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Derivatives of (*R*)-Lactic Acid for the Analysis of Chiral Alcohols by ^{1}H NMR Spectroscopy

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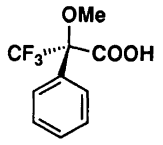
Diastereometric esters of *O*-arylated (*R*)-lactic acids have been studied by ^{1}H NMR spectroscopy with respect to their potential application as reagents for chiral analysis. The substitution pattern of the acid moiety of the ester was found to have a decisive influence on the magnitude of the resolution of the signals from the diastereomers. The best results were observed for derivatives of (*R*)-2-(β-naphthyloxy)propionic acid.

The great interest in asymmetric synthesis has created a demand for reagents aimed at determining the enantiomeric purity of the products.[1] A common way of making the measurement is to react the chiral compound with an enantiomerically pure reagent (chiral derivatizing reagent) in order to form diastereomers, which can subsequently be analyzed by a variety of methods, e.g., GLC, HPLC and NMR spectroscopy.[1,2]

The most well-known reagent for the determination of chiral alcohols and amines is α-methoxy-α-(trifluoromethyl)phenylacetic acid **1** (MPTA, Mosher's acid), where one takes advantage of the simplicity and usually good resolution of the ^{19}F NMR signals from the diastereomers.[3] An empirical model for the determination of the absolute configuration of the diastereomers by ^{1}H NMR spectroscopy has also been proposed.[3c] Recently, other reagents have been synthesized and successfully used. For example, the fluorinated acid **2** gives larger ^{19}F NMR Δδ values and is more reactive than Mosher's acid **1**, the phosphorus reagent **3** gives excellent separation on ^{31}P NMR spectroscopy and reacts even with tertiary alcohols, and the selenium reagent **4** makes possible the detection of very remote chiral centers by ^{77}Se NMR spectroscopy.[4–6]

However, the above-mentioned reagents present the disadvantage of not being easily synthesized from cheap and readily available starting materials. During our studies of the cyclization of *cis*-1,2-divinylcyclohexane with derivatives of (*R*)-lactic acid (e.g. **5**–**14**) as nucleophiles,[7] it occurred to us that it should also be possible to use these acids as chiral derivatizing agents. This



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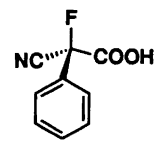

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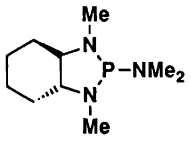

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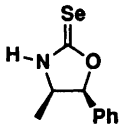

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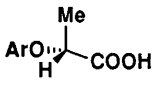
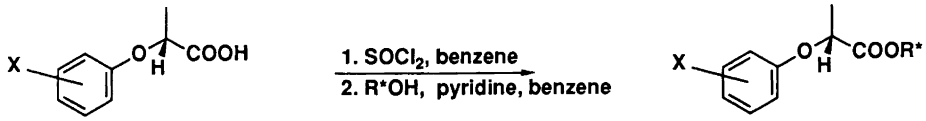


5-15

was recently investigated, and it was found that the fluorinated acids **5**–**7** give large Δδ values on ^{19}F NMR spectroscopy [eqn. (1)].[8] However, in order to obtain singlet peaks for the diastereomeric esters **16a/b**–**18a/b** the recording of ^{19}F NMR spectra requires access to spectrometers allowing proton decoupling. To avoid this disadvantage, we examined the ^{19}F NMR spectra for some alcohols derivatized with the acid **8**, which contains



(1)

5 X=*o*-F
6 X=*m*-F
7 X=*p*-F
8 X=*m*-CF_3

16 a/b X=*o*-F
17 a/b X=*m*-F
18 a/b X=*p*-F
19 a/b X=*m*-CF_3

a trifluoromethyl group [eqn. (1)].[9] The CF_3 group should then give singlets for the diastereomers **19a/b** without necessitating irradiation of the protons during the acquisition. Unfortunately, very poor resolution was observed.[10]

Recently, it has been pointed out that the frequent use of ^{19}F NMR spectroscopy in this field was originally due to the poor resolution by ^{1}H NMR spectroscopy obtained with the early low-field instruments (60–100 MHz), and to the fact that the fluorine nucleus is more sensitive to structural variations.[11] It was also suggested that the absolute configuration of natural products determined by ^{19}F NMR spectroscopy of their esters with Mosher's acid (MTPA esters) should be reexamined.[11a] This, together with the fact that our derivatives of (*R*)-lactic acid are easily synthesized in only two steps from cheap and readily available starting materials, prompted us to examine a few more acids in addition to the above-mentioned fluorinated acids in order to study the resolution by ^{1}H NMR spectroscopy.

Results and discussion

An initial comparison was made between esters differing only in the substitution pattern of the acid moiety (Table 1).[7c] The ^{1}H NMR signals from the diastereomers of the different esters **20–28** could be clearly distinguished since the bridgehead protons of the 7*R* diastereomer always resonated upfield relative to those of the 7*S* isomer and conversely, the allylic methylene proton in an *exo* position always resonated upfield in the 7*S* diastereomer compared with the 7*R* diastereomer. This shifting of protons can be ascribed to a ring current effect (*vide infra*) from the aromatic group in the acid moiety of the ester, and as can be seen in Table 1, the substitution pattern was found to influence the chemical shift differences between the diastereomers to different extents for the esters. The resonance of the allylic bridgehead proton C(1)H was in almost all cases the one most affected, with the β-naphthol ester showing the largest shift difference between the diastereomers (entry 3, Table 1). The other bridgehead proton, C(6)H, which is close to the carbonyloxy group, showed a large difference in chemical shift only for the naphthol derivatives **21** and **22** (entries 2 and 3, Table 1). In contrast, the allylic methylene proton in the *exo* position showed a rather small chemical shift difference between the diastereomers for all esters and very little sensitivity to the substitution pattern in the acid part of the molecule.

