Metal-Catalyzed Cycloetherification Reactions of β,γ - and γ,δ -Allendiols. Chemo-, Regio- and Stereocontrol in the Synthesis of Oxacycles

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Abstract: Versatile routes leading to a variety of functionalized enantiopure tetrahydrofurans, dihydropyrans, and tetrahydrooxepines are based on chemo-, regio- and stereocontrolled metal-catalyzed oxycyclization reactions of β,γ - and γ,δ -allendiols, which were readily prepared from (*R*)-

2,3-*O*-isopropylidene-glyceraldehyde. The application of Pd(II), Pt(II), Au(III) or La(III) salts as the catalysts gives controlled access to differently-sized oxacycles in enantiopure form. Usually, chemoselective cyclization reactions occurred exclusively by attack of the secondary hydroxy group (except for

the oxybromination of phenyl β,γ -allenic diols **3b** and **3d**) to an allenic carbon. Regio- and stereocontrol issues are mainly influenced by the nature of metal catalysts and substituents.

Keywords: allenes · cyclization · gold · palladium · platinum

Introduction

The development of synthetic methods for the preparation of different-sized oxacycles is important because they are present in a wide range of natural products and biologically active molecules.^[1] Among the possibilities, transition metal-catalyzed intramolecular addition of oxygen nucleophiles across an allene moiety is intriguing from the point of view of regioselectivity as well as it being one of the most rapid and convenient methods for the preparation of oxacycles.^[2] However, metal-catalyzed heterocyclizations of allenes bearing two contiguous nucleophilic centers have rarely been mentioned because of additional chemoselectivity problems.^[3] Namely, the product distribution must depend on the chemo- and regioselectivity of the heterocyclization, but in principle, eight different products are possible.^[4] In this context, even if the structure of the substrate suggests numerous possibilities for reactivity, metal-catalyzed processes can lead to specific control of the transition state and result in the controlled

formation of products with high selectivity. In continuation of our interest in heterocyclic and allene chemistry,^[5] we report here full details of the chemo- and regioselective palladium-catalyzed cycloetherification of β,γ - and γ,δ -allendiols,^[6] together with its extension to precious metals, namely, gold and platinum salts.

Results and Discussion

Precursors for the oxacycle formation, enantiopure β,γ -allenic diols **3a–d** and γ,δ -allenic diols **4a** and **4b**, were made starting from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde **1** and (*R*)-2-(benzyloxy)-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde **2**,^[7] respectively, via regio- and stereocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media, followed by protecting groups manipulation (Scheme 1 and Scheme 2). Whereas the allenylation of aldehyde **1** using 1-bromobut-2-yne did take place with complete diastereoselectivity forming **5a**, the carbonyl–addition reaction of its benzyloxy homologue **2** gave α -allenols **7a** with poor syn/anti stereoselectivity (ratio **7aM**:**7am** = 60:40). Fortunately, the diastereomeric α -allenols **7aM** and **7am** were separated by column chromatography. By contrast, coupling reactions of aldehydes **1** and **2** with organoindium reagent generated *in situ* from indium and (3-bromoprop-1-ynyl)benzene were totally diastereoselective, affording α -allenols **5b** and **7b** as single isomers. The absolute configurations of the new carbinolic stereocenters on α -allenols **5a** and **7aM** were determined according to Trost's empirical model, through esterification with (*S*)- and (*R*)-*O*-methylmandelic acids.^[8] The calculated ¹H NMR chemical shift differences for the protons of their acetylmandelates allowed us to tentatively attribute the (*S*) configuration to α -allenol **5a** and the (*R*) configuration to α -allenol **7aM**.

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Scheme 1. Preparation of enantiopure β,γ -allenic diols **3a–d**. Reagents and conditions: i) 1-Bromobut-2-yne or (3-bromoprop-1-ynyl)benzene, In, THF/ NH_4Cl (aq. sat.), RT, 5 h. ii) PMPCOCl, Et_3N , DMAP, CH_2Cl_2 , RT, 18 h; or TPSCl, imidazole, CH_2Cl_2 , reflux, 24 h; or Me_2SO_4 , NaOH, TBAI, DCM- H_2O , RT, 12 h. iii) 20 mol% BiCl_3 , MeCN- H_2O , RT, 24 h. PMP = 4-MeOC $_6\text{H}_4$. TPS = *t*-Butyldiphenylsilyl.

Scheme 2. Preparation of enantiopure γ,δ -allenic diols **4**. Reagents and conditions: i) 1-Bromobut-2-yne or (3-bromoprop-1-ynyl)benzene, In, THF/ NH_4Cl (aq. sat.), RT, 16 h. ii) PMPCOCl, Et_3N , DMAP, CH_2Cl_2 , reflux, **8aM**: 28 h; **8b**: 48 h; **8aM**: 24 h. iii) 20 mol% BiCl_3 , MeCN- H_2O , RT, **4aM**: 48 h; **4b**: 18 h; **4aM**: 48 h. PMP = 4-MeOC $_6\text{H}_4$. **M** = Major isomer; **m** = minor isomer.

