

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 ¹⁸O 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

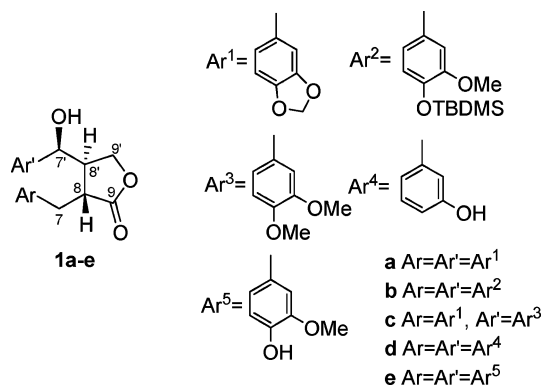
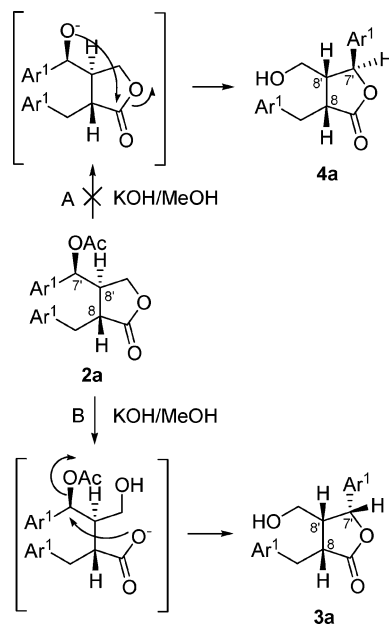


Fig. 1 7'-Hydroxylignano-9,9'-lactones and their aromatic substitution pattern.

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 reported⁴ 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 Ar¹ 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 transactonization 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, $J_{\text{H-7'/H-8'}} = 8$ 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, $J_{\text{H-7'/H-8'}} = 2.6$ 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, $J_{\text{H-7'/H-8'}} = 9.3$ 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 reactonization (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 ¹⁸O labeled compounds and monitoring the results by mass spectroscopy (MS). A variety of rearrangement conditions were investigated using different

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† Dedicated to Prof. E. J. Corey on the occasion of his 80th birthday.

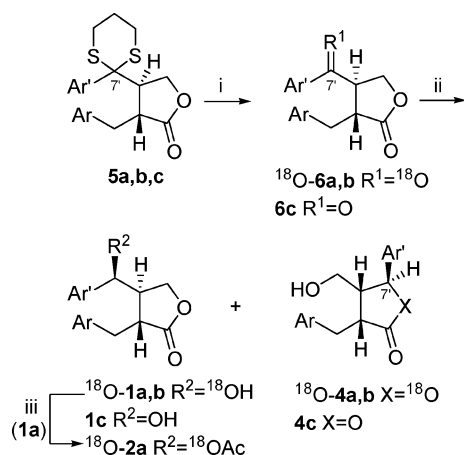
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unlabeled substrates, such as 8-methylparabenzlactone, a lignan derivative lacking α carbonyl protons, and diversely aromatic-substituted lignanolactones.

Results and discussion

Translactonization of ^{18}O labeled substrates

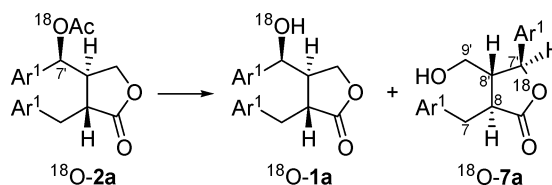
To distinguish between the translactonization and the $\text{S}_{\text{N}}2$ rearrangement mechanism, we prepared (Scheme 2) the labeled silyl protected 7'-*S*-hydroxymatairesinol ^{18}O -**1b** and the parabenzlactone derivative ^{18}O -**2a**, and looked by MS for the conservation vs. loss of the label under the translactonization (L-Selectride[®]) or the $\text{S}_{\text{N}}2$ 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 $\text{S}_{\text{N}}2$ mechanism.