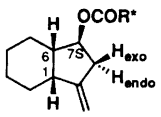
An attempt to assess the importance of the α-oxygen of the acid moiety in the ester for the resolution of the diastereomers by NMR spectroscopy was made by comparing the bicyclic esters formed from reactions with the phenoxy acid **9** and the commercially available (*R*)-3-phenylpropionic acid **15**.[12] The diastereomeric esters from **9** were found to give a larger shift difference for C(1)H than for the corresponding diastereomers from **15** (entries 1 and 9, Table 1).

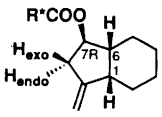
The resolution by NMR spectroscopy of other diastereomers from enantiomerically pure derivatives of (*R*)-lactic acid was studied by converting three acids with different substitution patterns in the aromatic ring (**9**, **10** and **11**) into their corresponding acid chlorides, which were subsequently reacted with primary and secondary alcohols. The best results were found for (*R*)-2-(β-naphthyloxy)propionic acid (**11**), which even separated the diastereomers obtained from reaction with 2,2-dimethyl-1,3-dioxolan-4-ylmethanol (entry 8, Table 2). This is known to be a difficult case,[13] and the signals from the corresponding MTPA esters could not be resolved by NMR spectroscopy (^{1}H and ^{19}F). Furthermore, this acid, when reacted with the pheromone component ipsdienol, also gave diastereomers that were well resolved by ^{1}H NMR spectroscopy (entry 10, Table 2).[14] It should be noted that in this case the signals from the corresponding MTPA esters could also not be resolved by NMR spectroscopy. The resolution of the signals from the diastereomers **38a/b**, derived from 1-phenylethyl alcohol, was found to be comparable to that for the corresponding diastereomers derived from Mosher's acid, and measurement could also be carried out by using two aromatic peaks for which baseline separation was observed (entry 7, Table 2).[15]

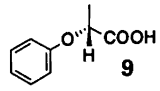
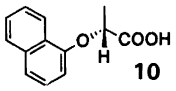
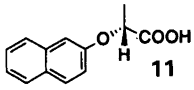
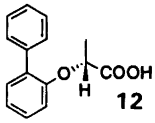
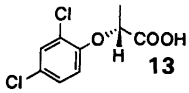
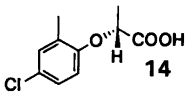
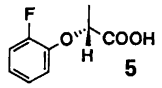
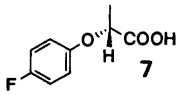
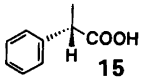
The enantiomeric purity of menthol was then examined. It was found that the two methyl doublets originating from the isopropyl group of the (−)-menthyl esters derived from acids **9–11** were in all cases shifted upfield compared with those of the esters prepared from (+)-menthol, whereas the doublet originating from the remaining methyl group in the alcohol moiety of the (−)-menthyl esters appeared at lower field than the corresponding peak of the esters of (+)-menthol. These peaks could be used for measurement of the enantiomeric excess, the most useful of these reagents being **9**. In this case, two methyl doublets originating from different diastereomers were close in chemical shift (at δ 0.73 and 0.76) but well separated from a methyl doublet from only one diastereomer (at δ 0.57, entry 3, Table 2). For the menthol esters of the naphthol derivatives **10** and **11** the peaks from the α-hydrogen of the alcohol moiety were best suited to the measurement (entries 6 and 9, Table 2). However, even when there is no overlap with other peaks this α-hydrogen is not generally useful for measurement as can be seen for the diastereomers **41a/b**.

A model for the determination of the absolute configurations of the diastereomers has previously been developed for the esters **16a/b–18a/b**.[16] It was shown by X-ray analysis and supported by NMR spectroscopy that the α-hydrogen of the acid as well as the α-hydrogen of the secondary alcohol is eclipsed with the carbonyl oxygen of the ester (Fig. 1). The substituent eclipsing the aromatic ring experiences a ring current effect and is therefore shifted upfield on NMR. Consequently, in a pair of diastereomeric esters one of the diastereomers will have the resonances of the R substituent shifted upfield and that of the R′ substituent shifted downfield compared with

Table 1. ^{1}H NMR spectral data for some bicyclic esters.[a]





Entry	R*COOH	Products	$\Delta\delta(C_1H)$[b]	$\Delta\delta(C_6H)$[b]	$\Delta\delta(C_8H_{exo})$[b]
1	 **9**	**20a/b**	−0.17	−0.14	0.13
2	 **10**	**21a/b**	−0.18[c]	−0.21	0.15[d]
3	 **11**	**22a/b**	−0.31[c]	−0.19	0.14[d]
4	 **12**	**23a/b**	−0.18[c]	−0.13	0.13[d]
5	 **13**	**24a/b**	−0.13	−0.12	0.13
6	 **14**	**25a/b**	−0.18	−0.13	*e*
7	 **5**	**26a/b**	−0.13	−0.11	0.12
8	 **7**	**27a/b**	−0.15	−0.12	0.13
9	 **15**	**28a/b**[f]	−0.12	−0.12	0.13