We decided to investigate the distinct reactivity of β,γ - and γ,δ -allenic diols depending on the nature of the metal catalyst that initiates electrophilic activation of the allene moiety. Recently, gold and platinum salts have emerged as powerful catalysts for the formation of C–C and C–heteroatom bonds.^[9] Indeed, in an initial screen with β,γ -allendiols **3**, it was found that AuCl_3 was a selective catalyst to perform the desired cycloetherification to exclusively access functionalized dihydropyrans **9** in reasonable yields (Scheme 3). These results could be explained through a 6-*endo* cycloisomerization by chemo- and regioselective attack of the secondary hydroxy group to the terminal allene carbon. Worthy of note, by contrast, the AuCl_3 -catalyzed cycloisomerization of γ,δ -allenic diols **4** represents a selective method to afford tetrahydrofurans **10** bearing a quaternary stereocenter (Scheme 3).^{[10],[11]} Thus, by using a benzyloxy allendiols homologue, the regioselectivity can be completely reversed, favoring the 5-*exo* cyclization of the secondary hydroxy group towards the internal allene carbon over the 6-*endo* cyclization towards the terminal allene carbon. The reason for the total diastereoselectivity for 5-*exo* cyclization toward the internal allene carbon on methyl-allendiols **4aM** to give adduct **10c** compared to the moderate diastereoselectivity of methyl-allendiols **4aM** to give adduct **10a** (Scheme 3), may be related to an increase ease of access of the incoming oxygen nucleophile to the allene group from the face *trans* to the benzyloxy and *p*-methoxybenzyloxy groups. Qualitative homonuclear NOE difference spectra allowed us to assign the stereochemistry at the newly formed stereocenter of tetrahydrofurans **10**. The *p*-methoxybenzyloxy group comprises a large substituent. Disappointingly, the presence of a large phenyl substituent in the allene moiety (**4b**) instead of the methyl group (**4aM**) did affect the reactivity, being oxacycle **10b** obtained within a complex reaction mixture.

Scheme 3. Gold-catalyzed preparation of dihydropyrans **9** and tetrahydrofurans **10**. Reagents and conditions: i) 5 mol % AuCl_3 , CH_2Cl_2 , RT, **9a**: 2.5 h; **9b**: 2 h; **10a**: 16 h; **10b**: 16 h; **10c**: 25 h. PMP = 4-MeOC $_6\text{H}_4$. **M** = Major isomer; **m** = minor isomer.

The use of gold catalysis in allene chemistry has already witnessed spectacular achievements. By contrast, the platinum-catalyzed reactions by using allenols as substrates are an almost unexplored field of noble metal catalysis.^[12] Nicely, upon exposure of β,γ -allenic diol **3a** to platinum catalysis, the carbaldehyde **11**, which is the result of a chemo- and regioselective cyclization of the secondary hydroxy group into the distal allene carbon with concurrent oxidation,^[13] was obtained as the sole product. The fact that the optimum reaction conditions required the addition of equimolecular amount of phosphine ligand for platinum, may suggest that the catalytically active species could be a platinum(II) monophosphine complex. Compound **11** was not particularly stable at room temperature. Thus, in order to avoid decomposition, the aldehyde must be trapped immediately. The trapping/derivatization was accomplished through the use of a stabilized Wittig reagent during the platinum-catalyzed oxycyclization step, giving rise to the α,β -unsaturated ester **12** (Scheme 4). By contrast, the cyclization of γ,δ -allenic diol **4aM** was not as rewarding, and the tetrahydrofuran **10a** was obtained in low yield (Scheme 4).

Scheme 4. Platinum-catalyzed preparation of dihydropyrans **11** and **12** and tetrahydrofurans **10**. Reagents and conditions: i) 5 mol % $[\text{PtCl}_2(\text{CH}_2=\text{CH}_2)_2]$, 10 mol % TDMPP, CH_2Cl_2 , RT, 2 h. ii) 5 mol % $[\text{PtCl}_2(\text{CH}_2=\text{CH}_2)_2]$, 10 mol % TDMPP, methyl (triphenylphosphoranylidene)acetate, CH_2Cl_2 , RT, 2 h. PMP = 4-MeOC $_6\text{H}_4$. TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

The lanthanide-catalyzed hydroalkoxylation of simple allenols has recently appeared in the literature.^[14] Our investigations began with β,γ -allenic diols **3a** and **3b** as model substrates. Attempts of a cyclization reaction of **3a** using $\text{La}[\text{N}(\text{SiMe}_3)_2]_3$ as catalyst failed, giving rise instead to the isomeric α,β -allenic diol **13**. However, the reaction of phenyl allenic diol **3b** using the lanthanide amide-catalyzed protocol afforded the furan **14** in good yield. It could be explained through a selective 5-*exo* cyclization by attack of the secondary hydroxy group to the central allene carbon to give the non-isolable dihydrofuran **15**, which under the reaction conditions suffers aromatization to form furan **14** (Scheme 5). Interestingly, the reaction of the γ,δ -allenic diol **4am** under identical conditions as above, could proceed smoothly with complete product selectivity to give tetrahydrofuran **10c** via 5-*exo* cycloisomerization of the secondary hydroxy group towards the internal allene carbon. It should be noted that the La-catalyzed oxycyclization of simple γ -allenols afforded six-membered cyclic ethers.^[14]

Scheme 5. Lanthanide amide-catalyzed preparation of furan **14**. Reagents and conditions: i) 5 mol % $\text{La}[\text{N}(\text{SiMe}_3)_2]_3$, toluene, reflux, **13**: 4 h; **14**: 24 h; **10c**: 3 h. PMP = 4-MeOC₆H₄.

To screen the reactivity of the allenic diol moiety under different palladium-based catalysts, heterocyclization was initially explored by the exposure of β,γ -allenic diol **3a** to Pd(0)-catalysis. The 2*H*-pyran **16**, arising from a totally chemo- and regioselective 6-*exo* oxycyclization of the primary hydroxy group to the central allene carbon with concurrent dehydration, was obtained in modest yield, together with a complicated mixture of side-products (Scheme 6). Next, **3a** was reacted with allyl bromide in the presence of a Pd(II) catalyst. Nicely, the functionalized dihydropyran **17a** was isolated as the sole isomer in a reasonable 65% yield. Similar behavior was observed for the phenyl-derivative **3b** (Scheme 6). This result could be explained through a 6-*endo* cyclization by chemo- and regiospecific attack of the secondary hydroxy group to the terminal allene carbon. The stage was thus set for the metal-catalyzed cycloetherification reaction of γ,δ -allenic diols **4**. The conversion to the corresponding oxacycle could not be satisfied with Pd(0) promoters. Interestingly, we found that under the allyl bromide reactions conditions, PdCl₂ could be an excellent catalyst for this purpose. The cycloetherification/coupling sequence of γ,δ -allenic diols **4** was attained and surprisingly, the regioselectivity was changed by inverting the configuration of the stereocentre near to the allene framework (Scheme 6). Thus, we were pleased to find that γ,δ -allenic diols **4aM** and **4b** did suffer a 7-*endo* oxycyclization into the distal allene carbon to give tetrahydrooxepines **18**, while γ,δ -allenic diol **4am** did follow a 5-*exo* heterocyclization pathway into the proximal allene carbon to afford tetrahydrofuran **19b**.

