A stereodivergent synthesis of β-hydroxy-α-methylene lactones *via* vinyl epoxides†

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A catalytic diastereoselective sulfonium ylide epoxidation of aldehydes furnished original vinyl epoxides, having an MBH backbone. These highly functionalised building blocks were used for a formal synthesis of the antibiotic conocandin, and opened up a stereodivergent route towards β-hydroxy-α-methylene lactones, core units of naturally occurring compounds. Under acidic conditions, the oxiranes were mainly transformed, with moderate to good yields, into *trans* β-hydroxy-α-methylene lactones. On the other hand, a user-friendly palladium-catalysed CO_2 insertion and cyclisation sequence gave the *cis* β-hydroxy-α-methylene lactone counterparts along with an interesting *cis–trans* equilibration of the π-allyl intermediates.

Introduction

Belonging to the wide-ranging naturally occurring family of α-methylene-γ-butyrolactones, the β-hydroxy-α-methylene lactone scaffold **I** is found within compounds having a large array of biological functions (Fig. 1).[1] Their pharmaceutical activities are related to their structures, from the simpliest motif to some more elaborate ones. For instance, the simple motif of tulipalin B[2] provides fungicidal activity, whereas the more complex waol A[3] (a *trans* lactone) and lincomolide B[4] (a *cis* lactone) feature, respectively, potent activity against cancer tumor cell lines and antitubercular properties.[5] In addition, the open-chain diol **II** displays the highly synthetically versatile Morita–Baylis–Hillman (MBH) backbone,[6] namely an α-methylene-β-hydroxycarbonyl structure, which is flanked by an extra alcohol function. These densely functionalised alk-1-en-3,4-diols have proved to be useful intermediates in organic synthesis.[7]

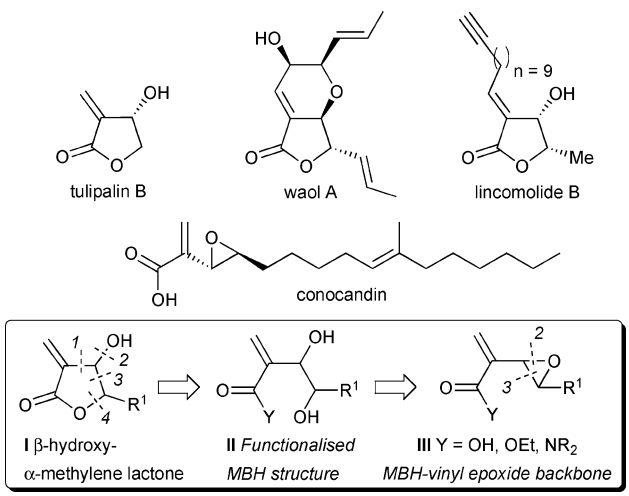

Fig. 1 β-Hydroxy-α-methylene lactones.

The synthetic endeavours towards β-hydroxy-α-methylene-γ-butyrolactones include the stereochemical control of C-4 and C-5 (in the relative and absolute sense) within such highly decorated five-membered rings. Early on, the stereoselective synthesis of these compounds was based on modifications of sugar derivatives.[8] In the 1980s, aldolisation reactions of esters derivatives to chiral aldehydes (with an α-alkoxy group) were developed and furnished a C–C bond-formation approach *via* disconnection 1 (**I**, Fig. 1). The lactone ring was subsequently formed by cyclisation of the obtained diol **II**, from which the alkene moiety was regenerated by β-elimination of a heteroatom (at the β or α position).[9] The direct inter- and intra-molecular addition of acrylates to chiral aldehydes in the presence of an amine (MBH reaction) was achieved with good *anti*:*syn* selectivities.[10] With respect to these methods, a chiral acrylamide derived from Oppolzer's sultam auxiliary was involved in a highly diastereoselective MBH reaction to form a readily available precursor of tulipaline B (Fig. 1).[2b] The addition of vinyl anion (Br–Li exchange of the corresponding vinyl bromide) to chiral aldehydes was also studied for the elaboration of target **I** in few steps.[11] Alternatively, a sequence involving a diastereoselective Schenck ene-reaction (singlet oxygen) to allylic alcohols was developed in order to introduce the alcohol at C-4 (disconnection 2).[12] On the other hand, the enantioselective Sharpless dihydroxylation of alkenes turned out to be the method of choice for the introduction of the diol moiety (disconnections 2 and 4). In that context, Liu and co-worker prepared an acetylenic diol from an ene-yne substrate with good ee. They subsequently performed an elegant cycloalkenation of the corresponding propargyltungsten intermediate with acetylenic aldehydes. The obtained oxacarbenium salt was subsequently

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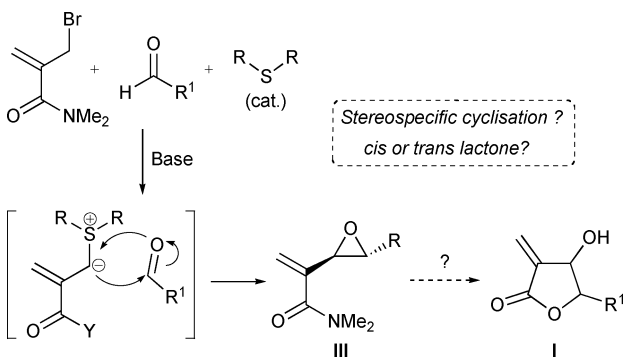
demetallated to β-hydroxy-α-methylene lactones.[13] Brückner and co-workers studied a straightforward regioselective dihydroxylation of α′,β′,α,β-unsaturated esters which led, after cyclisation, to lactones with moderate to good enantiomeric excesses.[14] The *cis* and *trans* derivatives were obtained with respect to the geometry of the starting dienes. Krische and Rhee have recently described an effective reductive cyclisation of acetylenic aldehydes catalysed by enantiopure rhodium complexes (disconnection 1).[15] All these methods have been providing elegant and new approaches to β-hydroxy-α-methylene lactone scaffolds but, in some cases, they suffer from a lack of generality due to the specificity of the starting materials. Moreover, the level of selectivities obtained so far leaves space for improvement.

We recently became interested in the use of epoxides **III** ($R^1 = NMe_2$), which are readily available by sulfonium ylide epoxidation of aldehydes R^1CHO (Fig. 1).[16] This skeleton displays both a vinyl epoxide and an MBH building block, which offer many synthetic transformation opportunities. Moreover, this motif is present within conocandin (Fig. 1), a potent antibiotic isolated by Müller and co-workers in 1976 from a strain of *Hormococcus conorum*.[17] In that context, we envisaged an alternative approach to β-hydroxy-α-methylene lactone structures based on disconnections 2 and 3. The open-chain intermediate diol **II** would be formed *via* a stereoselective ring-opening transformation of vinyl epoxides **III**, to allow a concise access to the lactone ring after cyclisation. To our knowledge, few publications bring confidence in the feasibility of this sequence. Kende and Toder described a single example showing the ability of a *trans* ester-epoxide **III** (Y = OEt, R^1 = Me, Fig. 1) to undergo cyclisation to a racemic *trans* β-hydroxy-α-methylene lactone in the presence of a Brønsted acid.[18] Carlson and Yang synthesized *in situ* carboxylic acid derivatives **III** (Y = OH, Fig. 1), from epoxidation of the corresponding aldehydes, which, upon an acidic work-up, furnished the methylene lactone **I** with moderate *cis* and *trans* ratios.[19] These lactonisation sequences were used as a key step towards bioactive compounds.[20]

Making use of allylic bromide derivatives having an acrylamide moiety (Scheme 1),[16] we recently described an organocatalytic sulfonium ylide epoxidation allowing a straightforward connective formation of vinyl epoxides **III** (Y = NMe_2) *via* C–C and C–O bond formation.[21–23] We established that the presence of an amide (instead of an ester or acid) was crucial to preserve the acrylate moiety integrity, which otherwise underwent polymerisation events in these basic conditions. But the ability of these robust epoxy-acrylamides to undergo lactonisation, in a stereospecific way, is uncertain. We report herein in full our attempts and successes to develop a route to β-hydroxy-α-methylene lactones *via* this epoxidation–cyclisation sequence, providing a stereodivergent entry to these compounds. The application of this epoxidation towards a novel formal synthesis of conocadin will also be described.

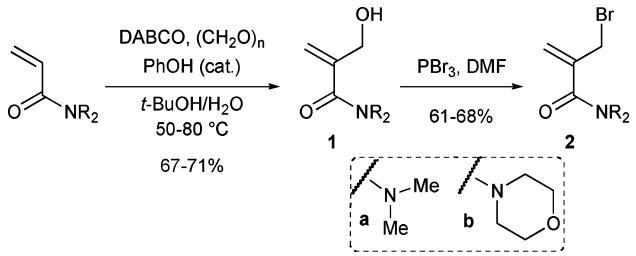


Scheme 1 Strategy.

Results and discussion

Synthesis of epoxidation precursors

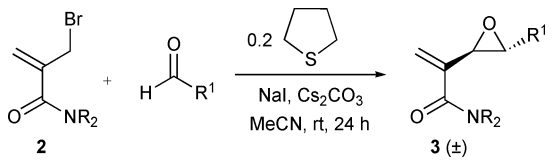
At the onset of this project, we developed a straightforward access to allylic bromide derivatives **2**, our epoxidation precursors. This synthesis was based on a successful two step MBH–bromination sequence from the weakly reactive tertiary dimethyl acrylamide (Scheme 2).[16,24] This reaction has been easily extended to morphonyl acrylamide.



Scheme 2 Synthesis of 2-bromomethylacrylamide derivatives.

Sulfonium ylide epoxidation

Both allylic precursors **2a** and **2b** reacted smoothly in one day at ambient temperature with various aromatic aldehydes, or cinnamaldehyde, in the presence of caesium carbonate and a substoichiometric amount of thiolane (Scheme 3).[16] This organocatalytic open-air process furnished the corresponding epoxides **3** with high *trans* selectivities (Table 1, entries 1–6) regardless of the amide moiety (entries 1 *vs.* 11).[22c] Aliphatic aldehydes, such as valeraldehyde, underwent epoxidation in 60 to 78% yield but with lower diastereoisomeric ratios (entries 7 and 12). Branched (more hindered) aldehydes gave lower yields due to a slower reaction of the ylide reagent (entries 8 and 10). Unfortunately, longer reaction times led only to moderate improvements in yield due to decomposition of the allylic reactant. Therefore, we used a stoichiometric amount of sulfonium salt, preformed *in situ* in water from **2** (entry 9),[25] and improved the yield of epoxide **3h** from 51 to 71%, albeit with lower dr.



Scheme 3 Epoxidation of aldehydes (see Table 1).