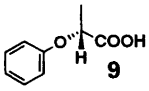
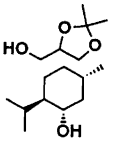
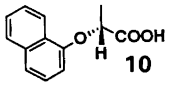
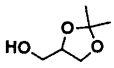
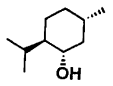
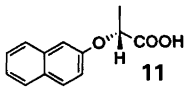
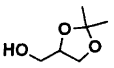
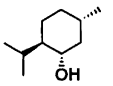
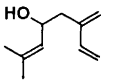
[a] 400 MHz. Synthesis, characterization, and determination of absolute configuration of the esters have been described elsewhere.[7c] [b] Chemical shift difference in ppm between the 7*R* and 7*S* diastereomers. [c] Overlap with C(8)H_{exo} from the 7*R* diastereomer. [d] Overlap with C(1)H from the 7*R* diastereomer. [e] Overlap with ArCH_3. [f] The absolute configurations were determined according to the method described in Ref. 12.

the corresponding substituents of the other diastereomer (Fig. 1).

Excellent agreement was found between this model and the results for the menthol esters obtained from reactions with the acids **9**–**11** (*vide supra*). The importance of the substitution pattern of the aromatic group is shown by the good resolution by NMR spectroscopy of the diastereomers **39a/b**, derived from 2-(β-naphthyloxy)-propionic acid (**11**), in contrast with the diastereomers **35a/b**, derived from 2-(α-naphthyloxy)propionic acid (**10**) or **31a/b**, derived from 2-phenoxypropionic acid (**9**) (entries 2, 5 and 8, Table 2). It seems reasonable to assume that this reflects the possibility of the aromatic group in **39a/b** being oriented in such a way that a proton in the alcohol moiety of the ester, for which there is no overlap with other peaks, can experience a ring current effect.

The free rotation around the bonds to the α-oxygen in the derivatives of (*R*)-lactic acid might be expected to reduce the effect of the ring current, since it seems likely that there would be a preference for sterically less hindered conformations where the aromatic group is

Table 2. NMR spectral data for the diastereomeric esters formed from the acids **9–11**.[a]

Entry	Acid	Alcohol	Products	Δδ(400 MHz)[b]	Δδ(250 MHz)[b]
1	 **9**		**30a/b**	0.09, $CH_3CHC_6H_5$[c]	
2	**9**		**31a/b**	No separation	
3	**9**		**32a/b**	*d*	
4	 **10**		**34a/b**	Baseline separation, aromatic 0.13, $CH_3CHC_6H_5$	
5	**10**		**35a/b**	No separation	
6	**10**		**36a/b**	−0.11, *CH*OCO	
7	 **11**		**38a/b**	0.08, aromatic 0.05, aromatic 0.10, $CH_3CHC_6H_5$	Baseline separation Baseline separation 0.09
8	**11**		**39a/b**	−0.06, CH_2CHCH_2O	No separation
9	**11**		**40a/b**	−0.10, *CH*OCO	
10	**11**		**41a/b**	−0.13, $CH_2{=}CH$ −0.08, $CHCH_2C{=}CH_2$	Baseline separation No separation

[a] Only significant peaks for which baseline separation was observed are reported. [b] Chemical shift difference in ppm between the *R,R* and *R,S* diastereomers. [c] Slight overlap with CH_3CH doublets. [d] The methyl peaks could be used for measurement; see the text.

oriented far away from the alcohol moiety of the ester. However, comparison of the esters formed from the phenoxy acid **9** and the acid **15**, which lacks an oxygen atom adjacent to the aromatic ring, showed better resolution for the diastereomers from **9** (entries 1 and 9, Table 1). A possible interpretation of these results could be that the α-oxygen might facilitate a closer orientation of the phenyl group to the allylic bridgehead proton C(1)H.

Ipsdienol has proved difficult to obtain in enantiomerically pure form.[14] The diastereomeric esters **22a/b**, derived from the acid **11**, showed promising resolution when chromatography on silica gel was performed, in contrast with the diastereomers of the acids **9** and **13** (entries 1, 3 and 5, Table 1).[17] Unfortunately, chromatography of the diastereomers of ipsdienol **41a/b** gave no enrichment of the diastereomers in any fraction containing the compound. This different behavior towards separation depending on the alcohol moiety of the ester was also observed for the acid **9**, for which the above-mentioned results can be compared with the fact that it has been possible to use **9** as a resolving agent.[18] HPLC also did not separate the diastereomers **41a/b**, and resolution of the diastereomers on a preparative scale was not further investigated.

The choice of reaction conditions for the esterification is important. Great care must be taken in order to avoid

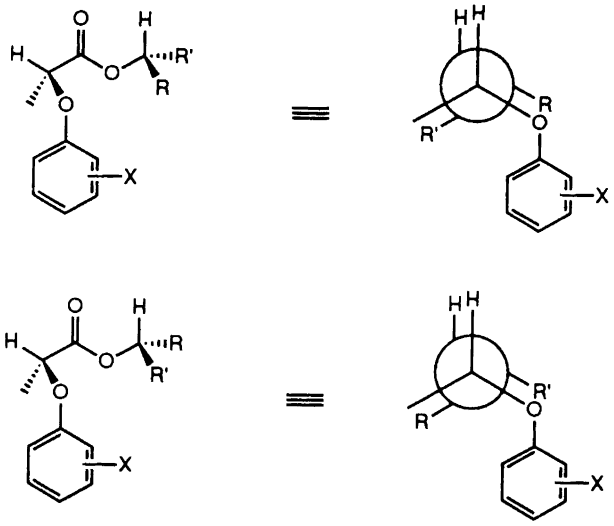


Fig. 1. Extended Newman projections of *O*-arylated lactic esters.

