Lewis Acid-Mediated Diastereoselective Reduction of *N*-Protected β-Amino Ketones: Influence of the Nature of the Metal Atom and of the Nitrogen Protecting Group

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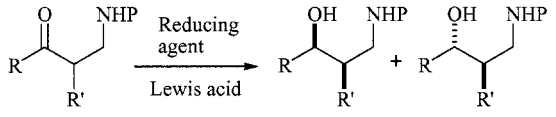
Lewis acid-mediated chelation and non-chelation control is one of the most fundamental and practical concepts in modern organic chemistry. Extension of these concepts to the reduction of different *N*-protected α-substituted β-amino ketones indicated that diastereoselectivity in the hydride addition step is strongly dependent on the nature of the metal atom and on the type of protecting group. Strongly chelating $TiCl_4$ and an electron-rich nitrogen protecting group promoted the *syn* diastereoselectivity in noncoordinating solvents (CH_2Cl_2) at −78 °C with BH_3·py as reducing agent. On the other hand, a Lewis acid as such as $CeCl_3$ and a bulky *N*-protecting group gave an excess of the *anti*-diastereomer in coordinating solvents (THF) at the same temperature with lithium borohydride ($LiBH_4$) as reducing agent.

Introduction

A variety of important compounds containing a 1,3-amino alcohol structure have been studied in detail due to their important role in biologically active natural products.[1] These structures have also been discovered to play a crucial role in the preparation of important alkaloids[2] as well as drugs for therapeutic purposes.[3] There has therefore been an increased interest in the synthesis of molecules containing an amino alcohol moiety. Among the plethora of methods that exist for their construction,[4] the classical method for the preparation of 1,3-amino alcohols usually involves reduction of their nearest precursors, namely the corresponding carbonyl compounds.[5] In particular, the reduction of *N*-protected β-amino ketones is one of the most attractive routes.[6] Recently, we published a preliminary communication on a new, straightforward method for the synthesis of *syn*-1,3-amino alcohols.[7] In the presence of $TiCl_4$, the borane/tetrahydrofuran complex reduces 2-alkyl-3-oxoamides to the corresponding *syn*-1,3-amino alcohols in good yield and high diastereoselectivity. During this same period we have also been engaged in the study of the addition of nucleophiles to a large variety of functionalized ketones with high efficiency and stereoselectivity by an appropriate choice of Lewis acid promoter.[8] In particular, extensive studies have been devoted to the reduction of β-functionalized carbonyl compounds with an asymmetric α-carbon in their racemic form, and have found that these protocols represent efficient and general approaches to access both *syn*- and *anti*-diastereomers from a common precursor.[9] The correct choice of hydrides, solvent, and especially Lewis acid, allows us to perform a simple and effective diastereoselective synthesis of the corresponding β-hydroxy derivatives.

Given the importance of the target at issue, it seemed very useful to investigate the possibility of applying these concepts to the diastereoselective reduction of α-substituted β-amino ketones in order to set up on operationally simple methodology. Taking into account the good results that we have obtained in the diastereoselective reduction of α-substituted β-functionalized ketones, we wish to report here that the efficiency and sense of diastereoselective reduction of β-amino ketones **1** is highly influenced by substrate structures and reaction conditions (Scheme 1). The ratio of *syn*-**2** and *anti*-**2** amino alcohols also depends highly on the kind of *N*-protecting group (P). Our procedure represents



Scheme 1. Diastereoselective reduction of *N*-protected α-substituted β-amino ketones **1**

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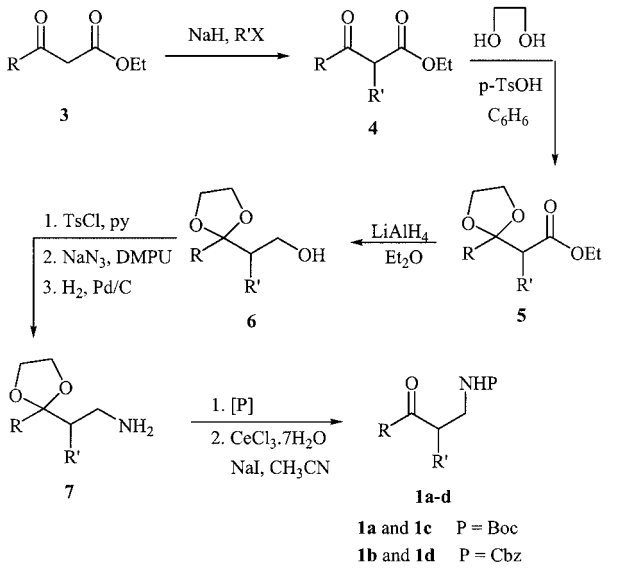
an effective alternative procedure for the diastereoselective synthesis of *syn*- or *anti*-α-alkyl-1,3-amino alcohols through the reduction of the corresponding β-amino ketones with BH_3·py or lithium borohydride in the presence of $TiCl_4$ or dry $CeCl_3$, respectively.

Results and Discussion

It is well established that the influence of Lewis acid promoters on the stereochemical selectivity of nucleophilic addition reactions to carbonyl compounds is instrumental in determining the stereochemical outcome of these reactions.[10] Lewis acids that possess two empty coordination sites, such as $TiCl_4$, usually form chelates when a second basic site is present in the carbonyl ligand.[11] In contrast, rare-earth element Lewis acids, such as $CeCl_3$, tend, in several circumstances, to be incapable of chelation because the resulting large coordination numbers lead to long and therefore unstable metal−ligand bonds.[12] A chelation and non-chelation control model has been proposed by us to justify the diastereofacial selectivity obtained in reductions of α-substituted β-functionalized carbonyl compounds. On the basis of these results, we have examined the reduction of *N*-protected α-substituted β-amino ketones (**1**) in the expectation of the formation of *syn*- and *anti*-1-amino-3-hydroxy compounds **2**.[13]

In order to study if this reduction reaction of β-amino ketones depends upon initial coordination of the nitrogen atom to Lewis acid, we required large quantities of these substrates. Among the methods for generating β-amino ketones,[14] the Mannich reaction is a classical method for the preparation of these molecules.[15] However, due to the drastic reaction conditions and the long reaction times, the classical Mannich reaction presents serious disadvantages.[16] The approach based on the Michael addition of amines to α,β-unsaturated carbonyl compounds affords an efficacious alternative.[17] The drawbacks encountered with this approach, such as basic conditions,[18] acid catalysis[19] or the problem of double-conjugate addition,[20] led us to develop a general synthesis for these β-amino ketone compounds.

