Asymmetric synthesis, stereochemistry and rearrangement reactions of naturally occurring 7′-hydroxylignano-9,9′-lactones

Barbara Raffaelli, Kristiina Wähälä* and Tapio Hase

Received 20th September 2005, Accepted 17th November 2005
First published as an Advance Article on the web 12th December 2005
DOI: 10.1039/b513303c

The asymmetric synthesis of a series of (7′*S*,8*R*,8′*R*)-7′-hydroxylignano-9,9′-lactones is presented, among them the mammalian lignan (7′*S*)-hydroxyenterolactone and (7′*S*)-parabenzlactone, allowing the stereochemistry of natural occurring (–)-parabenzlactone to be re-assigned. A hydroxylactone rearrangement and its possible mechanisms are discussed. Finally a brief survey of the current naming and numbering variants of 7′-hydroxylignano-9,9′-lactones is presented, along with a suggestion for harmonization of the nomenclature.

Introduction

(8*R*,8′*R*)-Dibenzylbutyrolactones [or (8*R*,8′*R*)-lignano-9,9′-lactones, according to IUPAC recommendations][1] represent a large class of naturally occurring lignans,[2] but only six compounds bearing a hydroxyl group at the 7′ position (7′-hydroxylignano-9,9′-lactones, 7′-HLL) are known up today (**1**–**6**, Fig. 1). Compounds **1**–**4** are plant lignans,[3,4,5] while **5** and its isomer **6** are so-called mammalian lignans,[6,7] products of intestinal bacterial metabolism. The current interest in **1**–**6** stems from their biological activities. For example, (7′*S*)-hydroxymatairesinol **1** [(7′*S*,8*R*,8′*R*)-4,4′,7′-trihydroxy-3,3′-dimethoxylignano-9,9′-lactone] and its 7′-epimer (7′*R*)-hydroxymatairesinol **2** [also called *allo*-hydroxymatairesinol, (7′*R*,8*R*,8′*R*)-4,4′,7′-trihydroxy-3,3′-dimethoxylignano-9,9′-lactone] have been in the last years under biological and clinical studies,[8,9] since it was discovered that they are precursors of the mammalian lignan enterolactone **7** (Fig. 1), which possesses antitumor activity.[9,10] (7′*R*)-parabenzlactone **4** [(7′*R*,8*R*,8′*R*)-7′-hydroxy-4,4′,5,5′-dimethylenedioxylignano-9,9′-lactone] showed immunosuppressive properties on certain human lymphocytes.[11] Biological effects of (7′*R*)-hydroxyarctigenin **3** [(7′*R*,8*R*,8′*R*)-4,7′-dihydroxy-3,3′,4′-trimethoxylignano-9,9′-lactone], (7′*S*)-hydroxyenterolactone **5** [(7′*S*,8*R*,8′*R*)-4,4′,7′-trihydroxylignano-9,9′-lactone] and its 7′-epimer (7′*R*)-hydroxyenterolactone **6** [(7′*R*,8*R*,8′*R*)-4,4′,7′-trihydroxylignano-9,9′-lactone] are not known at present, but compounds **5** and **6** are metabolites of **1** and/or **2** and possible precursors and/or metabolites of enterolactone **7**.[7]

Lack of synthetic enantiopure compounds has obstructed the assignment of absolute configuration of the molecules. In fact the first stereoselective synthesis of **1**–**3** and **8** appeared[12] only last year, while compounds **4**–**6** and **9** have been only prepared as a mixture of enantiomers.[13,14]

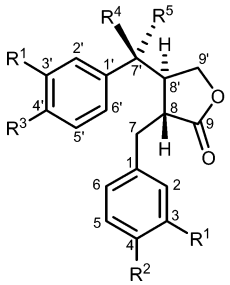
The plant derived lignans possess a *trans* 8*R*/8′*R* configuration, while the stereochemistry at 7′ has long been unclear owing to conflicting literature reports. The configurations of **1** and **2** were only recently indirectly determined as 7′*S* and 7′*R*,[15] respectively, by X ray analysis of the corresponding diols, opposite to those previously assigned.[16,17] Also for the natural compound **3** the configuration at the 7′ position was recently re-assigned as being 7′*R*.[12] The configuration of naturally occurring (–)-parabenzlactone has been inferred[18,19] as 7′*R*, after the absolute configurations at C-7 of the 7-hydroxylignanolactone podorhizol and its 7-epimer epipodorhizol were established as *S* and *R*, respectively.[20] The latter assignments were based on the intramolecular 7-OH hydrogen bonding to the lactone carbonyl, which was observed (and possible) in the epi compound only. The podorhizol and epipodorhizol 7-CH ^{1}H-NMR parameters (δ and J) were applied[18,19] to show that (–)-parabenzlactone possesses the 7′*R* configuration. Obviously this analysis is inherently prone to errors because of the different environment of the 7- and 7′-sites.

Compounds **5** and **6** have been both detected in human plasma, and being derived from the plant lignan **1** and/or **2**, are likely to have retained the *trans* 8*R*/8′*R* configuration, but they have never been isolated, synthesized nor characterized as pure isomers.

Several synthetic procedures exist in literature[12,21,22] for the formation of the *trans* 8*R*/8′*R* configuration leading to optically active lignanolactones, either lacking benzylic functionalities altogether or with a hydroxyl group at the C-7 position. The recent asymmetric synthesis[12] of (7′*S*,8*R*,8′*R*)- and (7′*R*,8*R*,8′*R*)-HLLs relied on a radical carboxylation approach. Enantiopure 7′-hydroxyarctigenin has also been obtained *via* a semi-synthetic route, by benzylic oxidation at C-7′ of arctigenin monoacetate, but at that time the stereochemistry of 7′-HLLs was still uncertain and in fact in the paper the *R* and *S* configurations are incorrectly assigned.[19]

In this paper we present a general approach for the stereoselective synthesis of several (7′*S*,8*R*,8′*R*)-HLLs. Thus, we report the first asymmetric synthesis of lignans **5**, **9** and **10**, together with the synthesis of **1** and **8**, which also serves to clarify the absolute configuration of naturally occurring (–)-parabenzlactone, which in our opinion has been erroneously assigned.[18] Additionally, we report the formation of a new HLL-related hydroxylactone arising from a rearrangement reaction in a hydride ketone reduction. The presumed mechanism of formation is presented and discussed, together with other possible mechanisms which may be responsible of the formation of related lactones described in literature. Finally we would like to point out the confusing naming and numbering systems used at present in the literature for the 7- and 7′-HLLs.

Department of Chemistry, Laboratory of Organic Chemistry, University of Helsinki, P.O. Box 55, FIN-00014, Finland. E-mail: kristiina.wahala@helsinki.fi; Fax: +358 9191 50357

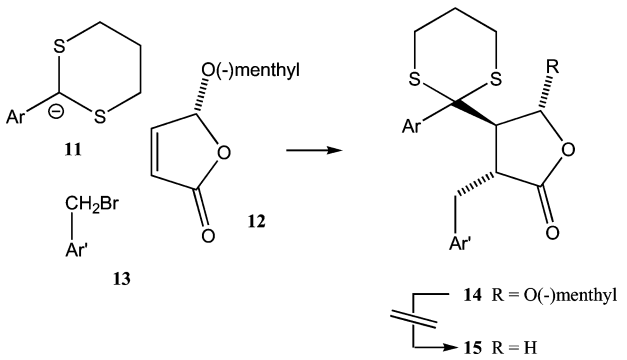


1 R^1=OMe, R^2=R^3=R^4=OH, R^5=H — 7′(*S*)-Hydroxymatairesinol
2 R^1=OMe, R^2=R^3=R^5=OH, R^4=H — 7′(*R*)-*Allo*-hydroxymatairesinol
3 R^1=R^3=OMe, R^2=R^5=OH, R^4=H — 7′(*R*)-Hydroxyarctigenin
4 R^1-R^2=R^1-R^3=OCH_2O, R^5=OH, R^4=H — (-)-Parabenzlactone [7′(*R*)]
5 R^1=R^4=OH, R^2=R^3=R^5=H — 7′(*S*)-Hydroxyenterolactone
6 R^1=R^5=OH, R^2=R^3=R^4=H — 7′(*R*)-Hydroxyenterolactone
7 R^1=OH, R^2=R^3=R^4=R^5=H — Enterolactone
8 R^1=R^3=OMe, R^2=R^4=OH, R^5=H — 7′(*S*)-Hydroxyarctigenin
9 R^1-R^2=R^1-R^3=OCH_2O, R^4=OH, R^5=H — 7′(*S*)-Parabenzlactone
10 R^1=R^4=OH, R^2=R^3=OMe, R^5=H — 7′(*S*)-Hydroxyprestegane B

Fig. 1 Naturally (**1**–**6**) and non-naturally occurring (**8**–**10**) 7′-hydroxylignano-9,9′-lactones. The metabolite enterolactone (**7**) is also shown. Note that the (7′*R*) configuration assigned in literature to (–)-parabenzlactone (**4**) is incorrect as shown in this work, and the true structure for the (–)-enantiomer is (**9**).

Results and discussion

For establishing the *trans* 8*R*/8′*R* stereochemistry, we first examined the well known tandem Michael addition–alkylation sequence,[23,24] employing a lithiated dithiane **11** as nucleophile, 5-(–)-menthyloxybutenolide **12**[25] as a chiral auxiliary and Michael acceptor, and a benzylic bromide **13** as an alkylating agent (Scheme 1).

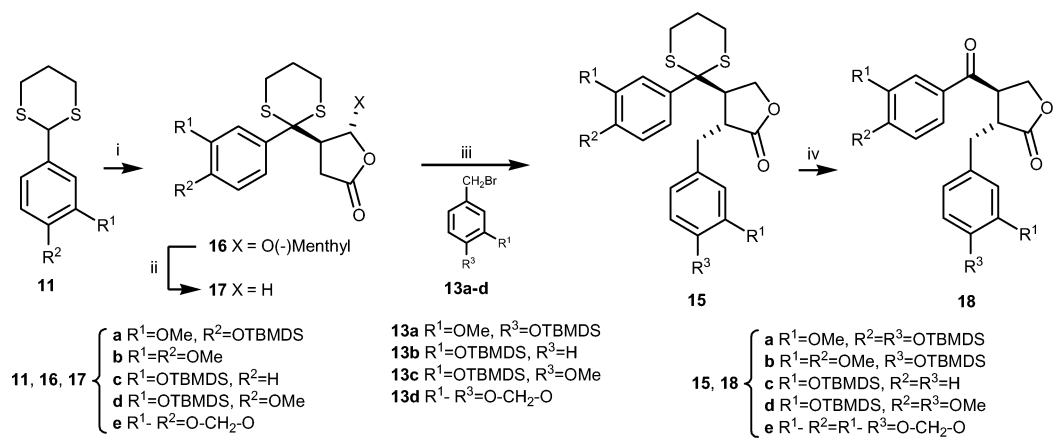


Scheme 1

Unfortunately the product **14**, obtained in 56% yield as a single isomer, resisted all attempts at removing the menthyloxy auxiliary to give **15**. The successful outcomes reported in the literature for certain related cases apparently all require the prior removal of the dithio attachment.[23,24] It would appear an attractive possibility to first carry out a deketalization on the tandem product **14** and then perform a double stereoselective reduction (on the ketone and the ring-opened lactone aldehyde), but such a streamlined sequence is frustrated by the two competing relactonization modes, *i.e.*, *via* either the primary or the secondary hydroxyl (see below). This is why in our experience also the silanyloxy–nitrile alternative (used in place of the dithiane moiety)[26] was not satisfactory due to the silanyloxy–nitrile hydrolysis which occurs in the menthyloxy removal step.