kinetic resolution and racemization/epimerization during the esterification. While the acid chlorides of the above-mentioned fluorinated acids **5–8** reacted easily with alcohols in the presence of pyridine, the corresponding acid chlorides of the acids **9–11** were found to be much less reactive. In the case of menthol, the addition of DMAP to a mixture of the acid chloride of **9** and pyridine resulted in a yield that was too low to be acceptable (55%). Use of triethylamine as the base instead of pyridine together with a catalytic amount of DMAP afforded quantitative yields, but some epimerization was observed for the acids **9** and **10** (25 and 7%, respectively). Fortunately, no epimerization was observed for the most successful acid **11**.[19] The necessity of using triethylamine as a base instead of pyridine for the esterification with the acid chlorides of **9–11** was presumably caused by formation of an unreactive acylpyridinium chloride complex. The same kind of complex is likely to be formed with the acid chlorides of **5–8** and pyridine, but the electron-withdrawing effect of the fluorine substituents makes them more reactive.

Conclusions

The cheap and easy synthesis of enantiomerically pure derivatives of (*R*)-lactic acid makes these compounds an interesting complement to existing chiral derivatizing agents for analysis by high resolution NMR spectroscopy. In some cases, better resolution in ^{1}H NMR spectra was observed for derivatives of 2-(β-naphthyloxy)propionic acid than for those of MTPA. These chiral reagents can be used for the determination of the absolute configuration of secondary alcohols.

Experimental

^{1}H NMR spectra were recorded at 250 and 400 MHz in $CDCl_3$ with Me_4Si as an internal standard.

Dry diethyl ether was obtained by distillation from sodium benzophenone ketyl. CCl_4 was distilled from $CaCl_2$ and stored over 4 Å molecular sieves. DMF was stored over 4 Å molecular sieves. Triethylamine was dried over potassium hydroxide. (*R*)-(−)-2-Phenylpropionic acid was purchased from Fluka, and oxalyl chloride, (1*R*, 2*S*, 5*R*)-(−)-menthol and racemic menthol were from Aldrich and used as received. (*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethanol had earlier been synthesized according to a literature procedure.[20] The synthesis and characterization of the acids **5–12** as well as the bicyclic esters in Table 1 have been described elsewhere (except **28a/b**).[7c]

Synthesis of the acid chlorides **29**, **33** *and* **37**. The acid (5 mmol) was dissolved in diethyl ether under a nitrogen atmosphere. Oxalyl chloride (2.5 ml) was added dropwise at 0 °C followed by DMF (50 µl). The reaction mixture was stirred for 30 min at 0 °C and 3 h at room temperature after which the ether and the oxalyl chloride were distilled off. In order to ensure complete removal of the excess of oxalyl chloride, CCl_4 was added to the residue and the distillation was repeated, after which the product was left under vacuum for approximately 1 h. The resulting acid chloride was obtained in high yield (92–99%) and was essentially pure as judged by NMR spectroscopy.

Esterification procedure. The acid chloride (0.15 mmol) was dissolved in CCl_4 (800 µl) under a nitrogen atmosphere. The alcohol (0.11 mmol) was added followed by triethylamine (36 µl, 0.26 mmol) and DMAP (3.5 mg, 0.03 mmol). The reaction mixture was stirred at ambient temperature overnight. Work-up procedure: an excess of 3-dimethylamino-1-propylamine was added (50–100 µl) in order to dissolve the precipitate formed. CH_2Cl_2 (5 ml) was added, and the organic phase was extracted with 1 M HCl (2 × 5 ml), a satd. aqueous solution of Na_2CO_3 (2 × 5 ml), and brine (2 × 5 ml). After drying ($MgSO_4$), the solvent was removed *in vacuo* and the NMR spectrum of the crude product was recorded. The yields were between 70 and 100%.*

The NMR spectra for all diastereomers were assigned from mixtures, except for spectra of the diastereomers derived from enantiomerically pure (1*R*, 2*S*, 5*R*)-menthol and (*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethanol. The assignment of the diastereomers derived from α-methylbenzyl alcohol was made by analogy with the results from an experiment with (*R*)-2-(β-naphthyloxy)propionic acid and this alcohol in which kinetic resolution was observed. The absolute configurations of **28a/b** were assigned according to the model described in Ref. 12. The model for

* Kinetic resolution was not observed under these reaction conditions. The varying yields were presumably due to the fact that, on this small scale, very slight loss of product during the work-up procedure resulted in a largely decreased yield.

the determination of the absolute configuration described in the text was used for assigning the diastereomers of ipsdienol.[16]

*(1*R, *6*S, *7*R*)-7-[(*R*)-1-Phenylethylcarbonyloxyl]-9-methylenebicyclo[4.3.0]nonane* (**28a**). ^{1}H NMR (400 Hz): δ 7.2–7.35 (m, 5 H), 4.8–4.96 (m, 3 H, CH_2=C and C*H*OCOR*), 3.63–3.75 (m, 1 H, C*H*CH_3), 2.85 [ddq, J = 18, 7 and 2 Hz, 1 H, C(8)H_{endo}], 2.55 [br s, $w_{1/2}$ = 14 Hz, 1 H, C(1)H], 2.37 [br d, J = 18 Hz, 1 H, C(8)H_{exo}], 1.92 [br s, $w_{1/2}$ = 23 Hz, 1 H, C(6)H], 1.7–1.8 (m, 1 H), 1.48 (d, J = 7 Hz, 3 H, CHCH_3), 1.1–1.65 (m, 6 H), 0.8–1.0 (m, 1 H).