Therefore, an interesting reversal of regioselectivity can be achieved by introducing the epimeric configuration at the allenic contiguous stereocenter. Probably, this fact is due to steric effects in the transition state. Thus, for β,γ -allenic diol **4aM** the reaction should take place more unfavorably for the pallada-tetrahydrofuran than for the pallada-tetrahydrooxepine intermediate due to destabilizing steric interactions around the reactive centers in the former. Qualitative homonuclear NOE difference spectra allowed us to assign the stereochemistry at the newly formed stereocenter of tetrahydrofuryl derivative **19b**.

Scheme 6. Palladium-catalyzed preparation of dihydropyrans **17**, tetrahydrooxepines **18**, and tetrahydrofuran **19b**. Reagents and conditions: i) 5 mol % $\text{Pd}(\text{PPh}_3)_4$, PhI, K₂CO₃, toluene, 80 °C, 24 h. ii) Allyl bromide, 5 mol % PdCl₂, DMF, RT, **17a**: 3 h; **17b**: 2 h; **18a**: 16 h; **18b**: 16 h; **19b**: 24 h. PMP = 4-MeOC₆H₄.

It was interesting at this point to test the reactivity of the allenic diol moiety under palladium-catalyzed oxybromination conditions.^[15] We found that when β,γ -allenic diols **3a** and **3c** (bearing a methyl group on the allene group) were treated with lithium bromide using a Pd–Cu bimetallic catalytic system, selectively led to the bromoetherification products **20** in reasonable isolated yields, ensuing from 6-*endo-trig* cyclization. We also tested the reactivity of β,γ -allendiols **3b** and **3d** bearing a phenyl rather than a methyl allene substituent. To our delight, in contrast to the oxybromination reaction of methyl-allendiols **3a** and **3c** which lead to a bromodihydropyran, the reaction of phenyl-allendiols **3b** and **3d** under identical conditions affords 2-(1-bromovinyl)tetrahydrofurans **21** bearing a quaternary stereocentre (Scheme 7).^[10] Thus, by a subtle variation in the substitution pattern of the β,γ -allenic diol (Ph versus Me) both the chemo- and the regioselectivity can be completely reversed. This apparently unusual result can be explained by pointing at the electron-withdrawing capacities of the phenyl substituent compared to the electron-donating methyl group. Probably, the presence of a Ph substituent in the allene moiety strengthened the electrophilicity of the benzylic carbon, favoring the 5-*exo* cyclization of the primary hydroxy group over the 6-*endo* cyclization of the secondary hydroxy group. The *p*-methoxybenzoyloxy group comprises a large substituent; however, the *cis* attack which would be disfavored with a larger ZO group, increases with **3b** (Z = COPMP) in comparison with **3d** (Z = Me). The reason for the total diastereoselectivity for 5-*exo* cyclization toward the internal allene carbon on phenyl-allenic diol **3d** to give

adduct **21b** compared to the moderate diastereoselectivity of phenylallendiol **3b** to give adduct **21a** in the examples of Scheme 7, may be related to unfavorable steric interactions between the ZO group and Pd in the π -allylpalladium intermediate derived from **3b**, hampering the required conformation for the *trans* attack. Unfortunately, the Pd–Cu bimetallic system could not induce a clean bromoheterocyclization reaction of γ,δ -allenic diols **4**; being formed a complex mixture of products under Pd(II)-catalyzed conditions.

Scheme 7. Palladium-catalyzed preparation of dihydropyrans **20** and tetrahydrofurans **21**. Reagents and conditions: i) 7 mol % Pd(OAc)₂, LiBr, Cu(OAc)₂, K₂CO₃, MeCN, O₂, RT, 2 h. PMP = 4-MeOC₆H₄, PMP = 4-MeOC₆H₄, TPS = *t*-Butyldiphenylsilyl.

A possible pathway for the gold-catalyzed achievement of tetrahydrofurans **10** may initially involve the formation of a complex **24** through coordination of the gold trichloride to the proximal allenic double bond of γ,δ -allenic diols **4**. Next, chemo- and regioselective 5-*exo* oxyauration forms zwitterionic intermediates **25**, which after loss of HCl generate neutral species **26**. Protonolysis of the carbon–gold bond of **26** liberates adduct **10** with concurrent regeneration of the Au(III) catalytic species (Scheme 8).

Scheme 8. Mechanistic explanation for the gold-catalyzed oxymercuration of γ,δ -allenic diols **4**.

A conceivable mechanism for the achievement of dihydropyran **11** may initially involve the formation of a π -complex **27** through coordination of the platinum catalyst to the 1,2-diene moiety of β,γ -allenic diol **3a**. Next, chemo- and regioselective 6-*endo* oxyplatination to form species **28** followed by loss of HCl,

demetalation, and proton transfer affords non-isolable (dihydropyran)lmethanol **9a** and regenerates the platinum catalyst (Scheme 9). Intermediate **9a** is transformed by aerobic oxidation into the (dihydropyran)lcarbaldehyde **11**. To support that adduct **9a** is an intermediate, we have performed the reaction of compound **9a**, which is the final product from the gold-catalyzed cycloisomerization of allenic diol **3a** (see Scheme 4), in the presence of [PtCl₂(CH₂=CH₂)]₂ and TDMPP under an oxygen atmosphere to afford aldehyde **11** in 70% yield.

Scheme 9. Mechanistic explanation for the platinum-catalyzed tandem oxymercuration/oxidation of β,γ -allenic diol **3a**.

