Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 14 August 2009, Revised 14 October 2009, Accepted 18 October 2009 Published online 25 November 2009 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1696

Influence of [^{2}H]-labelled acetic acid as solvent in the synthesis of [^{2}H]-labelled perhexiline

Søren Christian Schou*

Preparation of deuterium-labelled perhexiline from an unsaturated analogue was performed via reduction with deuterium gas and PtO_2 in acetic acid. Low incorporation was observed when using acetic acid as solvent (most abundant mass peak was M^+_{D0}), but when changing the solvent to deuterium-labelled acetic acid, e.g. acetic acid-OD or acetic acid-d_4, a higher incorporation was observed (most abundant mass peak was M^+_{D8}). Using hydrogen gas instead of deuterium gas with deuterium-labelled acetic acid, high levels of deuterium incorporation were observed (most abundant mass peak was M^+_{D5}). An attempt to reduce a precursor with a fully deuterated pyridine to obtain perhexiline with a higher content of deuterium failed.

Keywords: perhexiline; deuterium; platinum oxide; labelled acetic acid

Introduction

Racemic perhexiline (**1**) is used as a prophylactic agent for the treatment of angina and is thought to act by inhibiting mitochondrial carnitine palmitoytransferase-1. This shifts myocardial metabolism from fatty acid to glucose utilization that results in increased ATP production with the same O_2 consumption and consequently increases myocardial efficiency. Perhexiline is indicated to reduce the frequency of moderate to severe attacks of angina pectoris due to coronary artery disease in patients that have not responded to other conventional therapy or for patients where such therapy may be contraindicated. Its clinical use has been limited by its narrow therapeutic window and high inter and intraindividual pharmacokinetic variability (Figure 1).

In an attempt to make deuterated perhexiline to be used as internal standard for GC-MS analysis, direct H/D exchange protocols using $(PPh_3)_3RuCl_2$ or $(CO)_6Ru_2Cl_4$ as described in the literature were used.[1] Unfortunately, the outcome of these reactions was a low incorporation of deuterium into the molecule, affording a product which was useless as an internal standard. Thus, we decided to prepare deuterated perhexiline via catalytic reduction with deuterium gas of a suitable unsaturated precursor.

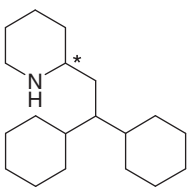
Results and discussion

The unsaturated analogue of perhexiline, 2-(2,2-dicyclohexyl-vinyl)-pyridine **4**, to be used as starting material for the catalytic reduction with deuterium gas, was synthesised in a one pot reaction in 59% yield. 2-Picoline (**2**) was deprotonated with *n*-BuLi at −78°C, and subsequently dicyclohexyl-methanone (**3**) was added at −20°C to the prepared lithium species. After 10 min, the reaction mixture was cooled to −78°C, and $SOCl_2$ was added to facilitate the dehydration during warm-up. Two unsaturated perhexiline precursors **4** (59%) and **5** (34%) were isolated (Scheme 1).

An alternative route to suitable precursors for deuterated perhexiline is shown in Scheme 2, where the intermediate **6** is isolated before dehydration.

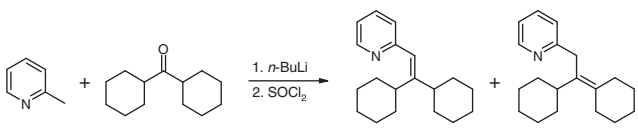
Dehydration was carried out by refluxing compound **6** in conc. HCl for 1 h, affording the two dehydration products **4** and **7** in 44 and 37% yield, respectively.

Following the same procedure as described above (Scheme 1) starting from 2-picoline-d_7, the deuterated perhexiline precursor **8** (Figure 2) was prepared, but in an unexpected low yield of 20%. When preparing compound **8,** two byproducts, the 6-butyl pyridine derivatives **9** and **10**, were observed and could be isolated as a



1

Figure 1. The structure of (±)-perhexiline.

