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Enantiopure Building Blocks for Marine Natural Products via Differentiation of Enantiotopic Groups

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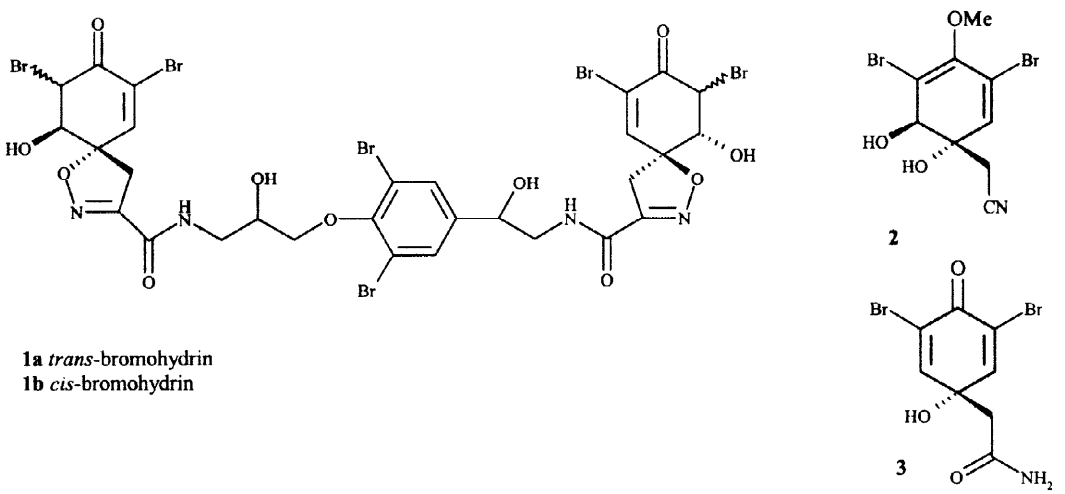
Abstract: The group and face-selective cycloaddition of the enantiopure cyclopentadiene **4** to the tyrosine-related spirocylohexadienone **10** provided a high yield of the enantiomerically pure cyclohexadienone **11**. Stereoselective transformations at the remaining double bond followed by a thermal retro-process, finally giving rise to the chromophore of the marine agelorin antibioticcs isolated from the sponge *Agelas oroides* Schmidt.

Introduction

The structurally most exciting subunits of the marine antibiotics agelorin A (**1a**) and agelorin B (**1b**) are the halogenated spirocyclohexenone rings (Fig. 1). They were isolated by König and Wright[1] from the barrier reef sponge *Agelas oroides* in 1993 and were subsequently shown to be active against *Bacillus subtilis* and *Micrococcus luteus*.[2]



1a *trans*-bromohydrin
1b *cis*-bromohydrin

Fig. 1. Brominated marine natural compounds

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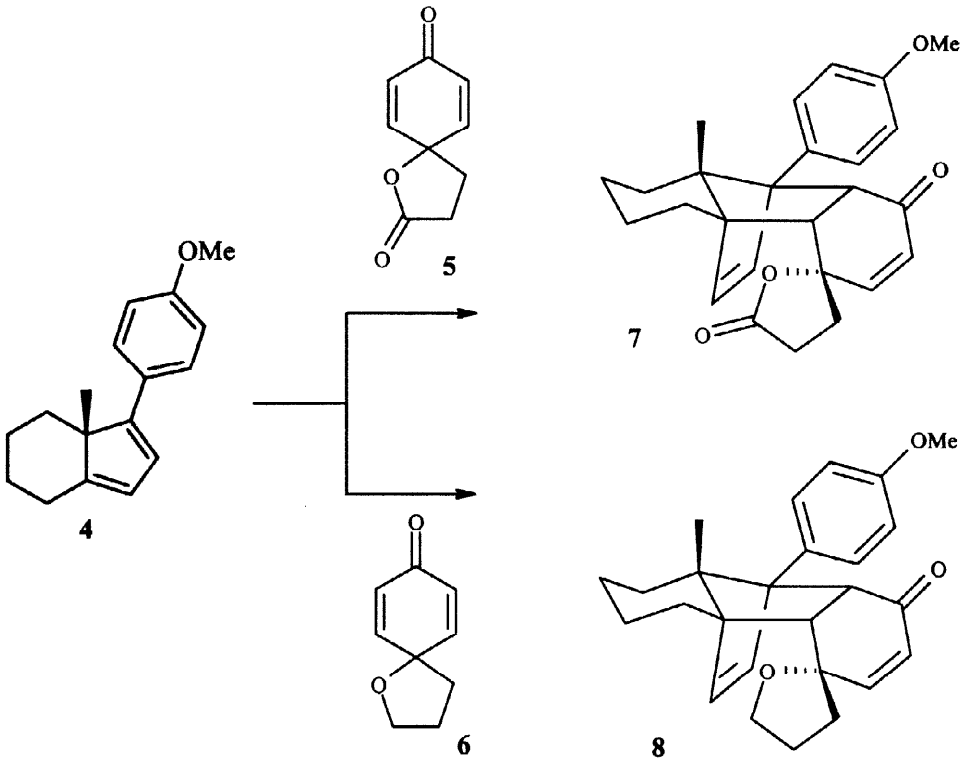
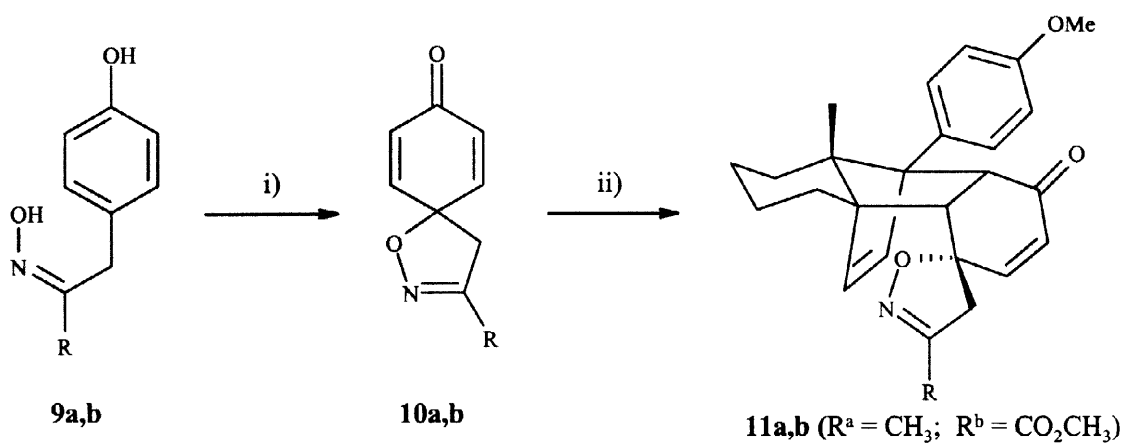
As earlier cycloaddition experiments with the optically pure cyclopentadiene **4**[3] and spirolactone **5** or spiroether **6** had resulted in clean and very efficient discrimination of the enantiotopic double bonds of the cyclohexadienone moiety, leading to the enantiomerically pure cyclohexenones **7** and **8**[4] (Scheme 1), we were confident of obtaining comparable results with spiroisoxazolines of the general structure **10**.



Scheme 1. Differentiation of enantiotopic groups

Since the face selectivity in this process is believed to be due to the lower spatial demand of an oxygen atom than a methylene group, formation of the cycloproducts **11** from this reaction, was expected (Scheme 2).



9a,b **10a,b** **11a,b** ($R^a = CH_3$; $R^b = CO_2CH_3$)

Scheme 2. i) PIFA, CH_3CN, reflux; ii) 6.5 kbar; **4**, CH_2Cl_2 (**11a** 88%; **11b** 78%)

Starting from the reasonable assumption that oxidative attack (hydroxylation, epoxidation) to the cylohexenone double bond would owing to the concave-convex structure of **11** take place from the β-side in a chemoselective manner, the *cis*-orientation of the hydroxy group and the methylene group of the spiro-ring (see **1a** and **1b**) should be easily accessible, culminating in a diastereoselective and enantioselective route to this important subunit.

Results and Discussion

To test all these assumptions, the simple spiro-cyclohexadienone **10a** was prepared in good yield using McKillops phenyliodine(III) bis(trifluoroacetate) (PIFA) oxidation of oxime **9**.[5]

We were pleased to note that the subsequent cycloaddition process indeed gave rise to one single cycloadduct in 88% yield and since the absolute configuration of this material could not be reliably deduced from NMR data and NOE experiments, structure **11a** was proven by an X-ray investigation (Fig. 2).

