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Stereochemistry and rearrangement reactions of hydroxylignanolactones†‡

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Various conflicting data on the rearrangement and absolute stereochemistry of hydroxylignano-9,7′-lactones are resolved using ^{18}O labeled compounds, also confirmed by an X-ray analysis of a pure lignano-9,7′-lactone enantiomer, obtained for the first time. Under NaH/DMF rearrangement conditions a silyl protected hydroxylignano-9,9′-lactone underwent an unexpected silyl migration.

Introduction

Lignans, as natural products widely distributed in the plant kingdom, are the topic of many investigations due to their numerous interesting biological properties, such as anticancer and immunosuppressive activity.[1] Besides clinical studies, much effort has been invested into finding strategies for the synthesis of the various subclasses.[2] We have recently reported the stereoselective synthesis of several (7′*S*,8*R*,8′*R*)-7′-hydroxylignano-9,9′-lactones (7′-HLLs **1a**,**b**,**d**,**e**, Fig. 1), among which the plant lignan (−)-parabenzlactone (**1a**) and the mammalian lignan 7′*S*-hydroxyenterolactone (**1d**) were obtained as enantiopure products for the first time.[3]

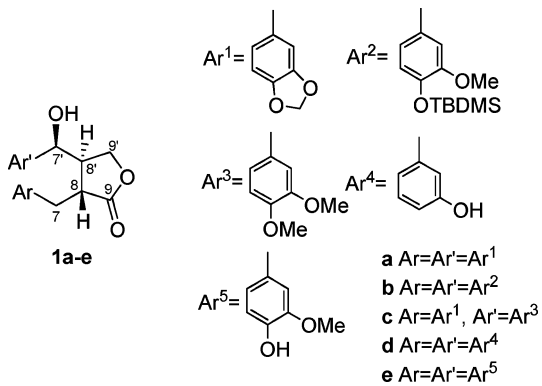
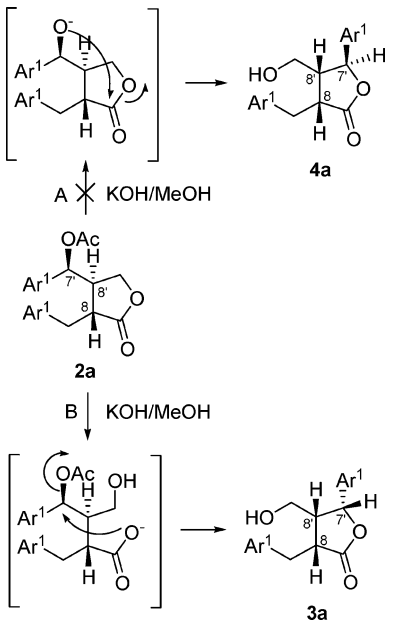


Fig. 1 7′*S*-Hydroxylignano-9,9′-lactones and their aromatic substitution pattern.

The total synthesis of 7′-HLLs allowed us to correct the stereochemistry of **1a**, and of its naturally occurring derivative acetylparabenzlactone (**2a**, Scheme 1) as 7′*S*,[3] as opposed to the previously reported[4] configuration. This adjustment also involved a re-examination of the lignano-9,7′-lactone obtained by Nishibe



Scheme 1 Proposed mechanism of formation of the rearranged lactone **3a** (route B).[3] For Ar[1] see Fig 1.

et al.[4] by basic hydrolysis (2% KOH–MeOH) of **2a** and originally described with a 7′/8′-*cis*-8/8′-*cis* configuration (**3a**). In fact, according to the corrected stereochemistry of the starting material **2a**, the rearranged product obtained by a simple translactonization should be the 7′/8′-*trans*-8/8′-*cis* isomer **4a** (Scheme 1, route A). However the reported NMR data (in particular the 7′-H signal, doublet at δ 5.13 ppm, $J_{H\text{-}7'/H\text{-}8'} = 8$ Hz) are not well-matched with such configuration which, as observed by Eklund *et al.*[5] and by us,[3] should have the 7′ proton as a doublet at δ 5.45 ppm, $J_{H\text{-}7'/H\text{-}8'} = 2.6$ Hz. On the other hand, since the NMR data were anyway consistent with a 7′/8′-*cis*-8/8′-*cis* configuration (7′-H doublet at δ 5.12 ppm, $J_{H\text{-}7'/H\text{-}8'} = 9.3$ Hz),[5] we suggested an S_N2 mechanism for the formation of the rearranged lactone **3a**, where, with OAc as the leaving group, an inversion of the configuration at 7′ has taken place during the relactonization (Scheme 1, route B).[3]

In continuation of our previous work we now present the results of mechanistic studies we undertook in order to clarify these questions. The studies were accomplished using ^{18}O labeled compounds and monitoring the results by mass spectroscopy (MS). A variety of rearrangement conditions were investigated using different

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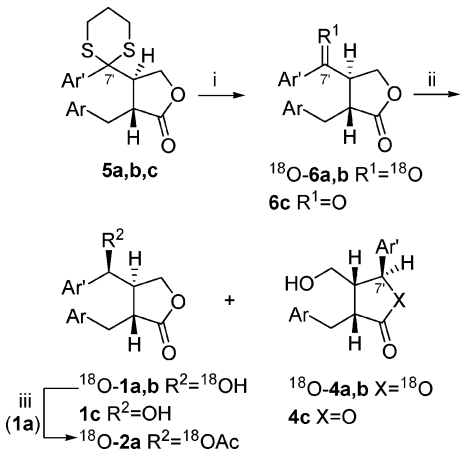
unlabeled substrates, such as 8-methylparabenzlactone, a lignan derivative lacking α carbonyl protons, and diversely aromatic-substituted lignanolactones.

Results and discussion

Translactonization of ^{18}O labeled substrates

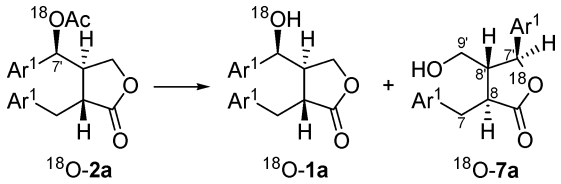
To distinguish between the translactonization and the S_N2 rearrangement mechanism, we prepared (Scheme 2) the labeled silyl protected 7′*S*-hydroxymatairesinol ^{18}O-**1b** and the parabenzlactone derivative ^{18}O-**2a**, and looked by MS for the conservation *vs.* loss of the label under the translactonization (L-Selectride®) or the S_N2 rearrangement (KOH–MeOH) conditions. In the translactonization route, the ^{18}O should be retained in the product, but should be missing in the rearranged lactone derived by the S_N2 mechanism.



Scheme 2 Reagents and conditions: (i) $(CF_3CO_2)_2IPh$, CH_3CN–$^{18}OH_2$ (for **5a**,**b**) or CH_3CN–H_2O (for **5c**), rt; (ii) L-Selectride®, THF, −78 °C; (iii) Ac_2O-Py, rt. For Ar and Ar′ see Fig. 1.

