

CHIRAL 2-ALKYLBRANCHED ACIDS, ESTERS AND ALCOHOLS. PREPARATION AND STEREOSPECIFIC FLAVOUR EVALUATION

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Abstract: Racemic 2-alkylbranched acids are transformed to diastereomeric derivatives with (S)-2-hydroxy-3-phenylpropionic acid-N-methylamide or (S)-(-)-1-phenylethylamine and separated by liquid chromatography to pure diastereoisomers, which are subsequently hydrolyzed to yield optically pure acids. Enantiomeric alcohols are generated by LiAlH₄-reduction of the corresponding acids, esters are synthesized by different methods. The odour impression of the enantiomeric compounds is investigated.

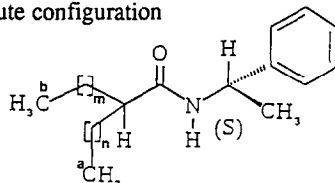
2-Alkylalkanoic acids, esters and alcohols are well appreciated aroma compounds of fruits and other foodstuffs ¹⁾. In particular 2-methylbutanoic acid and its esters are known to be important compounds of fruits like apples ²⁾ and pineapples ³⁾. Until now odour quality only was investigated with racemic substances of this type, although it is generally known that enantiomers may exhibit rather different odour sensations⁴⁾. 2-Alkylbranched acids and alcohols are important for pheromone synthesis and liquid crystal investigations, too. Recently, investigations on lipase-catalyzed enantioselective esterification of 2-methylalkanoic acids have been reported by Engel⁵⁾.

This paper now describes the generation of optically pure 2-methylbutanoic acid (**1**), 2-methylpentanoic acid (**2**), 2-methylhexanoic acid (**3**), 2-ethylhexanoic acid (**4**), the corresponding alcohols 2-methylbutan-1-ol (**5**), 2-methylpentan-1-ol (**6**), 2-methylhexan-1-ol (**7**), 2-ethylhexan-1-ol (**8**) and the esters ethyl-2-methylbutanoate (**9**) and prenyl-2-methylpentanoate (**10**).

In order to determine their absolute configurations racemic acids **1-4** were converted to diastereomeric amides with (S)-(-)-1-phenylethylamine (SPEA) and chromatographically (LC) separated into optically pure diastereoisomers. Diastereomeric amides were prepared either by a way earlier described by Kaneda⁶⁾ with equimolar ratio of free acid and free amide by catalysis of N,N'-Dicyclohexylcarbodiimide (DCC) in dry tetrahydrofuran (THF) or by an other way versus acid chloride and free amine under catalysis of 4-Dimethylaminopyridine (DMAP). Absolute configurations of the 2-alkylalkanoic acid moieties were elucidated by comparison with easily available (S)-2-methylbutanoic acid **1a** and by ¹H-NMR data of their diastereomeric (S)-1-phenylethylamides⁷⁾ (Helmchen's model), by chromatographic behaviour of these

amides in LC according to Helmchen *et al.*⁸⁾ and by comparison with gas chromatographic data from Sonnet⁹⁾ [For ¹H-NMR data of relevant shift of the two acyl-CH₃-groups see table 1, in LC on silica gel (R)-acid-SPEA eluted before (S)-acid-SPEA, in gas chromatography on Carbowax 20 m and DB 5 stationary phase (S)-acid-SPEA eluted prior to (R)-acid-SPEA].

Table 1: Characteristic ¹H-NMR-data (Acyl-CH₃-signals, δ-values, [ppm]; 300 MHz, CDCl₃/TMS) of diastereomeric (S)-1-phenylethylamine-derivatives of 2-alkylbranched acids used for the determination of the absolute configuration



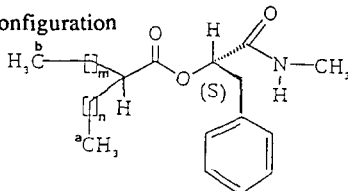
absolute configuration	(1) m=0;n=1		(2) m=0;n=2		(3) m=0;n=3		(4) m=1;n=3	
acyl-group	a-H t; 3H	b-H d; 3H	a-H t; 3H	b-H d; 3H	a-H t; 3H	b-H d; 3H	a-H t; 3H	b-H t; 3H
S	0,86	1,14	0,87	1,14	0,84	1,14	0,82	0,91
R	0,91	1,11	0,91	1,11	0,89	1,12	0,90	0,82

The optically pure amides were hydrolyzed (1:1/v+v; mixture of 25% HCl/glacial acetic acid, 8-15 h, 110 °C) to yield optically active acids **1-4**. Optical purity was not in all cases 100%, 2-methylbutanoic acid and especially 2-ethylhexanoic acid interconverted slightly during hydrolysis of the amides.

