The highly diastereoselective addition of organometallic derivatives of trimethylsilylacetylen to *N*-Boc-*O*-Me-L-thyrosinal – synthesis directed towards anisomycin

Henryk Gruza,[a] Dorota Gryko,[a] and Janusz Jurczak[*a,b]

[a] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw,*
[b] *Deparment of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland*
E-mail: jurczak@icho.edu.pl

Dedicated to Professor Mieczysław Mąkosza on the occasion of his 70th birthday
(received 30 Oct 03; accepted 15 Jan 04; published on the web 30 Jan 04)

Abstract
Anisomycin analogue precursor was synthesised starting from a suitably protected α-amino aldehyde - tyrosine. The crucial step involves the addition of acetylenic reagent to *N*-Boc-*O*-methyl-L-tyrosinal in the presence of zinc(II) bromide, affording a *syn*-acetylenic adduct with high diastereoselectivity.

Keywords: Anisomycin, α -amino aldehydes, acetylenic addition, asymmetric synthesis

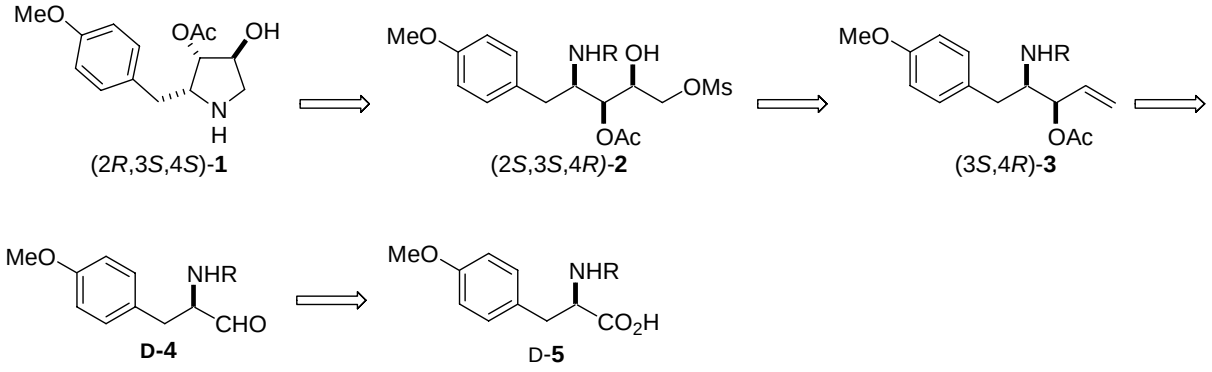
Introduction

Polyhydroxylated pyrrolidines and piperidines have received much attention since many representatives have been reported to exhibit interesting physiological effects. Anisomycin (**1**) is an antibiotic which was first isolated from the fermentation broths of *streptomyces* by Sobin and Tanner in 1954.[1] Since its isolation, this alkaloid has attracted much interest due to its potent and specific antibiotic activity[2] against several microorganisms. These properties have been successfully used in the clinical treatment of amoebic dysentery and *trichomonas vaginitis*.[2] Anisomycin (**1**) and its derivatives have also been employed as fungicides in plant infections.[3] Renewed interest in this antibiotic and its derivatives has arisen when high anti-tumor activity in vitro was reported.[4] The structure and relative stereochemistry of anisomycin (**1**) were studied chemically[5] and then determined by X-ray crystallographic analysis.[6] The absolute stereochemistry being (2*R*,3S,4*S*) was established on the basis of chemical correlation studies.[7] As a result, many approaches have been developed for the asymmetric synthesis of anisomycin (**1**)[8-15] but there is still a need for more efficient and elegant procedure In the continuation of our efforts on the application of a methodology with the use of α-amino aldehydes to the synthesis of

natural compounds,[16-24] we have undertaken an effort directed towards the synthesis of the title alkaloid.