However, the menthyloxy auxiliary is easily removed before alkylation.[27] Thus the Michael addition of lithiated dithianes **11a**–**e**[28] to the chiral butenolide **12** afforded **16a**–**e** in 75–88% yield as single isomers (Scheme 2), provided 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[29] was used as a co-solvent and complexing reagent (DMPU was also essential in the tandem Michael addition–alkylation reaction). The menthyloxy moiety was then smoothly detached by a basic lactone hydrolysis followed by the *in situ* $NaBH_4$ reduction of the aldehyde formed, giving the chiral lactones **17a**–**e** (60–82% yield) on ordinary acidic workup (pH 5–6). No isomerization was detected by ^{1}H NMR, using the chiral shift reagent Eu(hfc)$_3$ (ee $\geq$ 98%). Alkylation of **17a**–**e** with the appropriate benzylic bromides **13a**–**d** gave the lignanolactone derivatives **15a**–**e** in acceptable yields (66–78%) and with the wanted *trans* 8*R*/8′*R* configuration.[30]

For the unmasking of the 7′ keto group *via* dithiane hydrolysis, several literature methods were tested, but in our experience



Scheme 2 Reagents and conditions: (i) *n*-BuLi, THF, DMPU, **12**, −78 °C; (ii) (a) $NaBH_4$, KOH, EtOH, 0 °C, then rt, (b) 0.1 N HCl (pH 5–6); (iii) LDA or LHMDS, THF, DMI, −78 °C to rt; (iv) $(CF_3COO)_2IPh$, CH_3CN–H_2O, rt.

Table 1 L-Selectride® reduction of **18**

Entry	Ketone	Alcohol	ds[a] (%)	H-7′*S*	H-7′*R*	Yield[b] (%)
1	**18a**	**19a**	97	4.57	4.37	70
2	**18b**	**19b**	93	4.62	4.38	75
3	**18c**	**19c**	83	4.60	4.38	77
4	**18d**	**19d**	88	4.53	4.35	68
5	**18e**	**9**	96	4.61	4.38	80

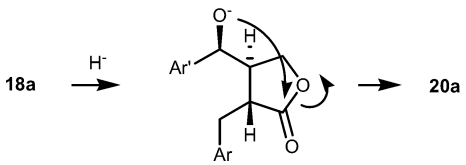
[a] Determined by ^{1}H NMR of crude products (7′S/7′R). [b] After flash chromatography (7′S +7′R).

only $(CF_3CO_2)_2IPh$[31] served satisfactorily, providing 7′-oxolignanolactones **18a**–**e** in 50–80% yield.

The reduction of the ketone moiety of **18a**–**e** by L-Selectride® produced **9**,**19a**–**d** in high enantiomeric excess (Scheme 3, Table 1). As expected of a hydride attack from the less hindered face of the ketone **18**, (7′*S*)-OH compounds were obtained in all cases (spectroscopic data of compound **19a** in agreement with those reported[12]), but considerable variations in the stereoselectivity were encountered with values of ds up to 97% in case of **19a** (Table 1, entry 1) and as low as 83% for compound **19c** (entry 3). The ds values were based on ^{1}H-NMR of the crude mixtures, confirming the trend previously described[12] for 7′-HLL derivatives, *i.e.* that the H-7′*S* signal is at about δ 4.6, while that of H-7′*R* is at about δ 4.4 (Table 1) irrespective of the aromatic substituents (OH, OMe, OTBDMS, OCH_2O). It is not immediately obvious why this reduction was so stereoselective for certain compounds, but less so for others, as the differences in structures reside at relatively remote locations. We are presently doing modelling studies to elucidate this question.

L-Selectride® reduction of **18e** provided (7′*S*)-parabenzlactone **9**, one of the target molecules. The physical and spectroscopic data obtained for synthetic **9** were in good agreement with those reported for the natural product,[5,18] confirming that the stereochemistry of (–)-parabenzlactone had been erroneously assigned as 7′*R* instead of 7′*S*.

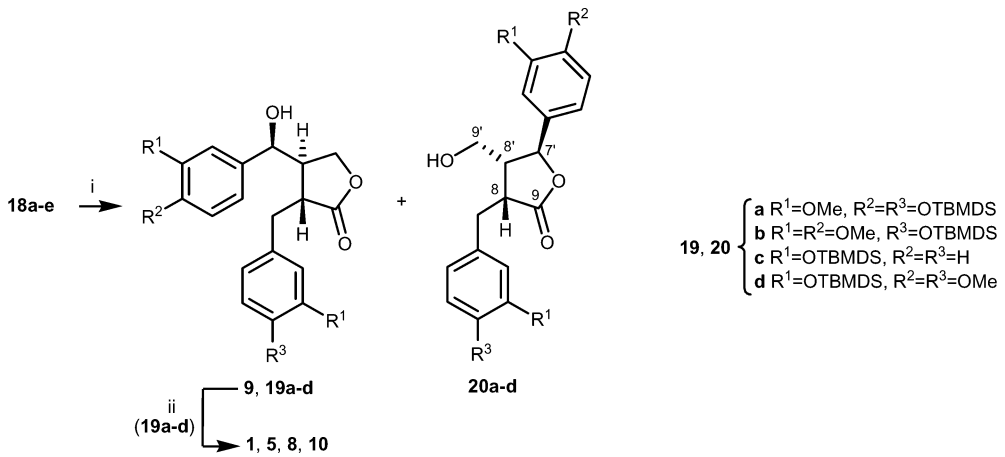
In the L-Selectride® reduction of **18a** a byproduct was isolated in about 10% yield. Spectroscopic data (IR, 1- and 2D NMR, MS) suggested that this compound was the rearranged hydroxylactone **20a** (Scheme 3). At the same time a paper by Eklund *et al.*[32] reported the isolation and characterization of two lariciresinol-type lactone lignans from the treatment of 7′-hydroxymatairesinols **1** and **2** with base. Comparison of NMR data suggested that the major compound (ratio between isomers was 5 : 1) found by Eklund *et al.* possesses the same skeleton and stereochemistry as our byproduct **20a**. In particular, the NMR signal for H-7′, which for both compounds is found at about δ 5.4 ($J_{H\text{-}7'\text{-}H\text{-}8'} = 2.6$ Hz), is diagnostic for a *trans* 7′/8′ configuration, which derives from the *S* configuration of the 7′-OH group of **19a**. The second lactone described by Eklund and coworkers is the 7′-epimer with a H-7′ signal at about δ 5.1, with a coupling constant of $J_{H\text{-}7'\text{-}H\text{-}8'} =$ 9.3 Hz, characteristic of a *cis* 7′/8′ configuration. The formation of our compound **20a** can be assumed to be the result of a translactonization reaction, where the 7′-alkoxyborane from the Selectride® reaction may act as nucleophile towards the lactone ring, with the formation of a primary alcohol as a consequence (Scheme 4).



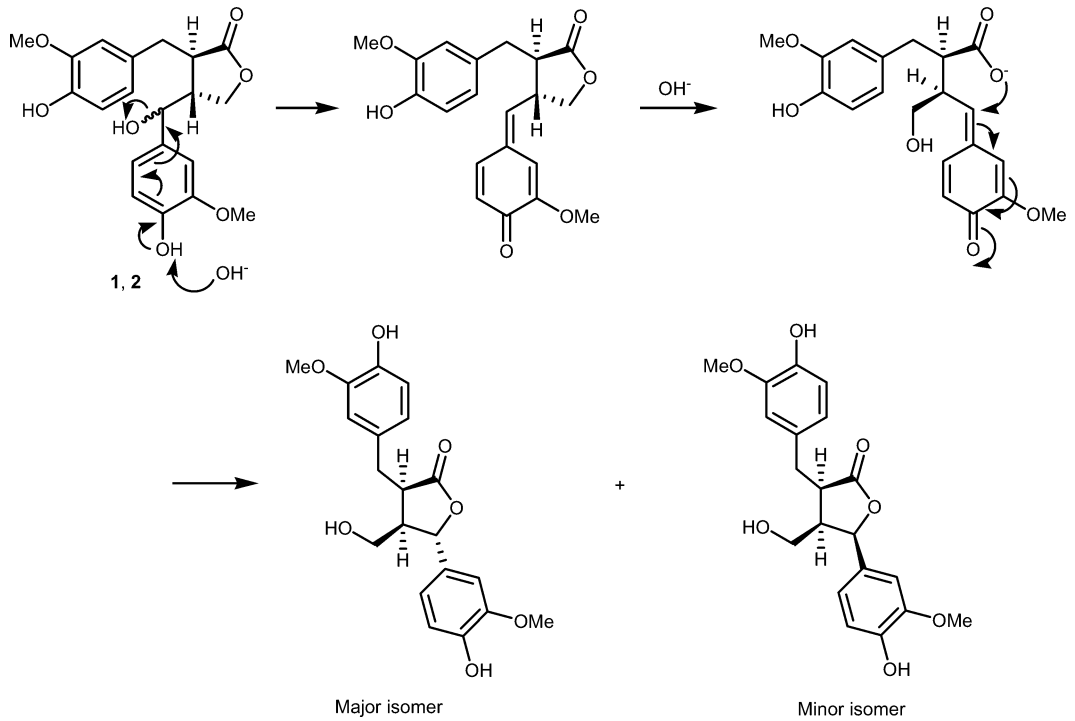
Scheme 4 Presumed mechanism of translactonization and formation of **20a**.

Eklund *et al.* suggest that their lactones are formed by a *p*-quinone methide mechanism (Scheme 5), only available when a free *p*-phenol moiety is present. In our case, the phenols are TBDMS protected, therefore this mechanism is unlikely, and in fact we did not detect any further rearranged lactones by NMR of the crude mixture, from the treatment of **18a** with L-Selectride®.