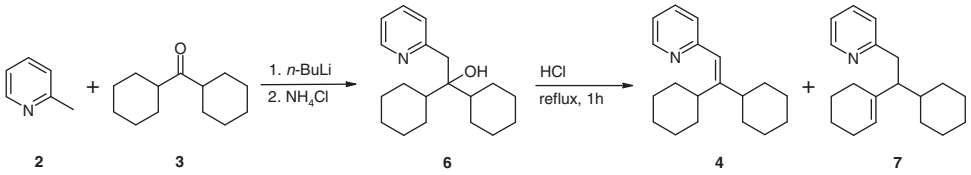


2 **3** **4** **5**

Scheme 1. Preparation of perhexiline precursors.

LEO Pharma, Medicinal Chemistry Research, Industriparken 55, DK-2750 Ballerup, Denmark

**Correspondence to: Søren Christian Schou, LEO Pharma, Medicinal Chemistry Research, 55 Industriparken, DK-2750 Ballerup, Denmark.*
E-mail: soeren.schou@leo-pharma.com



Scheme 2. Alternative route to suitable precursors.

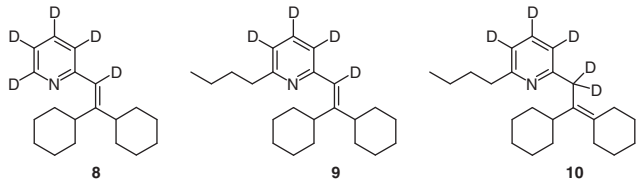
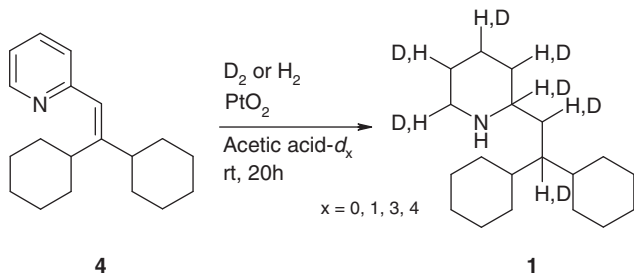


Figure 2. The structure of **8**, **9** and **10**.



Scheme 3. General reduction setup.

mixture in an amount corresponding to 37% yield. These byproducts (unlabelled) were not observed in the synthesis of compound **4**.

The formation of **9** and **10** occurred by reaction of the butyl anion from *n*-BuLi with the pyridine ring. Such addition products have been observed before.[2,3]

Compound **4** and the deuterium-labelled compound **8** were selected as precursors for the catalytic reduction experiments.

For the reduction of the pyridine moiety to the corresponding piperidine, a method recently reported by Birman *et al.*[4] was used, using PtO_2 in acetic acid at ambient pressure and temperature.

A straightforward reduction of compound **4** with deuterium gas should label perhexiline with 7 deuterium atoms (Scheme 3). An analysis of the reaction mixture using LC-MS showed that the most abundant mass was not M^+_{D7} but M^+_{D1}, demonstrating that the precursor had been reduced mainly with hydrogen (protium) and not deuterium. The source of protium had to be the acetic acid. Experiments using different variants of deuterium-labelled and non-labelled acetic acid as solvents should identify the protium source.

The crude reaction mixtures were filtered through a syringe filter before GC-MS analysis. The volatility of a compound changes with the degree of deuteration[5] which causes the mass spectra to change slightly across the GC-peak. To get a precise determination of the degree of deuteration, the mass, M^+_{D1}, M^+_{D2}, etc., were extracted from the chromatogram using the software Xcalibur (ver. 2.07 provided by Thermo), and thereby a 'corrected' mass spectrum, based on the area from the ion count, could be obtained. The 'corrected' mass spectra are shown in Table 1.

