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TETRAHEDRON:
ASYMMETRY

Stereoselective α-amidoalkylation reactions of phenylglycinol-derived bicyclic lactams

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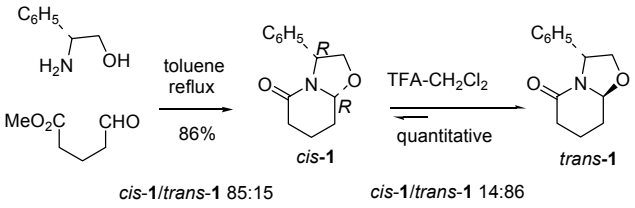
Abstract—The sterochemical outcome of α-amidoalkyltaion reactions from chiral non-racemic bicyclic lactams *trans*-**1** and *cis*-**1** using indole, allyltrimethylsilane, higher order organocuprates, TMSCN, and Grignard reagents is discussed.

1. Introduction

Chiral bicyclic lactams derived from *R*- or *S*-phenylglycinol have emerged as powerful tools for the enantioselective synthesis of piperidine derivatives.[1] In this context, in previous work we have reported the preparation of the phenylglycinol-derived lactams *cis*-**1** and *trans*-**1**.[2] Pure lactam *cis*-**1** is easily accessible by cyclocondensation of (*R*)-phenylglycinol with methyl 5-oxopentanoate under neutral conditions, followed by column chromatography of the resulting 85:15 diasteromeric mixture of lactams, while lactam *trans*-**1** is obtained by equilibration of the above mixture under acidic conditions followed by chromatographic purification (Scheme 1).[3]



Scheme 1.

Both lactams *cis*-**1** and *trans*-**1** have proven to be versatile chiral building blocks for the synthesis of diversely substituted enantiopure piperidines as they allow the stereocontrolled formation of C-C bonds at the different carbon positions of the piperidine ring.[4] In particular, the enantioselective synthesis of 2-alkyl- and 2-arylpiperidines from these lactams requires the stereocontrolled introduction of the substituent at the piperidine α-position by asymmetric α-amidoalkylation,[5,6] a process that has been reported to occur with moderate to high stereoselectivity from *trans*-**1**.[7] Thus, reaction of *trans*-**1** with indole in the presence of $TiCl_4$ leads to a 3:1 mixture of 6-indolyl-2-piperidones **2a** and **2b**,[8] whereas reaction of *trans*-**1** with allyltrimethylsilane in the presence of $TiCl_4$ gives a 9:1 mixture of the allylated products **3a** and **3b**[4b] (Table 1, entries 1 and 2).

Similarly, the addition of higher order alkyl and phenyl cyanocuprates in the presence of $BF_3.Et_2O$ takes place in good yields and high stereoselectivities to give the corresponding 6-alkyl- and 6-aryl-2-piperidones (**4-6**; Table 1, entries 3-5).[4b] In all the above cases the major stereoisomer results from an inversion of the configuration at the C-8a stereocenter. This stereoselectivity can be accounted for by considering that the iminium ion generated by interaction of *trans*-**1** with the Lewis acid undergoes nucleophilic attack upon the less hindered face as depicted in **A** (Figure 1).

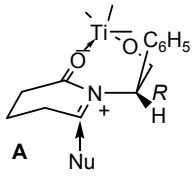


Figure 1.

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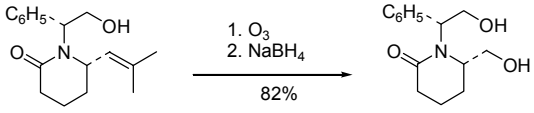
2. Results and discussion

In this article we report i) new α-amidoalkylation reactions from *trans*-**1**, which provide access to 2-piperidones bearing a functionalized substituent at C-6; ii) the dramatic change of stereoselectivity when Grignard reagents are used instead of higher order cyanocuprates, and iii) a comparative study of the behavior of *cis*-**1** and *trans*-**1** in α-amidoalkylation reactions.