Scheme 2 Reagents and conditions: (i) $(\text{CF}_3\text{CO}_2)_2\text{IPh}$, $\text{CH}_3\text{CN}-^{18}\text{OH}_2$ (for **5a,b**) or $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (for **5c**), rt; (ii) L-Selectride[®], THF, $-78\text{ }^\circ\text{C}$; (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 $^{18}\text{OH}_2$ 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 conditions⁴ (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 $\text{S}_{\text{N}}2$ 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' 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 results³ and those of Iwasaki⁷ and Eklund.⁵ Iwasaki had reported the concomitant translactonization/ α -epimerization whilst treating (\pm)-**1c** (Fig. 1) with NaH–DMF to obtain the all-*trans* (\pm)-**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, $J_{\text{H-7'/H-8'}} = 9.2$ 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 ($\text{S}_{\text{N}}2$).

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

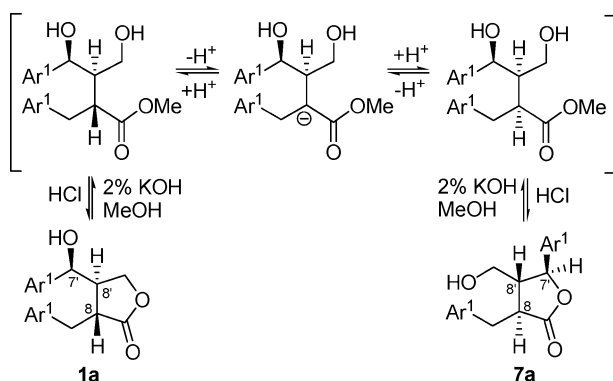
Table 1

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

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

the rearranged lactone **7a** in a 40 : 60 ratio, with a 33% yield of the latter, very different from Iwasaki's results⁷ (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 compound³ **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 ¹⁸O-**2a** (Scheme 3) and also as previously achieved by Nishibe⁴ 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 than **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 Ar¹ see Fig. 1.

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

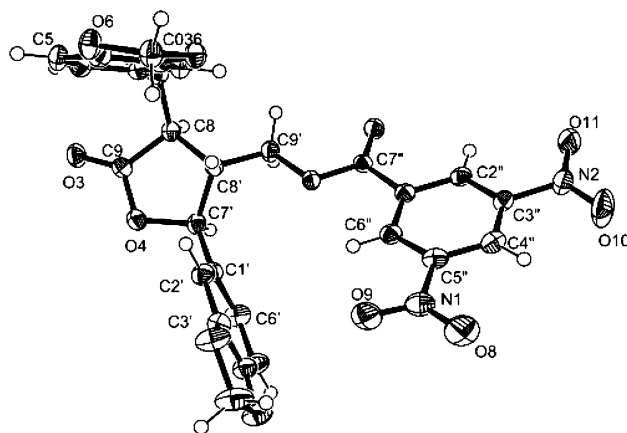
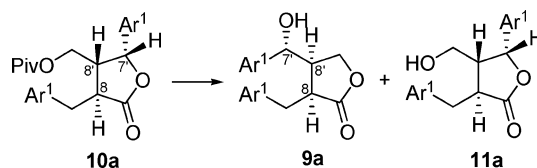


Fig. 2 Crystal structure of **8a** (50% probability ellipsoids).

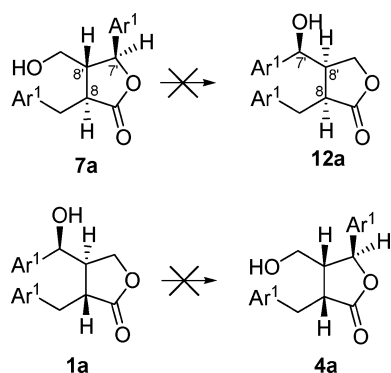
Translactonization studies with aq. NaOH–EtOH

Yamauchi and Kinoshita⁸ 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 Ar¹ see Fig. 1.

