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Oxazepines and Thiazepines. XIX [1] Synthesis of Optically Active 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones**

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Optically active 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**14**–**17**) have been synthesized *via* resolution and chemical transformation of nitrocarboxylic acids **6**–**9**. Starting from the latter various optically active substances have been synthesized as well. Optical purity was checked by NMR spectroscopy.

(Keywords: Resolution; Optical purity; Optically active benzothiazepines)

Oxazepine und Thiazepine, 19. Mitt.:
Synthese optisch aktiver 2,3-Dihydro-1,5-benzothiazepin-4(5H)-one

Optisch aktive 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-one (**14**—**17**) wurden mittels Racematspaltung und weiterer chemischer Umsetzungen der Nitrocarbonsäuren **6**—**9** hergestellt. Ausgehend von optisch aktiven Carbonsäuren wurden außerdem verschiedene optisch aktive Verbindungen synthetisiert. Die optische Reinheit wurde mit Hilfe der NMR-Spektroskopie überprüft.

Introduction

First representatives of optically active 1,5-benzothiazepines were prepared by the resolution of 2,3-dihydro-2-carboxymethyl-1,5-benzothiazepin-4(5*H*)-one with brucine as early as 1927 [2]. Later, optical resolution of thiazesim (2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-phenyl-1,5-benzothiazepin-4(5*H*)-one) [3] and *cis*-2,3-dihydro-3-[4-(methylpiperazinyl)methyl]-2-phenyl-1,5-benzothiazepin-4(5*H*)-one [4] was

** Dedicated to Prof. Dr. *G. Snatzke* on the occasion of his 60th birthday.

carried out using (+)-tartaric acid. For the synthesis of the diltiazem (2,3-dihydro-3(*S*)-acetoxy-5-[2-(dimethylamino)ethyl]-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one), an antianginal drug, one of its intermediates was resolved with brucine [5]. Very recently optically active 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one derivatives possessing angiotensin converting enzyme inhibitory activity were synthesized from natural amino acid precursors [6, 7].

In the course of our studies on benzothiazepines, synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones substituted in position 2 were studied [19, 8, 9]. Optically active derivatives of such benzothiazepinones have hitherto been prepared in case the starting materials had substituents capable of salt formation [2–4]. For this reason, it seemed expedient to develop a procedure which leads to these benzothiazepinones via the resolution of one of their intermediates.

Although optically active benzothiazepines were synthesized since 1927, to our knowledge, their chiroptical properties have not yet been investigated, whereas chiroptical studies of benzodiazepines were described in several papers [10–14]. One of the aims of our present work was, therefore, to synthesize appropriate optically active benzothiazepines for circular dichroism studies*.

Results and Discussion

Nitrocarboxylic acids **6–9** used as starting materials of the target optically active benzothiazepinones **14–17** were prepared by the reaction of 2-nitrothiophenols **1–3** with substances **4** and **5** [19]. Brucine salts of compounds **6–9** were crystallized from ethanol until each salts showed constant optical rotation. Diastereomeric salts were then decomposed with hydrochloric acid in aqueous acetone to yield enantiomers *S*(+)-**6**, *S*(+)-**7**, *S*(+)-**8**, *R*(+)-**9**, *R*(−)-**6**, *R*(−)-**7**, *R*(−)-**8**, and *S*(−)-**9**. Nitrocarboxylic acid enantiomers gave the optically active aminocarboxylic acids **10–13** on reduction with Zn powder in acetic acid. Benzothiazepines **14–17** were obtained by ring closure in boiling xylene (Scheme 1) [19].

Together with the circular dichroism studies of optically active benzothiazepinones synthesized in this way, the investigation of the chiroptical properties of their intermediates and related compounds was scheduled as well. For this reason, starting from the optically active nitrocarboxylic acids not only intermediates necessary for the synthesis of the corresponding benzothiazepinones were synthesized.

