

WYKŁAD 6

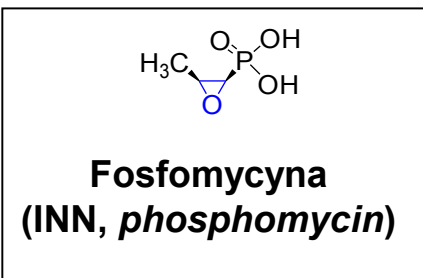
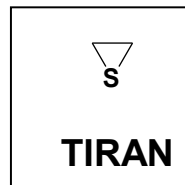
Zalecana literatura

1. Johnson, D. S.; Li, J. J. *The art of drug synthesis*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2007.
2. Torrence P. F. *Antiviral drug discovery for emerging diseases and bioterrorism threats*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2005.
3. Li, J. J.; Johnson, D. S.; Sliskovic, D. R.; Roth B. D. *Contemporary Drug Synthesis*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2004.
4. GAD, S. C. *Drug discovery handbook*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2005.
5. Rolski, S. *Chemia środków leczniczych*, PZWL, Warszawa, 1968.
6. Lednicer, D. *Strategies for organic drug synthesis and design*, John Wiley & Sons, Inc., Hoboken, New Jersey, 1998.
7. Vardanyan, R.; Hruby, V. *Synthesis of essential drugs*, Elsevier B. V. Amsterdam, 2006.
8. Fischer, J.; Ganellin, R. *Analogue-based drug discovery*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2006.
9. Ogólnodostępne podręczniki do chemii organicznej oraz literatura źródłowa.

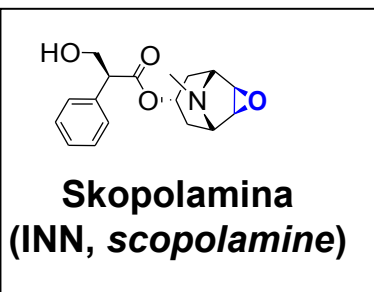
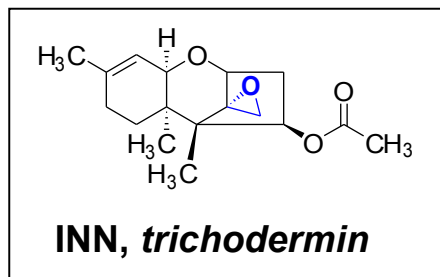
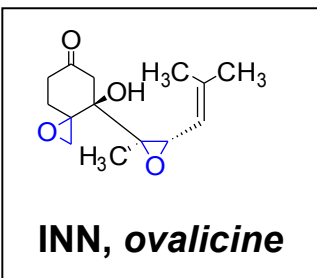
Polskie nazwy omawianych preparatów farmaceutycznych zaczerpnięto z rozporządzenia Komisji (WE) Nr 1549/2006 z dnia 17 października 2006 r. oraz rozporządzenia Rady (WE) nr 129/2007 z dnia 12 lutego 2007 r., załącznik 3: „Wykaz międzynarodowych niezastrzeżonych nazw preparatów farmaceutycznych (INN) przewidzianych przez Światową Organizację Zdrowia, które są zwolnione z cła”.

INN - międzynarodowa niezastrzeżona nazwa preparatu farmaceutycznego przewidziana przez Światową Organizację Zdrowia.

