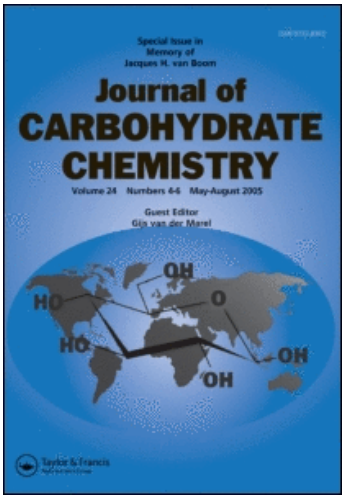

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SYNTHESIS OF ANELLATED PYRANOSE DERIVATIVES ON THE BASIS OF LEVOGLUCOSENONE☆

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☆ Dedicated to Professor Dr. *Rüdiger Selke* on the occasion of his 65th birthday.

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ABSTRACT

1,6-Anhydro-2-(dicyanomethylene)-2,3-dideoxy-4-*S*-ethyl-4-thio-β-D-*erythro*-hexopyranose (**1**) reacted with tosyl azide or sulfur and triethylamine to furnish the 5-aza-10,11-dioxatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-3-carbonitrile **2** and the 10,11-dioxa-5-thiatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-3-carbonitrile **3**, respectively. The reactions of **1** with arylisothiocyanates furnished the 11,12-dioxa-5-thiatricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3-diene-3-carbonitriles **4** and **5**. **3** underwent cyclization with triethyl orthoformate and ammonia or hydrazine hydrate to afford the 5,7-diaza-14,15-dioxa-9-thiatetracyclo[10.2.1.$0^{2,10}$.$0^{3,8}$]pentadecatetra(tri)enes **7** and **8**, respectively.

INTRODUCTION

Pyran rings are part of the structure of numerous natural products.[1-3] It has been found that a great number of these compounds containing anellated pyrans exhibit biological activity, for example as cancerostatics or antibiotics.[4-7] Fused ring systems with at least one pyran moiety are also very interesting as potential inhibitors of glycosidases.[8,9] Therefore, the development of new methods for the synthesis of anellated pyranose derivatives has become a topic of current interest in synthetic organic chemistry in recent years.[10-13]

Levoglucosenone is a bicyclic enone that can be obtained by pyrolysis of cellulose. In recent years this compound has been intensively used as chiral precursor in the synthesis of natural products[14-16] as well as different carbohydrate derivatives such as thiosugars,[17-19] C-glycosyl compounds[15,20] and anellated pyranosides,[13,21,22] some of them showing interesting characteristics from a biological point of view.[17,22]

In continuation of our investigations on the preparation of derivatives of levoglucosenone we now report a new method for the synthesis of anellated monosaccharides using the 1,6-anhydro-2-(dicyanomethylene)-2,3-dideoxy-4-*S*-ethyl-4-thio-β-D-*erythro*-hexopyranose **1** as starting material, which can be obtained in two steps from levoglucosenone in good overall yields.[23] We used the 1,2-aminonitrile substructure of the synthesized anellated heterocycles to obtain new tetracyclic pyrimidine derivatives.

RESULTS AND DISCUSSION

It is known that sulfonyl azides react with acidic methylene compounds. These reactions have mostly been used for the preparation of diazo compounds.[24,25] Treatment of 1,6-anhydro-2-(dicyanomethylene)-2,3-dideoxy-4-*S*-ethyl-4-thio-β-D-*erythro*-hexopyranose **1** with tosyl azide in DMF in the presence of triethylamine afforded the (1*R*,7*S*,8*R*)-4-amino-7-ethylsulfanyl-5-tosyl-5-aza-10,11-dioxatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-3-carbonitrile (**2**) in 37% yield. Similarly, a substituted [1,3]dioxino[4′,5′:5,6]pyrano[4,3-b]pyrrol-7-carbonitrile was obtained by reaction of methyl-4,6-*O*-