The first set of β-amino ketones used in this study was prepared by the sequence shown in Scheme 2 in an approach that takes advantage of the easy availability of β-keto ester **3**. The procedure consists of alkylation of the dianion keto ester[21] followed by treatment of the adducts with one equivalent of sodium hydride and α-alkylation of the monoanions to give **4**. Ketalisation of **4** to **5**, followed by reduction with lithium aluminum hydride, afforded the corresponding alcohol.[22] Conversion into the tosylate and displacement with sodium azide gave the desired azides in good yields. The reduction of these azides was accomplished by catalytic hydrogenation, and the resulting amines **7** were then protected as either the *tert*-butyl carbamate or benzyl carbamate using standard protocols.[23] Subsequent hydrolysis of the ketal moiety[24] provided the corresponding *N*-protected amino ketones in excellent overall yield.



Scheme 2. A general synthesis of β-amino ketone compounds **1a−d**

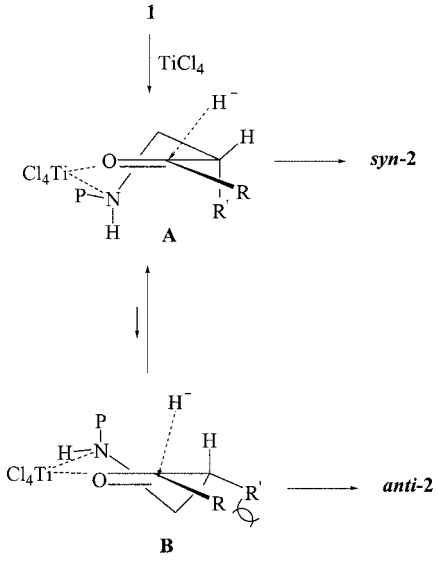
The choice of carbamate groups as protecting groups for β-amino ketones **1a−d** arises from the fact that stereocontrol in the reduction of carbamate-protected amino ketones tends to favor chelation control since both the ketone oxygen and the carbamate nitrogen are sterically accessible for coordination to a Lewis acid.[25] In fact, we found that the reduction of α-alkyl-β-amino ketones **1a−d** in dry dichloromethane at low temperature (−78 °C) with borane-pyridine complex (BH_3·py)[26] in the presence of $TiCl_4$ gave moderate to good *syn*-selectivity (Table 1). This is clearly due to chelation[27] by the metal atom, which creates a bridge between the oxygen atom of the carbonyl group and the nitrogen atom of the amine group. In the resulting six-membered cyclic intermediate, the most populated conformation **A** is preferentially attacked by the incoming hydride ion at the less-hindered side opposite R′ (Scheme 3).

In contrast to the corresponding β-functionalized keto compound O-derivatives,[9] these N-derivatives are reduced with a lower level of diastereoselectivity. The presence of a strongly electron-withdrawing group probably causes a decrease in the electron density on the nitrogen atom of the carbamate group, weakening the interaction between the n-electrons of nitrogen and Ti^{IV}; the cyclic complex **A** therefore becomes less rigid with a consequent decrease in the stereofacial discrimination. Thus, with the primary aim of understanding the factors that influence this reduction reaction more completely, and with the secondary aim of improving the diastereoselective ratios, we decided to explore the effect of changing the nature of the nitrogen protecting group. Tolylsulfonyl is an attractive protecting group because sulfonamides are usually stable, crystalline solids that are easy to purify and handle. However, in our methodology they were less reactive and the *N*-tolylsulfonyl-β-amino ketones were recovered completely. Therefore, in order to establish whether replacement of the nitrogen protecting

Table 1. Stereoselective reduction of β-amino ketones **1** to 1,3-amino alcohols **2** by hydrides (H^-) in the presence of Lewis acids[a]

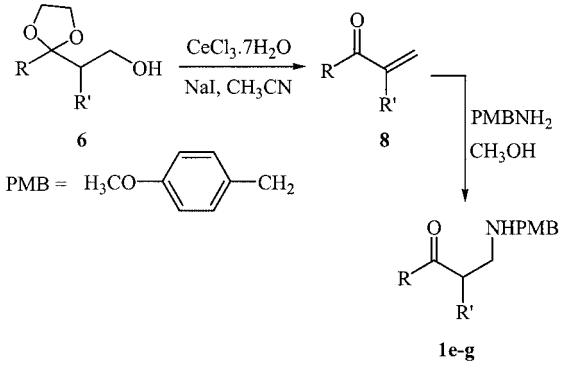
Entry	**1**	R	R′	P	Reducing agent	Lewis acid	Product **2**[b]	*syn*/*anti* [c]	Yield (%)[d]
1	**1a**	*n*Pr	Bn	Boc	$LiBH_4$	$CeCl_3$	**2a**	15:85	98
2	**1a**	*n*Pr	Bn	Boc	BH_3·py	$TiCl_4$	**2a**	62:38	97
3	**1b**	*n*Pr	Bn	Cbz	$LiBH_4$	$CeCl_3$	**2b**	22:78	91
4	**1b**	*n*Pr	Bn	Cbz	BH_3·py	$TiCl_4$	**2b**	80:20	98
5	**1b**	*n*Pr	Bn	Cbz	$LiEt_3BH$[e]	$CeCl_3$	**2b**	50:50	98
6	**1c**	Me	Bn	Boc	BH_3·py	$TiCl_4$	**2c**	60:40	92
7	**1c**	Me	Bn	Boc	$LiBH_4$	$CeCl_3$	**2c**	18:82	93
8	**1d**	Me	Bn	Cbz	BH_3·py	$TiCl_4$	**2d**	80:20	98
9	**1e**	Ph	Et	PMB	BH_3·py	$TiCl_4$	**2e**	93:7	96
10	**1e**	Ph	Et	PMB	$LiBH_4$	$CeCl_3$	**2e**	33:67	91
11	**1f**	*n*Bu	Et	PMB	BH_3·py	$TiCl_4$	**2f**	90:10[f]	90
12	**1f**	*n*Bu	Et	PMB	Me_2S·BH_3	$TiCl_4$	**2f**	90:10[f]	95
13	**1f**	*n*Bu	Et	PMB	$LiBH_4$	$CeCl_3$	**2f**	30:70[f]	90
14	**1g**	Ph	*n*Pr	PMB	$LiBH_4$	$CeCl_3$	**2g**	30:70	90