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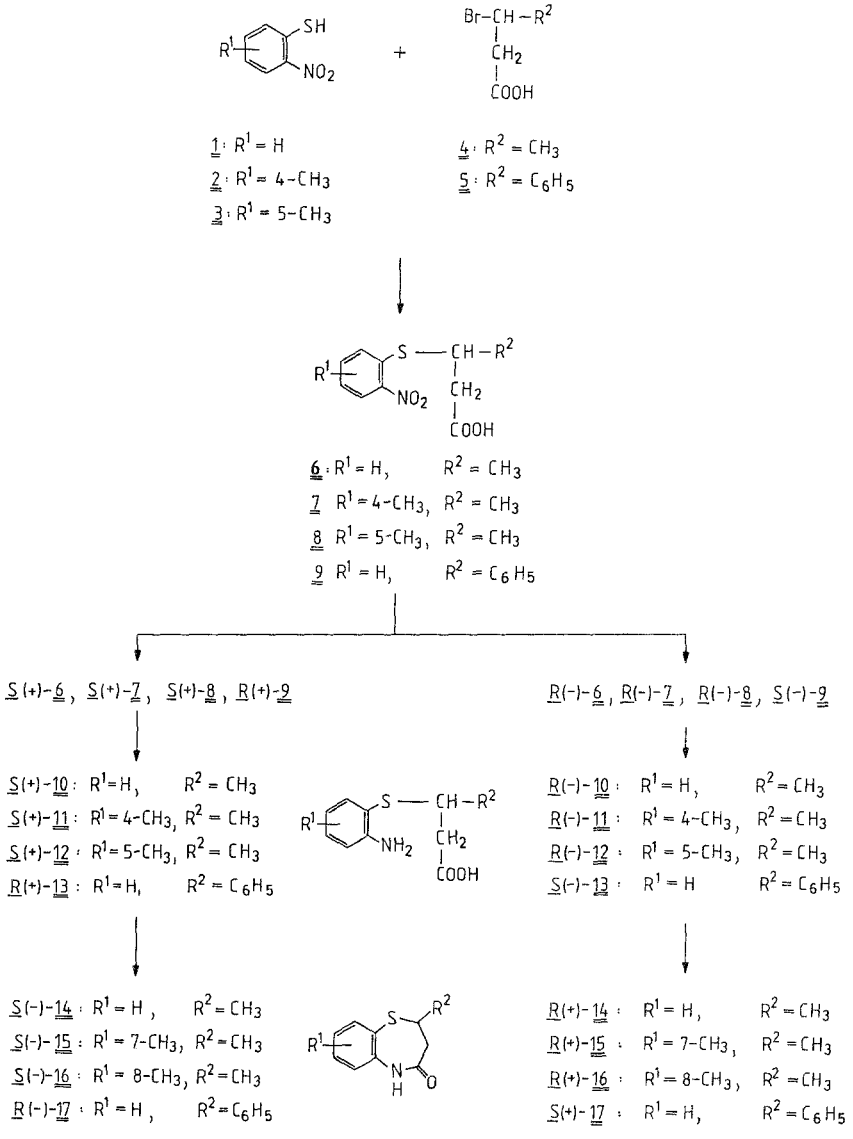
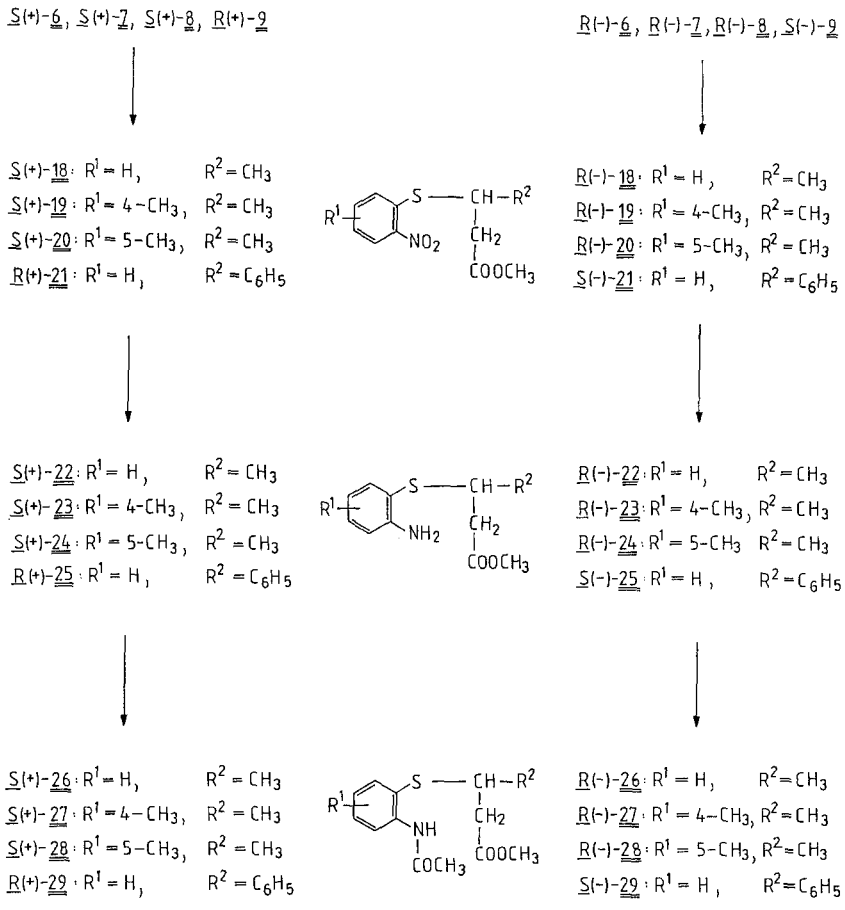
* Circular dichroism measurements of compounds prepared will be published in a separate paper.