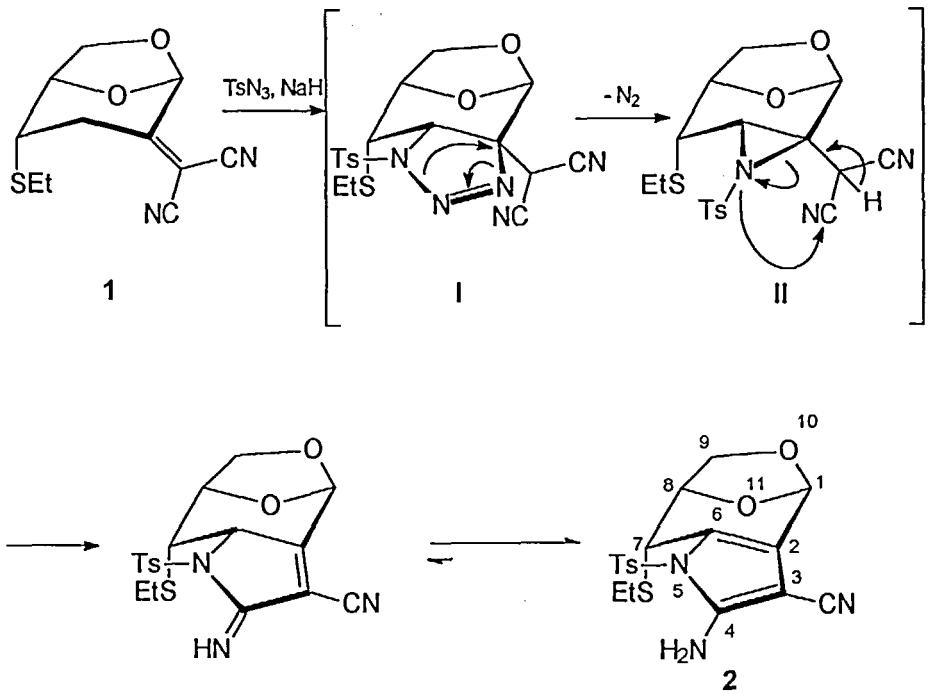
benzyliden-2,3-didesoxy-α-D-*erythro*-hexopyranosid-2-ylidenemalononitrile with tosyl azide.[26]

For the reaction of tosyl azide with carbonyl compounds, a 1,3-dipolar addition mechanism[27] has been postulated. We propose a similar mechanism for the reaction of tosyl azide with **1** where the intermediate triazoline **I** is formed first, then undergoes a loss of nitrogen to give the intermediate aziridine **II**. The rearrangement of **II** then would lead to the formation of compound **2** (Scheme 1).

The mass spectrum of compound **2** showed the molecular peak at $m/z = 405$ and the IR spectrum proved the presence of just one cyano group as well as an amino group. All the other analytical data were in accordance with the proposed structure as well.

The synthesis of thiophene derivatives with biological activity by reaction of either non-carbohydrate "Knoevenagel" compounds or ketones and malononitrile with elementary sulfur mostly in ethanol using amines as bases has already been reported.[28-30] The reaction of compound **1** with sulfur and triethylamine in ethanol as solvent did not lead to the desired result. Therefore, *N,N*-dimethylformamide was used as solvent. Under these conditions the reaction was finished after approximately 15 minutes. In this fashion the (1*R*,7*R*,8*R*)-4-amino-7-ethylsulfanyl-10,11-dioxa-5-thiatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-3-carbonitrile (**3**) was prepared (Scheme 2). All analytical data were in accordance with the proposed structure **3**. Furthermore, an X-ray structure of compound **3** could be obtained. The crystallographic data are given in Table 1. An ORTEP drawing of **3** is shown in Figure 1, and displays the numbering scheme of the atoms.