In order to prepare optically pure 2-methylbutanoic acid (**1**), 2-methylpentanoic acid (**2**) and 2-ethylhexanoic acid (**4**) the chiral auxiliary (S)-2-hydroxy-3-phenylpropionic acid-N-methylamide was used. Diastereomeric (S)-2-[2-alkylalkanoyloxy]-3-phenylpropionic acid-N-methylamides were separated by LC and subsequently hydrolyzed with a small excess of alkali to yield optically pure 2-alkylbranched acids¹⁰⁾. Diastereomeric derivatives of this type were synthesized under DMAP-catalysis by the reaction of an equimolar ratio of the acid chloride of racemic 2-alkylakanoic acid with (S)-2-hydroxy-3-phenylpropionic acid in dry methylene chloride. After isolation the (S)-2-[2-alkylalkanoyloxy]-3-phenylpropionic acid was treated with oxalylchloride. The resulting acid chloride reacted with a 33% solution of methylamine in dry ethanole (Fluka). After purification diastereoisomers were separated by liquid chromatography on silica gel, to yield optically pure acids alkaline hydrolysis was performed (1.1 mol excess of KOH in dist. water after solution of the derivative in acetone, stirring 5h at room temperature, extraction after acidification).

The absolute configurations of these acids were assigned via the corresponding (S)-1-phenylethylamides⁷⁻⁹⁾. The optical purity control of the free acids was performed by capillary gas chromatography (CGC)-analysis on heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (permethyl-β-cyclodextrin) or heptakis(2,3,6-tri-O-ethyl)-β-cyclodextrin (perethyl-β-cyclodextrin) as stationary phases^{10,12)}. Additionally ¹H-NMR-spectroscopy was applied, analogously to the model of Helmchen for (S)-(-)-1-phenylethylamides⁷⁾. All acids were chemically purified by LC on silicagel with a pentane/diethylether-gradient¹⁰⁾.

Table 2: $^1\text{H-NMR}$ -data (Acyl- CH_3 -signals, δ -values, [ppm]; 300 MHz, CDCl_3/TMS) of diastereomeric (S)-2-hydroxy-3-phenylpropionic acid derivatives of 2-alkylbranched acids used for the determination of the absolute configuration



absolute configuration	(1) m=0;n=1		(2) m=0;n=2		(4) m=1;n=3	
	a-H t; 3H	b-H d; 3H	a-H t; 3H	b-H d; 3H	a-H t; 3H	b-H t; 3H
S	0,84	1,05	0,87	1,05	0,85	0,74
R	0,78	1,09	0,83	1,09	0,84	0,81

An X-ray structural analysis¹¹⁾ was made of (S)-2-[(R)-2-methylpentanoyloxy]-3-phenylpropionic acid-N-methylamide (**11**) (fig. 1).

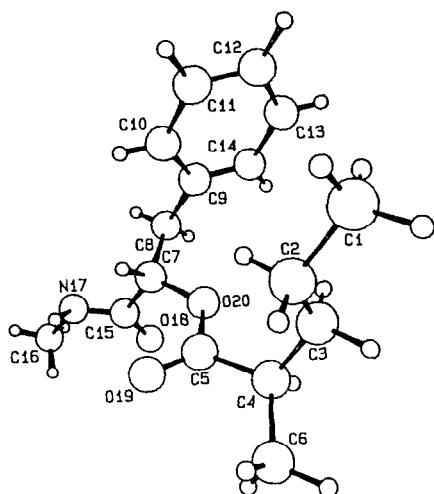


Figure 1. Molecular structure of (S,R)-11. Selected bond distances (Å) and angles ($^\circ$) for the molecule shown are as follows: O18-C15 1.225(8), O19-C5 1.194(8), O20-C5 1.353(7), O20-C7 1.435 (7), C4-C5 1.52 (1), C4-C6 1.51 (1), C7-C8 1.531 (8), C7-C15 1.522(8) Å, C5-O20-C7 114.8(5), C3-C4-C5 109.91(7), C3-C4-C6 116.9(8), O20-C5-C4 110.9(6), O20-C7-C8 106.7(5), O20-C7-C15 110.2(5), C8-C7-C15 110.7(5) $^\circ$

As outlined in table 3 rather different odour qualities of enantiomers (optical purity $>98\%$ ee) were found. It can be observed that the odour of (S)-2-methylbutanoic acid is similar to that one of (R)-2-methylpentanoic acid, while the corresponding enantiomers show different odour qualities. It is known that (S)-2-methylbutanoic acid and (S)-2-methylbutan-1-ol are found in natural food in a high excess¹⁰⁾. About the absolute configuration of the other 2-alkylalkanoic acids, esters and alcohols in food nothing is known until now.