1. Układy trójczłonowe – pochodne oksiranu i azyrydyny



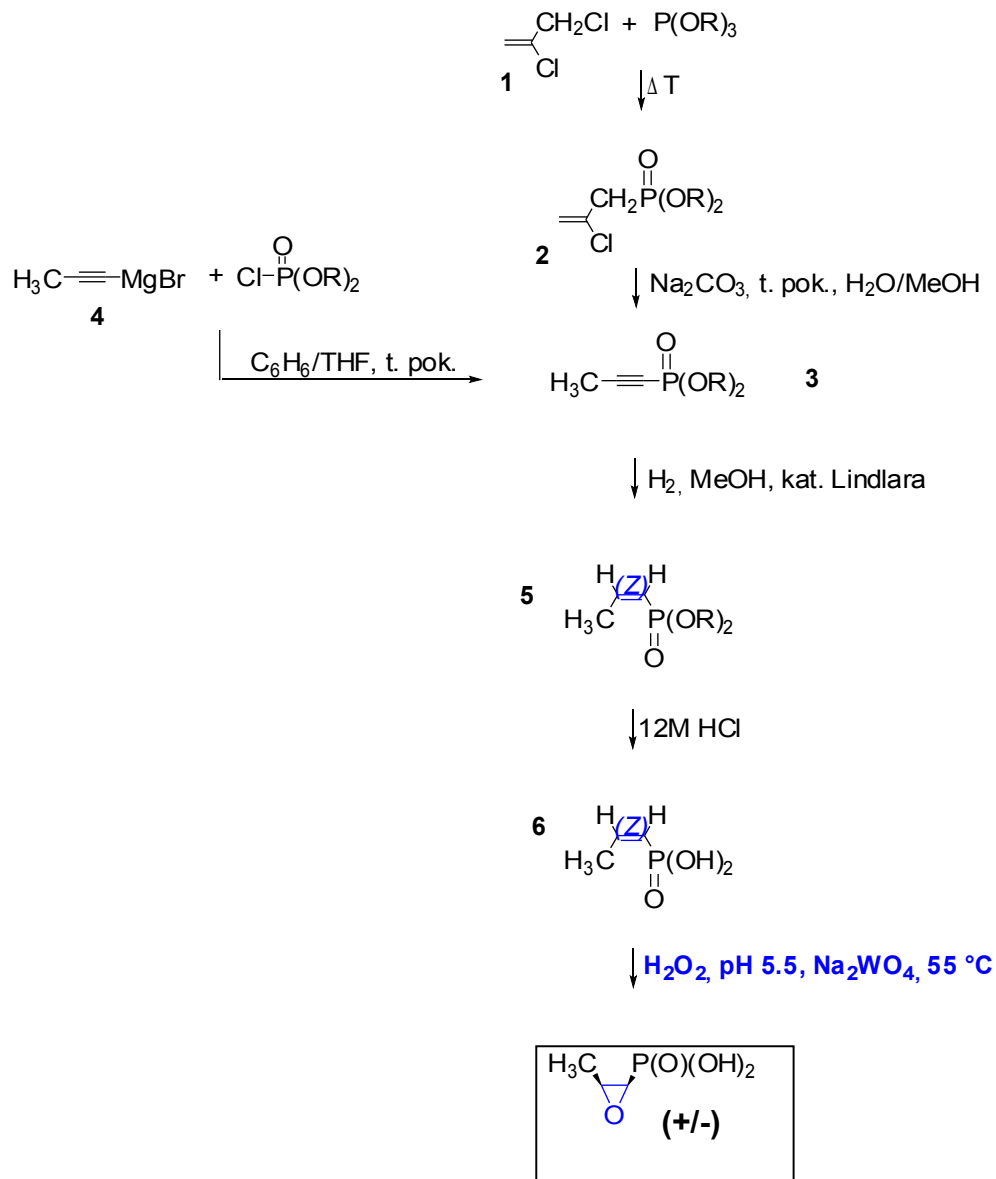
Wyizolowana w 1969 r. ze *Streptomyces fradiae*; antybiotyk o szerokim spektrum działania, aktywna przeciwko bakteriom Gram-dodatnim i Gram-ujemnym.

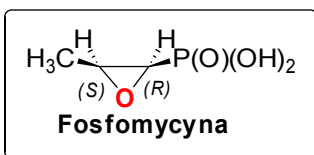
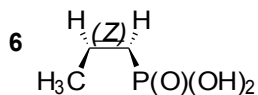
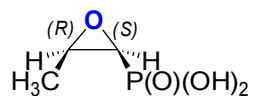


BIELUŃ DZIEDZIERZAWA

1.1. Fosfomycyna

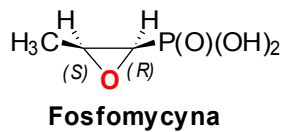
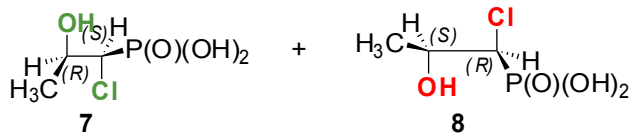
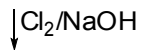
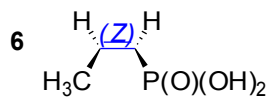
1.1.A. Metoda 1 – utlenianie alkenu





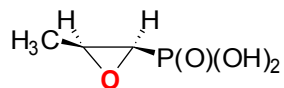
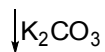
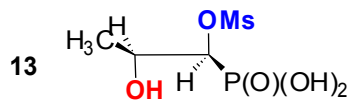
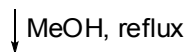
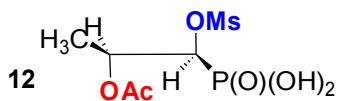
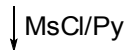
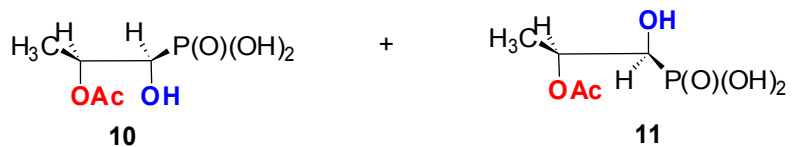
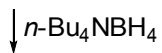
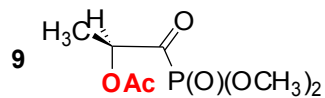
Chem. Ind. (London) 1978, 430.

