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O-Methylatrolactic acid as a new reagent for determination of the enantiomeric purity and absolute configuration of chiral alcohols and amines

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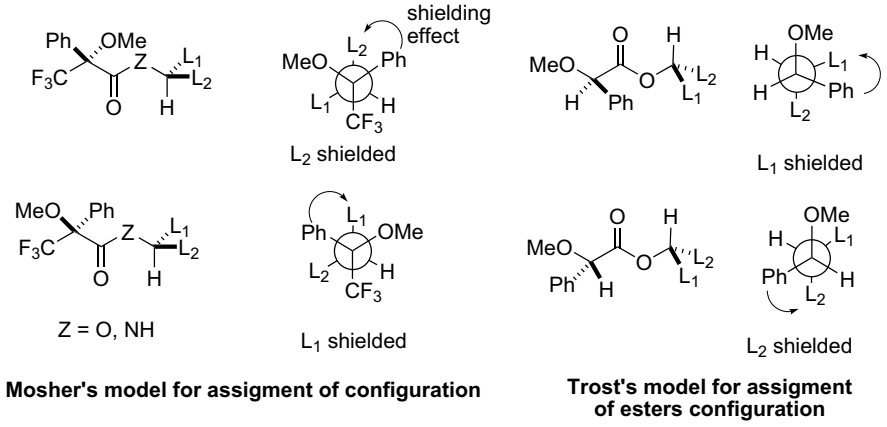
Abstract—Easily available in both enantiomeric forms, *O*-methylatrolactic acid (MAA) was successfully used as a new chiral derivatizing agent. Enantiomeric purities and the absolute configurations of chiral secondary alcohols and amines were determined using the observed differences in ^{1}H NMR chemical shifts. The Mosher's stereochemical model explains the conformational preferences of the respective diastereomeric MAA esters and amides. This was confirmed by the results of DFT calculations for the respective conformers.

1. Introduction

Chiral α-substituted-α-arylacetic acids are known as resolving agents that allow for the separation of racemic mixtures as well as chiral derivatizing agents (CDA), useful in the determination of enantiomeric composition of chiral alcohols and amines.[1] The pioneering works of Raban and Mislow dealt with the esters and amides of *O*-methylmandelic acid (MPA).[2] Subsequent developments have led to the application of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, Mosher's reagent)[3] designed to avoid epimerization at the hydrogen alpha to the carbonyl, that was problematic with the MPA derivatives.[4] In the NMR spectra of the thus obtained diastereomeric derivatives of CDA, the signals coming from the new diastereotopic centers (anisochronous) appear at the different fields (difference in chemical shift, $\Delta\delta$). In order to account for the observed sign of $\Delta\delta$ and its value, two simple stereochemical models were adopted by Mosher[4] and Trost[5] (Scheme 1). The models were based on the anisotropy effect imposed by



Scheme 1.

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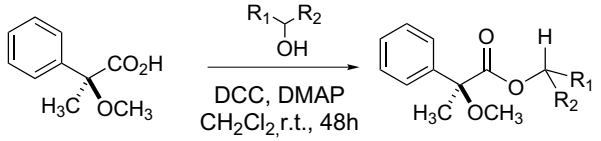
the aryl group. They were derived empirically analyzing a large set of data for the diastereomeric products of known configurations. Moreover, on this basis and with both enantiomers of the acid in hand, it was possible to determine the absolute configurations of chiral α-amines and alcohols.

Since then, many new CDAs have been reported, including some structural analogues of MPA.[6] This allowed for the identification of the key structural features essential for CDA effectiveness.[7] Consequently, the theoretical analysis of the population of the respective conformers for each diastereomer rationalized the essentially empirical, correlative method.[8] Despite some limited use of atrolactic acid as a CDA,[4] its *O*-methyl derivative, that is, *O*-methylatrolactic acid **1** (MAA) has never been applied in this role. This compound fulfills the CDA structural requirements and its fully substituted stereogenic α-carbon center is inert towards racemization. Recently, we have improved the synthesis and deracemization of **1**[9] and herein we report the results of its application as an enantiomeric resolution reagent and CDA.

2. Results and discussion

2.1. Derivatization

Firstly, in order to obtain the MAA amides from the hydrochlorides of methyl esters of α-amino acids we used the procedure advocated for the respective MPA amides by Trost (DCC, DMAP, Et_3N).[10] However, in our case the reaction was sluggish and the yield of the desired products was insufficient (ca. 20%), even after a long reaction time. The MAA amides were successfully prepared by activating MAA with oxalyl chloride and DMF and running the reaction in the presence of anhydrous K_2CO_3. (*S*)-MAA and the enantiomeric amino acid derivatives gave single diastereomeric amides (ca. 60% isolated yield). Moreover, the reaction of (*S*)-MAA with the racemic amino acid ester hydrochloride resulted in an exactly 1:1 diastereomeric mixture, as documented by GC and NMR (see, below). The same method of MAA activation and the reaction in the presence of pyridine was used for the derivatization of the free amine (73% yield) with no trace of epimerization nor kinetic resolution in the reaction of the racemate (Scheme 2). In the case of the aminoalcohol, this acylation method led to mixtures of the corresponding amide and ester, which were difficult to separate chromatographically. However, the aminoalcohols were selectively N-acylated with the acyl chloride prepared from MAA with DMF–oxalyl chloride and used under the modified Schotten–Baumann conditions. We obtained the corresponding amides in almost quantitative yield (98%) while the corresponding crude products were pure enough for spectral analysis.

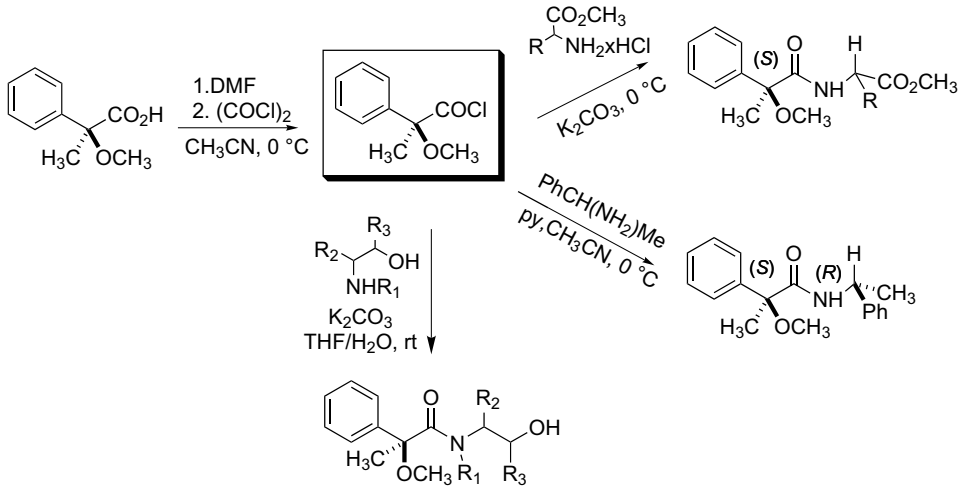


Scheme 3.

The same MAA activation method and the reaction in the presence of pyridine was applied for the preparation of the corresponding esters, but proved only successful for 2-butanol. More sterically hindered hydroxy groups were acylated (ca. 60% yield) using the DCC/DMAP method (Scheme 3).[5] As before, neither epimerization nor kinetic resolution were observed when the reactions were carried out with the enantiomeric or racemic substrates. Thus, the methods adopted for the preparation of MAA amides and esters seemed to be suitable for its use as CDA.

2.2. Chiral discrimination: separation of diastereomers (GC)

Gas chromatography offers a simple and fast method for the determination of enantiomeric composition.[1] If an



Scheme 2.