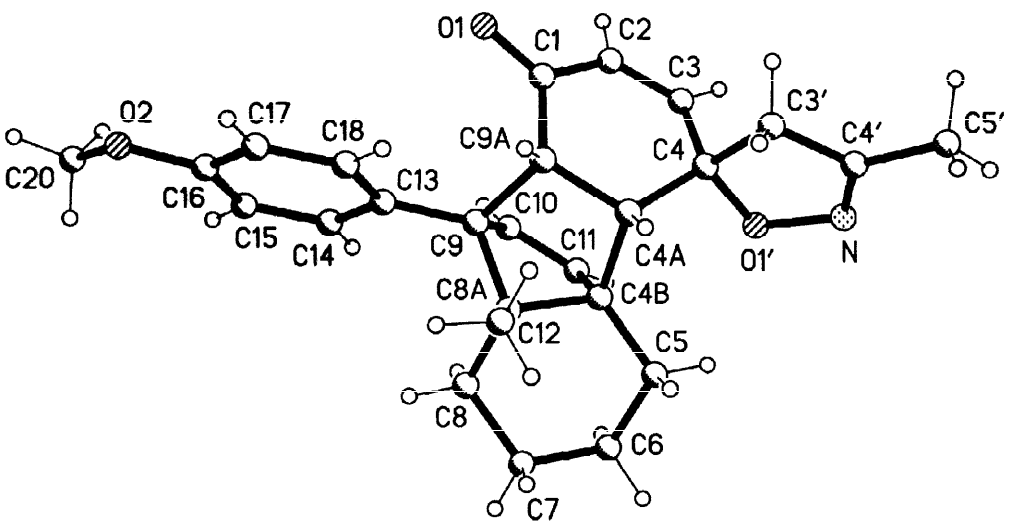
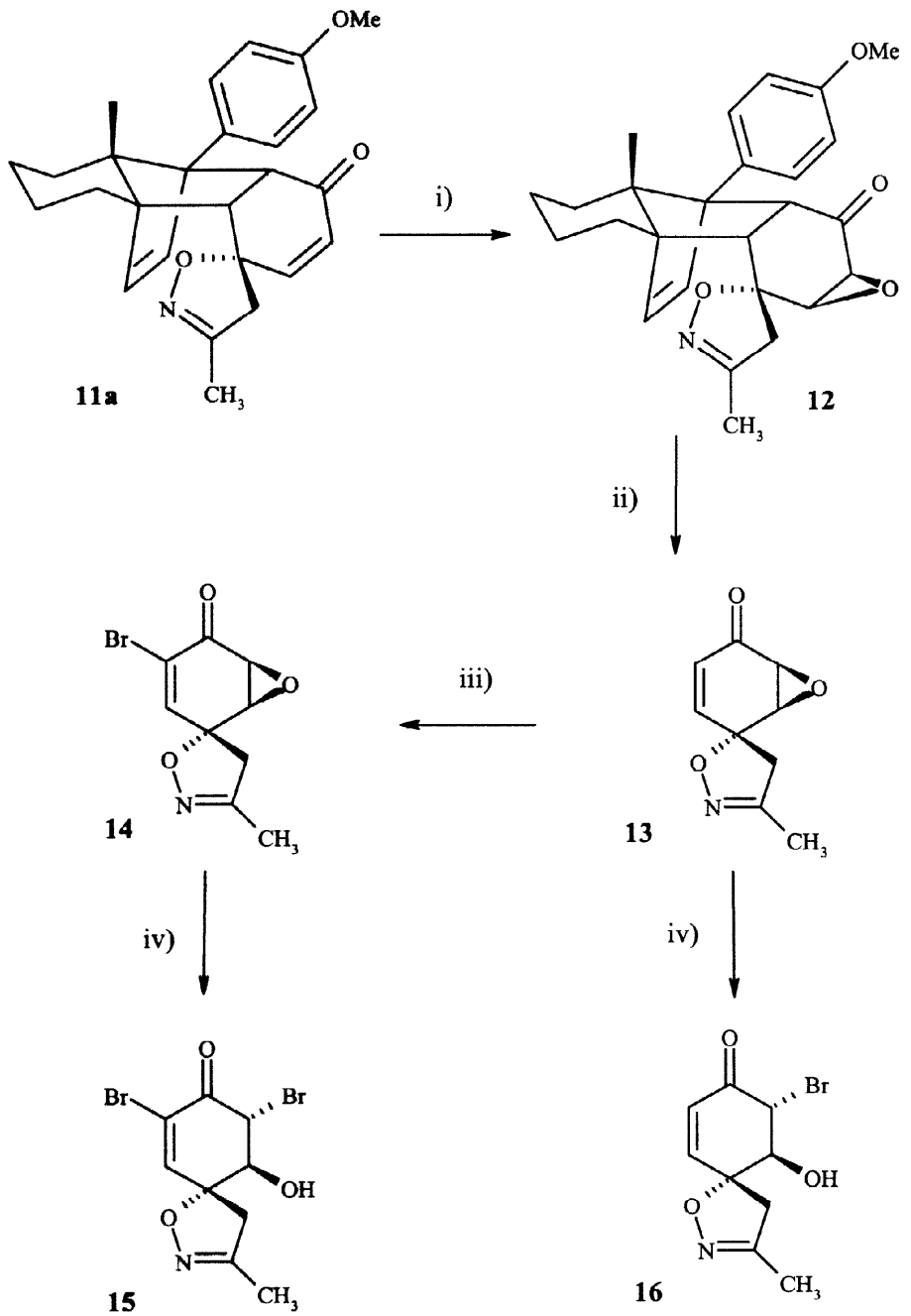


Fig. 2. Structure of compound **11a** in the crystal. Radii are arbitrary.

As expected, nucleophilic epoxidation of this adduct provided β-epoxide **12** as one stereoisomer exclusively in 96% yield. After these diastereoselective manipulations at the enantiotopic double bonds, the stage was set for the thermal retro-reaction, which took place at 300 °C and gave rise to the enantiopure epoxycyclohexenone **13** in 83% yield and with ee >98% (Scheme 3).

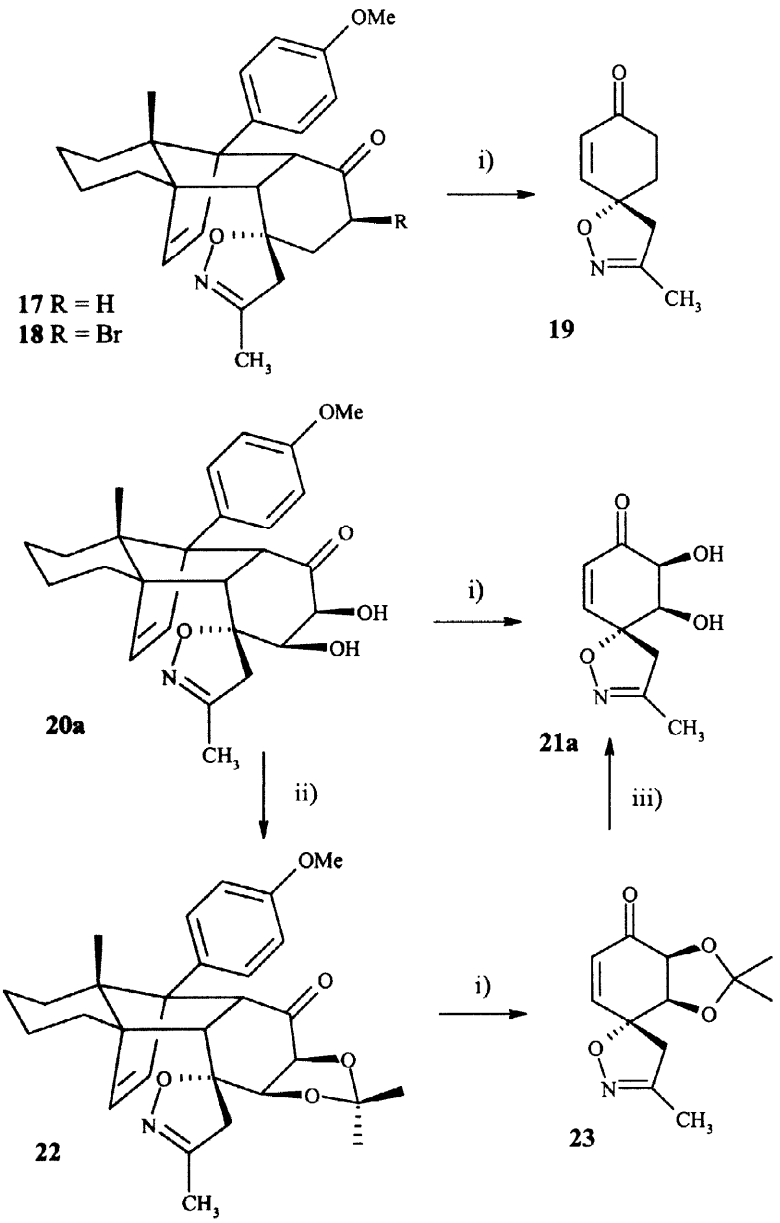


Scheme 3. i) KOH, H_2O_2, aq. THF, 0 °C (96%); ii) 300 °C, $1\cdot10^{-2}$ mbar (83%); iii) Br_2, NEt_3, CH_2Cl_2, 0 °C (48%); iv) $Ph_3P{\cdot}Br_2$, CH_2Cl_2 (79%).

The bromination of the remaining double bond in the presence of triethylamine proceeded uneventfully to provide vinyl bromide **14** and to stereoselectively establish the substitution pattern of the Agelorin chromophore, this intermediate was treated with triphenylphosphine-dibromide as described by Caputo and his colleagues[6] to yield dibromide **15** which meets all requirements for the core-structure of *epi*-agelorin A.

According to our expectations this regioselective opening of the epoxide was also observed with the more simple spiro-cyclohexenone **13** and provided bromohydrin **16** in 79% yield.

