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A novel asymmetric reduction of dihydro-β-carboline derivatives using calix[6]arene/chiral amine as a host complex

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Abstract—A novel approach to the asymmetric reduction of dihydro-β-carboline derivatives to the corresponding tetrahydro-β-carboline is described based on the supramolecular complex formed from calix[6]arene/chiral amine as an enzyme mimetic and $NaBH_4$ as the reducing agent.

1. Introduction

During the course of our recent total synthesis of the arborescidine alkaloids,[1] the opportunity arose to investigate a new approach to the asymmetric reduction of imines through a host–guest mediated process. Although numerous methods for the synthesis of optically active amines are known, few are based on asymmetric synthesis and chiral catalysis; among the most popular are the asymmetric hydrogenation of ketimines or enamides using chiral biphosphine-rhodium(I) complexes,[2] iridium(I)[3] or ruthenium(II) complexes,[4] chiral titanium complexes,[5] chiral amino alcohol–borane,[6] and β-hydroxysulfoximine–borane complexes.[7] A particularly efficient method for the reduction of dihydro-β-carbolines is the asymmetric transfer hydrogenation but chemists are certainly in need of more general catalytic systems.[8] Therefore the search for new enantioselective imine reduction methods were inspired by the cyclodextrin (CD)/$NaBH_4$ asymmetric reduction of carbonyl compounds.[9] α-, β- and γ-CD are cyclic molecules (host) composed of 6, 7, and 8 glucose residues, respectively, linked with *O*-α-D-glucopyranosyl-(1,4)-bonds, possessing chiral hydrophobic cavities that encapsulates appropriate hydrophobic guest molecules.[10] The intrinsic chirality of the cyclodextrins is responsible for the enantioselectivity of these reactions, which relies on the affinity of the carbonyl derivatives to the hydrophobic site of the cyclodextrins (CDs). These reactions have often been classified as enzyme mimetic in comparison to the carbonyl reduction in nature with oxyredutase/NADH or NADPH.[11]

Herein we report novel results on the enantioselective reduction of dihydro-β-carboline derivatives with two enzyme mimetic systems, one composed of α- or β- or γ-CD and $NaBH_4$ and a second one based on the chiral complex calix[6]arene/(*R*)-phenylethylamine, which has never been reported in the literature in connection with enantioselective reductions.

We first set out to investigate the reduction of imine **1a** in aqueous solution in the presence of α-, β- or γ-CD and $NaBH_4$ (Table 1) at 0°C. In all cases, the reaction proceeded efficiently and easily with overall yields of **2a**[12] ranging from 70–90%, after quenching with aqueous HCl followed by silica gel filtration. However the level of enantioselection was consistently low (10–30% *ee* for **2a**). Aiming for a better enantiomeric excess, several conditions were tested (Table 1). The use of a sodium bicarbonate buffer improved the solubility of the host–guest complex while triethylamine (TEA) proved to be beneficial to the face selectivity in the chiral induction, but despite these attempts the best enantiomeric excess during this set of experiments was observed in the reduction of **1a** encapsulated in β-CD in the presence of triethylamine (Table 1, entry 3). The influence of TEA in CD-$NaBH_4$ reduction has already been observed by Deratani et al. during the enantioselective reduction of acetophenone by the $NaBH_4$–CD–

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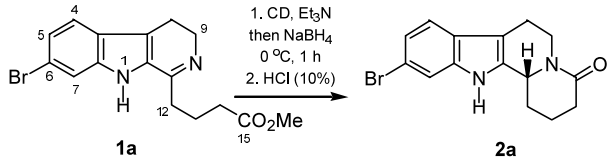
TEA system.[13] The authors assigned this fact to the formation of a three-component complex (acetophenone, triethylamine and CD).

The reaction conditions depicted in entry 3 (Table 1) were applied to imines **1b–d** and afforded the corresponding carbamates **2b**,**c** and lactam **2d** in high yields but in poor enantiomeric excess (Scheme 1).[14] The poor selectivity observed can be based on the: (1) low CD/imine **1a**/TEA binding constant; (2) lower reactivity of the CD/imine **1a**/TEA complex regarding that of free **1a**; and/or (3) the topology of the complex does not favor facial selectivity.[15]

^{1}H NMR analysis of a sample of **1a**/β-CD before the addition of the reducing agent (ROESY 1D, rOe experiments with shaped pulse and field gradient in z) confirmed the formation of the complex by depicting dipolar interactions between H-4, H-5 and H-7 of the imine **1a** and H-3 and H-5 of the β-CD. We have therefore suggested that the aromatic moiety of imine **1a** was inside the CD cavity thus possessing the complex topology as shown in Fig. 1. In such a case the facial selectivity is not expected to be high and indeed the imine reduction produced **2a** in 30% *ee*, (Table 1, entry 3).

