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SYNTHESIS OF 1-AZAFAGOMINE BASED ON RASEMIC DIETHYL-3-(HYDROXYMETHYL)-3,6-DIHYDROPYRIDAZINE-1,2-DICARBOXYLATE

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Rasemic diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate was synthesized following Diels-Alder reaction in the presence of achiral (2E)-penta-2,4-dien-1-ol and diethylazodicarboxylate. Dienophile 4-phenyl-1,2,4-triazole-3,5-dione (PTAD)) was substituted for diethylazodicarboxylate. Achiral (2E)-penta-2,4-dien-1-ol was obtained by repeating the literature procedure.Due to the two bulky groups in the diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate, the duplication of peaks in the ^{1}H and ^{13}C NMR spectrum was typical for some regions. C=C double bond of the diethyl-3-(hydroxymethyl)-3,6 dihydropyridazine-1,2-dicarboxylate was oxidized in the presence of OsO_4 and N-methylmorpholineN-oxide. It revealed that diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate subjected tocis-dihydroxylated, not trans-dihydroxylated. Duplication of signals in the ^{1}H and ^{13}C IMR spectrums was observed in triol intermediate as well. Based on a modified Bols's protocol, 5-epi-1-azafagomine synthesized by cleavage of groups attached to six-membered ring nitrogen atoms. The target compounds were obtained in good yields. Structures of synthesized compounds approved by NMR, Mass, Infrared spectroscopies.
Keywords:*1-Azafagomine, Diels–Alder reaction , azasugar, Bols protocol*

INTRODUCTION

1-Azasugars are a series of synthetic nitrogen-containing sugar analogues consisting of a monosaccharide structure where the anomeric carbon was replaced by a nitrogen atom.The name 1-azasugar is used here rather than the name iminosugar in accordance with IUPAC nomenclature that recommends that carbohydrates in which the ring-oxygen was substituted with N be called iminosugars, and those where a carbon was substituted with N be called azasugars[1].

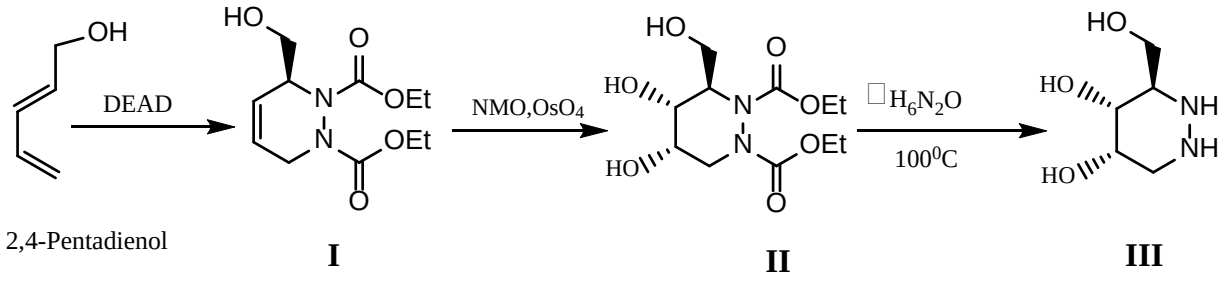
Interest in these compounds is based on the discovery that many of them are potent glycosidase inhibitors [2,3]. So far glycosidase inhibitors were investigated as antidiabetic, antiviral or antimetastatic agents, work which resulted in the antidiabetes drug acarbose[4] and the new antiinfluenza drug Zanamivir[5].

At present, the field of azafagomine is a very exciting area of research because of biological activity.

