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Synthesis and transformations of 2-(phenylhydroxymethyl)cyclohexylamines

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Abstract—Diastereomeric 2-(phenylhydroxymethyl)cyclohexylamines were synthesised by reduction of 2-benzoylcyclohexylamines. (1*S**,2*R**)-2-Benzoylcyclohexylamine can be reduced diastereoselectively to the corresponding γ-amino alcohol with sodium borohydride; for the *trans* counterpart (1*R**,2*R**)-2-benzoylcyclohexylamine, lithium aluminium hydride was found to be a selective reducing agent. In both cases, high *syn* selectivities were observed. The amino alcohols were transformed to the corresponding cyclohexane-fused tetrahydro-1,3-oxazin-2-ones and -2-thiones. The γ-amino alcohols reacted with arylimidates to afford 4,5-dihydro-6*H*-1,3-oxazines. Their cyclization with phenyl isothiocyanate yielded 2-phenyliminotetrahydro-1,3-oxazines.

1. Introduction

The stereocontrolled synthesis of 1,3-amino alcohols has attracted much attention recently because of their pharmacological properties and their utility as building blocks for the preparation of potential pharmacons.[1–6] Alicyclic amino alcohol derivatives have also been introduced into therapy. For example, ciramadol and tramadol are used as analgesics.[7]

The methods most generally applied for the preparation of stereoisomeric 1,3-amino alcohols involve reduction reactions.[8] These include mainly the reductions of the corresponding β-amino carbonyl derivatives or the cleavage of *N*,*O*-heterocycles.[9] The alicyclic amino alcohols can also be obtained via these two procedures. However, various methods can be used for the stereoselective preparation of alicyclic 1,2-disubstituted 1,3-amino alcohols possessing two stereogenic centres.[10–12] The preparation of the corresponding stereohomogeneous alicyclic amino alcohols possessing three stereogenic centres is more difficult and is dependent on the selectivity of the reduction reaction. On the other hand, as the number of possible stereoisomers increases, only some of them can be prepared with good stereoselectivity. The literature syntheses of alicyclic amino alcohols containing three stereogenic centres commonly involve the reductions of β-amino ketones,[13–15] enaminones[16–18] or isoxazolines.[19,20]

In recent years, the synthesis of cycloalkane-fused heterocycles has been one of our main research topics. A number of alicycle-condensed oxazines, thiazines and pyrimidines have been prepared by ring closure of the corresponding 1,3-difunctional compounds. The chemistry and stereochemistry of the partially saturated heterocycles obtained has been widely investigated.[21] As a continuation of our earlier investigations, our present aim was the diastereoselective synthesis of hydroxymethylcyclohexylamines containing a phenyl substituent on the carbon atom adjacent to the anellation. The synthesised amino alcohols were transformed to different alicycle-condensed 1,3-oxazines for further conformational studies.

2. Synthesis

For the preparation of amino alcohols **3** and **6**, amino ketones **2** and **5** were chosen as key intermediates. *N*-Substituted derivatives of **2** and **5** were earlier prepared for pharmacological studies of their analgesic activity.[17] The partially unsaturated derivative of **2**, (1*R**,2*S**)-*N*-(*tert*-butoxycarbonyl)-2-[(3′,4′-methylenedioxy)benzyl]-4-cyclohexenylamide was used as a building block in the synthesis of montanine-type *Amaryllidaceae* alkaloids.[22,23] To obtain

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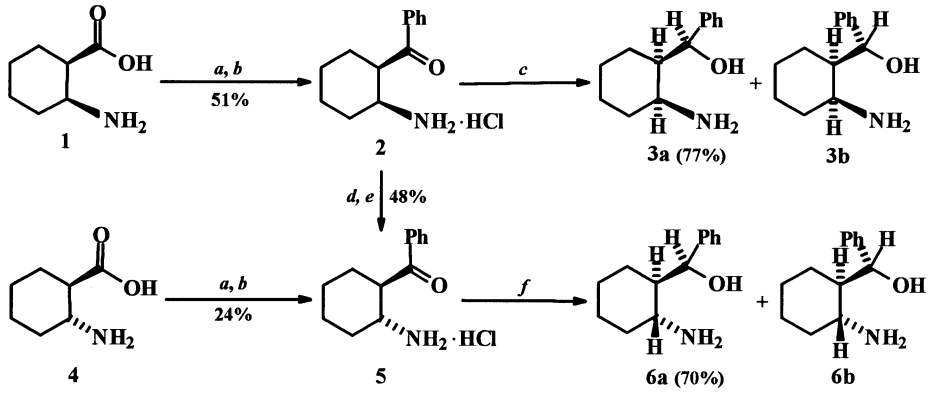


Scheme 1. (a) 1 equiv. PCl_5, CH_2Cl_2, 0°C–rt, 2 h; (b) 3 equiv. $AlCl_3$, benzene, 60°C, 4 h; (c) 4 equiv. $NaHB_4$, EtOH, −10°C–rt, 3 h (d) conc. HCl, 70°C; (e) recrystallization from EtOH; (f) $LiAlH_4$, Et_2O, 0°C, 1 h–rt, 3 h.

the amino ketones **2** and **5** with known stereochemistry, β-amino acids **1** and **4** were employed as starting materials (Scheme 1).