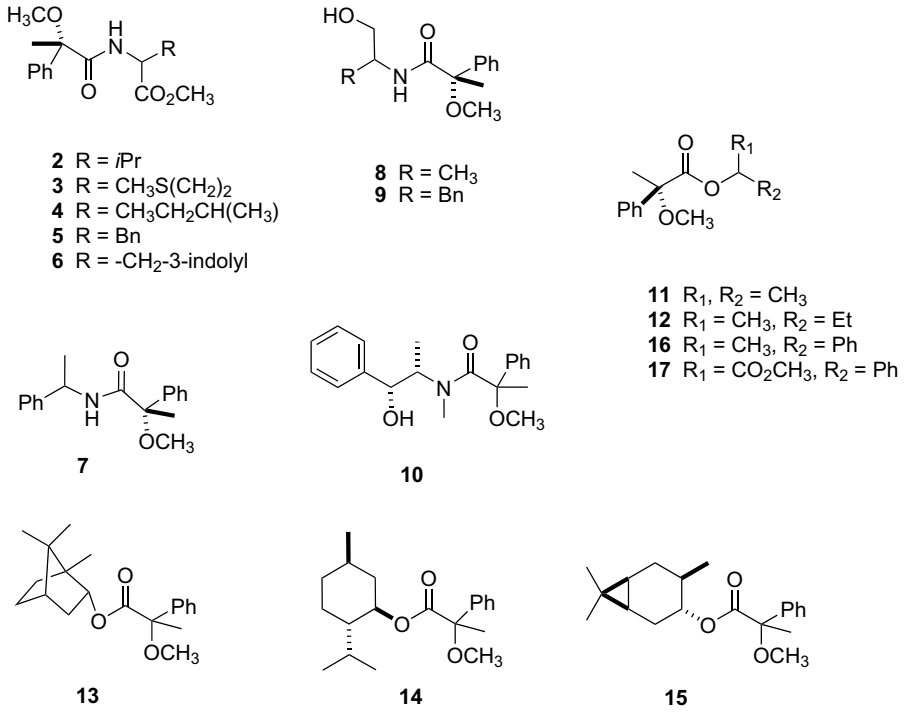


Figure 1.

achiral stationary phase is used, an enantiomeric mixture has to be derivatized with CDA into the corresponding diastereomers. Separation efficiency depends mainly on the CDA used while the influence of the stationary phase is rather limited.[12] Under these circumstances a new CDA with nonracemizing and sterically congested stereogenic centers are highly desirable.[13] In order to test MAA in this role we analyzed the equimolar mixtures of diastereomeric amides prepared from the esters of α-amino acids and α-methylbenzylamine (Fig. 1). The results are presented in Table 1. For all the compounds analyzed the (*S*,*S*)-isomers exhibited a weaker affinity toward the stationary phase (diphenyl-5%–dimethyl-95%–polysiloxane), thus a shorter retention time was observed for them than for the respective (*S*,*R*)-isomers. The resolution factor (R_s)[14] value differed in the examined cases. Thus, for amides **8**–**10**, the respective GC peaks were not separated completely which could be the result of their conformational flexibility. Furthermore, the diastereomeric MAA esters of chiral secondary alcohols differed poorly in GC while the peaks were insufficiently separated ($R_s < 1.15$ and $\Delta t_R < 0.50$ min), except for borneol, where $\Delta t_R = 0.99$ min, $R_s = 1.13$. Moreover, the application of the cyanopropylated (70%) polysiloxane capillary column did not improve the separation of diastereomers. Therefore, the use of MAA as CDA in GC is regarded as rather limited.

Table 1. Retention times in minutes and resolution factor R_s of (*S*)-MAA amides

Compound	t_{R1}	t_{R2}	R_s[a]
2	45.56 (*S*)	45.87 (*R*)	1.633
3	26.97 (*S*)	27.39 (*R*)	1.569
4	48.13 (*S*)	48.83 (*R*)	1.105
5	41.09 (*S*)	41.34 (*R*)	0.700
6	42.22 (*S*)	43.18 (*R*)	2.122

The absolute configuration of the amine was given in parentheses.

[a] Resolution, R_s, is defined as $(t_{R2} - t_{R1})/(w_{h1} + w_{h2})$, where w_{hi} is a width of a peak at a half of its height.[14]

2.3. Chiral discrimination: quantification of enantiomers by CDA-^{1}H NMR

Another technique commonly used for the determination of enantiomeric composition is CDA-NMR.[15] In the ^{1}H NMR spectra of the diastereomeric derivatives of CDA, the specific signals differ in chemical shift which, if not overlapped, can be integrated individually, thus providing information about the composition. For the MAA derivatives, as for those of MPA and MTPA this possibility is offered by the resonance of the corresponding methoxy groups. To learn the scope of application of this technique with MAA, we analyzed differences in chemical shifts $\Delta\delta^{OMe}$ for various diastereomeric amides and esters (Table 2). For all but **8**, **12**, and **13** compounds the observed differences were far beyond the NMR spectrum accuracy limit. Thus the method seemed to be suitable for the mentioned analytical purpose. Additionally, for the amides of methyl esters of amino acids **2**–**7** resonances of the ester methyl group also differed and their integration can serve the same aim (see below). Unfortunately, for the esters **12** and **13** the signal separation observed was insufficient and it did not improve with a solvent change or in the presence of achiral lanthanide shift reagent Eu(fod)$_3$. Likewise for MAA-**12**, the $\Delta\delta^{OMe}$ reported for MTPA-**12** did not allow for its practical analytical use ($\Delta\delta^{OMe} < 0.04$). Other examples (Table 2) showed that MAA, MTPA, and MPA performed quite similarly in this respect.

Table 2. $\Delta\delta^{OMe}$ values of corresponding amides and esters of MAA in $CDCl_3$

Compound	$\Delta\delta^{OMe}_{acid}$
2	0.074
3	0.072
4	0.030
5	0.110
6	0.136
7	0.071
	MTPA: 0.050[a]
	MPA: 0.038[c]
8	0.000
9	0.045
10	0.307
12	0.012 (0.008)
	MTPA: 0.033[a] (0.000)[b]
13	0.009 (0.014)
14	0.046 (0.041)
15	0.060 (0.011)
16	0.061 (0.100)
	MTPA: 0.083[a] (0.100)[b]
17	0.106 (0.147)
	MTPA: 0.150[a] (0.160)[b]

In parentheses values obtained in CCl_4 as a solvent.
[a] Data from Ref. 3.
[b] Data from Ref. 16.
[c] Data from Ref. 17.

2.4. MAA-derivatives applied for the determination of absolute configuration of α-chiral alcohols and primary amines. Stereochemical analysis

Thus, in the ^{1}H NMR spectra of the diastereomeric derivatives of enantiomeric CDA, the signals arising from the anisochronous protons, even far removed from the stereogenic centers, appear at different fields ($\Delta\delta$). Essentially, this effect comes from the diamagnetic influence of the aromatic moiety of the CDA. In order to evaluate this influence in both diastereomers of the MAA derivatives one should consider $\Delta\delta^{S,R}L_n = \delta^S L_n - \delta^R L_n$ defined as a difference between the chemical shifts for a given proton L_n for the (*S*)-MAA and (*R*)-MAA derivative of the same enantiomeric amine or alcohol. Moreover, $\Delta\delta^{S,R}L_n$ can be obtained as the difference between the chemical shift for the (*S*)-MAA derivative of the (*S*)-amine/alcohol and the shift for the (*S*)-MAA derivative of the (*R*)-amine/alcohol.

