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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of 2-(α-hydroxyalkyl)benzimidazoles

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Abstract

Lithiated oxazolo[3,4-*a*]benzimidazole **4** reacted with various alkyl halides to give oxazolo[3,4-*a*]benzimidazoles **5a**–**d** in good yields as single diastereoisomers. (*R*)-Benzimidazol-2-yl carbinols **6a**–**d** were obtained upon hydrolysis under acidic conditions of 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole derivatives.

1. Introduction

2-(α-Hydroxybenzyl)benzimidazoles and related 2-(α-hydroxyalkyl)benzimidazoles are compounds with high biological potential, as shown by the numerous reports on their various physiological actions: respiratory, analeptic, analgesic, spasmolytic, antiinflammatory and antihypertensive.[1a–d] QSAR studies and biological tests demonstrated that, of the two optical isomers of 2-(α-hydroxybenzyl)benzimidazole derivatives, the (*R*)-enantiomer is more active and selective than the (*S*)-enantiomer.[2] Previous synthetic approaches to 2-(α-hydroxybenzyl)benzimidazoles have involved lithiation of an N-protected benzimidazole, followed by the electrophilic attack of a carbonyl compound[3a–c] or direct reaction of a benzimidazole with a ketone,[1d] these approaches provide the products as racemic mixtures.

We now report the synthesis of enantiomerically pure 2-(α-hydroxyalkyl)benzimidazoles **6b**–**d** utilizing 1*H*,3*H*-oxazolo[3,4-*a*]benzimidazoles **5b**–**d** as key intermediates, themselves derived from chiral (*R* or *S*)-2-(α-hydroxyethyl)benzimidazole **3** obtained from *o*-phenylenediamine **1** and the appropriate enantiomer of lactic acid (*R* or *S*)-**2**.

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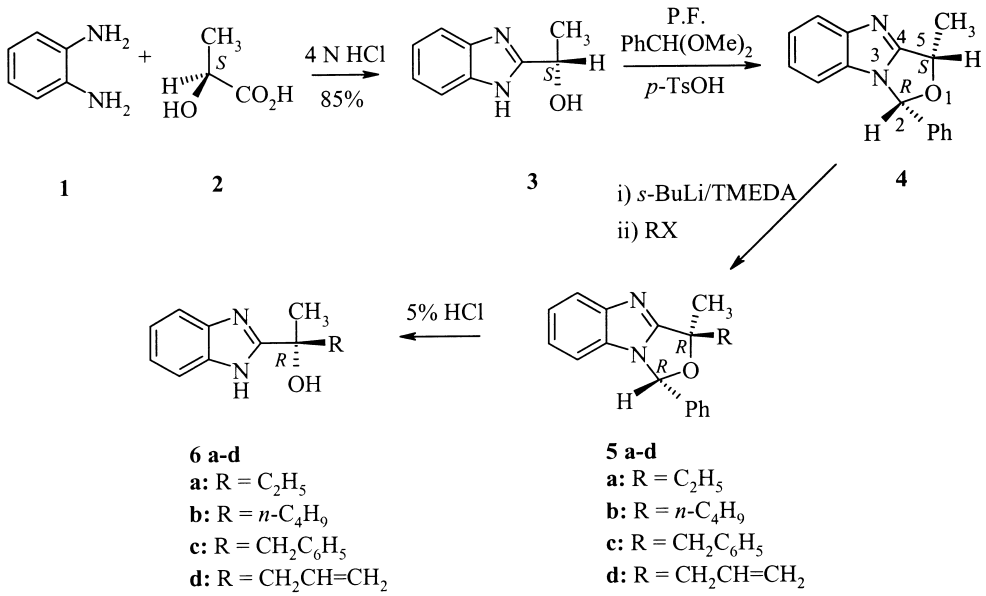
2. Results and discussion

*2.1. Synthesis of (1*R,*3*R*)-3-alkyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazoles and 2-(α-hydroxyalkyl)benzimidazoles*

We previously obtained excellent diastereoselectivity in the synthesis of 5-ethyl-5-methyl-1*H*,3*H*-oxazolo[3,4-*a*]benzimidazole **5a** by the route shown in Scheme 1.[4] Condensation of **3** (obtained from *o*-phenylenediamine **1** with (*S*)-lactic acid **2**) with benzaldehyde dimethyl acetal in refluxing perfluorocarbon fluid using catalytic *p*-toluenesulfonic acid, following our previous work,[4] yielded 50% of compound **4** as a single diastereoisomer.