Treatment of *cis*-2-aminocyclohexanecarboxylic acid **1** with phosphorus(V) chloride, and subsequent Friedel–Crafts acylation in the presence of $AlCl_3$, gave amino ketone **2** in relatively good yield (51%). The *trans* amino ketone **5** was prepared similarly, starting from amino acid **4**, but in only moderate yield (24%). Epimerisation of the *cis* amino ketone **2** in concentrated hydrochloric acid at 70°C for three days resulted in a 1:9 mixture of **2** and **5**. From this mixture, the *trans* amino ketone **5** was obtained in 48% yield by recrystallization from ethanol. By this method, **5** can be prepared directly from the readily available *cis*-2-amino-cyclohexanecarboxylic acid **1**.

The reduction of β-amino ketones with metal hydrides usually occurs with *syn* selectivity,[24] a preference consistent with a β-chelated transition state.[25] The different reductions of the *cis* amino ketone **2** also provided *syn* amino alcohol **3a** as the major product. The *cis* amino ketone **2** could be reduced diastereoselectively with $NaBH_4$ in ethanol at −10°C (Table 1). For the *trans* amino ketone **5**, lithium aluminium hydride proved to be a selective reducing agent. The ^1H NMR spectrum of the crude product of the reduction of **5** revealed a 9:1 mixture of **6a** and **b**.

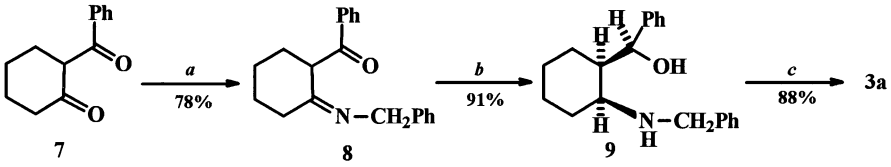
An alternative synthesis of **3a** is shown in Scheme 2. β-Imino ketone **8** was prepared from β-diketone **7** and benzylamine. The catalytic reduction of **8** with 5% Pt/C at room temperature afforded **9** diastereoselectively. After recrystallization from diisopropyl ether, the $Pd(OH)_2$/C-catalysed hydrogenolysis of **9** provided amino alcohol **3a** in a yield of 88% (Scheme 2). For the preparation of amino alcohols possessing structures similar to that of **3a**, selective reductions were performed with PtO_2, starting from the corresponding enamino ketones.[16,18]

Alternatively, the addition of thiocyanic acid, generated from potassium thiocyanate in 50% sulfuric acid, to

Table 1. Selectivity of the reduction of *cis*-amino ketone **2**

	Reducing agent	Reaction conditions	**3a** (%)	**3b** (%)
HCl salt	$NaBH_4$ (4 equiv.)	EtOH, rt (3 h)	89	11
HCl salt	$NaBH_4$ (4 equiv.)	EtOH, −10°C–rt (3h)	98	2
Base	$LiAlH_4$ (2 equiv.)	Et_2O, 0°C (1 h)–rt (3 h)	71	29
Base	L-Selectride[a] (3 equiv.)	THF, −78°C (6 h)–rt (4 h)	42	58
Base	Na (10 equiv.)	*i*-PrOH/THF, rt (4 h)	43	57
Base	10% Pd/C[b]	EtOH, rt (6 days)	70	30
Base	Raney-Ni[c]	EtOH, rt (5 days)	92	8

[a] Traces of *trans* isomers **6a** and **b** were also detected.
[b] 0.1 g/1 g **2**.
[c] 0.2 g/1 g **2**.



Scheme 2. (a) 1.04 equiv. benzylamine, toluene, reflux, Dean–Stark trap, 3 h; (b) 5% Pt/C, H_2 (60 bar), EtOH, rt, six days; (c) 20% $Pd(OH)_2$/C, H_2 (60 bar), MeOH, rt, 48 h.

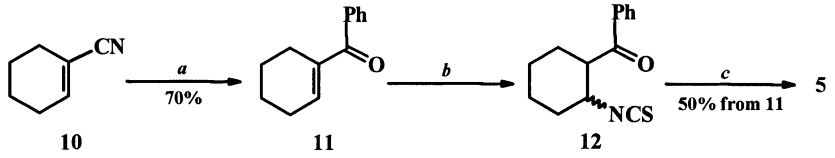
1-benzoylcyclohexene **11** afforded the isothiocyanate intermediate **12**, which was converted to amino ketone **5** via acidic hydrolysis (Scheme 3). A similar addition to 1-acetylcyclohexene was earlier performed for the preparation of (1*R**,2*R**)-2-acetylcyclohexylamine.[26]

Amino alcohols **3a** and **6a** were transformed to different alicycle-condensed 1,3-oxazines (Schemes 4 and 5).

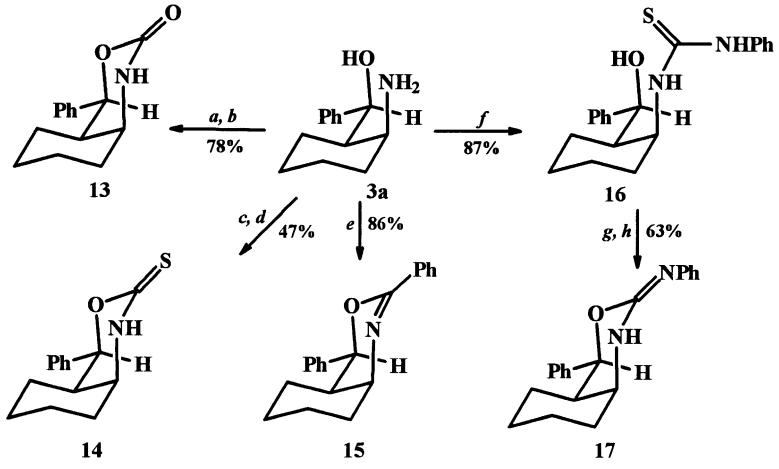
The reactions of **3a** and **6a** with ethyl chloroformate provided urethane intermediates, which were converted with sodium methoxide to tetrahydro-1,3-oxazin-2-ones **13** and **18** in good yields. The corresponding 2-thiones **14** and **19** were prepared from **3a** and **6a** by reaction with carbon disulfide in the presence of triethylamine. The triethylammonium dithiocarbamate intermediates formed were transformed without isolation to 2-thioxo-1,3-oxazines by ethyl chloroformate treatment.[27] In these cases, only moderate yields were obtained. The cyclizations of **3a** and **6a** with ethyl benzimidate in ethanol, under acid catalysis, resulted in 4,5-dihydro-6*H*-1,3-oxazines **15** and **20**. Treatment of **3a** and **6a** with phenyl isothiocyanate provided the thiourea derivatives **16** and **21**. With methyl iodide, **16** and **21** gave thioethers, which were transformed in alkaline medium to 2-phenyliminotetrahydro-1,3-oxazines **17** and **22**.