As could be expected from previous results, treatment of lactam *trans*-**1** with lithium 2-methyl-1-propenyl-cyanocuprate in the presence of $BF_3.Et_2O$ gave the 6-substituted 2-piperidone **7a** in 52% yield as the only isolable product (entry 6). Very minor amounts (<5%) of the C-6 diastereomer were detected from the crude reaction mixture. The interest of the above vinylation lies in the fact that lactam **7a** could be converted to alcohol **8** in excellent yield by ozonolysis followed by $NaBH_4$ reduction (Scheme 3), thus opening a simple route for the stereoselective introduction of a hydroxymethyl substituent at the piperidine 2-position, an appendage present in many natural and synthetic azasugars.[9] A similar stereoselectivity was observed in the addition of trimethylsilyl cyanide in the presence of $TiCl_4$: a 95:5 mixture of nitriles **9a** and **9b**, respectively, was obtained in 74% yield (Table 1, entry 7).



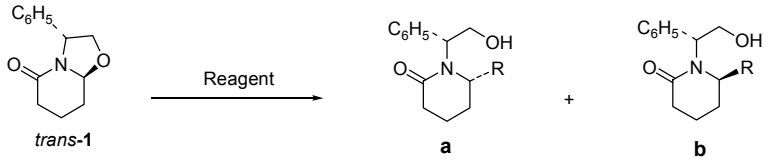
7a **8**

Scheme 3.

The absolute configuration of the new stereogenic center of 6-substituted lactams **7** and **9** was assigned from the NMR data following the correlation observed in a series of related diastereomeric phenylglycinol-derived lactams.[10] Thus, in the major isomers **a** the benzylic proton appears more shielded than in the minor isomers **b**, whereas the benzylic and C-6 carbons are more deshielded.

In sharp contrast with the uniform stereoselectivity of the above reactions, Grignard reagents reacted with lactam *trans*-**1** with retention of the configuration at C-8a to give diastereomers **b** as the major products. Thus, reaction of *trans*-**1** with methylmagnesium bromide gave a 15:85 mixture of piperidones **4a** and **4b** in 73% yield (Table 1, entry 8). *n*-Propylmagnesium bromide (entry 9) also reacted with excellent yield (72%) and stereoselectivity (**5a**:**5b**; 5:95 ratio).[11] As expected reaction of *trans*-**1** with phenylmagnesium bromide (entry 10) and 2-methyl-1-propenylmagnesium bromide (entry 11) took also place with high stereoseelectivity to give piperidones **6b** and **7b**, respectively, in 72% and 56% yield.

Table 1. Stereoselective α-amidoalkylation reactions from lactam *trans*-**1**



trans-**1** **a** **b**

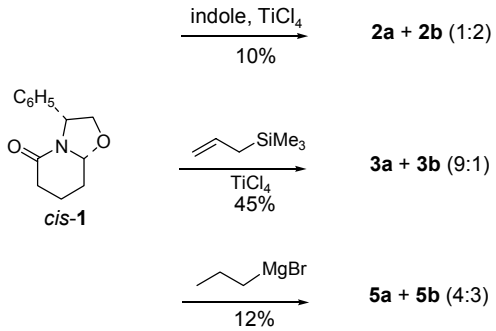
Entry	Reagents and conditions	Product	R	Yield %	**a**:**b** ratio
1	Indole, $TiCl_4$	**2a** + **2b**	3-In	80[a]	3:1
2	CH_2=CH-CH_2SiMe_3, $TiCl_4$	**3a** + **3b**	CH_2-CH=CH_2	91[b]	9:1
3	$Me_2Cu(CN)Li$, $BF_3.Et_2O$	**4a** + **4b**	CH_3	70[b]	>95:5
4	*n*-$Pr_2Cu(CN)Li$, $BF_3.Et_2O$	**5a** + **5b**	$CH_2CH_2CH_3$	65[b]	93 :7
5	$(C_6H_5)_2Cu(CN)Li$, $BF_3.Et_2O$	**6a** + **6b**	C_6H_5	75[b]	9 :1
6	$(Me_2C=CH)_2Cu(CN)Li$, $BF_3.Et_2O$	**7a** + **7b**	CH=CMe_2	52	>95 :5
7	TMSCN, $TiCl_4$	**9a** + **9b**	CN	74	95:5
8	CH_3MgBr	**4a** + **4b**	CH_3	73	15:85
9	*n*-PrMgBr	**5a** + **5b**	$CH_2CH_2CH_3$	72	5:95
10	C_6H_5MgBr	**6a** + **6b**	C_6H_5	72	<5:95
11	Me_2C=CHMgBr	**7a** + **7b**	CH=CMe_2	56	<5:95

[a]Reference 8.

