

## SYNTHESIS OF OPTICALLY ACTIVE TETRAHYDRO-3-BENZAZEPINE-2-CARBOXYLIC ACID DERIVATIVES VIA THE RING EXPANSION REACTION OF ISOQUINOLINES AND ENZYMATIC RESOLUTION

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**Abstract** – The facial approach to 3-benzazepine-2-carboxylic acid derivatives (**1**) via the ring expansion reactions of 10b-hydroxymethyloxazoloisoquinolines (**3**) to 3-benzazepines (**2**) is described. Utilizing enzymatic resolution, the synthesis of (-)-(*S*)-*N*-Cbz-3-benzazepine-2-carboxylic acid (**1b**) was achieved.

2,3,4,5-Tetrahydro-1*H*-3-benzazepine derivatives have been of interest in synthesis<sup>1</sup> due to their pharmacological activities,<sup>2</sup> such as dopaminometric or antidopaminergic agents<sup>3</sup> and the inhibitory effect<sup>4</sup> of reverse transcriptase. In our laboratory, the synthesis of isoindolobenzazepine alkaloids, such as lennoxamine and chilenine, utilizing the ring expansion reaction of isoindoloisoquinoline to isoindolobenzazepine has been reported.<sup>5</sup> We attempted to apply this strategy to the synthesis of 2,3,4,5-tetrahydro-1*H*-3-benzazepine derivatives. In this paper, the facial synthesis of benzazepine derivatives, especially 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (**1**) ( $R^1, R^2, R^3 = H$ ),<sup>6,7</sup> which is used as a replacement for phenylalanine in the peptide,<sup>8</sup> via the ring-expansion reaction of 10b-hydroxymethyloxazoloisoquinolines (**3**) is described (Figure 1).

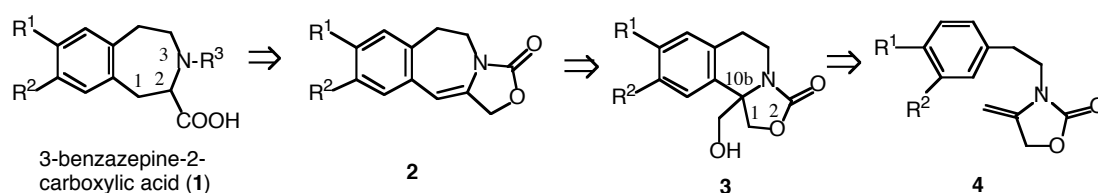
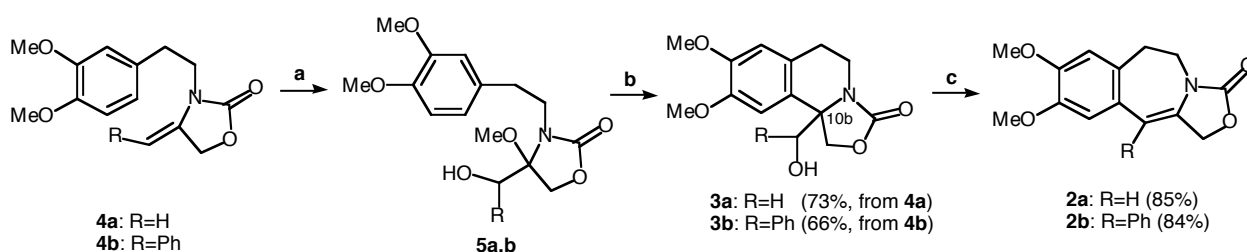


Figure 1

There are many reports involving the ring expansions of isoquinoline-rings to 3-benzazepine rings *via* azirizines.<sup>9</sup> In a similar method, the ring expansion of spirocyclic ammonium ylides for the synthesis of 3-benzazepines has been reported by Padwa *et al.*<sup>10</sup> In addition, ring expansions through the 1,2-aryl migrated reaction without the formation of azirizine have been reported.<sup>9</sup> However, only one such example of a ring expansion to form an acyliminium ion intermediate has been reported by ourselves.<sup>5</sup> At first, the synthesis of isoquinoline derivatives (**3**) as key compounds from alkylidenelactams (**4**)<sup>11</sup> *via* the acyliminium ion equivalents (**5**) was conducted according to our previous report.<sup>12</sup> The results are shown in Scheme 1.