For experiments carried out under a deuterium atmosphere, using acetic acid-OD or acetic acid-d_4 as solvent gave the highest incorporation level of deuterium (M^+_{D7} was dominant peak). Using acetic-d_3 acid low incorporation of deuterium was observed and the most dominant peak was M^+_{D1}. Using acetic acid, a higher M^+_{D1} peak was observed (85 versus 26 in perhexiline), but still with M^+_{D0} as the most dominant peak.

Table 1. Corrected mass spectra from the different experiments

		Peak intensities found in the GC-MS														
Solvent	Gas	M^+_{D0}	M^+_{D1}	M^+_{D2}	M^+_{D3}	M^+_{D4}	M^+_{D5}	M^+_{D6}	M^+_{D7}	M^+_{D8}	M^+_{D9}	M^+_{D10}	M^+_{D11}	M^+_{D12}	M^+_{D13}	M^+_{D14}
Acetic acid	D_2	100	85	47	15	5	1	—	—	—	—	—	—	—	—	—
Acetic acid-OD	D_2	1	1	2	3	8	19	53	90	100	68	33	6	4	—	—
Acetic-d_3 acid	D_2	93	100	38	32	—	—	—	—	—	—	—	—	—	—	—
Acetic acid-d_4	D_2	2	1	3	3	5	10	100	68	100	85	49	15	3	2	—
Acetic acid	H_2	100	25	3	1	—	—	—	—	—	—	—	—	—	—	—
Acetic acid-OD	H_2	9	18	41	76	94	100	78	38	16	6	2	—	—	—	—
Acetic-d_3 acid	H_2	100	20	4	3	—	—	—	—	—	—	—	—	—	—	—
Acetic acid-d_4	H_2	6	15	29	71	92	100	81	51	24	7	3	—	—	—	—
Perhexiline		100	26	—	—	—	—	—	—	—	—	—	—	—	—	—

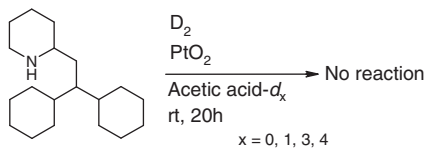
When performing the reduction under a hydrogen atmosphere, a high degree of incorporation was seen in the experiments using acetic acid-OD or acetic acid-d_4 (M^+_{D5} was dominant peak). Using acetic-d_3 acid or acetic acid as solvents, no incorporation of deuterium was observed. This showed that the exchangeable acidic protons were involved in the reduction. The catalyst promotes the exchange of the exchangeable acidic deuterium with the hydrogen gas affording deuterium gas. Such effects have been reported before, not with deuterium-labelled acetic acid but with deuterated ammonium formate in deuterated methanol[6] or D_2O.[7–10] Derdau[6] has reported the preparation of labelled piperidines, piperazines and tetrahydroquinolines using Pd/C and deuterated ammonium formate in deuterated methanol, and Sajiki *et al.*[9] showed that D_2 can be generated *in situ* by stirring D_2O under a H_2 atmosphere with Pd/C as catalyst for the exchange reaction.

An equilibrium mixture of acetic acid (-OD) and H_2-gas in our experiments would have an approximate molar ratio D/H = 93/7 (500 μL acetic acid-OD = 8.3 mmol D and 7 mL H_2-gas = 0.6 mmol H). The outcome of the reduction with such a mixture would result in labelled perhexiline with a predicted highest molar ion at M^+_{D6}. A fast reduction with H_2-gas, before any substantial exchange of H and D has taken place, would result in no or little deuterium incorporation. The highest peak was observed at M^+_{D5}, which shows that reduction takes place with a fully (or nearly) equilibrated H/D-mixture.

Esaki and co-workers[11] have reported a direct deuterium transfer from D_2O to the product when performing H/D exchange reactions in alkyl-substituted benzene derivatives in a Pd/C–H_2–D_2O system.

