# Asymmetric synthesis of trans-4,5-disubstituted γ-butyrolactones involving a key allylboration step. First access to (-)-nicotlactone B and (-)-galbacin

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# Asymmetric synthesis of *trans*-4,5-disubstituted γ-butyrolactones involving a key allylboration step. First access to (−)-nicotlactone B and (−)-galbacin†

S. Henrion,[a] A. Macé,[a] M. M. Vallejos,[b] T. Roisnel,[a] B. Carboni,[a] J. M. Villalgordo[c] and F. Carreaux *[a]

An efficient asymmetric synthesis of *trans*-4,5-disubstituted γ-butyrolactones from aldehydes and enantioenriched γ-carbamate alkenylboronates is reported. The cornerstone of this strategy is the implementation of sequential [3,3]-allyl cyanate rearrangement/allylboration/nucleophilic addition/cyclisation reactions. Diverse γ-butyrolactones such as the flavouring compounds, (+)-*trans*-whiskey lactone and (+)-*trans*-cognac lactone, as well as an advanced intermediate towards the first synthesis of natural products, (−)-nicotlactone B and (−)-galbacin, have thus been obtained.

## Introduction

*trans*-4,5-Disubstituted-γ-butyrolactones represent a class of compounds whose structural units can be encountered in widespread naturally occurring substances as sex-attractant pheromones **1** as well as the flavouring components **2** and **3** (Fig. 1).[1] Their structural motif can also be used as a construction platform to access biologically significant α-alkylidene γ-butyrolactones,[2] such as the α-methylene derivative **4** which inhibits *in vitro* the growth of HL-60 myeloid leukemia cells by activating apoptosis with no obvious toxic side effects in T-lymphocytes or in murine splenocytes.[3] In addition, the 4,5-disubstituted five-membered ring lactones were also considered as useful synthetic intermediates to prepare lignans having a 2,5-diaryl-3,4-disubstituted tetrahydrofuran scaffold by alkylation and subsequent introduction of an aromatic group, respectively, at the C3 and C2 positions.[4] As an example, the biologically active natural product (+)-galbacin has been obtained by using this approach.[5] To the best of our knowledge, the synthesis of its optical antipod, (−)-galbacin **5**, has not been reported to date. For all these reasons, the development of new asymmetric syntheses of such compounds is always of interest and more specially when the sequential one-pot procedure is implemented in order to reduce the purification steps, and minimize time and efforts.

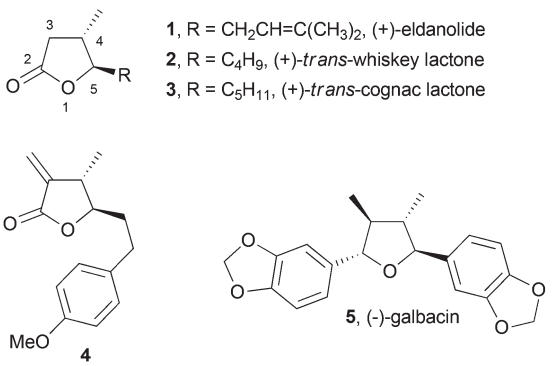


**Fig. 1** Structure of some biologically active substituted γ-butyrolactones and 2,5-diaryl-3,4-disubstituted tetrahydrofuran lignans.

Several strategies have been hitherto developed for the stereoselective synthesis of γ-lactones, but only a few allow access to a broad structural and stereochemical diversity.[6] Taking into account the fact that functionalized homoallylic alcohols can be considered as potential building blocks for the preparation of a lactone skeleton, the stereoselective allylboration of carbonyl compounds has been successfully incorporated in various synthetic approaches.[7] Regarding the preparation of *trans*-4,5-disubstituted-γ-butyrolactones, chiral unfunctionalized (*E*)-substituted allylboron reagents were used to give the

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final products with excellent enantioselectivities.[8] However, it requires several steps since the resulting homoallylic alcohols must be converted into diols *via* a hydroboration-oxidation sequence followed by a selective oxidation of primary alcohols before obtaining the expected five membered-rings. The reaction of chiral (*E*)-α-sulfonamidocrotylboronate with aldehydes provides a more straightforward access to the disubstituted γ-lactones *via* the formation of γ-sulfonamido homoallyl alcohols which can be further easily cyclized into lactol ethers.[9] Nevertheless, the reactivity of this boronic ester with aldehydes is lower than usual, which means that either heating at elevated temperature, or the use of high pressure at room temperature for several days to obtain good yields. In all cases, the purification of the key starting allylboronates can be tedious depending upon the nature of the chiral auxiliary located on the boron atom and (or) the presence of a functional group at the alpha position to the boronate ester.

