Enantioselective Lutidine-Tetrahydrobenzoxanthene Receptors for Carboxylic Acids

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Receptors based on *cis*- and *trans*-tetrahydrobenzoxanthene skeletons combined with benzoxazoles and pyridines have shown enantioselective binding to sulfonylamino acids. The keto-enol tautomeric equilibrium of the receptors shifts towards the keto form upon complexation. X-ray analysis of the *trans* receptor complex with L-leucine triflamide (H) reveals an unexpected structure, in which the basic pyridine nitrogen accepts the strong H-bond of the guest, while the benzoxazole acts as a counterpart for the sulfonamide group. l-Carbamoyllactic acid (C) is a suitable guest for the resolution of the racemic mixture of the *trans* receptor, which can be performed by impregnating TLC plates with the guest. Extraction of racemic carbamoyllactic acid (C) and its ammonium salt from a chloroform/water system with the *trans* receptor **4** provided a procedure for the resolution of the guest.

Introduction

Carboxylic acids are of great technical importance,[1] but large scale resolution of the racemic mixtures of these compounds is still a challenging issue. The use of synthetic molecular receptors is a promising possibility for the resolution of these mixtures,[2] especially if a device such as the "Cram machine" is used, because a small amount of the enantiomerically pure receptor may enable the resolution of large amounts of the guests.[3]

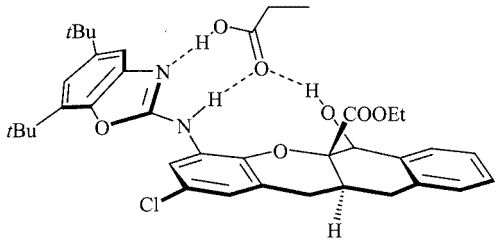

Figure 1. Structure of the complex of the *trans*-benzoxanthene receptor **2** and propionic acid obtained through X-ray analysis

Results and Discussion

Receptors **1** and **2**, based on the *cis*-[4] and *trans*-benzoxanthene[5] skeletons (Scheme 1), have previously been shown to be suitable for the complexation of carboxylic acids. The geometry of these complexes was confirmed by X-ray analysis (Figure 1).

In order to establish a new receptor for an amino acid derivative, a pyridine unit was attached to these molecules, as shown in Scheme 1.

Both receptors are present as the keto-enol tautomers in solution; the *cis* compound **3** in a 2:1 ratio in favour of the enol, and the *trans* structure with equal amounts of both tautomers. This behaviour is already known for α-pyridylketones.[6] The enol protons of **3** and **4** can be detected in the ^{1}H NMR at δ = 16.2 ppm and 15.6 ppm, respectively (see the Supporting Information). The signals from the enol form vanish from the spectrum when trifluoroacetic acid is added, probably because protonation of the pyridine takes place and the enol can no longer profit from the intramolecular H-bond.

Separation of the racemates of these receptors by TLC was then attempted, by impregnating silica gel with solutions of several enantiomerically pure acids. Table 1 shows the results obtained for both the *cis* receptor **3** and the *trans* receptor **4**. The resolution of the receptor depends on its stereochemistry. L-Lactic acid (**A**) and L-leucine *N*-phenylurea (**F**) were able to split the enantiomers of **3**, although no separation was observed for the enantiomers of **4**; these