The ^{18}O label was introduced during the deprotection of the dithiane moiety of **5** using $^{18}OH_2$ as the co-solvent. Since no rearranged product had been previously observed in the treatment of oxoparabenzlactone **6a** with L-Selectride®,[3] we decided to perform the reduction also on ^{18}O-**6b** to follow the destiny of the label in a simple translactonization. The treatment of ^{18}O-**6a** or ^{18}O-**6b** with L-Selectride® (Scheme 2, step ii) furnished, as expected, the 7′*S*-HLL alcohols ^{18}O-**1a** or ^{18}O-**1b**, along with the rearranged 9,7′-lactones ^{18}O-**4a** or ^{18}O-**4b**, in a *ca.* 85 : 15 ratio according to NMR and MS.§ In particular the mass spectra showed that for a simple translactonization the ^{18}O label is totally conserved. The acetylated derivative ^{18}O-**2a** was submitted to hydrolytic conditions[4] (Scheme 3) to reinstate ^{18}O-**1a** and the presumed rearranged lactone in a 2 : 1 ratio, as indicated by Nishibe.[4] However the MS analysis of the latter showed that the molecule still contained the ^{18}O label. This result was in conflict with a possible S_N2 mechanism, which therefore was ruled out. On the other hand a simple translactonization would have furnished the product ^{18}O-**4a**, easily distinguished from the hydrolysis

§ The minor product **4a** was not observed in our previous experiment.[3] The studies about the L-Selectride® side reaction will be the subject of another paper of the series where full characterization of **4a** will be reported.



Scheme 3 Reagents and conditions: (1) 2% KOH–MeOH, rt; (2) 2 N HCl. For Ar[1] see Fig 1.

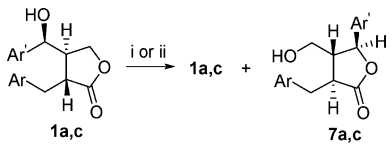
product ^{18}O-**1a**. Since spectroscopic analyses showed the presence of a trisubstituted butyrolactone ring, two piperonyl groups and a primary alcohol, it was evident that the lignan skeleton was conserved and the new compound must be a stereoisomer of **3a** and **4a**. A NOESY experiment of the product showed no correlation between the protons 7′ and 8′ (good evidence for a 7′/8′-*trans* configuration), nor between H-8 and H-8′. Instead, a NOESY correlation was detected between H-7′/8, 7′/9, 8/9′ and 7/8′. On the basis of these results it was deduced that this compound is the previously reported (in unlabeled form)[4,6] 7′/8′-*trans*-8/8′-*trans* (7′*S*,8*S*,8′*R*) isomer ^{18}O-**7a** (Scheme 3), which arises from a translactonization accompanied by an α-epimerization.

Translactonization studies with NaH–DMF or 2% KOH–MeOH

The present findings also clarify the discrepancy between our previous results[3] and those of Iwasaki[7] and Eklund.[5] Iwasaki had reported the concomitant translactonization/α-epimerization whilst treating (±)-**1c** (Fig. 1) with NaH–DMF to obtain the all-*trans* (±)-**7c** (confirmed by X-ray analysis). In our earlier paper we assumed, supported by Eklund's results,[5] that the 7′-H doublet at δ 5.1 ppm was sign of a *cis* 7′/8′configuration, and could not explain how the all-*trans* **7c** could give such a similar signal (doublet at δ 5.16 ppm, $J_{H\text{-}7'/H\text{-}8'} = 9.2$ Hz).[3] It is now understandable that, although a different mechanism of formation is involved, the same configuration 7′/8′-*trans*-8/8′-*trans* is obtained with both NaH–DMF and KOH–MeOH, as the similarity between the NMR of **7c** and **7a** clearly shows. Also it is evident that the coincidental NMR resemblance between the all-*cis* and the all-*trans* lactones is misleading and leads to proposal of the wrong mechanism (S_N2).

To compare directly the two reactions (Table 1), **1a**[3] was submitted to both Nishibe's (2% KOH–MeOH)[4] and Iwasaki's (NaH–DMF)[7] rearrangement conditions. In our hands the reaction with NaH–DMF furnished a mixture of the starting material **1a** and

Table 1



	1 : 7 ratio[a]		Yield (%)[b]			
	1a : 7a	1c : 7c	1a	7a	1c	7c
(i) 2%KOH–MeOH	64 : 36	57 : 43	61	31	58	31
(ii) NaH–DMF	40 : 60	36 : 64	23	33	26	38[c]

[a] From the ^1H NMR of the crude material. [b] Yields after flash chromatography. [c] Reported yield of (±)-**7c** was 75%.[7]

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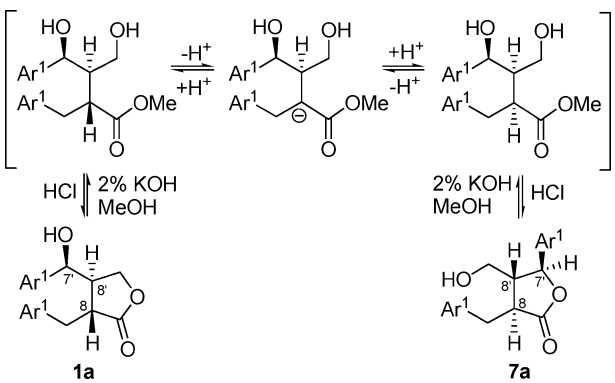
the rearranged lactone **7a** in a 40 : 60 ratio, with a 33% yield of the latter, very different from Iwasaki's results[7] (75% yield with no recovery nor detection of starting material reported). To exclude any effects due to the unlike aromatic substituents, Nishibe's and Iwasaki's rearrangement conditions were repeated on the enantiopure compound[3] **1c** (Scheme 2). With NaH–DMF **1c** gave results (**1** : **7** ratio and yields) comparable to those obtained for **1a** (Table 1). Thus the nature of phenolic protection does not play a role in these reactions. With KOH–MeOH **1a** or **1c** each furnished a mixture of starting material and rearranged lactone in a *ca.* 60 : 40 ratio, in agreement with the results of the hydrolysis of ^{18}O-**2a** (Scheme 3) and also as previously achieved by Nishibe[4] with **2a** as the substrate.

The difference in the **1** : **7** ratios under conditions (i) and (ii) (Table 1), and a change of the predominant product in these reactions, may be explained by the reactions mechanisms. When NaH–DMF is employed the lactone moiety of **1** undergoes a nucleophilic attack by the formed alkoxide ion and the α-epimerization occurs more or less simultaneously to give the thermodynamically more stable product **7**. In the case of KOH–MeOH (Scheme 4) the lactone moiety of **1** undergoes transesterification by the action of MeO^- present in the reaction medium, forming the methyl ester diol intermediate, which can be deprotonated at the α position. After acidification, relactonization can occur with either hydroxy group present in the intermediate, but the preference is determined by the selectivity of α-proton reinsertion into the molecule, prior to relactonization. A reprotonation from the less hindered upper face leads back to the starting material **1**, whereas protonation from the lower face will lead to the rearranged **7**. From the **1** : **7** ratio values it is clear that the structure **1** is preferred. Evidence for this equilibrium was obtained by treating **7a** with 2% KOH–MeOH. Translactonization/α-epimerization is observed and the ratio **1a** : **7a** = 66 : 34 was obtained after 48 h (compared to the 1.5 h required when **1a** was the starting material). Probably the 9,7′-lactone **7a** is more hindered then **1a**, making transesterification less favorable. Furthermore, when **1a** and **7a** were treated with 2% KOH–*t*-BuOH no rearrangement was observed.



Scheme 4 Mechanism of translactonization/α-epimerization in 2% KOH–MeOH. For Ar[1] see Fig. 1.

The absolute configuration of **7a** was confirmed by X-ray analysis of the 3,5-dinitrobenzoate derivative **8a** (Fig. 2).