Thus, we calculated $\Delta\delta^{S,R}$ values from the spectra of pure (*S*,*S*)-amide or ester and the diastereomeric mixture of the (*S*,*S*) and (*S*,*R*) compounds of (*S*)-MAA, analogously to the Trost procedure[5] (for details see Section 4). The results obtained, together with the reference data[3,6,8c,18] for the MTPA compounds are depicted on Figure 2. As can be seen, for the amides, the observed $\Delta\delta$ values were large enough to distinguish both diastereomers. The signs of $\Delta\delta^{S,R}$ (negative or positive) were in agreement with those noted for the MTPA analogues of the same known configuration (Fig. 2, **2**–**6**). Namely, when the hydrogens on one side of the amide bond plane gave $\Delta\delta^{S,R} > 0$, the hydrogens on the opposite side of the plane gave $\Delta\delta^{S,R} < 0$. Therefore, we tentatively adopted the Mosher's stereochemical model (Scheme 1). A comparison of the MAA derivatives with the Mosher's model suggested that in our case the dominating conformation of the amide has the methyl group coplanar with the amide bond, as it was for CF_3– in the case of the MTPA compounds. On this basis we derived a similar model explaining the magnetic anisotropy imposed by the phenyl group of *O*-methylatrolactic acid (Scheme 4).

Additionally, the ^{1}H NMR NOESY spectra for both diastereomers of **3** corroborated this interpretation showing the respective correlations and the absence of the other ones (Scheme 4). If the Trost's model (Scheme 1) was applied to the MAA derivative of the amine of known configuration, the resulting absolute configuration of the amine was opposite to the real one.

In order to verify the qualitative stereochemical interpretation we performed semiempirical (PM3) calculations optimizing the structures of (*S*,*S*)-**3** and (*R*,*S*)-**3** and changing the value of torsion angle H_3CC_α–C=O every 10°. Additionally, the structures close to that of the energy minimum were further optimized. For (*S*,*S*)-**3**, three energy minima structures finally resulted (the angle: 15°, 101°, and 106°) and for (*R*,*S*)-**3** two minima were observed (−1.3° and 113°). Thus the conformers obtained were subjected to the more advanced DFT [B3LYP/6-31G (d) − DFT] calculations. For each diastereomer of **3**, only two conformations were obtained (Scheme 5). Their structures differed substantially, however only those of the lowest energy [7.0 kcal/mol for (*S*,*S*)-**3** and 5.8 kcal/mol for (*R*,*S*)-**3**] less than the next ones should be taken into account. In spite of the fact that these preferred conformations differed somewhat from that of the Mosher's model, in both cases the diamagnetic influence of the phenyl group was in full agreement with that expected within the simplified model.

The ^{1}H NMR spectrum of the isopropyl ester of MAA demonstrated the discrimination of diastereotopic methyl groups, $\Delta\delta = 0.005$ (0.082 in CCl_4). Therefore, we examined the signs and values of the anisochrony for the MAA esters of various α-chiral secondary alcohols. The respective $\Delta\delta^{S,R}$ values were obtained from the spectra of (*S*)-MAA esters of enantiomeric and racemic alcohols, analogously as it was done for the amides. For the enantiomeric terpenic alcohols obtained **13**–**15**, we analyzed the corresponding esters of (*R*)- and (*S*)-MAA. The results are presented in Figure 2. Unfortunately, the corresponding $\Delta\delta^{S,R}$ values ($CDCl_3$) were smaller than those for the MPA and MTPA derivatives.[6] Furthermore, for esters **12**–**14**, the sign of $\Delta\delta^{S,R}$ for the hydrogens on the one side of the ester bond plane did not differ from the sign for the hydrogens on the opposite side of the plane (Fig. 2, underlined values). However, the corresponding spectra in CCl_4 gave the expected distribution of the $\Delta\delta^{S,R}$ signs, along with an increase of their values (Fig. 2, bolded values), in effect allowing for the determination of absolute configuration of the analyzed alcohols. A solvent of decreased polarity seemed to favor a conformer with the lowest dipole moment. This conformer should give the largest contribution to the shielding/deshielding effects observed for the respective protons. At the same time, the influence of the other, more polar conformers should be diminished. This reasoning is in agreement with the results of the DFT calculations that we carried out for the MAA ester of

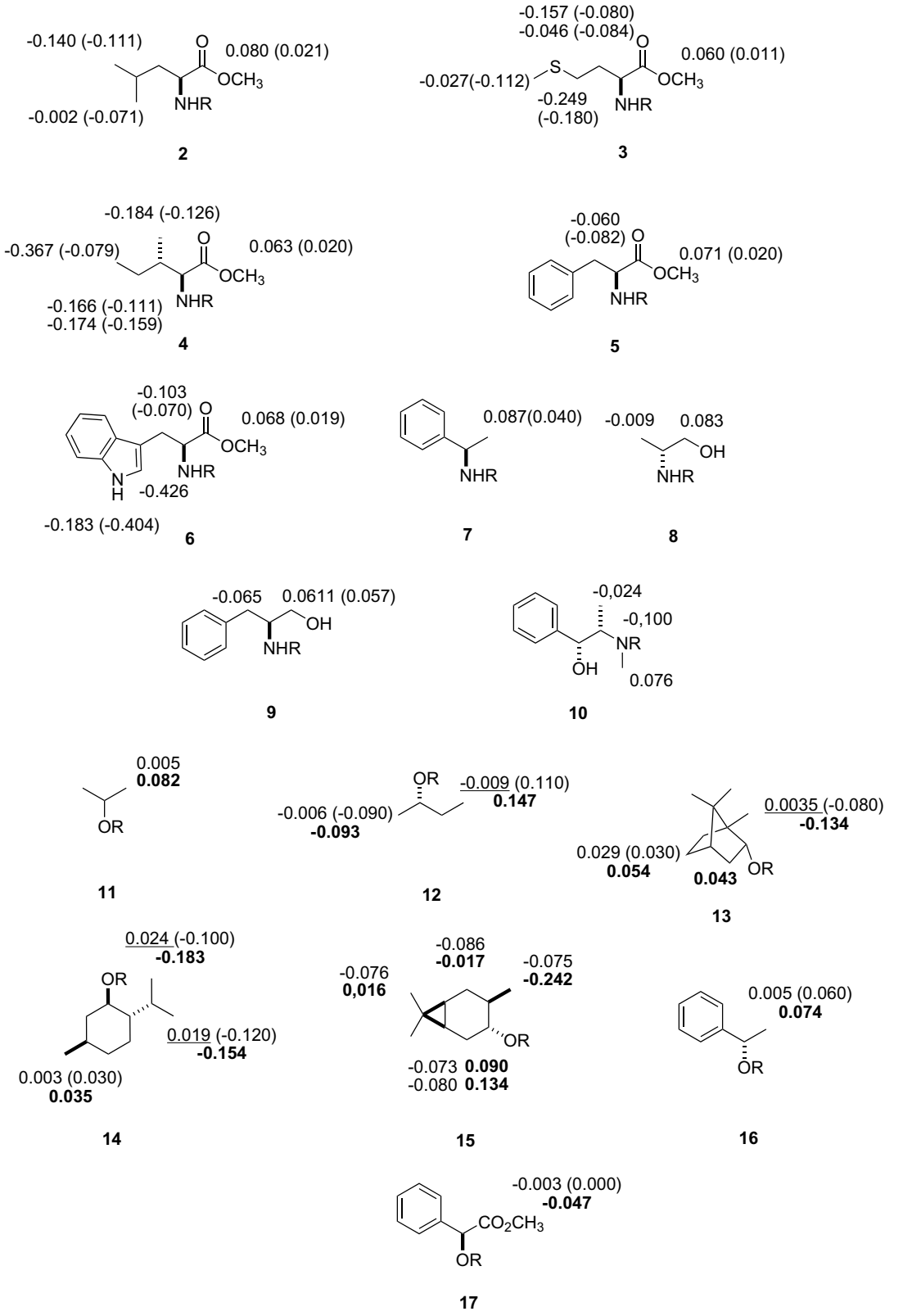
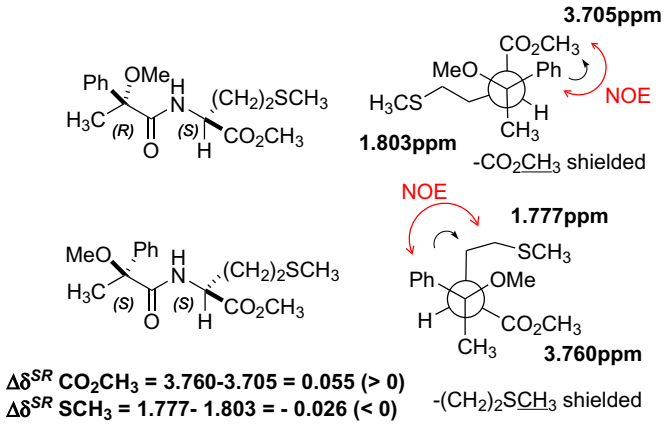
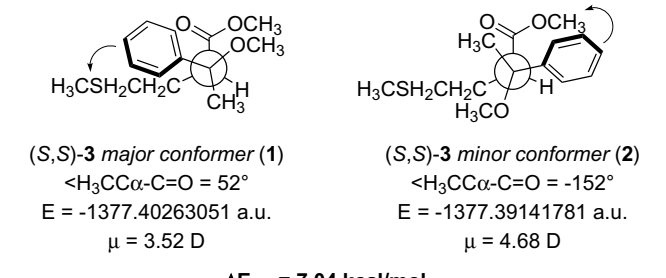