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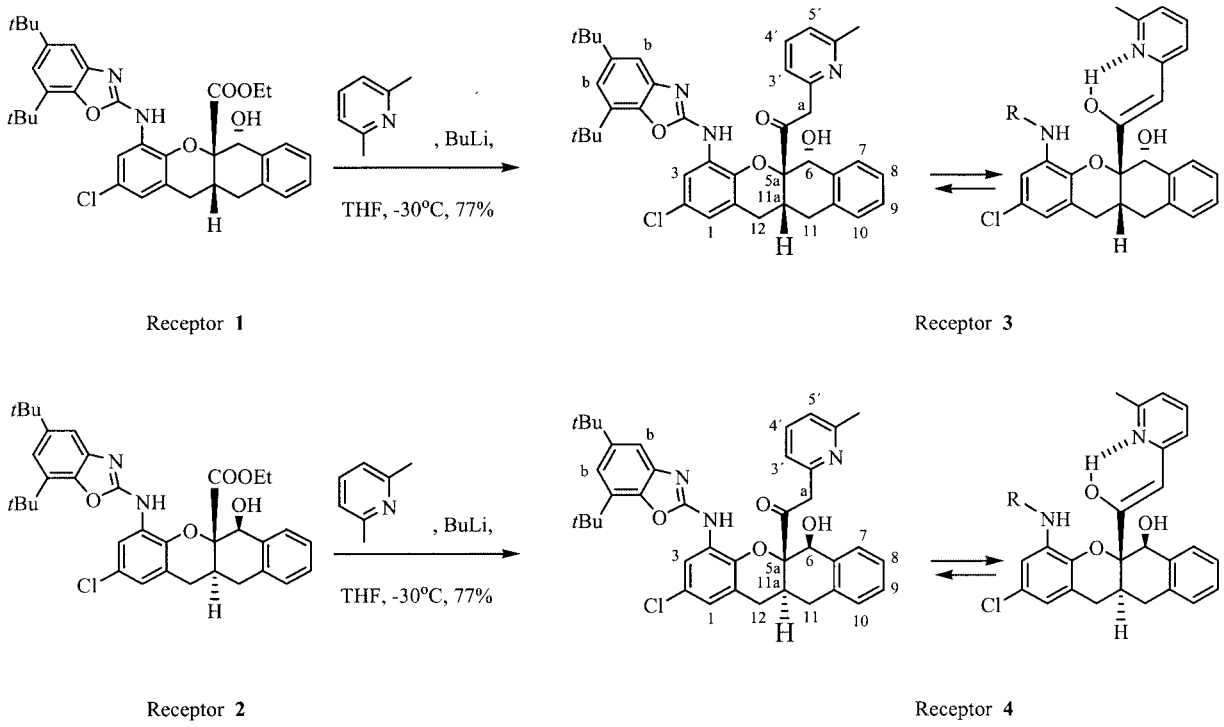


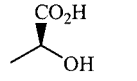
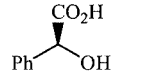
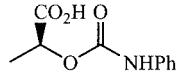
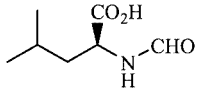
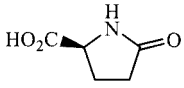
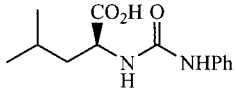
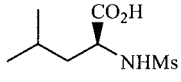
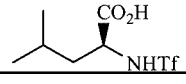
Scheme 1. Preparation of *cis*- and *trans*-benzoxanthene receptors **3** and **4**

compounds were better separated by L-leucine triflamide (**H**), which provided, however, only a very small separation for compound **3**. The best results were obtained for both *cis* and *trans* hosts using L-carbamoyllactic acid (**C**). This host produced a large separation between the enantiomers of both receptors.

Despite the presence of the keto-enol equilibrium, a conventional titration[7] could be carried out by adding a solution of L-leucine triflamide (**H**) to receptor **4**. The 3-H proton in the keto form becomes more shielded during the titration (from $\delta = 8.54$ ppm to 7.92 ppm), probably due to a change in the benzoxazole conformation. A graphical representation of the chemical shift of this proton as a function of the amount of guest added, and the use of a Monte Carlo based curve-fitting program provided an apparent constant of $K_{ass} = 3.1 \times 10^4\ M^{-1}$ (see Figure S5 in the Supporting Information). Job plots of this data indicate a 1:1 stoichiometry (see Figure S6 in the Supporting Information). A graphical representation of the chemical shift of the 3-H proton of the keto form as a function of the chemical shift of the 6-H proton in the enol form throughout the course of the titration revealed that the binding with the ketone was four times stronger than with the enol (Figure S7 in the Supporting Information).