With respect to the synthesis of agelorin A, this route turned out to be unsuccessful however, because all efforts to generate the epoxide of **11b** failed. Thus we began to study additional typical double bond transformations with **11a**, including reduction or hydrogenation and the flash-hydroxylation with ruthenium tetroxide.[7] In spite of the presence of the more strained electron rich cyclopentene double bond, both reactions proceeded with excellent chemoselectivity and yielded spiro-cyclohexanone **17** and its corresponding *cis*-diol **20a** very efficiently (Scheme 4).

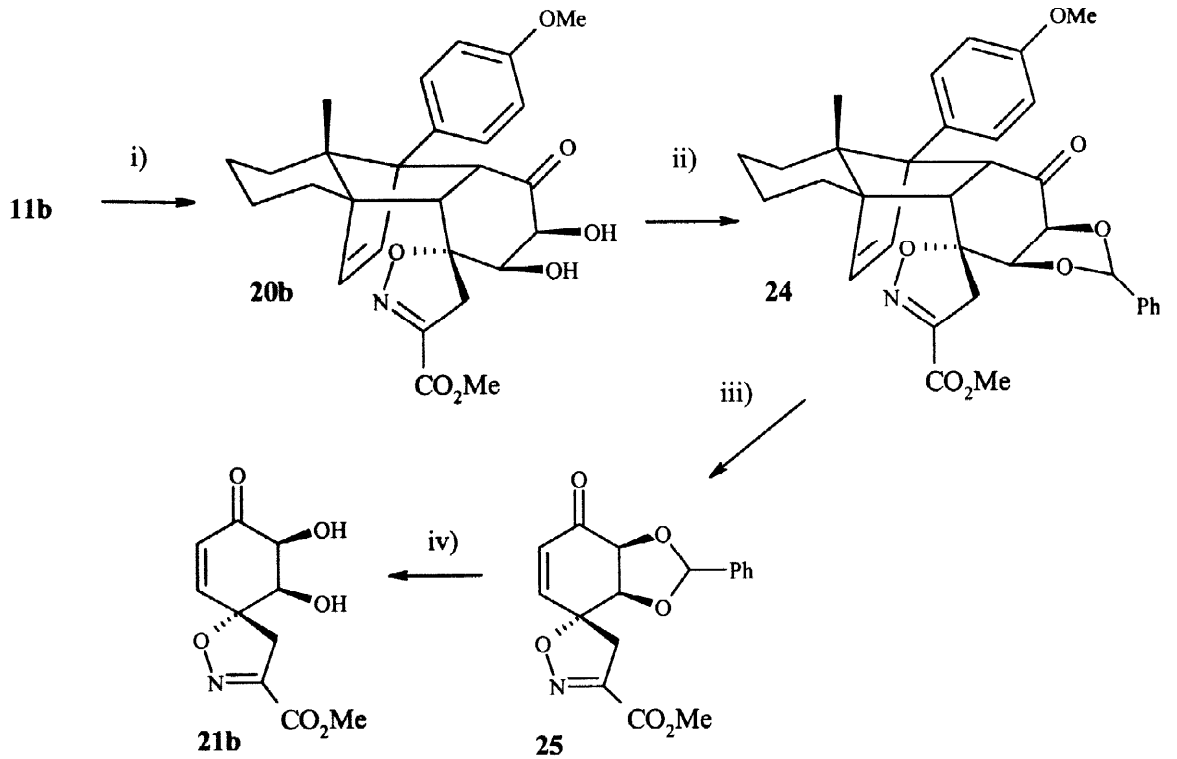


Scheme 4. i) 300 °C, $1 \cdot 10^{-2}$ mbar (**19** 87%; **21a** 32%; **23** 87%); ii) 2,2-dimethoxypropane, *p*TsOH, DMF (95%); iii) 2 N HCl, aq. THF (24%).

Although the dihydro compounds **17** provided a high yield of cyclohexenone **19** in the retro-Diels-Alder process, its corresponding monobromide **18**, which had been obtained with pyridinium tribromide in 73% yield, failed completely under comparable conditions. Unsatisfactory results at this stage were also noticed with diol **20a** which gave rise to a meager 32% of the dihydroxycyclohexenone **21a**. In this case however preceding acetonide formation changed the situation completely. Excellent recovery of both retro-products was secured after pyrolysis at 300 °C.

This is obviously due to the high stability of acetonide **23**, which turned out to be a mixed blessing, however. In the subsequent hydrolysis to generate diol **20a** the forcing conditions necessary for this splitting (2N HCl) led to a quite low yield of the hydrolysis product (24%).

This was the main reason to switch from acetone to benzaldehyde as the protecting reagent in our approach to the ester derivative **21b**, which is the real and crucial intermediate en route to the agelorins and their analogues (Scheme 5).



Scheme 5. i) $RuCl_3$, $NaIO_4$, EtOAc/CH_3CN/H_2O, 0 °C (89%); ii) α,α'-dimethoxytoluene, *p*TsOH, CH_3CN (90%); iii) 300 °C, $1\,10^{-2}$ mbar (69%); iv) 2 N HCl, aq. acetone (72%).

With this protecting group, satisfactory thermal stability should, because of higher cation-stability, be accompanied by high reaction rates in the deprotecting step. To our delight this was borne out by experiment. When diol **20b**, which had been prepared from **11b** in the usual way was transformed into acetal **24** it cleanly underwent pyrolysis to generate a 69% yield of

spirocyclohexenone **25** and the good yield (72%) in the subsequent hydrolysis proved our prediction to be correct and opened a reliable route to an enantiopure intermediate, representing the agelorin chromophore.

A few compounds of this type were selected for tests with cell-lines from adenocarcinoma (HM02) and coloncarcinoma (KATO III) and as tables I and II demonstrate very clearly the analogues **16** and **19** are even more active than the dibromide **15** corresponding to the agelorins. As even the simple cyclohexenone **19** shows this activity one may speculate that spiro-cyclohexenones of this type are cytotoxic in general. These results coincide with the biological evaluation of related marine compounds, e.g. the brominated tyrosine metabolites aeroplysinin-1 (**2**) and **3** (Fig. 1), described by Proksch and his colleagues.[8]

Table I. Antitumor activity measured toward HM02 cells

Compound	GI_{50}	TGI	LC_{50} ($\mu mol \cdot l^{-1}$)
15	0.05	0.04	0.05
16	<0.01	<0.01	0.03
19	<0.01	<0.01	<0.01
cis-platinum	0.1	3	10

GI_{50}: drug concentration causing 50% growth inhibition
TGI: drug concentration causing 100% growth inhibition
LC_{50}: drug concentration causing 50% reduction of the cells present at time point zero, i.e. at 24 h

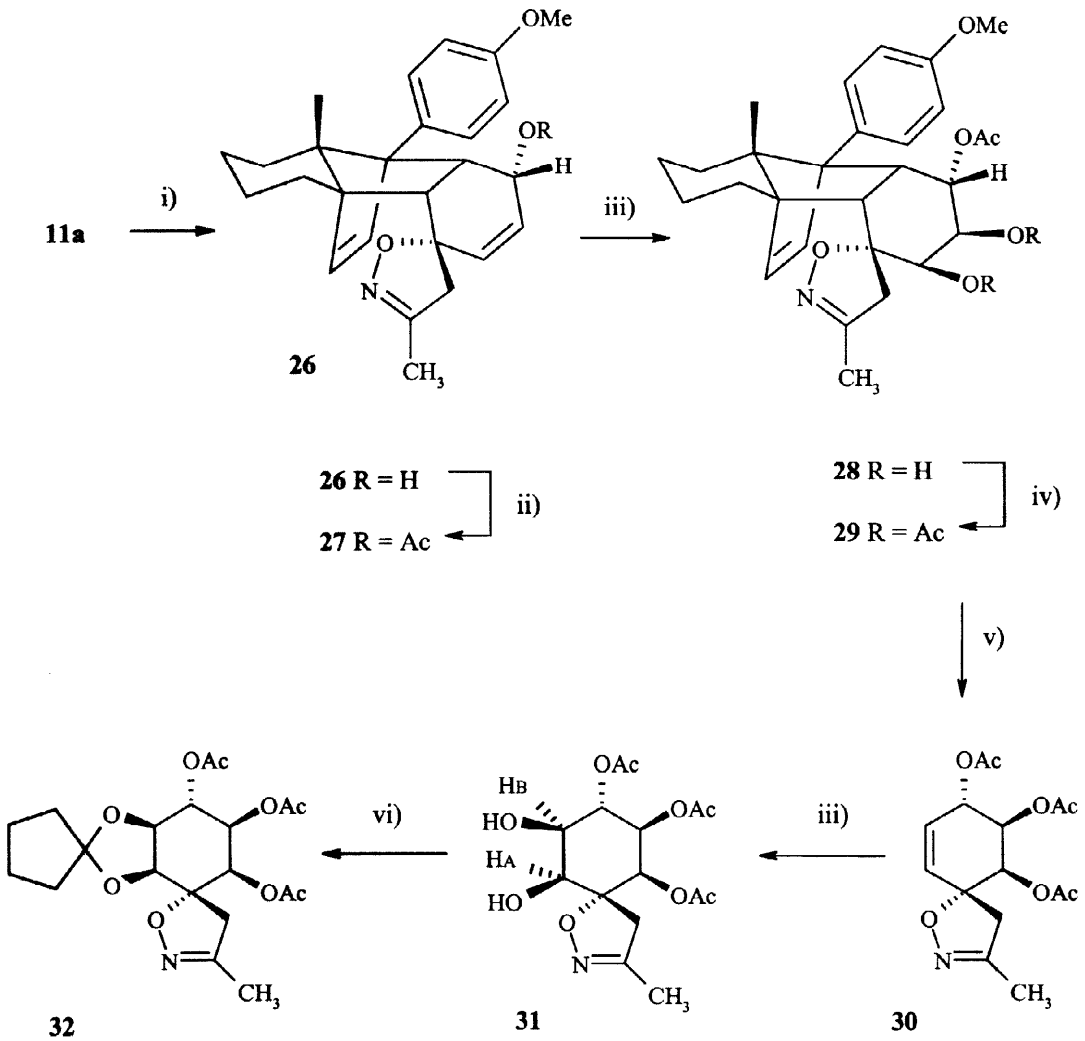
Table II. Antitumor activity measured toward KATO III cells

