α-Azido ketones, Part 6.[†] Reduction of acyclic and cyclic α-azido ketones into α-amino ketones: old problems and new solutions

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Dedicated to Prof. Henk van der Plas on the occasion of his 80th birthday

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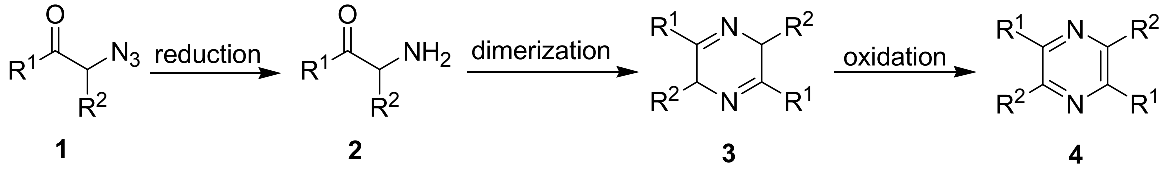
Abstract

Comparative experiments on the selective reduction of α-azido ketones to α-amino ketones revealed that tin(II) chloride reduction followed by immediate protection with Boc group is the method of choice. This methodology proved to be useful for more complex substrates, too. Chromium(II) acetate also resulted in the desired products but in lower yields due to a competitive deazidation procedure. A mechanism to explain this deazidation was suggested.

Keywords: α-Amino ketones, α-azido ketones, chromium(II), selective reduction, tin(II)

Introduction

α-Azido ketones **1** represent useful precursors of the synthetically important 1,2-amino alcohols. The survey of the literature revealed that this transformation is usually executed in two steps. Either the carbonyl or the azide groups can be reduced chemoselectively and numerous protocols have also been published for the synthesis of enantiomerically pure or enriched 2-azido-1-alcohols. The major problem during the reduction of α-azido ketones **1** to the corresponding α-amino ketones **2** lies in the well-known propensity of the products to the intermolecular condensation followed by dehydrogenation affording pyrazines **4** (Scheme 1).



Scheme 1

Anselme and his co-workers [1] studied the catalytic reduction of various phenacyl azides and aliphatic α-azido ketones **2** (R^1 = *i*-Pr, R^2 = H; R^1 = Me, R^2 = Et) over Pd-C in ethanol in the presence of a few drops of acetic acid at 3.4 atm. pressure and isolated the corresponding pyrazines **4**. In one case, the intermediate dihydropyrazine **3** has also been obtained which oxidized to the pyrazine **4** spontaneously by standing in air. However, the outcome of the reaction was somewhat structure dependent. Suzuki and his co-workers[2] have also reported the formation of symmetrical 2,5-substituted- or 2,3,5,6-tetrasubstituted-pyrazines **4** by treating α-azido ketones **2** with sodium hydrogen telluride in ethanol. The reaction could be performed in a "crossed" manner to synthesize complex pyrazines such as the naturally occurring cephalostatin 7, cephalostatin 12, and ritterazin K.[3]

In some cases the catalytic reduction over Pd-charcoal, [4] Pd-calcium carbonate[5] or platinum oxide[6] was reported to give stable α-amino ketones but usually the products should be protected by their immediate transformation into a salt or an acylated / alkoxycarbonylated derivative to avoid the pyrazine formation. Hydrogen chloride or perchloric acid was added to the solution of the substrate prior to the hydrogenation[7-11], or as an alternative, concentrated hydrochloric acid or dry hydrogen chloride was added to the reaction mixture just after filtering the catalyst off. [8,9] *In situ* derivatization of amino ketones was accomplished by adding acetic anhydride[12] or di-*tert*-butyl dicarbonate[13] (Boc anhydride) to the solution of the substrate prior to the hydrogenation. Acetylation[12] or aroylation by an active ester[10] immediately after the reduction has also been reported.

Only sporadic reports are available on the use of other reducing agents. Pulici *et al.*[14] applied tin(II) chloride dihydrate in ethanol for the preparation of 2-acylamino ketones but they presented 2-amino-1-phenylpropane-1-one (**2**, R^1 = Ph, R^2 = Me) as an only example in their paper. In a systematic study on the reduction of azides to amines by the combination of zinc and bismuth (III) chloride in water or aqueous ethanol, phenacyl azide was shown as a single example. [15] Trivalent phosphorus compounds such as phosphines and phosphites are generally useful reagents to convert azides to amines but this methodology is not applicable for the reduction of α-azido ketones because of the concurrent secondary reactions such as pyrazine[16-18] or aziridin[19,20] formation. In the only reported exception, triphenylphosphine was applied in the presence of *p*-toluenesulfonic acid and the intermediate iminophosphoranes were immediately cleaved and the formed α-amino ketone were trapped as their tosylates. [21]

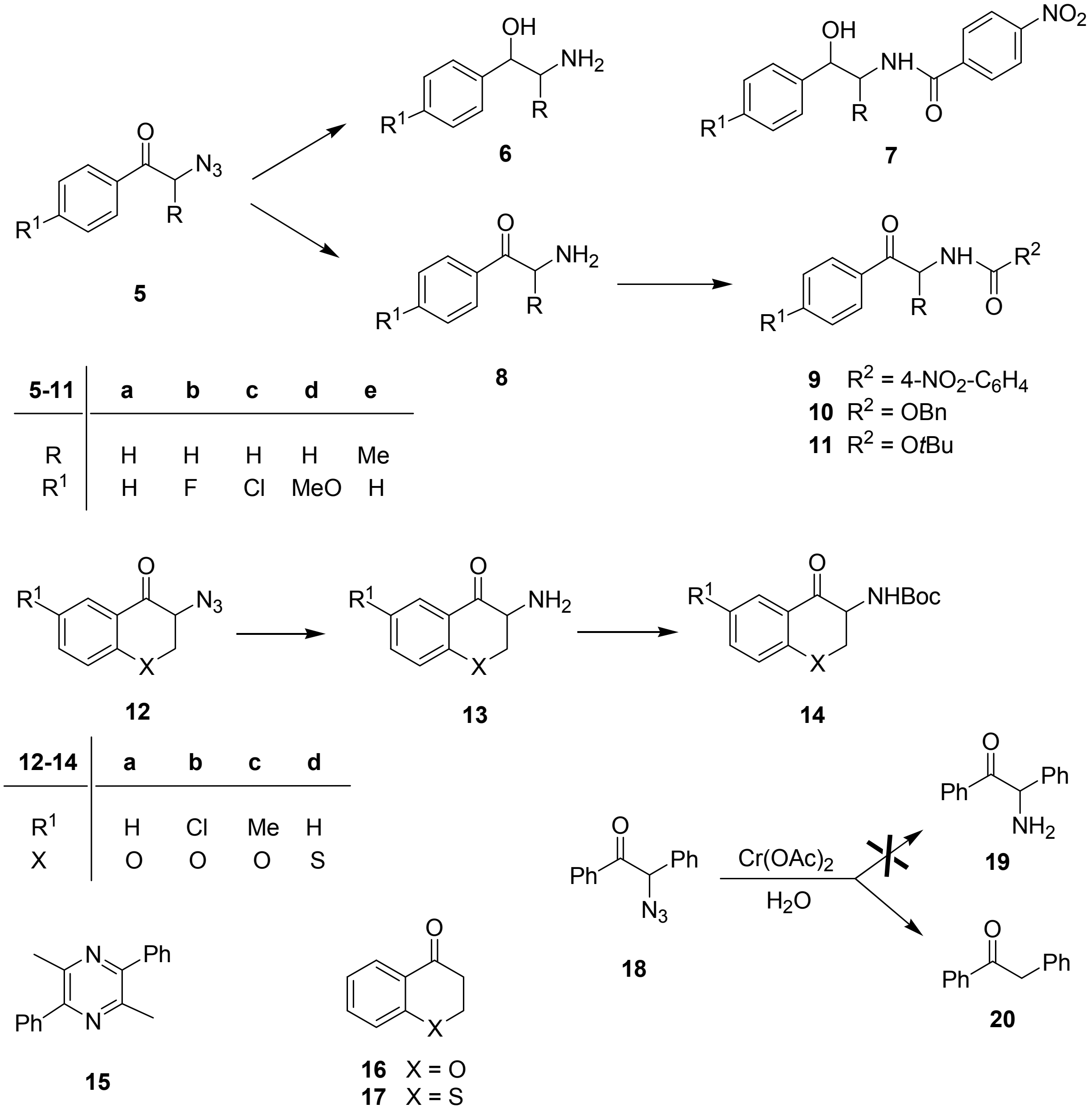
Another reduction method leading directly to N-acylated α-amino ketones using thioacids as reducing and acylating agent has also been reported. The method which was originally developed for the reduction of simple azides by Rosen *et al.*[22] was successfully applied first to α-azido ketones having a protected amino group in their α' position, the reducing and acylating thioacids were *N*-protected *L*-aminothiocarboxylic S-acids.[23] This methodology was also applied by other research groups for the reduction of complex α-azido ketones using thioacetic or thiobenzoic acid.[24,25] A mechanism involving an interesting triathiazoline intermediate has also been proposed. [25]

Consequently, an efficient method for the transformation of α-azido ketones into α-amino ketones is still a need. In this contribution we wish to present our comparative studies using various reducing systems and to demonstrate the usefulness of tin(II) chloride in this transformation.

Results and Discussion

The usefulness of the transfer hydrogenation using ammonium formate as hydrogen source in the presence of palladium on charcoal in hot methanol was investigated first; this methodology has not been tested so far. Unfortunately, the reaction 2-azidoacetophenone (**5a**) or 2-azidopropiophenone (**5e**) did not result in the desired aminoketones **8a,e**, only the corresponding 1,2-amino-alcohols **6a,e** were obtained in low or moderate yields. 2-Amino-1-phenylethanol (**6a**) was isolated as its *p*-nitrobenzoate, **7a** (Scheme 2). Interestingly, the reduction of azido ketone **5e** afforded *anti*-2-amino-1-phenyl-1-propanol (*anti*-**6e**) in nearly diastereo-pure form, only traces (≤5 %) of *syn*-**6e** was detected in the worked-up reaction mixture. The relative configurations of amino-alcohol *anti*-**6e** [26] and the minor product *syn*-**6e** [27] were verified by comparison of the chemical shifts with the literature data. We can conclude that the afore-mentioned chemoselectivity of the reduction was completely lost under these conditions.

