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A practical guide for the assignment of the absolute configuration of alcohols, amines and carboxylic acids by NMR

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Abstract—A practical guide for the assignment of the absolute configuration of alcohols, amines and carboxylic acids by NMR is presented. The guide includes information required for the judicious selection of the most suitable auxiliary reagent (MPA, MTPA, BPG, 9-AMA and 9-AHA), derivatization procedures and NMR conditions (solvent and temperature) for each substrate, as well as a critical account on the reliability, scope and limitations of these applications.

Contents

1. Introduction

In recent years there has been a marked increase in the number of papers describing the use of NMR for the assignment of the absolute stereochemistry of organic compounds. The general procedure consists of the derivatization of the substrate of unknown configuration with the two enantiomers of an auxiliary reagent. The proton NMR spectra of the resulting diastereoisomeric derivatives are compared and the differences in chemical shifts measured to give a $\Delta\delta^{RS}$ value. Although several auxiliary reagents have been described for this purpose,[1] very few have been subjected to detailed theoretical or experimental studies. Indeed, in many cases the experimental conditions for their application have not been optimized or the procedure tested with a sufficiently large and varied number of sub-

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strates of known absolute stereochemistry to offer the highest possible confidence in the configuration assigned.

Among these auxiliary reagents we include MPA (methoxyphenylacetic acid), MTPA (methoxytrifluormethylphenylacetic acid), 9-AMA (9-anthrylmethoxyacetic acid), 9-AHA (9-anthrylhydroxyacetic acid ethyl ester) and BPG (Boc-phenylglycine). These reagents are all currently being used for the assignment of the configuration of secondary alcohols, primary alcohols, primary amines and carboxylic acids (Fig. 1).

From a practical point of view, those wishing to use this method for configurational assignment may find some difficulties in the selection of the most suitable reagents and conditions for a certain substrate, or simply in the choice of the derivatization procedure (e.g. coupling of an alcohol/amine with the acids MPA or 9-AMA or with the corresponding acid chlorides). This difficulty is compounded by the absence of a comprehensive single source to provide information on this topic.

For instance, to choose between MPA, MTPA and 9-AMA for the assignment of a secondary alcohol, the actual structure of the alcohol and the complexity of its spectrum must be considered and the outcome of the study not left to chance.

Another aspect of this method that requires careful choice arises when the signals in the NMR spectra of the diastereoisomeric derivatives are too close to be distinguished (small $\Delta\delta^{RS}$). In this instance a change to a more powerful reagent can be a costly solution in some cases (e.g. MPA for 9-AMA with secondary alcohols) because the preparation of new derivatives is necessary. Valuable alternatives to increase the $\Delta\delta^{RS}$ values include acquiring the NMR spectra at lower temperatures[2] or adding a barium salt to the NMR sample,[3] but these work only with MPA as the auxiliary reagent and secondary alcohols as the substrates. These techniques do not show any significant improvement with other reagents (e.g. 9-AMA) or with MPA and different substrates (e.g. MPA/primary amines). Similarly, lowering the polarity of the NMR solvent leads to increased $\Delta\delta^{RS}$ values in MPA amides only.[4]

Recent developments have shown that the absolute configuration of alcohols and amines can also be obtained using only one derivative[3,5,6] (either with the *R* or with the *S* auxiliary). Information about the advantages and/or limitations of this single derivatization option are particularly relevant for the researcher in terms of saving time and sample quantity: in the double derivatization procedures sufficient substrate is needed to obtain good quality ^{1}H NMR spectra of the two derivatives, whereas in the single derivatization procedure only one derivative has to be prepared.

In order to facilitate the use of this methodology, we present here a short guide for the assignment of the absolute configuration that has been specially written for those who are interested only in the practical application of this technique.

For the sake of simplicity, this guide is ordered by substrate type and presented in schematic form. It begins with general information about the method and then provides relevant information about the appropriate reagents and the differences between them. In addition, the experimentally established NMR conditions (solvent, temperature) for each functional group are given. Changes to other conditions not previously tested (i.e. the use of solvent systems different from those mentioned in this work) are not recommended and could lead to misleading results. A short, representative experimental description of the derivatization procedures and the availability of the reagents is included at the end of the paper.

2. Methodology

This paper refers exclusively to the assignment of the configuration of monofunctional primary and secondary alcohols, primary amines and carboxylic acids (substrates) in conjunction with MPA, MTPA, 9-AMA, 9-AHA and BPG (auxiliary reagents). Procedures are described based on both the double and the single derivatization methods.

The procedure for the assignment of the absolute configuration by double derivatization of a substrate

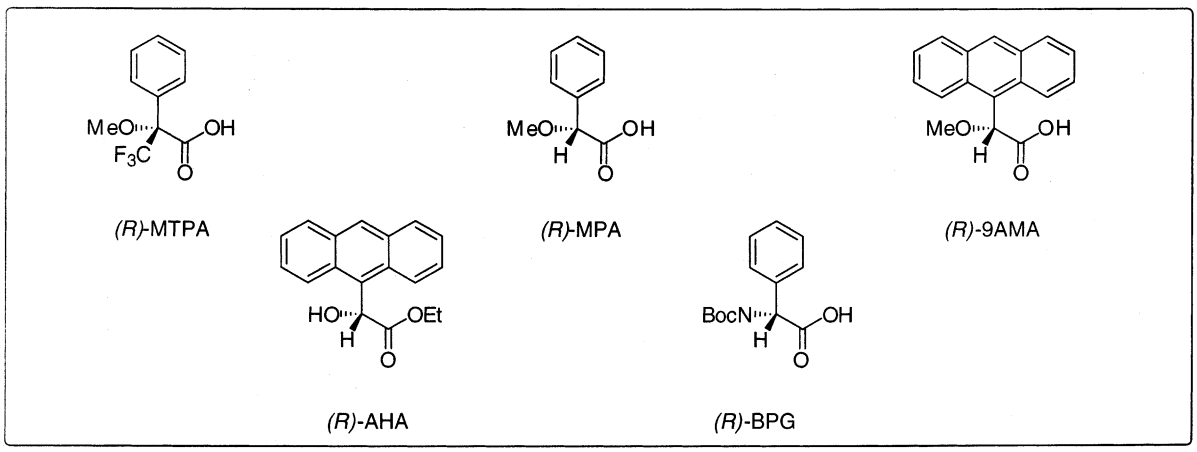

Figure 1.

bearing the functional group and substituents L_1 and L_2 (this choice is arbitrary), directly bonded to the stereogenic carbon, consists of a series of steps. These steps are as follows:

Step 1 – Derivatization of the substrate with the *R* and the *S* enantiomers of the selected auxiliary reagent (Fig. 2a). The use of only one enantiomer will be explained later.

