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Determining the absolute configuration of secondary alcohols by means of a chiral auxiliary and NOESY☆

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Abstract—The absolute configuration of secondary alcohols can be determined by NOE between the diastereotopic protons of the lactam and the protons of the alcohol moieties in some 1-(alkoxymethyl)-methyl-2-pyrrolidone-5-carboxylate derivatives. Two simple methods based on conformational analysis and ^{1}H NMR data have been developed. The main conformer, in all cases, was established by means of MM, semi-empirical, and ab initio calculations.

1. Introduction

Absolute stereochemistries and enantiomeric purities of chiral compounds are frequently determined by nuclear magnetic resonance and studies on molecular mechanics.[1] Most of the chiral auxiliaries used for this purpose show magnetic anisotropies caused by π systems. This effect is reflected on the chemical shift in the nuclear magnetic resonance spectra obtained for the different derivatives. The most common reagent used for absolute stereochemistry determination is α-methoxy-α-(trifluoromethyl)phenyl acetic acid (Mosher's acid, MTPA).[2] Some analogues, such as 2-(2′-methoxy-1′-naphthyl)-3,5-dichlorobenzoic acid (MNCB) and 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (MBNC), have been used to determine the absolute stereochemistry of secondary alcohols, when forming the ester derivatives. In this case, the absolute stereochemistry is determined by observing NOEs that take place among the protons of the MBNC or MNCB and the protons of the alcohol moieties in the diastereomers.[3,4] The carbonyl group shows anisotropy effects due to its conical magnetic distribution.[5] Smith et al. have used this advantage to determine the enantiomeric composition of chiral non-racemic alcohols by using 1-(chloromethyl)-5-(*R*)-methyl-2-pyrrolidinone **1** to produce *N*-alkoxymethyl lactams **2**.[6]

In such derivatives, carbonyl anisotropy generates an AB system in the ^{1}H NMR spectra for the NCH_2O protons, essential for enantiomeric ratio determination. The conformational analyses of these derivatives were proposed by Latypov based on a molecular mechanics model. In this conformation, the five membered ring is planar with a pseudoaxial C-5 methyl group. The facility of rotation around the N–C bond results in two important rotamers, which are slightly different in energy. Steric interactions between the C-5 methyl group and the alkoxy moiety are responsible for these results. The relative positions of the protons within the NCH_2O fragment, in terms of the carbonyl group, modify the chemical shift. Furthermore, the absolute stereochemistry of the chiral alcohols can be established by taking the principal conformation into consideration. Latypov argues that both chiral alcohol enantiomers must be studied and that the procedure works well when substituents L_1 and L_2 are different in size[7] (Scheme 1).

Methyl pyroglutamate **3**, the starting material used to obtain compound **4**, is an important chiral auxiliary used in asymmetric syntheses of *N*-acyl pyroglutamic esters, radical cyclization, and Diels Alder reactions.[8]

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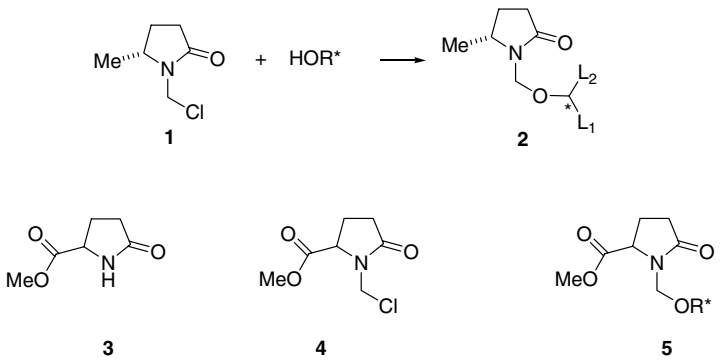


Scheme 1.

We decided to use 1-(chloromethyl)-methyl-2-pyrrolidone-5-carboxylate **4**, which can follow two synthetic steps that avoid the formation of **1**,[9a] compound obtained through a long synthetic route. This auxiliary is highly relevant for ^{1}H NMR spectroscopy since the methoxy singlet is ideal for ratio determination and the overlapping of signals is considerably reduced due to the ester moiety. Herein we report the results on the use of **4** as an auxiliary to obtain different analogues of **5**; compounds used to determine the absolute stereochemistry of the secondary alcohols by comparison of the NOE observed for the *N*-alkoxymethyl derivatives.

MM+, semi-empirical, and ab initio methods were used to calculate the conformation and distance interactions between the protons that could give rise to NOE.

2. Results and discussion

The chiral auxiliary was prepared by cyclization of either the L- or D-glutamic acids used as starting materials. Pyroglutamic acid was esterified with thionyl chloride and methanol as solvent.[9b] Compound **3** was transformed into **4** using paraformaldehyde and trimethylchlorosilane, to obtain an unstable oil that decomposes even in Kugelrohr distillation. The crude mixture was analyzed by ^{1}H NMR spectroscopy where a minimum of impurities was observed. *N*-Alkoxy derivatives were prepared using Smith conditions.[6] NaH in THF was used to obtain the sodium salts, these alkoxides were then reacted with **4** to obtain *N*-alkoxy derivatives **5**.[6] For the absolute stereochemistry determination, two methodologies were used. When both enantiomers of the alcohol were available, only one enantiomer of the chiral auxiliary was used (Method A). On the other hand, if only one of the enantiomers of the chiral alcohol was available, both enantiomers of the chiral auxiliary were used (Method B) (Fig. 1). In both methods, the following convention was applied: H_b is the deshielded proton of the AB system, that is, the hydrogen located in the lactam carbonyl plane. In method **A**, structures $\mathbf{A}_1$ and in $\mathbf{A}_2$ show H_b on the same side of the ring; R_2 is more deshielded in $\mathbf{A}_1$ than $\mathbf{A}_2$ due to its proximity to the carbonyl of the lactam; R_1 remains unaffected. This proximity is reflected in the chemical shift observed in the ^{1}H NMR spectrum. The proton attached to the asymmetric center plays an important role in this analysis, since, in $\mathbf{A}_1$, this proton is located over the carbonyl plane, thus decreasing the distance between R_2 and the carbonyl of the lactam. However in $\mathbf{A}_2$, the proton is behind the lactam ring. In addition, it would be more protected in $\mathbf{A}_1$ than $\mathbf{A}_2$. Thus, in $\mathbf{A}_1$, this proton would only show NOE with H_b while the interactions in $\mathbf{A}_2$ would be related to both protons in the AB system. For method B, we used L- and D-pyroglutamate derivatives and established structures $\mathbf{B}_1$ and $\mathbf{B}_2$. In these models, different fragments of the alcohol moiety are deshielded depending on the carbonyl orientation. It is important to state that this deshielding pattern was confirmed in a ^{1}H NMR spectrum based on the chemical shift.