To investigate whether a direct deuterium/hydrogen exchange takes place between acetic acid-OD and the aromatic precursor **4** prior to reduction, remaining starting material from the reduction was analysed. MS-Analysis showed the same mass peak as for non-reacted precursor, with 269 as the dominant peak. Thus, no direct deuterium transfer from acetic acid-OD to the precursor occurred.

In an attempt to make perhexiline with a higher content of deuterium, **8** was used as the precursor. Surprisingly, neither D_2 nor H_2 could reduce compound **8** to the corresponding piperidine using the same conditions as used for the reduction of **4**.



1

Scheme 4. Setup to investigate a potential H/D exchange.

To investigate a potential H/D exchange in the final product formed by the reduction, a set of experiments was performed using the same conditions as used for the reduction (Scheme 4).

These experiments showed that no H/D exchange took place in the product perhexiline under the standard conditions given in Scheme 4 (Table 2).

To obtain high levels of deuterium incorporation, reductions should be performed in OD-solvents.

Conclusion

In conclusion, the deuterium found in the product comes from reduction of the double bonds. No subsequent H/D exchange reaction was observed. The highest level of deuterium incorporation was observed when acetic acid-OD and deuterium gas was used. Using acetic acid (-OH) lower levels of incorporation was observed, proving that the exchangeable proton is taking part in the reduction. No direct deuterium transfer from OD-labelled acetic acid was observed. Due to the fast equilibrium $2CH_3COOD + H_2 \rightleftharpoons 2CH_3COOH + D_2$, catalysed by PtO_2, reduction of the unsaturated perhexiline precursor **4** will give perhexiline labelled with deuterium at a level that reflects the amount of deuterium in the total proton/hydrogen-gas pool.

Experimental

General

All reactions were performed in a stainless steel manifold purchased from RC Tritec, Teufen, Switzerland. D_2 (99.8 atom % D) was purchased from Isotec, H_2 (99.996%) was purchased from Sigma-Aldrich. THF was dried over molecular sieves (4 Å). All other solvents and reagents were used as received, purchased from Sigma-Aldrich.

^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AV600 spectrometer with a 5 mm TCI-Cryoprobe or a Bruker DRX500 spectrometer with a 5 mm PAPPI-probe. Chemical shifts are reported in ppm with tetramethylsilane (TMS, $\delta = 0.00$) as internal reference. All air and moisture sensitive reactions were carried out in oven-dried (120°C) glassware under an inert atmosphere of argon. Column chromatography was performed using silica gel 60 (Merck) (70–230 mesh).

Standard procedure for reduction

PtO_2 (8 mol%) was weighed into a 4 mL round bottom reaction flask containing a Teflon-coated stir bar (3 × 10 mm). The substrate (0.037 mmol), dissolved in dry solvent (500 μL), was added. The reaction mixture was frozen in liquid N_2 and evacuated (below 3.5×10^{-3} mbar), thawed and then stirred

Table 2. Corrected mass spectra from the experiments investigating a possible H/D exchange reaction

	Peak intensities found in GC-MS							
Solvent	M^+_{D0}	M^+_{D1}	M^+_{D2}	M^+_{D3}	M^+_{D4}	M^+_{D5}	M^+_{D6}	M^+_{D7}
Acetic acid	100	25	4	1	—	—	—	—
Acetic acid-OD	100	28	5	1	—	—	—	—
Acetic-d_3 acid	100	35	6	1	—	—	—	—
Acetic acid-d_4	100	31	5	1	—	—	—	—
Perhexiline	100	26	—	—	—	—	—	—

under D_2- or H_2-atmosphere (1340–722 mbar) for 20 h at rt. The reaction mixture was filtered through a syringe filter (Whatman, 0.45 μm) and concentrated *in vacuo* affording a colourless film.