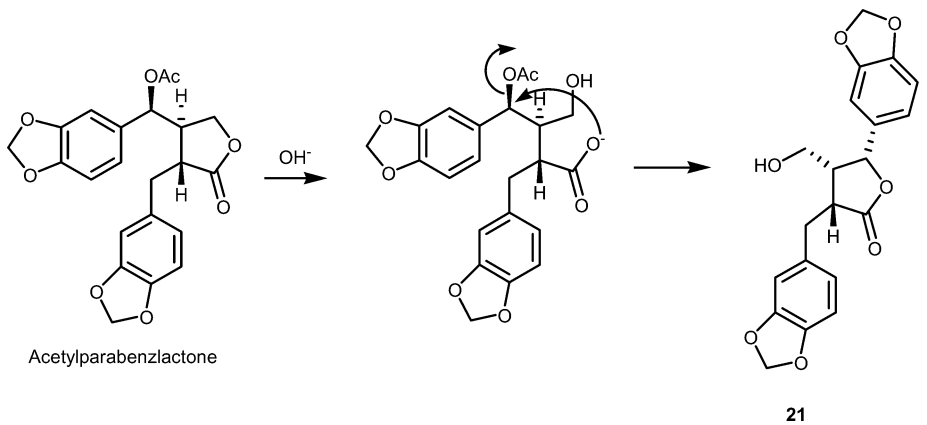
In literature two other examples of formation of compounds similar to **20a** can be found. Niwa *et al.*[18] reported the formation of a rearranged lactone obtained as a side product from the treatment of natural acetylparabenzlactone with KOH. The authors suggested the structure **21** (Scheme 6) for this compound, which according to ^{1}H NMR (H-7′, δ 5.13, d, $J_{H\text{-}7'\text{-}H\text{-}8'} = 8.0$ Hz) is analogous with the minor isomer obtained by Eklund *et al.*[32] However there is a problem in that the configuration of natural parabenzlactone, as shown above, is 7′*S*, while the configuration



Scheme 3 Reagents and conditions: (i) L-Selectride®, THF, −78 °C; (ii) TBAF–CH_3COOH, THF, 0 °C.



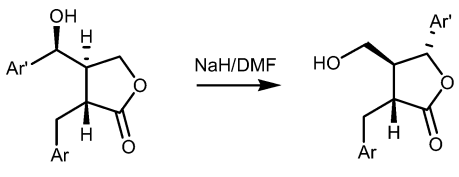
Scheme 5 Hydroxylactone rearrangement *via* a quinone methide intermediate.[32]



Scheme 6 Niwa's rearranged lactone[18] and possible mechanism of formation of **21**.

of the rearranged lactone could only come from a 7′*R* center, assuming the same mechanism of translactonization presumed for **20a** (attack by 7′-O^- on the lactone ring). This discrepancy may be resolved by taking into account that the starting material is acetylparabenzlactone and that AcO, in contrast to OH, is a sufficiently good leaving group. In competition with the hydrolysis of the AcO group, the lactone also may undergo hydrolysis with the formation of a primary alcohol and a carboxyl group. The COO^- generated can now act as a nucleophile and attack the 7′ center *via* a S_N2 mechanism, with simultaneous detachment of the AcO group. The final result would be a new lactone ring with inversion of configuration at 7′ position, in agreement with Niwa's paper and our own results. One should notice that for acetylparabenzlactone mere AcO hydrolysis is not sufficient to trigger the lactone rearrangement, and no other rearranged lactones were mentioned.

Moritani *et al.*[33] obtained a rearranged lactone **22** by treating a (7′*S**,8*R**,8′*R**)-7′-HLL **23** with NaH in DMF (Scheme 7). The authors assumed that during this reaction complete epimerization had occurred at the β-carbon of the new lactone ring to give a *trans* 8/8′-*trans* 7′/8′ configuration, determined by X-ray crystallography. However looking at the NMR data of this compound, one notes that H-7′ is reported to appear at δ 5.16, with a



Scheme 7 Lactone isomerization reported by Moritani *et al.*[33]

$J_{H\text{-}7'\text{-}H\text{-}8'} = 9.2$ Hz, which however indicates a *cis* 7′/8′ configuration according to Eklund's results. Therefore in our opinion Moritani's finding is incompatible with our results and those of Eklund *et al.*[32] and this discrepancy remains unexplained at present.

Thus three different mechanisms may operate in the lactone isomerisations, depending on finely tuned substituent effects and reaction conditions, one of them involving the quinone methide route. The expected stereochemical consequences at C-7′ of the three alternatives are: retention (7′-OH), inversion (7′-OAc) and racemization (*via* quinone methide). Concerning Moritani's lactone, none of the three possible mechanisms can explain the formation of a *trans*/*trans* configured lactone, as reported.

Treatment of **18b–e** with L-Selectride® furnished the 7′-HLLs **19b–e**, and in all cases, except for oxo-parabenzlactone **18e**, small quantities of the rearranged lactones **20b–d** were detected by ^{1}H NMR of the crude mixture (doublet at about δ 5.4), but were not isolated. Finally, the TBDMS ethers **19a–d** were deprotected with TBAF–AcOH[34] (Scheme 3) to furnish compounds **1**, **8** and, for the first time, (7′*S*)-hydroxyenterolactone **5** together with the previously unknown (7′*S*)-hydroxyprestegane B **10**, also fully characterized.

Nomenclature of 7′-hydroxylignano-9,9′-lactones

The nomenclature and numbering of carbon atoms in the 7′-HLL series, as used in the literature, is often confusing or misleading, or even quite erroneous at times. This situation largely arises from the fact that these compounds may be considered as derived from any of a number of parent structures, with different numbering being applied for example to the benzylic carbon atoms. A naturally occurring lactone lignan where the two arylpropyl units are joined at their 8/8′ sites usually possesses a trivial name. However, such a compound may also be named as a lignano-9,9′-lactone (IUPAC recommendations),[1] dibenzylbutyrolactone, or 2(3*H*)-dihydrofuranone (*Chemical Abstracts*), or tetrahydrofuranone (preferably avoided). The site of the benzylic hydroxy group of hydroxymatairesinols **1** and **2** is variously given as matairesinol C-7,[6,8,12,15,17] or 7′,[1,4,14,16] or even 5.[19] Speaking in terms of a butyrolactone parent, the hydroxybenzyl moiety may be viewed as a lactone 3-[35] or 4-[36] substituent. Other papers using the butyrolactone framework assign the benzylic sites variously as 5/6,[37] or 6/7,[24] or 7′/7″.[38] Furthermore, some authors including ourselves have changed their nomenclature in their more recent work without actually alerting unwary readers to this effect. If one adheres to lignano-9,9′-lactone based numbering (IUPAC recommendations),[1] there is the obvious advantage that the hydroxybenzyl site of hydroxymatairesinol is 7′ because the alternative benzylic site, being closer to the carbonyl, has priority and is thus 7. It would undoubtedly be very helpful if this numbering would be more generally adopted. This numbering may of course be used for hydroxymatairesinol and other similar trivial names as well.

Conclusions

Asymmetric synthesis of optically active 7′-hydroxylignano-9,9′-lactones concerns a subclass of lignans which possess or may possess certain interesting biological properties. We report here a general asymmetric synthesis route that can be applied for the synthesis of several (7′*S*)-HLLs, irrespective of their aromatic substituents. This has allowed the preparation of (7′*S*)-hydroxymatairesinol **1**, (7′*S*)-hydroxyarctigenin **8** and for the first time (7′*S*)-hydroxyenterolactone **5**, (7′*S*)-parabenzlactone **9**, and (7′*S*)-hydroxyprestegane B **10**, a previously unknown isomer of (7′*S*)-hydroxymatairesinol. In connection with this work we demonstrated that the reported (*R*) configuration for the 7′ position in the natural (–)-parabenzlactone was erroneous.

In one step of our synthetic procedure, performing a hydride reduction of a keto group, a rearranged hydroxylactone was formed as a byproduct, presumably by a translactonization mechanism. Altogether, three different mechanisms may be responsible for the formation of similar lactones reported in literature, depending on the aromatic substituents, the configuration of the 7′ center and the reaction conditions, giving an explanation for all observed cases except one, which remained unsolved.

Finally, in a discussion of the nomenclature of the HLL lignans, we examine the many confusing or misleading variants in the naming and numbering systems used in literature, and suggest the adoption of an unequivocal naming system for these compounds, as recommended by the IUPAC.

Experimental

General

THF and Et_2O were freshly distilled from sodium benzophenone ketyl, DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) and DMI (*N*,*N*-dimethyl-2-imidazolidinone) from CaH_2 under reduced pressure. Lithium diisopropylamide (LDA) was prepared from freshly distilled diisopropylamine and *n*-butyllithium in THF. Other commercially available chemicals were used as supplied by the manufacturers. 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 ethanol. Silica gel 60 (230–400 mesh, Merck) was used for flash column chromatography. Compounds were homogeneous on TLC. Optical rotation values were measured with a JASCO DIP-1000 digital polarimeter at ambient temperature. NMR spectra were recorded on a 200 MHz Varian GEMINI 2000, or a 500 MHz Bruker Avance 500 spectrometer. Chemical shifts are given in δ and *J* values in Hz, using tetramethylsilane (TMS) as internal standard. Mass spectra were obtained using a JEOL JMS-SX102 mass spectrometer operating at 70 eV. Melting points were determined in open capillary tubes with an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR instrument equipped with ATR reflection top plate. HPLC separations were performed using Waters 600 pump, CYCLOBOND I RSP 2000 (10 μm) column (250 × 10 mm), Waters 996 UV photodiode array detector and Waters 717 plus autosampler. Compounds **11b**, **11e**,[39] **12**[40] and **13a–d**[41] were prepared according to literature procedures.

2-(4-*tert*-Butyldimethylsilanyloxy-3-methoxyphenyl)-1,3-dithiane (11a). 4-*tert*-Butyldimethylsilanyloxy-3-methoxybenzaldehyde (1.94 g, 7.29 mmol) in dry Et_2O (8.0 ml) was added at rt to a stirred solution of propane-1,3-dithiol (0.8 ml, 8.0 mmol) and $MgBr_2$ (2.0 g, 1.10 mmol) in dry Et_2O (10 ml) under Ar, and the mixture was stirred overnight. The reaction was then diluted with

Et_2O and washed with 10% NaOH, saturated NH_4Cl solution and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product purified by flash chromatography (eluent hexane–EtOAc 4 : 1) to obtain **11a** as a viscous oil (2.4 g, 92%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.99 (s, 9H), 1.88–2.21 (m, 2H), 2.85–3.14 (m, 4H), 3.82 (s, 3H), 5.12 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.92 (dd, J = 2.0, 8.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.6, 18.4, 25.1, 25.7, 32.2, 51.4, 55.5, 111.6, 120.1, 120.8, 132.4, 145.1, 150.9. EIMS m/z (relative intensity): 356 (M^+, 5%), 299 (100), 284 (20), 210 (80) 179 (10). HRMS (EI) m/z calcd for $C_{13}H_{19}O_2SiS_2$ $(M-57)^+$, 299.0596; found, 299.0610.

2-(3-*tert*-Butyldimethylsilanyloxyphenyl)-1,3-dithiane (11c). Following the same procedure as for **11a**, compound **11c** was prepared in 90% yield as a viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.98 (s, 9H), 1.83–2.22 (m, 2H), 2.84–3.13 (m, 4H), 5.10 (s, 1H), 6.77 (ddd, J = 1.2, 2.4, 8.0 Hz, 1H), 6.97 (t, J = 2.0 Hz, 1H), 7.05 (dt, J = 1.2, 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.4, 18.2, 25.1, 25.7, 32.1, 51.3, 119.6, 120.1, 120.6, 129.6, 140.4, 155.8. EIMS m/z (relative intensity): 326 (M^+, 80%), 269 (60), 195 (90). HRMS (EI) m/z calcd for $C_{16}H_{26}OSiS_2$ (M^+), 326.1194; found, 326.1183.