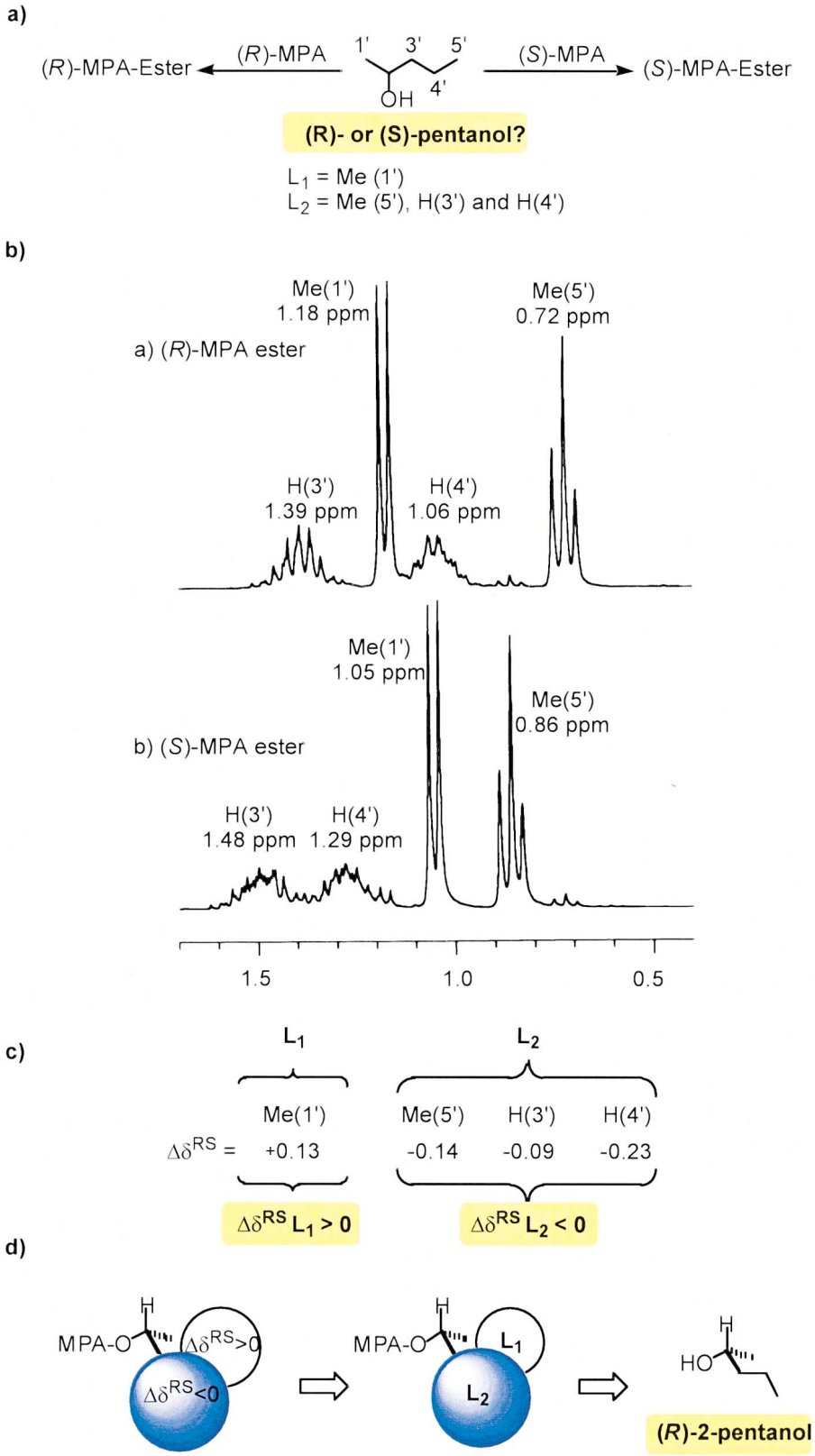

Figure 2. Procedure for the assignment of the configuration of (*R*)-2-pentanol.

Step 2 – Assignment of the proton NMR signals of L_1 and L_2 in both derivatives (see Fig. 2b). Correct assignment is a prerequisite in this method and 2D NMR should be used if necessary.

Step 3 – Comparison of the chemical shifts of the signals due to protons in L_1 and L_2 in both the *R* and the *S* derivatives and calculation of the corresponding differences expressed as $\Delta\delta^{RS}$. The parameter $\Delta\delta^{RS}$ represents the differences between the NMR spectra of the two derivatives and is defined as the chemical shift of the signal for a certain proton or substituent L_1 in the derivative prepared from the *R*-auxiliary minus the chemical shift of the same proton in the derivative prepared from the *S*-auxiliary ($\Delta\delta^{RS}L_1 = \delta^{R}L_1 - \delta^{S}L_1$). The sign of $\Delta\delta^{RS}$ (+ or −) corresponds to the signals for all of the protons of substituent L_1 and the opposite sign should result for all the protons in L_2 (Fig. 2c). Two points must be stressed: (a) the use of identical internal referencing of chemical shifts for the two spectra being compared, especially when small shift differences are observed (i.e. TMS or solvent resonance) and (b) the comparison of solutions of similar concentrations to avoid possible concentration dependent shift differences.

Step 4 – Consider the model in Fig. 2 and insert the substituent with a positive $\Delta\delta$ and that with a negative $\Delta\delta$ value in the appropriate place. This process will allow the assignment of the *R*/*S* configuration (Fig. 2d).

In some cases, the assignment can be carried out using only one of the two derivatives (prepared from either the *S* or the *R* enantiomer of the auxiliary). For the single derivatization procedure other parameters are used that are different but still fairly similar to $\Delta\delta^{RS}$ (i.e. $\Delta\delta^{T1T2}$, $\Delta\delta^{Ba}$, $\Delta\delta^{AR}$, $\Delta\delta^{AS}$). The significance of these parameters and their interpretation will be discussed below for each case.

A number of details related to the structure and/or requirements of the substrate, the NMR spectra and the $\Delta\delta$ parameter are of utmost importance[7] for the correct application of this technique and these warrant mention here:

(a) – The substrates should present clearly distinguishable and identifiable NMR signals in the two substituents L_1/L_2. If a substrate does not have protons on one substituent (L_1 or L_2) or does not give distinct NMR signals, the method cannot be used for assignment.

(b) – The most important protons for assignment purposes are those located in the neighborhood of the stereogenic carbon, an area where the maximum magnetic shielding and, therefore, the larger $\Delta\delta$ values occur (two or three bonds away from the stereogenic carbon is acceptable). However, protons located in more remote positions along the chain of L_1 or L_2 can also be used if their $\Delta\delta$ values are sufficiently high. These signals are particularly useful when the most efficient reagents are used. Nevertheless, protons located in the plane of the reagent (MeO–C–C=O) should not be considered (Fig. 3).