Next, we tested the synthetic value of the catalytic hydrogenation by using Lindlar's catalyst instead of the previously reported Pd-charcoal, [4] Pd-calcium carbonate[5] or platinum oxide. [6] This catalyst was found effective in the reduction of azido group[28] but has never been tried in the case of α-azido ketones. The 2-Azidoacetophenones **5a**,**b**, 2-azidopropiophenone (**5e**), and the heterocyclic α-azido ketones **12a**,**d** were hydrogenated at atmospheric pressure in the presence of Lindlar's catalyst. The product was immediately derivatized with $(Boc)_2O$ in the presence of sodium hydrogencarbonate to avoid the formation of pyrazines from the primary product α-amino ketones **8a**,**b,e** and **13a**,**d**. The corresponding Boc-protected derivatives **11a**,**b**,**e** and **14a**,**d** were isolated but the yields were low or moderate (7.6-32%) in all cases. No other products could be isolated from the reaction mixture by column chromatography. In conclusion, although this reduction method works for the α-azido ketones, the observed low efficiency, particularly keeping the high price of the catalyst in mind, diminishes its synthetic value.



5, **6**, **7**, **8**

9 R^2 = 4-NO_2-C_6H_4
10 R^2 = OBn
11 R^2 = O*t*Bu

5-11	a	b	c	d	e
R	H	H	H	H	Me
R^1	H	F	Cl	MeO	H

12, **13**, **14**

12-14	a	b	c	d
R^1	H	Cl	Me	H
X	O	O	O	S

18, **19**, **20**, **15**

16 X = O
17 X = S

Scheme 2

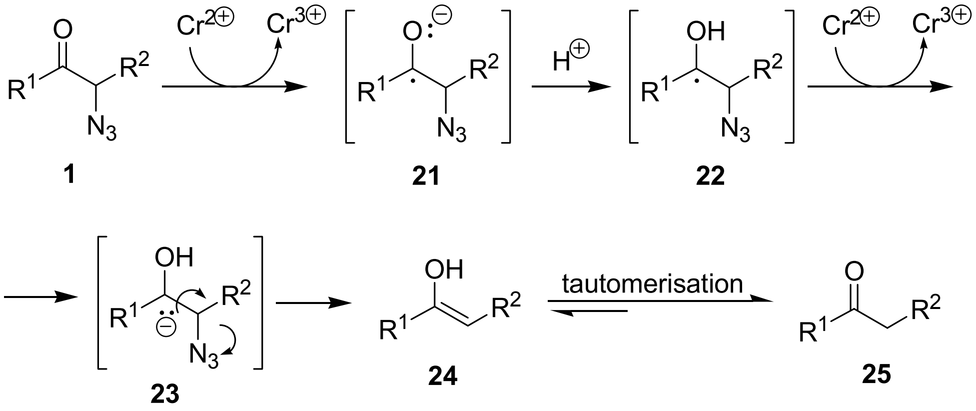
Low-valent transition (LVT) metal ions offer another possibility to reduce the azido group. Recently, we have applied successfully chromium(II) acetate to reduce prochiral ketones into alcohols and this reduction could be performed with moderate-to-good enantioselectivity in the presence of α-amino acids.[29] The same reducing system was also used for the enantioselective reduction of C=N double bonds.[30,31] LVT metal ions such as tin(II), iron(II) and chromium(II) were used in the reduction of simple azides into the corresponding amines,[32] but this approach has never been tested in the case of α-azido ketones. First, we investigated the reduction of α-azido ketones with chromium(II) ions. When 2-azidopropiophenone (**5e**) was treated with chromium(II) acetate in water-dioxane medium and the worked-up reaction mixture was purified by column chromatography, 2,5-dimethyl-3,6-diphenylpyrazine (**15**) was the only isolable product. This observation provided a further proof for the necessity of the immediate protection of the α-amino ketone products. We studied various protecting groups such as 4-nitrobenzoyl, benzyloxycarbonyl and *tert*-butoxycarbonyl but no marked difference was found in the yields (Table 1). Moreover, the same moderate yields were observed when intermediate **8e** was treated with $(Boc)_2O$ under different conditions. These results support that reason of the low yields is in the reduction and in not the protection step.

Table 1. Yields of the protected amines by using low-valent transition metal ions

Substrate	Protecting group	Product	Yield (%)	
			$Cr(OAc)_2$	$SnCl_2$
5a	Boc	**11a**	30	84
5b	Boc	**11b**	37	-
5c	Boc	**11c**	-	33
5d	Boc	**11d**	27	63
5e	$4\text{-}NO_2\text{-}C_6H_4$	**9e**	44	-
5e	Cbz	**10e**	25	-
5e	Boc	**11e**	21,[a] 27[b]	62
12a	Boc	**14a**	0[c]	73
12b	Boc	**14b**	-	24
12c	Boc	**14c**	-	67
12d	Boc	**14d**	0[d]	48

[a]The α-amino ketone intermediate **8e** was derivatized with $(Boc)_2O$/TEA/DMAP. [b]The α-amino ketone intermediate **8e** was derivatized with $(Boc)_2O$/MeCN. [c]The chromanone (**16**) was isolated as the only product (see Experimental Section). [d]The 1-thiochroman-4-one (**17**) was isolated as the only product (see Experimental Section).

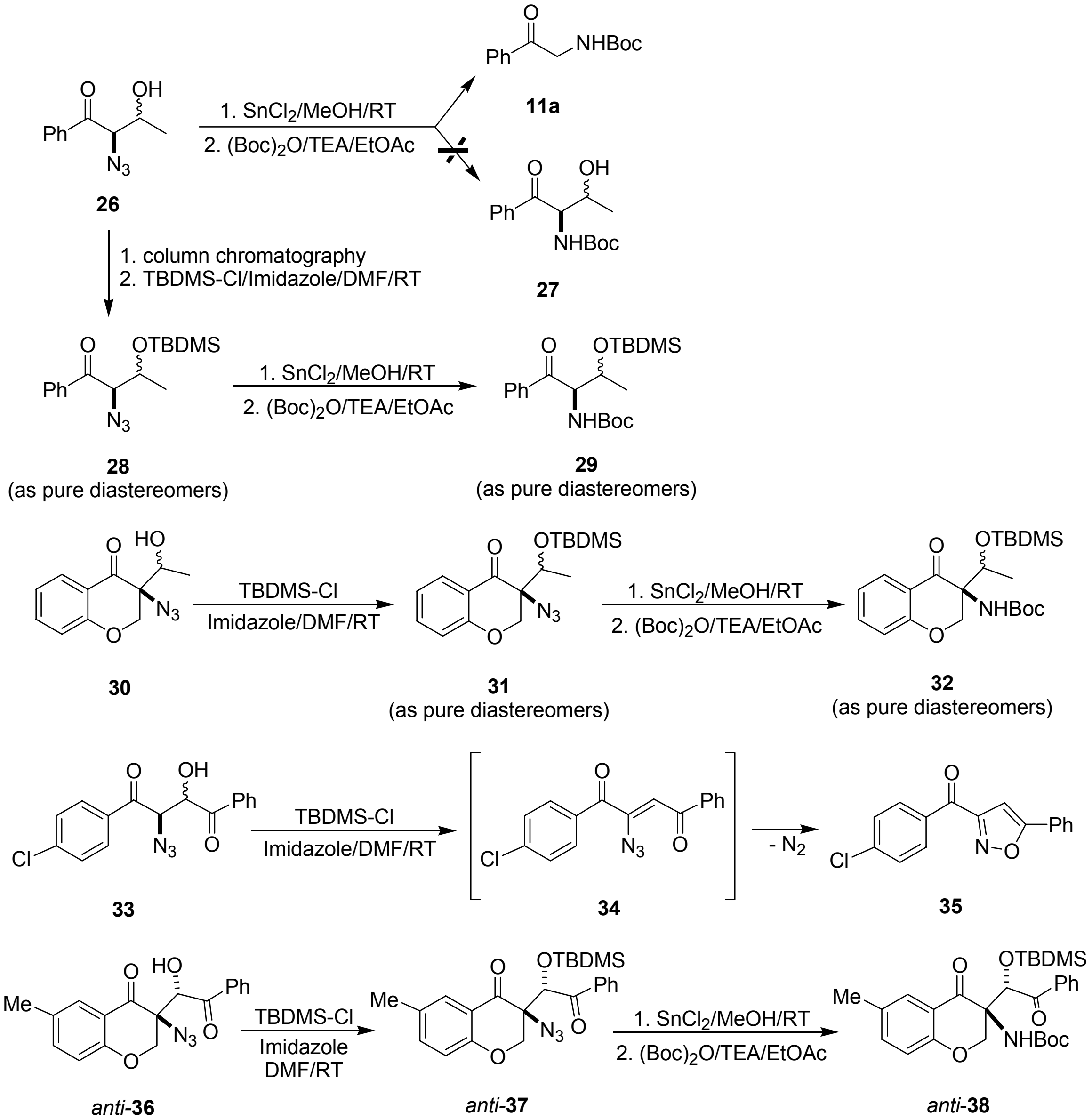
The reduction and derivatization of the phenacyl azides **5a**,**b**,**d** also gave similarly low yields. More surprisingly, the reduction of 3-azidochromanone (**12a**) and 3-azido-1-thiochromanone (**12d**) with chromium(II) acetate did not result in any expected products **14a**,**d**, only compounds **16**,**17,** the products of a deazidation reaction, were obtained. The same deazidation was observed in the case of another open-chain substrate. The treatment of 2-azido-1,2-diphenylethanone (**18**) with chromium(II) acetate gave deoxybenzoin (**20**) exclusively. Therefore, it is very likely that this side-reaction is responsible for the lower yields in the case of other substrates. The de-azidation may be explained in terms of the SET mechanism of the reduction. The second SET step of the reduction leads to anion **23** which, instead of a protonation, loses an azide ion giving enol **24**. The tautomerization of the enol **24** yields the final product ketone **25** (Scheme 3).