Keeping this in mind, one-pot procedures *in situ* generating the allylboron reagents, before the subsequent addition to carbonyl compounds, have emerged as efficient synthetic tools to achieve such transformation. In this respect, Miyaura's group described an elegant and short synthesis of *trans*-4,5-disubstituted-γ-butyrolactones starting from (*R*,*R*)-tartrate allyl boronate.[10] The reaction with methyl 3-butenoate under cross-metathesis conditions led to the stereoselective formation of the linear (*E*)-allylboronate, which is directly trapped with aldehydes before carrying out the last lactonization step. Unfortunately, this process suffers from low enantioselectivity.

As part of our efforts to develop sequential reactions involving an allylboration step,[11] we recently reported a [3,3]-sigmatropic rearrangement/allylboration/cyclisation sequence allowing us to obtain optically pure functionalized seven-membered ring carbamates from enantioenriched compounds **6** (Fig. 2).[12] From a similar approach and taking advantage of the fact that the homoallylic alcohols resulting from the addition of α-isocyanato allylboronic esters **7** to aldehydes are obtained as their protected O-Bpin form, we envisaged that such intermediates could be subjected to an intermolecular trapping by the addition of a nucleophile to afford the corresponding acyclic enecarbamates **8**. An acid-catalyzed cyclization should lead to (tetrahydrofuran-2-yl)ethers **9** as precursors to the γ-lactone framework.[13] In this paper, we report our efforts regarding the implementation of this new approach for a stereocontrolled synthesis of *trans*-4,5-disubstituted γ-butyrolactones **11**. Asymmetric one-pot sequential transformations were employed permitting the synthesis of desired γ-butyrolactones without any purification of intermediates.

A large variety of compounds have thus been obtained as well as γ-butyrolactone natural products like the (+)-*trans*-whiskey lactone and (+)-*trans*-cognac lactone. As evidence for the efficiency of this strategy, the first total syntheses of (−)-nicotlactone B and (−)-galbacin were also described.

## Results and discussion

The enantioenriched carbamate (*S*,*E*)-**6a** (98% ee) was first chosen as the starting material for the optimization of the strategy. This compound was prepared in multigram-scale quantities from (*S*)-but-3-yn-2-ol.[12] The dehydration reaction of carbamate into cyanate groups can be performed mainly under two conditions.[14] In our case, we favoured the use of trifluoroacetic anhydride (TFAA) as the reagent in place of triphenylphosphine in order to avoid the formation of the corresponding oxide which can be difficult to remove. After 1 h at room temperature in the presence of triethylamine, the formation of the α-isocyanato allylboronate **7a** resulting from the domino dehydration/rearrangement sequence was evaluated as complete by NMR-spectroscopic analysis of the crude mixture (Scheme 1).[15] The allyl boronate **7a** was directly treated without purification with aromatic aldehydes, and then followed by addition of methanol. Using the 4-nitro benzaldehyde, the acyclic enecarbamate **8aa** was formed as a single diastereomer (determined by $^1$H NMR) and obtained with 89%

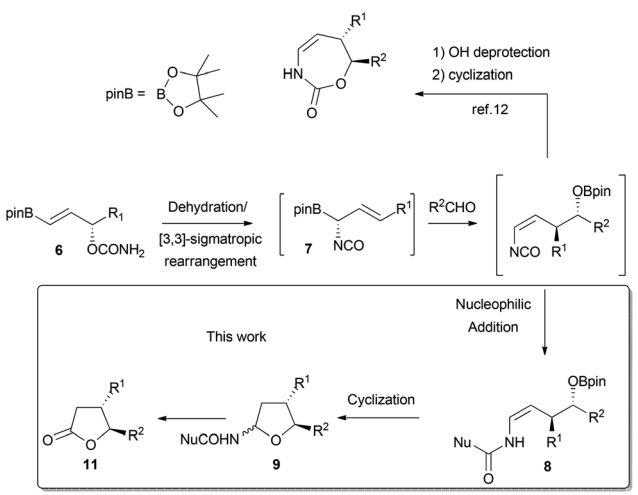
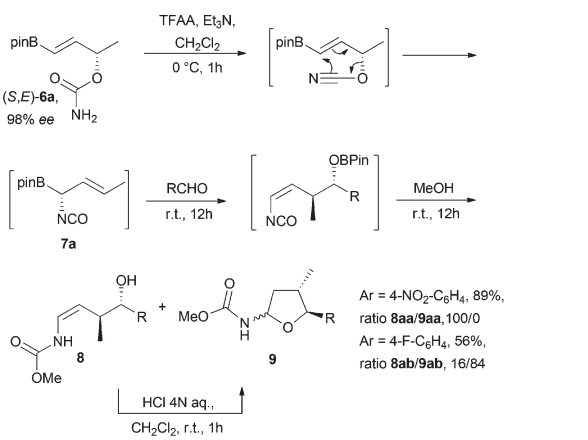



