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Application of the Palladium-Catalysed Norbornene-Assisted Catellani Reaction Towards the Total Synthesis of (+)-Linoxepin and Isolinoxepin

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Our ongoing effort towards the development of highly selective transition-metal-catalysed C–H activation processes has led to the expansion of the Catellani reaction. In a $Pd^0/Pd^{II}/Pd^{IV}$-catalysed domino reaction, an aryl iodide, alkyl iodide and *tert*-butyl acrylate were combined to synthesize the carbon framework of the novel lignan (+)-linoxepin. The enantioselective synthesis highlights the work accomplished in our group and provides an excellent procedure for the reliable and scalable synthesis of architecturally complex scaffolds. This report outlines the synthetic approaches towards this interesting class of biologically active molecules. After the key Catellani/Heck reaction, our synthesis features a Leimeux–Johnson oxidation and a titanium tetrachloride mediated aldol condensation. Finally, a tuneable Mizoroki–Heck reaction was performed to furnish not only the natural product (+)-linoxepin but also its isoform, which we have named isolinoxepin.

Introduction

Since 2000 our group has advanced the C–H functionalization methodology first reported by Catellani. This remarkable multi-component domino process has been shown to doubly *ortho* alkylate an aryl iodide and then undergo an aryl–Pd^{II} coupling reaction to form up to three C–C bonds in a single step.[1] In recent years we demonstrated the synthetic utility of this catalytic process by the formation of tetrasubstituted helical olefins, the synthesis of 2-arylindoles and the formal synthesis of nitidine and NK109.[2] Having developed different protocols for the synthesis of these scaffolds, we looked towards showcasing our developments in this growing field by applying the Catellani reaction in a complex natural product synthesis. In 2008, we became intrigued by the novel structure of the newly discovered lignan, (+)-linoxepin (**1**), and initiated a project to utilize a selective C–H functionalization for its synthesis.

(+)-Linoxepin (**1**) was first isolated by Schmidt et al. in 2007 from the aerial parts of the *Linum perenne* flower (Figure 1).[3] Although no known biological activity has been reported, lignans with similar structures have shown to have tremendous health benefits.[4] Etoposide and podophyllotoxin, two molecules with similar structures to **1**, have both been approved as anti-cancer agents and are in use today.[5]

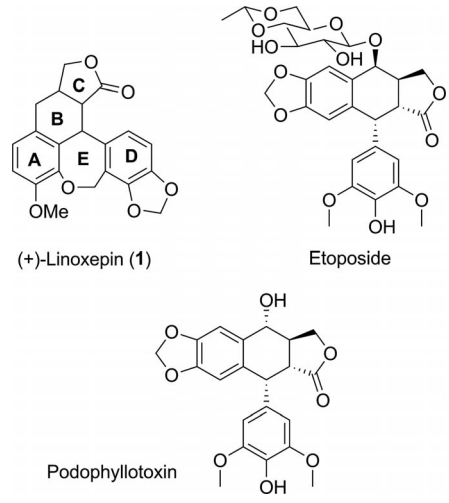

Figure 1. (+)-Linoxepin, etoposide and podophyllotoxin.

The racemic linoxepin was first synthesized by Tietze et al. in 2013 through a domino Heck reaction. Tietze et al. were able to obtain an X-ray crystal structure of the unnatural (*S*) enantiomer of linoxepin to support the absolute stereochemistry in the reported structure.[6] Shortly after their synthesis, we published an enantioselective synthesis featuring the first use of the Catellani reaction in a complex natural product synthesis.[7] Herein we provide a full account of the routes towards the synthesis of **1** with a focus on scalable C–H functionalization processes.

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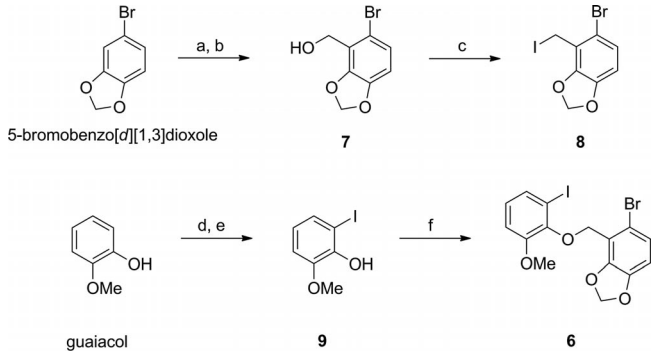
Results and Discussion

We initially approached the retrosynthetic analysis of (±)-linoxepin by disconnecting the B and C rings. Advanced intermediate (±)-**2** can be viewed as arising from a dihydroxylation followed by a Yamaguchi cyclization of alkene (±)-**3**. Intramolecular 1,4-addition of the α,β-unsaturated ester **4** would yield (±)-**3**. At this stage the stereochemistry is irrelevant because the final oxidation would eliminate the doubly benzylic stereocentre. Alkene **4** can be synthesized by elimination from alkyl bromide **5**, which would be the direct product of the Catellani reaction (Scheme 1).

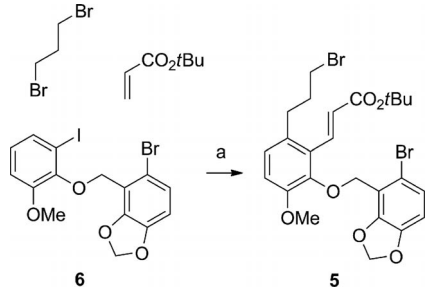
The synthesis of the Catellani precursor **6** began with the formylation of commercially available 5-bromobenzo[*d*]-[1,3]dioxole. Reduction of the intermediate aldehyde with $NaBH_4$ led to benzylic alcohol **7**, which was subsequently transformed into the corresponding benzyl iodide **8** with TMSCl and NaI. These three steps did not require any chromatographic purification and with an overall yield of 91% we were able to quickly and efficiently gain access to the D ring. The A ring was synthesized starting with the THP-directed *ortho* iodination of the commercially available guaiacol to give aryl iodide **9**. The coupling of the A and D rings proceeded smoothly under the Williamson ether synthesis protocol to give **6** (Scheme 2).

The power of the Catellani reaction was showcased in the next step. Aryl iodide **6**, 1,3-dibromopropane and *tert*-butyl acrylate were combined in a multi-component domino process[8] to give the product bromide **5** in 82% yield. After optimization, this reaction was performed on a 10 mmol scale, which at the time represented the largest-scale Catellani reaction to date (Scheme 3). The palladium(0) catalyst, formed in situ from palladium acetate and triphenylphosphine, preferentially inserts into the aryl–I bond over the aryl–Br bond of **6** to give intermediate **I**. With two types of olefins in the reaction mixture the Pd^{II} catalyst carbopalladates onto the electronically more activated olefin of norbornane to form intermediate **II**, which

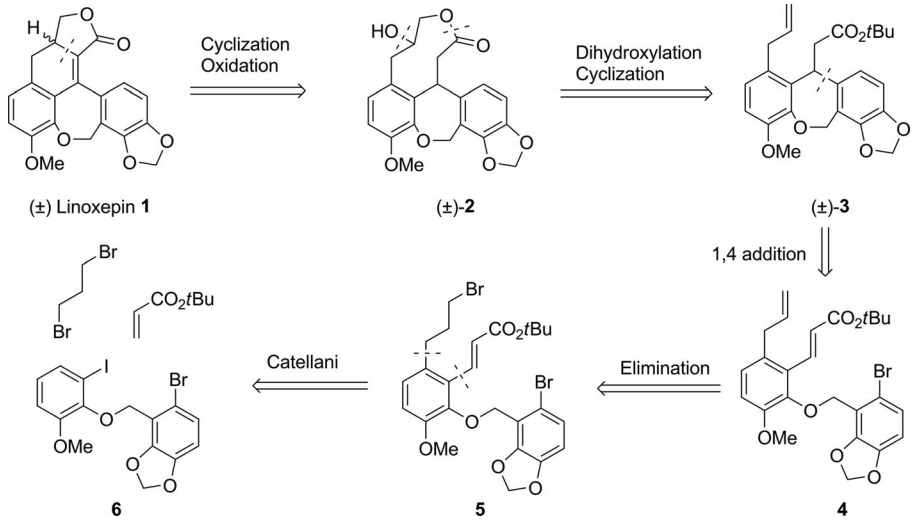


Scheme 2. Synthesis of the Catellani precursor **6**. Reagents and conditions: a) i) diisopropylamine, *n*BuLi, THF, –78 °C, 1 h; ii) DMF, THF, –78 °C→r.t., 95%; b) $NaBH_4$, THF, reflux, 90 min, 97%; c) TMSCl, NaI, CH_3CN, r.t., 1 h, 99%; d) DHP, PPTS, CH_2Cl_2, r.t., 4 h, 95%; e) i) *n*BuLi, THF, r.t., 7 h; ii) I_2, THF, –78 °C→r.t., 16 h, 98%; f) **8**, K_2CO_3, acetone, reflux, 94%; DHP = 3,4-dihydro-2*H*-pyran; PPTS = pyridinium *p*-toluenesulfonate.

contains no β-hydrogen atoms in the correct orientation for elimination, and therefore electrophilic attack on the electron-rich A ring can occur. Following deprotonation by Cs_2CO_3 a five-membered palladacycle **III** forms.[9] By using bipyridine ligands, Catellani was able to crystallize this in-



Scheme 3. Catellani reaction. Reagents and conditions: a) $Pd(OAc)_2$ (10 mol-%), triphenylphosphine, norbornene, Cs_2CO_3, *tert*-butyl acrylate, 1,3-dibromopropane, CH_3CN (sealed tube), 90 °C, 16 h, 82%.



Scheme 1. Retrosynthetic analysis of (±)-linoxepin.

termediate palladacycle to support its formation during the catalytic cycle.[10a] With palladium in the +2 oxidation state the normal course of events would lead to reductive elimination to regenerate the palladium(0) catalyst. In this case the product would form a highly strained cyclobutane ring fused to an aryl ring. Although the formation of products such as these is known, they require prolonged heating at higher temperatures.[10b,10c] The mechanism of the next step remains under some debate. Catellani proposed a pathway that involves a second round of oxidative addition, this time to an alkyl–Br bond to produce a Pd^{IV} intermediate **IV**, which reductively eliminates to *ortho* alkylate the aromatic ring to generate **V**. With both *ortho* positions substituted, the steric congestion around the palladium centre increases, driving the decarbopalladation of norbornene to give the aryl–Pd^{II} intermediate **VI**. sp^3–sp^3 coupling between the alkyl and norbornyl groups is not seen, presumably due to the high activation barrier of this type of coupling with a monodentate triarylphosphine ligand.[11] Echavarren and co-workers proposed an alternative mechanism involving a dinuclear Pd^{II} species that proceeds via intermediate **VII**.[12] In either case the *ortho* position is alkylated and intermediate **VI** undergoes a Mizoroki–Heck reaction with *tert*-butyl acrylate to give **5** (Figure 2).[13]

The next step involved the installation of the terminal alkene to give **4**. Displacing the bromide with acetate anion followed by base hydrolysis led to an intermediate alcohol. Under the Grieco[14] protocol the corresponding selenide was formed and then eliminated to give alkene **4**. Lithiation of **4** with *n*BuLi followed by transmetallation with CuCN/LiCl according to Knochel's procedure[15] led to a 65% yield of the 1,4-addition product (±)-**3** (Scheme 4).

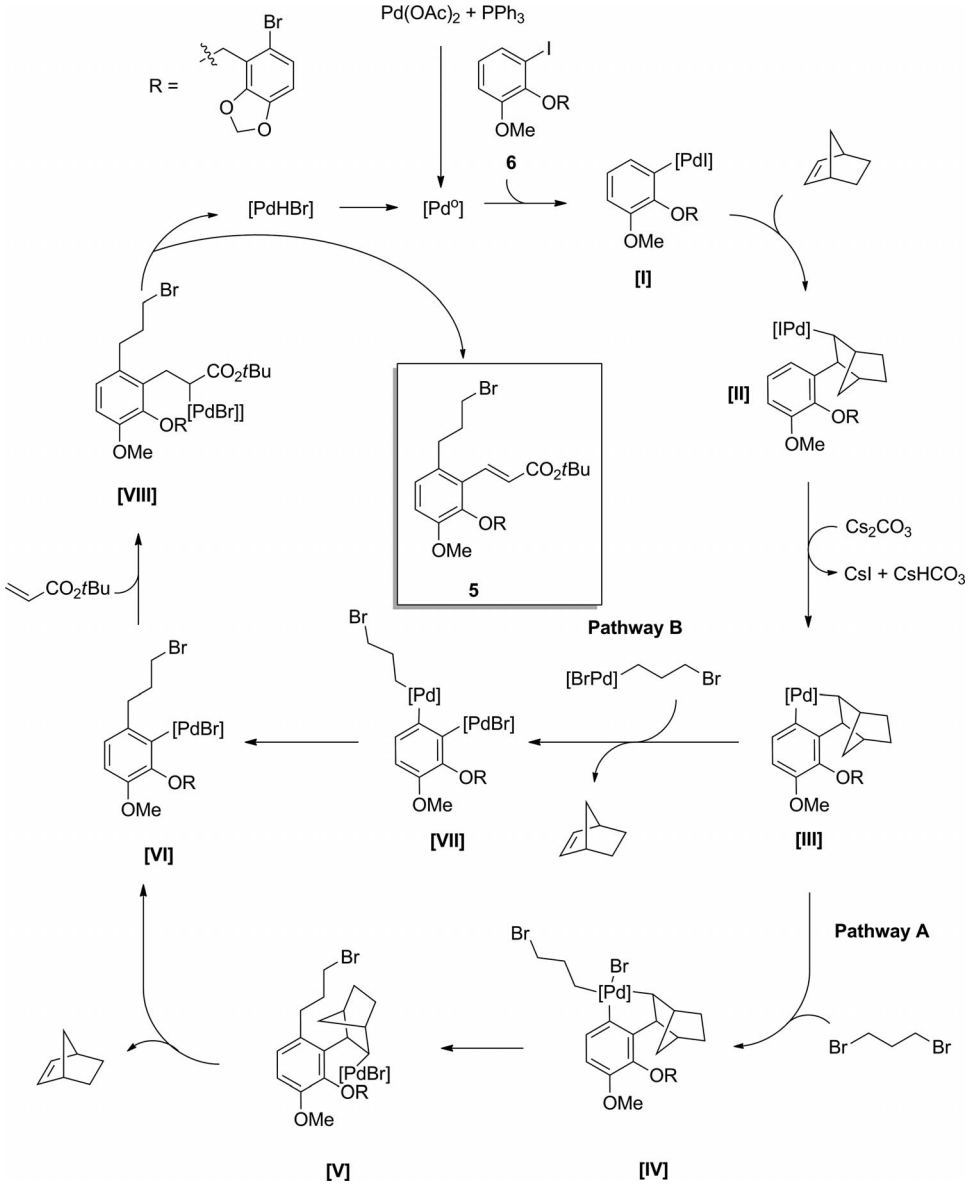
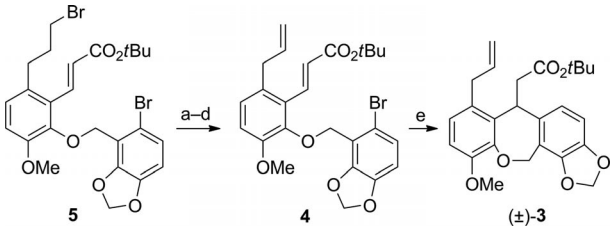
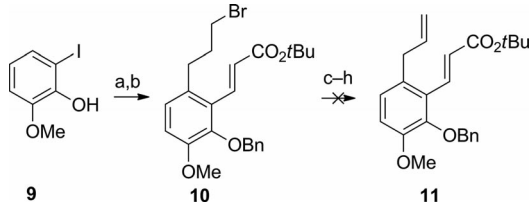


Figure 2. Catellani catalytic cycle.



