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Determination of the absolute configuration of chiral benzylic alcohols and their esters or ethers, by ruthenium-mediated oxidative degradation

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Abstract

A sensitive analytical method for the reliable determination of the absolute configuration of chiral benzylic alcohols and the corresponding methyl ethers is described. After protection of the hydroxy function by acylation, they are degraded by Ru(VIII)-mediated oxidation, yielding chiral α-oxygenated carboxylic acids, whose stereoanalysis is achieved by GC–MS on a chiral phase. The method easily works down to 1 mg of the analyte.

1. Introduction

Chiral α-hydroxyalkyl aryl partial structures **1** occur in a broad series of natural products, among them are dihydrophenanthrenes such as **2**,[1] benzofuranes such as **3**,[2] anthraquinones of type **4**,[3,4] and chromenes such as **5**.[5] They are also found in compounds of synthetic origin, for example in hydrosilylation/oxidation products of stilbenes[6,7] or in reduction or alkylation products of acetophenones or benzaldehydes, e.g. when new chiral hydrogen or alkyl transfer reagents are tested,[8–11] as in the axially chiral biaryl compound **6**, which has been synthesized stereoselectively in our group (Fig. 1).[11]

Despite the availability of modern methods for the elucidation of the absolute configuration of secondary alcohols,[12–15] many of these structures are, even nowadays, published without assignment (or even discussion) of the absolute configuration at the stereogenic center.[1–3,5,16] We have recently established a fast and reliable method for the elucidation of the configuration of the stereocenters in tetrahydroisoquinolines and tetrahydro-β-carbolines,[17] by ruthenium(VIII)-mediated oxidative degradation to give simple amino acids, which can be analyzed by GC–MS

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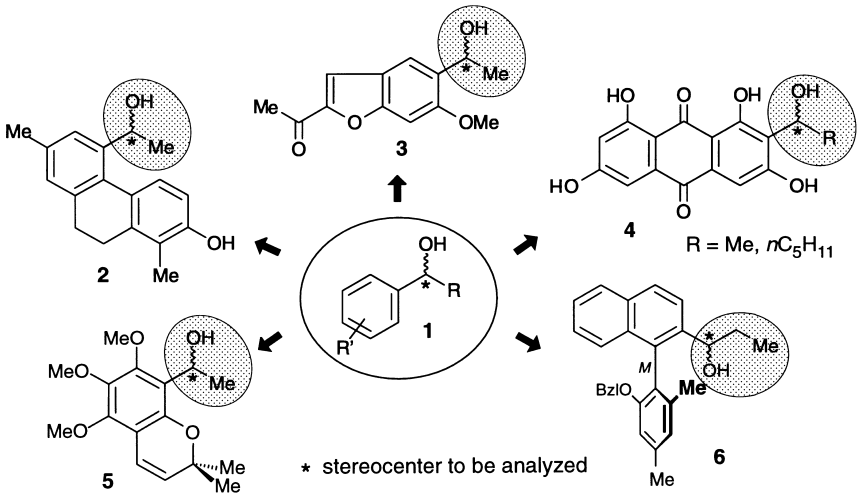
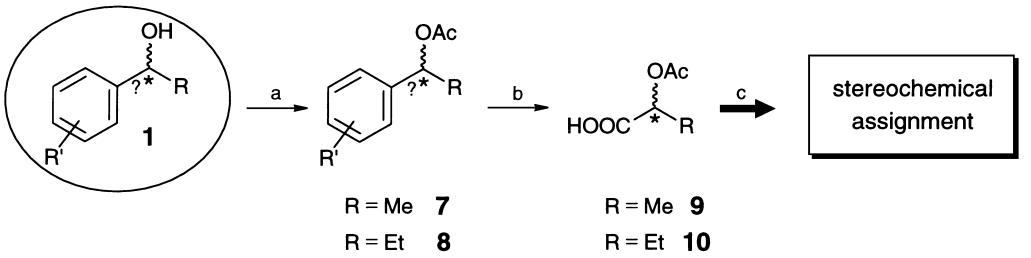


Figure 1. Aromatic natural and synthetic products with chiral α-hydroxyalkyl side chains

after Mosher-type derivatization. More recently, we have extended the procedure to the degradation of natural tetralones, which give rise to α-branched chiral carboxylic acids.[18]