1.1.B. Metoda 2 – cyklizacja kwasu (1*R*,2*S*)-1-chloro-2-hydroksypropylofosfonowego (8)



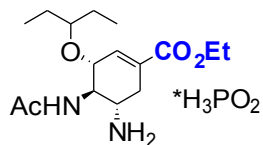
Tetrahedron Lett. 1969, 4647.

1.1.C. Metoda 3 – cyklizacja kwasu (1S,2S)-2-hydroxy-1-(metylosulfonyloksy)propylofosfonowego (13)

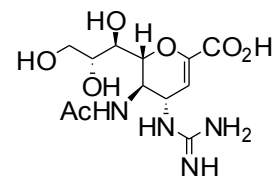


Fosfomycyna

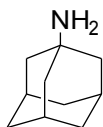
Leki przeciwgrypowe



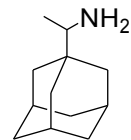
Osetamiwir
(INN, *oseltamivir*, TAMIFLU)



Zanamiwir
(INN, *zanamivir*, RELENZA)

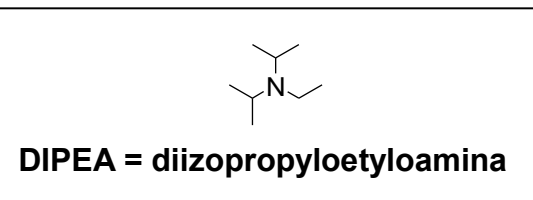
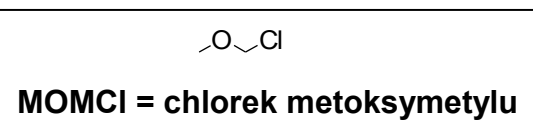
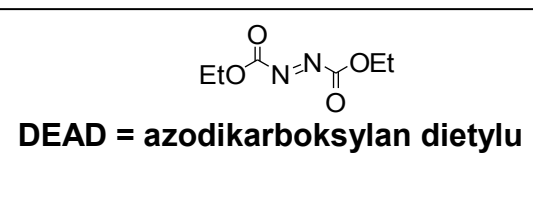
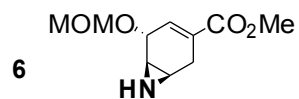
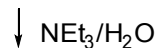
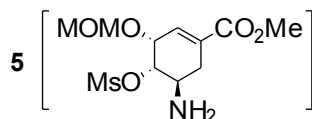
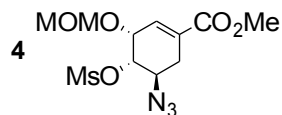
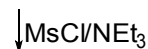
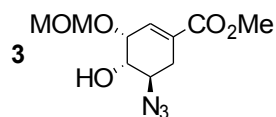
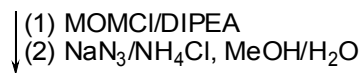
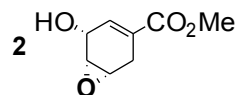
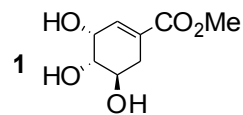
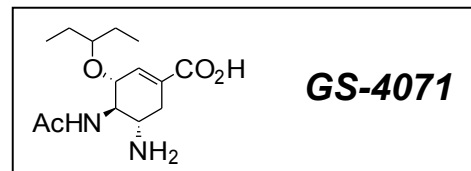


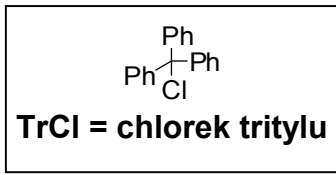
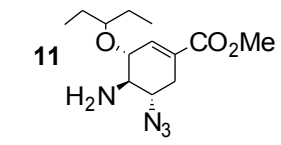
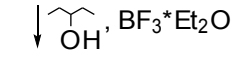
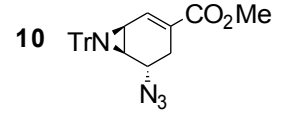
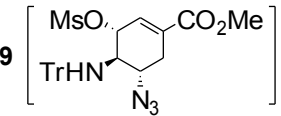
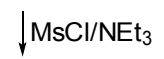
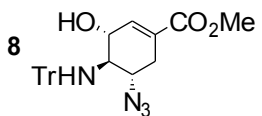
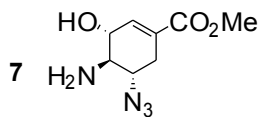
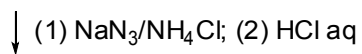
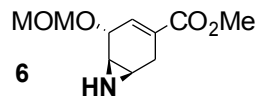
Amantadyna
(INN, *amantadine*)

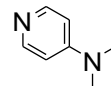


Rymantadyna
(INN, *rimantadine*)