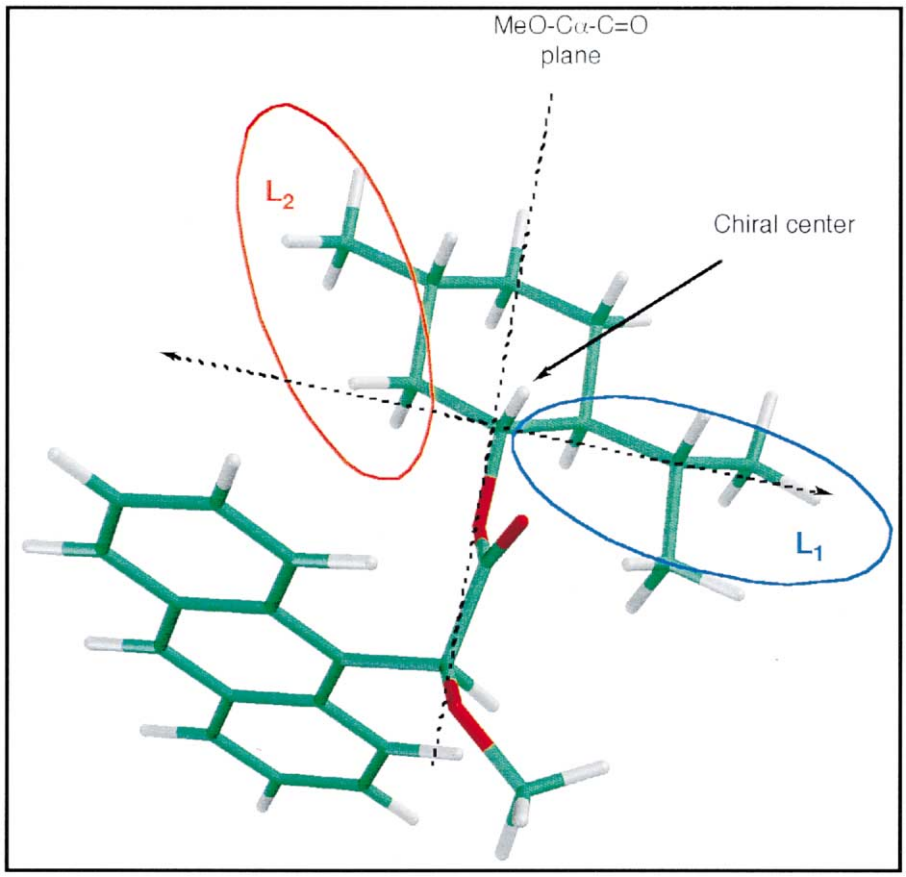

Figure 3. Illustration of L_1/L_2 and the MeO–C–C=O plane in the (*S*)-9-AMA ester of (−)-menthol.

(c) – All of the protons along L_1 should present the same $\Delta\delta$ sign, which should be opposite to that obtained for all the protons along L_2. In this way a different sign corresponds to each substituent (i.e. positive for L_1 and negative for L_2). If such an homogenous distribution of signs is not obtained, the data may well produce an erroneous assignment of configuration. This is particularly critical if it occurs with the protons that are closer to the stereogenic carbon and, in such a case, the only solution is to use a more effective auxiliary reagent.

(d) – The $\Delta\delta$ values should be sufficiently large, be clearly positive or negative and be well above the experimental error of the NMR measurements.

3. Applications

3.1. Primary alcohols by double derivatization

Substrate: primary alcohols with the stereogenic carbon in the β-position.

Auxiliary reagent: (*R*)- and (*S*)-9-AMA; both enantiomers are required.

NMR conditions: $CDCl_3$; room temperature.

General: Only one auxiliary reagent has been sufficiently studied and tested for the assignment of the configuration of primary alcohols.[8–10] This reagent is 9-AMA, which has been demonstrated to give the correct configuration with 13 examples of primary alcohols that have the stereogenic carbon in the β-position.[10] In three cases out of sixteen the method was found to give the incorrect configuration. Nevertheless, the uncertainty about its usefulness for novel, unstudied primary alcohols can be predicted by semiempirical calculations.

Procedure: The sample is divided into two with one half esterified with (*R*)-9-AMA and the other with (*S*)-9-AMA. The spectra of both derivatives are recorded, the signals assigned, the $\Delta\delta^{RS}$ values calculated for substituents L_1 and L_2 (do not forget that the signs for L_1 and L_2 should be opposite) and use the model shown in Fig. 4 to place the substituents L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{RS}$.

3.2. Carboxylic acids by double derivatization

Substrate: carboxylic acids with the stereogenic carbon in the α-position.

Auxiliary reagent: (*R*)- and (*S*)-9-AHA; both enantiomers are required.

NMR conditions: $CDCl_3$; room temperature.

General: This auxiliary reagent has been widely tested for the assignment of configuration by NMR. The reliability of 9-AHA has been demonstrated with the assignment of the correct configuration of 16 examples of structurally diverse carboxylic acids having the stereogenic carbon in the α-position.[8,11,12] Some other reagents can also be found in the literature but the number of test cases investigated is much lower and theoretical foundations are not described.

Procedure: The sample is divided into two halves with one half esterified with (*R*)-9-AHA and the other with (*S*)-9-AHA. The spectra of both derivatives are recorded, the signals assigned, the $\Delta\delta^{RS}$ value calculated for substituents L_1 and L_2 (do not forget that the signs for L_1 and L_2 should be opposite) and the model shown in Fig. 5 used to place the substituents L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{RS}$.

3.3. Primary amines by double derivatization

Substrates: primary amines with the stereogenic carbon in the α-position.

Auxiliary reagents: (*R*)- and (*S*)-MPA; (*R*)- and (*S*)-MTPA; (*R*)- and (*S*)-BPG; both enantiomers are required in all three cases.

