HETEROCYCLES, Vol. 69, 2006, pp. 303 - 310. © The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2006, Accepted, 17th August, 2006, Published online, 22nd August, 2006. COM-06-S(O)34

ADDITION REACTION OF *O*-TOLUAMIDES WITH CHIRAL AUXILIARY DERIVED FROM 2-AMINO-1,3-PROPANEDIOLS TO IMINES

Maria Chrzanowska* and Agnieszka Dreas

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland, e-mail: marylch@amu.edu.pl

Abstract – Stereoselectivity of the addition reaction of *o*-toluamides, incorporating 2-amino-1,3-propanediols as chiral auxiliary to imines has been studied. Addition products, diastereomerically enriched, after column chromatography separation were obtained and further transformed to (*S*)-(–)-or (*R*)-(+)-8-oxoberbines with ee up to 97%.

INTRODUCTION

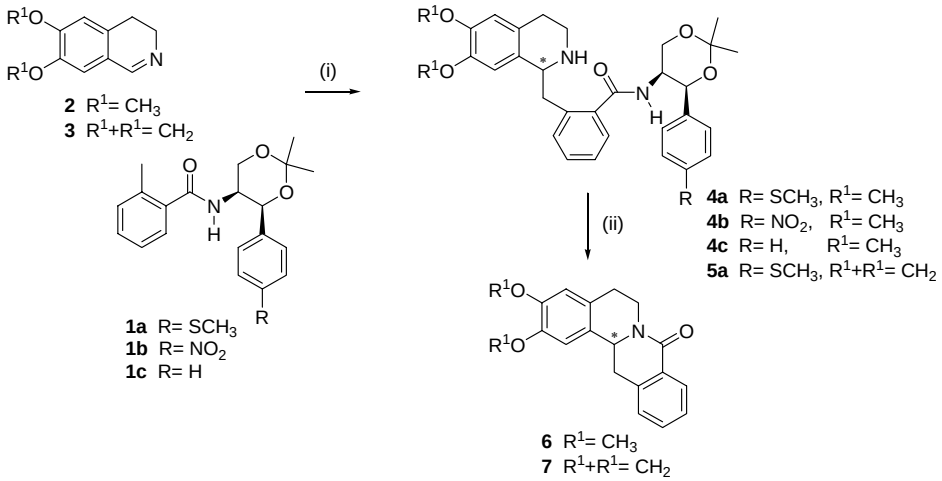
A study of stereoselectivity of the addition reaction of chiral *o*-toluamides to imines is a part of our project connected with asymmetric synthesis of protoberberine system.[1-4] The key step of the synthesis, in which a new stereogenic centre was created, involved the addition of laterally lithiated chiral *o*-toluamide to imine. The lateral lithiation methodology has been developed for the synthesis of several heterocyclic ring systems including different types of alkaloids i.e. benzophenantridinone,[5,6] benzo[*c*]phenantridine,[7,8] protoberberine,[8,9] isocoumarin.[10-12] A stereoselective tandem addition/cyclization of lithiated *o*-toluamides to imines led to formation of 3-substituted dihydro-*2H*-isoquinolin-1-ones.[13-15] Recently this methodology has been applied to the stereoselective synthesis of protoberberine system.[2-4,16-18]

Condensation of *o*-toluamides incorporating chiral auxiliaries with 3,4-dihydroisoquinolines led to non-chiral 8-oxoberbine system.[2,3,16] (*S*)- And (*R*)-α-phenylethylamine[16] as well as 2-aminopropanols: (1*R*,2*S*)-norephedrine[2] and (*S*)- and (*R*)-phenylalaninol[3] were applied as inductors of chirality.