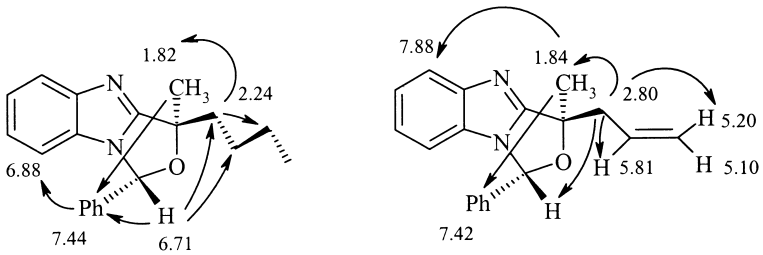


Scheme 1.

As before,[4] lithiation of compound **4** with *s*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), followed by quenching with ethyl bromide gave compound **5a** as a single diastereoisomer and novel compounds **5b**–**d** were obtained similarly in yields of 78–80%. Thus this lithiation at the 5-C of the oxazole ring proceeded by the attack of the electrophile with retention of configuration (Scheme 1). NOEDIF measurements together with earlier X-ray findings for compounds **4** and **5a**[4] prove that the newly formed chiral center has a (*R*)-configuration, as is further discussed below.

The analysis of the ^{1}H-NMR and GC–MS spectra of the crude reaction mixtures of products **5a**–**d** showed that the isomers of **5a**–**d** with an inverted configuration at C-5 were formed in less than 5%, and substitution in position 2 does not occur. However, the regioselectivity of the method does not prove a higher thermodynamic acidity of the proton attached to 5-C, as steric effects may be involved. The stereoselectivity is strongly influenced by the molarity of the reaction mixture: when the concentration is higher than 8×10^{-3} M, the ratio between the two diastereomers increases up to 1:1 for a concentration of 2×10^{-2} M.

The structures assigned to compounds **5a**–**d** were confirmed by ^{1}H- and ^{13}C-NMR. All compounds present signals characteristic for the 5-methyl group: a singlet in the ^{1}H-NMR spectra at about 1.80–1.90 ppm, and a signal at 25–26 ppm in the ^{13}C-NMR spectra, the latter was unequivocally assigned to



5b **5d**

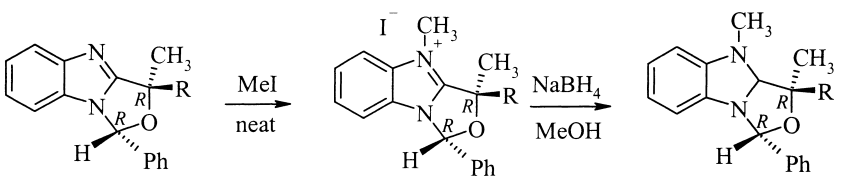
Fig. 1. Results of NOE experiments for compounds **5b** and **5d**

a methyl group by 'attached proton test' experiments. The ^{1}H-NMR spectra of compounds **5a–d** all feature the characteristic benzimidazole coupling pattern: *d–t–t–d* with 8.10–8.40 Hz coupling constants (*ortho* coupling), corresponding to four adjacent aromatic protons (exceptionally for compound **5c** the aromatic signals of the benzyl group overlap those of benzimidazole). In the ^{13}C-NMR spectra, the six benzimidazole ring signals are also well defined, at about 160, 149, 135, 123, 122, 120 and 110 ppm. The chemical shifts of the hydrogen (5.70–6.70 ppm, singlet) and carbon (88 ppm) in the 2-position of the oxazole ring are deshielded, due to the presence of vicinal heteroatoms.

The results of NOEDIF experiments for compounds **5b** and **5d** are depicted in Fig. 1. In compound **5b**, irradiating the 2-H induced positive NOE's at the signals characteristic for the 5-butyl group. Interestingly, there is a higher positive NOE on the β-CH_2 of the *n*-butyl group than on the α-CH_2, which may suggest that the molecule adopts a specific conformation in solution. Irradiating the signal characteristic for the phenyl group caused a positive NOE to be observed at the 5-CH_3 hydrogen atoms. In compound **5d**, irradiation of the allylic methylene produced a positive NOE at the hydrogen in position 2. In agreement with this, irradiation of the 5-CH_3 protons produced a positive NOE on the phenyl ring protons.

