

论文

d-生物素的不对称全合成研究

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摘要:

目的:探索工业生产可行的*d*-生物素的全合成方法。方法和结果:以(1*S*,2*S*)-(+) -苏式-1-(对硝基苯基)-2-氨基-1,3-丙二醇与顺-1,3-二苄基-四氢-4*H*-呋喃并[3,4-*d*]咪唑-2,4,6-三酮(2) 缩合而成的顺-1,3-二苄基-5-[(1*S*,2*S*)-(+) -苏式-1-羟甲基-2-(对硝基苯基)-2-羟乙基]-四氢-4*H*-吡咯并[3,4-*d*]咪唑-2,4,6-三酮(3) 经高立体选择性还原、水解内酯化成(3*aS*,6*aR*)-1,3-二苄基-四氢-4*H*-呋喃并[3,4-*d*]咪唑-2,4(1*H*)-三酮(6),再经硫代、格氏反应、还原制成(3*aS*,6*aR*)-1,3-二苄基-4-羟基-4-(3-乙氧基丙基)-四氢-4*H*-噻吩并[3,4-*d*]咪唑-2(3*H*)-酮(9),后者经脱水、还原、裂解环合、脱苄4步反应合成(3*aR*,8*aS*,8*bS*)-2-氧代-十氢咪唑并[4,5-*c*]噻吩并[1,2-*a*]硫鎓溴化物(12),继而缩合开环、水解即得*d*-生物素,以2 计算,总收率25-7%。结论:此法原料易得、操作简便、成本较低,适合工业化生产。

关键词: *d*-生物素 (1*S*,2*S*)-(+) -苏式-1-(对硝基苯基)-2-氨基-1,3-丙二醇 手性辅助剂 立体选择还原 胶态金属镍 全合成

STUDY ON THE ASYMMETRIC TOTAL SYNTHESIS OF *d*-BIOTIN

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Abstract:

AIM: To investigate feasible method for total synthesis of *d*- biotin on a large scale. METHODS AND RESULTS: *cis*-1,3-Dibenzyl-5-[(1*S*,2*S*)-(+) -threo-1-hydroxymethyl-2-(*p*-nitrophenyl)-2-hydroxyethyl] tetrahydro 4*H* pyrro[3,4-*d*]imidazole-2,4,6-trione (3) prepared from (1*S*,2*S*)-(+) -threo-(*p*-nitro-phenyl)-2-amino-1,3-propanediol and *cis*-1,3-dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]imidazole-2,4,6-trione. (2) by melting condensation was converted to (3*aS*,6*aS*)-1,3-dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]imidazole-2,4(1*H*)-dione(6) via highly stereoselective reduction, hydrolytic lactonization. Compound 6 was subjected to sulfurization, Grignard reaction, reduction to give (3*aS*,6*aS*)-1,3-dibenzyl-4-hydroxy-4-(3-ethoxypropyl)-tetrahydro-4*H*-thieno[3,4-*d*]imidazole-2(3*H*)-one(9). Compound 9 underwent dehydration, reduction, cleavage cyclization, debenzylation in four steps procedure to lead to the formation of (3*aS*,8*aS*,8*bS*)-2-oxo-decahydro imidazo[4,5-*c*]thieno[1,2-*a*]thiolium bromide(12), which was transformed into *d*-biotin by condensation/ring opening, hydrolysis and decarboxylation in an overall yield of 25.7% from compound 2. CONCLUSION: A practical and cost effective process for the manufacture of *d*-biotin was developed.

Keywords: (1*S*,2*S*)-(+) -threo-(*p*-nitrophenyl)-2-amino-1,3-propanediol chiral auxiliaries stereoselective reduction colloidal state metallic nickel total synthesis *d*-biotin

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