuration and Enantiomeric Composition of Partially Resolved Mandelic, Atrolactic and Lactic Acids by ^{1}H NMR of their (*S*)-2-Methylbutyl Esters

Francisco A. da C. Andrade,* Maricleide P. de L. Mendes and Neuracy C. da Fonseca

Departamento de Química Orgânica, Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, 40170-280 Salvador-BA, Brazil

Ésteres dos ácidos mandélico, atrolático e lático com o (*S*)-2-metil-1-butanol foram examinados como derivados diastereoméricos para análise estereoquímica por ressonância nuclear magnética (NMR) de ^{1}H a 300 MHz dos ácidos mencionados. Diastereômeros destes ésteres apresentaram ressonâncias com diferenças evidentes na região de absorção do grupo metilena alquílico (O–$\underline{CH_2}$–CH). Por análise dos espectros dos derivados, nesta região, foram atribuídas suas configurações absolutas, especificadas as absorções dos hidrogênios pró-*R* e pró-*S* do grupo metilena e determinadas as composições enantioméricas dos ácidos de origem parcialmente resolvidos.

The mandelic, atrolactic and lactic acid esters of the (*S*)-2-methyl-1-butanol were examined as diastereomeric derivatives for the stereochemical analysis of the mentioned acids by ^{1}H nuclear magnetic resonance (NMR) at 300 MHz. The diastereomeric esters showed distinctive signals in the methylenic absorption range (O–$\underline{CH_2}$–CH) of the alcoholic moieties. By spectral analysis at this region, absolute configurations were attributed, chemical shifts of the correspondent pro-(*R*) and pro-(*S*) hydrogens from the methylene group of the alcohol moiety were assigned and enantiomeric compositions were determined for the original partially resolved acids.

Keywords: absolute configuration, enantiomeric composition, NMR spectroscopy, chiral hydroxyacid, chiral primary alcohol

Introduction

A general procedure for the enantiomeric composition of chiral alcohols (and acids) consists in the conversion of the enantiomers into a diastereomeric ester mixture, by using an enantiomerically pure chiral acid (or chiral alcohol) and examining the resultant mixture by nuclear magnetic resonance (^{1}H NMR) spectroscopy.[1-4] Those conversions are also used for assignment of chiral alcohol (and acid) configurations.[5,6]

An empirical correlation between the configuration and the observed resonances for esters of such acids as the mandelic, atrolactic, α-methoxy-α-(trifluoromethyl) phenylacetic and *O*-methylmandelic[5] has been used for the deduction of the absolute configuration of the secondary alcohols from which they were prepared. This correlation was extended[7] to valine esters and applied for the stereochemical analysis of some primary chiral alcohols. ^{1}H NMR spectroscopy of 2-methyl-1-alkanol valine ester derivatives showed that geminal diastereotopic protons, in O–$\underline{CH_2}$–CH of the alcoholic moiety, display measurable chemical shift non-equivalents for their epimers, at 300 MHz. The chemical shifts caused by H_R and H_S protons, around 4 ppm, were farther from each other for one of the valine ester enantiomer while were closer from each other for the correspondent epimer.

To extend the procedure to other derivatives, it seemed interesting to inspect esters of the primary chiral alcohol with mandelic, atrolactic and lactic acids, this last an inexpensive chiral α-hydroxyacid. The referred NMR features led to infer the configuration, assign the H_R and H_S resonances and determine the enantiomeric composition of the original acid.

Experimental

Instruments

Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were

*e-mail: fandrade@ufba.br

obtained in a Perkin Elmer-283B spectrometer. Optical rotations were determined in a Zeiss polarimeter. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini (300 MHz) spectrometer, using approximately 0.2 mol L^{-1} solutions in $CDCl_3$ and the following conditions: spectral width 4,500 Hz; pulse width 9.1 μs; flip angle 45°; acquisition time 1.767 s; no recycle delay; number of transients 128. Reported chemical shifts (δ units) are in ppm from internal TMS (tetramethylsilane), coupling constants (*J*) are in hertz, multiplicity are indicated as s, d, t, q, m, respectively for singlet, doublet, triplet, quartet and multiplet, and the ABX patterns of the chiral derivatives are listed in Table 1.

Chemicals

(*S*)-2-Methyl-1-butanol 99%, (–)-ephedrine, quinine hydrochloride, (±)-lactic acid 85% aq., (*S*)-(+)-lactic acid 85% aq., *p*-toluenesulphonic acid, inorganic reagents and analytical grade solvents, available as commercial products (Aldrich or Merck or Reagen), were used without further purification. Benzaldehyde was distilled before use. Other substances, referred below, were prepared by well known literature procedures.

(±)-Mandelic acid, mp 115-116 °C (118 °C),[8] was prepared from benzaldehyde through formation and posterior hydrolysis of the mandelonitrile.[8]

(*R*)-(–)-Mandelic acid 78.8% ee, was prepared by partial resolution of the (–)-mandelic acid through re-crystallization of their (–)-ephedrine salts in ethanol,[9] followed by acidification of the less soluble crop, ether extraction and re-crystallization of the (*R*)-(–)-mandelic acid in acetone. The partially resolved product showed mp. 127-128 °C, and $[\alpha]_D^{26}$ –123.7° (c 1.1 H_2O) [mp 133.5 °C, $[\alpha]_D^{20}$ –156.9° (c 2 H_2O)].[9]

(±)-Atrolactic acid, mp 84-88 °C (88-90 °C),[10] was prepared from acetophenone through formation and hydrolysis of the cyanohydrin.[10]

(*S*)-(+)-Atrolactic acid 60.6% e.e. was obtained by resolution of its quinine salt.[11] After six re-crystallizations from ethanol, the quinine salt melted at 220-225 °C and presents $[\alpha]_D^{30}$ –109° (c 0.55, ethanol) $[\alpha]_D^{30}$ –109° (c 0.54, ethanol)].[11] The atrolactic acid regenerated from this salt melted at 92-95oC and presented $[\alpha]_D^{30}$ +22.6° (c 2.54, ethanol) $[\alpha]_D^{30}$ +37.3° (c 2.53, ethanol)].[11]

Analytical samples of esters

Esters were prepared by adapting a reported procedure[12] to a smaller scale and substituting the catalyst from sulfuric acid for *p*-toluenesulfonic acid. A mixture of the acid (0.2 mmol), alcohol (0.22 mmol), *p*-toluenesulphonic acid (5 mg) and benzene (5 mL) was refluxed (4 h) using a trap for water separation. The cold reaction mixture was taken in ether and the extract washed with water, sodium bicarbonate (5%), water again, and dried over anhydrous sodium sulfate. The crude esters (0.12-0.14 mmol) were obtained as yellowish or colorless liquids, after removing drying agent, alcohol excess and the solvent.

