Carbasugars

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Regiodivergent Addition of Phenols to Allylic Oxides: Control of 1,2- and 1,4-Additions for Cyclitol Synthesis**

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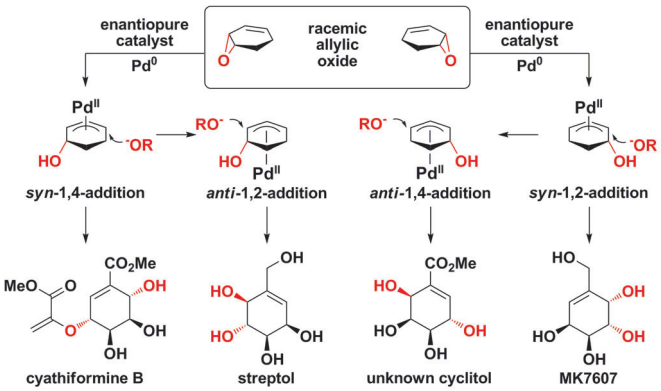
Abstract: *Control of 1,2- and 1,4-addition of substituted phenols to allylic oxides is achieved by intercepting palladium π-allyl complexes. The interconversion of palladium complexes results in the total synthesis of MK7607, cyathiformine B type, streptol, and a new cyclitol.*

Carbasugars,[1] owing to their biomimicry of carbohydrates, possess a wide range of biological activities from antitumor to antibiotic to antifungal, and therefore are attractive targets for synthesis. Several classes of carbasugars, including MK7607, streptol, and cyathiformines, have been isolated as enantiopure products or racemates (Scheme 1). The contiguous array of stereogenic hydroxy groups has relegated current syntheses to diastereocontrol beginning from the chiral pool (carbohydrates, quinic acid, tartrates), enzymatic benzene dihydroxylation, or Diels–Alder cycloaddition.[1] With more than 140 known carbasugars, a strategy for enantio-, diastereo-, and regioselective access from a common synthon could afford access to the gamut of biologically active carbasugars.

The majority of the carbasugars have *syn*- or *anti*-1,2- and -1,4-cyclohexenediol motifs. The four possible regioisomers (*syn*-1,2; *syn*-1,4; *anti*-1,2; *anti*-1,4) are notable for their relationship to a single precursor, an allylic oxide (Scheme 1). Ideally, a single synthon would provide all possible stereoisomers and streamline the preparation of several carbasugars. We propose the term allylic oxide regio-resolution (AORR) for this process of resolving a racemic allylic oxide to regioisomeric products using the Tsuji–Trost reaction.[2,3] Regioselective substitution[4] of enantioenriched allylic acetates with malonates has been investigated with chiral molybdenum[5] and palladium[6] complexes, resulting in regioisomeric products of 1,2- and 1,4-additions. Our efforts resulted in a catalyst-controlled AORR that delivers asymmetric 1,2 and 1,4 products that can be relayed to carbasugar natural products (see Scheme 1).



Scheme 1. Strategic allylic oxide regio-resolution (AORR) to access targeted carbasugar motifs.

We began with a simplified carbasugar synthon (**1**) to study the influence of catalyst structure, substrate, and nucleophile on the AORR. Racemic allylic oxide **1** was exposed to $[Pd_2(dba)_3]$ and PPh_3 with *p*-cresol, which favored *syn*-1,4-addition over *syn*-1,2-addition (Table 1, entry 1). The regioselectivity proved to be phosphine-dependent, and (*R*)-binap was gauged ineffectual (entry 2). The Trost ligand[2] (**4**) provided high enantioinduction in lower yields (entry 3) compared to the Van-Vranken–Trost diphenylethylenediamine (dpen) ligand **5** (entry 4).[7] The high conversion and enantioinduction of **2** and **3** and the absence of kinetic resolution of **1** (e.r. 57:43 after reaction) suggested that each epoxide enantiomer proceeds to a different regioisomer. To test this hypothesis, we examined each enantioenriched epoxide of **1** under optimized conditions to gauge the "match"[8] to a single enantiomer of ligand **5** and confirm the anticipated selectivity toward either *syn*-1,2- or *syn*-1,4-addition (entries 5 and 6). As predicted, the enantioenriched oxides smoothly converted to the *syn* products with an improved e.r. value. Notably, the (+) oxide matched the *S,S* ligand to provide 1,2 and 1,4 products in an 8.5:1 ratio (entry 5), and the (−) oxide switched the selectivity to a 1:4.6 ratio (entry 6). The recovered oxide showed no change in enantiopurity for either entry (5 or 6). 4-Hydroxyanisole[9] (entry 7) provided high levels of regiocontrol, enantioinduction, and conversion. The oxidative removal of 4-hydroxyanisole liberates the stereogenic hydroxy group and is vital to carbasugar preparation via AORR (see Scheme 2).