**Fig. 2** Strategy for the asymmetric synthesis of *trans*-4,5-disubstituted γ-butyrolactones from γ-carbamate alkenylboronates **6**.

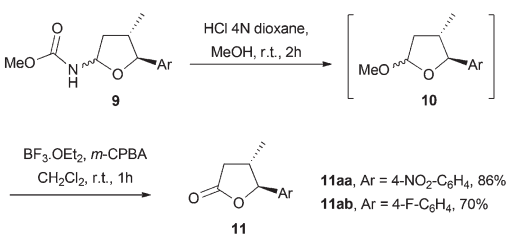



**Scheme 1** Synthesis of carbamates **8** and **9** from (*S*,*E*)-**6a**.

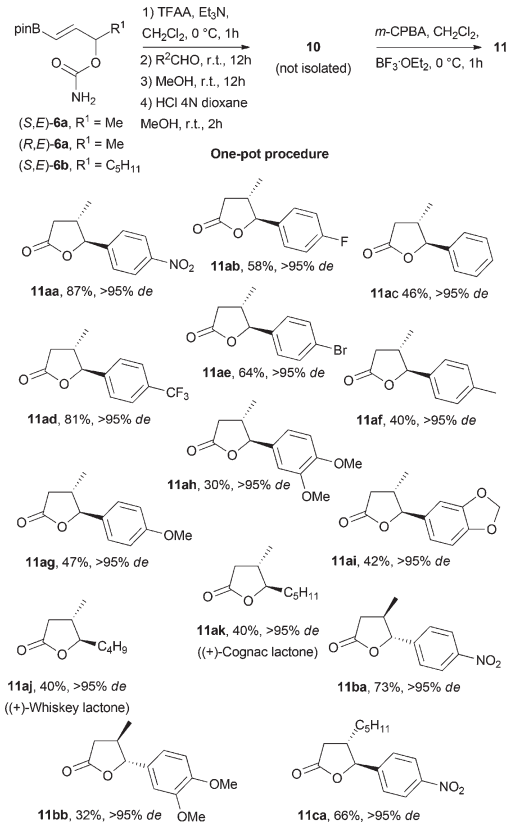
overall yield from **6a** after chromatographic purification. In the case of the 4-fluoro benzaldehyde, an $^1$H NMR study of the crude product showed that the formation of the desired enecarbamate **8ab** was accompanied by an important quantity of the five-membered ring **9ab** (ratio of 16/84, respectively), which probably comes from **8ab** *via* an intramolecular addition of the secondary alcohol to an iminium species. These two structurally isomeric compounds cannot be separated easily by purification on a silica gel. Fortunately, treatment under acidic conditions allowed the complete conversion of enecarbamates **8** into substituted 3-aminotetrahydrobenzofurans, **9**.

The latter can be considered as suitable intermediates to access γ-butyrolactones. Indeed, the *N*,*O*-acetals **9aa** and **9ab** can be efficiently transformed into the corresponding γ-lactol methyl ethers **10** with methanol using a 4N hydrogen chloride solution in dioxane.[16] Subsequent oxidation by *m*-CPBA in the presence of boron trifluoride etherate led to the expected lactones **11aa** and **11ab** (Scheme 2). At this point, the enantiomeric excess was measured by chiral HPLC to be 98% (see ESI†). Compared to the starting material (*S*,*E*)-**6a**, we can conclude that during all these transformations, no loss of chirality occurred.[17]