2-Methylbutyl mandelates (**1**): enriched (*S,R*)-2-methylbutyl mandelate 78.8% d.e. was obtained from (*R*)-mandelic acid 78.8% e.e. and pure (*S*)-2-methyl-1-butanol. An equimolar epimeric pair of (*S,R*) plus (*S,S*)-2-methylbutyl mandelate was obtained from racemic mandelic acid and (*S*)-2-methyl-1-butanol. ^{1}H NMR δ 7.45-7.26 (m, 5H, C_6H_5), 5.17 (d, 1H, *J* 5.6, ArC<u>H</u>), 4.09-3.91 (2H, ABX, OC<u>H</u>$_2$), 3.55 (d, 1H, *J* 5.6, OH), 1.73-1.56 (m, 1H, MeC<u>H</u>), 1.36-1.18 (m, 1H, MeC<u>H</u>H), 1.16-0.98 (m, 1H, MeCH<u>H</u>), 0.85-0.76 (m, 6H, $2CH_3$).

2-Methylbutyl atrolactates (**2**): enriched (*S,R*)-2-methylbutyl atrolactate 60.6% d.e. was obtained from (*R*)-atrolactic acid 60.6% e.e. and pure (*S*)-2-methyl-1-butanol. The equimolar epimeric pair (*S,R* plus *S,S*)-2-methylbutyl atrolactate was obtained from racemic atrolactic acid and

Table 1. ABX resonances for OCH_2CH protons of the ester derivatives

entry	Epimer	R^1	R^2	δ / ppm				*J* / Hz		
				H_R	H_S	H_X	$\Delta\delta$	H_RH_S	H_RH_X	H_SH_X
Mandelic acid ester										
1a	*S,R*	Ph	H	4.06	3.95	1.64	0.11	10.6	6.0	7.2
1b	*S,S*	H	Ph	3.97	4.02	1.64	0.05	10.6	6.7	5.6
Atrolactic acid ester										
2a	*S,R*	Ph	Me	4.01	4.01	1.70	0	–	6.2	6.2
2b	*S,S*	Me	Ph	4.07	3.93	1.70	0.14	10.7	6.0	6.6
Lactic acid ester										
3a	*S,R*	Me	H	4.11	3.96	1.75	0.15	10.6	6.0	6.6
3b	*S,S*	H	Me	4.01	4.05	1.75	0.04	10.6	6.6	6.1

pure (*S*)-2-methyl-1-butanol. ^{1}H NMR δ 7.60-7.25 (m, 5H, C_6H_5), 4.11-3.90 (2H, ABX, O–CH_2), 3.86 (s, 1H, OH), 1.80 (s, 3H, C–CH_3), 1.78-1.62 (m, 1H, MeCH), 1.39-1.25 (m, 1H, MeC<u>H</u>H), 1.21-1.06 (m, 1H, MeCH<u>H</u>), 0.89-0.83 (m, 6H, 2CH_3).

2-Methylbutyl lactates (**3**): enriched (*S,S*)-2-methylbutyl lactate was obtained from (*S*)-2-methyl-1-butanol and almost pure (*S*)-lactic acid. An equimolar epimeric mixture of (*S,R*)-plus (*S,S*)-2-methylbutyl lactates was obtained from pure (*S*)-2-methyl-1-butanol and racemic lactic acid. ^{1}H NMR δ 4.28 (q, 1H, *J* 6.7, HO–C<u>H</u>), 4.14-3.93 (2H, ABX, O–CH_2), 3.10 (d, 1H, *J* 6.4, OH), 1.83-1.67 (m, 1H, EtC<u>H</u>), 1.43 (d, 3H, *J* 6.7, CO–CHC<u>H</u>$_3$), 1.51-1.36 (m, 1H, MeC<u>H</u>H), 1.28-1.13 (m, 1H, MeCH<u>H</u>), 0.95-0.89 (m, 6H, 2CH_3).

Results and Discussion

The ^{1}H NMR spectra of the diastereomeric ester mixtures examined in this work showed that the more distinctive signs were observed in the region of absorption for the methylenic protons in O–<u>CH_2</u>–CH of the alcoholic moiety.

Oxymethylene resonances of individual epimers

The identification of resonances for oxymethylenic protons of the diastereomeric esters were made by contrasting the spectra, around the 4 ppm region, of the equimolar diastereomeric mixture with an enriched mixture of known diastereomeric excess or with a pure enantiomer. Example of this procedure for esters of (*S*)-2-methyl-1-butanol with mandelic, atrolactic and lactic acids are shown in Figure 1. For each ester, equimolar mixture is displayed on top of the mixture enriched by the next esters.

Upon inspection of the 2-methylbutyl mandelic and lactic acid ester spectra, shown in Figure 1, the (*S,R*)- or (*R,S*)-isomers are recognized by their larger chemical shift differences of the geminal protons, represented as A and B, and the (*S,S*)- or (*R,R*)-isomers by their smaller chemical shift differences, represented as A' and B'.

Unexpectedly, the atrolactic ester showed inverted signals. The (*S,R*)- or (*R,S*)-isomers were recognized by their smaller chemical shift differences of the geminal protons, and the (*S,S*)- or (*R,R*)-isomers by their larger chemical shift differences.

Absolute configurations

Absolute configuration of one of the mentioned chiral acids or alcohols could be determined by the observations of the NMR signals of their esters prepared using the optically pure alcohol or acid, respectively.