Scheme 3

Finally, we studied the reduction of α-azido ketones **5a**,**c**,**d**,**e** and **12a-d** with tin(II) chloride in methanolic solution under nitrogen atmosphere, the α-amino ketone intermediates **8a**,**c**,**d**,**e**, **13a-d** were derivatized with $(Boc)_2O$ in the presence of TEA. Although the yields varied in relatively wide range (24-84%), the values were generally better than by using any previous method (Scheme 2, Table 1). We can conclude that tin(II) chloride is the reagent of choice for the reduction of α-azido ketones.

The usefulness of tin(II) chloride as reducing agent was also tested in the case of other, more complex substrates such as 2-azido-3-hydroxy ketones **26**, **30**, **33**, **36** obtained by trapping the carbanions of the corresponding α-azido ketones with various carbonyl compounds.[20,33-35] In our first attempt the sequential reduction and protection of 2-azido-3-hydroxy-1-phenyl-1-butanone (**26**) according to the procedure described above resulted in 2-(N-*tert*-butoxycarbonylamino)-1-phenyl-1-ethanone (**11a**) as the only product instead of the expected compound **27**. Obviously, a competitive and faster *retro*-aldol cleavage leading to the phenacyl azide (**5a**) took place prior to the reduction. To avoid this side reaction the 3-hydroxy group should be blocked with an appropriate protecting group. Previously, we reported[33] on the efficient *tert*-butyldimethylsilylation of this compound by treating the azido-alcohol **26** with *tert*-butyldimethylsilyl chloride in DMF and in the presence of imidazole to give silyl ether **28** and demonstrated the lack of any epimerization during the protection step. Fortunately, we managed to find proper chromatographic conditions for the separation of the *syn* and *anti* diastereomers of azide **28**. The reduction of the pure diastereomers of azides **28** followed by reaction with $(Boc)_2O$ in the presence of TEA afforded the expected derivatives **29** in good (66-72%) yields and in diastereomerically pure form.



This methodology was also found to work in the case of heterocyclic systems. The silylation of chromanone **30** followed by chromatographic separation resulted in the pure diastereomers of protected compound **31**. These azide derivatives were reduced and derivatized with Boc protecting groups successfully and the desired compounds **32** were obtained in good (54-79%) yields.

Attempted silylation of 2-azido-3-hydroxy-1,4-diketone **33** did not give the desired product but only 3-(4-chlorobenzoyl)-5-phenylisoxazole (**35**), probably *via* the vinyl azide **34**. Similar elimination reaction of 2-azido-3-hydroxy-1,4-diketones during benzoylation or mesylation have been observed previously.[34] Since the dimethyl-*tert*-butylsilyloxy unit is a group with moderate leaving group ability, it seems 2-azido-3-hydroxy-1,4-diketones show exceptional willingness to loss their substituted hydroxyl group. The crucial role of the α-hydrogen which is a prerequisite of the elimination process is shown by the fact that *anti*-3-azido-3-(1-*tert*-butyldimethylsilyloxy-2-oxo-2-phenylethyl)-6-methylchroman-4-one (**37**) having a quaternary carbon at position α resulted in the expected product *anti*-**38** without any problem.

Conclusions

In conclusion, tin(II) chloride gave the best results in the selective reduction of α-azido ketones and proved to be useful in the wide range of substrates. Immediate protection of the amino group without any attempted purification seems necessary to avoid the secondary dimerization by condensation followed by dehydrogenation. Another low-valent metal ion, chromium(II), has also considerable reducing potential but this procedure suffers from a competitive de-azidation reaction.

Experimental Section

General Procedures. Chromatographic separations were performed using silica gel (Merck, 70-230 mesh). Thin-layer chromatography was carried out on Kieselgel 60 F_{254} (0.25 mm layer thickness, Merck). Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. ^1H- and ^{13}C- NMR spectra were recorded with a Bruker AM 360 (360 MHz for ^1H-; 90 MHz for ^{13}C- nuclei) or a Bruker WP 200 SY (200 MHz for ^1H- nuclei) spectrometer in $CDCl_3$ solution unless otherwise specified (internal standard TMS, $\delta = 0$ ppm). IR spectra were recorded with a Perkin-Elmer 16 PC-FT-IR instrument in KBr disks. Elemental analyses were performed in house with a Carlo Erba 1106 EA instrument.

Transfer hydrogenation

2-(4-Nitrobenzoylamino)-1-phenylethanol (7a). A mixture of the α-azido-acetophenone (**5a**) (200 mg, 1.20 mmol), 10% palladium on charcoal (140 mg) and ammonium-formate (1.60 g) in methanol (60 mL) was heated at reflux temperature for 90 min. The catalyst was filtered off, washed with methanol and the filtrate was concentrated *in vacuo*. The obtained residue was dissolved in abs. pyridine (5 mL) and cooled to 0 °C. 4-Nitrobenzoyl chloride (1.473 g, 7.94 mmol) was added and the mixture was stirred at room temperature. When the reaction was complete (2 hrs, TLC monitoring: hexane-ethyl acetate = 4:1, *v:v*), the mixture was poured into ice-cold water, extracted with dichloromethane (3 x 50mL). The organic layer was washed with sodium hydrogen carbonate (2 x 70 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was submitted to column chromatography (hexane-ethyl acetate = 1:1, *v/v*) to give amide **7a** (14 mg, 15 %) as white crystals. Mp: 49.5-52 °C. IR: ν_{max} 3417 (NH), 3304 (OH), 1594 (Amide-I), 1550 (Amide-II), 1521 (NO_2), 1352 (NO_2), 1321, 1064, 706 cm^{-1}; ^1H- NMR ($CDCl_3$ + acetone-d_6): δ 3.53, 3.83 (2xm, 2xH, 1'-H), 4.98 (m, 1H, 2'-H), 7.24-7.44 (m, 5H, Ph), 7.96 (s, 1H, NH), 8.09 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 8.28 (d, *J* = 8.8 Hz, 2H, 3',5'-H). Anal. Calcd. for $C_{15}H_{14}N_2O_4$ (286.28): C, 62.93; H, 4.93; N, 9.79. Found: C, 63.11; H, 4.71; N, 9.85%.

***anti*- 2-Amino-1-phenyl-1-propanol (6e)**. α-Azidopropiophenone (**5e**) (500 mg, 2.85 mmol) was reduced as given for α-azido-acetophenone (*vide supra*), reaction period: 40 min. The residue obtained after the work-up was dissolved in diethyl ether (50 mL) and washed with water (3 x 15 mL). The aqueous phase was adjusted to pH = 11 with sodium hydroxide, extracted with diethyl ether (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give *anti*-**6e** (229 mg, 53%) as white crystals. Mp: 94-97 °C, lit.[36] mp: 98-100 °C. IR: ν_{max} 3372 (OH), 3270 (NH), 1606, 1574, 1480, 1454 cm^{-1}; ^{1}H- NMR: δ 0.96 (d, *J* = 7.2 Hz, 3H, 3-H), 1.8 (brs, 3H, NH, OH), 3.19 (m, 1H, 2-H), 4.52 (d, *J* = 5.1 Hz, 1H, 1'-H), 7.33 (m, 5H, Ph); ^{13}C NMR: δ 18.0 (C-3), 51.9 (C-2), 77.6 (C-1), 126.7 (C-2',6), 127.6 (C-4'), 128.3 (C-3',5'), 141.6 (C-1'). Anal. Calcd. for $C_9H_{13}NO$ (151.20): C, 71.49; H, 8.67; N, 9.26%. Found: C, 71.72; H, 8.47; N, 9.02%.

Catalytic hydrogenation in the presence of Lindlar's catalyst

2-(*N*-*tert*-Butoxycarbonylamino)-1-phenyl-1-ethanone (11a). A solution of 2-azido-acetophenone (**5a**) (750 mg, 4.65 mmol) in methanol (5 mL) was added under hydrogen atmosphere to the stirred mixture of 1.05 g of 5% Lindlar's catalyst and methanol (15 mL) previously saturated with hydrogen. The reaction was monitored by TLC (toluene-ethyl acetate = 6:1, *v/v*). After the completion of the reduction (3 h.) a solution of di-*tert*-butyl dicarbonate (3.55 g, 16.29 mmol) in methanol (3 mL) and sodium hydrogencarbonate (391 mg, 4.65 mmol) was added to the reaction mixture. The carbamoylation was monitored by TLC (hexane-ethyl acetate = 4:1, *v/v*). The catalyst was filtered off, washed with methanol and the filtrate was evaporated. The residue was washed with acetone (50 mL), the inorganic salts were filtered off and the organic phase was concentrated *in vacuo*. The residue was submitted to column chromatography (hexane-ethyl acetate = 4:1, *v/v*) to give carbamate **11a** (86 mg, 7.9%) as white crystals. Mp: 49-51 °C, lit.[37] mp: 56 °C, lit.[38] mp: 55-58 °C. IR: ν_{max} 3382 (NH), 2977, 1719, 1690 (Amide-I), 1595 (Amide-II), 1518, 1365, 1228, 1171 (C-O-C), 690 cm^{-1}; ^{1}H- NMR: δ 1.48 (s, 9H, *t*-BuO), 4.67 (d, *J* = 4.3 Hz, 2H, 2-H), 5.56 (s, 1H, NH), 7.49 (m, 7.9 Hz, 2H, 3',5'-H), 7.61 (m, 1H, 4'-H), 7.96 (d, *J* = 7.2 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ 28.2 (Me_3), 47.4 (C-2), 79.6 (**C**Me_3), 127.7, 128.7 (C-2',6' + C-3',5'), 133.7 (C-4'), 134.4 (C-1'), 155.7 (C=O, carbamate), 194.4 (C-1). Anal. Calcd. for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28, N 5.95. Found: C, 66.56; H, 7.01; N, 6.02%.

