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Determining Factors in the Assignment of the Absolute Configuration of Alcohols by NMR. The Use of Anisotropic Effects on Remote Positions.

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Dedicated to the memory of Professor Luigi Minale, a pioneer in the Chemistry of Marine Natural Products.

Abstract: The factors governing the efficiency of arylmethoxyacetic acids (AMAAs) for the determination of the absolute configuration of alcohols by NMR, have been identified and their influence studied. The largest $\Delta\delta^{RS}$ values are obtained either increasing the size of the aryl ring (i.e. α-(9-anthryl)-α-methoxyacetic acid, **5**), or the population of the most stable conformer (i.e. reagent **3** at low temperature). The use of **5** to induce useful shifts on remote protons of complex molecules (i.e. androsterone) is described. © 1997 Elsevier Science Ltd.

INTRODUCTION

The absolute stereochemistry of an organic compound determines important aspects of its properties, reactivity and biological activity. Several methods are regularly used to determine the configuration at the asymmetric centers.[1] The heavy-atom phase-shifted X-ray crystallographic analysis being the most general and reliable is nevertheless limited by the necessity to get adequate monocrystals and requires specialized equipment. Other methods are used in solution and provide the absolute configuration of certain asymmetric centers that are then correlated to the rest of the molecule. These procedures require the presence in the molecule of a handle, a functional group necessary to link the substrate to the reagent and therefore are specifically used with certain classes of compounds. Thus, esterification with a benzoic acid or analog is used for alcohols in Harada and Nakanishi's CD method; esterification with α-phenylbutiric acid followed by saponification of the corresponding esters is the basis of Horeau's method; in the NMR based methods the chiral substrate (i.e. a secondary alcohol or amine) of unknown absolute stereochemistry *(?)*-**A**, is separately esterified with the *(R)*- and *(S)*-enantiomers of an auxiliary reagent **B**, and the NMR spectra of the two resulting diastereomers *(?)*-**A**-*(R)*-**B** and *(?)*-**A**-*(S)*-**B** are compared (Figure 1a). The two spectra should be different and the assignment of configuration is based on the existence of a fixed association between the absolute stereochemistry at the chiral centre of the auxiliary reagent **B**, and the chemical shifts of L_1/L_2 in the two derivatives.

For this relationship to exist, some conditions have to be fulfilled:

a) the conformational composition and preference should be the same in the two diasteroisomeric derivatives and independent of the nature of substituents L_1 and L_2 of **A**.

b) substituent **Y** at the auxiliary reagent **B**, should be able to affect in a selective and recognized way the chemical shifts of substituents L_1/L_2 at the substrate part, and

c) there should exist in both derivatives a significantly more populated conformer where group **Y** acts strongly on L_1/L_2.

Figure 1a illustrates the relative position of group **Y** in relation to L_1 and L_2 in each of the three main conformers **a, b** and **c**. Naturally, due to the conformational equilibrium, a substantial part of the overall capability of group **Y** for shielding/deshielding L_1/L_2 is lost in the average with the other conformers. The average NMR spectra thus reflects the balance between the relative population and the intensity of action of **Y** in each conformer and for simplicity, is usually interpreted as originated from a single NMR-relevant conformer. Therefore, a perfect knowledge of the main conformations and of the intensity and characteristics of the effect of **Y** on the chemical shifts of L_1/L_2 in each conformer is essential to correlate NMR to the absolute stereochemistry.

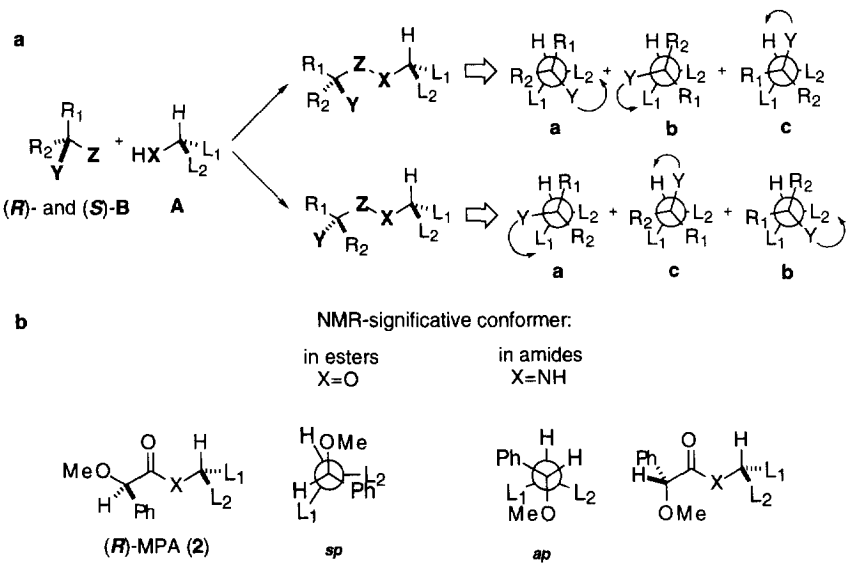


Figure 1.

In its more widely extended version, **Y** is an aromatic or an unsaturated group that produces shielding/deshielding on L_1 or L_2 through space, and R_1 and/or R_2 are polar groups. Frequently used reagents for secondary alcohols and primary α-substituted amines are arylmethoxyacetic acids (AMAAs) and particularly *(R)*- and *(S)*-methoxytrifluormethylacetic acid, MTPA (**1**), and *(R)*- and *(S)*-methoxyphenylacetic acid, MPA (**2**), that are commercially available. In the case of MPA, conformer ***sp*** (Figure 1b) is the relevant one, while in amides, ***ap*** is the NMR-significant conformer. In this way, the prediction of the absolute configuration of the alcohol or amine moiety is straightforward knowing which substituent (L_1 or L_2), resonates at lower (or higher) field in the (*R*)- or (*S*)-ester/amide and comparing that information with the structure of the significant conformer.

Other reagents where the phenyl group has been replaced by different aryl rings (in general AMAAs, **3-8**, Figure 2)[1], axially chiral compounds[3], diazaphophamidic chlorides[4] and even a glucoside[5] have been reported.

In this paper we wish to present our results on the study of the main factors that play a role in this method and to propose new, more efficient and reliable reagents for the determination of the absolute stereochemistry of secondary alcohols. Application of these reagents to molecules with chiral centers at longer distance from the auxiliary reagent is discussed too. Short accounts of some of these results have been recently communicated.[2]

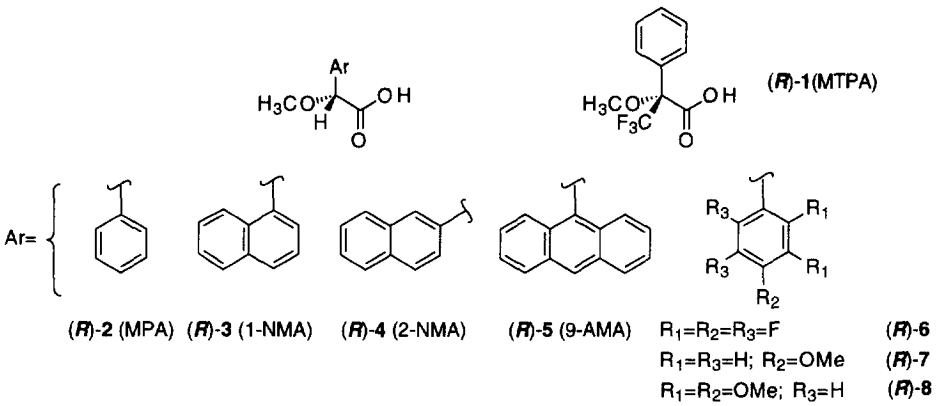


Figure 2.

STRUCTURE AND CONFORMATION OF THE AMAAs AND THE MAGNITUDE OF $\Delta\delta^{RS}$

The AMAAs esters exist in solution as a conformational equilibrium composed by essentially two forms: ***sp***, (the more stable one)[6] and ***ap*** , independently of the alcohol structure. They are shown in Figure 3a-b. In both conformers, the C_α-OMe, C=O and C_1'-H bonds are approximately co-planar and this necessarily leads to an arrangement where the C_α-Ar bond is ca. perpendicular to the C=O and C_1'-H bonds (the calculated Ar-C_α-C=O dihedral angles are 92.3° (102.1°), 104.9° (90.1°) and 103.8° (96.7°) for MPA (**2**), 1-NMA (**3**) and 9-AMA (**5**) acids respectively (data in parenthesis correspond to the ***ap*** form).

For its part, the aryl ring plane is in those two conformers, practically co-planar with the C_α–H bond and perpendicular to the C_α-C=0 bond (angles ranging from 8 to 16 in the ***sp*** and from 14 to 23 degrees in the ***ap*** conformer, for MPA, 1-NMA and 9-AMA esters. Those values mean that substituent L_1 in the ***ap*** conformer and L_2 in the ***sp*** one, are located in the zone of maximum effect of the shielding magnetic field[7] for an (***R***)-ester. In fact, the area of the maximum shielding is ca. 3-4 bonds apart from the chiral center and about 0.6 Å over L_2, (Figure 3c). Maximum shielding increments of 0.3-1.0 ppm would then be expected in that zone for L_1/L_2 if the ester derivative were composed by only the ***sp*** conformer, but due to the fast conformational exchange in NMR time scale, the experimental shielding on L_1/L_2 is weight averaged between those in the ***sp*** and those of the ***ap*** conformers.

The importance of the contributions from the less abundant ***ap*** rotamers to the time-averaged NMR chemical shifts of L_1 and L_2 are evident from Figures 3a-b. The expected signs for the $\Delta\delta^{RS}$ values obtained according to these models are shown in Figure 3d. In the (***R***)-ester, the shift of L_2 (shielded in conformer ***sp***) is averaged with that of conformer ***ap*** where L_2 is not affected by the phenyl ring, and therefore resonates at lower field than in ***sp***. In the (***S***)-ester, L_2 is shielded in ***ap*** but this upfield shift is partially cancelled by averaging with the ***sp*** rotamer where L_2 is not affected by the aryl ring.

As a result, the magnitude of $\Delta\delta^{RS}$ is clearly smaller than the maximum 0.3-1.0 ppm calculated for rotamer ***sp*** and values lower than 0.001 ppm. are frequently observed for protons located in the proximity of the asymmetric carbon. For protons far away from the asymmetric center (outside the zone of effective anysotropic effect), the experimental $\Delta\delta^{RS}$ are practically negligible.

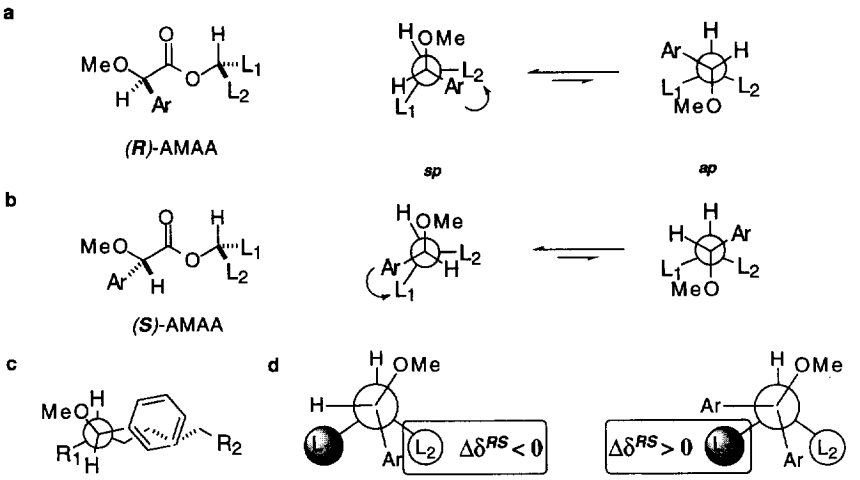


Figure 3.

Of course, the higher the relative abundance of the ***sp*** rotamer, the larger the shielding and the $\Delta\delta^{RS}$ have to be observed experimentally.

To sum it up, the magnitude of $\Delta\delta^{RS}$ depends on:

a) the relative population of conformers ***sp*** and ***ap***,

b) the distance and orientation of the aryl ring with respect to the substrate, and

c) the nature of the aromatic system.