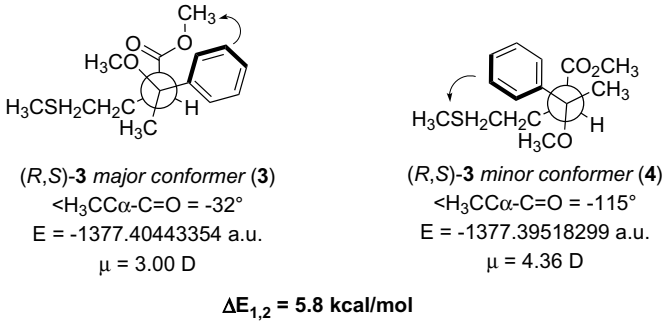
Figure 2. $\Delta\delta^{S,R}$ values ($CDCl_3$) for the tested MAA amides and esters. Underlined are values of unexpectedly opposite sign. Bold values are those recorded in CCl_4 solutions. In brackets, reference values ($CDCl_3$) for the corresponding MTPA derivatives: **2**–**6**, **9**;[8c] **7**;[3] **12**, **16**;[18] **13**, **14**;[6] **17**[3] are given.

(−)-menthol (Scheme 6). There, one of two low-energy conformers, the less polar one (calculated $\mu = 1.48$ D) demonstrated a large magnetic anisotropy, while the second one, that of higher energy (1.5 kcal/mol) and more polar

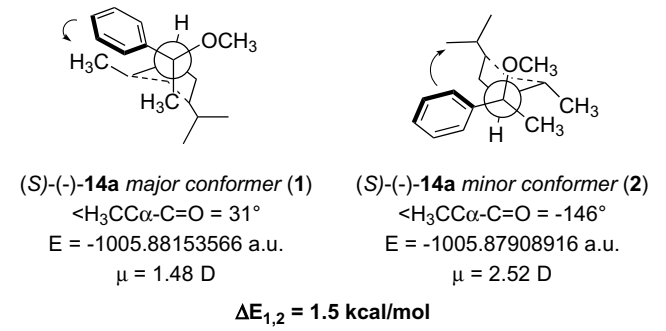


Scheme 4.





Scheme 5.



Scheme 6.

(calculated $\mu = 2.52$ D), was much less sensitive to the magnetic influence of the phenyl group. A quite similar interpretation was adopted to explain the rise of the $\Delta\delta$ values in the less polar solutions of the MPA derivatives.[8a]

Table 3. Solvent effect of observed $\Delta\delta$ values in representative amides and esters

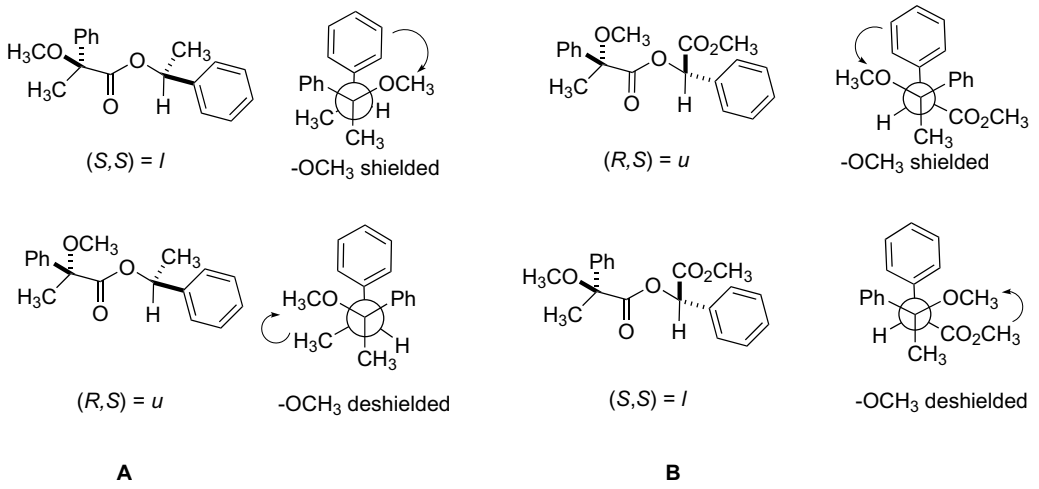
Compound	Group	$CDCl_3$	C_6D_6	CS_2	CCl_4
6	OMe	0.123	0.134	0.125	0.171
	CO_2CH_3	0.068	0.069	0.063	0.065
	C=CH	0.426	0.279	0.454	0.354
7	OMe	0.071	0.058	0.125	0.093
	CH_3	0.087	0.131	0.084	0.085
8	OMe	0.000	0.009	0.000	0.000
	CH_3	0.009	0.000	0.020	0.021
12	OMe	0.012	0.000	0.019	0.014
	CH_3	0.060	0.061	0.084	0.093
	CH_2CH_3	0.009	0.085	0.132	0.147
17	OMe	0.106	0.193	0.164	0.147
	CO_2CH_3	0.003	0.020	0.039	0.047

We next examined the spectra of amides **6**–**8** and esters **12** and **17** in solvents less polar than $CDCl_3$ (Table 3). For the esters we observed an increase of the $\Delta\delta$ values for the MAA methoxy group as well as for the other easily identifiable signals. For the amides however, the effect for $\Delta\delta^{OMe}$ holds on but for the other signals it was less pronounced or even reversed.