These outcomes are in agreement with the recently proposed mechanism by Aggarwal and Harvey explaining the diastereoselectivity of the epoxidation of aldehydes by aryl sulfonium ylides.[26–28]

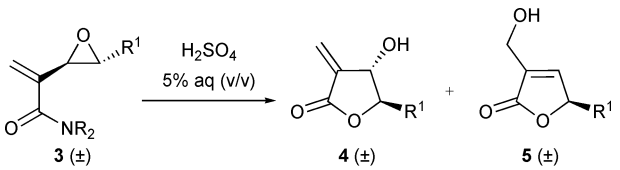
Table 1 Epoxidation of aldehydes (see Scheme 3)[a]

Entry	NR_2	R^1	Product	Yields[b] (%)	dr (*trans*/*cis*)
1	NMe_2	C_6H_5	**3a**	90	>95 : 5
2	NMe_2	4-$CF_3C_6H_4$	**3b**	92	93 : 7
3	NMe_2	4-$NO_2C_6H_4$	**3c**	83	94 : 6
4	NMe_2	4-$MeOC_6H_4$[c]	**3d**	73[d] (33[e])	>95 : 5
5	NMe_2	2-Furyl	**3e**	75[d]	95 : 5
6	NMe_2	PhCH=CH	**3f**	85[d] (67[e])	92 : 8
7	NMe_2	*n*-Butyl	**3g**	78	77 : 23
8	NMe_2	*i*-Butyl	**3h**	51	78 : 22
9[f]	NMe_2	*i*-Butyl	**3h**	71	63 : 37
10	NMe_2	Cy	**3i**	39	62 : 38
11	NC_4H_8O	C_6H_5	**3j**	93	>95 : 5
12	NC_4H_8O	*n*-Butyl[c]	**3k**	66	71 : 29

[a] General reaction conditions: 0.25 mmol of benzaldehyde (0.5 M), allylbromide (1.3 eq.), thiolane (0.2 eq.), Cs_2CO_3 (1.8 eq.), NaI (0.2 eq.), MeCN, rt, 24 h. [b] Isolated yield after column chromatography on silica gel. [c] After 48 h. [d] NMR yield with an internal standard. [e] Purification on neutral alumina. [f] Preformation of the sulfonium salt in water between allylbromide (1 eq.), thiolane (1 eq.) for 5 h, followed by the addition of *t*-BuOH (9 : 1 *t*-BuOH–H_2O), aldehyde (1 eq.), NaOH (2 eq.).

Lactonisation of the obtained vinyl epoxides

Having the original epoxides **3** in hand, we undertook the direct lactonisation reaction under acidic conditions according to Scheme 4.



3a R = NMe_2, R^1 = Ph
3b R = NMe_2, R^1 = *p*-$CF_3C_6H_4$
3g R = NMe_2, R^1 = *n*-Butyl
3j R = NC_4H_8O, R^1 = Ph
3k R = NC_4H_8O, R^1 = *n*-Butyl

Scheme 4 Lactonisation under acidic conditions (see Table 2).

We screened many Brønsted and Lewis acids, eventually finding that the best conditions involved the use of an aqueous sulfuric acid solution (Table 2).[29] The epoxides **3a** and **3j** led to the corresponding major *trans* lactone **4a** (R^1 = Ph) in poor yield irrespective of the amide moiety (entries 1–3). The slow diastereospecific cyclisation at room temperature (entry 1) was speeded up at 60 °C (entries 1 *vs.* 2–3) but this was detrimental to the *trans*/*cis* ratio. At this stage, the relative stereochemistry was fully determined by NMR NOE experiments.[29] The epimerisation event was not observed when an electron-poor aryl group was present (entry 4). Much better results were obtained with oxiranes **3g** and **3k**, having an alkyl chain, which were transformed into the main *trans* derivatives **4c** in a diastereospecific manner and with more than 60% yield (entries 5 and 7). We also observed the formation of the furanone isomer **5** (R^1 = *n*-Bu).[30] The amount of this derivative increased with the reaction time (entry 6). We supposed that the furanone **5** is the thermodynamic product of the whole process, coming from the β-hydroxy-α-methylene lactone, *via* acid-catalysed isomerisation of the allylic alcohol unit.[31] Accordingly, this forced us to run these reactions for a short period of time (20 minutes) to minimize the amount of furanone **5**.

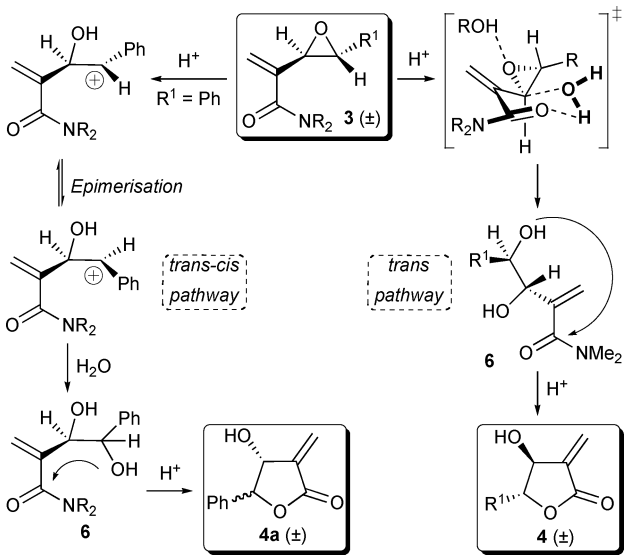
This method constitutes a very simple entry to *trans* β-hydroxy-α-methylene lactones and affords useful yields with derivatives having an alkyl group at the 5 position giving, moreover, diastereospecific cyclisations. The access to *trans* lactones having an aryl groups at C-5 was limited by poor yields, and/or epimerisation of the main *trans* epoxides. In order to get a reasonable working hypothesis, we established a mechanistic explanation of these outcomes (Scheme 5).

We assumed that a molecule of water (solvent) adds directly to the activated allylic carbon under acid catalysis, in an S_N2 manner, to lead to the corresponding diol **6** with inversion of configuration (*trans* pathway).[32] Although not required, we suppose that an extra hydrogen bond between the incoming water nucleophile and the amide could also stabilize the transition state. Then, the diol easily cyclises into lactone and the cleavage of the robust amide function is facilitated due to the intramolecular nature of this step.[33] In the case of a phenyl group (R^1 = Ph) a carbocation at

Table 2 Lactonisation of epoxides **3** in acidic conditions (see Scheme 4)

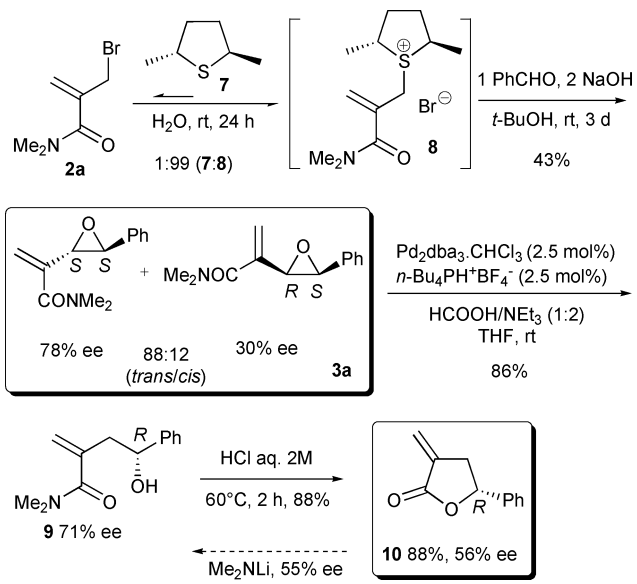
Entry	Epoxide **3**[a] (*trans*/*cis*)	Time	Temp.	Lactone **4**[a] (*trans*/*cis*)	Yield[b](%)	**4**/**5**[a]
1	**3a** (95 : 5)	21 h	rt	**4a** (92 : 8)	15	100 : 0
2	**3a** (95 : 5)	30 min	60 °C	**4a** (64 : 36)	13	100 : 0
3	**3j** (95 : 5)	30 min	60 °C	**4a** (72 : 28)	24	100 : 0
4	**3b** (93 : 7)	60 min	60 °C	**4b** (90 : 10)	20	100 : 0
5	**3g** (78 : 22)	20 min	60 °C	**4c** (79 : 21)	62	90 : 10
6	**3g** (78 : 22)	6.5 h	60 °C	**4c** (76 : 24)	30	38 : 62
7	**3k** (71 : 29)	20 min	60 °C	**4c** (72 : 28)	66	92 : 8

[a] Determined by ^1H NMR spectroscopy of the crude product. [b] Isolated yield of both *trans* and *cis* lactone.



Scheme 5 Mechanistic proposal.

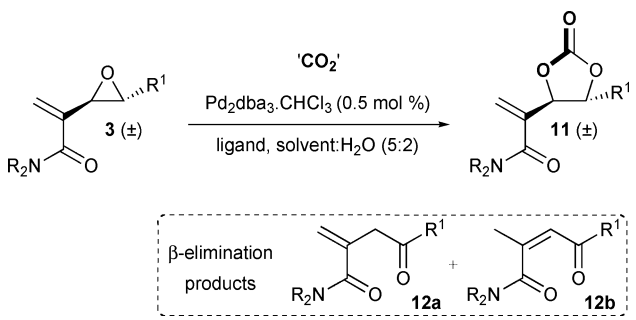
the benzylic position would be stabilized for a period of time long enough to allow the attack of a molecule of water on either face of the sp^2 carbon (*trans*/*cis* pathway). Once again, the diol **6** would easily cyclise into a mixture of *trans* and *cis* lactones with regard to the previous epimerisation event.[34] Some indirect proof of this hypothesis arose from previous studies that we performed to determine the absolute configuration of the enantioenriched epoxide **3a** (Scheme 6).[16] Our first attempts towards an enantioselective epoxidation gave the best result with NaOH as a base, but showed that the addition of a bulkier C_2-symmetrical sulfide **7** (with respect to thiolane) to allylic bromide **2a** was slow. A moderate yield was obtained (34% yield) and concurrent side reactions with the unreacted reactants occurred.[35] Therefore, we established a user-friendly protocol in order to preform the sulfonium salt before adding other reagents. It was shown that a mixture of sulfide **7** and **2a** resulted in complete



Scheme 6 Determination of the absolute configuration of the enantioenriched epoxide **3a**.

formation of the corresponding sulfonium salt **8** in the presence of water.[25] This protocol allowed the subsequent *in situ* addition of the other components, and led to an improved yield and enantioselectivity (Scheme 6). The enantiomeric excess of both *trans* and *cis* vinyl oxiranes **3a** (whose absolute configuration was *a priori* unknown) was determined by HPLC. We then successfully carried out Tsuji's palladium-catalysed reduction on the mixture of epoxides **3a** to form the corresponding secondary alcohol **9**.[36] This alcohol underwent smooth cyclisation, with slight racemisation, into α-methylene lactone **10**, for which the absolute configuration had previously been determined in the literature.[37] The addition of lithium dimethylamide allowed the reverse synthesis of the secondary alcohol with the same absolute configuration (comparison of HPLC analysis), showing, thereby, that the lactonisation mainly took place with a retention of configuration. Therefore, we could deduce the absolute configuration of the original epoxides **3a**. To explain these results, the lactonisation (**9** to **10**) should go mainly through the attack of the alcohol to the amide (retention of configuration).[33] The concomitant formation of the other enantiomer) occurs likely *via* the formation of a carbocation followed by the attack of a molecule of water, which is reminiscent of the proposal in Scheme 5. On the other hand, we can not rule out the direct attack of the amide moiety onto the carbocation, followed by the hydrolysis of the obtained iminium into lactone **10**.[34] Nevertheless, this shows that the amide bond is easily cleaved in the presence of a γ-hydroxy group, and therefore that our challenge would be the clean formation of the corresponding diol **6** (Scheme 5) to form a β-hydroxy-α-methylene-γ-butyrolactone.

The successful formation of π-allyl intermediates with vinyl epoxide **3a** (Scheme 6) prompted us to envisage a carbon dioxide insertion into this catalytically formed reagent, as shown in Scheme 7.[38] Thereby, the carbonate derivatives **11** would be obtained, and this masked diol could easily be cyclised into a lactone.



Scheme 7 CO_2 insertion (see Tables 3 and 4).

