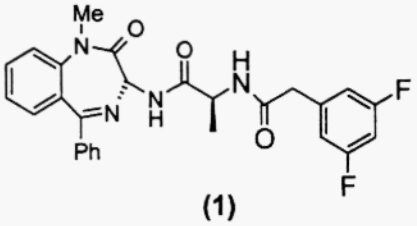
SYNTHESIS OF SOME NOVEL SPIRO BENZODIAZEPINES INCLUDING A PYROLIDINE RING

H. Ali Dondas[a]* and Sultan Sönmez[b]

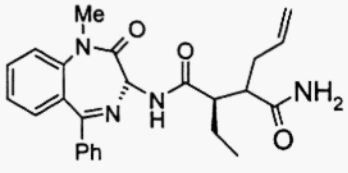
a. Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Mersin-Turkey
b. Mersin University, Science and Arts, Faculty, Chemistry Department, Mersin-Turkey

Abstract: Some novel spiro-benzodiazepines derivatives were prepared via thermal and metal catalysed imine-azomethine ylide-1,3-dipolar cycloaddition cascades reactions. This substrate allows the influence of the new stereocentres on the cascade to be assessed with respect to the configuration of the azomethine ylide that is generated and the facial selectivity of the subsequent cycloaddition.

Introduction: Benzodiazepines have been known to posses important medicinal properties for the last several years. Some benzodiazepines derivatives have been found to be potent antagonist of the peptide hormones cholecystokinin (CCK) and gastrin[1-4] The 1,4-benzodiazepines have constitutes a class of widely used anxiolytic and anticonvulsant drug[5]. Recently some amino and succinoylamino benzodiazepines such as **(1-2)** have been useful in treatment of neurologic disorders related to β-amyloid production such as Alzheimer's disease and Down's Syndrome[6].



(1)



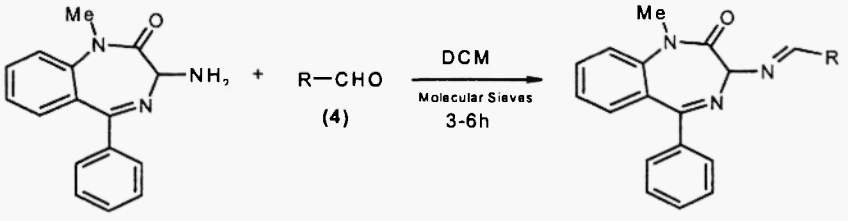
(2)

Grigg *et al* have recently reported a range of imine -> azomethine ylide -> cycloaddition cascades reactions furnishing azomethine ylide and their cycloadduct in good yields[7-9] Inter- and intra-molecular cycloaddition reactions of azomethine ylide have attracted much attention because they provide a potentially flexible entry into the complex molecular framework of natural products[10-12]. We have previously shown that amines of benzodiazepine react with aldehyde to generate imine which then gave azomethine ylide via thermal and metal catalysed processes. 1,3-dipolar cycloaddition cascades reactions with chiral and achiral dipolarophiles afforded cycloadduct in good to excellent yield[12]

Results and Discussion: We now report a study of cycloaddition cascades reactions to imines of 1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one. This substrate allows the influence of the new stereocentres on the cascade to be assessed with respect to the configuration of the azomethine ylide that is generated and the facial

selectivity of the subsequent cycloaddition. The reactions proceed via intermediate NH azomethine ylides (scheme 2) and litho azomethine ylides (scheme 3) respectively.

Imines derived from benzodiazepine **(3)** and aldehydes **(4)** undergo either the 1,2-prototropic schift to give azomethine ylides or in presence of metal salts to give metallo azomethine ylides then undergo 1,3-dipolar cycloaddition with dipolarophiles. Imines of 1-methyl-3-amino-1,3-dihidro-5-phenyl-(2H)-1,4-benzodiazepine-2-one which was liberated from its p-toluene sulphonic acid salt by treatment with ammonium hydroxide and extraction into dichloromethane (scheme 1). The imines were then underwent thermal (toluene 110 °C or xylene 140 °C) regio- and stereo-specific cycloaddition to achiral dipolarophiles N-phenylmaleimide (NPM) and N-methylmaleimide (NMM) gave racemic spiro-cycloadducts in good to excellent yield.



