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A very short asymmetric synthesis of enantiomerically pure methyl substituted tetrahydro-3-benzazepines

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ABSTRACT

An efficient synthesis of both enantiomers of methyltetrahydro-3-benzazepines **10** and **15** has been elaborated following a very short reaction sequence. The two diastereomeric oxazolo[3]benzazepinones **6** and **7** were prepared by condensation of keto acid **4** with (*R*)-phenylglycinol **5**. Benzylation of **6** and **7** was controlled by the newly established N/O-acetalic stereogenic center leading to products **11** and **12**. Reduction of the diastereomeric pairs **6**, **7** and **11**, **12** with $LiAlH_4/AlCl_3$ (3:1) occurred under retention of configuration yielding tetrahydro-3-benzazepines **8** and **9** with de >98%, as well as **13** and **14** with complete diastereoselectivity. Hydrogenolytic cleavage of the N-substituent led to the enantiomerically pure 2-methyltetrahydro-3-benzazepines (*R*)-**10** and (*S*)-**10** and 1-benzyl-4-methyltetrahydro-3-benzazepines (*R*,*R*)-**15** and (*S*,*S*)-**15**. The relative and absolute configuration of the formed products were deduced from X-ray crystal structure analysis of the 3-benzazepine **14**·HCl still bearing the original stereochemical information in the N-substituent.

1. Introduction

Seven-membered nitrogen heterocycles, such as 3-benzazepines, are constituents of several compounds with interesting pharmacological properties.[1–3] Derivatives with the 3-benzazepine framework are well known for their agonistic and antagonistic activity at dopamine D_1[4,5] and dopamine D_3 receptors.[6] They also show neuroprotective effects by activation of D_1 receptors.[7] Very recently, 1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines have been described as selective 5-HT_{2C} receptor agonists, which can be used for the treatment of obesity.[8,9] Furthermore, 3-benzazepines are also active in animal models of various neurological disorders, for example, Parkinson's disease[10] and Alzheimer's disease.[11]

Recently, we have shown that racemic[12] and enantiomerically pure 1-substituted 3-benzazepines[13,14] **1** show moderate to high affinity to the phencyclidine (PCP) binding site of the NMDA receptor. The NMDA receptor, which is the best investigated subtype of the class of glutamate receptors, plays a crucial role in processes such as learning and memory. However, overactivation of the NMDA receptor results in neuronal damage due to uncontrolled opening of the NMDA associated Ca^{2+}-channel (excitotoxicity). Therefore, NMDA receptor antagonists are of great interest for the prevention of neuronal damage, for example, following ischemic conditions and traumatic brain injuries.[15,16]

In order to find novel potent antagonists for the NMDA receptor, we focused our attention on the tetrahydro-3-benzazepine system bearing various substituents in different ring positions. For this purpose, a general method for the preparation of enantiomerically pure tetrahydro-3-benzazepines is required allowing the flexible introduction of various substituents at different ring positions. Herein, we report on a very short and efficient synthesis of enantiomerically pure tetrahydro-3-benzazepines bearing one substituent at the 2 position or two substituents at the 1 and 4 positions (see compounds **2** and **3** in Fig. 1).

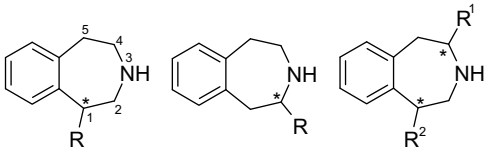

Figure 1. Lead compound **1** in comparison with new potential NMDA receptor antagonists **2** and **3**.