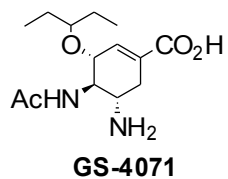
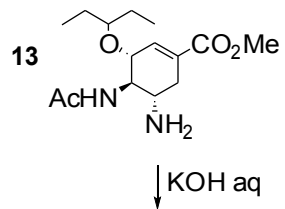
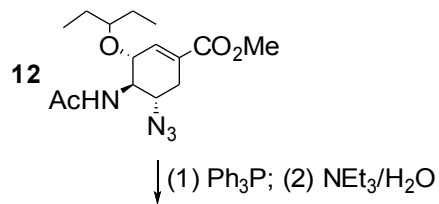
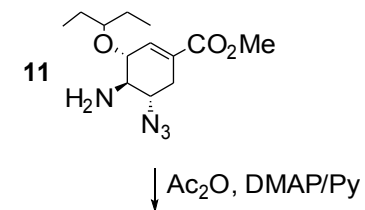
1.2. GS-4071, prekursor oseltamiwiru







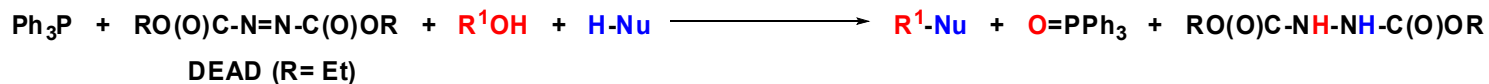
DMAP = 4-dimethylaminopyridyna



***J. Med. Chem.* 1998, 41, 2451**

1.2.A. Wyjaśnienie przebiegu wybranych etapów

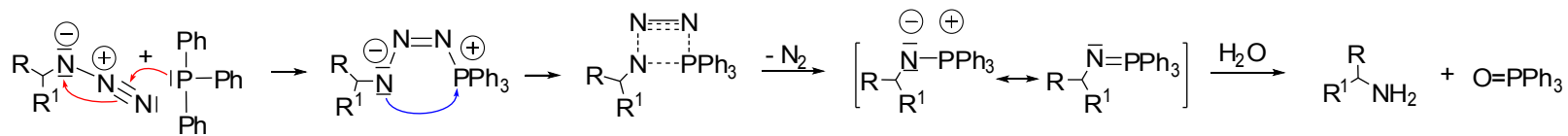
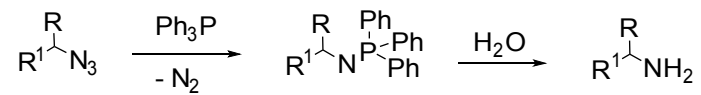
1.2.A1. Reakcja Mitsunobu



Nu	R ¹ -Nu	
N ₃	R ¹ -N ₃	azydki
NR ₂	R ¹ -NR ₂	aminy, azyrydyny
OR lub OAr	R ¹ -OR	etery, oksirany
RC(O)O	R ¹ -O(O)CR	estry
RNHC(O)R ²	R ¹ RNC(O)R ²	amidy
ArSH	R ¹ -S-Ar	tioetery

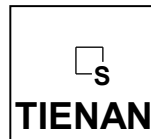
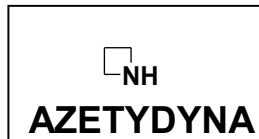
<http://www.organic-chemistry.org/namedreactions>

1.2.A2. Reakcja Staudingera

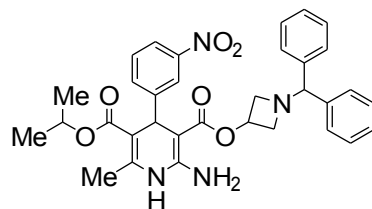


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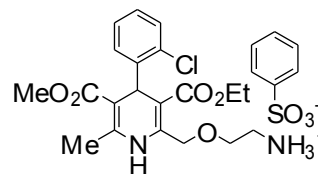
2. Układy czteroczłonowe - azetydyna



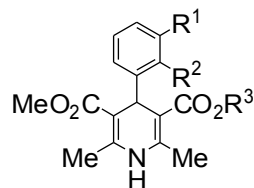
Leki obniżające ciśnienie krwi



Azelnidypina
(INN, *azelnidipine*)



Amlodypina
(INN, *amlodipine*, **AMLOZEK**)

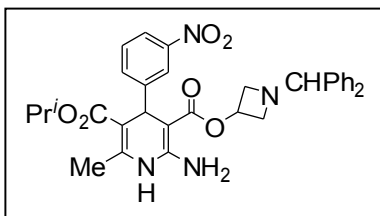
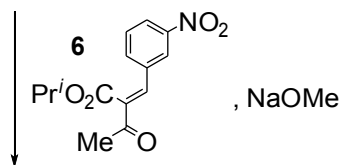
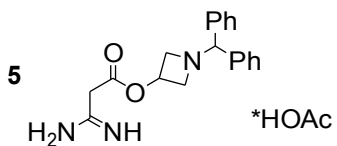
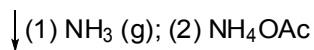
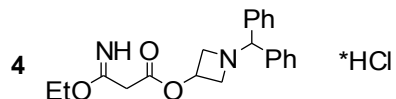
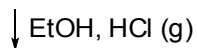
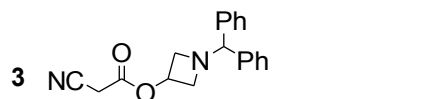
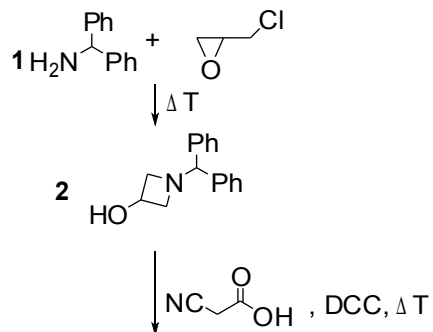