(3)

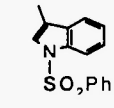
(5)

a. R = , 76%

b. R = , 88%

c. R = , 82%

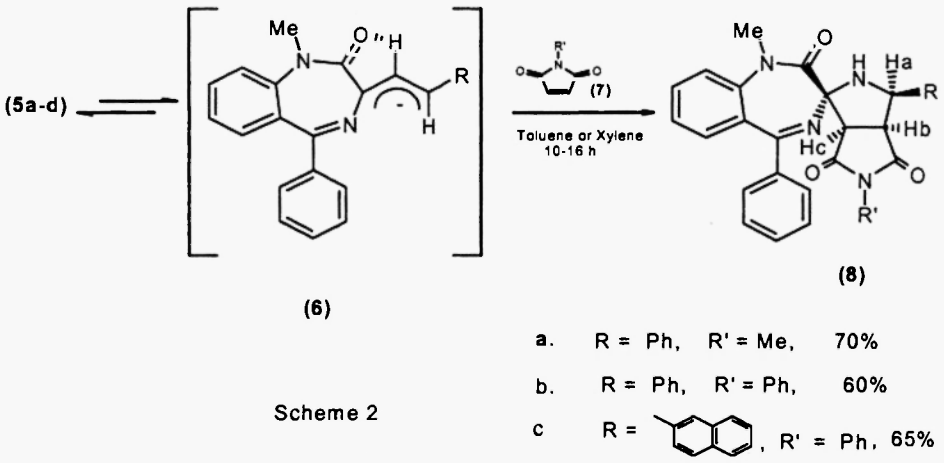
d. R = , 84%



Scheme 1

When the imines **(5a-c)** were boiled under reflux in toluene in presence of (NPM) and (NMM) cycloaddition occured stereospecifically to afford the cycloadducts **(8a-c)** in 65-70% yield(scheme 2). In case of imine **(5d)** did not undergo thermal cycloaddition under the standart conditions with NPM. When the solvent changed to xylene at 140 °C, only trace amount of desired product and some possible decomposition products were obtained (^{1}Hnmr). This is probably due to the solubility and reactivity of the corresponding imine.

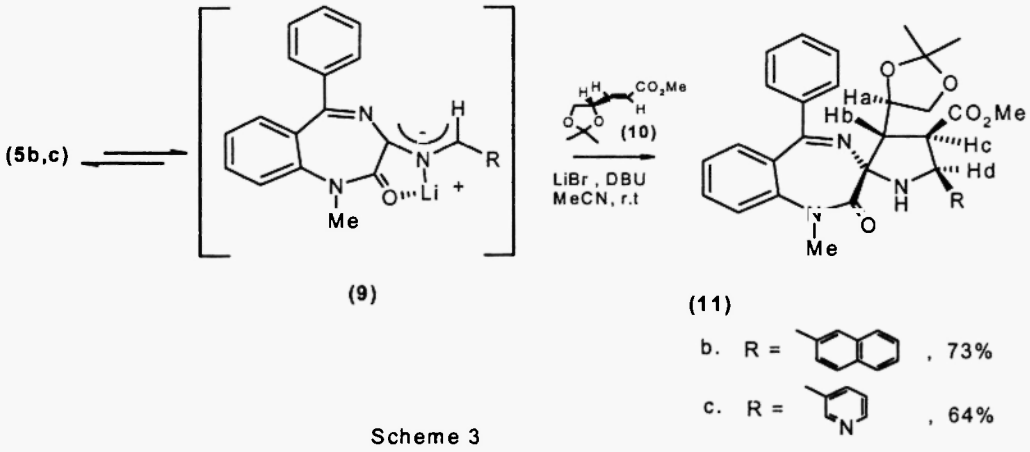
During these cycloadditions a purple colour developed and then largely discharged. This colour is ascribed to the resonance stabilised 1,3-dipole **(6)**. The cis stereochemistry of Ha, Hb and Hc was readily established from n.O.e data and conforms to that expected [9,10] whilst the C2-stereochemistry is assigned on the basis of previous studies[11,12] and an X-ray crystal structure of analogue[12]. These structure agree also with the previous studies on the cycloaddition of NMM and NPM to the similar systems[13,14]. The formation of single stereoisomers in these kinetically controlled cycloaddition indicates stereospecific formation of a single dipole (scheme 2) via 1,2-prototropy.