Our first attempt, with a poorly coordinated phosphite ligand under CO_2 atmosphere, led to the corresponding carbonate **11a** with 63% yield and a very good 92 : 8 ratio of *trans*/*cis* isomers (Table 3, entry 1). However, this process was accompanied by the formation of ketones **12** (Scheme 7), arising from a β-elimination reaction. Pleasingly, a much better result was obtained by making use of bicarbonate as a user-friendly carbon dioxide surrogate (entry 2), which was originally described by Trost and McEachern.[39] Only traces of **12** could be seen in the NMR of the crude product. Probing the scope of these conditions, we observed no reaction with sodium carbonate as a base (entry 3)

Table 3 CO_2 insertion into epoxide **3a** (R^1 = Ph)[a]

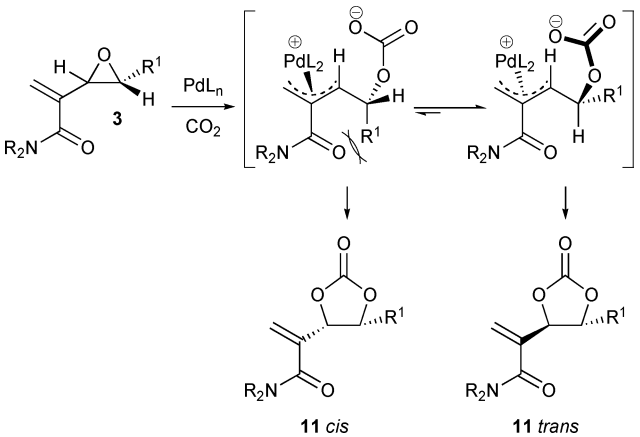
Entry	Ligand	CO_2 source	Solvent	Conv.[b](%)	Yield[b](%)	rd **11a**[c] (*trans*/*cis*)	**11a** : **12a** : **12b**[c]
1	P(O*i*-Pr)$_3$	CO_2[d]	CH_2Cl_2	100	63	92 : 8	84 : 3 : 13
2	P(O*i*-Pr)$_3$	$NaHCO_3$	CH_2Cl_2	100	80	92 : 8	>99 : 1 : 1
3	P(O*i*-Pr)$_3$	Na_2CO_3	CH_2Cl_2	7	—	—	—
4	P(O*i*-Pr)$_3$	$NaHCO_3$	THF	0	—	—	—
5	P(O*i*-Pr)$_3$	$NaHCO_3$	MeCN	0	—	—	—
6	PPh_3	$NaHCO_3$	CH_2Cl_2	90	52	90 : 10	76 : 6 : 19
7	dppe	$NaHCO_3$	CH_2Cl_2	93	—	94 : 6	62 : 6 : 32
8	dppb	$NaHCO_3$	CH_2Cl_2	5	—	—	—

[a] The reactions were performed at rt for 30 hours with the epoxide **3a** having a >95 : 5 ratio (*trans*:*cis*). [b] For both *trans* and *cis* carbonates. [c] Determined on the ^{1}H NMR of the crude product. [d] Under CO_2 atmospheric pressure without water as solvent.

or with more coordinating solvents (entries 4–5). The use of a more electron-rich phosphine such as PPh_3 led to an increase in side products **12** (entry 6). Eventually, we found that bidentate phosphine ligands resulted in a slower reaction, or an increase in β-elimination products, depending on their bite-angle (entries 7 and 8). It seems that a strongly coordinating environment (solvent or ligand) renders more difficult either the coordination or the oxidative insertion to the vinyl epoxide moiety, by hindering and/or saturating the metal. Moreover, for successful π-allyl derivative formation, the subsequent reaction of CO_2 is retarded, favouring the β-elimination process.[40]

We next focused on the scope and limitation of this easily performed reaction with various epoxides **3** (Table 4). The reaction worked well with both dimethyl or morpholinyl amides (entries 1 and 2). It was found that an electron-withdrawing group on the aryl moiety slowed down the process (entry 3), or completely suppressed the CO_2 insertion in favour of the β-elimination reaction (entry 4). This constitutes a chemical limitation of this metal–ligand couple. However, a very interesting observation was made with epoxides **3g–i** having an alkyl moiety. With *n*-butyl (entry 5), *i*-butyl (entry 6) and cyclohexyl groups (entry 7), a virtually complete re-equilibration of the initial *trans*/*cis* mixture of epoxides into *trans* carbonates took place. Although this palladium-promoted isomerisation is well-described with vinyl aziridines,[41] this event has been scarcely reported with vinyl epoxides.[42] In our case, this original process is highly useful, as the sulfonium ylide epoxidation of aliphatic aldehydes usually occurs with moderate diastereoselectivities. Therefore, we achieved an excellent *trans*/*cis* ratio for this CO_2 insertion step.

An explanation of this phenomenon could stem from the observation depicted in Scheme 8. The distribution of both π-allylpalladium complexes (*via* π–σ–π interconversion), or the cyclisation transition states thereof, would be dictated by the minimization of the *A*(1,3) repulsion between amide and R^1 groups of the *cis*-carbonate precursor. On one hand, the selectivity would be controlled by the fastness of the cyclisation step into carbonates **11** and a kinetic dynamic resolution would take place (as long as a fast equilibrium occurs). On the other hand, the *trans* and *cis* ratio of compounds **11** could also reflect the thermodynamic stability of both π-allylpalladium intermediates.



Scheme 8 Mechanistic proposal.

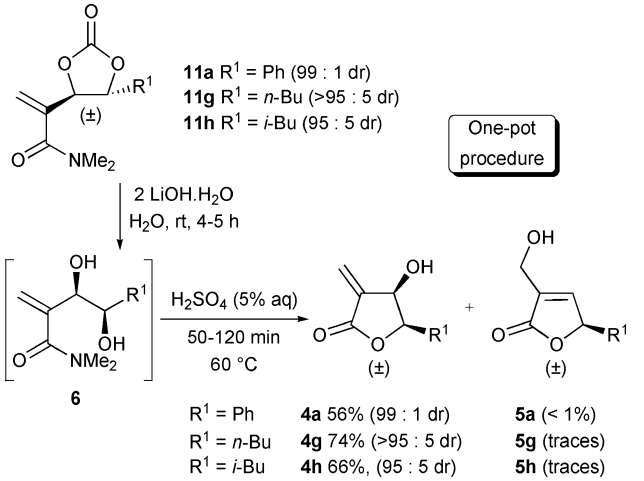
We carried out the direct transformation of these masked diols **11** into their corresponding methylene lactones **4**. However, under various conditions (Brønsted and Lewis acids), we obtained the lactones in low yields. It turned out that the carbonate deprotection was slower than the diol lactonisation so that the accumulated lactone **4** decomposed during the reaction time. Therefore, we

Table 4 CO_2 insertion into of epoxide **3**[a]

Entry	Epoxide (*trans*/*cis*)	R^1	NR_2	Conv.[b](%)	Yield[b] (%)	Carbonate **11** (*trans*/*cis*)[d]
1	**3a** (>95 : 5)	Ph	NMe_2	100	80	**11a** (92 : 8)
2	**3j** (>95 : 5)	Ph	NC_4H_8O	100	77	**11j** (>95 : 5)
3	**3b** (93 : 7)	4-$CF_3C_6H_4$	NMe_2	45	—	**11b** (94 : 6)
4	**3c** (96 : 4)	4-$NO_2C_6H_4$	NMe_2	100	0[c]	—
5	**3g** (77 : 23)	*n*-Bu	NMe_2	100	91	**11g** (>95 : 5)
6	**3h** (78 : 22)	*i*-Bu	NMe_2	100	85	**11h** (95 : 5)
7	**3i** (62 : 38)	Cy	NMe_2	100	71	**11i** (>98 : 2)

[a] General reaction conditions: 1.15 mmol of epoxides **3**, $NaHCO_3$ (6 eq.), $Pd_2dba_3{\cdot}CHCl_3$ (0.5 mol%), P(O*i*-Pr$_3$) (3 mol%), CH_2Cl_2–H_2O (5 : 2), rt, 30 h. [b] For both *trans* and *cis* carbonates. [c] Exclusive formation of ketones **12**. [d] Determined on the NMR of the crude product.

focused our attention on a two-step, but one-pot procedure (Scheme 9).[42a]

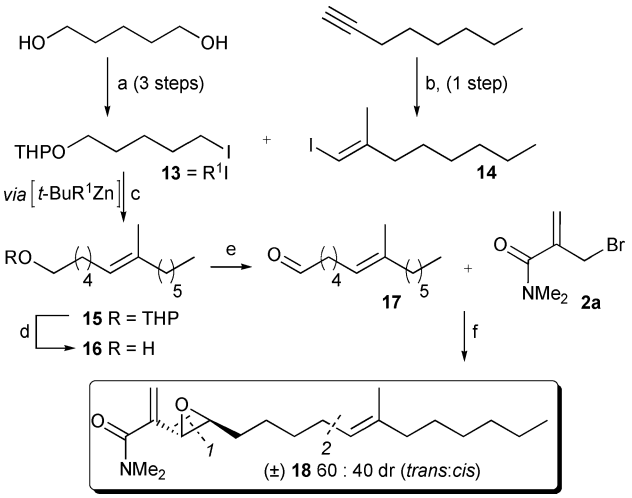


Scheme 9 Synthesis of *cis* lactone.

An easy saponification proceeded in the presence of lithium hydroxide in water to furnish the desired diol **6** *in situ*. All attempts to isolate this compound were unsuccessful due to its high polarity. The addition of dilute sulfuric acid solution then smoothly performed the lactonisation into products **4**. Once again, the reaction time for the cyclisation step had to be as short as possible to prevent a formation of a large amount of furanone **5**, likely to be the thermodynamic product (seen on the NMR of the crude product). This lactonisation sequence was achieved at 60 °C in a stereospecific fashion even with the phenyl-substituted carbonate. In contrast to acid-catalysed lactonisation of epoxides **3** (Scheme 5 *vs.* Scheme 9), one can suppose that the diol **6** ring-closing step is fast enough to prevent any epimerisation. However, the lactones **4g–h** with a 5-alkyl group gave the best results once again, certainly due to their higher stability in acidic conditions compared to aryl lactones (Scheme 9). It is noteworthy that the overall process furnished *cis* lactones, thanks to the epoxide transformation into carbonate taking place with retention of configuration. So, this approach is complementary to the acid-catalysed cyclisation of vinyl epoxides **3**, which mainly afforded *trans* lactones. Therefore, we have developed a stereodivergent methodology to both *cis* and *trans* lactones from our *trans* vinyl oxiranes **3**.