Compound	GI_{50}	TGI	LC_{50} ($\mu mol \cdot l^{-1}$)
15	0.026	0.036	0.05
16	<0.01	<0.01	<0.01
19	<0.01	<0.01	<0.01

Since in all these cases conjugated ketones had been formed in the retro-Diels-Alder process benefiting from conjugation energy. We wanted to compare these results to the corresponding

allylic acetates (e.g. **30**) and, as hydroxylation and epoxidation operate extremely well in this series this compound should also lend itself to the preparation of optically active carba-sugar derivatives such as **32**.

Borohydride reduction of **11a** proceeded as expected with excellent diastereoselectivity to generate the corresponding α-carbinol exclusively, which was converted into acetate **27** in quantitative yield (Scheme 6). Flash hydroxylation of this acetate turned out to be highly efficient (88 %) and for the crucial pyrolysis step this diol was transformed into triacetate **29** to avoid the problems encountered with diol **20a**.



Scheme 6. i) $NaBH_4$, $CeCl_3$, CH_2Cl_2/MeOH, 0 °C (78%); ii) Ac_2O, DMAP, CH_2Cl_2, 0 °C (98%); iii) $RuCl_3$, $NaIO_4$; EtOAc/CH_3CN/H_2O; 0 °C (**28** 88%; **31** 89%); iv) Ac_2O, pyridine, 0 °C (89%); v) 300 °C, $1\cdot10^{-2}$ mbar (81%); vi) 1,1-dimethoxycyclopentane, *p*TsOH, THF (95%).

Although in the subsequent retro-step conjugation energy is lacking one secured an 81 % yield of the spiroisoxazoline **30** which was shown to be optically pure (> 98 %) by shift measurements.

For further functionalisation flash hydroxylation was employed again and the exclusive formation of a *β*-diol (see **31**) was concluded from the coupling pattern of protons H_A (J = 3.5 Hz) and H_B (J = 3.5; 9.5 Hz) which was observed after deuterium exchange and proves the *cis*-*β*-configuration in diol **31**. For structural characterisation ketal **32** was formed in quantitative yield, which represents a stable and highly flexible carba-sugar derivative.

EXPERIMENTAL

General procedures: Melting points were determined on a Büchi melting point microscope and are uncorrected. UV spectra were measured on a Beckman 3600 instrument and IR spectra on a Perkin Elmer 581 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP 200 and Bruker AM 400. δ_H Values are given relative to TMS = 0; J values in Hz; δ_C values are given relative to $CDCl_3$ = 77.05; multiplicities of ^{13}C NMR were determined by DEPT (90°/135°). MS were determined with a Finnigan MAT 312 instrument and VG Autospec at 70 eV. Elemental analyses were recorded on a Heraeus CHN rapid analyzer. For flash chromatography silica gel (30-60 mesh; Baker) was used at 0.3 bar. The high pressure reactions were performed in a Nova Swiss apparatus. For retro-Diels-Alder reactions a special flash vacuum pyrolysis apparatus was used. All solvents were dried by standard methods. Cyclopentadiene **4** was prepared according to the procedure described by Winterfeldt et al.[9], oximes **9** were prepared as described[10], spiroisoxazolines **10** were prepared according to a procedure described by McKillop et al.[5]

Methods of the biological assay: The antitumor activity of the test compounds was determined in two human cancer cell lines, according to the NCI guidelines.[11] The cell lines used were HM02 (human gastric carcinoma)[12] and KATO III (human colon carcinoma). Cells were grown in 96-well microtitre plates (Greiner) of RPMI tissue culture medium supplemented with 10% fetal calf serum (Life Technologies) at 37 °C in a humidified atmosphere (10 nmol·l^{-1} - 1 μmol·l^{-1}) were added to the cells. Stock solutions of the test compounds were prepared in methanol. After 48 h incubation in the presence of the test drugs the cells were fixed by addition of trichloroacetic acid and cell protein was assayed with sulforhodamine B.[13] For each compound tested the GI_{50}, TGI and LC_{50} values was determined.

Experimental procedures: (2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydrospiro[1*H*-4b,9-etheno-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-one (**11a**): A solution of diene **4** (3.84 g, 16.0 mmol) and spiroisoxazoline **10a** (2.36 g, 14.5 mmol) in dichloromethane (5ml) was introduced into a teflon hose and submitted to 6.5 kbar in a high pressure autoclave for 21 days. Purification of the raw material by flash chromatography (diethyl ether/light petroleum, 2:1) yielded 5.14 g (88%) of **11a** as colorless crystals; M.p. 149 °C; $[\alpha]_D^{20}$ = -271.6° (c = 0.99, $CHCl_3$); UV/Vis (MeOH): λ_{max} = 221 nm; IR ($CHCl_3$): ν = 2924 (s), 1664 (vs), 1612 (m), 1516 (vs), 1248 (vs), 824 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.44 (1H, d_{br}, 13 Hz), 0.79 (3H, s), 1.19 (1H, m), 1.33-1.45 (2H, m), 1.55-1.67 (1H, m), 1.85 (1H, d_{tr}, 13/3.5 Hz), 2.02 (3H, s), 2.52 (1H, m), 2.77 (1H, d, 8 Hz), 2.98 (2H, s_{br}), 3.80 (3H, s), 3.81 (1H, d, 8 Hz), 5.80 (1H, d, 10 Hz), 5.84 (1H, d, 6 Hz), 6.16 (1H, d, 6 Hz), 6.55 (1H, d, 10 Hz), 6.87 (2H, d, 9 Hz), 7.30 (2H, d, 9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.22 (q), 15.31 (q), 21.18 (t), 23.87 (t), 27.06 (t), 28.58 (t), 50.21 (d), 51.16 (d), 55.14 (q), 56.72 (t), 61.13 (s), 62.23 (s), 71.07 (s), 83.87 (s), 113.02 (d), 129.07 (s), 129.08 (d), 130. 66 (d), 135.33 (d), 139.03 (d), 149.26 (d), 154.38 (s), 158.23 (s), 198.73 (s); HRMS: m/z calc.for $C_{26}H_{29}N_1O_3$: 403.2147; found: 403.2147; calc. C 77.39, H 7.24, N 3.47; found C 77.17, H 7.16, N 3.60.

Crystal structure analysis of compound 11a: *Crystal data*: $C_{26}H_{29}NO_3$, M_r = 403.50, orthorhombic, $P2_12_12$, a = 1360.7(2), b = 1555.9(2), c = 1004.4(2) pm, U = 2.1265 nm^3, Z = 4, D_x = 1.260 Mg m^{-3}, $F(000)$ = 864, λ(Mo $K\alpha$) = 71.073 pm, μ = 0.08 mm^{-1}, T = -130°C. *Data collection and reduction*: Colourless tablet 0.7 × 0.45 × 0.25 mm, Stoe STADI-4 diffractometer, 3022 independent intensities to $2\theta_{max}$ 55°. *Structure refinement*: anisotropic on F^2 (Program SHELXL-93, G.M. Sheldrick, University of Göttingen); H atoms with riding model or rigid methyl groups; $wR(F^2)$ 0.121 (all refl.), $R(F)$ 0.052 ($F > 4\sigma(F)$) for 274 parameters and 303 restraints; max. Δρ 174 e nm^{-3}, S = 1.11. The absolute configuration could not be directly determined by anomalous dispersion, but was clear from the known configuration of the precursor **4**.[14]

(2S,2′S,3R,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydrospiro[1*H*-2,3-epoxy-4b,9-etheno-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-one (**12**): To a solution of adduct **11a** (1.02 g, 2.53 mmol) in THF (10 ml) were added 35% H_2O_2 (1.3 ml) in water (5 ml) and aq. KOH (850 mg, 15 mmol) at 0 °C. After 2 h the reaction mixture was extracted with dichloromethane. The organic phase was washed twice with 5% aq. $FeSO_4$ and brine and dried ($MgSO_4$). Evaporation of the solvent yielded 1.02 g (96%) of **12** as a white foam; $[\alpha]_D^{20}$ = -36.3° (c = 1.02, $CHCl_3$); IR ($CHCl_3$): ν = 2928 (s), 1716 (vs), 1516 (vs), 1248 (vs), 1228 (vs), 1180 (s) cm^{-1};

