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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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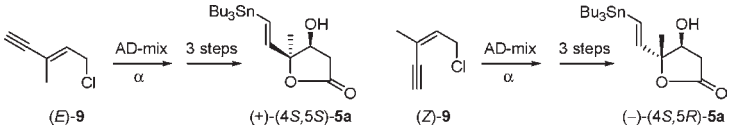
ABSTRACT



En route to a comprehensive set of hydroxylactone building blocks (4*R*,5*R*)-, (4*R*,5*S*)-, (4*S*,5*R*)-, and (4*S*,5*S*)-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 methyl-bearing stereocenter, form the core not only of a variety of natural products[1−3] but also of analogs of pharmaceutical interest[4] (Figure 1). In continuation of our interest in this kind of compound, which was aroused by establishing the configuration of a *Plagiomnium* lactone through synthesis,[5] we conceived sets of stereochemically homogeneous metal—C=C-containing hydroxylactones **5** (L_nM = Bu_3Sn, pinacolB, Cp_2ClZr, 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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(1) For example, see: (a) Trifonov, L.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Rast, D. M.; Hoesch, L. *Tetrahedron* **1982**, *38*, 397–403. (b) Andrade, R.; Ayer, W. A.; Trifonov, L. S. *Aust. J. Chem.* **1997**, *50*, 255–257. (c) Shirota, O.; Pathak, V.; Hossain, C. F.; Sekita, S.; Takatori, K.; Satake, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2961–2964. (d) Abe, N.; Murata, T.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2120–2126. See also: Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011–10014. (e) Sugaya, K.; Koshino, H.; Hongo, Y.; Yasunaga, K.; Onose, J.-i.; Yoshikawa, K.; Abe, N. *Tetrahedron Lett.* **2008**, *49*, 654–657.

(2) For example, see: (a) Sunazuka, T.; Obata, R.; Zhuorong, L.; Takamatsu, S.; Komiyama, K.; Ōmura, S.; Smith, A. B., III. *Tetrahedron Lett.* **1994**, *35*, 2635–2636. (b) Bell, P. J. L.; Karuso, P. *J. Am. Chem. Soc.* **2003**, *125*, 9304–9305. (c) Stierle, D. B.; Stierle, A. A.; Bugni, T. *J. Org. Chem.* **2003**, *68*, 4966–4969. (d) Mulholland, D. A.; McFarland, K.; Randrianarivelojosia, M.; Rabarison, H. *Phytochemistry* **2004**, *65*, 2929–2934. (e) Tu, L.; Zhao, Y.; Yu, Z.-Y.; Cong, Y.-W.; Xu, G.; Peng, L.-Y.; Zhang, P.-T.; Cheng, X.; Zhao, Q.-S. *Helv. Chim. Acta* **2009**, *91*, 1578–1587.

(3) For example, see: (a) Zampella, A.; Giannini, C.; Debitus, C.; D'Auria, M. V. *Tetrahedron* **2001**, *57*, 257–263. (b) Kanayama, M.; Nishiwaki, K.; Matsuo, K. *Heterocycles* **2006**, *68*, 233–236.

(4) For example, see: (a) Bühler, H.; Bayer, A.; Effenberger, F. *Chem.—Eur. J.* **2000**, *6*, 2564–2571. (b) Tan, L.; Chen, C.-y.; Chen, W.; Frey, L.; King, A. O.; Tillyer, R. D.; Xu, F.; Zhao, D.; Grabowski, E. J. J.; Reider, P. J.; O'Shea, P.; Dagneau, P.; Wang, X. *Tetrahedron* **2002**, *58*, 7403–7410. (c) Toyama, K.-i.; Tauchi, T.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2006**, *47*, 7163–7166; *corrigendum* 8793.

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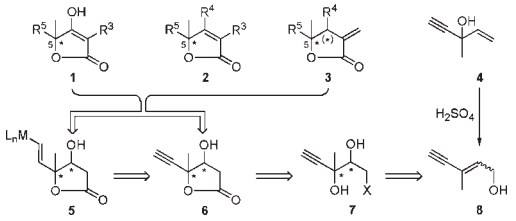
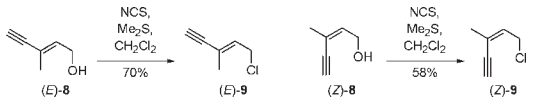


Figure 1. Retrosynthetic analysis of tetronic acids **1**, butenolides **2**, and methylidenebutanolides **3**, all with a quaternary methyl-bearing stereocenter at C-5.

