Asymmetric Proline-Catalyzed Addition of Aldehydes to 3*H*-Indol-3-ones: Enantioselective Synthesis of 2,3-Dihydro-1*H*-indol-3-ones with Quaternary Stereogenic Centers

by **Magnus Rueping***, **Ramesh Rasappan**, and **Sadiya Raja**

Institute of Organic Chemistry, RWTH-Aachen University, Landoltweg 1, DE-52074 Aachen (fax +49(241)8092665; e-mail: Magnus.Rueping@rwth-aachen.de)

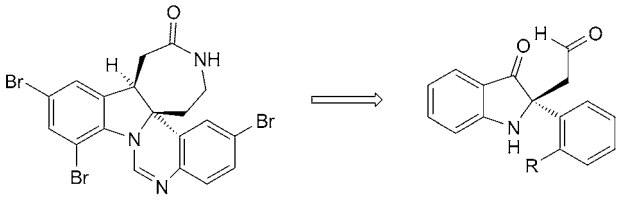
Meinem verehrten Lehrer, Herrn Prof. *Dieter Seebach*, zum 75. Geburtstag gewidmet

The proline-catalyzed addition of various aliphatic aldehydes to sterically hindered 2-aryl-substituted 3*H*-indol-3-ones affords 2,2-disubstituted 2,3-dihydro-1*H*-indol-3-one derivatives with excellent enantioselectivities. In addition, the synthesis of a chiral derivative, (*S*)-2-(2-bromophenyl)-2,3-dihydro-2-(2-hydroxyethyl)-1*H*-indol-3-one, which can be used as an intermediate for the preparation of the natural product hinckdentine A was accomplished with a high level of enantioselectivity.

Introduction. – The stereoselective construction of C–C bonds is a valuable tool in preparing complex natural products and pharmaceutically important compounds. However, the synthesis of stereogenic quaternary C-centers with a high level of enantioselectivity *via* C–C bond-formation is still demanding [1]. In particular, the preparation of compounds bearing N or other heteroatoms next to the quaternary C-center constitutes a challenging task in organic chemistry.

Indole derivatives are privileged structures [2] present in numerous pharmaceutical drugs. Dihydroindol-2- and -3-one derivatives are also found in many natural products and active compounds against cancer, atherosclerosis, arthritis, and restenosis [3]. 2,3-Dihydro-1*H*-indol-3-ones are valuable synthons for the synthesis of more complex molecules, for example, for the synthesis of the natural product hinckdentine A[1]) (*Scheme*) [5].

Scheme



[1]) For isolation and X-ray characterization of hinckdentine A, see [4].

© 2012 Verlag Helvetica Chimica Acta AG, Zürich

The *Mannich* reaction is a classic atom economic process for the construction of C–C bonds that has especially been applied in the preparation of amino acids, natural products, and biologically active compounds [6]. Proline-mediated *Mannich* reactions are known to provide excellent enantioselectivities with various aldehydes and ketones [6][7]. However, the use of acetaldehyde (MeCHO) as a nucleophile is very limited in organic synthesis due to the rapid self-aldol-condensation reaction which leads to the formation of polymers. Also, the *Mannich* product from MeCHO might undergo further reaction, since the α-C-atom can be further activated by proline [8].

Results and Discussion. – Recently, we showed that the 3*H*-indol-3-ones can be utilized to synthesize dihydro-indolone derivatives with a quaternary stereogenic center bearing a N-atom [9][2]). Here, we report our studies on the synthesis of chiral quaternary 2,2-disubstituted 2,3-dihydro-1*H*-indol-3-ones *via* proline-mediated *Mannich* reaction of 3*H*-indol-3-ones with various aldehydes as efficient nucleophiles. Moreover, the precursor for the synthesis of hinckdentine A was synthesized with a good enantioselectivity [10a][3]).

With 3*H*-indol-3-ones **1** in our hands [5c][12], we investigated their usefulness as substrates in the proline-catalyzed *Mannich* reactions with MeCHO[4]). Initial studies were carried out by varying the catalyst loading, solvent, and temperature. 3*H*-Indol-3-one **1a** was treated with 6 equiv. of MeCHO (**2a**) in the presence of L-proline at room temperature, and the resulting *Mannich* adduct **3a** was reduced with $NaBH_4$ in MeOH to give **4a**. When 20 mol-% of L-proline were used, an excellent enantioselectivity of 96% ee was observed (*Table 1*, *Entry 2*). A slightly lower level of enantioselectivity was observed by decreasing the catalyst loading to 10 mol-% (*Table 1*, *Entry 1*). Increasing the catalyst loading did not improve the enantioselectivity (*Table 1*, *Entry 3*). Interestingly, excellent enantioselectivities were observed in most of the tested solvents (*Table 1*, *Entries 2–7*). CH_2Cl_2 proved to be the most efficient solvent, with regard to yield and selectivity (*Table 1*, *Entry 6*, 56% yield, 98% ee). To improve the yield of the reaction by suppressing the side-product formation, we carried out reactions by varying the temperature and the amount of MeCHO (**2a**). Lowering the reaction temperature did not improve the reaction yield; however, significant improvement in the yield was observed when **2a** was added in two portions. Under these conditions, the desired product **4a** was obtained in 71% yield with 98% ee (*Table 1*, *Entry 9*).