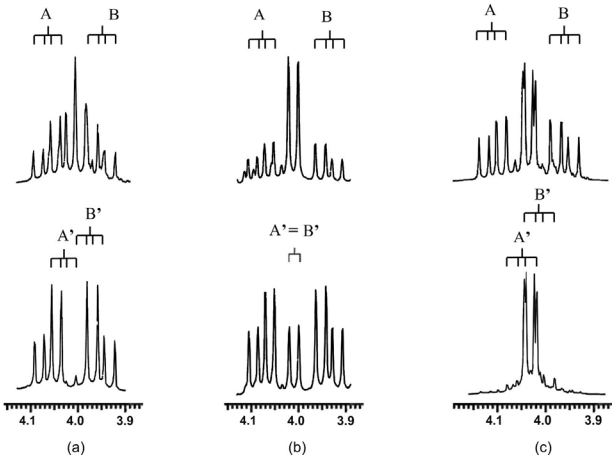


Figure 1. Methylene resonances from (a): equimolar and partially resolved (*S,R*)-2-methylbutyl mandelate; (b): equimolar and partially resolved (*S,S*)-2-metylbutyl atrolactate; and (c): equimolar and partially resolved (*S,S*)-2-metylbutyl lactate.

Similar correlations of the chemical shifts for oxymethylenic protons with attached groups to C-2 of some primary chiral alcohols were developed by the extension of the Mosher empirical model.[5] The extended model, limited for the (*S*)-2-methylbutyl esters, is represented by the chemical structure represented in Figure 2.

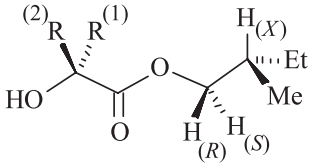


Figure 2. Chemical structure of (*S*)-2-methylbutyl esters.

The determined chemical shifts for the oxymethylene protons of (*S*)-2-methybutyl esters, corresponding to ABX systems, are shown in Table 1. In this table, all (*S*)-2-methybutyl (*R*)-carboxylic acid esters are designated as **a** entries and named as (*S,R*)-epimers. The (*S,S*)-diastereomers are designated as **b** entries. Resonances for the (*R,S*)- and (*R,R*)-diastereomers are expected to be coincident to those shown by their enantiomers, i.e., by **a** and **b** entries, respectively.

Applying the above structural model for the (*S,R*)-mandelic acid ester (**1a**) and (*S,R*)-lactic acid ester (**3a**), the phenyl group of mandelate and the methyl group of lactate have the power to displace to higher magnetic field the absorptions of the oxymethylene proton situated in the same face. Absorption in higher magnetic field of the pro-*S* hydrogen (H_S), relative to the absorption of pro-*R* hydrogen (H_R), must be presented by

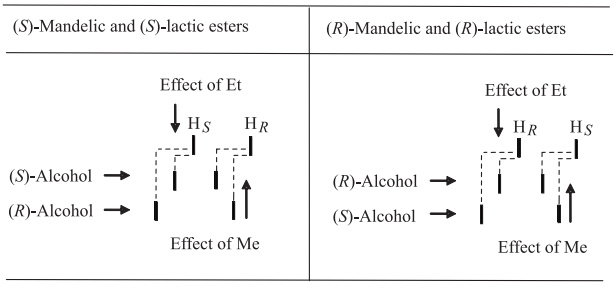
the (*S,R*)-mandelate and the (*S,R*)-lactate. Absorption in higher magnetic field of the pro-*R* hydrogen (H_R), relative to the absorption of pro-*S* hydrogen (H_S), must be presented by the (*S,S*)-mandelate (**1b**) and the (*S,S*)-lactate (**3b**).

The mentioned correlation resulting in higher magnetic field absorption of the pro-*R* oxymethylene hydrogen of the (*S*)-carboxylic acid esters was proved by comparing the following ^{1}H NMR spectra: butyl (*S*)-*O*-acetylmandelate versus (*R*)-[1-^{2}H]-butyl (*S*)-*O*-acetylmandelate[13] and octyl (1*S*)-camphanate *versus* (*R*)-(1-^{2}H)-octyl (1*S*)-camphanate.[14]

The Mosher model can not be applied to the prediction of the magnetic field for the H_S and H_R absorptions of atrolactic esters. In this case, bound on the acidic moiety, the methyl group would have a greater effect than the phenyl group over the geminal protons. Accurate effects are observed by comparing the differences between the H_R and H_S absorptions ($\Delta\delta$) for the mandelic and lactic acid esters.

The displacement of the germinal proton absorptions affected by the neighbor substituent is greater by the ethyl group than by the methyl group. It should be pointed out that the ethyl group can cause more shielding or more deshielding effect than the methyl group. Differences between the germinal proton absorptions ($\Delta\delta$) do not change using those effects.

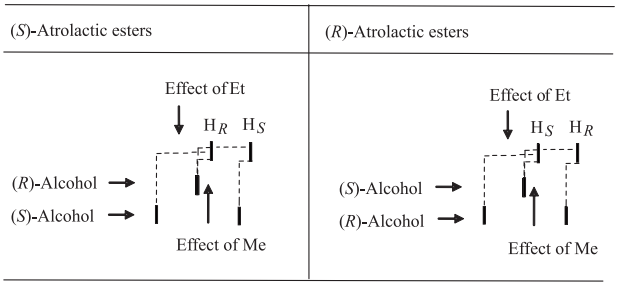
The chemical shifts for the germinal protons of valine esters have been modeled considering the shielding effects of the ethyl and methyl groups over the protons situated in the same face.[7] Chemical shifts for the germinal protons of the current (*S*)-2-methylbutyl esters were presented considering the deshielding effects of the ethyl and methyl groups. Structural model correlates the deshielding effects of the ethyl and methyl groups over the protons situated in the opposite face. The relative chemical shifts for mandelic and lactic esters can be assigned based on the Scheme 1.



Scheme 1. Relative chemical shifts of pro-*S* (H_S) and pro-*R* (H_R) protons for 2-methylbutyl mandelates and lactates.

