An Efficient and Simple Synthesis of 3,4,5,6-Tetrahydro-2*H*-1,2-oxazines by Sodium Cyanoborohydride Reduction of 5,6-Dihydro-4*H*-1,2-oxazines

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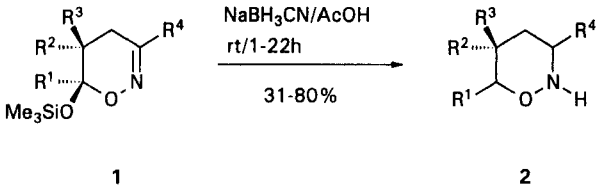
3,4,5,6-Tetrahydro-2*H*-1,2-oxazines are prepared by reduction of the corresponding 5,6-dihydro-4*H*-1,2-oxazines with sodium cyanoborohydride as the reducing agent in acetic acid. This reaction gives the 3,5-disubstituted compounds **2a–c**, **2f–g**, and **5a,b** with good to excellent *cis* selectivities, while a 3,6-disubstituted 1,2-oxazine leads to a *trans* configurated product as the major isomer. Under the same reaction conditions the bicyclic heterocycle **14** affords two products, the expected compound **15** and the cyclopentenol derivative **16** as a byproduct. Also, the formation of trifluoromethylated ketoximes **18** and **21** starting from the precursors **17** and **19** is described.

Tetrahydro-2*H*-1,2-oxazines have gained increasing interest in organic synthesis as useful intermediates[1] and are key compounds in the synthesis of natural products[2] and of unnatural cyclic amino acids.[3] They also play an important role as partial structures in agricultural and horticultural fungicides, herbicides, and broad spectrum bacteriocides.[4] Motivated by these applications we investigated the preparation of these N,O-compounds and found a simple and efficient synthesis starting from easily accessible 6-trimethylsiloxy(6-alkoxy)-substituted 5,6-dihydro-4*H*-1,2-oxazines.[5–9]

Reaction of trimethylsiloxy-substituted 4*H*-1,2-oxazines **1** with reducing agents transforms these heterocycles into γ-hydroxyketoximes ($NaBH_4$), to *N*-hydroxypyrrolidine derivatives (DIBAL), and to amines or to proline derivatives (H_2/Pd–C).[10] We report here our results employing sodium cyanoborohydride[11] which adds hydride to the oxime ether unit, thus smoothly affording a series of 3,4,5,6-tetrahydro-2*H*-1,2-oxazines. As constitutional isomers of morpholine derivatives interesting pharmacological activities of those heterocycles are conceivable. When $R^4 = CO_2Et$ (Scheme 1) these compounds are of particular interest because they can be regarded as oxahomologs of proline derivatives or as carbahomologs of cycloserine.[3]

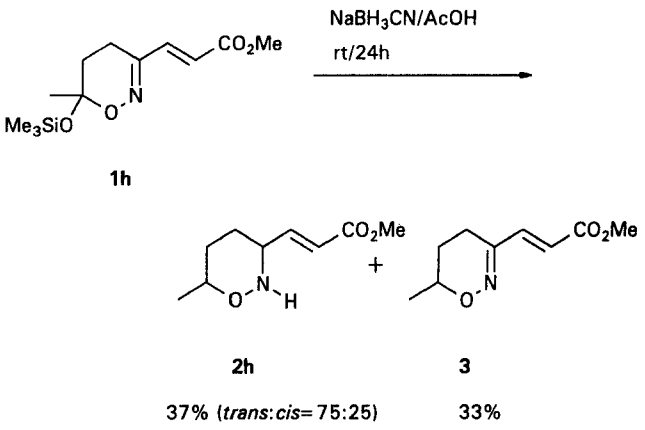
Reductions of the C=N unit in oximes,[12] oxime ethers,[13] and isoxazoles[14] with sodium cyanoborohydride ($NaBH_3CN$) are commonly known. However, Henning et al.[15] have only described one example of a 5,6-dihydro-4*H*-1,2-oxazine reduction with this agent leading to an oxime derivative, but they did not observe hydride addition to C-3. We performed the reactions with an excess of $NaBH_3CN$ in acetic acid at room temperature. Scheme 1 collects the individual examples of 6-siloxy-substituted 4*H*-1,2-oxazines, reflecting the scope of this reduction. Interestingly, in addition to the hydride transfer to C-3, heterocycles **1** are also reduced at the acetal moiety. The formation of compounds **2** is generally highly diastereoselective leading to *cis* isomers as major products (entries a–c, f–g in Scheme 1). It is remarkable that 1,2-oxazines with the electron-withdrawing group CO_2Et at C-3 show lower diastereoselectivities compared to their 3-phenyl analogs. The stereochemical outcome of the reaction is apparently independent of the *trans*/*cis* ratio of the precursor (see entries a, b in Scheme 1). We therefore assume that the siloxy group of **1** is removed in the first step and the remaining substituents determine the attack of the reducing agent towards the oxime ether function. The reduction at C-6 probably starts with acetolysis to form the 6-acetoxy intermediate **A** as illustrated in Scheme 2. Intermediate **A** is converted under the acidic reaction conditions via an carboxonium ion **B** into **C** which is further reduced to afford the isolated 2*H*-1,2-oxazine **2**. Reaction of 4*H*-1,2-oxazine **1h**[7] under standard conditions provides a mixture of the expected 3,4,5,6-tetrahydro-2*H*-1,2-oxazine **2h** and the partially reduced product **3**. This result is also in accordance with the sequence of reduction steps as proposed above (Scheme 2).



1 2

Entry	Precursor 1 (*trans*:*cis*)	R^1	R^2	R^3	R^4	Product 2 (*cis*:*trans*)	Yield (%)
a	**1a** (15:85)	H	H	Me	Ph	**2a** (96:4)	73
b	**1b** (75:25)	H	Me	H	Ph	**2a** (95:5)	64
c	**1c** (>97:3)	H	$OSiMe_3$	H	Ph	**2c**[a] (83:17)	80
d	**1d**		$-(CH_2)_4-$	H	Ph	**2d**[b]	57
e	**1e**	H	H	H	CO_2Et	**2e**	31
f	**1f** (77:23)	H	Me	H	CO_2Et	**2f** (73:27)	65
g	**1g** (95:5)	H	$OSiMe_3$	H	CO_2Et	**2g**[a] (70:30)	48

[a] R^2 = OH.
[b] Four diastereomers (35:25:25:15).