With the optimized reaction conditions in hand, we explored the scope of 3*H*-indol-3-one derivatives as substrates (*Table 2*). Substrates bearing electron-donating substituents such as Me, Et, and MeO gave the 2,3-dihydro-1*H*-indol-3-ones **4a**–**4c** with excellent enantioselectivities (*Table 2*, *Entries 1–3*). Substrates with electron deficient phenyl rings bearing substituents including F, Cl, and Br afforded the corresponding products with excellent enantioselectivities as well (*Table 2*, *Entries 4–6*). Notably, most of the reactions require less than 1 h for completion. Even the bulkier napthalen-2-yl indol-3-one **1h** provided the product in 81% yield and 98% ee (*Table 2*,

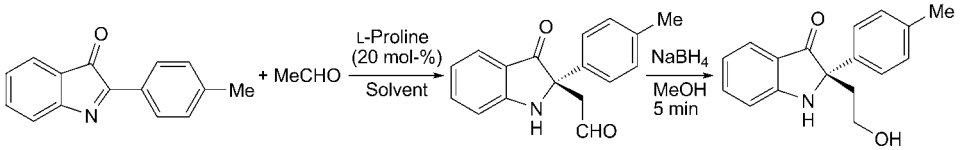
---

[2]) For similar studies, see [10].

[3]) For achiral *Lewis* and *Brønsted* acid catalyzed versions, see [11].

[4]) With regard to the mechanism in proline catalysis, see [13].

Table 1. *Screening of Catalyst Loading, Various Solvents, and Temperature*[a])

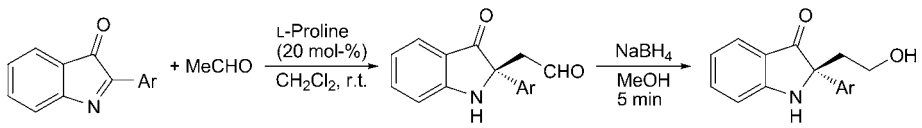


1a **2a** **3a** **4a**

Entry	Solvent	Catalyst [mol-%]	Temp. [°]	Time [h]	Yield [%][b])	ee [%][c])
1	DMSO	10	r.t.	1	44	87
2	DMSO	20	r.t.	1	46	96
3	DMSO	30	r.t.	1	48	96
4	Toluene	20	r.t.	1	53	97
5	$CHCl_3$	20	r.t.	0.75	51	97
6	CH_2Cl_2	20	r.t.	0.75	56	98
7	MeCN	20	r.t.	1	42	97
8	Benzene	20	r.t.	2	44	81
9[d])	CH_2Cl_2	20	r.t.	0.75	71	98
10[d])	CH_2Cl_2	20	0	1	68	98

[a]) 1 equiv. of **1a**, 6 equiv. of MeCHO, L-proline. [b]) Yields after CC (over two steps). [c]) Determined by SFC. [d]) Addition of 4 equiv. of MeCHO in two portions.

Table 2. Mannich *Addition of Acetaldehyde to 3*H*-Indol-3-ones*[a])



1a – 1h **2a** **3a – 3h** **4a – 4h**

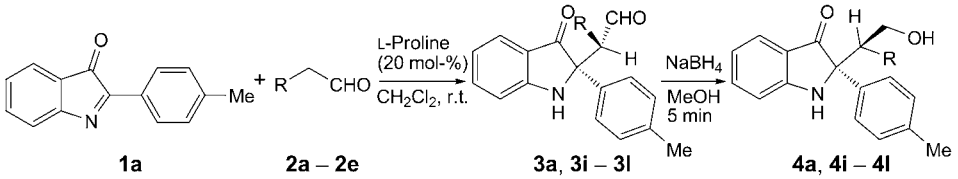
Entry	Ar	**1**	Time [h]	**4**	Yield [%][b])	ee [%][c])
1	4-Me–C_6H_4	**1a**	0.75	**4a**	71	98
2	4-Et–C_6H_4	**1b**	0.33	**4b**	76	97
3	4-MeO–C_6H_4	**1c**	0.5	**4c**	74	96
4	4-F–C_6H_4	**1d**	1	**4d**	52	94
5	4-Cl–C_6H_4	**1e**	1	**4e**	66	96
6	4-Br–C_6H_4	**1f**	1	**4f**	51	98
7	Ph	**1g**	1	**4g**	48	95
8	Naphthalen-2-yl	**1h**	0.5	**4h**	81	98

[a]) 1 equiv. of 3*H*-indol-3-one **1**, 4 equiv. of MeCHO in two portions. [b]) Yields after CC (over two steps). [c]) Determined by HPLC or supercritical fluid chromatography (SFC).