[a] The reaction was performed by adding a 2 M solution of $LiBH_4$ in THF to a THF solution of **1**/$CeCl_3$ at −78 °C or by adding the BH_3 complex to a CH_2Cl_2 solution of **1**/$TiCl_4$ at −78 °C. [b] All products were identified by IR and NMR spectroscopy, and GC/MS. [c] Determined by ^1H and ^{13}C NMR spectroscopy. [d] Calculated on the mixture of diastereomers isolated by column chromatography. [e] Reaction performed by a adding a 1 M solution of $LiEt_3BH$ in THF to a THF solution of **1**/$CeCl_3$ at −78 °C. [f] Assignment of configuration from the ^1H NMR spectrum of the corresponding cyclic carbamate.



Scheme 3. Chelation control in the $TiCl_4$-mediated reduction of α-alkyl β-amino ketones

group would influence the *syn*-**2** to *anti*-**2** ratio, we investigated reduction of *N*-(*p*-methoxybenzyl)-β-amino ketones **1e**−**g**. Unfortunately, the methodology in Scheme 2 was not good enough for the preparation of these derivatives. Among the methods for generating this class of *N*-protected β-amino ketones, the methodology shown in Scheme 4 gave us excellent results. The β-hydroxy ketals **6e**−**g** were transformed into the corresponding α,β-unsaturated derivatives **8e**−**g** by dehydration upon treatment with the $CeCl_3$·$7H_2O$/NaI system in refluxing acetonitrile.[28] Subsequent Michael addition of *p*-methoxybenzylamine to these α,β-unsaturated ketones provided the corresponding *N*-(*p*-methoxybenzyl)-amino ketones **1e**−**g**.[29] The reduction with BH_3·py in the presence of $TiCl_4$ gave the corresponding *N*-(*p*-methoxybenzyl)-1,3-amino alcohols in excellent yields and with better diastereoselectivity than with the *N*-carbamate protecting groups (Table 1, entries 9 and 11). Thus *N*-substitution by an electron-donating protecting group seems to be required to realize major levels of diastereoselectivity in these reductions. This confirms that a chelation model concerning the nitrogen and carbonyl moiety could be involved as a control element in determining the stereochemical outcome.

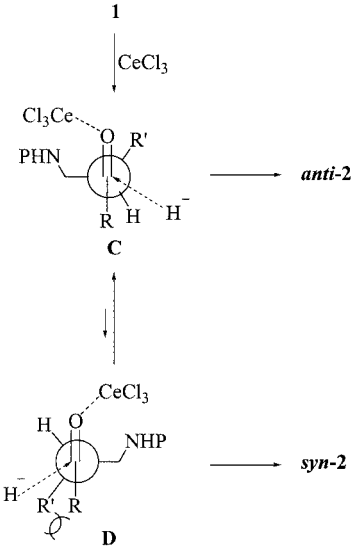


Scheme 4. Preparation of β-[(*p*-methoxybenzyl)amino] ketones **1e**−**g**

Apart from the general diastereoselectivity argument a very brief discussion should also mention the observed temperature behavior. It is known that the diastereoselectivity can either decrease, increase or stay the same when performing the reaction at higher temperatures. We have observed that our methodology follow the first case, that is, a decrease of diastereoselectivity with an increase of reaction temperature. Moreover, attempts to perform the reduction reaction of our β-amino ketones **1a**−**g** in the absence of $TiCl_4$ gave no diastereoselectivity, which is obviously due to the conformational flexibility of the alkyl chain.

The reduction of β-amino ketones **1** with BH_3·py in the presence of $TiCl_4$ was also studied in different solvents, such as CH_2Cl_2, THF and Et_2O. The diastereoselectivity was favored with noncoordinating solvents (CH_2Cl_2), presumably promoting association between $TiCl_4$ and the NHP group, whereas diethyl ether and THF led to the complete loss of diastereoselectivity. This situation did not change when the reduction of β-amino ketones was performed with borane-dimethyl sulfide reagent (Table 1, entry 12), a reductive system with lower basicity than amine boranes.[30]

