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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 have thus been obtained 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.

Introduction

Trans-4,5-disubstituted-γ-butyrolactones represent a class of compounds whose the structural unit can be encountered in widespread naturally occurring substances as sex-attractant pheromones **1** as well as the flavouring components **2** and **3** (Figure 1).[1] That structural motif can also be used as a construction platform to access biologically significant α-alkylidene y-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 was 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 this approach.[5] To the best of our knowledge, the synthesis of its optical antipod, (-)-galbacin **5**, was not reported to date. For all these reasons, the development of new asymmetric syntheses of such compounds is always of interest and more specially when sequential one-pot procedure is implemented in order to reduce purification steps, and minimize time and efforts.
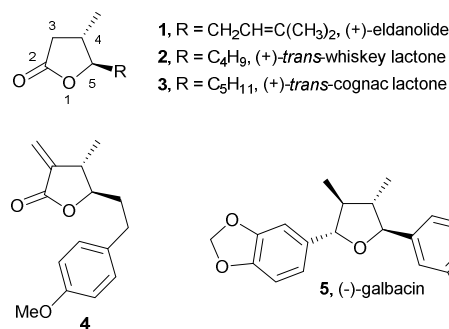

1, R = CH₂CH=C(CH₃)₂, (+)-eldanolide
2, R = C₄H₉, (+)-*trans*-whiskey lactone
3, R = C₅H₁₁, (+)-*trans*-cognac lactone

5, (-)-galbacin

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, only a few allow access to a broad structural and stereochemical diversity.[6] Taking into account that functionalized homoallylic alcohols can be considered as potential building blocks for the preparation of 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 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 implies, either

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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 chiral auxiliary located on the boron atom and (or) the presence of a functional group at alpha position to the boronate ester.

Keeping this in mind, one-pot procedures *in situ* generating the formation of allylboron reagents, before the subsequent addition to carbonyl compounds, have emerged as efficient synthetic tools to achieve such transformation. In this respect, the 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 to obtain optically pure functionalized seven-membered ring carbamates from enantioenriched compounds **6** (Figure 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 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.
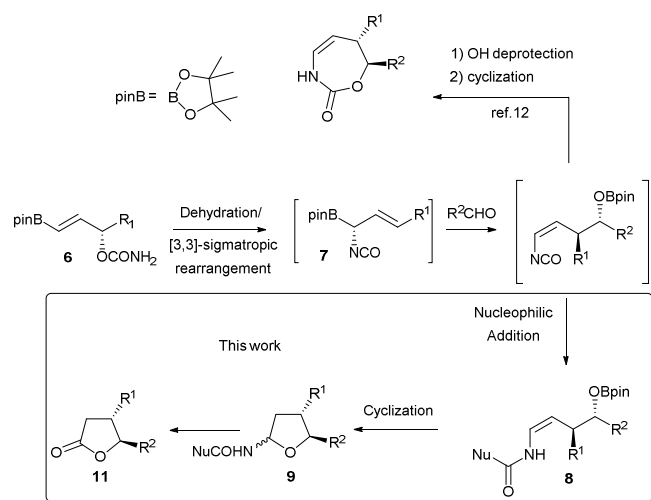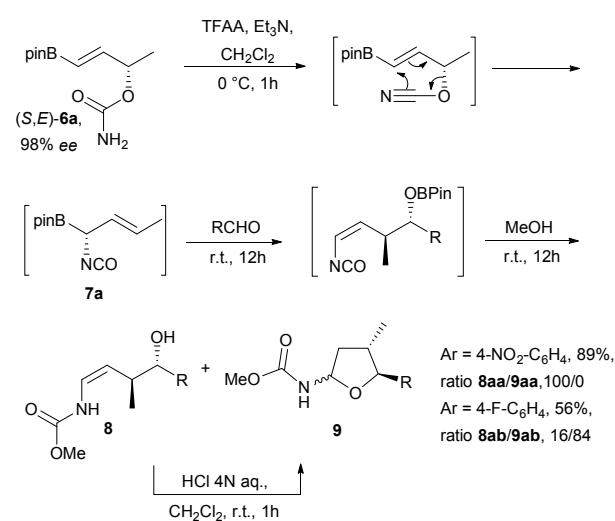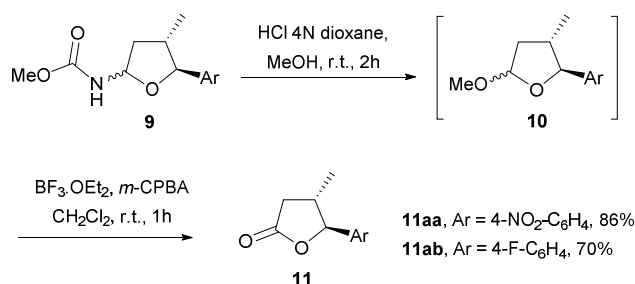
A large variety of compounds have thus been obtained as well as γ-butyrolactone natural products like the (+)-*trans*-whiskey lactone and (+)-*trans*-cognac lactone. As evidence of the efficiency of this strategy, the first total syntheses of (-)-nicotlactone B and (-)-galbacin were also described.