In agreement with this methodology, the carbonyl anisotropy is the key to determining, which part of the molecule is affected by the different fragments. The success of this method necessarily depends on identifiable signals from R_1 and R_2. With this in mind, we used

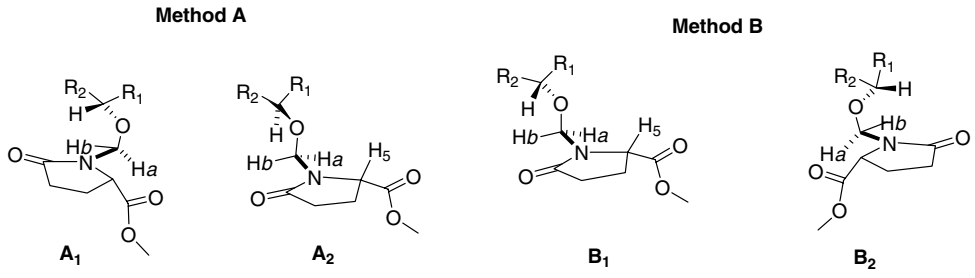


Figure 1. Shielding and deshielding effects for *N*-alkoxymethyl derivatives and interactions between protons that could give rise to NOE.

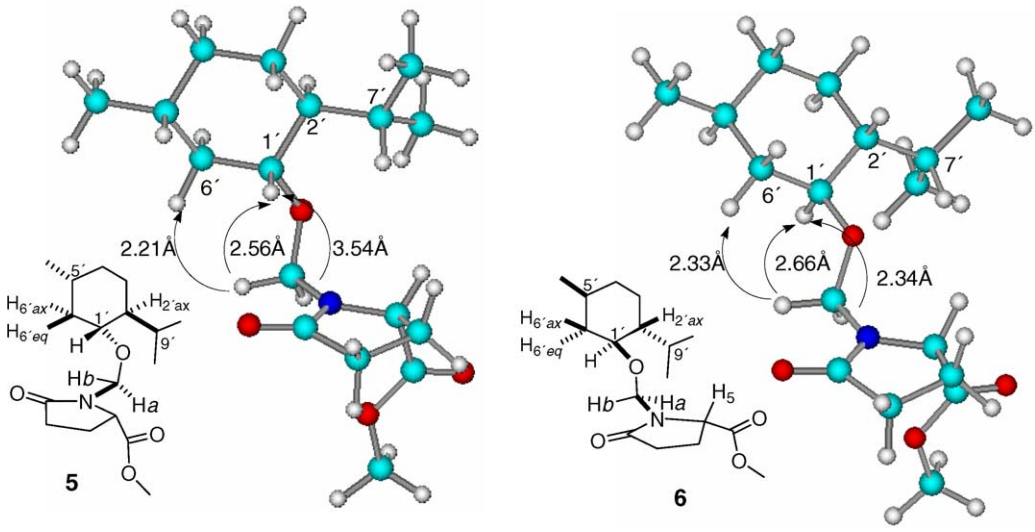


Figure 2. Conformational preference of **5** and **6** derivatives obtained by ab initio calculations.

2D NMR correlation experiments as well as a solvent change to guarantee the accurate assignment of the signals. To determine the absolute stereochemistry of (−)- and (+)-menthol we prepared derivatives **5** and **6** using method **A**, where only (*S*)-**4** was required (Fig. 2). In the ^{1}H NMR spectrum of **5**, the AB system was observed at 5.3 and 4.3 ppm ($J = 11.1$ Hz), H_b was the downfield proton.

The NOESY spectra obtained for product **5** showed H_b interactions with H_a, H-1′$_{ax}$, and H-6′$_{eq}$, H-1′$_{ax}$ is in proximity to H-5′$_{ax}$, H-6′$_{eq}$, and H-3′$_{ax}$. On the other hand, an NOE was observed between H-5 and H-9′. It is important to notice that H-1′$_{ax}$ showed an interaction with only one of the protons of the AB system: H_b. These observations indicate that compound **5** corresponds to structure $\mathbf{A}_1$, establishing R_1 as the isopropyl fragment and R_2 as C-6′, thus concluding that the stereochemistry of the center is *R*. In the ^{1}H NMR spectrum obtained for compound **6**, H_b was located at 5.26 ppm; an NOE interaction between this doublet with H-1′$_{ax}$ and H-6′$_{eq}$ was observed. In the case of **6**, H-1′$_{ax}$ interacts with the two protons of the AB system. This interaction suggests a proximity between these protons and H-1′$_{ax}$, in contrast with **5** where only one proton of the AB system interacts with H-1′$_{ax}$. As expected, **6** corresponds to structure $\mathbf{A}_2$, deduced by comparison of the chemical shift of H-1′$_{ax}$, which is downfield in $\mathbf{A}_2$, since it is not affected by the carbonyl of the lactam. A comparison of the carbonyl effect showed a difference in H-6′$_{eq}$ chemical shift; in **5** it was more deshielded than in **6** due to their distance to the conical distribution of the π system (Table 1).

It is important to point out that R_1 and R_2 are the same fragments of the molecule in both models and that the

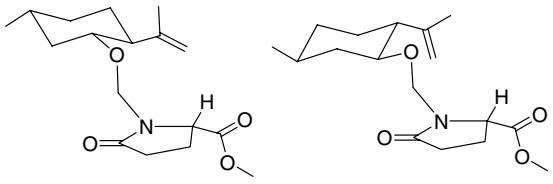


Table 1. Chemical shifts (ppm in $CDCl_3$), and NOESY interactions for **5**, **6**, **7**, and **8** using method A

Entry	Proton	δ	NOE	Entry	Proton	δ	NOE
5[a]	H_b	5.30	H_a, H-1′$_{ax}$, H-6′$_{eq}$	6[a]	H_b	5.26	H_a, H-1′$_{ax}$, H-6′$_{eq}$
	H_a	4.30	H_b		H_a	4.38	H_b, H-1′$_{ax}$
	H-6′$_{eq}$	2.22	H_b, H-5′$_{ax}$, H-1′$_{ax}$		H-6′$_{eq}$	1.91	H-1′$_{ax}$, H-7′
	H-1′$_{ax}$	3.16	H-6′$_{eq}$, H-5′$_{ax}$, H-3′$_{ax}$, H_b		H-1′$_{ax}$	3.22	H_a, H_b, H-6′$_{eq}$, H-5′$_{ax}$
	H-5	4.41	H-9′		H-5	4.44	—
7[b]	H_b	5.27	H_a, H-6′$_{eq}$, H-1′$_{ax}$	8[b]	H_b	5.26	H_a, H-1′$_{ax}$, H-6′$_{eq}$
	H_a	4.29	H_b		H_a	4.31	H_b, H-1′$_{ax}$
	H-6′$_{eq}$	2.22	H-1′$_{ax}$, H_b		H-6′$_{eq}$	1.90	H-5′$_{ax}$, H_b
	H-1′$_{ax}$	3.28	H-6′$_{eq}$, H-10′, H-5′$_{ax}$, H_b		H-1′$_{ax}$	3.34	H_a, H_b, H-6′$_{eq}$

[a] 300 MHz.
[b] 400 MHz.

main difference between these two derivatives is the orientation of H-1′$_{ax}$. These results confirm the unambiguous assignment of configuration for both compounds.