Synthetic application

The epoxidation methodology allowed us to achieve an alternative formal synthesis of the naturally occurring metabolite conocandin (Fig. 1), based on disconnections 1 and 2 (Scheme 10).[17] The elaboration of this potent antibiotic has been studied by two groups, who have pointed out the challenging stereocontrol of the trisubstituted C–C double bond and the vinyl epoxide units,[43] requiring multi-step strategies. However, the sulfonium ylide epoxidation of **17** (Scheme 10), at a later stage of the synthesis, afforded the opportunity of a convergent synthesis of this aldehyde from commercial pentan-1,5-diol and 1-octyne. For that purpose, we wanted to use Negishi's methodologies,[44] namely zirconium-catalysed carboalumination and zinc cross-coupling reactions. The precursor **14** was readily formed in high regioselectivity by



Scheme 10 Formal synthesis of conocandin. *Reagents and conditions*: a) i. DHP, *p*-TSA; ii. MsCl, Et_3N; iii. NaI (ref. 46); b) i. Me_3Al (3 eq.), Cp_2ZrCl_2 (0.2 eq.), H_2O (1.5 eq.), CH_2Cl_2, 0 °C, 1h; ii. I_2, THF (76%), (ref. 45); c) i. **13** (1.5 eq. with respect to **14**), $ZnCl_2$ (1.9 eq.), *t*-BuLi (6 eq.), ether, −78 °C; ii. **14** (1 eq.), $Pd(PPh_3)_4$ (0.02 eq.), ether (73%, estimated with an NMR internal standard); d) *p*-TSA, MeOH (50% from **14**); e) TPAP, NMO, acetone (58%); f) i. allyl bromide **2a**, thiolane (1 eq.), H_2O, rt, 5 h; ii. Aldehyde **17** (1 eq.), NaOH (2 eq.), *t*-BuOH (*t*-BuOH–H_2O 9 : 1), rt, 39 h (62%).

a carboalumination–iodation sequence, in the same flask, based on Wipf's protocol.[45] Then, the known iodide **13**[46] was expected to react with vinyl iodide **14** by means of a metal-catalysed cross-coupling reaction to form the challenging trisubstituted alkene.[43] In our hands, the only successful protocol made use of the *in situ* pre-formation of the *tert*-butyl alkylzinc derivative from **13** (*t*-BuR^1Zn) according to Smith's conditions.[47] After optimisation, this reagent allowed a palladium-mediated coupling process to take place with vinyl iodide **14** to give **15** in 73% yield (determined by NMR with an internal standard). Nearly 10% of diene and the hydrolysed C_5H_{11}OTHP derivatives were also formed, and, unfortunately the latter was inseparable from **15** by column chromatography. However, the THP deprotection led to the known alcohol **16**,[17c] which was easily purified on silica gel. TPAP oxidation furnished the aldehyde **17**,[48] which turned out to be unstable on silica. Then, **17** was subsequently engaged in the sulfonium ylide epoxidation reaction to give the target epoxide **18** in 62% yield and a moderate diastereoselectivity in favour of the *trans* isomer. Although the epoxidation deserves further optimisation, this reaction is performed late in the synthesis and thus allows a convergent strategy towards the precursor aldehyde **17**.[49] Therefore, the alkyl chains flanking the alkene moiety could be easily and rapidly modified *en route* to the elaboration of analogues of conocandin. The hydrolysis of the amide moiety is currently under investigation by taking advantage of the *trans*-amido-esterification sequence used in the aforementioned lactonisation.

Conclusions

We have described a straightforward organocatalytic sulfur ylide epoxidation of aldehydes, furnishing vinyl epoxides with an MBH backbone. This useful building block allowed a stereodivergent

synthesis of both *cis* and *trans* β-hydroxy-α-methylene lactones, the core structure of some naturally occurring compounds. The *cis* lactones were formed in two steps *via* the corresponding carbonates, which were synthesized by a user-friendly palladium-catalysed carbon dioxide insertion into epoxides making use of $NaHCO_3$ as a CO_2 source. During this process, an interesting isomerisation of *cis* oxiranes into *trans* carbonates was observed, resulting in a synthesis of *cis* lactones with high selectivities. The main *trans* lactones were obtained by a direct cyclisation of the corresponding oxiranes functionalised by aryl or alkyl groups. The latter gave the best results in terms of yields and diastereospecificity. This study has also pointed out the limitations of the currently used conditions, by showing that certain aryl-functionalised epoxides could not be transformed in good yield (low reactivity or product instability). Seeking to extend the scope of this methodology, we have also succeeded in the synthesis of enantioenriched *trans* (*S*,*S*)-vinyl epoxides by a C_2 symmetrical sulfide, but in moderate yields and selectivities so far. We are currently focusing on the improvement of these results. Indeed, the non-racemic epoxides would open straightforward enantioselective routes towards either *trans* or *cis* β-hydroxy-α-methylene lactones. Moreover, the convergent synthesis of the metabolite conocandin, achieved in this paper, could be extended to both enantiomers of this potent antibiotic.

Experimental

General

NMR spectra were recorded on Bruker DPX 250 (^{1}H: 250 MHz, ^{13}C: 63 MHz) or Bruker DRX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instruments in $CDCl_3$ unless indicated otherwise. Multiplicities in ^{13}C were determined by DEPT135 experiments. IR spectra were recorded on a Perkin-Elmer Spectrum-One ATR spectrophotometer. Mass spectra were recorded on a Varian GC/MS/MS instrument equipped with CP 3800 (GC) and Saturn 2000 (MS/MS) modules. Microanalyses were obtained using a ThermoQuest instrument. Exact mass spectra were recorded on a Waters Q-TOF Micro apparatus (LC/MS) with an Xterra MS column. Purification by flash chromatography of compounds was achieved with Merck 60 silica gel (40–63 μm). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (1.1 mm, Merck). Compounds **1–2a** and **3a–g** have been previously described.[16] All reagents were used without any purification unless noted otherwise.

4-[2-(Hydroxymethyl)acryloyl)]morpholine (1b). Paraformaldehyde (901 mg, 30 mmol), DABCO (693 mg, 6 mmol) and phenol (141 mg, 1.5 mmol) were introduced into a 10 mL flask with a stirring bar. The vessel was fitted with a septum and gently flushed with argon. A *t*-BuOH–H_2O (3 : 7) solvent mixture (370 μL) and 4-acryloylmorpholine (780 μL, 6.0 mmol) were then added *via* a syringe. The resulting mixture was stirred for 27 h at 55 °C (oil bath temperature) and was then allowed to cool to room temperature. Water was co-evaporated with toluene under vacuum. The crude mixture was then filtered over Celite with dichloromethane and concentrated *in vacuo*. Purification by column chromatography (AcOEt–EtOH 5 : 1, R_f = 0.33) afforded the desired product (688 mg, 67%) as colorless crystals. Mp 91–92 °C. δ_H(250 MHz): 5.49 (s, 1H), 5.17 (s, 1H), 4.28 (d, 2H, J = 5.3 Hz), 3.65 (brs, 8H), 3.05 (t, 1H, J = 5.3 Hz, OH, disappears after D_2O exchange). δ_C(100 MHz): 169.9 (C), 143.4 (C), 115.6 (CH_2), 66.99 (CH_2), 66.96 (CH_2), 63.9 (CH_2), 47.9 (CH_2), 42.2 (CH_2). ν_{max}/cm^{-1} (neat) 3313, 2859, 1597, 1431, 1279, 1110, 1068, 1032, 911, 844. MS (ESI) m/z (%): 172 (37, $[M + H]^+$), 154 (30), 114 (100), 100 (14), 88 (60), 85 (30). Found: C, 55.74; H, 7.61; N, 8.14. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18.

4-[2-(Bromomethyl)acryloyl)]morpholine (2b). The alcohol **1b** (644 mg, 3.76 mmol) was dissolved in anhydrous diethyl ether (3 mL) in a round-bottomed flask under nitrogen pressure. Dimethylformamide (1.46 mL, 18.90 mmol) was added and the mixture was cooled to −5 °C. A solution of PBr_3 (176 μL, 1.90 mmol) in anhydrous diethyl ether (685 μL) was then added dropwise. A white precipitate then appeared. The reaction was stirred at room temperature and monitored by TLC (AcOEt–EtOH 4 : 1). After 15 h, the mixture was quenched by hydrolysis with water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The organic layers were combined and washed with water (2 × 100 mL) to remove dimethylformamide. Then, the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt–pentane 4 : 1, R_f = 0.33) provided **2b** (595 mg, 68%) as white crystals. Mp 41–43 °C. δ_H(400 MHz): 5.51 (s, 1H), 5.12 (s, 1H), 4.20 (s, 2H), 3.67 (brs, 8H). δ_C(100 MHz): 168.0 (C), 139.6 (C), 118.2 (CH_2), 67.1 (CH_2), 66.9 (CH_2), 47.8 (CH_2), 42.3 (CH_2), 33.2 (CH_2). ν_{max}/cm^{-1} (neat): 2855, 1643, 1614, 1433, 1110, 1030, 842. MS (ESI) m/z (%): 234 (12, $[M + H]^+$), 147 (100), 119 (47), 100 (3). (Found: C, 41.03; H, 5.30; N, 6.20. Calc for $C_8H_{12}BrNO_2$: C, 41.05; H, 5.17; N, 5.98).

General procedure for the synthesis of vinyl epoxides 3. To a solution of the allylic bromide (0.33 mmol, 1.3 eq.), the aldehyde (0.25 mmol, 1 eq.) and sodium iodide (7.5 mg, 0.05 mmol, 0.2 eq.) in acetonitrile (0.5 mL), was added tetrahydrothiophene (4.5 μL, 0.05 mmol, 0.2 eq.). The reaction mixture was stirred for 5 min, then, caesium carbonate (147 mg, 0.45 mmol, 1.8 eq.) was added. The resulting mixture was vigorously stirred at 20 °C for 24 h. The salts were filtered and washed with CH_2Cl_2, and the filtrate was concentrated *in vacuo*. Purification by column chromatography afforded the desired epoxides. *Note*: the asymmetric synthesis of vinyl epoxide **3a** is described after compound **4c**.

***N*,*N*-Dimethyl-2-(3-isobutyloxiranyl)acrylamide (3h).** After 24 h of reaction and purification by column chromatography (AcOEt–pentane 1 : 1, R_f = 0.28), the inseparable *trans* and *cis* epoxides (78 : 22) were obtained as a colorless oil (25.2 mg, 51%). δ_H(400 MHz): *trans* 5.40 (s, 1H), 5.14 (s, 1H), 3.13 (d, J = 1.6 Hz, 1H), 3.05–2.86 (m, 7H), 1.80–1.65 (m, 1H), 1.45–1.25 (m, 2H), 0.86–0.84 (m, 6H). *cis* 5.32 (s, 1H), 5.26 (s, 1H), 3.56 (d, J = 4.4 Hz, 1H), 3.10–3.05 (m, 1H), 3.05–2.86 (m, 6H), 1.80–1.65 (m, 1H), 1.45–1.25 (m, 1H), 1.25–1.15 (m, 1H), 0.86–0.84 (m, 6H). δ_C(100 MHz): *trans* 168.7 (C), 142.4 (C), 116.4 (CH_2), 59.6 (CH), 57.9 (CH), 41.0 (CH_2), 38.7 (CH_3), 34.4 (CH_3), 26.2 (CH), 22.8 (CH_3), 22.3 (CH_3). *cis* 169.6 (C), 138.7 (C), 117.3 (CH_2), 58.5 (CH), 55.7 (CH), 35.2 (CH_2), 34.7 (CH_3), 34.7 (CH_3), 26.4 (CH), 22.64 (CH_3), 22.57 (CH_3). ν_{max}/cm^{-1} (neat): 2956, 1643, 1619, 1397, 1111, 905. MS (ESI) m/z (%): 198 (100, $[M + H]^+$), 180 (27), 153 (26), 152 (23), 135 (50), 123 (25), 111 (43), 107 (62), 97 (19).

HRMS (ESI): calcd for $C_{11}H_{20}NO_2$ $[M + H]^+$: 198.1494, found: 198.1485.

Stoichiometric epoxidation protocol for 3h. Thiolane (25 μL, 0.28 mmol) was added to a solution of the allylic bromide (53.1 mg, 0.28 mmol) in water (50 μL) at rt. Under vigorous stirring, the initial heterogeneous solution became homogeneous after 5 h. *t*-BuOH (450 μL), benzaldehyde (25 μL, 0.25 mmol) and NaOH (20 mg, 0.5 mmol) were subsequently added to the solution. The mixture was vigorously stirred for 24 h at room temperature and then diluted with water. The aqueous layer was extracted by dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (AcOEt–pentane = 1 : 1, $R_f = 0.28$) afforded the desired epoxides (35 mg, 71%) as an inseparable mixture of *trans* and *cis* diastereoisomers (63 : 37). See above for analyses.