On the basis of these experimental results, we assumed that there was still room for improvement of the procedure. In fact, using appropriate acidic conditions in the presence of methanol, the enecarbamate intermediates **8** could be directly transformed into the corresponding γ-lactol methyl ethers **10**. After some adjustments, we selected the optimized protocol, shown in Scheme 3. Starting from (*S*,*E*)-**6a**, the γ-lactol methyl ethers **10** were easily obtained according to a one-pot sequence. After evaporation of volatile components, the crude mixture was directly engaged in an oxidation reaction for 1 h at 0 °C. The single purification stage of this multistep sequence was further carried out. Using this simplified protocol, a large variety of hithertho unknown *trans*-4,5-disubstituted-γ-butyrolactones **11** have been thus obtained from various aldehydes with modest to good overall yields (5 steps from (*S*,*E*)-**6a**) and in a highly diastereoselective manner (>95%, evaluated by $^1$H NMR before purification). It is interesting to note that this excellent diastereoselectivity was maintained even with aromatic aldehydes possessing strongly electron donating groups on the ring (+M effect).[18] In order to highlight the versatility of this approach, other enantioenriched carbamates (*R*,*E*)-**6a** and **6b** have been prepared and used as starting




**Scheme 2** Transformation of **9** into γ-butyrolactones **11**.




**Scheme 3** Selected process for the asymmetric synthesis of *trans*-4,5-disubstituted γ-lactones **11**.

materials.[12,19] In all cases, the corresponding γ-butyrolactones **11ba**, **11bb** and **11ca** were obtained in a highly stereoselective way as previously observed, showing the good level of reliability and generalization of this approach.

This multi-stage procedure was also applied to the synthesis of γ-butyrolactone natural products, such as (+)-*trans*-whiskey lactone **11aj**[20] and (+)-*trans*-cognac lactone **11ak**,[21] giving compounds which showed NMR and optical properties in full agreement with those reported in the literature.

(−)-Galbacin is a natural product isolated, *inter alia*, from *Talauma hodgsonii Hook*, F & Thoms,[22] which inhibits in particular the growth of several human tumor cell lines.[23,24] Among all the γ-butyrolactones previously prepared, we speculated that compound **11ai** could be a key intermediate for the asymmetric synthesis of (−)-galbacin, *via* several transformations on the scaffold such as a stereoselective alkylation step and an electrophilic aromatic substitution reaction (EArS) as reported in Fig. 3.

For the purpose of developing the first asymmetric synthesis of this tetrahydrofuran lignan, the methylation reaction of **11ai** was tried under several basic conditions using MeI as the alkylating agent (Scheme 4). When the enolate was generated using LiHMDS as the base, the major product of alkylation was the stereoisomer **12** having a *cis*-configuration between C3 and C4. The origin of this π-facial stereoselectivity could be mainly attributed to the presence of the substituent

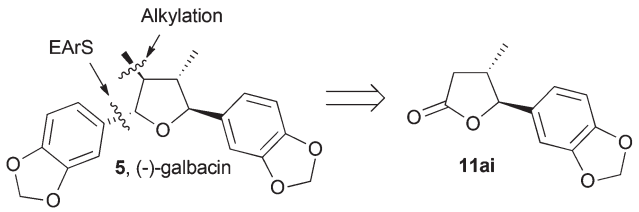
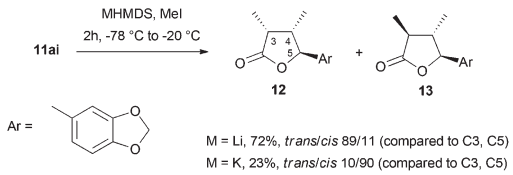
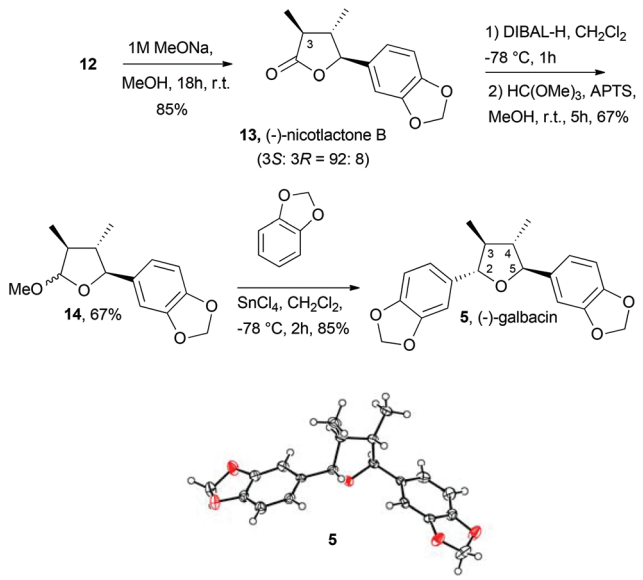



Fig. 3 Strategy for the synthesis of (–)-galbacin from the advanced intermediate **11ai**.




Scheme 4 Diastereoselectivity of the alkylation reaction of **11ai** using diverse bases.