Good crystals were obtained for the complex of the *trans* receptor **4** and L-leucine triflamide (**H**), which allowed an X-ray diffraction study to be undertaken. The structure of the complex is shown in Figure 2. The keto tautomer is the only one present, but it does not correspond to the previously predicted geometry. Instead of the Watson−Crick-

Table 1. R_f ratios of the *cis* receptor **3** and *trans* receptor **4** on silica gel plates impregnated with 1% of the enantiomerically pure guests **A**−**H**, and eluted with chloroform/diethyl ether 9:1; R_f ratios were obtained by dividing the R_f for one of the diastereomeric complexes by the other

	Guest	R_f ratio for **3**	R_f ratio for **4**
A		1.2	1.0
B		1.0	1.0
C		2.2	1.8
D		1.0	1.0
E		1.0	1.0
F		1.3	1.0
G		1.0	1.0
H		1.1	1.3

like H-bonds observed for other receptors (due to the interaction of the carboxylic group of the guest and the benzoxazole), a more unusual structure was present, in which the basic pyridine nitrogen atom formed a bond to the hydrogen atom of the carboxylic acid, thus resulting in a 12-membered ring containing the C-6 hydroxyl and the C=O group of the guest.

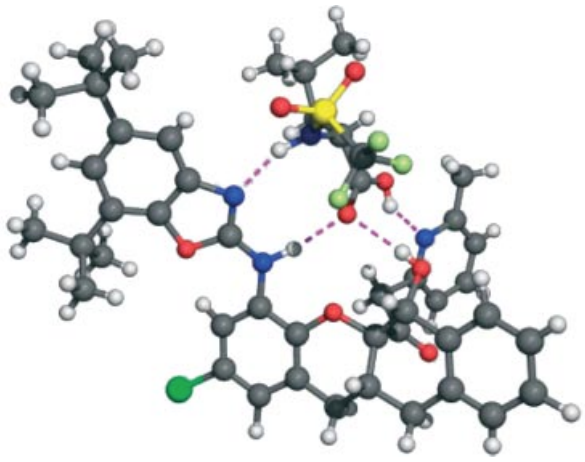


Figure 2. X-ray structure of the complex between receptor **4** and L-leucine triflamide (**H**)

Pyridines are known to be as much as 10,000 times more basic than oxazoles,[8] and this may be the reason for the preference for the structure shown in Figure 2. The H-bond lengths are in agreement with this hypothesis, since the distance is 2.57 Å when the pyridine nitrogen atom is the H-bond acceptor of the guest hydroxyl, and 2.66 Å when the benzoxazole nitrogen atom is the acceptor (the values given are the observed distances between the receptor **2** and propionic acid[5] in the X-ray crystal structure).

The geometry of the complex of *trans* receptor **4** and L-leucine triflamide (**H**) offers a good explanation for the source of the chiral recognition, because in the alternative diastereomeric complex, the guest would be in a strained conformation in which the isobutyl group is close to the sulfonamide oxygens (Figure 3).

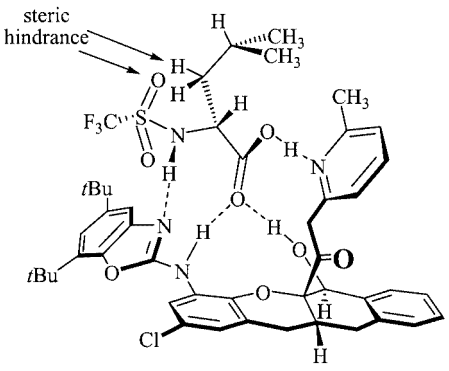


Figure 3. Proposed structure of the weak complex between receptor **4** and L-leucine triflamide (**H**)

