Asymmetric Dihydroxylations of Enynes with a Trisubstituted C=C Bond. An Unprecedented Route to γ -Lactone Building Blocks with a Quaternary Stereocenter

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En route to a comprehensive set of hydroxylactone building blocks (4R,5R)-, (4R,5S)-, (4S,5R)-, and (4S,5S)-5a, Sharpless asymmetric dihydroxylations of allylic chlorides (*E*)- and (*Z*)-9 were performed. They delivered the four stereoisomers of diol 10 with up to 92% *ee* and absolute configurations, which were proven to be in accordance with the Sharpless mnemonic.

Enantiomerically pure tetronic acids 1,¹ butenolides 2,² and 3-methylidenebutanolides 3,³ all with a quaternary

10.1021/ol103061g © 2011 American Chemical Society **Published on Web 01/27/2011** methyl-bearing stereocenter, form the core not only of a variety of natural products^{1–3} but also of analogs of pharmaceutical interest⁴ (Figure 1). In continuation of our interest in this kind of compound, which was aroused by establishing the configuration of a *Plagionnium* lactone through synthesis,⁵ we conceived sets of stereochemically homogeneous metal—C=C-containing hydroxylactones **5** ($L_nM = Bu_3Sn$, pinacolB, Cp₂ClZr, etc.) and C=C-containing hydroxylactones **6** as versatile precursors of such structures. We intended to derive **5** via **6** from functionalized diols **7** and those from the isomeric pentenynols

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Figure 1. Retrosynthetic analysis of tetronic acids 1, butenolides 2, and methylidenebutanolides 3, all with a quaternary methylbearing stereocenter at C-5.

Scheme 1. Stereoselective Syntheses of Chlorides (*E*)- and (*Z*)-9 (Isomeric Purity of All Compounds > 99:1)



(*E*)- and (*Z*)-8. The latter are [1,3]-rearrangement products⁶ of alcohol 4, which result from the 1,2-addition of metal acetylides to methylvinylketone⁷ or to cyclopentadiene-protected methylvinylketone⁸ (followed by a [2 + 4] cycloreversion). The originally obtained 15:85 (*E*)-8/(*Z*)-8 mixture⁹ can be separated by careful distillation.^{9a,10} The resulting isomers or the mentioned mixture are established C_6 building blocks for the synthesis of oligoterpenes.¹¹

We began by converting the allyl alcohols (*E*)- and (*Z*)-8 into the corresponding chlorides (*E*)- (70% yield) and (*Z*)-9 (58% yield), respectively, by the nonoxidizing variant of the Corey–Kim reaction (Scheme 1).¹² We are unaware of

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Scheme 2. Asymmetric Dihydroxylations of Allylic Chloride (*E*)-9 in the Presence of Buffer (NaHCO₃/K₂CO₃) and Me-SO₂NH₂



another synthesis of **9** from **8** or of any prior selective preparation of (*E*)-**9** at all. Only (*Z*)-**9** has been described but not its isomeric purity; it was prepared from alcohol **4**.¹³

Asymmetric Sharpless dihydroxylations¹⁴ of (E)-9 using AD-mix α or β^{15} and stoichiometric MeSO₂NH₂ led to incomplete conversions (15% after 8 d and 19% after 3 d. respectively) and less satisfactory ee values (69% and 83%, respectively). Accordingly we varied the amount of K₂OsO₂(OH)₄ [between 0.2 mol % (in the AD-mixes) and 2.0 mol %], the amount of phthalazine ligand [between 1.0 mol % (in the AD-mixes) and 10 mol %], and the ratio of these reagents [going from 0.2 (in the ADmixes) to 1.0]. Employing 1.0 mol % of K₂OsO₂(OH)₄ and 2.0 mol % of the phthalazine ligand resulted in the asymmetric dihydroxylation ("AD") giving better yields (Scheme 2). With (DHQ)₂PHAL as the ligand stereocontrol reached 85% ee^{16} (64% yield), but using (DHQD)₂-PHAL we obtained up to $92\% ee^{16}$ (69% yield). ADs of the same chloride (E)-9 in the presence of 1.0 mol % of $K_2OsO_2(OH)_4$ and 2.0 mol % of the anthraquinones (DHQ)₂AQN or (DHQD)₂AQN¹⁷ furnished 73% and 86% yields of the diol, respectively. Enantiocontrol dropped to 54% ee^{16} in the former case but matched the (DHQD)₂-PHAL value in the latter ($92\% ee^{16}$).

The same ligands mediated ADs of allylic chloride (Z)-9 (Scheme 3). Enanticocontrol was ca. 90% *ee*, but yields were only 41 and 47% with the PHAL-containing and 22–23% with the AQN-containing ligands. Since the substrate was completely consumed (as indicated by TLC) we assume that it suffered some competing hydrolysis.¹⁸ This would have led via pentenynol **8** to a triol sufficiently polar that it could have escaped our monitoring and workup procedures.