RESULTS AND DISCUSSION

The synthesis of homochiral 1-azafagomine was accomplished by Bols and coworkers through a synthetic sequence based on the Diels-Alder cycloaddition to 4-phenyl-

1,2,4-triazole-3,5-dione (PTAD) to achiral dienes: 2,4-pentadienoic acid, methyl 2,4-pentadienoate and 2,4-pentadienol [2]. In this article we report on new synthesis of 5-epi-1-azafagomine through the modification [6] of Bols protocol. 2,4-Pentadienol was obtained by following the literature procedure [7]. Rasemic cycloadduct (I) was obtained in a good yield by a modification of this protocol, by changing the dienophile/diethyl- azodicarboxylate instead of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD).



2,4-Pentadienol **I** **II** **III**

Synthesis of 5-epi-1-azafagomine (III).

^{1}H NMR spectrum of compound (I) showed 1:1ofrotamers A and B. In some regions of the ^{1}H NMR spectrum there is the duplication of peaks.^{13}C NMR spectrum shows either broad peaks or duplication of signals for all carbons.These phenomena are probably related to the difficulty of nitrogen's inversion due to the two bulky groups attached thereto. It found that diethyl-3-(hydroxymethyl)-3,6-dihydro-pyridazine-1,2-dicarboxylate (I)cis-dihydro-xylated with OsO_4 in good yield and total selectivity, but not trans-dihydroxylated; in this case the selectivity dropped to zero. cis-Dihydroxylation of diethyl-3-(hydroxymethyl)-3,6-dihydropyridazine-1,2-dicarboxylate (I) with OsO_4 leads to triol (II). Duplication of signalswere observed for triol intermediate in^{13}C and ^{1}H NMR spectrum. Hydrazinolysis of the urethane group furnished 5-epi-1-azafagomine (III) in 81% yield.The structure of the obtained compounds was confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS (ESI) spectra.

EXPERIMENTAL PART

Solvents were distilled under anhydrous conditions. All reagents were purchased and used without further purification. Glassware was dried prior to use. TLC plates (silica gel 60 F254) were visualized either at a UV lamp or in I_2. ^{1}H NMR and ^{13}C NMR were run on a Bruker Avance III 400 spectrometers.(Measuring frequency: ^{1}H NMR= 400 MHz, ^{13}C NMR= 100.6 MHz) Infrared spectra were recorded on a Bomem MB 104. Samples were run as oils of thin films. Mass spectra were recorded on a VG Autopsic Mass spectrometer.

I. Diethyl-3-(hydroxymethyl)-3,6-dihydro-pyridazine-1,2-dicarboxylate

To a solution of 2,4-pentadienol 1.33 g (16.0 mmol) in dry toluene (10 ml) was added diethyldiazodicarboxylate 7.30 ml (40% in toluene, 16.0 mmol) under magnetic stirring at rt. The stirring was continued for 24 h and the solvent removed to give cycloadduct (I) as an orange oil (4.32 g; 99%).

II. ***cis-Dihydroxylationofdiethyl-3-(hydroxyl-methyl)-3,6-dihydropyridazine-1,2dicarboxylate***

Cycloadduct (I) 1.85 g (7.17 mmol) was dissolved in acetone (18.4 mL) and water (2.05 mL), N-methylmorpholineN-oxide (1.25 g; 9.30 mmol) was added followed by a solution of OsO4 in water (4%; 0.76 mL; 0.12 mmol). The mixture was stirred for 1 day at rt. The reaction was quenched by addition of 5% aqsoln $Na_2S_2O_3$ (10 mL). The acetone was removed by evaporation and the residue redissolved in AcOEt, filtered through a pad of silica, washed with AcOEt, and concentrated to give a yellow oil (II) (2.00 g; 96%).

III. *Synthesis of 5-epi-1-azafagomine*

Triol (II) (1.40 g; 4.80 mmol) was dissolved in hydrazine hydrate (82 mL) and heated at 100 ^{0}C for 18 h. The solution was concentrated and the crude product subjected to dry-flash chromatography in EtOH/NH4OH (25%) 99:1 giving pure (III) (0.57 g; 81%).