For the (*S*,*R*)-2-methylbutyl mandelate (**1a**) (Table 1), the relative effect between phenyl and hydrogen groups resulted in $\Delta\delta$ = 0.11, while for the (*S*,*R*)-2-methylbutyl lactate (**3a**), the relative effect between methyl and hydrogen groups resulted in $\Delta\delta$ = 0.15.

The referred inversion of the substituent effects for atrolactic esters may be due to the described difference between the effects of the methyl and phenyl groups on the acidic moiety, and to the larger difference between the effects of the ethyl and methyl groups on the alcoholic moiety, which must result in higher magnetic field for H_S than for H_R oxymethylene proton for the (*S,S*)-atrolactate (**2b**). The relative chemical shifts for atrolactic esters can be assigned, approximately, based on the Scheme 2.



Scheme 2. Relative chemical shifts of pro-*S* (H_S) and pro-*R* (H_R) protons for 2-methylbutyl atrolactates.

The above mentioned relative effects of the phenyl and methyl groups over the oxymethylene protons of the atrolactic esters of the primary chiral alcohol are the same of the phenyl and trifluoromethyl groups found for the α-methoxy-α-(trifluoromethyl) phenylacetic esters.[15]

Enantiomeric compositions

Enantiomeric compositions are based on the machine integration of non-overlapping peaks of the methylenic protons from the diastereomeric derivatives. The conditions to optimize integral measurements were not determined. The procedure was already detailed in the literature[7] for valine esters of 2-methyl-1-alkanols. For the components that display the ABX pattern, to simplify identification, an ordering number from left to right is used to indicate the positions of resulting signals from A and then from B. In a mixture of (*S,R*)- plus (*S,S*)-2-methylbutyl mandelate esters (Figure 1a), for exemplification, the peak 1 of the (*S,R*) epimer, referred as 1/*SR*, is non-overlapped with the peak 1 of the (*S,S*) epimer, and the peaks 4 and 5 of the (*S,S*) epimer, referred as 4,5/*SS*, are non-overlapped with peaks of the (*S,R*) epimer. For coincident absorptions of the geminal protons of atrolactic acid ester, one peak of the resultant H-X duplet is referred as d1/*SR* or d2/*SR*. Calculations of enantiomeric compositions for acids presented in Figure 1 are indicated in Table 2.

Table 2. Enantiomeric composition of mandelic, atrolactic and lactic acids

Selected peak	Mandelic acid		Atrolactic acid		Lactic acid	
	1/*SR*	4,5/*SS*	d2/*SR*	5/*SS*	1-3/*SR*	3-6/*SS*
Enriched	11.6	5.3	11.1	16.4	4.6	66.4
Equimolar	6.3	22.9	24.2	10.0	24.6	62.8
Enriched/Equimolar	1.84	0.23	0.46	1.64	0.19	1.06
Composition / %	88.9	11.1	21.9	78.1	15.2	84.8

The integral values for areas of non-overlapped selected peaks from each component of the epimeric pair in the sample are compared with the values shown by the same peaks in an equimolar mixture of epimers. The proportional values obtained from the relations between enriched and equimolar amounts of the epimers are used for the calculations of their enantiomeric compositions.

Conclusions

Assignment of absolute configuration of β-chiral primary alcohols by ^{1}H NMR has been done by correlation of the anisotropic effect of aromatic groups over the oxymethylene protons absorption.[16] (*S*)-Valine, (*S*)-mandelic and (*S*)-lactic esters of (*S*)-2-methyl-1-butanol presented oxymethylene absorptions that show similar effects caused by isopropyl, phenyl and methyl groups, appears as proof for the absence of this anisotropic effect of aromatic groups over the methylene protons.

Our results for the (*R*)-mandelic acid and the (*R*)-lactic acid esters show that H_S is more shielded than H_R, while for the (*R*)-atrolactic acid ester, H_R is more shielded than H_S. The shielding effects for H_R and H_S found for the (*R*)-MTPA ester[15] were the same than for the above referred (*R*)-atrolactic acid ester.

Correlation between structure and absorptions of the methylene protons seems to be associated to the differences of conformations that can favor the flow of electron density of the adjacent nonbonding oxygen orbital, more for the H_R or more for the H_S proton. While the bright nonbonding orbital (Figure 3) is attracted by the carbonyl conjugation,

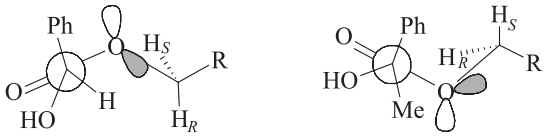


Figure 3. Bright and dark nonbonding orbitals.

the dark nonbonding orbital interacts more effectively with the antibonding orbital of the adjacent C–H bond, causing more shielding for the bound proton.

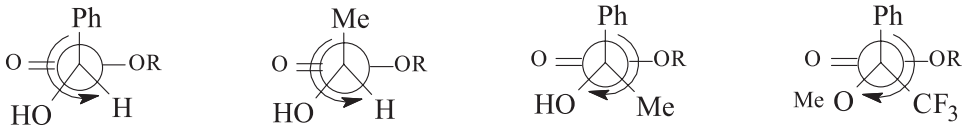
One assumption about the conformation that causes the preferential C=O conjugation with one of the nonbonding orbitals is related with the different steric effects of the hydrogen and methyl groups of the acidic moiety, observed by comparing the above structures.

Another assumption is related to the different screw patterns around the C–CO bond, as represented in Figure 4 for the cited acid esters, resultant from the decrease of the determined refractivity values[17] correlated to the electron polarizability.[18]

Referring to the enantiomeric composition, the (*S*)-2-methyl-1-butanol was a good derivatizing agent for the analysis of the α-hydroxi-acids. Equally, a pure α-hydroxyl-acid can serve as a derivatizing agent for the enantiomeric composition of the 2-methyl-1-butanol.

Supplementary Information

The ^{1}H NMR spectra for structural identification and composition determination of the esters are available free of charge at http://jbcs.sbq.org.br as PDF file.