*(1*S, *6*R, *7*S*)-7-[(*R*)-1-Phenylethylcarbonyloxyl]-9-methylenebicyclo[4.3.0]nonane* (**28b**). ^{1}H NMR (400 MHz): δ 7.2–7.35 (m, 5 H), 4.8–4.96 (m, 3 H, CH_2=C and C*H*OCOR*), 3.63–3.75 (m, 1 H, C*H*CH_3), 2.80 [ddq, J = 18, 7 and 2 Hz, 1 H, C(8)H_{endo}], 2.67 [br s, $w_{1/2}$ = 15 Hz, 1 H, C(1)H], 2.24 [br d, J = 18 Hz, 1 H, C(8)H_{exo}], 2.04 [br s, $w_{1/2}$ = 22 Hz, 1 H, C(6)H], 1.7–1.8 (m, 1 H), 1.48 (d, J = 7 Hz, 3 H, CHCH_3), 1.1–1.65 (m, 6 H), 0.8–1.0 (m, 1 H).

*(*R*)-2-Phenoxypropionyl chloride* (**29**). ^{1}H NMR (250 MHz): δ 7.23–7.36 (m, 2 H), 6.98–7.08 (m, 1 H), 6.83–6.92 (m, 2 H), 4.95 (q, J = 7 Hz, 1 H), 1.75 (d, J = 7 Hz, 3 H). IR (film): 1822, 1777 cm^{-1}.

*(*R*)-1-Phenylethyl (*R*)-2-phenoxypropionate* (**30a**). ^{1}H NMR (400 MHz): δ 7.15–7.4 (m, 7 H), 6.79–7.0 (m, 3 H), 5.93 (q, J = 7 Hz, 1 H, C_6H_5CH), 4.78 (q, J = 7 Hz, 1 H, CH_3CHOAr), 1.61 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.56 (d, J = 7 Hz, 3 H, $CH_3CHC_6H_5$).

*(*S*)-1-Phenylethyl (*R*)-2-phenoxypropionate* (**30b**). ^{1}H NMR (400 MHz): δ 7.15–7.4 (m, 7 H), 6.79–7.0 (m, 3 H), 5.94 (q, J = 7 Hz, 1 H, C_6H_5CH), 4.75 (q, J = 7 Hz, 1 H, CH_3CHOAr), 1.62 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.47 (d, J = 7 Hz, 3 H, $CH_3CHC_6H_5$).

*(*R*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (*R*)-2-phenoxypropionate* (**31a**). ^{1}H NMR (400 MHz): δ 7.16–7.35 (m, 2 H), 6.94–7.05 (m, 1 H), 6.8–6.94 (m, 2 H), 4.81 (q, J = 7 Hz, 1 H, C*H*OAr), 4.14–4.32 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.98 (dd, J = 8.5 and 6 Hz, 1 H, CH_2CHCH_2), 3.62 (dd, J = 8.5 and 5.5 Hz, 1 H, CH_2CHCH_2O), 1.64 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.40 (s, 3 H), 1.35 (s, 3 H).

*(*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (*R*)-2-phenoxypropionate* (**31b**). ^{1}H NMR (400 MHz): δ 7.16–7.35 (m, 2 H), 6.94–7.05 (m, 1 H), 6.8–6.94 (m, 2 H), 4.81 (q, J = 7 Hz, 1 H, C*H*OAr), 4.16–4.29 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.94 (dd, J = 8.5 and 6 Hz, 1 H, CH_2CHCH_2), 3.63 (dd, J = 8.5 and 5.5 Hz, 1 H, CH_2CHCH_2O), 1.64 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.42 (s, 3 H), 1.35 (s, 3 H).

*(1*R, *2*S, *5*R*)-Menthyl (*R*)-2-phenoxypropionate* (**32a**). ^{1}H NMR (400 MHz): δ 7.22–7.3 (m, 2 H), 6.9–7.0 (m, 1 H), 6.83–6.9 (m, 2 H), 4.74 (q, J = 7 Hz, 1 H, CH_3CHOAr), 4.67 (td, J = 11 and 4.5 Hz, 1 H, C*H*OCO), 1.97–2.04 (m, 1 H), 1.62 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.55–1.71 (m, 2 H), 1.3–1.55 (m, 3 H), 0.90 [d, J = 7 Hz, 3 H, $CH_2CH(CH_3)CH_2$], 0.8–1.1 (m, 3 H), 0.71 [d, J = 7 Hz, 3 H, $CH(CH_3)_2$], 0.56 [d, J = 7 Hz, 3 H, $CH(CH_3)_2$].

*(1*S, *2*R, *5*S*)-Menthyl (*R*)-2-phenoxypropionate* (**32b**). ^{1}H NMR (400 MHz): δ 7.22–7.3 (m, 2 H), 6.9–7.0 (m, 1 H), 6.83–6.9 (m, 2 H), 4.74 (td, J = 11 and 4.5 Hz, 1 H, C*H*OCO), 4.72 (q, J = 7 Hz, 1 H, CH_3CHOAr), 1.83–1.96 (m, 1 H), 1.61 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.55–1.72 (m, 2 H), 1.3–1.55 (m, 3 H), 0.91 [d, J = 7 Hz, 3 H, $CH(CH_3)_2$], 0.87 [d, J = 7 Hz, 3 H, $CH(CH_3)_2$], 0.8–1.1 (m, 3 H), 0.75 [d, J = 7 Hz, 3 H, $CH_2CH(CH_3)CH_2$].