Scheme 1


SH
NO2
Br–CH–R2
CH2
COOH
1: R1 = H
2: R1 = 4-CH3
3: R1 = 5-CH3
4: R2 = CH3
5: R2 = C6H5
S
CH–R2
CH2
COOH
NO2
6: R1 = H, R2 = CH3
7 R1 = 4-CH3, R2 = CH3
8 R1 = 5-CH3, R2 = CH3
9 R1 = H, R2 = C6H5
S(+)-6, S(+)-7, S(+)-8, R(+)-9
R(–)-6, R(–)-7, R(–)-8, S(–)-9
S(+)-10: R1 = H, R2 = CH3
S(+)-11: R1 = 4-CH3, R2 = CH3
S(+)-12: R1 = 5-CH3, R2 = CH3
R(+)-13: R1 = H, R2 = C6H5
NH2
R(–)-10: R1 = H, R2 = CH3
R(–)-11: R1 = 4-CH3, R2 = CH3
R(–)-12: R1 = 5-CH3, R2 = CH3
S(–)-13: R1 = H R2 = C6H5
S(–)-14: R1 = H, R2 = CH3
S(–)-15: R1 = 7-CH3, R2 = CH3
S(–)-16: R1 = 8-CH3, R2 = CH3
R(–)-17: R1 = H, R2 = C6H5
N
H
O
R(+)-14: R1 = H, R2 = CH3
R(+)-15: R1 = 7-CH3, R2 = CH3
R(+)-16: R1 = 8-CH3, R2 = CH3
S(+)-17: R1 = H, R2 = C6H5

Scheme 2



The methyl esters **18–21** of the nitrocarboxylic acids were prepared in boiling methanol with catalytic amounts of sulfuric acid. Compounds **18–21** gave aminocarboxylic acid methyl esters **22–25** on reduction [19]. Acetylation of substances **22–25** afforded their N-acetyl derivatives **26–29** (Scheme 2). To obtain model compounds for the circular dichroism studies deamination of the enantiomers of **22–24** has also been achieved to yield methyl carboxylates **30–32**.

Optical purity of the optically active benzothiazepines synthesized prior to our work was not investigated. In the course of our present studies

Scheme 3

S(+)-22, R(-)-22
S(+)-23, R(-)-23
S(+)-24, R(-)-24

S(+)-30, R(-)-30: $R^1 = H$, $R^2 = CH_3$
S(+)-31, R(-)-31: $R^1 = 4\text{-}CH_3$, $R^2 = CH_3$
S(+)-32, R(-)-32: $R^1 = 3\text{-}CH_3$, $R^2 = CH_3$

the known NMR shift reagent technique was utilized for this purpose. The enantiomeric purities of **18**–**21** were investigated by ^{1}H NMR using the chiral lanthanide shift reagent (CLSR) tris-[3-(heptafluoropropylhydroxymethylene)-*D*-camphorato]-europium (III). The acetyl-CH_3 and the —CH_2-resonances were well suited for this purpose: with approx. 0.5 mol of shift reagent the CH_3-singlet showed a splitting of ca. 0.025 ppm, the CH_2-dublet a splitting of 0.032 ppm. All enantiomers described in this study showed a high enantiomeric purity (ee $> 99.9\%$) with the exception of *S*(+)-**20** which contained approx. 0.5% of *R*(−)-**20** in spite of a considerable effort invested into the resolution process (the diastereomeric salt was recrystallized over 30 times). ^{1}H NMR proved to be a most sensitive method for determining the enantiomeric purity of these derivatives using the CLSR technique.

On the basis of the ^{1}H NMR spectra it can be stated that both enantiomers of **18**, **19**, **21**, and *R*(−)-**20** can be considered as highly pure for all practical purposes.