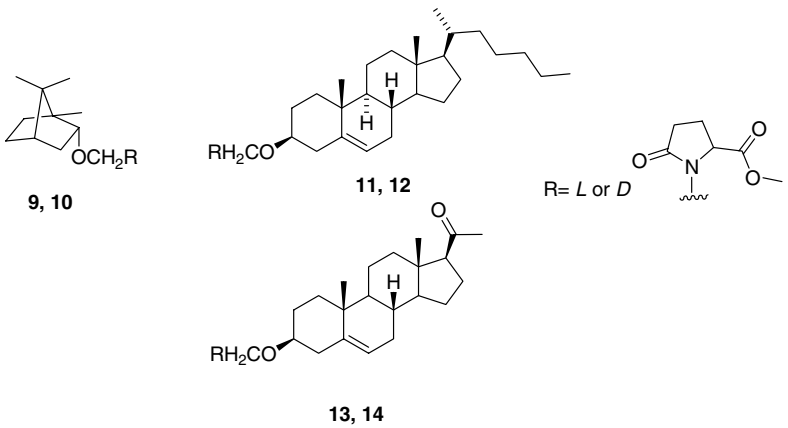
This method was also used with (−)- and (+)-isopullegol, **7** and **8**, respectively, for which similar data were obtained (Table 1).

Initially, the spectroscopic data obtained are in agreement with the theoretical calculations (Fig. 2). For menthol derivatives, the conformation and proton distances were scanned by ab initio optimization, with a modification of the key dihedral bonds. The rotation around the N–C bond presents a tendency toward the formation of a main conformer, in which the carbomethoxy and alcohol moieties have an *anti*-orientation. The lactam ring is planar with the ester moiety downwards. For conformational searching, the main dihedral angle (N–C–O–C) was rotated from 0° to 360° in 5° increments, obtaining the most stable conformation. The same analysis was carried out with semi-empirical and MM methods, which showed the same tendency. These results suggested the use of MM (MM+ force field) optimization for the remaining molecules. Calculation facilitated the rationalization of the NOESY information obtained for each derivative. Theoretical predictions for menthol and isopulegol derivatives showed important similarities. In both cases, the proton attached to the asymmetric center was responsible for the assignment of configuration.

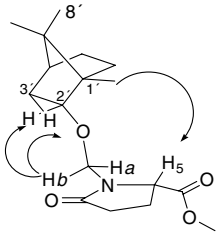
An important factor in the determination of the main conformer in derivatives **5** and **7** was the distance between H-1′$_{ax}$ and the π system of the carbonyl of the lactam. The lowest repulsion was observed when the distance between them was 1.54 Å; at this point the energy is 40.62 kcal/mol. This proximity explains the difference in chemical shift for H-1′$_{ax}$. In addition, the distances between H-1′$_{ax}$ and the protons of the AB system in **5** are 3.54 and 2.56 Å, respectively. Only the NOE interaction of H-1′$_{ax}$ with H_b was observed. In MM calculations for **6**, H-1′$_{ax}$ is up and behind the lactam ring, thus avoiding the shielding from the carbonyl group. Furthermore, in this case, both protons of the AB system interact with H-1′$_{ax}$. The distance between H-6$_{eq}$ and the carbonyl plane in **5** was 3.73 Å, while in **6** this distance was longer (4.06 Å), which explains the stronger field effect over H-6′$_{eq}$ causing deshielding. All these observations are in agreement with the experimental methods. Method B was applied for (−)-borneol, cholesterol, and pregnenolone (Scheme 2).

In this model, the chemical shift of the deshielded proton (H_b) depends on the enantiomer of the chiral auxiliary used. In our analysis, the key is to establish the deshielded fragment in the alcohol moiety. Important differences in the NOESY experiment were found in (−)-borneol derivatives **9** and **10** (with L-**4** and D-**4**, respectively). In the ^{1}H NMR spectrum obtained for **9**, the deshielded proton resonates at 5.09 ppm and H_a is placed at 4.48 ppm, with both protons showing a correlation with H-2′$_{exo}$ but the effect being stronger with H_b, which can be explained by its proximity. Furthermore, H_b shows an NOE with H-3′$_{endo}$, which establishes the main conformer of the molecule. The most important observation was the NOE between Me-10′ and H-5, which was the last feature to determine absolute configuration. Similar results were observed in the NOESY experiment for **10**, H-2′$_{exo}$ is in the proximity of the two protons of the AB system, but such effect is stronger with H_b. In this case, H-5 shows an NOE with H-3′$_{endo}$. This allowed us to establish the correct assignment of the stereochemistry. Another important key is the chemical shift for H-3′$_{endo}$ which is more deshielded in **9** than **10** due to its proximity to the carbonyl group. MM calculations for these derivatives show an anomalous behavior, which suggests a more complicated conformational situation not consistent with the experimental results.

The same methodology was used for cholesterol (**11** and **12**, with L-**4**- and D-**4**-, respectively), and pregnenolone (**13** and **14**, with L-**4**- and D-**4**-, respectively). To avoid signal overlapping, different solvents were tested in the acquisition of the NMR spectra. C_6D_6 offered the best results (Table 2). Derivatives of cholesterol **11** and **12** showed important interactions in the NOESY experiment; H-2′$_{eq}$ and H-4′$_{eq}$ protons are responsible for the following results. In **11** (Fig. 3); H_b shows a NOE



Scheme 2.



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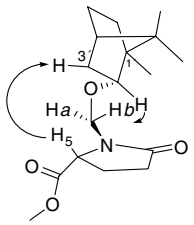

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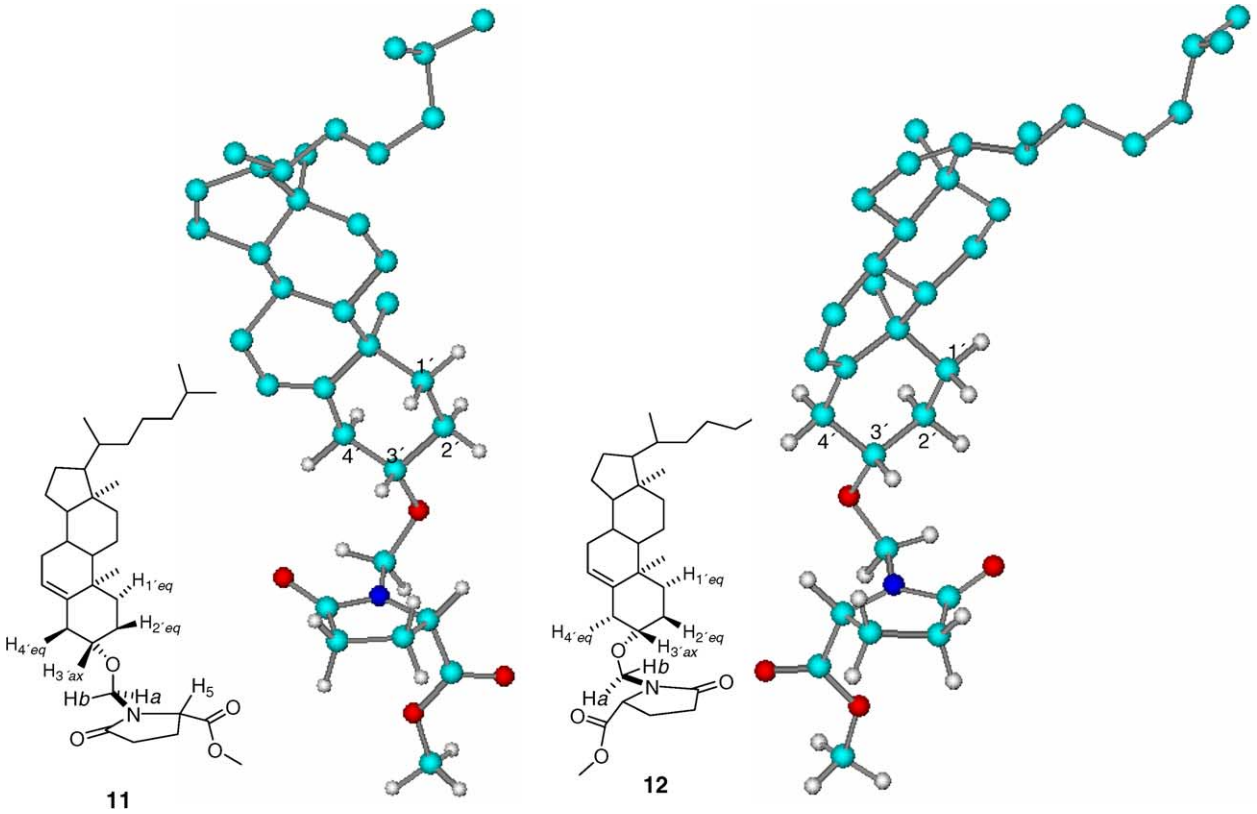
Table 2. Chemical shifts (ppm) and NOESY interactions for **9**, **10**, **11**, **12**, **13**, and **14** using method B