Scheme 5 Asymmetric syntheses of (–)-nicotlactone B and (–)-galbacin with an X-ray crystallographic structure of **5**.

at C5 favouring the *anti*-selectivity with respect to the aromatic group by a combination of different effects in the transition state already reported in the literature.[25] A computational study on the alkylation of lithium enolate showed that the *anti*-transition structure is 0.6 kcal $mol^{-1}$ more favourable than the *syn*-transition structure in Gibbs free energy, difference which corresponds quite exactly to the ratio observed experimentally (see ESI†). The stereoselectivity was reversed when the alkylation reaction was performed employing KHDMS as the base under the same conditions of temperature, solvent and time. Unfortunately, the stereoisomer **13** with the required stereochemistry to access (–)-galbacin was obtained with a low yield and cannot be separated from **12** by purification.[26]

To overcome this drawback, an epimerization of **12** under basic conditions was planned. Treatment of **12** (ratio 89/11) with MeONa in MeOH for 18 h at room temperature resulted in the inversion of configuration at chiral center C3 (ratio of 8/92 in favour of **13**) (Scheme 5). It is interesting to note that **13**, also named (–)-nicotlactone B,[27] is a natural product present in the Australian endemic plant *Austrobaileya scandens* whose asymmetric synthesis had not yet been reported. The reduction of **13** with DIBAL-H, followed by an acidic treatment in the presence of methylorthoformate and *para*-toluenesulfonic acid (APTS) in methanol led to γ-lactol methyl ether **14** in 67% yield as an anomeric mixture. The final step of our synthesis is the crucial building of remaining chiral center C2 by the introduction of a 1,2-methylenedioxybenzene moiety. To this end, a Friedel-Craft type arylation was carried out in the presence of a stoichiometric quantity of $SnCl_4$ in $CH_2Cl_2$ at −78 °C for 2 h. Under these conditions, the desired natural product **5** was obtained in good yield (85%) as a single stereoisomer. All the spectroscopic data of this synthetic compound are identical to those of natural (–)-galbacin.[24] The relative configurations of all chiral centers of (–)-galbacin were afterwards confirmed by the analysis of its X-ray crystallographic structure.[28]

## Conclusion

We described in this paper a new asymmetric synthesis of *trans*-4,5-disubstituted-γ-butyrolactones through an approach based on sequential one-pot transformations including a [3,3] allyl cyanate rearrangement/allylboration/nucleophilic addition followed by a cyclization reaction and an oxidation step. The value and the efficiency of this method was clearly demonstrated by the synthesis of various lactone natural products, including (–)-nicotlactone B, as well as a bioactive tetrahydrofuran lignan, (–)-galbacin, whose synthesis had never been reported to date.

## Experimental section

### General information

Tetrahydrofuran (THF) was distilled over sodium/benzophenone, and dichloromethane (DCM) was distilled over $P_2O_5$. Amines were distilled over potassium hydroxide. Trifluoroacetic anhydride was distilled over $P_2O_5$. Alcohols were distilled over calcium hydride ($CaH_2$). Triethylamine was distilled over KOH and stored under an argon atmosphere. All aldehydes used were distilled under *vacuum*. NMR spectra were recorded on Bruker apparatus at 300, 400 or 500 MHz for $^1H$ and 75, 101 or 126 MHz for $^{13}C$. Chemical shifts of $^1H$ and $^{13}C$ NMR were referenced to $Me_4Si$ as internal reference. Data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant *J* (Hz) and integration. All

high-resolution mass spectra (HRMS) were recorded on a Bruker Micro-Tof-Q II or on a Waters Q-Tof 2 at the CRMPO (Centre Régional de Mesures de Physiques de l'Ouest – Rennes – France) using positive ion electrospray. Purifications on a silica gel were carried out on an Acros silica gel 0.006–0.200 mm, 60 A. Analytical thin layer chromatography was performed on Merck Silica gel 60 $F_{254}$ plates. X-ray crystallographic data were collected on an APEXII crystal diffractometer. The optical rotations were measured on a PerkinElmer Model 341 polarimeter (sodium D-line: 589 nm and mercury I-line: 365 nm). Melting points were measured on a melting point apparatus Stuart SMP10. All analytical high-performance liquid chromatography (HPLC) were performed on an Agilent Technologies equipped with diode array UV detectors, using a Chiralcel OD-H column. Enantioenriched compounds **6** were prepared according to a literature procedure.[12]