RESULTS AND DISCUSSION

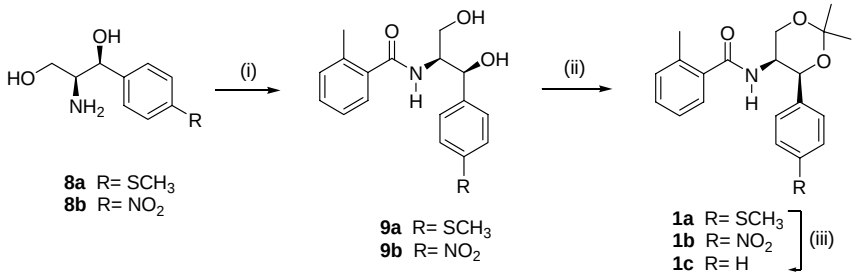
We would like to extend further our project using commercially available, enantiomerically pure, 2-amino-1,3-propanediols to check whether they will act as efficient chiral auxiliaries. At first we have

used *o*-toluamide (**1a**)[2] with a chiral auxiliary derived from (+)-thiomicamine (**8a**) {(1*S*,2*S*)-2-amino-1-[4-(methylthio)phenyl]-1,3-propanediol}, an industrial waste product. Although the diastereoselectivity of the addition reaction of anion generated from *o*-toluamide (**1a**) to cyclic imines [6,7-dimethoxy-3,4-dihydroisoquinoline (**2**)[19] or 6,7-methylenedioxy-3,4-dihydroisoquinoline (**3**)[20]] was very low, 26% de and 20% de, respectively, the addition products (**4a** and **5a**) were further transformed to 8-oxoberbines (**6** and **7**)[2,3] (Scheme 1).



Scheme 1 *Reagents and conditions:* (i) *n*-BuLi (2.2 equiv), THF, Ar, –72 °C; (ii) toluene, reflux.

To improve the diastereoselectivity of the addition reaction we tried to use another chiral auxiliary with different substituents in aromatic ring of aminodiol, e.g. with a nitro group or hydrogen in place of the thiomethyl one. The nitro derivative (**1b**) was obtained by the same reaction sequence as the (+)-thiomicamine derivative (**1a**), according to literature procedure.[2] Reaction of commercially available (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**8b**) and *o*-toluoyl chloride led to amide (**9b**) in 77% yield (Scheme 2).



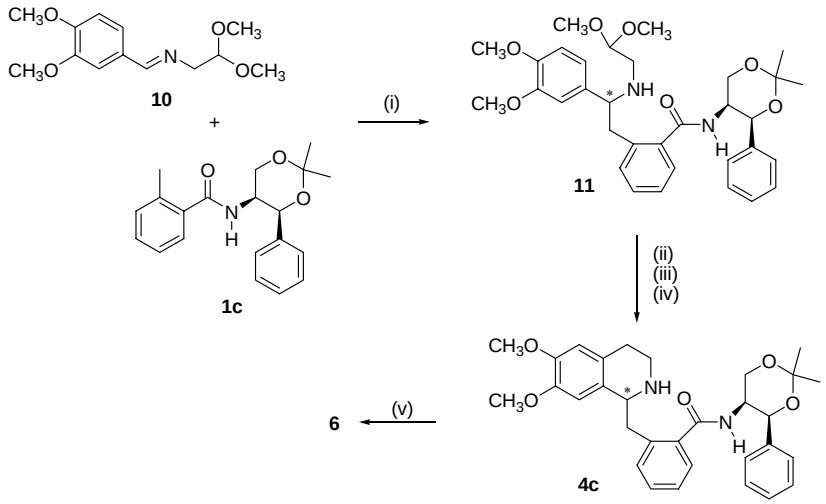
Scheme 2 *Reagents and conditions:* (i) *o*-toluoyl chloride, 0.5M KOH, CH_2Cl_2, 0 °C; (ii) $(CH_3O)_2C(CH_3)_2$, acetone, H_2SO_4, rt; (iii) Raney nickel, EtOH, rt.

The two hydroxyl groups in compound (**9b**) were protected as a 1,3-*O*-isopropylidene derivative in reaction with 2,2-dimethoxypropane. Compound (**1b**) was obtained as an oil in 66% yield. Amide (**1c**) was prepared by desulfurization reaction of amide (**1a**) (Raney nickel, EtOH) in 75% yield.