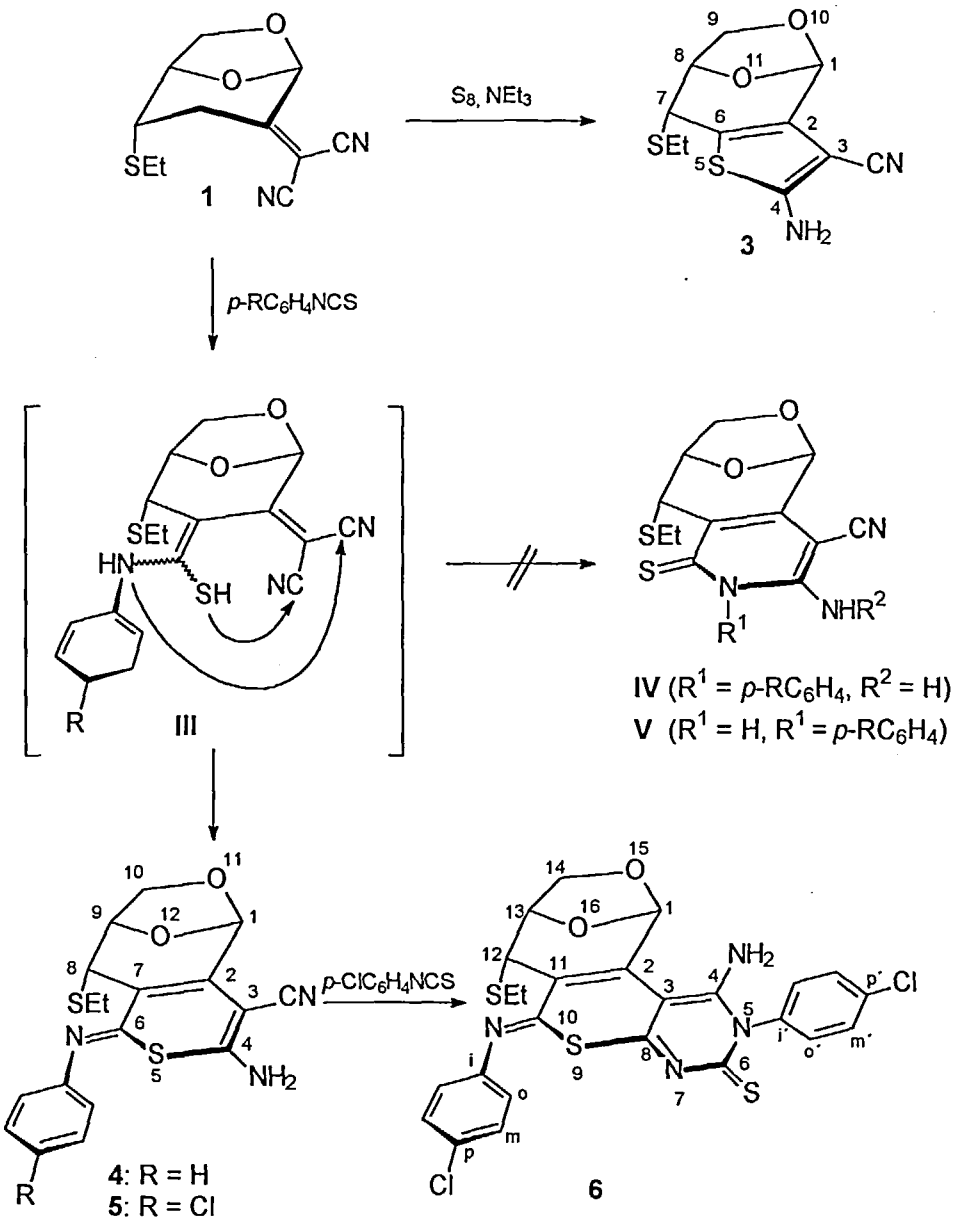
Gewald et al.[31] described the reactions of noncarbohydrate dicyanomethylene compounds with isothiocyanates in the presence of amines to give thiopyrans and dihydropyridines, respectively. It has been reported that performing this reaction at room temperature preferably led to the formation of the thiopyran ring while the pyridine structure is formed as a major product at higher temperatures.[32] Treatment of anhydrosugar **1** with phenylisothiocyanate as well as with *p*-chlorophenylisothiocyanate furnished the (1*R*,8*S*,9*R*)-4-amino-6-arylimino-8-ethylsulfanyl-11,12-dioxa-5-thia-tricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3-diene-3-carbonitriles **4** and **5**, respectively. The reaction proceeds through an open chain intermediate **III** which can cyclize to form either a thiopyran **4**, **5** or a pyridine ring **IV**, **V**. The analytical data confirmed the thiopyran structure. An X-ray structure of compound **4** could be obtained (see Table 1, Figure 1).



Scheme 1

Reaction of **1** with *p*-chlorophenylisothiocyanate afforded the (1*R*,12*S*,13*R*)-4-amino-5- (4-chlorophenyl) -10- (4-chlorophenylimino) -12-ethylsulfanyl-5,7-diaza-15,16-dioxa-9-thiatetracyclo[11.2.1.$0^{2,11}$.$0^{3,8}$]hexadeca-2(11),3,7-triene-6-thione (**6**) as a byproduct in very small amounts. The mass spectrum of this compound showed the molecular peak at *m/z* = 574. The formation of this byproduct can be explained by attack of a second molecule of *p*-chlorophenylisothiocyanate on the amino group of **5** to give a substituted thiurea which undergoes the nitrile cyclization.

The ^{13}C NMR spectrum of **6** showed two signals at δ 121.0 and 129.9 corresponding to the *ortho* and *meta* carbon atoms (in relation to the nitrogen atom) in a *p*-chlorophenyl ring bounded to an imino nitrogen atom. These signals are in agreement with the corresponding signals in compound **5**. On the other hand, the spectrum of **6** contained four additional signals in this region (δ 131.1, 130.7, 130.6, 130.2) that were assigned to the corresponding *ortho* and *meta* carbon atoms in the other *p*-chlorophenyl



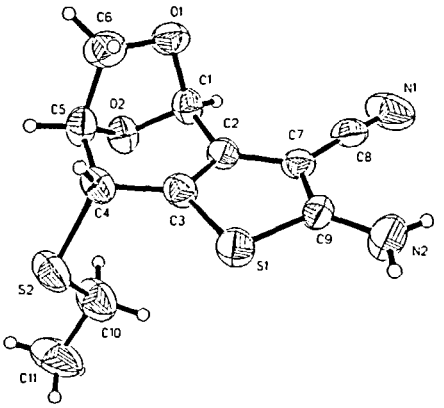
Scheme 2

Table 1. Crystallographic data of **3** and **4**.