2. Results and discussion

2.1. Synthesis

The tricyclic oxazolo[3]benzazepinones **6** and **7** represent key compounds in the planned asymmetric synthesis. In analogy to

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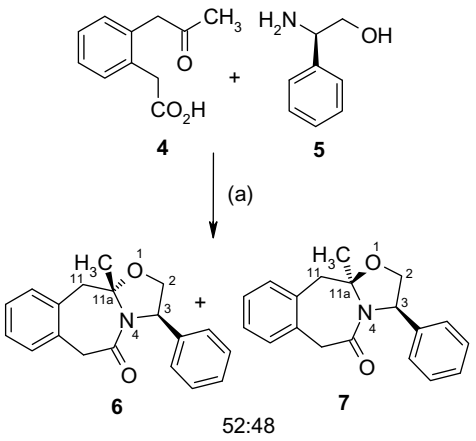
the procedure of Meyers,[17] the keto acid **4**[18,19] was heated at reflux with (*R*)-phenylglycinol **5** in toluene for 3 days to provide, in a single reaction step, the diastereomeric tricyclic lactams **6** and **7**, which were separated by flash chromatography (**6**: yield 41%; **7**: yield 31%) (Scheme 1). This transformation occurred without diastereoselectivity leading to a 52:48 mixture of the tricyclic lactams **6** and **7**. The ratio of the two diastereomers was determined by ^{1}H NMR spectroscopy of the crude reaction mixture (Fig. 2, spectrum e).



Scheme 1. Reagents and conditions: (a) toluene, reflux, 3 d, 72% (**6**:**7** = 52:48); yield of **6**: 41%, yield of **7** 31%.

The configuration at position 11a of the two diastereomers **6** and **7** was determined by NOE experiments. After irradiation at 4.93 ppm (3-H of **7**), the intensity of the singlet for the CH_3-moiety (1.55 ppm) increased indicating a *cis* arrangement of these groups. However, in the control experiment with diastereomer **6**, no such increase in intensity was observed after irradiation at 5.44 ppm (3-H of **6**) confirming the *trans*-configuration of 3-H and 11a-CH_3.

In order to obtain one of the two diastereomers **6** or **7** stereoselectively in high yield, the condensation of **4** and **5** was performed at lower temperatures. Stirring the reaction mixture in toluene for 3 days at room temperature (Fig. 2, spectrum a) and for 3 days at 50 °C (Fig. 2, spectrum b) did not result in formation of either **6** or **7** at all, but gave a side product (or intermediate) exhibiting a dd at 5.20 ppm. However, heating of the mixture at reflux, even for 2 h led to the production of both diastereomers **6** and **7** (Fig. 2, spectrum c). Although the conversion was as low as 10%, the ratio of **6** and **7** was 1:1. The same reaction mixture was heated at reflux for an additional 3 days giving the same ratio (1:1) of **6** and **7** (Fig. 2, spectrum d). So we assume that the diastereomeric ratio is not the result of a thermodynamic equilibrium between **6** and **7**. This assumption was confirmed by the fact that an interconversion of the purified diastereomers **6** and **7** into each other by refluxing of the corresponding solutions in toluene (3 days) and $CHCl_3$ (6 days) with trifluoroacetic acid did not take place.

The diastereomeric lactams **6** and **7** were reduced using a 3:1 mixture of $LiAlH_4$ and $AlCl_3$, which forms alane (AlH_3) in situ (Scheme 2). As described in the literature,[20] this reduction took place with retention of configuration and provided the diastereomeric 3-benzazepines **8** and **9**, respectively. The retention of configuration is explained by coordination of Al of the Lewis acid AlH_3 to the oxygen atom of the oxazolidine ring, and subsequent delivery of a hydride from the same side as the departing oxygen, which provides the observed products **8** and **9**. Prior to purification, the diastereomeric excess was 86%[21] for crude **8** and 95%[21] for crude **9**; after purification the diastereomeric purity was greater than 98% for both diastereomers (**8**: de >98%, yield 36%; **9**: de >99%, yield 63%). In the final step, the N-substituent was cleaved