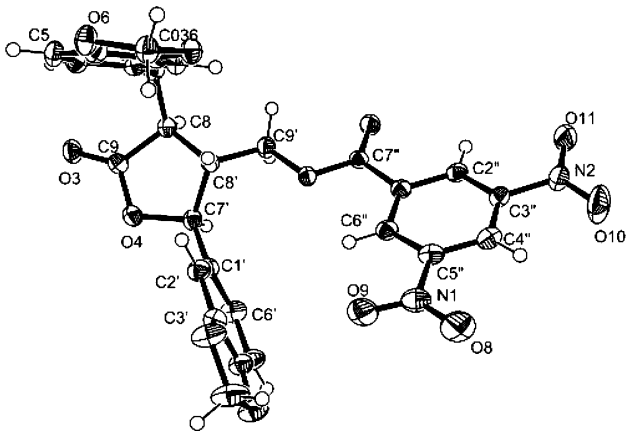
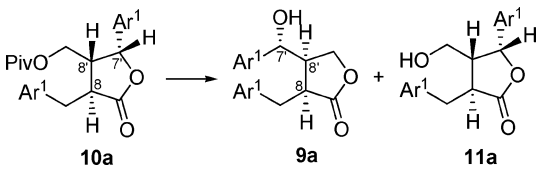


Fig. 2 Crystal structure of **8a** (50% probability ellipsoids).

Translactonization studies with aq. NaOH–EtOH

Yamauchi and Kinoshita[8] exploited the translactonization reaction for the synthesis of the unnatural (7′*R*/8*S*/8′*R*)-8/8′-*cis*-parabenzlactone **9a**. In this case the starting material was the 7′/8′-*cis*-8/8′-*trans* pivaloyl protected lignano-9,7′-lactone **10a**, which was treated with 1M aq NaOH–EtOH (50 : 50) to give a mixture of deprotected 7′-HLL **9a** and the lignano-9,7′-lactone **11a** in a 1 : 2 ratio (Scheme 5). This mixture is also obtained using the alcohol **11a** directly as starting material. Working in an aqueous medium, the α-epimerization cannot take place on the carboxylate intermediate. For this reason the sterically more favored 8/8′-*trans*-7′-HLL was not formed.



Scheme 5 Translactonization reaction for the synthesis of 8/8′-*cis*-parabenzlactone **9a**.[8] Reagents and conditions: (1) 1M aq NaOH, EtOH, rt; (2) 6M HCl. For Ar[1] see Fig. 1.

In trying to obtain **12a**, the 7′ epimer of **9a**, the above conditions were tested on **7a** (Scheme 6), but surprisingly no translactonization was observed and only **7a** was recovered. Since the only difference in the starting materials **11a** and **7a** is the stereochemistry at the 7′ site, this must play a crucial role in the formation of an 8/8′-*cis*-7′-HLL under these conditions. To confirm that steric hindrance is the key feature in this type of reactions, **1a** was also treated with 1M aq NaOH–EtOH (Scheme 6). As expected this reagent did not furnish the rearranged lactone **4a**, owing to the unfavourable 8/8′-*cis* configuration, which was nevertheless obtained under different conditions (L-Selectride®, Scheme 2). Thus it is evident that α-epimerization is necessary in the translactonization of **1** and **7**, due to their configuration. In support of these considerations, **1a** and **7a** when treated with 2% aq KOH–MeOH (50:50) only gave the starting materials in both cases.

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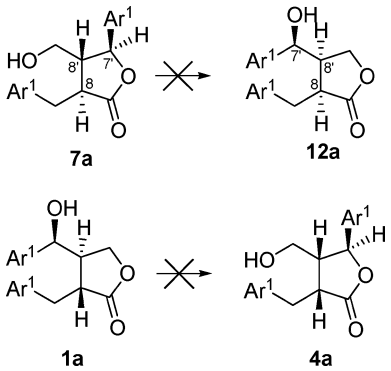
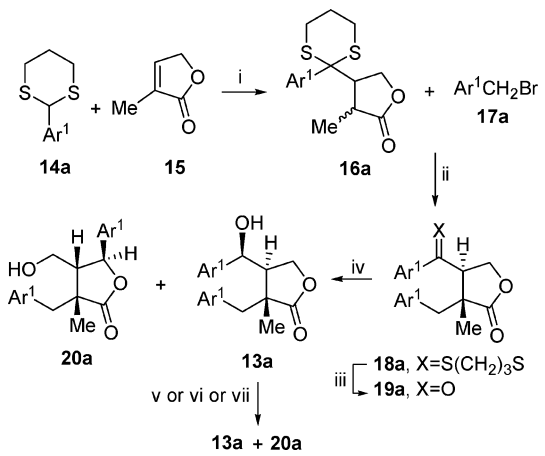


Scheme 6 Reagents and conditions: (1) 1M aq NaOH, EtOH, rt; (2) 2 N HCl. For Ar^1 see Fig. 1.

Translactonization studies of (±)-8-methylparabenzlactone 13a

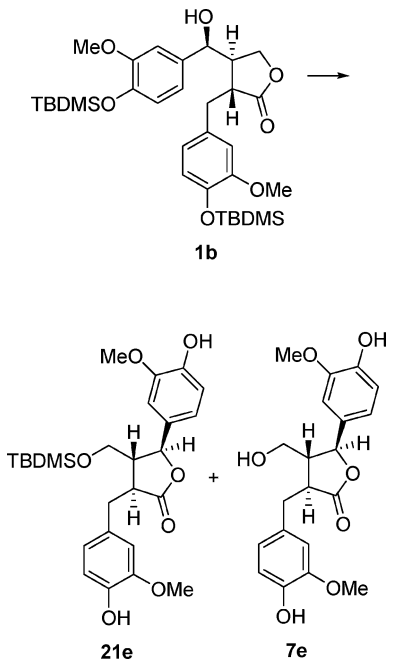
Because of the importance of α-epimerization under basic conditions, these reactions were further tested on (±)-8-methylparabenzlactone **13a**, a compound where no α protons are available. Compound **13a** was synthesized as shown in Scheme 7. A Michael addition[3] between the dithiane **14a**[9] and the methylbutenolide **15** gave a mixture of the α/β-*trans* and α/β-*cis* isomers **16a** in a 2 : 1 ratio. The diastereoselective alkylation[3] with piperonyl bromide **17a**[10] afforded only the α/β (8/8′)-*trans* compound **18a**, due to the bulky substituent present at the chiral β carbon (1,2 asymmetric induction).[11] The relative configuration was confirmed by the lack of correlation between the methyl and the H-8′ in a NOESY experiment. Ketone **19a**, obtained after removal of the dithiane functionality, was reduced diastereoselectively (*de* 99%) with L-Selectride®, furnishing (±)-8-methylparabenzlactone **13a** and the translactonized product **20a** (ratio 84 : 16). Lactone **13a** was subjected to the various conditions discussed above (2% KOH–MeOH, NaH–DMF and 1M aq. NaOH–EtOH), furnishing in all cases the rearranged product **20a** and the starting material **13a** in a *ca.* 35 : 65 ratio. Thus the presence of the methyl group at C-8 clearly affects the behaviour of the rearrangement reaction. In the case of 1M aq. NaOH–EtOH, the presence of the water in the reaction medium does not prevent (as seen for **1a**) the reaction from occurring, providing the same results as with 2% KOH–MeOH, which is in turn comparable with those obtained for **1a** and **1c** (Table 1). On the other hand NaH–DMF furnished less rearranged lactone **20a** when compared with the results obtained with **1a** and **1c** (Table 1), likely due to steric hindrance exerted by the 8-methyl in the nucleophilic attack.



Scheme 7 Reagents and conditions: (i) *n*-BuLi, THF, DMPU, −78 °C→rt; (ii) LHMDS, THF, DMI, −78 °C→rt; (iii) $(CF_3COO)_2IPh$, CH_3CN–H_2O, rt; (iv) L-Selectride®, THF, −78 °C; (v) 1) 2% KOH–MeOH, rt; 2) 2 M HCl; (vi) (1) NaH–DMF, 0°C; (2) 2 N HCl; (vii) (1) 1M aq. NaOH, EtOH, rt; (2) 2 M HCl. For Ar^1 see Fig. 1.