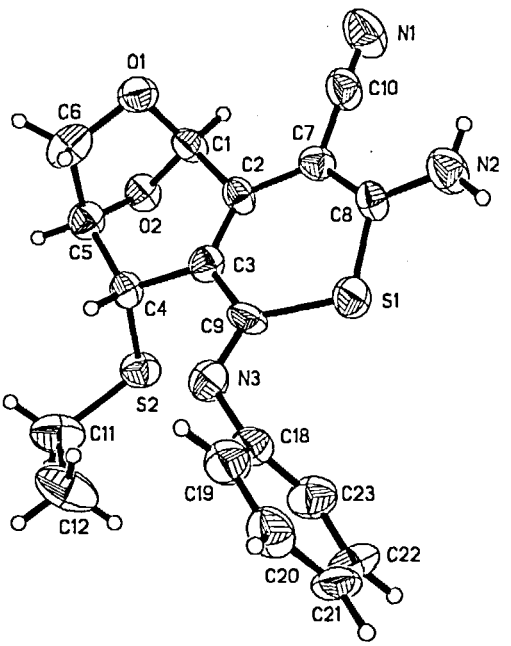
	3	**4**
Crystal size [mm]	0.66 x 0.46 x 0.1	0.24 x 0.16 x 0.16
Crystal system	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	P1
a [Å]	8.183(1)	8.671(1)
b [Å]	9.788(2)	8.709(1)
c [Å]	15.556(3)	13.731(2)
α [°]	90	78.52(1)
β [°]	90	81.54(1)
γ [°]	90	60.44(1)
V [Å^3]	1246.0(4)	882.4(2)
Z	4	2
ρ_{calc} [g cm^{-3}]	1.431	1.398
μ ($Mo_{K\alpha}$) [mm^{-1}]	0.418	0.319
F(000)	560	388
2θ limits [°]	4.92/44	5.40/ 44
hkl Ranges	-8/8; -10/10; -16/16	-9/9; -9/9; -14/14
Reflections collected	1826	4290
Independent reflections	1530	4289
Reflections observed	1300	3605
Parameters refined	154	451
R_1 ($2\sigma(I)$)	0.0476	0.0570
R_1 (all data)	0.0620	0.0734
wR_2 (all data)	0.1212	0.1497
Goodness of fit	1.063	1.031

a. Standard deviations given in parentheses.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-112401 and CCDC-112402. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).



Compound 3



Compound 4

Fig. 1. ORTEP drawings of **3** and **4**.
(only one molecule of the asymmetric unit is shown)

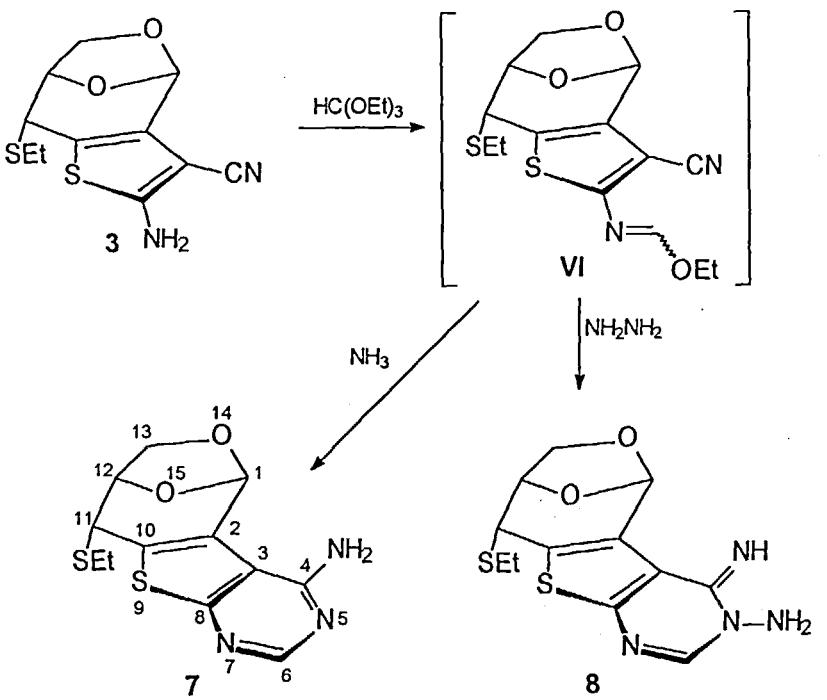
ring (determined by a DEPT experiment). Furthermore, the ^{1}H NMR spectrum confirmed the structure **6** as well. It showed two doublets of two protons each one at δ 6.94 (*meta* to nitrogen atom) and δ 7.55 (*ortho* to nitrogen atom) having similar chemical shifts as the corresponding protons in compound **5.** The other aromatic ring gave three different signals at δ 7.34, 7.47 and 7.69 which proved that there is no free rotation around the C-N bond which is also in accordance with the proposed structure for **6**.[33]

The reaction of **1** with *p*-chlorophenylisothiocyanate was repeated with a molar ratio of 1:2 and a longer reaction time. In this fashion compound **6** could be obtained as principal product of the reaction in 30% yield.