1h

2h 37% (*trans*:*cis* = 75:25) **3** 33%

Scheme 1

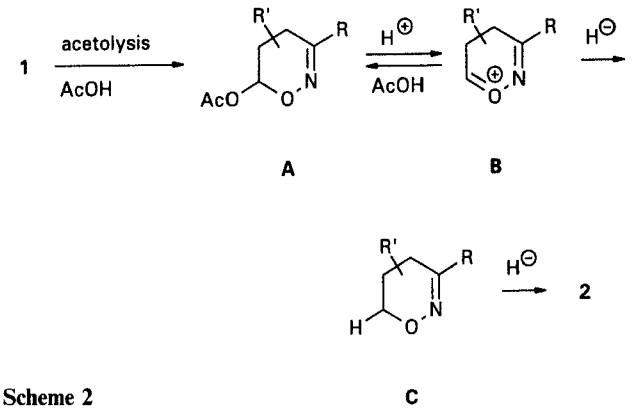
Table 1. Prepared Compounds **2a, 2c–h, 3, 5a,b, 7, 9a–c, 11, 13, 15, 16, 18**, and **21**

Educt[a]	Product[a,b]	Time (h)	Yield (%)	Solvent for chromatography	mp (°C)	IR[c] ν (cm^{-1}) (N–H)
1a (15 : 85)	**2a** (4 : 96)	1	73	Et_2O/pentane (2 : 1)	41–44	3420, 3240, 3100–3020 (=CH)
1b (75 : 25)	**2a** (5 : 95)	1	64			
1c (> 97 : 3)	**2c** (17 : 83)	1	80	*t*-BuOMe/pentane (2 : 1)	112–115	3700–3100, 3080–3020 (=CH)
1d	**2d**[d]	22	57	pentane/EtOAc (7 : 3)	oil	3200, 3060, 3030 (=CH)
1e	**2e**	18	31	*t*-BuOMe/EtOAc (4 : 1)	oil	3400–3250, 1730 (C=O)
1f (77 : 23)	**2f** (27 : 73)	5	65	*t*-BuOMe/EtOAc (4 : 1)	oil	3400, 3240, 1735 (C=O)
1g (95 : 5)	**2g** (30 : 70)	20	48	*t*-BuOMe/EtOAc (2 : 1)	oil	3500–3100, 1740 (C=O)
1h	**2h** (75 : 25)	24	37	hexane/EtOAc (3 : 2)	oil	3350–3200, 1725 (C=O), 1640 (C=C)
	3		33			1720 (C=O), 1630 (C=N, C=C)
4a	**5a** (4 : 96)	6	72	hexane/EtOAc (1 : 1)	112–115	3380, 3340, 3120–3020 (=CH)
4b	**5b** (7 : 93)	6	87	[e]	oil	3400–3300, 1735 (C=O)
6	**7**[f]	6	48	hexane/EtOAc (1 : 1)	oil	3300, 3240, 1735 (C=O)
8a	**9a** (87 : 13)[g]	16	68[h]	hexane/*t*-BuOMe (4 : 1)	117–121	3400, 1345, 1160 (SO_2)
8b	**9b** (56 : 44)[g]	18	61[h]	hexane/*t*-BuOMe (4 : 1)	188–195	3470–3400, 1730 (C=O), 1350, 1170 (SO_2)
8c	**9c** (61 : 39)[g]	17	65[h]	hexane/*t*-BuOMe (4 : 1)	195	3420, 1355, 1165 (SO_2)
10	**11** (79 : 21)[g]	17	65[h]	hexane/*t*-BuOMe (7 : 3)	oil	3450
12	**13** (96 : 4)	2	65	[e]	48–49	3190, 3050, 3030 (=CH)
14	**15** (57 : 43)[g]	1.5	67	[e]	oil	3270, 3060–3020 (=CH), 1600 (C=C)
	16[i]		15		oil	ref.[20]
17 (70 : 30)	**18**[j]	15	41	[e]	oil	3600–3100 (O–H), 1620 (C=N), 1185, 1130 (CF_3)
19	**21**[j]	24	40	*t*-BuOMe/EtOAc (1 : 1)	oil	3600–3150 (O–H), 3110–2780 (=CH), 1640, 1620 (C=C, C=N), 1190, 1125 (CF_3)

[a] Values in parentheses refering to isomeric ratio (*trans* : *cis*).
[b] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.30, N ± 0.22, exceptions **2f**: C – 0.48, H + 0.43; **13**: N – 0.48; **20**: C + 0.50.
[c] Oils as film, solids as KBr pellets.
[d] Four diastereomers (35 : 25 : 25 : 15), assignment is not possible.
[e] Purification by Kugelrohr distillation; bp 120 °C/0.01 Torr.
[f] After work up the crude material was transformed into the 4,5-isopropylidene protected compound by *p*-TsOH/2,2-dimethoxypropane treatment (3 h, r.t.).
[g] The relative configuration is not sure; the diastereomeric ratio of **9c** was determined after chromatography.
[h] Two isomers; **9a**: $[\alpha]_D = -85$ ($c = 1.6$, $CHCl_3$); **9b**: $[\alpha]_D = -79$ ($c = 0.8$, $CHCl_3$); **9c**: major isomer $[\alpha]_D = -60$ ($c = 1.9$, $CHCl_3$), minor isomer $[\alpha]_D = -2$ ($c = 1.5$, $CHCl_3$); **11**: $[\alpha]_D = +88$ ($c = 3.2$, $CHCl_3$).
[i] Four isomers (30 : 30 : 30 : 10).
[j] **18**: $E : Z = 95 : 5$; **21**: $E : Z = 85 : 15$.

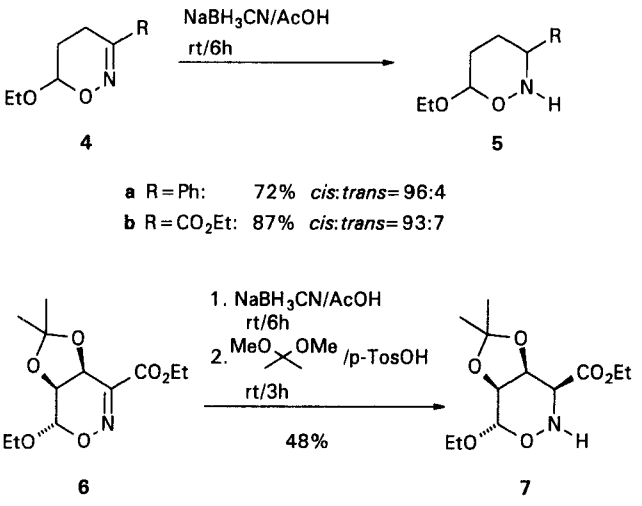
The relative stereochemistry at the centers 3 and 5 in *cis*-**2a** as a model compound for 3,5-disubstituted 1,2-oxazines could be determined by means of ^1H NMR NOE measurements. Irradiation of 5-Me resonance signal induces a NOE at protons 6-H_{eq}, 5-H, 4-H_a and 4-H_b. On the other hand, in a different NOE experiment when the 4-H_b signal is irradiated, signals of 3-Ph, 5-Me protons and the 4-H_a proton are enhanced, whereas no appreciable NOE is observed between 3-H and 4-H_b. These results of NOE investigations and the observed coupling constants (see Table 2) are in accord with a chair conformation and the proposed *cis* configuration.