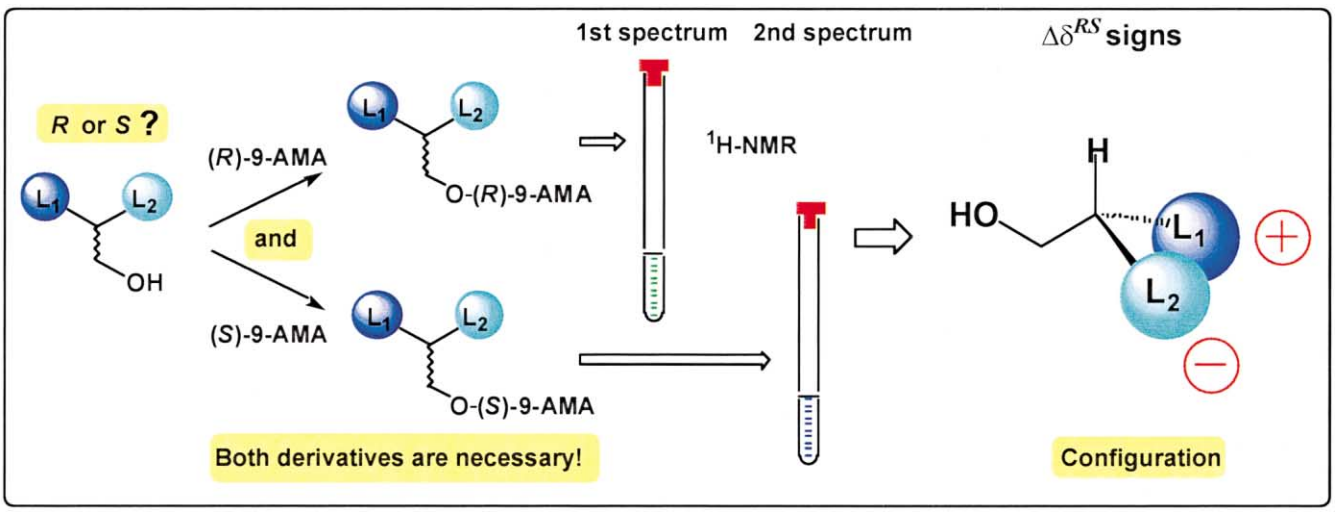

Figure 4. Model for the assignment of the absolute configuration of primary alcohols.

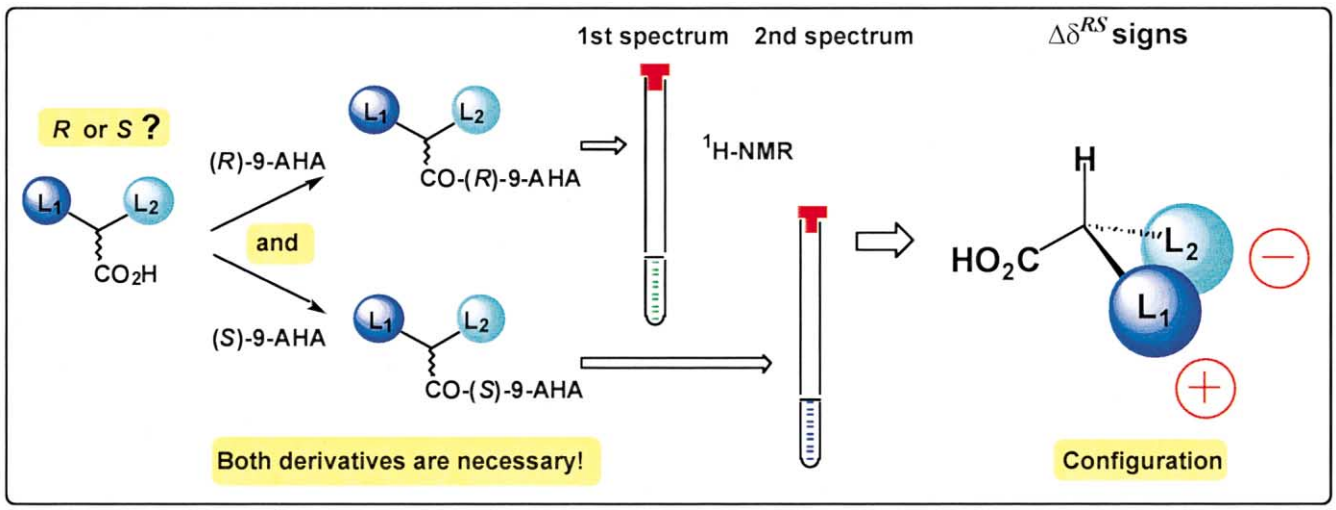

Figure 5. Model for the assignment of the absolute configuration of carboxylic acids.

NMR conditions: $CDCl_3$; room temperature.

General: Several auxiliary reagents have been used in the double derivatization procedure for the assignment of the configuration of primary amines with the stereogenic center in the α-position. MPA[13,4] and MTPA[14,15] are the classical examples of this type of reagent and BPG is a more recent one.[16] All of these compounds have been widely studied and tested with numerous compounds of known absolute stereochemistry.

MPA and MTPA produce similar $\Delta\delta$ values,[15] but MTPA is more prone to produce an irregular distribution of signs. Lowering the polarity of the NMR solvent can improve the $\Delta\delta^{RS}$ values in the case of MPA amides only.[4] Auxiliary BPG not only produces greater $\Delta\delta$ values but is also the cheapest choice of the three reagents.[16]

One case that requires special attention is when MTPA derivatives are to be prepared from the free acid or from the corresponding acid chloride. One must bear in mind that, due to the standard rules of nomenclature, the (*R*)-MTPA acid and the (*S*)-MTPA chloride have an identical absolute configuration. This means that to produce the (*R*)-MTPA ester or amide derivative, the (*S*)-MTPA chloride or the (*R*)-MTPA acid should be used.[17,18] In addition, it must also be noted that most of the literature data on MTPA derivatives report $\Delta\delta^{SR}$ differences ($\Delta\delta^{SR}L_1=\delta^{S}L_1-\delta^{R}L_1$) rather than $\Delta\delta^{RS}$ differences.

Procedure: The sample is divided into two halves and one half esterified with the (*R*)- and the other with the (*S*)-reagent. The spectra of both derivatives are recorded, the signals assigned, the $\Delta\delta^{RS}$ value calculated for substituents L_1 and L_2 and the models shown in Figs. 6 and 7 used to place the substituents L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{RS}$.