Entry 8). The absolute configurations of the products **4a**–**4h** were assigned by comparison with the literature data [10a].

To extend the scope of the reaction, various aldehydes **2a**–**2e** were treated with 3*H*-indol-3-one **1a**, and the results are compiled in *Table 3*. Propanal (**2b**) and butanal (**2c**) gave products with excellent ee values and very good yields (*Table 3*, *Entries 2* and *3*),

Table 3. *Evaluation of Aldehydes in the Asymmetric* Mannich *Reaction*[a])



1a **2a – 2e** **3a, 3i – 3l** **4a, 4i – 4l**

Entry	R	**2**	Equiv. (**2**)	Time [h]	**4**	Yield [%][b])	dr	ee [%][c])
1	H	**2a**	4	0.75	**4a**	71	–	98
2	Me	**2b**	2	2	**4i**	84	10:1	98
3	Et	**2c**	2	3	**4j**	91	3:1	98
4	Pr	**2d**	1.1	1.3	**4k**	84	2:1	85
5[d])	Pr	**2d**	1.1	3	**4k**	87	2:1	85
6	^{i}Pr	**2e**	2	3	**4l**	72	1:1	56

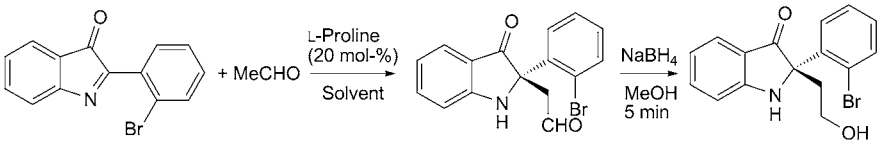
[a]) 1 equiv. of 3*H*-indol-3-one, L-proline 20 mol-%, CH_2Cl_2, r.t. [b]) Yields after CC (over two steps). [c]) Enantioselectivity of the major diastereoisomer, determined by HPLC or SFC. [d]) Reaction performed at 0°.

but the reactions required longer times compared to the addition of MeCHO (**2a**). The products **4i** and **4j** were obtained with a 10:1 and a 3:1 diastereoisomer ratio (dr), respectively. Extending the alkyl chain of the aldehyde led to a decrease in enantioselectivity (*Table 3*, *Entries 4* and *5*). The branched-chain aldehyde **2e** afforded the corresponding product **4l** only with moderate enantioselectivity (*Table 3*, *Entry 6*). The absolute configurations of the products **4i**–**4l** were assigned by comparison with the literature data [10a].

The natural product hinckdentine A has a unique structure consisting of a seven-membered lactam ring fused to a tribromo-indolo[1,2-*c*]quinazoline with a stereogenic quaternary and a stereogenic tertiary C-centers (*Scheme*), which attracted the interest of several chemists [4][5]. Despite considerable interest in the synthesis of hinckdentine A, its enantioselective synthesis still remains a challenge due to the construction of sterically crowded vicinal stereogenic quaternary and tertiary C-centers present in the structure.

Racemic indolinone **4m** was used as an intermediate in the synthesis of 8-debromo-hinckdentine A derivative [5c]. Hence, our attention was drawn to the enantioselective synthesis of this molecule. In this particular case, the addition of MeCHO (**2a**) is more challenging due to the presence of bulky 2-Br substituent on the phenyl ring. As anticipated, the product **4m** was isolated with a lower level of enantioselectivity (70% yield, 60% ee), when the reaction was performed under the standard conditions (*Table 4*, *Entry 2*). Use of a stoichiometric amount of L-proline did not improve the enantioselectivity (*Table 4*, *Entry 3*). However, by lowering the reaction temperature, the enantioselectivity was improved, but the reaction required longer time for the complete conversion. Accordingly, 2,3-dihydro-1*H*-indol-3-one **4m** was isolated with 75% ee, when the reaction was performed at 0° (*Table 4*, *Entry 4*). Lowering the temperature to –35° afforded the desired product with the best enantioselectivity of

Table 4. *Addition of Acetaldehyde to 2-(4-Bromophenyl)-3*H*-indol-3-one* (**1i**)[a])



1i **2a** **3m** **4m**

Entry	Proline	Loading [mol-%]	Time	Temp [°]	Yield [%][b])	ee [%][c])
1	DL	20	1.3 h	r.t.	65	–
2	L	20	1.3 h	r.t.	70	60
3	L	100	1 h	r.t.	72	55
4	L	20	6 h	0	70	75
5	L	20	4 d	−35	77	87
6	L	20	4 d	−78 to −30	50	87
7	L	20	10 d	−78 to −50	10	83

[a]) 1 equiv. of 3*H*-indol-3-one **1i**, 4 equiv. of MeCHO in two portions. [b]) Yields after CC (over two steps). [c]) Determined by SFC.

