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SYNTHESES OF THE STEREOISOMERS OF 17,21-DIMETHYLHEPTATRIACONTANE - SEX RECOGNITION PHEROMONE OF THE TSETSE FLY[1,2]

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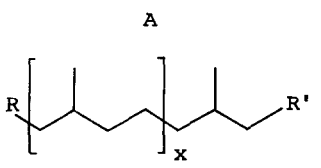
S.The title compounds were obtained both by application of directed resolution via diastereomeric amides and a novel asymmetric synthesis via ester enolates.

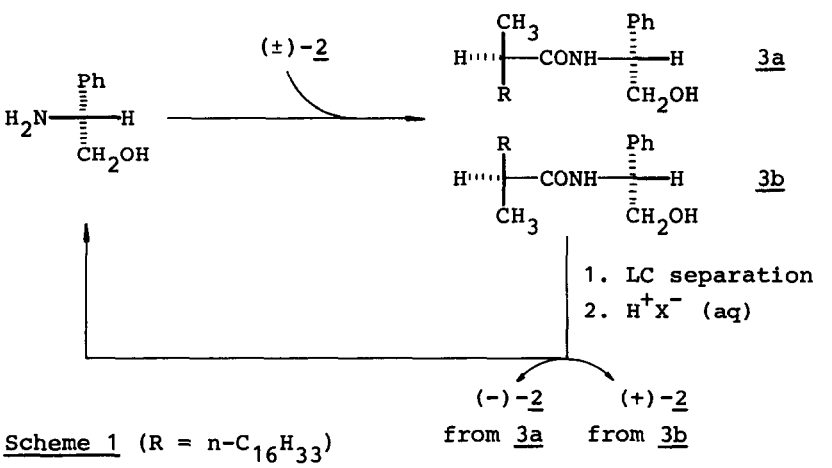
A number of branched hydrocarbons of general structure A (R,R' = n-alkyl) were recently demonstrated in various fly species and were shown to release mating behaviour in the male at short range or upon contact:



x	R	R'		
0	$C_{13}H_{27}$	$C_{17}H_{35}$		Stable fly (Stomoxys calcitrans)[3]
1	$C_{13}H_{27}$	$C_{13}H_{27}$		
1	$C_{15}H_{31}$	$C_{15}H_{31}$	(1)	Tsetse fly (Glossina morsitans morsitans)[4]
1	$C_{13}H_{27}$	$C_{17}H_{35}$		
2	$C_{13}H_{27}$	$C_{13}H_{27}$		

As information about stereochemical aspects of these compounds (configuration of the natural hydrocarbons, relationship between configuration and biological activity) was not available we have synthesized the complete set of stereoisomeric 17,21-dimethylheptatriacontanes, (R,R)-, (S,S)- and (R,S)-1. In addition to being biologically relevant, simple pheromones such as these are excellent models for the demonstration of new stereochemical methods[5]. In the present case 2-methyloctadecane derivatives (scheme 2, compounds 2,4,8) served as chiral building blocks. They were obtained by either enantiomer resolution or asymmetric synthesis methods developed in this laboratory.

Using our method of directed resolution of carboxylic acids via liquid chromatography (LC) of diastereomeric amides with (R)-phenylglycinol (or similar amino alcohols) we can obtain both enantiomers of any 2- or 3-methylalkanoic acid in a completely controlled way and in high yield[6]. The application of this method to 2-methyloctadecanoic acid ((±)-2) is depicted by scheme 1 and fig. 1. Reaction of the carboxylic acid chloride of (±)-2 with (-)(R)-phenylglycinol (ep = 99 %)[7] gave a mixture of the diastereomeric amides 3a and 3b. Their complete separation was achieved at a throughput of ca. 4 g per hour on a high performance preparative LC system developed in this laboratory[8] (chromatographic conditions see fig. 1). Purity of the final fractions was ascertained by HPLC[9].