3. Spectroscopic studies

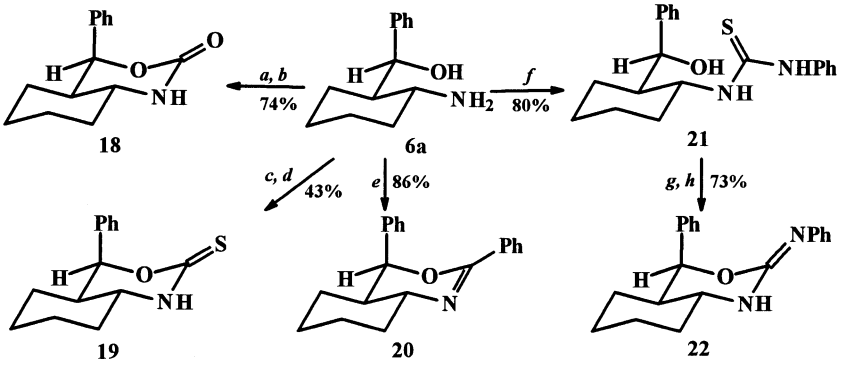
The IR, ^{1}H and ^{13}C NMR spectral data on compounds **2**, **3**, **5**, **6**, **8**, **9** and **13**–**22** are given in Tables 2 and 3 and prove the structures unambiguously. The numbering of the chemical names (compounds **2**, **3**, **5**, **6**, **8** and **9**) according



Scheme 3. (a) 1.2 equiv. PhMgBr, Et_2O, reflux, 6 h; (b) 1 equiv. KSCN, 0.5 equiv. 50% H_2SO_4, 50°C, 6 h; (c) conc. HCl, 70°C, three days.



Scheme 4. (a) 1.1 equiv. ClCOOEt, 4.4 equiv. 10% NaOH in H_2O/toluene, 30 min; (b) 0.11 equiv. NaOMe, 130°C, 1 h; (c) 11 equiv. CS_2, 1.1 equiv. Et_3N, $CHCl_3$, 0°C–rt, four days; (d) 1.1 equiv. ClCOOEt, 1.1 equiv. Et_3N, $CHCl_3$, 0°C, 5 min rt, 30 min reflux, 3 h; (e) 1 equiv. ethyl benzimidate, cat. CH_3COOH, ethanol, reflux, 36 h; (f) 1 equiv. PhSCN, toluene, 8 h; (g) 10 equiv. MeI, methanol, rt, 3 h; (h) 38 equiv. 15% KOH in methanol, rt, two days.



Scheme 5. (a) 1.1 equiv. ClCOOEt, 4.4 equiv. 10% NaOH in H_2O/toluene, 30 min; (b) 0.11 equiv. NaOMe, 130°C, 1 h; (c) 1.1 equiv. CS_2, 1.1 equiv. Et_3N, $CHCl_3$, 0°C–rt, four days; (d) 1.1 equiv. ClCOOEt, 1.1 equiv. Et_3N, $CHCl_3$, 0°C, 5 min rt, 30 min reflux, 3 h; (e) 1 equiv. ethyl benzimidate, cat. CH_3COOH, ethanol, reflux, 36 h; (f) 1 equiv. PhSCN, toluene, 8 h; (g) 10 equiv. MeI, methanol, rt, 3 h; (h) 38 equiv. 15% KOH in methanol, rt, two days.

Table 2. Characteristic IR frequencies (in KBr discs, cm^{-1}) and ^1H NMR data (in $CDCl_3$ solution, for **2**, **3b** and **5** in D_2O, at 500 MHz. Chemical shifts in ppm, $\delta_{TMS}=0$ ppm, coupling constants in Hz) on compounds **2**, **3**, **5**, **6**, **8**, **9** and **13**–**22** (assignments were supported by 2D-HSC (HMQC) and for **13**, **14**, **17**, **19**, **20** and **22** also by DNOE measurements)