[b]Reference 4b.

The remarkable change of stereoselectivity in the above reactions with Grignard reagents can be explained by considering that, in the absence of an additional Lewis acid, the magnesium may coordinate with the oxygen of the oxazolidine ring. Subsequent delivery of the alkyl or aryl group from the same face of the C-O bond would account for the observed retention of configuration.

We then decided to study the stereochemical outcome of α-amidoalkylation reactions from the C-8a epimeric lactam *cis*-**1**. In fact, α, β-unsaturated lactams derived from *cis*-**1** and *trans*-**1** undergo conjugate addition reactions with opposite facial selectivity.[12] Somewhat surprisingly, lactam *cis*-**1** was recovered unchanged after treatment with indole (25 ºC, 30 min) or allyltrimethylsilane (25 ºC, 4 h) in the presence of $TiCl_4$, under the conditions previously employed in the reactions from *trans*-**1**. These α-amidoalkylations required longer reaction times (25 h) and took place in lower yields (**2a** + **2b**: 10%; **3a** + **3b**: 45%) than the similar reactions from *trans*-**1** (Scheme 4). In both cases, bicyclic lactam *trans*-**1**, formed by equilibration of the unreacted starting lactam *cis*-**1**, was also isolated to a considerable extent. The observed stereoselectivity in the reaction with indole is a consequence of an equilibration process after prolonged exposure of the resulting indolylpiperidones to $TiCl_4$.[8] On the other hand, under the reaction conditions successfully used in the reaction with *trans*-**1**, *cis*-**1** reacted with *n*-propylmagnesium bromide with very low yield and stereoselectivity to give a 4:3 diastereomeric mixture of the corresponding lactams **5a** and **5b**, most of the starting material *cis*-**1** being recovered unchanged. Finally, only complex mixtures were formed from phenylmagnesium bromide. As a consequence of these discouraging results, no further α-amidoalkylation reactions using *cis*-**1** were studied.



Scheme 4.

In conclusion, starting from a single enantiomer of phenylglycinol, via a common lactam *trans*-**1**, either piperidones **4a**-**7a** or their epimers **4b**-**7b** are easily accessible by choosing the appropriate organometal derivative, which gives access to the two enantiomeric series of 2-alkyl substituted piperidines.

3.Experimental

2.1. General

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 200 or 300 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C) and chemical shifts are reported in δ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. Column chromatography was carried out using the flash chromatography technique. All non-aqueous reactions were performed under inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried following standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre D'Investigació i Desenvolupament (CSIC), Barcelona.

3.2. (6*S*)-6-(2-Methyl-1-propenyl)-1-[(1*R*)-1-phenyl-2-hydroxyethyl]-2-piperidone, 7a. *Lithium 2-methyl-1-propenylcyanocuprate.* 1-Bromo-2-methylpropene (1.13 mL, 11.04 mmol) was added to a suspension of cut up lithium (154 mg, 22.1 mmol) in Et_2O (36 mL) at −20 ºC and the mixture was stirred for 45 min at this temperature until the metal was dissolved. This suspension was added via canula to a mixture of CuCN (495 mg, 5.52 mmol) in THF (24 mL) at −78 ºC, and the stirring was continued for 1.5 h.