Thus, the small values and non-homogeneous distribution of the $\Delta\delta$ signs potentially leading to mistakes in ascribing absolute configuration can be overcome by the use of appropriate solvent. Another difficulty arises when the magnetic anisotropy effect of the CDA aromatic moiety is disturbed by the influence of the additional α or β-located polar or aryl group. In such a case the Mosher's model can lead to a wrong outcome.[8b] However, a simple stereochemical model of Kelly (Scheme 7) relays the sign of $\Delta\delta^{OMe}$ of CDA to the absolute configuration of the alcohol analyzed.[11] In this model the shielding of the CDA methoxy group results from the influence of the alcohols phenyl group for a *like* (*S*,*S* or *R*,*R*) diastereomer only, and the absence of this effect for an *unlike* (*S*,*R* or *R*,*S*) form. Thus, in our hands, a positive sign for $\Delta\delta^{OMe} = \delta_u^{OMe} - \delta_l^{OMe}$ confirmed the (*S*)-configuration for 2-phenylethanol (Scheme 7, A). On the other hand, in the presence of an α-polar group, an opposite trend was observed[11] while the respective negative sign of $\Delta\delta^{OMe}$ confirmed the (*S*)-configuration for the methyl ester of mandelic acid (Scheme 7, B). The corresponding $\Delta\delta$ values of –OMe signals of MAA are given in Table 4.

3. Conclusion

In conclusion we have developed an *O*-methylatrolactic acid as a new chiral derivatizing reagent (CDA) suitable for the determination of enantiomeric purity and absolute configuration of chiral secondary alcohols and amines. The Mosher's stereochemical model explains the conformational preferences of the respective diastereomeric MAA esters and amides. This is easily available in both enantiomeric forms, while the non-racemizing CDA supplements an existing kit of such compounds.



Scheme 7.

Table 4. $\Delta\delta$ values of –OMe signals in secondary alcohols with α aromatic moiety (see Scheme 7)

Compound	δ_u^{OMe}	δ_l^{OMe}	$\Delta\delta_{u-l}^{OMe}$	Configuration
16	3.315	3.254	0.061	*S*
	3.114	**3.015**	**0.099**	
17	3.318	3.424	−0.106	*S*
	3.108	**3.256**	**−0.147**	

Bolded values obtained from CCl_4 as a solvent.

4. Experimental

4.1. General methods

All commercially available materials were used without purification. The methyl ester of (*S*)-mandelic acid,[19] (−)-*cis*-caran-*trans*-4-ol[20] and the hydrochlorides of methyl ester of amino acids[21] were prepared according to the literature procedures. ^{1}H NMR spectra of the samples in $CDCl_3$ (ca. 5–8 mg in 0.5 ml) were recorded using a Bruker CPX (^{1}H, 300 MHz) and Bruker Avance II (600 MHz) spectrometer and the chemical shifts (ppm) were internally referenced to the TMS signal. GC analyses were carried out on a Hewlett–Packard 5890 II gas chromatograph (HP5MS 30m capillary column) or a Shimadzu GC-17A gas chromatograph (BPX 70 25 m capillary column). Melting points were measured using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer operating on the electron impact (EI, 70 eV) or chemical ionization (CI, isobutane) mode. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck).

The reproducibility of the chemical shift difference was verified for **6**. We measured six independent values of $\Delta\delta^{COOMe}$ (independent spectra). The mean value $\overline{\Delta\delta} = (0.0667883 \pm 0.0000010135)$ ppm.

Computational methods: The theoretical studies supporting the search for the low-energy conformers were performed applying semiempirical PM3 (GAUSSIAN-03) method. Thus the emerged structures were further optimized using the density functional theory (DFT) method. The DFT approach utilized Backe's three-parameter functional[22] with the local correlation part of Vosco et al.[23] and the non-local part of Lee et al.[24] (abbreviated as B3LYP). The calculation were performed in the standard 6-13G* atomic basis set.[25] The enthalpy differences were calculated for the theoretically optimized structures. The results reported here were obtained using the GAUSSIAN-03 package.[26] The calculations were performed at the Wroclaw Center for Networking and Supercomputing.

4.2. General method for the preparation of diastereomeric amides from (*S*)-*O*-methylatrolactic acid and corresponding amines

Method A. Oxalyl chloride (26 μl, 0.30 mmol, 1.1 equiv) was added slowly to a mixture of DMF (32 μl, 0.42 mmol, 1.5 equiv) in CH_3CN (0.5 ml) and stirred vigorously on an ice-water bath. Then, to the resulting suspension, a solution of MAA (50 mg, 0.28 mmol, 1 equiv) in CH_3CN (1.0 ml) was added dropwise via syringe. The mixture was stirred for 15 min at 0 °C, and then K_2CO_3 (116 mg, 0.83 mmol, 3 equiv) was added followed by the portionwise addition of the corresponding hydrochloric salt of amino acid methyl ester (0.30 mmol, 1.1 equiv) for 1 h. After 4 h at 0 °C the suspension was quenched with ether (20 ml), washed with water (10 ml), dried over Na_2CO_3, and evaporated. The products were purified by column chromatography on silica gel eluting with PET–AcOEt (4:1, v/v).

Method B. In this method, the active acylating agent was generated as mentioned above in method A. After the acid chloride preparation step, a solution of (*R*)-α-methylbenz-

ylamine (0.078 ml, 0.061 mmol, 1.1 equiv) in pyridine (2 equiv) was added in one portion via syringe and the resulting mixture stirred for 1 h, diluted with ether (25 ml), washed with aqueous $CuSO_4$ (satd, 2 × 8 ml), dried over $MgSO_4$, and evaporated. The crude product was purified as above.

Method C. The acid chloride generated as it was described in method A (0.41 mmol, 1.5 equiv) in anhydrous THF (2 ml) was added dropwise at room temperature to the vigorously stirred mixture of corresponding aminoalcohol (0.28 mmol, 1 equiv) and K_2CO_3 (172 mg, 1.2 mmol, 4.5 equiv) in water (3 ml). The resulted yellow solution was stirred for 48 h diluted with diethyl ether (10 ml), the phases were separated and the aqueous layer was washed with ether (10 ml). The combined organic layers were dried over Na_2CO_3 and the solvent evaporated to give the pure product (>98%, GC).

4.2.1. (*S*)-2-((*S*)-2-Methoxy-2-phenyl-propionylamino)-4-methyl-pentanoic acid methyl ester 2. Colorless oil; $R_f = 0.38$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = +12.7$ (*c* 0.88, CH_2Cl_2); IR (film): *v* 3357, 3061, 2957, 2872, 2835, 1745, 1683, 1510, 1446, 1368, 1273, 1205, 1159, 1072, 1047, 732, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45 (2H, d, $J = 7.2$ Hz, *o*-ArH), 7.30–7.36 (3H, m, ArH), 7.18 (1H, br d, $J = 7.4$ Hz, N*H*), 4.57 (1H, m, C*H*), 3.74 (3H, s, CO_2CH_3), 3.27 (3H, s, OMe), 1.78 (3H, s, Me), 1.41–1.67 (3H, m, CH_2 and $CH(CH_3)_2$), 0.79–0.86 (6H, m, 2 × Me); ^{13}C NMR ($CDCl_3$): δ 173.5, 173.4, 141.0, 128.3, 127.8, 125.9, 81.9, 52.2, 51.3, 50.4, 41.5, 24.8, 22.8, 21.7, 20.3; HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{25}NO_4$: 307.1784. Found: 307.1794.

4.2.2. (*S*)-2-((*S*)-2-Methoxy-2-phenyl-propionylamino)-4-methylsulfanyl-butyric acid methyl ester 3a. Colorless oil; $R_f = 0.26$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = +36.4$ (*c* 0.84, CH_2Cl_2); IR (film): *v* 2982, 2952, 2916, 2834, 1744, 1681, 1510, 1444, 1366, 1222, 1173, 1072, 1047, 732, 700, 670 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38–7.47 (3H, m, ArH and N*H*), 7.24–7.37 (3H, m, ArH), 4.62–4.69 (1H, m, C*H*), 3.76 (3H, s, CO_2CH_3), 3.27 (3H, s, OMe), 2.26–2.32 (2H, m, SCH_2), 2.07–2.17 (1H, m, $SCH_2CH_AH_B$), 1.95 (3H, s, Me), 1.85–1.94 (1H, m, $SCH_2CH_AH_B$), 1.78 (3H, s, SCH_3); ^{13}C NMR ($CDCl_3$): δ 173.5, 172.3, 141.2, 128.4, 127.8, 125.8, 82.0, 52.5, 51.4, 51.1, 31.9, 29.8, 20.2, 15.4; HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{23}NSO_4$: 325.1348. Found: 325.1354.