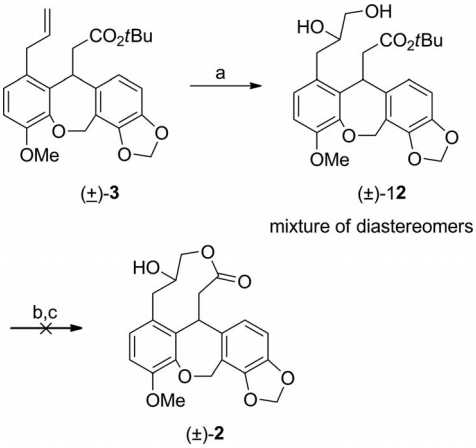
Scheme 4. Formation of the E ring. Reagents and conditions: a) KOAc, 18-crown-6, CH_3CN, 80 °C, 16 h, 91%; b) K_2CO_3, CH_2Cl_2/MeOH (1:1), r.t., 2 h, 96%; c) 1-nitro-2-selenocyanatobenzene, PBu_3, THF, r.t., 3 h, 88%; d) 30% H_2O_2 in H_2O, THF, r.t., ON, 97%; e) i) *n*BuLi, THF, –78 °C, 10 min; ii) CuCN, LiCl, THF, –78 °C→r.t., ON, 65%.

We attempted the direct elimination of the alkyl bromide to give the alkene from the model system **10**, but unfortunately this was unsuccessful under a myriad of conditions (Scheme 5).



Scheme 5. Attempted direct elimination of alkyl bromide. Reagents and conditions: a) benzyl bromide, K_2CO_3, acetone, 50 °C, 1 h, 99%; b) $Pd(OAc)_2$ (10 mol-%), triphenylphosphine, norbornene, Cs_2CO_3, *tert*-butyl acrylate, 1,3-dibromopropane, CH_3CN (sealed tube), 90 °C, 16 h, 64%; c) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), NaI, dimethoxyethane, 90 °C, ON; d) DBU, DMF, 80 °C, 24 h; e) DBU, AgOTf, DCM, r.t., 17 h; f) KO*t*Bu, dimethoxyethane, 90 °C, 2 d; g) NaHMDS, THF, r.t., ON; h) NiI_2, NaHMDS, *i*PrOH, 60 °C, 19 h.

Dihydroxylation of the terminal olefin (±)-**3** with catalytic K_2OsO_4 and *N*-methylmorpholine *N*-oxide as a stoichiometric oxidant gave the intermediate diol (±)-**12** in 74% yield. We attempted the acidic deprotection of the *tert*-butyl ester with TFA and the crude acid was subjected to Yamaguchi macrolactonization. Unfortunately we were unable to obtain any appreciable amounts of (±)-**2** (Scheme 6). Although we had to abandon this route, our success in applying the Catellani reaction to substrate **6** on a large scale encouraged us to devise alternate synthetic pathways to take advantage of this achievement.

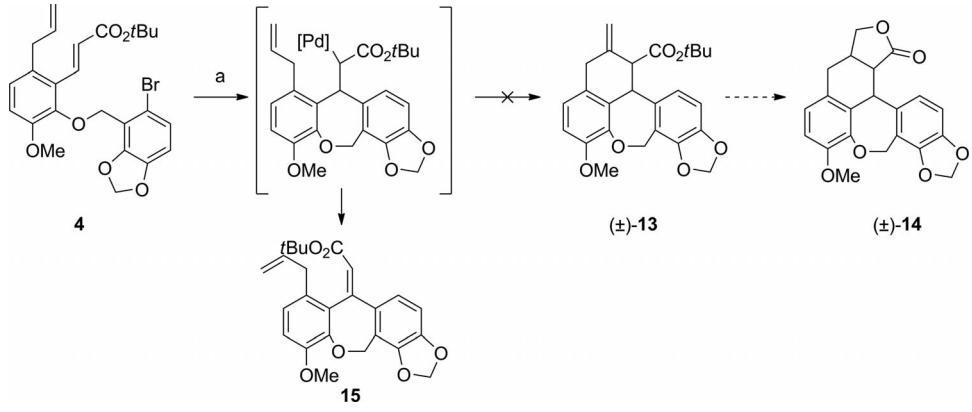


Scheme 6. Formation of the macrocycle (±)-**2**. Reagents and conditions: a) $K_2OsO_4{\cdot}2H_2O$, *N*-methylmorpholine *N*-oxide, acetone/water (4:1), r.t., ON, 74%; b) TFA; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene, 90 °C, 2 h.

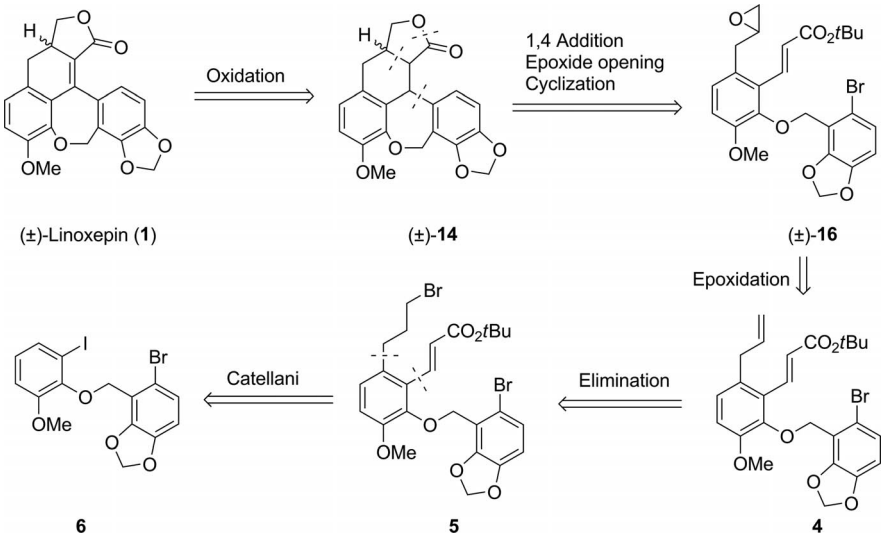
Beginning with alkene **4**, we envisioned a Heck zipper strategy that could close both the E and C rings sequentially in a one-pot domino process. Hydroboration of the resulting *exo*-cyclic olefin in (±)-**13** followed by ring closure would yield dihydrolinoxepin, (±)-**14**. However, upon examination of the reaction of **4** with 20 mol-% $PdCl_2$ we observed the clean formation of the mono-Heck product **15**. β-Hydride elimination to form the congested trisubstituted olefin was energetically favoured over the second carbopalladation at 130 °C under microwave irradiation (Scheme 7).

With the versatile intermediate **4**, we developed a new strategy to incorporate a different endgame (Scheme 8).

Intermediate (±)-**16** could be synthesized by the epoxidation of alkene **4**. A domino 1,4-addition, ring-opening/ring-closing step was envisioned to form dihydrolinoxepin



Scheme 7. Synthesis of the mono-Heck product **15**. Reagents and conditions: a) $PdCl_2$ (20 mol-%), PPh_3, Et_3N, DMF, 130 °C MW, 7 h, 63%.



Scheme 8. Retrosynthetic strategy towards a revised endgame.

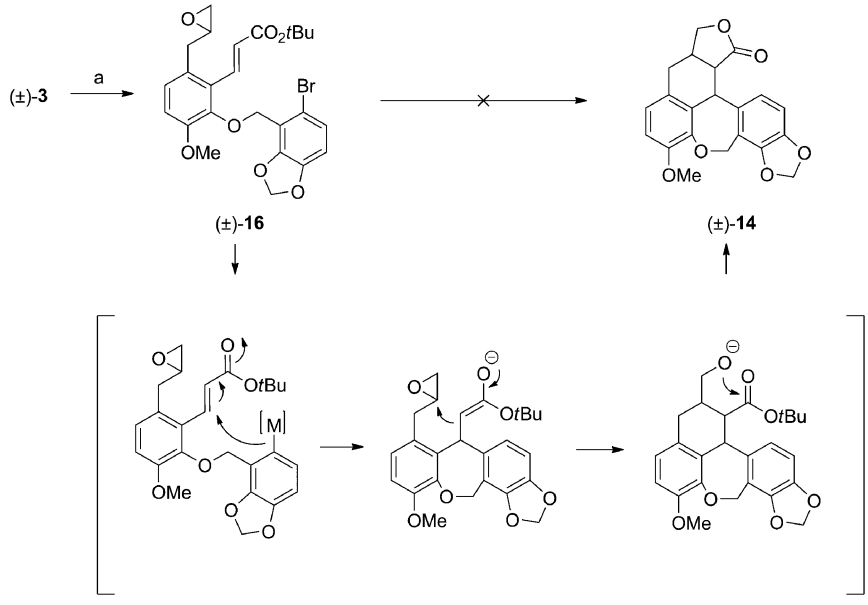
(±)-**14**. Metallation of the aryl bromide would initiate the 1,4-addition of the aryl moiety to the cinnamyl ester to form the seven-membered E ring. The resulting enolate could then be trapped by the appended epoxide, which opens by a 6-*exo*-*tet* pathway, to close the B ring. The resulting primary alkoxide could then close by nucleophilic attack of the ester to form the final C ring to give dihydrolinoxepin (±)-**14** (Scheme 9, Table 1).

The metallation to a nucleophilic aryl anion followed by the 1,4-addition proceeded as planned, as evidenced by the formation of (±)-**17**, unfortunately the epoxide remained intact. A closer look at the reaction mixture revealed the formation of another product, the chlorohydrin (±)-**18** (Figure 3). The enolate generated by the 1,4-addition was not sufficiently nucleophilic, however, the Cl anion used as an additive was able to open the epoxide.[16] Both (±)-**17** and (±)-**18** could be seen in the mass spectrum of the crude reaction mixture, however, no attempt was made to isolate these products (Figure 3).

Table 1. Domino 1,4-addition, epoxide opening and lactonization.

Entry	Base	Metal	Additives	*T* [°C]
1	*n*BuLi[a]	CuCN	$Et_2AlCl/LiCl$	–78
2	*n*BuLi[b]	CuCN	$Et_2AlCl/LiCl$	–78
3	*t*BuLi[a]	CuCN	LiCl	–78
4	*t*BuLi[a]	CuI	PBu_3	–78
5	*t*BuLi[b]	CuI	PBu_3	–100
6	*i*PrMgCl·LiCl[b]	CuI	PBu_3	–10
7	*i*PrMgCl·LiCl[b]	CuI	PBu_3	–10
8	*i*PrMgCl·LiCl[b]	CuI	PBu_3	–10
9[c]	–	Zn	TFA/PhBr	r.t.

[a] 1 equiv. [b] 10 equiv. [c] $CoBr_2/ZnBr_2$ used as a catalyst.



Scheme 9. Domino 1,4-addition, epoxide opening and lactonization: a) *m*CPBA, DCM, r.t., 16 h, 96%.

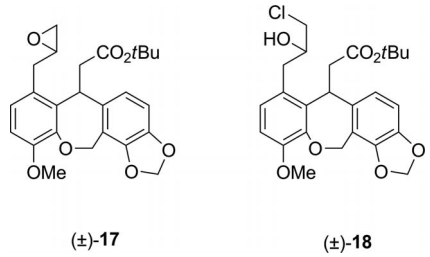
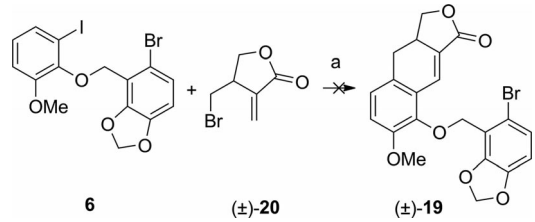


Figure 3. Products formed during the domino reaction.

Our approaches thus far have relied on the late-stage formation of the bond between the B and C rings. The next strategy was to synthesize this bond prior to the key Catellani step and thus a more convergent route was envisioned. Our group has reported the use of tethered olefins as intramolecular Heck acceptors for the termination step of the Catellani reaction (Figure 4).[17] Therefore a Catellani reaction between aryl iodide **6** and bromolactone **20** was proposed. Compound **20** contains the crucial bond between the B and C rings. From our previous success with the intramolecular Heck reaction of **4** we were confident that (±)-**19** could be cyclized to give **1**.

The bromolactone (±)-**20** was synthesized starting from the commercially available tulipalin A according to the procedure of Clark and co-workers.[18] Dibromination with trimethylphenylammonium tribromide followed by regioselective elimination of the dibromide intermediate gave the allyl bromide **21** in 68% yield over the two steps. To append an extra carbon, a Barbier reaction was employed.[19] The zinc-mediated addition of allylic bromides to aldehydes reported by Clark and co-workers failed with formaldehyde as the electrophile. However, by performing the reaction in the presence of indium(0) we were able to obtain the known addition product (±)-**22**, albeit in a modest 34% yield. Compound (±)-**22** was then converted into the desired bromolactone (±)-**20** by an Appel-type reaction (Scheme 10).

With bromolactone (±)-**20** in hand, the Catellani reaction was attempted with aryl iodide **6**. Unfortunately the reaction did not provide us with (±)-**19**. We saw no evidence of the incorporation of (±)-**20** into aryl iodide **6**, which was retrieved, whereas (±)-**20** was unstable to the basic conditions of the reaction and decomposed during the course of the reaction. Elimination to a diene is the most likely decomposition path (Scheme 11).