A solution of lithium 2-methyl-1-propenylcyanocuprate (30 mL, 3 equiv) was added via canula (the rest of the cyanocuprate solution was kept cool at −78 ºC) to a solution of *trans*-**1** (200 mg, 0.92 mmol) and $BF_3.Et_2O$ (0.22 mL, 1.84 mmol) in anhydrous THF (8 mL) at −78 ºC. The mixture was stirred at −78 ºC during 2.5 h. Then, additional $BF_3.Et_2O$ (0.22 mL, 1.84 mmol) and lithium 2-methyl-1-propenylcyanocuprate (30 mL, 3 equiv) were added, and the resulting suspension was stirred for 3 additional hours. The mixture was quenched with saturated aqueous NH_4Cl and saturated aqueous Na_2CO_3. The aqueous phase was extracted with AcOEt, and the combined organic extracts were dried and concentrated. The resulting residue was chromatrographed (AcOEt) to give unreacted lactam *trans*-**1** (30 mg) and pure **7a** (130 mg, 52%) as a white solid: IR (NaCl) 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 1.65-1.93 (m, 4H), 1.73 (s, 3H), 2.51-2.57 (m, 2H), 4.00 (dd, *J* = 12.3, 3.0 Hz, 1H), 4.02 (m, 1H), 4.18 (dd, *J* = 12.3, 6.6 Hz, 1H), 4.42 (dd, *J* = 6.6, 3.0 Hz, 1H), 5.22 (dm, *J* = 9.3 Hz, 1H), 7.24-7.33 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 17.5 (CH_2), 17.9 (CH_3), 25.8 (CH_3), 29.9 (CH_2), 33.1 (CH_2), 56.9

(CH), 64.7 (CH_2), 66.2 (CH), 125.1 (CH), 127.4 (CH), 127.5 (2 CH), 128.5 (2 CH), 135.7 (C), 137.6 (C), 172.0 (C); $[\alpha]^{22}_D$ +54 (*c* 1, EtOH); m.p. 112-115 ºC (Et_2O). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69: H, 8.48; N, 5.12. Found: C, 74.75; H, 8.61; N, 5.09.

2.3. (6*S*)-6-Hydroxymethyl-1-[(1*R*)-1-phenyl-2-hydroxyethyl]-2-piperidone, 8. A stream of ozone gas was bubbled through a cooled (−78 ºC) solution of **5a** (100 mg, 0.36 mmol) in CH_2Cl_2 (1 mL) and methanol (4 mL) until it turned pale blue. The solution was purged with O_2, and the temperature was raised to room temperature. Then, $NaBH_4$ (14 mg, 0.36 mmol) was added to the mixture, and the resulting suspension was cooled at −78 ºC and stirred for 1 h. Additional $NaBH_4$ (14 mg, 0.37 mmol) was added, and the temperature was raised to room temperature. After 1 h of stirring, the mixture was concentrated, and the residue was dissolved in $CHCl_3$. The organic solution was washed with 5% aqueous HCl, dried, and concentrated. The residue was chromatographed (9:1 AcOEt-MeOH) to give pure **8** (75 mg, 82%): IR (NaCl) 3359, 1619 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.69 (m, 1H, H-4), 1.79-1.97 (m, 3H, H-4, 2 H-5), 2.37-2.44 (m, 2H, 2 H-3), 3.51 (m, 1H, H-6), 3.61 (dd, *J* = 12.0, 5.0 Hz, 1H, CH_2OH), 3.75 (dd, *J* = 12.0, 4.8 Hz, 1H, CH_2OH), 3.99 (dd, *J* = 10.0, 4.0 Hz, 1H, NCHjC*H*$_2$O), 4.15 (br s, 2H, 2 OH), 4.63 (dd, *J* = 10.0, 4.0 Hz, 1H, NCH), 4.70 (t, *J* = 10.0 Hz, 1H, NCHC*H*$_2$O), 7.27-7.31 (m, 5H, Ar); ^{13}C-NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 17.2 (C-4), 26.2 (C-5), 32.5 (C-3), 60.2 (C-6), 62.8 (NCH*C*H$_2$), 64.1 (CH_2OH), 66.3 (NCH), 127.2 (2 CH), 128.5 (CH), 127.5 (2 CH), 137.5 (C), 172.7 (CO); $[\alpha]^{22}_D$ −4.6 (*c* 1.5, EtOH); HRMS calcd for $C_{14}H_{19}NO_3$ (M^+–H_2O) *m*/*z* 231.1252, found 231.1259.