Nifedypina (INN, *nifedipine*) $R^1 = H$, $R^2 = NO_2$, $R^3 = Me$

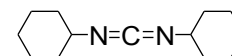
Felodypina (INN, *felodipine*) $R^1 = R^2 = Cl$, $R^3 = Et$

2.1. Azelnidypina

Wyjaśnienie przebiegu w dalszej części wykładu



U.S. Patent 4,772,596.

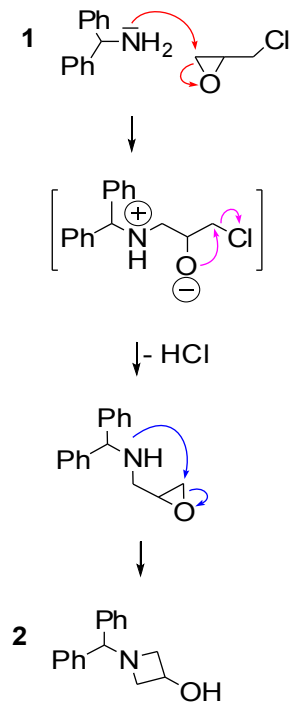


DCC = 1,3-dicykloheksylokarbodiimid

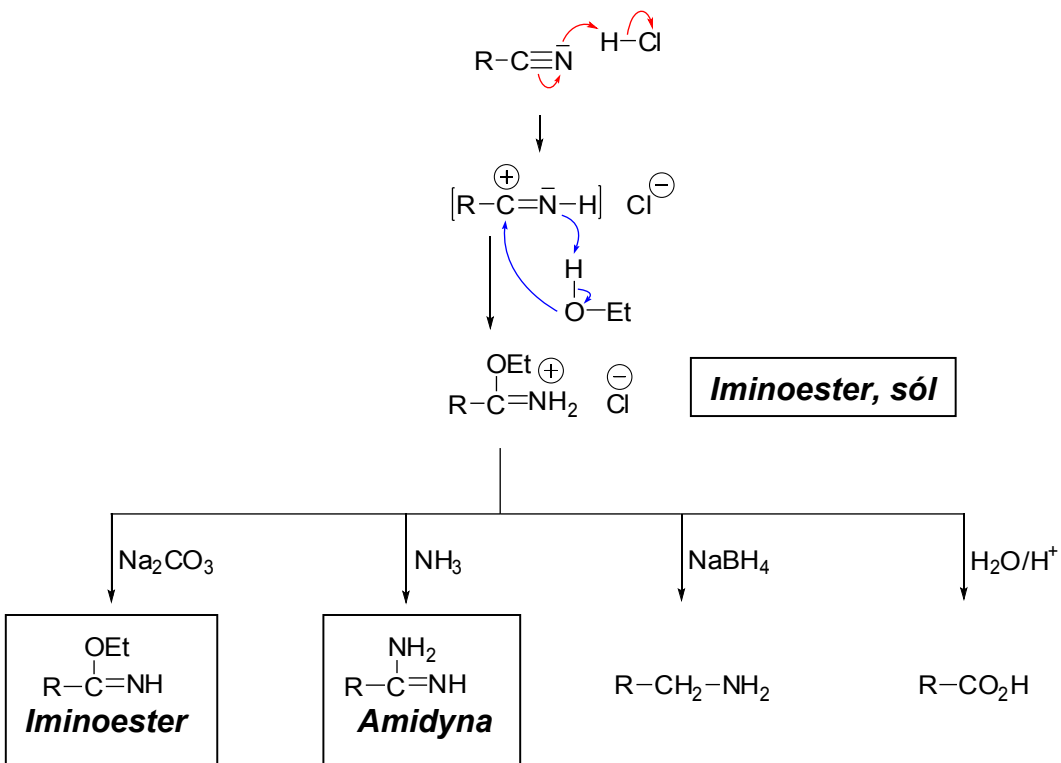
15

2.1.A. Wyjaśnienie przebiegu wybranych etapów

2.1.A1. Synteza 3-hydroksyazetydyny (2)