Points a and c are characteristics of each reagent while point b is a property of the substrate.

The power of the "auxiliary" reagent to induce selective shifts on L_1 and L_2 is represented by the expression:

$$\Delta\delta^{RS} = f(\Phi, \Delta E, T) = \Phi(\text{aryl ring}) \times [p^{sp}(\Delta E, T) - p^{ap}(\Delta E, T)] \qquad \text{eq. (1)}$$

Were Φ is a function of the aryl ring (effective area of the shielding cone, ring current intensity), and p^{sp} and p^{ap} are the relative populations of those conformers that depend on their energy difference and the temperature. In consequence, higher $\Delta\delta^{RS}$ values could be obtained by increasing 1) the relative population of the conformer ***sp*** over the ***ap*** or 2) by introducing an aryl ring with a more effective aromatic shielding cone.

The first point could be addressed by either modification of the energy gap (ΔE) between the two conformers or by variation of the NMR probe temperature, while the second approach involves the study of different aryl systems.

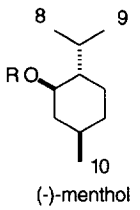
Let us to consider each approach in a more detailed way.

THE EFFECT OF THE SUBSTITUENTS ON THE ARYL RING

Our first attempt to improve the capacity of the auxiliary reagents to effectively separate the resonances of enantiotopic protons, was to investigate how the introduction of acceptor or donor substituents on the phenyl

ring of the model compound MPA (**2**), would affect the $\Delta\delta^{RS}$ values. To this end, the (***R***)- and (***S***)-enantiomers of acids **6**, **7**, **8** and their esters with (-)-menthol (**9**) (compounds **10**, **11** and **12** respectively) were prepared and the corresponding ^{1}H NMR spectra and $\Delta\delta^{RS}$ analyzed.

Table 1. Selected $\Delta\delta^{RS}$ values of the (-)-menthyl esters (**10-14**) of different AMA acids.



	$\Delta\delta^{RS}$			
Acid	Me(10')	Me(8')	Me(9')	Compound
6	0.07	-0.04	-0.10	**10**
7	0.05	-0.021	-0.25	**11**
8	0.06	-0.022	-0.25	**12**
MTPA	0.07	-0.017	-0.04	**13**
MPA	0.05	-0.021	-0.26	**14**

The data obtained are presented in Table 1 and show $\Delta\delta^{RS}$values smaller or similar than those obtained with MPA ester (**14**). In the case of **10** the values are smaller for all the protons investigated and in the same order to those obtained with MTPA ester (**13**). Analogously, esters **11** and **12**, produced $\Delta\delta^{RS}$ values larger than **10** and equivalents to those obtained with MPA.

Calculations have shown that the replacement of the unsubstituted Ph for the trimethoxy- or pentafluor-derivatives (**7** and **8**) do modify the relative populations and geometries of the low energy forms and as a result, the closer (in size) populations and distorted geometries explain the small $\Delta\delta^{RS}$ values observed.

All these data lead us to conclude that no much improvement of $\Delta\delta^{RS}$ values could be expected by changing substituents on the aryl rings of AMAAs.

THE SIZE OF THE ARYL SYSTEM

In a different approach, we decided to change the phenyl group of MPA by another aromatic system. Two different actions can be expected to outcome from this change: one is the modification of the relative populations of the ***sp*** and ***ap*** conformers as a result of the size of the aromatic system, and the other is related not to conformation, but to the intensity, size and shape of the shielding cone area, properties intrinsically characteristic of each aryl system. We will discuss the first point now and leave the second one to the final part of this article.

Modification of the energy gap between ***ap*** and ***sp*** conformers should be achieved by replacement of the substituents at the C_α chiral center of the reagent AMAA. Geometry optimization in HF 3-21 G basis set and energy calculation in 6-31 G*[8] for the low energy conformers of several AMAA esters of methanol, revealed a clear dependence of the ***sp-ap*** energy gap on the aryl ring. Values ranging from 0.19 up to 1.45 kcal/mol are obtained when MPA (**2**), 1-NMA (**3**) and 9-AMA (**5**) esters are considered (a summary of the calculations is given in Table 2). These results indicate that replacement of the phenyl ring of MPA by a larger aromatic system should produce not only a larger area of shielding but it can also be used to tune the conformational equilibrium to a more favorable position. In addition, it is reasonable to expect that the larger effective shielding cone of a naphthyl or anthryl aromatic system should also play an important role to increase the $\Delta\delta^{RS}$ values. Calculations of aromatic shielding effects have in fact demonstrated the importance of this factor.

Table 2. Results of *ab initio* calculations.

AMAA	Conformation	HF 3-21G//HF 3-21G	HF 6-31*//HF 3-21G
		kcal/mol	kcal/mol
MPA	*sp*	0.00	0.00 (0.00)[a]
	ap	1.51	0.19 (0.26)[a]
1-NMA	*sp*	0.00	0.00
	sp[b]	0.57	1.63
	ap	1.85	
	ap[b]	0.88	
9-AMA	*sp*	0.00	0.00
	ap	1.76	1.45

[a]HF 6-31*//HF 6-31*

[b]Conformers with an anti orientation of the 1-naphtyl ring and the $C_\alpha H$.

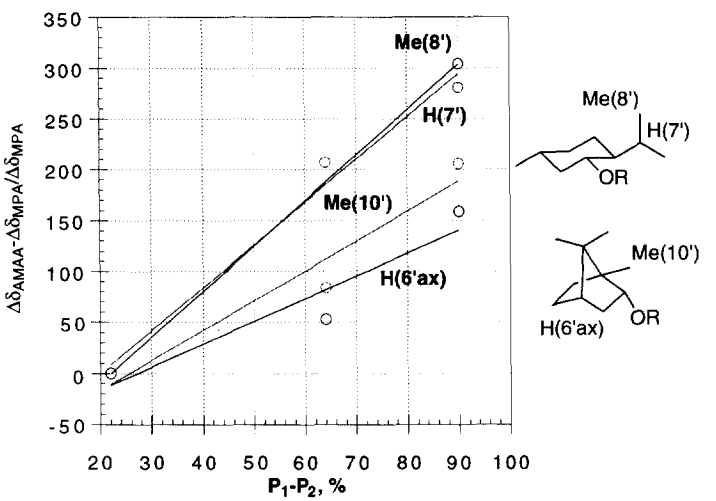


Figure 4. Dependence of $\Delta\delta^{RS}$ with the difference of the ***sp*** and ***ap*** populations (evaluated according to the Boltzman equation on the basis of calculated $\Delta E^{sp/ap}$).

In accordance with the calculations that predicted changes in the conformational ratio with the size of the system, a good correlation of the experimental $\Delta\delta^{RS}$ values with the energy difference of ***sp*** and ***ap*** conformers (*ab initio* calculated) was obtained.

The plot of $\Delta\delta^{RS}$ versus the ***sp/ap*** population difference calculated by the Boltzman equation, for ***(R)***- and ***(S)***-AMAA esters of (-)-menthol and (-)-isopulegol is shown on Figure 4. The experimental data are given in Figure 5.

Thus, we prepared the ***(R)***- and the ***(S)***-2-NMA, 1-NMA and 9-AMA acids (**4**, **3** and **5**) and tested their

ability to produce separate signals for enantiomeric protons in the esters of different alcohols of known stereochemistry [(-)-menthol (**9**), *(**R**)*-3,3-dimethyl-γ-butyrolactone (**15**), *(**S**)*-(3,3-dimethyl butanol (**16**), *(**R**)*-2-butanol (**17**), *((**S**)*-2-hydroxy-3-methyl butiric acid methyl ester (**18**), *(**R**)*-1-(1-naphthylethyl) methanol (**19**), *(**R**)*-1-(2-naphthylethyl) methanol (**20**), *(**S**)*-1-phenethyl alcohol (**21**), methyl *(**S**)*-mandelate (**22**), (+)-isopinocampheol (**23**), (-)-borneol (**24**), (-)-isopulegol (**25**)]. The results, that are in full accordance with the absolute stereochemistry of the alcohols and the predictions made on the basis of the conformational composition (Figure 3d), are shown in Figure 5 and demonstrate that in fact, replacement of the phenyl group for 2-naphthyl, 1-naphthyl or 9-anthryl produce a spectacular increase of $\Delta\delta^{RS}$ values that are in all cases higher, sometimes by a factor of 3, than those found in MPA derivatives. Altogether, they confirm the advantages and reliability of this method and recognizes 2-NMA, 1-NMA and principally 9-AMA, as the most effective reagents known, for the determination of the chirality of secondary alcohols by ^{1}H NMR.

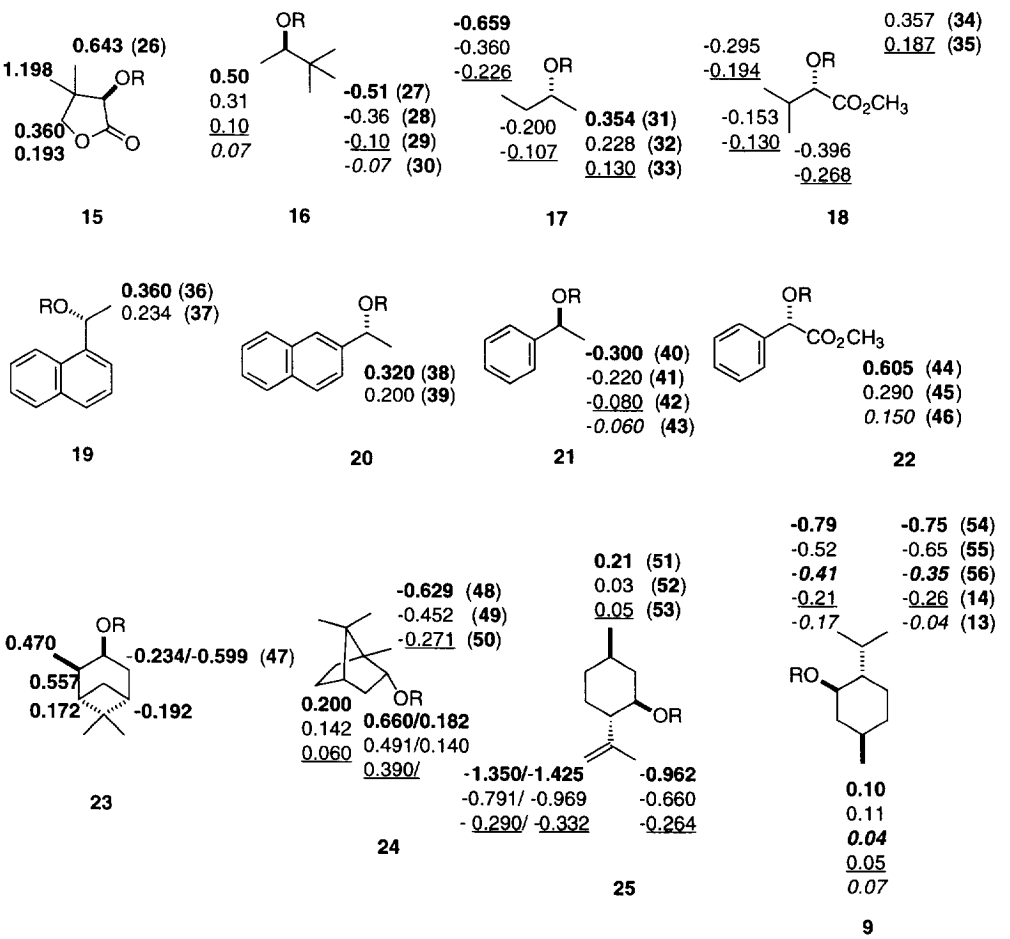


Figure 5. $\Delta\delta^{RS}$ values of AMA esters (**bold: 9-AMA**, plain: 1-NMA, ***bold italic: 2-NMA***, underlined: MPA, *plain italic: MTPA*).

Also, these conclusions strongly support the finding that the conformational characteristics of AMAA

esters are of utmost importance in their ability to produce NMR differentiation, that it is practically unaffected by the nature of the alcohol moiety and, hence, that these reagents and concepts can be of general use with any secondary alcohol.