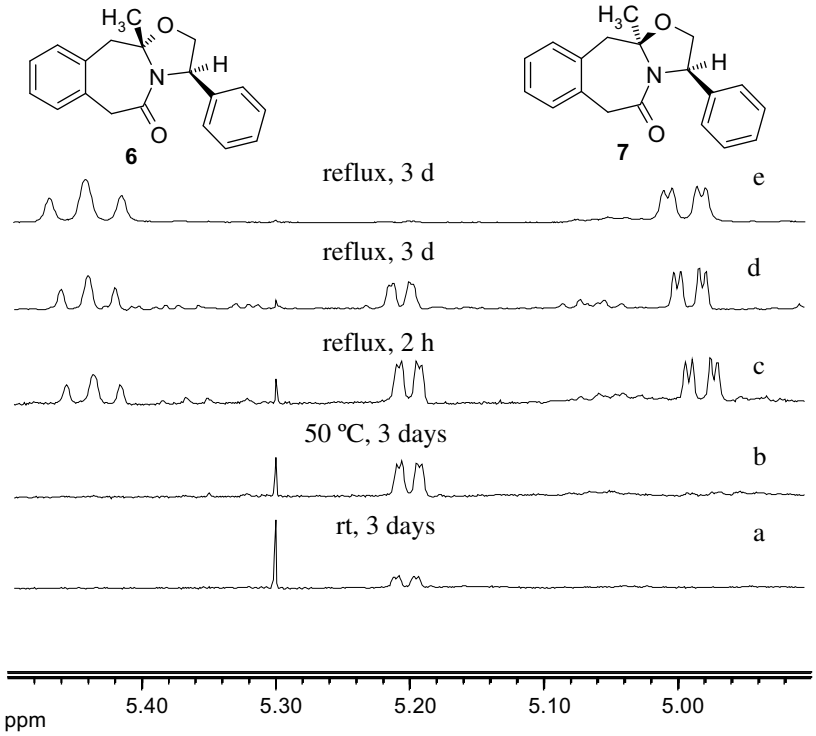
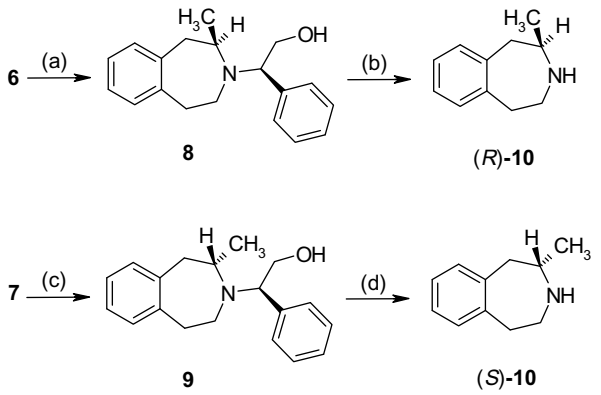


Figure 2. ^{1}H NMR spectra were recorded after the reaction of **4** with **5** under various reaction conditions using toluene as a solvent. Compound **6** gives a characteristic triplet at 5.44 ppm (3-H), whereas compound **7** gives a characteristic dd at 4.93 ppm (3-H). The signal at 5.20 ppm is caused by a side product (or intermediate). Spectra a–d were recorded from the same experiment reacting **4** with **5** in toluene using increasing temperature and time, whereas ^{1}H NMR spectrum e was recorded after heating **4** and **5** at reflux for 3 days in toluene.



Scheme 2. Reagents and conditions: (a) $AlCl_3$ 1.0 equiv, $LiAlH_4$ 3.0 equiv, THF, 0 °C, 2 h, 67%, dr (**8**:**9**) = 93:7; after fc purification dr (**8**:**9**) > 99:1, yield 36%;[20] (b) H_2, 1 bar, Pd/C (10%), aq HCl (1 M) 1.0 mL, MeOH, rt, 88%; (c) $AlCl_3$ 1.0 equiv, $LiAlH_4$ 3.0 equiv, THF, 0 °C, 2 h, 62%, dr (**8**:**9**) = 11:89; after fc purification dr (**8**:**9**) = 0.4:99.6, yield 63%;[20] (d) H_2, 1 bar, Pd/C (10%), aq HCl (1 M), 1.0 mL, MeOH, rt, 73%.

off with H_2 in the presence of Pd/C and HCl to afford the enantiomeric 2-methyl-3-benzazepines (*R*)-**10** (ee >98%) and (*S*)-**10** (ee >99%) in 88% and 73% yield (Scheme 2).[22]

According to the literature[13,14] the diastereomeric lactams **6** and **7** were deprotonated with LDA and subsequently trapped with benzyl bromide to yield the monobenzyl derivatives **11** (80%) and **12** (78%), respectively. The configuration of the new stereogenic center at the 6-position was determined to be (6*R*) for **11** and (6*S*) for **12** by NOE experiments. Obviously, the formation of the stereogenic center at the 6-position was controlled by the N/O-acetalic stereogenic center at the 11a-positions, leading to *like* configuration at the 6- and 11a-positions, respectively, irrespective of the configuration of the chiral auxiliary (Scheme 3).