3.4. (6*S*)-6-Cyano-1-[(1*R*)-1-phenyl-2-hydroxyethyl]-2-piperidone (9a) and (6*R*)-6-cyano-1-[(1*R*)-1-phenyl-2-hydroxyethyl]-2-piperidone (9b). Trimethylsilyl cyanide (0.69 mL, 5.52 mmol) and titanium tetrachloride (0.30 mL, 2.76 mmol) were added to a solution of *trans*-**1** (600 mg, 2.76 mmol) in CH_2Cl_2 (24 mL). The mixture was stirred for 18 h at room temperature, poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed (AcOEt) to furnish **9a** (470 mg, 70%) and **9b** (30 mg, 4%). **9a**: IR (NaCl) 2247, 1619 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.94-2.19 (m, 4H), 2.55 (dt, *J* = 18.3, 10.0 Hz, 1H), 2.72 (dm, *J* = 18.3 Hz, 1H), 2.80 (br s, 1H), 4.13 (dd, *J* = 11.9, 4.9 Hz, 1H), 4.18 (dd, *J* = 11.9, 7.0 Hz, 1H), 4.42 (dd, *J* = 4.3, 2.7 Hz, 1H), 5.46 (dd, *J* = 7.0, 4.9 Hz, 1H), 7.37-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 17.6 (CH_2), 27.4 (CH_2), 31.5 (CH_2), 46.2 (CH), 60.3 (CH), 61.6 (CH_2), 117.7 (C), 128.5, 128.6, 128.8 (5CH), 135.4 (C), 170.6 (CO); $[\alpha]^{22}_D$ −121.6 (*c* 0.5, EtOH). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 1/4H_2O$: C, 67.58; H, 6.65; N, 11.26. Found: C, 67.70; H, 6.65; N, 11.01. **9b**: IR (NaCl) 2238, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.73 (tdd, *J* = 13.2, 5.0, 4.0 Hz, 1H), 1.93-2.21 (m, 3H), 2.52 (ddd, *J* = 18.0, 10.1, 7.3 Hz, 1H), 2.73 (dddd, *J* = 18.0, 7.0, 3.0, 1.4 Hz, 1H), 4.16 (ddd, *J* = 5.1, 2.6, 1.4 Hz, 1H), 4.29 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.35 (dd, *J* = 11.6, 7.5 Hz, 1H), 5.93 (t, *J* = 6.6 Hz, 1H), 7.32-7.40 (m, 5H) ; ^{13}C-NMR ($CDCl_3$, 75.4 MHz) δ 17.9 (CH_2), 27.5 (CH_2), 31.3 (CH_2), 44.6 (CH), 58.4 (CH), 61.0 (CH_2), 118.9 (C), 128.1 (2 CH), 129.0 (CH), 128.5 (2 CH), 135.3 (C), 170.3 (CO).

3.5. General procedure for the reaction of lactam *trans*-1 with Grignard reagents. A solution of *trans*-**1** (1 equiv) in anhydrous THF (2 mL) was added via canula to a solution of the Grignard reagent (3 equiv) in THF or Et_2O at 0 ºC, and the mixture was stirred at this temperature for 8 h. The reaction was quenched by addition of saturated aqueous NaCl, and the mixture was extracted with AcOEt. The combined organic extracts were dried and concentrated.

3.5.1. With methylmagnesium bromide. Operating as described in the general procedure, from *trans*-**1** (300 mg, 1.38 mmol) and methylmagnesium bromide (3 M in Et_2O, 1.4 mL, 4.14 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave **4a**[4b] (36 mg, 11%) and **4b**[10b] (199 mg, 62%). **4b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, *J* = 6.5 Hz, 3H), 1.58 (m, 1H), 1.69-1.80 (m, 2H), 1.93 (m, 1H), 2.48-2.54 (m, 2H), 3.45 (m, 1H), 4.16 (dd, *J* = 11.5, 4.5 Hz), 4.25 (dd, *J* = 11.5, 7.5 Hz, 1H), 5.22 (dd, *J* = 7.5, 4.5 Hz, 1H), 7.26-7.34 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 50.4 MHz) δ 16.6 (CH_2), 21.2 (CH_3), 30.3 (CH_2), 32.1 (CH_2), 52.3 (CH), 63.4 (CH), 64.3 (CH_2), 127.4 (CH), 127.6 (2 CH), 128.5 (2 CH), 137.2 (C), 172.4 (CO); $[\alpha]^{22}_D$ −24.5 (*c* 1.0, EtOH); *m*/*z* 234 (1), 215 (26), 203 (31), 202 (100), 188 (7), 186 (6); HRMS calcd for $C_{14}H_{19}NO_2$ (M^+) *m*/*z* 233.1416, found 233.1419.