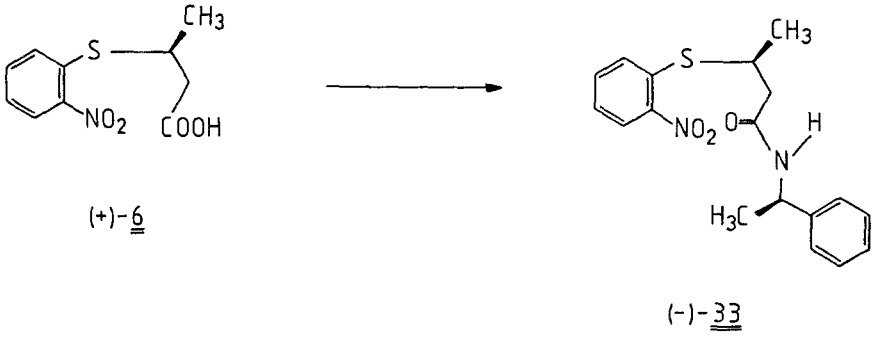
Table 1. *Measured senses of nonequivalence of the indicated protons in the CLSR experiments*

	Substituent		Sense of δ_H nonequivalence					
	R^1	R^2	OCH_3	$\ominus$ R^1	R^2	OCH_3	$\oplus$ R^1	R^2
18	H	CH_3	*H*	—	*H*	*L*	—	*L*
19	4-CH_3	CH_3	*H*	*L*	*H*	*L*	*H*	*L*
20	5-CH_3	CH_3	*L*	*H*	*	*H*	*L*	*
21	H	C_6H_5	*L*	—	—	*H*	—	—

* Magnitude of nonequivalence is too small to be detected; [CLSR]/[*S*] 0.17–0.20

The senses of chemical shift nonequivalence upon CLSR complexation for different groups on the substrates **18**–**21** are recorded in Table 1. The amount of the data is clearly insufficient to draw conclusions concerning the geometry of the CLSR-substrate complexes. This was, in fact, not the subject of this study. It is interesting, however, to note that the sense of nonequivalence depends, even for the same substituent group, on the structure of the substrate in a very sensitive manner. Thus, e.g. the OCH_3 resonance in *R*(−)-**19** (methyl group in position 4 on the aromatic ring) shows a high sense (*H*) of nonequivalence whereas a low sense (*L*) (Table 1) was observed for the same signal in *R*(−)-**20** (methyl group in position 5 in the aromatic ring).

Scheme 4



The absolute configuration of the centre of chirality was determined by X-ray analysis. Compound (+)-**6** was allowed to react with 1*R*-phenylethylamine to give substance (−)-**33** suitable for such an investigation (Scheme 4). The X-ray analysis revealed that the absolute configuration of (+)-**6** is *S*. Together with circular dichroism (CD) measurements this reference substance made possible the determination of the absolute configuration of all optically active compounds prepared [20].

Acknowledgements

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Experimental

M.p.'s were measured on a Reichert micro-melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ solutions with *TMS* as internal standard on Bruker WP-80, WH-200, and WH-400 instruments. IR spectra were recorded with Perkin-Elmer 283B or 221 instruments. Mass spectra were determined with Varian MAT CH-5, CH-7 or V.G. Micromass 7035 instruments (70 eV, direct inlet). UV spectra (in acetonitrile) were run on a Cary 17 spectrometer. Optical rotation was measured on a Perkin-Elmer 141 apparatus in chloroform. For column chromatography silica gel (0.06–0.2 mm) from Hermann (Köln) was used. Thin-layer chromatography was performed on Kieselgel 60 F_{254} (Merck) layer using toluene: ethyl acetate: acetic acid = 15:4:1 (*v/v*) or petroleum ether: acetone = 5:2 (*v/v*) developing mixtures.

2-Nitrothiophenol (**1**) [15], 4-methyl-2-nitrothiophenol (**2**) [16], 3-bromobutyric acid (**4**) [17], and 3-bromo-3-phenylpropionic acid (**5**) [18] were synthesized according to known procedures.

Starting nitrocarboxylic acids **6–9**, optically active aminocarboxylic acids **10–13**, benzothiazepinones **14–17**, and methyl esters **18–25** were synthesized as described for the corresponding racemic compounds [19].

5-Methyl-2-nitrothiophenol (**3**)

The method described for compound **1** [15] was applied to (5,5'-dimethyl-2,2'-dinitrophenyl)disulfide (20.0 g) to afford 15.0 g (75.0%) yellow powder, m.p. 68–72 °C; ν_{max} (KBr) 2 527 (SH), 1 497 and 1 332 (NO_2); δ_H (60 MHz) 2.37 (3 H, s, CH_3), 3.96 (1 H, s, SH), 6.90 (1 H, d, 4-H), 7.10 (1 H, s, 6-H), and 7.96 (1 H, d, 3-H); *m/z* 169 (M^+).