4.2.3. (*S*)-2-((*R*)-2-Methoxy-2-phenyl-propionylamino)-4-methylsulfanyl-butyric acid methyl ester 3b. Colorless oil; $R_f = 0.26$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = -28.6$ (*c* 0.86, CH_2Cl_2); IR (film): *v* 3406, 3052, 2977, 2951, 2833, 1743, 1680, 1511, 1444, 1367, 1225, 1196, 1148, 1071, 733, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51 (1H, br s, N*H*), 7.46 (2H, d, $J = 7.2$ Hz, *o*-ArH), 7.27–7.37 (3H, m, ArH), 4.60–4.67 (1H, m, C*H*), 3.70 (3H, s, CO_2CH_3), 3.20 (3H, s, OMe), 2.53 (2H, t, $J = 7.5$ Hz, SCH_2), 1.99–2.33 (2H, m, SCH_2CH_2), 2.11 (3H, s, SCH_3), 1.80 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 173.5, 172.1, 140.1, 128.3, 127.9, 126.5, 81.8, 52.4, 51.3, 51.1, 31.9, 30.1, 20.3, 15.5.

4.2.4. (2*S*,3*S*)-2-((*S*)-2-Methoxy-2-phenyl-propionylamino)-3-methyl-pentanoic acid methyl ester 4. Colorless oil; $R_f = 0.39$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = +35.8$ (*c* 0.30, CH_2Cl_2); IR (film): *v* 3424, 2964, 2879, 1742, 1685, 1507, 1449, 1245, 1210, 1152, 1072, 730, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (2H, dd, $J = 7.0$, 1.8 Hz, *o*-ArH), 7.24–7.37 (4H, m, ArH and N*H*), 4.52 (1H, dd, $J = 9.0$, 5.0 Hz, C*H*), 3.77 (3H, s, CO_2CH_3), 3.27 (3H, s, OMe), 1.79–1.89 (1H, m, C*H*), 1.78 (3H, s, Me), 1.34 (1H, m, CH_AH_B), 1.08 (1H, m, CH_AH_B), 0.84 (3H, t, $J = 7.4$ Hz, Me), 0.78 (3H, d, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 173.3, 172.4, 141.1, 128.3, 127.7, 125.9, 82.0, 56.0, 51.9, 51.3, 37.9, 25.0, 20.2, 15.4, 11.4; HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{25}NO_4$: 307.1784. Found: 307.1781.

4.2.5. (*S*)-2-((*S*)-2-Methoxy-2-phenyl-propionylamino)-3-phenyl-propionic acid methyl ester 5. Colorless oil; $R_f = 0.29$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = +98.7$ (*c* 1.14, CH_2Cl_2); IR (film): *v* 3029, 2950, 2834, 1744, 1682, 1507, 1444, 1217, 1199, 1143, 1073, 733, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.14–7.37 (10H, m, ArH), 6.87 (1H, br s, N*H*), 4.84 (1H, m, C*H*), 3.74 (3H, s, CO_2CH_3), 3.21 (3H, s, OMe), 2.97–3.10 (2H, m, CH_2), 1.76 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 173.1, 172.0, 141.0, 135.8, 129.3, 128.4, 128.3, 127.7, 126.9, 126.0, 81.9, 52.8, 55.3, 51.3, 37.8, 20.4; HRMS (EI): *m*/*z* [M^+] calcd for $C_{20}H_{23}NO_4$: 341.1627. Found: 341.1621.

4.2.6. (*S*)-3-(1*H*-Indol-3-yl)-2-((*S*)-2-methoxy-2-phenyl-propionylamino)-propionic acid methyl ester 6. Colorless solid; $R_f = 0.17$ ($CHCl_3$); $[\alpha]_D = +75.6$ (*c* 0.24, CH_2Cl_2); IR (CCl_4): *v* 3490, 3423, 1748, 1686, 1512, 1215 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92 (1H, br s, indole-N*H*), 7.46 (1H, d, $J = 7.8$ Hz, ArH), 7.28–7.38 (7H, m, ArH and N*H*), 7.18 (1H, dt, $J = 7.4$, 0.9 Hz, ArH), 7.11 (1H, dt, $J = 7.4$, 0.9 Hz, ArH), 6.57 (1H, d, $J = 2.2$ Hz, C=C*H*), 4.89 (1H, m, C*H*), 3.69 (3H, s, CO_2CH_3), 3.23 (2H, m, CH_2), 3.17 (3H, s, OMe), 1.75 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 173.2, 172.4, 141.3, 130.0, 128.3, 127.6, 127.5, 126.0, 122.9, 122.1, 119.6, 118.6, 111.1, 109.9, 81.9, 52.4, 52.3, 51.3, 27.6, 20.5; HRMS (EI): *m*/*z* [M^+] calcd for $C_{22}H_{24}N_2O_4$: 380.1736. Found: 380.1738.

4.2.7. (*S*)-2-Methoxy-2-phenyl-*N*-((*R*)-1-phenyl-ethyl)-propionamide 7. Colorless oil; $R_f = 0.32$ (PET–AcOEt, 4:1, v/v); $[\alpha]_D = +130.3$ (*c* 0.26, CH_2Cl_2); IR (film): *v* 3332, 3069, 2981, 1936, 1677, 1507, 1149, 1072, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39 (2H, d, $J = 6.9$ Hz, *o*-ArH), 7.24–7.34 (7H, m, ArH), 7.19 (1H, t, $J = 7.6$ Hz, ArH), 7.13 (1H, br d, $J = 7.5$ Hz, N*H*), 5.07 (1H, m, C*H*), 3.22 (3H, s, OMe), 1.81 (3H, s, Me), 1.53 (3H, d, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.5, 142.2, 140.2, 128.5, 128.3, 127.7, 127.1, 126.2, 126.0, 82.0, 51.2, 48.2, 21.8, 20.3; HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1579.

4.2.8. (*R*)-2-Aminopropanol-(*R*)-*O*-methylatrolactic acid amide 8. Colorless oil; $R_f = 0.13$ ($CHCl_3$); $[\alpha]_D = -39.7$ (*c* 1.36, CH_2Cl_2); IR (film): *v* 3417, 2974, 2933, 2832, 1665, 1526, 1448, 1369, 1229, 1135, 733, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37 (2H, dd, $J = 6.9$, 1.6 Hz, *o*-ArH),

7.17–7.29 (4H, m, ArH and N*H*), 3.79 (1H, m, C*H*), 3.30 (1H, m, CH_AH_B), 3.13 (3H, s, OMe), 3.06 (1H, m, CH$_A$$H_B$), 2.60 (1H, br s, O*H*), 1.72 (3H, s, Me), 1.06 (3H, d, $J = 6.3$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 174.7, 140.7, 128.4, 127.8, 126.2, 81.9, 67.3, 51.1, 46.8, 20.8, 20.4; HRMS (EI): m/z [M^+] calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1372.