Translactonization studies of Ar-*O*-silylated 7′*S*-hydroxymatairesinol 1b

In connection with another study, we have observed that phenolic silyl ethers can be cleaved selectively in the presence of aliphatic silyl ethers by means of NaH in DMF.[12] Thus the aryl-*O*-silyl protected 7′*S*-hydroxymatairesinol **1b**[3] was subjected to the NaH–DMF translactonization conditions (Scheme 8). As anticipated the reaction proved to be a powerful desilylating tool, and some of the rearranged/α-epimerized product **7e** with free phenolic groups was obtained. However the major product of this reaction was the unexpected TBDMS-derivative **21e**, formed by a migration of the silyl group to the aliphatic hydroxyl. Traces of totally and partially silyl protected **1b** were also detected by NMR, but were not isolated. In this case the combined amount of rearranged lactones **7e** and **21e** (81%) is higher than under the same reaction conditions with **1a** and **1c** as starting materials. We believe that this is due to the formation of the silyl derivative **21e**, whose aliphatic protection group is not cleaved by NaH–DMF, making the retro-translactonization impossible. Detailed studies about the capability of NaH to cleave silyl protecting groups will be reported in due course.



Scheme 8 Reagents and conditions: (1) NaH–DMF, 0 °C; (2) 2 M HCl.

The ^{1}H NMR spectrum of **21e** shows signals very similar to those of the unprotected **7e**, which in turn resembles the spectra of **7a–d**, particularly regarding the diagnostic peak of H-7′ (d at δ 5.1 ppm, $J_{H\text{-}7'/H\text{-}8'}$ = 9 Hz). Thus the aromatic variation and

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Table 2

Starting material	Reagents	Product(s)	Outcome
1a (or **2a**)	2% KOH–MeOH	**1a** + **7a**	Translactonization and α-epimerization
1a	NaH–DMF	**1a** + **7a**	Translactonization and α-epimerization
1a	1M aq NaOH–EtOH	**1a**	No reaction
1a	2% KOH–*t*-BuOH	**1a**	No reaction
1a	2% aq KOH–MeOH	**1a**	No reaction
1b	NaH–DMF	**21e** +**7e**	Translactonization, α-epimerization, silyl cleavage and silyl migration
1c	2% KOH–MeOH	**1c** + **7c**	Translactonization and α-epimerization
1c	NaH–DMF	**1c** + **7c**	Translactonization and α-epimerization
7a	2% KOH–MeOH	**1a** + **7a**	Translactonization and α-epimerization
7a	1M aq NaOH–EtOH	**7a**	No reaction
7a	2% KOH–*t*-BuOH	**7a**	No reaction
7a	2% aq KOH–MeOH	**7a**	No reaction
13a	2% KOH–MeOH	**13a** + **20a**	Translactonization
13a	NaH–DMF	**13a** + **20a**	Translactonization
13a	1M aq NaOH–EtOH	**13a** + **20a**	Translactonization

derivatizations of the aliphatic hydroxy group of **7** (TBDMS, benzoate, MOM[7]) do not produce significant changes in the NMR chemical shift of the characteristic H-7′ signal. Similarities in the ^{1}H NMR spectra can also be observed for **4a–e**. This can be useful in determining the stereochemistry of the trisubstituted lignano-9,7′-lactones, as previously applied to the 7′-HLLs.[3,13] However, this may not be valid for the all-*cis* stereoisomers. In fact the only two reported all-*cis*-lignano-9,7′-lactones **3e**[5] and (±)-**22a**[6] (Fig. 3) present a remarkable difference for the H-7′ signals in both chemical shifts and coupling constants (δ 5.12 ppm, $J_{\text{H-7′/H-8′}}$ = 9.3 Hz for **3e**[5] *vs.* δ 5.43 ppm, $J_{\text{H-7′/H-8′}}$ = 5.4 Hz for (±)-**22a**[6]). The sizeable variation of these values could be caused by the bulky TBDMS group, which may significantly affect the conformation of **22a** and consequently modify the NMR signals, in contrast to those previously observed for **21e** and **7e**.

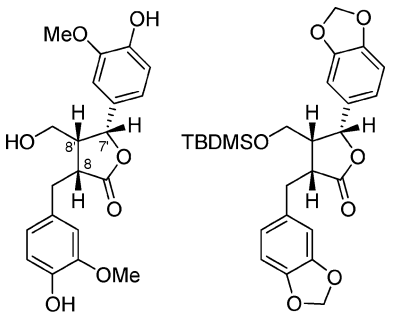

Fig. 3 Reported 7′/8′-*cis*-8/8′-*cis*-lignano-9,7′-lactones.[5,6]

As for the compounds possessing an 8-methyl **13a** and **20a**, while the H-7′ signal of **13a** is similar to that in the 7′*S*-HLL series (**1a–e**), the chemical shift of the H-7′ signal of **20a** (δ 4.8 ppm) is significantly different both from the **7a–d**,**21e** series (δ 5.1 ppm) and from the **4a–e** series (δ 5.4 ppm). Thus the methyl crucially affects both the reactivity (in **13a**) and the NMR signals (in **20a**).

Conclusion

In this study the rearrangement reactions of various hydroxylignano-9,9′- and -9,7′-lactones have been investigated and resolved as summarized in Table 2. The reaction mechanisms were studied using ^{18}O labeled substrates and the absolute stereochemistry of the rearranged lactone obtained by Nishibe[4] was determined as **7a**, thanks also to the X-ray analysis of its dinitrobenzoate derivative **8a**, obtained for the first time for this type of lignans. Compound **7a** derives from a translactonization accompanied by an α-epimerization and not, as we earlier proposed,[3] by an S_N2 mechanism. Different basic conditions were evaluated showing that the stereochemistry of the lactone determines whether a rearrangement or α-epimerization is observed or not. Rearrangement studies were also performed on the unnatural 8-methyl substituted lignanolactone **13a**. In this case the stereochemistry did not play a particular role in the formation of the rearranged lactone, which was obtained under all conditions. Finally the aromatic silyl protected lignan **1b** was treated with NaH–DMF causing rearrangement, α-epimerization and deprotection of the aryl silyl ethers, together with an unexpected migration of the silyl to the aliphatic hydroxy group. The resemblance observed in the ^{1}H NMR for this class of compounds can be a useful expedient for the assignment of the stereochemistries.

Experimental

Experiments were monitored by TLC using aluminium based, precoated silica gel sheets (Merck 60 F254, layer thickness 0.2 mm) and visualized under UV light and further with a mixture of vanillin and sulfuric acid in EtOH. Compounds were homogeneous on TLC. Silica gel 60 (230–400 mesh, Merck) was used for flash column chromatography. Optical rotation values were measured with a JASCO DIP-1000 digital polarimeter at rt. NMR spectra were recorded on a 500 MHz Varian Inova spectrometer or on a 300 MHz Varian Mercury. Chemical shifts are given in δ in ppm and J values in Hz, using TMS as an internal standard. Mass spectra were obtained using a JEOL JMS-SX102 mass spectrometer operating at 70 eV and for the ^{18}O compounds were measured with Bruker MicroTof$_{LC}$ (ESI) using Agilent ESI Tunemix as a calibration solution. Melting points were determined in open capillary tubes with a Büchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR instrument equipped with ATR reflection