THE INFLUENCE OF TEMPERATURE AND SOLVENT ON $\Delta\delta^{RS}$

A different way to improve the $\Delta\delta^{RS}$ values, would be to influence the thermodynamics of the conformational equilibrium and so to modify the relative populations of the ***ap*** and ***sp*** conformers. This approach should be very advantageous because no chemical modification of the structure of the auxiliary reagent is involved.

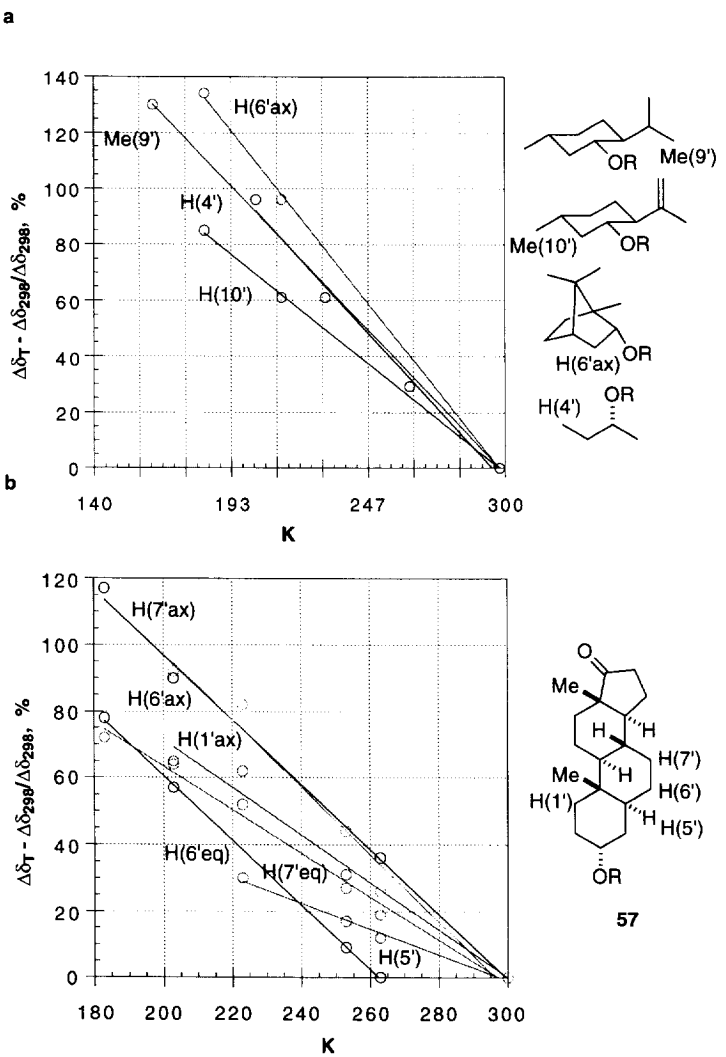


Figure 6. Temperature dependence of $\Delta\delta^{RS}$ in the MPA esters of (-)-menthol (**14**), (-)-isopulegol (**53**),

(-)-borneol (**50**), *(R)*-butan-2-ol (**33**) (a) and *cis*-androsterone (**58**) (b).

Table 3. Temperature dependence of $\Delta\delta^{RS}$ values for AMA derivatives of (-)-menthol, (-)-isopulegol, *(S)* borneol, *(S)*-(+)-2-hydroxy-3-methyl butiric acid methyl ester and *(R)*-(-)-2-butanol.

			$\Delta\delta^{RS}$			
Alcohol	AMMA	T, K	H(7')	Me(8')	Me(9')	Me(10')
9	2-NMA	298		0.269	0.286	0.063
	[**56**]	153		0.444	0.584	0.180
	1-NMA	298	0.930	0.462	0.506	0.059
	[**55**]	193		0.940	1.10	0.120
	9-AMA	298	1.715	0.787	0.85	0.189
	[**54**]	153	2.207	0.809	0.90	0.155
25			Me(9')	H(8'E)	H(H8'Z)	Me(10')
	1-NMA	293	-0.474	-0.608	-0.756	0.093
	[**52**]	213	-0.702	-0.954	-1.223	0.112
24			Me(8')	Me(9')	Me(10')	H(6'ax)
	1-NMA	298	-0.010	-0.028	-0.367	0.389
	[**49**]	261	-0.012	-0.029	-0.430	0.466
		232	-0.012	-0.021	-0.482	0.538
		203	-0.011	-0.019	-0.517	0.613
		186	-0.009	-0.017	-0.530	0.652
18				H(4')	H(5')	H(1')
	1-NMA	293		-0.224	-0.398	0.262
	[**34**]	213		-0.271	-0.442	0.372
		183		-0.290	-0.464	Br
17			H(1')		H(4')	
	1-NMA	293	0.192		-0.299	
	[**32**]	213	0.236		-0.549	
		183	0.260		-0.630	

Two experimental factors are amenable to be easily varied: a) the NMR solvent that acts on the conformational equilibrium according to the polarity of the rotamers involved, and b) the NMR probe temperature whose influence affects the relative stability of the conformers.

In the case of esters, the use of solvents of different polarity can be ruled out as an effective way to modify the ratio ***sp/ap***, because both rotamers present quite similar calculated dipole moments.

For its part, according to Boltzman's rule decreasing the temperature should increase the population of the low energy form in the equilibrium. An increment of the population of the more stable conformer ***sp*** over that of ***ap***, should then be expected when the NMR spectra is taken at low temperature. Crude evaluation of this change for MPA esters predict that a decrease of about 100° should lead to an enlargement of the ***sp*** population by about 10 % and, more important, this corresponds to a minimum increase of $\Delta\delta^{RS}$ of ca. 33 %.

Therefore, the ^{1}H NMR spectra of a MPA ester obtained at lower temperature, should present higher $\Delta\delta^{RS}$ values than those at room temperature.

Experimental evidence of that proposition was obtained by comparison of the MPA esters of (-)-menthol (**14**), (-)-isopulegol (**53**), (-)-borneol (**50**), *(**R**)*-(2)-butanol (a) and *cis*-androsterone (**58**) (b) obtained at different temperatures.

As expected, the $\Delta\delta^{RS}$ observed at low temperature are, for a variety of signals and compounds, larger than those obtained at room temperature (Figure 6a-b). The increment amounts to more than 100 % when the probe descends by about 100° and at the easily attainable 225 K, all the esters examined showed $\Delta\delta^{RS}$ values at least 50% higher than those at room temperature .

Figure 6a shows the plots with a very close slope in a wide temperature range. This is even so for a large molecule such as *cis*-androsterone (**57**) (Figure 6b) and for protons far away from the aryl ring. This result indicates that the thermodynamic parameters governing the conformational equilibrium of the MPA esters are essentially independent of the structure of the alcohol reinforcing the potential of this approach to determine the absolute configuration of any secondary alcohol.

A similar study of the variation of $\Delta\delta^{RS}$ with the temperature in the case of the *(**R**)*- and *(**S**)*-esters of other AMAAs (2-NMA, 1-NMA and 9-AMA acids (**3-5**) has been carried out and similar results were found (Table 3). However, the slope of the plot using reagents **3** and **5** is smaller than in MPA esters. This is particularly so for the 9-AMA ester of (-)-menthol whose ^{1}H NMR spectrum remained practically unchanged over all the temperature range. The most probable explanation for this finding is that the conformational equilibrium in molecules **3-5** is already biased in favor of the ***sp*** conformer at room temperature and therefore $\Delta\delta^{RS}$ can not grow in the same proportion than when MPA is used.

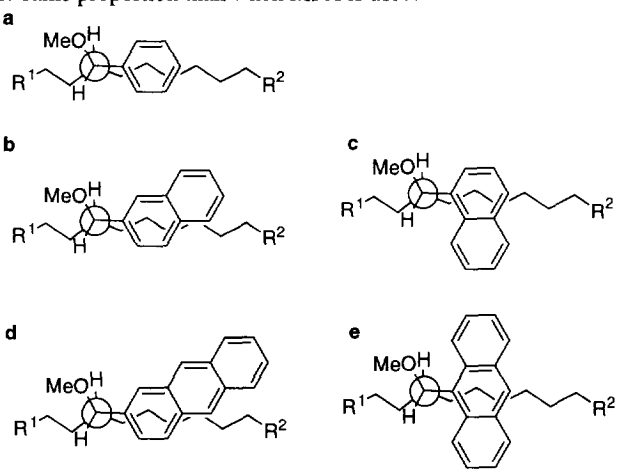


Figure 7.

THE SHAPE OF THE SHIELDING CONE AND ITS EFFECT AT REMOTE POSITIONS

The factors that determine the effectiveness of an AMAA reagent have been shown in Equation 1 as a function of the relative population of the conformers, their energy difference and the properties of the aromatic ring. In a practical application of this concept, we have described that substitution of the phenyl group of MPA by a larger aromatic system, as in 2-NMA, 1-NMA and 9-AMA, increments both the energy gap between ***sp*** and ***ap*** conformers and the area of effective shielding cone, leading to higher $\Delta\delta^{RS}$ values.

We know already that when different alcohols are used, no relevant perturbation of the conformational

equilibrium is produced, but obviously a good fitting between the structure of the alcohol and the aryl ring should lead to the highest $\Delta\delta^{RS}$ values on protons located in the zone of maximum shielding. This suggests that AMAA reagents could be specifically designed to produce large and selective shifts on protons located far away from the alcohol group just by judicious election of an aryl system that fits well to the substrate.

Figure 7a-e represents the situation expected when reagents with different aryl ring are attached to a linear substrate: A 2-substituted naphthalene or anthracene extend the zone of maximum influence along the axis determined by C_α-Ar bond (figure 7b and d), while in the 1-substituted naphthalene and 9-substituted anthracene it goes in the perpendicular direction so that one would expect reagents 2-NMA (**4**) and 2-ATMA (see Figure 7d) to be especially suitable for linear alcohols[2c,d] and 1-NMA (**3**) and 9-AMA (**5**) most probably useful for cyclic alcohols.

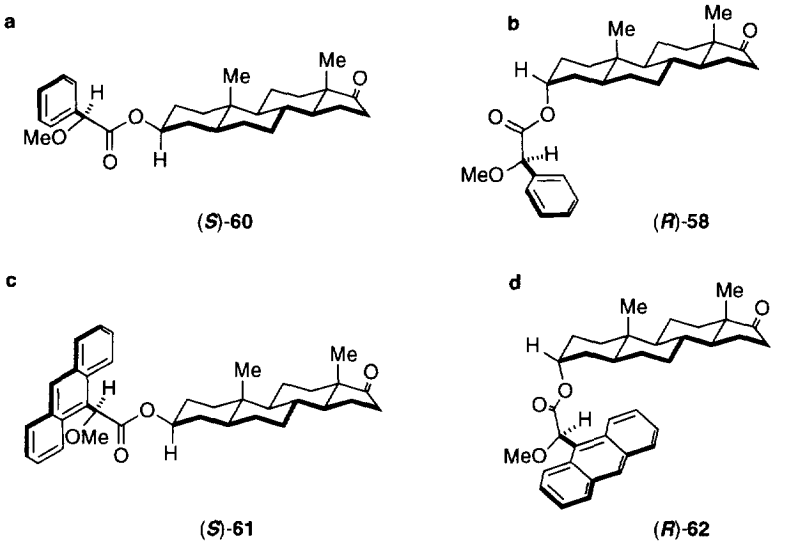


Figure 8.

In the case of cyclic alcohols, models a-d (Figure 8) indicate that if the ester linkage is axial, the disposition of the aryl ring is well suited to interact with the substrate. Again 9-AMA with its larger aryl system should affect the maximum number of protons. Experimental evidence of this supposition, using *cis*- and *trans*- androsterone (**57** and **59** respectively) as substrates, was obtained.