87% ee and in 77% yield, but the reaction was sluggish and took 4 d for the complete conversion (*Table 4*, *Entry 5*). Decreasing the reaction temperature further to −78° did not improve the enantioselectivity, and only traces of the product were observed even after several days. However, the acetaldehyde *Mannich* reaction provides access to a key building block for the synthesis of hinckdentine A.

In conclusion, we have developed an asymmetric synthesis of various 2,2-disubstituted 2,3-dihydro-1*H*-indol-3-ones with excellent enantioselectivities. The reaction is applicable to 3*H*-indol-3-ones bearing electron-withdrawing as well as electron-donating groups as electrophiles, and various aldehydes as nucleophiles. More importantly, a challenging intermediate for the synthesis of hinckdentine A was synthesized with good enantioselectivity. Further studies are focused on the total synthesis of hinckdentine A and exploring the scope of 3*H*-indol-3-ones in other organocatalyzed reactions.

Experimental Part

General. Solvents were obtained from *Fisher Scientific* and were purified before use by distillation. Starting materials were purchased from *Acros* and *Alfa Aesar* and were used without further purification. Optical rotations: *Perkin-Elmer 241* polarimeter. IR Spectra: *Jasco FT/IR-420* spectrometer, in KBr. NMR Spectra: *Mercury 300* or *Inova 400* spectrometer in CD_3OD, δ in ppm, J in Hz. EI-MS (70 eV): *GC/MS Shimadzu QP2010* (column *Equity-5*, length × i.d. 30 m × 0.25 mm, df 0.25 μm, lot # 28089-U, *Supelco*); *m*/*z*.

General Procedure. Acetaldehyde (**2a**; 4 equiv.) was added to the mixture of 3*H*-indol-3-one **1** (1 equiv.) and L-proline (20 mol-%) in 1.0 ml of CH_2Cl_2 at r.t. The mixture was stirred vigorously for 20 min. Subsequently, another 4 equiv. of **2a** were added. The reaction was monitored by TLC, and upon completion the solvent was removed, and the crude was taken in 1 ml of MeOH. $NaBH_4$ (2 equiv.) was added at 0°. After stirring for 5 min, the reaction was quenched with H_2O, and the mixture was extracted with AcOEt and washed with brine. The org. layer was dried (Na_2SO_4), filtered, and the solvent was

removed under reduced pressure. Purification of the crude product by column chromatography (CC) on SiO_2 afforded the corresponding product **4**.

*(2S)-2-(2-Hydroxyethyl)-2-(4-methylphenyl)-2,3-dihydro-1*H*-indol-3-one* (**4a**). Yellow gummy compound. Yield: 74%. $[\alpha]_D^{25} = +368$ ($c = 1.0$, CH_2Cl_2; 98% ee). IR: 3318, 3017, 2924, 2858, 2406, 1674, 1619, 1470, 1327, 1287, 1215, 1042, 1000, 894, 756. ^{1}H-NMR (400 MHz; CD_3OD): 7.48 – 7.43 (*m*, 1 H); 7.42 – 7.39 (*m*, 3 H); 7.11 (*d*, *J* = 8.0, 2 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.70 (*t*, *J* = 7.4, 1 H); 3.53 – 3.46 (*m*, 2 H); 2.36 – 2.29 (*m*, 1 H); 2.26 (*s*, 3 H); 2.19 (*dt*, *J* = 13.7, 7.8, 1 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.2; 161.5; 137.6; 136.9; 135.7; 128.7; 125.2; 124.3; 117.8; 117.7; 111.7; 70.4; 57.8; 40.2; 19.7. EI-MS: 268 (15, $[M+H]^+$), 267 (69, M^+), 223 (24), 222 (100).

*(2S)-2-(4-Ethylphenyl)-2-(2-hydroxyethyl)-1,2-dihydro-3*H*-indol-3-one* (**4b**). Yellow gummy compound. Yield: 76%. $[\alpha]_D^{25} = +265$ ($c = 1.0$, CH_2Cl_2; 97% ee). IR: 3361, 3012, 2964, 2928, 2876, 1687, 1617, 1488, 1325, 1151, 1098, 1042, 894, 755. ^{1}H-NMR (300 MHz; CD_3OD): 7.49 – 7.42 (*m*, 4 H); 7.15 (*d*, *J* = 8.1, 2 H); 6.99 (*d*, *J* = 8.3, 1 H); 6.72 (*t*, *J* = 7.4, 1 H); 3.59 – 3.45 (*m*, 2 H); 2.59 (*q*, *J* = 7.6, 2 H); 2.40 – 2.31 (*m*, 1 H); 2.27 – 2.17 (*m*, 1 H); 1.18 (*t*, *J* = 7.6, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 203.4; 161.6; 143.4; 137.6; 136.0; 127.6; 125.4; 124.4; 117.9; 117.7; 111.7; 70.4; 57.8; 40.1; 27.9; 14.7. EI-MS: 281 (60, M^+), 252 (56), 236 (100).