Scheme 10 comprises a mechanistic rationale for the La[N(SiMe₃)₂]₃-promoted conversion of β,γ -allenic diol **3b** into furan **14**. Firstly, lanthanum precatalyst formed the alkoxide–La compound **30** through protonolysis at the La–[N(SiMe₃)₂]₃ bond by allenic diol **3b**. Subsequently, one π -bond of the oxallene–La complex chemo- and regioselectively adds across the La–O functionality of **30** to afford oxacyclic intermediate **31** by 5-*exo* cyclization to the central allene carbon. The intervention of a second molecule of allenic diol **3b** facilitates the proton transfer step to afford species **33** via transition state **32**. Species **33** after complex dissociation delivers dihydrofuran **15**, which under the reaction conditions suffers aromatization to form furan **14**, thus re-initiating the catalytic cycle.

Scheme 10. Mechanistic explanation for the lanthanum-catalyzed oxycyclization of β,γ -allenic diol **3b**.

Scheme 11 outlines a mechanistic proposal for the achievement of tetrahydrooxepines **18**. Initial Pd(II)-coordination to the 1,2-diene moiety gave an allenepalladium complex **34**, which suffers a chemo- and regioselective 7-*endo* oxycyclization reaction to give the intermediate palladatetrahydrooxepine **35**. Species **35** reacted with allyl bromide via **36** to form intermediate **37**, which after a *trans* β -heteroatom elimination generates oxacycles **18** with concurrent regeneration of the Pd(II) catalyst (Scheme 11).

Scheme 11. Mechanistic explanation for the palladium-catalyzed oxycyclization of γ,δ -allenic diols **4**.

A likely mechanism for the generation of bromodihydropyrans **20** and tetrahydrofurans **21** should involve the initial formation of a

(π -allyl)palladium species. The allenepalladium complex **38** is formed initially and suffer a nucleophilic attack by the bromide to produce σ -allylpalladium species, which rapidly equilibrate to the corresponding (π -allyl)palladium intermediate **39**. Then, a chemo- and regiospecific intramolecular cycloetherification reaction by attack of either the secondary hydroxy group to the terminal allene carbon or the primary hydroxyl group to the internal allene carbon onto the (π -allyl)palladium complex must account for the formation of dihydropyrans **20** or tetrahydrofurans **21** (Scheme 12). Finally, in situ oxidation of Pd(0) to Pd(II) by Cu(OAc)₂ completes the catalytic cycle.

Scheme 12. Mechanistic explanation for the oxybromination reaction of β,γ -allendiols **3** under Pd–Cu bimetallic catalysis.

Abstract in Spanish: Se han encontrado rutas versátiles que conducen a tetrahidrooxepinas, dihidropiranos y tetrahidrofuranos funcionalizados enantiopuros, basadas en reacciones de oxidociclación quimio-, regio- y estereocontroladas de β,γ - y γ,δ -alenoalcoholes catalizadas por metales. Los alcoholes de partida se prepararon fácilmente a partir de (R)-2,3-O-isopropilidenglicerinaldehído. La utilización de sales de Pd(II), Pt(II), Au(III) ó La(III) como catalizadores da lugar a un método de preparación controlada de oxaciclos de diferente tamaño en forma enantiopura. Normalmente, las reacciones de ciclación quimioselectiva ocurren exclusivamente por ataque del grupo hidroxilo secundario (excepto en la oxibromación de los fenil β,γ -alenoalcoholes **3b** y **3d**) a uno de los carbonos alélicos. Tanto el control regio- como el estereoquímico están influidos por la naturaleza del metal y los sustituyentes.

Conclusion

In conclusion, the chemo-, regio-, and stereocontrolled cycloetherification of allenic diols bearing different substituents into differently-sized oxacycles has been realized by using various metal-based catalysts, such as Pd(II), Pt(II), Au(III) or La(III) salts. The scope of these protocols has been investigated and clearly demonstrates their utility for the selective preparation of several enantiopure cyclic ethers from structurally related substrates. At the present time, the application of this methodology into the selective

preparation of other types of heterocyclic compounds is ongoing in our group.

Experimental Section

General methods: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in CDCl_3 solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H , 0.0 ppm), or CDCl_3 (^{13}C , 76.9 ppm). Low and high resolution mass spectra were taken on a HP5989A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_{\text{D}}$ is given in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ at 20 $^\circ\text{C}$, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General procedure for the Au-catalyzed cyclization of allenic diols 3 and 4. Preparation of dihydropyrans 9 and tetrahydrofurans 10. AuCl_3 (0.05 mmol) was added to a stirred solution of the corresponding allenic diol 3 and 4 (1.0 mmol) in dichloromethane (1.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). The reaction was then quenched with brine (1.0 mL), the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried (MgSO_4) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts 9 and 10.^[16]

Dihydropyran (+)-9a. From 75 mg (0.27 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**9a** (49 mg, 75%) as a colorless oil; $[\alpha]_{\text{D}} = +75.1$ (c 1.8, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 6.94 and 8.02 (d, each 2H, $J = 9.0$ Hz, Ar), 5.70 (m, 1H), 5.61 (m, 1H), 4.26 (m, 2H), 3.88 (s, 3H), 3.70 (m, 3H), 1.73 (m, 3H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 166.5, 163.8, 132.3, 131.7, 124.4, 121.8, 113.8, 77.6, 67.6, 65.4, 62.4, 55.5, 18.4; IR (CHCl_3 , cm^{-1}): ν 3432, 1724; HRMS (ES): calcd (%) for $\text{C}_{14}\text{H}_{16}\text{O}_4[\text{M} + \text{H}]^+$: 248.1049; found: 248.1045.

Dihydropyran (+)-9b. From 50 mg (0.14 mmol) of β,γ -allendiol (–)-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**9b** (21 mg, 55%) as a colorless oil; $[\alpha]_{\text{D}} = +32.7$ (c 1.3, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 7.72 and 6.80 (d, each 2H, $J = 9.0$ Hz, Ar), 7.26 (m, 5H), 6.24 (m, 2H), 4.48 (t, 2H, $J = 2.7$ Hz), 3.82 (m, 3H), 3.81 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 163.6, 161.0, 137.2, 136.0, 132.3, 131.8, 128.4, 127.5, 126.9, 125.8, 113.6, 77.1, 65.4, 65.2, 62.1, 55.4; IR (CHCl_3 , cm^{-1}): ν 3428, 1722; HRMS (ES): calcd (%) for $\text{C}_{15}\text{H}_{18}\text{O}_4[\text{M} + \text{H}]^+$: 310.1205; found: 310.1210.