*(*R*)-2-(α-Naphthyloxy)propionyl chloride* (**33**). ^{1}H NMR (250 MHz): δ 8.26–8.36 (m, 1 H), 7.77–7.86 (m, 1 H), 7.45–7.58 (m, 3 H), 7.28–7.40 (m, 1 H), 6.64–6.72 (m, 1 H), 5.14 (q, J = 7 Hz, 1 H), 1.88 (d, J = 7 Hz, 3 H). IR (film): 1823, 1732 cm^{-1}.

*(*R*)-1-Phenylethyl (*R*)-2-(α-naphthyloxy)propionate* (**34a**). ^{1}H NMR (400 MHz): δ 8.32–8.4 (m, 1 H), 7.74–7.84 (m, 1 H), 7.4–7.52 (m, 3 H), 7.1–7.37 (m, 6 H), 6.63–6.68 (m, 1 H), 5.93 (q, J = 6.5 Hz, 1 H, $CH_3CHC_6H_5$), 4.97 (q, J = 7 Hz, 1 H, CH_3CHOAr), 1.73 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.54 (d, J = 6.5 Hz, 3 H, $CH_3CHC_6H_5$).

*(*S*)-1-Phenylethyl (*R*)-2-(α-naphthyloxy)propionate* (**34b**). ^{1}H NMR (400 MHz) 8.32–8.4 (m, 1 H), 7.74–7.84 (m, 1 H), 7.4–7.52 (m, 3 H), 7.1–7.37 (m, 6 H), 6.58–6.63 (m, 1 H), 5.94 (q, J = 6.5 Hz, 1 H, $CH_3CHC_6H_5$), 4.95 (q, J = 7 Hz, 1 H, CH_3CHOAr), 1.76 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.41 (d, J = 6.5 Hz, 3 H, $CH_3CHC_6H_5$).

*(*R*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (*R*)-2-(α-naphthyloxy)propionate* (**35a**). ^{1}H NMR (400 MHz): δ 8.3–8.37 (m, 1 H), 7.75–7.82 (m, 1 H), 7.42–7.53 (m, 3 H), 7.32 (t, J = 8 Hz, 1 H), 6.72 (d, J = 8 Hz, 1 H), 5.02 (q, J = 7 Hz, 1 H, CH_3CHOAr), 4.11–4.27 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.82–3.90 (m, 1 H, CH_2CH), 3.52–3.61 (m, 1 H, CH_2CHCH_2O), 1.78 (d, J = 7 Hz, 3 H, CH_3CHOAr), 1.37 (s, 3 H), 1.31 (s, 3 H).

*(*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (*R*)-2-(α-naphthyloxy)propionate* (**35b**). ^{1}H NMR (400 MHz): δ 8.3–8.37 (m, 1 H), 7.75–7.82 (m, 1 H), 7.42–7.53 (m, 3 H), 7.31 (t, J = 8 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H), 5.02 (q, J = 7 Hz, 1 H, CH_3CHOAr), 4.14–4.27 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.82–3.90 (m, 1 H, CH_2CHCH_2O), 3.52–3.61 (m, 1 H, CH_2CH), 1.78

(d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.37 (s, 3 H), 1.32 (s, 3 H).

(1R, 2S, 5R)-Menthyl (R)-2-(α-naphthyloxy)propionate (**36a**). ^{1}H NMR (400 MHz): δ 8.32–8.39 (m, 1 H), 7.74–7.82 (m, 1 H), 7.4–7.52 (m, 3 H), 7.30 (t, $J = 8$ Hz, 1 H), 6.71 (d, $J = 8$ Hz, 1 H), 4.94 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.63 (td, $J = 11$ and 4.5 Hz, 1 H, $CHOCO$), 1.98–2.06 (m, 1 H), 1.75 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.33–1.8 (m, 4 H), 1.18–1.29 (m, 1 H), 0.89 [d, $J = 6$ Hz, 3 H, $CH_2CH(CH_3)CH_2$], 0.72–1.09 (m, 3 H), 0.51 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$], 0.48 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$].

(1S, 2R, 5S)-Menthyl (R)-2-(α-naphthyloxy)propionate (**36b**). ^{1}H NMR (400 MHz): δ 8.32–8.39 (m, 1 H), 7.74–7.82 (m, 1 H), 7.4–7.52 (m, 3 H), 7.29 (t, $J = 8$ Hz, 1 H), 6.69 (d, $J = 8$ Hz, 1 H), 4.91 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.74 (td, $J = 11$ and 4.5 Hz, 1 H, $CHOCO$), 1.83–1.90 (m, 1 H), 1.74 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.33–1.8 (m, 4 H), 1.18–1.29 (m, 1 H), 0.91 [d, $J = 6.5$ Hz, 3 H, $CH(CH_3)_2$], 0.85 [d, $J = 6.5$ Hz, 3 H, $CH(CH_3)_2$], 0.76 [d, $J = 7$ Hz, 3 H, $CH_2CH(CH_3)CH_2$], 0.72–1.09 (m, 3 H).