*(2S)-2-(2-Hydroxyethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indol-3-one* (**4c**). Yellow gummy compound. Yield: 74%. $[\alpha]_D^{25} = +293$ ($c = 1.0$, CH_2Cl_2; 96% ee). IR: 3371, 2928, 1690, 1615, 1505, 1324, 1250, 1094, 1036, 756. ^{1}H-NMR (300 MHz; CD_3OD): 7.50 – 7.41 (*m*, 4 H); 6.98 (*dt*, *J* = 8.3, 0.8, 1 H); 6.89 – 6.84 (*m*, 2 H); 6.75 – 6.69 (*m*, 1 H); 3.74 (*s*, 3 H); 3.59 – 3.45 (*m*, 2 H); 2.37 – 2.29 (*m*, 1 H); 2.25 – 2.15 (*m*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 203.6; 161.5; 159.2; 137.6; 130.6; 126.5; 124.4; 117.9; 117.7; 113.5; 111.7; 70.1; 57.8; 54.3; 40.1. EI-MS: 283 (47, M^+), 254 (51), 238 (100).

*(2S)-2-(4-Fluorophenyl)-2-(2-hydroxyethyl)-2,3-dihydro-1*H*-indol-3-one* (**4d**). Yellow gummy compound. Yield: 52%. $[\alpha]_D^{25} = +251$ ($c = 1.0$, CH_2Cl_2, 94% ee). IR: 3370, 2927, 1693, 1617, 1502, 1382, 1325, 1229, 1158, 1091, 1041, 837, 756. ^{1}H-NMR (300 MHz; CD_3OD): 7.61 – 7.56 (*m*, 2 H); 7.51 – 7.43 (*m*, 2 H); 7.07 – 6.99 (*m*, 3 H); 6.74 (*td*, *J* = 7.4, 0.7, 1 H); 3.59 – 3.44 (*m*, 2 H); 2.37 – 2.29 (*m*, 1 H); 2.26 – 2.17 (*m*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 202.9; 162.3 (*d*, *J*(C,F) = 244.7); 161.4; 137.7; 134.9; 127.4 (*d*, *J*(C,F) = 13.7); 124.4; 117.9; 117.8; 114.7 (*d*, *J*(C,F) = 21.5); 111.8; 70.0; 57.7; 40.3. EI-MS: 271 (67, M^+), 242 (70), 226 (100), 224 (58).

*(2S)-2-(4-Chlorophenyl)-2-(2-hydroxyethyl)-2,3-dihydro-1*H*-indol-3-one* (**4e**). Yellow gummy compound. Yield: 66%. $[\alpha]_D^{25} = +234$ ($c = 1.0$, CH_2Cl_2; 96% ee). IR: 3346, 2921, 2851, 2320, 2081, 1904, 1790, 1677, 1616, 1582, 1465, 1386, 1324, 1290, 1152, 1092, 1009, 821, 750. ^{1}H-NMR (300 MHz; CD_3OD): 7.59 – 7.57 (*m*, 1 H); 7.55 – 7.54 (*m*, 1 H); 7.52 – 7.48 (*m*, 1 H); 7.47 – 7.43 (*m*, 1 H); 7.34 – 7.30 (*m*, 2 H); 7.01 (*dt*, *J* = 8.3, 0.8, 1 H); 6.77 – 6.72 (*m*, 1 H); 3.59 – 3.43 (*m*, 2 H); 2.37 – 2.28 (*m*, 1 H); 2.26 – 2.14 (*m*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 202.6; 161.5; 137.7; 133.1; 129.1; 128.1; 127.2; 124.4; 118.0; 117.8; 111.9; 70.1; 57.6; 40.2. EI-MS: 287 (67, M^+), 258 (64), 244 (46), 242 (100).

