

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)

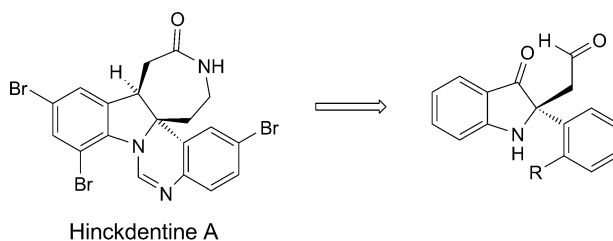
Meinem verehrten Lehrer, Herrn Prof. Dieter Seebach, zum 75. Geburtstag gewidmet

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 A¹⁾ (*Scheme*) [5].

Scheme



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

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).

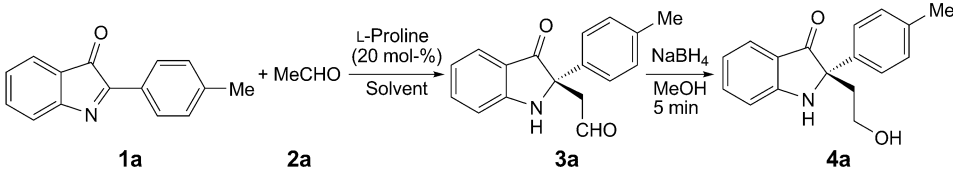
With 3*H*-indol-3-ones **1** in our hands [5c][12], we investigated their usefulness as substrates in the proline-catalyzed *Mannich* reactions with MeCHO⁴). Initial studies were carried out by varying the catalyst loading, solvent, and temperature. 3*H*-Indol-3-one **1a** was treated with 6 equiv. of MeCHO (**2a**) in the presence of L-proline at room temperature, and the resulting *Mannich* adduct **3a** was reduced with NaBH₄ 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). CH₂Cl₂ 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 naphthalen-2-yl indol-3-one **1h** provided the product in 81% yield and 98% ee (Table 2,

²) For similar studies, see [10].

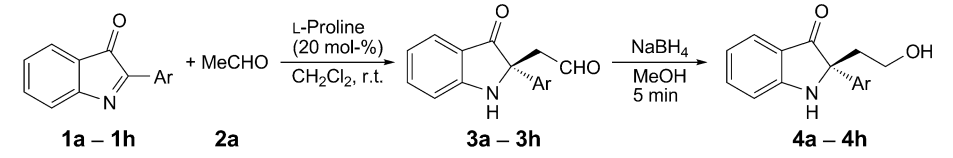
³) For achiral *Lewis* and *Brønsted* acid catalyzed versions, see [11].

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

Table 1. Screening of Catalyst Loading, Various Solvents, and Temperature^{a)}


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 ₂ Cl 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 ₂ Cl ₂	20	r.t.	0.75	71	98
10 ^{d)}	CH ₂ Cl 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 3H-Indol-3-ones^{a)}


Entry	Ar	1	Time [h]	4	Yield [%] ^{b)}	ee [%] ^{c)}
1	4-Me-C ₆ H ₄	1a	0.75	4a	71	98
2	4-Et-C ₆ H ₄	1b	0.33	4b	76	97
3	4-MeO-C ₆ H ₄	1c	0.5	4c	74	96
4	4-F-C ₆ H ₄	1d	1	4d	52	94
5	4-Cl-C ₆ H ₄	1e	1	4e	66	96
6	4-Br-C ₆ H 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 3H-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 3H-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)}

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-%, CH₂Cl₂, 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)-3H-indol-3-one (**1i**)^{a)}

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 3H-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-1H-indol-3-ones with excellent enantioselectivities. The reaction is applicable to 3H-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 3H-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 CD₃OD, δ in ppm, J in Hz. EI-MS (70 eV): GC/MS Shimadzu QP2010 (column Equity-5, length $\times$ i.d. 30 m $\times$ 0.25 mm, df 0.25 μ m, lot # 28089-U, Supelco); m/z .