Compound	H-2 *d* (1H)[a]	H-4a *m* (1H)[b]	H-8a (1H)[c]	CH_2 (Pos. 5–8) 4-8 *m*'s (8H)	H-2,6, H-3,5, H-4 Phenyl in pos. 2	H-2,6, H-3,5, H-4 Phenyl in side-chain	νOH &νNH band	νC═N band[d]
2	–	3.84	3.65	1.4–2.0	7.82, 7.44, 7.58	–	3200–2800	1675
3a	4.99	~1.6[e]	3.35	1.0–1.6[e]	7.20[f], ~7.3	–	3400–2800	–
3b[g]	4.67	2.07	3.62	1.2–1.9	7.25–7.40[e]	–	3400–2700	–
5	–	3.55	1.0–2.1	7.89	7.46, 7.60	–	3200–2800	1674
6a	4.70	1.61	2.40	0.7–1.7	7.1–7.3[e]	–	3400–2700	–
8	–	–	–	1.4–2.5	7.40, ~7.33[e], ~7.33[e]	7.26	–	–
9	5.02	1.65	3.23	1.0–2.1	7.20[f], 7.25–7.40 [e]	7.25–7.40[e]	3300–2600	–
13	5.42	1.99	3.95	1.0–1.9	7.25[f], 7.3–7.4	–	3235	1721
14	5.46	2.09	3.97	1.1–2.0	~7.3[e]	–	3185	1543
15	5.45	2.07	4.02	1.0–2.25	7.30[f], 7.35–7.5	8.09, 7.3–7.4[e]	–	1651
16	4.72	1.81	~4.6[h]	1.1–2.25	~7.25[e]	7.25, 7.42, 7.20	3500–3000	1234
17	5.36	~2.0[e]	3.92	1.1–2.0[e]	7.25–7.4[e]	7.25–7.40[e], 6.95	3250–2700	1669
18	5.34	~1.95[e]	2.93	0.6–2.0[e]	7.16, ~7.35[e]	–	3215, 3115	1698
19	5.47	~2.0[e]	2.96	0.6–2.0[e]	7.12, ~7.35[e]	–	3160	1550
20	5.40	1.85	2.99	0.6–2.3	7.16, ~7.28[e]	8.04, 7.40, 7.44	–	1641
21	4.98	~1.3[e]	4.50	0.9–2.1[e]	~7.28[e]	7.22, 7.46, 7.18	3500–2700	1238
22	5.28	1.86	2.92	0.6–2.1	7.23, ~7.35[e]	7.35, 7.23, 6.93	3200–2700	1662

Further signals, N^+H_3, br *s* (3H): 4.65 (**2**, **5**), OH, br *s* (1H): ~ 3.3 (**3a**), ~2.2 (**16**), CH_2, *d* (2H): 4.48, *J*: 6.0 (**8**), 2×d (2×1H): 3.78 and 3.96, *J*: 12.5 (**9**), NH, sharp *s*(1H): 12. 4 (**8**), br *s* (1H): 6.6 (**13**), 8.1 and 8.3 (**16** and **21**, vicinal to phenyl), 7.4 (**17**), 6.65 (**18**), 8.3 (**19**), 5.8 (**22**), *d* 6.80, *J*: 7.3 (**16**), 5.92, *J*: 9.3 (**21**).

[a] *J*: 1.5 (**3a**, **9**), 3.5 (**6a**, **16**), 2.0 (**13**), 5.3 (**18**, **20**), 2.5 (**15**), 4.5 (**19**, **22**), 3.0 (**21**); singlet for **13** and **17**, triplet for **16**.

[b] Broad multiplet. Lines are resolved for **2** (*td*, *J*: 8.5, 4.2), **6a**, (*tt*, *J*: 12, 3.3) and **13** (*d*, *J*: 12.5).

[c] Lines are coalesced to broad signals for **14**, **16** and **17**. The multiplicity is identifiable for **6a** and **22** (*dt*) and **21** (*qa*), respectively. Lines are separated to *td*, *J*: 7.0 and 3.5, (**2**); *d*, *J*: 2.8 (**3a**, 9), *J*: 4.9 (**3**), *t*, *J*: 3.0 (**3b**), *qa*, *J*: 3.5 (**15**), *dt*, *J*: 11.0 and 4.0 (**18**–**20**).

[d] νC═O band for **2**, **5**, **13** and **18**; group frequency of the thiourethane/thiourea of β-NH or νC═S character for **14**, **16**, **19** and **21**.

[e] Overlapping signals.

[f] The separated signal (1H) of one of the *ortho*-hydrogens.

[g] Hydrochloride.

[h] Broad signal.

to the IUPAC nomenclature is not identical with that used in the text, or in Tables 2 and 3, in order to facilitate the comparison of spectroscopically analogous data. As concerns the stereostructures (the configurations and conformations), only the following remarks are necessary. Compound **8** is stabilized by chelation: via tautomeric rearrangement, **8** assumes a six-membered conjugated ring structure involving an intramolecular hydrogen bond. Such an association is very common for β-imino-oxo compounds.[28]

Compounds **2** and **5**, containing two asymmetric centres, can exist in *cis* or *trans* configurations. In accordance with expectations, compound **2** is the *cis* and **5** the *trans* isomer. The sum of the shifts of the carbons of the cyclohexane ring is 192.7 ppm for **2**, and 209.4 ppm for **5**. The sterically less favourable structure of the *cis* isomer **2** is revealed in the upfield shifts of the ^{13}C NMR lines, due to the steric compression shift.[29,30a] The 16.7 ppm difference in the sum of the shifts is unambiguous proof of the configurations. The heterobicycles **13**–**15**, **17**–**20** and **22** containing three asymmetric centres may exist as four stereoisomers and, in the case of the *cis*-anellated skeleton, as two stable (chair–chair) conformations each.