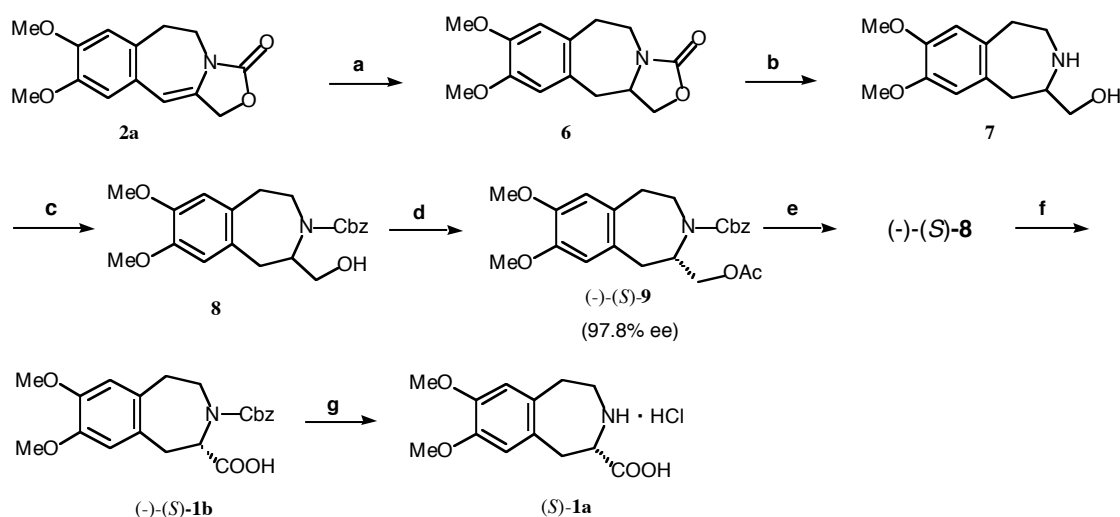


**Scheme 1** Reagents and conditions: (a) MCPBA (1.2 equiv.), MeOH, -50 °C to rt; (b)  $\text{BF}_3 \cdot \text{OEt}_2$  (2.1 equiv.),  $\text{CH}_2\text{Cl}_2$ , -40 to 0 °C; (c)  $\text{SO}_2\text{Cl}_2$  (3 equiv.),  $\text{Et}_3\text{N}$  (5 equiv.),  $\text{CHCl}_3/\text{Py}$  (4:1), -78 °C to rt.

The conversion of **4** into the acyliminium ion equivalent (**5**) through the oxidation<sup>13</sup> of the exocyclic enamide moiety with MCPBA was performed in quantitative yields, followed by cyclization<sup>14</sup> *via* an acyliminium ion in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  to afford **3**<sup>15</sup> in a satisfactory isolated yield. The obtained isoquinoline derivatives (**3**) in hand were then applied to the ring expansion<sup>5</sup> with  $\text{SO}_2\text{Cl}_2$  in the presence of  $\text{Et}_3\text{N}$  and pyridine in order to construct the 3-benzazepine ring system. When the ring expansion of **3a** was conducted with 3 equiv. of  $\text{SO}_2\text{Cl}_2$ , the reaction proceeded smoothly to give the corresponding seven-membered ring compound (**2a**) in a good yield (85%).<sup>16</sup> Furthermore, the ring expansion of **3b** (R = Ph) possessing the secondary hydroxy group at the 10b-position of the oxazoloisoquinoline ring progressed to 1-phenyl-3-benzazepine (**2b**) in 84% yield. After this efficient synthesis of 3-benzazepines (**2**), compound (**2a**) was used for the synthesis of tetrahydrobenzazepine-2-carboxylic acid (Scheme 2).