(*R*)-Mandelic (*R*)-Lactic (*R*)-Atrolactic (*R*)-MTPA

Figure 4. The different screw patterns around the C–CO bond for the acid esters.

Acknowledgment

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Supplementary Information

Absolute Configuration and Enantiomeric Composition of Partially Resolved Mandelic, Atrolactic and Lactic Acids by ^{1}H NMR of their (*S*)-2-Methylbutyl Esters

Francisco A. da C. Andrade,* Maricleide P. de L. Mendes and Neuracy C. da Fonseca

Departamento de Química Orgânica, Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, 40170-280 Salvador-BA, Brazil

Identifications (Figures S1-S6)

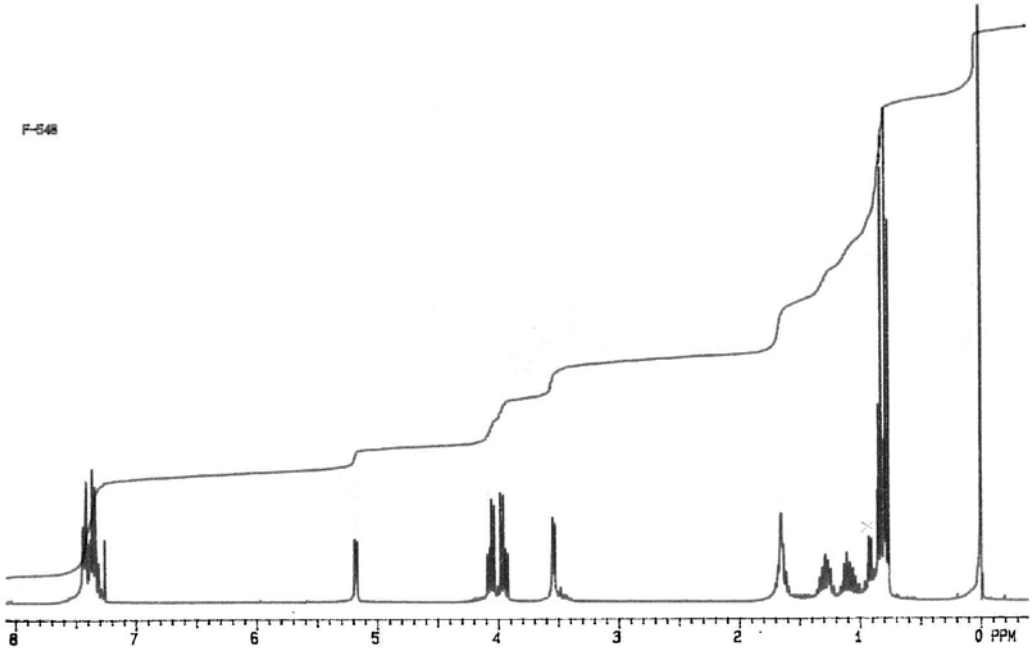

Figure S1. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of partially resolved (*S,R*)-2-methylbutyl mandelate.

*e-mail: fandrade@ufba.br

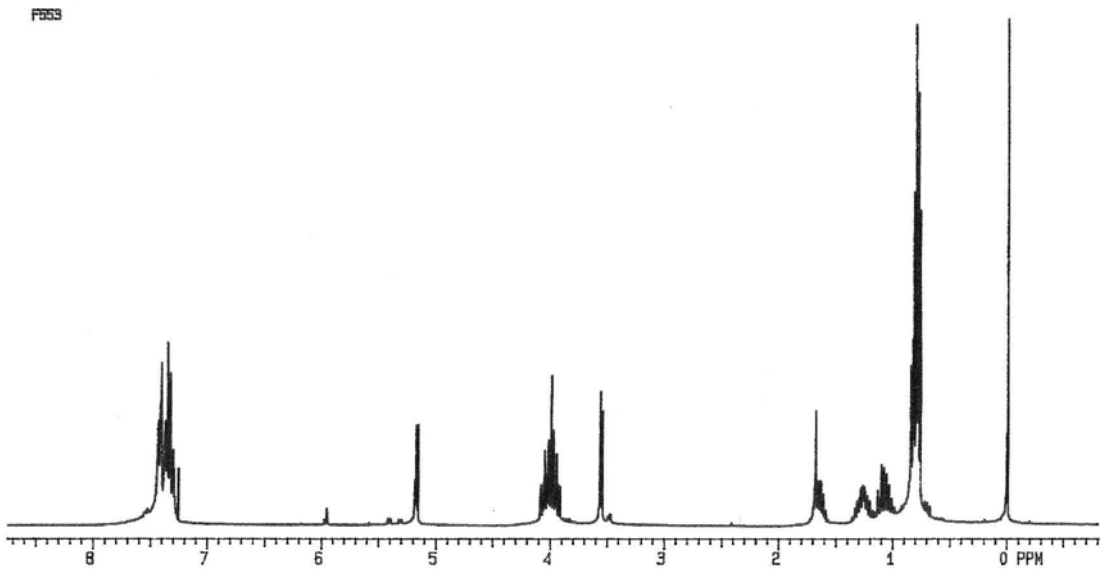

Figure S2. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of equimolar (*S,R*+*S,S*)-2-methylbutyl mandelate.

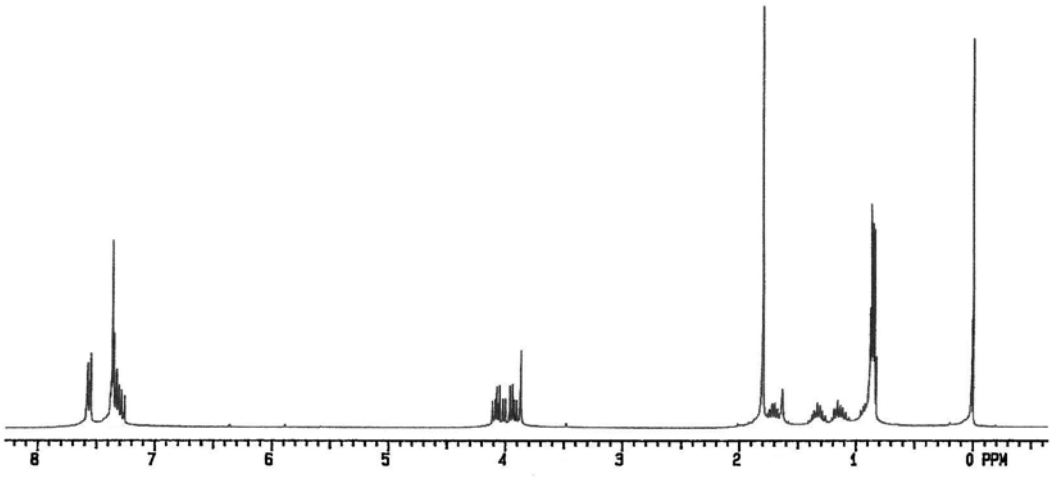

Figure S3. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of partially resolved (*S,S*)-2-methylbutyl atrolactate.