Compounds **18**–**20** and **22** are *trans*-anellated. This follows from (i) the double triplet fine structure of the H-8a signal due to two diaxial vicinal couplings of ca. 11 Hz, and (ii) the downfield shifts of the C-4a lines in comparison with those for the *cis* counterparts, in accordance with the expected upfield shifts of these signals in the more crowded *cis* isomers (field effect). While the C-4a shifts are 41.4±0.8 ppm for **18**–**20** and **22**, they are 37.6±0.5 ppm for the isomers **13**–**15** and **17**. The smaller and opposite difference in the C-8a shifts suggests conformationally homogeneous, quasi-rigid structures for the *cis* isomers with N(1) in a quasi-axial position. This is in accordance with our earlier finding[31–34] concerning the conformation of the cyclohexane-fused oxazines: of the two stable chair–chair conformers of 3,1-oxazines containing NH(1) or sp^2 N-1 vicinal to the anellated carbon, the N(1)-*in* form is preferred. In compounds **13**–**15** and **17**, this situation is more probable, in consequence of the bulkier CHPh group in position 4 bonded to the other anellated carbon instead of the methylene group in the same position in the molecules investigated earlier.

The relative configuration of C-4 was determined by means of DNOE measurements (Table 3). For the *trans*-anellated isomers, the interactions between H-8aax and the *ortho* hydrogens of the 4-phenyl ring and the similar interactions of the latter with H-5ax and between H-4 and H-5eq confirm the axial position of the 4-phenyl substituent *trans* to H-4a and *cis* to H-8a.

The DNOE results on the *cis*-anellated isomers **13**, **15** and **17** prove the equatorial orientation of the 4-phenyl group *trans* to both H-4a and H-8a. The most relevant NOE in this respect was observed between H-4a and H-8a in the 1,3-diaxial position.

The analogous stereostructures of **15** and **18** with those of the other *cis* and *trans*-anellated compounds follow directly from the very similar chemical shifts of the relevant H/C atoms.

For the monocyclic compounds, it is easy to determine the relative configurations of the substituted ring carbons and the substituents, respectively, but this is not possible for the third asymmetric carbon in the side-chain (position 4). The tt and dt multiplicities of the H-4a and H-8a signals of **6a** (two large couplings of about 12 Hz), characteristic of diaxial vicinal interactions,[35] are proof of the *trans*-diequatorial position of the substituents. The upfield shift (field effect) of the C-4a line (by 2.2 ppm) and the downfield

Table 3. ^{13}C NMR chemical shifts (in ppm, $\delta_{TMS}=0$ ppm), at 125.7 MHz. Solvent: $CDCl_3$ (for **2**, **3b** and **5**: D_2O) of compounds **2**, **3**, **5**, **6**, **8**, **9** and **13**–**22** (assignments were supported by DEPT and 2D-HSC (HMQC), and for **8** and **9** also by 2D-COLOC (HMBC) measurements)

Compound	C-2[a]	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Phenyl in position 4				Phenyl in side-chain			
									C-1	C-2,6	C-3,5	C-4	C-1	C-2,6	C-3,5	C-4
2	–	206.5	44.7	26.3	23.0	21.0	27.9	49.8	135.5	128.9	129.5	134.8	–	–	–	–
3a	–	78.3	47.3	26.1	18.3	19.9	35.8	52.2	144.1	126.3	128.2	126.8	–	–	–	–
3b[b]	–	74.7	43.7	24.6	21.1	23.0	28.0	50.3	142.7	129.2	128.7	127.0	–	–	–	–
5	–	204.4	49.3[c]	30.9	24.1	24.7	29.7	50.7[c]	135.1	129.0	129.5	135.0	–	–	–	–
6a	–	78.3	49.5	28.3	25.0	25.6	39.5	51.1	143.1	127.1	127.6	126.6	–	–	–	–
8[d]	–	194.4	100.7	27.9	23.4	22.0	26.2	164.2	138.2	126.6	127.8	128.4	143.0	127.0	128.8	127.4
9	–	77.9	47.1	25.4	20.0	18.4	28.1	58.0	139.5	125.8	127.8	126.4	143.6	128.5	128.7	127.4
13	155.4	81.8	38.1	24.9	18.8	19.7	31.0	50.8	137.8	125.8	128.6	128.1	–	–	–	–
14	187.5	83.9	37.1	19.4	24.6	19.9	30.5	52.7	136.6	125.9	128.8	128.4	–	–	–	–
15	154.8	79.5	37.6	25.0	19.6	20.7	33.1	53.1	139.1	125.4	127.2[c]	127.3	133.9	128.0[c]	128.2[c]	130.3
16	179.4	75.9	47.1	25.1	21.1[c]	21.0[c]	30.5	54.3	136.3	125.8[c]	128.2	127.0[c]	143.4	124.9[c]	130.0	127.3[c]
17	148.5	81.1	38.6	25.4	20.6	19.5	33.0	52.3	138.8	125.8	128.7	129.2	141.9	119.8	127.9	121.9
18	154.0	82.5	41.5	26.1	23.3	25.3	32.3	49.2	137.1	126.5	128.2[e]	128.2[e]	–	–	–	–
19	186.4	84.8	40.7	26.5	25.4	23.7	31.6	50.8	136.3	126.8	129.0	128.9	–	–	–	–
20	154.3	80.0	41.1	27.7	25.7	25.1	34.5	50.1	139.1	126.6	127.3[c]	127.8	134.0	128.0[c]	128.1[c]	130.3
21	180.1	70.2	51.3	25.3	25.1	22.8	33.5	56.0	135.7	125.8	127.8	127.6[c]	142.4	125.2	130.4	126.3[c]
22	148.3	81.6	42.2	27.7	26.2	25.1	35.1	50.2	138.9	127.1	128.6	129.2	141.8	119.8	128.4	121.9

[a] Urethane (**13**, **17**, **18** and **22**), thiourethane (**14** and **19**), thiocarbamide (**16** and **21**) or –O–C=N– group (**15** and **20**).
[b] Chlorohydrate, the major component in the 97:3 mixture.
[c] Interchangeable assignments.
[d] NCH_2: 46.3.
[e] Overlapping lines.

shift of the H-8a signal (by 0.95 ppm) for **3a** in comparison with **6a** suggest an equatorial→axial change in the position of the NH_2 group and thus the *cis* arrangement of the substituents (H-8a is more shielded in the axial position, in accordance with the literature). In the salt of **3b**, the main component is *cis*-anellated, as indicated by the small *t* splitting of the H-8a signal.