^{1}H NMR (400 MHz; $CDCl_3$): δ = 0.55 (1H, d_{br}, 13 Hz), 0.75 (3H, s), 1.15-1.48 (4H, m), 1.60 (1H, d_{br}, 12 Hz), 1.80 (1H, d_{br}, 11 Hz), 1.98 (1H, dd, 13/4 Hz), 2.04 (3H, s), 2.98 (1H, d, 10 Hz), 3.18 (1H, d, 18 Hz), 3.31 (1H, d, 5.5 Hz), 3.33 (1H, d, 5.5 Hz), 3.39 (1H, d, 18 Hz), 3.78 (3H, s), 3.94 (1H, d, 10 Hz), 6.08 (1H, d, 6 Hz), 6.12 (1H, d, 6 Hz), 6.84 (2H, d, 9 Hz), 7.12 (2H, d, 9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.11 (q), 15.63 (q), 21.05 (t), 23.36 (t), 26.66 (t), 28.00 (t), 51.33 (t), 52.88 (d), 53.06 (d), 55.08 (q), 56.00 (d), 60.06 (s), 60.86 (s), 61.30 (d), 63.67 (s), 84.50 (s), 113.32 (d), 127.68 (d), 130.64 (s), 134.77 (d), 139.22 (d), 154.89 (s), 157.95 (s), 204.68 (s); HRMS: m/z for $C_{26}H_{29}N_1O_4$: calc.: 419.2097; found: 419.2082

(5S,9S,10R)-9,10-Epoxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**13**): Epoxide adduct **12** (250 mg, 597 μmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/$2\cdot10^{-2}$ mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **13** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 2:1) yielded 89 mg (83%) of **13** as a white solid; M.p. 116 °C; $[\alpha]_D^{20}$ = -379.0° (c = 0.88, $CHCl_3$); ee >98% (determined by ^{1}H NMR; (+)-Eu(hfc)$_3$/$CHCl_3$); IR ($CHCl_3$): ν = 2960 (w), 1692 (vs), 1436 (m), 1228 (w) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.10 (3H, s), 3.13 (1H, d, 18 Hz), 3.40 (1H, d, 18 Hz), 3.55 (1H, dd, 3.5/2 Hz), 3.73 (1H, dd, 3.5/3 Hz), 6.06 (1H, dd, 10/2 Hz), 6.47 (1H, dd, 10/2.5 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): 12.96 (q), 48.79 (t), 53.54 (d), 57.79 (d), 80.11 (s), 127.62 (d), 142.91 (d), 155.74 (s), 191.79 (s); HRMS: m/z for $C_9H_9N_1O_3$ calc.: 179.0582; found: 179.0576.

(5S,9S,10R)-9-Bromo-10-hydroxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**16**): To a solution of Ph_3P (48 mg, 183 μmol) in dry dichloromethane (2 ml) was added a solution of Br_2 in dry dichloromethane (180 μl -1M solution; 180 μmol) at 0 °C. After 5 min a solution of **13** (30 mg; 168 μmol) in dry dichloromethane (3ml) was added dropwise. After 5 h at room temp. the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with methyl-*tert.*-butyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (diethyl ether/light petroleum, 1:1) yielded 35 mg (79%) of **16** as a colorless oil; $[\alpha]_D^{20}$ = -161.6° (c = 0.38, $CHCl_3$). UV/Vis (MeOH): λ_{max} = 218 nm; IR ($CHCl_3$): ν = 3588 (w), 1696 (vs), 1328 (m), 1076 (m) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.05 (3H, s), 2.78 (1H, d, 17 Hz), 3.10 (1H, d, 3.5 Hz), 3.58 (1H, d, 17 Hz), 4.31 (1H, dd, 12/3.5 Hz), 4.47 (1H, d, 12 Hz), 6.17 (1H, d, 10 Hz), 6.99 (1H, d, 10 Hz); HRMS: m/z for $C_9H_{10}N_1O_3{}^{79}Br_1$ calc.: 258.9844; found: 258.9847.

(5S,9S,10R)-7-Bromo-9,10-epoxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**14**): To a solution of **13** (45 mg, 251 μmol) in chloroform (3 ml) was added a solution of Br_2 in dry dichloromethane (256 μl -1M solution; 256 μmol) at 0 °C. After 1h Et_3N (68 μl, 502 μmol) was added at 0 °C. The solution was stirred for 5 h at room temp. and than diluted with diethyl ether. The organic layer was washed with water, 1 N HCl solution, sat. aq. $NaHSO_5$ and brine. The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (diethyl ether/light petroleum, 1:2) yielded 31 mg (48%) of **14** as a white foam; $[\alpha]_D^{20}$ = -287.3° (c = 0.89, $CHCl_3$); IR ($CHCl_3$): ν = 2928 (m), 1704 (vs), 1608 (m), 1228 (m), 1132 (vs) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.10 (3H, s), 3.17 (1H, dd, 18/1 Hz), 3.42 (1H, dd, 18/1 Hz), 3.73 (1H, d, 3.5 Hz), 3.77 (1H, dd, 3.5/2.5 Hz), 6.93 (1H, d, 2.5 Hz); HRMS: m/z for $C_9H_8N_1O_3{}^{79}Br_1$ calc.: 256.9688; found: 256.9691.

(5S,9S,10R)-7,9-Dibromo-10-hydroxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**15**): To a solution of Ph_3P (37 mg, 128 μmol) in dry dichloromethane (2 ml) was added a solution of Br_2 in dry dichloromethane (128 μl -1M solution; 128 μmol) at 0 °C. After 5 min a solution of **14** (30 mg; 116 μmol) in dry dichloromethane (3ml) was added dropwise. After 5 h at room temp. the reaction was quenched with sat. aq. $NaHCO_3$-Lsg. and extracted with methyl-*tert.*-butyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (diethyl ether/light petroleum, 1:1) yielded 31 mg (79%) of **15** as a colorless oil; $[\alpha]_D^{20}$ = -7.5° (c = 0.47, MeOH); IR ($CHCl_3$): ν = 3400 (m_{br}), 1712 (vs), 1604 (s), 1328 (s), 1092 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$; Cosolvent CD_3OD): δ = 2.04 (3H, s), 2.82 (1H, dd, 17/1 Hz), 3.60 (1H, dd, 17/1 Hz), 4.22 (1H, d, 12 Hz), 4.52 (1H, d, 12 Hz), 7.42 (1H, s); HRMS: m/z for $C_9H_9N_1O_3{}^{79}Br_1$ calc.: 257.9766; found: 257.9767.

(2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[1*H*-4b,9-ethe-no-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-one (**17**): A solution of adduct **11a** (1.0 g, 2.48 mmol) in dry THF (15 ml) after addition of Pd/C (100 mg 10% Pd; 90 μmol) was hydrogenated for 5 h at room temp. The catalyst was filtered off, and the solution was concentrated. Crystallisation from light petroleum yielded 948 mg (94%) of **17** as colorless crystals; M.p. 164 °C; $[\alpha]_D^{20}$ = -40.3° (c = 1.11, $CHCl_3$); IR ($CHCl_3$): ν = 2928 (s), 1704 (s), 1612 (w), 1516 (vs), 1248 (vs), 1036 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.50 (1H, d_{br}, 12.5 Hz), 0.76 (3H, s), 1.30-1.48 (4H, m), 1.61 (1H, d_{br}, 12.5 Hz), 1.83-1.99 (4H, m), 2.00 (3H, s), 2.21 (1H, ddd_{br}, 19/6/2.5 Hz), 2.39 (1H, ddd, 19/12/6 Hz), 2.83 (1H, d_{br}, 18 Hz), 2.85 (1H, d, 10 Hz), 3.06 (1H, d_{br}, 18 Hz), 3.68 (1H, d, 10 Hz), 3.79 (3H, s), 6.05 (1H, d, 5.5 Hz), 6.15 (1H, d, 5.5 Hz), 6.85 (2H, d, 9 Hz), 7.19 (2H, d, 9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.51 (q), 16.11 (q), 21.12 (t), 23.54 (t), 26.86 (t), 28.28 (t), 33.52 (t), 35.36 (t), 51.68 (t), 54.15 (d), 54.70 (d), 55.10 (q), 59.84 (s), 61.21 (s), 66.53 (s), 84.64 (s), 113.10

(d), 127.99 (d), 131.12 (s), 134.86 (d), 139.51 (d), 154.97 (s), 157.78 (s), 210.65 (s); HRMS: m/z for $C_{26}H_{31}N_1O_3$ calc.: 405.2304; found: 405.2304.

(5R)-3-Methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**19**): Adduct **17** (650 mg, 1.61 mmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/2·10^{-2} mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **19** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 1:1) yielded 230 mg (87%) of **19** as a white foam; $[\alpha]_D^{20}$ = -6.4° (c = 0.25, $CHCl_3$); UV (MeOH): λ_{max} = 220 nm; IR ($CHCl_3$): ν = 3012 (vs), 2924 (s), 1716 (s), 1436 (s), 1264 (s) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 2.04 (3H, s), 2.11-2.19 (1H, m), 2.34-2.46 (2H, m), 2.68 - 2.78 (1H, m), 3.00 (2H, s), 6.02 (1H, d, 10 Hz), 6.82 (1H, d, 10 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.27 (q), 33.74 (t), 34.61 (t), 48.75 (t), 82.10 (s), 130.13 (d), 148.98 (d), 155.01 (s), 197.87 (s); HRMS: m/z for $C_9H_{11}N_1O_2$ calc.: 165.0790; found: 165.0791.