Table 1. CD-mediated asymmetric reduction of **1a**



Entry	Cond.	Host	Maj.	Yield (%)[a]	*ee*%[b]
1	A	β-CD	*R*	88	10
2	B	β-CD	*R*	90	14
3	C	β-CD	*R*	85	30
4	D	β-CD	*R*	70	22
5	E	α-CD	*R*	86	14
6	F	γ-CD	*R*	70	20

[a] Determined for isolated product.

[b] Determined by HPLC (ChiralCell OD or Welk-01 Column- hexane:*iso*-propanol, 85:15). Condition **A**: β-CD/H_2O:**1a**:$NaBH_4$, 1:1:7; **B**: β-CD/Na_2CO_3 (0.2 mol/L):**1a**:$NaBH_4$, 1:1:7; **C**: β-CD/Na_2CO_3 (0.2 mol/L):Et_3N:**1a**:$NaBH_4$, 1:1:1:7 or 2:2:1:7; **D**: β-CD/DMSO:Et_3N:**1a**:$NaBH_4$, 1:1:1:7; **E**: α-CD/Na_2CO_3 (0.2 M):Et_3N:**1a**:$NaBH_4$, 1:1:1:7 or 2:2:1:7; **F**: γ-CD/Na_2CO_3 (0.2 M):Et_3N:**1a**:$NaBH_4$, 1:1:1:7.

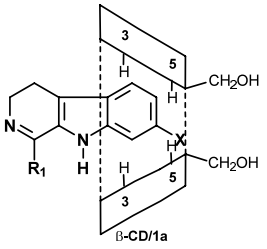


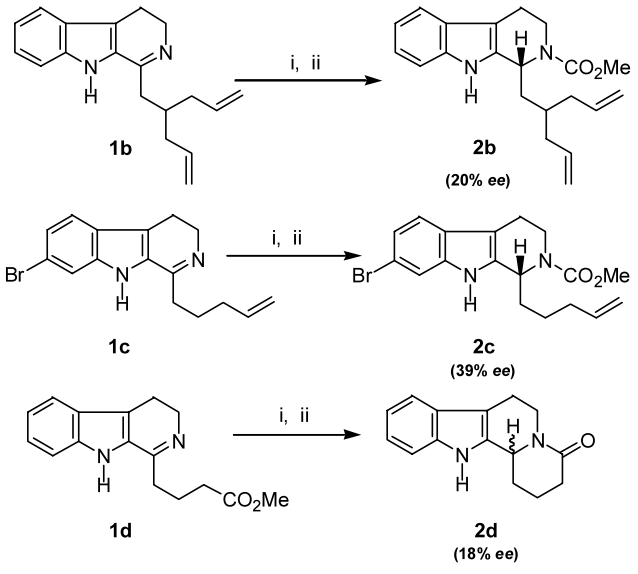
Figure 1. Proposed topology of the two-component complex (imine **1a**:β-cyclodextrin) based on NMR experiments.

At this stage we concluded that we needed to change the structure of the host either by modifying the natural CDs or by selecting a different class of encapsulating molecule.

Inspired by our recent results with calix[6]arene(calix) and (*R*)-phenylethylamine (*R*)-PEA, we proposed the reduction of imine **1a** with $NaBH_4$ in chloroform and in the presence of the calix/(*R*)-PEA complex. This system was never used before for enantioselective reductions but our own observation of the power of this complex in discriminating racemic sulfoxides gave us an idea that we were dealing with an interesting complex.[16]

A controlled experiment where racemic phenylethylamine, calix[6]arene and $NaBH_4$ in $CHCl_3$ were employed affording lactam **2a** in 82% yield and estimulated us to evaluate its enantiomerically pure form. Our initial experiments were conducted with imine **1a**, calix[6]arene/(*R*)-phenylethylamine as the encapsulating agent and $NaBH_4$. The use of (*R*)-phenylethylamine provided lactam **2a** in good yield and 50% enantiomeric excess when excess $NaBH_4$ (7 equiv.) was employed. Not unexpectedly, a decrease in the amount of the reducing agent resulted in a significant increase in the enantiomeric excess of **2a** (77% *ee*, entry 2). In the absence of calix[6]arene, racemic **2a** was formed which established the need for the three-component complex.