Reduction of the benzylated derivatives **11** and **12** with $LiAlH_4$/$AlCl_3$ (3:1) provided the trisubstituted 3-benzazepines **13** (72%) and **14** (66%) in diastereomerically pure form, respectively. Finally, the N-substituent of **13** and **14** was hydrogenolytically removed to give the enantiomeric 1-benzyl-4-methyl-3-benzazepines (*R*,*R*)-**15** (73%) and (*S*,*S*)-**15** (94%).[23]

2.2. X-ray crystal structure analysis of 14·HCl

In order to unequivocally prove the configuration of the products, in particular the retention of configuration during the reductive opening of the oxazolidine moiety, the reduced trisubstituted 3-benzazepine **14** was transformed into its HCl salt by the addition of HCl to a solution of **14** in CH_2Cl_2. The solid formed was recrystallized from CH_2Cl_2/*n*-hexane to give crystals, which were suitable for X-ray crystal structure analysis. The X-ray crystal structure of **14**·HCl (Fig. 3) clearly demonstrates (*S*)-configuration at the 1-position (corresponds to the 6-position of **12**) and an (*S*)-configuration at the 4-position (corresponds to the 11a-position of **12**). The (*S*)-configuration at the 4-position confirms the retention of configuration during AlH_3 reduction of the N/O-acetal. Furthermore, the (*S*)-configuration at the 1-position demonstrates the attack of benzyl bromide opposite to the 11a-methyl moiety.

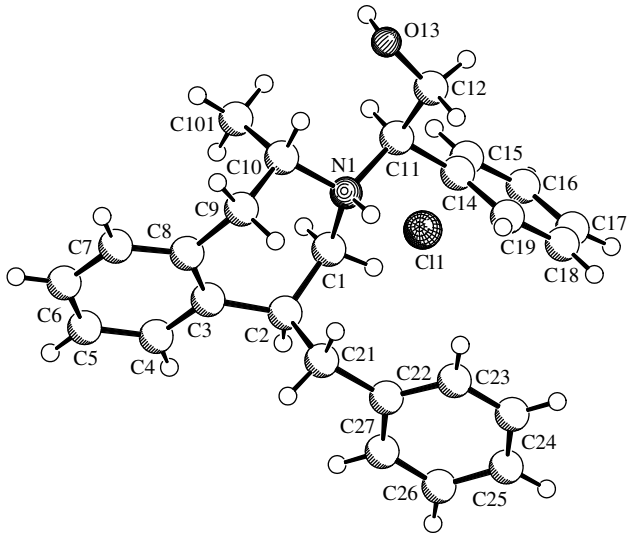
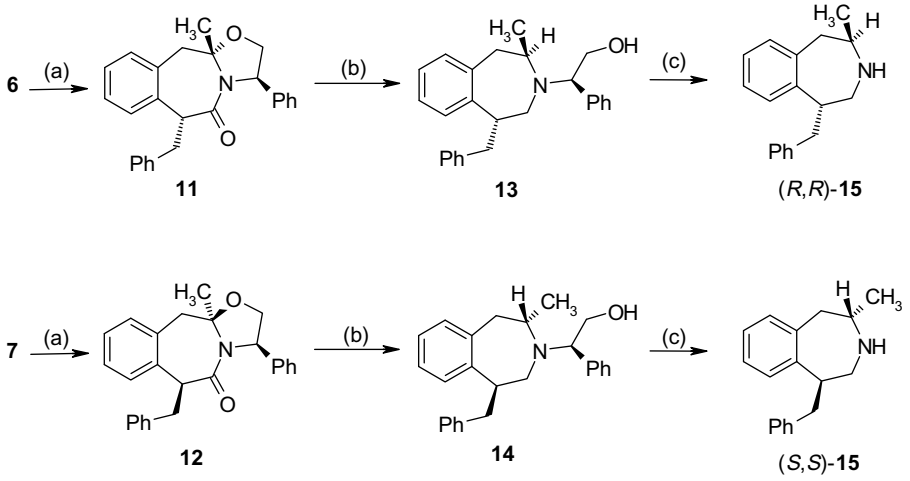


Figure 3. X-ray crystal structure analysis of **14**·HCl.