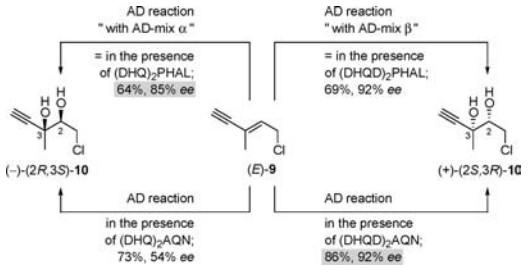
Scheme 1. Stereoselective Syntheses of Chlorides (*E*)- and (*Z*)-**9** (Isomeric Purity of All Compounds > 99:1)



(*E*)- and (*Z*)-**8**. The latter are [1,3]-rearrangement products[6] of alcohol **4**, which result from the 1,2-addition of metal acetylides to methylvinylketone[7] or to cyclopentadiene-protected methylvinylketone[8] (followed by a [2 + 4] cycloreversion). The originally obtained 15:85 (*E*)-**8**/(*Z*)-**8** mixture[9] 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 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]

Scheme 2. Asymmetric Dihydroxylations of Allylic Chloride (*E*)-**9** in the Presence of Buffer ($NaHCO_3/K_2CO_3$) and $MeSO_2NH_2$



Asymmetric Sharpless dihydroxylations[14] of (*E*)-**9** using AD-mix α or *β*[15] and stoichiometric $MeSO_2NH_2$ 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 $K_2OsO_2(OH)_4$ [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 AD-mixes) to 1.0]. Employing 1.0 mol % of $K_2OsO_2(OH)_4$ 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 $(DHQD)_2AQN$[17] 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). Enantiocontrol 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

(5) Kapferer, T.; Brückner, R.; Herzig, A.; König, W. A. *Chem.—Eur. J.* **2005**, *11*, 2154–2162.

(6) Cymerman, J.; Heilbron, I. M.; Jones, E. R. H. *J. Chem. Soc.* **1945**, 90–94.

(7) (a) Hennion, G. F.; Lieb, D. J. *J. Am. Chem. Soc.* **1944**, *66*, 1289–1290. (b) Jung, M. E.; Duclos, B. A. *Tetrahedron Lett.* **2004**, *45*, 107–109.

(8) Pasedach, H. U.S. Patent 2879308, 1959; *Chem. Abstr.* **1959**, *53*, 18889c.

(9) (a) Mori, K.; Ohki, M.; Sato, A.; Matsui, M. *Tetrahedron* **1972**, *28*, 3739–3745. (b) Zacharuas, M. T.; Pushpakumari, T.; Sreevalsan, S. V.; Pillai, G. N. *Indian J. Chem.* **1991**, *30B*, 59–62.

(10) Oroshnik, W. *J. Am. Chem. Soc.* **1956**, *78*, 2651–2652.

(11) For example, see: (a) Isler, O.; Ronco, A.; Huber, W.; Kofler, M. *Helv. Chim. Acta* **1947**, *30*, 1911–1927. (b) Manchard, P. S.; Rüegg, R.; Schwieter, U.; Siddons, P. T.; Weedon, B. C. L. *J. Chem. Soc.* **1965**, 2019–2026. (c) Davies, A. J.; Khare, A.; Mallams, A. K.; Massy-Westtropp, R. A.; Moss, G. P.; Weedon, B. C. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2147–2157. (d) Pattenden, G.; Robson, D. C. *Tetrahedron Lett.* **1987**, *28*, 5751–5754.

(12) Method: Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339–4342.

(13) (a) Surmatis, J. D. U.S. Patent 2760998, 1956; Chem. Abstr. 1956, 50, 8705i. (b) Santelli, M.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1973**, 2331–2335. (c) Preparation of an (*E*)-**9**/(*Z*)-**9** mixture from alcohol **4**: ref 9a.

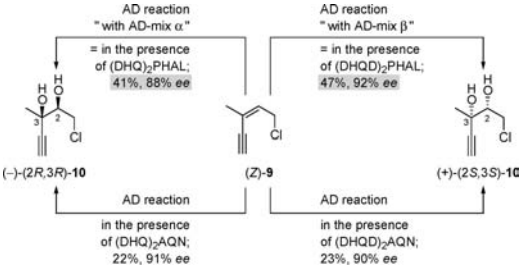
(14) Recent reviews: (a) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; pp 275−298; Vol. 2. (b) Noe, M. C.; Letavic, M. A.; Snow, S. L.; McCombie, S. *Org. React.* **2005**, *66*, 109–625. (c) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725–1756.

(15) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771 (in the presence of $MeSO_2NH_2$). (b) Footnote 6 in Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833–3836 (in the absence of $MeSO_2NH_2$).