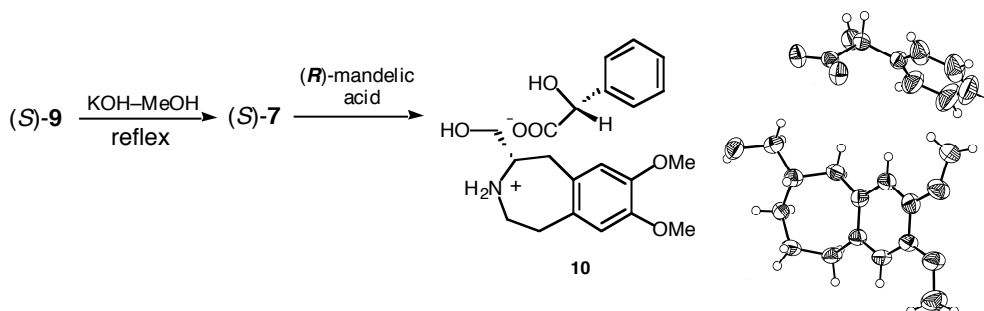
We initially attempted to convert **2a** into **6** or **7**, however, neither the catalytic reduction of enamide (**2a**) to **6** nor the hydrolysis of the carbamate moiety of **2a** occurred. Then, the reduction of **2a** utilizing  $\text{BF}_3 \cdot 2\text{AcOH}$ – $\text{Et}_3\text{SiH}$  system *via* an acyliminium ion intermediate was conducted to afford **6** in 94% yield. Saponification (10%  $\text{KOH}$ – $\text{MeOH}$ ) of **6** followed by protection of the amino moiety of **7** afforded **8** in 92% yield. Next, the asymmetric synthesis of **1** was attempted by enzyme-mediated chiral resolution utilizing lipase. To the best of our knowledge, there is no report for asymmetric synthesis of **1**. The lipase (Novozym 435®)-catalyzed acylation of alcohol (**8**) was performed with vinyl acetate as the acylating agent in THF at 20 °C. The *ca.* 50%-conversion was achieved within 30 min, and then the acylated

alcohol and the unreacted alcohol were separated by silica gel column to give (*S*)-(-)-**9** (97% ee) in 49% isolated yields.<sup>17</sup> However, in the gram-scales, their enantiomeric excess yields decreased to 92–94% ee. The low-temperature method<sup>18</sup> (at 0 °C for 45 min) in the gram-scale resolution of **8** succeeded in overcoming this disadvantage and the reproducible ee yields (96–97.8%) of (*S*)-**9** were obtained. The removal of the acetyl group on (*S*)-**9** using 0.05N NaOH<sup>19</sup> gave (*S*)-**8** in a good isolated yield.<sup>17</sup> On the other hand, the conversion of **7** to **1a** by Jones oxidation was carried out, but the isolation of amino acid (**1a**) was unsuccessful. Then, the oxidation of (*S*)-**8** was carried out according to Zao's method<sup>20</sup> to afford (*S*)-**1b**<sup>21</sup> in 92% yield. The subsequent hydrogenolysis of the Cbz-group of (*S*)-**1b** proceeded smoothly to afford (*S*)-**1a** as a rigid analogue of L-(*S*)-phenylalanine.<sup>22</sup>



**Scheme 2** Reagents and conditions: (a) Et<sub>3</sub>SiH (5 equiv.), BF<sub>3</sub>·2AcOH (1.2 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, rt, 94%; (b) KOH (10 equiv.), MeOH, reflux; (c) CbzCl (1.3 equiv.), NaHCO<sub>3</sub> (1.3 equiv.), THF–H<sub>2</sub>O (1:1), rt, 92% (from **6**); (d) Novozym 435®, CH<sub>2</sub>=CHOAc, THF, 0 °C, 46 %; (e) 0.05N NaOH, MeOH, 0 °C, 94%; (f) NaClO<sub>2</sub> (2 equiv.), 5% NaClO (cat.), TEMPO (cat.), MeCN, pH 6.86 buffer, 35 °C, 92%; (g) 5% Pd–C (cat.), H<sub>2</sub> (1 atm), MeOH, rt, then, 4N HCl, AcOEt, 88%.