The topology of the complex calix[6]arene/(*R*)-PEA/imine **1a** was investigated by ^{1}H NMR using ROESY 1D experiments (Fig. 2). The main dipolar interactions are between CH and CH_3 of the (*R*)-PEA and H-*m* and H-*p* of the calix[6]arene; H-9, H-12 and H-13 of the imine **1a** and H-*m* and H-*p* of the calix[6]arene. No



Scheme 1. *Reagents and conditions*: (i) β-CD, Et_3N, $NaBH_4$, 0°C, 1 h, then HCl (10%); (ii) $ClCO_2Me$, Et_3N, CH_2Cl_2.

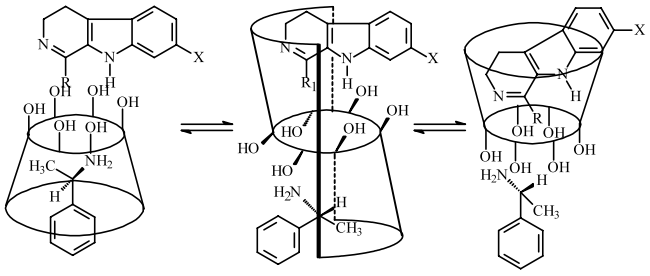


Figure 2. Proposed topology of the three-component complex imine **1a**/calix[6]arene/(*R*)-(−)-phenylethylamine based on NMR experiments.

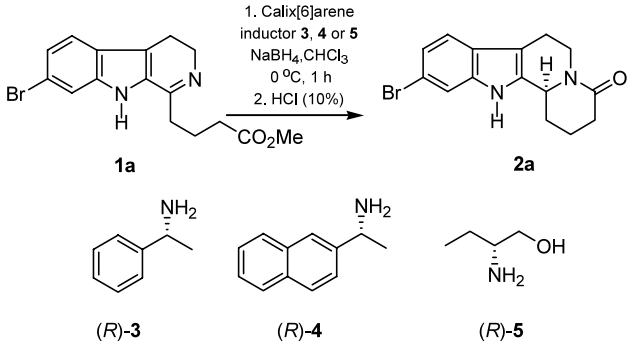
dipolar interactions between PEA and the imine **1a** were observed. In order to fit all these dipolar interactions we suggested the formation of a three-component complex. Searching for more evidence we measured the diffusion coefficient of the pure species **1a**, calix and (*R*)-PEA and that of the complex by ^{1}H NMR (pulsed field gradient spin echo, DgcsteSL) which is the perfect technique to probe encapsulation.[16] As expected the diffusion coefficients in deuterochloroform of free **1a** and (*R*)-PEA (about $\boldsymbol{D}_{\mathbf{1a}} = 11.3\times10^{-10}$ m^2 s^{-1} and $\boldsymbol{D}_{(R)\text{-PEA}} = 18.9\times10^{-10}$ m^2 s^{-1}) were higher than that of the calix[6]arene (7.9×10^{-10} m^2 s^{-1}) and higher than the diffusion coefficients of these three species in solution ($\boldsymbol{D}_{\mathbf{1a}} = 10.2\times10^{-10}$ m^2 s^{-1}; $\boldsymbol{D}_{(R)\text{-PEA}} = 16.4\times10^{-10}$ m^2 s^{-1} and $\boldsymbol{D}_{\text{calix[6]}} = 7.8\times10^{-10}$ m^2 s^{-1}) clearly indicating an association between **1a**/PEA/calix. Thus the diffusion coefficients and the dipolar interactions support the interaction between the three molecules. These can exist in a fast equilibrium regime (coherent with only one set of signals for all species Fig. 2) of two or more supramolecules or in assemblies of supramolecules.

Low temperature ^{1}H NMR experiments (varying from 213 to 298 K) revealed that the methylene hydrogens of the calix[6]arene/PEA/imine which absorbed at 3.89 ppm as a broad singlet at room temperature split into four sharp doublets at 3.50; 3.66; 4.02 and 4.35 ppm in a 1:2:1:2 ratio at 213 K. The two doublets of higher amplitude belong to the same spin system observed by 2D NMR (H,H COSY). The same is true for the doublet in 3.66 and 4.35 ppm, suggesting a slow equilibrium (for the NMR timescale) between the two cone conformations (Fig. 2). To determine the predominance of one supramolecule in relation to the others is beyond the scope of the present investigations.