Resolution of Nitrocarboxylic Acids **6–9**

30.0 mmol of nitrocarboxylic acid and (−)-brucine × 2 H_2O (32.0 mmol) were dissolved in ethanol (**6–8**: 250 ml; **9**: 800 ml) at 60 °C and the solution was allowed to cool down overnight. The precipitated crystals were filtered off and recrystallized several times (**6** and **9** from ethanol; **7** and **8** from 50% methanol). The mother liquor was evaporated under reduced pressure and the residue crystallized as mentioned at the precipitated materials.

Decomposition of the Brucine Salts of **6–9**

The brucine salt was dissolved in a mixture of acetone: 10% hydrochloric acid = 4:6 (*v/v*), then the free acid extracted with dichloromethane. The solution was dried with $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography to yield pure optically active nitrocarboxylic acid (Scheme 1, Tables 2 and 3).

Acetylation of the Aminocarboxylic Acid Methyl Esters

A mixture of 1.0 mmol of **22–25**, dichloromethane (20.0 ml), and acetic anhydride (1.0 ml) was stirred overnight, then the solvent removed and the oily residue purified by column chromatography to obtain compounds **26–29** (Scheme 2, Tables 2 and 3).

Deamination of Compounds **22–24**

A mixture of aminocarboxylic acid methyl ester (0.25 mmol), 2*N* sulfuric acid (10.0 ml) and 50% hypophosphorous acid (6.0 ml) was treated with equimolar

Table 2. *Physical constants and mass spectral data of compounds prepared*

Compound	Yield %	M.p. °C	$[\alpha]_D^{25}$*	Formula	*m/z* (M^+)
S(+)-**6**	55	oil	+ 121	$C_{10}H_{11}NO_4S$	241
R(−)-**6**	90	oil	− 121		
S(+)-**7**	65	56–62	+ 108	$C_{11}H_{13}NO_4S$	255
R(−)-**7**	70	56–62	− 114		
S(+)-**8**	11	92–96	+ 106	$C_{11}H_{13}NO_4S$	255
R(−)-**8**	36	92–96	− 113		
R(+)-**9**	70	110	+ 94	$C_{15}H_{13}NO_4S$	303
S(−)-**9**	70	109	− 91		
S(+)-**10**	70	69	+ 50	$C_{10}H_{13}NO_2S$	211
R(−)-**10**	75	71	− 52		
S(+)-**11**	60	56–59	+ 52	$C_{11}H_{15}NO_2S$	225
R(−)-**11**	60	oil	− 45		
S(+)-**12**	65	oil	+ 35	$C_{11}H_{15}NO_2S$	225
R(−)-**12**	70	oil	− 40		
R(+)-**13**	80	134–137	+ 270	$C_{15}H_{15}NO_2S$	273
S(−)-**13**	75	133–138	− 270		
S(−)-**14**	60	237–239	− 255	$C_{10}H_{11}NOS$	193
R(+)-**14**	75	237–238	+ 255		
S(−)-**15**	60	237–246	− 260	$C_{11}H_{13}NOS$	207
R(+)-**15**	50	237–246	+ 262		
S(−)-**16**	40	255–264	− 247	$C_{11}H_{13}NOS$	207
R(+)-**16**	35	255–264	+ 245		
R(−)-**17**	40	190	− 552	$C_{15}H_{13}NOS$	255
S(+)-**17**	35	190	+ 551		
S(+)-**18**	100	oil	+ 121	$C_{11}H_{13}NO_4S$	255
R(−)-**18**	100	oil	− 119		
S(+)-**19**	100	oil	+ 119	$C_{12}H_{15}NO_4S$	269
R(−)-**19**	100	oil	− 125		
S(+)-**20**	100	oil	+ 110	$C_{12}H_{15}NO_4S$	269
R(−)-**20**	100	oil	− 114		
R(+)-**21**	100	60	+ 86	$C_{16}H_{17}NO_4S$	317
S(−)-**21**	100	61	− 84		
S(+)-**22**	60	oil	+ 55	$C_{11}H_{15}NOS$	225
R(−)-**22**	30	oil	− 52		
S(+)-**23**	65	oil	+ 52	$C_{12}H_{17}NO_2S$	239
R(−)-**23**	70	oil	− 51		
S(+)-**24**	75	oil	+ 42	$C_{12}H_{17}NO_2S$	239
R(−)-**24**	75	oil	− 42		
R(+)-**25**	75	92	+ 251	$C_{16}H_{17}NO_2S$	287
S(−)-**25**	65	93	− 253		
S(+)-**26**	80	49	+ 81	$C_{13}H_{17}NO_3S$	267
R(−)-**26**	85	50	− 84		
S(+)-**27**	60	38–40	+ 82	$C_{14}H_{19}NO_3S$	281
R(−)-**27**	50	40–41	− 82		
S(+)-**28**	65	oil	+ 63	$C_{14}H_{19}NO_3S$	281
R(−)-**28**	70	oil	− 63		
R(+)-**29**	70	94	+ 273	$C_{18}H_{19}NO_3S$	329
S(−)-**29**	70	94	− 275		
S(+)-**30**	30	oil	+ 29	$C_{11}H_{14}O_2S$	210
R(−)-**30**	35	oil	− 33		
S(+)-**31**	40	oil	+ 25	$C_{12}H_{16}O_2S$	224
R(−)-**31**	35	oil	− 27		
S(+)-**32**	40	oil	+ 25	$C_{12}H_{16}O_2S$	224
R(−)-**32**	45	oil	− 23		