Results and discussion

The enantioenriched carbamate (*S*,*E*)-**6a** (98% *ee*) was first chosen as starting material for the optimization of the strategy. This last one can be prepared in multigram-scale quantities from (*S*)-but-3-yn-2-ol.[12] Dehydration reaction of carbamate into cyanate group can be performed mainly under two conditions.[14] In our case, we favoured the use of the trifluoroacetic anhydride (TFAA) as reagent in place of triphenylphosphine in order to avoid the formation of the corresponding oxide which can be difficult to remove. After 1h 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 3).[15] The allyl boronate **7a** was directly treated without purification with aromatic aldehydes, and then followed by addition of methanol. Using the 4-nitrophenyl benzaldehyde, the acyclic enecarbamate **8aa** was formed as single diastereomer (determined by ^{1}H NMR) and obtained with 89% overall yield from **6a** after chromatographic purification. In the case of the 4-fluorophenyl 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 silica gel. Fortunately, treatment under acidic conditions allowed the complete conversion of enecarbamates **8** into substituted 3-aminotetrahydrobenzofurans, **9**.
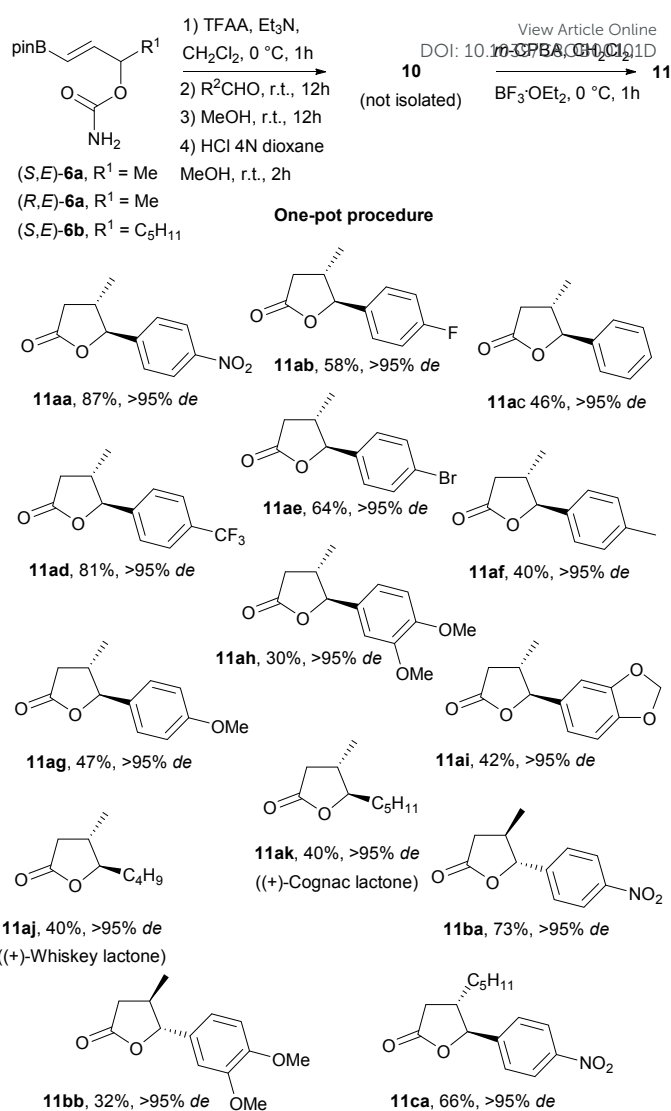

Fig. 2 Strategy for the asymmetric synthesis of *trans*-4,5-disubstituted γ-butyrolactones from γ-carbamate alkenylboronates **6**.

Scheme 3 Synthesis of carbamates **8** and **9** from (*S*,*E*)-**6a**.

**Scheme 4** Transformation of **9** into γ-butyrolactones **11**.

These 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 4). At this point of the work, the enantiomeric excess was measured by chiral HPLC as being of 98% (see supporting information). 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 5. 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 during 1h 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 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.