*2-(2,2-Dicyclohexyl-vinyl)-pyridine (**4**)*

*2-(2-Cyclohexyl-2-cyclohexylidene-ethyl)-pyridine (**5**)*. Preparation A: 2-Methyl-pyridine (5 mmol, 465 mg, 494 μL) was dissolved in dry THF (15 mL) in a dry flask charged with argon. The solution was cooled to −78°C and *n*-BuLi (1.6 M in hexanes, 5 mmol, 3.125 mL) was added dropwise. The clear, colourless solution turned red/orange and became milky during the addition. The reaction mixture was allowed to warm-up to −20°C and dicyclohexyl-methanone (5 mmol, 971 mg, 985 μL, dissolved in dry THF (5 mL)) was added dropwise. The colourless solution was stirred at −20°C for 10 min and cooled to −78°C. $SOCl_2$ (7.5 mmol, 892 mg, 544 μL) was dissolved in dry THF (5 mL) and added dropwise affording a yellow reaction mixture. The reaction mixture was stirred for an additional 5 min at −78°C and then allowed to warm-up to rt. During warm-up the yellow solution turned beige and milky. The reaction mixture was stirred at rt for 30 min and then poured into a separation funnel containing sat. Na_2CO_3 (30 mL), EtOAc (30 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* affording 1.43 g of pale yellow oil. The oil was purified by silica gel chromatography using a gradient of heptane:ethyl acetate [100:0 → 83:17] affording compound **4** as a colourless oil in 59% yield (793 mg, 2.94 mmol) and compound **5** as colourless oil in 34% yield (460 mg, 1.70 mmol).

Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$)δ8.57 (dd, *J* = 4.8, 0.8, 1H), 7.59 (td, *J* = 7.7, 1.9, 1H), 7.14 (d, *J* = 7.9, 1H), 7.05 (ddd, *J* = 7.5, 4.9, 0.9, 1H), 6.31 (s, 1H), 3.07 (tt, *J* = 11.7, 3.4, 1H), 2.09 (dd, *J* = 13.8, 5.7, 1H), 1.76 (ddd, *J* = 16.2, 14.8, 8.7, 8H), 1.66–1.52 (m, 2H), 1.51–1.13 (m, 10H).

^{13}C NMR (126 MHz, $CDCl_3$)δ158.00, 149.23, 135.67, 123.64, 123.02, 120.40, 40.81, 40.08, 35.13, 30.70, 27.16, 26.31, 26.26, 26.15.

Compound **5**: ^{1}H NMR (600 MHz, $CDCl_3$)δ8.53–8.48 (m, 1H), 7.54 (td, *J* = 7.7, 1.9, 1H), 7.13 (d, *J* = 7.9, 1H), 7.05 (dd, *J* = 6.8, 5.2, 1H), 3.63 (s, 2H), 2.62 (ddd, *J* = 11.5, 7.5, 3.4, 1H), 2.32 (t, *J* = 5.4, 2H), 2.13–2.06 (m, 2H), 1.66 (dd, *J* = 10.1, 2.5, 2H), 1.61–1.54 (m, 5H), 1.48 (dd, *J* = 7.5, 4.0, 2H), 1.37 (d, *J* = 10.7, 2H), 1.29–1.16 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$)δ162.24, 148.96, 136.13, 135.96, 130.67, 121.92, 120.54, 40.92, 36.84, 31.78, 31.72, 30.21, 28.71, 28.14, 27.09, 26.75, 26.08.