In order to probe the importance of the intermolecular forces and how they affect the superstructure and the final product stereochemistry we have changed the (*R*)-PEA to (*R*)-naphthylethylamine **4** affording **2a** in a somewhat lower yield (75%) and selectivity (61% *ee*). Interestingly, inversion of the configuration of **2a** was achieved with (*R*)-2-amine-1-butanol **5**. Unfortunately, the enantiomeric excess of (*R*)-**2a** was very low (6% *ee*) as depicted in Table 2 (entry 6). Thus we concluded that the π–π interactions or hydrogen bonding play a significant role in the complex formation.

Next we extended the method to imines **1b–d**, synthesized as described previously (Scheme 2).[1] Structurally similar dihydro-β-carboline **1c** afforded the corresponding carbamate **2c**, after nitrogen protection with methyl chloroformate, in 88% yield and 65% *ee*. However, the bromine substituent in the aromatic ring proved to be essential for good facial discrimination as the debrominated β-carboline **1d** afforded the corresponding lactam **2d**,[17] in good yield but in disappointingly low enantiomeric excess (*ee* 20%). The same behaviour was

Table 2. Calix[6]arene/chiral-inductor mediated asymmetric reduction of **1a**

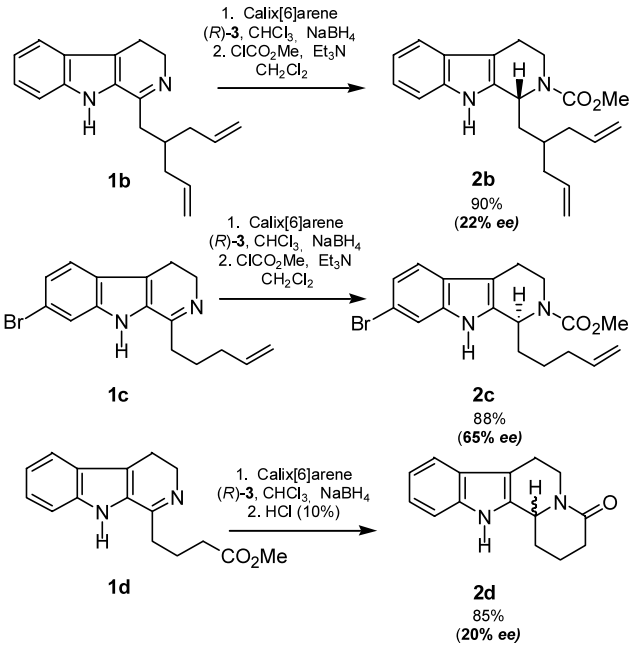


Entry	Cond.	Host	Inductor	Maj.	Yield (%)[a]	*ee*%[b]
1	A	Calix[6]arene	(*R*)-**3**	*S*	90	50
2	B	Calix[6]arene	(*R*)-**3**	*S*	85	77
3	B	Calix[6]arene	(±)-**3**	–	95	–
4	C	–	(*R*)-**3**	–	82	–
5	B	Calix[6]arene	(*R*)-**4**	*S*	75	61
6	B	Calix[6]arene	(*R*)-**5**	*R*	75	6

[a] Determined after isolation.

[b] Determined by HPLC (ChiralCell OD or Welk-01 Column- hexane: *iso*-propanol, 85:15). Conditions: **A**: calixarene:amine:**1a**:$NaBH_4$, 1:1:1:7; **B**: calixarene:amine:**1a**:$NaBH_4$, 1:1:1:1; **C**: amine:**1a**:$NaBH_4$, 1:1:1.

observed for dihydro-β-carboline **1b** (90% yield, 22% *ee*).[18] The decrease in selectivity found in the debromo compounds **1b** and **1d** can be rationalized as a weaker π–π interaction between the calix and **1b** and **1d** as compared to that of **1a** (Scheme 2).



Scheme 2.

In conclusion, the potential use of the supramolecular complex calix[6]arene/(*R*)-phenylethylamine in the enantioselective $NaBH_4$ reduction of β-carboline derivatives has been established. We continue to explore this conceptually novel approach to the enantioselective reduction of cyclic imines as well as the origin of the asymmetric induction observed.

2. Experimental

2.1. General information

NMR spectra were recorded on either a Varian-Gemini 2000 (300 MHz) or a Bruker instruments (400 MHz). HRMS were run on MicroMass-VG Autospec equipment. HPLC analyses were performed in a Hewlett Packard HP1050 equipment. The λ_{max} were measured in an Agilent 8453 equipment.