4.2.9. (*S*)-Phenylalanin-2-ol-(*R*)-*O*-methylatrolactic acid amide 9. Colorless crystals; mp 132–133 °C; $[\alpha]_D = -43.0$ (c 0.64, CH_2Cl_2); IR (KBr): ν 3398, 3368, 2930, 1649, 1522, 1458, 1151, 1097, 1046, 955, 731, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34 (2H, dd, $J = 8.3$, 1.9 Hz, ArH), 7.11–7.29 (8H, m, ArH), 7.04 (1H, br d, $J = 7.4$ Hz, N*H*), 3.98–4.01 (1H, m, C*H*), 3.56 (1H, m, AB-system, $J = 11.1$, 3.5 Hz, CH_AH_B), 3.47 (1H, m, AB-system, $J = 11.1$, 5.5 Hz, CH$_A$$H_B$), 2.99 (3H, s, OMe), 2.86 (1H, m, AB-system $J = 13.9$, 7.0 Hz, CH_AH_B), 2.75 (1H, m, AB-system $J = 13.9$, 8.0 Hz, CH$_A$$H_B$), 2.69 (1H, br s, O*H*), 1.61 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 174.2, 140.9, 137.9, 127.3, 128.5, 128.4, 127.8, 126.6, 125.7, 81.9, 64.1, 52.9, 51.7, 41.4, 19.5; HRMS (EI): m/z [M^+] calcd for $C_{19}H_{23}NO_3$: 313.1678. Found: 313.1674.

4.2.10. (−)-Ephedrine-(*R*)-*O*-methylatrolactic acid amide 10. Sticky colorless oil; $R_f = 0.25$ ($CHCl_3$); $[\alpha]_D = +3.4$ (c 0.76, CH_2Cl_2); IR (film): ν 3417, 3061, 3029, 2990, 2935, 1620, 1490, 1450, 1401, 1369, 1257, 1193, 1125, 1075, 1046, 765, 736, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.07–7.34 (10H, m, ArH), 4.74 (1H, m, C*H*OH), 4.49 (1H, m, NC*H*), 3.59 (1H, br s, O*H*), 3.23 (3H, s, OMe), 2.39 (3H, s, NMe), 1.50 (3H, s, Me), 1.18 (3H, d, $J = 7.0$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.9, 143.8, 141.6, 128.35, 128.29, 127.7, 126.9, 126.8, 123.8, 83.8, 77.1, 57.3, 51.5, 32.5, 26.2, 12.6; HRMS (CI): m/z [M+H$^+$] calcd for $C_{20}H_{26}NO_3$: 328.1913. Found: 328.1916.

4.3. Preparations of the diastereomeric esters from the corresponding alcohols and *O*-methylatrolactic acid

Preparations of the diastereomeric esters from the corresponding alcohols and *O*-methylatrolactic acid were carried out with DCC–DMAP according to the procedure described by Trost[5] and the products were purified by column chromatography on silica gel eluting with PET–AcOEt (20:1.5, v/v).

4.3.1. (*R*)-Propan-2-ol-*O*-methylatrolactate 11. Colorless oil; $R_f = 0.34$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = +24.4$ (c 0.31, CH_2Cl_2); IR (film): ν 2984, 2937, 1729, 1451, 1374, 1260, 1140, 1103, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, dd, $J = 7.2$, 1.5 Hz, o-ArH), 7.28–7.38 (3H, m, ArH), 5.07 (1H, h, $J = 6.2$ Hz, –C*H*(CH$_3$)$_2$), 3.30 (3H, s, OMe), 1.77 (3H, s, Me), 1.20 (6H, two d, $J = 6.2$ Hz, 2 × Me); ^{13}C NMR ($CDCl_3$): δ 172.5, 141.1, 128.2, 127.8, 125.9, 81.7, 68.2, 52.0, 22.2, 21.6; HRMS (CI): m/z [M+H$^+$] calcd for $C_{13}H_{19}O_3$: 223.1330. Found: 223.1334.

4.3.2. (*R*)-*sec*-Butyl-(*S*)-*O*-methylatrolactate 12. Colorless oil; $R_f = 0.52$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = +40.4$ (c 0.76, CH_2Cl_2); IR (film): ν 2938, 2975, 1728, 1450, 1257, 1109, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, m, o-ArH), 7.25–7.37 (3H, m, ArH), 4.85–4.95 (1H, m, C*H*), 3.31 (3H, s, OMe), 1.78 (3H, s, Me), 1.54 (2H, m, CH_2), 1.17 (3H, d, $J = 6.3$ Hz, Me), 0.78 (3H, t, $J = 7.3$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.1, 141.2, 128.2, 127.7, 125.8, 81.8, 73.4, 52.0, 28.7, 22.1, 22.0, 19.3; HRMS (CI): m/z [M+H$^+$] calcd for $C_{14}H_{21}O_3$: 237.1491. Found: 237.1488.

4.3.3. (−)-Bornyl-(*S*)-*O*-methylatrolactate 13a. Colorless oil; $R_f = 0.52$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -37.9$ (c 0.83, CH_2Cl_2); IR (film): ν 2954, 2831, 1733, 1453, 1256, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, d, $J = 7.7$ Hz, o-ArH), 7.36 (2H, t, $J = 7.7$ Hz, m-ArH), 7.27–7.33 (1H, m, p-ArH), 4.90 (1H, m, C*H*), 3.32 (3H, s, OMe), 2.24–2.35 (1H, m, C*H*), 1.81 (3H, s, Me), 1.61–1.81 (3H, m, C*H* and CH_2), 1.18–1.27 (1H, m, C*H*), 1.00–1.10 (1H, m, C*H*), 0.88 (3H, s, Me), 0.84 (3H, s, Me), 0.78–0.84 (1H, m, C*H*), 0.75 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 173.0, 141.1, 128.2, 127.8, 126.0, 81.7, 80.8, 52.1, 48.9, 47.8, 44.9, 36.4, 27.9, 27.1, 21.8, 19.6, 18.9, 13.4; HRMS (EI): m/z [M^+] calcd for $C_{20}H_{28}O_3$: 316.2038, Found: 316.2034.

4.3.4. (−)-Bornyl-(*R*)-*O*-methylatrolactate 13b. Colorless oil; $R_f = 0.48$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -11.1$ (c 0.92, CH_2Cl_2); IR (film): ν 2593, 2828, 1730, 1452, 1372, 1256, 1120, 763, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.80 (2H, dd, $J = 8.3$, 1.4 Hz, o-ArH); 7.35 (2H, m, m-ArH), 7.29 (1H, m, p-ArH), 4.86–4.91 (1H, m, C*H*), 3.31 (3H, s, OMe), 2.26–2.38 (1H, m, C*H*), 1.81 (3H, s, Me), 1.67–1.79 (2H, m, 2 × C*H*), 1.64 (1H, d, $J = 4.1$ Hz, C*H*), 1.15–1.27 (1H, m, C*H*), 1.04–1.11 (1H, m, C*H*), 0.88 (3H, s, Me), 0.84 (3H, s, Me), 0.78–0.81 (1H, m, C*H*), 0.71 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 173.1, 141.1, 128.2, 127.8, 126.0, 81.7, 80.9, 52.1, 48.8, 47.8, 44.8. 36.7, 27.9, 27.0, 21.7, 19.6, 18.9, 13.4.

4.3.5. (−)-Menthyl-(*S*)-*O*-methylatrolactate 14a. Colorless oil; $R_f = 0.47$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -73.3$ (c 0.63, CH_2Cl_2); IR (film): ν 2953, 2869, 1728, 1454, 1254, 1120, 769, 726, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, d, $J = 7.0$ Hz, o-ArH), 7.27–7.36 (3H, m, ArH), 4.71 (1H, dt, $J = 10.9$, 4.3 Hz, C*H*), 3.32 (3H, s, OMe), 1.94 (1H, m, C*H*), 1.77 (3H, s, Me), 1.64 (2H, m, CH_2); 1.47–1.57 (2H, m, CH_2), 1.27–1.40 (1H, m, C*H*); 0.84–1.07 (3H, m, CH_2 and C*H*), 0.88 (3H, d, $J = 6.5$ Hz, Me), 0.74 (3H, d, $J = 6.9$ Hz, Me), 0.59 (3H, d, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.5, 141.4, 128.1, 127.7, 125.6, 81.9, 75.4, 52.1, 46.9, 40.5, 34.2, 31.4, 25.7, 23.0, 22.2, 22.0, 20.7, 15.8; HRMS (EI): m/z [M^+] calcd for $C_{20}H_{30}O_3$: 318.2195. Found 318.2194.