***N*,*N*-Dimethyl-2-(3-cyclohexyloxiranyl)acrylamide (3i).** After 24 h of reaction and purification by column chromatography (AcOEt–pentane 1 : 1, R_f(*cis*) = 0.43, R_f(*trans*) = 0.37), parts of the *trans* and *cis* epoxides (60 : 40) were obtained separately as colorless oils (21.9 mg, 39%). δ_H(400 MHz): *trans* 5.46 (s, 1H), 5.21 (s, 1H), 3.31 (d, $J = 2.0$ Hz, 1H), 3.00 (s, 3H), 2.95 (s, 3H), 2.79 (dd, $J = 2.0$ and 6.7 Hz, 1H), 2.00–1.61 (m, 5H), 1.24–1.06 (m, 6H). *cis* 5.45 (t, $J = 1.3$ Hz, 1H), 5.34 (s, 1H), 3.71 (dd, $J =$ 1.3 and 4.4 Hz, 1H), 3.08 (s, 3H), 3.00 (s, 3H), 2.83 (dd, $J = 4.4$ and 8.5 Hz, 1H), 1.88–1.84 (m, 1H), 1.73–1.62 (m, 4H), 1.20–1.12 (m, 6H). δ_C(100 MHz): *trans* 168.9 (C), 142.8 (C), 116.4 (CH_2), 65.0 (CH), 56.8 (CH), 40.2 (CH_3), 38.9 (CH_3), 34.7 (CH), 29.3 (CH_2), 28.9 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 25.6 (CH_2). *cis* 169.5 (C), 138.7 (C), 117.5 (CH_2), 64.2 (CH), 56.5 (CH), 39.0 (CH_3), 35.1 (CH_3), 35.1 (CH), 30.4 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 25.5 (CH_2), 25.5 (CH_2). ν_{max}/cm^{-1} (neat): 2924, 1644, 1617, 1396, 1102, 870. MS (ESI) *m*/*z* (%): 224 (57, $[M + H]^+$), 206 (52), 161 (100), 133 (63), 128 (34), 97 (24), 91 (15). HRMS (ESI): calcd for $C_{13}H_{22}NO_2$ $[M + H]^+$: 224.1651, found: 224.1649.

4-[2-(3-Phenyloxiranyl)acryloyl]morpholine (3j). After 24 h of reaction and purification by column chromatography (AcOEt–pentane 2 : 1, $R_f = 0.39$), the epoxides were obtained as yellow crystals (60.3 mg, 93%) as an inseparable mixture of *trans* and *cis* diastereoisomers (95 : 5). δ_H(400 MHz): *trans* 7.35–7.27 (m, 5H), 5.61 (s, 1H), 5.36 (s, 1H), 4.00 (d, $J = 2.0$ Hz, 1H), 3.90–3.53 (m, 8H), 3.52 (d, $J = 2.0$ Hz, 1H). *cis* 5.57 (s, 1H), 5.16 (s, 1H), 4.30 (d, $J = 4.5$ Hz, 1H), 3.20 (d, $J = 4.5$ Hz, 1H). The other protons could not be observed for the *cis* diastereoisomer. δ_C(100 MHz): *trans* 167.1 (C), 141.4 (C), 136.4 (C), 128.7 (CH), 128.6 (CH), 125.7 (CH), 118.2 (CH_2), 67.05 (CH_2), 67.02 (CH_2), 62.1 (CH), 59.9 (CH), 47.8 (CH_2), 42.2 (CH_2). IR (neat): 2855, 1643, 1615, 1434, 1111, 1031, 844, 754, 698. MS (ESI) *m*/*z* (%): 260 (32, $[M + H]^+$), 242 (9), 173 (100), 145 (22), 117 (21), 100 (47), 91 (21), 88 (10). HRMS (ESI): calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$: 260.1287, found: 260.1279

4-[2-(3-Butyloxiranyl)acryloyl]morpholine (3k). After 48 h of reaction and purification by column chromatography (AcOEt–pentane 2 : 1, $R_f = 0.26$), the epoxides were obtained as a yellow oil (39.5 mg, 66%) as an inseparable mixture of *trans* and *cis* diastereoisomers (71 : 29). δ_H(400 MHz): *trans* 5.53 (s, 1H), 5.27 (s, 1H), 3.70–3.45 (m, 8H), 3.26 (d, $J = 2.1$ Hz, 1H), 3.02 (ddd, $J = 2.1$, 4.8 and 6.5 Hz, 1H), 1.72–1.30 (m, 6H), 0.91 (t, $J =$ 7.1 Hz, 3H). *cis* 5.47 (s, 1H), 5.37 (s, 1H), 3.02 (dd, $J = 3.3$ and 10.6 Hz, 1H). The other protons could not be observed for the *cis* diastereoisomer. δ_C(100 MHz): *trans* 167.3 (C), 142.0 (C), 117.2 (CH_2), 66.8 (CH_2), 66.8 (CH_2), 60.3 (CH), 57.8 (CH), 47.6 (CH_2), 41.9 (CH_2), 31.5 (CH_2), 27.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3). *cis* 168.0 (C), 138.1 (C), 117.7 (CH_2), 66.8 (2 CH_2), 59.7 (CH), 56.1 (CH), 47.6 (CH_2), 41.9 (CH_2), 28.3 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 13.9 (CH_3). ν_{max}/cm^{-1} (neat): 2958, 1644, 1619, 1432, 1112, 1031, 844. MS (ESI) *m*/*z* (%): 240 (100, $[M + H]^+$), 222 (29), 194 (7), 170 (21), 153 (39), 135 (60), 114 (76), 107 (34), 97 (7). HRMS (ESI): calcd for $C_{13}H_{22}NO_3$ $[M + H]^+$: 240.1600, found: 240.1606.

Representative procedure for the lactonisation of vinyl epoxides 3 to 4 under acidic conditions (Table 2). The vinyl epoxide (0.09 mmol, 1 eq.) and an aqueous solution of H_2SO_4 (2 mL, 5% v/v) were introduced into a Schlenk flask at 20 °C and were stirred at 60 °C (oil bath). After allowing to cool, the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (6 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (AcOEt–pentane) provided the desired lactones as a mixture of *trans* and *cis* diastereoisomers.

4-Hydroxy-3-methylene-5-phenyl-γ-butyrolactone (4a). After 30 min of reaction with epoxide **3a**, purification by column chromatography (AcOEt–pentane 1 : 1, R_f(*trans*) = 0.47, R_f(*cis*) = 0.33) gave the *trans* and *cis* lactones **4a** partly separated as yellow oils (24%, 72 : 28 dr). δ_H(400 MHz): *trans* 7.41–7.34 (m, 5H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.00 (d, $J = 2.2$ Hz, 1H), 5.22 (d, $J = 5.2$ Hz, 1H), 4.74 (brs, 1H), 2.76 (brs, 1H). *cis* 7.45–7.30 (m, 5H), 6.52 (d, $J = 2.0$ Hz, 1H), 6.02 (d, $J = 2.0$ Hz, 1H), 5.60 (d, $J = 6.1$ Hz, 1H), 5.05 (brs, 1H), 1.46 (d, $J = 6.1$ Hz, 1H). δ_C(100 MHz): *trans* 168.5 (C), 138.3 (C), 137.2 (C), 129.1 (CH), 129.0 (CH), 126.1 (CH_2), 125.6 (CH), 85.8 (CH), 75.8 (CH). *cis* 168.9 (C), 137.6 (C), 133.1 (C), 129.4 (CH), 129.1 (CH), 127.2 (CH_2), 126.8 (CH), 82.4 (CH), 70.5 (CH). ν_{max}/cm^{-1} (neat): 3422, 1748, 1146, 1069, 996, 696. MS (ESI^-) *m*/*z* (%): 189 (100, $[M\text{-}H]^-$), 161 (10), 159 (5), 145 (17), 143 (10), 133 (25), 127 (12), 117 (16), 115 (4). HRMS (ESI^-): calcd for $C_{11}H_9O_3$ $[M - H]^-$: 189.0552, found: 189.0549.

4-Hydroxy-3-methylene-5-(4-trifluoromethylphenyl)-γ-butyrolactone (4b). After 60 min of reaction with epoxide **3b**, purification by column chromatography (AcOEt–pentane 2 : 3, R_f(*trans*) = 0.32, R_f(*cis*) = 0.28) gave the *trans* and *cis* lactones **4b** separately as colorless oils (20%, dr 90 : 10). δ_H(250 MHz): *trans* 7.69 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 6.53 (d, $J = 2.6$ Hz, 1H), 6.04 (d, $J = 2.6$ Hz, 1H), 5.29 (d, $J = 5.2$ Hz, 1H), 4.73 (brs, 1H), 2.66 (d, $J = 6.4$ Hz, 1H). *cis* 6.56 (d, $J = 1.7$ Hz, 1H), 6.07 (d, $J = 1.7$ Hz, 1H), 5.64 (d, $J = 4.6$ Hz, 1H), 5.12 (brs, 1H). The other protons could not be observed for the *cis* diastereoisomer. δ_F(235 MHz): −62.7. δ_C(100 MHz): *trans* 167.9 (C), 141.3 (C), 137.8 (C), 131.3 (q, $^2J_{C\text{-}F} = 32.6$ Hz, C), 126.6 (CH_2), 126.1 (q, $^3J_{C\text{-}F} = 3.7$ Hz, CH), 125.8 (CH), 124.0 (q, $^1J_{C\text{-}F} =$ 272.4 Hz, C), 84.7 (CH), 75.8 (CH). ν_{max}/cm^{-1} (neat): 3239, 1754, 1330, 1114, 1071, 979, 838. MS (ESI^-) *m*/*z* (%): 256 (100, $[M - H]^-$), 229 (16), 213 (67), 201 (27), 193 (28), 165 (30), 145 (16). HRMS (ESI^-): calcd for $C_{12}H_8O_3F_3$ $[M - H]^-$: 257.0426, found: 257.0419.