In contrast to the siloxy derivatives **1**, reaction of 6-alkoxy-substituted 1,2-oxazines leads only to reduction of the oxime ether unit.[16] As depicted in Scheme 3, 6-alkoxy-4*H*-1,2-oxazines **4a** and **4b** provide the 3,6-disubstituted compounds **5a** and **5b** with excellent *cis* se-



Scheme 2

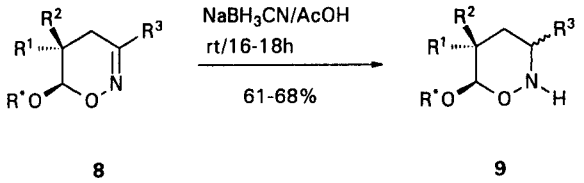
lectivities and in good yields. The *cis* configuration of the major diastereomer of **5a** is determined by a 500 MHz ^{1}H NMR spectrum. That **5a** assumes a chair conformation[17] with the 6-ethoxy group occupying an axial position is indicated by the coupling constants (see Table 2). The reduced crude product from **6** was deprotected at C-4/C-5 under the usual acidic reaction conditions. The subsequent reacetalization at these positions is performed under standard conditions providing the isolated compound **7** as one single diastereomer in moderate yield (Scheme 3).



Scheme 3

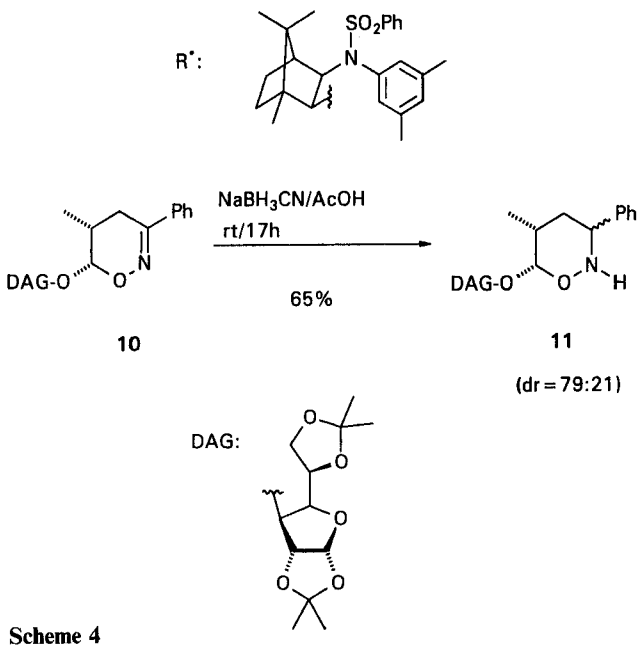
The $NaBH_3CN$ reduction was also successfully applied to optically pure 6-alkoxy-substituted 4*H*-1,2-oxazines, e.g. **8a–c** and **10**,[18] to form the corresponding 2*H*-1,2-oxazine derivatives **9a–c** and **11**. The best results in terms of diastereoselectivity are obtained with **9a** (Scheme 4) and compound **11** which contains diacetone glucose as chiral auxiliary.[19] It must be pointed out that the stereochemical assignment at C-3 in **9a–c** and **11** is so far ambiguous considering the NMR data, but according to the mechanistic considerations (see below) the major isomer should be *cis* configurated.

We have also studied the behaviour of 4*H*-1,2-oxazines lacking the 6-donor function. While the reduction of 6-oxygen-substituted 4*H*-1,2-oxazines preferentially provides *cis* isomers, the reaction of 6-(trimethylsilyl)methyl-substituted 1,2-oxazine **12** affords the expected product **13** with very high *trans* selectivity (96:4). On the other hand, the preparation of the bicyclic compound **15**, starting from **14**, is accompanied by the unexpected cyclopentene derivative **16**[20] as byproduct. This is the only case where we observed cleavage of the N–O bond, possibly because of the increased strain of precursor **15**.



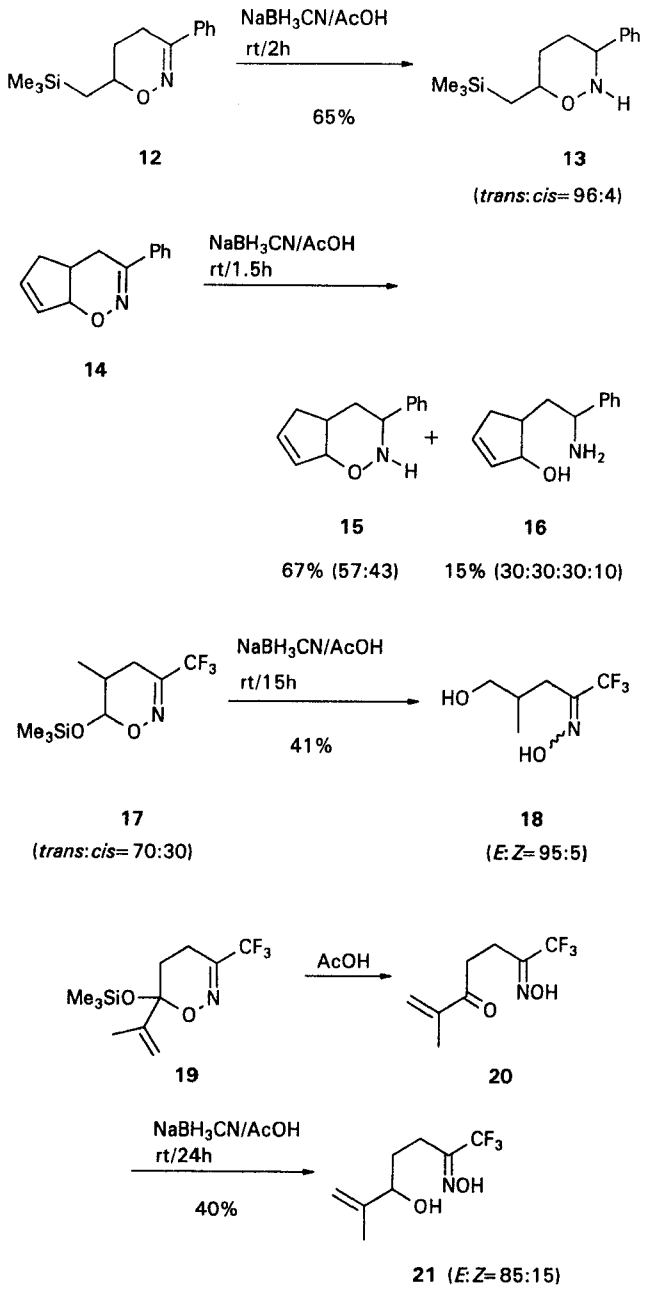
Precursor **8**	R^1	R^2	R^3	Product **9** (dr)	Yield (%)
8a	H	Me	Ph	**9a** (87:13)	68
8b	H	Me	CO_2Et	**9b** (56:44)	61
8c	Me	H	Ph	**9c** (61:39)[a]	65