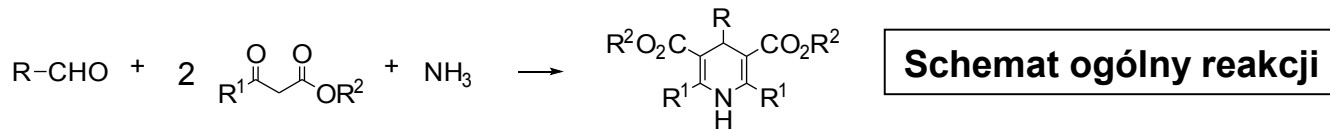


2.1.A2. Synteza Pinnera – otrzymywanie soli iminoestrów



S. Patai, Ed. (John Wiley & Sons, NY, 1975), pp. 385-489

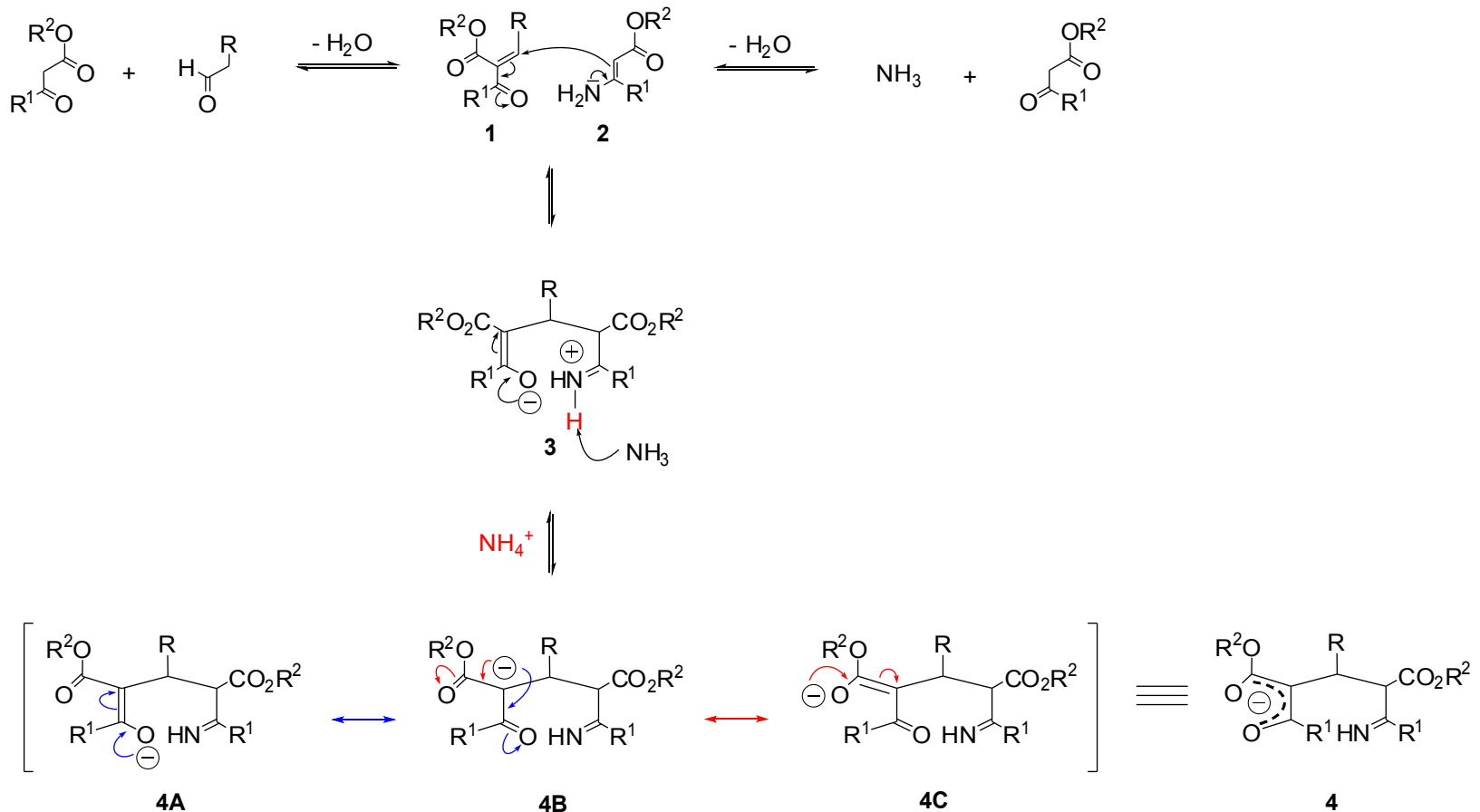
2.1.A3. Hantzsch metoda syntezy dihydropirydyn