Scheme 1 (R = n-$C_{16}H_{33}$)

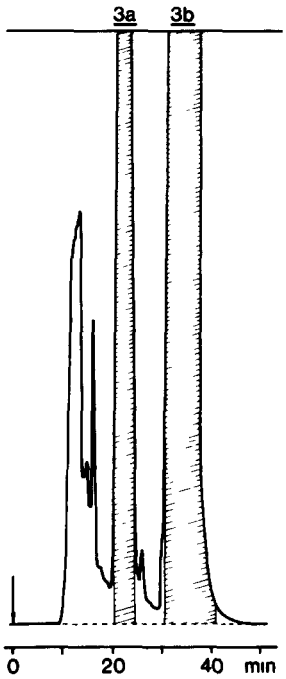
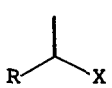
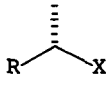
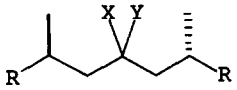


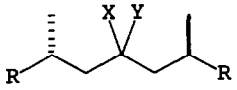
Fig. 1. Preparative LC separation of the diastereomeric amides 3a and 3b. Column: 45 × 4 cm, 270 g silica gel Merck LiChroprep 15-25 µm (9000 theoretical plates, standard test conditions: naphthalene, hexane-ethyl acetate 95/5 (50 ml/min));eluent: chloroform-ethyl acetate 6/4 (30 ml/min); detector: UV 254 nm; substance load: 3 g of raw reaction product, dissolved in 60 ml eluent.

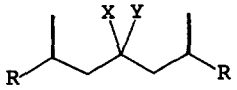
Scheme 2 (R = n-$C_{16}H_{33}$)


(R)


(S)


(17R,21R)


(17S,21S)

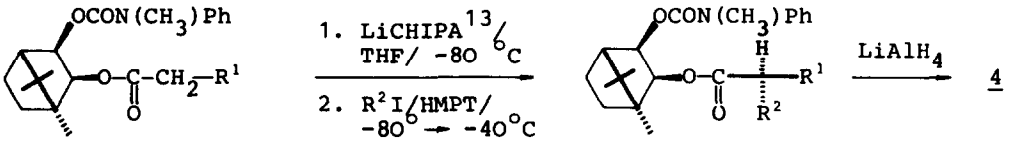

(17R,21S) (meso)

	X
2	COOH
4	CH_2OH
8	CH_2I
9	$CH(COO\text{-}n\text{-}Bu)_2$

	X	Y
10	COO-n-Bu	COO-n-Bu
11	COOH	COOH
12	H	COOH
13	H	I
1	H	H

Saponification of 3a (dioxane-H_2SO_4 (aq)) produced (-)(R)-2 which was crystallized once from methanol (80 % yield from (±)-2), mp 53.5-54 °C, $[\alpha]_D^{25} = -9.7°$ (c = 9.0, $CHCl_3$). In the same manner (+)(S)-2 was obtained from the amide 3b. Both acids were 99 ± 0.5 % enantiomerically pure (HPLC of diastereomeric 1-phenylethylamides[10]). Their absolute configuration is assigned by our rules described in [6]. The assignment is in agreement with a previous chemical correlation[11]. Reduction of the carboxylic acids ($LiAlH_4$) proceeded quantitatively to give the alcohols (+)(R)- and (-)(S)-4, mp 44-45 °C, $[\alpha]_D^{22} = \pm 5.5°$ (c = 5.0, benzene).

In an alternative synthesis, the enantiomerically pure alcohols (R)- and (S)-4 were obtained via asymmetric alkylation of ester enolates derived from novel chiral reagents recently developed in this laboratory[12]:



	R^1
5	CH_3
7	n-$C_{16}H_{33}$

	R^1	R^2
6a	CH_3	n-$C_{16}H_{33}$
6b	n-$C_{16}H_{33}$	CH_3

Alkylation of the propionate 5 with n-hexadecyl iodide proceeded with very high asymmetric induction to give esters 6a/6b. The ratio of the diastereomers was determined as 93:7 (de = 86 %) by HPLC. The minor component was easily separated off on the aforementioned preparative LC system (α = 1.3, petroleum ether-ethyl acetate 92/8). Reduction of the pure major isomer, 6a, obtained in 83 % yield from 5, followed by filtrative chromatographical removal of 2,3-bornanediol furnished enantiomerically pure (-)(S)-4 (95 % yield). Exchange of the two alkyl groups, i. e. alkylation of the n-octadecanoate 7 with methyl iodide, resulted in a mixture 6a/6b with the diastereomer ratio reversed to 10:90. Further processing as above yielded (+)(R)-4 (80 % yield from 7).