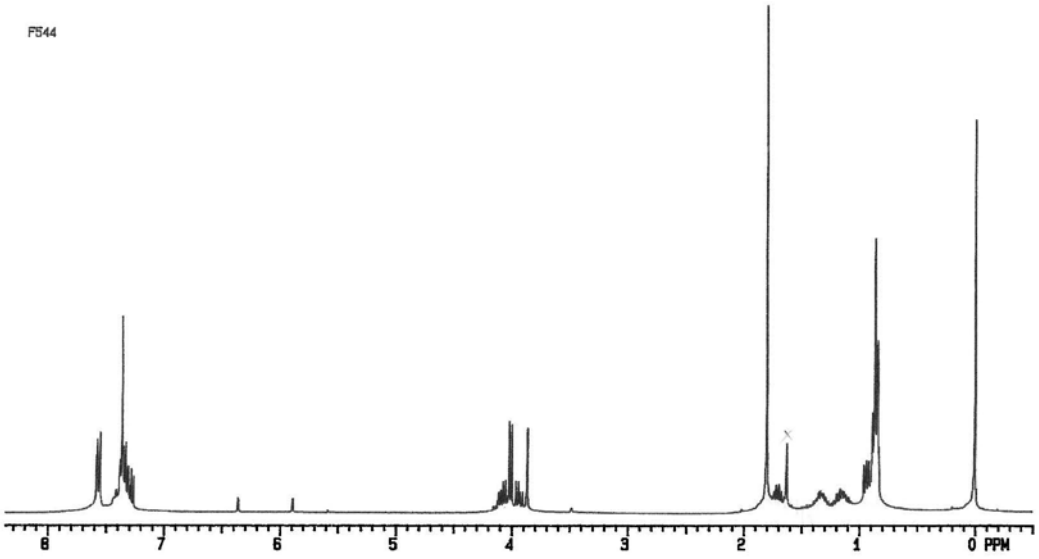

Figure S4. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of equimolar (*S,R*+*S,S*)-2-methylbutyl atrolactate.

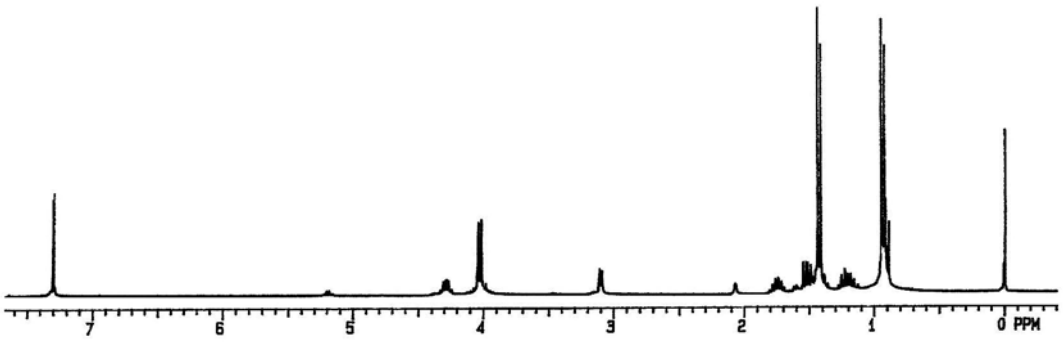

Figure S5. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of partially resolved (*S,S*)-2-methylbutyl lactate.

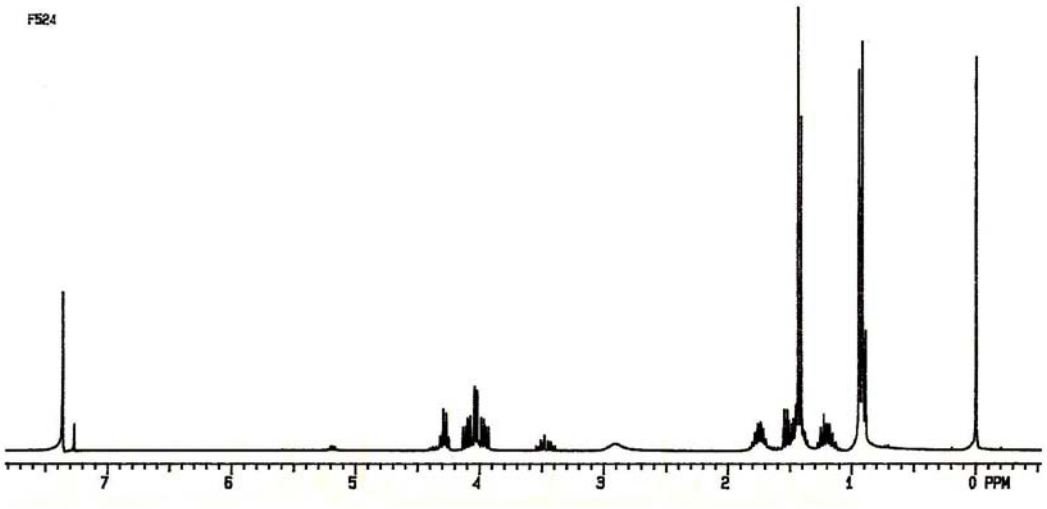

Figure S6. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of equimolar (*S,R*+*S,S*)-2-methylbutyl lactate.