2-(3-*tert*-Butyldimethylsilanyloxy-4-methoxyphenyl)-1,3-dithiane (11d). Following the same procedure as for **11a**, compound **11d** was prepared in 89% yield as a white solid: mp 101 °C (hexane). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.99 (s, 9H), 1.81–2.21 (m, 2H), 2.83–3.12 (m, 4H), 3.78 (s, 3H), 5.07 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 2.0, 8.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.6, 18.4, 25.1, 25.7, 32.2, 50.8, 55.5, 112.0, 120.5, 120.9, 131.6, 145.0, 151.0. EIMS m/z (relative intensity): 356 (M^+, 5%), 299 (100), 284 (15), 210 (60) 179 (10). HRMS (EI) m/z calcd for $C_{13}H_{19}O_2SiS_2$ $(M-57)^+$, 299.0596; found, 299.0585.

(3*R*,4*R*)-3-[(Propane-1,3-diyldithio)-(4-*tert*-butyldimethylsilanyloxy-3-methoxyphenyl)methyl]-4-[(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methyl-1-cyclohexyloxy]butano-4-lactone (16a). To a solution of thioacetal **11a** (750 mg, 2.10 mmol) in THF (20 ml) at −78 °C under Ar, a solution of *n*-BuLi in hexane (1.3 M, 1.80 ml, 2.34 mmol) was added dropwise and the mixture was stirred for 1 h. Then DMPU (0.40 ml, 4.65 mmol) was added dropwise followed by slow addition of **12** (550 mg, 2.31 mmol) in THF (5 ml). The reaction was stirred for 2 h at the same temperature and then quenched with saturated NH_4Cl and extracted with Et_2O. Organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound purified by flash chromatography (eluent CH_2Cl_2 to CH_2Cl_2–EtOAc 15 : 1) to obtain **16a** as an amorphous solid (1.10 g, 88%): $[\alpha]_D^{27}$ −57.0° (c 1.0, $CHCl_3$); IR (thin film) ν_{max} 1788 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.67–0.98 (m, 3H), 0.73 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.00 (s, 9H), 1.10–1.15 (m, 1H), 1.30–1.32 (m, 1H), 1.56–1.60 (m, 2H), 1.81–2.02 (m, 4H), 2.60 (dd, J = 9.9, 18.4 Hz, 1H), 2.65–2.78 (m, 5H), 2.84 (dd, J = 3.6, 18.4 Hz, 1H), 3.42 (dt, J = 4.2, 10.7 Hz, 1H), 3.82 (s, 3H), 5.79 (d, J = 1.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 2.4, 8.4 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, 15.6, 18.4, 20.9, 22.3, 23.1, 24.6, 25.4, 25.7, 27.0, 27.2, 30.2, 31.3, 34.3, 39.6, 47.7, 54.2, 55.8, 60.9, 77.4, 101.1, 113.3, 120.7, 122.4, 132.2, 144.7, 151.2, 175.5; EIMS m/z (relative intensity): 594 (M^+, 1%), 579 (9), 537 (100), 399 (50) 355 (80), 299 (60), 210 (40); HRMS (EI) m/z calcd for $C_{27}H_{41}O_5SiS_2$ $(M-57)^+$, 537.2165; found, 537.2134.

(3*R*,4*R*)-3-[(Propane-1,3-diyldithio)-(3,4-dimethoxyphenyl)-methyl]-4-[(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methyl-1-cyclohexyloxy]butano-4-lactone (16b). Following the same procedure as for **16a**, compound **16b** was prepared in 82% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2 to CH_2Cl_2–EtOAc 15 : 1): $[\alpha]_D^{26}$ −71.4° (c 1.0, $CHCl_3$); IR (thin film) ν_{max} 1786 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60–0.96 (m, 3H), 0.71 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 1.07–1.12 (m, 1H), 1.24–1.29 (m, 1H), 1.55–1.61 (m, 2H), 1.79–1.99 (m, 4H), 2.60 (dd, J = 10.5, 18.5 Hz, 1H), 2.65–2.77 (m, 5H), 2.84 (dd, J = 3.8, 18.5 Hz, 1H), 3.39 (dt, J = 4.0, 10.6 Hz, 1H), 5.75 (s, 1H), 6.87 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.50 (dd, J = 2.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 20.8, 22.1, 23.0, 24.5, 25.3, 26.9, 27.10, 30.0, 31.2, 34.2, 39.6, 47.6, 54.1, 55.8, 56.1, 60.7, 77.6, 101.2, 110.8, 112.3, 122.3, 131.2, 148.5, 149.2, 175.3; EIMS m/z (relative intensity): 494 (M^+, 100%), 310 (60), 256 (100), 236 (100), 208 (100), 176 (90), 139 (40). HRMS (EI) m/z calcd for $C_{26}H_{38}O_5S_2$ (M^+), 494.2160; found, 494.2155.

(3*R*,4*R*)-3-[(Propane-1,3-diyldithio)-(3-*tert*-butyldimethylsilanyloxyphenyl)methyl]-4-[(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methyl-1-cyclohexyloxy]butano-4-lactone (16c). Following the same procedure as for **16a**, compound **16c** was prepared in 75% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2): $[\alpha]_D^{26}$ −70° (c 1.0, $CHCl_3$); IR (thin film) ν_{max} 1789 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.22 (s, 6H), 0.60–0.98 (m, 3H), 0.72 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.1 Hz, 3H), 1.00 (s, 9H), 1.08–1.13 (m, 1H), 1.26–1.32 (m, 1H), 1.56–1.64 (m, 2H), 1.84–2.00 (m, 4H), 2.63 (dd, J = 10.0, 18.4 Hz, 1H), 2.65–2.78 (m, 5H), 2.87 (dd, J = 3.5, 18.4 Hz, 1H), 3.39 (dt, J = 4.2, 10.7 Hz, 1H), 5.73 (d, J = 1.5 Hz, 1H), 6.79 (ddd, J = 0.9, 2.4, 8.6 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 2.0 Hz, 1H), 7.55 (ddd, J = 0.9, 2.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.3, 15.6, 18.3, 20.8, 22.2, 23.1, 24.5, 25.4, 25.7, 27.0, 27.1, 30.1, 31.3, 34.3, 39.6, 47.6, 54.0, 60.6, 77.6, 101.1, 119.7, 121.1, 122.5, 129.8, 140.7, 156.4, 175.4; EIMS m/z (relative intensity): 564 (M^+, 1%), 507 (100), 369 (80), 325 (70), 217 (50). HRMS (EI) m/z calcd for $C_{26}H_{39}O_4SiS_2$ $(M-57)^+$, 507.2059; found, 507.2044.

(3*R*,4*R*)-3-[(Propane-1,3-diyldithio)-(3-*tert*-butyldimethylsilanyloxy-4-methoxyphenyl)methyl]-4-[(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methyl-1-cyclohexyloxy]butano-4-lactone (16d). Following the same procedure as for **16a**, compound **16d** was prepared in 81% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2 to CH_2Cl_2–EtOAc 15 : 1): $[\alpha]_D^{26}$ −76.6° (c 1.0, $CHCl_3$); IR (thin film) ν_{max} 1789 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.63–0.99 (m, 3H), 0.72 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.00 (s, 9H), 1.09–1.14 (m, 1H), 1.25–1.32 (m, 1H), 1.56–1.62 (m, 2H), 1.83–2.00 (m, 4H), 2.63 (dd, J = 10.0, 18.4 Hz, 1H), 2.65–2.77 (m, 5H), 2.85 (dd, J = 3.4, 18.4 Hz, 1H), 3.39 (dt, J = 4.2, 10.6 Hz, 1H), 3.82 (s, 3H), 5.74 (d, J = 1.4 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.48 (dd, J = 2.5, 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, 15.7, 18.5, 20.9, 22.2, 23.1,

24.7, 25.4, 25.8, 27.0, 27.1, 31.0, 31.3, 34.3, 39.7, 47.7, 54.0, 55.5, 60.3, 77.5, 101.1, 111.7, 122.0, 123.2, 131.0, 145.3, 150.6, 175.5; EIMS *m/z* (relative intensity): 594 (M^+, 1%), 579 (3), 537 (100), 399 (70), 355 (40), 247 (20), 203 (10). HRMS (EI) *m/z* calcd for $C_{27}H_{41}O_5SiS_2$ $(M-57)^+$, 537.2165; found, 537.2199.

(3*R*,4*R*)-3-[(Propane-1,3-diyldithio)-(3,4-methylenedioxyphenyl)-methyl]-4-[(1*R*,2*S*,5*R*)-2-(1-methylethyl)-5-methyl-1-cyclohexyloxy]-butano-4-lactone (16e). Following the same procedure as for **16a**, compound **16e** was prepared in 80% yield as a white solid after flash chromatography (eluent CH_2Cl_2 to CH_2Cl_2–EtOAc 15 : 1) and trituration with hexane–Et_2O: mp 118–120 °C, (lit.[27] 128 °C): $[\alpha]_D^{25}$ −73.6° (*c* 1.0, $CHCl_3$), (lit.[27] −71.8, *c* 0.96, $CHCl_3$); IR (thin film) ν_{max} 1784 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.62–0.99 (m, 3H), 0.71 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 6.0$ Hz, 3H), 1.08–1.12 (m, 1H), 1.25–1.32 (m, 1H), 1.55–1.62 (m, 2H), 1.78–1.98 (m, 4H), 2.63 (dd, $J = 10.5$, 18.5 Hz, 1H), 2.64–2.77 (m, 5H), 2.85 (dd, $J = 3.5$, 18.5 Hz, 1H), 3.38 (dt, $J = 4.0$, 10.6 Hz, 1H), 5.71 (s, 1H), 5.99 (s, 2H), 6.81 (d, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.47 (dd, $J = 2.0$, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 20.8, 22.1, 23.0, 24.4, 25.3, 26.9, 27.0, 30.0, 31.2, 34.2, 39.6, 47.6, 54.1, 60.6, 77.6, 101.1, 101.4, 108.0, 109.6, 123.4, 132.8, 147.1, 148.5, 175.3; EIMS *m/z* (relative intensity): 478 (M^+, 60%), 294 (40), 256 (60), 239 (90), 220 (60), 166 (95), 149 (100). HRMS (EI) *m/z* calcd for $C_{25}H_{34}O_5S_2$ (M^+), 478.1847; found, 478.1828.