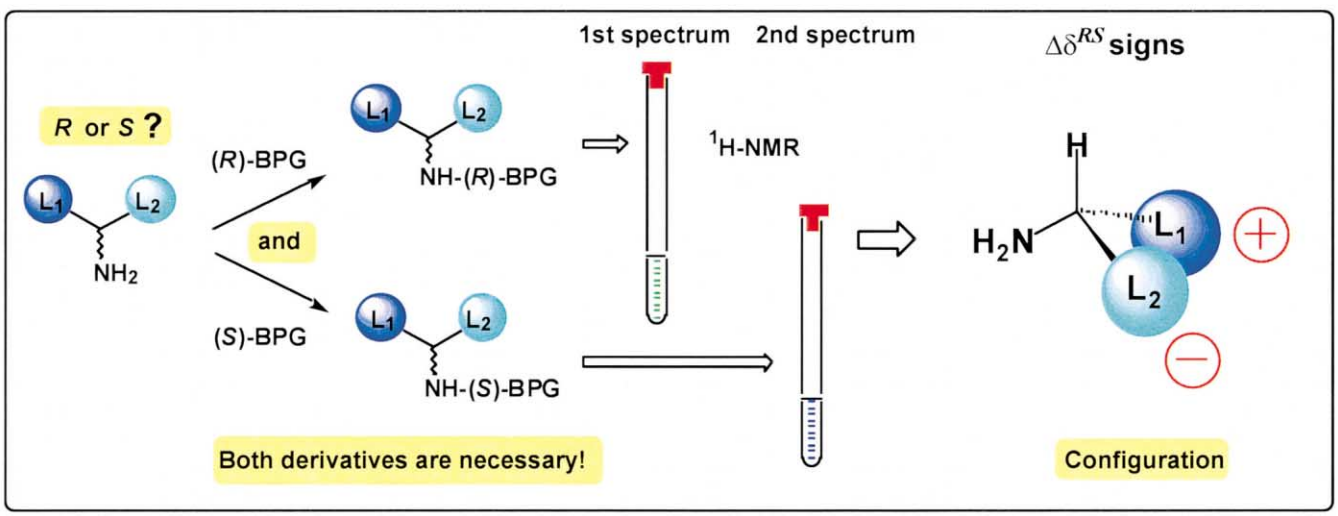

Figure 6. Model for the assignment of the absolute configuration of primary amines by double derivatization (BPG as reagent).

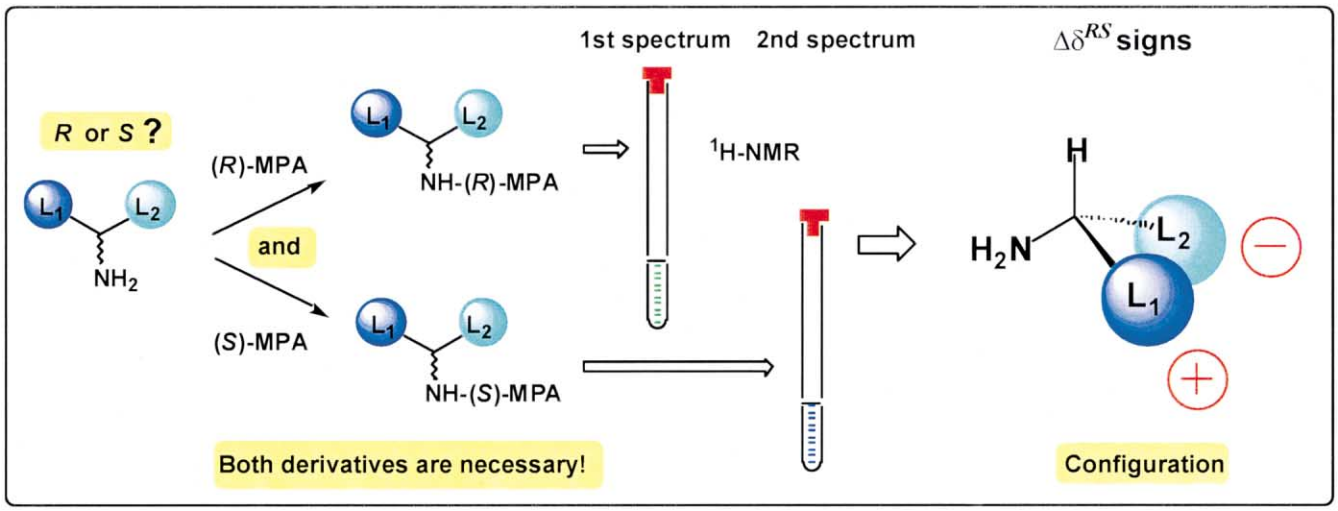

Figure 7. Model for the assignment of the absolute configuration of primary amines by double derivatization (MPA as reagent).

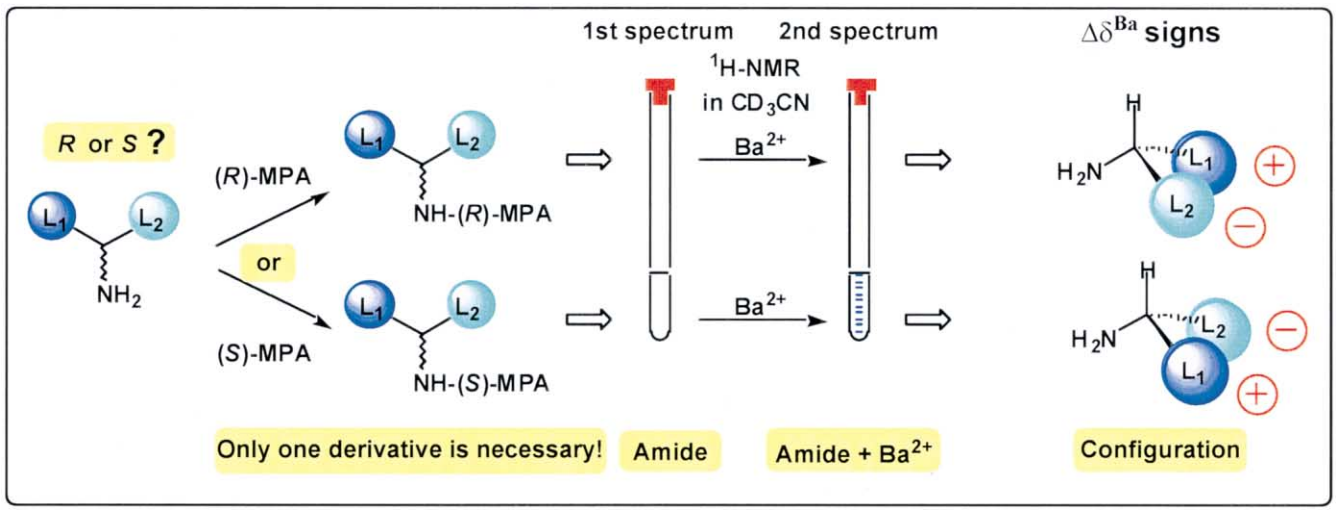

Figure 8. Model for the assignment of the absolute configuration of primary amines by single derivatization.

3.4. Primary amines by single derivatization: complexation with Ba^{2+}

Substrate: primary amines with the stereogenic carbon in the α-position, preferably without groups near to the stereogenic carbon that are able to complex with Ba^{2+} (i.e. 4-oxo-α-amino acids).

Auxiliary reagents: (*R*)- and (*S*)-MPA; only one enantiomer is required in this procedure.

NMR conditions: $CD_3CN/Ba(ClO_4)_2$; room temperature.