The only previous attempt of subjecting an allylic chloride with a trisubstituted C=C bond to an AD reaction

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Scheme 3. Asymmetric Dihydroxylations of Allylic Chloride (Z)-9 in the Presence of Buffer (NaHCO₃/ K_2CO_3) and Me-SO₂NH₂



Scheme 4. Attempted Asymmetric Dihydroxylation of Prenyl Chloride in the Presence of Buffer (NaHCO₃/K₂CO₃) and $MeSO_2NH_2^{-19}$



affected prenyl chloride (Scheme 4).¹⁹ This rendered none of the expected chlorodiol **12** yet 50% of the dihydroxylation product **14** (absolute configuration uncertain) of the surmised in situ hydrolysates **13** and *iso*-**13**. Apart from our own results ADs of allylic chlorides seem to be limited to the parent compound (i.e., allyl chloride²⁰) and to derivatives with a *trans*-disubstituted C=C bond.²¹

The isomeric chlorodiols **10** were C_1 elongated with KCN and crown ether²² giving the cyanodiols **15** shown in Schemes 5 and 6. When the latter compounds were treated with concentrated hydrochloric acid, they rendered

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Scheme 5. Elaboration of the *ul*-Configured Chlorodiols (2*R*,3*S*)- and (2*S*,3*R*)-10 into Two Sets of *lk*-Configured *tert*-Lactone Building Blocks 6 and 5a



Scheme 6. Elaboration of the *lk*-Configured Chlorodiols (2R,3R)- and (2S,3S)-10 into Two Sets of *ul*-Configured *tert*-Lactone Building Blocks 6 and 5a



a stereochemically comprehensive set of C=C-containing hydroxylactones 6. These were hydrostannylated²³ furnishing the Bu₃Sn-C=C-containing hydroxylactones 5a *trans*-selectively. The *lk*-configured hydroxylactones 5a resulted with 100:0 regioselectivities (Scheme 5), but their *ul*-configured counterparts as 86:14 mixtures (Scheme 6). Further elaboration of these building blocks is under study.

One enantiomer of each diastereomer of the Bu₃Sn— C=C-containing hydroxylactones **5a** was elaborated further by cross-coupling with *trans*-1-iodobut-2-ene²⁴ (Scheme 7). Standard Stille couplings²⁵ suffered from loss of the configurational integrity of the ethyl-substituted C=C bond. The Pd-free alternative²⁶ ("Liebeskind coupling") in the presence of 1.5 equiv of Cu(I) thiophene-2-carboxylate accomplished these transformations selectively (0 °C \rightarrow room temp, \leq 30 min). The diene-substituted hydroxylactones (-)-(4*R*,5*R*)and (-)-(4*R*,5*S*)-**16** resulted in yields of 68% and 95%, respectively.

We proved the configurational assignments of Schemes 2, 3, and 5–7 for one AD per allylic chloride. The bis(4-bromobenzoate) **17** of the AD product (+)-(2S,3R)-**10** of allylic chloride (*E*)-**9** crystallized so that its stereostructure could be unraveled by anomalous X-ray diffraction

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Scheme 7. Liebeskind Couplings of Diastereomeric *tert*-Lactone Building Blocks (-)-(4R,5R)- and (+)-(4R,5S)- $5a^{a}$



^{*a*}95% yield was calculated referring to the alkenylstannane precursor, which contains the *trans*-disubstituted C=C bond. The yield of (-)-(4R,5S)-**16** relative to the total amount of the two alkenylstannane substrates was 82%.

Scheme 8. Absolute Configuration of One of the *ul*-Configured Chlorodiols 10



(Scheme 8). The proof of the absolute configuration of AD-product (+)-(2*S*,3*S*)-10 of allylic chloride (*Z*)-9 focused on its tertiary stereocenter. It was incorporated in a sevenstep sequence²⁷ in the optically active lactone (-)-(*S*)-18 with a single stereocenter (Scheme 9). Its 3D structure became clear when its antipode (+)-(*R*)-18 resulted in seven analogous steps²⁷ from chlorodiol (+)-(2*S*,3*R*)-10, the configuration of which had been elucidated after the esterification shown in Scheme 8.

The steric course of the AD reactions of pentenynyl chlorides (*E*)- and (*Z*)-9 concurs with the outcome of ADs of allylic chlorides where the steric course was not just postulated (e.g., refs 19 and 21a,c,d,g,j) but evidenced by X-ray crystallography, identification with independently synthesized reference compounds, conversion into natural products of established stereo-structure, or NMR analysis of diastereomeric derivatives.^{21b,e,f,h,i,k,28} It should be emphasized that the *diagnosis of such a stereochemical analogy* is only meaningful if the following presupposition is made: in the transition state of the AD of an allylic chloride with either a tri- or disubstituted C=C bond, the orientation of the only C_{sp^2} -H bond in the former substrate or the orientation

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Scheme 9. Determination of the Absolute Configuration of One of the *lk*-Configured Chlorodiols 10 (Top Row)





Figure 2. Facial selectivity of the AD of allylic chlorides. A common stereochemical control element for substrates with a trisubstituted C=C bond (left) and a disubstituted C=C bond (right) is highlighted.

of any one of the two C_{sp^2} -H bonds in the latter substrate determines the facial selectivity of attack by a Sharpless-type OsO₄ complex. Figure 2 underscores this point. This selectivity conforms with the stereoselectivity, which the "Sharpless mnemonic" predicts for the ADs of *all kinds of substrates* with a trisubstituted or a *trans*-disubstituted C=C bond.²⁹

Disconcertingly, our stereoselectivities (E)-9 + AD-mix $\alpha \rightarrow (2R,3S)$ -10 and (Z)-9 + AD-mix $\alpha \rightarrow (2R,3R)$ -10 were the exact opposite of what was reported for the ADs of some ethers, which share a methylated pentenynyl unit with our substrates.³⁰ These inconsistencies are the subject of the following paper and resolved therein.

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Supporting Information Available. Experimental procedures, characterization data, copies of gas chromatograms, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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