Asymmetric [4+2] cycloaddition of cyclopentadiene to N'-tosylimine of N-glyoxyloyl-(2R)-bornane-10,2-sultam

Tomasz Bauer[*],[a] Sławomir Szymański,[a] Artur Jeżewski,[b] Przemysław Gluziński[b] and Janusz Jurczak[*],[a,b,*]

[a] Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland
[b] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland

Abstract: The first synthesis of the N'-tosylimine of N-glyoxyloyl-(2R)-bornane-10,2-sultam using a modified Holmes method is described. The N'-tosylimine was used as a dienophile in the Lewis acid-catalyzed diastereoselective imino-Diels–Alder reaction with cyclopentadiene to give cycloadducts with good diastereoisomeric excess. The direction of the asymmetric induction depends on the Lewis acid used. © 1997 Elsevier Science Ltd

The hetero-Diels–Alder reaction of imines with 1,3-dienes is a potent tool in the synthesis of six-membered heterocycles, being the backbone of several alkaloids and antivirial compounds.[1] The pioneering work of Grieco and Bahsas,[2] who used the methylene iminium species derived from α-methylbenzylamine has been extended by Waldman *et al.*[3] to include α-amino acid derived imines. Stella *et al.*[4] and Bailey *et al.*[5] have introduced glyoxylate imino derivatives and obtained excellent diastereoselectivities. In all cases chiral auxiliaries were attached to the nitrogen atom. Recently, Holmes *et al.*[6] have developed a new, mild method for the synthesis of imines of chiral glyoxylates derived from ethyl (S)-lactate.[7] The hetero-Diels–Alder reaction of such imine with cyclopentadiene furnished the appropriate derivatives of azabicyclo[2.2.1]heptane with 76% diastereoisomeric excess (d.e.).

Our previous work[8,9] on the hetero-Diels–Alder reaction of N-glyoxyloyl-(2R)-bornane-10,2-sultam **2**, obtained by the thermal degradation of the stable, crystalline hemiacetal **1**[10] (Scheme 1), has shown very good diastereofacial differentiation properties of this new glyoxylic acid derivative bearing the very efficient chiral auxiliary -(R)-bornane-10,2-sultam.[11]
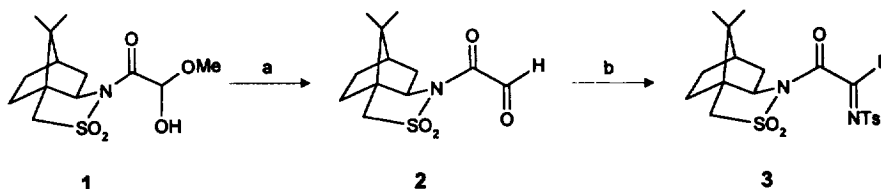

Scheme 1. Reagents and reaction conditions: (a) 110°C, 0.1 mmHg, 2 h; (b) *p*-TsNCO, toluene, 110°C, 32 h.

The nitrogen–carbonyl group bond in N-glyoxyloyl-(2R)-bornane-10,2-sultam **2** is highly base-sensitive and so far all our attempts at the synthesis of this type of chiral imine by classical methods have failed. In such a situation, we tried the method introduced recently by Holmes *et al.*[6,7] The reaction of compound **2** with *p*-toluenesulfonyl isocyanate in refluxing toluene afforded the expected imine **3**, which we employed to the diastereoselective [4+2] cycloaddition with cyclopentadiene (Scheme 2).

The [4+2] cycloaddition of cyclopentadiene to chiral heterodienophile **3** theoretically could give rise to four stereoisomers: two *exo* diastereoisomers **4** and **5**, and two *endo* diastereoisomers. However,

---

* Corresponding author. Email: jurczak@ichf.edu.pl
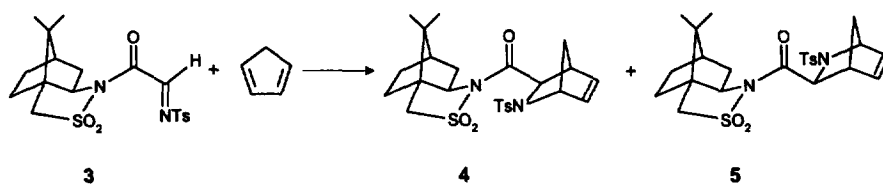
Scheme 2.