Table 1. Spectral analysis of **I-III** compounds

IR spectra (ν_{max}) **(I)**	3483, 1707 cm^{-1}
^{1}H NMRδ_H (400 MHz, $CDCl_3$) **(I)**	1.23–1.30 (12H, m, 4CH_3, A+B), 2.58 (1H, br s, OH), 3.35 (1H, dd, J 12.3, 9.5 Hz, H-30, A), 3.45 (1H, dd, J 12.0, 9.8 Hz, H-30, B), 3.56–3.69 (2H, m, 2H-3′, A+B), 3.77 (1H, dd, J 13.5, 4.3 Hz, H-6, A), 3.91 (1H, br s, H-6, B), 4.11–4.26 (8H, m, 4CH_2, A+B), 4.30 (1H, tdd, J 6.0, 3.9, 2.2 Hz, H-6, B), 4.34–4.44 (1H, m, H-6, A), 4.72 (2H, br s, H-3, A+B), 5.66–5.88 (4H, m, H-4+H-5, A+B) ppm.
^{13}C NMRδ_C (100 MHz, $CDCl_3$)**(I)**	14.3 (CH_3, A), 14.4 (CH_3, B), 42.2 (C-6, A), 43.6 (C-6, B), 55.9 (C-3, A), 56.9 (C-3, B), 61.9 (C-30, A+B), 62.6, 62.7, 62.8, 62.9 (CH_2, A+B), 123.4, 124.2, 124,6, 125.2 (C-4 or C-5, A+B), 154.9, 155.7, 156.2, 156.3 (C=O, A+B) ppm.
HRMS (ESI) **(I)**	Calculated : $C_{11}H_{18}N_2NaO_5$, 281.1108; found: 281.1109.
IR spectra (ν_{max}) **(II)**	3419, 2983, 2937, 1698 cm^{-1}
^{1}HNMR δ_H (400 MHz, $CDCl_3$) **(II)**	1.23–1.32 (12H, m, 4CH_3, A+B), 3.12 (1H, br d, J 10.8 Hz, H-6, A), 3.21 (1H, br d, J 10.8 Hz, H-6, B), 3.50 (2H, t, J 11.6 Hz, H-30, A), 3.62 (1H, d, J 8.0 Hz, H-30, B), 3.65–3.95 (4H, br s, H-4+H-5, A+B), 4.01 (2H, dd, J 13.2, 5.6 Hz, H-6, A), 4.10–4.25 (9H, m, H-6, B+4CH_2, A+B), 4.52–4.64 (2H, br s, H-3, A+B) ppm.
^{13}C NMRδ_C (100 MHz, $CDCl_3$)**(II)**	14.3, 14.4 (CH3, A,B), 44.0, 45.7 (C-6, A,B), 58.4, 59.0 (C-3, A,B), 61.9, 62.8 (C-30, A,B), 63.0, 63.1 (2CH_2, A or B), 63.2, 63.3 (2CH_2, A or B), 64.0, 64.3 (C-4 or C-5, A,B), 66.4, 66.7 (C-4 or C-5, A,B), 155.2, 156.5 (C=O, A,B), 157.1, 157.3 (C=O, A,B) ppm.
HRMS (ESI) **(II)**	Calculated: $C_{11}H_{20}N_2NaO_7$ 315.1163; found: 315.1163
^{1}H NMRδ_H (300 MHz, D_2O) **(III)**	3.00 (1H, d, J 14.4 Hz, H-6), 3.07 (1H, ddd, J 9.6, 6.4 e 3.2 Hz, H-3), 3.10 (1H, d, J 14.4 e 2.8 Hz, H-6), 3.64 (1H, dd, J 12.0 e 3.2 Hz, H-30), 3.67 (1H, d, J 6.4 Hz, H-4), 3.84 (1H, dd, J 12.0 e 2.8 Hz, H-30), 4.00 (1H, d, J 1.6 Hz, H-5) ppm.