Scheme 2

Some examples of room temperature, lithium bromide catalysed cascade cycloaddition reactions of (**5b, c**) was carried out with chiral dipolarophile (**10**). Thus imine (**5b,c**) reacted regiospecifically with methyl (S)-(+)-(3-(2,2-dimethyl-1,3-dioxalan-4yl)-trans-2-propenoate under the influence of LiBr and DBU in acetonitrile over 5-6h to give cycloadduct (**11b,c**) in 3:2 mixture of diastereoisomer in 64-68% yield (Scheme 3).

Similar results were observed by Kanemasa[15] and Annunziata[16] in their studies on azomethine ylide cycloaddition to unsaturated esters bearing either alylic stereocenter or alkoxy chirotopic but non stereogenic substituent imbedded in a chiral imidazoline ring. As in our case , the formation of only two diastereoisomeric products was observed, resulting from a totally regioselective endo-cycloaddition of a W-shaped dipole[7,17].



Scheme 3

In conclusion we have shown that 1,3-dipolar cycloaddition of azomethine ylide to imines, derived from a benzodiazepine, with achiral and chiral dipolarophile gave spirocycloadduct in good to excellent yield. The reaction

occurs regio- and stereo- specific under thermal and metal catalyst conditions and a flexible approach to potentially bioactive heterocycles has beeen developed.

EXPERIMENTAL

Microanalyses were obtained using a Carlo - Erba Model 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. Nuclear magnetic resonance spectra and decoupling experiments were determined at 300 MHz. on a Q.E 300 instrument and at 400 MHz on a Bruker AM400 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad and brs= broad singlet. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF_{254} (Merck 7730). Petroleum ether refers the fraction with b.p 40-60 °C unless otherwise specified. Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

General Procedure for Imine Formation

A mixture of aldehyde(1eq), amine(1.05 eq) and activated 4A molecular sieves in dry DCM was stirred either at room temperature (5a-c) or 40 °C for (5d) for an appropriate time(3-6h). After removal of the molecular sieves the solvent was evaporated under reduced pressure (bath temperature not higher than 30 °C) and the residue was crystallised from an appropriate solvent.

N-(2'-Phenylmethylidene)-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one (5a)
The product (76%) crystallised from ether-petroleum ether as colourless prisms, m.p. 146-149 °C.
δ(300 MHz): 9.42(s, 1H, CH=N), 7.84-7.14(m, 14H, ArH), 5.41(s, 1H, CHN) and 3.49(s, 3H, NMe). m/z (%): 353 (M+, 45), 237(100), 77(55) and 51(30).

N-(2'-Naphthylmethylidene)-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one (5b)[12].
The product (88%) crystallised from ether-petroleum ether as colourless prisms, m.p. 179-181 °C.
(Found: C, 78.6; H, 5.25; N, 9.9, $C_{27}H_{21}N_3O.0.5H_2O$ requires: C, 78.6; H, 5.55; N, 10.2 %) δ(300 MHz): 9.39(s, 1H, CH=N), 8.4-7.19(m, 16H, ArH), 5.48(s, 1H, CHN) and 3.45(s, 3H, NMe). m/z (%): 404 (M+1, 100), 266(40), 249(49), 221(53) and 141(9).