2-(*N*-*t*-Butoxycarbonylamino)-1-(4-fluorophenyl)-1-ethanone (11b). 2-Azido-(4'-fluoro-phenyl)-1-ethanone (**5b**) (500 mg, 2.78 mmol) was reduced and derivatized as given for carbamate **11a**. Purification by column chromatography (chloroform) afforded compound **11b** (54 mg, 7.6%) as white crystals. Mp: 87-89 °C. IR: ν_{max} 3372 (NH), 1685 (Amide-I), 1597 (Amide-II), 1513, 1249, 1227 (C-F), 1168 (C-O-C), 845 cm^{-1}; ^{1}H- NMR: δ 1.48 (s, 9H, *t*-BuO), 4.64 (d, *J* = 4.4 Hz, 2H, 2-H), 5.52 (s, 1H, NH), 7.19 (dd, *J* = 8.7, 8.5 Hz, 2H, 3',5'-H), 8.00 (m, 2H, 2',6'-H); ^{13}C- NMR: δ 28.3 (Me_3), 47.3 (C-2), 79.8 (**C**Me_3), 115.5 (C-2',6', $^3J_{C\text{-}F}$ = 22.6 Hz), 130.5 (C-3',5', $^4J_{C\text{-}F}$ = 9.2 Hz), 131.0 (C-1'), 156.3 (C=O, carbamate), 166.1 (C-4', $^2J_{C\text{-}F}$ = 257

Hz), 193.4 (C-1). Anal. Calcd. for $C_{13}H_{16}FNO_3$ (253.27): C, 61.65; H, 6.37; N 5.53%. Found: C, 61.43; H, 6.32; N, 5.67%.

2-(*N*-*t*-Butoxycarbonylamino)-1-phenyl-1-propanone (11e). 2-Azidopropiophenone (**5e**) (750 mg, 4.28 mmol) was reduced and derivatized as given for carbamate **11a**. Purification by column chromatography (hexane-ethyl acetate = 4:1, *v/v*) gave product **11e** (201 mg, 19%) as a white crystals. Mp: 79.5-81.5 °C, lit.[39] mp: 80.3-81 °C. IR: ν_{max} 3336 (NH), 2973, 1715, 1674 (Amide-I), 1596 (Amide-II), 1526, 1449, 1365, 1286, 1251, 1174 (C-O-C), 1016, 966, 701 cm^{-1}; ^1H-NMR: δ 1.40 (d, *J* = 6.8 Hz, 3H, 3-H), 1.46 (s, 9H, *t*-BuO), 5.29 (m, 1H, 2-H), 5.31 (br s, *J* = 6.9 Hz, 1H, NH), 7.49 (m, 2H, 3',5'-H), 7.59 (m, 1H, 4'-H), 7.98 (d, *J* = 7.3 Hz, 2H, 2',6'-H); ^{13}C-NMR: δ 19.6 (C-3), 28.2 (Me_3), 50.9 (C-2), 79.5 (**C**Me_3), 128.5, 128.7 (C-2',6' + C-3',5'), 133.5 (C-4'), 134.1 (C-1'), 155.1 (C=O, carbamate), 199.0 (C-1). Anal. Calcd. for $C_{14}H_{19}NO_3$ (249.30): C, 67.45; H, 7.68; N, 5.62%. Found: C, 67.21; H, 7.89; N, 5.21%.

3-(*N*-*t*-Butoxycarbonylamino)-4-chromanone (14a). 3-Azido-4-chromanone (**12a**) (750 mg, 3.96 mmol) was reduced and derivatized as given for carbamate **11a**. Purification by column chromatography (hexane-ethyl acetate = 4:1, *v/v*) gave compound **14a** (105 mg, 10%) as white crystals. Mp: 154-156 °C. IR: ν_{max} 3353 (NH), 1712, 1690 (C=O and Amide-I), 1608, 1525, 1478, 1339, 1287, 1170 (C-O-C), 767 cm^{-1}; ^1H- NMR: δ 1.48 (s, 9H, *t*-BuO), 4.04 (dd, *J* = 13.3, 10.5 Hz, 1H, 2-H_{ax}), 4.67 (br m, 1H, 2-H_{eq}), 4.88 (br m, 1H, 3-H), 5.46 (br s, 1H, NH), 6.99 (d, *J* = 8.4 Hz, 1H, 8-H), 7.04 (m, 1H, 6-H), 7.51 (m, 1H, 7-H), 7.88 (dd, *J* = 7.8, 2.1 Hz, 1H, 5-H); ^{13}C- NMR: δ 28.2 (Me_3), 53.8 (C-3), 69.7 (C-2), 80.4 (**C**Me_3), 117.8 (C-8), 119.6 (C-4a), 121.6 (C-6), 127.3 (C-5), 136.4 (C-7), 155.4 (C=O, carbamate), 161.7 (C-8a), 190.4 (C-4). Anal. Calcd. for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32%. Found: C, 64.09; H, 6.27; N, 5.37%.

3-(*N*-*t*-Butoxycarbonylamino)-1-thiochroman-4-one (14d). 3-Azido-1-thiochroman-4-one (**12d**) (640 mg, 3.12 mmol) was reduced and derivatized as given for carbamate **11a**. Purification by column chromatography (dichloromethane) gave product **14d** (293 mg, 32%) as white crystals. Mp: 144-145 °C. IR: ν_{max} 3368 (NH), 1707, 1686 (C=O and Amide-I), 1590 (Amide-II), 1526, 1460, 1437, 1364, 1263, 1171 (C-O-C), 759 cm^{-1}; ^1H- NMR: δ 1.48 (s, 9H, *t*-BuO), 3.21 (t, *J* = 13.4 Hz, 1H, 2-H_{ax}), 3.54 (br m, 1H, 2-H_{eq}), 4.72 (br m, 1H, 3-H), 5.93 (s, 1H, NH), 7.18 (m, 1H, 6-H), 7.25 (d, *J* = 7.9 Hz, 1H, 8-H), 7.40 (m, 1H, 7-H), 8.06 (dd, *J* = 7.9, 1.8 Hz, 1H, 5-H); ^{13}C- NMR: δ 28.3 (Me_3), 31.3 (C-2), 56.7 (C-3), 80.1 (**C**Me_3), 124.8, 127.2 (C-6 + C-8), 129.6 (C-4a), 129.7 (C-5), 133.8 (C-7), 141.9 (C-8a), 155.3 (C=O, carbamate), 191.7 (C-4). Anal. Calcd. for $C_{14}H_{17}NO_3S$ (279.35): C, 60.19; H, 6.13; N, 5.01%. Found: C, 59.87; H, 6.36; N, 4.78.

Reductions by chromium(II) acetate

2,5-Dimethyl-3,6-diphenylpyrazine (15). A solution of 2-azidopropiophenone (**5e**) (263 mg, 1.50 mmol) in dioxane (2 mL) was added to a degassed and stirred solution of chromium(II) acetate (705 mg, 3.70 mmol) in water (12 mL) at room temperature under N_2 atmosphere. The reaction was monitored through a septum by TLC (toluene-ethyl acetate-formic acid = 5:4:1, *v/v*/v) and the mixture was stirred for 22 hr at room temperature. The reaction mixture was poured into water, extracted with diethyl ether (2 x 40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the unreacted starting material **5e**. The aqueous phase was adjusted to pH = 11 by 8% aqueous sodium hydroxide solution, extracted with diethyl ether (4 x 40 mL) and dried (Na_2SO_4). After evaporation the residue was submitted to column chromatography (toluene-ethyl acetate = 4:1, *v/v*) to give the pyrazine **15** (35 mg, conversion: 78%, normalized yield: 23%) as a white crystals. Mp: 125-128 °C, lit.[40] mp 125-126 °C. IR: ν_{max} 2924, 1450, 1398, 1230, 1162, 772, 698 cm^{-1}; ^1H- NMR: δ 2.64 (s, 3H, Me), 7.43-7.54 (m, 3H, 3',4',5'-H), 7.64 (dd, *J* = 8.0, 1.9 Hz, 2H, 2',6'-H).

2-(4-Nitrobenzoylamino)-1-phenyl-1-propanone (9e). 2-Azidopropiophenone (**5e**) (530 mg, 3.00 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. The concentrated ethereal extract of the alkaline aqueous phase was dissolved in abs. pyridine (5 mL) and cooled to 0 °C. 4-Nitrobenzoyl chloride (1.12 g, 6.00 mmol) was added and the mixture was stirred at room temperature for 1 hr then poured into ice-cold water and extracted with diethyl ether (50 mL). The organic layer was washed with saturated sodium hydrogencarbonate solution (4 x 50 mL) and water (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was crystallized from hexane to give (393 mg, 44%) as white crystals, mp 96.5-99 °C. IR: ν_{max} 3410 (NH), 1691 (C=O), 1648 (Amide-I), 1600, 1514 (NO_2), 1449, 1340 (NO_2), 1322, 1296, 850, 724, 708, 701 cm^{-1}; ^1H- NMR: δ 1.57 (d, *J* = 7.0 Hz, 3H, 3-H), 5.71-5.79 (m, 1H, 2-H), 7.52-7.56 (m, 3H, 3',4',5'-H), 7.65 (d, *J* = 7.5 Hz, 1H, NH), 8.02-8.05 (overlapping doublets, 4H, 2',6',2'',6''-H), 8.31 (d, *J* = 9.1 Hz, 2H, 3",5"-H). Anal. Calcd. for $C_{16}H_{14}N_2O_4$ (298.29): C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.26; H, 4.59; N, 9.04%.