(R)-2-(β-Naphthyloxy)propionyl chloride (**37**). ^{1}H NMR (250 MHz): δ 7.68–7.83 (m, 3 H), 7.34–7.51 (m, 2 H), 7.15–7.22 (m, 1 H), 7.02–7.07 (m, 1 H), 5.10 (q, $J = 7$ Hz, 1 H), 1.81 (d, $J = 7$ Hz, 3 H). IR (film): 1831, 1780 cm^{-1}.

(R)-1-Phenylethyl (R)-2-(β-naphthyloxy)propionate (**38a**). ^{1}H NMR (400 MHz): δ 7.7–7.8 (m, 2 H), 7.57–7.62 (m, 1 H), 7.1–7.45 (m, 8 H), 6.97–7.0 (m, 1 H), 5.93 (q, $J = 7$ Hz, 1 H, C_6H_5CH), 4.92 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 1.66 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.56 (d, $J = 7$ Hz, 3 H, $CH_3CHC_6H_5$).

(S)-1-Phenylethyl (R)-2-(β-naphthyloxy)propionate (**38b**). ^{1}H NMR (400 MHz): δ 7.7–7.8 (m, 2 H), 7.5–7.54 (m, 1 H), 7.1–7.45 (m, 8 H), 6.92–6.95 (m, 1 H), 5.97 (q, $J = 7$ Hz, 1 H, C_6H_5CH), 4.89 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 1.69 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.47 (d, $J = 7$ Hz, 3 H, $CH_3CHC_6H_5$).

(R)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (R)-2-(β-naphthyloxy)propionate (**39a**). ^{1}H NMR (400 MHz): δ 7.74–7.79 (m, 2 H), 7.67–7.72 (m, 1 H), 7.4–7.46 (m, 1 H), 7.32–7.38 (m, 1 H), 7.17–7.22 (m, 1 H), 7.04–7.09 (m, 1 H), 4.96 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.14–4.32 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.97 (dd, $J = 8.5$ and 6.5 Hz, 1 H, CH_2CHCH_2O), 3.66 (dd, $J = 8.5$ and 5.5 Hz, 1 H, CH_2CHCH_2), 1.70 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.39 (s, 3 H), 1.32 (s, 3 H).

(S)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (R)-2-(β-naphthyloxy)propionate (**39b**). ^{1}H NMR (400 MHz): δ 7.74–7.79 (m, 2 H), 7.67–7.72 (m, 1 H), 7.4–7.46 (m, 1 H), 7.32–7.38 (m, 1 H), 7.17–7.22 (m, 1 H), 7.04–7.09 (m, 1 H), 4.96 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.17–4.28 (m, 3 H, CH_2OCO and CH_2CHCH_2), 3.91 (dd, $J = 8.5$ and 6 Hz, 1 H, CH_2CHCH_2O), 3.62 (dd, $J = 8.5$ and 5.5 Hz, 1 H, CH_2CHCH_2), 1.70 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.41 (s, 3 H), 1.32 (s, 3 H).

(1R, 2S, 5R)-Menthyl (R)-2-(β-naphthyloxy)propionate (**40a**). ^{1}H NMR (400 MHz): δ 7.72–7.78 (m, 2 H), 7.62–7.68 (m, 1 H), 7.38–7.44 (m, 1 H), 7.30–7.36 (m, 1 H), 7.16–7.22 (m, 1 H), 7.02–7.06 (m, 1 H), 4.89 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.67 (td, $J = 11$ and 4.5 Hz, 1 H, $CHOCO$), 1.98–2.05 (m, 1 H), 1.68 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.21–1.73 (m, 5 H), 0.89 [d, $J = 6.5$ Hz, 3 H, $CH_2CH(CH_3)CH_2$], 0.72–1.10 (m, 3 H), 0.53 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$], 0.38 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$].

(1S, 2R, 5S)-Menthyl (R)-2-(β-naphthyloxy)propionate (**40b**). ^{1}H NMR (400 MHz): δ 7.72–7.78 (m, 2 H), 7.62–7.68 (m, 1 H), 7.38–7.44 (m, 1 H), 7.30–7.36 (m, 1 H), 7.16–7.22 (m, 1 H), 7.02–7.06 (m, 1 H), 4.86 (q, $J = 7$ Hz, 1 H, CH_3CHOAr), 4.77 (td, $J = 11$ and 4.5 Hz, 1 H, $CHOCO$), 1.82–1.91 (m, 1 H), 1.67 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), 1.21–1.73 (m, 5 H), 0.94 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$], 0.83 [d, $J = 7$ Hz, 3 H, $CH(CH_3)_2$], 0.75 [d, $J = 7$ Hz, 3 H, $CH_2CH(CH_3)CH_2$], 0.72–1.1 (m, 3 H).

(R)-Ipsdienyl (R)-2-(β-naphthyloxy)propionate (**41a**). ^{1}H NMR (400 MHz): δ 7.6–7.8 (m, 3 H), 7.3–7.46 (m, 2 H), 7.15–7.23 (m, 1 H), 6.97–7.03 (m, 1 H), 6.23 (dd, $J = 17.5$ and 11 Hz, 1 H, $CH_2{=}CH$), 5.67–5.83 (m, 1 H, $CHCH_2C{=}CH_2$), 4.75–5.35 (m, 6 H), 2.56 (A part of ABX, $J_{AB} = 14$ Hz, $J_{AX} = 7.5$ Hz, 1 H, $CHCH_2C{=}CH_2$), 2.34 (B part of ABX, $J_{AB} = 14.5$ Hz, $J = 6.5$ Hz, 1 H, $CHCH_2C{=}CH_2$), 1.65 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), two of the signals: 1.73, 1.65, 1.62, 1.58 (d, $J = 1$ Hz, 6 H).