The preparation of pyrimidine derivatives starting from compounds containing the 1,2-aminonitrile unit has been known since several years.[35] We performed the reaction of **3** with triethyl orthoformate and ammonia which led to the (1*R*,11*R*,12*R*)-11-ethylsulfanyl-5,7-diaza-14,15-dioxa-9-thiatetracyclo[10.2.1.$0^{2,10}$.$0^{3,8}$]pentadeca-2(10), 3(8),4, 6-tetraen-4-ylamine (**7**) in 68% yield. On the other hand, the treatment of **3** with triethyl orthoformate and hydrazine hydrate provided the (1*R*,11*R*,12*R*)-11-ethylsulfanyl-5-amino-5,7-diaza-14,15-dioxa-9-thiatetracyclo[10.2.1.$0^{2,10}0^{3,8}$]pentadeca-2(10),3(8),6-trien-4-ylideneamine (**8**) in 53% yield. The analytical data obtained for both compound were in accordance with the proposed structures (Scheme 3).

EXPERIMENTAL

General procedures. Melting points were determined with a Boëtius apparatus and are corrected. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. Specific optical rotations were measured with a Gyromat HP (Dr. Kernchen). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker instruments ARX 300 and AC 250 with $CDCl_3$ or DMSO-d_6 as solvent. The calibration of spectra was carried out by means of solvent peaks (DMSO-d_6: δ ^{1}H= 2.50; δ ^{13}C= 39.7; $CDCl_3$: δ ^{1}H= 7.25; δ ^{13}C= 77.0). The ^{13}C NMR signals were assigned by DEPT and/or ^{1}H,^{13}C COSY experiments. The mass spectra were recorded on an AMD 402/3 spectrometer AMD Intectra GmbH). For chromatography Merck silica gel 60 (230-400 mesh) was used. TLC was performed on



Scheme 3

silica gel 60 GF_{254} (Merck) with detection by charring with sulfuric acid. Elemental analysis were performed on a Leco CHNS-932 instrument. Table 1 provides a summary of the crystallographic data of compounds **3** and **4.** The crystals were sealed onto a glass fiber and mounted on a Siemens P4 automated four circle diffractometer ($Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å, $T = 298$ K. The structures were solved by direct methods (XS program for crystal structure solution, version 4.2 for MS-DOS, copyright Siemens Analytical Xray Inst. Inc.) and refined by the full-matrix least-squares method of SHELXL-93. Non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed into theoretical positions and were refined by using the riding model. The weighting scheme was calculated according to $w = 1/[\sigma^2(Fo^2)+(0.0627P)^2+0.0000P]$, where $P = (Fo^2+2Fc^2)/3$.

(1*R*,7*S*,8*R*)-4-Amino-7-ethylsulfanyl-5-tosyl-5-aza-10,11-dioxatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-3-carbonitrile (2). Tosyl azide (98 mg, 0.5 mmol) and

triethylamine(0.07 mL, 0.05 mmol) were added to a stirred solution of 1,6-anhydro-2-(dicyanomethylene)-2,3-dideoxy-4-*S*-ethyl-4-thio-β-D-*erythro*-hexopyranose (**1**, 118 mg, 0.5 mmol) in anhydrous DMF (10 mL) at 0 °C. The mixture was stirred for 3 h, then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to leave a syrup. The product was chromatographed on a column of silica gel with 6:1 toluene/ethyl acetate to give a colorless syrup, that crystallized after several hours and yielded **2**, 75 mg, 37 % (in order to obtain an analytical pure sample HPLC was used): mp 73-80 °C (decomposition); $[\alpha]^{24}_D$ -11.1° (*c* 0.5 chloroform); IR(KBr) 3448.1, 3332.7 (NH_2), 2212.7 (CN), 1603.8 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.3 Hz, SCH_2CH_3), 2.44 (s, 3H, $C_6H_4CH_3$), 2.60 (m, 2H, SCH_2), 3.37 (d, 1H, $J_{7\text{-}8}$ = 1.2 Hz, H-7), 3.45 (dd, 1H, $J_{8\text{-}9e}$=2.3 Hz, H-9e Hz), 4.04 (dd, 1H, $J_{9a\text{-}9e}$ = 7.9 Hz, $J_{8\text{-}9a}$ = 6.4 Hz, H-9a), 4.82 (m, 1H, H-8), 5.29 (brs, 2H, NH_2), 6.50 (s, 1H, H-1), 7.35 (m, 2H, m- C_6H_4), 7.84 (m, 2H, o-C_6H_4); ^{13}C NMR ($CDCl_3$) δ 147.5, 146.5 (C-4, p-C_6H_4), 128.9, 124.6, 123.2 (i, o, m-C_6H_4), 133.6 (C-6), 118.0, 113.8 (CN, C-2), 94.8 (C-1), 78.8 (C-8), 74.4 (C-3), 66.9 (C-9), 42.8 (C-7), 25.0 (SCH_2), 20.9 ($C_6H_4CH_3$), 14.6 (SCH_2CH_3). Mass spectrum: *m/z* (%) = 405 (12, $M^{+\cdot}$), 91 (100).

Anal. Calcd for $C_{18}H_{19}N_3O_4S_2$ (405.49): C, 53.32; H, 4.72; N, 10.36; S, 15.81. Found: C, 53.50; H, 5.01; N, 10.10; S, 15.58.