*1,1-Dicyclohexyl-2-pyridin-2-yl-ethanol (**6**)*

2-Methyl-pyridine (3 mmol, 279 mg) was dissolved in dry THF (10 mL) in a dry flask charged with argon. The solution was cooled to −78°C and then *n*-BuLi (3 mmol, 1.9 mL) was added dropwise. The colourless clear solution turned red/orange during the addition of *n*-BuLi. The reaction mixture was allowed to warm-up to −20°C and dicyclohexyl-methanone (3 mmol, 583 mg, in dry THF (4 mL)) was added. The coloured reaction mixture turned colourless during the addition. The reaction mixture was stirred at −20°C for 10 min and the reaction was quenched with sat. NH_4Cl (20 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the desired product as colourless oil in quantitative yield (862 mg, 3 mmol) and Used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$)δ8.44 (d, *J* = 4.8, 1H), 7.60 (t, *J* = 7.7, 1H), 7.15 (d, *J* = 7.8, 1H), 7.14–7.10 (m, 1H), 6.32 (s, 1H), 2.97–2.84 (m, 2H), 1.83 (d, *J* = 12.6, 2H), 1.73 (dd, *J* = 28.4, 13.0, 6H), 1.61 (t, *J* = 11.7, 2H), 1.52 (t, *J* = 11.8, 2H), 1.36–1.02 (m, 8H), 0.96 (q, *J* = 12.2, 2H).

^{13}C NMR (151 MHz, $CDCl_3$)δ161.95, 147.82, 136.75, 124.52, 120.96, 77.81, 46.16, 39.15, 27.98, 27.94, 27.32, 27.18, 26.78.

*2-(2,2-Dicyclohexyl-vinyl)-pyridine (**4**)*

*2-(2-Cyclohex-1-enyl-2-cyclohexyl-ethyl)-pyridine (**7**)*. Preparation B: 1,1-Dicyclohexyl-2-pyridin-2-yl-ethanol (**6**) was dissolved in conc. HCl (50 mL) and heated to reflux for 1 h. The reaction mixture was allowed to cool to rt, and pH was adjusted to 10 using sat. Na_2CO_3. The basified reaction mixture was extracted with EtOAc (4 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* affording 798 mg crude product as colourless oil. The oil was purified by silica gel chromatography using a gradient of heptane:ethyl acetate [100:0 → 83:17] affording compound **4** as colourless oil in 44% yield (353 mg, 1.31 mmol) and compound **7** as colourless oil in 37% yield (302 mg, 1.12 mmol).

Compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$)δ8.50–8.45 (m, 1H), 7.50 (td, *J* = 7.6, 1.8, 1H), 7.02 (dd, *J* = 7.5, 4.8, 2H), 5.10 (s, 1H), 3.08 (dd, *J* = 13.2, 4.6, 1H), 2.62 (dd, *J* = 13.2, 11.2, 1H), 2.18–2.08 (m, 1H), 2.00–1.89 (m, 2H), 1.88–1.80 (m, 1H), 1.79–1.72 (m, 1H), 1.72–1.58 (m, 5H), 1.54–1.28 (m, 5H), 1.26–1.07 (m, 3H), 1.05–0.93 (m, 1H), 0.91–0.78 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$)δ162.19, 148.88, 137.53, 135.45, 123.87, 123.61, 120.43, 54.43, 40.09, 39.48, 31.73, 31.33, 26.73, 26.69, 26.66, 25.78, 25.23, 22.97, 22.73.

*2-(2,2-Dicyclohexyl-vinyl)-pyridine-d_5 (**8**)*

2-Methyl-pyridine-d_7 (2.5 mmol, 250 mg) was dissolved in dry THF (10 mL) in a dry flask charged with argon. The solution was cooled to −78°C and *n*-BuLi (1.6 M in hexanes, 2.5 mmol, 1.55 mL) was added dropwise. The clear, colourless solution turned red/orange and became milky during addition. The reaction mixture was allowed to warm-up to −20°C and then dicyclohexyl-methanone ((2.5 mmol, 486 mg, 492 μL) in dry THF (2 mL)) was added dropwise. The colourless solution was stirred at −20°C for 10 min and cooled to −78°C. $SOCl_2$ (3.75 mmol, 446 mg, 272 μL) in dry THF (2 mL) was added dropwise affording a yellow reaction mixture. The reaction mixture was stirred for an additional 5 min at −78°C and allowed to warm-up to rt. During warm-up, the yellow solution became beige and milky. The reaction mixture was stirred at rt for 30 min, poured into a separation funnel containing sat. Na_2CO_3 (20 mL), diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* affording 963 mg of light brown oil. The oil was purified by silica gel chromatography using a gradient of heptane:ethyl acetate [100:0 → 83:17] affording compound **8** as colourless oil in 20% yield (140 mg, 0.51 mmol).