Alcohols were made by reduction of the chemically purified acids with LiAlH_4 . For odour of chiral alcohols see table 3. A control of optical purity is possible by gas chromatography on perethylated β -cyclodextrin phase^{10,12)}.

Esters were made in different ways. Prenyl (3-methyl-2-buten-1-yl) esters of 2-methylpentanoic acid, whose odour has been described as black currant-like¹³⁾, were synthesized via acid chlorides of optically

pure (R)- and (S)- 2-methylpentanoic acid. A slight interconversion (enantiomer distribution 90:10) was observed. Optically pure ethyl-2-methylbutanoates were prepared via the potassium salts of 2-methylbutanoic acid (1 mmol) with ethyliodid (5 mmol) in dry dimethylformamide (7,5 ml) according to Mosandl ¹⁴). For sensory description of the esters, see table 3; optical purity control of ethyl-2-methylbutanoates was carried out by CGC on perethylated β -cyclodextrin-phase ¹²).

Table 3: Odour of the investigated enantiomers

Substance	(R)-enantiomer	(S)-enantiomer
1	penetrating cheesy-sweaty note	pleasant sweet, fine fruit note
2	pleasant sweet, fruit note	sweet, pungent, heavy
3	sweet, sweaty	sour, pungent, musty
4	herbaceous-earthly	sweet-herbaceous, mild musty
5	pleasant, earthy musty	pungent, etheric fruity
6	etheric, musty	first bloomy, then earthy musty
7	violetlike, bloomy-sweet, heavy	sweet, some bloomy with musty note
8	heavy, earthy, some bloomy note	light, sweet bloomy odour
9	first medical-phenolic note, then fruity-sweet but unspecific	etheric, sweetly, unspecific, pleasant apple note at extreme dilution
10	musty, sweetly, fruity, weak chemical	reminiscent of black currant

References and Notes

- H. Maarse, C.A. Visscher, Volatile Compounds in Food, Qualitative and Quantitative Data, Vol. I-III., CIVO-TNO, Zeist, the Netherlands (1989) and references cited therein.
- R.A. Flath, D.R. Black, W.H. Guadagni, W.H. McFadden, T.H. Schultz, J. Agric Food Chem. **15** (1967) 29.
- H. Ohta, S. Kinjo, Y. Osajima, J. Chromatogr. **409** (1987) 409.
- G. Ohloff, Experientia **42** (1986) 271.
- K.-H. Engel, Tetrahedron Asymm. **2** (1991) 165
- T. Kaneda, J. Chromatogr. **366** (1986) 217.
- G. Helmchen, Tetrahedron Lett. (1974) 1527.
- G. Helmchen, H. Völter, W. Schühle, Tetrahedron Lett (1977) 1417.
- P.E. Sonnet, A.T. Proveaux, E. Adamek, H. Sugie, R. Sato, Y. Tamaki, J. Chem. Ecol. **13** (1987) 547.
- K. Rettinger, Chirale Fruchtaromastoffe - 2-alkylverzweigte Säuren, Ester und Alkohole, doctoral thesis Univ. Frankfurt (1991).
- Crystal data: *II*, O₃NC₁₆H₂₃, monoclinic, space group P2₁, a = 9.302(2) b = 9.332(2) c = 9.550(2) β = 95.02(2) V = 825.8 Å³, (Z = 2, density = 1.76 mg/mm³), MoK α -Strahlung, λ = 0.70930 Å, Graphit-Monochromator, ω Θ -Abtastung). Of 1647 measured intensities 1451 were considered observed ($I_{\text{obs}} > 3 \sigma(I_{\text{obs}})$). The use of direct methods to the received data (SHELXS86) allowed to solve the structure. Subsequent refinement (least-squares) afforded R₁ and R₂-values of 0,049 and 0,043 respectively. Complete data have been deposited at the Fachinformationszentrum Energie, Physik, Mathematik, D-7514 Eggenstein-Leopoldshafen 2; deposition No. CSD 555 99.
- K. Rettinger, V. Karl, H.-G. Schmarr, F. Dettmar, U. Hener, A. Mosandl, Phytochem. Anal. (1991), in press.
- R.D. Schmid, Fette, Seifen, Anstrichmittel **88** (1986) 555.
- A. Mosandl, Struktur und Geruch substituierter Glycidsäureester, Habilitationsschrift Würzburg (1981), p. 111.