2-(*N*-Benzyloxycarbonylamino)-1-phenyl-1-propanone (10e). 2-Azidopropiophenone (**5e**) (265 mg, 1.50 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. To the ethereal extract of the alkaline aqueous phase benzyl chloroformate (0.14 mL, 0.93 mmol) and sodium hydrogencarbonate (179 mg, 0.21 mmol) in water (9 mL) was added and the mixture was stirred for 20 hrs. The phases were separated, the aqueous part was acidified with concentrated hydrochloric acid, extracted with diethyl ether (3 x 30 mL), this ethereal extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was submitted to column chromatography (hexane-ethyl acetate = 6:1, *v/v*) to give carbamate **10e** (61 mg, conversion: 56%, normalized yield: 25%) as white crystals. Mp: 79-82 °C, lit.[41] mp: 73-74 °C (data for pure *S* enantiomer). IR ν_{max} 3338 (NH), 1727, 1687 (C=O and Amide-I), 1534, 1497, 1448, 1288, 1259, 1176 (C-O-C), 1069, 730, 696 cm^{-1}; ^1H- NMR: δ 1.44 (d, *J* = 7.1 Hz, 3H, 3-H), 5.13 (s, 2H, CH_2), 5.35 (m, 1H, 2-H), 5.88 (m, 1H, NH), 7.31-7.40 (m, 5H, Ph of Cbz group), 7.50 (m, 2H, 3',5'-H), 7.98 (d, *J* = 7.7 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ 19.9 (C-3), 51.6 (C-2), 66.8 (CH_2Ph), 128.0, 128.1, 128.5, 128.6, 128.8 (C-2',6' + C-3',5' + C-2",6" + C-3",5" + C-4"), 133.8 (C-4'), 133.9, 136.4 (C-1' + C-1"), 155.6 (C=O, carbamate), 198.8 (C-1). Anal. Calcd. for $C_{17}H_{17}NO_3$ (283.32): C, 72.07; H, 6.05; N, 4.94%. Found: C, 71.95; H, 6.33; N, 4.80%.

2-(*N*-*t*-Butoxycarbonylamino)-1-phenyl-1-propanone (11e).

(a) 2-Azidopropiophenone (**5e**) (263 mg, 1.50 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. To the ethereal extract of the alkaline aqueous phase di-*tert*-butyl dicarbonate (480 mg, 2.19 mmol), triethylamine (0.18 mL, 1.32 mmol) and 4-(*N,N*-dimethylamino)pyridine (27 mg, 0.22 mmol) was added and the mixture was stirred at room temperature. When the reaction was completed (3.5 hrs), the mixture was concentrated under reduced pressure and the residue was purified by column chromatography (toluene-ethyl acetate = 4:1, *v/v*) to give carbamate **11e** (56 mg, 21%) as white crystals.

(b) 2-Azidopropiophenone (**5e**) (263 mg, 1.50 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. To the ethereal extract of the alkaline aqueous phase, di-t-butyl dicarbonate (316 mg, 1.45 mmol) in dry acetonitrile (25 mL) was added and stirred for 42 hrs at room temperature. The evaporated reaction mixture was submitted to column chromatography (toluene-ethyl acetate = 4:1, *v/v*) to give carbamate **11e** (73 mg, 27%) as white crystals.

2-(*N-tert*-Butoxycarbonylamino)-1-phenyl-1-ethanone (11a). 2-Azido-acetophenone (**5a**) (500 mg, 3.10 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. To the ethereal extract of the alkaline aqueous phase di-*tert*-butyl dicarbonate (2.36 g, 10.80 mmol), triethylamine (0.91 mL, 6.50 mmol) and 4-(*N,N*-dimethylamino)pyridine was added and the mixture was stirred at room temperature for 23 hrs. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (hexane-ethyl acetate: 4:1, *v/v*) to give the carbamate **11a** (183 mg, 30%) as white crystals.

2-(*N-tert*-Butoxycarbonylamino)-1-(4-fluorophenyl)-1-ethanone (11b). 2-Azido-(4'-fluorophenyl)-1-ethanone (**5b**) (500 mg, 2.78 mmol) was treated with chromium(II) acetate and worked up as given for pyrazine **15**. To the ethereal extract of the alkaline aqueous phase a solution of di-*tert*-butyl dicarbonate (3.55 g, 16.29 mmol) in diethyl ether (25 mL) and a solution of sodium hydrogencarbonate (234 mg, 2.78 mmol) in water (10 mL) was added and stirred for 23 hrs at room temperature. The mixture was diluted with water extracted with diethyl ether (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was triturated with hexane to give carbamate **11b** (263 mg, 37%) as a white crystals.

2-(*N-tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)-1-ethanone (11d). 2-Azido-(4'-methoxyphenyl)-1-ethanone (**5d**) (436 mg, 2.30 mmol) was treated with chromium(II) acetate, worked up and derivatized with Boc_2O as given above for product **11b**. Purification by column chromatography (toluene-ethyl acetate = 6:1, *v/v*) afforded carbamate **11d** (158 mg, 27%) as pale yellow crystals. Mp: 38-41.5 °C. IR: ν_{max} 3424 (NH), 2978, 2842 (MeO), 1715, 1682 (C=O and Amide-I), 1601 (Amide-II), 1514, 1455, 1366, 1261 (C-O-C), 1166 (C-O-C) cm^{-1}; ^{1}H- NMR: δ 1.49 (s, 9H, *t*-BuO), 3.89 (s, 3H, MeO), 4.62 (s, 2H, 2-H), 5.59 (s, 1H, NH), 6.97 (d, *J* = 8.4 Hz, 2H, 3',5'-H), 7.95 (d, *J* = 8.4 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ 28.3 (Me_3), 47.0 (C-2), 55.4 (OMe), 79.6 (**C**Me_3), 114.0 (C-3',5'), 127.5 (C-1'), 130.0 (C-2',6'), 155.8 (C=O, carbamate), 164.0 (C-4'), 193.1 (C-1). Anal. Calcd. for $C_{14}H_{19}NO_4$ (265.30): C, 63.38; H, 7.22; N, 5.28%. Found: C, 63.29; H, 7.45; N, 7.13%.

4-Chromanone (16)

(a) 3-Azido-4-chromanone (**12a**) (170 mg, 0.90 mmol) was treated with chromium(II) acetate as given for pyrazine **15**. The reaction mixture was diluted with water (50 mL), extracted with diethyl ether (5 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was submitted to column chromatography (hexane-ethyl acetate = 4:1, *v/v*). 52 mg of unreacted starting material **12a** eluted first followed by 4-chromanone (**16**) (24 mg, conversion: 76%, normalized yield: 18%) as a yellow oil. The product was identified by comparison to standard sample.

(b) When the reaction was repeated by using 5 equivalents chromium(II) acetate, no unreacted starting material **12a** was detected and the column chromatography gave 71 mg (53%) of 4-chromanone (**16**).

1-Thiochroman-4-one (**17**). 3-Azido-1-thiochroman-4-one (90 mg, 0.44 mmol) was treated with chromium(II) acetate (3.5 equiv.) as given for pyrazine **15**. The reaction mixture was diluted with water (30 mL), extracted with diethyl ether (4 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by repeated column chromatography (first elution: toluene-ethyl acetate = 4:1, *v/v*, second elution: toluene) to give 1-thiochroman-4-one (**17**) (61 mg, 50 %) as a yellow oil. The product was identified by comparison to standard sample.

Deoxybenzoin (20). 2-Azido-1,2-diphenyl-1-ethanone (**18**) (286 mg, 1.21 mmol) was treated with chromium(II) acetate as given for pyrazine **15**. The reaction mixture was diluted with water (20 mL), extracted with diethyl ether (3 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from hexane to give deoxybenzoin (**20**) (151 mg, 64%) as pale yellow crystals. The product was identified by comparison to standard sample.

Reductions by tin(II) chloride

2-(*N-tert*-Butoxycarbonylamino)-1-phenyl-1-ethanone (11a). (a) To a degassed solution of 2-azido-acetophenone (**5a**) (300 mg, 1.86 mmol) in methanol (10 mL) a solution of tin(II) chloride monohydrate (1.27g, 5.65 mmol) in methanol (15 mL) was added and the mixture was stirred at room temperature under nitrogen atmosphere. The reaction was monitored by TLC (hexane-ethyl acetate = 2:1, *v/v*). When the reaction completed (2 hrs), the reaction mixture was diluted with water (15mL), adjusted to pH = 10 with 8% sodium hydroxide solution, extracted with ethyl acetate (3 x 25 mL) and dried ($MgSO_4$). The drying agent was filtered off, di-*tert*-butyl dicarbonate (489 mg, 2.24 mmol) and triethylamine (0.49 mL, 3.53 mmol) was added and the mixture was stirred at room temperature with TLC monitoring (hexane-ethyl acetate = 2:1, *v/v*). When the reaction completed (15 hrs), the solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane-ethyl acetate = 2:1, *v/v*) to give carbamate **11a** (363 mg, 84%).

(b) A mixture of *syn-* and *anti*-2-azido-3-hydroxy-1-phenyl-1-butanone (**26**) (*syn/anti* = 53:47) (275 mg, 1.34 mmol) was treated with tin(II) chloride and derivatized with Boc_2O in the presence of TEA as given above. Purification by column chromatography (hexane-ethyl acetate = 2:1, *v/v*) gave afforded product **11a** (206 mg, 65%).

