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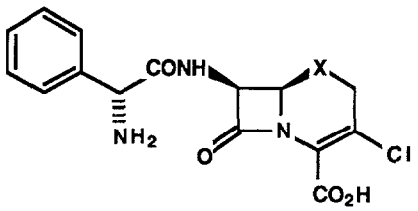
AN ENANTIOSELECTIVE SYNTHESIS OF LORACARBEF (LY163892/KT3777)

C. C. Bodurow,* B. D. Boyer, J. Brennan, C. A. Bunnell, J. E. Burks,
M. A. Carr, C. W. Doecke,* T. M. Eckrich,* J. W. Fisher, J. P. Gardner, B. J. Graves,
P. Hines, R. C. Hoying, B. G. Jackson, M. D. Kinnick, C. D. Kochert, J. S. Lewis,
W. D. Luke,* L. L. Moore, J. M. Morin, Jr.,* R. L. Nist, D. E. Prather, D. L. Sparks,
and W. C. Vladuchick.
Lilly Research Laboratories, Eli Lilly and Co.
Lilly Corporate Center, Indianapolis, Indiana 46285

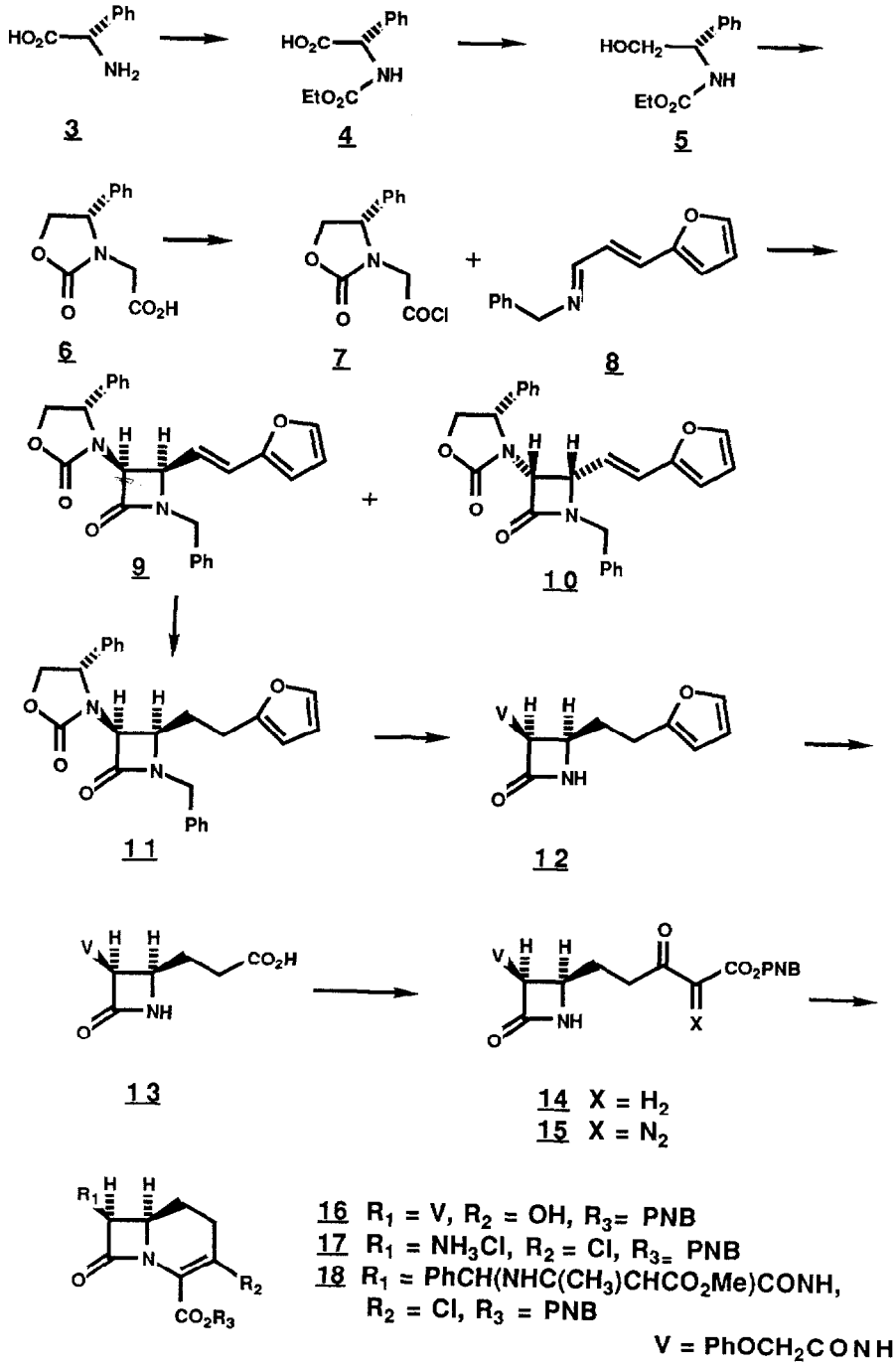
Summary: An enantioselective synthesis of the new, orally absorbable, totally synthetic β-lactam antibiotic, loracarbef (LY163892/KT3777) is described.