We also examined the reduction of α-substituted *N*-protected β-amino ketones **1a**−**g** with hydrides in the presence of dry cerium trichloride as the Lewis acid. We first tested the reduction of **1a** in CH_2Cl_2 with BH_3·py complex, a convenient reducing agent because of its solubility in many organic solvents, in the presence of dry $CeCl_3$. No reaction with $CeCl_3$ was observed, and the starting material was quantitatively recovered after 4 h at −78 °C. Prolonged reaction times and higher reaction temperatures were also ineffective. A complex between cerium(III) chloride and β-amino ketone was formed, since the addition of the substrate to a suspension of the cerium salt resulted in a clear solution after about 2 h. The paramagnetism of the cerium salt prevented useful NMR information on the structure of this complex from being obtained.[31] On the other hand, the reduction of *N*-protected β-amino ketones **1a**−**g** proceeded successfully when a 2 M THF solution of $LiBH_4$ was employed in the presence of dry $CeCl_3$ and at low temperature (−78 °C). The reaction was slower (4 h vs. 15 min) with respect to the titanium reduction and gave the expected *N*-protected α-alkyl-1,3-amino alcohols **2a**−**g** in excellent yields, but with reversed selectivity with respect to the BH_3·py/$TiCl_4$ system (Table 1). These findings strongly support an open-chain mechanism, and the Felkin−Anh model[32] explains the stereochemical outcome of the reaction. In fact, the sterically demanding alkyl chains favor the **C** over the **D** conformation, and the hydride anion attacks the carbonyl at the opposite side to the *N*-protected amino group leading to the *anti* diastereomers (Scheme 5). This explanation was further supported by the fact that in the $TiCl_4$-reducing system, the relative *syn*-diastereoselectivity decreases in the order PMB > Cbz > Boc, and in particular with Boc being more bulky than Cbz, so favouring the **A** conformation (Scheme 3), where P is equatorial, over the **B** conformation, where P is axial. In the $CeCl_3$-reducing system, however, the *anti*-diastereoselectivity was enhanced in the reduction of the more bulky *N*-protecting group (Table 1, entries 1, 3 and 10): because P is more bulky a large stereodifferentation between the **C** and **D** conformations is observed. For this reason, we believe that the cerium atom is not able to be chelated under these conditions, even though $CeCl_3$ is apparently a good Lewis acid and its anhydrous form is highly hygroscopic.[33] However, the presence of the cerium salt is essential for obtaining high yields and good stereochemical efficiency, since the reaction can then be carried out at lower temperatures. According to Boltzman's law, the population of the more stable conformer increases as the temperature decreases. The reduction can be carried out at −78 °C with a powerful hydride reducing agent such as $LiEt_3BH$,[34] but no diastereoselectivity was observed (Table 1, entry 5). Although several types of metal hydride complexes are available for this reduction of *N*-protected α-substituted β-amino ketones, the lithium borohydride is among the best.[35]

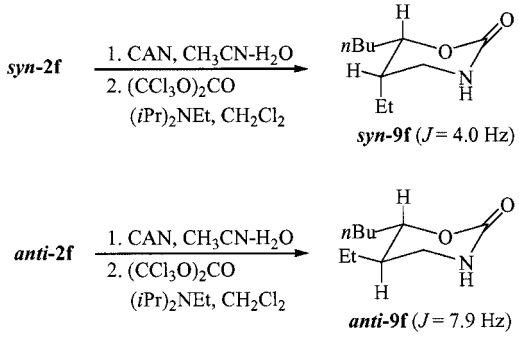


Scheme 5. Nonchelation control in the $CeCl_3$-mediated reduction of α-alkyl β-amino ketones

As we have previously noted for the $TiCl_4$ reaction, there are also remarkable solvent effects in the reduction with the $LiBH_4$/$CeCl_3$ system at −78 °C. Coordinating solvents such as diethyl ether and THF, which were mostly employed in analogous low-temperature studies, proved to be the best media; non-coordinating solvents led to low selectivity and pentane was less suitable than dichloromethane. Considering the conversion, diethyl ether apparently slows the reaction, although yields were good in all cases. In conclusion, THF was chosen for reductions with $CeCl_3$.

The stereochemistry of the products obtained in these reductions was not established unambiguously but was assumed on the basis of the results for *N*-protected 1,3-amino alcohols reported in the literature.[36] The assignment for the *syn*- and *anti*-diastereomers was based on the coupling constant between the C2- and C3 protons, which is usually slightly larger for the *anti*- than for the *syn*-diastereomer.[37] Moreover, the stereochemistry of the *syn*- and *anti*-diastereomers was determined from the ^{13}C NMR chemical shifts of the carbinol carbon in comparison with the data for similar compound. It was also shown that the *syn*/*anti* ratios of the crude products were very similar or identical to those of the purified *N*-protected 1,3-amino alcohols. The *syn*- and *anti*-diastereomers can be separated by flash chromatography (eluent: hexanes/ethyl acetate, 70:30, $\Delta R_f = 0.15$) and, therefore, we can reasonably assume that the observed *syn*/*anti* ratio at the 1,3-amino alcohol compound stage reflects the diastereofacial selectivity of the hydride-addition step. The vicinal coupling constant method for the assignment of relative stereochemistry cannot, how-

ever, be applied for *N*-*p*-methoxybenzyl-1,3-amino alcohols **2f** (Table 1, entries 11, 12 and 13).[38] Thus, the relative stereochemistry of compounds *syn*-**2f** and *anti*-**2f** was determined by converting the corresponding amino alcohol into the cyclic carbamate *syn*-**9f** and *anti*-**9f** by reaction with bis(trichloromethyl)carbonate and Hunig's base (Scheme 6).[39] Deprotection of reduction products **2f** by cerium ammonium nitrate[40] gave the corresponding 1,3-amino alcohols, which were transformed into the final cyclic carbamate **9**. The diastereomers *syn*-**2f** gave carbamates *syn*-**9f**, which have a smaller vicinal coupling constant (J = 4.0 Hz) than the carbamates *anti*-**9f** (J = 7.8 Hz) formed from the corresponding *anti*-**2f** diastereomers. Therefore, the diastereoselectivity of the BH_3·py/$TiCl_4$ and $LiBH_4$/$CeCl_3$ systems determined previously on the basis of NMR spectroscopic data was confirmed by the defined cyclic structure of the corresponding carbamates.



