Synthesis of 2,5-Diisoxazolyltetrahydrofurans

D. Chiarino and M. Fantucci*

Zambon Research S.p.A., Medicinal Chemistry Department,
Via Lillo Del Duca, 10, 20091 Bresso,
Milan, Italy

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The synthesis of 2,5-bis(3-bromo-5-isoxazolyl)tetrahydrofuran (**2**) and 2,5-bis(3-methoxy-5-isoxazolyl)tetrahydrofuran (**3**) have been accomplished in three and four steps respectively. *Cis*- and *trans*-isomers have been separated and fully characterized. Differently from synthetic schemes so far utilized for the preparation of the 2,5-diheteroaryltetrahydrofuran analogs, our approach involves the direct synthesis of a key intermediate containing both isoxazole rings and diol function for the final cyclization. Starting from succinic aldehyde, the new 1,7-octadiyne-3,6-diol (**4**) was prepared and was submitted to a double cycloaddition with bromonitrile oxide to yield the key intermediate 1,4-bis(3-bromo-5-isoxazolyl)-1,4-butanediol. The methoxy analogs **3** were obtained by methanolysis of the bromo derivatives **2**.

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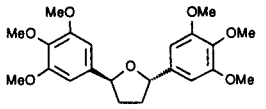
Platelet-activating factor (PAF) [1] is an endogenous phospholipidic mediator of many physiological processes responsible for a large group of diseases such as inflammatory disease, cardiovascular disorder, hypotension, shock, allergic and skin diseases, asthma, lung edema, peptic or stomach ulcer and dental pain. Therefore more and more scientific investigation has been focused on the search of a PAF antagonist for treating or preventing these common diseases. Among the PAF antagonists discovered in these years, 2,5-diaryltetrahydrofurans constitute a well known class of natural and synthetic agents [2]. One of the most active has been found to be the *trans*-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran (**1**).

Our studies on the effectiveness of the 3-bromo and 3-methoxy-5-isoxazolyl moieties as bioisosters of hydroxylated and methoxylated phenyl groups [3], led us to synthesize compounds **2** and **3**, initiating a new class of molecules, the 2,5-diisoxazolyltetrahydrofurans, and to test their affinity for the PAF binding sites.



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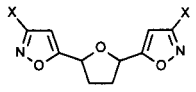


2 X = Br
3 X = MeO

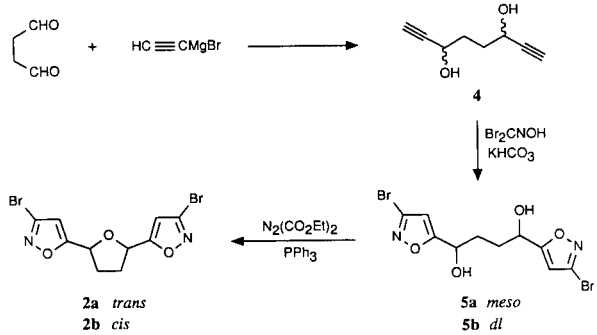
Previously a large number of 2,5-diaryltetrahydrofurans have been synthesized, but only a few 2,5-diheteroaryltetrahydrofurans are known. To our knowledge, only 2,5-bis(3-pyridyl)tetrahydrofuran [4], 2,5-bis(2-thienyl)tetrahydrofuran [4] and 2,5-bis(2-furanyl)tetrahydrofuran (2',3',-4',5'-tetrahydro-2,2':5',2''-terfuran) [5], which has not been characterized because of its instability, have been described so far.

In both diaryl- and diheteroaryltetrahydrofuran compounds, the tetrahydrofuran ring was built by cyclization of a γ-diol, obtained by reduction of a γ-diketone. The latter was the key intermediate in most of these synthesis. In the heterocyclic compounds mentioned above, the γ-diketones were prepared by oxidative dimerization of lithium enolates of the heteroaryl methyl ketones [6], or by condensation between aldehydes and vinyl ketones catalyzed by cyanide ion or thiazolium halides [4]. The terfuran system was prepared by oxidative cyclization of 1,4-bis(2-furanyl)-1-butanol [5], but it has been reported by the authors that this reaction has limited application.

Our synthesis did not involve the above schemes owing to the instability of the isoxazole ring towards the strong reduction conditions required in order to avoid the formation of the intermediate γ-hydroxyketone which easily cyclizes to 2-hydroxytetrahydrofuran, resistant to further reductions. Furthermore, the easily accessible 3-bromo-5-acetylisoxazole [6] failed to provide an enolate to perform the dimerization.