The addition reaction of carbanion generated from amide (**1b**), by the action of *n*-BuLi (2.2 equiv), to imine (**2**), led to addition product (**4b**) with 14% de (HPLC). The crude reaction mixture was further transformed to dextrorotatory (*R*)-2,3-dimethoxy-8-oxoberbine (**6**) in 72% yield and with 17% ee, by reflux in toluene under an argon atmosphere. A similar reaction of amide (**1c**) with imine (**2**) gave addition product (**4c**) with 10% de. The crude reaction mixture was chromatographed on a silica gel column to give the diastereomerically enriched fractions of the more polar diastereomer (12% yield, 71% de HPLC) and the less polar diastereomer (40% yield, 60% de HPLC). The last one was cyclized to afford dextrorotatory (*R*)-2,3-dimethoxy-8-oxoberbine (**6**) in 82% yield with 23% ee.

It turned out that the replacement of the thiomethyl group in aromatic ring coming from aminodiol part by a nitro group or by hydrogen had no influence on stereoselectivity. Although the diastereoselectivity of the addition process was low we were able to obtain diastereomerically enriched fractions of addition products (**4a**,**b**,**c** and **5a**) with 38 – 98% de by column chromatography on silica gel. The cyclization of the separated diastereoisomers, by reflux in toluene, led to enantiomerically enriched all enantiomers of lactams (**6** and **7**) with ee up to 97%.

In the next part of our study we have investigated the stereoselective outcome of the addition reaction of *o*-toluamide (**1c**) to acyclic imine (**10**), the so called Pomeranz-Fritsch imine[21] [(3,4-dimethoxybenzylidene)-(2,2-dimethoxyethyl)amine]. Addition of carbanion generated from *o*-toluamide (**1c**) by the action of *n*-BuLi (2.2 equiv) to imine (**10**) led to formation of a diastereomeric mixture (**11**) in 65% yield and 22% de (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) *n*-BuLi (2.2 equiv), THF, Ar, –72 °C; (ii) column chromatography separation; (iii) 6M HCl, rt; (iv) H_2, Pd/C, HCl/MeOH; (v) toluene, reflux.

Column chromatography on silica gel led to enantiomerically enriched fractions of two diastereoisomers: the less polar (21% yield, 59% de HPLC) and more polar (56% yield, 49% de HPLC). The last one was transformed to 8-oxoberbine (**6**) using the Pomeranz-Fritsch-Bobbitt methodology, which involved acid hydrolysis (6M HCl, rt, 48 h) followed by hydrogenation (H_2, 10% Pd/C, 0.3 Mpa, 18 h). The so obtained crude product (**4c**) was refluxed in toluene under an argon atmosphere giving (*S*)-(−)-2,3-dimethoxyberbine (**6**) in 26% yield with 53% ee, $[\alpha]_D$ −188.3° (*c* 0.60, $CHCl_3$) {lit.,[3] $[\alpha]_D$ −413.8° (*c* 0.359, $CHCl_3$), >99% ee}. The above transformations present another synthetic strategy for the preparation of enantiomerically enriched protoberberines using the Pomeranz-Fritsch-Bobbitt cyclization.[4]

EXPERIMENTAL

IR spectra: Bruker FT-IR IFS 113V. NMR spectra: Varian Gemini 300 with TMS as the internal standard. Mass spectra (EI): instrument AMD 402. Optical rotations: Perkin-Elmer polarimeter 242B, at 20 ºC. Merck Kieselgel 60 (70-230 mesh) was used for column chromatography; Merck DC-Alufolien Kieselgel 60_{254} for TLC. Analytical HPLC: Waters HPLC system with Mallinkrodt –Baker Chiralcel OD-H column. THF and Et_2O were freshly distilled from $LiAlH_4$. Imines (**2**),[19] (**3**)[20] and (**10**)[21] and *o*-toluamide (**1a**)[2] were prepared as previously described.