### A general experimental procedure for γ-butyrolactones synthesis

To a solution of carbamate **6a–c** (1 eq.) in dry dichloromethane (0.10 M), under an argon atmosphere were added trifluoroacetic anhydride (3 eq.) and triethylamine (4.5 eq.). The solution was stirred at 0 °C for one hour and then, aldehyde was added. The resulting solution was stirred at 25 °C for 12 hours. Methanol was added and the solution was stirred at 25 °C for an additional 12 hours. Methanol (20 eq.) and HCl 4 N in dioxane (10 eq.) were added and the solution was stirred at room temperature for an additional 2 hours. The reaction medium was diluted with dichloromethane and neutralized with NaOH 2 M. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. To the crude reaction in dry dichloromethane (0.15 M), cooled at 0 °C, were added $Et_2O{\cdot}BF_3$ (3 eq.) and a solution of *m*-CPBA (3 eq.) in dry dichloromethane (0.50 M). The mixture was stirred at 0 °C for 1 hour and quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography to give the desired lactone **11**.

**(4*S*,5*S*)-4-Methyl-5-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (11aa).** Yield: 87%, orange oil; $[\alpha]_D^{20}$ = +13 (*c* 1.60, $CH_2Cl_2$); $^1$H NMR (400 MHz, acetone-$d_6$, $\delta$ ppm) 8.29 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.7 Hz 2H), 5.21 (d, *J* = 8.5 Hz, 1H), 2.78 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.61–2.52 (m, 1H), 2.47 (dd, *J* = 16.3, 10.5 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (101 MHz, acetone-$d_6$, $\delta$ ppm) 175.8, 148.9, 147.2, 128.1, 124.5, 86.8, 40.7, 37.2, 16.1; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$ 244.0580; found 244.0579.

**(4*S*,5*S*)-5-(4-Fluorophenyl)-4-methyldihydrofuran-2(3*H*)-one (11ab).** Yield: 58%, yellow oil; $[\alpha]_I^{20}$ = +30 (*c* 1.05, $CH_2Cl_2$); $^1$H NMR (300 MHz, acetone-$d_6$, $\delta$ ppm) 7.56–7.44 (m, 2H), 7.23–7.14 (m, 2H), 5.02 (d, *J* = 8.6 Hz, 1H), 2.74 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.55–2.53 (m, 1H), 2.41 (dd, *J* = 16.0, 10.7 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H); $^{19}$F NMR (282 MHz, acetone-$d_6$, $\delta$ ppm) −115.2; $^{13}$C NMR (75 MHz, acetone-$d_6$, $\delta$ ppm) 176.0, 163.6 (d, *J* = 245.0 Hz), 135.8 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 8.5 Hz), 116.2 (d, *J* = 21.8 Hz), 87.7, 40.6, 37.5, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}FO_2Na$ $[M + Na]^+$ 217.0635; found 217.0636.

**(4*S*,5*S*)-4-Methyl-5-phenyldihydrofuran-2(3*H*)-one (11ac).**[20c] Yield: 46%, colourless oil; $[\alpha]_D^{20}$ = −9 (*c* 0.75, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm) 7.45–7.34 (m, 5H), 5.01 (d, *J* = 8.5 Hz, 1H), 2.74 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.60–2.46 (m, 1H), 2.40 (dd, *J* = 16.0, 10.6 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$, $\delta$ ppm) 176.1, 139.7, 129.4, 129.3, 127.2, 88.4, 40.6, 37.6, 16.1; HRMS (EI) *m*/*z* calcd for $C_{11}H_{12}O_2Na$ $[M + Na]^+$ 199.0729; found 199.0729.

**(4*S*,5*S*)-4-Methyl-5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (11ad).** Yield: 81%, orange oil; $[\alpha]_I^{20}$ = +15 (*c* 0.40, $CH_2Cl_2$); $^1$H NMR (300 MHz, acetone-$d_6$, $\delta$ ppm) 7.78 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 5.15 (d, *J* = 8.3 Hz, 1H), 2.77 (dd, *J* = 15.9, 7.0 Hz, 1H), 2.64–2.50 (m, 1H), 2.45 (dd, *J* = 15.9, 10.4 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H); $^{19}$F NMR (282 MHz, acetone-$d_6$, $\delta$ ppm) −63.1; $^{13}$C NMR (75 MHz, acetone-$d_6$, $\delta$ ppm) 175.9, 144.5 (q, *J* = 1.3 Hz), 130.9 (q, *J* = 32.2 Hz), 127.8, 126.4 (q, *J* = 3.9 Hz), 125.2 (q, *J* = 271.3 Hz), 123.4, 87.3, 40.7, 37.3, 16.2; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{11}F_3O_2Na$ $[M + Na]^+$ 267.0603; found 267.0604.