* $c = 0.1$–0.2, $CHCl_3$

Table 3. *UV, IR, and ^1H NMR spectral data*

Compound	UV λ_{max} [nm] (ε)	IR ν [cm^{-1}]	^1H NMR δ_H [ppm]
S(+)-**6** *R*(−)-**6**	370 (2 500), 265 sh (5 000), 255 (13 000), 190 (15 000)	3 300–2 300, 1 708, 1 511, 1 330	1.49 (3 H, d), 2.49–2.90 (2 H, oct), 3.78–4.00 (1 H, hex), 7.24 (3 H, m), 8.13 (1 H, d)
S(+)-**7** *R*(−)-**7**	380 (3 100), 265 sh (7 200), 245 (17 500), 195 sh (25 000)	3 300–2 500, 1 709, 1 515, 1 332	1.41 (3 H, d), 2.40 (3 H, s), 2.32–2.92 (2 H, oct), 3.59–4.00 (1 H, hex), 7.38–7.48 and 7.88 (3 H, m)
S(+)-**8** *R*(−)-**8**	368 (3 500), 280 (3 500), 250 (15 000), 202 (15 000)	3 300–2 500, 1 690, 1 516, 1 327	1.45 (3 H, d), 2.49–2.90 and 2.45 (5 H, m and s), 3.55–4.10 (1 H, hex), 7.00 (1 H, d), 7.20 (1 H, s), 7.87 (1 H, d)
R(+)-**9** *S*(−)-**9**	365 (4 000), 270 sh (6 000), 240 (14 000)	3 500–2 500, 1 712, 1 516, 1 338	3.05 (2 H, m), 4.90 (1 H, t), 7.20–7.50 (8 H, m), 8.10 (1 H, d)
S(+)-**10** *R*(−)-**10**	306 (3 200), 241 (7 400) 208 (27 500)	3 300–2 400, 3 460, 3 354, 1 710	1.28 (3 H, d), 2.59–2.65 (2 H, oct), 3.30–3.52 (1 H, hex), 6.62–6.78 (2 H, m), 7.10 (1 H, t), 7.35 (1 H, d)
S(+)-**11** *R*(−)-**11**	305 (3 600), 240 (7 100), 211 (30 000)	3 490, 3 395, 2 980, 2 925, 3 600–2 500, 1 719, 1 610	1.30 (3 H, d), 2.24 (3 H, s), 2.24–2.79 (2 H, oct), 3.17–3.59 (1 H, hex), 6.25 (3 H, br), 6.35–6.50 and 7.12–7.24 (3 H, m)
S(+)-**12** *R*(−)-**12**	310 (4 300), 242 (9 700), 210 (34 000)	3 490, 3 395, 2 985, 2 922, 3 600–2 500, 1 712, 1 618	1.30 (3 H, d), 2.20 (3 H, s), 2.28–2.81 (2 H, oct), 3.12–3.66 (1 H, hex), 6.28 (3 H, br), 6.64 (1 H, d), 6.94 (1 H, d), 7.18 (1 H, s)
R(+)-**13** *S*(−)-**13**	308 (4 300), 240 sh (9 000), 206 (35 000)	3 459, 3 358, 3 200–2 400, 1 710	3.00 (2 H, d), 4.45 (1 H, t), 5.00 (3 H, br), 6.50–6.70 and 7.05–7.40 (9 H, m)
S(−)-**14** *R*(+)-**14**	260 (4 000), 241 (15 000), 197 (30 000)	3 177, 1 683	1.35 (3 H, d), 2.30–2.51 and 2.60–2.70 (2 H, oct), 3.80–3.99 (1 H, hex), 7.10–7.20 (2 H, m), 7.35 (1 H, t), 7.57 (1 H, d), 8.30 (1 H, br)