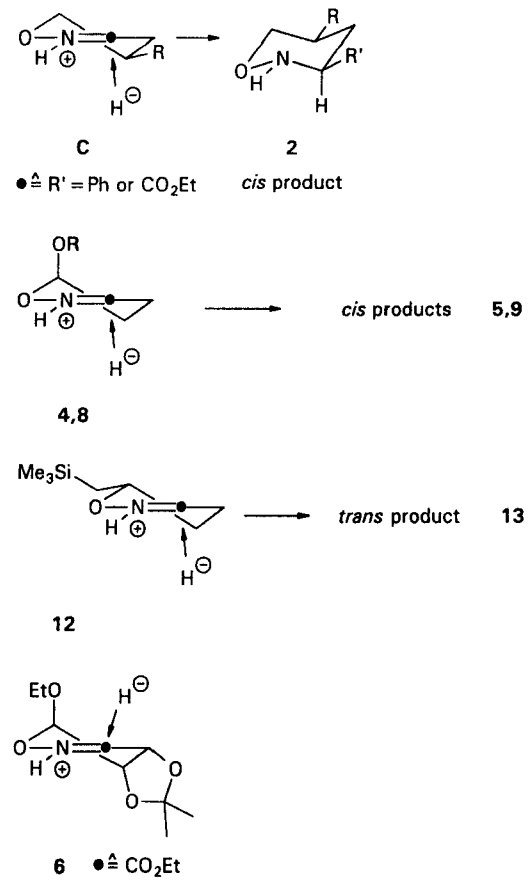
[a] Diastereomeric ratio was determined after chromatography.



Scheme 4

Interestingly, treatment of 3-trifluoromethyl functionalized 4*H*-1,2-oxazines such as **17** and **19** under the same reduction conditions as above provides only oximes **18** and **21** in moderate yields but with high predominance of *E*-oxime configuration. The intermediate enone **20** was further reduced by $NaBH_3CN$. Therefore, we conclude that a nitrogen protonation starts the reduction, and this step is unfavourable for 3-trifluoromethyl containing 1,2-oxazines. The electrophilicity of the C=N unit of **17** and **19**, respectively, is highly increased by the adjacent trifluoromethyl group, which possesses a strong electron-withdrawing effect. This observation is in agreement with previous results, in which the acid-catalyzed isomerization of 5-methylene-3-trifluoromethyl-4*H*-1,2-oxazine into the corresponding 6*H*-1,2-oxazine failed.[21]





Scheme 5

We explain our observed stereochemical results as illustrated in Scheme 5. Intermediate **C** should accommodate a half-chair conformation, where the C-5 substituent R occupies a *pseudo* equatorial position. Under these prerequisites the hydride transfer to C-3 occurs in the stereoelectronically favourable axial direction and the stereochemical outcome of **2** is less dependent on steric effects. In accordance with this hypothesis 4*H*-1,2-oxazines **4a,b** and **8a–c** lead to *cis* products **5a,b** and **9a–c**. The 6-alkoxy group in **4** and **8**, respectively, occupies a *pseudo* axial position due to the anomeric effect. 6-(Trimethylsilyl)methyl-substituted compound **12** provides *trans*-**13** as the major isomer (see Scheme 5). However, the hydride attacks the C=N bond in 4*H*-1,2-oxazine **6** exclusively from the sterically less hindered face thus providing product **7**. This result must be attributed to the dominating steric effect of the *cis*-fused dioxolane ring.

In summary, starting from the corresponding 5,6-dihydro-4*H*-1,2-oxazines, we have achieved a general and convenient access to a variety of 3,4,5,6-tetrahydro-2*H*-1,2-oxazines containing a 3-phenyl- or 3-alkoxycarbonyl group by reduction of the C=N moiety with sodium cyanoborohydride. Furthermore, we have demonstrated a ring-opening reaction of 3-trifluoromethyl-4*H*-1,2-oxazines using the same reducing agent. This transformation demonstrates a suitable preparation of polyfunctional fluorinated oximes which can serve as precursors of ketones bearing a CF_3 group. These compounds are of growing interest as enzyme inhibitors.[22]

Sodium cyanoborohydride and acetic acid were commercially available and were used as received. IR spectra were measured with a Perkin-Elmer spectrometer IR-325. ^1H and ^{13}C NMR spectra were obtained on a Bruker WM 300 and a Bruker AMX 500 in $CDCl_3$ solution. The chemical shifts are given in ppm relative to TMS from solvent ($CDCl_3$) signal ($\delta_H = 7.27$, $\delta_C = 77.0$). Optical rotations were obtained at 20°C using a Perkin-Elmer polarimeter 141. Neutral alumina (activity III, Fa. Macherey-Nagel) was used for column chromatography. Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohr oven. Melting points (uncorrected) were measured with an apparatus (SMP 20) from Büchi. Synthesis of starting materials: 6-siloxy-substituted 1,2-oxazines **1a–1f**,[5] **1h**,[7] **17**,[6] and **19**;[6] 6-alkoxy-substituted 1,2-oxazines **4a**,[23] **4b**,[24] **6**,[25] **8a–8c**,[18] and **10**;[18] 1,2-oxazines **12**[5] and **14**.[20]

Ethyl 5,6-Dihydro-5,6-bis(trimethylsiloxy)-4*H*-1,2-oxazine-3-carboxylate (1g):

According to ref.[5] a suspension of 3-bromopyruvate oxime (1.05 g, 5.00 mmol), 1,2-bis(trimethylsiloxy)ethene (5.57 g, 27.3 mmol; *E*:*Z* = 30:70), and freshly ground Na_2CO_3 (2.65 g, 25.0 mmol) in *t*-BuOMe (150 mL) was stirred at r.t. for 5 d. After workup radial

Table 2. ^{1}H NMR Data of Tetrahydro-2*H*-1,2-oxazines **2a, 2c–h, 3, 5a,b, 7, 9a–c, 11, 13**, and **15**