Due to above problems, it was developed a new synthetic scheme in which the skeleton of the target products was directly built with the 1,4-diol function. Our synthesis is reported in Scheme I. The first step involved a double condensation between ethynylmagnesium bromide and succinic aldehyde, freshly prepared from the commercial precursor 2,5-dimethoxytetrahydrofuran [8]. We obtained

Scheme I

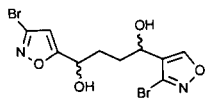


a good yield of the new 1,7-octadiyne-3,6-diol (**4**), diastereoisomers of which were indistinguishable by tlc, glc or 200 MHz ^{1}H nmr.

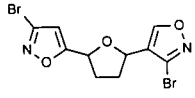
The second step involved a double cycloaddition between the diyne **4** and the bromonitrile oxide obtained "*in situ*" from dibromoformaldoxime [9]. We obtained both regiospecific and chemical high yields of the desidered 1,4-bis(3-bromo-5-isoxazolyl)-1,4-butanediols **5a** and **5b**, as the regioisomers 1-(3-bromo-4-isoxazolyl)-4-(3-bromo-5-isoxazolyl)1,4-butanediols **6** were found to be present in less than 10% and the whole of the recovered products amounted to 95%.

The cyclization to form the tetrahydrofuran ring was accomplished by using diethyl azodicarboxylate and triphenylphosphine in THF [10]. When the above butanediols mixture was submitted to the same reaction, after repeated chromatographies, it was possible to isolate besides the major products **2a** and **2b**, also the isomeric compounds **7a** and **7b** which were fully characterized.

The geometric configuration of the new products (**2a**, **2b**, **7a** and **7b**) was investigated and established by using the relative ^{1}H nmr chemical shifts of furanic methine protons [11-13], retention times in glc [12,13] and retention factors in tlc [12]. The *trans*-configuration was attributed to compounds **2a** and **7a**, for their delta values, retention times and retention factors were higher than for compounds **2b** and **7b**, which were assigned the *cis*-configuration. This observation is in agreement with data reported on tetrahydrofuranic analogs [11-13]. We also noted that hplc retention times on RP-18 of these compounds were higher for the *trans*- than for the *cis*-isomers due to the greater polarity of *cis*-isomers.



6

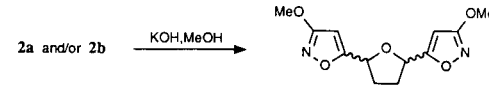


7a *trans*
7b *cis*

From the reaction mixture of butanediols we isolated, by crystallization, the pure isomer **5a**, which was submitted to the same cyclization method as described above, yielding the *trans*-isomer **2a**. Inasmuch as the stereochemical pathway of etherification is known [14], we were able to attribute the *meso*-configuration to compound **5a**.

With regard to the bis(3-methoxy-5-isoxazole) derivatives, they were obtained by nucleophilic substitution of the bromo-analogues. As described in Scheme II, the reaction was carried out by refluxing the bromo derivatives **2a** or **2b** in aqueous methanolic solution of potassium hydroxide. The strong alkaline conditions caused a complete equilibration at the two stereogenic centres, resulting in the same mixture of **3a** and **3b** (29/21, hplc) starting either from **2a** or **2b**. This is due to the easy deprotonation of the stereocenter bonded to the isoxazole ring in the 5-position

Scheme II



3a *trans*
3b *cis*

[15]. The two isomers **3a** and **3b** were then separated by chromatography. Their analytical data, together with data for the other couples of isomers showing the assignment of *cis*- and *trans*-configurations are given in Table 1.

Table 1

Analytical Values Used to Assign the Geometry of the 2,5-Diisoxazolyltetrahydrofurans Prepared [a]

Product	^{1}H NMR [b] δ (ppm)	GC [c] Rt [min]	TLC [d] Rf	HPLC [e] Rt [min]
2a	5.32-5.45 (2H) [f]	5.78	0.54	17.0
2b	5.21-5.34 (2H) [f]	5.38	0.40	14.2
7a	5.05 (1H), 5.35 (1H)	6.42	0.49	14.9
7b	4.39 (1H), 5.23 (1H)	6.02	0.44	13.7
3a	5.20 (2H)	3.29	0.37	6.8
3b	5.10 (2H)	3.12	0.31	6.3

[a] Complete analyses are reported in the experimental. [b] CH-O-CH multiplets in DMSO-d_6 with TMS as the internal standard. [c] Recorded on a HP-5840 Gas Chromatograph with 1.5 m SE-30 + OV-17 column, at 220°, 30 ml/minute He flow. [d] On silica gel using 7:3 petroleum ether/ethyl acetate as eluents. [e] On RP-18 column using 55:45 water/acetonitrile as mobile phase at a flow rate of 1 ml/minute (see also general introduction to the experimental. [f] Wide multiplet.