Scheme 6. The vicinal coupling constant method for assignment of relative stereochemistry

Conclusion

We have investigated a new application of our diastereoselective reduction of β-functionalized carbonyl compounds with a stereogenic center in the α-position. In particular, a diastereoselective procedure to obtain both *syn*- and *anti*-*N*-protected 1,3-amino alcohols, which are key intermediates for the stereoselective preparation of complex functionalized molecules, is now available. The present work confirms that the correct choice of Lewis acid is essential in determining the diastereoselective outcome of these reductions. Strongly chelating $TiCl_4$ led to the *syn*-diastereomer with BH_3·py as reducing agent, while non-chelating $CeCl_3$ gave an excess of the *anti*-diastereomer with $LiBH_4$ as reducing agent. Moreover, the nature of the protecting group also significantly influences the diastereoselectivity of the reduction of *N*-protected α-substituted β-amino ketones. Finally, although the number of examples is limited, it may be safely stated that with these *N*-protected β-amino ketones our procedure for hydride addition is less diastereoselective with respect to our reductions of the corresponding β-functionalized keto compound O derivatives.[9] Thus, studies are in progress in our laboratories to extend this protocol to other kinds of β-amino ketones as well as the introduction of a functionalized carbon chain at the β-carbon.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on Varian Gemini 200 spectrometer. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz on Varian Gemini 200 spectrometer, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. Infrared spectra were recorded on a Perkin−Elmer FTIR Paragon 500 spectrometer using thin films on NaCl plates. Only the characteristic peaks are quoted. Mass spectra were recorded on a Hewlett−Packard 5988 gas chromatography with a mass-selective detector MSD HP 5790 MS, utilizing electron ionisation (EI) at an ionizing energy of 70 eV. A fused silica column (30 m × 0.25 mm HP-5; cross-linked 5% Ph-Me siloxane, 0.10 μm film thickness) was used with a helium carrier flow of 30 mL/min. The temperature of the column was varied, after a delay of 3 min from the injection, from 65 °C to 300 °C with a slope of 15 °C min^{-1}.

All air-sensitive reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were distilled under nitrogen, tetrahydrofuran (THF), diethyl ether (Et_2O), and pentane from sodium benzophenone ketyl and dichloromethane (CH_2Cl_2) from calcium hydride. Solutions were evaporated to dryness under reduced pressure with a rotary evaporator and the residue was chromatographed on a Baker silica gel (230−400 mesh) column using a 30% ethyl acetate in hexane mixture as the eluent. Analytical thin layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm) and/or by dipping the plates into Von's reagent (1.0 g of ceric sulfate and 24.0 g of ammonium molybdate in 31 mL of sulfuric acid and 470 mL of water).

All *N*-protected β-amino ketones **1a**−**d** and **1e**−**g** were prepared from β-keto ester **3** in according to Scheme 2[21−24] and Scheme 4,[28,29] respectively.

General Procedure for the Diastereoselective Reduction of *N*-Protected α-Alkyl-β-Amino Ketones 1 with $LiBH_4$ in the Presence of Dry $CeCl_3$: Finely ground $CeCl_3$·$7H_2O$ (3.2 mmol) was dried by heating at 140 °C/0.1 Torr for 2 h.[32] It was then suspended in 10 mL of dry THF and left to stir overnight at room temperature. At this temperature, a solution of **1** (1.0 mmol) in 5 mL of THF was added and left to stir for 1 h. The mixture was then cooled to −78 °C, and $LiBH_4$ (3.0 mmol, solution 2 M in THF) was added by syringe. The resulting mixture was left to stir until TLC indicated that no substrate **1** remained (4 h). The reaction mixture was quenched with dilute HCl (10%), extracted with Et_2O, and the combined organic extracts were washed with water and brine and dried over Na_2SO_4. Finally, evaporation of the solvents afforded the crude diastereomeric mixture of *N*-protected 1,3-amino alcohols **2**. The diastereomeric ratios[41] were measured by NMR analysis, and clean separation of the *anti*- and *syn*-diastereomers could be achieved by flash column chromatography.[42] The reported yields listed in Table 1 are the weight recovery of the major *anti*-diastereomer and of a minor amount of the *syn*-diastereomer.

***tert*-Butyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxyhexyl)carbamate (*anti*-2a):** Yield: 256 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3348, 3029, 1690, 1595 cm^{-1}. ^{1}H NMR: δ = 0.91 (t, J = 6.9 Hz, 3 H), 1.32−1.60 (m, 5 H), 1.62 (s, 9 H), 2.40 (dd, J = 3.9, 8.1 Hz, 1 H), 2.88 (dd, J = 3.9, 4.9 Hz, 1 H), 3.01 (br. s, 1 H), 3.25−3.36 (m, 1 H), 3.70−3.80 (m, 1 H), 4.15 (dt, J = 7.0, 7.8 Hz, 1 H), 4.70−4.78 (m, 1 H), 7.17−7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 14.9, 19.7, 28.3, 39.3, 42.4, 45.3, 56.3, 74.5, 79.6, 126.6, 128.0, 128.7, 142.5, 158.7

ppm. MS: *m*/*z* = 289 [$M^+ - H_2O$], 250, 198, 131, 91 (100), 77, 65, 57, 41. $C_{18}H_{29}NO_3$ (307.43): calcd. C 70.32, H 9.51, N 4.56; found C 70.27, H 9.48, N 4.38.

Benzyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxyhexyl)carbamate (*anti*-2b): Yield: 243 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3388, 3045, 1685 cm^{-1}. ^1H NMR: δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 1.20−1.62 (m, 4 H), 1.77−1.83 (m, 1 H), 2.43 (dd, *J* = 10.2, 14.0 Hz, 1 H), 2.73−2.81 (m, 1 H), 2.93−3.01 (m, 1 H), 3.20−3.33 (m, 2 H), 3.49−3.55 (m, 1 H), 4.97 (dt, *J* = 7.0, 12.2 Hz, 1 H), 5.12 (d, *J* = 12.2 Hz, 1 H), 5.39−5.44 (m, 1 H), 7.11−7.34 (m, 10 H) ppm. ^{13}C NMR: δ = 14.3, 19.4, 32.7, 36.0, 41.9, 45.7, 67.0 71.9, 126.2, 128.4, 128.7, 128.9, 129.2, 129.3, 136.7, 140.4, 157.8 ppm. MS: *m*/*z* = 323 [$M^+ - H_2O$], 232, 142, 117, 91 (100), 79, 65, 41. $C_{21}H_{27}NO_3$ (341.44): calcd. C 73.87, H 7.97, N 4.10; found C 73.81, H 7.69, N 4.02.