Tetrahydrofuran (+)-10a. From 66 mg (0.16 mmol) of γ,δ -allendiol (–)-**4aM**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**10a** (34 mg, 51%), containing ca. 20% of its epimer, as a colorless oil; the diastereoisomers of **10a** are inseparable by column chromatography (their ^1H NMR and ^{13}C NMR data were obtained by analyzing the NMR spectra of the mixtures; however, IR and MS spectroscopic data could not be assigned individually for them); $[\alpha]_{\text{D}} = +2.0$ (c 2.1, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 8.00 and 6.95 (d, each 0.4H, $J = 9.0$ Hz), 7.94 and 6.92 (d, each 1.6H, $J = 9.0$ Hz), 7.13 (m, 5H), 6.07 (dd, 0.2H, $J = 17.3$, 10.7 Hz), 5.90 (dd, 0.8H, $J = 17.3$, 10.7 Hz), 5.47 (d, 0.2H, $J = 2.2$ Hz), 5.41 (m, 0.2H), 5.34 (d, 0.8H, $J = 2.0$ Hz), 5.35 (dd, 0.8H, $J = 17.3$, 1.5 Hz), 5.23 (dd, 0.2H, $J = 10.7$, 1.2 Hz), 5.12 (dd, 0.8H, $J = 11.0$, 1.5 Hz), 4.76 and 4.56 (d, each 0.2H, $J = 17.9$ Hz), 4.82 and 4.59 (d, each 0.8H, $J = 17.6$ Hz), 4.19 (m, 1H), 4.10 (dd, 0.8H, $J = 5.0$, 1.8 Hz), 4.08 (m, 0.2H), 3.88 (s, 0.6H), 3.87 (s, 2.4H), 3.86 (m, 1H), 3.69 (dd, 0.8H, $J = 11.8$, 4.3 Hz), 3.65 (dd, 0.2H, $J = 12.4$, 3.9 Hz), 1.56 (s, 2.4H), 1.55 (s, 0.6H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 165.3 (m), 165.1 (M), 163.7 (m), 163.6 (M), 138.1 (M + m), 137.6 (M), 137.5 (m), 131.8 (m), 131.7 (M), 128.5 (M), 128.4 (m), 127.8 (M), 127.7 (m), 127.6 (M + m), 122.0 (M), 121.8 (m), 114.8 (M), 114.2 (m), 113.8 (m), 113.7 (M), 84.9 (m), 84.8 (M), 84.7 (M), 84.6 (m), 81.9 (M), 81.3 (m), 77.2 (M + m), 72.3 (M), 72.2 (m), 62.8 (M), 62.7 (m), 55.5 (m), 55.4 (M), 22.9 (M), 22.1 (m); IR (CHCl_3 , cm^{-1}): ν 3432, 1722; HRMS (ES): calcd (%) for $\text{C}_{23}\text{H}_{27}\text{O}_6[\text{M} + \text{H}]^+$: 399.1808; found: 399.1803.

Tetrahydrofuran (+)-10c. From 48 mg (0.12 mmol) of γ,δ -allendiol (–)-**4am**, and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**10c** (22 mg, 46%) as a colorless oil; $[\alpha]_{\text{D}} = +2.4$ (c 1.3, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 8.07 and 6.94 (d, each 2H, $J = 9.0$ Hz), 7.23 (m, 5H), 5.98 (dd, 1H, $J = 17.3$, 10.5 Hz), 5.47 (d, 1H, $J = 4.2$ Hz), 5.36 (d, 1H, $J = 17.3$ Hz), 5.16 (d, 1H, $J = 10.5$ Hz), 4.62 and 4.42 (d, each 1H, $J = 11.5$ Hz), 4.16 (m, 2H), 3.88 (s, 3H), 3.85 (m, 1H), 3.64 (dd, 1H, $J = 12.0$, 3.9 Hz), 1.40 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 165.6, 163.7, 142.1, 137.5, 131.9, 128.4, 127.9, 127.8, 122.1, 114.1, 113.8, 84.1, 80.5, 77.2, 75.6, 73.0, 62.5, 55.5, 21.8; IR (CHCl_3 , cm^{-1}): ν 3434, 1724; HRMS (ES): calcd (%) for $\text{C}_{23}\text{H}_{27}\text{O}_6[\text{M} + \text{H}]^+$: 399.1808; found: 399.1804.

General procedure for the Pt-catalyzed cyclization of allenic diols 3 and 4. **Preparation of tetrahydrofuran 10a and dihydropyrans 11 and 12.** $[\text{PtCl}_2(\text{CH}_2=\text{CH}_2)]_2$ (0.01 mmol) and tris(2,6-dimethoxyphenyl)phosphine (0.02 mmol) were sequentially added [for the preparation of adduct 12, 1.1 mmol of methyl (triphenylphosphoranylidene)acetate was also added] to a stirred solution of the corresponding allenic diol 3 and 4 (1.0 mmol) in dichloromethane (1.0 mL) under argon. The resulting mixture was stirred at room temperature until disappearance of the starting material (TLC). The reaction was then quenched with brine (1.0 mL), the mixture was extracted with ethyl acetate (3 x 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried (MgSO_4) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts 10–12.

Dihydropyran (+)-11. From 50 mg (0.18 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:2) as eluent gave compound (+)-**11** (36 mg, 62%) as a colorless oil; $[\alpha]_{\text{D}} = +3.2$ (c 0.6, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 10.2 (d, 1H, $J = 8.1$ Hz), 8.06 and 6.95 (d, each 2H, $J = 9.0$ Hz), 6.33 (m, 2H), 5.89 (d, 1H, $J = 8.1$ Hz), 4.38 (m, 2H), 3.88 (s, 3H), 2.09 (d, 3H, $J = 1.2$ Hz); IR (CHCl_3 , cm^{-1}): ν 1732, 1725.