^{1}H NMR (600 MHz, $CDCl_3$)δ3.06 (tt, *J* = 11.9, 3.3, 1H), 2.10 (ddd, *J* = 11.2, 8.2, 3.2, 1H), 1.83–1.71 (m, 6H), 1.71–1.63 (m, 2H), 1.59 (dd, *J* = 13.3, 1.6, 2H), 1.42 (qd, *J* = 12.3, 3.1, 2H), 1.37–1.14 (m, 8H).

^{13}C NMR (151 MHz, $CDCl_3$)δ157.90 (d, *J* = 29.5), 148.87 (dd, *J* = 52.5, 25.4), 135.32 (dd, *J* = 46.7, 22.1), 123.30 (dd, *J* = 49.1,

24.4), 122.61, 119.95 (dd, $J = 46.9$, 22.4), 40.75, 40.03, 35.11, 30.60 (d, $J = 17.1$), 27.14, 26.29, 26.23, 26.13.

Acknowledgement

I am grateful to my colleague, Gunnar Grue-Sørensen, Department of Medicinal Chemistry Research at LEO Pharma, for fruitful discussions and invaluable assistance and support, Lars Dencker Nielsen and Maj-Britt Sund, Department of New Products, for the GC-MS analysis and the Department of Spectroscopy and Physical Chemistry at LEO Pharma for obtaining high resolution NMR-spectra.

References

[1] E. Alexakis, M. J. Hickey, J. R. Jones, L. P. Kingston, W. J. S. Lockley, A. N. Mather, T. Smith, D. J. Wilkinson, *Tetrahedron Lett.* **2005**, *46*, 4291–4293. http://dx.doi.org/10.1016/j.tetlet.2005.04.095.

[2] A. O'Byrne, P. Evans, *Tetrahedron* **2008**, *64*, 8067–8072. http://dx.doi.org/10.1016/j.tet.2008.06.073.

[3] M. Parmentier, P. Gros, Y. Fort, *Tetrahedron* **2005**, *61*, 3261–3269. http://dx.doi.org/10.1016/j.tet.2004.10.100.

[4] V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, *9*, 3237–3240. http://dx.doi.org/10.1021/ol071064i.

[5] Ed. Hoffmann, Th. Baudson, B. Tilquin, *J. High Resolut. Chromatogr. Chromatogr. Commun.* **1987**, *10*, 153–155.

[6] V. Derdau, *Tetrahedron Lett.* **2004**, *45*, 8889–8893. http://dx.doi.org/10.1016/j.tetlet.2004.09.165.

[7] N. Ito, T. Watahiki, T. Maesawa, T. Maegawa, H. Sajiki, *Synthesis* **2008**, *2008*, 1467–1478. http://dx.doi.org/10.1055/s-2008-1067017.

[8] E. Hiroyoshi, A. Fumiyo, U. Miho, K. Masatsugu, M. Tomohiro, M. Yasunari, S. Hironao, *Chemistry* **2007**, *13*, 4052–4063. http://dx.doi.org/10.1002/chem.200601615.

[9] H. Sajiki, T. Kurita, H. Esaki, F. Aoki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 3521–3523. http://dx.doi.org/10.1021/ol048591b.

[10] H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Hirota, *Org. Lett.* **2004**, *6*, 1485–1487. http://dx.doi.org/10.1021/ol0496374.

[11] H. Esaki, F. Aoki, F, M. Umemura, M. Kato, T. Maegawa, Y. Monguchi, H. Sajiki, *Chemistry* **2007**, *13*, 4052–4063. http://dx.doi.org/10.1002/chem.200601615.