(2S,2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[1*H*-2-bromo-4b,9-etheno-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-one (**18**): To a solution of **17** (500 mg, 1.23 mmol) in dry THF abs. (10 ml) was added pyridiniumperbromide (434 mg, 1.36 mmol) in dry THF (5 ml) at 0 °C. After 2 h at room temp. the reaction mixture was quenched with sat. aq. $NaHSO_5$. The aqueous phase was extracted with methyl *tert.*-butyl ether. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Chromatographic purification (diethyl ether/light petroleum, 1:2) yielded 435 mg (73%) of **18** as a colorless oil; IR ($CHCl_3$): ν = 2936 (s), 1720 (s), 1612 (w), 1516 (vs), 1248 (vs), 1180 (m), cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 0.55 (1H, d_{br}, 13 Hz), 0.78 (3H, s), 1.09-1.49 (5H, m), 1.61 (1H, d_{br}, 12.5 Hz), 1.84 (1H, d, 12 Hz), 2.00 (3H, s), 2.37 (1H, dd, 13.5/12 Hz), 2.56 (1H, dd, 13.5/6.5 Hz), 2.84 (1H, d_{br}, 18 Hz), 2.90 (1H, d, 10 Hz), 3.07 (1H, d_{br}, 18 Hz), 3.79 (3H, s), 4.05 (1H, d, 10 Hz), 4.34 (1H, dd, 12/6 Hz), 6.09 (1H, d, 6 Hz), 6.11 (1H, d, 6 Hz), 6.86 (2H, d, 9 Hz), 7.19 (2H, d, 9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.40 (q), 16.06 (q), 21.05 (t), 23.47 (t), 26.88 (t), 28.35 (t), 45.26 (d), 45.53 (t), 51.17 (t), 53.24 (d), 54.87 (d), 55.17 (q), 59.87 (s), 61.69 (s), 66.16 (s), 84.78 (s), 113.30 (d), 127.96 (d), 130.40 (s), 135.26 (d), 139.28 (d), 155.17 (s), 158.03 (s), 203.44 (s); HRMS: m/z for $C_{26}H_{30}N_1O_3{}^{79}Br_2$ calc.: 483.1409; found: 483.1408.

(2S,2′S,3R,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[1*H*-2,3-dihydroxy-4b,9-etheno-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-one (**20a**): To a solution of **11a** (1.00 g, 2.48 mmol) in EtOAc (20 ml) and CH_3CN (20 ml) was added with vigorous stirring a solution $RuCl_3 \cdot xH_2O$ (320 mg) and $NaIO_4$ (640 mg) in deionised water at 0 °C. After 5min the reaction mixture was quenched with sat. aq. $NaHSO_5$. The aqueous phase is extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash

chromatography (methyl *tert.*-butyl ether) yielded 932 mg (86%) of **20a** as a white solid; $[\alpha]_D^{20}$ = -50.3° (c = 0.72, $CHCl_3$); IR (KBr): ν = 3428 (m_{br}), 2924 (s), 1708 (vs), 1612 (m), 1516 (vs), 1248 (vs), 1180 (s), 1108 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.50 (1H, d_{br}, 13 Hz), 0.79 (3H, s), 1.32-1.48 (3H, m), 1.60-1.70 (2H, m), 1.84-2.02 (2H,m), 2.03 (3H, s), 2.80 (1H, s_{br}), 2.86 (1H, d_{br}, 18 Hz), 2.92 (1H, d, 9 Hz), 3.55 (1H, d_{br}, 17.5 Hz), 3.58 (1H, s_{br}), 3.72 (1H, s_{br}), 3.81 (3H, s), 3.89 (1H, d, 9 Hz), 4.21 (1H, s_{br}), 5.93 (1H, d, 6 Hz), 6.48 (1H, d, 6 Hz), 6.88 (2H, d, 9 Hz), 7.30 (2H, d, 9 Hz); HRMS: m/z for $C_{26}H_{31}N_1O_5$ calc.: 437.2202; found: 437.2200.

Acetonide of **20a**: To a solution of **20a** (900 mg, 2.06 mmol) in dry DMF (20 ml) were added 2,2-dimethoxypropane (1 ml) and a catalytic amount of *p*TsOH at 0 °C. After 12 h at room temp. the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with methyl *tert.*-butyl ether. The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by flash chromatography (diethyl ether/light petroleum, 1:3) yielded 933 mg (95%) of **22** as a white foam; $[\alpha]_D^{20}$ = -1.3° (c = 0.54, $CHCl_3$); IR ($CHCl_3$): ν = 2932 (s), 1732 (m), 1648 (w), 1516 (vs), 1384 (s), 1252 (vs), 1180 (s), 1064 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.62 (1H, d_{br}, 13 Hz), 0.77 (3H, s), 1.19 (3H, s), 1.34 (3H, s), 1.35-1.52 (6H, m), 1.99 (3H, s), 2.02 (1H, d, 13 Hz), 2.91 (1H, d, 17 Hz), 3.07 (1H, d, 10.5 Hz), 3.17 (1H, d, 17.5 Hz), 3.79 (3H, s), 4.19 (1H, d, 8 Hz), 4.20 (1H, d, 10.5 Hz) 4.43 (1H, d, 8 Hz), 6.09 (1H, d, 6 Hz), 6.19 (1H, d, 6 Hz), 6.85 (2H, d, 9 Hz), 7.18 (2H, d, 9 Hz); HRMS: m/z for $C_{29}H_{35}N_1O_5$ calc.: 477.2515; found: 477.2516.

Acetonide of **21a**: Acetonide adduct **22** (200 mg, 419 μmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/2·10^{-2} mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **23** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 1:1) yielded 86 mg (87%) of **23** as a white solid; M.p. 146 °C; $[\alpha]_D^{20}$ = -9.8° (c = 0.65, $CHCl_3$); IR ($CHCl_3$): ν = 2992 (m), 1692 (vs), 1228 (s), 1088 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 1.34 (3H, s), 1.41 (3H, s), 2.08 (3H, s), 3.02 (1H, d, 18 Hz), 3.48 (1H, d, 18 Hz), 4.45 (1H, dd, 5/2 Hz), 4.51 (1H, d, 5 Hz), 6.20 (1H, d, 10 Hz), 6.70 (1H, dd, 10/2 Hz); HRMS: m/z for $C_{11}H_{12}N_1O_4$ calc.: 222.0766; found: 222.0763.

(5S,9S,10R)-9,10-Dihydroxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-8-one (**21a**): a) Adduct **20a** (55 mg, 126 μmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/2·10^{-2} mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **21a** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 1:1) yielded 8 mg (32%) of **21a** as a colorless oil.

b) To a solution of **23** (40 mg, 169 μmol) in THF (3 ml) was added 2 N aq. HCl (3 ml) at room temp. After 15 h the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Chromatographic purification (methyl *tert.*-butyl ether) yielded 8 mg (24%) of **21a** as a colorless oil; IR ($CHCl_3$): ν = 3576 (m), 3496 (m_{br}), 1700 (vs), 1436 (m), 1384 (m), 1228 (s), 1112 (s), cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 2.07 (3H, s), 2.94 1H, s_{br}), 2.96 (1H, d, 17.5 Hz), 3.54 (1H, d, 17.5 Hz), 3.74 (1H, s_{br}), 4.20 (1H, m), 4.67 (1H, d, 3 Hz), 6.22 (1H, d, 10 Hz), 6.62 (1H, dd, 10/2 Hz).

(2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydro spiro[1*H*-4b,9-etheno-4*H*-fluorene-4,2′-4′-carboxylic acid methyl ester-isoxazoline]-1-one (**11b**): A solution of diene **4** (2.26 g, 9.42 mmol) and spiroisoxazoline **10b** (1.77 g, 8.55 mmol) in dichloromethane (5 ml) was introduced into a teflon hose and submitted to 6.5 kbar in a high pressure autoclave for 21 days. Purification of the raw material by flash chromatography (diethyl ether/light petroleum, 1:2) yielded 2.98 g (78%) of **11b** as colorless crystals; M.p. 131 °C; $[\alpha]_D^{20}$ = -29.8° (c = 0.25, $CHCl_3$); IR ($CHCl_3$): ν = 2928 (m), 1728 (s), 1668 (s), 1516 (s), 1248 (vs), 1040 (w) cm^{-1}; ^1H-NMR (400 MHz; $CDCl_3$): δ = 0.47 (1H, d_{br}, 12.5 Hz), 0.79 (3H, s), 1.10-1.48 (4H, m), 1.53-1.68 (1H, m), 1.80-1.91 (1H, m), 1.85 (1H, m), 2.33-2.43 (1H, m), 2.86 (1H, d, 8.5 Hz), 3.25 (1H, d, 18 Hz), 3.31 (1H, d, 18 Hz), 3.80 (3H, s), 3.83 (1H, d, 8.5 Hz), 3.92 (3H, s), 5.87 (1H, d, 10.5 Hz), 5.90 (1H, d, 6 Hz), 6.18 (1H, d, 6 Hz), 6.52 (1H, d, 10.5 Hz), 6.88 (2H, d, 9 Hz), 7.29 (2H, d, 9 Hz); HRMS: m/z for $C_{27}H_{29}N_1O_5$ calc.: 447.2046; found: 447.2043.