(3*R*)-3-[(Propane-1,3-diyldithio)-(4-*tert*-butyldimethylsilanyloxy-3-methoxyphenyl)methyl]butano-4-lactone (17a). To a solution of **16a** (720 mg, 1.21 mmol) and $NaBH_4$ (320 mg, 8.47 mmol) in EtOH (98%) at 0 °C under Ar, a solution of KOH in 98% EtOH (0.4 M, 4.5 ml, 1.80 mmol) was slowly added *via* syringe. The mixture was stirred at 0 °C for 1 h and then at room temperature for a further 2 h. The mixture was then gently poured into a saturated NH_4Cl solution containing ice and acidified (pH 5–6) with 0.1 N HCl. The mixture was extracted with EtOAc and the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude compound was dissolved in CH_2Cl_2 and allowed to cyclize overnight. After solvent removal, the crude compound was purified by flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1) to obtain **17a** as an amorphous solid (410 mg, 71%): $[\alpha]_D^{24}$ +6.6° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 6H), 1.00 (s, 9H), 1.87–1.98 (m, 2H), 2.41 (dd, $J = 9.1$, 17.9 Hz, 1H), 2.66–2.74 (m, 4H), 2.85 (dd, $J = 9.2$, 17.9 Hz, 1H), 3.00–3.05 (m, 1H), 3.82 (s, 3H), 4.18 (dd, $J = 8.2$, 9.5 Hz, 1H), 4.42 (dd, $J = 8.1$, 9.5 Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 2.4$, 8.4 Hz, 1H), 7.47 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.4, 24.8, 25.7, 27.2, 30.2, 48.2, 55.7, 60.8, 68.6, 113.0, 120.9, 121.9, 132.2, 144.7, 151.2, 175.8; EIMS *m/z* (relative intensity): 440 (M^+, <1%), 425 (6), 383 (100), 355 (70), 283 (65), 235 (60), 209 (60), 149 (40), 73 (50); HRMS (EI) *m/z* calcd for $C_{17}H_{23}O_4SiS_2$ $(M-57)^+$, 383.0807; found, 383.0821.

(3*R*)-3-[(Propane-1,3-diyldithio)-(3,4-dimethoxyphenyl)methyl]-butano-4-lactone (17b). Following the same procedure as for **17a**, compound **17b** was prepared in 60% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{28}$ +10.2° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.85–1.99 (m, 2H), 2.43 (dd, $J = 9.3$, 18.0 Hz, 1H), 2.65–2.79 (m, 4H), 2.87 (dd, $J = 9.3$, 18.0 Hz, 1H), 2.99–3.10 (m, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 4.19 (dd, $J = 8.2$, 9.5 Hz, 1H), 4.43 (dd, $J = 8.0$, 9.5 Hz, 1H), 6.89 (d, $J = 9.0$ Hz, 1H), 7.48–7.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 27.2, 30.2, 48.2, 55.9, 56.1, 60.8, 68.6, 111.1, 112.3, 122.0, 131.3, 148.5, 149.3, 175.8; EIMS *m/z* (relative intensity): 340 (M^+, 90%), 255 (100), 181 (80); HRMS (EI) *m/z* calcd for $C_{16}H_{20}O4S_2$ (M^+), 340.0803; found, 340.0796.

(3*R*)-3-[(Propane-1,3-diyldithio)-(3-*tert*-butyldimethylsilanyloxy-phenyl)methyl]butano-4-lactone (17c). Following the same procedure as for **17a**, compound **17c** was prepared in 64% yield as a viscous oil after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{28}$ +13.2° (*c* 0.09, $CHCl_3$); IR (thin film) ν_{max} 1789 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.99 (s, 9H), 1.87–1.97 (m, 2H), 2.41 (dd, $J = 9.1$, 17.9 Hz, 1H), 2.66–2.75 (m, 4H), 2.83 (dd, $J = 9.4$, 17.9 Hz, 1H), 2.98–3.05 (m, 1H), 4.18 (dd, $J = 8.3$, 9.4 Hz, 1H), 4.41 (dd, $J = 8.3$, 9.4 Hz, 1H), 6.80 (dd, $J = 2.0$, 8.0 Hz, 1H), 7.28 (t, $J = 8.0$ Hz, 1H), 7.46 (t, $J = 2.0$ Hz, 1H), 7.54 (ddd, $J = 0.8$, 2.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.3, 18.3, 24.8, 25.7, 27.2, 30.2, 48.0, 60.6, 68.5, 119.7, 120.7, 122.0, 130.1, 140.9, 156.5, 175.7; EIMS *m/z* (relative intensity): 410 (M^+, <1%), 353 (65), 325 (50), 249 (90), 216 (80), 149 (30); HRMS (EI) *m/z* calcd for $C_{16}H_{21}O_3SiS_2$ $(M-57)^+$, 353.0701; found, 353.0693.

(3*R*)-3-[(Propane-1,3-diyldithio)-(3-*tert*-butyldimethylsilanyloxy-4-methoxyphenyl)methyl]butano-4-lactone (17d). Following the same procedure as for **17a**, compound **17d** was prepared in 63% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{24}$ +6.9° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 6H), 1.00 (s, 9H), 1.84–1.98 (m, 2H), 2.41 (dd, $J = 9.1$, 17.9 Hz, 1H), 2.64–2.76 (m, 4H), 2.83 (dd, $J = 9.2$, 17.9 Hz, 1H), 2.98–3.05 (m, 1H), 3.83 (s, 3H), 4.18 (dd, $J = 8.3$, 9.5 Hz, 1H), 4.40 (dd, $J = 8.2$, 9.5 Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 1H), 7.45 (d, $J = 2.5$ Hz, 1H), 7.48 (dd, $J = 2.5$, 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.5, 24.9, 25.7, 27.2, 30.2, 48.2, 55.6, 60.3, 68.6, 112.0, 121.7, 122.8, 131.2, 145.3, 150.5, 175.8; EIMS *m/z* (relative intensity): 440 (M^+, <1%), 425 (2), 383 (100), 355 (70), 263 (70), 247 (65), 209 (30), 149 (20), 73 (15); HRMS (EI) *m/z* calcd for $C_{17}H_{23}O_4SiS_2$ $(M-57)^+$, 383.0807; found, 383.0782.

(3*R*)-3-[(Propane-1,3-diyldithio)-(3,4-methylenedioxyphenyl)-methyl]butano-4-lactone (17e). Following the same procedure as for **17a**, compound **17e** was prepared in 82% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{28}$ +10.5° (*c* 1.0, $CHCl_3$), (lit.[27] $[\alpha]_D^{25}$ +10.2°, *c* 0.51, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 27.2, 30.2, 48.2, 60.6, 68.5, 101.5, 108.3, 109.3, 123.1, 132.9, 147.2, 148.6, 175.7; IR, ^1H NMR and EIMS were in agreement with reported data.[27]; HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_4S_2$ (M^+), 324.0490; found, 324.0503.

(8*R*,8′*R*)-4,4′-Bis(*tert*-butyldimethylsilanyloxy)-3,3′-dimethoxy-7′-(propane-1,3-diyldithio)lignano-9,9′-lactone (15a). A solution of **17a** (394 mg, 0.90 mmol) in THF (2 ml) was added dropwise to a solution of LDA (0.98 mmol, 1.1 eq.) in THF (1 ml) under Ar at −78 °C. The reaction mixture was stirred for 2 h and then DMI (0,11 ml, 0.98 mmol) was added dropwise followed by a solution of benzylic bromide **13a** (324 mg, 0.98 mmol) in THF

(2 ml). The reaction mixture was stirred at the same temperature for 3 h and then left to reach the ambient temperature overnight. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. Organic phase was dried over anhydrous Na_2SO_4, filtered, evaporated and the crude compound was purified by flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1) to obtain **15a** as an amorphous solid (340 mg, 68%): $[\alpha]_D^{25}$ +60.2° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.18 (s, 3H), 0.18 (s, 3H), 0.98 (s, 9H), 1.00 (s, 9H), 1.83–1.95 (m, 2H), 2.30 (dd, J = 5.7, 14.0 Hz, 1H), 2.58–2.72 (m, 5H), 3.19 (dd, J = 4.5, 14.0 Hz, 1H), 3.18–3.21 (m, 1H), 3.72 (dd, J = 9.1, 9.8 Hz, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 4.45 (dd, J = 5.6, 9.8 Hz, 1H), 6.40 (dd, J = 2.0, 8.0 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 2.4, 8.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.6, 18.4, 24.8, 25.7, 27.1, 27.2, 35.7, 42.6, 49.9, 55.4, 55.7, 62.3, 67.6, 113.3, 113.4, 120.6, 121.0, 122.0 122.1, 130.3, 132.6, 143.9, 144.7, 150.9, 151.2, 178.7; EIMS m/z (relative intensity): 690 (M^+, 10%), 675 (5), 633 (100), 513 (50), 355 (80), 179 (90); HRMS (EI) m/z calcd for $C_{31}H_{45}O_6Si_2S_2$ $(M-57)^+$, 633.2196; found, 633.2224.

(8*R*,8′*R*)-4-(*tert*-Butyldimethylsilanyloxy)-3,3′,4′-trimethoxy-7′-(propane-1,3-diyldithio)-lignano-9,9′-lactone (15b). Following the same procedure as for **15a**, but using lithium hexamethyldisilazide (LHMDS, 1.6 M in THF, 1.1 eq.) in place of LDA, compound **15b** was prepared from **17b** and **13a** in 78% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2); $[\alpha]_D^{28}$ +68.9° (*c* 0.66 $CHCl_3$); IR (thin film) ν_{max} 1770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.98 (s, 9H), 1.82–1.96 (m, 2H), 2.45 (dd, J = 5.2, 14.0 Hz, 1H), 2.58–2.74 (m, 5H), 2.98 (dd, J = 5.0, 14.0 Hz, 1H), 3.15–3.19 (m, 1H), 3.73 (s, 3H), 3.77 (dd, J = 9.0, 10.0 Hz, 1H), 3.88 (s, 3H), 3.92 (s, 3H), 4.52 (dd, J = 5.2, 10.0 Hz, 1H), 6.40 (dd, J = 2.0, 8.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 7.43 (dd, J = 2.0, 8.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, 18.4, 24.7, 25.7, 27.0, 27.1, 35.9, 42.8, 50.1, 55.3, 55.9, 60.0, 62.2, 67.6, 111.0, 112.4, 113.1, 120.6, 122.0, 122.1, 130.2, 131.5, 143.9, 148.4, 149.1, 150.9, 178.7; EIMS m/z (relative intensity): 590 (M^+, 30%), 533 (100), 255 (100), 179 (60); HRMS (EI) m/z calcd for $C_{26}H_{33}O_6SiS_2$ $(M-57)^+$, 533.1487; found, 533.1461.