Results and Discussion

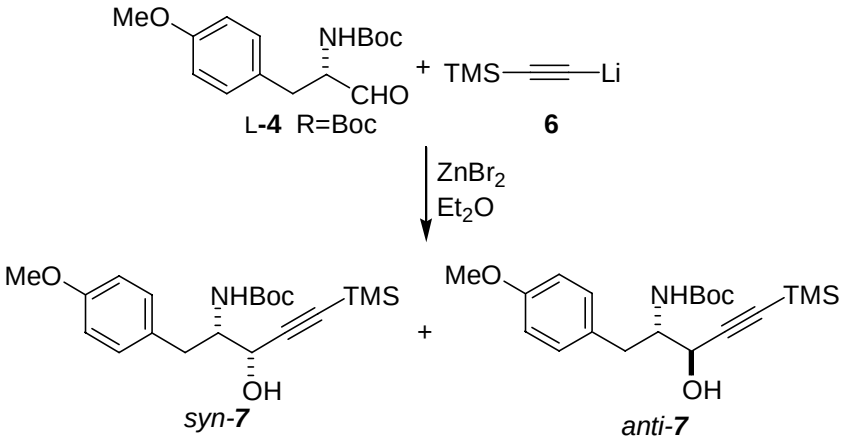
The retrosynthetic analysis, shown in Scheme 1, suggested that *N,O*-protected-D-thyrosinal of type **4** could serve as a starting material. Following our successful studies concerning the addition of various organometallic compounds[16,25-28] to α-amino aldehydes, we envisaged that a propargylic addition to a suitably protected D-thyrosinal would be a key step. On the basis of earlier investigations[25] we assumed that the use of *N*-monoprotected-*O*-methyl derivative of D-thyrosinal (D-**4**) in the addition reaction should give desired *syn*-adduct predominantly. Among several possible *N*-protecting groups, the Boc group was selected since it can be easily removed under mild conditions.



Scheme 1

Recently we have reported the highly diastereoselective addition of the lithium derivative of *tert*-butyldimethylsilyl propargyl ether to *N*-Boc-*N,O*-isopropylidene-L-serinal.[28] It was found that the *syn*-selectivity was observed when the propargylic addition was carried out in the presence of most of the commonly used Lewis acid whereas *anti*-isomer predominated when HMPA or anhydrous $CeCl_3$ was used as an additive. Moreover, it has recently been reported[13] that the addition of ethynylmagnesium bromide to *N*-monoprotected-D-tyrosinal gave *syn*-diastereoisomer predominantly. Having in mind our synthetic goal, we selected *N*-monoprotected α-amino aldehyde and because it is known that the *N*-protecting groups strongly influences the stereochemical course of the nucleophilic addition to the carbonyl group,[25] we extended our model studies to *N*-Boc-*O*-Me-L-thyrosinal (L-**4**).[29] Addition of lithium derivative of trimethylsilylacetylen (**6**) proceeded with moderate *anti*-stereoselectivity (82:18) and in a good yield (Scheme 2, Table 1, Entry 1). When the same reaction was carried out in the presence of HMPA as an additive, only *anti*-diastereoisomer **7** was isolated in 92% yield (Entry 2). The

direction of asymmetric induction was the same as for the addition of an acetylenic reagent to the Garner's aldehyde[28] and it can be explained by the Felkin-Anh model **A** (Figure 1).[30, 31] Then the addition reaction of **6** to L-**4** was carried out in the presence of various Lewis acids. It was found that when anhydrous $CeCl_3$ was used, *anti*-isomer **7** predominated (Entry 3) whereas the use of $ZnCl_2$ afforded *syn*-isomer **7** as the major product in 68% yield. *syn*-Selectivity as well as the yield was further improved when the reaction was catalysed by $ZnBr_2$ instead of $ZnCl_2$ (Entries 4, 5). In this case the etynyl reagent attacks carbonyl group from the less hindered side of the chelation-controlled cyclic Cram model **B** (Fig. 1).[32]



Scheme 2

Table 1. Addition of acetylenic reagent to tyrozinal L-**4**

Entry	Additive	Yield [%]	Ratio *anti:syn*
1	none	87	82:18
2	$CeCl_3$	90	>95:5
3	HMPA	92	>95:5
4	$ZnCl_2$	68	10:90
5	$ZnBr_2$	90	>5:95