General: Only the auxiliary reagent MPA has been reported for the assignment of the configuration of primary amines from the NMR spectra of a single amide derivative.[3] The procedure is based on selective chelation at the MPA moiety and is carried out by comparison of the NMR spectrum of the MPA amide with that of its complex with Ba^{2+} formed in situ. Comparison of the spectra is made through the $\Delta\delta^{Ba}$ parameter, which is defined as the chemical shift of a signal for one substituent (e.g. L_1) in the MPA amide after addition of Ba^{2+} salt minus the chemical shift of the same signal before addition of the Ba^{2+} salt [$\Delta\delta^{Ba}L_1 = (\delta L_1$ of MPA amide+$Ba^{2+}) - (\delta L_1$ of MPA amide); idem $\Delta\delta^{Ba}L_2$]. As in the double derivatization, the signs should be opposite for L_1 and L_2. Numerous examples (13 in all) of amines of known absolute configuration demonstrate the reliability of this procedure.

If the substrate contains in L_1 or L_2 groups that are able to form a complex with Ba^{2+}, the configuration assigned by this method may not be reliable.

Procedure: The sample is reacted with either the (*R*)- or the (*S*)-MPA reagent. The corresponding MPA amide is then isolated, its spectrum recorded in CD_3CN (i.e. 5 mg of MPA amide of bornylamide in 0.5 mL of CD_3CN), and the signals for substituents L_1 and L_2 assigned. Two equiv. of a 0.5 M solution of $Ba(ClO_4)_2$

in CD_3CN (50 μL) are added to the sample and a new spectrum recorded. The new signals are then assigned and the $\Delta\delta^{Ba}$ value calculated. The model shown in Fig. 8 is then be used to place L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{Ba}$.

3.5. Secondary alcohols by double derivatization

Substrate: secondary alcohols with the stereogenic carbon in the α-position.

Auxiliary reagents: (*R*)- and (*S*)-MPA; (*R*)- and (*S*)-MTPA; (*R*)- and (*S*)-9-AMA; both enantiomers are required.

NMR conditions: $CDCl_3$; room temperature.

General: Several auxiliary reagents can be used in the double derivatization procedure for the assignment of the configuration of secondary alcohols in which the stereogenic center is in the α-position. MPA[8,19–21] and MTPA[7,14,22–24] are the classical reagents and 9-AMA is the more recent one.[8,20,21] All of these compounds have been studied in depth and tested with numerous compounds of known absolute stereochemistry. However, there are several important points and differences that should be noted:

– MTPA sometimes produces very small $\Delta\delta^{SR}$ values and an irregular distribution of signs, a situation that may lead to erroneous assignments.[7,24] In addition, the use of ^{19}F instead of ^{1}H NMR spectroscopy for the assignment of configuration with MTPA derivatives has been reported to be unreliable.[22] MTPA therefore does not present any special advantages over the other two reagents and we do not recommend its use.[7]

– MPA does not suffer from the disadvantages outlined above and, in addition, it allows the possibility of increasing the $\Delta\delta^{RS}$ values by simply recording the NMR spectra at lower temperature.[2] Furthermore, MPA can be used in the single derivatization procedure.[5]

9-AMA is the most powerful reagent of all three. It produces the greatest $\Delta\delta^{RS}$ values and is particularly suited for substrates with complex or overlapping spectra and long chains.[21] 9-AMA can also be used for primary alcohols.[9,10] The reagent can be easily prepared (see Section 4) and, although it is not available from the normal suppliers, samples can be obtained from the authors upon request.

Procedure: The sample is divided into two halves with one half reacted with the (*R*)- and the other with the (*S*)-reagent. The spectra of both ester derivatives are recorded, the signals assigned, the $\Delta\delta^{RS}$ value calculated for substituents L_1 and L_2 and the model shown in Fig. 9 used to place the substituents L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{RS}$.

3.6. Secondary alcohols by single derivatization: low-temperature NMR

Substrate: secondary alcohols with the stereogenic carbon in the α-position.

Auxiliary reagents: (*R*)- and (*S*)-MPA; only one enantiomer is required.

NMR conditions: CS_2/CD_2Cl_2 (4:1)/variable temperature (from rt to e.g. −70°C).

General: Only MPA has been described for the assignment of the configuration of secondary alcohols using this procedure.[5] The method is based on selective modification of the conformational equilibrium by lowering the temperature of the NMR probe.

The assignment of the configuration is carried out, using the $\Delta\delta^{T1T2}$ parameter, by comparison of the NMR spectrum of a single derivative taken at room temperature and another spectrum recorded at lower temperature. For a given substituent, $\Delta\delta^{T1T2}L_1$ (for example) is the difference between the chemical shift of a signal of L_1 in the MPA ester at room temperature

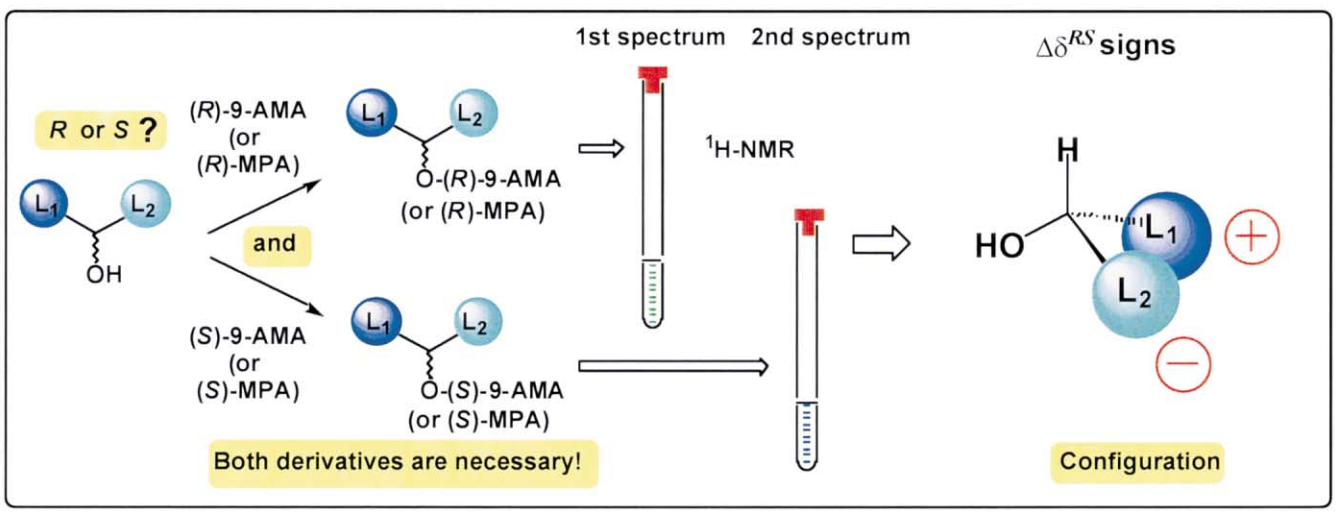

Figure 9. Model for the assignment of the absolute configuration of secondary alcohols by double derivatization.