Dihydropyran (+)-12. From 50 mg (0.18 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**12** (32 mg, 54%) as a colorless oil; $[\alpha]_{\text{D}} = +3.4$ (c 0.8, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 8.07 and 6.96 (d, each 2H, $J = 9.0$ Hz, Ar), 7.81 (dd, 1H, $J = 15.1$, 12.0 Hz), 6.94 (m, 1H), 6.07 (m, 2H), 5.85 (d, 1H, $J = 15.1$ Hz), 4.34 (dd, 2H, $J = 5.6$, 1.6 Hz), 3.89 (s, 3H), 3.77 (s, 3H), 2.00 (s ancho, 3H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 163.6, 163.2, 163.0, 141.9, 139.2, 132.6, 132.3, 126.7, 120.0, 113.7, 63.6, 55.5, 53.4, 51.5, 40.9, 21.0; IR (CHCl_3 , cm^{-1}): ν 1724, 1720; HRMS (ES): calcd (%) for $\text{C}_{19}\text{H}_{23}\text{O}_6[\text{M} + \text{H}]^+$: 347.1495; found: 347.1499.

General procedure for the La-catalyzed cyclization of allenic diols 3 and 4. Preparation of tetrahydrofuran 10c, diol 13, and furan 14. $\text{La}[\text{N}(\text{SiMe}_3)_2]_3$ (0.05 mmol) was added to a stirred solution of the corresponding allenic diol 3 and 4 (1.0 mmol) in toluene (10.0 mL) under argon. The resulting mixture was stirred at reflux temperature until disappearance of the starting material (TLC). The reaction was then filtered through a celite plug before being concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure adducts 10, 13, and 14.

Diol (+)-13. From 50 mg (0.18 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**13** (19 mg, 37%) as a colorless oil; $[\alpha]_{\text{D}} = +2.6$ (c 1.6, CHCl_3); ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 8.02 and 6.93 (d, each 2H, $J = 9.0$ Hz, Ar), 4.86 (m, 2H), 4.52 (d, 2H, $J = 4.6$ Hz), 4.17 (m, 1H), 4.03 (dd, 1H, $J = 10.2$, 4.6 Hz), 2.58 (br s, 2H), 1.80 (t, 3H, $J = 3.3$ Hz); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 205.5, 167.0, 163.6, 131.8, 122.1, 113.7, 98.9, 77.5, 72.9, 71.8, 65.7, 55.4, 15.0; IR (CHCl_3 , cm^{-1}): ν 3440, 2990, 1942, 1724; MS (ES): m/z (%): 279 (100) $[\text{M} + \text{H}]^+$, 278 (6) $[\text{M}]^+$.

Furan 14. From 50 mg (0.14 mmol) of β,γ -allendiol (–)-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (5:1) as eluent gave compound **14** (24 mg, 88%) as a colorless oil; ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 7.38 (m, 5H, Ar), 6.44 (s, 1H), 4.62 (s, 2H), 3.88 (br s, 1H), 2.46 (s, 3H); ^{13}C -NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 151.6, 148.0, 133.9, 128.6, 127.4, 126.4, 121.6, 109.5, 57.5, 13.1; IR (CHCl_3 , cm^{-1}): ν 3432; MS (ES): m/z (%): 189 (100) $[\text{M} + \text{H}]^+$, 188 (19) $[\text{M}]^+$.

Procedure for the Pd(0)-catalyzed preparation of dihydropyran 16. $[\text{Pd}(\text{PPh}_3)_4]$ (11 mg, 0.0093 mmol) was added to a mixture of the β,γ -allendiol (–)-**1a** (50 mg, 0.18 mmol), iodobenzene (22 μL , 0.19 mmol), and silver carbonate (99 mg, 0.36 mmol) in DMF (1.5 mL) under Ar, and the resulting mixture was heated at 80 $^\circ\text{C}$ until disappearance of the starting material (TLC, 24 h). The reaction was then quenched with brine (1.8 mL) and the mixture was extracted with ethyl acetate (3 x 3 mL). The organic extract was washed with brine, dried (MgSO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes (1:3) as eluent gave compound **16** (16 mg, 35%) as a colorless oil.

Dihydropyran 2. ^1H -NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ : 8.02 and 6.90 (d, each 2H, $J = 9.0$ Hz), 6.26 (s, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 2.22 (br s, 3H), 1.94 (br s, 3H); IR (CHCl_3 , cm^{-1}): ν 1725; MS (ES): m/z (%): 275 (100) $[\text{M} + \text{H}]^+$, 274 (11) $[\text{M}]^+$.

General procedure for the Pd(II)-catalyzed cyclization of allenic diols 3 and 4 in presence of allyl bromide. **Preparation of dihydropyrans 17, tetrahydrooxepines 18, and tetrahydrofuran (+)-19b.** Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding allenic diol 3 and 4 (0.10 mmol) and allyl bromide (0.50 mmol) in *N,N*-dimethylformamide (0.6 mL). The reaction was stirred under argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being extracted with ethyl acetate (3 x 4 mL). The organic phase was washed with water (2 x 2 mL), dried (MgSO_4) and concentrated under reduced pressure.

Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts 17–19.

Dihydropyran (+)-17a. From 75 mg (0.27 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (4:1) as eluent gave compound (+)-**17a** (76 mg, 65%) as a colorless oil; $[\alpha]_D = +21.9$ (c 1.1, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 8.02 and 6.94 (d, each 2H, $J = 9.0$ Hz), 5.74 (m, 1H), 5.61 (d, 1H, $J = 7.8$ Hz), 5.11 (dd, 1H, $J = 9.3, 1.7$ Hz), 5.04 (t, 1H, $J = 1.8$ Hz), 4.16 (m, 2H), 3.88 (s, 3H), 3.68 (m, 3H), 2.87 and 2.68 (dd, each 1H, $J = 15.5, 6.0$ Hz), 1.67 (br s, 3H); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 166.7, 163.2, 134.0, 132.0, 131.9, 125.6, 121.9, 116.0, 113.7, 77.2, 68.3, 67.8, 62.4, 55.5, 33.2, 13.4; IR (CHCl₃, cm^{–1}): ν 3420, 1720; HRMS (ES): calcd (%) for C₁₈H₂₂O₅[M]⁺: 318.1467; found: 318.1459.