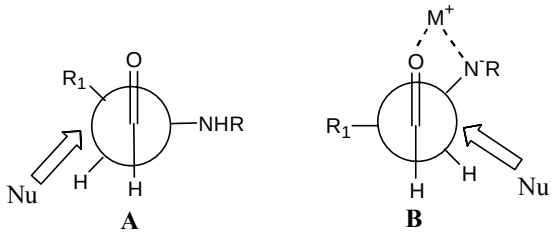
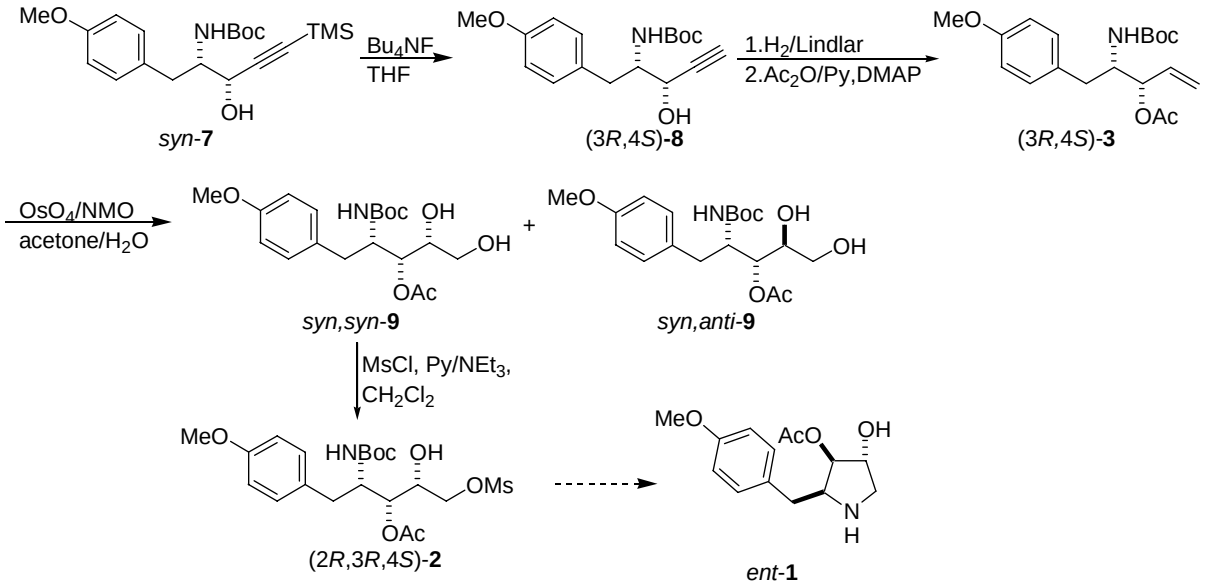


Figure 1

Having in hand highly stereoselective method for the preparation of *syn*-**7** and *anti*-**7** acetylenic adduct derivatives of *N*-Boc-*O*-Me-L-thyrosinal L-**4** we directed our efforts towards the synthesis of unnatural anisomycin *ent*-**1**. We pursued our studies exploiting compound *syn*-**7** (Scheme 3).



Scheme 3

syn-Adduct **7** was treated with crystalline $Bu_4NF{\cdot}3H_2O$[33] giving desilylated compound (3*R*,4*S*)-**8** in 88% yield. Subsequent hydrogenation, in the presence of a Lindlar catalyst,[34] yielded the vinyl adduct which was treated with acetic anhydride[35] affording (3*R*,4*S*)-**3**. This compound could be obtained by the direct addition of a vinyl organometallic reagent to *N*,*O*-diprotected-L-thyrosinal L-**4** but there is no highly effective procedure for this transformation. *syn*-Dihydroxylation of (3*R*,4*S*)-**3** with NMO and OsO_4[36] gave a mixture of diastereoisomeric polyhydroxylated amines **9**. The diastereoisomeric ratio was 4:1 in favour of the desired isomer *syn*,*syn*-**9**. After the chromatographic separation the primary hydroxy group of *syn*,*syn*-**9** was mesylated[37] in order to facilitate five-membered ring formation but unfortunately all attempts to do so failed to afford the desired antibiotic *ent*-**1**. Similar transformation was successfully accomplished using the Appel procedure by Jäger *et al*.[38] In his case, a polyhydroxylated amine with the neighbouring *N*-Bn and *O*-Bn triol, was used as pyrrolidine precursor. In this situation we did not further investigate our approach to the synthesis of anisomycin **1**.

In summary, we have presented highly diastereoselective addition of lithium trimethylsilylacetylen (**6**) to *N*-Boc-*O*-Me- L-thyrosinal (L-**4**), affording *anti*- or *syn*-adduct **7** depending on the conditions used. The synthetic interest of these transformations was illustrated by the preparation of the anisomycin precursor (2*R*,3*R*,4*S*)-**2**.