(8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-7′-(propane-1,3-diyldithio)lignano-9,9′-lactone (15c). Following the same procedure as for **15a**, but using LHMDS (1.6 M in THF, 1.1 eq.) in place of LDA, compound **15c** was prepared from **17c** and **13b** in 71% yield as viscous oil after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{24}$ +54.5° (*c* 0.19, $CHCl_3$); IR (thin film) ν_{max} 1771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.18 (s, 3H), 0.21 (s, 6H), 0.97 (s, 9H), 1.0 (s, 9H), 1.82–1.96 (m, 2H), 2.40 (dd, J = 5.7, 13.8 Hz, 1H), 2.59–2.72 (m, 5H), 3.04 (dd, J = 4.8, 13.8 Hz, 1H), 3.22–3.25 (m, 1H), 3.67 (dd, J = 8.9, 9.8 Hz, 1H), 4.45 (dd, J = 5.3, 9.8 Hz, 1H), 6.58 (t, J = 1.9 Hz, 1H), 6.62 (br d, J = 7.6 Hz, 1H), 6.69 (ddd, J = 0.8, 2.4, 8.0 Hz, 1H), 6.80 (ddd, J = 0.8, 2.4, 8.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 2.0 Hz, 1H), 7.53 (ddd, J = 0.8, 2.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.4, −4.3, 18.2, 18.3, 24.6, 25.7, 27.0, 27.1, 36.0, 42.6, 49.8, 62.1, 67.3, 118.9, 119.6, 121.0, 121.3, 122.2, 122.9, 129.4, 130.0, 138.2, 141.0, 155.8, 156.5, 178.3; EIMS m/z (relative intensity): 630 (M^+, 2%), 573 (70), 449 (60), 325 (100), 251 (15), 149 (20); HRMS (EI) m/z calcd for $C_{29}H_{41}O_4Si_2S_2$ $(M-57)^+$, 573.1984; found, 573.1971.

(8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-4,4′-dimethoxy-7′-(propane-1,3-diyldithio)lignano-9,9′-lactone (15d). Following the same procedure as for **15a**, compound **15d** was prepared from **17d** and **13c** in 65% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2–MeOH 100 : 1): $[\alpha]_D^{24}$ +67.5° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.17 (s, 3H), 0.18 (s, 3H), 0.99 (s, 9H), 1.01 (s, 9H), 1.82–1.95 (m, 2H), 2.35 (dd, J = 5.5, 13.9 Hz, 1H), 2.58–2.72 (m, 5H), 3.00 (dd, J = 4.7, 13.9 Hz, 1H), 3.16–3.19 (m, 1H), 3.63 (dd, J = 9.0, 9.8 Hz, 1H), 3.76 (s, 3H), 3.83 (s, 3H), 4.43 (dd, J = 5.1, 9.8 Hz, 1H), 6.59 (dd, J = 2.1, 8.2 Hz, 1H), 6.62 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 2.5, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.4, 18.5, 24.8, 25.7, 27.0, 27.1, 35.5, 42.8, 50.0, 55.4, 55.5, 61.8, 67.4, 111.9, 112.0, 121.9, 122.3, 122.9, 123.0, 129.2, 131.4, 144.9, 145.2, 150.0, 150.4, 178.5; EIMS m/z (relative intensity): 690 (M^+, 15%), 675 (10), 633 (80), 513 (60), 355 (60), 251 (50), 179 (100); HRMS (EI) m/z calcd for $C_{31}H_{45}O_6Si_2S_2$ $(M-57)^+$, 633.2196; found, 633.2225.

(8*R*,8′*R*)-4,4′,5,5′-Bis(methylenedioxy)-7′-(propane-1,3-diyldithio)-lignano-9,9′-lactone (15e). Following the same procedure as for **15a**, but using LHMDS (1.6 M in THF, 1.1 eq.) in place of LDA, compound **15e** was prepared from **17e** and **13d** in 66% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2): $[\alpha]_D^{27}$ +35° (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 1769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.81–1.97 (m, 2H), 2.58 (dd, J = 5.2, 14.0 Hz, 1H), 2.60–2.75 (m, 5H), 2.84 (dd, J = 6.5, 14.0 Hz, 1H), 3.04–3.08 (m, 1H), 3.95 (dd, J = 8.5, 10.0 Hz, 1H), 4.62 (dd, J = 5.0, 10.0 Hz, 1H), 5.91 (part A of AB system, J = 1.5 Hz, 1H), 5.94 (part B of AB system, J = 1.5 Hz, 1H), 6.00 (part A of AB system, J = 1.5 Hz, 1H), 6.03 (part B of AB system, J = 1.5 Hz, 1H), 6.45 (dd, J = 1.5, 8.0 Hz, 1H), 6.48 (d, J = 1.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 2.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 26.9, 27.1, 36.2, 42.9, 50.4, 62.3, 67.7, 101.9, 101.6, 108.0, 108.1, 109.5, 109.7, 122.6, 123.3, 130.4, 133.0, 146.4, 147.1, 147.6, 148.5, 178.3; EIMS m/z (relative intensity): 458 (M^+, 40%), 383 (10), 239 (100), 192 (30), 135 (50); HRMS (EI) m/z calcd for $C_{23}H_{22}O_6S_2$ (M^+), 458.0857; found, 458.0880.

(8*R*,8′*R*)-4,4′-Bis(*tert*-butyldimethylsilanyloxy)-3,3′-dimethoxy-7′-oxolignano-9,9′-lactone (18a). $(CF_3CO_2)_2IPh$ (470 mg, 1.09 mmol) was added to a solution of **15a** (250 mg, 0.36 mmol) in 10% aq. CH_3CN (5 ml) at room temperature. The mixture was stirred for 30 min and then quenched with saturated $NaHCO_3$ 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 80 : 1) to obtain **18a** (118 mg, 55%) as a viscous oil: $[\alpha]_D^{24}$ +19.3° (*c* 0.28, $CHCl_3$), (lit.[12]: $[\alpha]_D^{20}$ +16.7° *c* 0.96, $CHCl_3$); EIMS m/z (relative intensity): 600 (M^+, 2%), 543 (100), 291 (10), 193 (40), 179 (35); HRMS (EI) m/z calcd for $C_{32}H_{48}O_7Si_2$ (M^+), 600.2939; found, 600.2901; ^1H NMR and ^{13}C NMR ($CDCl_3$) were in agreement with reported data.[12]

(8*R*,8′*R*)-4-*tert*-Butyldimethylsilanyloxy-3,3′,4′-trimethoxy-7′-oxolignano-9,9′-lactone (18b). Following the same procedure as for **18a**, compound **18b** was prepared in 50% yield as an amorphous solid after flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1): $[\alpha]_D^{27}$ +13.8° (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 1772, 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.97 (s, 9H), 3.00 (dd, J = 7.5, 14.0 Hz, 1H), 3.05 (dd, J = 5.5, 14.0 Hz, 1H), 3.50–3.54 (m, 1H), 3.65 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 4.05 (apparent t, J = 8.2 Hz, 1H), 4.08–4.13 (m, 1H), 4.35 (apparent t, J = 8.2 Hz, 1H), 6.53 (dd, J = 1.8, 8.0 Hz, 1H), 6.60 (d, J = 1.8 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 1.8, 8.0 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.7, 18.4, 25.7, 34.5, 44.5, 46.4, 55.2, 56.0, 56.1, 68.2, 109.9, 110.3, 113.0, 120.8, 121.7, 122.9, 128.7, 130.5, 144.0, 149.5, 151.0, 154.2, 177.3, 194.9; EIMS m/z (relative intensity): 500 (M^+, 5%), 443 (100), 236 (80), 179 (90), 165 (50); HRMS (EI) m/z calcd for $C_{27}H_{36}O_7Si$ (M^+), 500.2230; found, 500.2245.

(8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-7′-oxolignano-9,9′-lactone (18c). Following the same procedure as for **18a**, compound **18c** was prepared in 70% yield as a viscous oil after flash chromatography (eluent CH_2Cl_2–Et_2O 80 : 1): $[\alpha]_D^{24}$ +25.9° (*c* 1.77, $CHCl_3$); IR (thin film) ν_{max} 1778, 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.21 (s, 6H), 0.95 (s, 9H), 0.99 (s, 9H), 3.01 (dd, J = 6.5, 14.0 Hz, 1H), 3.07 (dd, J = 6.0, 14.0 Hz, 1H), 3.51–3.55 (m, 1H), 4.01–4.06 (m, 1H), 4.10 (apparent t, J = 8.5 Hz, 1H), 4.36 (apparent t, J = 8.5 Hz, 1H), 6.63–6.70 (m, 3H), 7.03–7.07 (m, 2H), 7.22–7.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.4, 18.1, 18.2, 25.5, 25.6, 34.8, 43.8, 47.0, 68.0, 118.8, 119.4, 120.9, 121.3, 122.3, 129.7, 129.9, 136.8, 138.4, 156.0, 156.3, 177.1, 196.0; EIMS m/z (relative intensity): 540 (M^+, 20%), 483 (100), 275 (80), 235 (70), 73 (80); HRMS (EI) m/z calcd for $C_{26}H_{35}O_5Si_2$ (M-57)$^+$, 483.2023; found, 483.2027.

(8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-4,4′-dimethoxy-7′-oxolignano-9,9′-lactone (18d). Following the same procedure as for **18a**, compound **18d** was prepared in 57% yield as a viscous oil after flash chromatography (eluent CH_2Cl_2–Et_2O 80 : 1): $[\alpha]_D^{24}$ +28.4° (*c* 0.45, $CHCl_3$); IR (thin film) ν_{max} 1775, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.16 (s, 6H), 0.96 (s, 9H), 1.00 (s, 9H), 2.96 (dd, J = 5.7, 14.2 Hz, 1H), 3.00 (dd, J = 6.3, 14.2 Hz, 1H), 3.49 (apparent dt, J = 6.0, 8.5 Hz, 1H), 3.74 (s, 3H), 3.87 (s, 3H), 3.99–4.04 (m, 1H), 4.08 (apparent t, J = 8.6 Hz, 1H), 4.30 (apparent t, J = 8.6 Hz, 1H), 6.64–6.68 (m, 3H), 6.81 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 2.2, 8.5 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.6, 18.3, 18.4, 25.6, 25.7, 34.0, 44.0, 46.3, 55.4, 55.5, 68.1, 110.9, 112.2, 120.3, 122.2, 122.5, 123.5, 128.7, 145.1, 145.4, 150.0, 156.2, 177.4, 194.6; EIMS m/z (relative intensity): 600 (M^+, 2%), 585 (3), 543 (100), 305 (20), 179 (45); HRMS (EI) m/z calcd for $C_{32}H_{48}O_7Si_2$ (M^+), 600.2939; found, 600.2955.