4.3.6. (−)-Menthyl-(*R*)-*O*-methylatrolactate 14b. Colorless oil; $R_f = 0.42$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -49.5$ (c 1.10, CH_2Cl_2); IR (film): ν 3061, 2955, 2870, 1727, 1452, 1252, 1136, 1117, 776, 729, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.47 (2H, d, $J = 6.9$ Hz, o-ArH), 7.28–7.40 (3H, m, ArH), 4.36 (1H, dt, $J = 10.8$, 4.3 Hz, C*H*), 3.28 (3H, s, OMe), 1.95 (1H, m, C*H*), 1.79 (3H, s, Me), 1.57–1.67 (2H,

m, CH_2), 1.39–1.47 (2H, m, CH_2), 1.30 (1H, m, CH), 0.79–1.01 (3H, m, CH_2 and CH), 0.88 (3H, d, $J = 6.4$ Hz, Me), 0.72 (3H, d, $J = 6.9$ Hz, Me), 0.57 (3H, d, $J = 6.9$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.5, 140.8, 128.2, 127.8, 126.1, 81.5, 75.3, 51.9, 46.9, 40.5, 34.2, 31.4, 26.6, 23.0, 22.0, 21.4, 20.7, 15.7.

4.3.7. (−)-*cis*-Caran-*trans*-4-yl-(*S*)–*O*-methylatrolactate 15a. Colorless oil; $R_f = 0.55$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -74.2$ (*c* 0.90, CH_2Cl_2); IR (film): *v* 3062, 2988, 2936, 1728, 1451, 1256, 1122, 771, 727, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.40 (2H, dd, $J = 7.7$, 1.2 Hz, *o*-ArH), 7.17–7.29 (3H, m, ArH), 4.32 (1H, m, CH), 3.24 (3H, s, OMe), 1.83–2.01 (2H, m, CH_2), 1.69 (3H, s, Me), 1.43–1.54 (1H, m, CH), 1.30–1.42 (1H, m, CH), 0.87 (6H, s, 2 × Me), 0.73–0.84 (1H, m, CH), 0.54–0.66 (2H, m, 2 × CH), 0.55 (3H, d, $J = 6.4$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.7, 141.3, 128.2, 127.7, 125.8, 81.8, 78.7, 52.0, 33.6, 28.7, 28.3, 26.4, 22.1, 21.3, 20.0, 17.7, 17.5, 15.9; HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{20}H_{28}O_3$: 316.2038. Found: 316.2036.

4.3.8. (−)-*cis*-Caran-*trans*-4-yl-(*R*)-*O*-methylatrolactate 15b. Colorless oil; $R_f = 0.55$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -42.3$ (*c* 1.03, CH_2Cl_2); IR (film): *v* 3062, 2988, 2938, 2867, 1728, 1450, 1254, 1135, 11217, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45–7.49 (2H, m, *o*-ArH), 7.25–7.37 (3H, m, ArH), 4.36 (1H, m, CH), 3.30 (3H, s, OMe), 2.06 (1H, m, CH), 1.91–1.99 (1H, m, CH), 1.77 (3H, s, Me), 1.48–1.53 (1H, m, CH), 1.41–1.47 (1H, m, CH), 0.955 and 0.948 (6H, two s, 2 × Me), 0.80–0.91 (1H, m, CH), 0.62–0.73 (2H, m, 2 × CH), 0.54 (3H, d, $J = 6.5$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.9, 141.0, 128.2, 127.8, 126.0, 81.7, 78.8, 52.1, 33.5, 28.7, 28.3, 26.4, 21.9, 21.2, 20.0, 17.72. 17.66, 16.0.

4.3.9. (*S*)-1-Phenylethyl-(*S*)-*O*-methylatrolactate 16. Colorless oil; $R_f = 0.36$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = -44.2$ (*c* 0.75, CH_2Cl_2); IR (film): *v* 3062, 2984, 1732, 1494, 1451, 1249, 1127, 1055, 763, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.44 (2H, dd, $J = 8.0$, 1.7 Hz, *o*-ArH), 7.25–7.33 (6H, m, ArH), 7.17–7.19 (2H, m, ArH), 5.92 (1H, q, $J = 6.6$ Hz, CH(CH$_3$)Ph), 3.25 (3H, s, OMe), 1.80 (3H, s, Me), 1.48 (3H, d, $J = 6.6$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 172.2, 141.2, 140.8, 128.4, 128.3, 127.9, 127.8, 126.1, 126.0, 81.7, 73.2, 52.1, 22.0, 21.98; HRMS (CI): *m*/*z* [M+H$^+$] calcd for $C_{18}H_{21}O_3$: 285.1491. Found: 285.1488.

4.3.10. (*S*)-Methylmandelate-(*S*)-*O*-methylatrolactate 17. Colorless oil; $R_f = 0.24$ (hexane–AcOEt, 10:1, v/v); $[\alpha]_D = +61.3$ (*c* 1.05, CH_2Cl_2); IR (film): *v* 3063, 2992, 2951, 2837, 1749, 1495, 1450, 1222, 1113, 1033, 768, 734, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.57 (2H, d, $J = 7.0$ Hz, *o*-ArH), 7.30–7.38 (8H, m, ArH), 5.94 (1H, s, CH), 3.68 (3H, s, CO_2CH_3), 3.42 (3H, s, OMe), 1.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 172.6, 169.0, 140.5, 133.5, 129.2, 128.7, 128.3, 128.0, 127.4, 126.1, 81.8, 75.1, 52.6, 52.5, 22.7; HRMS (CI): *m*/*z* [M+H$^+$] calcd for $C_{19}H_{21}O_5$: 329.1389. Found: 329.1397.

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References

1. Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley-Interscience: New York, 2001; pp 143–196.
2. Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, 4249–4253.
3. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
4. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
5. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
6. Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
7. Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541–8564.
8. (a) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538–1545; (b) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577; (c) Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569–7574.
9. Kowalczyk, R.; Skarżewski, J. *Tetrahedron* **2005**, *61*, 623–628.
10. Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202–4205.
11. Kelly, D. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2927–2934.
12. Karger, B. L.; Stern, R. L.; Keane, W. *Anal. Chem.* **1967**, *39*, 228–230.
13. Lindner, W. In *Houben-Weyl Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. 1, pp 225–252.
14. Walter, J. *Analytical Gas Chromatography*; Academic Press: Orlando, 1987; pp 1–24.
15. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
16. Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2827–2830.
17. Jacobus, J.; Raban, M.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 1142–1145.
18. Omata, K.; Fujiwara, T.; Kabuto, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1655–1662.
19. Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397–406.
20. Uzarewicz, I.; Uzarewicz, A. *Rocz. Chem.* **1975**, *49*, 1113–1118.
21. (a) Zielinski, T.; Achmatowicz, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2053–2059; (b) Cambie, M.; D'Arrigo, P.; Fasoli, E.; Servi, S.; Tessaro, D.; Canevotti, F.; Del Corona, L. *Tetrahedron: Asymmetry* **2003**, *14*, 3189–3196.
22. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
23. Vosco, S. H.; Wilk, L.; Nusiar, M. *Can. J. Phys.* **1980**, *58*, 1200–1211.
24. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
25. Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
26. Frisch, M. J. et al. *Gaussian-03*; Gaussian: Wallingford CT, 2004.