Compounds **5a–d** were hydrolyzed under mild acidic conditions (Et_2O, 5% HCl) to give enantiomerically pure 2-(α-hydroxyalkyl)-benzimidazoles **6a–d**. The enantiomeric purity was determined by measuring the rotation angles of the polarized light: α_D values for compounds **5a–d** range between 66 and 94, while for compounds **6a–d** are found between 16.3 and 89.1.

1*H*,3*H*-Oxazolo[3,4-*a*]benzimidazole derivatives **5b–d** were converted to the benzimidazolium iodides **7b–d**, which were reduced, in the presence of sodium borohydride, to compounds **8b–d** (Scheme 2). Surprisingly, the hydrolysis of compounds **8b–d** under mild acidic conditions as described by Mukaiyama for the cleavage of similar imidazole derivatives[5a,b] did not afford the expected α-hydroxy aldehydes, but decomposition products, perhaps due to the extended conjugation of the unshared pair of electrons of the nitrogen atom in position 3 with the fused benzene ring.



5 b-d
b: R = *n*-C_4H_9
c: R = $CH_2C_6H_5$
d: R = $CH_2CH{=}CH_2$

7 b-d
b: R = *n*-C_4H_9
c: R = $CH_2C_6H_5$
d: R = $CH_2CH{=}CH_2$

8 b-d
b: R = *n*-C_4H_9
c: R = $CH_2C_6H_5$
d: R = $CH_2CH{=}CH_2$

Scheme 2.

3. Conclusions

In the present work the yield of compound **5a** was significantly improved compared to that previously reported.[4] 1*H*,3*H*-Oxazolo[3,4-*a*]benzimidazoles **5a**–**d** were converted into 2-(α-hydroxyalkyl)-benzimidazoles **6a**–**d** in excellent yields, thus providing an efficient approach to stereoselective synthesis of 2-(α-hydroxyalkyl)benzimidazoles as pure (*R*)-enantiomers.

4. Experimental

*4.1. General procedure for the synthesis of compounds **5a**–**d***

A solution of 5-methyl-2-phenyl-oxazolo[3,4-*a*]benzimidazole **4** (1 equiv.) in THF at −78°C under an argon atmosphere was treated with *s*-BuLi (1.1 equiv., 1.3 M in cyclohexane) and TMEDA (1 equiv.), with stirring. The resulting suspension was kept at −78°C for 2 h, when the appropriate electrophile (alkyl halide) (1 equiv.) was added. The reaction mixture was stirred at −78°C for 2 h, and then at room temperature overnight. The reaction was quenched with saturated NH_4Cl, extracted with diethyl ether, and the organic layer dried (Na_2SO_4). The solvent was removed under vacuum to give the product as a yellow oil. The crude product was purified by column chromatography on silica gel using a 1:2 mixture of hexane:diethyl ether as eluent.

*4.1.1. (1*R,*3*R*)-3-Ethyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**5a**)*[4]

Yield 85%, m.p. 122–123°C (lit.[4] 122–124°C); $[\alpha]_D$=103.0.

*4.1.2. (1*R,*3*R*)-3-Butyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**5b**)*

Yield 80%, m.p. 120–121°C; $[\alpha]_D$=78.4 at 25°C (c=0.01 g/ml, chloroform); δ_H ($CDCl_3$): 7.78 (d, *J*=8.1 Hz, 1H), 7.42 (s, 5H), 7.23 (t, *J*=7.2 Hz, 1H), 7.08 (t, *J*=7.5 Hz, 1H), 6.85 (d, *J*=7.9 Hz, 1H), 6.70 (s, 1H), 2.07–2.02 (m, 2H), 1.83 (s, 3H), 1.59–1.57 (m, 1H), 1.37–1.22 (m, 3H), 0.88 (t, *J*=6.0 Hz, 3H); δ_C ($CDCl_3$): 161.5, 149.2, 136.1, 130.3, 130.0, 129.0, 127.1, 122.4, 122.4, 120.1, 110.0, 88.4, 82.2, 39.9, 26.0, 25.9, 22.7, 13.8. Anal. calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.08; H, 7.36; N, 9.16.