**(4*S*,5*S*)-5-(4-Bromophenyl)-4-methyldihydrofuran-2(3*H*)-one (11ae).** Yield: 64%, slight yellow oil; $[\alpha]_I^{20}$ = +41 (*c* 1.45, $CH_2Cl_2$); $^1$H NMR (300 MHz, acetone-$d_6$, $\delta$ ppm) 7.60 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 5.02 (d, *J* = 8.4 Hz, 1H), 2.74 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.58–2.46 (m, 1H), 2.41 (dd, *J* = 15.7, 10.7 Hz, 1H), 1.16 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$, $\delta$ ppm) 175.9, 139.1, 132.5, 129.3, 122.8, 87.5, 40.6, 37.4, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}BrO_2Na$ $[M + Na]^+$ 276.9835; found 276.9837.

**(4*S*,5*S*)-4-Methyl-5-(*p*-tolyl)dihydrofuran-2(3*H*)-one (11af).** Yield: 40%, orange oil; $[\alpha]_I^{20}$ = +30 (*c* 0.35, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 7.25–7.14 (m, 4H), 4.91 (d, *J* = 8.3 Hz, 1H), 2.78 (dd, *J* = 16.9, 7.6 Hz, 1H), 2.56–2.39 (m, 1H), 2.36 (s, 3H), 2.33 (dd, *J* = 16.9, 10.5 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.3, 138.8, 135.0, 129.5, 126.1, 88.4, 39.9, 37.5, 21.3, 16.6; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}O_2Na$ $[M + Na]^+$ 213.0886; found 213.0887.

**(4*S*,5*S*)-5-(4-Methoxyphenyl)-4-methyldihydrofuran-2(3*H*)-one (11ag).**[29] Yield: 47%, orange oil; $[\alpha]_D^{20}$ = +13 (*c* 0.75, $CHCl_3$); litt.: $[\alpha]_D^{20}$ = +12 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 7.26 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.88 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 2.78 (dd, *J* = 16.9, 7.7 Hz, 1H), 2.54–2.43 (m, 1H), 2.33 (dd, *J* = 16.9, 10.7 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.2, 160.1, 129.8, 127.7, 114.2, 88.3, 55.5, 39.8, 37.6, 16.4. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}O_3Na$ $[M + Na]^+$ 229.0835; found 229.0836.

**(4*S*,5*S*)-5-(3,4-Dimethoxyphenyl)-4-methyldihydrofuran-2(3*H*)-one (11ah).** Yield: 30%, green oil; $[\alpha]_I^{20}$ = +37 (*c* 0.33, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 6.90–6.81 (m, 3H), 4.88 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.80 (dd, *J* = 16.9, 7.6 Hz, 1H), 2.53–2.43 (m, 1H), 2.34 (dd, *J* = 16.9, 10.8 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.3, 149.6, 149.5, 130.3, 119.0, 111.1, 109.1, 88.5,

56.2, 56.1, 39.9, 37.6, 16.5; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0940; found 259.0940.

**(4*S*,5*S*)-5-(Benzo[*d*][1,3]dioxolo-5-yl)-4-methyldihydrofuran-2(3*H*)-one (11ai).** Yield: 42%, colourless oil; $[\alpha]_I^{20}$ = +94 (*c* 0.35, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 6.86–6.77 (m, 3H), 5.98 (s, 2H), 4.84 (d, *J* = 8.5 Hz, 1H), 2.78 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.51–2.40 (m, 1H), 2.32 (dd, *J* = 16.8, 10.8 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.0, 148.3, 148.2, 131.7, 120.2, 108.4, 106.5, 101.5, 88.4, 39.9, 37.5, 16.5; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{12}O_4Na$ $[M + Na]^+$ 243.0628; found 243.0628.

**(4*S*,5*R*)-5-Butyl-4-methyldihydrofuran-2(3*H*)-one (11aj) [(+)-*trans*-whiskey lactone](2).**[20c] Yield: 40%, colourless oil; $[\alpha]_D^{20}$ = +50 (*c* 0.6, $CHCl_3$); litt.: $[\alpha]_D^{25}$ = +59.6 (*c* 0.71, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 4.00 (ddd, *J* = 8.2, 7.3, 4.1 Hz, 1H), 2.71–2.61 (m, 1H), 2.25–2.12 (m, 2H), 1.73–1.54 (m, 3H), 1.41– 1.31 (m, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.7, 87.6, 37.3, 36.2, 33.8, 28.0, 22.6, 17.6, 14.0. HRMS (ESI) *m*/*z* calcd for $C_9H_{16}O_2Na$ $[M + Na]^+$ 179.1042; found 179.1043.