Scheme 11. Catellani/double Heck reaction. Reagents and conditions: a) $Pd(OAc)_2$ (10 mol-%), triphenylphosphine, norbornene, Cs_2CO_3, CH_3CN (sealed tube), 90 °C, 16 h.

Our desire to incorporate the fully formed lactone in (±)-**20** led us to reason that removal of the *exo*-methylene unit might make the new halolactones (±)-**27** and (±)-**28** less likely to decompose. The synthesis of (±)-**27** began by dibrominating 3,3-dimethylacrylic acid. Base-mediated ring closure led to the unsaturated lactone **23**.[20] Direct hydrogenation of bromide **23** with H_2 over Pd/C, hydrazine, Stryker's reagent,[21] Wilkinson's catalyst and $CoCl_2$/$NaBH_4$[22] all failed to produce (±)-**27**. Although use of the stronger Pt/C catalyst with H_2 led to the reduction of the olefin, it also reduced the alkyl bromide to the corresponding alkane (±)-**29**. Consequently, an alternate pathway, similar to the route used in the conversion of **4** into **5**, was used. Displacement of the primary bromide with acetate (**24**), hydrolysis of the acetate (**25**), hydrogenation of the intermediate allylic alcohol [(±)-**26**] and an Appel reaction gave us the desired halolactones (±)-**27** and (±)-**28** (Scheme 12).

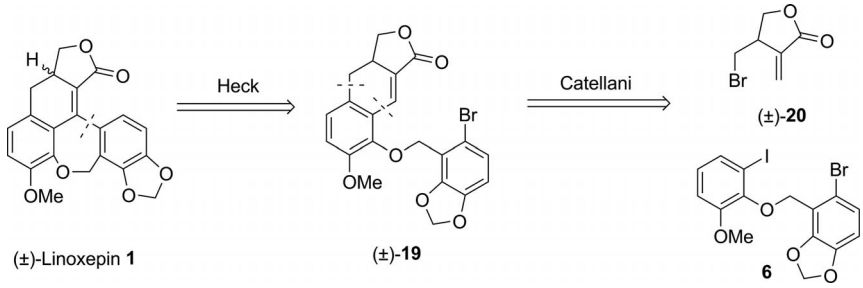
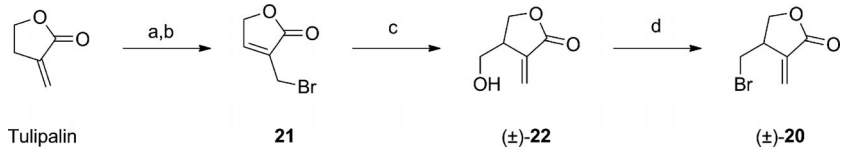
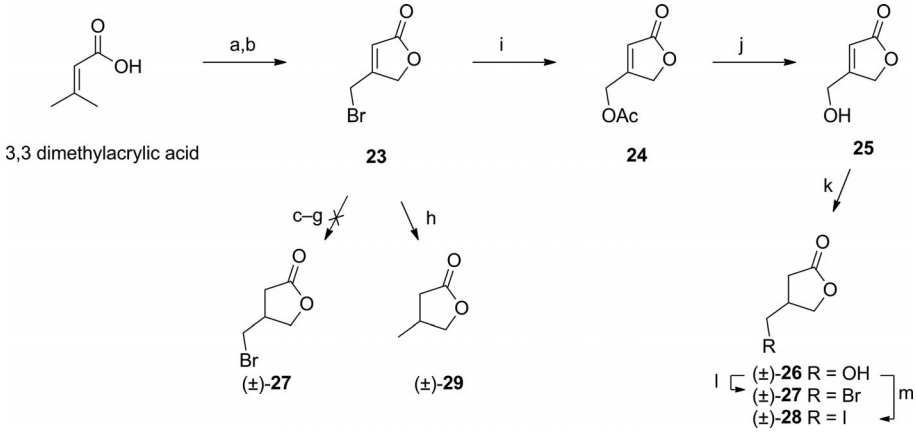


Figure 4. Catellani/Heck approach to (±)-linoxepin (**1**).



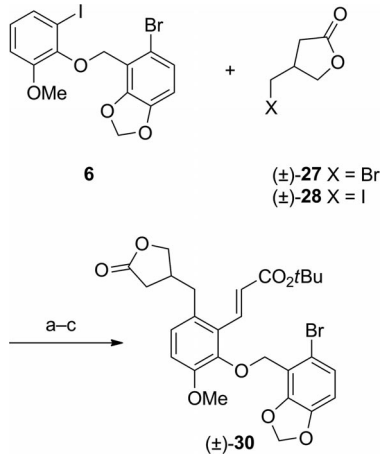
Scheme 10. Synthesis of bromolactone (±)-**20**. Reagents and conditions: a) $PhNMe_3Br_3$, dioxane, r.t., 15 h; b) Li_2CO_3, LiBr, dimethylformamide, 70 °C, 1 h, 68% over two steps; c) 37% CH_2O solution, indium powder, HCl, THF/H_2O (1:1), r.t., 24 h, 34%; d) CBr_4, PPh_3, CH_2Cl_2, 0 °C→r.t., 3 h, 76%.



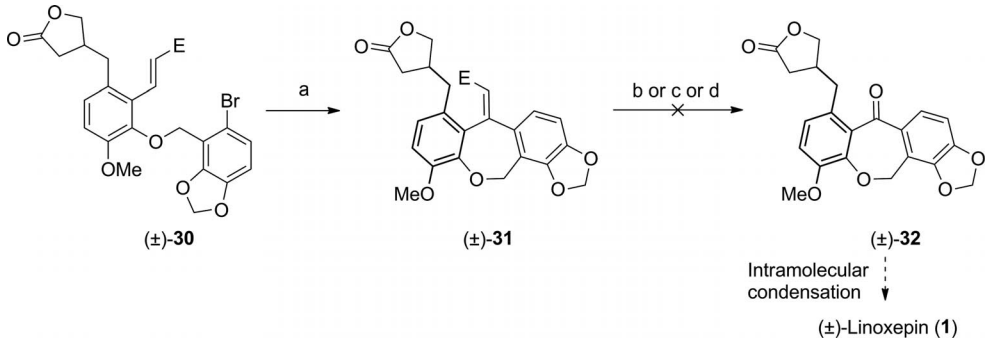
Scheme 12. Synthesis of halolactones (±)-**27** and (±)-**28**. Reagents and conditions: a) NBS, benzoyl peroxide, benzene, 100 °C, 2 h, 82%; b) NaOH, H_2O, r.t., ON, 63%; c) H_2, Pd/C, MeOH, r.t., ON; d) N_2H_4, NaOAc, THF/H_2O (1:1), 70 °C, ON; e) $[CuH(PPh_3)]_6$, PhH, r.t., ON; f) H_2, $[Rh(PPh_3)_3Cl]$; g) $CoCl_2$ (1 mol-%), 1,3 diaminopropane, $NaBH_4$, EtOH/DMF (1:1), r.t., 48 h; h) H_2, Pt/C, MeOH, r.t., ON, 90%; i) NaOAc, 15-crown-5, MeCN, r.t., ON, 60%; j) AcCl, MeOH, r.t., ON, 99%; k) H_2, Pd/C, MeOH, r.t., ON, 98%; l) Br_2, PPh_3, imidazole, CH_2Cl_2, 89%; m) I_2, PPh_3, imidazole, CH_2Cl_2, 86%.

As predicted, the halolactone (±)-**27** lacking the *exo*-methylene substituent was stable during the course of the Catellani reaction and the desired product was obtained in 72% yield. Optimization revealed that DMF and a reaction time of 5 h gave an excellent isolated yield (92%) of (±)-**30** on a 13 mmol scale. To the best of our knowledge this represents the largest-scale Catellani reaction reported to date. Moreover, this key step served to introduce all the carbon atoms needed in the final product (Scheme 13).

With (±)-**30** in hand, our previous method for the intramolecular Heck reaction of aryl bromides and disubstituted cinnamyl esters led to a near quantitative yield of the seven-membered oxepine (±)-**31**. Following this success, we were eager to convert the α,β-unsaturated ester into the corresponding ketone (±)-**32**. Intramolecular condensation of (±)-**32** would lead to our target molecule. Unfortunately the trisubstituted double bond of (±)-**31** could not be cleaved under the reaction conditions used (Scheme 14). Lemieux–Johnson conditions also failed to produce any reaction, presumably because the bulky osmium catalyst could not interact with the extremely hindered olefin. The



Scheme 13. Catellani reaction with more stable alkyl halides. Reagents and conditions: a) (±)-**27**, $Pd(OAc)_2$ (10 mol-%), triphenylphosphine, norbornene, Cs_2CO_3, *tert*-butyl acrylate, MeCN (sealed tube), 90 °C, 16 h, 72%; b) same conditions as (a) but with (±)-**28**, 89%; c) with (±)-**28**, DMF as solvent and reaction time shortened to 5 h, 92% on a 13 mmol scale.



Scheme 14. Attempted synthesis of (±)-linoxepin (**1**). Reagents and conditions: a) $PdCl_2$ (20 mol-%), PPh_3 (44 mol-%), Et_3N (10 equiv.), MW, DMF, 130 °C, 7 h, 99%; b) O_3, CH_2Cl_2/MeOH (4:1), then dimethyl sulfide; c) OsO_4, $NaIO_4$, THF, H_2O, then Na_2SO_3, r.t.; d) $KMnO_4$, THF, H_2O, r.t.; e) H_2O_2, NaOH, MeOH, 0 °C→r.t., then $NaIO_4$; E = CO_2tBu.

olefin geometry of (±)-**31** was confirmed by X-ray crystallographic analysis (Figure 5). All other oxidation methods (O_3, $KMnO_4$ and H_2O_2/NaOH) led to decomposition. It is assumed that the highly electron-rich aromatic rings are oxidized before the trisubstituted olefin (Scheme 14).

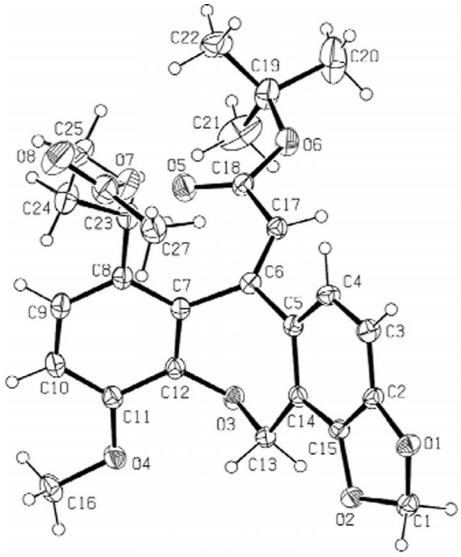


Figure 5. X-ray crystal structure of trisubstituted ester (±)-**31**.

Because the B ring could not be closed after the closure of the E ring we decided to switch the order of ring formation. Oxidative cleavage of (±)-**30** yielded aldehyde (±)-**33** in excellent yield. Subsequent treatment of (±)-**33** with $TiCl_4$ and triethylamine[23] gave the advanced intermediate (±)-**19** with the closed B ring (Scheme 15).

Under our developed conditions for the intramolecular Heck reaction we isolated a product that closely resembled the natural product. After a detailed analysis of this new molecule, it was apparent that we had synthesized a structural isomer of **1**. Our rationale for the formation of this new molecule, which we have called isolinoxepin [(±)-**34**], is that after the initial *syn* carbopalladation the faster *syn* β-hydride elimination occurs rather than the desired elimination (Scheme 16). Fortunately we were able to obtain crystallographic evidence of (±)-**34** to confirm our hypothesis (Figure 6).

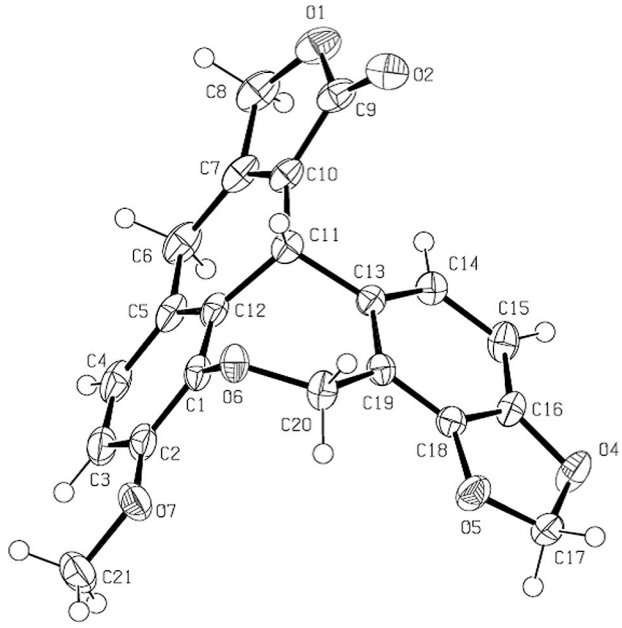
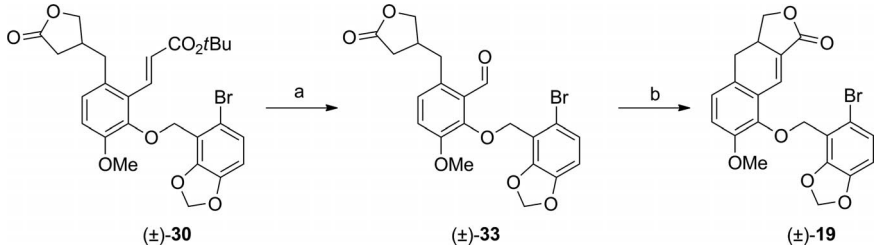
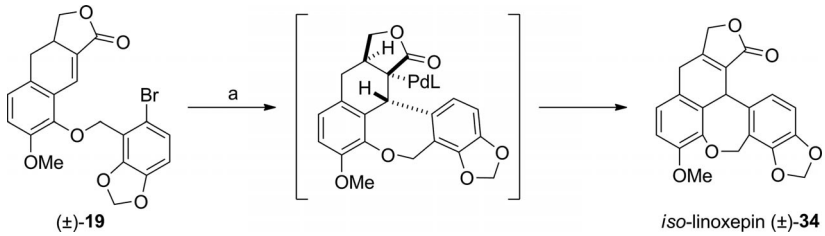


Figure 6. X-ray crystal structure of isolinoxepin [(±)-**34**].

Rhodium and ruthenium are known to isomerize olefins to yield conjugated systems and therefore the thermodynamically favoured products.[24] Owing to the highly conjugated system of (±)-**1** we predicted that (±)-isolinoxepin

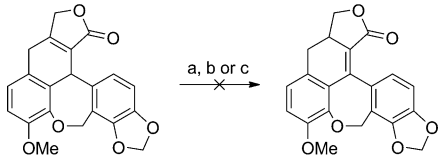


Scheme 15. Synthesis of advanced intermediate (±)-**19**. Reagents and conditions: a) OsO_4, $NaIO_4$, triethylbenzylammonium chloride, THF/H_2O (5:3), r.t., 99%; b) $TiCl_4$, NEt_3, CH_2Cl_2, –78 °C, 4 h, 53%.