(8*R*,8′*R*)-4,4′,5,5′-Bis(methylenedioxy)-7′-oxolignano-9,9′-lactone (18e). Following the same procedure as for **18a**, compound **18e** was prepared in 80% yield as a white solid after flash chromatography (eluent CH_2Cl_2–Et_2O 20 : 1) and trituration with hexane: mp 90–92 °C, (lit.[5] 113–115 °C); $[\alpha]_D^{28}$ +26.5° (*c* 0.33, $CHCl_3$); IR (thin film) ν_{max} 1769, 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.91 (dd, J = 7.5, 14.0 Hz, 1H), 3.05 (dd, J = 5.5, 14.0 Hz, 1H), 3.40–3.48 (m, 1H), 3.98–4.04 (m, 1H), 4.13 (apparent t, J = 8.5 Hz, 1H), 4.39 (apparent t, J = 8.5 Hz, 1H), 5.89 (d, J = 1.5 Hz, 2H), 6.06 (s, 2H), 6.52 (dd, J = 1.0, 8.0 Hz, 1H), 6.60 (d, J = 1.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 1.5 Hz, 1H), 7.27 (dd, J = 1.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 34.6, 44.8, 46.7, 68.1, 101.0, 102.1, 107.9, 108.0, 108.2, 109.6, 122.5, 124.8, 130.3, 130.7, 146.6, 147.9, 148.5, 152.6, 176.7, 194.5; EIMS m/z (relative intensity): 368 (M^+, 30%), 192 (40), 149 (40), 81 (50), 69 (100); HRMS (EI) m/z calcd for $C_{20}H_{16}O_7$ (M^+), 368.0896; found, 368.0879.

(7′*S*,8*R*,8′*R*)-4,4′-Bis(*tert*-butyldimethylsilanyloxy)-7′-hydroxy-3,3′-dimethoxylignano-9,9′-lactone (19a) and (2*R*,3*R*,4*S*)-2-(4-*tert*-butyldimethylsilanyloxy-3-methoxyphenyl)methyl-3-hydroxymethyl-4-(4-*tert*-butyldimethylsilanyloxy-3-methoxyphenyl)butano-4-lactone (20a). L-Selectride® (1 M in THF, 0.10 ml, 0.10 mmol) was added dropwise to a solution of **16a** (50 mg, 0.083 mmol) in dry THF (1.5 ml) under Ar at −78 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction was then stopped with saturated NH_4Cl and extracted with EtOAc. Organic phase was washed with oxalic acid 0.1 N, dried over anhydrous Na_2SO_4, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–EtOAc 5 : 1) to yield 35 mg (70%) of compound **19a** (ds 97%) as a viscous oil and 4.5 mg (9%) of compound **20a** as an amorphous solid.

Compound **19a**: $[\alpha]_D^{27}$ −0.8° (*c* 0.4, $CHCl_3$), lit.[12] $[\alpha]_D^{19}$ −1.5° (*c* 0.95, $CHCl_3$); EIMS m/z (relative intensity): 602 (M^+, 2%), 600 (2), 585 (5), 543 (100), 277 (20), 179 (50); HRMS (EI) m/z calcd for $C_{32}H_{50}O_7Si_2$ (M^+), 602.3095; found, 602.3116; IR, ^1H NMR and ^{13}C NMR ($CDCl_3$) were in agreement with reported data.[12]

Compound **20a**: $[\alpha]_D^{24}$ +37.5° (*c* 0.3, $CHCl_3$); IR (thin film) ν_{max} 3486, 1769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.15 (s, 6H), 0.98 (s, 9H), 0.99 (s, 9H), 2.59–2.63 (m, 1H), 2.75 (dd, J = 10.6, 15.1 Hz, 1H), 3.09 (ddd, J = 4.5, 8.2, 10.6 Hz, 1H), 3.23 (dd, J = 4.5, 15.1 Hz, 1H), 3.73–3.78 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 3.93 (dd, J = 4.0, 10.5 Hz, 1H), 5.45 (d, J = 2.6 Hz, 1H), 6.65 (dd, J = 2.0, 8.0 Hz, 1H), 6.71–6.73 (m, 2H), 6.74–6.77 (m, 2H), 6.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.4, 25.7, 30.8, 41.3, 47.6, 55.6, 55.6, 60.7, 81.1, 109.0, 112.4, 117.3, 120.2, 120.9, 120.9, 132.0, 132.3, 143.8, 145.0, 151.0, 151.2, 178.1; EIMS m/z (relative intensity): 602 (M^+, 5%), 545 (90), 543 (50), 277 (20), 179 (100); HRMS (EI) m/z calcd for $C_{32}H_{50}O_7Si_2$ (M^+), 602.3095; found, 602.3124.

(7′*S*,8*R*,8′*R*)-4-*tert*-Butyldimethylsilanyloxy-7′-hydroxy-3,3′,4′-trimethoxylignano-9,9′-lactone (19b). Following the same procedure as for **19a**, compound **19b** was prepared in 75% yield (ds 93%) after flash chromatography (eluent CH_2Cl_2–Et_2O 8 : 1) as a viscous oil: IR (thin film) ν_{max} 3497, 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer 7′*S*) δ 0.14 (s, 6H), 0.99 (s, 9H), 2.60–2.65 (m, 1H), 2.92 (dd, J = 5.5, 13.5 Hz, 1H), 2.95–2.98 (m, 1H), 3.08 (dd, J = 5.2, 13.5 Hz, 1H), 3.75 (s, 3H), 3.82 (apparent t, J = 9.0 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (dd, J = 6.5, 9.5 Hz, 1H), 4.61 (dd, J = 2.8, 6.8 Hz, 1H), 6.58 (dd, J = 2.0, 8.5 Hz, 1H), 6.68 (d, J = 1.0 Hz, 1H), 6.73 (dd, J = 2.0, 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer 7′*S*) δ −4.7, 18.4, 25.7, 35.2, 43.9, 45.1, 55.4, 55.9,

68.3, 75.4, 109.0, 111.2, 113.4, 118.4, 120.6, 122.0, 131.0, 134.0, 143.8, 149.1, 149.3, 150.9, 179.1; EIMS *m/z* (relative intensity): 502 (M^+, 10%), 445 (100), 193 (40), 179 (70), 167 (40); HRMS (EI) *m/z* calcd for $C_{23}H_{29}O_7Si$ (M-57)$^+$, 445.1682; found, 445.1674.

(7′*S*,8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-7′-hydroxylignano-9,9′-lactone (19c). Following the same procedure as for **19a**, compound **19c** was prepared in 77% yield (ds 83%) after flash chromatography (eluent CH_2Cl_2–EtOAc 5 : 1) as a viscous oil: IR (thin film) ν_{max} 3473, 1756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer 7′*S*) δ 0.19 (s, 6H), 0.20 (s, 6H), 0.98 (s, 9H), 0.99 (s, 9H), 2.59–2.65 (m, 1H), 2.87 (dd, J = 6.0, 13.5 Hz, 1H), 2.97–3.01 (m, 1H), 3.11 (dd, J = 5.2, 13.5 Hz, 1H), 3.77 (apparent t, J = 9.0 Hz, 1H), 3.90 (dd, J = 6.8, 9.0 Hz, 1H), 4.60 (dd, J = 2.8, 7.2 Hz, 1H), 6.69–6.83 (m, 4H), 7.11 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer 7′*S*) δ −4.5, −4.4, 18.2, 25.6, 25.7, 35.3, 45.0, 68.1, 75.3, 117.8, 118.6, 119.0, 120.1, 121.4, 122.8, 129.4, 129.9, 139.0, 143.0, 155.8, 156.2, 178.8; EIMS *m/z* (relative intensity): 542 (M^+, 5%), 485 (100), 437 (30), 307 (10), 221 (30); HRMS (EI) *m/z* calcd for $C_{26}H_{37}O_5Si_2$ (M-57)$^+$, 485.2180; found, 485.2152.

(7′*S*,8*R*,8′*R*)-3,3′-Bis(*tert*-butyldimethylsilanyloxy)-7′-hydroxy-4,4′-dimethoxylignano-9,9′-lactone (19d). Following the same procedure as for **19a**, compound **19d** was prepared in 68% yield (ds 88%) after flash chromatography (eluent CH_2Cl_2–EtOAc 5 : 1) as a viscous oil: IR (thin film) ν_{max} 3487, 1761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer 7′*S*) δ 0.14 (s, 6H), 0.15 (s, 6H), 0.99 (s, 9H), 1.00 (s, 9H), 2.57–2.63 (m, 1H), 2.83 (dd, J = 5.5, 13.7 Hz, 1H), 2.93 (dt, J = 5.3, 6.9 Hz, 1H), 3.07 (dd, J = 5.1, 13.7 Hz, 1H), 3.70 (dd, J = 8.4, 9.3 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.83 (dd, J = 6.8, 9.4 Hz, 1H), 4.51 (dd, J = 1.9, 7.4 Hz, 1H), 6.70–6.74 (m, 4H), 6.75–6.77 (m, 2H), 6.78–6.79 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer 7′*S*) δ −4.7, −4.6, 18.4, 25.7, 34.7, 44.1, 45.1, 55.4, 55.4, 68.1, 75.2, 112.0, 112.1, 118.8, 119.5, 122.3, 122.9, 130.1, 134.0, 145.0, 145.3, 149.9, 151.0, 179.0; EIMS *m/z* (relative intensity): 602 (M^+, 4%), 585 (2), 545 (70), 543 (100), 305 (20), 179 (60).

(7′*S*,8*R*,8′*R*)-7′-hydroxy-4,4′,5,5′-bis(methylenedioxy)lignano-9,9′-lactone, [(7′*S*)-parabenzlactone (9)]. Following the same procedure as for **19a**, compound **9** was prepared in 80% yield (ds 96%) after flash chromatography (eluent CH_2Cl_2–Et_2O 8 : 1). Trituration with hexane gave a white solid: mp 155–158 °C, (lit.[5] 159–161 °C); $[a]_D^{22}$ −15.0 °C (*c* 0.3, $CHCl_3$), (lit.[5]-11.0°, *c* 1.15, $CHCl_3$); IR (thin film) ν_{max} 3457, 1754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54–2.60 (m, 1H), 2.90 (dd, J = 6.0, 12.0 Hz, 1H), 2.94–3.00 (m, 2H), 3.91 (m, 2H), 4.61 (dd, J = 2.8, 6.2 Hz, 1H), 5.91 (part A of AB system, J = 1.5 Hz, 1H), 5.93 (part B of AB system, J = 1.5 Hz, 1H), 5.96 (part A of AB system, J = 1.5 Hz, 1H), 5.97 (part B of AB system, J = 1.5 Hz, 1H), 6.58 (dd, J = 1.5, 8.0 Hz, 1H), 6.61 (d, J = 1.0 Hz, 1H), 6.67 (dd, J = 1.0, 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 1.5 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1, 43.7, 45.1, 68.4, 75.5, 100.9, 101.3, 106.2, 108.1, 108.2, 109.9, 119.4, 122.7, 131.2, 135.3, 146.3, 147.5, 147.6, 148.1, 178.9; EIMS *m/z* (relative intensity): 370 (M^+, 90%), 352 (10), 175 (20), 151 (100), 135 (80); HRMS (EI) *m/z* calcd for $C_{20}H_{18}O_7$ (M^+), 370.1052; found, 370.1035.