Table 1. The asymmetric [4+2] cycloaddition of cyclopentadiene to imine 3[a)

Entry	Pressure [atm]	Temp. [°C]	Catalyst	Time [h]	Yield[b) [%]	Asymmetric induction (6'R)-4:(6'S)-5
1	1	20	none	48	64	36:64
2	15000	20	none	24	34	27:73
3	1	20	2%Eu(fod)₃	24	65	34:66
4	15000	20	2%Eu(fod)₃	96	64	25:75
5	1	-78	10%SnCl₄	2.5	20	47:53
6	1	-78	50%SnCl₄	2.5	14	53:47
7	1	-78	100%SnCl₄	2.5	14	73:27
8	1	-78	20%TiCl₄	2	17	80:20
9	1	-78	50%TiCl₄	2	38	80:20

[a)]All the reactions were carried out in toluene as a solvent.

[b)]Isolated yields, calculated on the starting compound 1.

when the reaction was carried out under ambient conditions without any catalyst only the two *exo* diastereoisomers **4** and **5** were obtained in a ratio of 36:64 (Table 1, Entry 1). Both diastereoisomeric adducts are crystalline compounds. Their absolute configuration was established by X-ray analyses, which revealed that adduct **4** has (6'R) and adduct **5** (6'S) configuration, with *exo* disposition of the carbonyloxysultam moiety and *endo* disposition of the tosyl group (Figs 1 and 2, respectively). The results of the [4+2] cycloaddition of cyclopentadiene to chiral imine **3**, carried out under various conditions, are presented in Table 1.

Several aspects of the data shown in Table 1 are noteworthy. The reaction carried out at ambient temperature and pressure afforded the diastereoisomeric cycloadducts in a relatively good yield, but with rather low asymmetric induction (Entry 1). Therefore we decided to enhance asymmetric induction by application of high-pressure techniques[12] and/or by Eu(fod)₃ catalysis.[13,14] As in the case of the atmospheric pressure experiment with Eu(fod)₃ (Entry 3) the application of high-pressure methodology without catalyst (Entry 2) and with Eu(fod)₃ (Entry 4) did not change substantially the yield and the diastereoisomeric composition of the product. In all the above-mentioned cases (Entries 1–4) the (S) absolute configuration was generated at the newly formed stereogenic center of the major diastereoisomer. Upon application of stronger Lewis acid type catalysts: SnCl₄ (Entries 5–7) and TiCl₄ (Entries 8,9) we observed the change of the direction of asymmetric induction, namely the major diastereoisomer possesed the (R) absolute configuration on the new stereogenic center. The extent of asymmetric induction depended on the concentration of a catalyst in the case of SnCl₄ (Entries 6,7) and it was independent in the case of TiCl₄ (Entries 8,9). In all the cases studied (Entries 5–9) the yield was low and the diastereoisomeric excess of the major cycloadduct was rather moderate.