Entry	Proton	δ	NOE	Entry	Proton	δ	NOE
9[a,b]	H_b	5.09	H_a, H-2′$_{exo}$, H-3′$_{endo}$	**10**[a,c]	H_b	5.07	H_a, H-2′$_{exo}$
	H_a	4.48	H-2′$_{exo}$, H_b		H_a	4.53	H_b
	H-5	4.35	H-10′		H-5	4.39	H-3′$_{endo}$
	H-2′$_{exo}$	3.60	H-10′, H_b		H-2′$_{exo}$	3.68	H_b, Me-10
	H-3′$_{endo}$	1.03	H_b		H-3′$_{endo}$	0.85	H-5
11[c,d]	H_b	5.15	H_a, H-3′$_{ax}$, H-4′$_{eq}$	**12**[c,d]	H_b	5.15	H_a, H-3′$_{ax}$, H-2′$_{eq}$
	H_a	4.93	H_b, H-3′$_{ax}$, H-2′$_{eq}$		H_a	4.84	H_b, H-3′$_{ax}$, H-4′$_{eq}$
	H-3′$_{ax}$	3.53	H-4′$_{eq}$, H-2′$_{eq}$, H_b, H_a		H-3′$_{ax}$	3.49	H-4′$_{eq}$, H-2′$_{eq}$, H_b, H_a
13[c,d]	H_b	4.97	H_a, H-3′$_{ax}$, H-4′$_{eq}$	**14**[c,d]	H_b	5.13	H_a, H-3′$_{ax}$, H-2′$_{eq}$
	H_a	4.86	H_b, H-3′$_{ax}$, H-2′$_{eq}$		H_a	4.86	H_b, H-3′$_{ax}$, H-4′$_{eq}$
	H-3′$_{ax}$	3.45	H-4′$_{eq}$, H-2′$_{eq}$, H_b, H_a		H-3′$_{ax}$	3.49	H-4′$_{eq}$, H-3′$_{eq}$, H_b, H_a
	H-6′	5.38	H-4′$_{eq}$, H-4′$_{ax}$,		H-6′	5.43	H-4′$_{eq}$, H-4$_{ax}$

[a] $CDCl_3$.
[b] 300 MHz.
[c] 400 MHz.
[d] C_6D_6.



11

12

Figure 3. Conformational preference of **11** and **12** derivatives obtained by molecular mechanics.

with H-4′$_{eq}$ and H_a with H-2′$_{eq}$. On the other hand, compound **12** presented this effect between H-2′$_{eq}$ and H_b; as well as between H_a and H-4′$_{eq}$. In both cases, the NOE between H_a and H-3′$_{ax}$ was weak. MM calculations for derivatives **11**–**14** showed a main conformer, which was in agreement with experimental results; the H_b–H-4′$_{eq}$ distance is 2.23 Å in compound **11**. A similar distance was observed between H_b–H-2′$_{eq}$ (2.24 Å) in conformer **12**.

Non-racemic mixtures were also studied. A 60:40 mixture of (−) and (+)-menthol was treated with 1.5 equiv of L-**4**. The analysis of the OMe signals showed a 54:46 ratio after the chromatographic procedure. The ^{1}H NMR spectrum showed two AB systems that were identified by means of their coupling constants. Protons were labeled as u for upfield and d for downfield (Fig. 4). H_{bd} (5.31 ppm) coupled with H_{au} (4.33 ppm) and H_{bu} (5.28 ppm) with H_{ad} (4.39 ppm); the chemical shift is related to the orientation of the carbonyl of the lactam.

According to the models proposed in method A, H-2′$_{eq}$ would be affected in different ways in the different diastereoisomers: H-2′$_{eqd}$ resonates at 2.21 ppm and H-2′$_{equ}$ at 1.86 ppm. H_{bd} showed NOE with H-2′$_{eqd}$ as well as with H-1′$_{axu}$. This suggests that the proton attached to the asymmetric center is over the lactam plane increasing the proximity of H-2′$_{eq}$ to the carbonyl group.

On the other hand, H_{bu} showed an NOE with H-2′$_{equ}$ and H-1′$_{axd}$. The H-2′$_{equ}$ chemical shift is modified because H-1′$_{ax}$ is behind the lactam plane decreasing the anisotropic effect on that alcohol moiety. In this case, the integration of the proton NMR signals and NOE correlations indicate an agreement with the composition of the mixture.

Our next task was to apply our method to the racemic mixtures obtained from carbonyl reductions. We treated 5-methoxytetralone **15** with $NaBH_4$ in EtOH and obtained a mixture of alcohols, **16** (Scheme 3).