Compositions (Figures S7-S12)

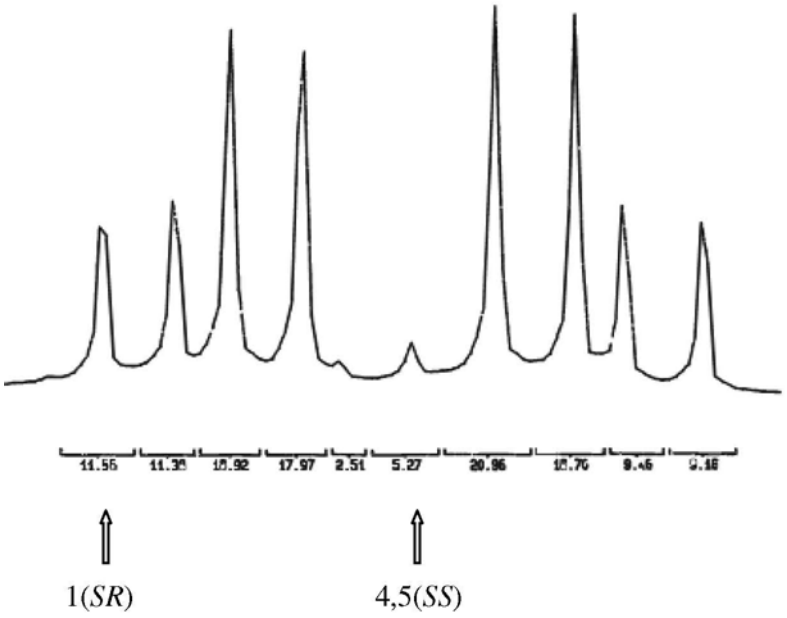

Figure S7. Methylene integration for partially resolved (*S,R*)-2-methylbutyl mandelate.

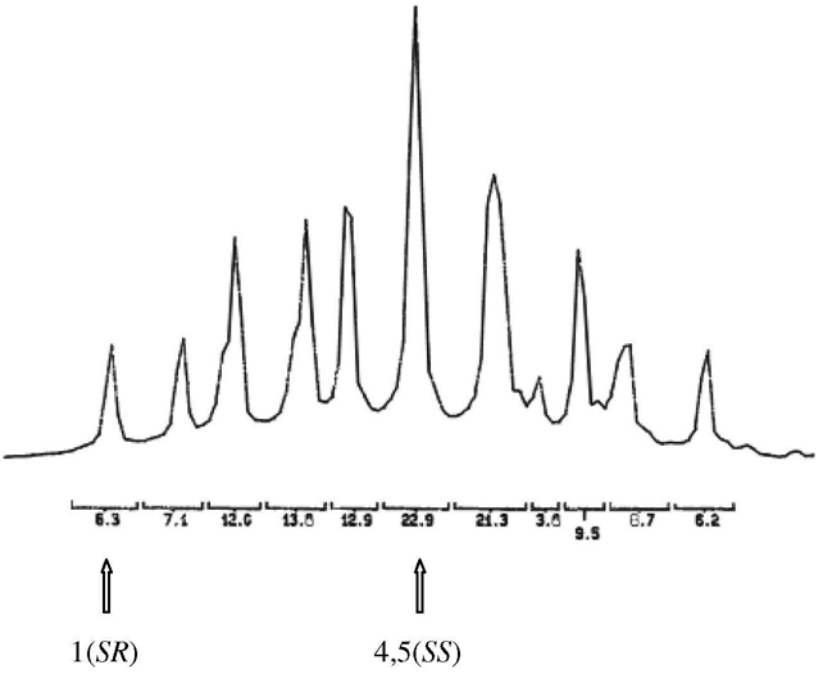

Figure S8. Methylene integration for equimolar (*S,R*+*S,S*)-2-methylbutyl mandelate.

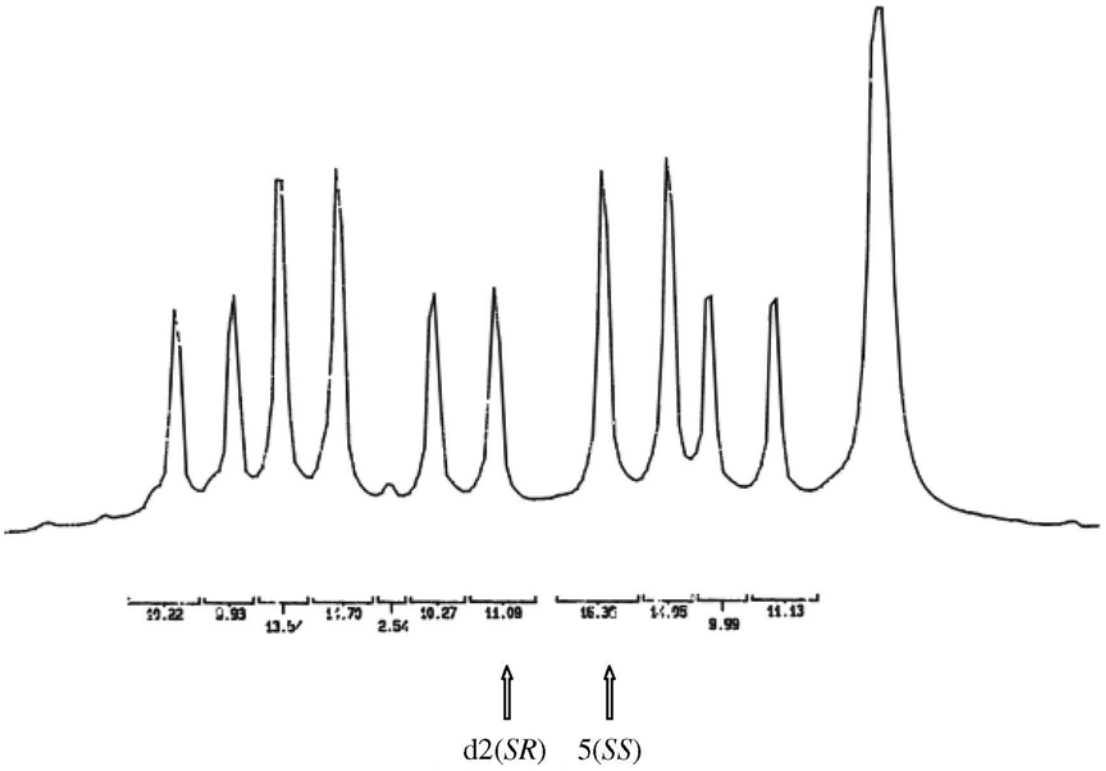

Figure S9. Methylene integration for partially resolved (*S,S*)-2-methylbutyl atrolactate.