Rationalization of our results obtained for the noncatalyzed thermal as well as high pressure [4+2]
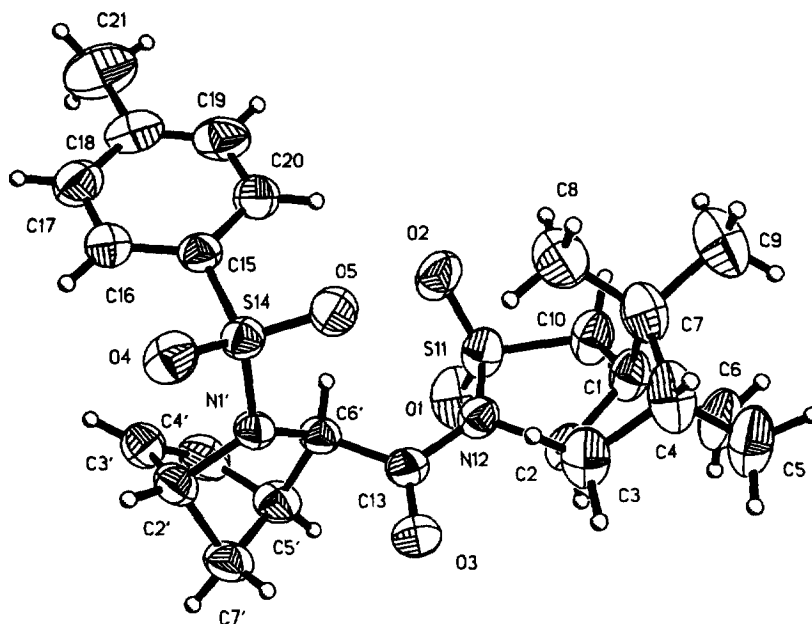
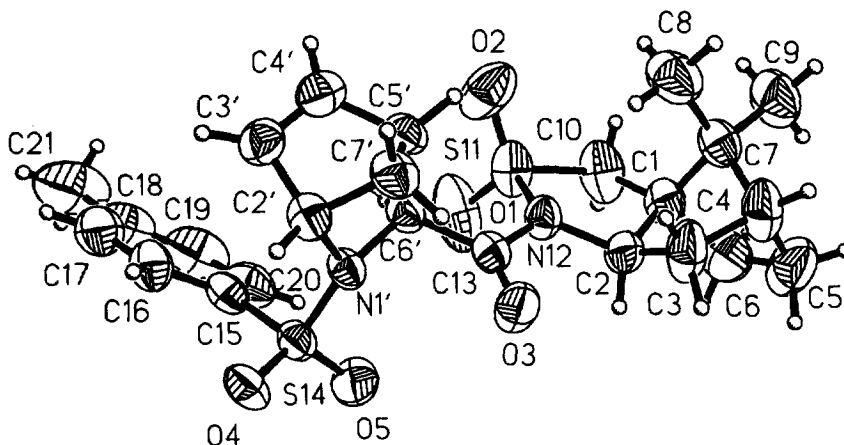Figure 1. ORTEP diagram of compound 4 showing labelling scheme and (R) configuration at C6'.

Figure 2. ORTEP diagram of compound 5 showing labelling scheme and (S) configuration at C6'.

cycloaddition may be based on two concepts: (a) the sterically controlled approach of a diene to the thermodynamically more stable SO_2/CO antiperiplanar, CO/CHNTs s-*cis* planar conformer **A**, as proposed by Oppolzer *et al.*[10,15] and by Curran *et al.*[16] for *N*-acryloyl- and *N*-crotonoyl-(2R)-bornane-10,2-sultam; and (b) the high reactivity of the less stable SO_2/CO synperiplanar, CO/CHNTs s-*cis* planar conformer **B**, reinforced by the cooperative stereoelectronic effect, as recently formulated by Chapuis *et al.*[9,17] for *N*-glyoxyloyl-(2R)-bornane-10,2-sultam **2**. The conformational equilibrium may be even more complicated in the view of, as recently proposed by Pindur *et al.*,[18] reactive SO_2/CO antiperiplanar, CO/CHNTs s-*trans* planar conformation **C** which cannot be excluded in our case (Scheme 3).

Analogous to the case of *N*-glyoxyloyl-(2R)-bornane-10,2-sultam **2**, for its *N'*-tosylimine derivative
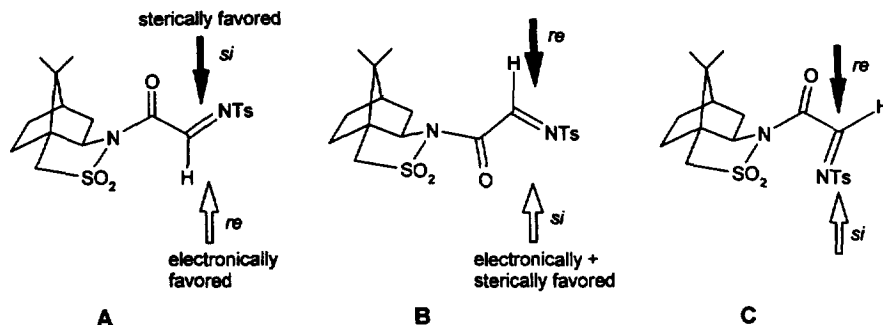
Scheme 3.