4-Hydroxy-3-methylene-5-butyl-γ-butyrolactone (4c). After 20 min of reaction with epoxide **3k** and purification by column chromatography (AcOEt–pentane 2 : 1, $R_f = 0.42$), the inseparable *trans* and *cis* lactones **4c** were obtained as a colorless oil (66%, 72 : 38 dr). δ_H(400 MHz): *trans* 6.43 (d, $J = 2.2$ Hz, 1H), 5.98 (d, $J = 2.2$ Hz, 1H), 4.56–4.50 (m, 1H), 4.26 (ddd, $^3J_{H-H} = 4.4$ Hz, $^3J_{H\text{-}CH_2} = 5.4$ Hz and $^3J_{H\text{-}CH2} = 7.8$ Hz, correlated by ^{1}H NMR decoupling experiment, 1H), 2.31 (d, $J = 6.8$ Hz, 1H), 1.85–1.60 (m, 2H), 1.60–1.30 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H). *cis* 6.40 (d, $J = 1.7$ Hz, 1H), 5.98 (d, $J = 1.7$ Hz, 1H), 4.84–4.83 (m, 1H), 4.44 (dt, $^3J_{H\text{-}H} = {}^3J_{H\text{-}CH2} = 5.5$ Hz and $^3J_{H\text{-}CH2} = 8.4$ Hz, correlated by irradiated proton spectra, 1H), 2.21 (brs, 1H), 1.84–1.73 (m, 2H), 1.72–1.26 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H). δ_C(100 MHz): *trans* 168.8 (C), 139.1 (C), 126.0 (CH_2), 85.6 (CH), 73.2 (CH), 33.5 (CH_2), 27.1 (CH_2), 22.5 (CH_2), 14.0 (CH_3). *cis* 169.3 (C), 139.1 (C), 126.3 (CH_2), 82.5 (CH), 69.5 (CH), 28.4 (CH_2), 27.6 (CH_2), 22.7 (CH_2), 14.0 (CH_3). ν_{max}/cm^{-1} (neat): 3426, 2957, 1740, 1271, 1167, 1112, 984. MS (ESI) *m/z* (%): 171 (79, $[M + H]^+$), 153 (80), 135 (77), 125 (19), 111 (79), 109 (16), 107 (100), 101 (11). HRMS (ESI): calcd for $C_9H_{15}O_3$ $[M + H]^+$: 171.1021, found: 171.1020. The furanone side product was also isolated: **3-(hydroxymethyl)-5-butylfuran-2(5*H*)-one (5)**. δ_H(400 MHz): 7.28–7.25 (m, 1H), 4.97 (brt, $J = 5.6$ Hz, 1H), 4.43 (brs, 1H), 2.46 (brs, 1H), 1.81–1.60 (m, 2H), 1.52–1.28 (m, 4H), 0.91 (t, $J = 6.8$ Hz, 3H). δ_C(100 MHz): 172.9 (C), 149.4 (CH), 133.5 (C), 82.3 (CH), 57.3 (CH_2), 33.1 (CH_2), 27.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3). ν_{max}/cm^{-1} (neat): 3435, 1732, 1018. MS (ESI) *m/z* (%):171 (100, $[M + H]^+$), 153 (61), 135 (31), 111 (34), 107 (49). HRMS (ESI): calcd for $C_9H_{15}O_3$ $[M + H]^+$: 171.1021, found: 171.1019.

Asymmetric synthesis of *N*,*N*-dimethyl-2-(3-phenyloxiranyl)-acrylamide (3a). A solution of (2*R*,5*R*)-2,5-dimethylthiolane **7** (100 mg, 0.86 mmol) with allylic bromide **2a** (215 mg, 1.12 mmol) in water (172 µL) was stirred at 20 °C for 24 h. The starting biphasic mixture became gradually a homogenous solution. *t*-BuOH (1.55 mL), benzaldehyde (88 µL, 0.86 mmol), and sodium hydroxide powder (69 mg, 1.72 mmol) were then added. The reaction mixture was stirred at 20 °C for 3 days. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt–pentane 3 : 1, $R_f = 0.43$) afforded the desired epoxides **3a** (81 mg, 43%) as an inseparable mixture of enantio-enriched *trans* and *cis* isomers (88 : 12). The epoxides were then analyzed by HPLC in order to determine the enantiomeric excess. HPLC: AS-H Daicel Chiralpak column 250 × 4.6 mm, 5 µm. t_r(*trans*) = 12.3 and 16.3 min [(*S*,*S*) and (*R*,*R*) enantiomers]. UV maximum absorption of *trans*: 202 nm. Absolute configurations: 3*S*,2*S* for the major enantiomer. t_r(*cis*) = 19.5 and 44.4 min [(*R*,*S*) and (*S*,*R*) enantiomers]. UV maximum absorption of *cis*: 202 nm. Absolute configurations: 3*S*,2*R* for the major enantiomer.

4-Hydroxy-*N*,*N*-dimethyl-2-methylidene-4-phenylbutanamide (9). $Pd_2(dba)_3.CHCl_3$ (6.6 mg, 6.38 µmol) and tri-*n*-butylphosphonium tetrafluoroborate (2 mg, 6.38 µmol) were introduced into a Schlenk flask under nitrogen. A solution of formic acid (20 µL, 0.51 mmol) and triethylamine (142 mL, 1.02 mmol) in anhydrous THF (0.5 mL degassed) were added *via* a syringe. The resulting purple mixture was stirred for 5–10 min. A solution of the enantioenriched vinylepoxide **3a** (56 mg, 0.26 mmol, 78% ee for the *trans*, 30%, ee for the *cis*) in THF (0.5 mL) was then added dropwise and the reaction mixture became yellow. The reaction was stirred at 20 °C and was monitored by TLC (AcOEt–pentane 4 : 1). After 2.5 h, the solution was passed through a short pad of silica with CH_2Cl_2, and the filtrate was concentrated *in vacuo*. Purification by column chromatography (AcOEt–pentane 4 : 1, $R_f = 0.19$) afforded the desired alcohol **9** (48 mg, 86%, 71% ee) as a colorless oil. δ_H(250 MHz): 7.42–7.21 (m, 5H), 5.31 (s, 1H), 5.21 (s, 1H), 5.03 (d, $J = 3.4$ Hz, 1H), 4.88 (m, 1H, after D_2O exchange: dd, $J = 2.7$ and 9.1 Hz), 3.08 (s, 3H), 3.03 (s, 3H), 2.69 and 2.53 (AB part of ABX system, 2H, $J_{AX} = 2.7$, $J_{BX} = 9.1$ and $J_{AB} = 14.0$ Hz). δ_C(63 MHz): 172.9 (C), 144.3 (C), 140.6 (C), 128.3 (CH), 127.3 (CH), 125.9 (CH), 119.6 (CH_2), 74.1 (CH), 44.7 (CH_2), 39.4 (CH_3), 35.2 (CH_3). ν_{max}/cm^{-1} (neat): 3378, 2931, 1598, 1396, 1057, 700. MS (ESI) *m/z* (%): 220 (30, $[M + H]^+$), 202 (100), 174 (2), 173 (8), 129 (1). HRMS (ESI): calcd for $C_{13}H_{17}NO_2Na$ (MNa^+): 242.1157, found: 242.1154. HPLC: AD–H Daicel Chiralpak column 250 × 4.6 mm, 5 µm. t_r = 13.4 and 15.9 min [(*S*) and (*R*) enantiomers]. UV maximum absorption: 202 nm. Absolute configuration: (*R*) for the major enantiomer.

3-Methylene-5-phenyl-γ-butyrolactone (10). The β-hydroxy-amide **9** (40 mg, 0.182 mmol) was added to an aqueous solution of 2 M HCl (4.2 mL). The mixture was warmed to 60 °C and stirred for 2 h. After allowing to cool, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The resulting organic layer was washed with a saturated aqueous solution of K_2CO_3 (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt–pentane 1 : 1, $R_f = 0.40$) afforded the lactone (28 mg, 88%, 56% ee) as yellow crystals, identified by comparing its NMR spectrum with that of the known compound.[37] Mp 54–55 °C. δ_H(250 MHz): 7.40–7.31 (m, 5H), 6.32 (t, $J = 2.5$ Hz, 1H), 5.70 (t, $J = 2.5$ Hz, 1H), 5.49 (dd, $J = 6.5$ and 8.0 Hz, 1H), 3.23 (ddt, $J = 2.5$, 8.0 and 17.0 Hz, 1H), 2.80 (ddt, $J = 2.5$, 6.5 and 17.0 Hz, 1H). $[\alpha]_D^{18}$ −10.5 ($c = 1$, $CHCl_3$), lit. (*R*) enantiomer $[\alpha]_D^{125}$ −19.0 ($c = 1$, $CHCl_3$).[37] HPLC: OD-H Daicel Chiralpak column 250 × 4.6 mm, 5 µm. *n*-heptane–*iso*-propanol 95 : 5 at 15 °C. t_r = 18.5 and 21.3 min [(*R*) and (*S*) enantiomers]. UV maximum absorption: 208 nm. Absolute configuration: (*R*) for the major enantiomer.

4-Hydroxy-*N*,*N*-dimethyl-2-methylidene-4-phenylbutanamide (9) from the lactone 10. Dimethylamine (73 µL, 0.144 mmol, 2.0 M commercial solution in THF) and anhydrous THF (0.25 mL) were introduced *via* a syringe into a Schlenk flask under nitrogen. The mixture was cooled to −78 °C and *n*-BuLi (64 µL, 0.144 mmol, 2.25 M) was added dropwise. After stirring for 10 min, a solution of the lactone **10** (25 mg, 0.144 mmol, 56% ee) in THF (0.5 mL) was dropped into the mixture at −78 °C. The resulting mixture was stirred at −20 °C for 2.5 h, and hydrolyzed with a saturated aqueous solution of NH_4Cl (1.2 mL). It was then allowed to reach room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the resulting organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification by column chromatography (AcOEt–pentane 4 : 1, $R_f = 0.20$), the pure alcohol was obtained (13 mg, 41%). HPLC analysis showed that the (*R*)-enantiomer was the major enantiomer, with 55% ee.

General procedure for the synthesis of vinylcarbonates 11. $Pd_2(dba)_3{\cdot}CHCl_3$ (6 mg, 5.75 μmol, 0.005 eq.) and $NaHCO_3$ (580 mg, 6.9 mmol, 6 eq.) were introduced into a Schlenk flask under nitrogen. Triisopropylphoshite (9 μL, 34.5 μmol, 0.03 eq.) was then added *via* a syringe under nitrogen pressure. These compounds were dissolved with anhydrous CH_2Cl_2 (6.5 mL, degassed). The purple mixture was vigorously stirred at 20 °C, and became bright yellow after 10 min, the time needed for the complete formation of the organometallic complex. At this stage, a solution of vinyl epoxide **3** (1.15 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL, degassed) was added dropwise *via* a syringe. Water (4.6 mL) was finally added to the mixture, which was vigorously stirred at 20 °C for 30 h. The biphasic mixture was then passed through a short pad of (silica/Celite 1 : 9) which was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo.* Purification by chromatography column afforded the desired carbonate **11**. *Note*: The products **12a** and **12b**, which resulted from the β-elimination pathway, were also obtained in this reaction, depending on the epoxide (see Table 3): ***N*,*N*-Dimethyl-2-methylene-4-oxo-4-phenylbutanamide (12a)**. δ_H(250 MHz): 7.95–7.43 (m, 5H), 5.39 (s, 1H), 5.31 (s, 1H), 4.12 (s, 2H), 3.25 (brs, 3H), 3.05 (brs, 3H). MS (EI) *m*/*z* (%): 217 (43, M^+), 174 (98), 173 (100), 172 (100), 144 (52), 131 (23), 112 (49), 105 (100), 78 (100), 73 (66). ***N*,*N*,2-Trimethyl-4-oxo-4-phenylbut-2-enamide (12b)**. δ_H(250 MHz): mixture of *E* and *Z* 7.95–7.43 (m, 5H), 6.84 (s, 1H), 3.06 (s, 3H), 2.92 (s, 3H), 2.34 (d, $J = 1.5$ Hz, 3H, diastereoisomer A), 2.18 (d, $J = 1.5$ Hz, 3H, diastereoisomer B). MS (EI) *m*/*z* (%): 217 (43, M^+), 174 (98), 173 (100), 172 (100), 144 (52), 131 (23), 112 (49), 105 (100), 78 (100), 73 (66).