*4.1.3. (1*R,*3*R*)-3-Benzyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**5c**)*

Yield 78%, oil; $[\alpha]_D$=94.1 at 25°C (c=0.01 g/ml, chloroform); δ_H ($CDCl_3$): 7.78 (d, *J*=8.4 Hz, 1H), 7.39–6.98 (m, 12H), 6.64 (d, *J*=8.1 Hz, 1H), 5.74 (s, 1H), 3.44 (d, *J*=13.8 Hz, 1H), 3.25 (d, *J*=13.8 Hz, 1H), 1.91 (s, 3H); δ_C ($CDCl_3$): 160.5, 149.1, 135.6, 135.4, 130.2, 130.1, 129.8, 128.8, 127.9, 127.6, 127.0, 126.8, 122.2, 120.0, 109.7, 88.4, 82.3, 46.1, 26.3. HRMS (POS FAB NBA) m/e calcd for $C_{23}H_{20}N_2O+H^+$: 341.1653. Found: 341.1659 (M+1).

*4.1.4. (1*R,*3*R*)-3-Allyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**5d**)*

Yield 79%, oil; $[\alpha]_D$=66.7 at 25°C (c=0.01 g/ml, chloroform); δ_H ($CDCl_3$): 7.76 (d, *J*=8.4 Hz, 1H), 7.42 (m, 5H), 7.22 (t, *J*=7.4 Hz, 1H), 7.07 (t, *J*=7.4 Hz, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 6.69 (s, 1H), 5.87–5.75 (m, 1H), 5.20 (d, *J*=17.0 Hz, 1H), 5.11 (d, *J*=10.2 Hz, 1H), 2.81–2.72 (m, 2H), 1.83 (s, 3H); δ_C ($CDCl_3$): 161.0, 149.3, 135.9, 131.8, 130.4, 130.1, 129.0, 127.1, 122.5, 122.4, 120.2, 119.9, 110.0, 88.5, 81.6, 44.2, 25.7. Anal. calcd for $C_{19}H_{18}N_2O$: H, 6.25; N, 9.65. Found: H, 6.50; N, 9.88.

4.2. General procedure for the synthesis of 2-(α-hydroxyalkyl)benzimidazoles **6a–d**

A solution of compound **5** (4 mmol) in ether was treated with an excess of 5% HCl and the reaction mixture stirred for 2 days at room temperature. The mixture was extracted with chloroform (2×100 ml), the aqueous layer was neutralized with 5% $NaHCO_3$ aqueous solution and extracted with chloroform (2×50 ml). This second organic layer was dried (Na_2SO_4) and evaporated under vacuum to give a white solid.

4.2.1. (2R)-2-(1H-Benzimidazo-2-yl)-1-butan-2-ol (**6a**)

Yield 78%, m.p. 170–172°C; $[\alpha]_D$=16.3 at 25°C (c=0.01 g/ml, methanol) δ_H (DMSO-d_6): 7.49–7.47 (m, 2H), 7.12–7.09 (m, 2H), 5.44 (s, 1H), 3.37 (br s, 1H), 1.88–1.83 (m, 2H), 1.54 (s, 3H), 0.76 (t, *J*=7.2 Hz, 3H); δ_C (DMSO-d_6): 160.5, 125.6, 123.0, 121.1, 121.0, 120.9, 112.8, 71.6, 35.2, 27.8, 8.3. Anal. calcd for $C_{11}H_{14}N_2O$: N, 14.72. Found: N, 14.82. HRMS (POS FAB NBA) m/e calcd for $C_{11}H_{14}N_2O$ 190.1106. Found: 190.1106 (M).

4.2.2. (2R)-2-(1H-Benzimidazo-2-yl)-1-hexan-2-ol (**6b**)

Yield 80%, m.p. 158–160°C; $[\alpha]_D$=22.8 at 25°C (c=0.01 g/ml, methanol); δ_H (DMSO-d_6): 12.07 (br s, 1H), 7.48 (s, 2H), 7.12–7.09 (m, 2H), 5.45 (s, 1H), 1.91–1.74 (m, 2H), 1.56 (s, 3H), 1.40–1.00 (m, 4H), 0.80 (t, *J*=6.9 Hz, 3H); δ_C (DMSO-d_6): 160.6, 120.8, 114.0, 112.9, 71.2, 42.3, 28.1, 25.6, 22.3, 13.8 (the benzimidazole signals are not always observable). Anal. calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.34; H, 8.49; N, 12.92.