(1*R*,7*R*,8*R*)-4-Amino-7-ethylsulfanyl-10,11-dioxa-5-thiatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-diene-3-carbonitrile (3). Elementary sulfur (16 mg, 0.5 mmol) and triethylamine (0.07 mL, 0.5 mmol) were added to a solution of **1** (118 mg, 0.5 mmol) in anhydrous DMF (10 mL). The mixture was stirred for 1 h, then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to leave a syrup. The product was chromatographed on a column of silica gel with 8:1 toluene/ethyl acetate to give, after recrystallization from dichloromethane/hexane, white crystals **3** (78 mg, 58 %): mp 140 °C; $[\alpha]^{25}_D$ -216.4° (*c* 0.5, chloroform); IR(KBr) 3303.1, 3202.8 (NH_2), 2199.5 (CN), 1630.4, 1510.9 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J= 7.5 Hz, CH_3), 2.63 (m, 2H, SCH_2), 3.55 (d, 1H, $J_{7\text{-}8}$ = 1.2 Hz, H-7), 3.62 (dd, 1H, $J_{8\text{-}9e}$ = 1.8 Hz, H-9e), 4.05 (dd, 1H, $J_{9a\text{-}9e}$ = 7.9 Hz, $J_{8\text{-}9a}$ = 6.1 Hz, H-9a), 4.92 (m, 1H, H-8), 4.84 (brs, 2H, NH_2), 6.00 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 163.8 (C-4), 135.9 (C-6), 119.8, 113.6 (C-2,

CN), 95.1 (C-1), 84.5 (C-3), 78.9 (C-8), 67.9 (C-9), 45.1 (C-7), 24.4 (SCH_2), 14.8 (CH_3). Mass spectrum: *m/z* (%) = 268 (8, $M^{+\cdot}$), 177 (100).

Anal. Calcd for $C_{11}H_{12}N_2O_2S_2$ (268.35): C, 49.24; H, 4.51; N, 10.44; S, 23.89. Found: C, 48.80; H, 4.72; N, 10.46; S, 23.33.

(1*R*,8*S*,9*R*)-4-Amino-8-ethylsulfanyl-6-phenylimino-11,12-dioxa-5-thiatricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3-diene-3-carbonitrile (4). Phenylisothiocyanate (0.04 mL, 0.05 mmol), and triethylamine (0.07 mL, 0.5 mmol) were added to a stirred solution of **1** (118 mg, 0.5 mmol) in anhydrous DMF (10 mL) at 22 °C. The mixture was stirred for 2 h, then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to leave a yellow syrup. The product was chromatographed on a column of silica gel with 8:1 toluene/ethyl acetate to give, after recrystallization from dichloromethane/hexane, yellow crystals of **4** (85 mg, 51%): mp 202-204 °C; $[\alpha]^{24}_D$ -91.6° (*c* 0.5 chloroform); IR(KBr) 3313.3, 3198.8 (NH_2), 2197.9 (CN), 1582.1 (C=C); ^{1}H NMR (DMSO-d_6) δ 1.23 (t, 3H, J = 7.6 Hz, CH_3), 2.79 (m, 2H, SCH_2), 3.77 (d, 1H, $J_{8\text{-}9}$ = 1.2 Hz, H-8), 3.66 (dd, 1H, $J_{9\text{-}10e}$ =1.9 Hz, H-10e), 3.95 (dd, 1H, $J_{10a\text{-}10e}$ = 8.3 Hz, $J_{9\text{-}10a}$ = 6.1 Hz, H-10a), 4.95 (m, 1H, H-9), 5.92 (s, 1H, H-1), 6.86 (m, 2H, m-Ph), 7.15 (m, 1H, p-Ph), 7.44 (m, 2H, o-Ph), 8.25 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 162.4 (C-4), 150.1 (C-6), 139.5, 130.1, 124.4, 119.4 (Ph), 126.0, 115.4, 112.8 (C-2, C-7, CN), 96.9 (C-1), 79.3 (C-9), 72.2 (C-3), 66.6 (C-10), 44.3 (C-8), 27.1 (SCH_2), 15.4 (CH_3). Mass spectrum: *m/z* (%) = 372 (2, $(M+H)^+$), 136 (100).

Anal. Calcd for $C_{18}H_{17}N_3O_2S_2$ (371.47): C, 58.20; H, 4.61; N, 11.31; S, 17.26. Found: C, 57.92; H, 4.53; N, 11.39; S, 17.06.