3 the more stable conformer **A** should be preferred over conformer **B** due to electrostatic and/or dipole–dipole repulsion between the sultam oxygen and the glyoxyloyl moiety.[19] It is also noteworthy that under high-pressure conditions, the CO/CHO s-*cis* conformation of chiral glyoxylates is favoured.[12,20] Therefore, the approach of cyclopentadiene to the dienophile **3** should occur from the top side of the bornane skeleton (*si* attack) as it has been observed earlier for similar cycloadditions.[15] On the other hand, the less stable but highly reactive conformer **B** shows also that *si* attack of cyclopentadiene is favoured for thermal and high-pressure [4+2] cycloadditions.[9,17] The s-*cis* conformations are also postulated for *N'*-tosylimine **3**, similarly as in the case of *N*-crotonoyl-[15] and *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2**,[9] complexed with a weak Lewis acid such as Eu(fod)₃, involving the same transition states and rationalization as used for the noncatalyzed reaction.

The opposite direction of asymmetric induction observed for the [4+2] cycloaddition of cyclopentadiene to *N'*-tosylimine **3** catalyzed by a stronger Lewis acid like TiCl₄ and SnCl₄, could be explained as a *re* attack of diene on the SO₂/CO synperiplanar, CO/CNTs s-*trans* conformation **D** or s-*cis* conformation **E** (Scheme 4). Similar conformations, where the catalyst chelates both the SO₂ and CO groups to rigidify the side chain, have earlier been postulated by Oppolzer *et al.*[11] for rationalization of asymmetric induction in the reaction of cyclopentadiene with *N*-enoylsultams.

M = Ti, Sn
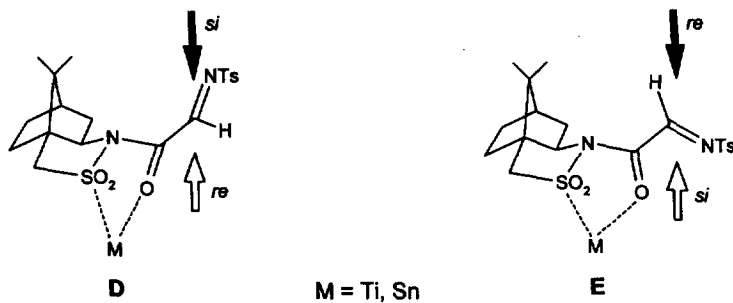
Scheme 4.

Experimental

General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. ¹H NMR spectra were recorded using a Bruker AM 500 (500 MHz) spectrometer, and ¹³C NMR spectra were recorded using a Bruker AM 500 (125 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer in KBr pellets. Mass

spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Single-crystal X-ray diffraction analysis was performed on an Enraf-Nonius MACH 3 diffractometer. Flash-column chromatography was performed according to Still et al.[21] on silica gel (Kieselgel-60, Merck, 200–400 mesh). Cyclopentadiene was prepared prior to use by distillation of a commercially available cyclopentadiene dimer. Methyl hemiacetal of N-glyoxyloyl-(2R)-bornane-10,2-sultam 1 was prepared according to our own methodology.[10]

[4+2] Cycloaddition of cyclopentadiene to dienophile 3. General procedures.