Carbacephalosporins have been shown to be extremely potent antibiotic substances displaying microbiological activity comparable to that of their cephalosporin analogs.[1] One of these derivatives, loracarbef[2] (1: LY163892/KT3777), the 1-carbadethia-analog of cefaclor (2),[3] has been shown to be a potentially useful clinical candidate, displaying activity against a broad spectrum of microbiological pathogens. We report herein an enantioselective synthesis of loracarbef suitable for the preparation of kilogram quantities for clinical trial evaluation.



1 X = CH_2, loracarbef
2 X = S, cefaclor

Our synthesis takes advantage of the observations of Evans and Sjogren[4] on the use of chiral 4-aryl-2-oxazolidinones as directing groups in asymmetric Staudinger type [2 + 2] cycloaddition reactions.[5] Preparation of the requisite (S)-4-phenyl-2-oxazolidinone followed directly from their work. Carbamoylation of L-(+)-phenylglycine (3) performed under Schotten-Baumann conditions ($ClCO_2CH_2CH_3$, CH_2Cl_2-aq. NaOH) afforded the ethyl carbamate 4 in 95% yield. Borane reduction (BH_3, THF) to alcohol 5, followed by cyclization (NaH, THF), *in situ* alkylation on nitrogen ($BrCH_2CO_2Et$), and saponification (aq. NaOH) afforded the


HO2C
Ph
NH2
3
EtO2C
NH
4
HOCH2
5
CO2H
6
COCl
7
8
9
10
11
12
13
CO2PNB
X
14 X = H2
15 X = N2
R1
R2
CO2R3
16 R1 = V, R2 = OH, R3= PNB
17 R1 = NH3Cl, R2 = Cl, R3= PNB
18 R1 = PhCH(NHC(CH3)CHCO2Me)CONH,
R2 = Cl, R3 = PNB
V = PhOCH2CONH

oxazolidinone 6 in 51% overall yield. Following activation of 6 as its acid chloride 7 and preparation of the aldimine 8, the key cycloaddition reaction was performed. Reaction of 7 and 8 in the presence of triethylamine (CH_2Cl_2) afforded a 92:8 diastereomer ratio (determined *in situ*) of β-lactams 9 and 10, respectively. Isolation of 9 could be effected by crystallization, however, olefin reduction (H_2-Pd/C, CH_2Cl_2) followed by selective crystallization of the saturated derivative 11 was preferred. This process afforded a 60% overall yield of 11 in 99% purity and 100% diastereomeric excess.[6]

Removal of the chiral auxiliary and cleavage of the benzyl group from the β-lactam nitrogen was accomplished in one step by Birch reduction (Li/NH_3, t-BuOH, THF). *In situ* acylation with phenoxyacetyl chloride (aq. $NaHCO_3$-CH_3CN) afforded the desired amide 12 in 78% yield. Ozonolysis and oxidative work up (O_3, H_2O_2, CH_2Cl_2-MeOH) afforded a 77% yield of the acid 13 . The keto-ester 14 was prepared in 80% yield by the procedure of Masamune and Brooks (carbonyl diimidazole, $Mg(O_2CCH_2CO_2PNB)_2$, THF).[7] Diazotization (p-dodecyl-SO_2N_3, TEA, CH_3CN) of derivative 14 afforded 15 in 85% yield. A rhodium-catalyzed intramolecular carbenoid-insertion reaction ($Rh_2(O_2CC_7H_{15})_4$, CH_2Cl_2)[8] afforded the enol 16 in 72% yield.

In contrast to a previous report,[9] side-chain cleavage and vinyl chloride preparation occurred in a single step without incident with Hatfield's reagent[10] ($(PhO)_3PCl_2$, CH_2Cl_2, pyridine, i-BuOH, HCl, EtOAc) to afford a 72% yield of nucleus hydrochloride 17. Liberation of the free base of 17 (Et_3N, EtOH, H_2O), followed by acylation with the isobutyl carbonic anhydride of enamine-protected D-phenylglycine (TEA, DMBA (cat.), i-BuOCOCl, DMF) afforded derivative18. The fully-protected intermediate 18 was doubly deprotected with zinc and acid, and residual methyl acetoacetate scavenged with semicarbazide [(i) Zn, HCl; (ii) semicarbazide, HCl; (iii) TEA] to afford the DMF-solvate of 1 in 75% yield. The product was recrystallized from water to afford the desired monohydrate form of the drug substance, loracarbef (1).

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6. Satisfactory spectral and analytical data were obtained for all new compounds; the diastereomeric excess for compound 11 was determined by HPLC analysis (on a Pirkle L-naphthylalanine column) of the corresponding 3,5-dinitrobenzamide derivative prepared by Birch reduction of 11 followed by acylation with 3,5-dinitrobenzoyl chloride.

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