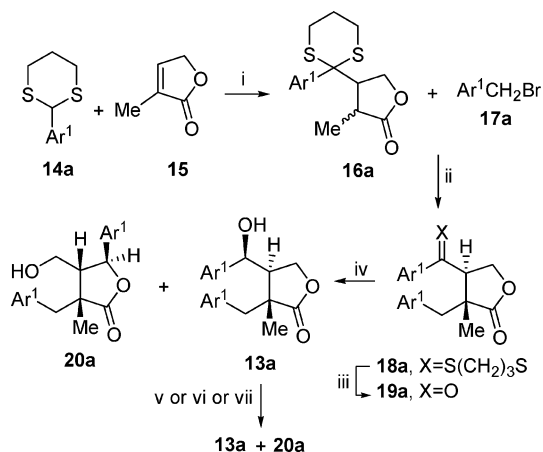
In trying to obtain **12a**, the *7'* epimer of **9a**, the above conditions were tested on **7a** (Scheme 6), but surprisingly no translactonization was observed and only **7a** was recovered. Since the only difference in the starting materials **11a** and **7a** is the stereochemistry at the *7'* site, 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.



Scheme 6 Reagents and conditions: (1) 1M aq NaOH, EtOH, rt; (2) 2 N HCl. For Ar¹ 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 addition³ 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 alkylation³ 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.

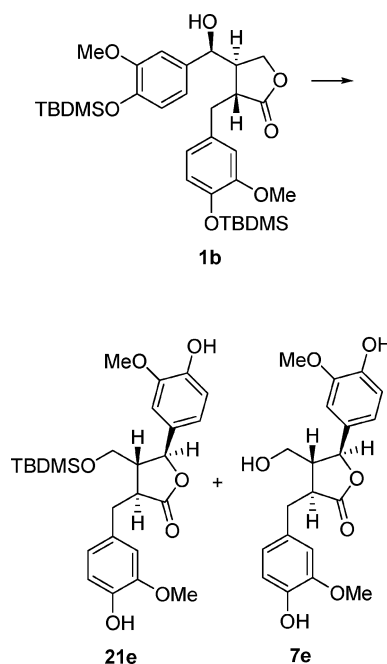


Scheme 7 Reagents and conditions: (i) *n*-BuLi, THF, DMPU, $-78\text{ }^\circ\text{C}\rightarrow\text{rt}$; (ii) LHMDS, THF, DMI, $-78\text{ }^\circ\text{C}\rightarrow\text{rt}$; (iii) $(\text{CF}_3\text{COO})_2\text{IPh}$, $\text{CH}_3\text{CN}-\text{H}_2\text{O}$, rt; (iv) L-Selectride[®], THF, $-78\text{ }^\circ\text{C}$; (v) 1) 2% KOH–MeOH, rt; 2) 2 M HCl; (vi) (1) NaH–DMF, $0\text{ }^\circ\text{C}$; (2) 2 N HCl; (vii) (1) 1M aq. NaOH, EtOH, rt; (2) 2 M HCl. For Ar¹ see Fig. 1.

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.

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, $0\text{ }^\circ\text{C}$; (2) 2 M HCl.

The ¹H 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, $J_{\text{H-7'/H-8'}} = 9$ Hz). Thus the aromatic variation and

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– <i>t</i> -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– <i>t</i> -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, MOM⁷) do not produce significant changes in the NMR chemical shift of the characteristic H-7' signal. Similarities in the ¹H 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 (\pm)-**22a**⁶ (Fig. 3) present a remarkable difference for the H-7' signals in both chemical shifts and coupling constants (δ 5.12 ppm, $J_{\text{H-7'}/\text{H-8'}} = 9.3$ Hz for **3e** vs. δ 5.43 ppm, $J_{\text{H-7'}/\text{H-8'}} = 5.4$ Hz for (\pm)-**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**.

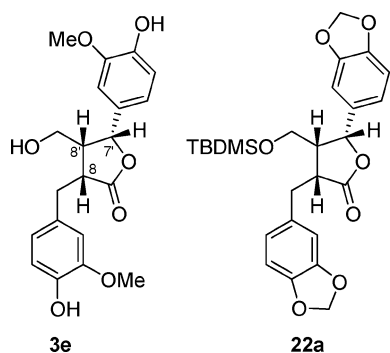


Fig. 3 Reported 7'/8'-*cis*-8/8'-*cis*-lignano-9,7'-lactones.^{5,6}

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 ¹⁸O labeled substrates and the absolute stereochemistry of the rearranged lactone obtained by Nishibe⁴ 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 ¹H 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, pre-coated 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 ¹⁸O 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

top plate. THF, CH₃CN and Py were dried by distillation from Na, P₂O₅ and CaH₂ 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 ($\lambda = 1.5418 \text{ \AA}$), on an Oxford Diffraction Gemini-S-Ultra diffractometer. 17995 reflections were measured at 150 K, and merged to give 3252 unique reflections, $R_{\text{merge}} = 0.0431$, in space group $P2_1$. The structure was refined to an R -factor of 0.0299 (for all data) and Flack parameter of $-0.19(14)$. \ddagger