The absolute configuration of (*S*)-**9** was determined by single-crystal X-Ray diffraction analysis. Figure 2 shows the crystal structure of the salt (**10**) consisting of (*R*)-mandelic acid and amino alcohol ((*S*)-**7**) obtained by saponification of (-)-**9** (Figure 2).<sup>23</sup>



**Figure 2** ORTEP drawing of salt (**10**)

In conclusion, the authors have established a new method for the synthesis of 3-benzazepine-2-carboxylic acid derivatives utilizing the ring-expansion of isoquinolines. Furthermore, the synthesis of (*S*)-**1b** was achieved. The investigations into their biological activities are now in progress.

## ACKNOWLEDGEMENTS

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## REFERENCES AND NOTES

1. For reviews, see: (a) T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931. (b) S. Kaspark, 'Advances in Heterocyclic Chemistry' Vol. 39, ed. by A. R. Katritzky, Academic Press, Inc., New York, 1986, p. 45.
2. J. Weinstock, J. P. Hieble, and J. W. Wilson, *Drugs Future*, 1985, **10**, 645.
3. For some recent examples, see: (a) C. N. Haile, G. Carey, G. B. Varty, and V. L. Coffin, *Eur. J. Pharmacol.*, 2000, **388**, 125. (b) M. R. Weed, W. L. Woolverton, and I. A. Paul, *Eur. J. Pharmacol.*, 1998, **361**, 129. (c) M.-Y. K. Brusniak, R. S. Pearlman, K. A. Neve, and R. E. Wilcox, *J. Med. Chem.*, 1996, **39**, 850. (d) H. Wikström, B. Andersson, T. Elebring, and S. Lagerkvist, *J. Med. Chem.*, 1992, **35**, 3984.
4. (a) L. Berek, I. B. Petri, E. Varga, J. Molnár, M. Kawase, S. Saito, and N. Motohashi, *Int. J. Antimicrob. Agents*, 2000, **14**, 221. (b) M. Kawase, S. Saito, and N. Motohashi, *Int. J. Antimicrob. Agents*, 2000, **14**, 193.
5. (a) Y. Koseki, S. Kusano, H. Sakata, and T. Nagasaka, *Tetrahedron Lett.*, 1999, **40**, 2169. (b) Y. Koseki, S. Katsura, S. Kusano, H. Sakata, H. Sato, Y. Monzen, and T. Nagasaka, *Heterocycles*, 2003, **59**, 527. (c) Y. Koseki, H. Sato, Y. Watanabe, and T. Nagasaka, *Org. Lett.*, 2002, **4**, 885.
6. (a) S. E. Gibson, J. O. Jones, R. McCague, M. J. Tozer, and N. J. Whitcombe, *Synlett*, 1999, 954. (b) S. E. Gibson, N. Guillo, R. J. Middleton, A. Thuilliez, and M. J. Tozer, *J. Chem. Soc., Perkin Trans. 1*, 1997, 447.
7. The other examples of carboxylic acid or aldehyde derivatives, see: (a) J. R. Fuchs and R. L. Funk, *Org. Lett.*, 2001, **3**, 3349. (b) M. Okada, T. Takahashi, M. Yokota, T. Kawasaki, and S. Nagaoka, Jpn. Kokai Tokkyo Koho JP 02,193,971, 1990 (*Chem. Abstr.*, 1990, **114**, 81626). (c) D. Ben-Ishai, I. Sataty, N. Peled, and R. Goldshare, *Tetrahedron*, 1987, **43**, 439. (d) H. Bieräugel, H.-P. Soetens, and U. K. Pandit, *Heterocycles*, 1977, **7**, 37. (e) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Am. Chem. Soc.*, 1968, **90**, 776. (f) K. Dimroth and H. Freyschlag, *Chem. Ber.*, 1956, **89**, 2602.
8. (a) S. E. Gibson, N. Guillo, J. O. Jones, I. M. Buck, S. B. Kalindjian, S. Roberts, and M. J. Tozer,

*Eur. J. Med. Chem.*, 2002, **37**, 379. (b) S. E. Gibson, N. Guillo, S. B. Kalindjian, and M. J. Tozer, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1289.