Compound	^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ, J (Hz)
cis-**2a**[a]	1.08 (d, 3H, J = 6.5, 5-Me), 1.37, 2.25–2.44 (m_c, m, 1H, 2H, 4-H, 5-H), 2.88 (dd, 1H, J = 3.5, 10, 6-H), 3.00 (t, 1H, J = 10, 6-H), 3.80 (dd, 1H, J = 7, 11, 3-H), 5.50 (br s, 1H, NH), 7.20–7.40 (m, 5H, Ph)
trans-**2a**[b]	1.07 (d, 3H, J = 6.5, 5-Me), 2.48 (t, 1H, J = 13.5, 6-H), 3.17 (dd, 1H, J = 4.5, 13, 6-H), 4.23 (dd, 1H, J = 6.5, 13, 3-H)
cis-**2c**	1.70–1.85, 2.63 (m, 1H, td, 1H, J = 7.5, 14, 4-H), 2.90 (dd, 1H, J = 6.5, 11, 6-H), 3.20 (br d, 1H, $J \approx$ 11, 6-H), 3.63 (dd, 1H, J = 7.5, 11, 3-H), 4.20–4.35 (m, 1H, 5-H), 5.35 (br s, 2H, NH, OH), 7.28 (m_c, 5H, Ph)
trans-**2c**[b]	2.07–2.16 (m, 2H, 4-H), 2.87 (dd, 1H, J = 4.5, 11.5, 6-H), 2.98 (br d, 1H, $J \approx$ 7, 3-H), 3.52 (dd, 1H, J = 6, 11.5, 6-H), 4.36–4.43 (m, 1H, 5-H)
2d	0.81–2.96 (m, 11H, 4a-H, 5CH_2), 3.37 (dt, 0.35H, J = 4, 10, 8a-H), 3.45–3.69 (m, 0.25H, 8a-H), 3.75 (dd, 0.25H, J = 8, 10.5, 3-H), 3.86 (td, 0.15H, J = 5, 11.5, 8a-H), 3.96 (br d, 0.25H, $J \approx$ 3, 8a-H), 4.09 (dd, 0.15H, J = 3, 11, 3-H), 4.17 (dd, 0.25H, J = 2.5, 11, 3-H), 4.34 (dd, 0.35H, J = 2.5, 12, 3-H), 5.15 (br s, 1H, NH), 7.21–7.41 (m, 5H, Ph)
2e	1.27 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.75–2.28 (m, 4H, 4-H, 5-H), 2.79–3.36 (m, 2H, 6-H), 3.62 (dd, 1H, J = 8, 8.5, 3-H), 4.19 (q, 2H, J = 7, OCH_2), 7.00 (br s, 1H, NH)
cis-**2f**	1.06 (t, 3H, J = 6.5, 5-Me), 1.27 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.33–1.52, 2.35–2.55 (2m, 1H, 2H, 4-H, 5-H), 2.96 (dd, 1H, J = 5, 10.5, 6-H), 3.12 (dd, 1H, J = 8.5, 10.5, 6-H), 3.72 (dd, 1H, J = 8, 9.5, 3-H), 4.19 (q, 2H, J = 7, OCH_2), 6.40 (br s, 1H, NH)
trans-**2f**[b]	1.07 (t, 3H, J = 6.5, 5-Me), 3.48 (dd, 1H, J = 6.5, 9.5, 6-H), 3.65 (dd, 1H, J = 8.5, 9.5, 6-H), 4.12 (q, 2H, J = 7, OCH_2), 4.32 (dd, 1H, J = 7, 13.5, 3-H)
cis-**2g**	1.28 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.84–1.95, 2.56–2.72 (2m, 1H each, 4-H), 2.98 (dd, 1H, J = 6, 11, 6-H), 3.38 (br d, 1H, $J \approx$ 11, 6-H), 3.54 (t, 1H, J = 9, 3-H), 4.21 (q, 2H, J = 7, OCH_2), 4.35 (m_c, 1H, 5-H), 5.00 (br s, 2H, NH, OH)
trans-**2g**[b]	1.27 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 2.05–2.32 (m, 2H, 4-H), 2.78 (dd, 1H, J = 3, 10, 6-H), 3.34 (dd, 1H, J = 6, 10, 6-H), 3.78 (dd, 1H, J = 6, 8.5, 3-H), 4.51 (m_c, 1H, 5-H)
trans-**2h**	1.16 (d, 3H, J = 6, 6-Me), 1.30–2.20 (m, 4H, 4-H, 5-H), 2.23–3.00, 3.63–3.70 (2m, 1H each, 3-H, 6-H), 3.74 (s, 3H, $CO_2\underline{Me}$), 4.35 (br s, 1H, NH), 5.95 (dd, 1H, J = 1.5, 16, =CH), 6.79 (dd, 1H, J = 6, 16, =CH)
cis-**2h**[b]	1.21 (d, 3H, J = 6, 6-Me), 3.77–3.90 (m, 1H, 6-H), 3.73 (s, 3H, $CO_2\underline{Me}$), 6.00 (dd, 1H, J = 1.5, 16, =CH), 6.96 (dd, 1H, J = 6, 16, =CH)
3	1.12 (d, 3H, J = 6, 6-Me), 1.50–1.95 (m, 2H, 5-H), 2.56 (td, 1H, J = 8, 14, 4-H), 2.75–2.92, 3.68–3.78 (2m, 1H each, 4-H, 6-H), 3.79 (s, 3H, $CO_2\underline{Me}$), 6.25, 7.28 (2d, 1H each, J = 16, HC=CH)
cis-**5a**[a]	1.39 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.96 (dddd, 1H, J = 2.5, 3.4, 4.9, 14.5, 4-H), 2.07 (dddd, 1H, J = 1.5, 2.5, 4.4, 13.8, 5-H), 2.21 (dddd, 1H, J = 3.5, 4.9, 13.6, 13.8, 5-H), 2.51 (dddd, 1H, J = 4.4, 13.4, 13.6, 14.5, 4-H), AB part of ABX_3 system (δ_A = 4.10, δ_B = 3.76, 2H, $J_{AX} = J_{BX}$ = 7, J_{AB} = 10.1, OCH_2), 4.37 (ddd, 1H, J = 3.4, 10.4, 13.4, 3-H), 5.21 (dd, 1H, J = 1.5, 3.5, 6-H), 7.38–7.51 (m, 6H, NH, Ph)