*(2S)-2-(4-Bromophenyl)-2-(2-hydroxyethyl)-2,3-dihydro-1*H*-indol-3-one* (**4f**). Yellow gummy compound. Yield: 51%. $[\alpha]_D^{25} = +222$ ($c = 1.0$, CH_2Cl_2; 98% ee). IR: 3331, 3018, 2923, 2856, 1677, 1619, 1583, 1471, 1215, 1007, 756. ^{1}H-NMR (300 MHz; CD_3OD): 7.52 – 7.43 (*m*, 6 H); 7.02 – 6.98 (*m*, 1 H); 6.78 – 6.72 (*m*, 1 H); 3.59 – 3.44 (*m*, 2 H); 2.37 – 2.27 (*m*, 1 H); 2.26 – 2.15 (*m*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 202.5; 161.5; 138.4; 137.8; 131.2; 127.5; 124.4; 121.1; 118.0; 117.8; 111.9; 70.1; 57.6; 40.2. EI-MS: 333 (50), 331 (52, M^+), 288 (79), 286 (100).

*(2S)-2-(2-Hydroxyethyl)-2-phenyl-2,3-dihydro-1*H*-indol-3-one* (**4g**). Yellow gummy compound. Yield: 48%. ^{1}H-NMR (400 MHz, CD_3OD): 7.55 – 7.53 (*m*, 2 H); 7.49 – 7.41 (*m*, 2 H); 7.32 – 7.28 (*m*, 2 H); 7.25 – 7.23 (*m*, 1 H); 6.99 (*d*, *J* = 8.3, 1 H); 6.71 (*t*, *J* = 7.4, 1 H); 3.55 – 3.46 (*m*, 2 H); 2.38 – 2.32 (*m*, 1 H); 2.26 – .18 (*m*, 1 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.0; 161.5; 138.8; 137.6; 128.1; 127.1; 125.3; 124.3; 117.8; 111.7; 70.5; 57.8; 40.3.

*(2S)-2-(2-Hydroxyethyl)-2-(naphthalen-2-yl)-2,3-dihydro-1*H*-indol-3-one* (**4h**). Yellow gummy compound. Yield: 81%. $[\alpha]_D^{25} = +223$ ($c = 1.0$, CH_2Cl_2; 98% ee). IR: 3366, 3057, 3013, 2925, 1687, 1617, 1487, 1325, 1215, 1152, 1040, 754. ^{1}H-NMR (400 MHz; CD_3OD): 8.01 – 8.00 (*m*, 1 H); 7.80 – 7.76 (*m*, 3 H); 7.68 (*dd*, *J* = 8.7, 1.9, 1 H); 7.50 – 7.46 (*m*, *J* = 1.3, 1 H); 7.45 – 7.40 (*m*, 3 H); 7.03 (*dt*, *J* = 8.3, 0.8, 1 H); 6.74 – 6.70 (*m*, *J* = 0.8, 1 H); 3.60 – 3.48 (*m*, 2 H); 2.50 – 2.44 (*m*, *J* = 4.6, 1 H); 2.35 – 2.28 (*m*, *J* = 7.6, 1 H). ^{13}C-NMR (101 MHz, CD_3OD): 202.9; 161.5; 137.7; 136.2; 133.3; 132.7; 127.8; 127.6; 127.0; 125.7; 125.6;

124.4; 124.1; 123.5; 117.9; 117.8; 111.8; 70.7; 57.9; 40.2. EI-MS: 304 (15, $[M+H]^+$), 303 (63, M^+), 259 (26), 258 (100).

(2S)-2-[(1R)-2-Hydroxy-1-methylethyl]-2-(4-methylphenyl)-2,3-dihydro-1H-indol-3-one (**4i**). Yellow gummy compound. Yield: 84%. $[\alpha]_D^{25} = +360$ ($c = 1.0$, CH_2Cl_2, 98% ee). IR: 3396, 3292, 2934, 1912, 1673, 1614, 1465, 1379, 1322, 1222, 1035, 892, 752. ^{1}H-NMR (400 MHz, CD_3OD): 7.45 – 7.40 (*m*, 3 H); 7.38 – 7.36 (*m*, 1 H); 7.12 – 7.10 (*m*, 2 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.69 – 6.65 (*m*, 1 H); 3.42 (*dd*, *J* = 10.6, 5.0, 1 H); 3.27 – 3.24 (*m*, 1 H); 2.75 – 2.71 (*m*, 1 H); 2.27 (*s*, 3 H); 0.85 (*d*, *J* = 6.9, 3 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.4; 161.6; 137.3; 136.9; 135.8; 128.7; 125.3; 124.0; 118.8; 117.4; 111.3; 73.9; 62.8; 43.6; 19.5; 11.2. EI-MS: 281 (16, M^+), 223 (19), 222 (100).