Table 3 *(continued)*

Compound	UV λ_{max} [nm] (ε)	IR ν [cm^{-1}]	^{1}NMR δ_H [ppm]
S(−)-**15** *R*(+)-**15**	260 (5200), 242 (15000), 211 (34000)	3185, 1679	1.31 (3H, d), 2.11–2.70 and 2.28 (5H oct and s), 3.59–4.02 (1H, hex), 6.85 and 6.95 (2H, s and d), 7.41 (1H, d), 7.81 (1H, br)
S(−)-**16** *R*(+)-**16**	250 (5200), 237 (18000), 198 (33000)	3495, 1672	1.43 (3H, d), 2.18–2.77 and 2.35 (5H, oct and s), 3.66–4.09 (1H, hex), 6.96 (1H, d), 7.16 (1H, s), 7.42 (1H, s), 7.90 (1H, br)
R(−)-**17** *S*(+)-**17**	272 (7000), 243 (2000)	3184, 1670	2.75–3.00 (2H, m), 4.90 (1H, q), 7.17–7.45 (7H, m), 7.58 (1H, t), 7.67 (1H, d), 8.70 (1H, br)
S(+)-**18** *R*(−)-**18**	370 (3500), 265 sh (8000), 245 (35000)	1736, 1520, 1335	1.45 (3H, d), 2.41–2.75 (2H, oct), 3.67 (3H, s), 3.80–3.95 (1H, hex), 7.30 (1H, t), 7.52 (1H, d), 7.58 (1H, t), 8.10 (1H, d)
S(+)-**19** *R*(−)-**19**	378 (4000), 265 sh (7000), 246 (20000), 195 (27500)	1740, 1525, 1340	1.38 (3H, d), 2.39 (3H, s), 2.43–2.72 (2H, oct), 3.69 (3H, s), 3.78–3.87 (1H, m), 7.36 (1H, d), 7.41 (1H, d), 7.88 (1H, s)
S(+)-**20** *R*(−)-**20**	367 (3600), 278 (5600), 249 (16000), 203 (17500)	1736, 1510, 1332	1.42 (3H, d), 2.42 (3H, s), 2.47–2.77 (2H, oct), 3.71 (3H, s), 3.82–3.91 (1H, m), 7.05 (1H, d), 7.28 (1H, s), 8.03 (1H, d)
R(+)-**21** *S*(−)-**21**	365 (3600), 270 sh (8000), 246 (17000)	1740, 1510, 1334	2.90–3.10 (2H, oct), 3.65 (3H, s), 4.93 (1H, t), 7.20–7.50 (8H, m), 8.10 (1H, d)
S(+)-**22** *R*(−)-**22**	308 (4100), 242 (9000), 208 (33500)	3467, 3360, 1734	1.28 (3H, d), 2.40–2.67 (2H, oct), 3.37–3.55 (1H, hex), 3.65 (3H, s), 4.72 (2H, br), 6.63–6.76 (2H, m), 7.15 (1H, t), 7.39 (1H, d)
S(+)-**23** *R*(−)-**23**	306 (6300), 240 (12000), 212 (55000)	3462, 3360, 1737	1.25 (3H, d), 2.23 (3H, s), 2.30–2.52 (2H, q), 3.10–3.60 (1H, hex), 3.60 (3H, s), 4.30 (2H, br), 6.30–6.40 (2H, m), 7.10 (1H, d)