(1*R*,8*S*,9*R*)-4-Amino-6-(4-chlorophenylimino)-8-ethylsulfanyl-11,12-dioxa-5-thiatricyclo[7.2.1.$0^{2,7}$]dodeca-2(7),3-diene-3-carbonitrile (5). *p*-Chlorophenylisothiocyanate (85 mg, 0.5 mmol), and triethylamine (0.07 mL, 0.5 mmol) were added to a stirred solution of **1** (118 mg, 0.5 mmol) in anhydrous DMF (10 mL) at 22 °C. The mixture was stirred for 1.5 h, then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to leave a yellow syrup. The product was chromatographed

on a column of silica gel with 8:1 toluene/ethyl acetate to give, after recrystallization from dichloromethane/hexane, yellow crystals of **5** (90 mg, 44%): mp 185-187 °C; $[\alpha]^{25}_D$ -62.9° (*c* 0.5 chloroform); IR(KBr) 3311.8, 3196.0 (NH_2), 2199.2 (CN), 1579.5, 1628.9 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.3 Hz, CH_3), 2.78 (m, 2H, SCH_2), 3.66 (d, 1H, $J_{8\text{-}9}$ = 1.5 Hz, H-8), 3.65 (dd, 1H, $J_{9\text{-}10e}$ = 2.0 Hz, H-10e), 4.01 (dd, 1H, $J_{10a\text{-}10e}$ = 7.6 Hz, $J_{9\text{-}10a}$ = 6.1 Hz, H-10a), 4.94 (m, 1H, H-9), 5.62 (brs, 2H, NH_2), 6.01 (s, 1H, H-1), 6.79 (m, 2H, m-C_6H_4), 7.34 (m, 2H, o-C_6H_4); ^{13}C NMR ($CDCl_3$) δ 160.9 (C-4), 148.1 (C-6), 138.9, 130.2, 130.0, 121.0 (C_6H_4), 121.1, 115.2, 114.6 (C-2, C-7, CN), 97.3 (C-1), 79.5 (C-9), 75.8 (C-3), 66.9 (C-10), 44.8 (C-8), 27.8 (SCH_2), 15.1 (CH_3). Mass spectrum: *m/z* (%) = 405 (28, $M^{+\cdot}$), 314 (100).

Anal. Calcd for $C_{18}H_{16}ClN_3O_2S_2$ (405.92): C, 53.26; H, 3.96; Cl, 8.73; N, 10.35; S, 15.80. Found: C, 52.95; H, 3.82; Cl, 8.38; N, 10.33; S, 15.57.

(1*R*,12*S*,13*R*)-4-Amino-5-(4-chlorophenyl)-10-(4-chlorophenylimino)-12-ethylsulfanyl-5,7-diaza-15,16-dioxa-9-thiatetracyclo[11.2.1.0^{2,11}.0^{3,8}]hexadeca-2(11),3,7-triene-6-thione (6). *p*-Chlorophenylisothiocyanate (170 mg, 1.0 mmol), and triethylamine (0.14 mL, 1.0 mmol) were added to a stirred solution of **1** (118 mg, 0.5 mmol) in anhydrous DMF (10 mL) at 22 °C. The mixture was stirred for 2.5 h, then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with water (3 x 20 mL), dried (Na_2SO_4) and concentrated to leave a yellow syrup. The product was chromatographed on a column of silica gel with 8:1 toluene/ethyl acetate to give, after recrystallization from ethyl acetate, yellow crystals of **5** (85 mg, 30 %): mp 225-227 °C; $[\alpha]^{25}_D$ 63.1° (*c* 0.1 chloroform); IR(KBr) 3312.5, 3213.4 (NH_2), 1632.3, 1536.9 (C=C); ^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3H, J= 7.2 Hz, CH_3), 2.80 (m, 2H, SCH_2), 3.82 (dd, 1H, $J_{13\text{-}14e}$ = 2.1 Hz, H-14e), 4.05 (s, 1H, H-12), 4.08 (dd, 1H, $J_{14a\text{-}14e}$ = 8.3 Hz, $J_{13\text{-}14a}$ = 5.7 Hz, H-14a), 5.09 (brd, 1H, H-13), 6.39 (s, 1H, H-1), 7.19 (brs, 2H, NH_2), 6.94 (m, 2H, m-C_6H_4), 7.55 (m, 2H, o-C_6H_4); 7.34 (m, 1H, o′-C_6H_4); 7.47 (m, 1H, o′-C_6H_4); 7.69 (m, 2H, m′-C_6H_4) ; ^{13}C NMR (DMSO-d_6) δ 177.6, 162.2 (C-8, C-6), 154.2, 156.3 (C-4, C-10), 148.2 (i′-C_6H_4), 137.0 (i-C_6H_4), 136.0, 134.3 (p, p′-C_6H_4), 131.1, 130.7, 130.6, 130.2 (o′, m′-C_6H_4)), 129.9 (m-C_6H_4), 121.0 (o-C_6H_4), 129.1, 123.4 (C-11, C-2), 98.0 (C-3), 95.1 (C-1), 78.9 (C-13), 67.1 (C-14), 44.8 (C-12), 27.3 (S*C*H_2), 16.2 (CH_3). Mass spectrum: *m/z* (%) = 574 (55, M^+), 154 (100).