Scheme 16. Mechanistic rationale for the formation of isolinoxepin [(±)-**34**]. Reagents and conditions: a) $PdCl_2$ (20 mol-%), PPh_3 (44 mol-%), NEt_3 (10 equiv.), MW, DMF, 130 °C, 7 h, 74%.

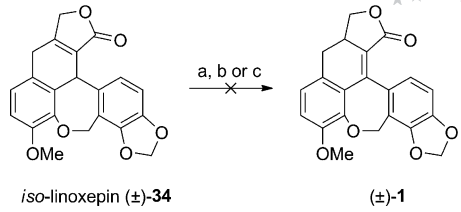
might isomerize to (±)-linoxepin under thermodynamic control. We modelled both molecules by DFT calculations and found that (±)-linoxepin is 14.46 kJ/mol more stable than (±)-isolinoxepin.[25] We attempted the isomerization of (±)-**34** under a variety of conditions, but unfortunately no conversion was observed with various rhodium and ruthenium complexes. We also attempted a base-mediated isomerization but to no avail. Our efforts to force the reaction (prolonged heating at elevated temperatures) only led to fluorescent decomposition products that could not be isolated and identified. Rather than devoting time to a process that would ultimately racemize the single stereocentre, we abandoned the isomerization route (Scheme 17).



Scheme 17. Attempted isomerization of isolinoxepin [(±)-**34**] to (±)-linoxepin (**1**). Reagents and conditions: a) $[HRh(PPh_3)_3]$; b) $[H_2Ru(CO)(PPh_3)_3]$; c) Bu_4NOAc.

Our focus then shifted towards a reductive Heck reaction that would lead to dihydrolinoxepin (±)-**14**. Palladium(II) catalysis with formate as base is known to produce products of formal 1,4-addition reactions.[26] With 10 mol-% palladium(II) acetate and 10 equiv. sodium formate we observed trace amounts of (±)-linoxepin (**1**) in the crude reaction mixture (Scheme 18). Surprisingly we did not observe the formation of (±)-**14**.

There are three possible explanations that account for the formation of (±)-**1** under these conditions. One option is a formal *anti* β-hydride elimination following the initial carbopalladation.[27] This phenomenon is typically seen when the palladium centre resides α to a carbonyl or at a



Scheme 18. Synthesis of (±)-linoxepin (**1**) by the Mizoroki–Heck coupling reaction. Reagents and conditions: a) $Pd(OAc)_2$ (10 mol-%), PPh_3 (20 mol-%), HO_2CNa (10 equiv.), DMF/MeCN (1:1), r.t. to 55 °C overnight.

benzylic centre[27a,27b] after the initial carbopalladation. In these cases the palladium can isomerize to the other face of the system to access a *syn* β-hydride. Ikeda et al. have reviewed formal *anti* elimination reactions leading to the formation of medium-sized rings through intramolecular Heck-type reactions.[27c] The second explanation invokes direct base-mediated *anti* β-hydride elimination. Takacs et al. have shown evidence for this mechanism with cyclic carbonates.[28] In this case the palladium centre undergoes an antiperiplanar elimination. Kikukawa et al. first postulated this type of elimination for β-stannylpalladium species.[29a] Lastly, a C–H activation following the initial oxidative addition could lead to linoxepin by a mechanism not involving carbopalladation. The switch in reactivity that is observed when using an inorganic carboxylate base lends credence to this type of mechanism. After oxidative addition to the aryl–Br bond of (±)-**19**, the carboxylate base can activate the vinylic C–H bond to form an eight-membered palladacycle. Reductive elimination would provide (±)-**1** (Figure 7).[30,31]

Screening different inorganic bases led to an improved method for the synthesis of our target. With caesium acetate we observed the formation of (±)-linoxepin (**1**) in 78% isolated yield on a 0.5 mmol scale (Scheme 19). We were also able to obtain the crystal structure of (±)-**1** (Figure 8).

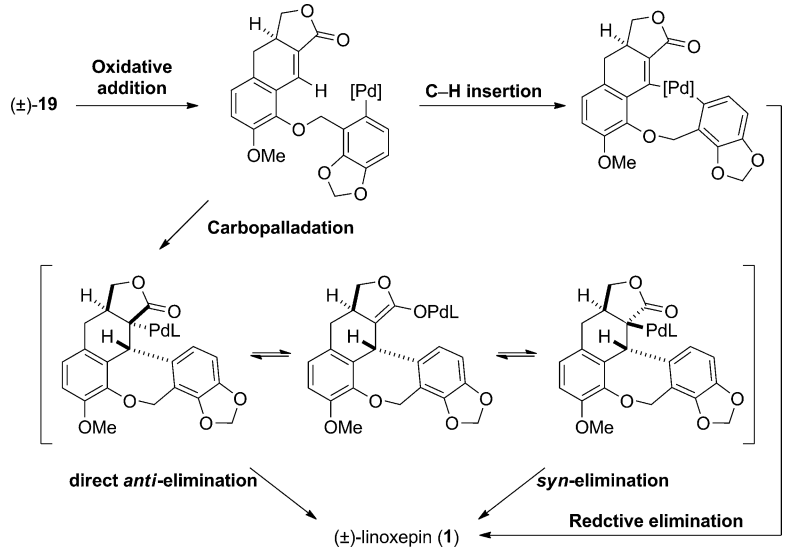
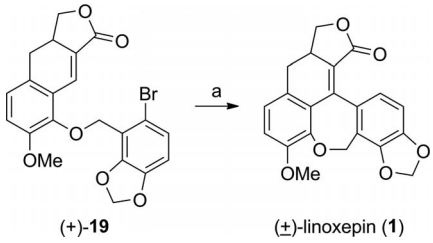


Figure 7. Possible mechanistic pathways from the formation of (±)-linoxepin (**1**).



Scheme 19. Optimized synthesis of (±)-linoxepin (**1**). Reagents and conditions: a) $PdCl_2$ (20 mol-%), PPh_3 (44 mol-%), CsOAc (10 equiv.), DMF, 75 °C, 4 h, 78% on a 0.5 mmol scale.

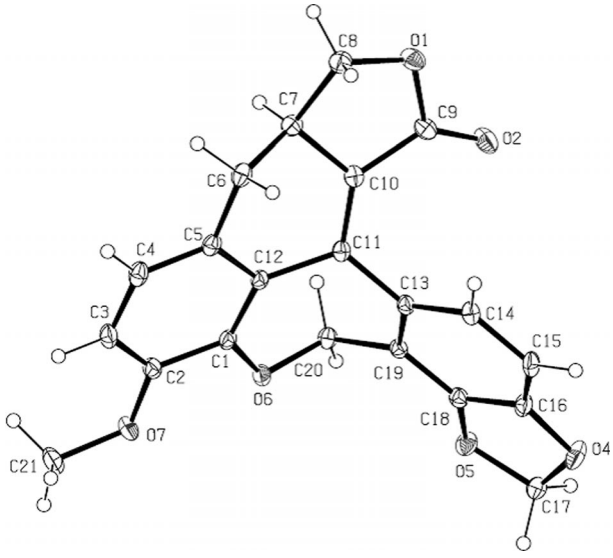
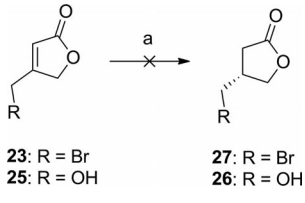


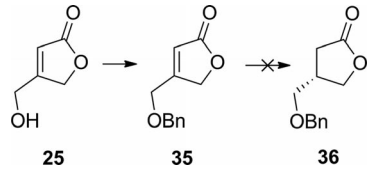
Figure 8. X-ray crystal structure of (±)-linoxepin (**1**).

With the completion of the racemic syntheses of both linoxepin and isolinoxepin, we looked towards an enantioselective synthesis of the natural product. The single stereogenic centre in (+)-linoxepin (**1**) was synthesized by hydrogenation (Scheme 12). Buchwald and co-workers have previously reported enantioselective hydrogenations of similar butenolides with a $CuCl_2$/(*S*)-*p*Tol-BINAP catalyst with $PhSiH_3$ as the stoichiometric reducing agent.[32] Unfortunately, bromide **23** and alcohol **25** showed no conversion under these conditions (Scheme 20).



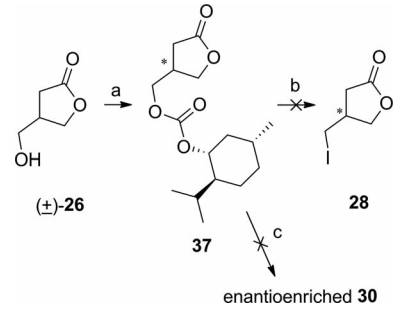
Scheme 20. Attempted asymmetric hydrogenation. Reagents and conditions: a) $CuCl_2$, (*S*)-tol-BINAP, $PhSiH_3$, toluene, 5 h.

Alcohol **25** was then benzyl-protected and treated with baker's yeast in an attempt at enzymatic hydrogenation.[33] This also failed to produce the chiral lactone (Scheme 21).



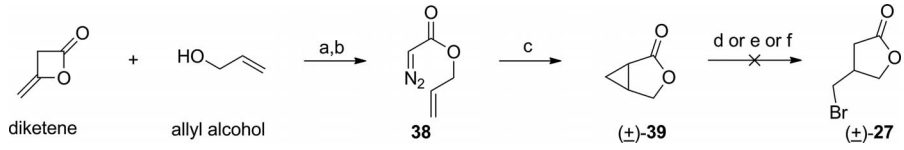
Scheme 21. Attempted enzymatic hydrogenation. Reagents and conditions: a) $PhCH_2OC(=NH)CCl_3$, NaH, CF_3CO_2H, diethyl ether, 75 min, 20%; b) baker's yeast, glucose, tap water, 36 °C.

We then turned out attention to kinetic resolution. By adding a chiral auxiliary to the racemic alcohol (±)-**26** we hoped to be able to separate the resulting diastereomers. Treatment of (±)-**26** with (–)-menthyl chloroformate produced a yield of **37** of about 50% as a crystalline solid. NMR analysis revealed the formation of only a single diastereomer. It is assumed that either only one of the enantiomers of alcohol (±)-**26** reacted or that only one diastereomer of the carbonate crystallized. Displacement of the carbonate with iodide by using TMSCl and NaI failed to give the alkyl iodide **28** and only led to decomposition (Scheme 22). Any type of hydrolysis, either acidic or basic, would have racemized the stereocentre once the alcohol was exposed.[34] Therefore **37** was used directly in the Catellani reaction. We reasoned that the alkyl carbonate could act as electrophile in place of the alkyl halide. Unfortunately the carbonate was not suitable for the reaction. No conversion was observed under different solvents (MeCN, DMF) or on addition of KI for in situ carbonate/iodide exchange.

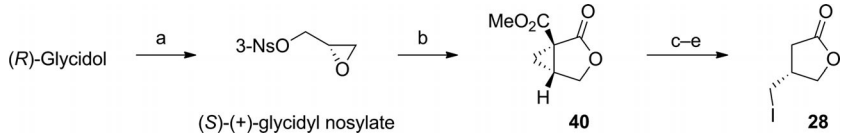


Scheme 22. Attempted synthesis of enantioenriched iodolactone **28** and Catellani product **30**. Reagents and conditions: a) (–)-menthyl chloroformate, pyridine, CH_2Cl_2, O°C→r.t., 2 h, 50%; b) TMSCl, NaI, MeCN, r.t., 15 min; c) Catellani conditions.

We then shifted our efforts towards enantioselective cyclopropanation chemistry. Both enantiomers of cyclopropane **39** were reported by Martin and co-workers in 1995.[35] Heating diketene and allyl alcohol at reflux under basic conditions followed by treatment with *p*-acetamidobenzenesulfonyl azide and then LiOH yielded allyl 2-diazoacetate (**38**). Diazo decomposition in the presence of a dirhodium(II) catalyst yielded cyclopropane (±)-**39**. The plan was to use a nucleophilic halide to open the cyclopropane ring to give the Catellani precursor. Unfortunately ring-opening to yield the bromolactone (±)-**27** was not successful under the reaction conditions attempted (Scheme 23).



Scheme 23. Attempted synthesis of (±)-**27** by cyclopropane ring-opening. Reagents and conditions: a) NaOAc, THF, TMSCl, NaI, 70 °C, 90 min, 49%; b) *p*-acetamidobenzenesulfonyl azide, Et_3N, CH_3CN, r.t., 30 min then aq. LiOH, r.t., 3 h, 77%; c) $[Rh_2(OAc)_4]$, CH_2Cl_2, 55 °C, 16 h, 25%; d) NaBr, TMSCl, CH_3CN, r.t., ON; e) NaBr, TMSCl, 15-crown-5, CH_3CN, r.t., ON; f) NaBr, TMSCl, 15-crown-5, CH_3CN, 50 °C, ON.



Scheme 24. Synthesis of enantioenriched iodolactone **28**. Reagents and conditions: a) 3-nitrobenzenesulfonyl chloride (1 equiv.), Et_3N (1.1 equiv.), DCM, 0 °C, 99%; b) dimethyl malonate (1.1 equiv.), CsF (5 equiv.), MeCN, r.t., 7 d, 68%; c) $AlCl_3$ (0.2 equiv.), HCl in dioxane (3 equiv.), DME, r.t., ON, 99%; d) *p*TsOH·H_2O, (2 equiv.), DMSO, 140 °C, 3 h, 76%; e) NaI (3 equiv.), Me(CO)Et, 80 °C, ON, 98%.

We hypothesized that if one carbonyl group was insufficient to drive cyclopropane ring-opening, installing a second would make the cyclopropane more reactive. On searching the literature we came across a publication by Zutter and co-workers for the synthesis of enantiopure iodolactone **28**.[36] Nosylation of (*R*)-glycidol gave us (*S*)-(+)-glycidyl nosylate, which was combined with dimethyl malonate to give cyclopropane **40** flanked by two carbonyl groups. Cyclopropane ring-opening was achieved by treatment with $AlCl_3$ and HCl. The resulting alkyl chloride was treated with *p*TsOH to remove the extra methyl ester. A Finklestein reaction gave **28** in an overall yield of 50% over five steps (Scheme 24).

With enantiopure iodolactone **28** in hand, the Catellani reaction and the subsequent oxidation, condensation and Heck reactions proceeded smoothly to furnish enantiopure (+)-linoxepin (**1**) in an overall yield of 30%.