We then decided to resolve the mixture of enantiomers of the *trans* receptor **4**. The previous experiment with L-carbamoyllactic acid (**C**) suggested that preparative TLC plates could be used to carry out the separation. A silica gel plate (16 g) was impregnated with a 2% solution of L-carbamoyllactic acid (**C**) in chloroform/diethyl ether 9:1. After solvent evaporation, the plate was loaded with 50 mg of the host racemic mixture, and eluted with chloroform/diethyl ether 98:2 containing 1% of the guest. Workup provided the complexes of both enantiomeric receptors, which could be obtained in the free form by washing the ethyl acetate solution with 4% aqueous sodium carbonate. Final crystallization from diethyl ether/hexane yielded 20 mg of each enantiomer. The optical rotation values were $[\alpha]_D^{20} = -140.2$ ($c = 0.8$, $CDCl_3$) for the enantiomer that forms the weak complex and $[\alpha]_D^{20} = +141.6$ ($c = 0.8$, $CDCl_3$) for the enantiomer that forms the strong complex. A possible application of these receptors is for the resolution of racemic mixtures of acids. Because the results were good with L-carbamoyllactic acid (**C**), this guest was chosen. A solution of (+)-**4** (18.1 μmol) and racemic carbamoyllactic acid (6.0 μmol) (**C**) in chloroform (0.7 mL) displayed two doublets of the same intensity at δ = 1.73 and 1.62 ppm, corresponding to the lactic acid methyl group in each diastereomeric complex. After treatment with a solution of the racemic ammonium salt of carbamoyllactic acid (61.5 μmol) (**C**) in water (250 μL), the doublet at δ = 1.73 ppm showed an integral 5.1 times larger than the more shielded methyl signal (Figure 4). Formation of the strong complex must therefore be the driving force for the exchange of the enantiomeric guests between the aqueous and organic phases.

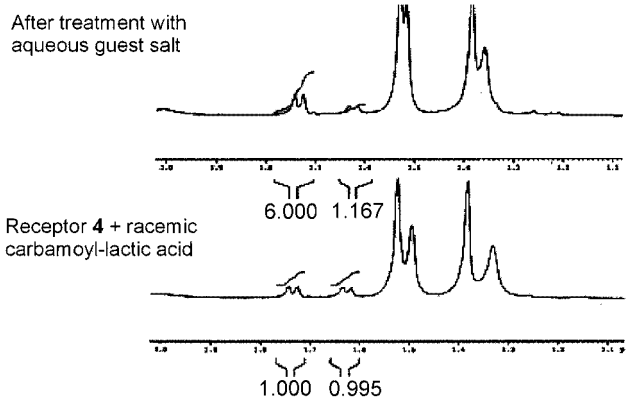


Figure 4. Spectra recorded during the extraction experiment; bottom: part of the spectrum of the mixture of diastereomeric complexes; top: part of the spectrum after extraction with an aqueous solution of the ammonium salt of racemic carbamoyllactic acid (**C**)

Conclusion

An enantiomerically pure receptor for carbamoyllactic acid (**C**) has been prepared. Extraction with a chloroform/water system provided a 67% enantiomeric excess of the

guest in a single extraction, due to the different stabilities of the diastereomeric complexes of the guest with receptor **4**.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance DRX 400 MHz spectrometer. Mass spectra were obtained with a VG. MOD. TS-250 spectrometer. IR spectra were recorded on a BONEN MB-100FT IR spectrometer. Melting points were obtained with a Stuart Scientific SMP3 Apparatus. Optical rotations were measured with a Perkin−Elmer 341 polarimeter**.** THF was distilled from sodium/benzophenone.

Synthesis of Receptors 3 and 4: BuLi (10.4 mL, 16.6 mmol) was added to a solution of 2,6-dimethylpyridine (2.0 mL, 17.2 mmol) in THF (10 mL) with stirring at −30 °C under an argon atmosphere. The ester **1** or **2** (1.00 g, 1.6 mmol) was dried by azeotropic distillation, dissolved in toluene (5 mL) and added to the reaction mixture. The reaction mixture was stirred for one hour (the temperature was allowed to rise to room temperature in the case of **2**) and extracted with ethyl acetate. The extracts were washed with aqueous HCl, aqueous Na_2CO_3 and water several times. The organic layer was dried over sodium sulfate and the solvents evaporated to dryness. The product was purified by crystallization from CH_2Cl_2/hexane, to give the product as a yellow solid (0.80−0.85 g, ca. 77%).