3. Conclusion

Enantiomerically pure 2-methyl and 1-benzyl-4-methyl substituted tetrahydro-3-benzazepines were synthesized in good yields, following a very short procedure (3–4 reaction steps). The configuration of the newly formed stereogenic centers was unequivocally proven by an X-ray crystal structure analysis of **14**·HCl.



Scheme 3. Reagents and conditions: (a) BnBr 1.0 equiv, LDA 1.2 equiv, THF, 3 h, **11**: 80%; **12**: 78%; (b) $AlCl_3$ 1.0 equiv, $LiAlH_4$ 3.0 equiv, THF, 0 °C, 2 h, **13**: 72%; **14**: 66%; (c) H_2, 1 bar, Pd/C (10%), aq HCl (1 M) 1.0 mL, MeOH, rt, (*R*,*R*)-**15**: 73%; (*S*,*S*)-**15**: 94%.

4. Experimental

4.1. Details for the X-ray crystal structure of 14·HCl

Formula $C_{26}H_{30}ClNO$, $M = 407.96$, colorless crystal $0.20 \times 0.15 \times 0.10$ mm, $a = 11.3379(1)$, $b = 9.2898(2)$, $c = 12.0980(1)$ Å, $\beta = 117.770(1)^\circ$, $V = 1127.48(2)$ Å^3, $\rho_{calc} = 1.202$ g cm^{-3}, $\mu = 1.61$ mm^{-1}, empirical absorption correction ($0.739 \leqslant T \leqslant 0.856$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223(2)$ K, ω and ϕ scans, 8666 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 2637 independent ($R_{int} = 0.073$) and 2637 observed reflections [$I \geqslant 2\sigma(I)$], 264 refined parameters, $R = 0.076$, $wR^2 = 0.210$, max. (min.) residual electron density 0.38 (-0.37) e Å^{-3}, Flack parameter 0.05(4), hydrogen atoms calculated and refined as riding atoms.

Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT,[24] data reduction DENZO-SMN,[25] absorption correction DENZO,[26] structure solution SHELXS-97,[27] structure refinement SHELXL-97,[28] and graphics SCHAKAL.[29]