Conclusions

We have provided a comprehensive account of the synthetic routes taken towards the synthesis of (+)-linoxepin (**1**). In the process, the Catellani reaction was advanced beyond all previous reports. Our work exemplifies the first use of the powerful palladium/norbornene catalytic system in the synthesis of a natural product. Extremely complex products have been synthesized in excellent isolated yields on a scale of up to 13 mmol, showcasing the successful realization of our goal to develop a synthetically viable C–H functionalization methodology. Along with a tunable late-stage Mizoroki–Heck reaction, a convergent synthesis of (+)-linoxepin (**1**) and its isoform isolinoxepin [(±)-**34**] has been accomplished in eight steps from commercially available materials.

Experimental Section

TLC was performed with EMD TLC silica gel 60 F254 aluminium sheets. Visualization was accomplished with 254 nm UV light followed by staining with potassium permanganate, anisaldehyde, phosphomolybdic acid or vanillin solution. Flash and gradient column chromatography were carried out with Silicycle Ultra-Pure 230–400 mesh silica gel. Melting points were measured with a Fisher-Johns melting-point apparatus. IR spectra were obtained by using a Perkin–Elmer Spectrum 1000 FT-IR spectrometer as neat films or as solutions ($CHCl_3$ or CH_2Cl_2) on a NaCl plate. Data is presented as the frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 23 °C in $CDCl_3$ with a Bruker Avance 400, Varian Mercury 400, Varian Unity 500 or Agilent DD2–600 spectrometer. Recorded shifts for protons and carbon resonances are reported in parts per million (δ scale) and are referenced to residual proton signals in the NMR solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m = multiplet, br. = broad, and combinations thereof), coupling constant (*J* [Hz]) and integration. High-resolution mass spectra were obtained with a SI2 Micromass 70S-250 (EI), AB Sciex QStar (ESI), or JEOL AccuTOF model JMS-T1000LC (DART) mass spectrometer. Crystal structures were obtained with a Bruker Kappa APEX-DUO CCD diffractometer equipped with a Bruker Triumph or multi-layer optics monochromator using Mo-K_α or Cu-K_α irradiation. Data collection was performed by using Bruker APEX2 software, data reduction by using Bruker SAINT[37], and structure solution by using SHELXS-97.[38] CCDC-929322 [for (±)-**19**], -929323 [for (±)-**33**], -929324 [for (±)-**31**], -929325 [for (±)-**34**], and -929326 [for (±)-**1**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

2-(2-Methoxyphenoxy)tetrahydro-2*H*-pyran (S1, Scheme 2): 3,4-Dihydro-2*H*-pyran (67.76 g, 73.0 mL, 805.5 mmol) and PPTS (200 mg, 8.05 mmol) was added to a solution of guaiacol (10.00 g, 80.55 mmol) in DCM (70 mL) . The reaction was stirred for 4 h at room temp. and then saturated NaOH (20 mL) was added. The reaction mixture was extracted with DCM three times and the combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (hexanes/EtOAc, 10:1) yielded **S1** as a colourless oil (15.95 g, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.09 (m, 1 H), 7.00–6.92 (m, 1 H), 6.91–6.79 (m, 2 H), 5.38 (t, *J* = 3.2 Hz, 1 H), 4.09–3.92 (m, 1 H), 3.81 (s, 3 H), 3.67–3.45 (m, 1 H), 2.15–1.76 (m, 4 H), 1.76–1.46

(m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.52, 146.49, 122.71, 121.10, 118.22, 112.64, 97.79, 62.34, 56.22, 30.53, 25.43, 19.06 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3063, 2943, 2874, 2843, 2361, 1593, 1501, 1454, 1358, 1254, 1211, 1115, 1026, 961, 914, 745 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 208.1099; found 208.1098.

2-Iodo-6-methoxyphenol (9): *n*-Butyllithium (1.70 M in *n*-hexane, 16.95 mL, 28.82 mmol) was added dropwise to a solution of THP-guaiacol **S1** (4.00 g, 19.21 mmol) in THF (40 mL) at 0 °C. The reaction was warmed to room temperature and stirred under N_2 for 7 h at which point it was cooled to –78 °C and I_2 (9.75 g, 38.42 mmol) dissolved in THF (60 mL) was added dropwise. After warming to room temperature overnight the reaction mixture was concentrated in vacuo and the residue was dissolved in water and extracted with DCM three times. The combined organic phases were washed with a saturated solution of Na_2SO_3 and then water. After drying over $MgSO_4$ and concentration under reduced pressure, the residue was adsorbed onto silica. Purification by column chromatography (hexanes/EtOAc, 3:1) yielded **9** as a colourless solid (4.70 g, 98%). Recrystallization (MeOH/H_2O) gave white needles, m.p. 48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.83 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.63 (t, *J* = 8.1 Hz, 1 H), 6.08 (s, 1 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.38, 145.88, 130.78, 121.81, 110.84, 81.56, 56.38 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3480, 2365, 1589, 1474, 1435, 1346, 1277, 1223, 1126, 1022, 799, 756, 714 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 249.9491; found 249.9485.

2-(Benzyloxy)-1-iodo-3-methoxybenzene (S2, Scheme 5): K_2CO_3 (6.9 g, 50 mmol) was added to a solution of phenol **9** (2.5 g, 10 mmol) and benzyl bromide (1.88, 11 mmol) in acetone (30 mL). The reaction was heated at reflux for 2 h. After cooling to room temp. the reaction mixture was diluted with water and the solution extracted with DCM three times. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo to obtain **S2** as a clear oil (3.44 g, 99%), which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.55 (m, 2 H), 7.45–7.31 (m, 4 H), 6.92 (dd, *J* = 8.2, 1.4 Hz, 1 H), 6.82 (t, *J* = 8.1 Hz, 1 H), 5.03 (s, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.19, 147.94, 137.29, 130.84, 128.66, 128.45, 128.42, 128.16, 126.15, 112.97, 93.22, 74.57, 56.16 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3063, 3032, 2870, 2361, 1597, 1562, 1485, 1454, 1377, 1285, 1231, 1018, 737, 694 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 339.9960; found 339.9959.

5-Bromobenzo[*d*][1,3]dioxole-4-carbaldehyde (S3, Scheme 2): *n*-Butyllithium (1.8 M in *n*-hexane, 17.3 mL, 31.13 mmol) was added dropwise to a solution of diisopropylamine (3.15 g, 4.37 mL, 31.13 mmol) in THF (60 mL) at –78 °C. After 15 min, 5-bromo-2*H*-1,3-benzodioxole (5.00 g, 3.00 mL, 24.90 mmol) was added and the mixture was stirred for –78 °C for 1 h. DMF (4.37 g, 4.6 mL, 59.8 mmol) was then added dropwise, which was then warmed to room temp. overnight. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc three times. The combined organic phases were concentrated without drying and purified by recrystallization from DCM/hexanes to give **S3** as yellow crystals (5.42 g, 95%), m.p. 163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.29 (s, 1 H), 7.11 (d, *J* = 8.2 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.16 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.50, 149.65, 148.89, 126.33, 117.58, 115.74, 113.70, 103.52, 100.13 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1678, 1616, 1582, 1451, 1397, 1242, 1207, 1115, 1045, 1015, 876, 806 cm^{-1}.

(5-Bromobenzo[*d*][1,3]dioxol-4-yl)methanol (7): Powdered $NaBH_4$ (897 mg, 23.67 mmol) was added in small portions to a solution of aldehyde **S3** (5.42 g, 23.67 mmol) in THF (50 mL). The reaction was heated at reflux for 90 min then quenched dropwise with water and extracted with EtOAc three times. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. After purification by column chromatography (hexanes/ethyl acetate, 3:1) **7** was obtained as a white solid (5.25 g, 96%), m.p. 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.01 (m, 1 H), 6.75–6.59 (m, 1 H), 6.09–6.00 (m, 2 H), 4.75 (s, 2 H), 2.26–2.07 (m, 1 H), 1.60–1.53 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.31, 147.27, 125.42, 121.80, 115.15, 109.32, 102.02, 59.67, 59.66 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3356, 1439, 1242, 995, 926, 775 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 252.9470; found 252.9476.

5-Bromo-4-(iodomethyl)benzo[*d*][1,3]dioxole (8): TMSCl (4.71 g, 5.55 mL, 43.28 mmol) and NaI (6.49 g, 43.28 mmol) were added successively to a solution of benzyl alcohol **7** (5.00 g, 21.64 mmol) in MeCN (30 mL) . The reaction mixture was stirred for 1 h at room temp. and then quenched with a saturated solution of Na_2SO_3, which caused a white solid to precipitate out of solution. The solid was collected and washed with water. Drying under vacuum gave iodide **8** (7.30 g, 99%), which was used without purification, m.p. 79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.3 Hz, 1 H), 6.62 (d, *J* = 8.3 Hz, 1 H), 6.06 (s, 2 H), 4.46 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.27, 146.79, 125.72, 120.67, 115.21, 109.23, 102.44, –2.11 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2905, 1493, 1458, 1420, 1250, 1215, 1126, 1049, 999, 922, 876, 810, 664 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 339.8596; found 339.8584.

5-Bromo-4-[(2-iodo-6-methoxyphenoxy)methyl]benzo[*d*][1,3]dioxole (6): Phenol **9** (4.70 g, 18.8 mmol) and iodide **8** (6.41 g, 18.8 mmol) were dissolved in acetone (200 mL). K_2CO_3 (12.78 g, 94 mmol) was added and the reaction mixture was heated at reflux for 2 h. The reaction was diluted with water (100 mL) and the solution extracted with DCM three times. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc, 10:1) to yield **6** as a white solid (8.70 g, 94%), which was recrystallized from hexanes/EtOAc at –25 °C, m.p. 62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.05 (d, *J* = 8.3 Hz, 1 H), 6.87 (dd, *J* = 8.2, 1.5 Hz, 1 H), 6.78 (dd, *J* = 8.0, 8.0 Hz, 1 H), 6.67 (d, *J* = 8.3 Hz, 1 H), 5.95 (s, 2 H), 5.21 (s, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.15, 148.78, 148.07, 147.10, 130.86, 126.07, 125.24, 118.86, 116.98, 112.85, 109.77, 102.01, 93.07, 68.54, 56.14 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2959, 2936, 2893, 1578, 1454, 1258, 1219, 1030, 961, 802, 764 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 484.8855; found 484.8852.

***tert*-Butyl (*E*)-3-[2-(Benzyloxy)-6-(3-bromopropyl)-3-methoxyphenyl]acrylate (10):** $Pd(OAc)_2$ (57.6 mg, 0.257 mmol) and PPh_3 (148.1 mg, 0.565 mmol) were dissolved in dry MeCN (3 mL) and stirred under argon for 10 min in a sealable reaction vessel. Cs_2CO_3 (4.19 g, 12.85 mmol), aryl iodide **S2** (874 mg, 2.57 mmol), *tert*-butyl acrylate (1.9 mL, 12.85 mmol) and 1,3-dibromopropane (2.6 mL, 25.7 mmol) were added successively to the reaction mixture. The vessel was closed by a septum and the mixture purged for 10 min with argon through a needle. Norbornene (1.2 g, 12.85 mmol) was added to the reaction mixture and the reaction mixture flushed rapidly with argon before the vessel was sealed. After 16 h at 90 °C the reaction mixture was filtered through Celite® with DCM as eluent and concentrated in vacuo. After purification by column chromatography (hexanes/EtOAc, 25:1→10:1), **10** (751 g, 64%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 16.2 Hz, 0.1 H), 7.63 (d, *J* = 16.2 Hz, 0.9 H), 7.51–7.40 (m, 2 H), 7.39–7.28 (m, 3 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.53 (d, *J* = 16.2 Hz, 0.9 H), 6.31 (d, *J* = 16.2 Hz, 0.1 H), 5.02 (s, 0.2 H), 4.92

(s, 1.8 H), 3.89 (s, 0.4 H), 3.88 (s, 2.6 H), 3.37 (t, J = 6.5 Hz, 2 H), 2.87–2.78 (m, 2 H), 2.16–2.01 (m, 2 H), 1.52 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.55, 166.24, 153.18, 151.60, 146.97, 138.21, 137.19, 137.16, 137.14, 137.05, 132.69, 129.42, 128.65, 128.63, 128.47, 128.45, 128.39, 128.38, 128.27, 128.25, 128.20, 128.17, 128.09, 128.02, 126.31, 125.44, 125.42, 124.24, 121.34, 118.86, 113.61, 112.95, 112.93, 80.26, 80.21, 75.53, 74.64, 55.99, 55.91, 33.80, 33.04, 31.35, 28.24, 28.23, 28.20 ppm. Due to dynamic effects, more signals than expected were observed. IR (neat): $\tilde{\nu}_{max}$ = 2977, 2934, 2876, 2358, 2338, 1727, 1722, 1709, 1699, 1617, 1603, 1497, 1477, 1468, 1454, 1386, 1262, 1156, 1150, 1070, 973, 917, 747, 700 cm^{-1}. HRMS (DART): calcd. for $[M + H]^+$ 461.13275; found 491.13373.

***tert*-Butyl (2*E*)-3-{2-[(5-Bromo-2*H*-benzo[*d*][1,3]dioxol-4-yl)methoxy]-6-(3-bromopropyl)-3-methoxyphenyl}prop-2-enoate (5):** $Pd(OAc)_2$ (224.5 mg, 1.0 mmol) and PPh_3 (557 mg, 2.2 mmol) were dissolved in dry MeCN (60 mL) and stirred under argon for 10 min in a sealable reaction vessel. Cs_2CO_3 (16.30 g, 50.0 mmol), iodophenol **6** (4.63 g, 10.0 mmol), *tert*-butyl acrylate (6.40 g, 7.26 mL, 50 mmol) and 1,3-dibromopropane (20.18 g, 10.15 mL, 100.0 mmol) were added successively to the reaction mixture. The vessel was closed by a septum and the mixture was purged for 10 min with argon through a needle. Norbornene (4.70 g, 50.0 mmol) was added to the reaction mixture and the reaction mixture flushed rapidly with argon before the vessel was sealed. After 16 h at 90 °C the reaction mixture was filtered through Celite® with DCM as eluent and concentrated in vacuo. After purification by column chromatography (hexanes/EtOAc, 25:1→10:1) **5** (4.79 g, 82%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, J = 16.2 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.40 (d, J = 16.2 Hz, 1 H), 5.94 (s, 2 H), 5.09 (s, 2 H), 3.87 (s, 3 H), 3.48 (t, J = 6.4 Hz, 2 H), 2.83–2.74 (m, 2 H), 1.99–1.90 (m, 2 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.30, 166.70, 151.82, 148.52, 147.07, 146.80, 137.00, 132.69, 128.99, 126.57, 125.69, 125.19, 118.86, 116.62, 112.91, 109.67, 102.13, 80.23, 68.45, 60.55, 56.16, 44.36, 33.83, 31.74, 30.29, 28.36, 22.80, 21.20, 14.35, 14.27 ppm. Due to dynamic effects, more signals than expected were observed. IR (neat): $\tilde{\nu}_{max}$ = 2970, 1705, 1632, 1454, 1366, 1261, 1153, 1053, 1022, 976, 802 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 605.0144; found 605.0114.