trans-**5a**[b]	3.41, 5.66 (2m_c, 1H each, 6-H, CH_2)
cis-**5b**	1.25, 1.28 (2t, 3H each, J = 7, $OCH_2C\underline{H}_3$), 1.75–2.07 (m, 4H, 4-H, 5-H), 3.47–3.59, 3.75–3.89 (2m, 1H, 2H, 3-H, OCH_2), 4.19 (q, 2H, J = 7, OCH_2), 4.73 (m_c, 1H, 6-H), 5.58 (br s, 1H, NH)
trans-**5b**[b]	2.11–2.21 (m, 2H, 4-H), 3.68 (m_c, 1H, 3-H)
7[c]	1.17, 1.24 (2t, 3H each, J = 7, $OCH_2C\underline{H}_3$), 1.32, 1.45 (2s, 6H, 2Me), AB part of ABX_3 system (δ_A = 3.86, δ_B = 3.63, 2H, $J_{AX} = J_{BX}$ = 7, J_{AB} = 10, OCH_2), 3.88, 4.21, 4.62 (3m_c, 1H, 3H, 2H, OCH_2, 3-H, 4-H, 5-H, 6-H), 6.07 (br s, 1H, NH)
9a major	0.53, 0.59, 1.07 (3s, 9H, 3Me), 1.49 (d, 3H, J = 7, 5-Me), 0.75–2.30 (m, 15H, 4-H, 5-H, NH, 2ArMe, CH, 2CH_2), 4.18 (m, 3H, 3-H, 2CH), 5.73 (d, 1H, J = 3.5, 6-H), 7.00–7.80 (m, 13H, CH_{arom})
9a[b] minor	0.51, 0.55, 0.92 (3s, 9H, 3Me), 1.28 (d, 3H, J = 7, 5-Me), 2.64 (s, 1H, NH), AB system (δ_A = 4.06, δ_B = 3.95, 2H, J_{AB} = 7, 2CH), 4.31 (dd, 1H, J = 2.5, 11.5, 3-H), 5.14 (d, 1H, J = 2, 6-H)
9b[d] major	0.41, 0.78 (2s, 6H, 2Me), 0.93 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.22 (s, 3H, Me), 1.50 (d, 3H, J = 7, 5-Me), 0.88–2.27 (m, 14H, 4-H, 5-H, 2 ArMe, CH, 2CH_2), 2.61 (s, 1H, NH), 3.63 (br dd, 1H, J = 3, 10, 3-H), 3.92 (q, 2H, J = 7, OCH_2), AB system (δ_a = 4.36, δ_B = 4.25, 2H, J_{AB} = 8, 2CH), 5.93 (d, 1H, J = 3, 6-H), 7.00–7.80 (m, 8H, CH_{arom})
9b[b, d] minor	0.33, 0.70 (2s, 6H, 2Me), 0.92 (t, 3H, J = 7, $OCH_2C\underline{H}_3$), 1.32 (s, 3H, Me), 1.37 (d, 3H, J = 7, 5-Me), 3.76 (dt, 1H, J = 4, 11, 3-H), 3.89 (q, 2H, J = 7, OCH_2), AB system (δ_a = 4.53, δ_B = 4.16, 2H, J_{AB} = 8, 2CH), 6.40 (d, 1H, J = 2, 6-H)
9c major	0.56, 0.60, 1.03 (3s, 9H, 3Me), 1.43 (d, 3H, J = 6.5, 5-Me), 1.00–2.38 (m, 15H, 4-H, 5-H, NH, 2ArMe, CH, 2CH_2), AB system (δ_A = 4.09, δ_B = 3.93, 2H, J_{AB} = 7, 2CH), 4.18 (dd, 1H, J = 3, 11, 3-H), 5.06 (d, 1H, J = 8, 6-H), 6.79–7.58 (m, 13H, CH_{arom})
9c[b] minor	0.52, 0.61, 0.94 (3s, 9H, 3Me), 1.36 (d, 3H, J = 7, 5-Me), 2.88 (s, 1H, NH), AB system (δ_A = 4.08, δ_B = 3.96, 2H, J_{AB} = 7, 2CH), 4.42 (br d, 1H, $J \approx$ 11, 3-H), 5.05 (d, 1H, J = 0.5, 6-H)
11 major	1.05 (d, 3H, J = 7, 5-Me), 1.27, 1.34, 1.42, 1.48 (4s, 12H, 4Me), 1.75–2.11 (m, 4H, 4-H, 5-H, NH), 3.95–4.37 (m, 6H, 3-H, 3CH, CH_2), 4.83, 4.89 (2d, 1H each, J = 3.5 and 3, 2CH), 5.90 (d, 1H, J = 3.5, 6-H), 7.00–7.80 (m, 5H, Ph)
11[b] minor	1.10 (d, 3H, J = 7, 5-Me), 1.32, 1.35, 1.44, 1.50 (4s, 12H, 4Me), 4.93 (d, 1H, J = 3, CH), 6.05 (d, 1H, J = 3, 6-H)
trans-**13**	0.12 (s, 9H, $SiMe_3$), 0.84, 1.00 (2dd, 2H, J = 7, 14.5, CH_2Si), 1.48–1.64, 1.94 (m, m_c, 2H each, 4-H, 5-H), 3.90 (dtd, 1H, J = 2, 7, 14.5, 6-H), 4.08 (dd, 1H, J = 3.5, 10.5, 3-H), 4.90 (br s, 1H, NH), 7.20–7.40 (m, 5H, Ph)
cis-**13**[b]	0.09 (s, 9H, $SiMe_3$), 0.95, 1.21 (2dd, 2H, J = 7, 14.5, CH_2Si), 1.57, 1.78–2.21 (m_c, m, 1H, 3H, 4-H, 5-H), 4.00 (dtd, 1H, J = 3.5, 7, 8, 6-H), 4.14 (t, 1H, J = 5, 3-H), 5.33 (s, 1H, NH)
15 major	1.91–2.61 (m, 5H, 4-H, 4a-H, 5-H), 4.12 (dd, 1H, J = 3, 11.5, 3-H), 4.72 (m_c, 1H, 7a-H), 5.44 (br s, 1H, NH), 5.88 (m_c, 1H, 7-H), 6.28 (td, 1H, J = 2, 6, 6-H), 7.30 (m_c, 5H, Ph)
15[b] minor	1.64 (td, 1H, J = 11.5, 13, 4-H), 4.03 (dd, 1H, J = 3.5, 11.5, 3-H), 4.95 (m_c, 1H, 7a-H), 5.96 (m_c, 1H, 6-H)