(7′*S*,8*R*,8′*R*)-4,4′,7′-Trihydroxy-3,3′-dimethoxylignano-9,9′-lactone, [(7′*S*)-hydroxymatairesinol (1)]. A solution of TBAF–AcOH (1 : 1, 1.0 M in THF, 0.30 ml, 0.30 mmol) was added dropwise to a solution of **19a** (18 mg, 0.03 mmol) in dry THF (0.4 ml) under Ar at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then for a further 3 h at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. Organic phase was dried over anhydrous Na_2SO_4, evaporated and the crude product was purified by flash chromatography (eluent CH_2Cl_2–Et_2O 1 : 1) to yield compound **1** (9 mg, 80%) as an amorphous solid: $[a]_D^{24}$ −9.3° (*c* 0.1, THF), (lit.[3] $[a]_D^{25}$ −11.0°, *c* 4, THF); HRMS (EI) *m/z* calcd for $C_{20}H_{22}O_7$ (M^+), 374.1366; found, 374.1345; IR, MS, ^{1}H NMR and ^{13}C NMR ($CDCl_3$) were in agreement with reported data.[12,16]

(7′*S*,8*R*,8′*R*)-4,7′-Dihydroxy-3,3′,4′-trimethoxylignano-9,9′-lactone, [(7′*S*)-hydroxyarctigenin (8)]. Following the same procedure as for **1**, compound **8** was prepared in 65% yield. Flash chromatography (eluent CH_2Cl_2–Et_2O 4 : 1) and HPLC purification gave (7′*S*)-**8** as a glassy material: $[a]_D^{22}$ −23.9° (*c* 0.56, $CHCl_3$), (lit.[12] $[a]_D^{21}$ −22.4°, *c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59–2.67 (m, 1H), 2.90–2.96 (m, 2H), 3.00–3.08 (m, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.91 (apparent t, J = 8.8 Hz, 1H), 3.96 (dd, J = 7.0, 9.5 Hz, 1H), 4.66 (dd, J = 1.5, 6.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.0 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 2.0, 8.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.0, 43.7, 45.0, 55.8, 55.9, 55. 9, 68.4, 75.2, 108.9, 111.0, 111.9, 114.0, 118.1, 122.5, 129.4, 134.0, 144.4, 146.5, 149.0, 149.3, 179.2; EIMS *m/z* (relative intensity): 388 (M^+, 100%), 370 (10), 194 (50), 167 (100), 137 (90); HRMS (EI) *m/z* calcd for $C_{21}H_{24}O_7$ (M^+), 388.1366; found, 388.1519; IR and ^{13}C NMR in agreement with reported data.[12]

(7′*S*,8*R*,8′*R*)-3,3′,7′-Trihydroxylignano-9,9′-lactone, [(7′*S*)-hydroxyenterolactone (5)]. Following the same procedure as for **1**, compound (7′*S*)-**5** was prepared in 60% yield after flash chromatography (eluent CH_2Cl_2–Et_2O 1 : 1) and HPLC as an amorphous solid: $[a]_D^{24}$ −1.32 (*c* 0.31, acetone); HRMS (EI) *m/z* calcd for $C_{18}H_{18}O_5$ (M^+), 314.1154; found, 314.1149; IR, MS, ^{1}H NMR and ^{13}C NMR (acetone-d_6) were in agreement with reported data (for the racemic material).[14]

(7′*S*,8*R*,8′*R*)-3,3′,7′-Trihydroxy-4,4′-dimethoxylignano-9,9′-lactone, [(7′*S*)-hydroxyprestegane B (10)]. Following the same procedure as for **1**, compound (7′*S*)-**10** was prepared in 81% yield after flash chromatography (eluent CH_2Cl_2–Et_2O 1 : 1) and HPLC as an amorphous solid: $[a]_D^{24}$ −1.50 (*c* 0.12, $CHCl_3$); IR (thin film) ν_{max} 3440, 1752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60–2.66 (m, 1H), 2.89–2.95 (m, 2H), 3.01 (dd, J = 8.0, 15.5 Hz, 1H), 3.85–3.88 (m, 1H), 3.87 (s, 3H), 3.89–3.92 (m, 1H), 3.90 (s, 3H), 4.57 (dd, J = 2.3, 6.7 Hz, 1H), 6.66 (dd, J = 2.0, 8.5 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.73–6.75 (m, 2H), 6.79 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9, 44.0, 45.1, 55.9, 56.0, 68.2, 75.4, 110.6, 110.7, 112.1, 115.9, 117.8, 121.2, 130.8, 134.6, 145.4, 145.5, 145.9, 146.6, 178.9; EIMS *m/z* (relative intensity): 374 (M^+, 50%), 356 (20), 298 (10), 232 (10), 177 (15), 153 (80), 137 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{22}O_7$ (M^+), 374.1366; found, 374.1349.

Acknowledgements

We thank the Finnish Academy (48931, 2100633), Bioorganic and Medicinal Chemistry Graduate School and University Research Funds for financial support. BR thanks the Research Foundation of the University of Helsinki and the Research Foundation of Orion Corporation for grants. This work was partially carried out within the EU project PHYTOHEALTH no QLRT-2001-02453. This study does not necessarily reflect the views of the Commission and in no way anticipates the Commission's future policy in this area.

References

1 G. P. Moss, *Pure Appl. Chem.*, 2000, **72**, 1493–1523.
2 D. C. Ayres and J. D. Loike, *Lignans: Chemical, Biological and Clinical Properties*, Cambridge University Press, Cambridge, 1990.
3 K. Freudenberg and L. Knof, *Chem. Ber.*, 1957, **90**, 2857–2869.
4 J. A. Marco, J. F. Sanz, F. Sancenon, A. Susanna, A. Rustaiyan and M. Saberi, *Phytochemistry*, 1992, **31**, 3527–3530.
5 K. Wada and K. Munakata, *Tetrahedron Lett.*, 1970, 2017–2019.
6 S. Heinonen, T. Nurmi, K. Liukkonen, K. Poutanen, K. Wähälä, T. Deyama, S. Nishibe and H. Adlercreutz, *J. Agric. Food Chem.*, 2001, **49**, 3178–3186.
7 A. Smeds and K. Hakala, *J. Chromatogr., B*, 2003, **793**, 297–308.
8 N. M. Saarinen, A. Wärri, S. I. Mäkelä, C. Eckerman, M. Reunanen, M. Ahotupa, S. M. Salmi, A. A. Franke, L. Kangas and R. Santti, *Nutr. Cancer*, 2000, **36**, 207–216.
9 N. M. Saarinen, R. Huovinen, A. Wärri, S. I. Mäkelä, L. Valentín-Blasini, L. Needham, C. Eckerman, Y. U. Collan and R. Santti, *Nutr. Cancer*, 2001, **41**, 82–90.
10 N. M. Saarinen, R. Huovinen, A. Wärri, S. I. Mäkelä, L. Valentín-Blasini, R. Sjöholm, J. Ämmälä, R. Lehtilä, C. Eckerman, Y. U. Collan and R. S. Santti, *Mol. Cancer Ther.*, 2002, **1**, 869–876 and references 5–7 therein.
11 T. Hirano, A. Wakasugi, M. Oohara, K. Oka and Y. Sashida, *Planta Med.*, 1991, **57**, 331–334.
12 J. Fischer, A. J. Reynolds, L. A. Sharp and M. S. Sherburn, *Org. Lett.*, 2004, **6**, 1345–1348.
13 Y. Asano, T. Kamikawa and T. Tokoroyama, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3232–3235.
14 T. H. Mäkelä, S. A. Kaltia, K. T. Wähälä and T. A. Hase, *Steroids*, 2001, **66**, 777–784.
15 P. Eklund, R. Sillanpää and R. Sjöholm, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1906–1910.
16 F. Kawamura, H. Ohashi, S. Kawai, V. Teratani and Y. Kai, *Mokuzai Gakkaishi*, 1996, **42**, 301–307.
17 J. Mattinen, R. Sjöholm and R. Ekman, *ACH Models Chem.*, 1998, **135**, 583–590.
18 M. Niwa, M. Iguchi, S. Yamamura and S. Nishibe, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3359–3360.
19 S. Nishibe, M. Chiba, A. Sakushima, S. Hisada, S. Yamanouchi, M. Takido, U. Sankawa and A. Sakakibara, *Chem. Pharm. Bull.*, 1980, **28**, 850–860.
20 M. Kuhn and A. von Wartburg, *Helv. Chim. Acta*, 1967, **50**, 1546–1565.
21 Latest review on stereoselective synthesis of *trans* 8/8′ lignanolactones: R. S. Ward, in Recent Advances in the Chemistry of Lignans ed. Atta-ur-Rahman, *Studiesin Natural Products Chemistry, Bioactive Natural Products, Part E*, Elsevier, Amsterdam, 2000, vol. 24, pp. 739–798.
22 M. P. Sibi, P. Liu, J. Ji, S. Hajra and J. Chen, *J. Org. Chem.*, 2002, **67**, 1738–1745.
23 A. Van Oeveren, J. F. G. A. Jansen and B. L. Feringa, *J. Org. Chem.*, 1994, **59**, 5999–6007.
24 A. Pelter, R. S. Ward, D. M. Jones and P. Maddocks, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2631–2637.
25 B. L. Feringa, B. de Lange and J. C. de Jong, *J. Org. Chem.*, 1989, **54**, 2471–2475.
26 A. Pelter, R. S. Ward and N. P. Storer, *Tetrahedron*, 1994, **50**, 10829–10838.
27 R. Van Speybroeck, H. Guo, J. Van der Eycken and M. Vandewalle, *Tetrahedron*, 1991, **47**, 4675–4682.
28 J. H. Park and S. Kim, *Chem. Lett.*, 1989, 629–632.
29 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385–391.
30 F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, 1978, **43**, 985–991.
31 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287–290.
32 P. C. Eklund, S. M. Willför, A. I. Smeds, F. J. Sundell, R. E. Sjöholm and B. R. Holmbom, *J. Nat. Prod.*, 2004, **67**, 927–931.
33 Y. Moritani, C. Fukushima, T. Ukita, T. Miyagishima, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, 1996, **61**, 6922–6930.
34 A. B. Smith, III and G. R. Ott, *J. Am. Chem. Soc.*, 1996, **118**, 13095–13096.
35 R. S. Ward, A. Pelter and A. Abd-El-Ghani, *Tetrahedron*, 1996, **52**, 1303–1336.
36 Y. Moritani, T. Ukita, H. Hiramatsu, K. Okamura, H. Ohmizu and T. Iwasaki, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2747–2753.
37 H. C. Kwon, S. U. Choi, J. O. Lee, K. H. Bae, O. P. Zee and K. R. Lee, *Arch. Pharmacal Res.*, 1999, **22**, 417–422.
38 B. Botta, G. Delle Monache, P. Ricciardi, A. Vitali, V. Vinciguerra, D. Misiti, J. P. Kutney and N. Stoynov, *Heterocycles*, 1996, **43**, 2443–2456.
39 N. Kiyoharu, N. Daisaku, Y. Kouichi, S. Toshio and N. Manabu, *Heterocycles*, 1997, **44**, 393–404.
40 B. L. Feringa and B. De Lange, *Tetrahedron*, 1988, **44**, 7213–7222.
41 T. Mäkelä, J. Matikainen, K. Wähälä and T. Hase, *Tetrahedron*, 2000, **56**, 1873–1882.