***tert*-Butyl (2*E*)-3-{6-[3-(Acetoxy)propyl]-2-[(5-bromo-2*H*-benzo[*d*]-[1,3]dioxol-4-yl)methoxy]-3-methoxyphenyl}prop-2-enoate (S4, Scheme 4):** In a sealable vessel, alkyl bromide **5** (4.87 g, 8.33 mmol) was dissolved in dry MeCN (40 mL) and 18-crown-6 (4.40 g, 16.67 mmol) and KOAc (1.64 g, 16.67 mmol) were added to the solution. The sealed vessel was heated at 80 °C overnight. The reaction was cooled to room temp. and diluted with H_2O. The aqueous phase was extracted with DCM three times and the organic phases were dried with $MgSO_4$ and concentrated in vacuo. After purification by column chromatography (hexanes/EtOAc, 10:1→3:1), **S4** (4.26 g, 91%) was obtained as a colourless solid, m.p. 74 °C. ^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.53 (d, J = 16.2 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.39 (d, J = 16.2 Hz, 1 H), 5.94 (s, 2 H), 5.09 (s, 2 H), 4.03 (t, J = 6.4 Hz, 2 H), 3.87 (s, 3 H), 2.75–2.64 (m, 2 H), 2.06 (s, 3 H), 1.88–1.79 (m, 2 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.21, 166.61, 151.59, 148.44, 146.98, 146.74, 137.12, 133.85, 133.10, 128.87, 126.24, 125.39, 125.31, 125.10, 121.70, 118.80, 116.54, 115.89, 112.91, 112.57, 109.62, 109.57, 102.05, 101.99, 80.07, 68.37, 65.80, 63.85, 63.64, 56.40, 56.08, 31.65, 30.36, 30.02, 29.49, 28.29, 21.07, 21.04 ppm. Due to dynamic effects, more signals than expected were observed. IR (neat): $\tilde{\nu}_{max}$ = 2974, 2940, 2901, 1736, 1705, 1632, 1458, 1366, 1242, 1153, 1049, 934, 802 cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 563.1275; found 563.1289.

***tert*-Butyl (2*E*)-3-{2-[(5-Bromo-2*H*-benzo[*d*][1,3]dioxol-4-yl)methoxy]-6-(3-hydroxypropyl)-3-methoxyphenyl}prop-2-enoate (S5, Scheme 4):** Acetate **S4** (850 mg, 1.51 mmol) was dissolved in DCM (3 mL) and MeOH (6 mL) and K_2CO_3 (208.7 mg, 1.51 mmol) was then added to the solution. After 2 h at room temp. the reaction mixture was quenched with water and extracted with DCM three times. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 3:1) to give **S5** (757 mg, 96%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 16.2 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.43 (d, J = 16.2 Hz, 1 H), 5.93 (s, 2 H), 5.09 (s, 2 H), 3.87 (s, 3 H), 3.63 (t, J = 6.3 Hz, 2 H), 2.77–2.63 (m, 2 H), 1.80–1.73 (m, 2 H), 1.69 (s, 1 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.96, 151.58, 148.49, 147.04, 146.84, 137.33, 134.06, 128.79, 126.20, 125.41, 125.19, 118.91, 116.64, 113.03, 109.63, 102.10, 80.23, 68.48, 62.21, 56.17, 34.25, 29.48, 28.36 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3433, 2970, 2936, 2835, 1701, 1628, 1454, 1366, 1258, 1153, 1053, 1015, 934 cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 521.1169; found 521.1188.

***tert*-Butyl (2*E*)-3-(2-[(5-Bromo-2*H*-benzo[*d*][1,3]dioxol-4-yl)methoxy]-3-methoxy-6-{3-[(2-nitrophenyl)selanyl]propyl}phenyl)prop-2-enoate (S6, Scheme 4):** Alcohol **S5** (337.8 mg, 0.65 mmol) and 1-nitro-2-selenocyanatobenzene (295 mg, 1.30 mmol) were dissolved in THF (6 mL). PBu_3 was added to the solution and the reaction mixture was stirred for 3 h at room temp. The solvent was evaporated under reduced pressure, and the residue was adsorbed on silica. Purification by column chromatography (hexanes/EtOAc, 5:1) gave **S6** (401 mg, 88%) obtained as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (dd, J = 8.3, 1.5 Hz, 1 H), 7.52 (d, J = 16.2 Hz, 1 H), 7.49 (ddd, J = 8.0, 7.2, 1.5 Hz, 1 H), 7.39 (dd, J = 8.1, 1.3 Hz, 1 H), 7.29 (ddd, J = 8.4, 7.2, 1.3 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.2 Hz, 1 H), 6.42 (d, J = 16.1 Hz, 1 H), 5.94 (s, 2 H), 5.10 (s, 2 H), 3.88 (s, 3 H), 2.88–2.77 (m, 4 H), 2.02–1.94 (m, 2 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.72, 151.82, 148.50, 147.06, 146.89, 137.08, 133.80, 133.55, 132.89, 129.03, 128.88, 126.61, 126.48, 125.62, 125.41, 125.20, 118.86, 116.61, 112.97, 109.69, 102.12, 80.29, 68.49, 56.17, 33.54, 30.01, 28.37, 25.30 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2974, 2936, 1701, 1589, 1512, 1454, 1304, 1261, 1053, 934, 729 cm^{-1}. HRMS (ESI): calcd. for $[M + H - C_4H_8]^+$ 649.9923; found 649.9903.

***tert*-Butyl (2*E*)-3-{2-[(5-Bromo-2*H*-benzo[*d*][1,3]dioxol-4-yl)methoxy]-3-methoxy-6-(prop-2-enyl)phenyl}prop-2-enoate (4):** Selenide **S6** (240 mg, 0.34 mmol) was dissolved in THF (4 mL) and H_2O_2 (30% in H_2O, 175 μL) was added at 0 °C. The reaction mixture was warmed to room temp. overnight and then diluted with water. The aqueous phase was extracted with EtOAc three times and the combined organic phases washed with a saturated solution of Na_2SO_3 and water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 5:1) yielded **4** (166 mg, 97%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, J = 16.2 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 6.32 (d, J = 16.2 Hz, 1 H), 5.94 (s, 2 H), 5.96–5.87 (m, 1 H), 5.10 (s, 3 H), 5.05 (dq, J = 10.1, 1.6 Hz, 2 H), 4.93 (dq, J = 17.1, 1.8 Hz, 2 H), 3.87 (s, 3 H), 3.36 (dt, J = 5.6, 1.4 Hz, 1 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.66, 151.73, 148.55, 147.06, 146.64, 137.57, 137.31, 131.56,

129.49, 126.17, 126.16, 125.80, 125.16, 118.84, 116.65, 116.09, 112.92, 109.62, 102.13, 80.09, 68.44, 56.16, 37.56, 28.35 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2974, 2932, 2901, 1705, 1636, 1454, 1366, 1261, 1153, 1053, 934, 802 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 525.0883; found 525.0885.

***tert*-Butyl 2-[7-Methoxy-4-(prop-2-enyl)-9,13,15-trioxatetracyclo-[9.7.0.0^{3,8}.0^{12,16}]octadeca-1(11),3,5,7,12(16),17-hexaen-2-yl]acetate (3):** *n*BuLi (1.78 M in hexane, 178 μL, 0.10 mmol) was added dropwise over 10 min to a solution of aryl bromide **4** (50 mg, 0.10 mmol) in dry THF (10 mL) at –78 °C. CuCN·2LiCl (1.0 M, 0.10 mL, 0.10 mmol) was then added dropwise to the mixture, which was then warmed to room temp. overnight. For work-up, saturated NH_4Cl was added and the reaction mixture was extracted with EtOAc three times. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 10:1 → 5:1) to obtain (±)-**3** (27.6 mg, 65%) as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, J = 8.4 Hz, 1 H), 6.80–6.72 (m, 2 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.00–5.83 (m, 3 H), 5.44 (d, J = 16.2 Hz, 1 H), 5.04–4.83 (m, 3 H), 4.49 (t, J = 7.5 Hz, 1 H), 3.86 (s, 3 H), 3.64–3.53 (m, 1 H), 3.43–3.34 (m, 1 H), 3.10 (dd, J = 7.5, 3.1 Hz, 2 H), 1.30 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.91, 171.28, 151.08, 146.43, 145.99, 143.90, 137.97, 137.42, 132.47, 129.83, 126.35, 126.17, 124.10, 124.05, 119.20, 115.90, 115.81, 110.87, 110.66, 106.64, 106.44, 101.51, 80.23, 67.82, 67.77, 60.54, 56.06, 55.96, 50.08, 43.31, 42.30, 37.68, 37.56, 34.82, 34.67, 31.74, 29.21, 28.13, 25.81, 25.43, 22.81, 22.77, 22.32, 21.19, 20.85, 18.91, 14.35, 14.26, 13.93, 11.58 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2974, 2936, 1724, 1447, 1366, 1261, 1146, 1084, 1049, 914, 806 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 447.1778; found 447.1783.

***tert*-Butyl (*Z*)-2-(7-Allyl-10-methoxy[1,3]dioxolo[4′,5′:3,4]benzo-[1,2-*e*]benzo[*b*]oxepin-6(12*H*)-ylidene)acetate (15):** $PdCl_2$ (8.9 mg, 0.049 mmol) and PPh_3 (28.1 mg, 0.107 mmol) were suspended in dry DMF (2 mL) in a sealable tube. The mixture was stirred under argon for 10 min at room temp. Aryl bromide **4** (123 mg, 0.244 mmol) and dry NEt_3 (0.34 mL, 2.44 mmol) were added to the tube. Before the tube was sealed, the mixture was flushed with argon and then heated in a microwave oven for 7 h at 130 °C. The reaction mixture was diluted with a mixture of hexanes/EtOAc (1:1) and washed with brine. The aqueous phase was extracted with hexanes/EtOAc (1:1) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuo. The dark residue was purified by column chromatography (hexanes/EtOAc, 10:1 → 5:1) to obtain **15** (65 mg, 63%) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.95–6.87 (m, 2 H), 6.83 (d, J = 8.5 Hz, 1 H), 6.68 (d, J = 8.1 Hz, 1 H), 6.21 (s, 1 H), 5.97 (d, J = 1.4 Hz, 1 H), 5.89 (d, J = 1.4 Hz, 1 H), 5.81–5.69 (m, 1 H), 5.35 (d, J = 16.2, 1 H), 5.01–4.93 (m, 1 H), 4.91 (d, J = 16.3 Hz, 1 H), 3.88 (s, 3 H), 3.36–3.29 (m, 1 H), 3.26–3.17 (m, 1 H), 1.31 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.87, 151.24, 150.04, 147.60, 143.77, 142.50, 137.03, 136.62, 132.27, 129.38, 125.34, 123.07, 121.70, 118.77, 116.18, 111.75, 106.88, 101.89, 80.36, 68.43, 56.18, 36.76, 27.99 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2974, 2936, 2905, 1717, 1694, 1620, 1601, 1470, 1451, 1362, 1258, 1204, 1150, 1045, 945, 810, 737 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 445.1621; found 445.1614.

***tert*-Butyl 2-[7-(2,3-Dihydroxypropyl)-10-methoxy-6,12-dihydro[1,3]-dioxolo[4′,5′:3,4]benzo[1,2-*e*]benzo[*b*]oxepin-6-yl)acetate (12):** NMO (144.8 mg, 1.237 mmol) and $K_2OsO_4·2H_2O$ (3.68 mg, 0.01 mmol) were added to a solution of alkene (±)-**3** (210 mg, 0.495 mmol) in acetone (1.6 mL) and water (0.4 mL). The reaction mixture was stirred at room temp. overnight after which a saturated solution of Na_2SO_3 was added. The reaction mixture was extracted with EtOAc three times and the combined organic phases dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 3:1 → 1:1) to obtain (±)-**12** (168 mg, 74%) as a colourless foam. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.90 (dd, J = 8.4, 7.6 Hz, 1 H), 6.83–6.71 (m, 2 H), 6.59 (dd, J = 8.0, 4.3 Hz, 1 H), 5.92 (d, J = 1.5 Hz, 1 H), 5.86 (d, J = 1.4 Hz, 1 H), 5.49–5.30 (m, 1 H), 4.97–4.70 (m, 1 H), 4.52 (dt, J = 18.1, 7.3 Hz, 1 H), 3.88–3.81 (m, 4 H), 3.79–3.41 (m, 2 H), 3.34–2.66 (m, 4 H), 1.30 (s, 6 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.58, 172.49, 151.26, 146.47, 146.43, 146.17, 144.07, 144.04, 138.39, 138.09, 132.35, 132.31, 128.14, 127.81, 127.32, 127.29, 123.44, 123.20, 119.03, 118.97, 110.95, 110.94, 106.75, 106.66, 101.59, 101.57, 80.79, 80.78, 73.05, 72.98, 67.78, 66.54, 65.56, 56.04, 43.45, 43.41, 42.43, 42.37, 37.03, 36.95, 28.10, 28.08 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3414, 2974, 2936, 1721, 1497, 1447, 1366, 1261, 1150, 1092, 1049, 910, 806, 733 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 481.1832; found 481.1855.

***tert*-Butyl (2*E*)-3-{2-[(5-Bromo-2*H*-benzo[*d*][1,3]dioxol-4-yl)methoxy]-3-methoxy-6-(oxiran-2-ylmethyl)phenyl}prop-2-enoate (16):** *m*CPBA (73%, 141 mg, 0.60 mmol) was added to a solution of aryl bromide **4** (350 mg, 0.50 mmol) in DCM (15 mL). The reaction was stirred overnight at room temp., a saturated solution of Na_2SO_3 was then added and the mixture was extracted with DCM three times. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 5:1) to give (±)-**16** as a colourless oil (248 mg, 96%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, J = 16.3 Hz, 1 H), 7.00 (dd, J = 8.3, 4.1 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 6.31 (d, J = 16.2 Hz, 1 H), 5.96–5.89 (m, 2 H), 5.10 (s, 2 H), 3.88 (s, 3 H), 3.07 (tdd, J = 5.2, 3.9, 2.6 Hz, 1 H), 2.89 (dd, J = 5.3, 3.7 Hz, 2 H), 2.75 (dd, J = 5.0, 3.9 Hz, 1 H), 2.48 (dd, J = 5.0, 2.6 Hz, 1 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.49, 152.11, 148.55, 147.05, 146.56, 137.37, 129.71, 128.77, 126.70, 126.22, 125.18, 118.78, 116.65, 112.87, 109.66, 102.14, 80.31, 68.44, 56.14, 52.17, 47.12, 35.70, 28.34 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2978, 2936, 1705, 1632, 1458, 1370, 1261, 1153, 1053, 934, 853, 802 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 541.0832; found 541.0823.