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

(-)-Galbacin is a natural product isolated, inter alia, from *Talauma hodgsonii Hook*, F & Thoms,[22] 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 Figure 6.
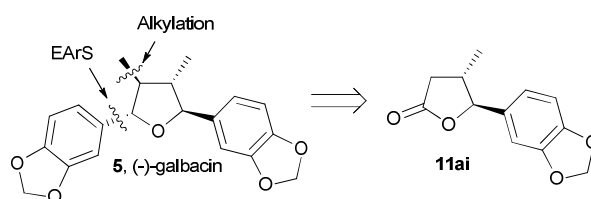
Fig.6 Strategy for the synthesis of (-)-galbacin from the advanced intermediate **11ai**.

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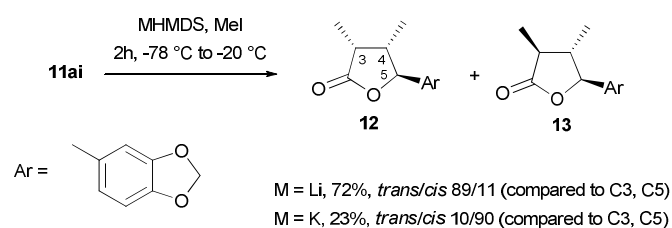
Scheme 7 Diastereoselectivity of the Alkylation reaction of **11ai** using diverse bases.

For the purpose of developing the first asymmetric synthesis of that tetrahydrofuran lignan, the methylation reaction of **11ai** was tried under several basic conditions using MeI as alkylating agent (Scheme 7). When the enolate was generated using LiHMDS as 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 at C5 favouring the *anti*-selectivity with respect to 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 more favourable than the *syn*-transition structure in Gibbs free energy, difference which corresponds quite exactly to the ratio observed experimentally (see supporting information). The stereoselectivity was inversed when the alkylation reaction was performed employing KHDMS as 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 18h at room temperature resulted in the inversion of configuration at chiral center C3 (ratio of 8/92 in favour of **13**) (Scheme 8). 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 no asymmetric synthesis had yet been reported so far. 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 introduction of a 1,2-methylenedioxybenzene moiety. To this end, a Friedel-Craft type arylation was carried out in the presence of a stoechiometric quantity of $SnCl_4$ in CH_2Cl_2 at -78 °C for 2h. 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 with those of natural (-)-galbacin.[24] The relative configurations of all chiral centers of (-)-galbacin were afterwards confirmed by analysis of its X-ray crystallographic structure.[28]
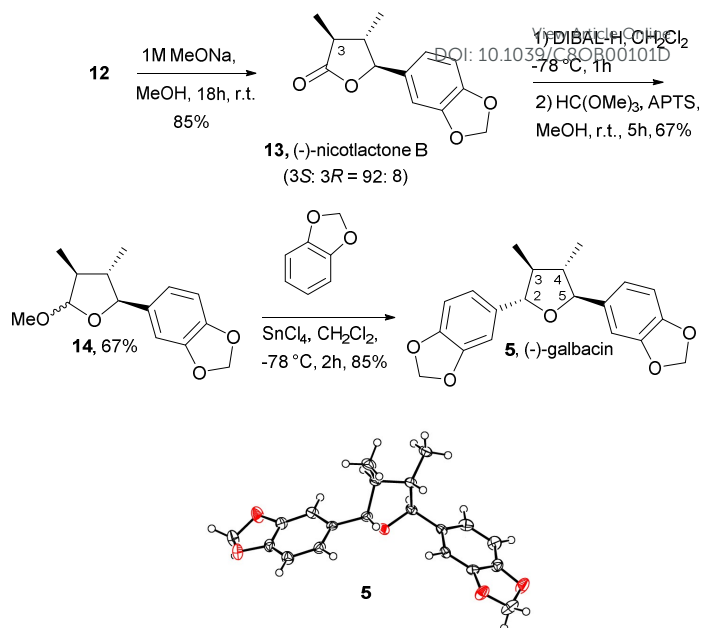
Scheme 8 Asymmetric syntheses of (-)-nicotlactone B and (-)-galbacin with an X-ray crystallographic structure of **5**.

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 the synthesis had never been reported to date.