A. Thermal reaction. Methyl hemiacetal 1 (303 mg, 1 mmol) was heated at 110°C/0.1 mmHg for 1 h. The oily residue was dissolved in 10 mL of freshly distilled toluene, then tosyl isocyanate (0.15 mL, 1 mmol) was added, and the solution was heated under reflux for 32 h. After cooling, 0.5 mL of freshly distilled cyclopentadiene was added, the reaction mixture was stirred at 20°C for 48 h, then evaporated, and the residue was subjected to flash chromatography on silica gel (hexane–ethyl acetate 8:2) yielding diastereoisomers in 64% overall yield, calculated on the starting hemiacetal 1.

B. High-pressure Eu(fod)$_3$-catalyzed reaction.[22] To a toluene solution of N'-tosylimine 3 (1 mmol) obtained as in the above procedure, Eu(fod)$_3$ (20 mg, 0.002 mmol) and cyclopentadiene (0.5 mL) were added, and the solution was charged into a Teflon ampoule, which was then placed in a high-pressure vessel, and pressure was slowly increased to 15 kbar at 20°C. After stabilization of pressure, the reaction mixture was kept under these conditions for 24 h. After decompression, the solvent was evaporated and the residue was subjected to flash chromatography as in the previous procedure.

C. TiCl$_4$-catalyzed reaction. To cold −78°C toluene, a solution of N'-tosylimine 3 (1 mmol) was added, under argon, TiCl$_4$ (95 mg, 0.5 mmol) and cyclopentadiene (0.5 mL). The reaction mixture was stirred under these conditions for 2 h, and then it was worked up as in the previous procedure.

Analytical and spectral data for (6'R)-4

Mp 156–158°C (dec.) (from acetone–n-hexane); $[\alpha]_D^{20}$ = +172.1 (c 1.02, CHCl$_3$); ν_{max} (KBr, cm^{-1}) 1696, 1331, 1161, 666; δ_H (500 MHz, CDCl$_3$) 7.81 (d, J=8.3, 2H), 7.29 (d, J=8.3, 2H), 6.15 (m, 1H), 5.94 (dd, J$_1$=2.0, J$_2$=5.5, 1H), 5.19 (bs, 2H), 4.64 (s, 1H), 4.00 (dd, J$_1$=4.8, J$_2$=7.8, 1H), 3.97 (s, 1H), 3.55 (s, 2H), 3.29 (s, 1H), 2.41 (s, 3H), 2.08 (dd, J$_1$=7.9, J$_2$=14.0, 2H), 2.04–1.88 (m, 4H), 1.43–1.25 (m, 3H), 1.16 (s, 3H), 0.99 (s, 3H); δ_C (125 MHz, CDCl$_3$) 168.4, 143.3, 136.2, 135.3, 129.5, 128.0, 126.2, 76.2, 65.2, 64.5, 52.8, 50.4, 48.7, 47.6, 45.2, 44.4, 38.1, 32.5, 26.1, 21.4, 20.7, 19.7; m/z (EIHR) calculated for C$_{24}$H$_{30}$N$_2$O$_5$S$_2$ (M)$^+$ 490.1600, found 490.1596.

Analytical and spectral data for (6'S)-5

Mp 189–191°C (dec.) (from acetone–n-hexane); $[\alpha]_D^{20}$ = +15.4 (c 1.01, CHCl$_3$); ν_{max} (KBr, cm^{-1}) 1706, 1329, 1163, 663; δ_H (500 MHz, CDCl$_3$) 7.70 (d, J=8.2, 2H), 7.25 (d, J=8.2, 2H), 6.10 (m, 1H), 5.82 (dd, J$_1$=2.3, J$_2$=5.3, 1H), 4.68 (s, 1H), 3.95 (bs, 2H), 3.79 (s, 1H), 3.53 (s, 2H), 3.39 (s, 1H), 2.40 (m, 4H), 2.23 (m, 1H), 2.07 (dd, J$_1$=7.2, J$_2$=15.6, 1H), 1.99–1.85 (m, 3H), 1.46–1.31 (m, 3H), 1.27 (s, 3H), 0.99 (s, 3H); δ_C (125 MHz, CDCl$_3$) 169.5, 143.5, 136.7, 135.1, 134.8, 129.5, 128.2, 120.3, 76.7, 65.6, 64.1, 58.1, 53.2, 49.6, 48.9, 47.8, 45.5, 44.6, 38.1, 32.8, 26.5, 21.5, 20.6, 19.9; m/z (EIHR) calculated for C$_{24}$H$_{30}$N$_2$O$_5$S$_2$ (M)$^+$ 490.1600, found 490.1596.