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top plate. THF, CH_3CN and Py were dried by distillation from Na, P_2O_5 and CaH_2 respectively. Compounds **1a**, **1b**, **5a–c**,[3] **14a**[9] and **17a**[10] were prepared according to reported procedures. Other commercially available chemicals were used as supplied by the manufacturers. The absolute configuration of **8a** was determined using Cu-K_α radiation, ($\lambda = 1.5418$ Å), on an Oxford Diffraction Gemini-S-Ultra diffractometer. 17995 reflections were measured at 150 K, and merged to give 3252 unique reflections, $R_{merge} = 0.0431$, in space group $P2_1$. The structure was refined to an *R*-factor of 0.0299 (for all data) and Flack parameter of −0.19(14).‡

(8*R*,8′*R*)-[7′-^{18}O]-4,4′-Bis(*tert*-butyldimethylsilyloxy)-3,3′-dimethoxy-7′-oxolignano-9,9′-lactone (^{18}O-6b)

$(CF_3COO)_2IPh$ (100 mg, 0.23 mmol) was added to a solution of **5b**[3] (55 mg, 0.08 mmol) in 10 : 1 CH_3CN-$^{18}OH_2$ (1.1 ml) at rt. The mixture was stirred for 30 min and then quenched with saturated $NaHCO_3$ (10 ml) and extracted with Et_2O (3 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH_2Cl_2) to obtain ^{18}O-**6b** (20 mg, 41%) as a viscous oil. IR and NMR were in agreement with data reported for the unlabeled **6b**.[3] HRMS (ESI-TOF) *m*/*z* calcd for $C_{32}H_{49}O_6{}^{18}OSi_2$ $[M + H]^+$ 603.3059, found 603.3054.

(8*R*,8′*R*)-[7′-^{18}O]-3,3′,4,4′-Bis(methylenedioxy)-7′-oxolignano-9,9′-lactone (^{18}O-6a)

Following the same procedure as for ^{18}O-**6b**, compound ^{18}O-**6a** was prepared from **5a**[3] in 86% yield after flash chromatography (eluent CH_2Cl_2-Et_2O 20:1). IR and NMR were in agreement with data reported for the unlabeled **6a**.[3] HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{16}NaO_6{}^{18}O$ $[M + Na]^+$ 393.0831, found 393.0836.

(7′*S*,8*R*,8′*R*)-[7′-^{18}O]-4,4′-Bis(*tert*-butyldimethylsilyloxy)-7′-hydroxy-3,3′-dimethoxylignano-9,9′-lactone (^{18}O-1b) and (7′*S*,8*R*,8′*R*)-[7′-^{18}O]-4,4′-bis(*tert*-butyldimethylsilyloxy)-8′-hydroxymethyl-3,3′-dimethoxylignano-9,7′-lactone (^{18}O-4b)

L-Selectride® (1M in THF, 0.026 ml, 0.026 mmol) was added dropwise to a solution of ^{18}O-**6b** (12 mg, 0.020 mmol) in dry THF (1 ml) under Ar at −78°C and the mixture was stirred at the same temperature for 2 h. The reaction was then stopped with saturated NH_4Cl (10 ml) and extracted with EtOAc (3 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2-Et_2O 20:1) to yield 8.5 mg (70%) of ^{18}O-**1b** and 2 mg (16%) of ^{18}O-**4b**. IR and NMR were in agreement with data reported for the unlabeled **1b** and **4b**.[3] For ^{18}O-**1b**: HRMS (ESI-TOF) *m*/*z* calcd for $C_{32}H_{50}NaO_6{}^{18}OSi_2$ $[M + Na]^+$ 627.3035, found 627.3030. For ^{18}O-**4b**: HRMS (ESI-TOF) *m*/*z* calcd for $C_{32}H_{50}NaO_6{}^{18}OSi_2$ $[M + Na]^+$ 627.3035, found 627.3030.

(7′*S*,8*R*,8′*R*)-[7′-^{18}O]-7′-Hydroxy-3,3′,4,4′-bis(methylenedioxy)-lignano-9,9′-lactone (^{18}O-1a) and (7′*S*,8*R*,8′*R*)-[7′-^{18}O]-8′-hydroxymethyl-3,3′,4,4′-bis(methylenedioxy)lignano-9,7′-lactone (^{18}O-4a)§

Following the same procedure as for ^{18}O-**1b** and ^{18}O-**4b**, compounds ^{18}O-**1a** and ^{18}O-**4a**§ were prepared from ^{18}O-**6a** in 72% and 15% yield respectively after flash chromatography (eluent CH_2Cl_2–Et_2O 8 : 1). IR and NMR of ^{18}O-**1a** were in agreement with data reported for the unlabeled **1a**.[3] For ^{18}O-**1a**: HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{18}NaO_6{}^{18}O$ $[M + Na]^+$ 395.0992, found 395.0998. For ^{18}O-**4a**: HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{18}NaO_6{}^{18}O$ $[M + Na]^+$ 395.0992, found 395.0996.

(7′*S*,8*R*,8′*R*)-[7′-^{18}O]-7′-Acetoxy-3,3′,4,4′-bis(methylenedioxy)lignano-9,9′-lactone (^{18}O-2a)

A solution of ^{18}O-**1a** (88 mg, 0.15 mmol) in 5 ml of Ac_2O-Py (4 : 1) was stirred overnight at rt. The residue was extracted with $CHCl_3$ (10 ml), washed with water (3 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1) to yield 85 mg (86%) of ^{18}O-**2a**: $[\alpha]_D{}^{22}$ −26.9° (*c* 0.3, dioxane), (for **2a** lit.[4] −19.6°, *c* 0.82, dioxane); IR (thin film) ν_{max} 1769, 1743, 1227, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 6.74–6.69 (m, 2H), 6.64–6.55 (m, 4H), 5.97 (part A of an AB system, $J = 1.5$ Hz, 1H), 5.95 (part B of an AB system, $J = 1.5$ Hz, 1H), 5.94 (part A of an AB system, $J = 1.5$ Hz, 1H), 5.93 (part B of an AB system, $J = 1.5$ Hz, 1H), 5.71 (d, $J = 6.9$ Hz, 1H), 3.99 (dd, $J = 8.1$, 9.6 Hz, 1H), 3.92 (dd, $J = 6.0$, 9.6 Hz, 1H), 2.96 (dd, $J = 6.9$, 13.8 Hz, 1H), 2.87 (dd, $J = 4.8$, 13.8 Hz, 1H), 2.83–2.68 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 178.0, 169.8, 148.1, 147.8 (2×), 146.5, 131.0, 130.7, 122.6, 120.1, 109.7, 108.3, 108.2, 106.5, 101.4, 101.0, 76.3, 68.0, 43.9, 43.4, 35.1, 21.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{20}NaO_7{}^{18}O$ $[M + Na]^+$ 437.1098, found 437.1093.

General procedure with 2% KOH–MeOH[4] (procedure A): (7′*S*,8*S*,8′*R*)-[7′-^{18}O]-3,3′,4,4′-bis(methylenedioxy)-8′-hydroxymethyl-3,3′-dimethoxylignano-9,7′-lactone (^{18}O-7a)

A solution of ^{18}O-**2a** (78 mg, 0.19 mmol) in 2% KOH–MeOH (5 ml) was stirred for 2 h at rt. The solution was acidified (pH 3) with 2 N HCl and extracted with CH_2Cl_2 (3 × 20 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 3 : 1) to yield 33 mg (47%) of ^{18}O-**1a** and 20 mg (29%) of ^{18}O-**7a**. For ^{18}O-**7a**: $[\alpha]_D{}^{27}$ + 66.97 (*c* 0.37, THF); IR (thin film) ν_{max} 3339, 1765, 1249, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.75 (d, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 7.5$ Hz, 1H), 6.72 (d, $J = 1.5$ Hz, 1H), 6.69 (dd, $J = 1.5$, 7.5 Hz, 1H), 6.66 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.60 (d, $J = 1.5$ Hz, 1H), 5.96 (s, 2H), 5.94 (s, 2H), 5.13 (d, $J = 8.5$ Hz, 1H), 3.55 (dd, $J = 3.5$, 11.0 Hz, 1H), 3.48 (dd, $J = 4.0$, 11.0 Hz, 1H), 3.15 (dd, $J = 5.0$, 14.0 Hz, 1H), 3.06 (ddd, $J = 5.0$, 7.0, 12.0 Hz, 1H), 2.95 (dd, $J = 7.0$, 14.0 Hz, 1H), 2.28–2.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 177.5, 148.3, 148.2, 148.1, 146.8, 132.4, 131.7, 122.5, 120.5, 109.8, 108.7, 108.4, 106.7, 101.5, 101.3, 81.2, 59.8, 50.9, 43.8, 35.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{18}NaO_6{}^{18}O$ $[M + Na]^+$ 395.0992, found 395.0998.