***tert*-Butyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxybutyl)carbamate (*anti*-2c):** Yield: 213 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3382, 3062, 1690, 1603 cm^{-1}. ^1H NMR: δ = 1.30 (d, *J* = 6.2 Hz, 3 H), 1.44 (s, 9 H), 2.39−2.51 (m, 1 H), 2.75−2.98 (m, 3 H), 3.20−3.36 (m, 1 H), 3.52−3.59 (m, 1 H), 3.77 (br. s, 1 H), 3.86 (dq, *J* = 6.2, 8.0 Hz, 1 H), 7.15−7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 19.4, 28.4, 32.7, 38.7, 48.2, 67.5, 79.7, 126.0, 128.7, 128.8, 141.0, 155.8 ppm. MS: *m*/*z* = 223, 205, 144, 118, 91, 77, 57 (100), 41. $C_{16}H_{25}NO_3$ (279.37): calcd. C 68.79, H 9.02, N 5.01; found C 68.70, H 9.03, N 4.97.

(1*RS*,2*RS*)-2-{[(4-Methoxybenzyl)amino]methyl}-1-phenylbutan-1-ol (*anti*-2e): Yield: 183 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3294, 3035 cm^{-1}. ^1H NMR: δ = 0.95 (t, *J* = 6.9 Hz, 3 H), 1.06−1.25 (m, 3 H), 1.90−1.97 (m, 1 H), 2.75−2.90 (m, 2 H), 3.54 (d, *J* = 3.3 Hz, 2 H), 3.65 (s, 3 H), 4.12 (br. s, 1 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 7.00−7.04 (m, 2 H), 7.20−7.42 (m, 7 H) ppm. ^{13}C NMR: δ = 14.4, 27.4, 44.5, 53.4, 54.8, 60.0, 76.2, 114.5, 125.5, 127.3, 128.9, 129.4, 131.0, 143.9, 160.7 ppm. MS: *m*/*z* = 281 [$M^+ - H_2O$], 224, 160, 121 (100), 104, 91, 77, 65. $C_{19}H_{25}NO_2$ (299.41): calcd. C 76.22, H 8.42, N 4.68; found C 76.18, H 8.32, N 4.67.

(3*RS*,4*SR*)-3-{[(4-Methoxybenzyl)amino]methyl}octan-4-ol (*anti*-2f): Yield: 176 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3345, 3035, 1660 cm^{-1}. ^1H NMR: δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 1.40−1.48 (m, 10 H), 2.71−2.74 (m, 2 H), 2.93−2.97 (m, 1 H), 3.41−3.48 (m, 1 H), 3.60−3.69 (m, 2 H), 3.91 (s, 3 H), 6.86−6.90 (m, 2 H), 7.25−7.30 (m, 2 H) ppm. ^{13}C NMR: δ = 12.2, 14.1, 22.9, 23.3, 35.7, 43.4, 51.6, 53.4, 55.3, 79.9, 113.8, 129.4, 137.3, 158.8 ppm. MS: *m*/*z* = 261 [$M^+ - H_2O$], 204, 163, 121 (100), 77, 65, 51, 41. $C_{17}H_{29}NO_2$ (279.42): calcd. C 73.07, H 10.46, N 5.01; found C 72.99, H 10.35, N 4.99.

(1*RS*,2*RS*)-3-{[(4-Methoxybenzyl)amino]methyl}-1-phenylpentan-1-ol (*anti*-2g): Yield: 197 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3400, 3028, 1668 cm^{-1}. ^1H NMR: δ = 0.85 (t, *J* = 7.0 Hz, 3 H), 1.06−1.20 (m, 5 H), 1.60−1.70 (m, 1 H), 2.75−2.90 (m, 2 H), 3.65 (d, *J* = 3.4 Hz, 2 H), 3.78 (s, 3 H), 4.00 (br. s, 1 H), 4.66 (d, *J* = 6.96 Hz, 1 H), 6.90−6.95 (m, 2 H), 7.20−7.42 (m, 7 H) ppm. ^{13}C NMR: δ = 14.4, 20.8, 29.3, 43.3, 50.6, 53.8, 55.5, 78.3, 114.1, 126.8, 127.1, 129.7, 129.9, 131.4, 142.8, 159.1 ppm. MS: *m*/*z* = 295 [$M^+ - H_2O$], 284, 224, 160, 121 (100), 104, 91, 77, 65. $C_{20}H_{27}NO_2$ (313.43): calcd. C 76.64, H 8.68, N 4.47; found C 76.59, H 8.65, N 4.45.

(1*SR*,2*RS*)-3-{[(4-Methoxybenzyl)amino]methyl}-1-phenylpentan-1-ol (*syn*-2g): Yield: 85 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3403, 3020, 1655 cm^{-1}. ^1H NMR: δ = 0.84 (t, *J* = 6.9 Hz, 3 H), 1.06−1.20 (m, 5 H), 2.03−2.06 (m, 1 H), 2.75−2.90 (m, 2 H), 3.74 (d, *J* = 2.9 Hz, 2 H), 3.83 (s, 3 H), 4.05 (br. s, 1 H), 4.98 (d, *J* = 3.3 Hz, 1 H), 6.85−6.95 (m, 2 H), 7.20−7.42 (m, 7 H) ppm. ^{13}C NMR: δ = 14.4, 20.3, 32.0, 44.0, 51.7, 53.6, 55.5, 80.1, 114.1, 126.7, 127.9, 128.2, 129.8, 131.3, 144.8, 159.1 ppm. MS: *m*/*z* = 295 [$M^+ - H_2O$], 284, 224, 160, 121 (100), 104, 91, 77, 65. $C_{20}H_{27}NO_2$ (313.43): calcd. C 76.64, H 8.68, N 4.47; found C 76.59, H 8.65, N 4.45.