In this paper, we describe the enlargement of the scope of the method to the stereoanalysis of α-hydroxyalkyl aromatics of type **1**. After protection of the hydroxy group (typically on a 1 mg scale), the resulting acetates **7** or **8** are oxidized to the corresponding α-acetoxy carboxylic acids **9** or **10** (Scheme 1). Similar degradation reactions previously described[19] required distinctly higher quantities of the analyte (ca. 1 mmol). The stereoanalysis of the degradation products is achieved by GC–MS analysis on a chiral phase without further derivatization, unequivocally establishing the absolute configuration of such chiral natural products with benzylic oxygen functions.



Scheme 1. The analytical oxidative degradation procedure: (a) AcCl, NEt_3; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral phase

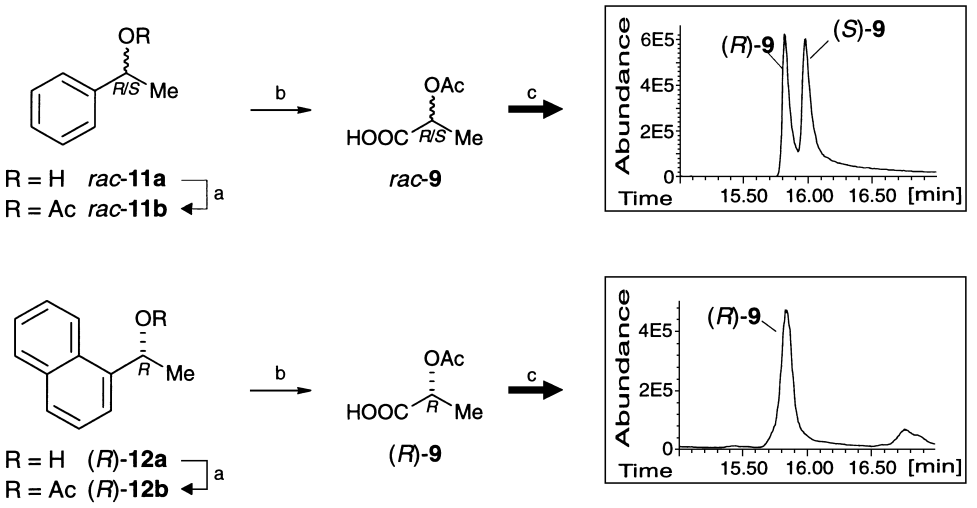
2. Results and discussion

2.1. (α-Hydroxyethyl)aryl compounds

As an important analytical 'building block' within the degradative stereoanalysis of aromatic alcohols of type **1** we first elaborated a GC–MS procedure for the separation of the acetate-protected

chiral carboxylic acids **9** and **10** expected to be formed in the degradation of ester-protected aromatic alcohols of types **7** and **8**, respectively (Scheme 1).[19,20] The free, non-protected α-hydroxy acids (although likewise analyzable for their absolute configuration[21,22]) were not investigated further because of the instability of chiral benzylic alcohols under the oxidative conditions, as evident already from the previous degradation of isoshinanolone[18] and from related work in the literature.[19,20,23]

The enantiomer resolution of α-acetoxypropionic and -butyric acids (**9** and **10**, respectively) was achieved by GC analysis on a chiral CDX-B column without further derivatization. By the use of a mass sensitive detector (MSD) in the selected ion monitoring mode (SIM mode), the significant base ion traces were recorded. The resulting clear chromatograms of the hydroxy acid derivatives **9** and **10** (see also Schemes 2 and 4) allowed us to register and characterize the degradation products in very small amounts and with high significance. The absolute configurations of the enantiomers were attributed to the respective signals by coelution experiments with references of known configuration. The structures and characteristic ions of the carboxylic acids **9** and **10**, their relative intensities, and the retention times (t_R) are presented in Table 1.