(1*S*,2*S*)-2-*o*-Toluamide-1-(4-nitrophenyl)-1,3-propanediol (**9b**)

The compound (**9b**) was prepared according to literature procedure[2] using (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**8b**) (2.12 g, 10 mmol), dichloromethane (135 mL), aqueous 0.5M KOH solution (65 mL) and *o*-toluoyl chloride (1.54 g, 10 mmol). Amide (**9b**) was obtained as a white precipitate (3.06 g, 93%), which was washed with Et_2O. Yield 2.54 g (77%), mp 142-146 °C, $[\alpha]_D$ +81.3° (*c* 0.59, MeOH); IR (KBr) ν: 3358 (OH, NH), 1623 (C=O), 1520 (NO_2), 1348 (NO_2) cm^{-1}; ^1H NMR (CD_3OD) δ: 2.11 (s, 3H, $ArCH_3$), 3.66-3.91 (m, 2H, CH_2O), 4.40-4.46 (m, 1H, C*H*NH), 5.21 (d, *J* = 2.7 Hz, 1H, C*H*OH), 7.16-7.31 (m, 4H, ArH), 7.72 (d, *J* = 8.5 Hz, 2H, ArH), 8.23 (d, *J* = 8.8 Hz, 2H, ArH); MS *m/z* (%): 312 ($M^+ - H_2O$, 0.04), 296 (0.07), 178 (19), 119 (100), 91 (28).

(1*S*,2*S*)-2-*o*-Toluamide-1-(4-nitrophenyl)-1,3-*O*-isopropylidenepropane (**1b**)

The compound (**9b**) was prepared according to literature procedure[2] using amide (**9b**) (2.93 g, 8.9 mmol), acetone (130 mL), 2,2-dimethoxypropane (5.5 g, 53 mmol) and concentrated H_2SO_4 (0.35 mL). After column chromatography purification amide (**1b**) was obtained as an oily compound (2.17 g). Yield 66%, $[\alpha]_D$ +137.4° (*c* 1.00, $CHCl_3$); IR (KBr) ν: 3311 (NH), 1663 (C=O), 1519 (NO_2), 1346 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.56 (s, 3H, $C(CH_3)_2$), 1.63 (s, 3H, $C(CH_3)_2$), 2.04 (s, 3H, $ArCH_3$), 3.99 (dd, *J* = 1.9, 12.1 Hz, 1H, CH_2O), 4.42 (dd, *J* = 1.9, 12.1 Hz, 1H, CH_2O), 4.60 (dd, *J* = 1.9, 9.9 Hz, 1H, C*H*NH), 5.36 (d,

J = 1.9 Hz, 1H, ArC*H*O), 6.42 (d, *J* = 9.9 Hz, 1H, CHN*H*), 7.02-7.30 (m, 4H, ArH), 7.61 (d, *J* = 8.2 Hz, 2H, ArH), 8.22 (d, *J* = 9.1 Hz, 2H, ArH); MS *m/z* (%): 355 ($M^+ - CH_3$, 3), 219 (2), 161 (44), 146 (3), 119 (100), 91(33).

(1*S*,2*S*)-2-*o*-Toluamide-1-phenyl-1,3-*O*-isopropylidenepropane (**1c**)