From this and related work[14] it appears that high induction asymmetric synthesis in combination with LC diastereomer purification constitutes a very efficient technique for the preparation of enantiomerically pure compounds in quantities of up to ca. 20 g.

As the synthons (R)- and (S)-4 were conveniently available, the final steps of the syntheses were straightforward (scheme 2). Treatment of (+)(R)-4 with hydroiodic acid gave the iodide (R)-8 (98 %, oil). Reaction of this with di-n-butyl malonate (n-butanol, NaOBu, 50 °C, 20 h) followed by LC separation of the products (gradient: petroleum ether-dimethoxyethane 0 → 0.8 %, UV detection at 220 nm) produced monoalkylmalonate (R)-9 (8 %, oil), dialkylmalonate (R,R)-10 (46 %),

mp 41-42 °C, $[\alpha]_D^{22}$ = + 4.6° (c = 10, benzene), and 2-methyloctadecene (20 %). (R,R)-10 was saponified and the product, (R,R)-11, decarboxylated to give monocarboxylic acid (R,R)-12 which without purification was subjected to iododecarboxylation[15] to afford iodide (R,R)-13 which was purified by LC (yield 78 % based on 10), mp 55-56 °C, $[\alpha]_D^{22}$ = - 5.5° (c = 5.0, CCl_4). Reduction of the latter (Zn/CH_3COOH) produced the hydrocarbon (R,R)-1 contaminated with ca. 5 % alkenes (GLC, OV 101, 270 °C) which were removed by filtration through a column of silica gel coated with silver nitrate (20 %, eluent hexane). (R,R)-1 crystallizes from pentane as large rectangular plates, mp 51.5 °C, $[\alpha]_D^{25}$ = - 0.3° (c = 5.0, hexane). The enantiomer, (S,S)-1, was obtained from (S)-4 via the same sequence of reactions and showed identical physical properties except for the sign of the optical rotation.

The meso-isomer (R,S)-1 was prepared by reacting monoalkylmalonate (R)-9 with the iodide (S)-8 to give the dialkylmalonate (R,S)-10 (61 %), optically inactive oil, from which the hydrocarbon (R,S)-1 was obtained as described above. (R,S)-1 crystallizes from the melt or from pentane solution as needles, mp 36-37.5 °C.

Tests are being carried out by Dr. Langley (Tsetse Research Laboratory, Bristol) to establish the biological activity of the three isomeric hydrocarbons.

1 Directed Resolution of Enantiomers via Liquid Chromatography of Diastereomeric Derivatives, Part 7; Part 6: G.Helmchen, G.Nill, Angew.Chem. 91, 66 (1979); Angew.Chem.Int.Ed.Engl. 18, 65 (1979).

2 Support of this research by the Deutsche Forschungsgemeinschaft (grant He 880/6) is gratefully acknowledged.

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7 Commercially available material (Sigma) was used. We have since found that this compound may be prepared easily by reducing the comparatively cheap (R)-phenylglycine with $LiAlH_2(OCH_3)_2$ and subsequently crystallizing the hydrochloride (ep = 99.8 %, yield > 90 %); G.Helmchen, A.Selim, to be published.

8 B.Glatz, G.Helmchen, to be submitted; a detailed description of the system is available from G.H. upon request: G.Helmchen, B.Glatz, Ein apparativ einfaches System und Säulen höchster Trennleistung zur präparativen Mitteldruck-Flüssigkeitschromatographie, Universität Stuttgart 1978; due to a very high separation factor, α = 2.6, separation of 3a and 3b would be possible with much less sophisticated equipment.

9 All the new compounds described herein gave correct elemental analyses and spectra.

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12 R.Schmierer, G.Heiligenmann, G.Helmchen, to be published.

13 LiCHIPA = lithium cyclohexylisopropylamide.

14 We have been using this technique over the last two years (asymmetric ester alkylations and Diels-Alder reactions) as have other investigators in the field of asymmetric synthesis, A.I.Meyers, J.Slade, R.K.Smith, E.D.Mihelich, F.M.Hershenson, C.D.Liang, J.Org.Chem. 44, 2247 (1979).

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