(2S,2′S,3R,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[1*H*-2,3-dihydroxy-4b,9-etheno-4*H*-fluorene-4,2′-4′-carboxylic acid methyl ester-isoxazoline]-1-one (**20b**): To a solution of **11b** (300 mg, 0.67 mmol) in EtOAc (5 ml) and CH_3CN (5 ml) was added with vigorous stirring a solution $RuCl_3 xH_2O$ (100 mg) and $NaIO_4$ (200 mg) in deionised water (3 ml) at 0 °C. After 5min the reaction mixture was quenched with sat. aq. $NaHSO_5$. The aqueous phase is extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (diethyl ether/light petroleum, 1:1) yielded 287 mg (89%) of **20b** as a white solid; $[\alpha]_D^{20}$ = -92.2° (c = 0.51, $CHCl_3$); IR ($CHCl_3$): ν = 3588 (w), 3468 (w_{br}), 2932 (m), 1728 (s), 1708 (s), 1516 (s), 1444 (m), 1252 (vs), 1108 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.51 (1H, d_{br}, 12.5 Hz), 0.79 (3H, s), 1.20-1.50 (5H, m), 1.60-1.65 (1H, m), 1.80-1.90 (1H, m), 2.95 (1H, d, 9 Hz), 3.08 (1H, d, 19 Hz), 3.74 (1H, s), 3.81 (3H, s), 3.83 (1H, d, 19 Hz), 3.92 (3H, s), 3.88-3.95 (1H, s), 4.19 (1H, s), 5.99 (1H, d, 5.5 Hz), 6.44 (1H, d, 5.5 Hz), 6.89 (2H, d, 9 Hz), 7.29 (2H, d, 9 Hz).

Benzaldehydeacetale of **20b**: To a solution of **20b** (148 mg, 308 μmol) in dry CH_3CN (5 ml) were added α,α'-dimethoxytoluene (234 mg, 1.54 mmol) and a catalytic amount of *p*TsOH at 0 °C. After 12 h at refluxing temp. the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with methyl *tert.*-butyl ether. The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by flash chromatography (diethyl ether/light petroleum, 1:3) yielded 158 mg (90%) of **24** as a white foam; IR ($CHCl_3$): ν = 2932 (m), 1728 (s_{br}), 1516 (m), 1252 (s), 1128 (vs), 1092 (vs) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.62 (1H, d_{br}, 12.5 Hz), 0.76 (3H, s), 1.10-1.70 (5H, m), 1.95-2.05 (2H, m), 3.22 (1H, d, 10.5 Hz), 3.26 (1H, d, 18.5 Hz), 3.59 (1H, d, 18.5 Hz), 3.78 (3H, s), 3.88 (3H, s), 4.28 (1H, d, 10.5 Hz), 4.31 (1H, d, 8 Hz), 4.50 (1H, d, 8 Hz), 5.86 (1H, s), 6.06 (1H, d, 5.5 Hz), 6.24 (1H, d, 5.5 Hz), 6.84 (2H, d, 9 Hz), 7.14 (2H, d, 9 Hz), 7.40-7.50 (3H, m), 7.51-7.55 (2H, m); HRMS: m/z for $C_{27}H_{29}N_1O_6$ calc.: 463.1995; found: 463.2016.

Benzaldehydeacetale of **21b**: Adduct **24** (776 mg, 1.36 mmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/$2\cdot10^{-2}$ mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **25** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 1:1) yielded 307 mg (69%) of **25** as a white foam; IR ($CHCl_3$): ν = 2956 (w), 1728 (vs), 1696 (vs), 1596 (m), 1260 (vs), 1228 (m), 1096 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 3.26 (1H, d, 18.5 Hz), 3.87 (1H, d, 18.5 Hz), 3.92 (3H, s), 4.65 (1H, dd, 6/4 Hz), 4.68 (1H, d, 6Hz), 5.98 (1H, s), 6.30 (1H, d, 10 Hz), 6.75 (1H, dd, 10/2 Hz), 7.34-7.40 (5H, m); HRMS: m/z for $C_{17}H_{15}N_1O_6$ calc.: 329.0899; found: 329.0892.

(5S,9S,10R)-9,10-Dihydroxy-8-oxo-1-oxa-2-aza-spiro[4,5]deca-2,6-diene-3-carboxylic acid methyl ester (**21b**): To a solution of **25** (200 mg, 610 μmol) in aq. acetone (3 ml) was added a catalytic amount of 2 N aq. HCl at room temp. After 20 h the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Chromatographic purification (methyl *tert.*-butyl ether) yielded 106 mg (72%) of **21b** as a colorless oil; $[\alpha]_D^{20}$ = -117.5° (c = 0.48, $CHCl_3$); IR ($CHCl_3$): ν = 3576 (w), 1728 (s), 1704 (vs), 1596 (m), 1260 (s), 1228 (m), 1112 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 3.21 (1H, d, 18.5 Hz), 3.85 (1H, d, 18.5 Hz), 3.93 (3H, s), 4.25 (1H, s_{br}), 4.68 (1H, d, 2.5 Hz), 6.29 (1H, d, 10 Hz), 6.62 (1H, dd, 10/2 Hz); HRMS: m/z for $C_{10}H_9N_1O_5$ calc.: 223.0481; found: 223.0479.

(1S,2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydrospiro[4b,9-etheno-4*H*-fluorene-4,2′-4′-methyl-isoxazoline]-1-ol (**26**): To a solution of **11a** (1.85 g, 4.58 mmol) in dichloromethane (70 ml) was added $CeCl_3 \cdot 7H_2O$ (5.12 g, 13.73 mmol) at 0 °C. After 15 min $NaBH_4$ (519 mg, 13.73 mmol) in MeOH (20 ml) was added and the solution was stirred for additional 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with chloroform. The combined organic layers were washed with brine and dried ($MgSO_4$). Purification by flash chromatography yielded 1.45 g (78%) of **26** as a white solid; M.p. 162 °C; $[\alpha]_D^{20}$ = -50.3° (c = 0.72, $CHCl_3$); IR ($CHCl_3$): ν = 3524 (w_{br}), 2928 (s), 1512 (vs), 1252 (s), 1180 (s), 1036 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.46 (1H, d_{br}, 13 Hz), 0.83 (3H, s), 1.13-1.66 (5H, m), 1.89 (2H, m), 2.00 (3H, s), 2.05 (1H, m), 2.49 (1H, d, 10 Hz), 2.91 (1H, d, 17.5 Hz), 3.02 (1H, d, 17.5 Hz), 3.26 (1H, dd, 10/6 Hz), 3.79 (3H, s), 4.28 (1H, m), 5.89 (1H, d, 9.5 Hz), 5.97 (1H, d, 5.5 Hz), 6.23 (1H, d, 5.5 Hz), 6.31 (1H, dd, 9.5/5.5 Hz), 6.87 (2H, d, 9 Hz), 7.25 (2H, d, 9 Hz); HRMS: m/z for $C_{26}H_{31}N_1O_3$ calc.: 405.2304; found: 405.2307.

(1S,2′S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-4,4a,4b,5,6,7,8,8a,9,9a-decahydrospiro[acetic acid-(1*H*-4b,9-etheno-4*H*-fluoren-1-yl-4,2′-4′-methyl-isoxazoline)] ester (**27**): To a solution of **26** (2.00 g, 4.94 mmol) and DMAP (905 mg, 7.41 mmol) in dry dichloromethane (35 ml) was added Ac_2O (741 µl, 7.41 mmol) at 0 °C. After 1h the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with methyl tert.-butyl ether. The combined organic layers were washed three times with 2 N aq. HCl and brine, dried ($MgSO_4$) and concentrated to yield 2.16 g (98%) of **27** as a white foam; $[\alpha]_D^{20}$ = -112.5° (c = 0.32, $CHCl_3$); IR ($CHCl_3$): ν = 2920 (m), 1728 (s), 1512 (s), 1248 (vs), 1180 (s), 1036 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.21 (1H, d_{br}, 12.5 Hz), 0.84 (3H, s), 1.11 (3H, s), 1.12-1.40 (4H, m), 1.50-1.60 (1H, m), 1.77 (1H, dt, 12.5/3), 2.00 (3H, s), 2.54 (1H, m), 2.66 (1H, d, 8.5 Hz), 2.71 (1H, dd, 16.5/1 Hz), 2.98 (1H, d, 16.5 Hz), 3.78 (3H, s), 3.75-3.81 (1H, m), 3.78 (3H, s), 5.34 (1H, dd, 10.5/2 Hz), 5.52 (1H, ddd, 9.5/3.5/2 Hz), 5.70 (1H, dd, 10.5/3.5 Hz), 5.78 (1H, d, 5.5 Hz), 5.93 (1H, d, 5.5 Hz), 6.84 (2H, d, 9 Hz), 7.14 (2H, d, 9 Hz); ^{13}C-NMR (100 MHz; $CDCl_3$): δ = 13.47 (q), 15.21 (q), 19.77 (q), 21.08 (t), 23.71 (t), 27.40 (t), 27.79 (t), 40.64 (d), 50.78 (d), 54.99 (t), 55.24 (q), 61.43 (s), 61.92 (s), 65.83 (s), 67.94 (d), 86.05 (s), 113.13 (d), 127.79 (d), 132.23 (s), 132.72 (d), 134.54 (d), 139.46 (d), 154.89 (s), 157.59 (s), 170.94 (s); HRMS: m/z for $C_{28}H_{33}N_1O_4$ calc.: 447.2410; found: 447.2409.