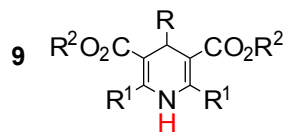
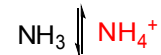
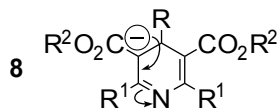
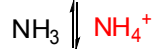
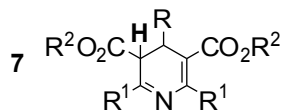
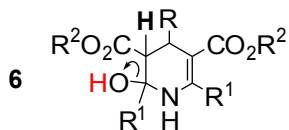
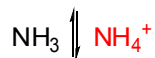
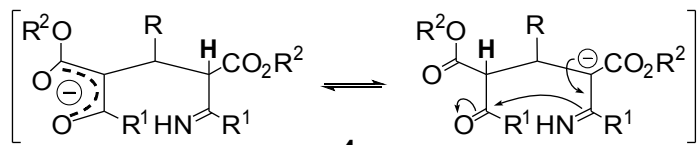


Addycja nukleofilowa do gr. karbonylowej:

(a) β -ketoester - aldehyd

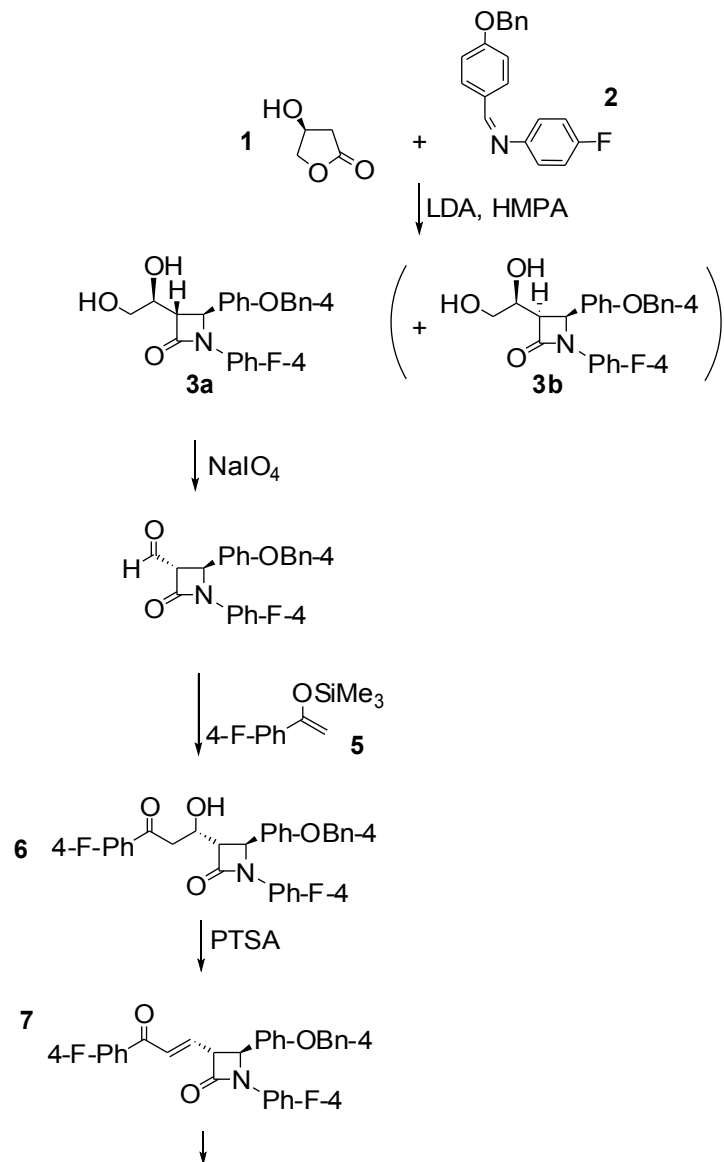
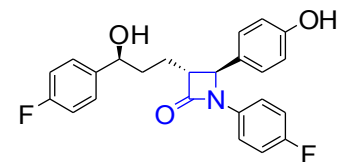
(b) amoniak - β -ketoester

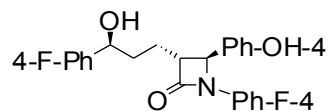
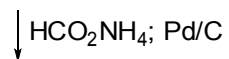
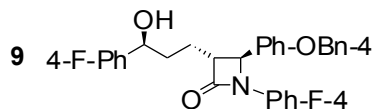
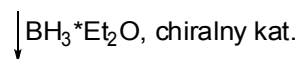
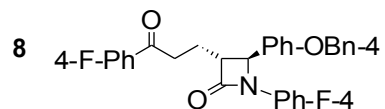
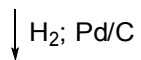
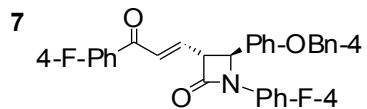




2.2. Ezetimib (*INN, ezetimibe*)

Lek obniżający poziom „złego” cholesterolu (LDL) we krwi.