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DİETİL-3-(HİDROKSİMETİL)-3,6-DİHİDROPİRİDAZİN-1,2-DİKARBOKSİLAT ƏSASINDA 1-AZAFAQOMİNİN SİNTEZİ

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Rasemik dietil-3-(hidroksimetil)-3,6-dihidropiridazin-1,2-dikarboksilat Dils-Alder reaksiyası əsasında axiral (2E)-penta-2,4-dien-1-ol və dietilazodikarboksilat əsasında sintez edilmişdir. Axiral(2E)-penta-2,4-dien-1-ol ədəbiyyata uyğun olaraq sintez edilmişdir. Dietil-3-(hidroksimetil)-3,6-dihidropiridazin-1,2-dikarboksilata birləşmiş iki ağır qrup səbəbindən ^{1}H and ^{13}C NMR spektrində piklərin ikiləşməsi müşahidə olunmuşdur. N-metilmorfolin N-oksid və OsO_4 iştirakında dietil-3-(hidroksimetil)-3,6-dihidropiridazin-1,2-dikarboksilat birləşməsində ikiqat rabitə C=C oksidləşdirilmişdir. Bu zaman müəyyən edilmişdir ki, OsO_4 addukt ilə trans deyil, cis-dihidroksilləşir. ^{1}H and ^{13}C NMR spektrində piklərin ikiləşməsi triol intermediatı üçün də qeydə alınır.Modifikasiya olunmuş Bols reaksiyası əsasında azota birləşmiş qruplar kənarlaşdırılaraq 5-epi-1-azafaqomin sintez olunmuşdur. Sintez edilmiş birləşmələrin quruluşları kütlə spektrometri, İQ və NMR analiz metodları ilə təsdiq olunmuşdur.

Açar sözlər:*1-azafaqomin,Dils-Alder reaksiyası**, dietilazodikarboksilat*

СИНТЕЗ 1-АЗАФАГОМИНА НА ОСНОВЕ ДИЕТИЛ-3-(ГИДРОКСИМЕТИЛ)-3,6-ДИГИДРОПИРИДАЗИН-1,2-ДИКАРБОКСИЛАТА

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Рацемат диэтил-3-(гидроксиметил)-3,6-дигидропиридазин-1,2-дикарбоксилата был синтезирован по реакции Дильса-Альдера в присутствии ахирального (2E)-пента-2,4-диен-1-ола и диэтилазодикарбоксилата. Диенофил 4-фенил-1,2,4-триазол-3,5-дион (ФТАД) был заменен на диэтилазодикарбоксилат (ДЭАД)). Ахиральный (2E)-пента-2,4-диен-1-ол был получен повторением литературной методики. Из-за наличия двух объемных групп в диэтил-3-(гидроксиметил)-3,6-дигидропиридазин-1,2-дикарбоксилате в некоторых областях ^{1}H и ^{13}C ЯМР спектров наблюдалось удвоение пиков. Кратная C=C связь диэтил-3-(гидроксиметил)-3,6-дигидропиридазин-1,2-дикарбоксилата была окислена в присутствии OsO_4 и N-метилморфолинN-оксида. Было установлено, что в присутствии OsO_4 диэтил-3-(гидроксиметил)-3,6-дигидропиридазин-1,2-дикарбоксилат подвергся не транс, а цис-дигидроксилированию. Удвоение сигналов ^{1}H и ^{13}C ЯМР спектров также наблюдалось и для триол интермедиата. Основанный на модифицированном протоколе Болса, 5-эпи-1-азафагомин был синтезирован отщеплением групп, которые присоединены к атому азота шестичленного цикла. Целевые продукты были получены в хороших выходах. Структуры синтезированных соединений были доказаны ЯМР, масс и ИК спектроскопиями.

***Ключевые слова**: азафагомин,диэтилазодикарбоксилат**,** реакция Дильса-Альдера**,** ахиральный (2E)-пента-2,4-диен-1-ол*