4.2.3. (2R)-2-(1H-Benzimidazo-2-yl)-1-phenylpropan-2-ol (**6c**)

Yield 71%, m.p. 207–208°C; $[\alpha]_D$=80.4 at 25°C (c=0.01 g/ml, methanol); δ_H (DMSO-d_6): 12.07 (br s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.14–7.05 (m, 7H), 5.71 (s, 1H), 3.19 (q, *J*=13.2 Hz, 2H), 1.54 (s, 3H); δ_C (DMSO-d_6): 160.5, 143.2, 137.4, 134.1, 130.4, 127.6, 126.1, 121.5, 120.9, 118.4, 111.4, 71.9, 48.1, 27.9. Anal. calcd for $C_{16}H_{16}N_2O$: N, 11.10. Found: N, 11.03. HRMS (POS FAB NBA) m/e calcd for $C_{16}H_{16}N_2O$ 252.1262. Found: 252.1259 (M).

4.2.4. (2R)-2-(1H-Benzimidazo-2-yl)-4-penten-2-ol (**6d**)

Yield 60%, m.p. 165–167°C; $[\alpha]_D$=89.1 at 25°C (c=0.01 g/ml, methanol); δ_H (DMSO-d_6): 12.13 (br s, 1H), 7.56–7.53 (m, 1H), 7.44–7.41 (m, 1H), 7.15–7.07 (m, 2H), 5.82–5.71 (m, 1H), 5.63 (s, 1H), 5.03–4.96 (m, 2H). 2.62 (d, *J*=6.9 Hz, 2H), 1.55 (s, 3H); δ_C (DMSO-d_6): 160.3, 143.1, 134.2, 134.2, 121.4, 120.8, 118.4, 117.6, 111.3, 71.1, 46.8, 27.6. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.89; H, 7.00; N, 13.90.

4.3. General procedure for the synthesis of compounds **7b–d**

A solution of (1*R*,3*R*)-3-alkyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole **5b–d** (1 equiv.) was stirred into an excess of MeI (10 equiv.), until no more starting material was observed (by GC). The excess MeI was evaporated under vacuum to give a yellow oil.

4.3.1. (1R,3R)-3-Butyl-3,4-dimethyl-1-phenyl-3H-[1,3]oxazolo[3,4-a]benzimidazol-4-ium iodide (**7b**)

Yield 93%, oil; $[\alpha]_D$=12.0 at 25°C (c=0.01 g/ml, chloroform), mixture of diastereomers A:B=1:1.5; δ_H ($CDCl_3$): 8.00–7.93 (m, 2H, A+B), 7.75–7.37 (m, 16H, A+B), 7.09 (d, *J*=8.4 Hz, 1H, A), 7.01 (d, *J*=8.4 Hz, 1H, B), 4.32 (s, 6H, A+B), 2.45–2.02 (m, 10H, A+B), 1.70–1.61 (m, 2H, A+B), 1.48–1.23 (m,

6H, A+B), 0.95–0.90 (m, 6H, A+B); δ_C ($CDCl_3$): 156.2 (A), 156.0 (B), 137.4 (B), 137.3 (A), 131.8 (A), 131.8 (B), 131.4 (A), 131.4 (B), 129.3 (A), 129.1 (B), 129.1 (A), 128.6 (B), 127.8 (B), 127.8 (A), 127.1 (B), 127.0 (A), 126.3 (A), 125.8 (B), 114.2 (B), 114.1 (A), 113.1 (A), 113.0 (B), 91.3 (B), 90.7 (A), 84.5 (B), 84.4 (A), 37.8 (B), 37.3(A), 33.8 (B), 33.2 (A), 25.9 (A), 25.5 (B), 24.1 (A), 24.1 (A), 22.1 (B), 22.0 (A), 13.6 (B), 13.5 (A) (the benzimidazole signals are not always observable). HRMS (POS FAB NBA) m/e calcd for $C_{21}H_{25}N_2O^+$ 321.1967. Found: 321.1967 ($M-I^-$).