All tetrahydrofuran derivatives were tested for their ability to displace tritium-labelled PAF from specific sites in rabbit-platelet preparations. No significant displacing activity was shown by these compounds.

EXPERIMENTAL

Melting points were determined on a Buchi 535 apparatus and are uncorrected. Elemental analyses were performed by "Università di Padova, Dipartimento Scienze Farmaceutiche". Mass spectra were obtained using a Finningam 8200 spectrometer with either EI or CI and isobutane as reacting gas. The ir spectra were recorded on a Pye Unicam SP3-200 spectrophotometer. The uv spectra were determined with a Shimadzu UV-260 spectrophotometer. The ^{1}H nmr spectra were obtained on a Varian Gemini 200 spectrometer with tms as internal standard.

The hplc was performed using a Beckman mod 344 chromatography being connected with a Shimadzu SPD-6A spectrophotometric detector set at 220 nm. All analyses were carried out on RP-18 column (Brownlee, RP-18 Spheri-5, 220 x 4.6 mm).

Pre-Coated tlc plates "Silica Gel 60 F-254" and silica gel (70-230 mesh) were purchased from Merck, Darmstadt, FRG. The tlc visualization was achieved by either irradiation at λ = 254 nm, or by iodine vapor.

Octa-1,7-diyne-3,6-diol (**4**).

A solution of ethynylmagnesium bromide, prepared from magnesium (2.67 g, 0.110 mole), ethyl bromide (13.33 g, 0.122 mole) and acetylene in dry THF (110 ml) according to Skallebol, Jones and Whiting [16] procedure, was rapidly cooled (−7°) and, maintaining passage of acetylene gas through the stirred light suspension, a solution of succinaldehyde (3.445 g, 0.040 mole) in THF (8 ml) was added (40 minutes). The stream was then interrupted and the mixture stirred at room temperature overnight. The reaction mixture was added to a saturated ammonium chloride aqueous solution (340 ml) and extracted with ether (3 x 150 ml). After drying (sodium sulfate) and evaporation of the solvent, the resulting crude product **4** was purified by chromatography on silica gel column (550 g, 70-230 mesh) using 95:5 dichloromethane/methanol as eluent, yield, 4.3 g (78%), mp 48-50°; ms: (m/e) 139 (M+1, 100), 121 (42); ir (potassium bromide): ν 3300 (br, O-H), 2950, 2930, 2120 (w, C≡C), 1055 (O-H), 1000, 885 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.58-1.68 (m, 4H, 2 CH_2), 3.23 (d, 2H, ^2J = 2, 2 C≡CH), 4.20 (m, 2H, 2 CH-O), 5.35 (d, 2H, J = 5.6, 2 OH).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.33; H, 7.35.

meso-1,4-Bis(3-bromo-5-isoxazolyl)-1,4-butanediol (**5a**).

By means of a diaphragm pump (ProMinent Duramatic by CFG, Heidelberg) running at 0.3 ml/minutes, a solution of dibromoformaldoxime (100 g, 0.493 mole) in ethyl acetate (500 ml) was added to a mixture of octa-1,7-diyne-3,6-diol (**4**, 20 g, 0.145 mole), ethyl acetate (400 ml), potassium hydrogen carbonate (174.2 g, 1.74 moles) and water (4 ml) under vigorous stirring, at room temperature.

Twenty hours after addition, the reaction mixture was diluted with water to obtain two clear layers which were then separated. After washing the organic layer with sodium chloride aqueous solution (20%, 600 ml) and drying (sodium sulfate), the solvent was removed under vacuum to obtain a highly odorous, irritating, viscous liquid (77 g). This was treated with dichloromethane (25 ml, ice-cooling for 48 hours) to obtain a crystalline product (37 g), being a mixture of wanted diols (45:55, hplc). After two crystallizations from acetonitrile (213 ml, 200 ml) nearly pure (95% hplc) isomer **5a** was obtained, yield, 13.21 g (24%), mp 166-169°; ms: (m/e) 383 (M+1, 88), 303 (100); ir (potassium bromide): ν 3420 (s, O-H), 3160, 2970, 2930, 1575 (C=N), 1435, 1340, 1315, 1080 (O-H), 960 cm^{-1}; uv (methanol): λ max 216 nm (log ϵ 4.20); ^1H nmr (DMSO-d_6): δ 1.64-1.93 (m, 4H, 2 CH_2); 4.70-4.83 (m, 2H, 2 CH-O); 5.94 (d, 2H, J = 5.6, 2 OH); 6.70 (s, 2H, 2 isox); hplc: water/methanol (75:25), flow 1 ml/minutes, Rt = 53 minutes (Rt (d1) form = 54 minutes).