Receptor 3: Mp.: 164−166 °C. IR (film): $\tilde{\nu}$ = 2963, 1636, 1576, 1507, 1458, 1406, 1265, 1211, 1103, 1045, 801, 756 cm^{-1}. ^{1}H NMR (400 MHz, DMSO, 25 °C): Enol tautomer: δ = 16.22 (s, 1 H, enol OH), 9.87 (s, 1 H, NH), 8.45 (d, *J* = 2 Hz, 1 H, 3-H), 7.67 (d, *J* = 8 Hz, 1 H, 7-H), 7.50 (t, *J* = 8 Hz, 1 H, 4′-H), 7.38 (s, 1 H, β-H), 7.22 (t, *J* = 8 Hz, 1 H, 8-H), 7.14 (t, *J* = 8 Hz, 1 H, 9-H), 7.05 (s, 1 H, β-H), 7.05 (d, *J* = 8 Hz, 1 H, 10-H), 6.82 (m, 2 H, 1-H, 3′-H), 6.71 (d, *J* = 8 Hz, 1 H, 5′-H), 5.72 (d, *J* = 12 Hz, 1 H, OH), 5.35 (s, 1 H, α-H), 4.99 (d, *J* = 12 Hz, 1 H, 6-H), 3.15−2.83 (m, 5 H), 2.43 (s, 3 H, CH_3), 1.43 (s, 9 H, *t*Bu), 1.32 (s, 1 H, *t*Bu) ppm. Keto tautomer: δ = 9.80 (s, 1 H, NH), 8.41 (d, *J* = 2 Hz, 1 H, 3-H), 7.62 (d, *J* = 8 Hz, 1 H, 7-H), 7.52 (t, *J* = 8 Hz, 1 H, 4′-H), 7.37 (s, 1 H, β-H), 7.22 (t, *J* = 8 Hz, 1 H, 8-H), 7.14 (t, *J* = 8 Hz, 1 H, 9-H), 7.05 (s, 1 H, β-H), 7.05 (d, *J* = 8 Hz, 1 H, 10-H), 7.05 (d, *J* = 8 Hz, 1 H, 3′-H), 6.96 (d, *J* = 8 Hz, 1 H, 5′-H), 6.82 (s, 1 H, 1-H), 6.22 (d, *J* = 12 Hz, 1 H, OH), 5.13 (d, *J* = 12 Hz, 1 H, 6-H), 4.36 (d, *J* = 17 Hz, 1 H, α-H), 3.84 (d, *J* = 17 Hz, 1 H, α-H), 3.15−2.83 (m, 5 H), 2.34 (s, 3 H, CH_3), 1.42 (s, 9 H, *t*Bu), 1.30 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (400 MHz, DMSO, 25 °C) δ = 208.81, 174.36, 157.47, 157.27, 157.12, 155.55, 153.73, 149.71, 146.6, 142.95, 142.07, 141.94, 140.30, 140.23, 138.88, 138.08, 136.92, 136.45, 134.15, 133.91, 131.95, 131.78, 128.29, 128.12, 127.92, 127.74, 127.27, 127.13, 126.84, 126.32, 126.18, 126.10, 124.54, 123.96, 122.61, 122.47, 121.45, 121.38, 120.99, 118.10, 116.55, 116.02, 115.89, 115.47, 111.96, 91.75, 87.70, 82.77, 72.24, 70.95, 47.28, 34.66, 33.82, 31.64, 30.12, 29.95, 29.89, 29.32, 29.09, 28.71, 28.11, 23.80, 21.43 ppm. MS (ESI): *m*/*z* (%) = 665 (100), 664 (M^+ +1, 88), 513 (75), 666 (57), 385 (55), 262 (40), 687 (M^+ + 23, 15).