*4.3.2. (1*R,*3*R*)-3-Benzyl-3,4-dimethyl-1-phenyl-3*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazol-4-ium iodide (**7c**)*

Yield 96%, oil; $[\alpha]_D$=27.8 at 25°C (c=0.01 g/ml, chloroform), mixture of diastereomers A:B=1:2; δ_H ($CDCl_3$): 8.11 (d, *J*=7.8 Hz, 1H, A), 7.87 (d, *J*=8.7 Hz, 1H, A), 7.84 (d, *J*=8.7 Hz, 1H, B), 7.63 (d, *J*=6.9 Hz, 1H, B), 7.59–7.00 (m, 12H, A+B), 6.91 (d, *J*=8.4 Hz, 1H, B), 6.84 (d, *J*=8.3 Hz, 1H, A), 4.38 (s, 3H, A), 4.00 (s, 3H, B), 3.69 (s, 2H, B), 3.61 (s, 2H, A), 2.17 (s, 3H, B), 2.14 (s, 3H, A); δ_C ($CDCl_3$): 155.7 (A), 155.2 (B), 137.3 (A), 137.2 (B), 133.3 (A), 133.1 (B), 131.6 (B), 131.5 (A), 131.5 (B), 131.3 (A), 130.2 (A), 130.2 (B), 129.2 (B), 128.9 (A), 128.8 (B), 128.6 (A), 128.0 (A), 128.0 (B), 127.9 (A), 127.9 (B), 127.5 (A), 127.4 (A), 127.2 (B), 127.1 (B), 126.3 (A), 125.8 (B), 116.1 (A), 114.1 (B), 113.1 (A), 112.9 (B), 91.4 (B), 91.1 (A), 85.1 (2C, A+B), 44.5 (B), 44.2 (A), 34.7 (A), 34.0 (B), 24.8 (A), 24.1 (B). Anal. calcd for $C_{24}H_{23}N_2OI$: N, 5.81. Found: N, 5.42. HRMS (POS FAB NBA) m/e calcd. for $C_{24}H_{23}N_2O^+$ 355.1810. Found: 355.1810 ($M-I^-$).

*4.3.3. (1*R,*3*R*)-3-Allyl-3,4-dimethyl-1-phenyl-3*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazol-4-ium iodide (**7d**)*

Yield 96%, oil; $[\alpha]_D$=7.1 at 25°C (c=0.01 g/ml, chloroform), mixture of diastereoisomers A:B=3:1; δ_H ($CDCl_3$): 7.90 (d, 1H, *J*=8.4 Hz, A), 7.89 (d, 1H, *J*=11.0 Hz, B), 7.74 (d, 1H, *J*=6.17 Hz, A), 7.68 (d, 1H, *J*=6.87 Hz, B), 7.62–7.35 (m, 7H, A+B), 7.06 (d, *J*=8.4 Hz, 1H, A), 7.00 (d, *J*=8.4 Hz, 1H, B), 6.00–5.89 (m, 1H, A+B), 5.45–5.38 (m, 1H, A+B), 5.31–5.25 (m, 1H, A+B), 4.31 (s, 3H, A), 4.27 (s, 3H, B), 3.25–3.06 (m, 2H, A+B), 2.14 (s, 3H, A), 2.12 (s, 3H, B); δ_C ($CDCl_3$): 155.4 (A), 155.4 (B), 137.4 (A+B), 131.7 (A), 131.4 (A+B), 131.2 (B), 129.9 (B), 129.5 (A), 129.3 (B), 129.2 (A), 128.7 (B), 127.9 (2C, A+B), 127.1 (A), 127.1 (B), 125.9 (A), 122.4(A), 121.4 (B), 114.1 (A), 114.0 (B), 113.1 (B), 113.0 (A), 91.4 (A), 90.8 (B), 84.6 (B), 84.4 (A), 42.7 (A), 42.0 (B), 34.5 (A), 34.2 (B), 24.2 (B), 24.1 (A). HRMS (POS FAB NBA) m/e calcd for $C_{20}H_{21}N_2O^+$ 305.1653. Found: 305.1653 ($M-I^-$).