While the spectra of the 9-AMA ester of *trans*- androsterone (**61**) show that only protons close to the OH group are really shifted by the reagent and small values of $\Delta\delta^{RS}$ are obtained, the spectra of the 9-AMA ester of *cis*-androsterone (**62**) show that practically all the protons located on its α–side are under the influence of the aromatic magnetic cone and efficiently shielded, so the massive overlapped ^{1}H NMR spectra of *cis*-androsterone is now extraordinarily simplified. For comparative purposes, the corresponding MPA esters of *cis*-androsterone (**58**) were also examined. Figure 9 shows the $\Delta\delta^{RS}$ values and signs obtained with both reagents. As expected, $\Delta\delta^{RS}$ values are, in the 9-AMA derivative, 3-4 times larger than those obtained with MPA, so practically all the protons can now be distinguished and assigned. More important, the shielding cone of the anthryl system strongly affects hydrogens located in remote positions, well outside the area of influence of MPA, [i.e. H(8'), H(12'), H(14'), H(15'), Me(18')]. At those distances, the $\Delta\delta^{RS}$ are practically negligible in MPA esters.

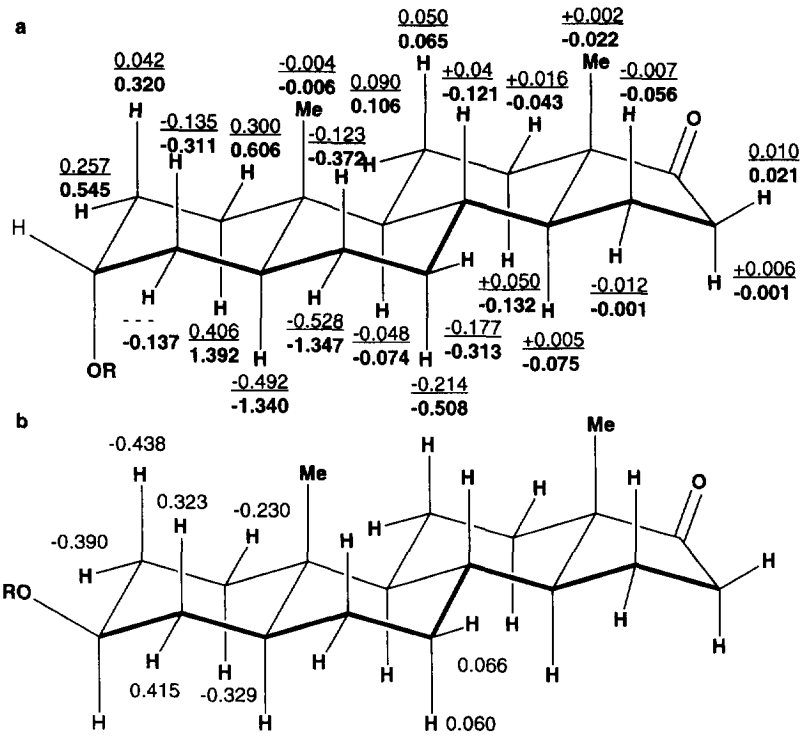


Figure 9.

Furthermore, comparison of the experimental $\Delta\delta^{RS}$ values obtained in the 9-AMA ester with those calculated according to semiclassical theory and a geometry optimized by MM showed a good correlation (Figure 10), being these results is in complete agreement with our previous findings and suggesting that the combined use of aromatic shielding effect calculations with experimental NMR data may constitute a very useful tool for structural analysis at remote positions from the hydroxy group used as a handle by comparison of the experimental shifts or $\Delta\delta^{RS}$ values with the calculated ones for all possible configurations.

CONCLUSIONS

All the above results show that the determination of absolute stereochemistry of secondary alcohols by ^{1}H NMR of AMAAs derivatives is a well founded method (theoretically and experimentally), and that an unequivocal relationship between the chirality of the AMAA reagent, the substrate and the NMR chemical shifts exists. The theoretical background relies on the conformational composition and the aromatic induced shifts produced by the aryl ring, so the intensity of the $\Delta\delta^{RS}$ depends on the orientation of the aryl ring with respect to the substrate in each conformer, their relative populations and the aromatic ring current intensity and extent of the magnetic cone of a particular aryl system.

Analysis of those factors indicate that new and more efficient reagents are obtained with aryl systems like 2-naphthyl, 1-naphtyl and principally 9-anthryl that gives $\Delta\delta^{RS}$ values up to 3 or 4 times higher than those observed with MPA. The reliability of reagents 2-NMA, 1-NMA and 9-AMA to predict the absolute

stereochemistry of secondary alcohols by comparison of the NMR of the *(R)*- and *(S)*- AMAA esters, has been demonstrated beyond any reasonable doubt, with a large number of alcohols of known configuration and varied structure. In an alternative approach, we found that an increment of the population of the conformer ***sp*** , and therefore higher $\Delta\delta^{RS}$, values can be obtained if the NMR spectra of MPA esters are taken at low temperature.

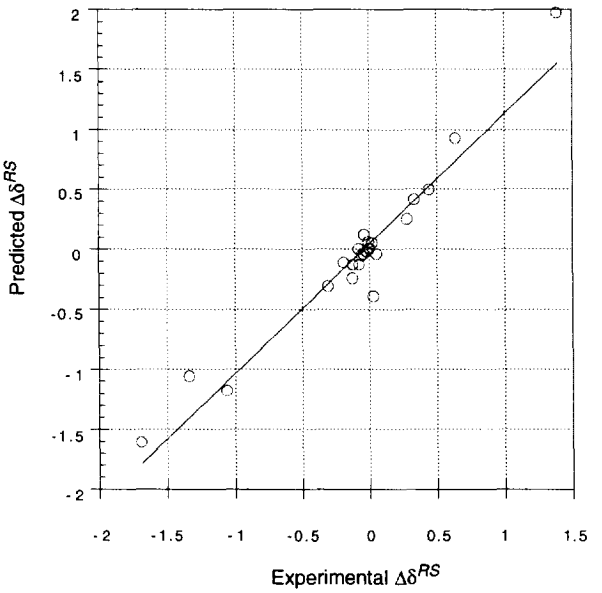


Figure 10. Correlation between predicted and observed $\Delta\delta^{RS}$ values in 9-AMA ester of *cis*-androsterone ($CDCl_3$).

Finally, we have demonstrated the possibility of selecting the aryl ring of the AMAA reagent on the basis of its fitting to a particular substrate. This is illustrated with 9-AMA ester of androsterone, where the anthryl ring induce strong and predictable shifts at long distances from the alcohol group. This can be used with advantage in stereochemical and structural analysis at remote positions in a molecule by comparison of the chemical shifts of the *(R)*- and *(S)*-9-AMA ester with the calculated ones for the configurations examined.

The exceptional conformational properties of 9-AMA esters with the aryl ring in a fixed position and the reliability of aromatic shielding effect calculations, suggest that the absolute stereochemistry of a secondary alcohol could be obtained by ^1H NMR of just one 9-AMA ester (*(R)*- or *(S)*- by comparison between the experimental chemical shifts and the calculated ones for the esters of the two enantiomers. Work is in progress to test this idea.

EXPERIMENTAL

Computational methods. Molecular mechanics (employing the pcff91 force fields[9]), AM 1 (PM3) were performed by the Insight II package on a Silicon Graphics Iris (SGI) computer. Initial molecular geometries were originated from the Builder Module of Insight II; 3D coordinates were then generated from the bond lengths, bond angles and dihedral angles by the DG-II package.[10] The conformational space of each compound was

scanned by MM optimization of the sterically allowed conformations around key single bonds. The MM simulations were carried out *in vacuo*. Analysis of conformational transitions, identification of the low energy conformers and calculation of the energy barriers between these conformers were all carried out by MM with an additional harmonic term of the form $k(1+\cos(n\theta-\theta_0)$ included in the force field. The energies of conformations were minimized in Cartesian coordinate space by the blockdiagonal Newton-Raphson method; minima corresponded to rms energy gradients < 0.001 kcal/mol A. The ground state energies of the geometries were then calculated by AM 1 (PM3) using the MOPAC 6.0 program. For all compounds, full geometry optimization used the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method and the PRECISE option.[11] *Ab initio* electronic structure calculations (at the restricted Hartree-Fock level of theory) were performed using GAUSSIAN 92.[8] During the *ab initio* calculations all internal coordinates were optimized by Berny algorithm and convergence was tested against criteria for the maximum force component, root-mean-square force, maximum step component and root-mean-square step. No symmetry options were implemented.

Shielding Effects calculations were carried out on a SGI computer by the program (written on Fortran 77) based to semi-classical model of Bovey and Johnson.[12] No corrections for local anisotropic contributions.[12d,e] were implemented. π-Current loops separated by 1.39 Å.[12b,f]

NMR Spectroscopy. ^{1}H NMR spectra of samples in 4:1 CS_2/CD_2Cl_2 or $(CD_3)_2CO$ (ca. 2-3 mg in 0.5 mL) were recorded in a Brüker AMX 500 NMR spectrometer. Chemical shifts (ppm) are internally referenced to the tetramethylsilane signal (0 ppm) in all cases. One- and two-dimensional NMR spectra were measured with standard pulse sequences. 2D Homo- (COSY) and heteronuclear (HMQC) shift correlation experiments were carried out using pulsed field gradient technique. Apodization with a shifted sine bell and base line correction was implemented to process 2D spectra.

1D ^{1}H NMR spectra. Size 32 K, pulse length 2.8 ms (30°), 16 acquisitions.

2D COSY spectra. Sequence: D1-90-t1- G_1-90-G_2-AQ; relaxation delay D1=1 s, 90° pulse 8.5 μs, gradient ratio 1:1.

2D TOCSY spectra. Relaxation delay D1=2 s; mixing time 41.3 ms; 90° pulse 8.5 μs; TPPI-mode, NS=64.

2D Proton-detected heteronuclear multiple quantum correlation (HMQC) experiments. Sequence: D190(^{1}H)-D2-90(^{13}C)-t_1/2-G1-180(^{1}H)-G2-t_1/2-90(^{13}C)-G3-D2-AQ (GARP(^{13}C)), relaxation delay D1=2s; D2=3.45 ms; 90° pulse (^{1}H) 8.5 μs; 90° pulse (^{13}C) 10.5 μs, gradient ratio 5:3:4.

For DNMR spectroscopy, the probe temperature was controlled by a standard unit calibrated using a methanol reference; samples were allowed to equilibrate for 15 min at each temperature before recording spectra.

General. Preparations of the diastereomeric esters from the corresponding alcohols and arylmethoxyacetic acids were carried out with DCC-DMAP. The reaction mixtures were filtered to remove the dicyclohexylurea and the esters purified by flash chromatography on silica gel eluting with dichloromethane. Further purifications were accomplished by HPLC (μ-Porasil, 3mm x 250mm or Spherisorb S5W 5μm, hexane-ethyl acetate). For experimental details on MPA esters **33**, **50**, **53** and **14** see reference [13].

(-)-menthyl *(R)*-α-methoxy-α-(1,2,3,4,5-pentafluorophenyl)acetate, *(R)*-10:

HPLC t_R= 16.81 min (hexane:ethyl acetate, 96:4, 2mL/min, spherisorb); [α]= -19.77 (c= 0.036, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.61 (d, J= 0.96 Hz, 3H), 0.71 (d, J= 7.01 Hz, 3H), 0.74-0.82 (m, 1H), 0.84 (d, J= 6.56 Hz, 3H), 0.90-1.01 (m, 2H), 1.22-1.30 (m, 1H), 1.32-1.48 (m, 2H), 1.54-1.64 (m, 2H)1.97-2.03 (m, 1H), 4.72 (ddd, J= 4.30, 10.88, 10.88 Hz, 1H), 4.99 (s, 1H); ^{13}C NMR (62.83 MHz,

$CDCl_3$) δ (ppm): 15.6, 20.5, 21.8, 23.1, 26.1, 31.3, 34.1, 40.3, 46.7, 58.5, 72.0, 76.5, 167.9;
MS (EI) m/z 393 (M^+); HRMS(EI) $C_{19}H_{22}F_5O_3$ obs. 393.14888 calc. 393.14891 Δm 0.03 mu.