(7′*S*,8*S*,8′*R*)-3,3′,4,4′-Bis(methylenedioxy)-8′-hydroxymethyl-3,3′-dimethoxylignano-9,7′-lactone (7a)

Compound **1a**[3] was treated as described in the procedure A to obtain after flash chromatography (eluent CH_2Cl_2–Et_2O 3 : 1) a mixture of starting material **1a** (61%) and rearranged lactone **7a** (31%). For **7a**: $[\alpha]_D{}^{22}$ + 90.14° (*c* 0.4, $CHCl_3$); IR and NMR were in

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agreement with the data of ^{18}O-**7a**; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{18}NaO_7$ $[M + Na]^+$ 393.0950, found 393.0956.

General procedure with NaH–DMF[7] (procedure B)

A solution of **1a**[3] (50 mg, 0.13 mmol) in DMF (2 ml) was added to a mixture of NaH (8 mg, 55–65% oil dispersion, previously rinsed with *n*-hexane) in DMF (2 ml) at 0°C under Ar. The reaction mixture was stirred at the same temperature for 1.5 h and then acidified (pH 3–4) with 2 N HCl. The mixture was extracted with EtOAc (3 × 10 ml) and the organic phase was washed with water (2 × 10 ml), dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 3 : 1) to yield 11.5 mg (23%) of compound **1a** and 16.5 mg (33%) of compound **7a**.

General procedure with 1M aq NaOH–EtOH[8] (procedure C)

A solution of **7a** (50 mg, 0.13 mmol) in 1M aq NaOH (1 ml) and EtOH (1 ml) was stirred overnight at rt and then acidified (pH 3–4) with 2 N HCl. The mixture was extracted with EtOAc (3 × 10 ml). The organic phase was washed with water (2 × 10 ml), dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 3 : 1) to yield only the starting material **7a** (80%).

(8*R*,8′*R*)-3′,4′-Dimethoxy-3,4-methylenedioxy-7′-(propane-1,3-diyldithio)-lignano-9,9′-lactone (5c)

LHMDS (1.6M in THF, 0.58 ml, 0.92 mmol) was added dropwise to a solution of (3*R*)-[(propane-1,3-diyldithio)-(3,4-dimethoxyphenyl)methyl]butano-4-lactone[3] (286 mg, 0.84 mmol) in THF (3 ml) at −78 °C under Ar. The reaction mixture was stirred for 2 h, then DMI (0.10 ml, 0.92 mmol) was added dropwise followed, after 30 min, by a solution of piperonyl bromide **17a**[10] (200 mg, 0.93 mmol) in THF (1 ml). The mixture was stirred at the same temperature for 1 h and then allowed to reach rt in 2 h, then quenched with saturated NH_4Cl (10 ml) and extracted with Et_2O (3 × 15 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 10 : 1) to obtain **5c** as a white solid (310 mg, 78%): mp 89–91°C (Et_2O–*n*-hexane); $[\alpha]_D^{25}$ + 72.17 ° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.48 (dd, J = 2.0, 8.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.41 (dd, J = 2.0, 8.0 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 5.95 (part A of an AB system, J = 1.5 Hz, 1H), 5.91 (part B of an AB system, J = 1.5 Hz, 1H), 4.68 (dd, J = 5.0, 10.0 Hz, 1H), 3.99 (dd, J = 9.0, 10.0 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.09–3.05 (m, 1H), 2.82 (dd, J = 7.0, 14.0 Hz, 1H), 2.77–2.57 (m, 5H), 2.49 (dd, J = 5.0, 14.0 Hz, 1H), 1.96–1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 178.3, 149.3, 148.5, 147.7, 146.5, 131.4, 130.4, 122.6, 122.3, 112.0, 110.7, 109.5, 107.9, 101.0, 67.8, 62.5, 55.8 (2×), 50.3, 42.8, 36.1, 27.2, 27.0, 24.7; EIMS *m/z* (relative intensity): 474 (M^+, 80%), 399 (50), 368 (49), 255 (100), 175 (80), 135 (90); HRMS (EI) *m/z* calcd for $C_{24}H_{26}O_6S_2$ (M^+), 474.1171; found, 474.1177.

(8*R*,8′*R*)-3′,4′-Dimethoxy-3,4-methylenedioxy-7′-oxolignano-9,9′-lactone (6c)

Following the same procedure as for ^{18}O-**6b**, using H_2O instead of $^{18}OH_2$, compound **6c** was prepared in 65% yield as a white solid after flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1): mp 153–154°C ($CHCl_3$–Et_2O) (lit.[7] 140–141°C (AcOEt–acetone)); $[\alpha]_D^{25}$ + 41.08 ° (*c* 0.1, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 195.0, 177.0, 154.2, 149.4, 147.8, 146.5, 130.7, 128.9, 122.9, 122.5, 110.3, 110.0, 109.8, 108.3, 101.0, 68.3, 56.2, 56.0, 46.5, 44.8, 34.5; IR, MS and ^{1}H NMR were in agreement with reported data;[7] HRMS (EI) *m/z* calcd for $C_{21}H_{20}O_7$ (M^+), 384.1209; found, 384.1204.

(7′*S*,8*R*,8′*R*)-7′-Hydroxy-3′,4′-dimethoxy-3,4-methylenedioxylignano-9,9′-lactone (1c) and (7′*S*,8*R*,8′*R*)-8′-hydroxymethyl-3′,4′-dimethoxy-3,4-methylenedioxylignano-9,7′-lactone (4c)

Following the same procedure as for ^{18}O-**1b** and ^{18}O-**4b**, compounds **1c** (*de* 97%) and **4c** were prepared in 61% and 7% yield, respectively, after flash chromatography (eluent CH_2Cl_2–Et_2O 10 : 1). For **1c** mp 122–124°C (Et_2O); $[\alpha]_D^{22}$ −20.09° (*c* 0.34, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 178.8, 149.3, 149.1, 147.7, 146.4, 133.9, 131.3, 122.7, 118.1, 111.1, 109.9, 108.8, 108.0, 101.0, 75.4, 68.4, 55.9, 55.8, 45.2, 43.6, 35.2; IR, MS and ^{1}H NMR were in agreement with reported data;[7] HRMS (EI) *m/z* calcd for $C_{21}H_{22}O_7$ (M^+), 386.1365; found, 386.1362. For **4c**: $[\alpha]_D^{24}$ + 44.47 ° (*c* 0.54, THF); IR (thin film) ν_{max} 3517, 1769 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.85 (d, J = 8.0 Hz, 1H), 6.82 (dd, J = 2.0, 8.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H), 6.65 (dd, J = 1.5, 8.0 Hz, 1H), 5.91 (s, 2H), 5.53 (d, J = 2.0 Hz, 1H), 3.96 (dd, J = 4.5, 11.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.78 (dd, J = 7.5, 11.0 Hz, 1H), 3.20 (dd, J = 5.0, 15.0 Hz, 1H), 3.04 (ddd, J = 5.0, 8.5, 11.0 Hz, 1H), 2.74 (dd, J = 11.0, 15.0 Hz, 1H), 2.62–2.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 177.8, 149.3, 148.9, 147.9, 146.3, 132.3, 131.5, 121.2, 116.9, 111.3, 108.6, 108.4, 108.2, 101.0, 80.9, 60.8, 56.0, 55.9, 47.4, 41.1, 30.7; EIMS *m/z* (relative intensity): 386 (M^+, 50%), 368 (40), 194 (20), 167 (100), 135 (70); HRMS (EI) *m/z* calcd for $C_{21}H_{22}O_7$ (M^+), 386.1365; found, 386.1378.