Raney nickel (2 g) and compound (**1a**) (0.41 g, 1.1 mmol) in EtOH (20 mL) were stirred at rt for 24 h. Next it was filtered through a pad of Celite and washed with EtOH. The filtrate was evaporated and the residue (0.36 g, 93%) was crystallized from Et_2O giving colorless crystals (0.26 g). Yield 75%, mp 108-111 °C, $[\alpha]_D$ +85.6° (*c* 1.07, $CHCl_3$); IR (KBr) ν: 3446 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 3H, $C(CH_3)_2$), 1.61 (s, 3H, $C(CH_3)_2$), 2.06 (s, 3H, $ArCH_3$), 4.01 (dd, *J* = 1.9, 12.1 Hz, 1H, CH_2O), 4.37 (dd, *J* = 1.9, 12.1 Hz, 1H, CH_2O), 4.49 (dd, *J* = 1.9, 9.4 Hz, 1H, C*H*NH), 5.31 (d, *J* = 1.9 Hz, 1H, ArC*H*O), 6.35 (d, *J* = 9.1 Hz, 1H, CHN*H*), 6.98-7.01 (m, 1H, ArH), 7.09-7.13 (m, 2H, ArH), 7.22-7.42 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$) δ: 18.6 (*C*H_3C), 19.2 (CH_3Ar), 29.7 (*C*H_3C), 46.9 (C-2), 64.9 (C-3), 71.8 (C-1), 99.6 (CH_3*C*), 125.3 (2C, CH), 125.5 (CH), 126.6 (CH), 127.6 (CH), 128.3 (2C, CH), 129.7 (CH), 130,7 (CH), 135.9 (C), 136.3 (C), 138.4 (C), 169.4 (C=O); MS *m/z* (%): 325 (M^++1, 0.09), 310 ($M^+ - CH_3$, 3), 267 (2), 161 (26), 119 (100), 105 (4), 91 (33). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N 4.30. Found: C, 73.91; H, 7.08; N, 4.12.

Addition to cyclic imine – product (4c) – *a representative procedure*

Amide (**1c**) (325 mg, 1mmol) was dissolved in dry THF (10 mL) under an argon atmosphere and the mixture cooled to −72 ºC. *n*-BuLi (1.6 M solution in hexanes, 1.4 mL) was introduced and the carbanion generated for 30 min at −72 ºC. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (**2**) (191 mg, 1 mmol) in dry THF (10 mL) was added and the mixture kept at −72 ºC for 4h and then treated at this temperature with 20% aqueous NH_4Cl (6mL). When the reaction mixture reached rt, the phases were separated and the aqueous one extracted with Et_2O (3x10 mL). The combined organic extracts were dried and solvents removed under reduced pressure yielding 519 mg of crude product. HPLC analysis of the crude reaction product indicated the presence of two diastereoisomers (**4c**) in a ratio 55:45 [hexane/propan-2-ol=65:35, t_R 26.5 min, t_R 29.5 min (major)] together with unreacted amide (**1c**) and imine (**2**). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 100:1 → 50:1) yielding diastereomerically enriched fractions of the more polar diastereomer (63 mg, 12% yield, 71% de HPLC, t_R 26.5 min) and the less polar diastereomer (201 mg, 40% yield, 60% de HPLC, t_R 29.5 min). ^{1}H NMR for more polar diatereoisomer ($CDCl_3$) δ: 1.54 (s, 3H, $C(CH_3)_2$), 1.61 (s, 3H, $C(CH_3)_2$), 1.82 (br s, 1H, NH disappeared with D_2O), 2.55-2.92 (m, 5H, CH_2), 3.27 (dd, *J* = 4.1, 13.5 Hz, 1H, CH_2), 3.86 (d, *J* = 1.9 Hz, 1H, ArC*H*NH), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.99 (dd, *J* = 1.9, 12.9 Hz, 1H, CH_2O), 4.33 (dd, *J* = 2.2, 12.9 Hz, 1H,

CH_2O), 4.53 (dd, *J* = 2.2, 8.8 Hz, 1H, C*H*(NHCO)), 5.30 (d, *J* = 1.4 Hz, 1H, ArCHO), 6.58 (s, 1H, ArH), 6.69 (s, 1H, ArH), 7.08 (d, *J* = 7.4 Hz, 1H, ArH), 7.12-7.19 (m, 5H, ArH), 7.20-7.36 (m, 3H, ArH), 8.09 (d, *J* = 8.8 Hz, 1H, CONH disappeared with D_2O).