***N*,*N*-Dimethyl-2-(2-oxo-5-phenyl-1,3-dioxolan-4-yl)acrylamide (11a).** After 30 h of reaction and purification by column chromatography (CH_2Cl_2–EtOH 40 : 1, $R_f = 0.48$), the inseparable *trans* and *cis* carbonates **11a** were obtained as a light-brown powder (80%, 92 : 8 dr). δ_H(400 MHz): *trans* 7.43–7.40 (m, 5H), 6.00 (d, $J = 7.2$ Hz, 1H), 5.54 (d, $J = 0.8$ Hz, 1H), 5.44 (d, $J = 0.8$ Hz, 1H), 4.99 (dt, $J = 0.8$ and 7.2 Hz, 1H), 3.10 (s, 3H), 3.03 (s, 3H). *cis* 7.37–7.31 (m, 3H), 7.25–7.21 (m, 2H), 6.06 (dt, $J = 1.8$ and 8.2 Hz, 1H), 5.86 (d, $J = 8.2$ Hz, 1H), 5.79 (d, $J = 1.8$ Hz, 1H), 5.32 (d, $J = 1.8$ Hz, 1H), 2.68 (s, 3H), 2.24 (s, 3H). δ_C(100 MHz): *trans* 167.7 (C), 154.0 (C), 138.1 (C), 135.6 (C), 129.6 (CH), 129.2 (CH), 126.0 (CH), 120.6 (CH_2), 84.9 (CH), 82.2 (CH), 39.1 (CH_3), 35.1 (CH_3). ν_{max}/cm^{-1} (neat): 2948, 1804, 1620, 1177, 1042, 761, 699. MS (ESI) *m*/*z* (%): 262 (24, $[M + H]^+$), 218 (19), 200 (100), 173 (15), 172 (34), 157 (3), 145 (24), 117 (9). HRMS (ESI): calcd for $C_{14}H_{16}NO_4$ $[M + H]^+$: 262.1079, found: 262.1080. Found: C, 64.57; H, 5.15; N, 5.48. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36.

***N*,*N*-Dimethyl-2-(2-oxo-5-(4-trifluoromethylphenyl)-1,3-dioxolan-4-yl)acrylamide (11b).** After 30 h, the reaction was incomplete (45% of conversion, 94 : 6 dr) and the carbonate was not separable from the starting epoxide. It was thus described from the crude product. δ_H(250 MHz): *trans* 7.69 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 6.11 (d, $J = 7.1$, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 4.94 (d, $J = 7.1$, 1H), 3.12 (s, 3H), 3.05 (s, 3H). *cis* 6.04 (dt, $J = 1.6$ and 8.0 Hz, 1H), 5.96 (d, $J = 8.0$ Hz, 1H), 5.79 (d, $J = 1.6$ Hz, 1H). The other protons could not be observed for the *cis* diastereoisomer.

***N*,*N*-Dimethyl-2-(2-oxo-5-butyl-1,3-dioxolan-4-yl)acrylamide (11g).** After 30 h of reaction and purification by column chromatography (AcOEt–pentane 3 : 1, $R_f = 0.42$), the inseparable *trans* and *cis* carbonates were obtained as a colorless oil (91%, >95 : 5 dr). δ_H(400 MHz): *trans* 5.67 (s, 1H), 5.44 (s, 1H), 4.86–4.84 (m, 2H), 3.11 (s, 3H), 3.02 (s, 3H), 1.85–1.71 (m, 2H), 1.55–1.37 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H). *cis* 5.89 (s, 1H), 5.61 (s, 1H), the other protons could not be observed for the *cis* diastereoisomer. δ_C(100 MHz): *trans* 167.7 (C), 154.2 (C), 139.0 (C), 119.2 (CH_2), 81.9 (CH), 81.8 (CH), 39.1 (CH_3), 35.0 (CH_3), 33.4 (CH_2), 26.6 (CH_2), 22.2 (CH_2), 13.8 (CH_3). ν_{max}/cm^{-1} (neat): 2933, 1795, 1618, 1173, 1048, 770. MS (ESI) *m*/*z* (%): 242 (100, $[M + H]^+$), 217 (24), 198 (6), 117 (3). HRMS (ESI): calcd for $C_{12}H_{20}NO_4$ $[M + H]^+$: 242.1392, found: 242.1389.

***N*,*N*-Dimethyl-2-(2-oxo-5-isobutyl-1,3-dioxolan-4-yl)acrylamide (11h).** After 30 h of reaction and purification by column chromatography (AcOEt–pentane 3 : 1, $R_f = 0.45$), the inseparable *trans* and *cis* carbonates were obtained as a colorless oil (85%, 95 : 5 dr). δ_H(400 MHz): *trans* 5.62 (s, 1H), 5.39 (s, 1H), 4.91 (ddd, $J = 3.8$, 6.8 and 9.4 Hz, 1H), 4.75 (d, $J = 6.8$ Hz, 1H), 3.06 (s, 3H), 2.97 (s, 3H), 1.86–1.79 (m, 1H), 1.72–1.64 (m, 1H), 1.57–1.51 (m, 1H), 0.93 (d, $J = 6.8$ Hz, 6H). *cis* 5.81 (s, 1H), 5.57 (s, 1H), the other protons could not be observed for the *cis* diastereoisomer. δ_C(100 MHz): *trans* 167.7 (C), 154.2 (C), 138.8 (C), 119.4 (CH_2), 82.5 (CH), 80.6 (CH), 42.7 (CH_2), 39.1 (CH_3), 35.0 (CH_3), 24.8 (CH), 22.9 (CH_3), 21.8 (CH_3). ν_{max}/cm^{-1} (neat): 2958, 1796, 1618, 1177, 1121, 1047, 770. MS (ESI) *m*/*z* (%): 242 (60, $[M + H]^+$), 198 (61), 180 (100), 135 (6). HRMS (ESI): calcd for $C_{12}H_{20}NO_4$ $[M + H]^+$: 242.1392, found: 242.1380.

***N*,*N*-Dimethyl-2-(2-oxo-5-cyclohexyl-1,3-dioxolan-4-yl)acrylamide (11i).** After 30 h of reaction and purification by column chromatography (AcOEt–pentane 3 : 1, $R_f = 0.35$), the *trans* carbonate was obtained as a slightly yellow oil (71%, > 98 : 2 dr). δ_H(400 MHz): *trans* 5.65 (d, $J = 1.2$ Hz, 1H), 5.42 (s, 1H), 5.00 (d, $J = 5.6$ Hz, 1H), 4.62 (t, $J = 5.6$ Hz, 1H), 3.09 (brs, 3H), 3.00 (brs, 3H), 1.81–1.66 (m, 6H), 1.23–1.11 (m, 5H). δ_C(100 MHz): *trans* 167.9 (C), 154.4 (C), 139.8 (C), 119.1 (CH_2), 85.0 (CH), 79.4 (CH), 41.3 (CH), 39.2 (CH_3), 35.1 (CH_3), 27.9 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.4 (CH_2). ν_{max}/cm^{-1} (neat): 2928, 1791, 1618, 1166, 1052, 769. MS (ESI) *m*/*z* (%): 268 (41, $[M + H]^+$), 224 (17), 206 (100), 178 (5), 161 (56), 133 (27). HRMS (ESI): calcd for $C_{14}H_{22}NO_4$ $[M + H]^+$: 268.1549, found: 268.1547.

4-[1-(Morpholin-4-ylcarbonyl)vinyl]-5-phenyl-1,3-dioxolan-2-one (11j). After 30 h of reaction and purification by column chromatography (CH_2Cl_2–EtOH 80 : 3, $R_f = 0.31$), the inseparable *trans* and *cis* carbonates were obtained as a yellow oil (77%, >95 : 5 dr). δ_H(400 MHz): *trans* 7.49–7.38 (m, 5H), 5.98 (d, $J = 7.2$ Hz, 1H), 5.51 (s, 1H), 5.41 (s, 1H), 4.97 (d, $J = 7.2$ Hz, 1H), 3.90–3.45 (m, 8H). *cis* 6.05 (dt, $J = 1.6$ and 8.2 Hz, 1H), 5.85 (d, $J = 8.2$ Hz, 1H), 5.83 (d, $J = 1.6$ Hz, 1H), 5.33 (d, $J = 1.6$ Hz, 1H). The other protons could not be observed for the *cis* diastereoisomer. δ_C(100 MHz): *trans* 166.3 (C), 153.8 (C), 137.7 (C), 135.4 (C), 129.7 (CH), 129.3 (CH), 126.0 (CH), 120.8 (CH_2), 84.8 (CH), 82.1 (CH), 66.9 (CH_2), 66.7 (CH_2), 47.9 (CH_2), 42.2 (CH_2). ν_{max}/cm^{-1} (neat): 2858, 1798, 1614, 1438, 1269, 1163, 1112, 1030, 698. MS (ESI) *m*/*z* (%): 304 (41, $[M + H]^+$), 260 (25), 242

(100), 173 (12), 164 (9), 145 (7), 114 (6). HRMS (ESI): calcd for $C_{16}H_{18}NO_5$ $[M + H]^+$: 304.1185, found: 304.1170.

Representative procedure for cyclisation of vinylcarbonates 11 to lactones 4. Vinylcarbonate (118 mg, 0.48 mmol) and water (2.5 mL) were first introduced in a Schlenk flask. Lithium hydroxide (23.4 mg, 0.98 μmol) was then added and the cloudy mixture was stirred vigorously at 20 °C (the solution became homogeneous). The carbonate deprotection step was monitored by TLC (AcOEt–pentane 4 : 1). After complete deprotection, a solution of sulfuric acid (7.6 mL, 5% v/v) was dropped onto the solution at 20 °C. The reaction mixture was then stirred at 60 °C by putting directly the Schlenk flask into a warm oil bath. The lactonisation step was also monitored by TLC (AcOEt–pentane 4 : 1). After cooling, the solution was dissolved with water and extracted with CH_2Cl_2. The organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (foam formation), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (AcOEt–pentane) afforded the desired lactones as a mixture of *trans* and *cis* diastereoisomers.

4-Hydroxy-3-methylene-5-phenyl-γ-butyrolactone (4a). After 4 h for the deprotection step followed by 2 h for the lactonisation, purification by column chromatography (AcOEt–pentane 1 : 1, $R_f(trans) = 0.47$, $R_f(cis) = 0.33$), provided the *trans* and *cis* lactones separately as yellow oils (56% global yield, 1 : 99 dr). See above for the analyses.

4-Hydroxy-3-methylene-5-butyl-γ-butyrolactone (4g). After 4 h for the deprotection step followed by 50 min for the lactonisation, purification by column chromatography (AcOEt–pentane 2 : 1, $R_f = 0.42$) provided the *trans* and *cis* lactones separately as colorless oils (74%, 5 : 95 dr). See above for the analyses.

4-Hydroxy-3-methylene-5-isobutyl-γ-butyrolactone (4h). After 5 h for the deprotection step followed by 50 min for the lactonisation, purification by column chromatography (AcOEt–pentane 2 : 3, $R_f = 0.35$) provided the inseparable mixture of *trans* and *cis* lactones as a colorless oil (66%, 6 : 94 dr). δ_H(400 MHz): *trans* 6.39 (d, $J = 2.4$ Hz, 1H), 5.97 (d, $J = 2.3$ Hz, 1H), 4.49–4.44 (m, 1H), 4.35–4.30 (m, 1H) the other signals overlapped with the major *cis* lactone. *cis* 6.38 (d, $J = 1.6$ Hz, 1H), 5.98 (d, $J = 1.2$ Hz, 1H), 4.85–4.75 (brt, 1H), 4.55–4,50 (m, 1H), 2.70 (d, $J = 5.6$ Hz, 1H), 1.92–1.82 (m, 1H), 1.72–1.65 (m, 1H), 1.60–1.53 (m, 1H), 0.98 (d, $J = 4.4$ Hz, 3H), 0.97 (d, $J = 4.4$ Hz, 3H). δ_C(100 MHz): *cis* 169.8 (C), 139.1 (C), 126.0 (CH_2), 81.0 (CH), 70.0 (CH), 37.3 (CH_2), 24.7 (CH), 23.4 (CH_3), 22.0 (CH_3). ν_{max}/cm^{-1} (neat): 3429, 2958, 1742, 1272, 1169, 1121, 986. MS (EI) *m/z* (%): 171 (59, $[M + H]^+$), 153 (100), 135 (21), 125 (25), 107 (78). HRMS (ESI): calcd for $C_9H_{15}O_3$ $[M + H]^+$: 171.1021, found: 171.1016.