(-)-menthyl *(S)*-α-methoxy-α-(1,2,3,4,5-pentafluorophenyl)acetate, *(S)*-10:

HPLC t_R= 15.81 min (hexane:ethyl acetate, 96:4, 2mL/min, spherisorb); [α]= -6.18 (c= 0.011, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.71 (d, J=6.95 Hz, 3H), 0.73-0.84 m, 2H), 0.82 (d, J= 7.00 Hz, 3H), 0.83 (d, J= 6.56 Hz, 3H), 0.93-1.03 (m, 1H), 1.25-1.32 (m, 1H), 1.38-1.48 (m, 1H), 1.60-1.63 (m, 2H), 1.72-1.79 (m, 1H), 1.87-1.93 (m, 1H), 3.41 (s, 3H), 4.76 (ddd, J= 4.47, 10.95, 10.95 Hz, 1H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 16.2, 20.5, 21.8, 23.4, 26.3, 31.3, 34.0, 40.1, 46.7, 58.3, 71.8, 76.5, 167.8; MS (EI) m/z 393 (M^+); Anal. Calcd for $C_{19}H_{22}F_5O_3$: C, 57.99; H, 5.64 ; F, 24.16; O, 12.21. Found: C, 57.98; H, 5.60.

(-)-menthyl *(R)*-α-methoxy-α-(p-methoxyphenyl) acetate, *(R)*-11:

HPLC tR= 35.38 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= -63.60 (c= 0.010, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.45 (d, J= 6.81 Hz, 3H), 0.65 (d, J= 6.81 Hz, 3H), 0.88 (d, J= 6.40 Hz, 3H), 0.89-1.05 (m, 1H), 1.20-1.31 (m, 2H), 1.36-1.47 (m 1H), 1.54-1.66 (m, 3H), 1.67-1.79 (m, 1H), 1.90-2.01 (m, 1H), 3.37 (s, 3H), 3.79 (s, 3H), 4.65 (s, 1H), 4.68 (ddd, J= 4.32, J′=J"= 10.89 Hz, 1H), 6.86 (J=8.67 Hz, 2H), 7.33 (d, J=8.67 Hz, 2H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 15.6, 16.1, 20.5, 21.8, 23.0, 23.2, 25.4, 26.1, 31.2, 31.3, 34.1, 40.2, 40.7, 47, 55.2, 57.0, 74.9, 75.1, 82.3, 113.8, 128.4, 128.6, 128.8, 160, 170.6;
IR (NaCl): MS (EI) m/z 334 (M^+); HRMS(EI) $C_{20}H_{30}O_4$ obs. 334.21440 calc. 334.21441 Δm 0.01 mu.

(-)-menthyl *(S)*-α-methoxy-α-(p-methoxyphenyl) acetate, *(S)*-11:

HPLC tR= 32.58 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= -4.36 (c= 0.0105, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCL_3$) δ (ppm): 0.70 (d, J=6.93Hz, 2H), 0.83 (d, J= 6.88 Hz, 2H), 0.86 (d, J= 7.3 Hz, 2H), 0.94-1.09 (m, 2H), 1.32-1.42 (m, 2H), 1.60-1.66 (m, 3H), 1.76-1.81 (m, 2H), 3.38 (s, 3H), 3.80 (s, 3H), 4.68 (s, 1H), 4.70 (ddd, J= 4.32, J′=J"= 10.89 Hz, 1H), 6.87 (d, J=8.67 Hz, 2H), 7.35 (d, J=8.67 Hz, 2H); ^{13}C NMR (62.83 MHz, CDCL3) δ (ppm): 16.1, 20.6, 21.8, 23.3, 26.1, 31.2, 34.1, 40.2, 46.8, 55.2, 57.0, 75, 82.3, 113.9, 128.4, 128.6, 160, 170.6; MS (EI) m/z 334 (M^+); HRMS(EI) $C_{20}H_{30}O_4$ obs.334.21448 calc. 334.21441 Δm 0.07 mu; Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.81; H, 9.05; O, 19.14. Found: C,71.84; H,9.21.

***(R)*-3,3-dimethyl-2-O-((*S*)-α-methoxy-α-(9-anthryl)acetyl)-γ-butyrolactone, *(S)*-26:**

[α]= 44.7 (c= 0.036, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): -0.17 (s, 3H), 0.50 (s, 3H), 3.52 (s, 3H), 3.58 (d, J= 9.02Hz, 1H), 3.75 (d, J= 9.10Hz, 1H), 5.33 (s, 1H), 6.45 (s, 1H), 7.44-8.57 (m, 9H); MS (EI) m/z 378 (M^+); HRMS(EI) $C_{23}H_{22}O_5$ obs. 378.14672 calc. 378.14672 Δm 0.00 mu. Anal. Calcd for $C_{23}H_{22}O_5$: C, 72.99; H, 5.86; O, 21.15. Found: C, 73.01; H, 5.89.

***(R)*-3,3-dimethyl-2-O-((*R*)-α-methoxy-α-(9-anthryl)acetyl)-γ-butyrolactone, *(R)*-26:**

[α]= -49.03 (c= 0.027, $CHCl_3$); ^1H NMR (250.13 MHz, CDCL3) δ (ppm): 1.02 (s, 3H), 1.14 (s, 3H), 3.50 (s, 3H), 3.94 (s, 2H), 5.34 (s, 1H), 6.44 (s, 1H), 7.44-8.57 (m, 9H); MS (EI) m/z 378 (M^+); HRMS(EI) $C_{23}H_{22}O_5$ obs. 378.14655 calc. 378.14672 Δm 0.17 mu.

(R)-(3,3-dimethyl)-1-butyl (R)-α-Omethyl-α-(9-anthryl) acetate, *(R)*-27:

HPLC t_R= 34.73 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= 10.4 (c= 0.007, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.17 (s, 9H), 1.11 (d, J= 6.41Hz, 3H), 3.43 (s, 3H), 4.55 (q, J= 6.41Hz, 1H), 6.27 (s, 1H), 7.45-8.62 (m, 9H); MS (EI) m/z 350 (M^+); HRMS(EI) $C_{23}H_{26}O_3$ obs.

350.18816 calc. 350.18819 Δm 0.03 mu. Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.81; H, 7.48; O, 13.7. Found: C, 78.84; H, 7.49.

(S)-(3,3-dimethyl)-1-butyl (R)-α-Omethyl-α-(9-anthryl) acetate, *(S)*-27:

HPLC t_R= 31.94 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= 24 (c= 0.008, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.61 (d, J=6.42 Hz, 3H), 0.68 (s, 9H), 3.41 (s, 3H), 4.67 (q, J= 6.42 Hz, 1H), 6.27 (s, 1H), 7.43-8.62 (m, 9H); MS (EI) m/z 350 (M^+); HRMS(EI) $C_{23}H_{26}O_3$ obs. 350.18819 calc. 350.18817 Δm 0.02 mu.

(S)-(3,3-dimethyl)-1-butyl (R)-α-methoxy-α-(1-naphthyl) acetate, *(S)*-28:

HPLC tR= 27.67 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= -6.50 (c= 0.004, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 9H), 0.81 (d, J=6.89Hz, 3H), 3.47 (s, 3H), 4.70 (q, 1H), 5.39 (s, 1H), 7.43-8.28 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 14.2, 25.4, 33.9, 57.4, 78.8, 81.0, 124.1, 125.2, 125.8, 126.3, 126.4, 128.6, 129.2, 170.5; MS (EI) m/z 300 (M^+) ; HRMS(EI) $C_{19}H_{24}O_4$ obs. 300.17258 calc. 300.17254 Δm -0.04 mu.

(R)-(3,3-dimethyl)-1-butyl (R)-α-methoxy-α-(1-naphthyl) acetate, *(R)*-28:

HPLC tR= 31.07 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= -2.66 (c= 0.012, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.42 (s, 9H), 1.12 (d, J=6.42 Hz, 3H), 3.45 (s, 3H), 4.63 (q, J= 6.41Hz, 1H), 5.35 (s, 1H), 7.42-8.33 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 14.8, 25.0, 33.8, 57.2, 78.7, 81.2, 124.3, 125.1, 125.8, 126.3, 126.7, 128.5, 129.2, 170.4; MS (EI) m/z 300 (M^+); HRMS(EI) $C_{19}H_{24}O_4$ obs.300.17243 calc. 300.17254 Δm 0.11 mu.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.11; H, 7.65; O, 20.24. Found: C, 72.14; H, 7.70.

(*R*)-2-butyl (*R*)-α-methoxy-α-(9-anthryl) acetate, *(R)*-31:

[α]= -120 (c= 0.012, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.14 (t, J= 7.40 Hz, 3H), 0.88 (m, 2H), 1.14 (d, J= 6.33 Hz, 3H), 3.43 (s, 3H), 4.85 (m, 1H), 6.24 (s, 1H), 7.44-8.58 (m, 9H); MS (EI) m/z 322 (M^+); HRMS(EI) $C_{21}H_{22}O_3$ obs.322.15682 calc. 322.15689 Δm 0.07 mu.

(*R*)-2-butyl (*S*)-α-methoxy-α-(9-anthryl) acetate, *(S)*-31:

[α]= 82 (c= 0.004, $CHCl_3$);^1H NMR (250.13 MHz, CDCL3) δ (ppm): 0.79 (d, J= 6.23 Hz, 3H), 0.80 (t, J= 7.40 Hz, 3H), 1.43 (m, 2H), 3.40 (s, 3H), 4.87 (m, 1H), 6.25 (s, 1H), 7.44-8.58 (m, 9H); MS (EI) m/z 322 (M^+); Anal. Calcd for CHO: C, 78.22; H, 6.88; O, 14.89. Found: C, 78.20; H, 6.86.

(*R*)-2-butyl (*S*)-α-methoxy-α-(1-naphthyl) acetate, *(S)*-32:

[α]= +100 (c=0.00048, EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.82 (t, J=7.21Hz, 3Hz), 0.96 (d, J=6.25Hz, 3H), 1.50 (m, 2H), 3.45 (s, 3H), 4.90 (m, 1H), 5.40 (s, 1H),, 7.20-8.3 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 9.4, 18.9, 28.5, 57.3, 73.4, 81.2, 124.1, 125.2, 125.8, 126.3, 126.4,128.6, 129.3, 170.6; MS (EI) m/z 272 (M^+); HRMS(EI) $C_{17}H_{20}O_3$ obs. 272.14128 calc. 272.14124 Δm -0.04 mu.

(*R*)-2-butyl (*R*)-α-methoxy-α-(1-naphthyl) acetate, *(R)*-32:

[α]= -133.84 (c=0.0013, EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.40 (t, J=7.20Hz, 3H), 1.18 (d, J=6.25Hz, 3H), 1.30 (m, 2H), 3.45 (s, 3H), 4.90 (m, 1H), 7.20-8.30 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 8.8, 19.3, 28.4, 57.3, 81.2, 124.2, 125.1, 125.8, 126.3, 126.7, 128.6, 129.3, 131.9, 132.5, 133.9, 170.6;

MS (EI) m/z 272 (M^+); Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.96; H, 7.41; O, 17.63. Found: C, 74.98; H, 7.49.

***(S)*-2-O-((*R*)-α-methoxy-α-(1-naphthyl)acetyl)-3-methyl butiric acid methyl ester, *(R)*-34:**

HPLC tR= 44.04 min (hexane:ethyl acetate, 96:4, 2mL/min, μ-Porasil); [α]= -63.33 (c= 0.003, $CHCl_3$); ^1H

NMR (500 MHz, CD_2Cl_2+CS_2, 4:1) δ (ppm): 0.81 (d, J= 6.84 Hz, 3H), 0.48 (d, J= 6.90 Hz, 3H), 2.06 (m, 1H), 3.35 (s, 3H), 3.45 (s, 3H), 4.68 (d, J= 4.36 Hz, 1H), 5.33 (s, 1H), 5.33 (s, 1H), 7.36-8.14 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 16.5, 18.0, 29.8, 52.1, 57.5, 77.1, 80.7, 124.2, 25.2, 125.9, 126.5, 126.8, 128.6, 129.5, 133.9, 158.7, 169.9; MS (EI) m/z 330 (M^+); HRMS(EI) $C_{19}H_{22}O_5$ obs. 330.14661 calc. 330.14672 Δm 0.11 mu.