In the thioureas **16** and **21**, this group is *cis*-axial and *trans*-equatorial, as proved by the small splitting and downfield shift of the H-8a signal in **16** and the upfield shifts of the C-4a and C-8a lines (field effect).

4. Experimental

4.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. The physical and analytical data on the compounds prepared are listed in Table 2. Amino acids **1** and **4** were prepared from the corresponding alicyclic 1,2-dicarboxylic anhydrides by ammonolysis, followed by Hoffmann degradation and ion-exchange chromatography.[45] For the preparation of β-diketone **7**, 4-cyclohex-1-enylmorpholine was reacted with benzoyl chloride and the intermediate 4-(2-benzoylcyclohex-1-enyl)morpholine was hydrolysed.[46] The synthesis of **10** started from cyclohexanone and sodium cyanide; the cyanohydrin formed was treated with phosphorus oxychloride in pyridine.[47] The Grignard reaction of 1-cyanocyclohexene with phenylmagnesium bromide afforded **11**.[48]

IR spectra were run in KBr discs on a Bruker IFS-S 5 FT spectrometer, controlled by OPUS 2.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes, at room temperature, on a Bruker DRX-500 spectrometer at 500.13 (^1H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. For DNOE measurements,[30b,36] the standard Bruker microprogram DNOEMULT.AU to generate NOE[37] was used with a selective pre-irradiation time. DEPT spectra[38] were run in a standard manner,[39] using only the $\theta=135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down.

The 2D-COSY,[40] 2D-HMQC[41,42] and 2D-HMBC[43,44] spectra were obtained by using the standard Bruker pulse programs COSYGSSW, HXCO.AU (INV4GSSW) and HXXCO.AU (*IN*V4GSLRNDSW), respectively.

4.1.1. (1*S,2*R**)-2-Benzoylcyclohexylamine hydrochloride (2).** To a suspension of phosphorus(V) chloride (21 g, 0.1 mol) in 300 mL of dichloromethane at 0°C, *cis*-2-aminocyclohexanecarboxylic acid 1 (14.32 g, 0.1 mol) was added and the mixture was stirred for 2 h. After evaporation of the solvent, the residue was dried in a vacuum desiccator at room temperature for 3 h. To the residue, 300 mL of dry benzene and anhydrous aluminium chloride (40 g, 0.3 mol) were added. The mixture was heated at 60°C for 4 h, cooled to room temperature, and then poured into 200 g of ice–water. The mixture was shaken in an ice-bath, and the precipitate formed was filtered off, washed twice with ethyl acetate and dried. After recrystallization from ethanol, the crystals were filtered off. The mother liquor was evaporated and the residue was recrystallized from ethanol. The two crystalline fractions were combined, and dissolved in 100 mL of cold water. The solution was made alkaline with potassium carbonate and extracted with ethyl acetate (3×80 mL). After drying (Na_2SO_4) and evaporation of the organic solvent, a pale-yellow oil was obtained, which was purified by recrystallization as the hydrochloride (white powder).

4.1.2. (1*S,2*R**)-2-[(*R**)-α-Hydroxybenzyl]cyclohexylamine (3a).** *Method A*. The hydrochloride salt of amino ketone **2** (5.56 g, 23.19 mmol) was suspended in 60 mL of ethanol. The suspension was stirred and cooled in salt–ice–water. Sodium hydrogen carbonate (1.97 g, 23.45 mmol) and then sodium borohydride (3.48 g, 92 mmol) were added, the temperature of the mixture being maintained below −10°C, and stirring was continued until the mixture warmed up to room temperature. It was then stirred for a further 3 h and processed in the usual way. The ^1H NMR spectrum of the crude product revealed a 98:2 mixture of **3a** and **b**. Trituration of the oily residue with diisopropyl ether gave **3a** as white crystalline powder.

Method B. A solution of diketone **7** (10.12 g, 50 mmol) and benzylamine (5.57 g, 52 mmol) was refluxed for 3 h in 75 mL of abs. toluene, using a Dean–Stark trap. After evaporation of the solvent, the red–brown oily residue was triturated with diisopropyl ether to give **8** as white crystalline powder.

β-Imino ketone **8** (5.00 g, 17.16 mmol) was dissolved in 50 mL of ethanol and hydrogenated for six days in the presence of 5% platinum on carbon (0.50 g) at room temperature and 60 bar. The catalyst was filtered off and the solvent was evaporated off, to afford a white crystalline powder. The ^1H NMR spectrum of the crude product revealed the presence of homogeneous **9**.

The recrystallized benzylamino alcohol **9** (2.43 g, 8.20 mmol) was dissolved in 50 mL of methanol and the solution was stirred for 48 h in the presence of 20% palladium hydroxide on carbon (0.12 g) at room temperature and 60 bar. After filtration and evaporation, the resulting crystalline product was triturated with diisopropyl ether to give **3a** as white crystalline powder.