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

(CF₃COO)₂IPh (100 mg, 0.23 mmol) was added to a solution of **5b**³ (55 mg, 0.08 mmol) in 10 : 1 CH₃CN-¹⁸OH₂ (1.1 ml) at rt. The mixture was stirred for 30 min and then quenched with saturated NaHCO₃ (10 ml) and extracted with Et₂O (3 \times 10 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH₂Cl₂) to obtain ¹⁸O-**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 C₃₂H₄₀O₆¹⁸OSi₂ [M + H]⁺ 603.3059, found 603.3054.

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

Following the same procedure as for ¹⁸O-**6b**, compound ¹⁸O-**6a** was prepared from **5a**³ in 86% yield after flash chromatography (eluent CH₂Cl₂-Et₂O 20:1). IR and NMR were in agreement with data reported for the unlabeled **6a**.³ HRMS (ESI-TOF) m/z calcd for C₂₀H₁₆NaO₆¹⁸O [M + Na]⁺ 393.0831, found 393.0836.

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

L-Selectride[®] (1M in THF, 0.026 ml, 0.026 mmol) was added dropwise to a solution of ¹⁸O-**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 NH₄Cl (10 ml) and extracted with EtOAc (3 \times 10 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH₂Cl₂-Et₂O 20:1) to yield 8.5 mg (70%) of ¹⁸O-**1b** and 2 mg (16%) of ¹⁸O-**4b**. IR and NMR were in agreement with data reported for the unlabeled **1b** and **4b**.³ For ¹⁸O-**1b**: HRMS (ESI-TOF) m/z calcd for C₃₂H₅₀NaO₆¹⁸OSi₂ [M + Na]⁺ 627.3035, found 627.3030. For ¹⁸O-**4b**: HRMS (ESI-TOF) m/z calcd for C₃₂H₅₀NaO₆¹⁸OSi₂ [M + Na]⁺ 627.3035, found 627.3030.

(7'*S*,8*S*,8'*R*)-[7'-¹⁸O]-7'-Hydroxy-3,3',4,4'-bis(methylenedioxy)-lignano-9,9'-lactone (¹⁸O-1a) and (7'*S*,8*R*,8'*R*)-[7'-¹⁸O]-8'-hydroxymethyl-3,3',4,4'-bis(methylenedioxy)-lignano-9,7'-lactone (¹⁸O-4a) \S

Following the same procedure as for ¹⁸O-**1b** and ¹⁸O-**4b**, compounds ¹⁸O-**1a** and ¹⁸O-**4a** \S were prepared from ¹⁸O-**6a** in 72% and

15% yield respectively after flash chromatography (eluent CH₂Cl₂-Et₂O 8 : 1). IR and NMR of ¹⁸O-**1a** were in agreement with data reported for the unlabeled **1a**.³ For ¹⁸O-**1a**: HRMS (ESI-TOF) m/z calcd for C₂₀H₁₈NaO₆¹⁸O [M + Na]⁺ 395.0992, found 395.0998. For ¹⁸O-**4a**: HRMS (ESI-TOF) m/z calcd for C₂₀H₁₈NaO₆¹⁸O [M + Na]⁺ 395.0992, found 395.0996.

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

A solution of ¹⁸O-**1a** (88 mg, 0.15 mmol) in 5 ml of Ac₂O-Py (4 : 1) was stirred overnight at rt. The residue was extracted with CHCl₃ (10 ml), washed with water (3 \times 10 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH₂Cl₂-Et₂O 20 : 1) to yield 85 mg (86%) of ¹⁸O-**2a**: $[\alpha]_{\text{D}}^{22} -26.9^\circ$ (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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 178.0, 169.8, 148.1, 147.8 (2 \times), 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 C₂₂H₂₀NaO₇¹⁸O [M + Na]⁺ 437.1098, found 437.1093.