*4.4. General procedure for the synthesis of compounds **8b–d***

A solution of (1*R*,3*R*)-3-alkyl-3-methyl-1-phenyl-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole **5b–d** (1 equiv.) was stirred in an excess of MeI (10 equiv.), until no more starting material was observed (by GC). The excess MeI was evaporated under vacuum and the resulting yellow oil was dissolved in 20 ml of MeOH at 0°C. To the stirred solution $NaBH_4$ (10 equiv.) was added portionwise, and the reaction mixture was refluxed for 18 h. The solvent was evaporated under vacuum, and the residue dissolved in methylene chloride (50 ml). The organic layer was washed with water (2×30 ml), dried (Na_2SO_4), and the solvent evaporated. Purification by flash chromatography (silica gel/hexane:ether=1:2) gave the product as a yellow oil.

*4.4.1. (1*R,*3*R*)-3-Butyl-3,4-dimethyl-1-phenyl-3a,4-dihydro-3*H*-[1,3]oxazolo[3,4-a]benzimidazole (**8b**)*

Yield 84%, oil; $[\alpha]_D$=6.02 at 25°C (c=0.01 g/ml, chloroform), mixture of diastereoisomers A:B=1:1, δ_H ($CDCl_3$): 7.55 (d, *J*=6.9 Hz, 2H, A+B), 7.40–7.30 (m, 3H, A+B), 6.78 (t, *J*=6.0 Hz, 1H, A), 6.75

(t, *J*=6.0 Hz, 1H, B), 6.52 (t, *J*=6.0 Hz, 1H, A), 6.50 (t, *J*=6.0 Hz, 1H, B), 6.39–6.29 (m, 2H), 5.55 (s, 1H, A), 5.49 (s, 1H, B), 4.91 (s, 1H, A), 4.86 (s, 1H, B), 2.83 (s, 3H, A+B), 2.76–1.17 (m, 9H, A+B), 0.95–0.84 (m, 3H, A+B); δ_C ($CDCl_3$): 145.7 (B), 145.7 (A), 140.8 (B), 140.6 (A), 128.7 (A), 128.6 (B), 128.4 (A), 128.3 (B), 127.1 (A), 127.0 (B), 122.3 (B), 122.0 (A), 118.2 (A), 118.0 (B), 110.9 (B), 110.2 (A), 105.7 (A), 105.2 (B), 95.1 (A), 94.8 (B), 94.7 (A), 93.0 (B), 85.0 (A), 84.4 (B), 39.7 (1C, A+B), 34.8 (A), 34.5 (B), 31.5 (A), 31.2 (B), 25.9 (A), 25.0 (B), 23.3 (A), 23.2 (B), 18.1 (1C, A+B), 14.0 (A), 13.9 (B). Anal. calcd for $C_{21}H_{26}N_2O$: N, 8.69. Found: N, 8.55.

*4.4.2. (1*R,*3*R*)-3-Benzyl-3,4-dimethyl-1-phenyl-3a,4-dihydro-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**8c**)*

Yield 88%, oil, mixture of diastereomers A:B=5:1; $[\alpha]_D$=118.5 at 25°C (c=0.01 g/ml, chloroform); δ_H ($CDCl_3$): 7.87 (d, *J*=6.9 Hz, 1H, A), 7.64–7.15 (m, 9H, A), 7.64–7.15 (m, 10H, B), 6.80 (t, *J*=6.0 Hz, 1H, A), 6.78 (t, *J*=6.0 Hz, 1H, B), 6.57 (t, *J*=6.0 Hz, 1H, A), 6.54 (t, *J*=6.0 Hz, 1H, B), 6.42 (t, *J*=8.7 Hz, 2H, A+B), 5.83 (s, 1H, A), 5.56 (s, 1H, B), 5.04 (s, 1H, A), 5.00 (s, 1H, B), 3.00 (d, *J*=14.4 Hz, 1H, B), 2.94, (d, *J*=19.2 Hz, 1H, A), 2.94 (s, 3H, A+B), 2.61 (d, *J*=19.2 Hz, 1H, A), 2.55 (d, *J*=14.4 Hz, 1H, B), 1.27 (s, 3H, A+B); δ_C ($CDCl_3$): 145.6 (2C, A+B), 140.7 (1C, A+B), 140.5 (1C, A+B), 137.1 (A), 139.4 (B), 130.8 (B), 130.5 (A), 128.9 (B), 128.8 (A), 128.5 (A), 128.4 (B), 128.1 (B), 127.9 (A), 127.3 (B), 127.0 (A), 126.7 (B), 126.2 (A), 122.4 (B), 122.2 (A), 118.4 (A), 118.2 (B), 110.8 (B), 110.3 (A), 105.7 (A), 105.7 (B), 95.1 (B), 95.0 (A), 94.9 (A), 91.6 (B), 84.9 (B), 84.3 (A), 46.0 (B), 37.4 (A), 35.1 (A), 31.6 (B), 23.3 (A), 22.6 (B). Anal. calcd for $C_{24}H_{24}N_2O$: N, 7.86. Found: N, 5.42.