***(S)*-2-O-((*S*)-α-methoxy-α-(1-naphthyl)acetyl)-3-methyl butiric acid methyl ester, *(S)*-34:**

HPLC tR= 35.08 min (hexane:ethyl acetate, 96:4, 2mL/min, μ-Porasil); [α]= 29.14 (c= 0.003, $CHCl_3$); ^1H NMR (500 MHz, CD_2Cl_2+CS_2, 4:1) δ (ppm): 0.48 (d, J= 6.91 Hz, 3H), 0.63 (d, J=6.84 Hz, 3H), 1.95 (m, 1H), 3.42 (s, 3H), 3.61 (s, 3H), 4.63 (d, J= 4.27 Hz, 1H), 5.34 (s, 1H), 7.36-8.17 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 16.9, 18.5, 29.9, 51.6, 77.3, 80.9, 124.2, 125.2, 126.3, 126.6, 128.6, 129.45, 159, 169.2; MS (EI) m/z 330 (M^+); Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.06; H, 6.72; O, 24.22. Found: C,70.01; H, 6.75.

***(S)*-2-O-((*R*)-α-methoxy-α-phenyl acetyl)-3-methyl butiric acid methyl ester, *(R)*-35:**

^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.65 (d, J= 6.90 Hz, 3H), 0.75 (d, J= 6.83 Hz, 3H), 2.10 (m, 1 H), 3.38 (s, 3H), 3.65 (s, 3H), 4.79 (d, J= 4.34 Hz, 1H), 4.84 (s, 1H), 7.27-7.41 (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 16.8, 18.3, 29.6, 30.1, 52.1, 57.5, 77.2, 82.2, 127.3, 128.6, 128.8, 136.3, 169.1, 170.4; MS (EI) m/z 280 (M^+); HRMS(EI) $C_{15}H_{20}O_5$ obs. 280.13102 calc. 280.13107 Δm 0.05 mu.

***(S)*-2-O-((*S*)-α-methoxy-α-phenyl acetyl)-3-methyl butiric acid methyl ester, *(S)*-35:**

^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 0.92 (d, J= 6.69 Hz, 3H), 0.94 (d, J= 6.90 Hz, 3H), 2.51 (m, 1H), 3.49 (s, 3H), 3.57 (s, 3H), 4.86 (s, 1H), 4.90 (d, J= 4.26 Hz, 1H), 7.33-7.49 (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 17.0, 18.5, 29.6, 30.0, 51.8, 57.5, 77.1, 82.6, 127.2, 128.4, 128.7, 169.8, 171.0; MS (EI) m/z 280 (M^+); Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.26; H, 7.2; O, 28.55 . Found: C, 64.30; H,7.12.

***(R)*-1-(1-Naphthylethyl)-*(R)*-α-methoxy-α-(9-anthryl)acetate, *(S)*-36:**

HPLC t_R= 7.69 min (hexane:ethyl acetate, 80:20, 5mL/min, spherisorb); [α]= 10.90 (c= 0.022, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.21 (d, J= 6.65 Hz, 3H), 3.42 (s, 3H), 6.31 (s, 1H), 6.61 (q, J= 6.57 Hz, 1H), 7.22-8.60 (m, 16H); MS (EI) m/z 420 (M^+); HRMS(EI) $C_{29}H_{24}O_3$ obs. 420.17244 calc. 420.17254 Δm 0.1 mu.

***(R)*-1-(1-Naphthylethyl)-*(R)*-α-methoxy-α-(9-anthryl)acetate, *(R)*-36:**

HPLC t_R= 9.86 min (hexane:ethyl acetate, 80:20, 5mL/min, spherisorb); [α]= 0.94 (c= 0.029, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.57 (d, J= 6.61 Hz, 3H), 3.46 (s, 3H), 6.40 (s, 1H), 6.46 (d, J= 7.11 Hz, 1 H), 6.62 (q, J= 6.61 Hz, 1H), 6.80 (t, J= 7.41 Hz, 1H), 7.10-7.14 (m, 1H), 7.28-7.34 (m, 1H), 7.40-7.52 (m, 5H), 7.65 (t, J= 9.17 Hz, 2H), 7.97-8.02 (m, 2H), 8.47-8.55 (m, 3H); MS (EI) m/z 420 (M^+); Anal. Calcd for $C_{29}H_{24}O_3$: C, 82.82; H, 5.76; O, 11.42. Found: C, 82.78; H,5.74.

***(R)*-1-(1-Naphthylethyl)-*(R)*-α-methoxy-α-(1-naphthyl)acetate, *(R)*-37:**

[α]= -130.66 (c= 0.003, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.66 (d, J= 6.52 Hz, 3H), 3.48 (s, 3H), 5.49 (s, 1H), 6.66 (q, J= 6.54 Hz, 1H), 6.89 (d, J= 7.11 Hz, 1H), 7.05 (t, J= 7.78 Hz, 1H), 7.24-7.26 (m, 1H), 7.34-7.86 (m, 10H), 8.25 (d, J= 8.77 Hz, 1H); MS (EI) m/z 370 (M^+); HRMS(EI) $C_{25}H_{22}O_3$ obs. 370.15678 calc. 370.15689 Δm 0.11 mu.

***(R)*-1-(1-Naphthylethyl)-*(S)*-α-methoxy-α-(1-naphthyl)acetate, *(S)*-37**

[α]= 134.5 (c= 0.004, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.42 (d, J= 6.66 Hz, 3H), 3.46 (s, 3H), 5.43 (s, 1H), 6.66 (q, J= 6.51 Hz, 1H), 7.35-8.33 (m, 14H); MS (EI) m/z 370 (M^+); Anal. Calcd for

$C_{25}H_{22}O_3$: C, 81.05; H, 5.99; O, 12.96. Found: C, 81.01; H, 6.01.

***(R)*-1-(2-Naphthylethyl)-*(R)*-α-methoxy-α-(9-anthryl)acetate, *(R)*-38:**

HPLC t_R= 18.47 min (hexane:ethyl acetate, 90:10, 4 mL/min, spherisorb); [α]= -38.66 (c= 0.013, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.48 (d, J= 6.64 Hz, 3H), 3.47 (s, 3H), 6.06 (q, J= 6.59 Hz, 1H), 6.40 (s, 1H), 6.73-8.55 (m, 16 H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 22.1, 57.5, 77.3, 123.2, 123.8, 124.5, 125.0, 125.7, 126.4, 127.3, 127.6, 127.9, 129.1, 129.2, 130.6, 131.5, 132.5, 132.7, 138.1, 170.6; MS (EI) m/z 420 (M^+); HRMS(EI) $C_{29}H_{24}O_3$ obs. 420.17251 calc. 420.17254 Δm 0.03 mu.

***(R)*-1-(2-Naphthylethyl)-*(S)*-α-methoxy-α-(9-anthryl)acetate, *(S)*-38:**

HPLC t_R= 10.76 min (hexane:ethyl acetate, 90:10, 4mL/min, spherisorb); [α]= 25.86 (c= 0.007, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.16 (d, J= 6.55 Hz, 3H), 3.41 (s, 3H), 6.09 (q, J= 6.52 Hz, 1H), 6.28 (s, 1H), 6.73-8.55 (m, 16H); MS (EI) m/z 420 (M^+); Anal. Calcd for $C_{29}H_{24}O_3$: C, 82.82; H, 5.76; O, 11.42. Found: C, 82.76; H,5.71.

***(R)*-1-(2-Naphthylethyl)-*(R)*-α-methoxy-α-(1-naphthyl)acetate, *(R)*-39:**

HPLC t_R= 23.49 min (hexane:ethyl acetate, 96:4, 5mL/min, spherisorb); [α]= -27.12 (c= 0.016, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.56 (d, J= 6.63 Hz, 3H), 3.47 (s, 3H), 5.49 (s, 1H), 6.07 (q, J= 6.52 Hz, 1 H), 6.95-7.89 (m, 14 H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 22.1, 57.4, 73.1, 81.1, 123.5, 124.1, 124.2, 125.2, 125.8, 125.9, 126.4, 126.9, 127.4, 127.8, 127.9, 128.6, 129.4, 132.1, 132.7, 133.9, 138.3, 170.1; MS (EI) m/z 370 (M^+); HRMS(EI) $C_{25}H_{22}O_3$ obs. 370.15670 calc. 370.15689 Δm 0.19 mu.

***(R)*-1-(2-Naphthylethyl)-*(S)*-α-methoxy-α-(1-naphthyl)acetate, *(S)*-39:**

HPLC t_R= 17.86 min (hexane:ethyl acetate, 96:4, 5 mL/min, spherisorb); [α]= 46 (c= 0.014, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.36 (d, J= 6.53 Hz), 3.45 (s, 3H), 5.44 (s, 1H), 6.10 (q, J= 6.52 Hz, 1H), 7.32-8.33 (m, 14 H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 21.6, 57.4, 73.4, 81.1, 124.0, 124.1, 125.1, 125.8, 126.1, 126.2, 126.4, 126.6, 127.6, 127.0, 120.1, 128.3, 128.7, 129.4, 131.1, 132.3, 133.1, 170.2; MS (EI) m/z 370 (M^+); Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99; O, 12.96. Found: C, 80.11; H, 6.01.

***(S)*-1-phenethyl *(S)*-α-methoxy-α-(9-anthryl) acetate, *(S)*-40:**

HPLC t_R= 13.19 min (hexane:ethyl acetate, 90:10, 4mL/min, spherisorb); [α]= 40 (c= 0.006, $CHCl_3$); ^1H NMR (250.13 MHz, CD3CL) δ (ppm): 1. 41 (d, J= 6.58 Hz, 3H), 3.46 (s, 3H), 3.46 (s, 3H), 5.90 (q, J= 6.57 Hz, 1H), 6.36 (s, 1H), 6.85-8.60 (m, 14 H); MS (EI) m/z 370 (M^+); HRMS(EI) $C_{25}H_{22}O_3$ obs. 370.15684 calc. 370.15689 Δm 0.05 mu.

***(S)*-1-phenethyl *(R)*-α-methoxy-α-(9-anthryl) acetate, *(R)*-40:**

HPLC t_R= 10.76 min (hexane:ethyl acetate, 90:10, 4mL/min, spherisorb); [α]= -62.5 (c= 0.003, EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.07 (d, J= 6.70 Hz, 3H), 3.41 (s, 3H), 5.93 (q, J=6.52 Hz, 1H), 6.28 (s, 1H), 7.13-8.58 (m, 14 H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 21.7, 57.5, 73.2, 77.4, 124.5, 125.0, 126.0, 126.4, 127.8, 128.4, 129.1, 130.1, 131.5, 141.1, 170.6; MS (EI) m/z 370 (M^+); Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99; O, 12.96. Found: C, 81.06; H, 5.91.

***(S)*-1-phenethyl *(S)*-α-methoxy-α-(1-naphthyl) acetate, *(S)*-41:**

HPLC t_R= 15.27 min (hexane:ethyl acetate, 96:4, 4mL/min, μ-Porasil); [α]= 26.7 (c= 0.018, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.48 (d, J= 7.82 Hz, 3H), 3.46 (s, 3H), 5.44 (s, 1H), 5.91 (q, J= 6.59 Hz, 1H), 6.83-7.86 (m, 12H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 22.1, 57.4, 73.1, 81.1, 124.1, 125.1, 125.5, 125.8, 126.4, 126.8, 127.5, 128.1, 128.5, 129.3, 131.2, 132.0, 140.9, 170.1; MS (EI) m/z 320

(M^+); HRMS(EI) $C_{21}H_{20}O_3$ obs. 320.14125calc. 320.14124 Δm -0.01 mu.

(*S*)-1-phenethyl (*R*)-α-methoxy-α-(1-naphthyl) acetate, (*R*)-41:

HPLC t_R= 13 min (hexane:ethyl acetate, 96:4, 4mL/min, μ-Porasil); [α]= -86.22 (c= 0.009, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 1.26 (d, J=7.81 Hz, 3H), 3.44 (s, 3H), 5.41 (s, 1H), 5.93 (q, J= 6.52 Hz, 1H), 7.22-7.88 (m, 12H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 21.6, 57.4, 73.3, 81.1, 124.1, 125.2, 125.8, 126.1, 126.4, 126.6, 128.0, 128.4, 128.6, 129.4, 132.3, 134.0, 141.1, 170.2; MS (EI) m/z 320 (M^+); Anal. Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.72 ; H, 6.3; O, 14.99. Found: C,78.69; H,6.25.