This racemate was treated with (*S*)-**4** to obtain diastereoisomers **17** and **18**. After many chromatographic procedures, we were unable to separate the stereoisomers, so we decided to analyze them as a mixture. The

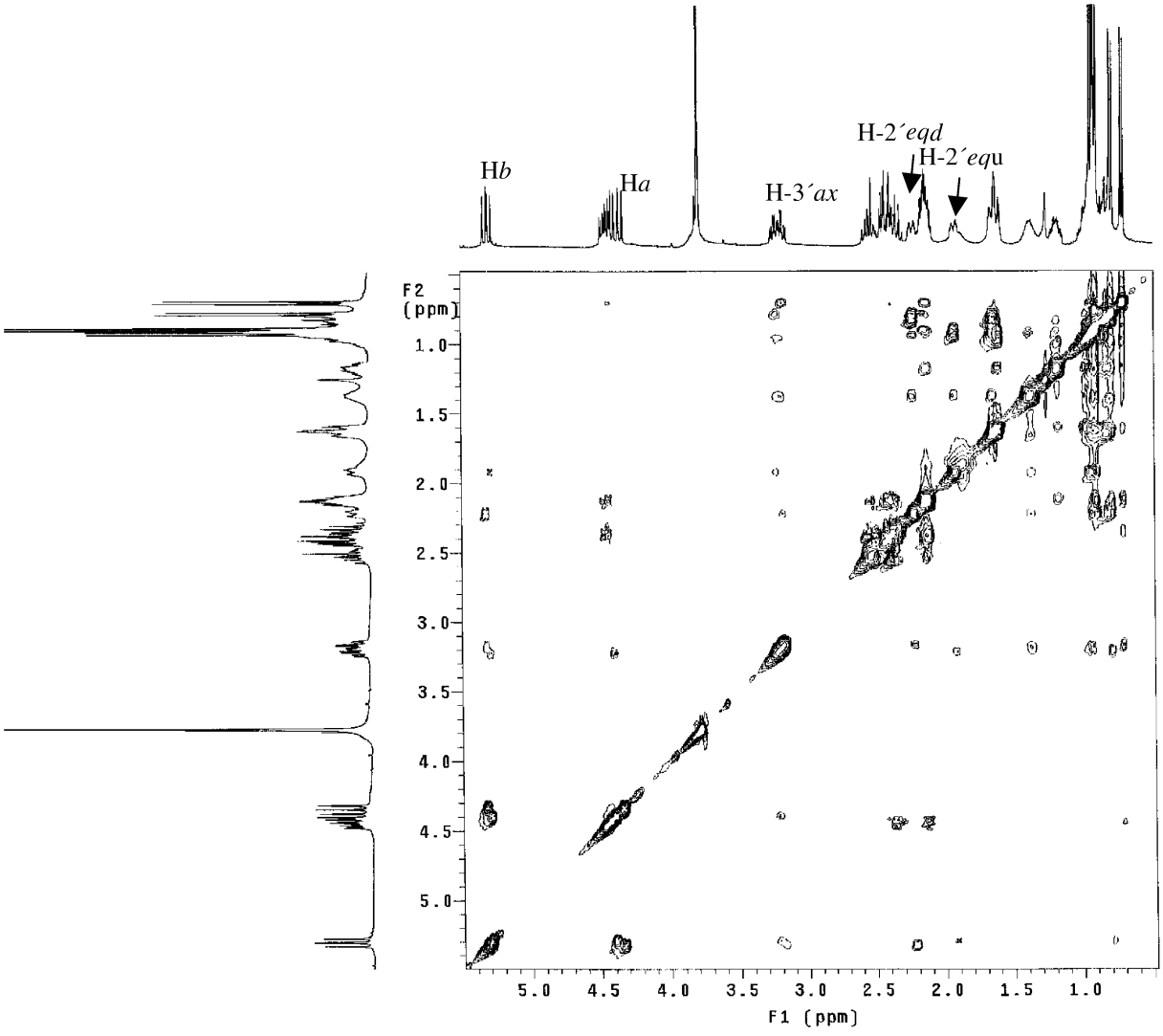
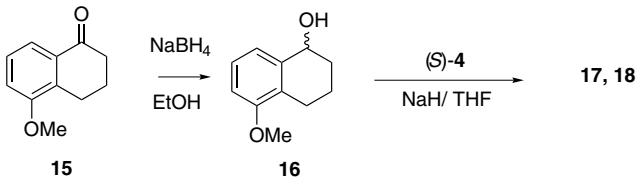


Figure 4. NOESY of a 54:46 mixture of **5** and **6** derivatives. 400 MHz, $CDCl_3$.



Scheme 3.

integration suggests a 56:44 ratio after the chromatography procedure. The ^{1}H NMR spectrum at 400 MHz showed overlapped signals when using $CDCl_3$. The best analysis was obtained with a 50:50 mixture of C_6D_6/$(CD_3)_2CO$. Molecular mechanic calculations show an important relationship with the experimental results (Fig. 5). A comparison between **17** and **18** allowed us to predict an important deshielding for H_b in **18**, due to aromatic anisotropy (H_{bd}); such an effect was absent in **17**. Experimentally, in **18** we observed NOE between H_{bd} and H-8′ while H_{bu} showed proximity with H-2′$_{eq}$. The protons attached to the asymmetric center had the same chemical shift in both derivatives. It is important to highlight that H_{bd} belongs to the abundant stereoisomer, which suggests that its absolute stereochemistry is *S*. These results were also observed when using C_6D_6 in NMR experiments.

3. Conclusions

We have demonstrated that NOE is a useful tool for determining the absolute stereochemistry of secondary alcohols and that it supports the validity of the proposed method. Experimentally, the deshielding produced by a carbonyl group is the key for the establishment of the correct interactions in NOESYs.

Ab initio, semi-empirical, and molecular mechanic optimizations showed a main conformer by rotation of the NCOC dihedral angle that is in agreement with the data obtained by spectroscopic means. The important role of the proton attached to the asymmetric center is also described.

The use of either method depends on alcohol availability. Spectroscopical results can be improved by solvent modification, thus increasing, even more, the utility of **4** as a chiral auxiliary.

4. Experimental section

^{1}H NMR were obtained on a Varian Unity System 400 MHz, a Varian Unity 300 MHz, and a Varian Mercury 200 MHz. The chemical shifts (ppm) are relative to internal TMS. One and two dimensional NMR spectra were obtained with a standard pulse sequence. The mixing time used for the NOESY spectra is 1.0 s or 1.5 s. Calculations were performed using the Gaussian 98 program. Conformational analysis was scanned by ab initio optimization using Hartree-Fock approximation with 6-31G* basis. Semi-empirical and molecular mechanics calculations were carried out using AM1 and MM+ force fields, respectively. The conformational analysis of each compound was scanned by MM optimization around key dihedral bonds.

4.1. 1-Chloromethyl-methyl-2-pyrrolidone-5-carboxylate 4

A mixture of methyl pyroglutamate (500 mg, 3.49 mmol), paraformaldehyde (170 mg, 5.6 mmol), and chlorotrimethylsilane (2.8 ml, 17.9 mmol) was refluxed for 2 h. The hexamethyldisiloxane formed and