9. For reviews, see: Ref. 1a. For recent some references not included in the above review, see: Ref. 5b; and references cited therein.
10. A. Padwa, L. S. Beall, C. K. Eidell, and K. J. Worsencroft, *J. Org. Chem.*, 2001, **66**, 2414.
11. **4a,b** were prepared as follows. Compound (**4a**): Treatment of propargyl 2-(3,4-dimethoxyphenyl)ethylcarbamate with  $\text{LiN}(\text{TMS})_2$  (0.3 equiv.) in THF at 66 °C afforded **4a** in 90% yield. Compound (**4b**): Treatment of 3-phenylprop-2-ynyl 2-(3,4-dimethoxyphenyl)ethylcarbamate with  $\text{NaN}(\text{TMS})_2$  (0.3 equiv.) in the presence of 18-crown-6 (0.3 equiv.) in toluene at 60 °C afforded **4b** in 97% yield. And also, see: Y. Tamaru, M. Kimura, S. Tanaka, S. Kure, and Z. Yoshida, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 2838; and references cited therein.
12. Y. Koseki, S. Kusano, D. Ich, K. Yoshida, and T. Nagasaka, *Tetrahedron*, 2000, **56**, 8855.
13. For the first example of oxidation of ethylidenetetrahydro-1,3-oxazin-2-one with MCPBA, see: T. G. Back, O. E. Edwards, and G. A. MacAlpine, *Tetrahedron Lett.*, 1977, 2651.
14. For some examples of similar cyclization to oxazolo- or thiazoloisoquinolines, see: (a) I. Osante, M. I. Collado, E. Lete, and N. Sotomayor, *Eur. J. Org. Chem.*, 2001, 1267. (b) M. I. Collado, N. Sotomayor, M.-J. Villa, and E. Lete, *Tetrahedron Lett.*, 1996, **37**, 6193.
15. The synthesis of **3a** has been reported, see: M. Bois-Choussy, S. Cadet, M. D. Paolis, and J. Zhu, *Tetrahedron Lett.*, 2001, **42**, 4503.
16. The general procedure for the ring expansion reaction of isoquinolines (**3**) (preparation of **2a**): To the solution of **3a** (12.5 g, 44.8 mmol) in a mixed solvent (dist.  $\text{CHCl}_3$ /pyridine = 120 mL/30 mL) was added  $\text{Et}_3\text{N}$  (31 mL, 224 mmol) and then, added dropwise  $\text{SO}_2\text{Cl}_2$  (10.8 mL, 134 mmol) at -78 °C under Ar. The solution was allowed to warm to rt over 0.5 h followed by stirring overnight. The reaction mixture was quenched with sat. aq  $\text{NaHCO}_3$ , and the mixture was extracted with  $\text{CHCl}_3$  followed by a conventional work-up. The residue was chromatographed (silica gel, hexane–AcOEt = 10:1) to give **2a** (9.9 g) in 85% yield.
17. The ee values of (*S*)-**9** and (*S*)-**8** were determined by HPLC on a CHIRALCEL OJ–H, (0.46 cm × 25 cm, DAICEL CHEMICAL IND. LTD.), with hexane/EtOH (100:1 to 50:1 over 40 min) as eluent, respectively. **Compound (-)-(S)-9**: colorless oil;  $[\alpha]_{\text{D}}^{24}$  -52.2° (c 1.01,  $\text{CHCl}_3$ ) (97% ee); HRMS (EI) *m/z* calcd for  $\text{C}_{23}\text{H}_{27}\text{NO}_6$  ( $\text{M}^+$ ) 413.1838, found: 413.1820. **Compound (-)-(S)-8**: colorless crystals; mp 97–99 °C (from *t*-BuOMe);  $[\alpha]_{\text{D}}^{22}$  -53.8° (c 1.01,  $\text{CHCl}_3$ ) (98.5% ee); Anal. Calcd for  $\text{C}_{21}\text{H}_{25}\text{NO}_5$ : C, 67.90; H, 6.78; N, 3.77. Found: C, 67.79; H, 6.78; N, 3.70.
18. For an example of low-temperature method in the kinetic resolution, see: T. Sakai, T. Kishimoto, Y. Tanaka, T. Ema, and M. Uta, *Tetrahedron Lett.*, 1998, **39**, 7881.