General procedure with 2% KOH–MeOH⁴ (procedure A): (7'*S*,8*S*,8'*R*)-[7'-¹⁸O]-3,3',4,4'-bis(methylenedioxy)-8'-hydroxymethyl-3,3'-dimethoxylignano-9,7'-lactone (¹⁸O-7a)

A solution of ¹⁸O-**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 CH₂Cl₂ (3 \times 20 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH₂Cl₂-Et₂O 3 : 1) to yield 33 mg (47%) of ¹⁸O-**1a** and 20 mg (29%) of ¹⁸O-**7a**. For ¹⁸O-**7a**: $[\alpha]_{\text{D}}^{27} +66.97$ (c 0.37, THF); IR (thin film) ν_{max} 3339, 1765, 1249, 1035 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₀H₁₈NaO₆¹⁸O [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 CH₂Cl₂-Et₂O 3 : 1) a mixture of starting material **1a** (61%) and rearranged lactone **7a** (31%). For **7a**: $[\alpha]_{\text{D}}^{22} +90.14^\circ$ (c 0.4, CHCl₃); IR and NMR were in

agreement with the data of ¹⁸O-**7a**; HRMS (ESI-TOF) *m/z* calcd for C₂₀H₁₈NaO₇ [M + Na]⁺ 393.0950, found 393.0956.

General procedure with NaH–DMF⁷ (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 Na₂SO₄, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH₂Cl₂–Et₂O 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–EtOH⁸ (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 Na₂SO₄, filtered, evaporated and the crude product was purified by flash chromatography (eluent CH₂Cl₂–Et₂O 3 : 1) to yield only the starting material **7a** (80%).

(*8R,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-lactone³ (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 NH₄Cl (10 ml) and extracted with Et₂O (3 × 15 ml). The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH₂Cl₂–Et₂O 10 : 1) to obtain **5c** as a white solid (310 mg, 78%): mp 89–91°C (Et₂O–*n*-hexane); [α]_D²⁵ + 72.17° (*c* 1.0, CHCl₃); IR (thin film) ν_{max} 1766 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₄H₂₆O₆S₂ (M⁺), 474.1171; found, 474.1177.

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

Following the same procedure as for ¹⁸O-**6b**, using H₂O instead of ¹⁸OH₂, compound **6c** was prepared in 65% yield as a white solid after flash chromatography (eluent CH₂Cl₂–Et₂O 20 : 1): mp 153–154°C (CHCl₃–Et₂O) (lit.⁷ 140–141°C (AcOEt–acetone)); [α]_D²⁵ + 41.08° (*c* 0.1, CHCl₃); ¹³C NMR (125 MHz, CDCl₃) 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 ¹H NMR were in agreement with reported data;⁷ HRMS (EI) *m/z* calcd for C₂₁H₂₀O₇ (M⁺), 384.1209; found, 384.1204.

(*7'S,8R,8'R*)-7'-Hydroxy-3',4'-dimethoxy-3,4-methylenedioxy-lignano-9,9'-lactone (**1c**) and (*7'S,8R,8'R*)-8'-hydroxymethyl-3',4'-dimethoxy-3,4-methylenedioxy-lignano-9,7'-lactone (**4c**)

Following the same procedure as for ¹⁸O-**1b** and ¹⁸O-**4b**, compounds **1c** (*de* 97%) and **4c** were prepared in 61% and 7% yield, respectively, after flash chromatography (eluent CH₂Cl₂–Et₂O 10 : 1). For **1c** mp 122–124°C (Et₂O); [α]_D²² –20.09° (*c* 0.34, CHCl₃); ¹³C NMR (125 MHz, CDCl₃) 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 ¹H NMR were in agreement with reported data;⁷ HRMS (EI) *m/z* calcd for C₂₁H₂₂O₇ (M⁺), 386.1365; found, 386.1362. For **4c**: [α]_D²⁴ + 44.47° (*c* 0.54, THF); IR (thin film) ν_{max} 3517, 1769 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₂O₇ (M⁺), 386.1365; found, 386.1378.