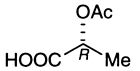
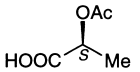
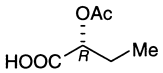
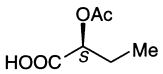


Scheme 2. GC–MS analysis of the degradation products of compounds *rac*-**11a** and (*R*)-**12a**: (a) AcCl, NEt_3; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral CDX-B phase

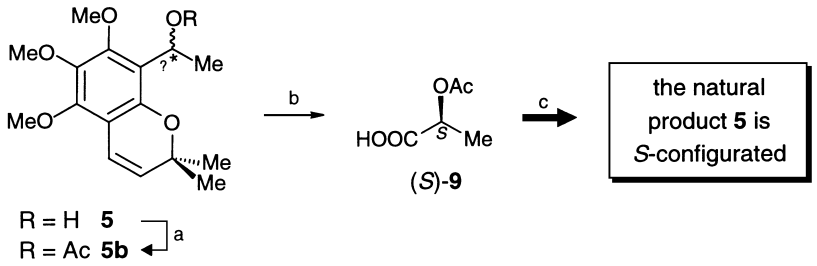
For the oxidative degradation, the standard conditions previously elaborated for the tetrahydropyridine system[17] were applied to different esters of type **7** obtained by acetate-protection of the hydroxy group of benzylic alcohols of type **1**. In the first instance, easily available model systems of known configuration were investigated by this procedure. Thus, as presented in Scheme 2, racemic α-phenylethyl acetate *rac*-**11b** yielded racemic α-acetoxypropionic acid *rac*-**9**, and (*R*)-α-(1-naphthyl)ethyl acetate *R*-**12b** gave enantiopure (*R*)-**9**, showing that, in agreement with related (preparative) investigations in the literature,[19,20,24] no racemization of the resulting acetoxy acid **9** had occurred.

The technique thus elaborated was then applied to the stereoanalysis of the benzopyran **5**, a natural product of as yet unknown absolute configuration isolated from the leaves of *Melicope ptelefolia* (Rutaceae).[5] As expected, the oxidative degradation offers a fast solution to this

Table 1
Structures, GC retention times (t_R), and characteristic ions of the α-acetoxypropionic and -butyric acid derivatives **9** and **10** (CG-column used: CDX-B)

structure		t_R (min)	*m/z*	rel. int. (%)
	(*R*)-**9**	16.1	43 $[CO_2]^+$	100
	(*S*)-**9**	16.3	87 $[M\text{-}CO_2H]^+$	30
	(*R*)-**10**	18.1	43 $[CO_2]^+$	100
	(*S*)-**10**	18.5	101 $[M\text{-}CO_2H]^+$	24

problem even on an analytical scale: Acetylation of **5** and oxidative degradation gave (*S*)-α-acetoxypropionic acid (*S*)-**9**, stereochemically again identified by GC–MS, thus establishing natural **5** to be *S*-configured (Scheme 3).

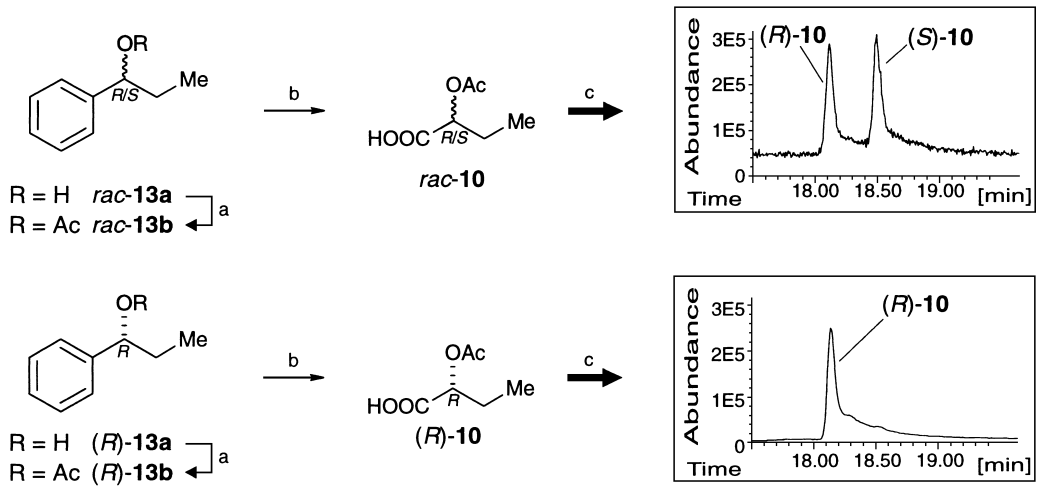


Scheme 3. Elucidation of the absolute configuration of the natural benzopyran **5** from *Melicope ptelefolia* (Rutaceae)[5] by the oxidative degradation method: (a) AcCl, NEt_3; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral CDX-B phase