N-(2'-Pyridylylmethylidene)-1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one (5c) [12]. The product (82%) precipitated from ether-petroleum ether as a pale yellow amorphous solid, m.p. 97-99 °C. (Found: C, 72.45; H, 4.95; N, 15.4, $C_{22}H_{18}N_4O.0.5H_2O$ requires: C, 72.7; H, 4.95; N, 15.4 %) δ(300MHz): 9.35(s,

1H, CH=N), 8.7 and 8.31(2xd, 2x1H, Pyridine-H), 7.82-7.21(m, 11H, ArH), 5.5(s, 1H, CHN) and 3.49(s, 3H, NMe). m/z(%): 354 (M^+, 3), 265(36), 235(89), 222(65), 194(74), 122(68), 79(99) and 52(100)

N-[3'-(N-phenylsulphonyl)-indolylmethylidene]1-methyl-3-amino-1,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepine-2-one(5d). The product (84%) crystallised from ether-ethanol as colourless prisms, m.p. 212-214 °C. (Found: C, 69.8; H, 4.4; N, 10.4; S, 6.1, $C_{31}H_{24}N_4O_3S$ requires: C, 69.9; H, 4.55; N, 10.5; S, 6.0 %). δ(300MHz): 9.39(s, 1H, CH=N), 8.81(d, 1H, Ar-H) , 8.03(s, 1H, indole-H), 8.02-7.21(m, 17H, ArH), 5.51(s, 1H, CHN) and 3.48(s, 3H, NMe). m/z(%) (FAB): 593 (M+1, 100), 393(8), 286(8), 266(38), 249(80) and 77(15).

General Procedure for Thermal Cycloaddition:

A solution of imine (1mmol), and N-phenylmaleimide (NPM) or N-methylmaleimide(NMM) (1mmol) in dry degassed toluene or xylene (30ml.) was heated at 110 °C and 140 °C under a nitrogen atmosphere for 9-16h. The solvent was then evaporated under reduced pressure and the residue crystallised from an appropriate solvent.

Cycloadduct (8a): After a reaction time of 8h and work up the product (70%) crystallised from petroleum ether-hexane as a colourless amorphous, m.p. 270-274 °C.(Found: C, 72.46, H, 4.8, N, 11.8., $C_{28}H_{24}N_4O_3$ requires: C, 72.4, H, 5.15, N, 12.0). δ (400 MHz): 7.75-7.2(m, 14H, ArH), 5.0.(d, 1H, J 8.4 Hz, Ha), 3.52(s, 3H, NMe), 3.12(br, 1H, NH), 3.0(t, 1H, J 7.4Hz, Hb), 2.75(s, 3H, NMe) and 2.35(d, 1H, J 7.2 Hz, Hc). m/z (%) (EI): 465 (M+1, 5), 447(45), 446(100) and 360(48).

n.O.e data:

Signal		Enhancement(%)			
Irradiated	H_a	H_b	H_c	NH	ArH
H_a		14.7		3.5	4.5
H_b	13.2		15.4		
H_c		13.5			
N_H	11.0				6.5

Cycloadduct (8b): After a reaction time of 16h and work up the product (66%) crystallised from dichloromethane-hexane as a pale violet amorphous, m.p. 196-198°C. (Found: C, 75.5, H, 4.9, N, 10.9, $C_{33}H_{26}N_4O_3$ requires: C, 75.3, H,4.9, N, 10.3%). δ (400 MHz): 8.3-7.3(m, 19H, ArH), 7.0.(d, 1H, J 7.6 Hz, Hc), 6.9(q, 1H, Hb), 5.1(d, 1H, J 7.2 Hz, Ha), 4.9(3.12(br, 1H, NH), 3.9(s, 3H, NMe). m/z (%) (FAB): 525 (M-1, 5), 510(24), 508(100) and 507(8).

Cycloadduct (8c): After a reaction time of 16h and work up the product (65%) crystallised from petroleumether-diethylether as a pale violet amorphous, m.p. 204-206. (Found: C, 77.25, H, 4.75, N, 9.75, $C_{37}H_{28}N_4O_3$ requires: C, 77.1, H,4.9, N, 9.73%). δ (400 MHz): 8.3-7.3(m, 21H, ArH), 7.0.(d, 1H, Hc), 6.8(t, 1H, Hb), 5.1(d, 1H, Ha), 4.9(d, 1H, NH), 3.9(s, 3H, NMe). m/z (%) (FAB): 575 (M-1, 5), 560(25), 558(100) and 557(11).