2.2. General method to CD-mediated reduction

An equimolar amount of imine (0.5 mmol) and Et_3N (0.5 mmol) was added to a suspension of dried CD (0.5 mmol) in 2.5 mL of aqueous sodium bicarbonate solution (0.2 mol/L). The mixture was stirred at room temperature overnight and the resulting slurry used without further processing. $NaBH_4$ (0.5–3.5 mmol) was then added to the mixture obtained previously and stirred at 0°C for 1 h. After acidification with aqueous solution of HCl (10%) the mixture was stirred for an additional period of 1 h at room temperature. Extraction with CH_2Cl_2 (3×10 mL), and the combined organic layer washed with water (2×10 mL) and dried with $MgSO_4$. After evaporation of solvent, the resulting title compound was filtered through silica using $CHCl_3$/MeOH. Analysis by NMR showed these compounds to be free of impurities. Enantiomeric excess (*ee*%) was determined by HPLC on a chiral column (Welk-01) using hexane:*iso*-propanol (10–15%) with a flow rate of 1.0 mL/min. The λ_{max} was measured in a Hewlett Packard equipment for each compound.

2.3. General method to calix[6]arene/chiral inductor mediated reduction

Chloroform was added to an equimolar amount of calix[6]arene (0.12 mmol) and chiral inductor (0.12 mmol) and stirred at room temperature overnight. The resulting mixture was then added to an equimolar amount of imine (0.12 mmol) and stirred for 1 h. $NaBH_4$ (0.12 mmol) was then added to the mixture and stirred at 0°C for 1 h. After acidification with an aqueous solution of HCl (10%), the mixture was stirred for an additional period of 1 h at room temperature. Extraction with CH_2Cl_2 (3×10 mL), and the combined organic layer washed with water (2×10 mL) and dried with $MgSO_4$. After evaporation of solvent, the resulting title compound was filtered through silica using $CHCl_3$/MeOH. Analysis by NMR showed these compounds to be free of impurities. Enantiomeric excess (*ee*%) was determined by HPLC on a chiral column (Welk-01) using hexane:*iso*-propanol (10–15%) with a flow rate of 1.0 mL/min. The λ_{max} was measured in a Hewlett Packard equipment for each compound.

2.4. Preparation of compounds 2a–d

Lactam (*S*)-2a: According to general procedures, the crude was purified by flash chromatography ($CHCl_3$/MeOH, 10%, R_f=0.7) to afford the lactam **2a** as a cream solid. $[\alpha]_D$=−0.7 (*c* 0.9, $CHCl_3$) to 77% *ee*. Mp 242–243°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71–1.94 (3H, m), 2.34–2.66 (2H, m), 2.73 (1H, m), 2.84 (2H, d, *J* 9.5), 2.94 (1H, d, *J* 11.5), 4.74 (1H, br dd, *J* 9.1 and 3.3), 5.16 (1H, d, *J* 8.8), 7.19 (1H, dd, *J* 8.4 and 0.7), 7.33 (1H, d, *J* 8.4), 7.46 (1H, s), 8.62 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.4, 21.0, 29.0, 32.5, 40.1, 54.4, 109.4, 113.9, 115.2, 119.5, 122.9, 125.7, 134.0, 137.0, 169.1. IR (KBr film) cm^{-1}: 3265, 3101, 2924, 2854, 1616, 1462, 1442, 1311, 1269, 1232, 1038, 754. HRMS (70 eV): $C_{15}H_{15}N_2OBr$ calcd 318.0368, found 318.0366.

Carbamate (*R*)-2b: According to general procedures, the crude was purified by flash chromatography ($CHCl_3$/MeOH, 3.3%, R_f=0.75) to afford the carbamate **2b** as a brown oil. $[\alpha]_D$=−0.2 (*c* 0.5, $CHCl_3$) to 22% *ee*. ^{1}H NMR (d^6-DMSO, 333 K, 400 MHz) δ: 1.68–1.72 (1H, m), 1.72 (1H, dt, *J* 9.0 and 1.6), 1.81 (1H, dt, *J* 10.6 and 2.9), 1.96 (1H, quint, *J* 7.1), 2.12–2.13 (2H, m), 2.34–2.39 (1H, m), 2.65 (1H, d, *J* 3.8), 2.68 (1H, dq, *J* 11.5 and 5.1), 3.14 (1H, dtd, *J* 11.1 and 4.7), 3.66 (3H, s), 4.23 (1H, br s), 4.99 (2H, dd, *J*