4-(Bromomethyl)-3-methylenedihydrofuran-2(3*H*)-one (20): CBr_4 (365 mg, 1.1 mmol) followed by PPh_3 (290 mg, 1.1 mmol) were added to a solution of the alcohol (±)-**22** (118 mg, 92 mmol) in dry DCM. The reaction mixture was stirred at room temp. for 3 h and then filtered through a short plug of silica. Purification with hexanes/DCM (4:1) as eluent gave the product bromide (±)-**20** (133 mg, 7 mmol, 76%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.41 (d, J = 2.5 Hz, 1 H), 5.79 (d, J = 2.2 Hz, 1 H), 4.51 (dd, J = 9.8, 8.1 Hz, 1 H), 4.22 (dd, J = 9.6, 4.7 Hz, 1 H), 3.60–3.54 (m, 1 H), 3.54–3.47 (m, 1 H), 3.42 (dd, J = 9.4, 8.0 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.66, 135.95, 124.55, 70.01, 40.73, 33.43 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3077, 3056, 2961, 2929, 2856, 1762, 1691, 1590, 1437, 1311, 1261, 1219, 1173, 1159, 1119, 1070, 1027, 997, 770, 722, 693 cm^{-1}. HRMS (DART): calcd. for $[M + NH_4]^+$ 207.99732; found 207.99717.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (5-Oxotetrahydrofuran-3-yl)methyl Carbonate (37): A solution of alcohol (±)-**26** (1.77 g, 15.3 mmol) in dry CH_2Cl_2 (25 mL) and pyridine (2.1 mL, 26.1 mmol) was cooled to 0 °C under Ar. (–)-Menthyl chloroformate (3.25 mL, 15.2 mmol) was added dropwise and the reaction was warmed to room temp. over 2 h. Water was added and the mixture was extracted with excess EtOAc. The organic phase was washed successively with 5% HCl, a saturated solution of $NaHCO_3$ and brine, then dried with $MgSO_4$. The white solid was crystallized

from hexanes to obtain the product **37** (2.42 g, 8.12 mmol, 53%) as white crystals, m.p. 107–110 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.52 (td, J = 10.9, 4.4 Hz, 1 H), 4.43 (dd, J = 9.4, 7.5 Hz, 1 H), 4.25–4.05 (m, 3 H), 3.09–2.89 (m, 1 H), 2.67 (dd, J = 17.8, 8.9 Hz, 1 H), 2.38 (ddd, J = 17.8, 6.8, 1.6 Hz, 1 H), 2.05 (dtd, J = 12.0, 4.0, 1.8 Hz, 1 H), 1.92 (quintd, J = 7.0, 2.7 Hz, 1 H), 1.72–1.65 (m, 2 H), 1.48 (tdt, J = 12.1, 6.6, 3.4 Hz, 1 H), 1.41 (ddt, J = 12.5, 10.8, 3.1 Hz, 1 H), 1.05 (td, J = 12.3, 11.0 Hz, 2 H), 0.91 (dd, J = 10.8, 6.8 Hz, 6 H), 0.89–0.81 (m, 1 H), 0.78 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.92, 154.70, 79.26, 70.04, 70.01, 67.25, 47.10, 40.81, 34.16, 31.54, 31.00, 26.29, 23.47, 22.09, 20.82, 16.42 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2956, 2928, 2871, 1784, 1472, 1453, 1370, 1340, 1259, 1171, 1026, 1008, 955, 916, 837, 789 cm^{-1}. HRMS (DART): calcd. for $[M + NH_4]^+$ 316.21240; found 316.21222.

***tert*-Butyl (*E*)-3-{2-[(5-Bromobenzo[*d*][1,3]dioxol-4-yl)methoxy]-3-methoxy-6-[(5-oxotetrahydrofuran-3-yl)methyl]phenyl}acrylate (30):** $Pd(OAc)_2$ (38.5 mg, 0.17 mmol, 0.10 equiv.), PPh_3 (99.1 mg, 0.38 mmol, 0.22 equiv.), Cs_2CO_3 (2.80 g, 8.58 mmol, 5.0 equiv.), aryl iodide **6** (797 mg, 1.72 mmol, 1.0 equiv.), *tert*-butyl acrylate (1.26 mL, 8.58 mmol, 5.0 equiv.) and iodolactone (+)-**28** (1.94 g, 8.58 mmol, 5.0 equiv.) were added successively to a sealable pressure flask under Ar. Degassed anhydrous DMF (2 mL) was added and the reaction mixture was stirred at room temp. as Ar was bubbled through the heterogeneous mixture. Norbornene (808.2 mg, 8.58 mmol, 5.0 equiv.) was added and the flask was again purged with Ar before being sealed and heated at 90 °C for 16 h. The reaction mixture was cooled to room temp. and quenched by the addition of a saturated solution of NH_4Cl. Water and EtOAc/hexanes (1:1) were added and the phases were separated. The organic layer was washed with brine, dried with $MgSO_4$ and the solvents removed under reduced pressure. The crude material was purified by silica gel column chromatography (hexanes/EtOAc, 3:1→2:1) to give lactone (–)-**30**. Recrystallization from EtOAc/hexanes gave a white solid (860 mg, 1.53 mmol, 89%), m.p. 113–116 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (dd, J = 16.1, 0.6 Hz, 1 H), 7.00 (d, J = 8.2 Hz, 1 H), 6.85 (s, 2 H), 6.65 (d, J = 8.3 Hz, 1 H), 6.42 (dd, J = 16.1, 0.7 Hz, 1 H), 5.96 (d, J = 0.6 Hz, 2 H), 5.11 (d, J = 0.6 Hz, 2 H), 4.25 (dd, J = 9.2, 6.8 Hz, 1 H), 3.96 (dd, J = 9.1, 6.2 Hz, 1 H), 3.89 (s, 3 H), 2.82–2.76 (m, 2 H), 2.72 (ddd, J = 14.5, 8.1, 6.8 Hz, 1 H), 2.52 (dd, J = 17.5, 8.0 Hz, 1 H), 2.22 (dd, J = 17.5, 7.0 Hz, 1 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.87, 166.56, 152.35, 148.50, 147.09, 147.05, 136.48, 130.09, 128.93, 127.02, 125.90, 125.22, 118.79, 116.55, 112.84, 109.77, 102.14, 80.52, 72.61, 68.46, 56.13, 36.63, 36.38, 34.30, 28.36 ppm. IR: (neat): $\tilde{\nu}_{max}$ = 3434, 2977, 1780, 1767, 1696, 1627, 1575, 1480, 1456, 1368, 1276, 1262, 1154, 1052, 1022, 764, 749 cm^{-1}. HRMS (ESI): calcd. for $[M + NH_4]^+$ 578.13895; found 578.13928. $[\alpha]_D^{20}$ = –4.1 (c = 0.29, $CHCl_3$). Scale-up of the racemic experiment: limiting compound **6** (6.34 g, 13.1 mmol, 1.0 equiv.), DMF as solvent (0.3 M), 5 h; yield: 92% (6.77 g, 12.0 mmol).

***tert*-Butyl (*Z*)-2-{10-Methoxy-7-[(5-oxotetrahydrofuran-3-yl)methyl][1,3]dioxolo[4′,5′:3,4]benzo[1,2-*e*]benzo[*b*]oxepin-6(12*H*)-ylidene}acetate (31):** $PdCl_2$ (3.16 mg, 0.018 mmol, 0.2 equiv.) and PPh_3 (10.3 mg, 0.039 mmol, 0.44 mmol) were suspended in dry DMF (1.5 mL) in a sealable tube. The mixture was stirred under argon for 10 min at room temp and then lactone (±)-**30** (50 mg, 0.089 mmol, 1.0 equiv.) and dry NEt_3 (126 μL, 0.89 mmol, 10 equiv.) were added. Before the tube was sealed, the content was flushed with argon for 5 min. The reaction mixture was heated in a microwave oven for 7 h at 130 °C. For work-up the reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic phases were dried with $MgSO_4$ and concentrated to dryness in vacuo. The dark residue was purified by column chromatography (hexanes/EtOAc, 4:1→3:1) to obtain tetracycle (±)-**31** (42 mg, 0.089 mmol, 99%) as an off-white solid, m.p. 212–214 °C. ^{1}H NMR (399 MHz, $CDCl_3$): δ = 6.92–6.81 (m, 3 H), 6.71 (dd, J = 8.1, 2.9 Hz, 1 H), 6.22 (s, 1 H), 5.98 (d, J = 1.4 Hz, 1 H), 5.92 (dd, J = 1.4, 0.7 Hz, 1 H), 5.35 (d, J = 16.3 Hz, 1 H), 4.95–4.86 (m, 1 H), 4.19–4.08 (m, 1 H), 3.93–3.90 (m, 0.5 H)*, 3.89 (s, 3 H), 3.69 (dd, J = 9.2, 5.8 Hz, 0.5 H)*, 2.79 (dt, J = 13.9, 7.0 Hz, 1 H), 2.71–2.58 (m, 1 H), 2.53 (ddd, J = 13.8, 7.7, 1.9 Hz, 1 H), 2.42 (ddd, J = 17.5, 8.1, 6.3 Hz, 1 H), 2.17 (dd, J = 17.5, 6.7 Hz, 0.5 H)*, 2.00 (dd, J = 17.5, 6.9 Hz, 0.5 H)*, 1.29 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.96, 176.83, 164.65, 164.63, 150.76, 150.71, 150.56, 150.53, 147.87, 147.86, 144.01, 143.99, 142.94, 142.85, 136.92, 136.87, 131.95, 131.91, 127.87, 127.78, 125.55, 125.45, 123.37, 123.31, 121.28, 121.26, 118.69, 118.67, 111.87, 111.80, 107.29, 107.22, 102.05, 80.60, 72.94, 72.76, 68.43, 56.14, 36.65, 36.41, 35.54, 35.44, 34.59, 34.48, 27.98 ppm. *Due to dynamic effects, more signals than expected were observed. IR: (neat): $\tilde{\nu}_{max}$ = 2975, 2916, 1779, 1771, 1712, 1693, 1493, 1471, 1456, 1368, 1253, 1164, 1149, 1043, 1019 cm^{-1}. HRMS (DART): calcd. for $[M + NH_4]^+$ 498.21393; found 498.21279.

2-[(5-Bromobenzo[*d*][1,3]dioxol-4-yl)methoxy]-3-methoxy-6-[(5-oxotetrahydrofuran-3-yl)methyl]benzaldehyde (33): $NaIO_4$ (480 mg, 2.25 mmol) and Et_3NBnCl (17.1 mg, 0.08 mmol) were added to a solution of lactone (–)-**30** (420 mg, 0.75 mmol) in THF/H_2O (5:3, 8 mL) at 0 °C. A catalytic amount of OsO_4 was added and after 10 min at 0 °C the reaction was stirred at room temp. for 5 h. For work-up a saturated solution of Na_2SO_3 was added and the reaction mixture extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography aldehyde (–)-**33** (347 mg, 99%) was obtained as a white solid, m.p. 110–112 °C. ^{1}H NMR**:** (600 MHz, $CDCl_3$): δ = 10.39 (s, 1 H), 7.08 (d, J = 8.3 Hz, 1 H), 7.04 (d, J = 8.3 Hz, 1 H), 6.87 (dd, J = 8.4, 0.8 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 5.96 (s, 2 H), 5.32 (s, 2 H), 4.28 (dd, J = 9.1, 7.0 Hz, 1 H), 3.99 (dd, J = 9.1, 6.3 Hz, 1 H), 3.95 (s, 3 H), 3.01 (dd, J = 13.1, 7.2 Hz, 1 H), 2.94 (dd, J = 13.1, 7.5 Hz, 1 H), 2.82–2.71 (m, 1 H), 2.48 (dd, J = 17.4, 8.2 Hz, 1 H), 2.24 (dd, J = 17.4, 7.2 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 193.19, 177.36, 152.89, 152.23, 148.63, 147.22, 131.99, 129.85, 128.97, 128.44, 127.22, 126.48, 125.63, 117.74, 117.35, 116.46, 110.35, 102.18, 72.98, 69.50, 56.30, 36.79, 36.42, 34.26, 30.11 ppm. IR: (neat): $\tilde{\nu}_{max}$ = 2917, 1775, 1730, 1684, 1574, 1488, 1457, 1401, 1369, 1257, 1226, 1169, 1052, 1021, 933, 853, 803 cm^{-1}. HRMS (DART): calcd. for $[M + NH_4]^+$ 463.03924; found 463.03942. $[\alpha]_D^{20}$ = –2.4 (c = 1.13, $CHCl_3$). HPLC analysis: enantiomers not separable, Chiralpak® AD-H, hexanes/IPA (70:30), 1 mL/min t_{R1} = 10.60 min, t_{R2} = not detectable.