2.2. (α-Hydroxypropyl)aryl compounds

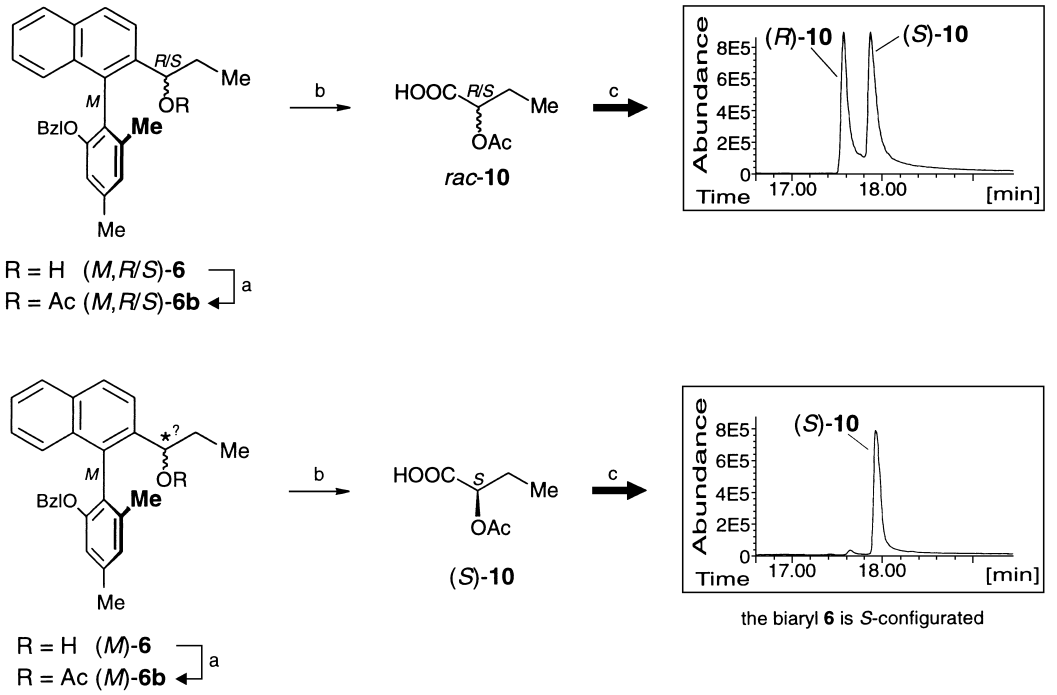
In a similar way the analytical method was then extended to the assignment of the absolute configuration of α-acetoxypropyl aromatics of type **8** (cf. Scheme 1). Again, the degradation was first tested with simple, easily available representatives (see Scheme 4). Thus, after acetylation and oxidation of the racemic alcohol *rac*-**13a** and of the pure *R*-enantiomer, (*R*)-**13a** (obtained by asymmetric addition of diethylzinc to benzaldehyde[25]), the expected α-acetoxybutyric acids, *rac*-**10** and (*R*)-**10**, respectively, were identified.

As a rewarding first substrate of as yet unkown absolute configuration, we chose the biaryl **6**, which had been prepared by atropisomer-selective alkylation of configuratively unstable biaryl aldehydes, with double—axial and central—stereodifferentiation.[11,26] While the assignment of its axial configuration was easily attributed through CD spectroscopy, the benzylic stereocenter had not been assigned as yet, but could now be elucidated by the Ru(VIII)-mediated oxidation



Scheme 4. Results of the degradation procedure of racemic and enantiopure α-phenylpropanol [*rac*-**13** and (*R*)-**13**]: (a) AcCl, NEt_3; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral CDX-B phase

presented here. Thus, application of the procedure led to *rac*-**10** for (*M*,*R*/*S*)-**6** and to stereochemically homogeneous (*S*)-**10** for the pure isomer of **6**, which was thus identified as (*M*,*S*)-**6** (Scheme 5)—a simple and fast way to analyze absolute configurations at benzylic stereocenters.