Receptor 4: $[\alpha]_D^{20}$ = −140.2 (*c* = 0.8, $CDCl_3$) and +141.6 (*c* = 0.8, $CDCl_3$). ^{1}H NMR (400 MHz, DMSO, 25 °C): Enol tautomer: δ = 15.67 (s, 1 H, enol OH), 9.83 (s, 1 H, NH), 8.46 (d, *J* = 2 Hz, 1 H, 3-H), 7.61 (d, *J* = 8 Hz, 1 H, 7-H), 7.42 (t, *J* = 8 Hz, 1 H, 4′-H), 7.42 (d, *J* = 2 Hz, 1 H, β-H), 7.18 (m, 3 H, 8-H, 9-H, 10-H), 7.09 (d, *J* = 2 Hz, 1 H, β-H), 6.80 (d, *J* = 2 Hz, 1 H, 1-H), 6.74 (d, *J* = 8 Hz, 1 H, 3′-H), 6.62 (d, *J* = 8 Hz, 1 H, 5′-H), 6.35 (d, *J* = 2 Hz, 1 H, OH), 5.35 (s, 1 H, α-H), 5.07 (d, *J* = 2 Hz, 1 H, 6-H), 3.30−2.50 (m, 5 H), 2.24 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*Bu), 1.33 (s, 9 H, *t*Bu) ppm. Keto tautomer: δ = 9.84 (s, 1 H, NH), 8.49 (d, *J* = 2 Hz, 1 H, 3-H), 7.61 (d, *J* = 8 Hz, 1 H, 7-H), 7.40 (t, *J* = 8 Hz, 1 H, 4′-H), 7.42 (d, *J* = 2 Hz, 1 H, β-H), 7.18 (m, 3 H, 8-H, 9-H, 10-H), 7.09 (d, *J* = 2 Hz, 1 H, β-H), 6.92 (m, 2 H, 3′-H, OH), 6.83 (d, *J* = 2 Hz, 1 H, 1-H) 6.74 (d, *J* = 8 Hz, 1 H, 5′-H), 5.16 (d, *J* = 2 Hz, 1 H, 6-H), 4.15 (d, *J* = 17 Hz, 1 H, α-H), 3.68 (d, *J* = 17 Hz, 1 H, α-H), 3.30−2.50 (m, 5 H), 2.29 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*Bu), 1.33 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (400 MHz, DMSO, 25 °C) δ = 207.81, 171.46, 157.51, 157.35, 156.89, 155.89, 153.89, 150.22, 146.7, 143.08, 142.20, 142.07, 140.62, 140.16, 138.45, 137.76, 136.14, 135.44, 135.02, 131.89, 131.81, 128.28, 128.02, 127.32, 127.15, 126.76, 126.23, 125.74, 125.46, 124.27, 123.82, 123.41, 122.91, 121.47, 121.10, 120.74, 118.07, 116.81, 116.00, 115.90, 115.40, 115.27, 112.10, 112.05, 94.50, 87.97, 83.83, 74.90, 74.67, 50.75, 34.68, 34.09, 34.03, 33.86, 33.20, 33.14, 31.65, 29.89, 28.47, 28.08, 23.64, 21.72 ppm. MS (FAB): *m*/*z* (%) = 134 (100), 664 (M^+ + 1, 40), 666 (20), 514 (15). IR (film): $\tilde{\nu}$ = 2965, 1699, 1653, 1576, 1458, 1404, 1364, 1265, 1215, 1159, 1038, 756 cm^{-1}. HRMS (FAB) for $C_{40}H_{43}ClN_3O_4$: calcd. 664.2942; found 664.2953 for the (−)-enantiomer and 664.2916 for the (+)-enantiomer. Elemental analysis for $C_{40}H_{42}ClN_3O_4$: calcd. C 72.33, H 6.31, N 6.33; found C 72.01, H 6.03, N 6.21.

X-ray Crystallographic Study: A single crystal of the complex of **4** and L-leucine triflamide (**H**) was subjected to X-ray diffraction studies on a Seifert 3003 SC four-circle diffractometer (Cu-K_α radiation, graphite monochromator) at 293(2) K. Crystal data for **1**: $C_{47}H_{54}N_4SO_8F_3Cl{\cdot}C_4H_{10}O$, *M* = 1001.57, triclinic, space group $P\bar{1}$ (no. 2), *a* = 13.202(3) Å, *b* = 14.554(3) Å, *c* = 19.104(4) Å, α = 97.04(3)°, β = 91.58(3)°, γ = 116.38(3)°, *V* = 3249.7(11) Å^3, *Z* = 2, D_c = 1.024 Mg/m^3, *F*(000) = 1060. Crystal size: 0.06 × 0.07 × 0.08 mm. 9258 reflections were collected, of which 5946 were considered to be observed with $I > 2\sigma(I)$. Absorption coefficient μ = 0.145 mm^{-1}, no absorption correction, 681 refined parameters. The structure was determined by direct methods using the SHELXTL™ suite of programs. Full-matrix least-squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors R_1 = 0.1231 and ωR_2 = 0.3233.

CCDC-225993 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].

Acknowledgments

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