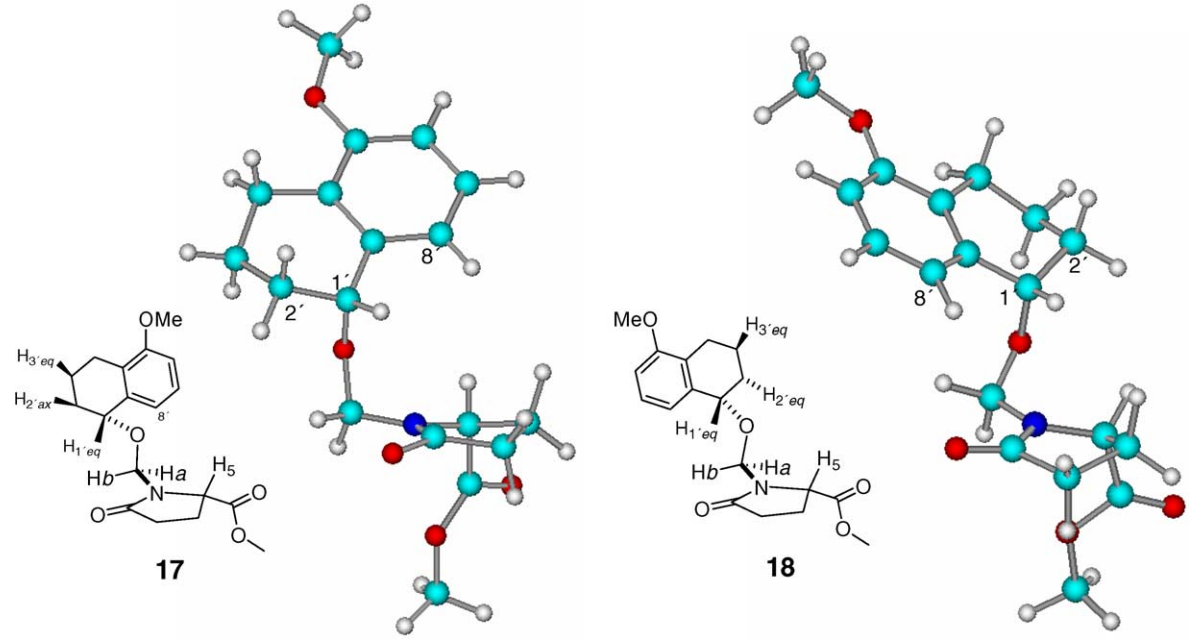


Figure 5. Conformational preference of **17** and **18** derivatives obtained by MM.

chlorotrimethylsilane excess was removed under vacuum for 1 h without heat. The colorless liquid was identical to the reported one. The crude ester was used for the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.7 (d, $J = 10.2$ Hz, 1H), 4.9 (d, $J = 10.2$ Hz, 1H), 4.4 (dd, $J = 8$, 4 Hz, 1H), 3.8 (s, 3H), 2.0–2.5 (m, 4H).

4.2. General procedure for the preparation 1-(alkoxymethyl)-methyl-2-pyrrolidone-5-carboxylate derivatives

Sodium hydride (1.2 equiv, 60% in mineral oil) was added to a solution of alcohol (1.0 equiv) in dried THF under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. Crude 1-(chloromethyl)-5-methyl-2-pyrrolidone carboxylate (1.5–2.0 equiv) in dried THF was then added dropwise under a nitrogen atmosphere. The solution was refluxed for 12–24 h. A saturated solution of NH_4Cl was added to eliminate the excess of sodium hydride. THF was distilled and the aqueous layer was extracted with methylene chloride. Organic extracts dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by chromatography using *n*-hexane/EtOAc as eluent.

4.3. 1-[(1*R*′,2*S*′,5*R*′)-Menthoxy-methyl]-methyl-(*S*)-2-pyrrolidone-5-carboxylate 5

A mixture of (−)-(1*R*,2*S*,5*R*)-menthol (1.40 g, 9.01 mmol), $[\alpha]_D^{20} = -50$ (*c* 10, EtOH), sodium hydride (0.43 g, 10.8 mmol, 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone 5-carboxylate (2.30 g, 12.1 mmol) in dried THF, was heated at reflux for 23 h, as described in the general procedure. The crude was purified by column chromatography to yield 1.61 g (57.5%) of **5** as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm) 5.3 (d, $J = 11.1$ Hz, 1H), 4.41 (dd, $J = 9.0$, 3.3 Hz, 1H), 4.33 (d, $J = 11.1$ Hz, 1H), 3.79 (s, 3H), 3.16 (td, $J = 10.5$, 4.2 Hz, 1H), 2.4–2.05 (m, 6H), 1.63 (m, 2H), 1.37 (m, 1H), 1.17 (m, 1H), 0.95–0.8 (m, 3H), 0.9 (d, $J = 6.6$ Hz, 3H), 0.9 (d, $J = 7.5$ Hz, 3H), 0.7 (d, $J = 6.6$ Hz, 3H); MS EI *m*/*z* (rel intensity): M^+ 311(2), 252(44), 172(36), 157(98), 156(100), 128(81), 98(36), 84(43), 68(16), 55(11), 41(11); HRMS FAB$^+$ *m*/*z*: $C_{17}H_{30}O_4N$ $[M+1]^+$ calculated 312.2097, observed 312.2180. $[\alpha]_D^{20} = -105.5$ (*c* 0.578, $CHCl_3$).

4.4. 1-[(1*S*′,2*R*′,5*S*′)-Menthoxy-methyl]-methyl-(*S*)-2-pyrrolidone-5-carboxylate 6

A mixture of (+)-(1*S*,2*R*,5*S*)-menthol (175 mg, 0.55 mmol), $[\alpha]_D^{23} = +48$ (*c* 10, EtOH), sodium hydride (28 mg, 0.67 mmol, 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone 5-carboxylate (192 mg, 1.34 mmol) in dried THF, was heated at reflux for 24 h. The crude was purified by column chromatography using *n*-hex/EtOAc as eluent. The reaction yields 270 mg (64.7%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 5.26 (d, $J = 10.2$ Hz, 1H), 4.44 (ddd, $J = 8.7$, 4.2, 0.6, 1H), 4.38 (dd, $J = 9.9$, 0.6 Hz, 1H), 3.75 (s, 3H), 3.2 (td, $J = 10.8$, 4.8 Hz, 1H), 2.4 (m, 3H), 2.11 (m, 2H), 1.91 (m, 1H), 1.62 (m, 1H), 1.35 (m, 1H), 1.17 (m, 2H), 1.05–0.83 (m, 3H), 0.88 (d, $J = 7.2$ Hz, 3H), 0.86 (d, 6.3, 3H), 0.77 (d, $J = 6.9$ Hz, 3H); MS EI *m*/*z* (rel intensity): M^+ 311(2), 252(18), 172(18), 157(76), 156(100), 128(43), 98(14), 85(27), 68(8), 55(8), 41(8). $[\alpha]_D^{20} = +11.8$ (*c* 0.204 $CHCl_3$).

4.5. 1-[(1*R*′,2*S*′,5*R*′)-2-Isopropenyl-5-methyl-cyclohexanoxy-methyl]-methyl-(*S*)-2-pyrrolidone-5-carboxylate 7

A mixture of (−)-isopulegol (147 mg, 0.95 mmol), $[\alpha]_D^{20} = -22$ (neat), sodium hydride (42 mg, 1.05 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (366 mg, 1.91 mmol) in dried THF, was heated at reflux for 26 h. The crude was purified by column chromatography to yield 0.165 g (55.75%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.27 (d, $J = 11.6$ Hz, 1H), 4.78 (t, $J = 1.6$, 1H), 4.73 (d, $J = 0.4$ Hz, 1H), 4.38 (dd, $J = 9.6$, 3.6 Hz, 1H), 4.29 (d, $J = 11.6$ Hz, 1H), 3.78 (s, 3H), 3.28 (td, $J = 10.4$, 4.0 Hz, 1H), 2.52–2.25 (m, 3H), 2.22 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.69 (s, 3H), 1.65 (m, 2H), 1.45 (m, 1H), 1.27 (m, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 1.0–0.8 (m, 2H); MS EI *m*/*z* (rel intensity): M^+ 309(2), 250(8), 167(8), 156(63), 128(100), 97(12), 84(12), 68(19); HRMS EI$^+$ *m*/*z*: $C_{17}H_{27}O_4N$ M^+ calculated 309.1940, observed 309.1903. $[\alpha]_D^{20} = -83.1$ (*c* 4.8 $CHCl_3$).