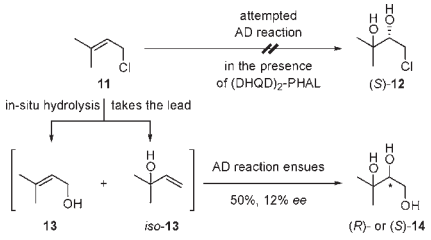
(16) The enantiopurity of this compound was determined by GLC after acetonide formation (for details see Supporting Information).

(17) Becker, H.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 447–449. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448–451.

Scheme 3. Asymmetric Dihydroxylations of Allylic Chloride (*Z*)-**9** in the Presence of Buffer ($NaHCO_3/K_2CO_3$) and $MeSO_2NH_2$



Scheme 4. Attempted Asymmetric Dihydroxylation of Prenyl Chloride in the Presence of Buffer ($NaHCO_3/K_2CO_3$) 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 chloride[20]) and to derivatives with a *trans*-disubstituted C=C bond.[21]

The isomeric chlorodiols **10** were C_1 elongated with KCN and crown ether[22] giving the cyanodiols **15** shown in Schemes 5 and 6. When the latter compounds were treated with concentrated hydrochloric acid, they rendered

(18) Product loss through epoxide formation appears to be an unlikely alternative since we dihydroxylated in the presence of a buffer ($NaHCO_3/K_2CO_3$). This is common[19,21a,21b,21f–21i,21k] yet not compulsory (footnote 4 in ref 19; ref 21c–e,j) in such cases.

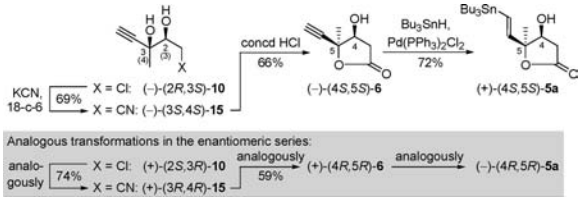
(19) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett*. **1994**, *35*, 3469–3472.

(20) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133–141.

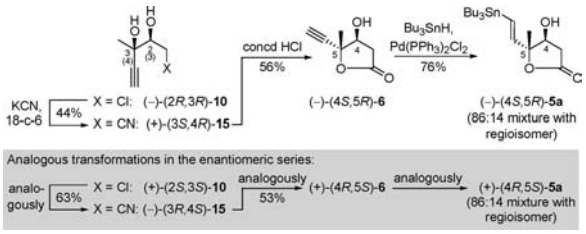
(21) For example, see: (a) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem*. **1997**, *62*, 8978–8979. (b) Marshall, J. A.; Jiang, H. *Tetrahedron Lett*. **1998**, *39*, 1493–1496. (c) Kobayashi, Y.; Nakayama, Y.; Yoshida, S. *Tetrahedron Lett*. **2000**, *41*, 1465–1468. (d) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem*. **2001**, 1873–1881. (e) Mayer, S. F.; Steinreiber, A.; Orru, R. V. A.; Faber, K. *J. Org. Chem*. **2002**, *67*, 9915–9121. (f) Chun, J.; Byun, H.-S.; Bittman, R. *J. Org. Chem*. **2003**, *68*, 348–354. (g) Plietker, B. *Org. Lett*. **2004**, *6*, 289–291. (h) Yadav, J. S.; Rajaiah, G. *Synlett* **2004**, 1743–1746. (i) Kumar, P.; Naidu, S. V. *J. Org. Chem*. **2005**, *70*, 4207–4210. (j) Faveau, C.; Mondon, M.; Gesson, J.-P.; Mahnke, T.; Gebhardt, S.; Koert, U. *Tetrahedron Lett*. **2006**, *47*, 8305–8308. (k) Li, X.; Manjunatha, U. H.; Goodwin, M. B.; Knox, J. E.; Lipinski, C. A.; Keller, T. H.; Barry, C. E.; Dowd, C. S. *Bioorg. Med. Chem. Lett*. **2008**, 2256–2262.

(22) Procedure: Groza, N. V.; Ivanov, I. V.; Romanov, S. G.; Myagkova, G. I.; Nigam, S. *Tetrahedron* **2002**, *58*, 9859–9863.