General Procedure for the Diastereoselective Reduction of *N*-Protected α-Alkyl-β-Amino Ketones 1 with BH_3·py in the Presence of $TiCl_4$: $TiCl_4$ (1.5 mmol, solution 1 M in CH_2Cl_2) was added to a cold (−78 °C) solution of β-amino ketones **1** (1.0 mmol) in 10 mL of dry CH_2Cl_2 to give immediately a clear solution, which was stirred for 15 min at this temperature. The complex BH_3·py (1.5 mmol) in 5 mL of CH_2Cl_2 was then added. After 15 min, 25 mL of 1 N HCl was added, and the reaction was warmed to room temperature. The organic layer was separated, the aqueous layer was washed with CH_2Cl_2, and the combined organics were concentrated in vacuo. The resulting residue was partitioned between Et_2O and H_2O. The ethereal layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvents afforded the crude diastereomeric mixture of *N*-protected 1,3-amino alcohols **2**. Diastereomer ratios were measured by NMR analysis, and cleaner separation of the *syn*- and *anti*-diastereomers could be achieved by flash column chromatography. The reported yields listed in Table 1 are the weight recovery of the major *syn*-diastereomer and of a minor amount of the *anti*-diastereomer.

***tert*-Butyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxyhexyl)carbamate (*syn*-2a):** Yield: 277 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3325, 3019, 1690, 1583 cm^{-1}. ^1H NMR: δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.22−1.40 (m, 5 H), 1.59 (s, 9 H), 2.40 (dd, *J* = 3.9, 8.1 Hz, 1 H), 2.88 (dd, *J* = 3.9, 4.9 Hz, 1 H), 3.01 (br. s, 1 H), 3.15−3.32 (m, 1 H), 3.59−3.67 (m, 1 H), 4.54 (dt, *J* = 2.8, 7.0 Hz, 1 H), 4.70−4.78 (m, 1 H), 7.22−7.38 (m, 5 H) ppm. ^{13}C NMR: δ = 15.6, 20.4, 27.6, 48.5, 49.9, 54.2, 68.9, 79.7, 126.6, 128.3, 128.7, 140.0, 158.7 ppm. MS: *m*/*z* = 289 [$M^+ - H_2O$], 250, 198, 131, 91 (100), 77, 65, 57, 41. $C_{18}H_{29}NO_3$ (307.43): calcd. C 70.32, H 9.51, N 4.56; found C 70.27, H 9.48, N 4.38.

Benzyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxyhexyl)carbamate (*syn*-2b): Yield: 268 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3407, 3028, 1698 cm^{-1}. ^1H NMR: δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.20−1.62 (m, 4 H), 1.77−1.83 (m, 1 H), 2.51 (dd, *J* = 9.1, 13.7 Hz, 1 H), 2.73−2.81 (m, 1 H), 3.07−3.15 (m, 1 H), 3.20−3.33 (m, 1 H), 3.36−3.44 (m, 1 H), 3.62−3.69 (m, 1 H), 5.05 (dt, *J* = 3.3, 12.5 Hz, 1 H), 5.11 (d, *J* = 12.5 Hz, 1 H), 5.35−5.41 (m, 1 H), 7.11−7.34 (m, 10 H) ppm. ^{13}C NMR: δ = 14.3, 20.0, 35.5, 37.2, 40.1, 45.9, 67.0, 70.6, 126.4, 128.3, 128.7, 128.8, 129.1, 136.7, 140.8, 157.6 ppm. MS: *m*/*z* = 323 [$M^+ - H_2O$], 232, 142, 117, 91 (100), 79, 65, 41. $C_{21}H_{27}NO_3$ (341.44): calcd. C 73.87, H 7.97, N 4.10; found C 73.81, H 7.69, N 4.02.

***tert*-Butyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxybutyl)carbamate (*syn*-2c):** Yield: 154 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3299, 3011, 1685, 1605 cm^{-1}. ^1H NMR: δ = 1.27 (d, *J* = 6.6 Hz, 3 H), 1.42 (s, 9 H), 2.39−2.51 (m, 1 H), 2.75−2.98 (m, 3 H), 3.20−3.36 (m, 1 H), 3.40−3.50 (m, 1 H), 3.75 (br. s, 1 H), 4.02 (dq, *J* = 3.0, 6.5 Hz, 1 H), 7.15−7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 20.9, 28.4, 35.0, 40.9, 47.1, 66.3, 79.9, 126.2, 128.5, 128.9, 140.2, 155.7 ppm. MS: *m*/*z* = 223, 205, 144, 118, 91, 77, 57 (100), 41. $C_{16}H_{25}NO_3$ (279.37): calcd. C 68.79, H 9.02, N 5.01; found C 68.70, H 9.03, N 4.97.

Benzyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxybutyl)carbamate (*syn*-2d): Yield: 246 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3397, 3035, 1698,

1604 cm^{-1}. ^1H NMR: δ = 1.25 (d, *J* = 6.5 Hz, 3 H), 1.70−1.85 (m, 1 H), 2.47 (dd, *J* = 3.9, 9.8 Hz, 1 H), 2.81 (dd, *J* = 3.9, 5.0 Hz, 1 H), 2.91 (br. s, 1 H), 3.00−3.09 (m, 1 H), 3.29−3.34 (m, 1 H), 3.96 (dq, *J* = 2.8, 6.5 Hz, 1 H), 5.09 (s, 2 H), 5.23 (s, 1 H), 7.15−7.36 (m, 10 H) ppm. ^{13}C NMR: δ = 19.5, 33.0, 41.6, 46.8, 66.9, 128.1, 128.2, 128.7, 130.0, 136.4, 140.0, 157.5 ppm. MS: *m*/*z* = 204, 143, 131, 91 (100), 74, 65, 51. $C_{19}H_{23}NO_3$ (313.39): calcd. C 72.82, H 7.40, N 4.47; found C 72.79, H 7.35, N 4.45.