(7′*S*,8*S*,8′*R*)-8′-Hydroxymethyl-3′,4′-dimethoxy-3,4-methylenedioxylignano-9,7′-lactone (7c)

Compound **1c** was treated according to the general procedures A and B and a mixture of **1c** and **7c** was obtained (for ratios and yields see Table 1). For **7c**: $[\alpha]_D^{27}$ + 47.45 (*c* 1.08, THF); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 177.5, 149.5, 149.4, 147.9, 146.4, 131.5, 130.7, 122.4, 119.2, 110.9, 109.7, 108.9, 108.4, 101.0, 81.0, 59.6, 55.9, 55.8, 50.3, 43.6, 34.6; IR, MS and ^{1}H NMR were in agreement with reported data;[7] HRMS (EI) *m/z* calcd for $C_{21}H_{22}O_7$ (M^+), 386.1365; found, 386.1362.

(7′*S*,8*S*,8′*R*)-3,3′,4,4′-Bis(methylenedioxy)-3,3′-dimethoxy-8′-(3,5-dinitrobenzoyloxy)methyllignano-9,7′-lactone (8a)

3,5-Dinitrobenzoyl chloride (100 mg, 0,46 mmol) was added to a solution of **7a** (40 mg, 0.11 mmol) in Py (4 ml) and the mixture was stirred overnight at rt. The reaction was stopped with water

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(10 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The organic phase was washed with water (2 × 10 ml), dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 4 : 1) to obtain **8a** as a yellow solid (40 mg, 65%): mp 182–183°C (CH_2Cl_2); $[\alpha]_D^{25}$ + 66.81 ° (*c* 0.31, THF); IR (thin film) ν_{max} 1771, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 9.20 (app. t, J = 2.0 Hz, 1H), 8.80 (d, J = 2.0 Hz, 2H), 6.75 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 6.71 (dd, J = 1.5, 7.5 Hz, 1H), 6.68 (dd, J = 1.5, 7.5 Hz, 1H), 6.63 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 5.93 (s, 2H), 5.92 (m, 2H), 5.04 (d, J = 9.0 Hz, 1H), 4.23 (d, J = 6.0 Hz, 2H), 3.22 (dd, J = 4.0, 14.0 Hz, 1H), 3.00 (dd, J = 7.5, 14.0 Hz, 1H), 2.91–2.87 (m, 1H), 2.82–2.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 175.8, 162.2, 148.8 (2×), 148.7, 148.5, 148.4, 147.1, 132.9, 131.2, 130.9, 129.4 (2×), 122.8, 122.5, 121.1, 109.6, 108.9, 108.4, 106.9, 101.8, 101.4, 82.9, 65.6, 47.7, 45.4, 35.3; EIMS m/z (relative intensity): 564 (M^+, 40%), 534 (20), 372 (100), 342 (40), 192 (70), 135 (90); HRMS (EI) m/z calcd for $C_{27}H_{20}O_{12}N_2$ (M^+), 564.1016; found, 564.1011.

(2*R**,3*R**)-2-Methyl-3-[(propane-1,3-diyldithio)-(3,4-methylendioxyphenyl)methyl]-butano-4-lactone (*trans*-16a) and (2*S**,3*R**)-2-methyl-3-[(propane-1,3-diyldithio)-(3,4-methylendioxyphenyl)methyl]-butano-4-lactone (*cis*-16a)

n-BuLi (1.3M in *n*-hexane, 1.80 ml, 2.29 mmol) was added dropwise to a solution of thioacetal **14a**[9] (500 mg, 2.08 mmol) in THF (10 ml) at −78 °C under Ar. The mixture was stirred for 1 h, then DMPU (0.28 ml, 2.29 mmol) was added dropwise followed, after 30 min, by slow addition of **15** (225 mg, 2.29 mmol) in THF (2 ml). The reaction mixture was stirred for 2 h at the same temperature, then quenched with saturated NH_4Cl and extracted with Et_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1) to obtain 547 mg (78%) of a 2 : 1 mixture of *trans*-**16a** and *cis*-**16a** (not separated): mp 88–90°C (Et_2O); IR (thin film) ν_{max} 1766 cm^{-1}; EIMS m/z (relative intensity): 338 (M^+, 60%), 239 (100), 165 (100); HRMS (EI) m/z calcd for $C_{16}H_{18}O_4S_2$ (M^+), 338.0646; found, 338.0653. For *trans*-**16a** (major product): ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.49–7.45 (m, 2H), 6.83 (d, J = 8.5 Hz, 1H), 6.01 (s, 2H), 4.42 (dd, J = 8.5, 9.5 Hz, 1H), 4.23 (dd, J = 9.0, 9.5 Hz, 1H), 2.84–2.57 (m, 6H), 1.99–1.84 (m, 2H), 1.42 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 179.0, 148.6, 147.2, 133.1, 123.3, 109.5, 108.2, 101.5, 67.0, 61.1, 55.4, 35.9, 27.2, 27.1, 24.7, 17.0. For *cis*-**16a** (minor product): ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.49–7.46 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 6.00 (s, 2H), 4.54 (app. t, J = 9.5 Hz, 1H), 4.20 (dd, J = 7.0, 9.5 Hz, 1H), 2.95 (app. q J = 8 Hz, 1H), 2.84–2.57 (m, 5H), 1.99–1.84 (m, 2H), 1.42 (d, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 178.8, 148.4 146.9, 134.4, 123.2, 109.4, 107.9, 101.5, 67.5, 59.2, 52.6, 38.4, 27.6, 27.5, 24.6, 13.1.

(8*R**,8′*R**)-8-Methyl-3,3′,4,4′-bis(methylenedioxy)-7′-(propane-1,3-diyldithio)-lignano-9,9′-lactone (18a)

Following the same procedure as for **5c**, compound **18a** was prepared from **16a** (*cis* and *trans*) and piperonyl bromide **17a**[10] in 66% yield after flash chromatography (eluent CH_2Cl_2): mp 118–120°C (Et_2O–*n*-hexane), IR (thin film) ν_{max} 1766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.42 (dd, J = 1.5, 8.0 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 6.76 (dd, J = 1.5, 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.00 (s, 2H), 5.92 (s, 2H), 4.48 (app t, J = 9.5 Hz, 1H), 3.81 (app t, J = 9.0 Hz, 1H), 3.07 (d, J = 13.5 Hz, 1H), 2.86–2.61 (m, 6H), 1.96–1.89 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 181.0, 148.4, 147.6, 146.9, 146.5, 134.8, 130.4, 124.2, 123.4, 111.2, 109.7, 108.0, 107.9, 101.5, 100.9, 65.9, 61.0, 51.2, 49.3, 44.1, 28.1, 27.6, 24.8, 21.9; EIMS m/z (relative intensity): 472 (M^+, 30%), 239 (80), 206 (50), 165 (20), 135 (100); HRMS (EI) m/z calcd for $C_{24}H_{24}O_6S_2$ (M^+), 472.1014; found, 472.1013.