4.1.3. (1*R,2*R**)-2-Benzoylcyclohexylamine hydrochloride (5).** *Method A*. The same method was used as for the *cis* counterpart **2**, but starting from the *trans* amino acid **4**. However, the work-up was performed as follows. After the reaction mixture was poured into 200 g of ice–water, the aqueous phase was separated, washed with ethyl acetate, and then neutralized with sodium carbonate. The precipitate was filtered off (suction), washed with ethyl acetate (2×200 mL), then stirred with chloroform (200 mL) and decanted. After filtration, the two phases were separated and the aqueous phase was extracted with chloroform (200 mL). The combined organic phases were dried (Na_2SO_4) and the organic solvents were evaporated off. A pale-yellow oil was obtained, which was purified as the hydrochloride (white crystalline powder).

Method B. To a stirred mixture of 1-benzoylcyclohexene **11** (2.80 g, 15 mmol), a 50% aqueous solution of potassium thiocyanate (1.48 g, 15 mmol) and 50% aqueous sulfuric acid (0.8 mL, 7.5 mmol sulfuric acid) were added simultaneously dropwise at 55°C. After the addition of the reagents was complete, the reaction mixture was stirred at 55°C for 6 h. It was next cooled to room temperature and extracted with diethyl ether (3×30 mL). The combined organic phases were extracted with 5% sodium hydrogencarbonate solution (2×20 mL) and water (20 mL), and the ether phase was dried (Na_2SO_4) and evaporated. To the 2.93 g of yellow oily residue obtained, 20 mL of concentrated hydrochloric acid was added and the reaction mixture was stirred at 70°C until it became homogeneous (three days). It was then allowed to cool down to room temperature and was extracted with diethyl ether (2×10 mL). After evaporation of the aqueous phase, a white crystalline powder was obtained, which was filtered off and washed with diethyl ether and acetone.

Method C. Amino ketone **2** (3.5 g, 17.22 mmol) was dissolved in 50 mL of concentrated hydrochloric acid and the reaction mixture was stirred at 70°C for three days. Evaporation in vacuo led to a white crystalline powder, which was filtered off and washed successively with diethyl ether and acetone. The ^{1}H NMR spectrum of the crude product revealed a 9:1 mixture of **5** and **2**.

4.1.4. (1*R,2*R**)-2-[(*R**)-α-Hydroxybenzyl]cyclohexylamine (6a).** To an ice-cooled, stirred suspension of lithium aluminium hydride (1.68 g, 44.26 mmol) in 100 mL of diethyl ether, the amino ketone base of **5** (4.50 g, 22.13 mmol) in 20 mL of diethyl ether was added dropwise during 1 h. Stirring was continued until the mixture warmed up to room temperature. It was then stirred for a further 3 h and processed in the usual way. Trituration of the oily residue with diisopropyl ether gave **6a** as white crystalline powder. The ^{1}H NMR spectrum of the crude product revealed a 9:1 mixture of **6a** and **b**.

4.1.5. (4*R,4a*R**,3a*S**)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (13).** Amino alcohol **3a** (0.52 g, 2.53 mmol) was dissolved in 20 mL of toluene. To this solution, sodium hydroxide (0.50 g, 11.12 mmol) dissolved in 5 mL of water was added. After the addition of ethyl chloroformate (0.30 g, 2.78 mmol), the reaction mixture was shaken intensely for 30 min. The phases were next separated and the aqueous phase was extracted with toluene (10 mL). The combined organic phases were extracted with water (10 mL), dried (Na_2SO_4) and evaporated, to give 0.62 g of an oily residue. This urethane derivative was thoroughly mixed with sodium methoxide (0.02 g, 0.38 mmol), and the mixture was maintained at 130°C for 1 h. The melt was dissolved in 10 mL of chloroform and was extracted with water (10 mL). The aqueous phase was extracted with chloroform (2×5 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. Trituration of the oily residue with diisopropyl ether gave **13** as a white crystalline powder.

4.1.6. (4*R,4a*R**,3a*R**)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazin-2(1*H*)-one (18).** Amino alcohol **6a** (0.72 g, 3.50 mmol) was dissolved in 25 mL of toluene. To this solution, sodium hydroxide (0.62 g, 15.40 mmol) dissolved in 10 mL of water was added. After the addition of ethyl chloroformate (0.42 g, 3.85 mmol), the reaction mixture was shaken intensely for 30 min. The phases were separated and the aqueous phase was extracted with toluene (10 mL). The combined organic phases were extracted with water (10 mL), dried (Na_2SO_4) and evaporated, to give 0.92 g of oily residue. Trituration with petroleum ether afforded the white crystalline urethane derivative, which was recrystallized from diisopropyl ether (mp: 117–118°C, 0.82 g, 85%, white powder).

This urethane derivative of **6a** (0.20 g, 0.72 mmol) was thoroughly mixed with sodium methoxide (0.02 g, 0.38 mmol), and the mixture was maintained at 130°C for 1 h. The melt was extracted with 10 mL of hot ethyl acetate, and the extract was filtered, dried (Na_2SO_4) and evaporated. The oily residue crystallized on trituration with diisopropyl ether (white crystalline powder).