Experimental Section

General Procedures. All chemicals were used as received unless otherwise noted. Reagent grade solvents ($CHCl_3$, CH_2Cl_2, hexanes, AcOEt) were distilled prior use. All reported NMR spectra were recorded with a Bruker spectrometer at 500 (^{1}H NMR) and 125 (^{13}C NMR) MHz or with a Varian Gemini spectrometer at 200 (^{1}H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS signal defined at δ = 0.00 (^{1}H NMR) or δ = 0.0 (^{13}C NMR). IR spectra were obtained on a Perkin-Elmer 1640 FTIR unit. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or LSIMS technique. Chromatography was performed on silica (Kieselgel 60, 200-400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell.

Compound L**-4.** [29] Yield 90%, ^{1}H NMR (500 MHz, DMSO-d_6) 1.34 (s, 9H), 2.65 (dd, *J* = 13.0 Hz, *J* = 10.0 Hz, 1H), 3.00 (dd, *J* = 13.0 Hz, *J* = 4.8, 1H), 3.70 (s, 3H), 4.00 (m, 1H), 6.8-7.1 (m, 4H), 7.2-7.3 (m, 1H), 9.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) 28.1, 32.5, 61.0, 78.3, 113.6, 129.5, 130.1, 155.5, 157.8, 201.3; IR (KBr) 770, 835, 1034, 1164, 1248, 1367, 1514, 1613, 1701, 2978, 3364; HR EIMS $C_{15}H_{21}NO_4$ $(M)^+$ calcd 279.1471, found 279.1470.

Compound *syn*-7. To the precooled to -50°C solution of trimethylsilylacetylen (12.3 mmol) in dry toluene (30 ml) the solution of *n*-BuLi in hexane (12 mmol, 7.5 ml, 1.6M) was added dropwise. The resulted mixture was stirred for 45 min during which time the temperature was raised to -30°C and then $ZnBr_2$ (1 mmol) was added. After 1 h, the reaction mixture was cooled to -78°C and the precooled solution of L-thyrosinal derivative L**-4** (6 mmol) in toluene (5 ml) was added. When the reaction was completed (TLC) the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into aqueous NH_4Cl_{sat}. It was then extracted three times with AcOEt and the organic layer was worked up in the usual manner. The column chromatography (silica, hexanes/AcOEt) afforded adduct *syn*-**7** as an amorphous solid, in the yield shown in Table 1. ^{1}H NMR (200 MHz, $CDCl_3$) 0.22 (s, 9H), 1.40 (s, 9H), 2.7-2.9 (m, 2H), 3.12 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 3.9-4.1 (m, 1H), 4.38 (dd, *J* = 3.0 Hz, *J* = 7.2 Hz, 1H), 4.7 (d, *J* = 8.0 Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) –0.13, 28.3, 36.6, 55.3, 56.8, 65.4, 77.5, 80.1, 103.1, 114.0, 129.3, 130.1, 130.3, 158.4; IR (KBr) 849, 1014, 1177, 1247, 1527, 1692, 2180, 2835, 2959, 3373; Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.61; H, 8.29; N, 3.71. Found: C, 63.59; H, 8.39; N, 3.51; $[\alpha]_D^{20}$ -1.8 (*c* 1, $CHCl_3$).

Compound *anti*-7. To the precooled to -50°C solution of trimethylsilylacetylen (12.3 mmol) in dry toluene (30 ml), the solution of *n*-BuLi in hexane (12 mmol, 7.5 ml, 1.6M) was added dropwise. The resulted mixture was stirred for 45 min during which time the temperature was raised to -30°C. Then it was cooled to -78°C and HMPA (0.1 mmol) was added. After 0.5 h, the precooled solution of L-thyrosinal derivative L**-4** (6 mmol) in toluene (5 ml) was added. When the reaction was completed (TLC) the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into aqueous NH_4Cl_{sat}. It was then extracted three times with with AcOEt, and the organic layer was worked up in the usual

manner. The column chromatography (silica, hexanes/AcOEt) afforded adduct *anti*-**7** as an amorphous solid, in the yield shown in Table 1. ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (s, 9H), 1.44 (s, 9H), 2.7-2.9 (m, 2H), 3.21 (d, *J* = 6.2 Hz, 1H), 3.68 (s, 3H), 3.9-4.1 (m, 1H), 4.31 (dd, *J* = 3.2 Hz, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.8 Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) -0.09, 28.3, 36.3, 55.2, 57.7, 66.3, 77.0, 8.21, 100.1, 113.3, 129.0, 130.3, 130.5, 158.9; IR (KBr) 760, 840, 1038, 1066, 1176, 1246, 1300, 1368, 1455, 1626, 1611, 1678, 2177, 2835, 2980, 3388; HR EIMS $C_{20}H_{31}NO_4Si$ $(M)^+$ calcd 377.2022, found 377.2022.$[\alpha]_D^{20}$ -2.6 (*c* 1, $CHCl_3$).