(*7'S,8S,8'R*)-8'-Hydroxymethyl-3',4'-dimethoxy-3,4-methylenedioxy-lignano-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**: [α]_D²⁷ + 47.45° (*c* 1.08, THF); ¹³C NMR (125 MHz, CDCl₃) 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 ¹H NMR were in agreement with reported data;⁷ HRMS (EI) *m/z* calcd for C₂₁H₂₂O₇ (M⁺), 386.1365; found, 386.1362.

(*7'S,8S,8'R*)-3,3',4,4'-Bis(methylenedioxy)-3,3'-dimethoxy-8'-(3,5-dinitrobenzoyloxy)methyl-lignano-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

(10 ml) and extracted with CH₂Cl₂ (3 × 20 ml). The organic phase was washed with water (2 × 10 ml), dried over anhydrous Na₂SO₄, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH₂Cl₂–Et₂O 4 : 1) to obtain **8a** as a yellow solid (40 mg, 65%); mp 182–183 °C (CH₂Cl₂); [α]_D²⁵ + 66.81 ° (c 0.31, THF); IR (thin film) ν_{max} 1771, 1733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₇H₂₀O₁₂N₂ (M⁺), 564.1016; found, 564.1011.

(2*R,3*R**)-2-Methyl-3-[(propane-1,3-diylidithio)-(3,4-methylenedioxyphenyl)methyl]-butano-4-lactone (*trans*-16a) and (2*S**,3*R**)-2-methyl-3-[(propane-1,3-diylidithio)-(3,4-methylenedioxyphenyl)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 NH₄Cl and extracted with Et₂O. The organic phase was dried over anhydrous Na₂SO₄, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH₂Cl₂–Et₂O 20 : 1) to obtain 547 mg (78%) of a 2 : 1 mixture of *trans*-**16a** and *cis*-**16a** (not separated): mp 88–90 °C (Et₂O); 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 C₁₆H₁₈O₄S₂ (M⁺), 338.0646; found, 338.0653. For *trans*-**16a** (major product): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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-diylidithio)-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 CH₂Cl₂): mp 118–

120 °C (Et₂O–*n*-hexane), IR (thin film) ν_{max} 1766 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₄H₂₄O₆S₂ (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 ¹⁸O-**6a**, using H₂O instead of ¹⁸OH₂, compound **19a** was prepared from **18a** in 60% yield after flash chromatography (eluent CH₂Cl₂): mp 113–114 °C (Et₂O–*n*-hexane); IR (thin film) ν_{max} 1763, 1668 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₁₈O₇ (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 ¹⁸O-**1b** and ¹⁸O-**4b**, compounds **13a** (*de* 99%) and compound **20a** were obtained in 70% and 9% respectively after flash chromatography (eluent CH₂Cl₂–Et₂O 20 : 1). For **13a**: mp 159–160 °C (Et₂O); IR (thin film) ν_{max} 3510, 1762 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₀O₇ (M⁺), 384.1209; found, 384.1194. For **20a**: viscous oil, IR (thin film) ν_{max} 3473, 1757 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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

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 $\text{C}_{21}\text{H}_{20}\text{O}_7$ (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,8S,8'R)-8'-tert-Butyldimethylsilyloxymethyl-4,4'-dihydroxy-3,3'-dimethoxylignano-9,7'-lactone (21e) and (7'S,8S,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**: $[\alpha]_{\text{D}}^{27} + 36.83$ (c 0.57, THF); IR (thin film) ν_{max} 1765 cm^{-1} ; ^1H 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 \times), 18.2, –5.6 (2 \times); EIMS m/z (relative intensity): 488 (M^+ , 40%), 431 (30), 401 (20), 277 (80), 151 (30), 137 (100); HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{36}\text{O}_7\text{Si}$ (M^+) 488.2230, found 488.2236. For **7e**: $[\alpha]_{\text{D}}^{27} + 52.68$ (c 0.2, THF); IR (thin film) ν_{max} 1748 cm^{-1} ; ^1H 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 $\text{C}_{20}\text{H}_{22}\text{O}_7$ (M^+) 374.1365, found 374.1360.

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