Anal. Calcd. for $C_{10}H_{10}Br_2N_2O_4$: C, 31.44; H, 2.64; Br, 41.83; N, 7.33. Found: C, 31.54; H, 2.67; Br, 41.71; N, 7.47.

From the pooled crystallization mother liquors, it was possible to recover a mixture of diols **5** together with a small amount of regioisomers **6** purifying them from the by-product 3,4-dibromofuroxan by chromotography (1 kg silica gel column, 95:5 then 9:1 dichloromethane methanol as eluent, yield 39.2 g, 71%). The total yield of this step was then 95%.

trans-2,5-Bis(3-bromo-5-isoxazolyl)tetrahydrofuran (**2a**).

Under a dry nitrogen atmosphere, diethyl azodicarboxylate (7.29 g, 0.0418 mole, 6.56 ml) in THF (10 ml) was added to a cooled (0°) solution of the diol **5a** (12 g, 0.0314 mole) and triphenylphosphine (8.66 g, 0.033 mole) in THF (150 ml). After one hour the cooling bath was removed and the solution was left to stand at room temperature for 15 hours.

The reaction solution was then washed with brine (25%, 2 x 100 ml) and the organic layer, after drying (sodium sulfate) was evaporated to obtain an oily residue (28.8 g) which on treatment with ether (35 ml) separated most of the dicarbetoxyhydrazine as white heavy crystals. The filtrate, after evaporation of the solvent, was chromatographed on silica gel column (1 kg) using 4:1 petroleum ether/ethyl acetate as eluent, yield, 9.1 g (80%), mp 79-81° (1:1 *tert*-butyl methyl ether/hexane); ms: (m/e) 365 (M+1, 100), 285 (20); ir (potassium bromide): ν 3140, 3125, 1590 (C=N), 1375, 1335, 1240, 1040 (C-O-C), 950 cm^{-1}; uv (methanol): λ max 218 nm (log ϵ 4.21); ^1H nmr (DMSO-d_6): δ 2.13-2.54 (m, 4H, 2 CH_2), 5.32-5.45 (m, 2H, 2 O-CH), 6.94 (s, 2H, 2 isox).

Anal. Calcd. for $C_{10}H_8Br_2N_2O_3$: C, 33.00; H, 2.22; Br, 43.91; N, 7.70. Found: C, 32.89; H, 2.17; Br, 44.16; N, 7.87.

cis-2,5-Bis(3-bromo-5-isoxazolyl)tetrahydrofuran (**2b**), *trans*- and *cis*-2-(3-Bromo-4-isoxazolyl)-5-(3-bromo-5-isoxazolyl)tetrahydrofuran (**7a** and **7b**).

A mixture of diols **5** and regioisomers **6** (39 g, 0.102 mole) was cyclized, following the method described above. Despite two subsequent chromatographies (1 kg silica each), only a series of enriched fractions were isolated. The purest fractions were crystallized from *tert*-butyl methyl ether/hexane to obtain crops of **2a** or **2b**, while the other fractions and crystallization mother liquors were re-chromatographed separately (silica-product ratio = 100) to finally obtain all four isomers, yield, **2a**, 4.9 g, (13%l), **7a**, 2.7 g, (7%), **7b**, 1.2 g, (3%) and **2b**, 17 g, (46%), listed in order of elution.

Compound **2b**.

This *cis*-isomer, *meso* form had mp 99-101°; ms: (m/e) 365 (M+1, 100), 285 (37); ir (potassium bromide): ν 3135, 1590 (C=N), 1375, 1335, 1240, 1065 (C-O-C), 950 cm^{-1}; uv (methanol): λ max 215 nm (log ϵ 4.21); ^1H nmr (DMSO-d_6): δ 2.10-2.55 (m, 4H, 2 CH_2), 5.21-5.34 (m, 2H, 2 O-CH), 6.87 (s, 2H, 2 isox).