General Procedure for The Lithium Bromide Catalysed Cycloaddition Reactions:

A mixture of the imine (1eq.), DBU(1.1 eq), dipolarophile (1eq.) and LiBr (1.5eq.) in freshly distilled acetonitrile was stirred at room temperature under an atmosphere of N_2 until reaction was complete. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution, and extracted with methylene chloride (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was crystallised from an appropriate solvent.

Cycloadduct (11a): After a reaction time of 6h and work up the product (73%) precipitated from hexane-ethanol as a pale brown oil which was obtained as a 3:2 mixture of diastereoisomer. (Found(HRMS): 589.2561, C36H35N3O5 requires: 589.2576. δ(400 MHz): 8,05-7,06(m,16 H, ArH), 4.99 and 4,80(2xd, 1H, J 8.6 Hz, Hd,isomer), 4.01(m, 1H, OCH), 3.65(m, 2H, OCH2), 3.52(s, 3H, NMe), 3.51(ms, 3H, CO_2Me), 3.41(br, 1H, NH) 2.64 and 2.47(2xm, 1H, Hc isomer), 2.53(d, 1H, J 5.3 Hz, Hb), 1.40 and 1.30(2xs, 3H, Me, isomer), 1.24 and 1.13(2xs, 3H, Me, isomer). m/z (%) (FAB): 590(M+1, 92), 572(77), 532(5), 403(9), 264(15), 237(100), 221(16), 194(11), 101(22).The protons were assigned on the basis of ^{1}H nmr and ^{2}D COSY studies.

Cycloadduct (11b): After a reaction time of 7 h and work up the product (64%) precipitated from ether-ethanol as a thick pale brown oil which was obtained as a 3:2 mixture of diastereoisomer. (Found(HRMS): 540.2377. $C_{32}H_{32}N_4O_5$ requires: 540.2372. δ(400 MHz): 8,2(m, 1H, pyridine-H), 7.58-7.15(m, 12H, ArH), 4.71 and 4.56(2xd, 1H, J 7.9 Hz, Hd, isomer), 4.22(m, 1H, OCH), 3.86 and 3.39(m, 2H, OCH2), 3.75(br, 1H, NH), 3.49(s, 3H, NMe), 3.45(2xs, 3H, CO_2Me, isomer), 2.73 and 2.63(2xm, 1H, Hc, isomer), 2.56(2xd, J 4.8 Hz, Hb), 1.24 and 1.21(2xs, 3H, Me, isomer), 1.10 and 1.08(2xs, 3H, Me, isomer). m/z (%) (EI): 540(M^+, 1), 522(46), 421(100), 405(14), 389(54), 363(69), 235(56), 221(41), 194(58), 165(22), 77(19) and 43(28). The protons were assigned on the basis of ^{1}H nmr and ^{2}D COSY studies and the stereochemistry was determined by n.O.e data.

n.O.e data:

Signal			Enhancement(%)			
Irradiated	H_d	H_c	H_b	Ha(OCH)	ArH	OCH2β
Hd		4,9		6.8	5.4	
H_c	4.5			7.5		
H_b	3.6			7.5		5.0
H_a	5.4	6.5				3.0
OCH2α	3.2		6.0		7.6	10.5
NH	5.3				8.0	

Acknowledgements: We thank University of Mersin for support.

REFERENCES

1. (a). Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whittler, W. L.; Veber, D. F.; Anderson, P. S. and Freidinger, R. M.; *J. Med. Chem.*, **1989**, 32, 13-16. (b). Lotti, V. J.; Chang, R. S. L.; *Eur. J. Pharmacol.*, **1989**, 162, 273. (c) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whittler, W. L.; Garsky, V. M.; Gilbert, K. F.; Leighton, J. L.; Carson, K. L.; Mellin, E. V.; Veber, D. F.; Chang, R. S. L.; Lotti, v-V. J.; Freedman, S. B.; Smith, A. J.; Patel, S.; Anderson, P. S.; Friedinger, R. M.; *J Med.Chem.*, **1993,** 36,4276-4292.