Benzyl (2*RS*,3*SR*)-*N*-(2-Benzyl-3-hydroxybutyl)carbamate (*anti*-2d): Yield: 61 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3402, 3028, 1698, 1599 cm^{-1}. ^1H NMR: δ = 1.28 (d, *J* = 6.3 Hz, 3 H), 1.70−1.85 (m, 1 H), 2.47 (dd, *J* = 3.9, 9.8 Hz, 1 H), 2.81 (dd, *J* = 3.9, 5.0 Hz, 1 H), 2.91 (br. s, 1 H), 3.00−3.09 (m, 1 H), 3.29−3.34 (m, 1 H), 3.68 (dq, *J* = 6.3, 7.3 Hz, 1 H), 5.12 (s, 2 H), 5.17 (br. s, 1 H), 7.15−7.36 (m, 10 H) ppm. ^{13}C NMR: δ = 21.1, 36.2, 39.8, 47.6, 68.0, 128.2, 128.5, 128.7, 128.9, 136.4, 140.4, 157.6 ppm. MS: *m*/*z* = 204, 143, 131, 91 (100), 74, 65, 51. $C_{19}H_{23}NO_3$ (313.39): calcd. C 72.82, H 7.40, N 4.47; found C 72.79, H 7.35, N 4.45.

(1*SR*,2*RS*)-2-{[(4-Methoxybenzyl)amino]methyl}-1-phenylbutan-1-ol (*syn*-2e): Yield: 267 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3334, 3015 cm^{-1}. ^1H NMR: δ = 0.94 (t, *J* = 6.9 Hz, 3 H), 1.06−1.35 (m, 3 H), 2.09−2.15 (m, 1 H), 2.75−2.93 (m, 2 H), 3.76 (d, *J* = 2.6 Hz, 2 H), 3.83 (s, 3 H), 4.00 (br. s, 1 H), 4.90 (d, *J* = 3.3 Hz, 1 H), 6.90−7.00 (m, 2 H), 7.20−7.43 (m, 7 H) ppm. ^{13}C NMR: δ = 14.9, 29.6, 45.3, 50.6, 54.2, 57.4, 78.9, 114.6, 125.9, 127.3, 128.2, 129.9, 131.6, 145.3, 160.7 ppm. MS: *m*/*z* = 281 [$M^+ - H_2O$], 224, 160, 121 (100), 104, 91, 77, 65. $C_{19}H_{25}NO_2$ (299.41): calcd. C 76.22, H 8.42, N 4.68; found C 76.18, H 8.32, N 4.67.

(3*RS*,4SR)-3-{[(4-Methoxybenzyl)amino]methyl}octan-4-ol (*syn*-2f): Yield: 239 mg of a colorless oil. IR (neat): $\tilde{\nu}$ = 3315, 3028, 1668 cm^{-1}. ^1H NMR: δ = 0.90 (t, *J* = 6.8 Hz, 3 H), 0.98 (t, *J* = 7.1 Hz, 3 H), 1.35−1.45 (m, 10 H), 2.68−2.74 (m, 2 H), 2.89−2.95 (m, 1 H), 3.60−3.69 (m, 1 H), 3.77−3.85 (m, 2 H), 3.91 (s, 3 H), 6.84−6.88 (m, 2 H), 7.23−7.29 (m, 2 H) ppm. ^{13}C NMR: δ = 11.4, 14.1, 22.7, 23.2, 28.7, 35.7, 50.6, 53.5, 55.3, 73.8, 113.7, 130.1, 131.3, 158.8 ppm. MS: *m*/*z* = 261 [$M^+ - H_2O$], 204, 163, 121 (100), 77, 65, 51, 41. $C_{17}H_{29}NO_2$ (279.42): calcd. C 73.07, H 10.46, N 5.01; found C 72.99, H 10.35, N 4.99.

Procedure for Synthesizing Cyclic Carbamates from *N*-Protected 1,3-Amino Alcohols: The synthesis of *syn*-**9f** from *syn*-**2f** is given as an example. Cerium(IV) ammonium nitrate (0.68 g, 1.25 mmol) was added to a solution of *syn*-3-{[(4-methoxybenzyl)amino]methyl}-octan-4-ol (*syn*-**2f**) (70 mg, 0.25 mmol) in acetonitrile (35 mL) and water (7.5 mL). The reaction was left to stir at room temperature overnight and the reaction was quenched with methanolic hydrogen chloride. The mixture was then evaporated to dryness. The residue was dissolved in 2 M HCl (22 mL) and washed with dichloromethane (3 × 5 mL). The aqueous solution was made alkaline with 3 M NaOH (35 mL), and then extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvents evaporated to give 1,3-amino alcohol as a colorless liquid (36 mg, 90% yield) which was used directly in the next step.

Triphosgene (121 mg, 0.41 mmol) was added to a stirred solution of crude 1,3-amino alcohol (30 mg, 0.19 mmol) and diisopropylethylamine (75 μL, 0.43 mmol) in dry dichloromethane (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature with stirring for 8 h. Water (16 mL) and ethyl acetate (25 mL) were added to the mixture, and the organic phase was separated. The resulting solution was washed with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution, and brine, and was then dried over Na_2SO_4. Evaporation of the solvents afforded the cyclic carbamate as colorless crystals.

(5*RS*,6*SR*)-6-Butyl-5-ethyl-1,3-oxazinan-2-one (*syn*-9f): ^1H NMR: δ = 0.90 (t, *J* = 6.9 Hz, 3 H), 1.02 (t, *J* = 7.2 Hz, 3 H), 1.20−1.45 (m, 6 H), 1.62−1.75 (m, 3 H), 3.25−3.36 (m, 2 H), 3.92 (dt, *J* = 4.0, 7.2 Hz, 1 H), 5.25 (br. s, 1 H) ppm. ^{13}C NMR: δ = 11.4, 15.1, 23.6, 27.9, 29.0, 30.5, 34.8, 36.2, 78.1, 157.3 ppm.

(5*RS*,6*SR*)-6-Butyl-5-ethyl-1,3-oxazinan-2-one (*anti*-9f): ^1H NMR: δ = 0.91 (t, *J* = 6.8 Hz, 3 H), 1.09 (t, *J* = 7.0 Hz, 3 H), 1.20−1.38 (m, 6 H), 1.59−1.75 (m, 3 H), 3.36−3.41 (m, 2 H), 4.50 (dt, *J* = 7.2, 7.9 Hz, 1 H), 5.07 (br. s, 1 H) ppm. ^{13}C NMR: δ = 12.6, 15.2, 23.0, 24.6, 28.6, 30.6, 35.2, 41.7, 73.7, 156.9 ppm.

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