Cyclization reaction – *a representative procedure*

The fractions consisting of more polar diastereomer (**4c**) (97 mg, 0.2 mmol, 60% de) were refluxed under argon in dry toluene (10 mL) for 24 h. After cooling to rt, it was evaporated to dryness and the remaining oil (97 mg) dissolved in Et_2O (30 mL) and washed with 5% aqueous HCl (4x2 mL). The organic phase was dried and evaporated yielding (*R*)-(+)-2,3-dimethoxy-8-oxoberbine (**6**) (51 mg) in 82% yield with 23% ee, HPLC [hexane/propan-2-ol=80:20, t_R 27.2 min (major), t_R 31.5 min].

Addition to acyclic imine (10) – product (11)

Amide (**1c**) (325 mg, 1mmol) was dissolved in dry THF (10 mL) under an argon atmosphere and the solution cooled to −72 ºC. *n*-BuLi (1.6 M solution in hexanes, 1.4 mL) was added and the carbanion generated for 30 min at −72 ºC. A solution of imine (**10**) (253 mg, 1 mmol) in dry THF (6 mL) was added and the mixture kept at −72 ºC for 4h and then treated at this temperature with 20% aqueous NH_4Cl (6mL). When the reaction mixture reached rt, the phases were separated and the aqueous one extracted with Et_2O (3x10 mL). The combined organic extracts were dried and the solvents removed under reduced pressure yielding crude product. HPLC analysis of the crude reaction product indicated the presence of two diastereoisomers (**11**) in a ratio 61:39 [hexane/propan-2-ol=80:20, t_R 19.9 min (major), t_R 21.4 min) together with unreacted amide (**1c**) and imine (**10**). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 200:1 → 50:1) yielding diastereomerically enriched fractions of the more polar diastereomer (321 mg, 56% yield, 49% de HPLC, t_R 19.9 min) and the less polar diastereomer (124 mg, 21% yield, 59% de HPLC, t_R 21.7 min). ^{1}H NMR for more polar diastereoisomer ($CDCl_3$) δ: 1.53 (s, 3H, $C(CH_3)_2$), 1.62 (s, 3H, $C(CH_3)_2$), 1.70 (br s, 1H, NH disappeared with D_2O), 2.48 (dd, *J* = 1.1, 5.8 Hz, 2H, CH_2), 2.76 (dd, *J* = 6.3, 13.2 Hz, 1H, CH_2), 2.89 (dd, *J* = 6.3, 13.2 Hz, 1H, CH_2), 3.21 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.74 (t, *J* = 7.1 Hz, 1H, C*H*(OCH_3)), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.04 (dd, *J* = 1.9, 12.1 Hz, 1H, CH_2O), 4.33 (t, *J* = 5.5 Hz, 1H, ArC*H*NH), 4.37 (dd, *J* = 2.2, 12.9 Hz, 1H, CH_2O), 4.49 (dd, *J* = 2.2, 8.8 Hz, 1H, C*H*(NHCO)), 5.32 (d, *J* = 1.9 Hz, 1H, ArCHO), 6.64 (d, *J* = 8.8 Hz, 1H, CONH), 6.68-6.79 (m, 1H, ArH), 6.91 (d, *J* = 7.4 Hz, 4H, ArH), 7.07-7.41 (m, 6H, ArH); IR (KBr) ν: 3446 (NH), 1662 (C=O) cm^{-1}; MS *m/z* (%): 579 (M^++1, 0.3), 563 (M^+ – CH_3, 0.7), 489 (2), 416 (16), 255 (16), 254 (100), 222 (35), 190 (10), 177 (6), 118 (6), 75 (22). Anal. Calcd for $C_{33}H_{42}N_2O_7$: C, 68.49; H, 7.32; N 4.84. Found: C, 68.07; H, 7.71; N, 4.42.