[a] Recorded on 500 MHz spectrometer.
[b] Missing signals are hidden by that of the major isomer.
[c] In acetone-d_6.
[d] In C_6D_6

Table 3. ^{13}C NMR Data[a] of Tetrahydro-2*H*-1,2-oxazines **2a, 2c–h, 3, 5a,b, 7, 9a–c, 11, 13** and **15**

Compound	C-3 (d)	C-4 (t)	C-5 (d)	C-6	Other signals
cis-**2a**	73.9	39.1	28.7	64.5 (t)	20.9 (q, 5-Me), 128.0, 128.3, 128.4, 138.5 (3d, s, Ph)
trans-**2a**[b]	77.6	37.1	29.5	70.9 (t)	21.6 (q, 5-Me), 129.8, 130.4, 131.2, 138.5 (3d, s, Ph)
cis-**2c**	67.5	41.5	72.4	66.1 (t)	127.8, 128.2, 128.4, 139.6 (3d, s, Ph)
trans-**2c**[b]	68.5	39.4	71.1	65.9 (t)	127.6, 127.9, 128.6, 140.0 (3d, s, Ph)
2d	57.4, 62.6, 63.3, 66.2	[c]	[c]	[c]	20.7, 20.9, 23.5, 25.0, 25.3, 25.6, 25.7, 25.8, 26.0, 26.1, 29.5, 29.7, 30.4, 30.6, 31.1, 31.9, 32.0, 36.6, 37.8, 38.5 (20 d, C-4, −5, −6, −7, −8), 33.6, 34.6, 35.6, 42.0 (4d, C-4a), 72.0, 77.1, 77.3, 83.8 (4 t, C-8a), 125.5–129.5, 140.2, 140.4, 143.8 (several d, 3s, Ph)
2e	69.6	25.8[d]	20.5[d] (t)	57.2 (t)	13.9, 60.7, 172.6 (q, t, s, $COOCH_2CH_3$)
cis-**2f**	70.8	35.4	29.5	64.6 (t)	20.4 (q, 5-Me), 14.5, 60.9, 172.8 (q, t, s, $COOCH_2CH_3$)
trans-**2f**[b]	69.1	34.4	28.7	65.1 (t)	19.5 (q, 5-Me), 14.5, 60.9, 173.0 (q, t, s, $COOCH_2CH_3$)
cis-**2g**	68.0[d]	36.7	68.6[d]	65.4 (t)	13.8, 61.0, 172.2 (q, t, s, $COOCH_2CH_3$)
trans-**2g**[b]	61.4	39.2	69.8	57.6 (t)	13.8, 60.3, 173.8 (q, t, s, $COOCH_2CH_3$)
trans-**2h**	58.0	31.7[d]	29.5[d] (t)	75.5 (d)	19.9 (q, 6-Me), 51.5, 166.4 (q, s, $COOCH_3$), 121.8, 145.9 (2d, HC=CH)
cis-**2h**[b]	61.3	27.9[d]	25.6[d] (t)	74.2 (d)	18.2 (q, 6-Me), 51.3, 166.4 (q, s, $COOCH_3$), 121.9, 147.8 (2d, HC=CH)
3	158.6 (s)	35.3[d]	20.3[d] (t)	66.8 (d)	22.9 (q, 6-Me), 51.8, 166.8 (q, s, $COOCH_3$), 122.3, 140.9 (2d, HC=CH)
cis-**5a**	67.7	27.6[d]	24.6[d] (t)	99.9 (d)	14.8, 65.4 (q, t, OCH_2CH_3), 127.9, 128.9, 129.4, 136.2 (3d, s, Ph)
trans-**5a**[b]	66.2	28.5[d]	26.1[d] (t)	103.3 (d)	128.2, 128.5, 129.0 (3d, Ph)
cis-**5b**	58.5	27.4[d]	21.8[d] (t)	97.3 (d)	13.7, 14.7, 60.6, 63.3 (2q, 2t, 2 OCH_2CH_3), 170.7 (s, CO)
trans-**5b**[b]	57.8	26.9[d]	21.7[d] (t)	99.4 (d)	60.8, 63.6 (2t, $2OCH_2CH_3$), 175.2 (s, CO)
7[e] major	60.9	76.2[d] (d)	74.3[d]	104.5 (d)	14.4, 15.6 (2q, $2OCH_2CH_3$), 26.5, 28.1 (2q, 2Me), 61.3, 66.0 (2t, OCH_2), 110.4 (s, CMe_2), 168.0 (s, CO)
7[e] minor		[c]	[c]	105.5 (d)	61.7, 66.3 (2t, OCH_2), 112.2 (s, CMe_2), 165.6 (s, CO)
9a major	61.3	29.1	34.5	99.8 (d)	13.7, 18.3, 20.7, 21.1, 21.7 (5q, 6Me), 33.2, 33.6 (2t, $2CH_2$), 46.9, 50.7 (2s, 2C), 48.4, 69.1, 86.1 (3d. 3CH)[f]
9a minor	56.6	28.8	31.3	106.2 (d)	11.5, 12.3, 20.9, 21.0, 21.1 (5q, 6Me), 32.5, 38.5 (2t, $2CH_2$), 46.8, 48.7 (2s, 2C), 47.8, 68.3, 90.5 (3d, 3CH)[f]
9b major	58.9	29.0	32.8	102.0 (d)	13.3, 14.1, 17.2, 20.8, 21.1, 21.6 (6q, 7Me), 30.5, 33.1 (2t, $2CH_2$), 47.0, 50.6 (2s, 2C), 48.3 (d, CH), 60.9 (t, OCH_2), 69.0, 86.8 (2d, 2CH), 171.7 (s, CO)[f]
9b minor	63.5	28.4	31.0	100.6 (d)	13.1, 13.8, 16.9, 20.5, 21.1, 21.8 (6q, 7Me), 28.7, 32.7 (2t, $2CH_2$), 47.1, 50.8 (2s, 2C), 48.5 (d, CH), 62.7 (t, OCH_2), 69.0, 87.3 (2d, 2CH), 168.4 (s, CO)[f]
9c major	62.2	28.9	36.5	108.1 (d)	12.8, 17.6, 20.8, 21.2, 21.8 (5q, 6Me), 32.6, 40.1 (2t, $2CH_2$), 48.2, 50.2 (2s, 2C), 47.0, 68.7, 88.2 (3d, 3CH)[f]
9c minor	55.3	29.1	30.9	104.7 (d)	13.0, 16.7, 20.7, 21.0, 21.1, 21.4 (6q, 6Me), 31.4, 33.1 (2t, $2CH_2$), 48.0, 50.1 (2s, 2C), 47.1, 68.3, 92.4 (3d, 3CH)[f]
11 major	61.2	32.9	34.4	101.9 (d)	16.6, 25.3, 26.3, 26.9, 27.0 (5q, 5Me), 68.0 (t, CH_2), 72.3, 81.2, 81.7, 83.7, 105.3 (5d, 5CH), 109.2, 111.8 (2s, 2C)[f]
11 minor	67.5	32.3	33.2	104.2 (d)	60.4 (t, CH_2), 71.8, 83.3, 105.0 (3d, 3CH), 109.5, 112.2 (2s, 2C)[f]
trans-**13**	62.3	34.1[d]	31.8[d] (t)	77.6 (d)	−0.7 (q, $SiMe_3$), 23.6 (t, CH_2Si), 127.4, 127.8, 128.4, 140.2 (3d, s, Ph)
cis-**13**[b]	59.4	29.3[d]	28.1[d] (t)	76.4 (d)	−0.9 (q, $SiMe_3$), 21.8 (t, CH_2Si), 126.9, 127.3, 128.5, 141.9 (3d, s, Ph)
15 major	58.3	[c]	[c]	[c]	32.9, 34.8 (2t, $2CH_2$), 36.6, 82.0, 133.7, 140.3 (4d, 4CH), 126.9–129.6, 141.9 (3d, s, Ph)
15 minor	59.8	[c]	[c]	[c]	34.1 (d, CH), 34.2, 38.2 (2t, $2CH_2$), 84.9, 131.9, 140.2 (3d, 3CH), 126.9–129.6, 141.6 (3d, s, Ph)

[a] 75.5 MHz, $CDCl_3$, δ.
[b] Minor isomer.
[c] See column "other signals".
[d] Assignment ambiguous; signals are exchangeable within the line.
[e] In acetone-d_6.
[f] 125–146 (several d and s, Ph, Ar).

chromatography (pentane/EtOAc, 9:1) gave pure 1,2-oxazine **1g** (*trans*:*cis* = 95:5) as a colourless oil that slowly crystallized at r.t. (mp 30–32°C); yield: 1.06 g (64%).