3.5.2. With *n*-propylmagnesium chloride. Operating as described in the general procedure, from *trans*-**1** (500 mg, 2.30 mmol) and *n*-propylmagnesium chloride (2 M in Et_2O, 3.45 mL, 6.91 mmol) a residue was obtained. Purification by column chromatography (97:3 AcOEt-EtOH) gave **5a**[4b] (36 mg, 6%) and **5b**[11] (397 mg, 66%) as colorless oils. **5b**: ^{1}H-NMR ($CDCl_3$, 300 MHz, COSY) δ 0.82 (t, *J* = 7.2 Hz, 3H, CH_3), 1.09 (m, 1H, C*H*$_2$CH$_3$), 1.25 (m, 1H, C*H*$_2$CH$_3$), 1.47-1.59 (m, 3H, C*H*$_2$CH$_2$CH$_3$, H-5), 1.65-1.75 (m, 2H, H-5, H-4), 1.84 (m, 1H, H-4), 2.45-2.50 (m, 2H, H-3), 3.22 (m, 1H, H-6), 4.14 (dd, *J* = 11.0, 5.5 Hz, 1H, C*H*$_2$OH), 4.22 (dd, *J* = 11.0, 7.5 Hz, C*H*$_2$OH), 5.25 (dd, *J* = 7.5, 5.5 Hz, NCH), 7.26-7.32 (m, 5H, Ar); ^{13}C-NMR ($CDCl_3$, 75.5 MHz, HETCOR) δ 13.7 (CH_3), 16.0 (C-4), 19.3 (*C*H$_2$CH$_3$), 25.5 (C-5), 31.5 (C-3), 35.1 (*C*H$_2$CH$_2$CH$_3$), 56.0 (C-6), 62.8 (NCH), 63.4 (CH_2OH), 127.2 (CH), 127.5 (2 CH), 128.2 (2 CH), 137.2 (C), 172.1 (CO); $[\alpha]^{22}_D$ +28 (*c* 1.0, CH_2Cl_2) {lit[11] $[\alpha]^{20}_D$ +21 (*c* 1.0, CH_2Cl_2)}; HRMS calc. for $C_{16}H_{24}NO_2$ (M^++H) *m*/*z* 262.1807, found 262.1796.

3.5.3. With phenylmagnesium bromide. Operating as described in the general procedure, from *trans*-**1** (200 mg, 1.38 mmol) and phenylmagnesium bromide (1 M in THF, 2.7 mL, 2.76 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave **6b**[4b] (196 mg, 72%).

3.5.4. With 2-methyl-1-propenylmagnesium bromide. Operating as described in the general procedure, from *trans*-**1** (300 mg, 1.38 mmol) and 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 8.3 mL, 4.14 mmol) a residue was obtained. Purification by column chromatography (AcOEt) gave starting material *trans*-**1** (30 mg, 10%) and **7b** (211 mg, 56%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 1.56 (m, 1H), 1.68-1.75 (m, 2H), 1.65 (s, 3H), 1.87 (m, 1H), 2.42-2.62 (m, 2H), 3.40 (br s, 1H), 3.94 (dt, *J* = 9.3, 4.5 Hz, 1H), 4.08-4.21 (m, 2H), 5.26 (dm, *J* = 9.3 Hz, 1H), 5.50 (dd, *J* = 8.0, 5.5 Hz, 1H), 7.21-7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50.4 MHz) δ 17.6 (CH_3), 17.6 (CH_2), 25.9 (CH_3), 30.4 (CH_2), 32.5 (CH_2), 53.6 (CH), 60.7 (CH), 63.5 (CH_2), 126.2 (CH), 127.5 (CH), 128.1 (2 CH), 128.4 (2 CH), 133.7 (C), 137.1 (C), 172.3 (CO); $[\alpha]^{22}_D$ −63 (*c* 1.0, EtOH); *m*/*z* 274 (2), 255 (14), 242 (30), 212 (9); HRMS calc. for $C_{17}H_{23}NO_2$ (M^+) *m*/*z* 273.1729, found 273.1722.

3. Acknoledgments

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