Anal. Calcd for $C_{25}H_{20}Cl_2N_4O_2S_3$ (575.55): C, 52.17; H, 3.50; Cl, 12.32; N, 9.73; S, 16.71. Found: C, 52.46; H, 3.79;Cl, 12.21; N, 9.95; S 16.47.

(1*R*,11*R*,12*R*) -11-Ethylsulfanyl-5,7-diaza-14,15-dioxa-9-thiatetracyclo[10.2.1.0^{2,10}.0^{3,8}]pentadeca-2(10),3(8),4,6-tetraen-4-ylamine (7). Compound **3** (134 mg, 0.5 mmol) was added to ethyl orthoformate (10 mL) and refluxed for 1 h. The reaction mixture was concentrated to a syrup, dissolved in 10 mL of a saturated solution of ammonia in ethanol and stirred at 22 °C for 30 min. The reaction mixture was concentrated to give a yellowish solid, dissolved in 20 mL acetone, treated with activated charcoal for 15 min and filtered. The solvent was evaporated under vacuum and the white solid recrystallized from dichloromethane/hexane to give white crystals **6** (100 mg, 68%): mp 193-197 °C; $[\alpha]^{25}_D$ 46.4° (*c* 0.1, chloroform); IR(KBr) 3415.0, 3330.2, 3234.1 (NH_2), 1652.0, 1568.2 (C=C); ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 7.3 Hz, CH_3), 2.67 (m, 2H, SCH_2), 3.63 (dd, 1H, $J_{12\text{-}13e}$ = 2.1 Hz, H-13e), 3.99 (dd, 1H, $J_{13a\text{-}13e}$ = 8.2 Hz, $J_{12\text{-}13a}$ = 6.4 Hz, H-13a), 4.15 (brs, 1H, H-11), 4.97 (brd, 1H, H-12), 6.84 (s, 1H, H-1), 7.10 (brs, 2H, NH_2), 8.25 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6) δ 167.1, 157.7 (C-8, C-4), 153.7 (C-6), 132.3, 130.2 (C-10, C-2), 111.0 (C-3), 94.7 (C-1), 77.5 (C-12), 67.1 (C-13), 44.6 (C-11), 24.7 (SCH_2), 15.1 (CH_3). Mass spectrum: *m/z* (%) = 295 (3, $M^{+\cdot}$), 204 (100).

Anal. Calcd for $C_{12}H_{13}N_3O_2S_2$ (295.37): C, 48.80; H, 4.44; N, 14.23; S, 21.71. Found: C, 48.60; H, 4.66; N, 13.97; S, 20.97.

(1*R*,11*R*,12*R*)-5-amino-11-ethylsulfanyl-5,7-diaza-14,15-dioxa-9-thiatetracyclo[10.2.1.0^{2,10}-0^{3,8}]pentadeca-2(10),3(8),6-trien-4-imine (8). Compound **3** (134 mg, 0.5 mmol) was added to ethyl orthoformate (10 mL) and the mixture refluxed for 1 h. The reaction mixture was concentrated to a syrup and dissolved in 10 mL of ethanol. Hydrazine hydrate (0.050 mL, 0.55 mmol) was added and the mixture was stirred at 22 °C for 30 min. The reaction mixture was concentrated to give a yellowish solid, dissolved in 20 mL acetone, treated with activated charcoal for 15 minutes and filtered. The filtrate was concentrated under vacuum and the white solid recrystallized from ethanol to give white crystals **7** (82 mg, 53%): mp 174-175 °C; $[\alpha]^{24}_D$ 42.5° (*c* 0.5, DMF); IR(KBr) 3334.0, 3271.9, 3229.9, 3143.1 (NH, NH_2), 1628.6, 1552.3 (C=C); ^{1}H NMR (DMSO-d_6) δ 1.19 (t, 3H, J = 7.3 Hz, CH_3), 2.63 (m, 2H, SCH_2), 3.59 (dd, 1H, $J_{12\text{-}13e}$= 1.8 Hz,

H-13e), 3.94 (dd, 1H, $J_{13a\text{-}13e}$ = 8.2 Hz, $J_{12\text{-}13a}$ = 6.7 Hz, H-13a), 4.16 (brs, 1H, H-11), 4.92 (brd, 1H, H-12), 5.63 (brs, 2H, NH_2), 6.83 (s, 1H, H-1), 7.24 (s, 1H, NH), 7.95 (brs, 1H, H-6); ^{13}C NMR δ (DMSO-d_6) 157.5, 150.7 (C-8, C-4), 149.2 (C-6), 133.9, 132.6 (C-2, C-10), 117.6 (C-3), 95.4 (C-1), 77.5 (C-12), 66.8 (C-13), 44.5 (C-11), 24.6 (SCH_2), 15.0 (CH_3). Mass spectrum: *m/z* (%) = 310 (23, $M^{+\cdot}$), 219 (100).

Anal. Calcd for $C_{12}H_{14}N_4O_2S_2$ (310.39): C, 46.44; H, 4.55; N, 18.15; S, 20.66. Found: C, 46.12; H, 4.69; N, 17.85; S, 20.87.

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