IR (KBr): ν = 2960, 2930, 2910, 2850, 1715, 1595 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$), *trans*-**1g**: δ = 0.11, 0.16 (2 s, 18 H, $OSiMe_3$), 1.35 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.49 (m_c, 2 H, 4-H), 3.89 (dt, 1 H, J = 3, 5 Hz, 5-H), 4.32 (q, 2 H, J = 7 Hz, OCH_2CH_3), 5.07 (d, 1 H, J = 3 Hz, 6-H); *cis*-**1g**: δ = 1.24, 4.10 (t, q, 3 H, 2 H, J = 7 Hz each, OCH_2CH_3), 5.23 (d, 1 H, J = 2 Hz, 6-H).

^{13}C NMR ($CDCl_3$), *trans*-**1g**: δ = 0.01 (q, $OSiMe_3$), 14.2 (q, OCH_2CH_3), 24.8 (t, C-4), 62.0 (t, OCH_2CH_3), 62.4 (d, C-5), 93.0 (d, C-6), 148.5 (s, C-3), 163.7 (s, CO); *cis*-**1g**: δ = 26.2 (t, C-4), 63.5 (d, C-5), 92.7 (d, C-6).

Reduction of 1,2-Oxazines by $NaBH_3CN$; General Procedure:
The corresponding 1,2-oxazine was dissolved in acetic acid (5 mL/1 mmol 1,2-oxazine) and sodium cyanoborohydride (0.200 g [3.15 mmol]/1 mmol 1,2-oxazine) was added in portions under Ar. The solution was stirred mechanically at r.t. for the time indicated. After consumption of starting material, the solution was slowly added to a sat. Na_2CO_3 solution (30 mL/1 mmol 1,2-oxazine) and was extracted with ethyl acetate. The combined organic layers were concentrated in vacuo, and the crude product was purified by chro-

matography on neutral alumina (activity III) or by Kugelrohr distillation.

NMR Data of **16**, **18**, and **21**:

5-[(2-Amino-2-phenyl)ethyl]cyclopent-2-en-1-ol (16):[20]
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.17–2.72 (m, 8H, CH, CH_2, OH, NH_2), 4.04 (dd, 0.7H, J = 3.5, 11.5 Hz, C<u>H</u>NH_2), 4.12 (dd, 0.3H, J = 3, 11.5 Hz, C<u>H</u>NH_2), 4.70, 4.92–4.98, 5.25, 5.42–5.50 (m_c, m, m_c, m, 0.3H, 0.3H, 0.1H, 0.3H, C<u>H</u>OH), 5.76–5.91, 5.94–6.02, 6.14–6.19 (3 m, 1H, 0.3H, 0.3H, =CH), 6.30 (td, 0.3H, J = 2, 5.5 Hz, =CH), 6.36 (td, 0.1H, J = 2, 5.5 Hz, =CH), 7.20–7.43 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$): δ = 29.7*, 32.0, 32.9 (3 t, CH_2), 33.8, 34.1, 35.4*, 36.6 (4 d, CH), 34.15, 34.8, 38.2, 38.7*, 39.0 (5 t, CH_2), 58.3, 59.8, 64.2*, 66.9 (4 d, <u>C</u>HNH_2), 82.0, 82.6, 84.3*, 85.0 (4 d, <u>C</u>HOH), 125.7–131.1 (several d, Ph, =CH), 133.5, 138.0, 140.3, 142.1* (4 d, =CH), 136.8, 137.0, 141.7 (3 s, Ph). The NMR data for the minor isomer are marked with an asterisk (*).

1,1,1-Trifluoro-5-hydroxy-4-methylpentan-2-one Oxime (18):
Major isomer (*E*-**18**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (d, 3H, J = 7 Hz, 4-Me), 2.12 (m_c, 1H, 4-H), AB part of ABX system (δ_A = 2.70, δ_B = 2.32, 2H, J_{AX} = 8.5 Hz, J_{BX} = 7 Hz, J_{AB} = 13.5 Hz, 3-H), 2.90 (br s, 1H, OH), AB part of ABX system (δ_A = 3.53, δ_B = 3.49, 2H, J_{AX} = 4.7 Hz, J_{BX} = 5.3 Hz, J_{AB} = 11 Hz, 5-H), 10.0 (br s, 1H, NOH).

^{13}C NMR ($CDCl_3$): δ = 16.9 (q, 4-Me), 27.5 (t, C-3), 33.4 (d, C-4), 66.9 (t, C-5), 121.0 (q, J_{CF} = 274 Hz, CF_3), 149.8 (q, J_{CF} = 32 Hz, C-2).

Further signals for the minor isomer (*Z*-**18**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (d, 3H, J = 7 Hz, 4-Me), 2.85 (dd, 1H, J = 5.5, 13.5 Hz, 3-H), 3.05 (dd, 1H, J = 6, 13.5 Hz, 3-H), 3.92–4.09 (m, 2H, 5-H)

^{13}C NMR ($CDCl_3$): δ = 18.1 (q, 4-Me), 29.0 (t, C-3), 29.4 (d, C-4), 65.1 (t, C-5).

1,1,1-Trifluoro-5-hydroxy-6-methylpent-6-en-2-one Oxime (21):
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.75–2.65 (m, 8H, 6-Me, 3-H, 4-H, OH), 4.10 (br t, 0.85H, J = 6 Hz, 5-H), 4.37 (t, 0.15H, J = 7 Hz, 5-H), 4.90 (quint, 1H, J = 1.5 Hz, 7-H), 4.99 (m_c, 1H, 7-H), 10.01 (br s, 1H, NOH).

^{13}C NMR ($CDCl_3$): δ = 17.5*, 17.7 (2 q, 6-Me), 20.2, 20.6*, 29.6*, 30.1 (4 t, C-3, C-4), 75.0, 76.1* (2 d, C-5), 111.7 (t, C-7), 121.1 (q, J_{CF} = 274 Hz, CF_3), 146.1 (s, C-6), 149.7 (q, J_{CF} = 32 Hz, C-2).
The NMR data for the minor isomer (*Z*-**21**) are marked with an asterisk (*).

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