General Procedure. Acetaldehyde (**2a**; 4 equiv.) was added to the mixture of 3H-indol-3-one **1** (1 equiv.) and L-proline (20 mol-%) in 1.0 ml of CH₂Cl₂ 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. NaBH₄ (2 equiv.) was added at 0°. After stirring for 5 min, the reaction was quenched with H₂O, and the mixture was extracted with AcOEt and washed with brine. The org. layer was dried (Na₂SO₄), filtered, and the solvent was

removed under reduced pressure. Purification of the crude product by column chromatography (CC) on SiO₂ afforded the corresponding product **4**.

(2S)-2-(2-Hydroxyethyl)-2-(4-methylphenyl)-2,3-dihydro-1H-indol-3-one (**4a**). Yellow gummy compound. Yield: 74%. $[\alpha]_D^{25} = +368$ ($c = 1.0$, CH₂Cl₂; 98% ee). IR: 3318, 3017, 2924, 2858, 2406, 1674, 1619, 1470, 1327, 1287, 1215, 1042, 1000, 894, 756. ¹H-NMR (400 MHz; CD₃OD): 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). ¹³C-NMR (101 MHz, CD₃OD): 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-(2-Hydroxyethyl)-2-(2-hydroxyethyl)-1,2-dihydro-3H-indol-3-one (**4b**). Yellow gummy compound. Yield: 76%. $[\alpha]_D^{25} = +265$ ($c = 1.0$, CH₂Cl₂; 97% ee). IR: 3361, 3012, 2964, 2928, 2876, 1687, 1617, 1488, 1325, 1151, 1098, 1042, 894, 755. ¹H-NMR (300 MHz; CD₃OD): 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). ¹³C-NMR (75 MHz, CD₃OD): 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-1H-indol-3-one (**4c**). Yellow gummy compound. Yield: 74%. $[\alpha]_D^{25} = +293$ ($c = 1.0$, CH₂Cl₂; 96% ee). IR: 3371, 2928, 1690, 1615, 1505, 1324, 1250, 1094, 1036, 756. ¹H-NMR (300 MHz; CD₃OD): 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). ¹³C-NMR (75 MHz, CD₃OD): 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-1H-indol-3-one (**4d**). Yellow gummy compound. Yield: 52%. $[\alpha]_D^{25} = +251$ ($c = 1.0$, CH₂Cl₂; 94% ee). IR: 3370, 2927, 1693, 1617, 1502, 1382, 1325, 1229, 1158, 1091, 1041, 837, 756. ¹H-NMR (300 MHz; CD₃OD): 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). ¹³C-NMR (75 MHz, CD₃OD): 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-1H-indol-3-one (**4e**). Yellow gummy compound. Yield: 66%. $[\alpha]_D^{25} = +234$ ($c = 1.0$, CH₂Cl₂; 96% ee). IR: 3346, 2921, 2851, 2320, 2081, 1904, 1790, 1677, 1616, 1582, 1465, 1386, 1324, 1290, 1152, 1092, 1009, 821, 750. ¹H-NMR (300 MHz; CD₃OD): 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). ¹³C-NMR (75 MHz, CD₃OD): 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-1H-indol-3-one (**4f**). Yellow gummy compound. Yield: 51%. $[\alpha]_D^{25} = +222$ ($c = 1.0$, CH₂Cl₂; 98% ee). IR: 3331, 3018, 2923, 2856, 1677, 1619, 1583, 1471, 1215, 1007, 756. ¹H-NMR (300 MHz; CD₃OD): 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). ¹³C-NMR (75 MHz, CD₃OD): 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-1H-indol-3-one (**4g**). Yellow gummy compound. Yield: 48%. ¹H-NMR (400 MHz, CD₃OD): 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); 2.26–2.18 (*m*, 1 H). ¹³C-NMR (101 MHz, CD₃OD): 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-1H-indol-3-one (**4h**). Yellow gummy compound. Yield: 81%. $[\alpha]_D^{25} = +223$ ($c = 1.0$, CH₂Cl₂; 98% ee). IR: 3366, 3057, 3013, 2925, 1687, 1617, 1487, 1325, 1215, 1152, 1040, 754. ¹H-NMR (400 MHz; CD₃OD): 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). ¹³C-NMR (101 MHz, CD₃OD): 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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. Fujii, *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. Córdova, 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. García 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