**(4*S*,5*R*)-4-Methyl-5-pentyldihydrofuran-2(3*H*)-one (11ak) [(+)-*trans*-cognac lactone](3).**[20b] Yield: 40%, colourless oil; $[\alpha]_D^{20}$ = +70 (*c* 0.27, $CHCl_3$); litt.: $[\alpha]_D^{25}$ = +72 (*c* 1.00, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm) 4.05–3.96 (m, 1H), 2.75–2.61 (m, 1H), 2.31–2.13 (m, 2H), 1.73–1.60 (m, 4H), 1.38–1.28 (m, 4H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 5.8 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm) 176.6, 87.5, 37.2, 36.1, 34.0, 31.6, 25.4, 22.5, 17.5, 14.0. HRMS (ESI) *m*/*z* calcd for $C_{10}H_{18}O_2Na$ $[M + Na]^+$ 193.1198; found 193.1199.

**(4*R*,5*R*)-5-Methyl-5-(4-nitrophenyl)dihydrofuran-2(3*H*)-one (11ba).** Yield: 73%, orange oil; $[\alpha]_D^{20}$ = −12 (*c* 1.60, $CH_2Cl_2$); $^1$H NMR (400 MHz, acetone-$d_6$, $\delta$ ppm) 8.29 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 8.5 Hz, 1H), 2.78 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.61–2.52 (m, 1H), 2.47 (dd, *J* = 16.3, 10.5 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (101 MHz, acetone-$d_6$, $\delta$ ppm) 175.8, 148.9, 147.2, 128.1, 124.5, 86.8, 40.7, 37.2, 16.1. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}NO_4Na$ $[M + Na]^+$ 244.0580; found 244.0581.

**(4*R*,5*R*)-5-(3,4-Dimethoxyphenyl)-4-methyldihydrofuran-2(3*H*)-one (11bb).** Yield: 32%, green oil; $[\alpha]_D^{20}$ = −35 (*c* 0.33, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 6.90–6.81 (m, 3H), 4.88 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.80 (dd, *J* = 16.9, 7.6 Hz, 1H), 2.53–2.43 (m, 1H), 2.34 (dd, *J* = 16.9, 10.8 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 176.3, 149.6, 149.5, 130.3, 119.0, 111.1, 109.1, 88.5, 56.2, 56.1, 39.9, 37.6, 16.5. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0940; found 259.0941.

**(4*S*,5*S*)-5-(4-Nitrophenyl)-4-pentyldihydrofuran-2(3*H*)-one (11ca).** Yield: 66%, orange oil; $[\alpha]_D^{20}$ = +15 (*c* 0.50, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm) 8.26 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 5.10 (d, *J* = 7.3 Hz, 1H), 2.89–2.71 (m, 1H), 2.48–2.28 (m, 2H), 1.71–1.55 (m, 1H), 1.55–1.42 (m, 1H), 1.39–1.17 (m, 6H), 0.92–0.80 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 175.3, 148.1, 145.7, 126.7, 124.1, 85.2, 53.4, 45.1, 34.9, 32.1, 31.6, 30.9, 22.4, 14.2, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{19}NO_4Na$ $[M + Na]^+$ 300.1206; found 300.1207.

**5,5′-((2*S*,3*S*,4*S*,5*S*)-3,4-Dimethyltetrahydrofuran-2,5-diyl)bis(benzo[*d*][1,3]dioxole), (−)-galbacin (5).**[24a] Yield from **14**: 85%, colourless oil; $[\alpha]_D^{20}$ = −103 (*c* 0.88, $CHCl_3$); litt.: $[\alpha]_D^{25}$ = −119 (*c* 0.02, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm) 6.91 (d, *J* = 1.6 Hz, 2H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 2H), 6.77 (d, *J* = 7.9 Hz, 2H), 5.94 (s, 4H), 4.59 (d, *J* = 9.2 Hz, 2H), 1.83–1.67 (m, 2H), 1.02 (d, *J* = 6.1 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$, $\delta$ ppm) 147.9, 147.1, 136.5, 119.9, 108.1, 106.7, 101.1, 88.4, 51.2, 13.9. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NaO_5$ $[M + Na]^+$ 363.1202; found 363.1203.

## Conflicts of interest

There are no conflicts to declare.

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