($\delta^{T1}L_1$) and the chemical shift of the same signal at the lower temperature ($\delta^{T2}L_1$). As in the double derivatization procedure, the signs should be opposite for L_1 and L_2. The reliability of the results from this method has been proven on many compounds of known absolute stereochemistry.

Procedure: The sample is reacted with the (*R*)-MPA or the (*S*)-MPA reagent. The spectrum of the MPA ester derivative is recorded at room temperature and the signals for L_1 and L_2 assigned. A spectrum is then recorded at lower temperature (e.g. −70°C) and the $\Delta\delta^{T1T2}$ value calculated (δ at the higher temperature T_1 minus δ at the lower temperature T_2). The model shown in Fig. 10 is then used to place L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{T1T2}$.

3.7. Secondary alcohols by single derivatization: complexation with Ba^{2+}

Substrate: secondary alcohols in which the stereogenic carbon is in the α-position, preferably without groups that are able to complex with Ba^{2+} (e.g. α- and β-hydroxyesters).

Auxiliary reagents: (*R*)- and (*S*)-MPA; only one enantiomer is required.

NMR conditions: $CD_3CN/Ba(ClO_4)_2$/room temperature.

General: Only MPA has been described for the assignment of the configuration of secondary alcohols

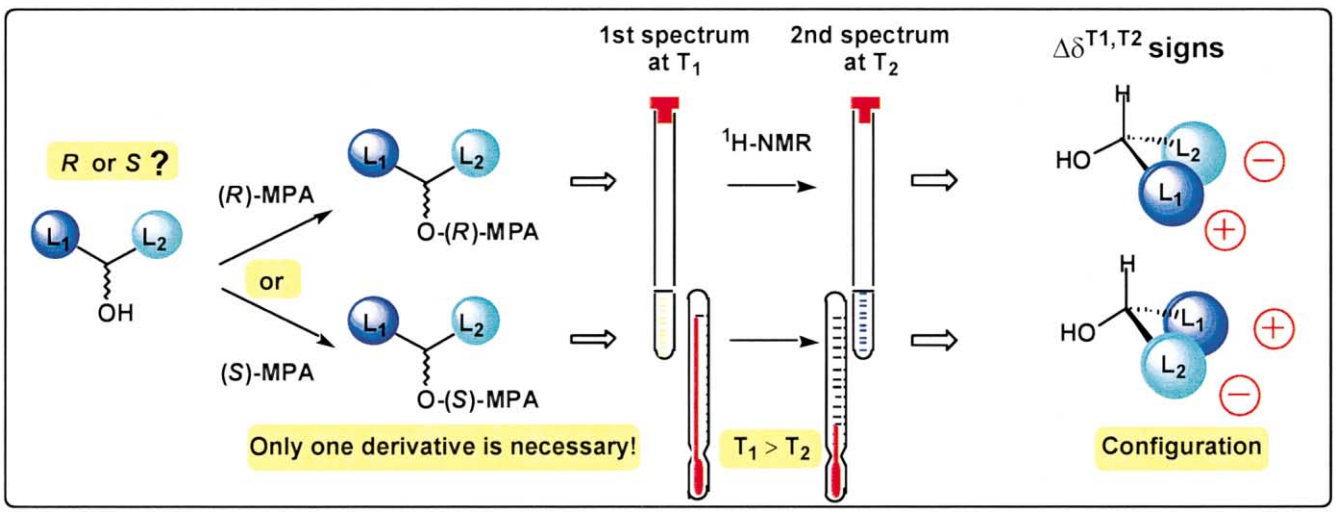

Figure 10. Model for the assignment of the absolute configuration of secondary alcohols by single derivatization.

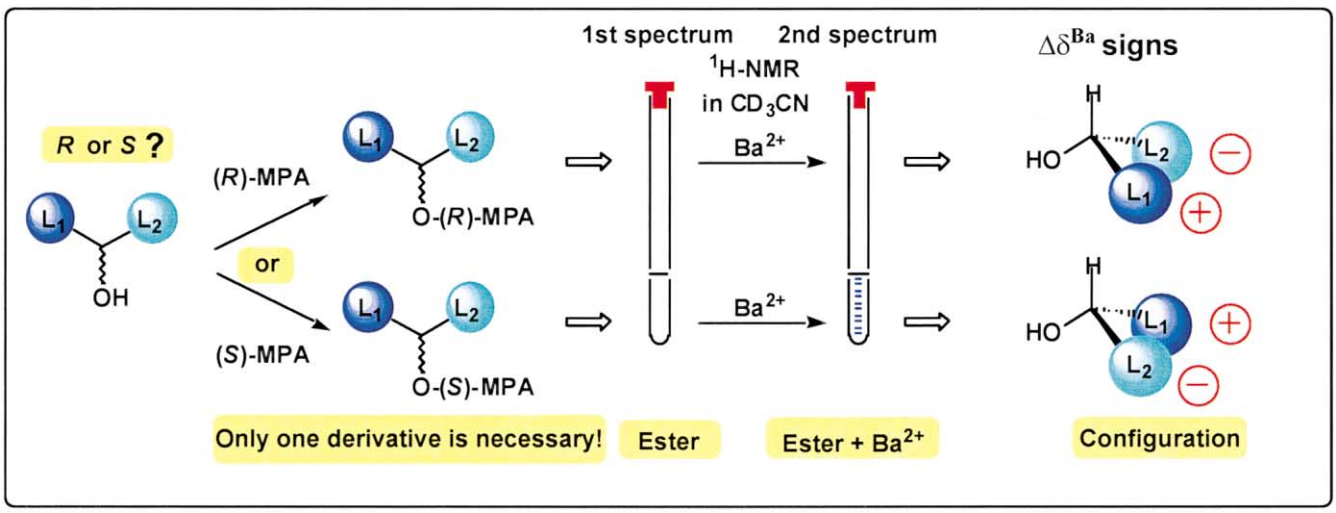

Figure 11. Model for the assignment of the absolute configuration of secondary alcohols by single derivatization (complexation with Ba^{2+}).

using a single derivative.[25] The procedure is based on selective chelation at the MPA moiety and is carried out by comparison of the NMR spectra of the MPA ester derivative with that of its complex with Ba^{2+}. The complex is formed in situ and the $\Delta\delta^{Ba}$ parameter is defined as the chemical shift of a substituent signal (e.g. L_1) in the MPA ester before addition of Ba^{2+} minus the chemical shift of the same signal after addition of Ba^{2+} [$\Delta\delta^{Ba}L_1 = (\delta L_1$ of MPA ester)–(δL_1 of MPA ester+Ba^{2+}); idem $\Delta\delta^{Ba}L_2$]. Numerous examples of substrates of known absolute configuration have been used to demonstrate the reliability of this procedure. It should be noted that if L_1 or L_2 contain functional groups that are able to complex with Ba, they will compete with the chelation at the MPA moiety and the configuration assigned may be erroneous.