Dihydropyran (–)-17b. From 50 mg (0.14 mmol) of β,γ -allendiol (–)-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (–)-**17b** (42 mg, 78%) as a colorless oil; $[\alpha]_D = -15.2$ (c 1.4, CHCl₃); ¹H-NMR (CDCl₃): δ 7.69 and 6.80 (d, each 2H, $J = 9.0$ Hz), 7.22 (m, 5H), 5.93 (br s, 1H), 5.69 (m, 1H), 5.05 (m, 2H), 4.41 and 4.28 (dd, each 1H, $J = 16.0, 2.0$ Hz), 3.82 (s, 3H), 3.76 (m, 3H), 2.72 (d, 2H, $J = 6.3$ Hz); ¹³C-NMR (CDCl₃): δ 166.3, 163.5, 136.8, 134.9, 132.0, 131.6, 128.7, 128.3, 128.1, 127.2, 121.8, 116.6, 113.5, 77.4, 67.7, 67.4, 62.3, 55.4, 34.5; IR (CHCl₃, cm^{–1}): ν 3424, 1715; MS (ES), m/z : 380 (M⁺, 17), 379 (M⁺ – 1, 100).

Tetrahydrooxepine (–)-18a. From 76 mg (0.19 mmol) of γ,δ -allendiol (–)-**4aM**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound (–)-**18a** (49 mg, 59%) as a colorless oil; $[\alpha]_D = -1.5$ (c 0.1, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 8.05 and 6.90 (d, each 2H, $J = 9.0$ Hz), 7.35 (s, 5H), 5.76 (m, 1H), 5.68 (d, 1H, $J = 3.6$ Hz), 5.06 (m, 1H), 4.81 and 4.57 (d, each 1H, $J = 11.6$ Hz), 4.49 (dd, 1H, $J = 16.3, 1.9$ Hz), 4.19 (dd, 1H, $J = 16.3, 1.7$ Hz), 3.87 (s, 3H), 3.84 (m, 1H), 3.66 (m, 2H), 3.51 (m, 1H), 2.78 (dd, 1H, $J = 15.6, 5.6$ Hz), 2.62 (dd, 1H, $J = 15.6, 6.3$ Hz), 1.93 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 165.8, 163.4, 137.7, 134.5, 134.2, 131.7, 128.4, 128.1, 127.9, 122.8, 115.9, 113.7, 80.7, 79.3, 74.9, 73.5, 72.7, 63.9, 55.4, 35.3, 20.6; IR (CHCl₃, cm^{–1}): ν 3431, 1728; HRMS (ES): calcd (%) for C₂₆H₃₁O₆[M + H]⁺: 439.2121; found: 439.2124.

Tetrahydrooxepine (+)-18b. From 28 mg (0.06 mmol) of γ,δ -allendiol (+)-**4b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**18b** (16 mg, 53%) as a colorless oil; $[\alpha]_D = +2.0$ (c 0.3, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 7.99 and 6.93 (d, each 2H, $J = 9.0$ Hz), 7.26 (m, 10H), 5.95 (d, 1H, $J = 2.1$ Hz), 5.69 (m, 1H), 5.03 (m, 2H), 4.73 and 4.52 (d, each 1H, $J = 11.3$ Hz), 4.71 and 4.41 (d, each 1H, $J = 16.6$ Hz), 3.88 (s, 3H), 3.82 (m, 2H), 3.71 and 3.56 (d, each 1H, $J = 11.9$ Hz), 2.69 (dd, 1H, $J = 15.0, 6.2$ Hz), 2.59 (dd, 1H, $J = 15.7, 6.5$ Hz); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 165.4, 163.4, 142.3, 138.5, 137.5, 135.4, 134.0, 131.8, 128.5, 128.4, 128.3, 128.2, 127.4, 126.9, 116.6, 113.7, 81.0, 79.4, 74.5, 73.3, 72.6, 64.0, 55.5, 36.7; IR (CHCl₃, cm^{–1}): ν 3430, 1725; HRMS (ES): calcd (%) for C₃₁H₃₂NaO₆[M + Na]⁺: 523.2097; found: 523.2095.

Tetrahydrofuran (+)-19b. From 46 mg (0.12 mmol) of γ,δ -allendiol (–)-**4am**, and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound (+)-**19b** (25 mg, 50%) as a colorless oil; $[\alpha]_D = +1.2$ (c 0.8, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 8.08 and 6.96 (d, each 2H, $J = 9.0$ Hz), 7.24 (m, 5H), 5.84 (m, 1H), 5.57 (d, 1H, $J = 5.0$ Hz), 4.58 and 4.42 (d, each 1H, $J = 11.5$ Hz), 4.21 (m, 1H), 4.08 (dd, 1H, $J = 8.0, 5.0$ Hz), 3.89 (s, 3H), 3.87 (dd, 1H, $J = 12.2, 3.0$ Hz), 3.66 (dd, 1H, $J = 11.9, 5.0$ Hz), 2.90 (d, 2H, $J = 7.0$ Hz), 1.44 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 165.6, 163.7, 150.8, 137.5, 136.4, 131.8, 128.3, 127.9, 127.8, 122.1, 116.7, 113.8, 111.3, 86.4, 80.3, 77.3, 74.8, 73.0, 62.9, 55.5, 36.2, 22.0; IR (CHCl₃, cm^{–1}): ν 3436, 1724; HRMS (ES): calcd (%) for C₂₆H₃₁O₆[M + H]⁺: 439.2121; found: 439.2118.