(1S,2R,2′S,3S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[acetic acid-(1*H*-4b,9-etheno-2,3-dihydroxy-4*H*-fluoren-1-yl-4,2′-4′-methyl-isoxazoline)] ester (**28**): To a solution of **27** (2.00 g, 4.47 mmol) in EtOAc (20 ml) and CH_3CN (20 ml) was added with vigorous stirring a solution $RuCl_3 \cdot xH_2O$ (577 mg, 252 µmol) and $NaIO_4$ (1.15 g, 5.37 mmol) in deionised water (10 ml) at 0 °C. After 5min the reaction mixture was quenched with sat. aq.

$NaHSO_5$. The aqueous phase is extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (methyl *tert.*-butyl ether) yielded 1.89 g (88%) of **28** as a white foam; $[\alpha]_D^{20}$ = -1.5° (c = 0.72, $CHCl_3$); IR ($CHCl_3$): ν = 3588 (w), 2932 (m), 1728 (m), 1612 (w), 1512 (s), 1252 (vs), 1076 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.39 (1H, d_{br}, 12.5 Hz), 0.76 (3H, s), 1.19 (3H, s), 1.30-2.02 (7H, m), 1.97 (3H, s), 2.68 (1H, d, 9.5 Hz), 2.73 (1H, d, 18 Hz), 3.45 (1H, d, 18 Hz), 3.66 (1H, 3.5 Hz), 3.79 (3H, s), 3.83 (1H, d, 10 Hz), 3.88 (1H, dd, 9.5/3.5 Hz), 5.38 (1H, dd, 10/9.5 Hz), 6.18 (1H, d, 5.5 Hz), 6.27 (1H, d, 5.5 Hz), 6.84 (2H, d, 9 Hz), 7.13 (2H, d, 9 Hz).

(1S,2R,2′S,3S,4aS,4bS,8aS,9R,9aR)-9-(4-Methoxyphenyl)-8a-methyl-dodecahydrospiro[acetic acid-(1*H*-4b,9-etheno-2,3-diacetoxy-4*H*-fluoren-1-yl-4,2′-4′-methyl-isoxazoline)] ester (**29**): To a solution of **28** (1.00 g, 2.08 mmol) in dry pyridine (10 ml) was added Ac_2O (520 µl, 5.02 mmol) at 0 °C. After 1h the reaction mixture was diluted with diethyl ether and washed three times with 2 N aq. HCl and brine. The organic phase was dried ($MgSO_4$) and concentrated to provide 1.05 g (89%) of **29** as a white foam; IR (KBr): ν = 2924 (m), 1748 (vs), 1612 (w), 1516 (m), 1240 (vs), 1040 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 0.38 (1H, d_{br}, 12.5 Hz), 0.78 (3H, s), 1.13 (3H, s), 1.15-1.71 (6H, m), 1.90 (3H, s), 1.90-2.02 (1H, m), 1.97 (3H, s), 2.17 (3H, s), 2.70 (1H, d, 9.5 Hz), 2.77 (1H, d, 17.5 Hz), 2.96 (1H, d, 17.5 Hz), 3.79 (3H, s), 3.85 (1H, dd, 10/10 Hz), 5.10 (1H, d, 3 Hz), 5.18 (1H, dd, 10/3 Hz), 5.56 (1H, dd, 10.5/10 Hz), 6.27 (1H, d, 5.5 Hz), 6.41 (1H, d, 5.5 Hz), 6.84 (2H, d, 9 Hz), 7.14 (2H, d, 9 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.13 (q), 15.78 (q), 19.78 (q), 20.74 (q), 20.99 (q), 21.15 (t), 23.63 (t), 26.72 (t), 28.34 (t), 43.81 (d), 50.01 (t), 52.82 (d), 55.26 (q), 61.46 (s), 61.69 (s), 66.47 (s), 68.39 (d), 71.54 (d), 86.70 (s), 113.28 (d), 127.90 (d), 131.51 (s), 134.10 (d), 141.22 (d), 154.55 (s), 157.81 (s), 169.74 (s), 170.06 (s), 170.61 (s); HRMS: m/z for $C_{32}H_{39}N_1O_8$ calc.: 565.2676; found: 565.2672.

(8R,9S,10S)-Acetic acid-9,10-diacetoxy-3-methyl-1-oxa-2-aza-spiro[4,5]deca-2,6-dien-8-yl ester (**30**): *tris*-Acetate adduct **29** (788 mg, 1.38 mmol) was brought into a flash vacuum pyrolysis apparatus and sublimed at 180 - 220 °C/$2 \cdot 10^{-2}$ mbar through a pyrolysis tube heated to 300 °C. After 2 h the whole starting material was sublimed off and a 1:1 mixture of **30** and diene **4** was trapped on a cooling finger. Chromatographic purification (diethyl ether/light petroleum, 1:1) yielded 364 mg (81%) of **30** as a white foam; $[\alpha]_D^{20}$ = +122.0° (c = 1.04, $CHCl_3$); ee >98% (determined by ^1H NMR; (+)-Eu(hfc)$_3$/$CHCl_3$).- IR ($CHCl_3$): ν = 3040 (w), 1744 (s), 1372 (m), 1228 (vs), 1048 (m) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 1.99 (3H, s), 2.04 (3H, s), 2.10 (3H, s), 2.11 (3H, s), 2.80 (1H, dd, 17.5/1 Hz), 2.97 (1H, d, 17.5 Hz), 5.38-5.44 (2H, m), 5.45-5.50 (1H, m), 5.80 (1H, d_{br}, 10 Hz), 5.85 (1H, dd, 10/2.5 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ = 13.03 (q), 20.70 (q), 20.75 (q),

20.87 (q), 45.64 (t), 68.31 (d), 70.12 (d), 70.42 (d), 83.61 (s), 127.75 (d), 130.21 (d), 155.21 (s), 169.38 (s), 169.94 (s), 170.32 (s); HRMS: m/z for $C_{12}H_{17}N_1O_4$ calc.: 325.1162; found: 325.1167.

(6R,7S,8R,9S,10S)-Acetic acid-9,10-diacetoxy-6,7-dihydroxy-3-methyl-1-oxa-2-aza-spiro [4, 5]deca-2-en-8-yl ester (31): To a solution of **30** (200 mg, 0.67 mmol) in EtOAc (5 ml) and CH_3CN (5 ml) was added with vigorous stirring a solution of $RuCl_3 \cdot xH_2O$ (100 mg) and $NaIO_4$ (200 mg) in deionised water (2 ml) at 0 °C. After 5min the reaction mixture was quenched with sat. aq. $NaHSO_5$. The aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (diethyl ether/light petroleum, 1:1) yielded 287 mg (89%) of **31** as a white foam; $[\alpha]_D^{20} = +33.3°$ (c = 0.84, $CHCl_3$); IR ($CHCl_3$): ν = 3468 (m_{br}), 2960 (w), 1744 (vs), 1372 (s), 1248 (vs), 1228 (vs), 1180 (s) cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ = 1.99 (3H, s), 2.00 (3H, s), 2.12 (3H, s), 2.16 (3H, s), 2.88 (1H, d, 18 Hz), 3.04 (1H, m), 3.10 (1H, m), 3.28 (1H, d, 18 Hz), 3.89 (1H, s_{br}), 4.00-4.05 (1H, m), 5.27 (1H, dd, 10/3.5 Hz), 5.38 (1H, d, 3.5 Hz), 5.40 (1H, dd, 10/9.5 Hz); H/D-Exchange (200 MHz; $CDCl_3/D_2O$): 3.87 (1H, d, 3.5 Hz); 4.01 (1H, dd, 9/3.5 Hz.

Cyclopentylacetale of **31**: To a solution of **31** (50mg, 139 μmol) in dry THF (3 ml) were added a catalytic amount of *p*TsOH and 1,1-dimethoxycyclopentane (91 mg, 696 μmol). After 1 h at refluxing temp. the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). Purification by flash chromatography (diethyl ether/light petroleum, 1:1) yielded 56 mg (95%) of **32** as a white foam; $[\alpha]_D^{20} = +9.2°$ (c = 1.48, $CHCl_3$); IR ($CHCl_3$): ν = 2960 (m), 1744 (vs), 1252 (s), 1228 (vs), 1120 (m) cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ = 1.50-2.20 (8H, m), 1.97 (3H, s), 2.01 (3H, s), 2.09 (3H, s), 2.17 (3H, s), 2.92 (1H, d, 18 Hz), 3.22 (1H, d, 18 Hz), 4.03 (1H, d, 5 Hz), 4.28 (1H, dd, 8/5 Hz), 5.22 (1H, dd, 11/3 Hz), 5.38 (1H, m), 5.49 (1H, dd, 11/8 Hz); HRMS: m/z for $C_{20}H_{27}N_1O_9$ calc.: 425.1686; found: 425.1689.

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14 Full details have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, from where this material can be obtained on quoting a full literature citation and the deposition number CSD 407937.