Compound 8. To the solution of *syn*-**7** (700 mg, 1.86 mmol) in dry THF (10 ml), Bu_4NF (50 mg) was added. After 5 min, the reaction mixture was extracted twice with Et_2O. The organic layer was washed with water and brine. Filtration through the silica pad gave 645 mg (yield 88%) of desilylated compound **8** as an viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) 1.40 (s, 9H), 2.5-2.8 (m, 3H), 3.78 (s, 3H), 4.00 (m, 1H), 4.38 (m, 1H), 4.80 (brs, 2H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) 28.2, 36.6, 55.2, 56.9, 62.5, 77.5, 80.1, 83.3, 114.0, 129.3, 130.1, 130.6, 158.9; IR (KBr) 1054, 1177, 1237, 1537, 1612, 1698, 2187, 2836, 2987, 3350; EIMS (m/z) $C_{17}H_{23}NO_4$ 306 $(M+H)^+$, 248, 150, 121, 86,57; $[\alpha]_D^{20}$ -5.4 (*c* 1, $CHCl_3$).

Compound (3*R*,4*S*)-3. Hydrogenation of compound **8** (610 mg, 2 mmol) in the mixture of toluene and quinoline (1:1, 14 ml) in the presence of Lindlar catalyst for 2 h at room temperature. After filtration, the reaction mixture was washed with water and brine. Column chromatography (silica, hexanes/AcOEt) afforded 530 mg of vinyl alcohol derivative which was treated with a mixture of Ac_2O and pyridine (1:1) in the presence of catalytic amount of DMAP. Standard workup, followed by filtration through a silica pad, gave (3*R*,4*S*)-**3** (600 mg, 97%) as an viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) 1.36 (s, 9H), 2.10 (s, 3H), 2.6-2.9 (m, 2H), 3.20 (brs, 1H), 3.74 (s, 3H), 3.8-4.0 (m, 1H), 4.20 (brs, 1H), 5.2-5.4 (m, 2H), 5.93 (ddd, *J* = 5.5 Hz, *J* = 10.4 Hz, *J* = 16.2 Hz, 1H), 6.8-7.2 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 29.3, 37.5, 50.6, 54.3, 55.1, 74.4, 79.4, 113.8, 118.0, 129.2, 130.1, 133.6, 155.3, 158.2, 169.6; IR (KBr) 840, 1053, 1176, 1300, 1357, 1445, 1606, 1611, 1678, 1704, 2838, 2987, 3388; ; HR EIMS $C_{19}H_{27}NO_5$ $(M)^+$ calcd 349.1892, found 349.1896; $[\alpha]_D^{20}$ +6.5 (*c* 1.3, $CHCl_3$).

Compound *syn,syn*-9. To a solution of (3*R*,4*S*)-**3** (52 mg, 0.15 mmol) in a mixture of acetone/H_2O (7:1, 2.4 ml), were added subsequently *N*-methylmorpholine (170 mg, 1.26 mmol) and the solution of OsO_4 (0.01 mmol) in *tert*-BuOH (0.2 ml). The reaction mixture was stirred until the disappearance of the starting material (TLC) then saturated $NaHSO_{3aq}$ (20 ml) and Et_2O were added. The organic layer was washed with saturated solution of NaH_2PO_{4aq} and brine. Column chromatography (silica, hexanes/AcOEt, 2:8) gave both oily diastereoisomers *syn,syn*-**9** (38 mg) and *syn,anti*-**9** (10 mg). ^{1}H NMR (200 MHz, $CDCl_3$) 1.40 (s, 9H), 2.10 (s, 3H), 2.50 (dd, *J* = 1.7 Hz, *J* = 6.9 Hz, 1H), 2.9-3.1 (m, 2H), 3.55 (dd, *J* = 10.1 Hz, *J* = 14.3 Hz, 1H), 3.76 (s, 3H), 4.1-4.3 (m, 2H), 4.6-4.8 (m, 1H), 5.20 (s, 1H), 6.8-7.2 (m, 4H); IR (KBr) 816, 1132, 1276, 1543, 1619, 1711, 2878, 2995, 3069, 3500; HR LSIMS $C_{19}H_{29}NO_7$ $(M)^+$ calcd 383.1944, found 383.1952; $[\alpha]_D^{20}$ +4.5 (*c* 1.0, $CHCl_3$).