General procedure for the Pd(II)-catalyzed cyclization of allenic diols **3 in presence of lithium bromide. Preparation of dihydropyrans **20** or tetrahydrofurans **21**.** Palladium(II) acetate (0.01 mmol), lithium bromide (0.74 mmol), potassium carbonate (0.18 mmol) and copper(II) acetate (0.32 mmol) were sequentially added to a stirred solution of the corresponding β,γ -allendiol **3** (0.15 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere until disappearance of the starting material (TLC). The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (3 x 5 mL), washed with brine (2 mL), dried (MgSO₄) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **20** or **21**.

Dihydropyran (+)-20a. From 100 mg (0.36 mmol) of β,γ -allendiol (–)-**3a**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**20a** (68 mg, 53%) as a colorless oil; $[\alpha]_D = +3.5$ (c 1.0, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 8.07 and 6.95 (d, each 2H, $J = 9.0$ Hz), 5.71 (m, 1H), 4.34 (m, 2H), 3.89 (s, 3H), 3.72 (m, 3H), 1.84 (d, 3H, $J = 1.0$ Hz); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 163.9, 164.0, 132.3, 132.0, 130.6, 119.7, 113.7, 77.3, 70.3, 68.7, 62.0, 55.5, 17.5; IR (CHCl₃, cm^{–1}): ν 3425, 1716; HRMS (ES): calcd (%) for C₁₅H₁₇BrO₅[M]⁺: 356.0259; found: 356.0268.

Dihydropyran (–)-20b. From 75 mg (0.20 mmol) of β,γ -allendiol (+)-**3c**, and after chromatography of the residue using hexanes/ethyl acetate (6:1) as eluent gave compound (–)-**20b** (47 mg, 51%) as a colorless oil; $[\alpha]_D = -22.8$ (c 0.5, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 7.72 (m, 4H), 7.32 (m, 6H), 4.14 (m, 3H), 3.72 (td, 1H, $J = 6.8, 3.1$ Hz), 3.46 (dd, 1H, $J = 7.3, 3.2$ Hz), 3.36 (dd, 1H, $J = 6.8, 5.1$ Hz), 1.80 (br s, 3H), 1.06 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 135.9, 135.8, 134.8, 133.3, 132.6, 130.0, 127.8, 127.7, 119.4, 79.5, 70.4, 68.9, 61.9, 27.1, 26.8, 19.8; IR (CHCl₃, cm^{–1}): ν 3429; MS (EI), m/z : 461 (M⁺, 23), 443 (100).

Tetrahydrofuran (+)-21a. From 50 mg (0.14 mmol) of β,γ -allendiol (–)-**3b**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (+)-**21a** (33 mg, 57%), containing ca. 40% of its epimer, as a colorless oil; the diastereoisomers of **21a** are inseparable by column chromatography (their ¹H NMR and ¹³C NMR data were obtained by analyzing the NMR spectra of the mixtures; however, IR and MS spectroscopic data could not be assigned individually for them); $[\alpha]_D = +5.9$ (c 0.8, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 8.11 and 6.98 (d, each 0.8H, $J = 9.0$ Hz), 7.61 (m, 2H), 7.40 (m, 3H), 6.59 and 5.80 (d, each 0.6H, $J = 2.0$ Hz), 6.28 and 5.68 (d, each 0.4H, $J = 1.7$ Hz), 6.12 (d, 0.4H, $J = 4.6$ Hz), 5.29 (m, 0.6H), 4.67 (dd, 0.6H, $J = 12.4, 3.2$ Hz), 4.07 (m, 2H), 3.89 (s, 1.8H), 3.87 (m, 0.4H), 3.77 (s, 1.2H); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 164.0 (m), 163.9 (M), 163.3 (m), 163.2 (M), 150.4 (M+m), 132.2 (M+m), 128.5 (m), 128.4 (M+m), 128.3 (M+m), 128.2 (M), 127.8 (M+m), 127.6 (M+m), 126.3 (M), 126.2 (m), 113.8 (m), 113.3 (M), 88.1 (M+m), 82.1 (M), 77.5 (m), 71.8 (m), 71.5 (m), 67.1 (m), 63.4 (M), 55.5 (M), 55.2 (m); IR (CHCl₃, cm^{–1}): ν 3435, 1718; MS (EI), m/z : 420 (M⁺ + 2, 98), 418 (M⁺, 100).

Tetrahydrofuran (–)-21b. From 65 mg (0.30 mmol) of β,γ -allendiol (+)-**3d**, and after chromatography of the residue using hexanes/ethyl acetate (3:1) as eluent gave compound (–)-**21b** (49 mg, 55%) as a colorless oil; $[\alpha]_D = -26.3$ (c 0.4, CHCl₃); ¹H-NMR (300 MHz, CDCl₃, 25 °C) δ : 7.52 (m, 2H), 7.37 (m, 3H), 6.26 and 5.70 (d, each 1H, $J = 1.7$ Hz), 4.30 (m, 2H), 3.99 (dd, 1H, $J = 9.5, 6.3$ Hz), 3.85 (dd, 1H, $J = 9.5, 4.9$ Hz), 3.74 (s, 3H), 3.48 (d, 1H, $J = 6.8$ Hz); ¹³C-NMR (75 MHz, CDCl₃, 25 °C) δ : 150.7, 128.5, 128.3, 128.1, 126.3, 118.7, 85.8, 77.2, 72.7, 71.2, 61.3; IR (CHCl₃, cm^{–1}): ν 3432; HRMS (ES): calcd (%) for C₁₃H₁₅BrO₅[M]⁺: 298.0205; found: 298.0212.

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Synthetic Methods

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Metal-Catalyzed Cycloetherification Reactions of β,γ - and γ,δ -Allendiols. Chemo-, Regio- and Stereocontrol in the Synthesis of Oxacycles

A chemo-, regio- and stereoselective methodology for the preparation of a variety of diversely functionalized enantiopure tetrahydrofurans, dihydropyrans, and tetrahydrooxepines involves the controlled Pd-, Pt-, Au- or La-catalyzed oxycyclization reactions of β,γ - and γ,δ -allenic diols.

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