(2S)-2-[(1R)-1-(Hydroxymethyl)propyl]-2-(4-methylphenyl)-2,3-dihydro-1H-indol-3-one (**4j**). Yellow gummy compound. Yield: 91%. $[\alpha]_D^{25} = +260$ ($c = 0.9$, CH_2Cl_2; 98% ee). IR: 3350, 3009, 2961, 2930, 2878, 1683, 1618, 1470, 1323, 1216, 1034, 893, 756. ^{1}H-NMR (400 MHz, CD_3OD): 7.45 – 7.42 (*m*, 2 H); 7.41 – 7.36 (*m*, 2 H); 7.10 (*d*, *J* = 8.1, 2 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.68 – 6.64 (*m*, 1 H); 3.52 – 3.43 (*m*, 2 H); 2.56 – 2.50 (*m*, 1 H); 1.36 – 1.23 (*m*, 2 H); 0.83 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.7; 161.6; 137.1; 136.8; 136.2; 128.7; 125.5; 124.1; 118.9; 117.4; 111.4; 74.5; 61.5; 49.9; 20.4; 19.5; 11.8. EI-MS: 295 (16, M^+), 223 (24), 222 (100).

(2S)-2-[(1R)-1-(Hydroxymethyl)butyl]-2-(4-methylphenyl)-2,3-dihydro-1H-indol-3-one (**4k**). Yellow gummy compound. Yield: 87%. $[\alpha]_D^{25} = +225$ ($c = 1.1$, CH_2Cl_2, 85% ee). ^{1}H-NMR (400 MHz, CD_3OD): 7.46 – 7.43 (*m*, 2 H); 7.41 – 7.39 (*m*, 1 H); 7.37 (*d*, *J* = 7.8, 1 H); 7.10 (*d*, *J* = 8.2, 2 H); 6.97 (*d*, *J* = 8.3, 1 H); 6.66 (*t*, *J* = 7.3, 1 H); 3.50 – 3.42 (*m*, 2 H); 2.64 – 2.58 (*m*, 1 H); 2.27 (*s*, 3 H); 1.41 – 1.30 (*m*, 1 H); 1.28 – 1.14 (*m*, 3 H); 0.75 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.7; 161.6; 137.1; 136.8; 136.2; 128.7; 125.5; 124.1; 119.0; 117.4; 111.4; 74.5; 62.0; 29.9; 21.1; 19.5; 13.2. EI-MS: 309 (15, M^+), 223 (24), 222 (100).

(2S)-2-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-2-(4-methylphenyl)-2,3-dihydro-1H-indol-3-one (**4l**). Yellow gummy compound. Yield: 72%. IR: 3387, 2959, 2925, 1689, 1618, 1471, 1384, 1322, 1216, 1149, 1104, 1045, 897, 756. ^{1}H-NMR (400 MHz, CD_3OD): 7.45 – 7.42 (*m*, 2 H); 7.41 – 7.35 (*m*, 2 H); 7.10 (*d*, *J* = 8.0, 2 H); 7.02 (*d*, *J* = 8.3, 1 H); 6.68 – 6.65 (*m*, 1 H); 3.67 (*dd*, *J* = 11.1, 6.3, 1 H); 3.49 (*dd*, *J* = 11.1, 6.7, 1 H); 2.74 – 2.70 (*m*, 1 H); 2.26 (*s*, 3 H); 1.78 – 1.70 (*m*, 1 H); 0.97 (*d*, *J* = 7.1, 3 H); 0.84 (*d*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 161.7; 136.8; 136.0; 128.7; 125.5; 124.0; 118.6; 117.4; 111.6; 74.8; 58.8; 52.7; 42.4; 26.5; 22.8; 19.5; 16.5. EI-MS: 309 (14, M^+), 223 (28), 222 (100).

(2S)-2-(2-Bromophenyl)-2-(2-hydroxyethyl)-2,3-dihydro-1H-indol-3-one (**4m**). Yellow gummy compound. Yield: 77%. $[\alpha]_D^{25} = -312$ ($c = 0.9$, CH_2Cl_2; 87% ee). IR: 3373, 3063, 3011, 2926, 1690, 1616, 1486, 1436, 1325, 1214, 1152, 1097, 1028, 894, 755. ^{1}H-NMR (400 MHz, CD_3OD): 7.62 – 7.57 (*m*, 2 H); 7.52 (*d*, *J* = 7.8, 1 H); 7.46 (*td*, *J* = 7.7, 1.1, 1 H); 7.36 – 7.31 (*m*, 1 H); 7.19 – 7.14 (*m*, 1 H); 6.90 (*d*, *J* = 8.3, 1 H); 6.78 – 6.74 (*m*, 1 H); 3.58 – 3.52 (*m*, 1 H); 3.47 – 3.40 (*m*, 1 H); 2.65 – 2.58 (*m*, 1 H); 2.46 – 2.38 (*m*, 1 H). ^{13}C-NMR (101 MHz, CD_3OD): 203.4; 161.2; 137.9; 137.4; 134.8; 129.4; 129.1; 127.0; 123.5; 122.8; 120.6; 118.0; 112.0; 70.6; 57.2; 39.3. EI-MS: 331 (7, M^+), 252 (100).