2-(*N*-*tert*-Butoxycarbonylamino)-1-(4-chlorophenyl)-1-ethanone (11c). 2-Azido-(4'-chlorophenyl)-1-ethanone (**5c**) (300 mg, 1.54 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. Purification by column chromatography (hexane-ethyl acetate = 3:1 *v/v*) gave carbamate **11c** (134 mg, 33%) as yellow crystals. Mp: 66-69 °C. IR: ν_{max} 3375 (NH), 2984, 1678 (C=O and Amide-I), 1590 (Amide-II), 1500, 1362, 1224, 1165 (C-O-C), 1091 (Ar-Cl) cm^{-1}; ^{1}H- NMR: δ 1.48 (s, 9H, *t*-BuO), 4.63 (d, *J* = 4.2 Hz, 2-H), 5.50 (s, 1H, NH), 7.47 (d, *J* = 8.4 Hz, 2H, 3',5'-H), 7.90 (d, *J* = 8.4 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ 28.3 (Me$_3$), 47.4 (C-2), 79.9 (**C**Me$_3$), 129.2 (C-2',6' + C-3',5'), 132.8 (C-1'), 140.3 (C-4'), 155.7 (C=O, carbamate), 193.4 (C-1). Anal. Calcd. for $C_{13}H_{16}ClNO_3$ (269.72): C, 57.89; H, 5.98%; N 5.19%. Found: C, 57.98; H, 6.16; N, 5.13%.

2-(*N*-*tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)-1-ethanone (11d). 2-Azido-(4'-methoxyphenyl)-1-ethanone (**5d**) (300 mg, 1.57 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The residue obtained by evaporation was crystallized from hexane to give carbamate **11d** (263 mg, 63%) as pale yellow crystals.

2-(*N*-*tert*-Butoxycarbonylamino)-1-phenyl-1-propanone (11e). 2-Azidopropiophenone (**5e**) (300 mg, 1.71 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. Purification by column chromatography (hexane-ethyl acetate = 2:1, *v/v*) yielded carbamate **11e** (265 mg, 62%) as white crystals.

3-(N-*tert*-Butoxycarbonylamino)-4-chromanone (14a). 3-Azido-4-chromanone (**12a**) (300 mg, 1.59 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The residue obtained by evaporation was crystallized from hexane to give carbamate **14a** (307 mg, 73%) as white crystals.

3-(*N*-*tert*-Butoxycarbonylamino)-6-chloro-4-chromanone (14b). 3-Azido-6-chloro-4-chromanone (**12b**) (300 mg, 1.34 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The residue was submitted to column chromatography (hexane-ethyl acetate = 6:1, *v/v*) to give carbamate **14b** (88 mg, 24%) as white crystals. Mp: 153-155 °C. IR: ν_{max} 3385 (NH), 1713, 1696 (C=O and Amide-I), 1607 (Amide-II), 1530, 1425, 1264, 1171, 1006 (Ar-Cl) cm^{-1}; ^{1}H- NMR: δ 1.48 (s, 9H, *t*-BuO), 4.04 (t, *J* = 12.0 Hz, 1H, 2-H$_{ax}$), 4.66 (br m, 1H, m, 2-H$_{eq}$), 4.87 (br m, 1H, 3-H), 5.42 (br s, 1H, NH), 6.96 (d, *J* = 8.8 Hz, 1H, 8-H), 7.45 (d, *J* = 8.8 Hz, 1H, 7-H), 7.83 (br s, 1H, 5-H); ^{13}C- NMR: δ 28.3 (Me$_3$), 53.9 (C-3), 69.9 (C-2), 79.6 (**C**Me$_3$), 119.6 (C-8), 120.4 (C-4a), 126.6 (C-5), 127.3 (C-6), 136.3 (C-7), 155.4 (C=O, carbamate), 160.2 (C-8a), 189.9 (C-4). Anal. Calcd. for $C_{14}H_{16}ClNO_4$ (297.73): C, 56.48; H, 5.42; N 4.70%. Found: C, 56.29; H, 5.77; N, 4.89%.

3-(*N*-*tert*-Butoxycarbonylamino)-6-methyl-4-chromanone (14c). 3-Azido-6-methyl-4-chromanone (**12c**) (300 mg, 1.47 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The residue obtained by evaporation was crystallized from hexane to give carbamate **14c** (307 mg, 73%) as yellow crystals. Mp: 138-140 °C. IR: ν_{max} 3381 (NH), 1705 (C=O and Amide-I), 1617 (Amide-II), 1421, 1365, 1332, 1289, 1156 (C-O-C) cm^{-1}; ^{1}H- NMR: δ 1.48 (s, 9H, *t*-BuO), 2.32 (s, 3H, Me) 4.00 (t,

J = 12.0 Hz, 1H, 2-H$_{ax}$), 4.64 (br m, 1H, 2-H$_{eq}$), 4.85 (br m, 1H, 3-H), 5.45 (s, 1H, NH), 6.89 (d, J = 9.0 Hz, 1H, 8-H), 7.4 (dd, J = 8.8, 1.8 Hz, 1H, 7-H), 7.66 (d, J = 1.8 Hz, 1H, 5-H); ^{13}C-NMR: δ 20.3 (6-Me), 28.2 (Me$_3$), 53.9 (C-3), 69.8 (C-2), 80.3 (**C**Me$_3$), 117.6 (C-8), 119.62 (C-4a), 126.8 (C-5), 131.1 (C-6), 137.5 (C-7), 155.4 (C=O, carbamate), 159.8 (C-8a), 190.6 (C-4). Anal. Calcd. for $C_{15}H_{19}NO_4$ (277.32): C, 64.97; H, 6.91; N, 5.05%. Found: C, 64.76; H, 7.10; N, 4.98%.

3-(*N-tert*-Butoxycarbonylamino)-1-thiochroman-4-one (14d). 3-Azido-1-thiochroman-4-one (**12d**) (300 mg, 1.46 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. Purification performed by column chromatography (hexane-ethyl acetate = 2:1, *v/v*) afforded carbamate **14d** (206 mg, 48%) as white crystals.

***syn*-2-(*N-tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-butanone** (*syn*-**29**). *syn*-2-Azido-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-butanone (*syn*-**29**) (300 mg, 0.94 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The obtained crude product was submitted to column chromatography (dichloromethane) and carbamate *syn*-**29** (203 mg, conversion: 77%, normalized yield: 72%) was obtained as a colorless oil. IR: ν_{max} 3444 (NH), 2930 (CH$_3$), 2857 (CH$_2$), 1715, 1698 (C=O and Amide-I), 1598, 1503, 1447, 1391, 1254 (C-O-C), 1168 (C-O-C), 1128, 1095, 1072, 837, 776, 701 cm^{-1}; ^{1}H- NMR: δ -0.28 (s, 3H, MeSi), -0.12 (s, 3H, MeSi), 0.78 (s, 9H, *t*-BuSi), 1.26 (d, J = 6.5 Hz, 3H, 4-H), 1.46 (s, 9H, *t*-BuO), 4.30 (m, 1H, 3-H), 5.17 (m, 1H, 2-H), 5.51 (br d, 1H, NH), 7.47 (m, 2H, 3’,5’-H), 7.57 (m, 1H, 4’-H), 7.92 (d, J = 8.2 Hz, 2H, 2’,6’-H); ^{13}C- NMR: δ -5.4, -4.6 (MeSi), 17.8 (Si**C**Me$_3$), 20.9 (C-4), 25.6 (SiC**Me**$_3$), 28.3 (**Me**$_3$CO), 61.4 (C-3), 68.9 (C-2), 79.6 (O**C**Me$_3$), 128.6 (C-2’,6’ + C-3’,5’), 133.3 (C-4’), 135.2 (C-1’), 156.1 (C=O, carbamate), 197.4 (C-1). Anal. Calcd. for $C_{21}H_{35}NO_4Si$ (393.59): C, 64.08; H, 8.96; N 3.56%. Found: C, 63.86; H, 9.02; N, 3.43%.

***anti*-2-(*N-tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-butanone** (*anti*-**29**). *anti*-2-Azido-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-butanone (*anti*-**29**) (130 mg, 0.41 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for **11a**. Purification of the crude product with column chromatography (dichloromethane) afforded carbamate *anti*-**29** (84 mg, conversion: 79%, normalized yield: 66%) as a yellowish oil. IR: ν = 3358 (NH), 2929 (CH$_3$), 2857 (CH$_2$), 1716, 1681 (C=O and Amide-I), 1502, 1448, 1252 (C-O-C), 1169 (C-O-C), 836 cm^{-1}; ^{1}H- NMR δ -0.18 (s, 3H, MeSi), -0.04 (s, 3H, MeSi), 0.67 (s, 9H, *t*-BuSi), 1.21 (d, J = 6.5 Hz, 3H, 4-H), 1.42 (s, 9H, *t*-BuO), 4.00 (m, 1H, 3-H), 5.24 (m, 1H, 2-H), 5.41 (br d, 1H, NH), 7.46 (m, 2H, 3’,5’-H), 7.57 (m, 1H, 4’-H), 8.01 (d, J = 8.0 Hz, 2H, 2’,6’-H); Anal. Calcd. for $C_{21}H_{35}NO_4Si$ (393.59): C, 64.08; H, 8.96; N 3.56%. Found: C, 64.21; H, 9.06; N, 3.57%.

***syn*-3-(*N-tert*-Butoxycarbonylamino)-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-chroman-4-one** (*syn*-**32**)**.** *syn*-3-Azido-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]chroman-4-one (*syn*-**31**) (155 mg, 0.45 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The obtained crude product was submitted to column chromatography (hexane-ethyl acetate = 3:1 *v/v*) and carbamate *syn*-**32** (135 mg, 72%) was obtained as a yellowish oil. IR: ν_{max} 3292 (NH), 2928 (CH_3), 2857 (CH_2), 1690 br (C=O and Amide-I), 1603, 1479, 1462, 1353, 1302, 1256 (C-O-C), 1181 (C-O-C), 1137, 1093, 1063, 833, 763 cm^{-1}; ^{1}H- NMR δ -0.37 (s, 3H, MeSi), -0.31 (s, 3H, MeSi), 0.91 (s, 9H, *t*-BuSi), 1.12 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.53 (s, 9H, *t*-BuO), 4.32 (q, *J* = 6.5 Hz, 1H, 1'-H), 4.57 (br m, 1H, one of 2-H), 4.81 (br m, 1H, one of 2-H), 5.09 (br s, 1H, NH), 6.95 (d, *J* = 8.7 Hz, 1H, 8-H), 7.01 (m, 1H, 6-H), 7.46 (m, 1H, 7-H), 7.94 (dd, *J* = 8.0, 1.9 Hz, 1H, 5-H); ^{13}C- NMR: δ -5.2, -4.5 (MeSi), 17.8 (C-4), 18.0 (Si**C**Me$_3$), 25.7 (SiC**Me**$_3$), 28.2 (**Me**$_3$CO), 65.6 (O**C**Me$_3$), 65.8 (C-1' + C-2), 80.0 (C-3), 117.7 (C-8), 120.5 (C-4a), 121.6 (C-6), 128.2 (C-5), 135.9 (C-7), 154.5 (C=O, carbamate), 161.0 (C-8a), 189.7 (C-4). Anal. Calcd. for $C_{22}H_{35}NO_5Si$ (421.60): C, 62.67; H, 8.37; N, 3.32%. Found: C, 62.79; H, 8.12; N. 3.19%.