Experimental section

General information

Tetrahydrofuran (THF) was distilled over sodium/benzophenone, 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 argon atmosphere. All aldehydes used were distilled under *vacuum*. NMR spectra were recorded on Bruker apparatus at 300, 400 or 500 MHz for ^{1}H and 75, 101 or 126 MHz for [13]C. Chemical shifts of ^{1}H 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, 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 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 Perkin Elmer 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 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 (0.10M), under 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 additional 12 hours. Methanol (20 eq.) and HCl 4N in dioxane (10 eq.) were added and the solution was stirred at room temperature for additionally 2 hours. The reaction medium was diluted with dichloromethane and neutralized with NaOH 2M. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under *vacuo.* To the crude reaction in dry dichloromethane (0.15M), cooled at 0 °C, were added $Et_2O \cdot BF_3$ (3 eq.) and a solution of *m*-CPBA (3 eq.) in dry dichloromethane (0.50M). 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 *vacuo.* 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(3H)-one (11aa)

Yield: 87%, orange oil; $[\alpha]_D^{20}$ = + 13 (c 1.60, CH_2Cl_2); ^{1}H NMR (400 MHz, Acetone-d6, δ 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-d6, δ 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(3H)-one (11ab)

Yield: 58%, yellow oil; $[\alpha]_I^{20}$ = + 30 (c 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, Acetone-d6, δ 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, δ ppm) -115.2; ^{13}C NMR (75 MHz, Acetone-d6, δ 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(3H)-one (11ac)[19c]

Yield: 46%, colourless oil; $[\alpha]_D^{20}$ = - 9 (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ 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-d6, δ 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(3H)-one (11ad)

Yield: 81%, orange oil; $[\alpha]_I^{20}$ = + 15 (c 0.40, CH_2Cl_2); ^{1}H NMR (300 MHz, Acetone-d6, δ 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-d6, δ ppm) -63.1; ^{13}C NMR (75 MHz, Acetone-d6, δ 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(3H)-one (11ae)

Yield: 64%, slight yellow oil; $[\alpha]_I^{20}$ = + 41 (c 1.45, CH_2Cl_2); ^{1}H NMR (300 MHz, Acetone-d6, δ 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-d6, δ 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(3H)-one (11af)

Yield: 40%, orange oil; $[\alpha]_I^{20}$ = + 30 (c 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, δ 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, $CDCl_3$, δ 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(3H)-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, $CDCl_3$, δ 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, $CDCl_3$, δ 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.

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(4S,5S)-5-(3,4-dimethoxyphenyl)-4-methyldihydrofuran-2(3H)-one (11ah)

Yield: 30%, green oil; $[\alpha]_I^{20}$ = + 37 (c 0.33, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$, δ 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$_3$, δ 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$_4$Na [M+Na]$^+$ 259.0940; found 259.0940.

(4S,5S)-5-(benzo[d][1,3]dioxolo-5-yl)-4-methyldihydrofuran-2(3H)-one (11ai)

Yield: 42%, colourless oil; $[\alpha]_I^{20}$ = + 94 (c 0.35, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$, δ 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$_3$, δ 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$_4$Na [M+Na]$^+$ 243.0628; found 243.0628.

(4S,5R)-5-butyl-4-methyldihydrofuran-2(3H)-one (11aj) [(+)-trans-whiskey lactone](2)[19c]

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$_3$, δ 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$_3$, δ 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$_9$H$_{16}$O$_2$Na [M+Na]$^+$ 179.1042; found 179.1043.

(4S,5R)-4-methyl-5-pentyldihydrofuran-2(3H)-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$_3$, δ 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$_3$, δ 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$_2$Na [M+Na]$^+$ 193.1198; found 193.1199.

(4R,5R)-5-methyl-5-(4-nitrophenyl)dihydrofuran-2(3H)-one (11ba)

Yield: 73%, orange oil; $[\alpha]_D^{20}$ = - 12 (c 1.60, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, Acetone-d6, δ 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-d6, δ 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$_4$Na [M+Na]$^+$ 244.0580; found 244.0581.

(4R,5R)-5-(3,4-dimethoxyphenyl)-4-methyldihydrofuran-2(3H)-one (11bb)

Yield: 32%, green oil; $[\alpha]_D^{20}$ = - 35 (c 0.33, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$, δ 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$_3$, δ 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$_4$Na [M+Na]$^+$ 259.0940; found 259.0941.

(4S,5S)-5-(4-nitrophenyl)-4-pentyldihydrofuran-2(3H)-one (11ca)

Yield: 66%, orange oil; $[\alpha]_D^{20}$ = + 15 (c 0.50, CH$_2$Cl$_2$); ^{1}H NMR (300 MHz, CDCl$_3$, δ 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$_3$, δ 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$_4$Na [M+Na]$^+$ 300.1206; found 300.1207.

5,5'-((2S,3S,4S,5S)-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$_3$, δ 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$_3$, δ 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.

Acknowledgements

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