Procedure: The sample is reacted with the (*R*)- or the (*S*)-MPA reagent, the spectrum of the resulting MPA ester is recorded in CD_3CN (5 mg of ester in 0.5 mL of CD_3CN), and the signals of L_1 and L_2 assigned. Solid anhydrous $Ba(ClO_4)_2$ is added to the NMR tube until saturation is attained (about 200 mg per tube) and a new spectrum recorded. The signals are assigned and the $\Delta\delta^{Ba}$ value calculated. The model shown in Fig. 11 is used to place L_1 and L_2 in space in accordance with the signs of $\Delta\delta^{Ba}$.

3.8. Secondary alcohols by single derivatization: esterification shifts

Substrate: secondary alcohols with the stereogenic carbon in the α-position.

Auxiliary reagents: (*R*)- and (*S*)-9-AMA; only one enantiomer is required.

NMR conditions: $CDCl_3$/room temperature.

General: The procedure is based on the NMR shifts observed when a secondary alcohol is derivatized with (*R*)- or (*S*)-9-AMA.[6] The study of numerous examples (22 in all) of substrates of known absolute configuration indicates that the sign of the esterification shift is related to the absolute configuration of the alcohol and to that of the auxiliary reagent. The differences between the chemical shifts of L_1 and L_2 in the free alcohol and those in the (*R*)-9AMA and (*S*)-9AMA ester are expressed as $\Delta\delta^{AR}$ and $\Delta\delta^{AS}$.

Procedure: The spectrum of the secondary alcohol is recorded and the signals due to L_1 and L_2 are assigned. The sample is converted into its (*R*)- or into (*S*)-MPA ester, the spectrum of the derivative recorded, the signals assigned and the $\Delta\delta^{AR}$ (or $\Delta\delta^{AS}$) value calculated. The model shown in Fig. 12 is used to place L_1 and L_2 in space in accordance with the $\Delta\delta$ values obtained.

4. Experimental

4.1. General

Auxiliary reagents MPA, MTPA and BPG are commercially available. Reagents 9-AMA and 9-AHA can be prepared by standard procedures[4,10] or acquired from the laboratories of the USC upon request to the authors. Numerous examples of derivatizations of alcohols, amines and carboxylic acids can be found in the literature cited. The two most generally used procedures for derivatization of alcohols and carboxylic acids, employ the auxiliary reagent (MPA, MTPA, BPG or 9-AMA) either as the free acid, or as the corresponding acid chloride while for derivatization of amines the acid is usually employed.

4.2. Preparation of the acid chlorides

Oxalyl chloride (5 mmol) was added to a mixture of the corresponding acid [MPA, 9-AMA, etc. (0.5 mmol)] and DMF (0.05 mmol) in hexane at room temperature. After 2 days, the solvent was evaporated to dryness at reduced pressure to afford the acid chloride.[26,27]

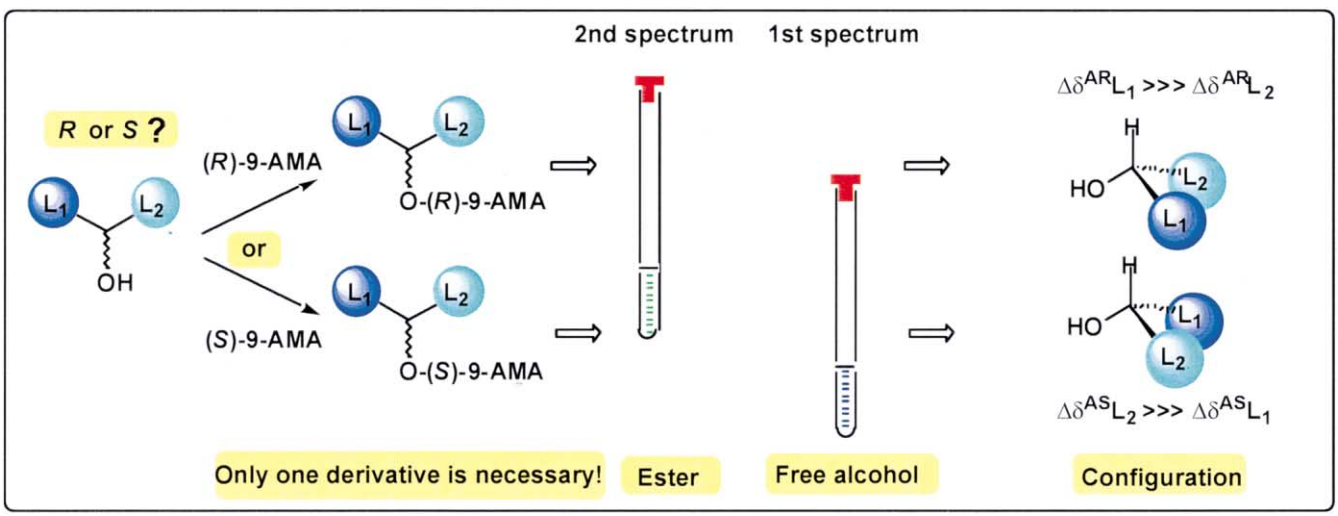

Figure 12. Model for the assignment of the absolute configuration of secondary alcohols by single derivatization (9-AMA esterification shifts).

4.3. Preparation of the esters from the acid chloride

The corresponding acid chloride [MPA-Cl, 9-AMA-Cl, etc. (0.5 mmol)], prepared as above, was dissolved in 5 mL of CH_2Cl_2 and added to a solution of the alcohol (0.1 mmol), Et_3N (1.2 mmol) and DMAP (12 mg, 0.1 mmol) in 10 mL of CH_2Cl_2. After 15 min the solution was washed with H_2O, dried and concentrated to a residue which was purified by flash chromatography on silica gel.[26,27]

4.4. Preparation of the esters from the free acid

The esters were prepared by treatment of alcohol (0.5 mmol) with the corresponding acid [MPA, 9-AMA, etc (0.5 mmol)] in the presence of DCC (0.6 mmol) and DMAP (catalytic) in 10 mL of CH_2Cl_2. The reaction mixture was filtered to remove the dicyclohexylurea and the ester purified by flash chromatography on silica gel eluting with hexane–ethyl acetate.[8,19]

4.5. Preparation of the amides from the free acid

Preparation of diastereomeric amides from either the free amine or the amine salt (0.5 mmol) and the corresponding acid [MPA, 9-AMA, etc (0.5 mmol)] was carried out with 0.6 mmol of DCC (free amine) or 0.6 mmol of DCC and 0.5 mmol of DMAP (amine salt) in 10 mL of CH_2Cl_2. The reaction mixture was filtered to remove the dicyclohexylurea and the amide purified by flash chromatography on silica gel eluting with dichloromethane.[4,13]

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