8-[(5-Bromobenzo[*d*][1,3]dioxol-4-yl)methoxy]-7-methoxy-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-one (19): Aldehyde (–)-**33** (110 mg, 0.24 mmol) was dissolved in anhydrous CH_2Cl_2 (8 mL) and the solution was cooled to –78 °C. $TiCl_4$ (29 μL, 0.26 mmol) and NEt_3 (83 μL, 0.60 mmol) were added and the solution was warmed to –25 °C while stirring was continued for 3 h. Additional $TiCl_4$ (29 μL, 0.26 mmol) and NEt_3 (83 μL, 0.60 mmol) were added and the reaction mixture was warmed to room temp. over 1 h before quenching the reaction by the addition of a saturated solution of $NaHCO_3$. The crude biphasic mixture was filtered through a short plug of Celite® and repeatedly washed with CH_2Cl_2. The phases were separated and the organic phase dried with $MgSO_4$. The solvents were removed under reduced pressure and the crude material purified by using column chromatography (hexanes/EtOAc,

4:1→3:1). Dihydronaphthalene (+)-**19** (56 mg, 0.23 mmol, 53%) was obtained as a white solid, m.p. 198–201 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, J = 3.3 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.94–6.90 (m, 1 H), 6.86 (d, J = 8.2 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.13 (d, J = 1.4 Hz, 1 H), 6.06 (d, J = 1.4 Hz, 1 H), 5.23 (d, J = 1.5 Hz, 2 H), 4.70 (t, J = 8.7 Hz, 1 H), 3.97 (t, J = 8.8 Hz, 1 H), 3.91 (s, 3 H), 3.13 (dtdd, J = 15.7, 8.8, 6.8, 3.3 Hz, 1 H), 2.94 (dd, J = 14.9, 6.9 Hz, 1 H), 2.65–2.55 (m, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.83, 152.38, 148.73, 147.33, 145.86, 128.73, 127.77, 127.42, 127.32, 125.29, 123.84, 118.27, 116.44, 113.59, 109.95, 102.47, 72.65, 68.97, 56.29, 34.59, 32.46 ppm. IR: (neat): $\tilde{\nu}_{max}$ = 3390, 2897, 1750, 1662, 1572, 1483, 1456, 1336, 1260, 1242, 1199, 1182, 1121, 1093, 1052, 1037, 999 cm^{-1}. HRMS (DART): calcd. for $[M + NH_4]^+$ 445.02868; found 445.02720. $[\alpha]_D^{20}$ = +103.3 (c = 1.05, $CHCl_3$). HPLC analysis: Chiralpak® AD-H, hexanes/IPA (70:30), 1 mL/min, t_{R1} = 10.51 min, t_{R2} = 12.79 min, 93% *ee*. Scale-up of the racemic experiment: limiting compound (±)-**33** (1.38 g, 3.0 mmol, 1.0 equiv.), yield: 49% (650 mg, 1.5 mmol).

(+)-Linoxepin (1): A flame-dried sealable vial was charged with dihydronaphthalene (+)-**19** (10.0 mg, 21.8 ìmmol, 1.0 equiv.), $PdCl_2$ (0.77 mg, 4.4 µmol), PPh_3 (2.5 mg, 9.6 µmol) and anhydrous CsOAc (41.8 mg, 218 µmol, 10.0 equiv.). The vial was flushed with Ar for 2 min before degassed anhydrous DMF (1 mL) was added. The suspension was stirred for 5 min at room temp. and purged with Ar. The vial was sealed and heated at 75 °C for 4 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl and the aqueous layer was extracted twice with EtOAc/hexanes (1:1). The combined organic layers were dried with $MgSO_4$ and the solvents removed under reduced pressure. The title compound (+)-**1** was obtained as a yellow solid (6.0 mg, 16.5 µmol, 76%) after column chromatography on silica gel (hexanes/EtOAc, 2:1), m.p. 228 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93–6.77 (m, 3 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.06–5.97 (m, 2 H), 5.39 (d, J = 12.5 Hz, 1 H), 5.14 (d, J = 12.5 Hz, 1 H), 4.68 (t, J = 8.9 Hz, 1 H), 4.03 (t, J = 8.7 Hz, 1 H), 3.85 (s, 3 H), 3.28 (dtd, J = 14.6, 8.8, 5.7 Hz, 1 H), 2.99 (dd, J = 14.7, 5.7 Hz, 1 H), 2.71–2.61 (m, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.96, 149.59, 149.18, 148.68, 145.82, 144.94, 129.59, 128.31, 124.52, 124.29, 122.37, 119.98, 116.65, 111.98, 108.26, 102.00, 70.15, 64.81, 56.33, 36.99, 34.61 ppm. IR: (neat): $\tilde{\nu}_{max}$ = 2900, 1748, 1661, 1572, 1481, 1464, 1436, 1300, 1277, 1264, 1244, 1199, 1183, 1102, 1032, 1013, 913, 760 cm^{-1}. HRMS (DART): calcd. for $[M + H]^+$ 365.10251; found 365.10195 $[\alpha]_D^{20}$ = +90.0 (c = 0.25, $CHCl_3$). Scale of the racemic experiment: limiting compound (±)-**19** (223 mg, 0.5 mmol, 1.0 equiv.); yield: 78% (142 mg, 0.39 mmol).

Isolinoxepin (34): $PdCl_2$ (0.52 mg, 3.0 µmol) and PPh_3 (1.7 mg, 6.0 µmol) were suspended in dry DMF (0.5 mL) in a sealable tube and the mixture was stirred under argon for 10 min at room temp. Dihydronaphthalene (±)-**19** (6.5 mg, 0.015 mmol, 1.0 equiv.) and dry NEt_3 (20 µL, 0.146 mmol) were added and the flask was flushed with argon for a further 5 min. The reaction vessel was sealed and heated in a microwave oven for 7 h at 130 °C. For work-up the reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$ and concentrated to dryness in vacuo. The dark residue was purified by column chromatography (hexanes/EtOAc, 2:1) to obtain isolinoxepin (±)-**34** (4 mg, 0.011 mmol, 74%) as an off-white solid, m.p. >380 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (d, J = 8.5 Hz, 1 H), 6.84 (d, J = 8.5 Hz, 1 H), 6.53 (d, J = 8.2 Hz, 1 H), 6.26 (dd, J = 8.1, 0.9 Hz, 1 H), 5.92 (d, J = 1.4 Hz, 1 H), 5.86 (d, J = 1.4 Hz, 1 H), 5.81 (s, 1 H), 5.59 (d, J = 15.6 Hz, 1 H), 5.18 (d, J = 15.5 Hz, 1 H), 5.12 (d, J = 17.1 Hz, 1 H), 4.98–4.87 (m, 1 H), 3.88 (s, 3 H), 3.76 (ddd, J = 22.2, 4.2, 1.2 Hz, 1 H), 3.62 (dd, J = 22.0, 3.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.96, 161.80, 151.16, 146.62, 144.81, 143.89, 134.41, 131.65, 126.46, 124.14, 121.88, 117.92, 117.20, 111.64, 106.45, 101.66, 71.86, 67.86, 56.25, 34.18, 28.23 ppm. IR: (neat): $\tilde{\nu}_{max}$ = 2956, 2934, 2922, 2852, 2359, 1750, 1738, 1733, 1727, 1722, 1709, 1699, 1618, 1603, 1497, 1477, 1468, 1454, 1410, 1277, 1262, 1248, 1205, 1156, 1070, 1029, 939, 917, 747 cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 387.0839; found 387.0852.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all new compounds; DFT calculations.

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[1] a) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119; *Angew. Chem.* **1997**, *109*, 142; b) E. Motti, M. Rossetti, G. Bocelli, M. Catellani, *J. Organomet. Chem.* **2004**, *689*, 3741.

[2] a) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1; b) H. Liu, M. El-Salfiti, M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 9846; *Angew. Chem.* **2012**, *124*, 9984; c) D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 3312; d) M. Blanchot, D. A. Candito, F. Larnaud, M. Lautens, *Org. Lett.* **2011**, *13*, 1486.

[3] T. J. Schmidt, S. Vβing, M. Klaes, S. Grimme, *Planta Med.* **2007**, *73*, 1574.

[4] a) J. L. Charlton, *J. Nat. Prod.* **1998**, *61*, 1447; b) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75; c) B. Kozik, J. Wilamowski, M. Gora, J. J. Sepiol, *Tetrahedron* **2008**, *64*, 6452.

[5] a) M. Gordaliza, P. A. García, J. M. D. Corral, M. A. Castro, M. A. Gómez-Zurita, *Toxicon* **2004**, *44*, 441; b) E. L. Baldwin, N. Osheroff, *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 363.

[6] L. F. Tietze, S.-C. Duefert, J. Clerc, M. Bischoff, C. Maaß, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3191; *Angew. Chem.* **2013**, *125*, 3273.

[7] H. Weinstabl, M. Suhartono, Z. Qureshi, M. Lautens, *Angew. Chem. Int. Ed.* **2013**, *52*, 5305; *Angew. Chem.* **2013**, *125*, 5413.

[8] a) L. F. Tietze, G. Brasche, K. M. Gericke, in: *Domino Reactions in Organic Synthesis* Wiley-VCH, Weinheim, Germany, **2006**; b) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929; c) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442.

[9] a) M. Catellani, *Pure Appl. Chem.* **2002**, *74*, 63; b) M. Catellani, M. C. Fagnola, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421; *Angew. Chem.* **1994**, *106*, 2559; c) M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1988**, *346*, C27.

[10] a) M. Catellani, B. E. Mann, *J. Organomet. Chem.* **1990**, *390*, 251; b) G. Bocelli, M. Catellani, G. P. Chiusoli, S. Larocca, *J. Organomet. Chem.* **1984**, *265*, C9; c) G. Bocelli, M. Catellani, *J. Organomet. Chem.* **1985**, *296*, C11.

[11] C. Mollar, M. Besora, F. Maseras, G. Asensia, M. Media-Simón, *Chem. Eur. J.* **2010**, *16*, 13390.

[12] D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033.

[13] For reviews on the Catellani reaction, see: a) R. Ferraccioli, *Synthesis* **2013**, *45*, 581; b) A. Martins, B. Mariampillai, M.

Lautens, *Top. Curr. Chem.* **2010**, *292*, 1; c) M. Lautens, D. Alberico, C. Bressy, Y. Q. Fang, B. Mariampillai, T. Wilhelm, *Pure Appl. Chem.* **2006**, *78*, 351; d) G. C. Tsui, M. Lautens, in: *Domino Reaction: Concepts for Efficient Organic Synthesis* (Ed.: L. F. Tietz), Wiley-VCH, Weinheim, Germany, **2013**, vol. 1, p. 80–96.
[14] P. A. Grieco, M. Miyashita, *J. Org. Chem.* **1974**, *39*, 120.
[15] C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983.
[16] S. K. Taylor, J. A. Fried, Y. N. Grassel, A. E. Marolewski, E. A. Pelton, T.-J. Poel, D. S. Rezanka, M. R. Whittaker, *J. Org. Chem.* **1993**, *58*, 7304.
[17] a) M. Lautens, S. Piguel, *Angew. Chem. Int. Ed.* **2000**, *39*, 1045; *Angew. Chem.* **2000**, *112*, 1087; b) M. Lautens, J. F. Paquin, S. Piguel, M. Dahlmann, *J. Org. Chem.* **2001**, *66*, 8127.
[18] D. M. Hodgson, E. P. A. Talbot, B. P. Clark, *Org. Lett.* **2011**, *13*, 2594.
[19] G. D. Bennett, L. A. Paquette, *Org. Synth.* **2000**, *77*, 107.
[20] E. S. Wang, Y. M. Choy, H. N. C. Wong, *Tetrahedron* **1996**, *52*, 12137.
[21] W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291.
[22] U. Leutenegger, A. Madin, P. Doz, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 61; *Angew. Chem.* **1989**, *101*, 54.
[23] The authors thank Prof. H. U. Reissig for suggesting the conditions for the transformations of (+)-**33** into (+)-**19**.
[24] See the Supporting Information for calculations.
[25] For rhodium-catalysed isomerizations, see: a) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc.* **1984**, *106*, 5208; b) F. A. Alphonse, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 11754; c) D. S. Tsang, S. Yang, F. A. Alphonse, A. K. Yudin, *Chem. Eur. J.* **2008**, *14*, 886; d) L.-G. Zhuo, Z.-K. Yao, Z.-X. Yu, *Org. Lett.* **2013**, *15*, 4634; for ruthenium-catalysed isomerizations, see: e) H. Suzuki, Y. Koyama, Y. Moro-Oka, T. Ikawa, *Tetrahedron Lett.* **1979**, *20*, 1415; f) P. Wipf, S. R. Spencer, *J. Am. Chem. Soc.* **2005**, *127*, 225; g) M. Arisawa, Y. Terada, K. Takahashi, M. Nakagawa, A. Nishida, *J. Org. Chem.* **2006**, *71*, 4255; h) S. Hanessian, S. Giroux, A. Larrson, *Org. Lett.* **2006**, *8*, 5481; i) D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592; j) T. J. Donohoe, T. J. C. O'Riordan, C. P. Rosa, *Angew. Chem. Int. Ed.* **2009**, *48*, 1014; *Angew. Chem.* **2009**, *121*, 1032; k) C. R. Larsen, D. B. Grotjahn, *J. Am. Chem. Soc.* **2012**, *134*, 10357.
[26] a) T. Tobrman, D. Dvořák, *Tetrahedron Lett.* **2004**, *45*, 273; b) P. Gao, S. P. Cook, *Org. Lett.* **2012**, *14*, 3340; c) K. C. Majumdar, T. Ghosh, S. Ponra, *Tetrahedron Lett.* **2013**, *54*, 4661.
[27] a) M. Lautens, Y.-Q. Fang, *Org. Lett.* **2003**, *5*, 3679; b) K. Maeda, E. J. Farrington, E. Galardon, B. D. John, J. M. Brown, *Adv. Synth. Catal.* **2002**, *344*, 104; c) M. Ikeda, S. A. A. El Bialy, T. Yakura, *Heterocycles* **1999**, *51*, 1957.
[28] J. M. Takacs, E. C. Lawson, F. Clement, *J. Am. Chem. Soc.* **1997**, *119*, 5956.
[29] For cine substitution of vinylstannanes, see: a) K. Kikukawa, H. Umekawa, T. Matsuda, *J. Organomet. Chem.* **1986**, *311*, C44; b) G. Stork, R. C. A. Isaacs, *J. Am. Chem. Soc.* **1990**, *112*, 7399; c) G. T. Crisp, P. T. Glink, *Tetrahedron* **1994**, *50*, 3213; for cine substitution of vinylzinc compounds, see: d) D. S. Ennis, T. L. Gilchrist, *Tetrahedron Lett.* **1989**, *30*, 3735; for cine substitution of vinylboron compounds, see: e) A. R. Hunt, S. K. Stewart, A. Whiting, *Tetrahedron Lett.* **1993**, *34*, 3599.
[30] C. C. Hughes, D. Trauner, *Angew. Chem. Int. Ed.* **2002**, *41*, 1569; *Angew. Chem.* **2002**, *114*, 1639.
[31] For recent reviews on C–H activation, see: a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.
[32] G. Hughes, M. Kimura, S. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253.
[33] K. Takabe, M. Tanaka, M. Sugimoto, T. Yamada, H. Yoda, *Tetrahedron: Asymmetry* **1992**, *3*, 1385.
[34] K. Mori, K. Yamane, *Tetrahedron* **1982**, *38*, 2919.
[35] M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. Zhou, S. F. Martin, *J. Am. Chem. Soc.* **1995**, *117*, 5763.
[36] J.-M. Adam, J. Foricher, S. Hanlon, B. Lohri, G. Moine, R. Schmid, H. Stahr, M. Weber, B. Wirz, U. Zutter, *Org. Process Res. Dev.* **2011**, *15*, 515.
[37] Bruker AXS Inc., Madison, Wisconsin, USA.
[38] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

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