4.6. 1-[(1*S*′,2*R*′,5*S*′)-2-Isopropenyl-5-methyl-cyclohexanoxy-methyl]-methyl-(*S*)-2-pyrrolidone-5-carboxylate 8

A mixture of (+)-(1*S*,2*R*,5*S*)-isopulegol (147 mg, 0.95 mmol), $[\alpha]_D^{20} = +22$ (neat), sodium hydride (57.4 mg, 1.43 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (366 mg 1.91 mmol), in dried THF, was refluxed for 25 h. The crude mixture was purified by column chromatography as in the general procedure. The reaction yields 188 mg (63.4%), of a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.26 (d, $J = 10.4$ Hz, 1H), 4.78 (m, 2H), 4.44 (dd, $J = 3.6$, 8.8 Hz, 1H), 4.31 (dd, $J = 10.0$, 0.4 Hz, 1H), 3.75 (s, 3H), 3.34 (td, $J = 10.8$, 4.4 Hz, 1H), 2.6–2.3 (m, 3H), 2.1 (m, 1H), 1.9 (m, 2H), 1.73 (t, $J = 0.8$ Hz, 3H), 1.62 (m, 2H), 1.48 (m, 1H), 1.31 (m, 1H), 1.0–0.8 (m, 2H), 0.91 (d, $J = 6.8$ Hz, 3H); MS EI *m*/*z* (rel intensity): M^+ 309(2), 281(8), 250(8), 156(68), 144(13), 128(100), 98(8), 81(10), 68(17); HRMS EI$^+$ *m*/*z*: $C_{17}H_{27}O_4N$ M^+ calculated 309.1940, observed 309.1928. $[\alpha]_D^{20} = -5.1$ (*c* 1.77 $CHCl_3$).

4.7. 1-[*endo*-(1*S*)-[1′,7′,7′-Trimethylbicyclo[2.2.1]heptan-2′-oxy-methyl]]-methyl-(*S*)-2-pyrrolidone-5-carboxylate 9

A mixture of *endo*-(1*S*)-[1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (540 mg, 3.44 mmol), $[\alpha]_D^{20} = -35.6$ (*c* 5 EtOH), sodium hydride (153 mg, 3.83 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (1.338 g, 6.98 mmol) in dried THF, was refluxed for 23 h. The reaction yielded 595 mg (55.1%) of product as a colorless oil after column chromatogra-

phy. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 5.09 (d, $J = 10.5$ Hz, 1H), 4.48 (d, $J = 10.8$ Hz, 1H), 4.35 (dd, $J = 6$, 2.4 Hz, 1H), 3.77 (s, 3H), 3.61 (ddd, $J = 9.3$, 3.3, 1.5 Hz, 1H), 2.6–2.1 (m, 5H), 1.93–1.60 (m, 3H), 1.20 (m, 2H), 1.0 (dd, 13.2, 3.3 Hz, 1H), 0.83 (s, 6H), 0.81 (s, 3H); MS EI m/z (rel intensity): M^+ 309(4), 250(3), 158(57), 157(100), 156(99), 128(54), 109(17), 98(24), 81(8), 68(12), 41(10); HRMS FAB$^+$ m/z: $C_{17}H_{28}O_4N$ $[M+1]^+$ calculated 310.1940, observed 310.2008. $[\alpha]_D^{20} = -66.8$ (c 0.774 $CHCl_3$).

4.8. 1-[*endo*-(1*S*)-[1′,7′,7′-Trimethylbicyclo[2.2.1]heptan-2′-oxy-methyl]]-methyl-(*R*)-2-pyrrolidone-5-carboxylate 10

A mixture of *endo*-(1*S*)-[1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (360 mg, 2.33 mmol), $[\alpha]_D^{20} = -35.6$ (c 5 EtOH), sodium hydride (100 mg, 2.56 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*R*)-2-pyrrolidone-5-carboxylate (670 mg, 3.49 mmol), in dried THF, was heated at reflux for 28 h. The reaction was purified by column chromatography to yield 0.434 mg (60.1%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.07 (d, $J = 10$ Hz, 1H), 4.53 (d, $J = 10$ Hz, 1H), 4.39 (dd, $J = 9.2$, 3.6 Hz, 1H), 3.77 (s, 3H), 3.68 (ddd, $J = 9.6$, 3.6, 2.0 Hz, 1H), 2.6–2.05 (m, 5H), 1.9–1.6 (m, 3H), 1.4–1.2 (m, 2H), 0.9 (m, 1H), 0.84 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H); MS EI m/z (rel intensity): M^+ 309(3), 250(3), 166(4), 158(61), 157(100), 156(96), 128(56), 109(21), 98(27), 81(12), 68(13), 55(13), 41(18), 28(12); HRMS FAB$^+$ m/z: $C_{17}H_{28}O_4N$ $[M+1]^+$ calculated 310.1940, observed 310.2029. $[\alpha]_D^{20} = -4.3$ (c 1.80 $CHCl_3$).

4.9. 1-[3′-β-Cholest-5′-en-3′-oxy-methyl]-methyl-5-(*S*)-2-pyrrolidone-5-carboxylate 11

A mixture of cholesterol (0.50 g, 1.29 mmol), $[\alpha]_D^{20} = -40$ (c 2, $CHCl_3$), sodium hydride (77.5 mg, 1.94 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (370 mg 1.94 mmol), in dried THF, was refluxed for 36 h and purified by column chromatography as described in the general procedure. The reaction yields 298 mg (42.5%), of a white solid: mp 145–147 °C; ^{1}H NMR (C_6D_6, 400 MHz) δ (ppm) 5.51 (m, 1 H), 5.12 (d, $J = 10.8$ Hz, 1H), 4.93 (d, $J = 10.8$ Hz, 1H), 4.07 (m, 1H), 3.53 (m, 1H), 3.3 (s, 3H), 2.66 (ddd, $J = 13.2$, 6.6, 2.8 Hz, 1H), 2.4 (m, 1H), 2.22 (dt, $J = 16.8$, 9.6 Hz, 1H), 2.1–1.15 (m, 29H), 1.04 (d, $J = 6.4$ Hz, 3H), 1.01 (s, 3H), 0.96 (d, $J = 6.4$ Hz, 6H), 0.70 (s, 3H); MS EI m/z (rel intensity): M^+ 541(4), 536(4), 478(10), 405(6), 355(9), 281(22), 253(13), 207(68), 167(21), 149(65), 119(35), 95(46), 69(100), 41(86); HRMS FAB$^+$ m/z: $C_{34}H_{56}O_4N$ $[M+1]^+$ calculated 542.4131, observed 542.4218. $[\alpha]_D^{20} = -55.6$ (c 1.86 $CHCl_3$).