1-Iodo-2-methyloct-1-ene (14). According to Wipf's protocol,[45b] Me_3Al (75 mL, 2 M solution in toluene, 150 mmol) was added to a solution of Cp_2ZrCl_2 (2.92 g, 10 mmol) in 200 mL of dry dichloromethane at rt. After cooling to 0 °C, water was slowly added dropwise (1.35 mL, 75 mmol). The reaction was allowed to warm to rt and, after 20 minutes, octyne (5.51 g, 50 mmol) was added. The reaction was stirred for 30 minutes and treated with a solution of iodine (14.15 g, 60 mmol) in THF (75 mL). After 30 minutes, the reaction was poured into a saturated aqueous solution of K_2CO_3 (500 mL). After filtration over a pad of Celite, the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo.* Purification by column chromatography (pentane, $R_f = 0.75$) yielded **14** as a colorless oil (9.8 g, 78%). δ_H(400 MHz): 5.84 (q, $J = 1.1$, 1H), 2.19 (t, $J = 6.6$ Hz, 2H), 1.80 (d, $J = 1.0$ Hz, 3H), 1.42 (m, 2H), 1.28–1.18 (m, 6H), 0.88 (t, $J = 6.7$ Hz, 3H). δ_C(100 MHz): 148.6 (C), 74.3 (CH), 39.6 (CH_2), 31.6 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 23.8 (CH_2), 22.6 (CH_3), 14.0 (CH_3). ν_{max}/cm^{-1} (neat) 3057, 2955, 2926, 2855, 1617, 1456, 1376, 1271, 1142, 1110, 1017, 892, 838, 765, 724, 680, 666.

2-[(7-Methyl-tridec-6-en-1-yl)]tetrahydro-2*H*-pyran (15). $ZnCl_2$ (1 M solution in ether, 0.75 mL, 0.75 mmol) was added to a solution of alkyl iodide **13** (180 mg, 0.60 mmol) in 0.7 mL of dry ether at −78 °C. The mixture was stirred 30 minutes and treated dropwise with *t*-BuLi (1.2 M solution in pentane, 2 mL, 2.4 mmol). The solution was gently allowed to warm to rt, and then cannulated over a mixture of vinyl iodide **5** (101 mg, 0.4 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in dry ether. The reaction was stirred overnight, protected from light. Water was added carefully and the organic layer was separated. The aqueous layer was extracted by ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Rapid column chromatography of the crude product (Et_2O–pentane = 1 : 1, $R_f = 0.25$) yielded 163 mg of the coupling product **15** (73% yield determined by NMR with an internal standard), contaminated with the hydrolyzed side-product $C_5H_{11}OTHP$. δ_H(400 MHz): 5.10 (tq, $J = 1.1$ and 7.1, 1H), 4.58 (dt, $J = 2.9$ and 4.6, 1H), 3.86 (m, 1H), 3.74 (ddd, $J = 6.9$, 9.5 and 13.8, 1H), 3.49 (m, 1H), 3.38 (ddd, $J = 6.6$, 9.3 and 13.3, 1H), 1.96 (m, 4H), 1.57 (m, 2H), 1.57 (m, 5H), 1.44 (m, 6H), 1.25 (m, 10H), 0.88 (t, 3H, $J = 6.7$). δ_C(100 MHz): 135.5 (C), 124.4 (CH), 98.9 (CH), 67.8 (CH_2), 62.4 (CH_2), 39.9 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 22.8 (CH_2), 19.8 (CH_2), 16.0 (CH_3), 14.2 (CH_3). ν_{max}/cm^{-1} (neat) 2925, 2855, 1668, 1465, 1455, 1441, 1381, 1364, 1352, 1322, 1283, 1260, 1200, 1184, 1164, 1136, 1120, 1078, 1065, 1034, 1022, 988; 974, 905, 869, 844, 816; 727. HRMS (ESI): calcd for $C_{19}H_{36}O_2$ $[M + Na]^+$: 319.2613, found: 319.2616. A diene side product **7** was also isolated (Et_2O–pent 1 : 4, R_f = 0.80): **10-dimethyl-hexadeca-7,9-diene**. δ_H(400 MHz): 5.99 (s, 2H), (t, $J = 7.1$, 4H), 1.72 (s, 6H), 1.42 (m, 4H), 1.26 (m, 12H), 0.89 (t, $J = 6.8$, 6H). δ_C(100 MHz): 136.8 (C), 120.8 (CH), 40.5 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 16.5 (CH_3), 14.3 (CH_3). ν_{max}/cm^{-1} (neat) 2956, 2924, 2855, 1615, 1457, 1379, 1105, 1017, 862, 724. MS (ESI) *m/z* (%): 250 (M).

7-Methyl-tridec-6-en-1-ol (16). *p*-Toluenesulfonic acid (2.98 mg, 0.016 mmol) was added to the obtained mixture of **15** and the reduced product (46.6 mg) in methanol (0.5 mL) at room temperature. The solution was heated at 45 °C until complete conversion (checked by TLC). After addition of ether, the organic layer was washed with water, an aqueous solution of $NaHSO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (Et_2O—pentane 1 : 2, $R_f = 0.31$) yielded alcohol **7** in 50% yield from **14**. δ_H(400 MHz): 5.10 (tq, $J = 1.1$ and 7.1, 1H), 3.63 (t, J = 6.6, 2H), 1.96 (m, 4H), 1.60–1.55 (m, 2H), 1.57 (s, 4H), 1.43–1.25 (m, 12H), 0.87 (t, $J = 6.8$, 3H). δ_C(100 MHz): 135.6 (C), 124.3

(CH), 63.2 (CH_2), 39.9 (CH_2), 32.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.1 (CH_2) 28.1 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 16.0 (CH_3), 14.2 (CH_3). ν_{max}/cm^{-1} (neat) 3323, 2955, 2925, 2855, 1668, 1457, 1379, 1122, 1073, 1055, 1011, 885, 841, 724. The analysis was in agreement with previous reports.[49]

7-Methyl-tridec-6-enal (17). Alcohol **16** (70 mg, 0.33 mmol) was diluted with acetone (10 mL) at 0 °C in the presence of *N*-methyl-morpholine-*N*-oxide (117 mg, 1 mmol). Then tetrapropylammonium perruthenate (6 mg, 0.017 mmol) was added and the reaction mixture was stirred until complete conversion of the starting material. The solution was concentrated *in vacuo* and pentane was added. The obtained crude mixture was filtered over a pad of Celite. Rapid purification by column chromatography (Et_2O–pentane 1 : 1, $R_f = 0.68$) gave aldehyde **17** as a light yellow oil (40 mg, 58%). This unstable aldehyde was subsequently used in the following epoxidation step. δ_H(400 MHz): 9.76 (t, $J = 1.8$, 1H), 5.09 (tq, $J = 1.1$ and 7.1, 1H), 2.42 (td, $J = 1.8$ and 7.3, 2H), 2.03–1.93 (m, 4H), 1.67–1.59 (m, 2H), 1.57 (s, 3H), 1.43–1.26 (m, 10H), 0.88 (t, $J = 7.1$, 3H). δ_C(100 MHz): 203.0 (C), 136.1 (C), 123.7 (CH), 44.0 (CH_2), 39.8 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 21.8 (CH_2), 16.1 (CH_3), 14.2 (CH_3). ν_{max}/cm^{-1} (neat) 3323, 2955, 2925, 2855, 1668, 1457, 1379, 1122, 1073, 1055, 1011, 885, 841, 724. The analysis was in agreement with the previous description.[49]

***N*,*N*-Dimethyl-2-[3-(6-methyldodec-5-en-1-yl)oxiran-2-yl]-acrylamide (18).** Thiolane (19 μL, 0.21 mmol) was added to a solution of allylic bromide **2a** (40.1 mg, 0.21 mmol) in water (40 μL) at rt. With vigorous stirring, the initial heterogeneous solution became homogenous within 6 h. *t*-BuOH (360 μL), aldehyde **17** (40.0 mg, 0.19 mmol) and NaOH (16 mg, 0.40 mmol) were subsequently added to the solution. The mixture was vigorously stirred for 39 hours at room temperature and diluted with water. The aqueous layer was extracted by dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt–heptane 1 : 1, $R_f = 0.32$) afforded a colourless oil corresponding to the desired epoxides (35 mg, 71%) as an inseparable mixture of *trans* and *cis* diastereoisomers (60 : 40). δ_H(400 MHz): *trans* 5.49 (s, 1H), 5.24 (s, 1H), 5.07 (t, $J =$ 5.8, 1H), 3.26 (d, $J = 2$ Hz, 1H), 3.12–2.96 (m, NMe_2 and 1H oxirane, 7H), 2.00–1.91 (m, 4H), 1.71–1.60 (m, 1H), 1.55 (s, 3H), 1.54–1.21 (m, 14H), 0.86 (t, $J = 6.8$, 3H). *cis* 5.43 (d, $J = 1.2$ Hz, 1H), 5.35 (s, 1H), 5.07 (t, $J = 5.8$ Hz, 1H overlapped with the *trans*), 3.68 (dd, $J = 1.2$ and 4.4 Hz, 1H), 3.12–2.96 (m, NMe_2 and 1H oxirane, 7H overlapped with the *trans*), 2.00–1.91 (m, 4H, overlapped with the *trans*), 1.71–1.60 (m, 1H, overlapped with the *trans*), 1.55 (s, 3H, overlapped with *trans*), 1.54–1.21 (m, 14H, overlapped with the *trans*), 0.91 (t, $J = 7.6$ Hz, 3H). δ_C(100 MHz): *trans* 169.5 (C), 142.7 (C), 135.7 (C), 124.1 (CH), 116.7 (CH_2), 60.8 (CH), 58.1 (CH), 39.8 (CH_2), 38.9 (CH_3), 34.7 (CH_3), 31.9 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 28.0 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 25.5 (CH_2, 22.7 (CH_2), 16.0 (CH_3), 14.2 (CH_3). *Cis* 168.9 (C), 138.8 (C), 135.6 (C), 124.0 (CH), 117.5 (CH_2), 59.8 (CH), 56.4 (CH), 39.8 (CH_2), 38.9 (CH_3), 35.0 (CH_3), 32.1 (CH_2), 29.8 (CH_2), 27.8 (CH_2), 26.0 (CH_2), 16.0 (CH_3 overlapped with the *trans*), 14.2 (CH_3 overlapped with *trans*). The chemical shift of four carbons of the *cis* isomer could not be determined because of the overlapping with the *trans* isomer. ν_{max}/cm^{-1} (neat) 2925, 2855, 1646, 1622, 1397, 1105, 924. HRMS (ESI): calcd for $C_{20}H_{35}NO_2$ $[M + H]^+$: 322.2746, found: 322.2758. MS (ESI) *m*/*z* (%): 172 (37, $[M + H]^+$), 154 (30), 114 (100), 100 (14), 88 (60), 85 (30).

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