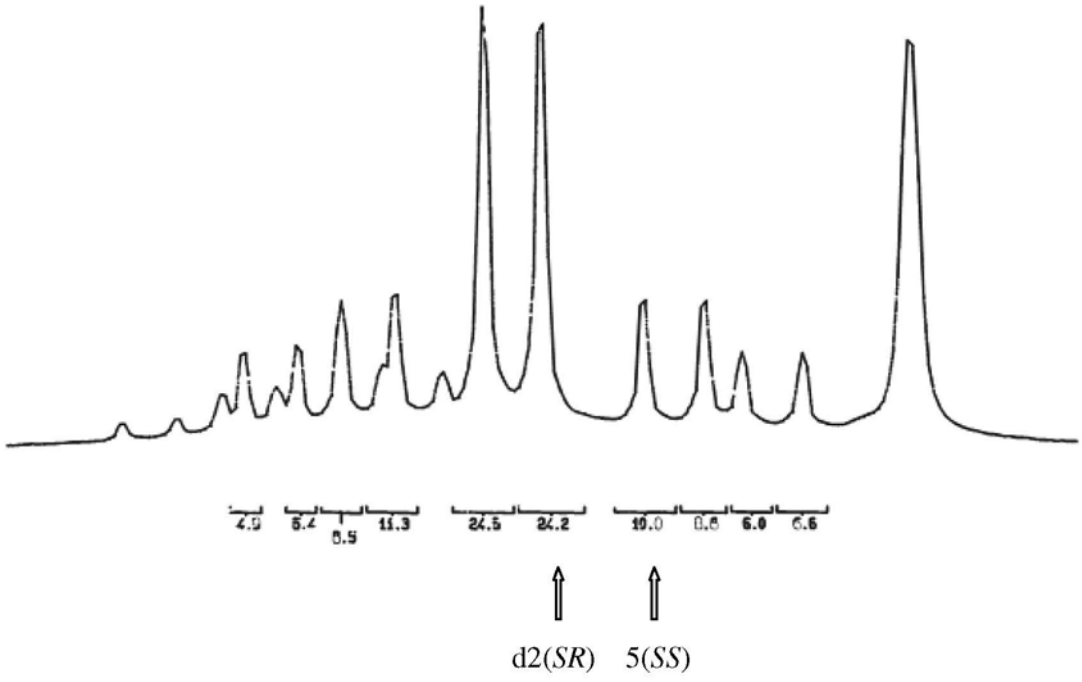

Figure S10. Methylene integration for equimolar (*S,R*+*S,S*)-2-methylbutyl atrolactate.

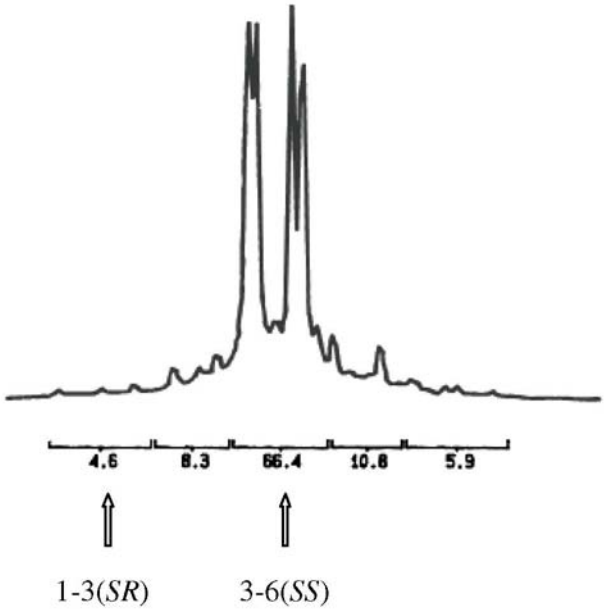

Figure S11. Methylene integration for partially resolved (*S,S*)-2-methylbutyl lactate.

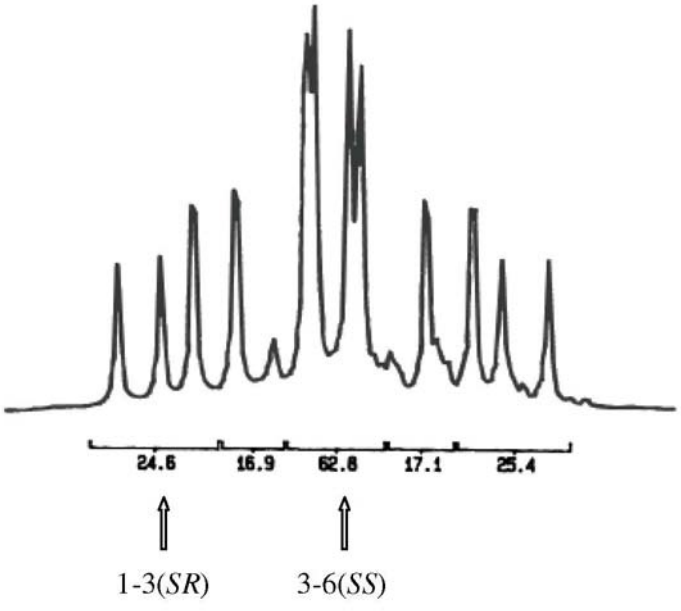

Figure S12. Methylene integration for equimolar (*S,R*+*S,S*)-2-methylbutyl lactate.