***anti*-3-(*N-tert*-Butoxycarbonylamino)-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-chroman-4-one** (*anti*-**32**). *anti*-3-Azido-3-[(1-*tert*-butyldimethylsilyloxy)ethyl]chroman-4-one (*anti*-**31**) (175 mg, 0.50 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The obtained crude product was submitted to column chromatography (dichloromethane) and carbamate *anti*-**32** (90 mg, conversion: 79%, normalized yield: 54%) was obtained as a colorless oil. IR: ν_{max} 3408 (NH), 2930 (CH_3), 2958 (CH_2), 1704, 1698 (C=O and Amide-I), 1609, 1484, 1470, 1252 (C-O-C), 1169 (C-O-C), 1147, 1104, 832, 778 cm^{-1}; ^{1}H- NMR δ -0.15 (s, 3H, MeSi), -0.05 (s, 3H, MeSi), 0.83 (s, 9H, *t*-BuSi), 1.31 (d, *J* = 6.4 Hz, 3H, 2'-H), 1.43 (s, 9H, *t*-BuO), 4.29 (m, 1H, 1'-H), 4.77 (d, *J* = 11.6 Hz, 1H, one of 2-H), 4.89 (d, *J* = 11.6 Hz, 1H, one of 2-H), 5.45 (s, 1H, NH), 6.92 (d, *J* = 8.4 Hz, 1H, 8-H), 7.02 (m, 1H, 6-H), 7.45 (m, 1H, 7-H), 7.90 (d, *J* = 8.4 Hz, 1H, 5-H); ^{13}C- NMR: δ -5.3, -4.5 (MeSi), 17.8 (Si**C**Me$_3$), 18.8 (C-4), 25.6 (SiC**Me**$_3$), 28.3 (**Me**$_3$CO), 64.4 (O**C**Me$_3$), 69.3 (C-1'), 70.3 (C-2), 79.8 (C-3), 117.6 (C-8), 120.6 (C-4a), 121.6 (C-6), 128.6 (C-5), 135.7 (C-7), 155.6 (C=O, carbamate), 160.1 (C-8a), 190.9 (C-4). Anal. Calcd. for $C_{22}H_{35}NO_5Si$ (421.60): C, 62.67; H, 8.37; N, 3.32%. Found: C, 62.79; H, 8.16; N, 3.19%.

***anti*-3-(*N-tert*-Butoxycarbonylamino)-3-[1-(*tert*-butyldimethylsilyloxy)-2-oxo-2-phenyl-ethyl]-6-methylchroman-4-one** (*anti*-**38**)**:** *anti*-3-Azido-3-[1-(*tert*-butyldimethylsilyloxy)-2-oxo-2-phenylethyl]-6-methylchroman-4-one (*anti*-**37**) (160 mg, 0.35 mmol) was treated with tin(II) chloride and derivatized with Boc$_2$O in the presence of TEA as given above for the product **11a**. The obtained crude product was submitted to column chromatography (hexane-ethyl acetate = 6:1, *v/v*) and carbamate *anti*-**38** (90 mg, conversion: 75%, normalized yield: 61%) was isolated as a yellow oil. IR: ν_{max} 3407 (NH), 2930 (CH_3), 2958 (CH_2), 1727, 1698 (C=O and Amide-I), 1494, 1367, 1277, 1252 (C-O-C), 1216, 1168 (C-O-C), 1139, 839, 780 cm^{-1}; ^{1}H- NMR δ -0.11 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.87 (s, 9H, *t-Bu*Si), 1.37 (s, 9H, *t-Bu*O), 2.25 (s, 3H, 6-Me), 4.79 (d, *J* = 12.1 Hz, 1H, one of 2-H), 4.88 (d, *J* = 12.1 Hz, 1H, one of 2-H), 5.59 (s, 1H, 1-H), 5.83 (br s, 1H, NH), 6.87 (d, *J* = 8.4 Hz, 1H, 8-H), 7.31-7.33 (m, 3H, 3",5",7-H), 7.46-7.52 (m, 2H, 4",5-H), 7.76 (d, *J* = 7.2 Hz, 2H, 2",6"-H); ^{13}C- NMR: -5.4, -4.8 (MeSi), 18.1 (Si**C**Me$_3$), 20.3 (6-Me), 25.6 (SiC**Me**$_3$), 28.2 (**Me**$_3$CO), 63.9 (O**C**Me$_3$), 69.3 (C-2), 70.9 (C-1), 80.8 (C-3), 117.4 (C-8), 120.3 (C-4a), 127.6 (C-5), 128.4, 128.7 (C-2",6" + C-3",5"), 131.4 (C-6), 133.5 (C-

4”), 136.3 (C-1”), 137.2 (C-7), 158.8 (C-8a), 188.6 (C-4), 198.3 (C-2’). Anal. Calcd. for $C_{29}H_{39}NO_6Si$ (525.71): C, 66.26; H 7.48; N 2.66%. Found: C, 65.99; H, 7.67; N, 2.54.

Synthesis of the starting materials for the reductions

Starting materials **5a-d**,[20] **5e,**[19] **12a-d,**[20] **18,**[33] **26,**[20,33] **30,**[19] **33**[34] and **36**[34] were prepared according to literature methods.

***syn-* and *anti-* 3-Azido-3-(1-hydroxy-2-oxo-2-phenylethyl)-6-methylchroman-4-one (36)**. Phenylglyoxal hydrate (2.17 g, 14.29 mmol) and DBU (0.13 ml, 0.89 mmol) was added to a stirred and cooled (0-4 °C) solution of 3-azido-6-methylchroman-4-one (1.65 g, 8.12 mmol) in dry tetrahydrofuran (25 mL). The reaction was monitored by TLC (toluene-ethyl acetate = 6:1, *v/v*). When the reaction was completed (22 hrs) the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (dichloromethane) to give azido-alcohol **36** (1.73 g, 63%) as yellow crystals, the product was a 79:21 mixture of *syn* and *anti* diastereomers. The mixture of the diastereomers was recrystallized from hexane-ethyl acetate (2:1) to give first the *anti*-**36** diastereomer (578 mg) as pale yellow crystals. Pure *syn*-**36** isomer (555 mg) was obtained from the evaporated mother liquor by repeated recrystallization from hexane-ethyl acetate (2:1) as pale yellow crystals.

***anti*-36.** Mp: 157-159°C. IR: ν_{max} 3459 (OH), 2126 (N_3), 1687 (C=O), 1617, 1597, 1578, 1491, 1420, 1291, 1261 (C-OH), 1212, 1142, 1099, 1026, 984, 840, 746 cm^{-1}; ^1H- NMR: δ 2.32 (s, 3H, 6-Me), 4.09 (d, *J* = 12.6 Hz, 1H, one of 2-H), 4.22 (d, *J* = 6.3 Hz, 1H, 1’-OH), 4.26 (d, *J* = 12.6 Hz, 1H, one of 2-H), 5.55 (d, *J* = 6.3 Hz, 1H, 1’-H), 6.87 (d, *J* = 8.3 Hz, 1H, 8-H), 7.30 (dd, *J* = 8.4, 2.1 Hz, 1H, 7-H), 7.44 (m, 2H, 3”,5”-H), 7.53 (d, *J* = 2.1 Hz, 1H, 5-H), 7.61 (m, 1H, 4”-H), 7.85 (dd, *J* = 8.4, 1.5 Hz, 2H, 2”,6”-H). ^{13}C- NMR: δ 20.3 (6-Me), 67.8 (C-3), 69.3 (C-1’), 72.9 (C-2), 117.4 (C-8), 119.2 (C-4a), 127.5 (C-5), 128.7, 128.8 (C-2”,6” + C-3”,5”), 132.2 (C-6), 134.1 (C-4”), 135.1 (C-1”), 137.9 (C-7), 158.6 (C-8a), 188.4 (C-4), 198.1 (C-2’). Anal. Calcd. for $C_{18}H_{15}N_3O_4$ (337.33): C, 64.09; H, 4.48; N, 12.46%. Found: C, 63.98; H, 4.55; H, 12.00.

***syn*-36.** Mp: 106-109°C. IR: ν_{max} 3433 (OH), 2125 (N_3), 1698 (C=O), 1665 (C=O), 1616, 1597, 1492, 1287, 1254 (C-OH), 1219, 1023, 973, 830, 749 cm^{-1}; ^1H- NMR: δ 2.31 (s, 3H, 6-Me), 3.97 (d, *J* = 8.4 Hz, 1H, 1’-OH), 4.19 (d, *J* = 12.0 Hz, 1H, one of 2-H), 4.72 (d, *J* = 12.0 Hz, 1H, one of 2-H), 5.63 (d, *J* = 8.4 Hz, 1H, 1’-H), 6.94 (d, *J* = 8.5 Hz, 1H, 8-H), 7.37-7.44 (overlapping m, 3H, 7,3”,5”-H), 7.51 (br s, 1H, 5-H), 7.62 (m, 1H, 4”-H), 7.74 (d, *J* = 7.9 Hz, 2H, 2”,6”-H). ^{13}C- NMR: δ 20.4 (6-Me), 67.2 (C-3), 69.6 (C-1’), 71.4 (C-2), 117.9 (C-8), 119.4 (C-4a), 127.6 (C-5), 128.7 (C-2”,6” + C-3”,5”), 132.1 (C-6), 134.4 (C-4”), 135.3 (C-1”), 138.3 (C-7), 158.9 (C-8a), 187.6 (C-4), 199.0 (C-2’). Anal. Calcd. for $C_{18}H_{15}N_3O_4$ (337.33): C, 64.09; H, 4.48; N, 12.46%. Found: C, 64.22; H, 4.56; N, 12.23.