*4.4.3. (1*R,*3*R*)-3-Allyl-3,4-dimethyl-1-phenyl-3a,4-dihydro-3*H*-[1,3]oxazolo[3,4-*a*]benzimidazole (**8d**)*

Yield 85%, oil; $[\alpha]_D$=23.6 at 25°C (c=0.01 g/ml, chloroform), mixture of diastereomers A:B=2:1; δ_H ($CDCl_3$): 7.54 (d, *J*=7.8 Hz, 2H, A+B), 7.39–7.23 (m, 3H, A+B), 6.79–6.73 (m, 1H, A+B), 6.53 (d, *J*=7.5 Hz, 1H, A), 6.50 (d, *J*=7.5 Hz, 1H, B), 6.38–6.32 (m, 2H, A+B), 5.95–5.83 (m, 1H, A+B), 5.85 (s, 1H, A), 5.57 (s, 1H, B), 5.16–5.01 (m, 2H, A+B), 4.92 (s, 1H, A), 4.90 (s, 1H, B), 2.82 (s, 3H, A), 2.79 (s, 3H, B), 2.46–2.37 (m, 2H, A), 2.11–2.04 (m, 2H, B), 1.36 (s, 3H, A), 1.17 (s, 3H, B); δ_C ($CDCl_3$): 145.4 (1C, A+B), 140.5 (1C, A+B), 133.2 (B), 133.0 (A), 128.7 (A), 128.6 (B), 128.4 (A), 128.3 (B), 128.2 (B), 127.9 (A), 127.1 (B), 126.9 (A), 122.4 (B), 122.1 (A), 118.5 (B), 118.2 (A), 118.2 (A), 117.8 (B), 110.9 (B), 110.1 (A), 105.8 (B), 105.4 (A), 95.0 (A), 94.9 (B), 94.1 (A), 92.0 (B), 84.2 (B), 83.7 (A), 44.3 (A), 36.5 (B), 34.8 (B), 34.7 (A), 23.2 (A), 18.5 (B). Anal. calcd for $C_{20}H_{22}N_2O$: N, 9.14. Found: N, 8.73.

References

1. (a) Tamm I.; Eggers H. J.; Bablanian R.; Wagner A. F.; Folkers K. *Nature* **1969**, *223*, 785–788; (b) Fauran C.; Eberle J.; Le Cloarec A. Y.; Raynaud G.; Dorme N. *Chem. Abstr*. **1973**, *79*, 137156f; (c) Fauran C.; Turin M.; Raynaud G.; Sergant M. *Chem. Abstr*. **1976**, *84*, 135658x; (d) Jpn Kokai Tokkyo Koho JP 61,145,165 *Chem. Abstr*. **1987**, *106*, 18565e.
2. Kadin S. B.; Eggers H. J.; Tamm I. *Nature* **1964**, *201*, 639–640.
3. (a) Wagner A. F.; Folkers K. A. *Chem. Abstr*. **1968**, *68*, 68992j; (b) Tertov B. A.; Koblik A. V.; Avdyunina N. I. *Chem. Abstr*. **1972**, *76*, 34326v; (c) Atkinson R. S.; Tughan G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2787–2796.
4. Katritzky A. R.; Aslan D. C.; Leeming P.; Steel P. J. *Tetrahedron: Asymmetry* **1997**, *8(9)*, 1491–1500 and references cited therein.
5. (a) Mukaiyama T.; Sakito Y.; Asami M. *Chem. Lett*. **1978**, 1253–1256; (b) Mukaiyama T. *Tetrahedron* **1981**, *37*, 4111–4119.