4.1.7. (4*R,4a*R**,3a*S**)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine-2(1*H*)-thione (14) and (4*R**,4a*R**,3a*R**)-4-Phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine-2(1*H*)-thione (19).** To a stirred solution of the amino alcohol **3a** or **6a** (0.30 g, 1.46 mmol) in chloroform (10 mL), triethylamine (0.16 g, 1.6 mmol) dissolved in 5 mL of chloroform was added dropwise. Carbon disulfide (0.12 g, 1.6 mmol) was then added under ice cooling and the mixture was kept at room temperature for four days. The solution was next evaporated to dryness, the residual oil was dissolved in 10 mL of chloroform, and triethylamine (0.16 g, 1.6 mmol) and ethyl chloroformate (0.17 g, 1.60 mmol) were added dropwise under ice cooling. The mixture was sirred for 30 min, then refluxed for 3 h and evaporated. The residual oil was dissolved in chloroform (15 mL) and washed with 1% aqueous HCl solution (10 mL). The organic phase was dried (Na_2SO_4) and evaporated. To the yellow oil obtained, diisopropyl ether was added to give white crystalline powder **14** or **19**.

4.1.8. (4*R,4a*R**,3a*S**)-2,4-Diphenyl-1,2,4a,5,6,7,8,8a-octahydro-4*H*-3,1-benzoxazine (15) and (4*R**,4a*R**,3a*R**)-2,4-Diphenyl-1,2,4a,5,6,7,8,8a-octahydro-4*H*-3,1-benzoxazine (20).** To a solution of amino alcohol **3a** or **6a** (0.30 g, 1.5 mmol) in dry ethanol (10 mL), ethyl benzimidate (0.22 g, 1.5 mmol) and two drops of glacial acetic acid in 1 mL of dry ethanol was added. The reaction mixture was refluxed for 12 h. Then, two drops of ethyl benzimidate were added and the solution was refluxed for a further 24 h. After evaporation, white crystalline powder of **15** or **20** was obtained.

4.1.9. Thiourea derivatives 16 and 21. Phenyl isothiocyanate (0.30 mL, 2.5 mmol) was added to amino alcohol **3a** or **6a** (0.50 g, 2.5 mmol) dissolved in 20 mL of dry toluene. The reaction mixture was stirred at room temperature for 8 h and evaporated. The white crystalline powder obtained was taken up in diisopropyl ether and the solution was filtered.

4.1.10. (4*R,4a*R**,3a*S**)-4-Phenyl-2(1*H*)-phenylimino-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine (17) and (4*R**,**

Table 4. Analytical data on the compounds prepared

Compound	Yield (%)	Mp (°C)	Formula	Analysis					
				C (%)		H (%)		N (%)	
				Calcd	Found	Calcd	Found	Calcd	Found
2	51	213–215[a]	$C_{13}H_{18}ClNO$	65.13	65.35	7.57	7.68	5.84	6.01
3a	77 (A)[b] 88 (B)[b,c]	119–121[d]	$C_{13}H_{19}NO$	76.06	75.77	9.33	9.14	6.82	6.72
5	24 (A)[b] 50 (B)[b] 48 (C)[b]	209–211[a,e]	$C_{13}H_{18}ClNO$	65.13	64.89	7.57	7.82	5.84	6.12
6a	70	121–122[d]	$C_{13}H_{19}NO$	76.06	75.83	9.33	9.27	6.82	6.84
8	78	75–77[d]	$C_{20}H_{21}ClNO$	82.44	82.32	7.26	6.97	4.81	5.15
9	91[f]	118–120[d]	$C_{20}H_{24}NO$	81.31	81.47	8.53	8.40	4.74	4.78
13	78	240–241[g]	$C_{14}H_{17}NO_2$	72.70	72.30	7.41	7.32	6.06	6.16
14	47	228–229[d]	$C_{14}H_{17}NOS$	67.98	68.43	6.93	7.23	5.66	5.50
15	86	106–109[e]	$C_{20}H_{21}NO$	82.44	82.37	7.26	7.43	4.81	5.12
16	87	155–157[h]	$C_{20}H_{24}N_2OS$	70.55	70.14	8.23	8.35	7.10	6.89
17	63	163–165[d]	$C_{18}H_{22}N_2O$	76.56	76.62	9.92	10.11	9.92	9.89
18	74	199–201[i]	$C_{14}H_{17}NO_2$	72.70	73.02	7.41	7.58	6.06	6.34
19	43	217–219[h]	$C_{14}H_{17}NOS$	67.98	68.32	6.93	6.70	5.66	5.47
20	88	171–172[e]	$C_{20}H_{21}NO$	82.44	82.32	7.26	7.45	4.81	4.84
21	80	166–168[i]	$C_{20}H_{24}N_2OS$	70.55	70.43	8.23	8.14	7.10	7.05
22	72	144–146[d]	$C_{18}H_{22}N_2O$	76.56	76.73	9.92	10.27	9.92	9.62

[a] Ethanol-diethyl ether (solvent for recrystallization).
[b] Corresponding methods in Section 4.
[c] Yield starting from **9**.
[d] Diisopropyl ether (solvent for recrystallization).
[e] Ethanol (solvent for recrystallization).
[f] Yield starting from **8** (solvent for recrystallization).
[g] Ethyl acetate-ethanol (solvent for recrystallization).
[h] Diisopropyl ether-ethyl acetate (solvent for recrystallization).
[i] Ethyl acetate (solvent for recrystallization).

4a*R,3a*R**)-4-Phenyl-2(1*H*)-phenylimino-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine (22).** Thiourea derivative **16** or **21** (0.23 g, 0.69 mmol) was dissolved in methanol (10 mL), methyl iodide (0.44 mL, 6.9 mmol) was added and the solution was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was stirred in 10 mL of 15% methanolic potassium hydroxide for two days. After evaporation, ice–water (10 mL) and chloroform (15 mL) were added, and the phases were separated. The aqueous phase was extracted with chloroform (10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The oxazines **17** and **22** were obtained as white crystalline powders (Table 4).

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