Acknowledgements

This work was supported by the Polish State Committee for Scientific Research, Grant PBZ 6.05/T09/1999.

References

1. Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053.
2. Korzybski, T.; Kowszyk-Gindifer, Z.; Kurylowicz, W. *Antibiotics*, Vol. 1, American Society of Microbiology, Washington DC, **1978**, 343.
3. *The Merck Index, 12th Edn*., Budavari, S., Ed.; Merck: Whitehouse Station, NJ, 1996, p 710.
4. Hosoya, Y.; Kameyama, T.; Naganawa, H.; Okami Y.; Takeuchi T. *J. Antibiotics* **1993**, *46,* 1300.
5. Bereboom, J. J.; Butler, K.; Pennington, F. C.; Solomons, I. A. *J. Org. Chem.* **1965**, *30*, 2334.
6. Schaefer, J. P.; Weatley, P. J. *J. Org. Chem*. **1968**, *33*, 166.
7. Wong, C. M. Can. *J. Chem.* **1968**, *46,* 1101.
8. Merino, P.; Frnco, S.; Lafuente, D.; Merchan, F.; Revuelta, J.; Tejero, T. Eur. *J. Org. Chem.* **2003**, 2877.
9. Chang, M-Y.; Chen, S-T.; Chang, N-C. *Heterocycles* **2003**, *60*, 1203.
10. Huang, P-Q.; Zheng, X. *ARKIVOC* **2003**, *(ii)*, 7.
11. Chandrasekhar, S.; Ramachandar, T.; Venkat Reddy, M. *Synthesis* **2002**, 1867.
12. Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4,* 265 and references cited herein.
13. Chang, K-T.; Chang Jang, K.; Park, H-Y.; Kim, Y-K.; Park, K. H.; Lee, W. S. *Heterocycles* **2001**, *55*, 1173.
    Huang, P. Q.; Tang, X.; Chen, A. Q. *Synth. Commun*. **2000**, *30*, 2259.
14. Jäger, V.; Öhrlein, R.; Wehner, V.; Poggendorf, P.; Steuer, B.; Raczko, J.; Greisser, H.; Keiss, F-M.; Menzel, A. *Enantiomer* **1999**, *4*, 205.
15. Ono, M.; Suzuki, K.; Akita, H. *Tetrahedron Lett*. **1999**, *40*, 8223.
16. Gryko, D.; Prokopowicz, P.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1103.
17. Jurczak, J.; Prokopowicz, P.; Gołębiowski, A. *Tetrahedron Lett*. **1993**, *34*, 7107.
18. Gryko, D.; Jurczak, J. *Polish J. Chem.* **2002,** *76*, 959.
19. Gryko, D.; Jurczak, J. *Tetrahedron Lett.* **1997**, *38,* 8275.
20. Krasiński, A.; Gruza, H.; Jurczak, J. *Tetrahedron: Asymmetry* **200**1, *12,* 111.
21. Krasiński, A.; Jurczak, J. *Tetrahedron Lett.* **2001**, *42*, 2019.
22. Gołębiowski, A.; Jurczak, J. *Synlett* **1993**, 241.
23. Kiciak, K.; Jakobson, U.; Gołębiowski, A.; Jurczak, J. *Polish J. Chem*. **1994**, *68*, 199.
24. Jurczak, J. In *Preparative Carbohydrate Chemistry*; Hanessian, S. Ed.; Dekker: NJ, 1997, p 593.
25. Gryko, D.; Chałko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

26. Kobrzycka, E.; Gryko, D.; Jurczak. *Tetrahedron: Asymmetry* **2002**, *13*, 2133.
27. Gryko, D.; Jurczak, J. *Helv. Chim. Acta* **2000**, *83*, 2705.
28. Gruza, H.; Kiciak, K.; Krasiński, A.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2627.
29. Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051.
30. Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 1245.
31. Anh, N. T. *Topics Curr. Chem.* **1980**, *88*, 114.
32. Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 5719.
33. Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732.
34. *Organic Synthesis* **1985**, 64, 108.
35. Höfle, I.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int., Ed.* **1978**, *17*, 569.
36. Jarosz, S. *Polish J. Chem*. **1992**, *66*, 1853.
37. Fürst, A.; Koller, F. *Helv. Chim. Acta.* **1947**, *30*, 1454.
38. Schwardt, O.; Veith, U.; Gaspard, Ch.; Jäger, V. *Synthesis* **1999**, 1473.