4.10. 1-[3′-β-Cholest-5′-en-3′-oxy-methyl]-methyl-5-(*R*)-2-pyrrolidone-5-carboxylate 12

A solution of cholesterol (392 mg, 1.01 mmol), $[\alpha]_D^{20} = -40$ (c 2, $CHCl_3$), sodium hydride (40.5 mg, 1.52 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*R*)-2-pyrrolidone-5-carboxylate (290 mg 1.52 mmol), in dried THF, was refluxed for 45 h. The reaction was purified by column chromatography to yield 275 mg (50.1%), of a white solid: mp 134–136 °C; ^{1}H NMR (C_6D_6, 400 MHz) δ (ppm) 5.48 (m, 1H), 5.15 (d, $J = 10.8$ Hz, 1H), 4.84 (d, $J = 10.8$ Hz, 1H), 4.06 (m, 1H), 3.49 (m, 1H), 3.25 (s, 3H), 2.62 (ddd, $J = 13.2$, 4.8, 2.4 Hz, 1H), 2.43 (m, 1H), 2.18 (dt, $J = 17.2$, 9.2 Hz, 1H), 2.09–1.22 (m, 29H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.97 (s, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.66 (s, 3H); MS EI m/z (rel intensity): M^+ 541(4), 536(10) 478(7), 393(7), 281(22), 207(54), 189(16), 159(15), 139(50), 119(35), 95(50), 60(100), 41(83); HRMS FAB$^+$ m/z: $C_{34}H_{56}O_4N$ $[M+1]^+$ calculated 542.4131, observed 542.4218. $[\alpha]_D^{20} = -63.2$ (c 0.95 $CHCl_3$).

4.11. 1-[17′-β-(1-Ketoethyl)-$\Delta^{5'}$-androsten-3′-β-oxy-methyl]-methyl-5-(*S*)-2-pyrrolidone-5-carboxylate 13

A mixture of pregnenolone (0.3 g, 0.95 mmol), $[\alpha]_D^{23} = +27$ (c 1, C_2H_5OH), sodium hydride (57 mg, 1.42 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (363 mg 1.89 mmol), in dried THF, was refluxed and purified by chromatotron as described in the general procedure. The reaction yielded 220 mg (49.3%), of a white solid: mp 151–153 °C; ^{1}H NMR (C_6D_6, 400 MHz) δ (ppm) 5.38 (m, 1H), 4.97 (d, $J = 10.8$ Hz, 1H), 4.86 (d, $J = 10.8$ Hz, 1H), 3.95 (dd, $J = 6.8$, 5.6 Hz, 1H), 3.45 (m, 1H), 3.22 (s, 3H), 2.56 (ddd, $J = 13.2$, 4.8, 2.8 Hz, 1H), 2.3 (m, 2H), 2.13 (dt, $J = 16.8$, 9.6 Hz, 1H), 2.02 (m, 2H), 1.82–0.64 (m, 18H), 1.747 (s, 3H), 0.83 (s, 3H), 0.50 (s, 3H); MS EI m/z (rel intensity): M^+ 471(2), 412(4), 299(24), 298(88), 283(12), 174(12), 156(100), 128(37), 68(8), 43(15), 18(7); HRMS FAB$^+$ m/z: $C_{28}H_{42}O_5N$ $[M+1]^+$ calculated 472.2985, observed 472.3053. $[\alpha]_D^{20} = -22.8$ (c 0.745 $CHCl_3$).

4.12. 1-[17′-β-(1-Ketoethyl)-$\Delta^{5'}$-androsten-3′-β-oxy-methyl]-methyl-5-(*R*)-2-pyrrolidone-5-carboxylate 14

A mixture of pregnenolone (0.5 g, 1.57 mmol), $[\alpha]_D^{23} = +27$ (c 1, C_2H_5OH), sodium hydride (94.2 mg, 2.35 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*R*)-2-pyrrolidone-5-carboxylate (605 mg, 3.16 mmol), in dried THF, was heated for 48 h and purified by column chromatography as in the general procedure. The reaction yielded 382 mg (51.3%), of a white solid: mp 137–139 °C; ^{1}H NMR (C_6D_6, 400 MHz) δ (ppm) 5.43 (m, 1H), 5.13 (d, $J = 10.8$ Hz, 1H), 5.86 (d, $J = 10.8$ Hz, 1H), 4.05 (dd, $J = 6.4$, 6.0 Hz, 1H), 3.49 (m, 1H), 3.25 (s, 3H), 2.62 (m 1H), 2.8 (m, 2H), 2.17 (dt, $J = 16.8$, 9.2 Hz, 1H), 2.08 (m, 2H), 1.81 (s, 3H), 0.88 (s, 3H), 0.56 (s, 3H), 1.8–0.65 (m, 18H); MS EI m/z (rel intensity): M^+ 471(2), 453(3), 412(3), 310(14), 299(27), 298(100), 174(14), 156(93), 128(39), 121(10), 68(9),43(14); HRMS FAB$^+$ m/z: $C_{28}H_{42}O_5N$ $[M+1]^+$ calculated 472.2985, observed 472.3062. $[\alpha]_D^{20} = +28.8$ (c 0.35 $CHCl_3$).

4.13. 1-[5′-Methoxy-1′,2′,3′,4′-tetrahydro-naphthalen-1′-oxy-methyl]-methyl-5-(*S*)-2-pyrrolidone-5-carboxylate 17 and 18

A mixture of 5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ol (500 mg, 2.80 mmol), sodium hydride (110 mg, 2.8 mmol in 60% mineral oil), and 1-(chloromethyl)-methyl-(*S*)-2-pyrrolidone-5-carboxylate (805 mg 4.21 mmol), in dried THF, was heated at reflux for 24 h. The reaction yields 410 mg (44.17%) of a colorless oil, obtained as a 56:43 diastereomeric mixture (analyzed as NMR ^{1}H integration); ^{1}H NMR (C_6D_6/$(CD_3)_2CO$, 50:50, 400 MHz) δ (ppm) 7.13 (m, 3H), 7.03 (m, 1H), 6.68 (m, 2H), 5.27 (d, $J = 10.4$ Hz, 1H), 5.18 (d, $J = 10.8$ Hz, 1H), 4.65 (dd, $J = 10.8$, 0.4 Hz, 1H), 4.64 (dd, $J = 10.4$, 0.8 Hz, 1H), 4.51 (t, $J = 4.4$ Hz, 1H), 4.49 (t, $J = 4.4$ Hz, 1H), 4.34 (dd, $J = 8.0$, 3.2 Hz, 1H), 4.31 (dd, $J = 8.0$, 3.2 Hz, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.55 (s, 3H), 2.75 (t, $J = 4.8$ Hz, 2H), 2.71 (t, $J = 4.8$ Hz, 2H), 2.5 (m, 2H), 2.35 (m, 2H), 2.18 (m, 4H), 1.91 (m, 4H), 1.75 (m, 2H), 1.62 (m, 2H); MS EI *m*/*z* (rel intensity): M^+ 333(2), 281(2), 244(3), 177(47), 161(58), 160(100), 145(16), 128(43), 98(36), 84(16), 68(21), 41(20). HRMS EI$^+$ *m*/*z*: $C_{18}H_{23}O_5N$ M^+ calculated 333.1576, observed 333.1557.

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