Scheme 5. Derivatization and degradation of (*M*,*R*/*S*)-**6** and of the diastereopure compound (*M*)-**6** with previously unknown configuration at the benzylic stereocenter, and stereoanalysis of the products: (a) AcCl, NEt_3; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral CDX-B phase

2.3. (α-Methoxyethyl)aryl compounds

In numerous natural products, the benzylic hydroxy groups occur in an *O*-methylated form, e.g. in benzofurans such as **15**,[2] chromenes like **16**,[5] dihydrophenanthrenes as for example **17**,[1] and anthraquinones such as **18**.[4] In many cases, the absolute configurations of the products have not yet been elucidated (Fig. 2).

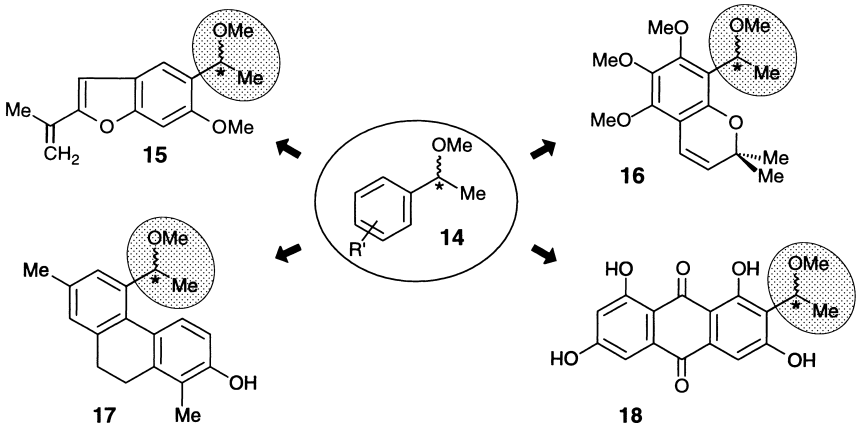
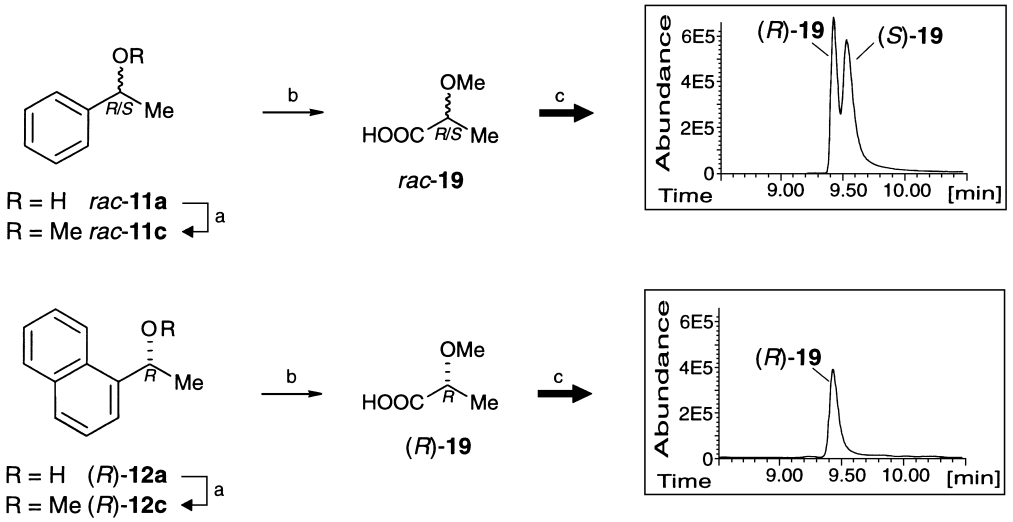