Table 3 *(continued)*

Compound	UV λ_{max} [nm] (ε)	IR ν [cm^{-1}]	^{1}NMR δ_H [ppm]
S(+)-**24** *R*(−)-**24**	315 (4700), 243 (11200), 209 (43000)	3460, 3360, 1735	1.32 (3H, d), 2.25 (3H, s), 2.25–2.80 (2H, oct), 3.28–3.70 (1H, m), 3.70 (3H, s), 4.00 (2H, br), 6.68 (1H, d), 6.98 (1H, d), 7.20 (1H, s)
R(+)-**25** *S*(−)-**25**	308 (5000), 240 sh (11500), 207 (35000)	3471, 3367, 1731	2.98 (2H, d), 3.60 (3H, s), 4.35 (2H, br), 6.56 (1H, t), 6.70 (1H, d), 7.05–7.28 (7H, m)
S(+)-**26** *R*(−)-**26**	285 (2000), 245 (13000), 210 (25000)	3328, 1732, 1694, 1510	1.37 (3H, d), 2.38 (3H, s), 2.60 (2H, d), 3.33–3.50 (1H, hex), 3.80 (3H, s), 7.12 (1H, t), 7.45 (1H, t), 7.60 (1H, d), 8.58 (1H, d), 895 (1H, br)
S(+)-**27** *R*(−)-**27**	283 (2700), 255 (13500), 246 (17000), 216 (36000)	3340, 1739, 1698, 1522	1.23 (3H, d), 2.18 (3H, s), 2.30 and 2.50 (5H, s and d), 2.95–3.40 (1H, hex), 3.70 (3H, s), 6.70 (1H, d), 7.23 (1H, d), 8.30 (1H, s), 8.60 (1H, br)
S(+)-**28** *R*(−)-**28**	292 (2300), 260 sh (10000), 247 (15000), 211 (25000)	3340, 1736, 1695, 1513	1.30 (3H, d), 2.29 and 2.33 (6H, 2s), 2.52 (2H, d), 3.13–3.57 (1H, hex), 3.72 (3H, s), 7.18 (1H, d), 7.31 (1H, s), 8.32 (1H, d), 8.72 (1H, br)
R(+)-**29** *S*(−)-**29**	285 (7400), 246 (33000), 204 (50000)	3316, 1727, 1692, 1524	2.11 (3H, s), 2.85–3.14 (2H, oct), 3.73 (3H, s), 4.31 (1H, q), 6.92 (1H, t), 7.00–7.40 (7H, m), 8.42 (1H, d), 8.85 (1H, br)
S(+)-**30** *R*(−)-**30**	256 (6000), 203 sh (17000), 190 (46000)	1739	1.35 (3H, d), 2.18–2.89 (2H, oct), 3.44–3.80 and 3.64 (4H, m and s), 7.14–7.57 (5H, m)
S(+)-**31** *R*(−)-**31**	257 (6500), 220 (11000), 195 (50000)	1740	1.26 (3H, d), 2.30–2.80 and 2.37 (5H, m and s), 3.20–3.66 and 3.58 (4H, m and s), 6.95–7.30 (4H, q)
S(+)-**32** *R*(−)-**32**	263 (6000), 209 sh (16000), 195 (50000)	1738	1.32 (3H, d), 2.33 and 2.27–2.82 (5H, s and m), 3.42–3.75 and 3.68 (4H, m and s), 7.00–7.30 (4H, m)

amount of sodium nitrite dissolved in water (1.0 ml). After stirring overnight, the product was extracted with dichloromethane, the organic layer was washed with 1.0% sodium carbonate and with water, dried over $MgSO_4$ and the solvent evaporated. The crude residue was subjected to low pressure chromatography (Lobar-Fertigsäule, Lichroprep Si60 (0.04–0.063 mm), light petroleum: ethyl acetate = 75 : 1 *v/v*, 1.5 bar), to give compounds **30**–**32** (Scheme 3, Tables 2 and 3).

Preparation of Compound **33**

100 mg of *S*(+)-**6** was dissolved in anhydrous dichloromethane (20.0 ml) and treated with 70 mg of 1*R*-phenylethylamine and 100 mg of N,N′-dicyclohexylcarbodiimide. The mixture was stirred overnight, the organic layer washed with water, dried over $MgSO_4$ and the solvent evaporated. The yellow oily residue was purified by column chromatography and the semisolid product obtained was recrystallized several times from *n*-hexane: ethyl acetate = 6 : 4 (*v/v*) mixture to afford 20 mg (15%) of pure **33**. M.p. 150 °C; $[\alpha]_D^{25} - 6$ ($c = 0.10$); ν_{max} ($CHCl_3$) 1 702 (amide I), 1 655 (amide II), 1 518 and 1 340 (NO_2); δ_H (80 MHz) 1.35 and 1.46 (6 H, 2 d, 2 CH_3), 2.16–2.78 (2 H, m, CH_2), 3.77–4.18 (1 H, m, CH), 4.92–5.28 (1 H, m, CH), 6.10 (1 H, d, NH), 7.10–7.70 (8 H, m, aromatic H), and 8.10 (1 H, d, 3 H); *m/z* 344 (M^+); λ_{max} [nm] (ε) 372 (2 200), 25 sh (4 000), 246 (10 000), and 195 (23 500).

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