19. N. Langlois and F. Rakotonradany, *Tetrahedron*, 2000, **56**, 2437.
20. M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, and P. J. Reider, *J. Org. Chem.*, 1999, **64**, 2564.
21. **Compound (-)-(S)-1b**: White paste,  $[\alpha]_D^{22} -29.5^\circ$  (c 1.32, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.80-3.40 (m, 5H), 3.82-3.84 (each s, 3H  $\times$  2, two rotamers), 4.25, 4.37 (each br d,  $J = 1.5$  Hz, 1H, two rotamers), 5.05-5.30 (m, 2H+1H, two rotamers), 6.56, 6.61, 6.64, 6.68 (each s, 1H  $\times$  2, two rotamers), 7.10-7.20 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, two rotamers)  $\delta$ : 34.7, 35.2, 36.1, 41.9, 42.4, 55.7, 55.9, 57.1, 57.5, 67.5, 67.7, 112.8, 112.9, 114.1, 114.4, 127.2, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 131.7, 136.2, 136.3, 146.8, 146.9, 147.5, 147.7, 155.8, 156.6, 175.6, 175.9; MS(ES)  $m/z$  408 (MNa<sup>+</sup>), 386 (MH<sup>+</sup>); HRMS (ES)  $m/z$  calcd for C<sub>21</sub>H<sub>24</sub>NO<sub>6</sub> (MH<sup>+</sup>) 386.1604, found 386.1601.
22. The analytical and spectral data of pure (S)-**1a** were not obtained because its insolubility in organic and aqueous solvents (e.g., CHCl<sub>3</sub>, THF, MeOH, toluene, H<sub>2</sub>O). To a suspension of the crude paste ((S)-**1a**) in AcOEt was added 4N HCl, and the solution was concentrated to give (S)-**1a**·HCl as a white solid. The spectral data for (S)-**1a**·HCl are as follows. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)  $\delta$ : 2.99 (m, 2H), 3.12 (m, 1H), 3.26 (m, 2H), 3.54 (m, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 4.06 (d,  $J = 8.2$  Hz, 1H), 6.80 (s, 1H), 6.86 (s, 1H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O)  $\delta$ : 31.38, 34.69, 45.49, 56.52, 56.58, 58.52, 113.9, 114.8, 129.4, 132.6, 147.4, 147.8, 171.5.
23. Crystal data of **10**: C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>7</sub>, MW 389.448, T 297 K, monoclinic, space group  $P2_1$ :  $a = 6.678$  (10) Å,  $b = 8.814$  (5) Å,  $\beta = 93.217$  (6) $^\circ$ ,  $c = 17.248$  (2) Å,  $V$  1013.6 (2) Å<sup>3</sup>,  $Z$  2,  $D_{\text{calc}}$  1.276 mg m<sup>-3</sup>,  $\rho$  range 2.60 to 27.18 $^\circ$ , prism 0.09 x 0.22 x 0.2 mm, Mo K $\alpha$  ( $K\alpha = 0.71073$  Å),  $\mu = 0.093$  mm<sup>-1</sup>, absorption correction: none, 2243 measured reflections, 2242 independent reflections ( $R_{\text{int}} = 0.024$ ), 1896 observed reflections [ $I > 2\sigma(I)$ ],  $R(\text{all})$  0.0483,  $R(\text{gt})$  0.0384,  $wR(\text{ref})$  0.1012,  $wR(\text{gt})$  0.0953,  $S(\text{ref})$  1.044, refinement on  $F^2$  (fullmatrix least squares refinement), 2242 reflections, 258 parameters,  $\sigma_{\text{max}} = 0.137\text{e}\text{\AA}^3$ ,  $\sigma_{\text{min}} = -0.163\text{e}\text{\AA}^3$ , all diagrams and calculations were performed using *maXus* crystallographic software package,<sup>24</sup> the refinement was performed using SHELX-97.<sup>25</sup>
24. a) S. Mackay, C. J. Gilmore, C. Edwards, N. Stewart, and K. Shankland, *maXus Computer Program for the Solution and Refinement of Crystal Structures*. Bruker Nonius, The Netherlands, MacScience, Japan and The University of Glasgow, 1999.
25. G. M. Sheldrick, *SHELXL-97*, Program for The Crystal Structure Refinement, University of Göttingen, Germany, 1997.