Pomeranz-Fritsch-Bobbitt cyclization

The fractions consisting of more polar diastereomer (**11**) (280 mg, 0.48 mmol, 49% de) were dissolved in 6M aqueous HCl (8 mL) and MeOH (1 mL) and the solution was stirred at rt for 48 h. It was then hydrogenated with hydrogen at 0.3 MPa in the presence of 10% palladium on carbon (280 mg) for 18 h. Next the catalyst was removed by filtration through a pad of Celite, the filtrate was basified with 20% NaOH and extracted with CH_2Cl_2. Organic extracts were dried and solvents removed under reduced pressure. The crude reaction product (**4c**) (124 mg, 50%) was refluxed under argon in dry toluene (10 mL) for 30 h. After work-up the crude reaction product was purified by column chromatography to give (*S*)-(−)-2,3-dimethoxyberbine (**6**) in 26% yield with 53% ee, HPLC [hexane/propan-2-ol=80:20, t_R 27.2 min, t_R 31.5 min (major)];$[\alpha]_D$ −188.3° (*c* 0.60, $CHCl_3$) {lit.,[3] $[\alpha]_D$ −413.8° (*c* 0.359, $CHCl_3$), >99% ee}.

ACKNOWLEDGEMENTS

This work was supported by research grants from the State Committee for Scientific Research in the years 2003−2006 (KBN Grant No. 4 T09A 078 24) and the Ministry of Sciences and Information Society Technologies in the years 2005−2006 (MNI Grant No. 3 T09A 102 28).

REFERENCES

1. M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341.
2. M. Chrzanowska, A. Dreas, and M. D. Rozwadowska, *Tetrahedron: Asymmetry*, 2004, **15**, 1113.
3. M. Chrzanowska and A. Dreas, *Tetrahedron: Asymmetry*, 2004, **15**, 2561.
4. M. Chrzanowska, A. Dreas, and M. D. Rozwadowska, *Tetrahedron: Asymmetry*, 2005, **16**, 2954.
5. M. Khaldi, F. Chretien, and Y. Chapleur, *Tetrahedron Lett.*, 1995, **36**, 3003.
6. S. Ibn-Ahmed, M. Khaldi, F. Chretien, and Y. Chapleur, *J. Org. Chem.*, 2004, **69**, 6722.
7. T. N. Le, S. G. Gang, and W.-J. Cho, *Tetrahedron Lett.*, 2004, **45**, 2763.
8. T. N. Le, S. G. Gang, and W.-J. Cho, *J. Org. Chem.*, 2004, **69**, 2768.
9. R. D. Clark, *Heterocycles*, 1985, **23**, 825.
10. M. Watanabe, M. Sahara, S. Furukawa, R. Billedeau, and V. Snieckus, *Tetrahedron Lett.*, 1982, **23**, 1647.
11. M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R. Billedeau, and V. Snieckus, *J. Org. Chem.*, 1984, **49**, 742.
12. R. A. Ward and G. Procter, *Tetrahedron*, 1995, **51**, 12301.
13. R. D. Clark, A. Jahangir, M. Souchet, and J. R. Kern, *J. Chem. Soc., Chem. Commun.*, 1989, 930.
14. V. Derdau and V. Snieckus, *J. Org. Chem.*, 2001, **66**, 1992.
15. D. Enders, V. Braig, M. Boudon, and G. Raabe, *Synthesis*, 2004, 2980.

16. R. N. Warrener, L. Liu, and R. A. Russell, *Chem. Commun.*, 1997, 2173.
17. L. Liu, *Synthesis*, 2003, 1705.
18. M. Boudou and D. Enders, *J. Org. Chem.*, 2005, **70**, 9486.
19. W. M. Whalley and M. Meadow, *J. Chem. Soc.*, 1953, **23**, 1067.
20. D. B. MacLean and R. Marsden, *Can. J. Chem.*, 1987, **62**, 1392.
21. D. Brózda, M. Chrzanowska, A. Głuszyńska, and M. D. Rozwadowska, *Tetrahedron:Asymmetry*, 1999, **10**, 4791.