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 (2*R*,3*R*)- and (2*S*,3*S*)-**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 hydrostannylated[23] furnishing the Bu_3Sn—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 Bu_3Sn—C=C-containing hydroxylactones **5a** was elaborated further by cross-coupling with *trans*-1-iodobut-2-ene[24] (Scheme 7). Standard Stille couplings[25] suffered from loss of the configurational integrity of the ethyl-substituted C=C bond. The Pd-free alternative[26] ("Liebeskind coupling") in the presence of 1.5 equiv of Cu(I) thiophene-2-carboxylate accomplished these transformations selectively (0 °C → room temp, ≤ 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 (+)-(2*S*,3*R*)-**10** of allylic chloride (*E*)-**9** crystallized so that its stereostructure could be unraveled by anomalous X-ray diffraction

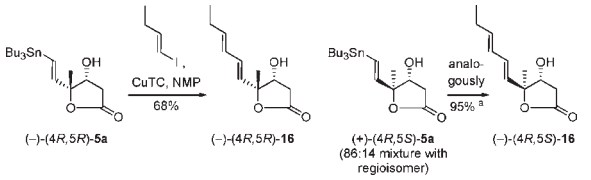
(23) Procedure: Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem*. **1997**, *62*, 7768–7780.

(24) *trans*-1-Iodobut-2-ene was prepared in 50% yield (63%: Alexakis, A.; Duffault, J. M. *Tetrahedron Lett*. **1988**, *29*, 5243–6246) from but-1-yne by successive treatments with DIBAH and iodine.

(25) Stille, J. K. *Angew. Chem*. **1986**, *98*, 504–519. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508–524. Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React*. **1997**, *50*, 1–652.

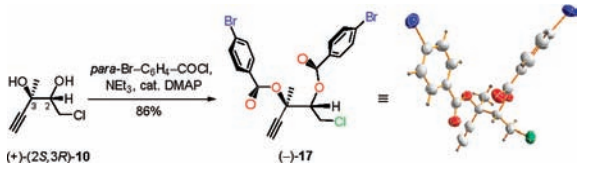
(26) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748–2749. Related earlier observations:Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc*. **1995**, *117*, 5973–5982.

Scheme 7. Liebeskind Couplings of Diastereomeric *tert*-Lactone Building Blocks (−)-(4*R*,5*R*)- and (+)-(4*R*,5*S*)-**5a**[a]



[a] 95% yield was calculated referring to the alkenylstannane precursor, which contains the *trans*-disubstituted C=C bond. The yield of (−)-(4*R*,5*S*)-**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**



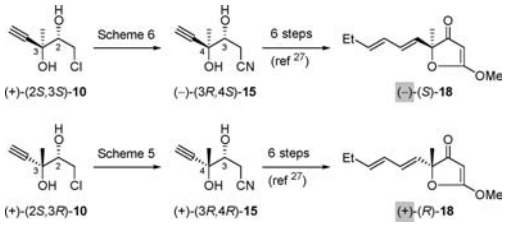
(Scheme 8). The proof of the absolute configuration of AD-product (+)-(2*S*,3*S*)-**10** of allylic chloride (*Z*)-**9** focused on its tertiary stereocenter. It was incorporated in a seven-step sequence[27] in the optically active lactone (−)-(*S*)-**18** with a single stereocenter (Scheme 9). Its 3D structure became clear when its antipode (+)-(*R*)-**18** resulted in seven analogous steps[27] 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 stereostructure, 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

(27) Burghart-Stoll, H.; Brückner, R. Manuscript in preparation. It is unlikely that the transformations of Scheme 9 are the shortest conceivable stereochemical correlation between the chlorodiols (+)-(2*S*,3*S*)-**10** and (+)-(2*S*,3*R*)-**10**. However, for reasons beyond the present context we needed a nonracemic sample of lactone **18**. What mattered was the efficiency of the route and not the configuration of **18**. At some point we had converted (+)-(2*S*,3*S*)-**10** into levorotatory **18** and (+)-(2*S*,3*R*)-**10** into dextrorotatory **18**. These transformations provided the latest stereochemical information for completing the configurational assignments of the present study as a spin-off result.

(28) Richardson, T. I.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 4219–4231.

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



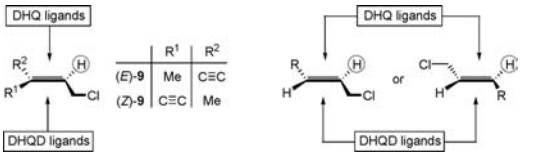


Figure 2. Facial selectivity of the AD of allylic chlorides. A common stereochemical control element for substrates with a trisubstituted C=C bond (left) and a disubstituted C=C bond (right) is highlighted.

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 OsO_4 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 α → (2*R*,3*S*)-**10** and (*Z*)-**9** + AD-mix α → (2*R*,3*R*)-**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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