Methyl (*S*)-α-O-((*S*)-α-methoxy-α-(9-anthryl)-acetyl)-phenyl acetate, (*S*)-44:

HPLC t_R= 20.17 min (hexane:ethyl acetate, 90:10, 4mL/min, spherisorb); [α]= 114.13 (c= 0.015, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 3.08 (s, 3H), 3.49 (s, 3H), 5.99 (s, 1H), 6.45 (s, 1H), 7.12-7.29 (m, 5H), 7.46-7.56 (m, 4H), 8.03-8.07 (m, 2H), 8.53-8.62 (m, 3H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 51.9, 57.7, 74.8, 77.4, 124.7, 124.9, 126.4, 126.8, 127.2, 128.6, 129.1, 129.2, 129.5, 130.7, 131.5, 133.4, 168.3, 170.4; MS (EI) m/z 414 (M^+); HRMS(EI) $C_{26}H_{22}O_5$ obs. 414.14666 calc. 414.14672 Δm 0.06 mu.

Methyl (*S*)-α-O-((*R*)-α-methoxy-α-(9-anthryl)-acetyl)-phenyl acetate, (*R*)-44:

HPLC t_R= 24.36 min (hexane:ethyl acetate, 90:10, 4mL/min, spherisorb); [α]= -0.014 (c= 0.021, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 3.49 (s, 3H), 3.71 (s, 3H), 5.90 (s, 1H), 6.53 (s, 1H), 6.98-7.14 (m, 5H), 7.43-7.58 (m, 4H), 7.98-8.01 (m, 2H), 8.46-8.66 (m, 3H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 52.6, 57.7, 74.7, 77.3, 124.6, 125.0, 126.6, 126.7, 128.3, 128.7, 129.1, 129.5, 130.6, 131.5, 132.9, 169.1, 170.1; MS (EI) m/z 414 (M^+); Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.34 ; H, 5.35; O, 19.31. Found: C, 75.31; H, 5.32.

Methyl (*S*)-α-O-((*R*)-α-methoxy-α-(1-naphthyl)-acetyl)-phenyl acetate, (*R*)-45:

[α]= 19.24 (c= 0.029, $CHCl_3$); ^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm): 3.53 (s, 3H), 3.68 (s, 3H), 5.63 (s, 1H), 5.96 (s, 1H), 7.19-7.86 (m, 12H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 52.5, 57.6, 74.7, 80.7, 124.1, 125.1, 125.8, 126.5, 126.8, 127.1, 128.5, 128.6, 128.9, 129.5, 131.0, 131.6, 133.9, 168.9, 170.3; MS (EI) m/z 364 (M^+); HRMS(EI) $C_{22}H_{20}O_5$ obs. 364.13101 calc. 364.13107 Δm 0.06 mu.

Methyl (*S*)-α-O-((*S*)-α-methoxy-α-(1-naphthyl)-acetyl)-phenyl acetate, (*S*)-45

[α]= 0.8 (c= 0.026, $CHCl_3$); ^1H NMR (250.13 MHz, CD3CL) δ (ppm): 3.39 (s, 3H), 3.68 (s, 3H), 5.63 (s, 1H), 5.96 (s, 1H), 7.19-8.33 (m, 12H); ^{13}C NMR (62.83 MHz, CD3CL) δ (ppm): 52.2, 57.6, 74.9, 80.7, 124.2, 125.2, 125.8, 126.4, 126.8, 127.1, 127.4, 128.5, 128.6, 129.2, 129.5, 131.6, 133.3, 133.9, 168.5, 170.2; MS (EI) m/z 364 (M^+); Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.5; H, 5.54; O, 21.96. Found: C, 72.48; H,5.50.

(-)-bornyl (*R*)-α-methoxy-α-(9-anthryl) acetate, (*R*)-48:

HPLC t_R= 54.24 min (hexane:ethyl acetate, 98:2, 2mL/min, Spherisorb); [α]= -8.33 (c= 0.0005, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): -0.22 (s, 3H), 0.56 (s, 3H), 0.57-0.61 (m, 1H), 0.67 (s, 3H), 0.69-0.80 (m, 2H), 0.86 (dd, J= 3.34, 13.66 Hz, 1H), 1.35-1.42 (m, 1H), 1.45 (t, J= 4.5 Hz, 1H), 2.18 (dddd, J= 3.39, 5.77, 9.98, 13.98 Hz, 1H), 3.39 (s, 3H), 4.78 (ddd, J= 2.71, 10.08 Hz, 1H), 6.21 (s, 1H), 7.37-8.55 (m, 9 H); ^{13}C NMR (62.83 MHz, $CDCL_3$) δ (ppm): 12.4, 18.6, 19.3, 26.2, 27.6, 36.4, 44.7, 47.5, 48.7, 57.5, 77.6, 80.6, 124.6, 124.9, 126.3, 127.9, 129.0, 129.1, 130.5, 131.5; MS (EI) m/z 402 (M^+); HRMS(EI) $C_{27}H_{30}O_3$ obs. 402.21961 calc. 402.21950 Δm -0.11 mu.

(-)-bornyl (*S*)-α-methoxy-α-(9-anthryl) acetate, (*S*)-48:

HPLC t_R= 57.22 min (hexane:ethyl acetate, 98:2, 2mL/min, Spherisorb); [α]= -78.43 (c= 0.00051, EtOH); ^1H

NMR (500 MHz, $CDCl_3$) δ (ppm): 0.03 (ddd, J= 4.66, 9.49, 12.41 Hz, 1H), 0.20 (dd, J= 3.23, 13.85 Hz, 1H), 0.60 (s, 3H), 0.62 (s, 3H), 0.60 (s, 3H), 0.73 (tq, J= 0.41, 10.12 Hz, 1H), 0.77-0.85 (m, 1H), 1.14-1.25 (m, 1H), 1.25 (t, J= 4.45 Hz, 1H), 1.97-2.03 (m, 1H), 3.39 (m, 3H), 4.72 (ddd, J= 3.03, 3.06, 9.72 Hz, 1H), 6.27 (s, 1H), 7.39-8.50 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCL_3$) δ (ppm): 13.2, 18.6, 19.4, 26.4, 27.1, 36.1, 44.4, 48.4, 57.6, 77.4, 81.1, 124.5, 124.9, 126.4, 128.9, 129.1, 130.5, 131.4, 171.5; MS (EI) m/z 402 (M^+); HRMS(EI) $C_{27}H_{30}O_3$ obs.402.21975 calc. 402.21950 Δm -0.25 mu.

Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.55; H, 7.52; O, 11.93. Found: C, 80.51; H, 7.53.

(-)-bornyl *(R)*-α-methoxy-α-(1-naphthyl) acetate, *(R)*-49:

HPLC t_R= 29.05 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= -224 (c= ,0.001 $CHCl_3$); ^1H NMR (500 MHz, CS_2+CD_2Cl_2, 4:1) δ (ppm): 0.32 (s, 3H), 0.80 (s, 3H), 0.92-0.97 (m, 2H), 1.05-1.09 (m, 1H), 1.37-1.42 (m, 1H), 1.57-1.62 (m, 2H), 2.22-2.33 (m, 1H), 3.48 (s, 3H), 4.88 (ddd, J= 2.24, 3.36, 7.33 Hz, 1H), 5.39 (s, 1H), 7.45-8.33 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 12.7, 18.6, 19.4, 26.5, 27.7, 36.4, 44.7, 47.6, 48.8, 57.4, 80.7, 81.3, 124.3, 125.1, 125.8, 126.4, 126.5, 128.6, 129.2, 132.7, 171.2; MS (EI) m/z 352 (M^+); HRMS(EI) $C_{23}H_{28}O_3$ obs. 352.20379calc. 352.20384 Δm 0.05 mu.

(-)-bornyl *(S)*-α-methoxy-α-(1-naphthyl) acetate, *(S)*-49:

HPLC t_R= 29.05 min (hexane:ethyl acetate, 96:4, 2mL/min, Spherisorb); [α]= 10 (c= 0.002, $CHCl_3$); ^1H NMR (500 MHz, CS_2+CD_2Cl_2, 4:1)δ (ppm): 0.46 (dd, J= 3.25, 13.78 Hz, 1H), 0.51-0.56 (m, 1H), 0.77 (s, 3H), 0.82 (s, 3H), 1.05-1.11 (m, 1H), 1.43-1.49 (m, 3H), 2.13-2.18 (m, 1H), 3.48 (s, 3H), 4.85 (ddd, J= 2.75, 2.68, 9.79 Hz, 1H), 5.39 (s, 1H), 7.45-8.31 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 13.3, 18.7, 19.4, 26.8, 27.4, 36.2, 44.5, 47.6, 48.6, 57.4, 81.0, 81.2, 124.2, 125.2, 125.8, 126.4, 126.6, 128.6, 129.2, 131.1, 132.6, 133.9, 131.1; MS (EI) m/z 352 (M^+); Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.36 ; H, 8.01; O, 13.62. Found: C,78.32; H, 8.11.

***(R)*-α-methoxy-α-(9-anthryl)acetate of (-)-isopulegol, *(R)*-51**

HPLC t_R= 52.94 (98:2, hexane-ethyl, 98-2, 2 mL/min, Spherisorb); [α]= 10 (c= 0.001, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.63 (m, 3H), 0.67 (ddd, J= 3.57, 12.89, 16.50 Hz, 1H), 0.80 (d, J= 6.45, 3H), 0.89 (q, J= 12.02 Hz, 1H), 1.03- (ddd, J= 3.37, 12.99, 26.31 Hz, 1H), 1.29 (dq, J= 3.48, 13.59 Hz, 1H), 1.35-1.49 (m, 3H), 1.99 (dddd, J= 2.24, 3.42, 4.33, 12.14 Hz, 1H), 3.18 (m, 1H), 3.34 (s, 3H), 3.39 (m, 1H), 4.62 (ddd, J= 4.38, 10.93, 10.93 Hz, 1H), 7.35-8.46 (m, 9H);

^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 18.3, 21.8, 30.1, 31.2, 33.8, 40.2, 50.1, 57.3, 74.5, 77.1, 110.7, 124.8, 126.1, 128.8, 128.9, 130.7, 131.5, 144.1, 170.6; MS (EI) m/z 402 (M^+); HRMS(EI) $C_{27}H_{30}O_3$ obs. 402.21927 calc. 402.21950 Δm 0.23 mu.

Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.55; H, 7.52; O, 11.93. Found: C, 80.48; H, 7.50.

***(S)*-α-methoxy-α-(9-anthryl)acetate of (-)-isopulegol, *(S)*-51:**

HPLC t_R= 54.09 (hexane-ethyl acetate, 98-2, 2 mL/min, Spherisorb); [α]= 18 (c= 0.0025, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.33 (q, J= 12.23 Hz, 1H), 0.59 (d, J= 6.57 Hz, 3H), 0.60-0.63 (m, 1H), 1.22 (ddd, J= 2.18, 13.18, 26.00 Hz, 1H), 1.27-1.34 (m, 1H), 1.42-1.53 (m, 3H), 1.59 (m, 3H), 1.80 (ddd, J= 3.79, 10.81, 12.51 Hz, 1H), 3.27 (s, 3H), 4.63 (m, 1H), 4.74 (m, 1H), 4.74 (ddd, J= 4.33, 9.91, 9.91 Hz, 1H), 6.09 (s, 1H), 7.37-8.45 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 19.4, 21.6, 30.1, 33.7, 39.3, 50.3, 57.3, 74.6, 77.1, 111.8, 124.6, 124.9, 126.2, 128.9, 129.1, 130.5, 131.4, 146.2, 170.9; MS (EI) m/z 402 (M^+); HRMS(EI) $C_{27}H_{30}O_3$ obs. 402.21916 calc. 402.21950 Δm 0.34 mu. Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.55; H, 7.52; O, 11.93. Found: C, 80.51; H, 7.54.