Figure 2. Natural products with chiral (α-methoxyethyl)aryl fragments

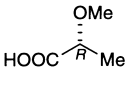
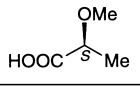
For the stereochemical analysis of such natural compounds, we have extended the above-described oxidative degradation method to (α-methoxyethyl)aryl ethers of type **14**. The reaction of *rac*-**11c** with $RuCl_3/NaIO_4$ (Scheme 6) resulted in the—expected—formation of racemic α-methoxypropionic acid (*rac*-**19**). The chromatographic racemate resolution of **19** was achieved without further derivatization, by GC–MS analysis on a chiral β-DEX 325 column. By co-elution



Scheme 6. Results of the oxidative degradation of the (α-methoxyethyl)aryl ethers *rac*-**11c** and (*R*)-**12C**: (a) NaH, Me_2SO_4; (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral β-DEX 325 phase

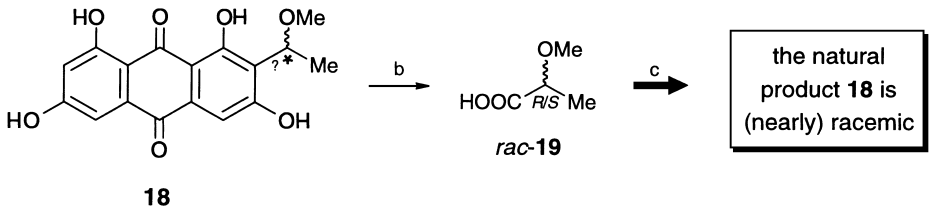
experiments with authentic (*R*)-**19**, easily prepared according to literature protocols,[27] the signals were attributed to the respective enantiomers (Table 2).

Table 2
Structures, GC retention times (t_R), and the characteristic ion of α-methoxypropionic acid (**19**) (GC column used: β-DEX 325)

structure		t_R (min)	*m/z*	rel. int. (%)
	(*R*)-**19**	9.45	58 $[M\text{-}CO_2H_2]^+$	100
	(*S*)-**19**	9.55		

Enantiomerically pure (*R*)-**19** was obtained by degradation of (*R*)-α-(1-naphthyl)ethyl methyl ether (*R*-**12c**), which, in turn, was prepared from commercially available (*R*)-**12a** (Scheme 6). As with the oxidation of α-arylethyl acetates of type **9** (see above), no racemization was observed, showing this degradation being well suited for the stereochemical assignment of chiral products with benzylic methoxy groups, too.

As a first example, oxidative degradation of 1,3,6,8-tetrahydroxyanthraquinone **18**[4] gave virtually racemic **19**, with no enantiomers of **19** significantly predominant, which explained the unexpectedly low CD $\Delta\varepsilon$ value of this natural product from an undescribed fungus of the genus *Microsphaeropsis*,[4] which thus seems to occur as a (nearly) racemic mixture in the sponge-associated fungus (Scheme 7).



Scheme 7. Elucidation of the absolute configuration of the natural anthraquinone **18**[4] by the oxidative degradation method: (b) $RuCl_3$, $NaIO_4$; (c) GC–MS analysis on a chiral CDX-B phase

3. Conclusion

In summary, the technique of the Ru(VIII)-mediated oxidative degradation has been extended to the analysis of the absolute configuration of a series of chiral compounds with stereocenters bearing a benzylic hydroxy or methoxy group. The procedure is simple, requires only small amounts of the analyte, and leads to reliable results.

4. Experimental

Optical rotations were measured on a Perkin–Elmer polarimeter. $RuCl_3 \cdot H_2O$ was purchased from Heraeus Feinchemikalien und Forschungsbedarf GmbH, Germany. Sodium phosphate buffer (0.1 M) was prepared by dissolving 1.38 g (10 mmol) $NaH_2PO_4 \cdot H_2O$ in 100 mL water and adjusting to pH 6 with 0.1 M NaOH. Reference material of racemic α-acetoxypropionic acid (*rac*-**9**) and 1-phenylethanol (*rac*-**11a**) were obtained from Fluka and the enantiopure (*R*)-α-acetoxypropionic acid [(*R*)-**9**] was purchased from Merck-Schuchardt. (*R*)-α-(1-Naphthyl)ethanol [(*R*)-**12a**] was obtained from Aldrich and *rac*- and (*R*)-1-phenylpropanol [*rac*- and (*R*)-**13a**, respectively] were prepared according to literature protocols.[25] Compounds **5**, **6**, and **18** were provided from Professor Dr. G. Adam, Dr. M. Breuning, and Professor Dr. P. Proksch, respectively.