***syn*- and *anti*- 2-Azido-3-(*tert*-butyldimethylsilyloxy)-1-phenyl-1-butanone** (*syn*- and *anti*-**28**). To a solution of 2-azido-3-hydroxy-1-phenyl-1-butanone (**26**) (1.00 g, 4.87 mmol) in DMF (10 mL) *tert*-butyldimethylsilyl chloride (875 mg, 5.82 mmol) and imidazole (780 mg, 12.15 mmol) was added and the mixture was stirred at room temperature by monitoring with TLC (hexane-ethyl acetate = 3:1, *v/v*). After completion, the reaction mixture was poured into water and extracted with dichloromethane (3x100 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and the residue was purified by column chromatography (hexane-ethyl acetate = 6:1, *v/v*). *syn*-**28** diastereomer (613 mg, 39%) eluted first followed by *anti*-**28** diastereomer (233 mg, 15%).

***syn*-28**. Pale yellow crystals. Mp: 54-57°C. IR: ν_{max} 2925 (CH_3), 2856 (CH_2), 2098 (N_3), 1691 (C=O), 1450, 1248, 1211, 1102, 1059, 982, 836, 776 cm^{-1}; ^{1}H- NMR δ -0.19 (s, 3H, MeSi), -0.02 (s, 3H, MeSi), 0.84 (s, 9H, *t-Bu*Si), 1.34 (d, *J* = 6.3 Hz, 3H, 4-H), 4.31 (d, *J* = 3.8 Hz, 1H, 2-H), 4.44 (m, 1H, 3-H), 7.49 (m, 2H, 3',5'-H), 7.60 (m, 1H, 4'-H), 7.89 (d, *J* = 8.0 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ -5.4, -4.5 (MeSi), 17.8 (Si**C**Me$_3$), 21.7 (C-4), 25.5 (SiC**Me**$_3$), 68.7, 70.4 (C-2 + C-3), 128.6, 128.9 (C-2',6' + C-3',5'), 133.7 (C-4'), 135.0 (C-1'), 196.2 (C-1). Anal. Calcd. for $C_{16}H_{25}N_3O_2Si$ (319.47): C, 60.15; H, 7.89; N, 13.15%. Found: C, 60.19; H, 7.58; N, 12.98 %.

***anti*-28**. Colorless oil. ^{1}H- NMR δ -0.14 (s, 3H, MeSi), 0.02 (s, 3H, MeSi), 0.70 (s, 9H *t-Bu*Si), 1.35 (d, *J* = 6.3 Hz, 3H, Me), 4.31 (m, 1H, 3-H), 4.50 (d, *J* = 7.2 Hz, 1H, 2-H), 7.48 (m, 2H, 3',5'-H), 7.59 (m, 1H, 4'-H), 7.96 (d, *J* = 6.9 Hz, 2H, 2',6'-H); ^{13}C- NMR: δ -4.6, -5.3 (MeSi), 17.7 (Si**C**Me$_3$), 20.9 (C-4), 25.5 (SiC**Me**$_3$), 67.1, 69.7 (C-2 + C-3), 128.7, 128.9 (C-2',6' + C-3',5'), 133.8 (C-4'), 136.1 (C-1'). The C-1 signal could not be assigned due to the long relaxation time. Anal. Calcd. for $C_{16}H_{25}N_3O_2Si$ (319.47): C, 60.15; H, 7.89; N, 13.15%. Found: C, 60.37; H, 7.77; N, 12.98%.

***syn*- and *anti*- 3-Azido-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]chroman-4-one** (*syn*- and *anti*-**31**). A mixture of *syn*- and *anti*- 3-azido-3-(1-hydroxyethyl)-chroman-4-one **30** (*syn/anti* = 55:45) (1.00 g, 4.31 mmol) was treated with *tert*-butyldimethylsilyl chloride and imidazole as given above for the silyl- ether **28**. Column chromatography (hexane-ethyl acetate = 20:1, *v/v*) resulted in *syn*-**31** diastereomer (175 mg, 12%) and *anti*-**31** diastereomer (361 mg, 24%).

syn-**31**. Yellow oil. ^{1}H- NMR δ -0.07 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.84 (s, 9H *t-Bu*Si), 1.34 (d, *J* = 6.3 Hz, 3H, 2'-H), 4.33 (d, *J* = 12.0 Hz, 1H, one of 2-H), 4.49 (q, *J* = 6.3 Hz, 1H, 1'-H), 4.72 (d, *J* = 12.0 Hz, 1H, one of 2-H), 6.99 (d, *J* = 8.5 Hz, 1H, 8-H), 7.06 (m, 1H, 6-H), 7.52 (m, 1H, 7-H), 7.91 (d, *J* = 7.7 Hz, 1H, 5-H); ^{13}C- NMR: δ -5.4, -4.5 (MeSi), 17.8 (C-2'), 17.9 (Si**C**Me$_3$), 25.6 (SiC**Me**$_3$), 67.6 (C-1'), 68.3 (C-3), 69.1 (C-2), 117.9 (C-8), 120.0 (C-4a), 122.1 (C-6), 128.0 (C-5), 136.5 (C-7), 161.1 (C-8a), 188.5 (C-4). Anal. Calcd. for $C_{17}H_{25}N_3O_3Si$ (347.48): C, 58.76; H, 7.25; N, 12.09%. Found: C, 58.93; H, 7.17; N, 11.89.

anti-**31**. Pale yellow crystals. Mp: 71-73.5 °C. IR: ν_{max} 2923 (CH_3), 2113 (N_3), 1700 (C=O), 1609, 1483, 1461, 1326, 1302, 1258 (C-O-C), 1214, 1101, 1038, 957, 833, 773, 756 cm^{-1}; ^{1}H- NMR δ -0.02 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.86 (s, 9H, *t-Bu*Si), 1.37 (d, *J* = 5.1 Hz, 3H, 2'-H), 4.17, 4.25 (AB q, *J* = 11.8 Hz, 1H, 2-H), 4.49 (q, *J* = 5.7 Hz, 1H, 1'-H), 6.97 (d, *J* = 8.3 Hz, 1H, 8-H), 7.09 (m, 1H, 6-H), 7.52 (m, 1H, 7-H), 7.91 (d, *J* = 6.9 Hz, 1H, 5-H); ^{13}C- NMR: δ -5.6, -4.6 (MeSi), 17.8 (Si**C**Me$_3$), 18.8 (C-2'), 25.5 (SiC**Me**$_3$), 67.3 (C-3), 69.3 (C-1'), 69.9 (C-2), 117.6 (C-8), 119.4 (C-4a), 122.2 (C-6), 128.0 (C-5), 136.3 (C-7), 160.6 (C-8a), 190.8 (C-4). Anal. Calcd. for $C_{17}H_{25}N_3O_3Si$ (347.48): C, 58.76; H, 7.25; N, 12.09%. Found: C, 58.54; H, 7.16; N, 12.24%.

***anti*- 3-Azido-3-(1-*tert*-butyldimethylsilyloxy-2-oxo-2-phenylethyl)-6-methylchroman-4-one** (**37**). *anti*-3-Azido-3-(1-hydroxy-2-oxo-2-phenylethyl)-6-methylchroman-4-one (*anti*- **36**) (500 mg, 1.48 mmol) was treated with *tert*-butyldimethylsilyl chloride and imidazole as given above for the silyl ether **28**. Column chromatography (toluene) afforded azide **37** (180 mg, conversion: 83%, normalized yield: 32%) as yellow crystals. Mp: 84-88°C. ^{1}H- NMR δ -0.08 (s, 3H, MeSi), 0.06 (s, 3H, MeSi), 0.81 (s, 9H, *t-Bu*Si), 2.33 (s, 3H, 6-Me), 4.51 (d, *J* = 13.3 Hz, 1H, one of 2-H), 4.86 (d, *J* = 13.3 Hz, 1H, one of 2-H), 5.85 (s, 1H, 1'-H), 6.92 (d, *J* = 8.0 Hz, 1H, 8-H), 7.35 (dd, *J* = 8.0, 2.2 Hz, 7-H), 7.49 (m, 2H, 3",5"-H), 7.61 (m, 1H, 4"-H), 7.71 (br s, 1H, 5-H), 8.02 (d, *J* = 8.0 Hz, 2H, 2",6'-H). Anal. Calcd. for $C_{24}H_{29}N_3O_4Si$ (451.59): C, 63.83; H, 6.47; N, 9.30%. Found: C, 63.96; H, 6.39; N, 9.11%.

Analogous reaction of *syn*-**36** failed to give any isolable products, only an extensive decomposition of the starting material was observed.

3-(4-Chlorobenzoyl)-5-phenylisoxazole (35). 2-Azido-3-hydroxy-4-phenyl-1-(4-chloro-phenyl)-butane-1,4-dione (**33**) (200 mg, 0.61 mmol) was treated with *tert*-butyldimethylsilyl chloride and imidazole as given above for the silyl- ether **28**. Column chromatography (dichloromethane) resulted in isoxazole **35** (75 mg, 44%, mp: 132-135 °C), the product was identified by comparison with a previously described[34] sample.

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References and Notes

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