REFERENCES

[1] S. F. Martin, *Tetrahedron* **1980**, *36*, 419; K. Fuji, *Chem. Rev.* **1993**, *93*, 2037; E. J. Corey, A. Guzman-Perez, *Angew. Chem., Int. Ed.* **1998**, *37*, 388; J. Christoffers, A. Mann, *Angew. Chem., Int. Ed.* **2001**, *40*, 4591; J. Christoffers, A. Baro, *Angew. Chem., Int. Ed.* **2003**, *42*, 1688; I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105; 'Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis', Eds. J. Christoffers, A. Baro, Wiley-VCH, Weinheim, 2005.

[2] R. J. Sundberg, in 'The Chemistry of Indoles', Eds. A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Academic Press, New York, 1996; K. S. Ryan, C. L. Drennan, *Chem. Biol.* **2009**, *16*, 351; R. K. Brown, in 'Indoles', Ed. W. J. Houlihan, Wiley-Interscience, New York, 1972; E. Lodyga-Chruscinska, M. Turek, *PharmaChem* **2009**, *8*, 6.

[3] I. Carletti, B. Banaigs, P. Amade, *J. Nat. Prod.* **2000**, *63*, 981; Z. Pang, O. Sterner, *J. Nat. Prod.* **1994**, *57*, 852; K. N. Kilminster, M. Sainsbury, *J. Chem. Soc., Perkin Trans. 1* **1972**, 2415; M. Hooper, W. N. Pitkethly, *J. Chem. Soc., Perkin Trans. 1* **1972**, 1607; A. Karadeolian, M. A. Kerr, *J. Org. Chem.* **2010**,

75, 6830; I. Coldham, H. Adams, N. J. Ashweek, T. A. Barker, A. T. Reeder, M. C. Skilbeck, *Tetrahedron Lett.* **2010**, *51*, 2457; R. Abonia, P. Cuervo, J. Castillo, B. Insuasty, J. Quiroga, M. Nogueras, J. Cobo, *Tetrahedron Lett.* **2008**, *49*, 5028; B. K. Banik, M. Cardona, *Tetrahedron Lett.* **2006**, *47*, 7385.

[4] A. J. Blackman, T. W. Hambley, K. Picker, W. C. Taylor, N. Thirasasana, *Tetrahedron Lett.* **1987**, *28*, 5561.

[5] a) A. D. Billimoria, M. P. Cava, *J. Org. Chem.* **1994**, *59*, 6777; b) N. Barnwell, R. L. Beddoes, M. B. Mitchell, J. A. Joule, *Heterocycles* **1994**, *37*, 175; c) Y. Liu, W. W. McWhorter Jr., *J. Am. Chem. Soc.* **2003**, *125*, 4240; d) K. Higuchi, Y. Sato, M. Tsuchimochi, K. Sugiura, M. Hatori, T. Kawasaki, *Org. Lett.* **2009**, *11*, 197.

[6] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29; M. M. B. Marques, *Angew. Chem., Int. Ed.* **2006**, *45*, 348; A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; H. Zhang, S. Syed, C. F. Barbas III, *Org. Lett.* **2010**, *12*, 708; R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940; D. Enders, M. Vrettou, *Synthesis* **2006**, 2155; E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138; R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem*. **2007**, 2575.

[7] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; J. W. Yang, M. Stadler, B. List, *Angew. Chem., Int. Ed.* **2007**, *46*, 609; Y. Chi, E. P. English, W. C. Pomerantz, W. S. Horne, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins, S. H. Gellman, *J. Am. Chem. Soc.* **2007**, *129*, 6050; B. List, J. W. Yang, *Science* **2006**, *313*, 1584.

[8] J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453; S. E. Denmark, T. Bui, *J. Org. Chem.* **2005**, *70*, 10190; A. Cordóva, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620.

[9] M. Rueping, S. Raja, A. Núñez, *Adv. Synth. Catal.* **2011**, *353*, 563.

[10] a) L. Li, M. Han, M. Xiao, Z. Xie, *Synlett* **2011**, 1727; b) Q. Yin, S.-L. You, *Chem. Sci*. **2011**, *2*, 1344; c) A. Parra, R. Alfaro, L. Marzo, A. Moreno-Carrasco, J. L. Garciá Ruano, J. Alemán, *Chem. Commun*. **2012**, *48*, 9759.

[11] K. Higuchi, Y. Sato, S. Kojima, M. Tsuchimochi, K. Sugiura, M. Hatori, T. Kawasaki, *Tetrahedron* **2010**, *66*, 1236.

[12] M. Rueping, S. Raja, *Beilstein J. Org. Chem.* **2012**, *8*, 1819.

[13] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425.

Received August 29, 2012