Anal. Calcd. for $C_{10}H_8Br_2N_2O_3$: C, 33.00; H, 2.22; Br, 43.91; N, 7.70. Found: C, 32.91; H, 2.18; Br, 43.83; N, 7.81.

Compound **7a**.

This *trans*-isomer was obtained as an oil; ms: (m/e) 364 (M+1, 100), 285 (23); ir (potassium bromide): ν 3130, 2955, 1590 (C=N), 1370, 1330, 1240, 1060 (C-O-C), 950 cm^{-1}; uv (methanol): λ max 217 nm (log ϵ 4.21); ^1H nmr (DMSO-d_6): δ 2.00-2.60 (m, 4H, 2 CH_2), 5.05 (m, 1H, O-CH-C_4), 5.35 (m, 1H, O-CH-C_5), 6.92 (s, 1H, isox H-C_4), 9.1 (s, 1H, isox H-C_5).

Anal. Calcd. for $C_{10}H_8Br_2N_2O_3$: C, 33.00; H, 2.22; Br, 43.91; H, 7.70. Found: C, 32.78; H, 2.12; Br, 44.13; N, 7.90.

Compound **7b**.

This *cis*-isomer had mp 82-84°; ms: (m/e) 365 (M+1, 100), 285 (82); ir (potassium bromide): ν 3135, 1590 (C=N), 1390, 1370, 1240, 1045 (C-O-C), 950 cm^{-1}; uv (methanol): λ max 216 nm (log ϵ 4.21); ^1H nmr (DMSO-d_6): δ 1.97-2.57 (m, 4H, 2 CH_2), 4.93 (m, 1H, O-CH-C_4), 5.23 (m, 1H, O-CH-C_5), 6.85 (s, 1H, isox H-C_4), 9.00 (s, 1H, ^2J = 0.8, isox H-C_5).

Anal. Calcd. for $C_{10}H_8Br_2N_2O_3$: C, 33.00; H, 2.22; Br, 43.91; N, 7.70. Found: C, 32.88; H, 2.16; Br, 43.87; N, 7.54.

trans- and *cis*-2,5-Bis(3-methoxy-5-isoxazolyl)tetrahydrofuran (**3a** and **3b**).

2,5-Bis(3-bromo-5-isoxazolyl)tetrahydrofuran (**2a**, **2b**, 8.30 g, 0.0228 mole) was dissolved in a solution of potassium hydroxide (27.4 g) in water (13.9 ml) and methanol (69 ml). The whole was heated at 80° for 5 hours. The solution was concentrated under vacuum, diluted with water, acidified to *p*H 5 with concentrated hydrochloric acid and extracted with chloroform (3 x 50 ml). The organic layers were washed with water until neutral to litmus and dried on sodium sulfate. The solvent was evaporated and the crude product mixture (3.4 g) was chromatographed on silica gel column (800 g) using 4:1 petroleum ether/ethyl acetate as eluent to separate the isomers.

The first fraction, **3a**, having a higer Rf value was the *trans*-isomer, yield, 1.8 g (30%); the second fraction, **3b**, having a lower Rf value and with a more crystalline appearance was the *cis*-isomer, yield, 1.2 g (20%).

Compound **3a**.

This *trans*-isomer had mp 60-62°; ms: (m/e) 267 (M + 1, 100); ir (potassium bromide): ν 3140, 2980, 2950, 1620 (C=N), 1515, 1455, 1410, 1070, 1035 (C-O), 925, cm^{-1}; uv (methanol): λ max 208 nm (log ϵ 4.21); ^1H nmr (DMSO-d_6): δ 2.06-2.50 (m, 4H, 2 CH_2), 3.90 (s, 6H, 2 CH_3), 5.20 (m, 2H, 2 O-CH), 6.31 (s, 2H, 2 isox).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.98; H, 5.44; N, 10.42.

Compound **3b**.

This *cis*-isomer, *meso* form had mp 45-46°, (1:1 *tert*-butyl methyl ether/hexane); ms: (m/e) 267 (M + 1, 100); ir (potassium bromide): ν 3140, 3120, 2950, 1620 (C=N), 1520, 1455, 1410, 1055, 1040 (C-O), 935, cm^{-1}; uv (methanol): λ max 209 nm (log ϵ 4.24); ^1H nmr (DMSO-d_6): δ 2.06-2.50 (m, 4H, 2 CH_2); 3.90 (s, 6H, 2 CH_3); 5.10 (m, 2H, 2 O-CH); 6.23 (s, 2H, 2 isox).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.31; H, 5.40; N, 10.51.

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