(S)-Ipsdienyl (R)-2-(β-naphthyloxy)propionate (**41b**). ^{1}H NMR (400 MHz): δ 7.6–7.8 (m, 3 H), 7.3–7.46 (m, 2 H), 7.15–7.23 (m, 1 H), 6.97–7.03 (m, 1 H), 6.36 (dd, $J = 17.5$ and 11 Hz, 1 H, $CH_2{=}CH$), 5.67–5.83 (m, 1 H, $CHCH_2C{=}CH_2$), 4.75–5.35 (m, 6 H), 2.64 (A part of ABX, $J_{AB} = 14$ Hz, $J_{AX} = 7.5$ Hz, 1 H, $CHCH_2C{=}CH_2$), 2.40 (B part of ABX, $J_{AB} = 14.5$ Hz, $J = 6$ Hz, 1 H, $CHCH_2C{=}CH_2$), 1.65 (d, $J = 7$ Hz, 3 H, CH_3CHOAr), two of the signals: 1.73, 1.65, 1.62, 1.58 (d, $J = 1$ Hz, 6 H).

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References

1. Morrison, J. D. *Asymmetric Synthesis*, Academic Press, New York 1983, Vol. I.
2. Parker, D. *Chem. Rev. 91* (1991) 1441.

3. (a) Dale, J. A. and Mosher, H. S. *J. Am. Chem. Soc. 90* (1968) 3732; (b) Dale, J. A., Dull, D. L. and Mosher, H. S. *J. Org. Chem. 34* (1969) 2543; (c) Dale, J. A. and Mosher, H. S. *J. Am. Chem. Soc. 95* (1973) 512; (d) Sullivan, G. R., Dale, J. A. and Mosher, H. S. *J. Org. Chem. 38* (1973) 2143.
4. Takeuchi, Y., Itoh, N., Note, H., Koizumi, T. and Yamaguchi, K. *J. Am. Chem. Soc. 113* (1991) 6318.
5. (a) Alexakis, A., Mutti, S., Normant, J. F. and Mangeney, P. *Tetrahedron: Asymmetry 1* (1990) 437; (b) Alexakis, A., Mutti, S. and Mangeney, P. *J. Org. Chem. 57* (1992) 1224.
6. (a) Silks, L. A., Dunlap, R. B. and Odom, J. D. *J. Am. Chem. Soc. 112* (1990) 4979; (b) Silks, L. A., Peng, J., Odom, J. D. and Dunlap, R. B. *J. Org. Chem. 56* (1991) 6733.
7. (a) Heumann, A. and Moberg, C. *J. Chem. Soc., Chem. Commun.* (1988) 1516; (b) Heumann, A., Tottie, L. and Moberg, C. *J. Chem. Soc., Chem. Commun.* (1991) 218; (c) Tottie, L., Baeckström, P., Moberg, C., Tegenfeldt, J. and Heumann, A. *J. Org. Chem. 57* (1992) 6579.
8. Heumann, A. and Faure, R. *J. Org. Chem. In press.*
9. Tottie, L., Moberg, C. and Heumann, A. *Unpublished results.*
10. The high cost of the *o*- and *p*-trifluoromethylphenols prevented us from synthesizing the regioisomers of **8**.
11. (a) Ohtani, I., Kusumi, T., Kashman, Y. and Kakisawa, H. *J. Am. Chem. Soc. 113* (1991) 4092; (b) Gordon, A. J. and Ford, R. A. *The Chemist's Companion*, Wiley, New York 1972, pp. 288.
12. Bravo, P., Ganazzoli, F., Resnati, G., De Munari, S. and Albinati, A. *J. Chem. Res.* (1988) (*S*) 216; (*M*) 1701.
13. Mukaiyama, T., Tanabe, Y. and Shimuzu, M. *Chem. Lett.* (1984) 401.
14. (a) Baeckström, P., Björkling, F., Högberg, H.-E. and Norin, T. *Acta Chem. Scand., Ser. B 37* (1983) 1; (b) Mustaparta, H., Tømmerås, B. Å., Baeckström, P., Bakke, J. M. and Ohloff, G. *J. Comp. Physiol. A 154* (1984) 591.
15. Nishiyama, H., Kondo, M., Nakamura, T. and Itoh, K. *Organometallics 10* (1991) 500.
16. Heumann, A. *Unpublished results.*
17. Tottie, L., Moberg, C., Heumann, A. and Looström, H. *Unpublished results.*
18. (a) Jacques, J., Collet, A. and Wilen, S. H. *Enantiomers, Racemates and Resolutions*, Wiley, New York 1981, p. 260; (b) Canceill, J., Collet, A. and Gottarelli, G. *J. Am. Chem. Soc. 106* (1984) 5997.
19. (a) Attempts to use DCC and DMAP in CH_2Cl_2 or DMF for esterification of the acids **10** and **11** resulted in incomplete reaction, low yields and kinetic resolution. However, it has been reported that DCC and DMAP in DMF can be used for esterification with the acid **9**: Ref. 18(b); (b) Racemic alcohols have been kinetically resolved with (*R*)-(2,4-dichlorophenoxy)propionic acid using DCC: Chinchilla, R., Nájera, C., Yus, M. and Heumann, A. *Tetrahedron: Asymmetry 1* (1990) 851.
20. Baldwin, J. J., Raab, A. W., Mensler, K., Arison, B. H. and McClure, D. E. *J. Org. Chem. 43* (1978) 4876.

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