CCDC 685859 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

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References

1. Weinstock, J.; Hieble, J. P.; Wilson, J. W., III. *Drug Future* **1985**, *10*, 645–697.
2. Kawase, M.; Saito, S.; Motohasho, N. *Int. J. Antimicrob. Agents* **2000**, *14*, 193–194.
3. Sorbera, L. A.; Castaner, J. *Drug Future* **2003**, *28*, 652–658.
4. Pettersson, I.; Liljefors, T.; Bogeso, K. *J. Med. Chem.* **1990**, *33*, 2197–2204.
5. Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Bass, L. S.; Clardy, J. *J. Med. Chem.* **1982**, *25*, 697–703.
6. Micheli, F.; Bonanomi, G.; Braggio, S.; Capelli, A. M.; Celestini, P.; Damiani, F.; Di Fabio, R.; Donati, D.; Gagliardi, S.; Gentile, G.; Hamprecht, D.; Petrone, M.; Radaelli, S.; Tedesco, G.; Terreni, S.; Worby, A.; Heidbreder, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 901–907.
7. Yu, Y.; Wang, J.; Sun, P. H.; Guo, Y.; Zhang, Z.; Jin, G.; Zhen, X. *J. Neurochem.* **2008**, *104*, 946–956.
8. Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Thomsen, W. J.; Saldana, H. R.; Whelan, K. T.; Menzaghi, F.; Webb, R. R.; Beeley, N. R. A. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1467–1470.
9. Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Dosa, P. I.; Covel, J. A.; Ren, A.; Webb, R. R.; Beeley, N. R. A.; Martin, M.; Morgan, M.; Espitia, S.; Saldana, H. R.; Bjenning, C.; Whelan, K. T.; Grottick, A. J.; Menzaghi, F.; Thomsen, W. J. *J. Med. Chem.* **2008**, *51*, 305–313.
10. Gnanalingham, K. K.; Hunter, A. J.; Jenner, P.; Marsden, C. D. *Psychopharmacology* **1995**, *117*, 403–412.
11. Medhurst, A. D.; Atkins, A. R.; Beresford, I. J.; Brackenborough, K.; Briggs, M. A.; Calver, A. R.; Cilia, J.; Cluderay, J. E.; Crook, B.; Davis, J. B.; Davis, R. K.; Davis, R. P.; Dawson, L. A.; Foley, A. G.; Gartlon, J.; Gonzalez, M. I.; Heslop, T.; Hirst, W. D.; Jennings, C.; Jones, D. N. C.; Lacroix, L. P.; Martyn, A.; Ociepka, S.; Ray, A.; Regan, C. M.; Roberts, J. C.; Schogger, J.; Southam, E.; Stean, T. O.; Trail, B. K.; Upton, N.; Wadsworth, G.; Wald, J. A.; White, T.; Witherington, J.; Woolley, M. L.; Worby, A.; Wilson, D. M. *J. Pharm. Exp. Therap.* **2007**, *321*, 1032–1045.
12. Krull, O.; Wünsch, B. *Bioorg. Med. Chem.* **2004**, *12*, 1439–1451.
13. Wirt, U.; Fröhlich, R.; Wünsch, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2199–2202.
14. Wirt, U.; Schepmann, D.; Wünsch, B. *Eur. J. Org. Chem.* **2007**, 462–475.
15. Watkins, J. C.; Jane, D. E. *Br. J. Pharmacol.* **2006**, *147*, 100–108.
16. Bräuner-Osborne, H. B.; Egebjerg, J.; Nielsen, E.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.
17. Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413–1419.
18. Husain, S. M.; Wünsch, B. *Synthesis* **2008**, in press.
19. In the following references, compound **4** is mentioned. However a preparative procedure and spectroscopic and analytical data are not available. (a) Bobranski, B.; Konieczny, M. *Pol. Roczniki Chemii* **1962**, *36*, 639–644; (b) Konieczny, M. *Pol. Bull Acad. Polon. Sci. Ser. Sci. Chim.* **1959**, *7*, 229–233.
20. Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
21. The de was determined by chiral HPLC, using CHIRALPAK AD-H column, isopropanol/*n*-hexane, flow rate 1 mL/min.
22. NMR data of compound **10:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, $J = 6.1$ Hz, 3H, CH_3), 2.72–2.91 (m, 5H, 1-H/2–H/4–H/5–H), 3.01 (ddd, $J = 14.7/10.6/1.9$ Hz, 1H, 4-H), 3.23 (ddd, $J = 12.9/6.5/2.90$ Hz, 1H, 5-H), 7.06–7.13 (m, 4H, Ph-*CH*). A signal for the NH proton could not be detected.
23. NMR data of compound **15**: ^{1}H NMR ($CDCl_3$): δ 1.13 (d, $J = 5.7$ Hz, CH_3), 2.61 (dd, $J = 13.2/8.4$ Hz, 1H, 2-H), 2.77 (br s, 1 H, *NH*), 2.84–2.95 (m, 4H, 4-H/5–H/CH_2Ph), 3.16 (dd, $J = 13.3/2.4$ Hz, 1H, CH_2Ph), 3.23 (dd, $J = 13.7/5.4$ Hz, 1H, 2-H), 3.32 (m, 1H, 1-H). 7.10–7.32 (m, 9H, arom).
24. 'COLLECT' data collection software. Nonius, B. V. Delft, The Netherlands, **1998**.
25. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.
26. Otwinowski, Z.; Borek, D.; Majewski, W.; Minor, W. *Acta Crystallogr., Sect. A* **2003**, *59*, 228–234.
27. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
28. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
29. Keller, E. SCHAKAL—*A Computer Program for the Graphic Representation of Molecular and Crystallographic Models*; Universität Freiburg, 1997.