17.1 and 9.9), 5.09 (1H, dd, *J* 17.1 and 7.4), 5.32 (1H, br s), 5.77 (1H, ddt, *J* 17.1, 9.4 and 7.4), 5.88 (1H, ddt, *J* 17.1, 9.4 and 7.4), 6.97 (1H, dt, *J* 7.9 and 0.7), 7.04 (1H, dt, *J* 7.9 and 0.9), 7.31 (1H, d, *J* 7.9), 7.36 (1H, d, *J* 7.9), 10.69 (1H, s). ^{13}C NMR (d^6-DMSO, 333 K, 100 MHz) δ: 20.5, 33.6, 36.6, 37.3, 49.2, 52.1, 78.8, 106.1, 110.7, 116.0, 117.2, 118.2, 120.5, 126.2, 134.9, 135.7, 136.5, 155.6. IR (KBr film) cm^{-1}: 3306, 3074, 3001, 2922, 2852, 1680, 1469, 1442, 1410, 802, 760. HRMS (70 eV): $C_{21}H_{26}N_2O_2$ calcd. 338.1994, found 338.1997.

Carbamate (*S*)-2c: According to general procedures, the crude was purified by flash chromatography ($CHCl_3$/MeOH, 2.5%, R_f=0.51) to afford the carbamate **2c** as a brown solid. $[\alpha]_D$=+23.5 (*c* 0.6, $CHCl_3$) to 65% *ee*. Mp 62–63°C. ^{1}H NMR (d^6-DMSO, 343 K, 400 MHz) δ: 1.45–1.55 (2H, m), 1.73–1.82 (1H, m), 1.89–1.91 (1H, m), 2.09 (2H, quint, *J* 5.9), 2.64 (1H, dd, *J* 5.9 and 2.2), 2.63–2.67 (1H, m), 3.16 (1H, ddd, *J* 12.8, 10.2 and 6.6), 3.66 (3H, s), 4.25 (1H, dd, *J* 15.2 and 3.2), 4.96 (1H, dd, *J* 10.3 and 1.5), 5.02 (1H, dd, *J* 17.1 and 1.5), 5.16 (1H, dd, *J* 9.2 and 4.1), 5.82 (1H, ddt, *J* 17.1, 10.3 and 6.7), 7.07 (1H, dd, *J* 8.4 and 1.5), 7.31 (1H, d, *J* 8.4), 7.48 (1H, d, *J* 1.5), 10.83 (1H, s). ^{13}C NMR (d^6-DMSO, 343 K, 100 MHz) δ: 20.3, 24.6, 32.5, 33.4, 37.5, 50.7, 51.9, 106.6, 113.1, 113.3, 114.3, 118.8, 121.0, 125.2, 135.6, 136.6, 138.1, 155.4. IR (KBr film) cm^{-1}: 3306, 3074, 3001, 2922, 2852, 1680, 1469, 1442, 1410, 802, 760. HRMS (70 eV): $C_{18}H_{21}N_2O_2Br$ calcd 376.0786, found 376.0789.

Lactam 2d: According to general procedures, the crude was purified by flash chromatography ($CHCl_3$/MeOH, 10%, R_f=0.85) to give lactam **2d** as a brown oil. $[\alpha]_D$=−0.3 (*c* 0.5, $CHCl_3$) to 20% *ee*. ^{1}H NMR ($CDCl_3$, 333 K, 300 MHz) δ: 1.74–2.02 (3H, m), 2.38–2.50 (2H, m), 2.63 (1H, m), 2.76–2.81 (2H, m, 2.87–2.92 (1H, m), 4.81 (1H, br dd, *J* 9.1 and 3.3), 5.15–5.22 (1H, m), 7.14 (1H, td, *J* 7.5 and 0.9), 7.20 (1H, td, *J* 7.5 and 0.9), 7.36 (1H, d, *J* 7.5), 7.52 (1H, d, *J* 7.5), 7.88 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.4, 21.0, 29.1, 32.4, 40.2, 54.4, 109.7, 110.9, 118.4, 119.9, 122.2, 126.9, 133.3, 136.3, 169.3. IR (KBr film) cm^{-1}: 3223, 2926, 2856, 1609, 1470, 1440, 1409, 1325, 1268, 1234, 1038, 741. HRMS (70 eV): $C_{15}H_{16}N_2O$ calcd. 240.1263, found 240.1259.

Acknowledgements

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