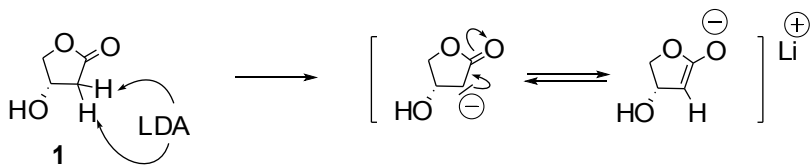
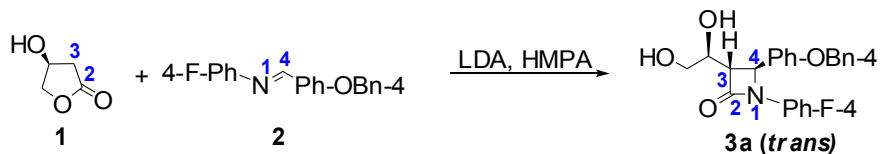




**J. Org. Chem. 1999, 64, 3714;
World (PTC) Patent WO9508532-A1;
U.S. Patent 5,631,365.**

2.2.A. Wyjaśnienie przebiegu wybranych etapów

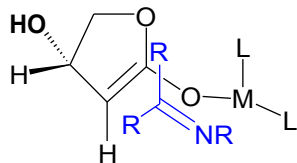
2.2.A1. Alkilowanie iminy (2)



LDA = diizopropylamide litu

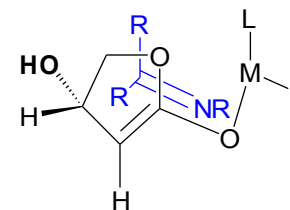


HMPA = heksametylfosforoamid

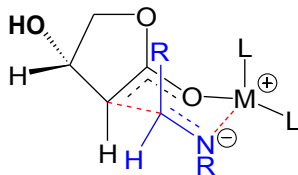


Wariant 1:

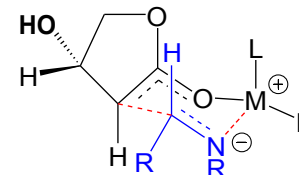
Zawada steryczna



Wariant 2:

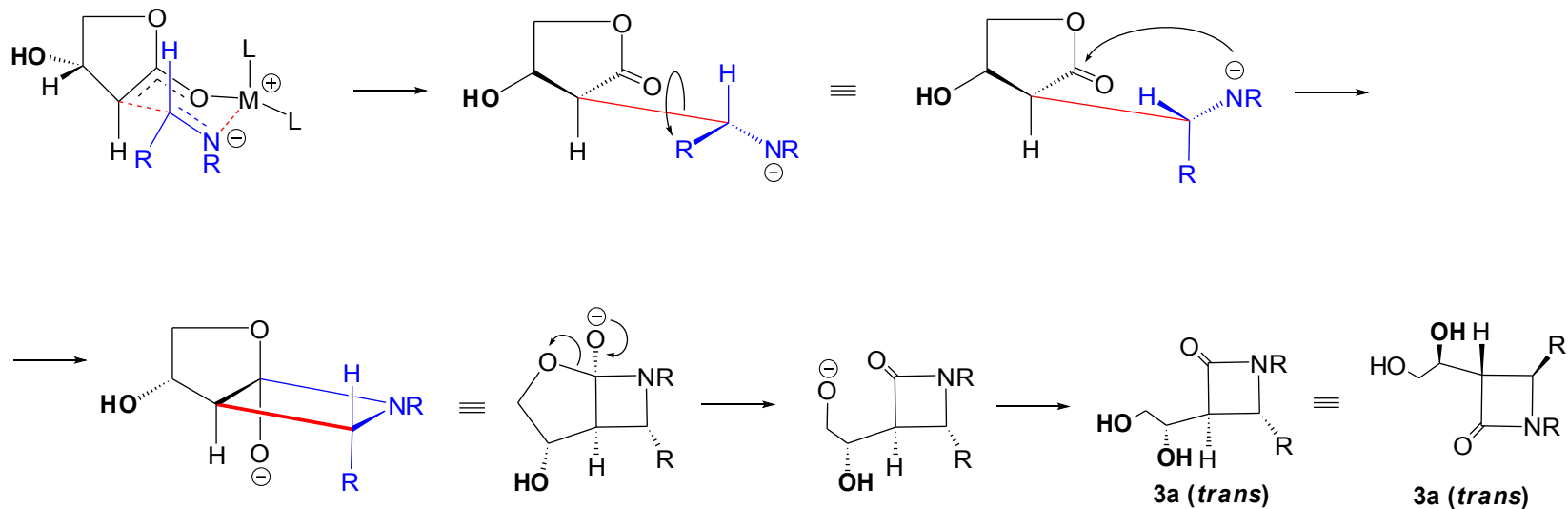


Wariant 1A:

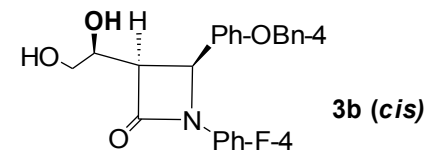


Wariant 1B:

Wariant 1B



Podobne rozumowanie w odniesieniu do „Wariantu 2” doprowadzi do izomeru 3b (*cis*)



Praca domowa

Wykazać, jakie orientacje początkowe substratów 1 i 2 doprowadziły by do związków