(8*R**,8′*R**)-8-Methyl-3,3′,4,4′-bis(methylenedioxy)-7′-oxolignano-9,9′-lactone (19a)

Following the procedure as for ^{18}O-**6a**, using H_2O instead of $^{18}OH_2$, compound **19a** was prepared from **18a** in 60% yield after flash chromatography (eluent CH_2Cl_2); mp 113–114 °C (Et_2O–*n*-hexane); IR (thin film) ν_{max} 1763, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.26 (dd, J = 1.5, 8.0 Hz, 1H), 7.20 (d, J = 1.5 Hz, 1H), 6.81 (d and d overlapping, J = 8.0 Hz, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.71 (dd, J = 1.5, 8.0 Hz, 1H), 6.07 (s, 2H), 5.99 (s, 2H), 4.58 (dd, J = 4.5, 9.0 Hz, 1H), 4.18 (dd, J = 4.5, 8.0 Hz, 1H), 3.93 (dd, J = 8.0, 9.0 Hz, 1H), 3.11 (d, J = 13.5 Hz, 1H), 2.72 (d, J = 13.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 196.3, 179.9, 152.5, 148.6, 148.1, 147.2, 131.9, 129.6, 124.7, 123.3, 110.3, 108.5, 108.0, 107.9, 102.1, 101.2, 66.7, 48.2, 47.0, 44.1, 20.7; EIMS m/z (relative intensity): 380 (M^+, 5%), 443 (100), 236 (80), 179 (90), 165 (50); HRMS (EI) m/z calcd for $C_{21}H_{18}O_7$ (M^+), 382.1052; found, 382.1039.

(7′*S**,8*R**,8′*R**)-7′-Hydroxy-8-methyl-3,3′,4,4′-bis(methylenedioxy)-lignano-9,9′-lactone [(±)-8-methylparabenzlactone, 13a] and (7′*S**,8*R**,8′*R**)-8′-hydroxymethyl-8-methyl-3,3′,4,4′-bis(methylenedioxy)-3,3′-dimethoxylignano-9,7′-lactone (20a)

Following the same procedure as for ^{18}O-**1b** and ^{18}O-**4b**, compounds **13a** (*de* 99%) and compound **20a** were obtained in 70% and 9% respectively after flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1). For **13a**: mp 159–160°C (Et_2O); IR (thin film) ν_{max} 3510, 1762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.93 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 1.5, 8.0 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 1.5, 8.0 Hz, 1H), 5.97 (part A of an AB system, J = 1.5 Hz, 1H), 5.96 (s, 2H), 5.94 (part B of an AB system, J = 1.5 Hz, 1H), 4.63 (dd, J = 2.0, 10.0 Hz, 1H), 3.55 (dd, J = 9.0, 11.0 Hz, 1H), 3.44 (app. t, J = 9.0 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H), 2.99 (d, J = 13.5 Hz, 1H), 2.74 (dt, J = 9.0, 11.0 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 181.4, 148.3, 148.0, 147.5, 146.3, 136.0, 131.2, 124.4, 119.7, 111.6, 108.4, 108.0, 106.4, 101.3, 100.8, 74.0, 66.3, 47.5, 45.2, 42.4, 18.9; EIMS m/z (relative intensity): 384(M^+, 50%), 366 (20), 151 (40), 135 (100); HRMS (EI) m/z calcd for $C_{21}H_{20}O_7$ (M^+), 384.1209; found, 384.1194. For **20a**: viscous oil, IR (thin film) ν_{max} 3473, 1757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.81 (d, J = 1.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.75 (m, 2H), 6.71 (d, J = 1.5 Hz, 1H), 6.67 (dd, J = 1.5, 8.0 Hz, 1H), 5.97 (AB system, J = 2.0 Hz, 2H), 5.94 (AB

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system, $J = 2.0$ Hz, 2H), 4.84 (d, $J = 10.5$ Hz, 1H), 4.01 (dd, $J =$ 8.0, 11.5 Hz, 1H), 3.84 (dd, $J = 5.5$, 11.5 Hz, 1H), 2.99 (d, $J =$ 13.5 Hz, 1H), 2.85 (d, $J = 13.5$ Hz, 1H), 2.44 (ddd, $J = 5.5$, 8.0, 10.5 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 179.1, 148.2, 148.1, 147.5, 146.7, 131.8, 129.5, 123.4, 120.3, 110.6, 108.3, 108.1, 106.6, 101.4, 101.0, 80.3, 58.9, 57.6, 48.0, 38.5, 23.7; EIMS m/z (relative intensity): 384 (M^+, 50%), 366 (20), 151 (40), 135 (100); HRMS (EI) m/z calcd for $C_{21}H_{20}O_7$ (M^+), 384.1209; found, 384.1201.

Compound **19a** was treated according to the general procedures A, B, and C, obtaining in all cases a mixture of starting material **13a** (19–28%) and rearranged lactone **20a** (41–65%).

(7′*S*,8*S*,8′*R*)-8′-*tert*-Butyldimethylsilyloxymethyl-4,4′-dihydroxy-3,3′-dimethoxylignano-9,7′-lactone (21e) and (7′*S*,8*S*,8′*R*)-4,4′-dihydroxy-8′-hydroxymethyl-3,3′-dimethoxylignano-9,7′-lactone (7e)

Compound **1b**[3] was treated according to the general procedure B, to give after flash chromatography (eluent CH_2Cl_2–MeOH 97 : 3) **21e** (55%) and **7e** (26%). For **21e**: $[\alpha]_D^{27}$ + 36.83 (c 0.57, THF); IR (thin film) ν_{max} 1765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.84 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 6.67 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.66 (dd, $J =$ 2.0, 8.0 Hz, 1H), 6.46 (d, $J = 2.0$ Hz, 1H), 5.11 (d, $J = 9.0$ Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.49 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.41 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.15–3.10 (m, 1H), 3.05 (d, $J =$ 5.5 Hz, 2H), 2.26–2.21 (m, 1H), 0.89 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 178.1, 146.9, 146.6, 146.1, 144.5, 130.2, 129.8, 122.4, 120.1, 114.2, 114.0, 111.9, 108.2, 81.0, 59.0, 55.9, 55.8, 50.6, 43.3, 34.4, 25.8 (3×), 18.2, −5.6 (2x); EIMS m/z (relative intensity): 488 (M^+, 40%), 431 (30), 401 (20), 277 (80), 151 (30), 137 (100); HRMS (EI) m/z calcd for $C_{26}H_{36}O_7Si$ (M+) 488.2230, found 488.2236. For **7e**: $[\alpha]_D^{27}$ +52.68 (c 0.2, THF); IR (thin film) ν_{nmax} 1748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 6.84 (d, $J = 8.0$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 1.5$ Hz, 1H), 6.70 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.69 (dd, $J = 1.5$, 8.0 Hz, 1H), 6.49 (d, $J = 2.0$ Hz, 1H), 5.11 (d, $J = 9.5$ Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.58 (dd, $J = 3.5$, 11.0 Hz, 1H), 3.50 (dd, $J = 4.0$, 11.0 Hz, 1H), 3.14–3.05 (m, 3H), 2.32–2.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 177.7, 146.9, 146.7, 146.2, 144.5, 130.1, 129.7, 122.3, 120.1, 114.4, 114.1, 111.9, 108.2, 81.2, 59.0, 56.0, 55.9, 50.1, 43.8, 34.4; EIMS m/z (relative intensity): 374 (M^+, 80%), 356 (20), 194 (20), 180 (90), 153 (30), 151 (30), 137 (100); HRMS (EI) m/z calcd for $C_{20}H_{22}O_7$ (M+) 374.1365, found 374.1360.

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