(*S*)-α-methoxy-α-(1-naphthyl)acetate of (-)-isopulegol, (*S*)-52:

[α]= +60.86 (c= 0.00046, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.69 (q, J= 12.27 Hz, 1H), 0.81 (d, J= 6.55 Hz, 3H), 0.83-0.91 (m, 1H), 1.26-1.46 (m, 2H), 1.53 (m, 3H), 1.58-1.66 (m, 3H), 1.97 (ddd, J= 3.66, 10.66, 12.51 Hz, 1H), 3.33 (s, 3H), 4.56 (m, 1H), 4.59 (m, 1H), 4.71 (ddd, J= 4.39, 10.89, 10.89 Hz, 1H), 5.13 (s, 1H), 7.24-8.09 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 19.3, 21.7, 26.3, 29.6, 30.2, 31.1, 33.8, 39.6, 50.5, 57.4, 74.6, 80.8, 111.9, 124.1, 125.2, 125.7, 126.3, 128.6, 129.2, 133.9, 146.0, 170.3;

MS (EI) m/z 352 (M^+); HRMS(EI) $C_{23}H_{28}O_3$ obs. 352.20380 calc. 352.20384 Δm 0.04 mu.

(*R*)-α-methoxy-α-(1-naphthyl)acetate of (-)-isopulegol, (*R*)-52:

[α]= -58, 33 (c= 0.0012, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.81-0.89 (m, 1H), 0.90 (d, J= 6.52 Hz, 3H), 0.94 (q, J= 11.09 Hz, 1H), 1.07 (m, 3H), 1.17-1.25 (m, 1H), 1.41-1.54 (m, 2H), 1.57-1.62 (m, 1H), 1.94-1.89 (m, 1H), 3.33 (s, 3H), 3.83 (m, 1H), 4.01 (m, 1H), 4.63 (ddd, J= 4.41, 10.93, 10.93 Hz, 1H), 5.09 (s, 1H), 7.22-8.11 (m, 7H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 18.8, 21.9, 29.6, 30.4, 31.2, 33.9, 40.3, 50.3, 57.3, 74.6, 81.4, 112.7, 124.5, 125.1, 125.7, 126.2, 127.0, 128.4, 129.2, 131.4, 134.1, 170.4; MS (EI) m/z 352 (M^+); Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.36; H, 8.01; O, 13.62. Found: C, 78.30; H, 8.21.

(*S*)-α-methoxy-α-(9-anthryl) acetate of (+)-isopinocampheol, (*S*)-57:

HPLC t_R= 68.57 (hexane-ethyl acetate, 98-2, 2 mL/min, Spherisorb); [α]= 25.5 (c= 0.004, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.53 (d, J= 7.41 Hz, 3H), 0.55 (d, J= 9.70 Hz, 1H), 0.75 (s, 3H), 1.02 (s, 3H), 1.33-1.37 (m, 1H), 1.42 (ddd, J= 2.22, 6.23 Hz, 1H), 1.57 (ddd, J= 3.16, 3.84, 14.4 Hz, 1H), 1.70-1.73 (m, 1H), 2.01-2.06 (m, 1H), 2.41-2.47 (m, 1H), 3.33 (s, 3H), 4.49 (m, 1H), 6.17 (s, 1H), 7.37-8.52 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 23.5, 27.2, 33.0, 35.3, 40.9, 43.3, 47.2, 57.5, 75.2, 77.5, 124.6, 124.9, 126.3, 129.0, 129.1, 130.5, 131.5, 171.4;

MS (EI) m/z 402 (M^+); HRMS(EI) $C_{27}H_{30}O_3$ obs. 402.21945 calc. 402.21949 Δm 0.04 mu.

(*R*)-α-methoxy-α-(9-anthryl) acetate of (+)-isopinocampheol, (*R*)-57:

HPLC t_R= 64.31 (hexane-ethyl acetate, 98-2, 2 mL/min, Spherisorb); [α]= 20 (c= 0.003, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.44 (d, J= 9.78 Hz, 1H), 0.76 (s, 3H), 0.97 (m, 1H), 1.00 (s, 3H), 1.02 (d, J= %.04 Hz, 3H), 1.51-1.54 (m, 1H), 1.59 (ddd, J= 2.32, 5.41, 5.41 Hz, 1H), 1.88-2.01 (m, 2H), 2.17-2.23 (m, 1H), 3.34 (m, 1H), 3.34 (s, 3H), 4.99 (ddd, J= 4.18, 4.18, 9.13 Hz, 1H), 6.19 (s, 1H), 7.36-5.53 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 20.3, 23.5, 27.2, 36.7, 34.9, 37.9, 40.7, 43.3, 47.1, 57.5, 75.1, 77.6, 124.6, 124.9, 126.3, 127.6, 129.1, 130.6, 131.5, 171.2; MS (EI) m/z 402 (M^+); Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.55; H, 7.52; O, 11.93. Found: C, 80.53; H,7.50.

3α-O-((*R*)-α-methoxy-α-phenylacetyl)-5α-androstan-17-one (*R*)-58.

[α]= 30.40 (c= 0.0025, $CHCl_3$); ^{1}H NMR (500 MHz, CS_2+CD_2CL_2, 4:1) δ (ppm): 0.55-0.63 (m, 1H), 0.75 (s, 3H), 0.76 (s, 3H), 0.77-0.83 (m, 1H), 0.92-0.98 (m, 2H), 1.02-1.34 (m, 7H), 1.37=1.47 (m, 3H), 1.54-1.72 (m, 5H), 1.84-1.98 (m, 2H), 2.26-2.33 (m, 1H), 3.32 (s, 3H), 4.57 (s, 1H), 4.88 (m, 1H), 7.19-7.36 (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 11.1, 13.7, 19.9, 21.6, 25.9, 27.7, 30.4, 31.5, 32.2, 32.7, 34.8, 35.7, 39.4, 47.7, 51.5, 54.2, 57.3, 71.0, 82.6, 127.3, 128.5, 128.6, 137.1, 170.1, 221.3; MS (EI) m/z 438 (M^+); HRMS(EI) $C_{28}H_{38}O_4$ obs.438.27689 calc. 438.27700 Δm 0.11 mu.

3α-O-((*S*)-α-methoxy-α-phenylacetyl)-5α-androstan-17-one (*S*)-58.

[α]= 72 (c= 0.003, $CHCl_3$); ^{1}H NMR (500 MHz, CS_2+CD_2CL_2, 4:1) δ (ppm): 0.60-0.66 (m, 1H), 0.75 (s,

3H), 0.76 (s, 3H), 0.78-0.85 (m, 1H), 0.90-0.98 (m, 1H), 1.08-1.22 (m, 5H), 1.26-1.53 (m, 9H), 1.67-1.70 (m, 1H), 1.73-1.78 (m, 1H), 1.85-1.97 (m, 2H), 2.26-2.44 (s, 1H), 3.32 (s, 3H), 4.56 (s, 1H), 4.86 (m, 1H), 7.17-7.29 (m, 5H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 11.2, 13.7, 19.8, 21.6, 25.5, 27.8, 30.7, 31.5, 32.3, 32.6, 34.9, 35.6, 35.7, 39.8, 47.7, 51.5, 54.3, 57.3, 71.1, 82.7, 127.2, 128.6, 136.9, 170.1, 221.3;

MS (EI) m/z 438 (M^+); Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.66; H, 8.74; O, 14.6. Found: C, 76.68; H, 8.76.

3β-O-((*R*)-α-methoxy-α-(9-anthryl)acetyl)-5α-androstan-17-one (*R*)-61.

[α]= -33.93 (c= 0.015, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.50-0.56 (m, 1H), 0.58 (s, 3H), 0.72 (s, 3H), 0.75-1.07 (m, 5H), 1.08-1.24 (m, 5H), 1.27-1.47 (m, 5H), 1.51-1.56 (m, 1H). 1.77-1.83 (m, 1H), 1.92-1.99 (m, 1H), 2.28-2.36 (m, 1H), 3.32 (s, 3H), 4.66 (m, 1H), 6.15 (s, 3H), 7.36-8.50 (m, 9H); MS (EI) m/z 538 (M^+); HRMS(EI) $C_{36}H_{42}O_4$ obs. 538.30830 calc. 538.30831 Δm 0.01 mu.

3β-O-((*S*)-α-methoxy-α-(9-anthryl)acetyl)-5α-androstan-17-one (*S*)-61.

[α]= 85.34 (c= 0.029, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.50-0.56 (m, 1H), 0.56 (s, 3H), 0.57-0.61 (m, 1H), 0.67 (s, 3H), 0.73-1.05 (m, 8H), 1.08-1.20 (m, 3H), 1.27-1.39 (m, 3H), 1.47-1.53 (m, 1H), 1.54-1.61 (m, 1H), 1.64-1.68 (m, 1H), 1.71-1.81 (m, 2H), 1.90-1.98 (m, 1H), 2.27-2.36 (m, 1H), 3.31 (s, 3H), 4.66 (m, 1H), 6.15 (s, 1H), 7.36-8.49 (m, 9H); MS (EI) m/z 538 (M^+);Anal. Calcd for $C_{36}H_{42}O_4$: C, 80.25; H, 7.86; O, 11.89. Found: C, 80.22; H,7.83.

3α-O-((*R*)-α-methoxy-α-(9-anthryl)acetyl)-5α-androstan-17-one (*R*)-62.

[α]= 26.66 (c= 0.0045, $CHCl_3$); ^{1}H NMR (500 MHz, CS2+CD2CL2, 4:1) δ (ppm): -0.62 (m, 1H), -0.52 (m, 1H), -0.06 (M, 2H), 0.40-0.47 (m, 1H), 0.49 (s, 3H), 0.55-0.63 (m, 1H), 0.71 (s, 3H), 0.76-0.82 (m, 1H), 0.91-1.00 (m, 3H), 1.05-1.47 (m, 7H), 1.51-1.56 (m, 1H), 1.57-1.64 (m, 1H), 1.85-1.91 (m, 1H), 2.01-2.12 (m, 1H), 2.33-2.41 (m, 1H), 3.47 (s, 3H), 4.87 (m, 1H), 6.18 (s, 1H), 7.37-8.60 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 10.7, 13.5, 19.6, 21.6, 25.8, 26.8, 29.4, 31.4, 32.2, 34.2, 34.8, 35.8, 38.3, 51.5, 53.2, 57.5, 70.8, 77.3, 124.8, 125.2, 126.4, 128.3, 129.0, 129.1, 130.5, 131.6, 170.0, 221.5; MS (EI) m/z 538 (M^+);

HRMS(EI) $C_{36}H_{42}O_4$ obs. 538.30827 calc. 538.30831 Δm 0.04 mu.

3α-O-((*S*)-α-methoxy-α-(9-anthryl)acetyl)-5α-androstan-17-one (*S*)-62.

[α]= 57.00 (c= 0.0045, $CHCl_3$); ^{1}H NMR (500 MHz, CS_2+CD_2Cl_2, 4:1) δ (ppm): -0.91-(-0.85) (m, 1H), -0.49 -(-0.43) (m, 1H), 0.09-0.44 (m, 1H), 0.46 (s, 3H), 0.48-0.56 (m, 1H), 0.61-0.66 (m, 1H), 0.67 (s, 3H), 0.81-0.88 (m, 1H), 0.91-1.14 (m, 7H), 1.18-1.25 (m, 3H), 1.34-1.42 (m, 1H), 1.54-1.62 (m, 1H), 1.81-1.87 (m, 1H), 1.94-2.03 (m, 1H), 2.28-2.35 (m, 1H), 3.42 (s, 3H), 4.79 (m, 1H), 6.12 (s, 1H), 7.35-8.55 (m, 9H); ^{13}C NMR (62.83 MHz, $CDCl_3$) δ (ppm): 10.8, 13.5, 19.4, 21.6, 25.1, 27.6, 30.5, 31.1, 31.4, 3.4, 34.5, 34.7, 35.7, 39.1, 47.7, 51.4, 53.2, 57.5, 71.1, 124.8, 125.1, 126.4, 128.3, 128.9, 129.1, 130.6, 131.6, 170.2, 221.6; MS (EI) m/z 538 (M^+); Anal. Calcd for $C_{36}H_{42}O_4$: C, 80.25; H, 7.86; O, 11.89. Found: C, 80.31; H,7.85.

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