X-Ray structure determination of compounds (6'R)-4 and (6'S)-5

Crystal data and measurement conditions are given in Table 2. The positions of the hydrogen atoms bonded to carbon atoms were generated from the assumed geometries. The structure was solved by the SHELXS 86[23] and refined with the SHELXL 93[24] programs. Lists of the fractional atomic coordinates, isotropic thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

Table 2. Crystal data and measurement conditions for compounds (6'R)-4 and (6'S)-5

	(6'R)-4	(6'S)-5
Formula	$C_{24}H_{30}N_2O_5S_2$	
Molecular weight	487.63	
Crystal system	orthorhombic	
a [Å]	7.512(9)	7.587 (1)
b [Å]	12.498 (1)	12.670 (1)
c [Å]	25.534 (4)	24.979 (4)
V [Å³]	2397.3 (3)	2401.2 (3)
Molecular multiplicity	Z = 4	
Calculated density [g x cm⁻³]	1.36	
Space group	$P2_12_12_1$	
Radiation (graphite monochromated)	Cu K$_\alpha$	
Wavelength [Å]	1.54178	
Linear absorption coeff. μ [mm⁻¹]	2.33	
Number of electrons F (000)	1040	
Crystal size [mm]	0.22 x 0.25 x 0.21	0.32 x 0.30 x 0.35
Temperature [°C]	22 ± 1	
Diffractometer	Enraf-Nonius MACH 3	
Scan mode	ω/2θ	
Scan range 2θ [°]	0 - 150	
Number of collected data:		
total measured	2858	5588
unique [with I > 2σ (I)]	2722	3898
R_1	0.0305	0.0530
WR$_2$	0.0835	0.1289
GoF	1.0360	1.0570

Acknowledgements

References

1. Weinreb, S. M.; Steib, R. R. *Tetrahedron* **1982**, *38*, 3087.
2. Grieco, P.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5745.
3. Waldmann, H., Braun, M.; Draeger, M. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1468, and references cited therein.
4. Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Leclercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2063.
5. Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337.
6. Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29.
7. Hamley, P.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; McKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1992**, 786.
8. Bauer, T.; Chapuis, C.; Kozak, J.; Jurczak, J. *Helv. Chim. Acta* **1989**, *72*, 482.
9. Bauer, T.; Chapuis, C.; Jeżewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391.
10. Bauer, T.; Jeżewski, A.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1385.
11. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.
12. Jurczak, J. *Polish J. Chem.* **1979**, *53*, 2539.
13. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
14. Jurczak, J.; Gołębiowski, A.; Bauer, T. *Synthesis* **1985**, 928.
15. Oppolzer, W.; Poli, G.; Starkeman, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559.

16. Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555.
17. Chapuis, C.; Saint Laumer, J.-Y.; Marty, M. *Helv. Chim. Acta* **1997**, 146.
18. Pindur, U.; Lutz, G.; Fischer, G.; Massa, W.; Schroder, L.; Schollmeyer, D. *Tetrahedron* **1993**, *49*, 2863.
19. Kim, K. S.; Kim, B. H.; Park, W. M.; Cho, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 7472.
20. Jurczak, J.; Tkacz, M. *J. Org. Chem.* **1979**, *44*, 4347.
21. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2939.
22. Gołębiowski, A.; Jacobsson, U.; Jurczak, J. *Tetrahedron* **1987**, *43*, 3063.
23. Sheldrick, G. M. SHELXS 86 *Program for the Solution of Crystal Structures*, **1985** University of Gottingen, Germany.
24. Sheldrick, G. M. SHELXL 93 *Program for the Refinement of Crystal Structures*, **1993** University of Gottingen, Germany.