2. Nishida, A.; Miyata, K.; Tsutsumi, R.; Yuki, H.; Akuzawa, S.; Kobayashi, A.; Kamato, T.; Ito, H.; Yamano, M.; Katuyama, Y.; Satoh, M.; Ohta, M.; Honda, K., *J. Pharmacol. Exp. Ther.*, **1994**, 269, 725-731.

3. Chang, R.S.L.; Lotti, V.J.; Monaghan, R.L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; AlbersSchonberg G.; Patchett, A. A.; Liesch , J. M.; Hensens, O. D. and Spinger, J. P.; *Science* **1985**, 230, 177-179.

4. Evans, B..E.; . Bock, M. G; . Rittle, K. E.; DiPardo, R. M.; Whittler, W. L.; Veber, D. F.; Anderson, P. S. and Freidinger, R. M.; *Proc. Natl. Acad. Sci. U.S.A.*, **1986**, 83, 4918-4922.

5. Van Dort, M.E.; Cliax, B. J.; Gildersleeve, D. L.; Sherman, P. S.; Rosenspire, K. C.; Young, A. B.; Joung, L.; Wieland, D. M; *J. Med. Chem.*, **1988**, 31, 2081-2086.

6. (a). Olson, R. E. ; *Du Pont Pharmaceutical Company* (USA). PCT int. Appl., WO 98/28268, **2000**, 256pp (Patent writtten in English) (b). Seiffert, D. ; Bardley, J. D. ; Rominger, C. M. ; Rominger, D. H. ;Yang, F. ; Meredith Jr, J. E. ; Wang, Q. ; Roach, A. H ; Thompson, L. A. ; Spitz, S. M. ; Higaki, J. N. ; Parakash, S. R. ; Combs, A. P. ; Copeland, R. A. ; Arneric, S. P. ; Hartig, P. R. ; Robertson, D. W. ; Cordell, B. ; Stern, A. M. ; Olson, R. E. and Zaczeg, R. ; *The Journal of Biological Chemistry*, **2000**, 275, 44, 34086-34091.

7. Grigg, R.; Sridharan, V.; *Adv. In Cycloaddition*, JAI Press Inc, **1993**, Vol. 3, 161-204.

8. Barr, D. A.; -Dorrity, M. J.; Grigg, R.; Hargreaves, S.; Malone, J. F.; Mondgomery, J.; Redpath, J.; Stevenson, P.; Thornton-Pett, M.; T*etrahedron*, **1995**, 51, 273-294

9. Barr, D. A.; Grigg, R.; Sridharan, V.; T*etrahedron Lett.*, **1989**, 30, 4727.

10. Grigg, R.; Mc.Meeckin, P.; Sridharan, V.; T*etrahedron*, **1995**, 51, 13347-13357.

11. Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J.; T*etrahedron*, **1995**, 51, 7791-7808.

12. Dondas, H. A.; Grigg, R.; Thornton-Pett, M ; *Tetrahedron* , **1996**, 52, 13455-13466.

13. Durust, Y.; Dondas, H.A.; Ozkoru, N.; *Heterocyclic Commun.*, **1999**, 5(2), 173-178.

14. Dondas, H. A.; Grigg, R.; Thornton-Pett, M ; *unpublished results.*

15. (a). Kanemasa, S.; Hayashi, T.; Tanaka; J.; Yamamoto, H.; Sakurai, T.; *J. Org. Chem.*; **1991**, ***56***, 4473.

(b). Tsuge, O.; Kanemasa, S.; Yoshioka, M.; *J. Org. Chem.*; **1988**, 53, 1384.

16. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T.; *Tetrahedron Asymetry,* **1991**, 2, 1329-1342.

17. (a). Review: Tsuge, O.; Kanemasa, S.; *Advanced in Heterocyclic Chemistry*, **1989, 45,** 231.(b). Barr, D. A.; Grigg, R.; Gunaratne, H. Q. N.; Kemp, J.; Mc.Meeckin, P.; Sridharan, V.; T*etrahedron*, **1988**, 44, 557. **(c).** Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H.; *Chem. Lett.*; **1990**, 105.

Received on August 17, 2002.