4.1. α-Acetoxybutyric acid *10*

Racemic material of **10** was obtained from racemic α-aminobutyric acid (purchased from Fluka) by reaction with $NaNO_2$ in acetic acid according to the literature[28] in 80% yield.

Enantiopure (*R*)-**10** was prepared by the same reaction, starting with (*R*)-α-aminobutyric acid (Fluka): $[\alpha]_D^{22}$ +30.7 (*c* 1.3, MeOH) [reported[29] $[\alpha]_D^{20}$ +36.2 (*c* 3.2, MeOH)].

4.2. α-Methoxypropionic acid *19*

Compound *rac*-**19** was prepared from racemic α-bromopropionic acid and sodium methoxide in 85% yield as described in the literature.[27]

The enantioseparation of **19** was achieved in analogy to the literature.[30] (–)-(*S*)-α-Methoxypropionic acid (*S*)-**19**: $[\alpha]_D^{22}$ –19.4 (*c* 1.0, $CHCl_3$) [reported[30] $[\alpha]_D^{20}$ –70.5 (pure liquid)].

4.3. General procedure for the acetylation of the benzylic alcohols

To a solution of the alcohol (ca. 1 mg) in 2 mL Et_2O, AcCl (3.0 equiv.) and NEt_3 (3.0 equiv.) were added and the mixture stirred for 6 h at room temperature. After extraction with 2 mL Et_2O, the organic solvent was dried over $MgSO_4$, evaporated and the resulting product was analyzed by oxidative degradation.

4.4. General procedure for the methylation of benzylic alcohols

The alcohol (ca. 1 mg) was dissolved in 1 mL Et_2O, NaH (1.0 equiv.) and Me_2SO_4 (1.0 equiv.) were added and the mixture was stirred at room temperature for 2 h. The reaction was stopped by adding 1 mL H_2O and the mixture extracted with 2 mL Et_2O. After evaporation of the organic solvent the product was analyzed by oxidative degradation.

4.5. Oxidative degradation procedure

The reactions were performed in analogy to the degradation of chiral amines as described previously.[17] To a stirred two-phase mixture of 150 μl of MeCN, 150 μl of CCl_4, and 300 μl of a 9.1 M sodium phosphate buffer (pH 6) in a 2.5 mL Wheaton screw-cap vial, an analytical amount (ca. 1 mg) of the chiral aryl compound and the catalyst $RuCl_3 \cdot H_2O$ (0.1 mg, 0.4 μmol) were added

at room temperature. Over a period of 60 min, 40 mg (183 μmol) of $NaIO_4$ were added in small portions, followed by stirring for another 1.5 h. To the resulting carboxylic acid, 700 μl of H_2O were added and the mixture was stirred for a short period. The aqueous solution was washed two times with 300 μl $CHCl_3$ and then lyophilized. The residue was extracted with 1.5 mL of dry MeOH, followed by separation of the insoluble inorganic salts by centrifugation. After evaporation of the solvent and dissolution in CH_2Cl_2 the mixture was filtered over a microfilter and the clear solution analyzed by GC–MS.

4.6. Capillary GC

GC–EI-MSD analyses were performed with a transfer-line temperature maintained at 280°C resulting in a source temperature of 170°C and an ionizing energy of 70 eV. Helium was used as the carrier gas with a column head pressure of 100 kPa. A CDX-B (J&W Scientific) column, 30 m×0.25 mm (i.d.)×0.25 μm with an on-column injector maintained at 210°C was used for enantiomer separation of α-acetoxypropionic acid **9** and α-acetoxybutyric acid **10**. Column temperature was programmed 5 min at 100°C, 5°C min^{-1} to 150°C for 5 min, 10°C min^{-1}, and finally held at 200°C for 5 min. For the separation of α-methoxypropionic acid **19** a β-DEX 325 (Supelco) column, 30 m×0.25 mm (i.d.)×0.25 μm was used. The on-column injector and column temperature were programmed as described before.

Acknowledgements

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