Similar to Trost's stereoinduction of allylic acetates and carbonates,[2] the C_2-symmetric ligand blocks one of the two sites of the π-allyl unit, diverting each oxide to a different constitutional isomer of 1,2- or 1,4-addition. The proposed

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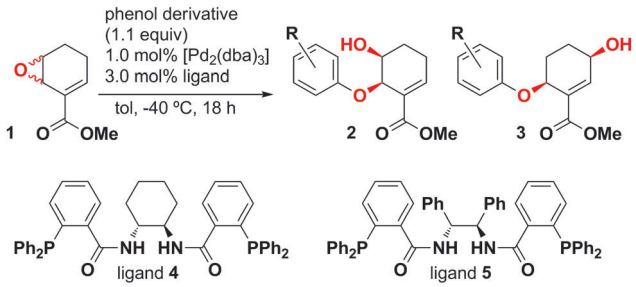
Table 1: Regiochemical control of enantioinduction.[a]



entry	oxide **1**	ligand	R of the phenol	e.r. of **1**[b]	e.r. of **2**[c]	e.r. of **3**[c]	yield [%] of **1**, **2**, **3**[d]
1	(±)	PPh_3	*p*-Me	–	–	–	20, 15, 50
2	(±)	(*R*)-binap	*p*-Me	–	–	–	n.d.[e]
3	(±)	(*R*,*R*)-**4**	*p*-Me	40:60	22:78	10:90	35, 29, 24
4	(±)	(*S*,*S*)-**5**	*p*-Me	57:43	96:4	93:7	2, 39, 34
5	(+)[f]	(*S*,*S*)-**5**	*p*-Me	92:8	**98:2**	32:68	31, **34**, **4**
6	(−)[g]	(*S*,*S*)-**5**	*p*-Me	10:90	24:76	**96:4**	28, **8**, **37**
7	(±)	(*S*,*S*)-**5**	*p*-MeO	56:44	85:15	95:5	1, 48, 35

[a] Enantiomers of **2** and **3** shown are the major enantiomers derived from the (*S*,*S*) ligand (entries 4–7); dba = dibenzylideneacetone, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [b] The enantiomeric ratio (e.r.) of recovered epoxides was determined with GC. [c] e.r. values determined with liquid chromatography against prepared racemic standards. [d] Yields after silica gel chromatography. [e] Decomposition of the epoxide. [f] Enantiomeric ratio of 92:8 favoring the (+)-**1** isomer. [g] Enantiomeric ratio of 10:90 favoring the (−)-**1** isomer.

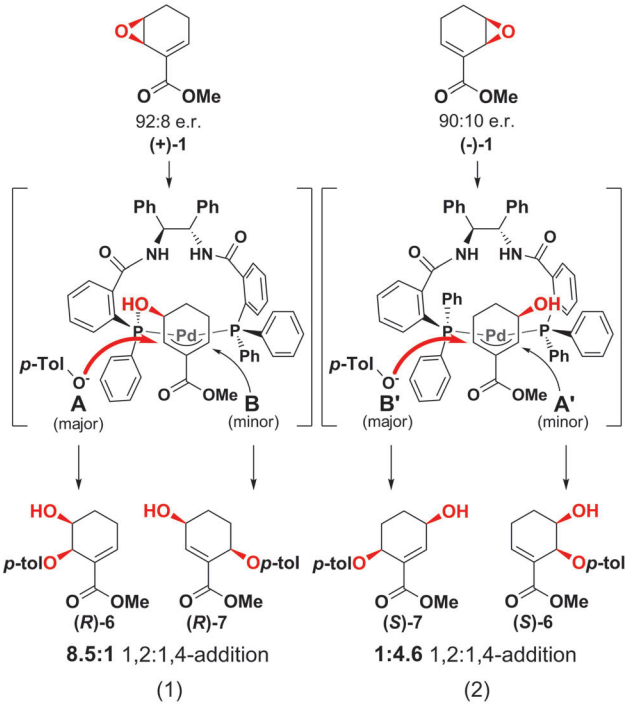


Figure 1. Proposed transition states for stereoinduction with observed product ratios.

Table 2: Predicted and observed e.r. values for the AORR reactions in Figure 1.

oxide **1**	(*R*)-**6**:(*S*)-**6**		(*R*)-**7**:(*S*)-**7**	
	predicted	observed	predicted	observed
92:8	99:1	98:2	67:33	68:32
10:90	40:60	24:76	1:99	4:96

model fits the observed enantioenriched-oxide data and provides a predictive basis for new studies of complex allylic oxides in total synthesis.[10]

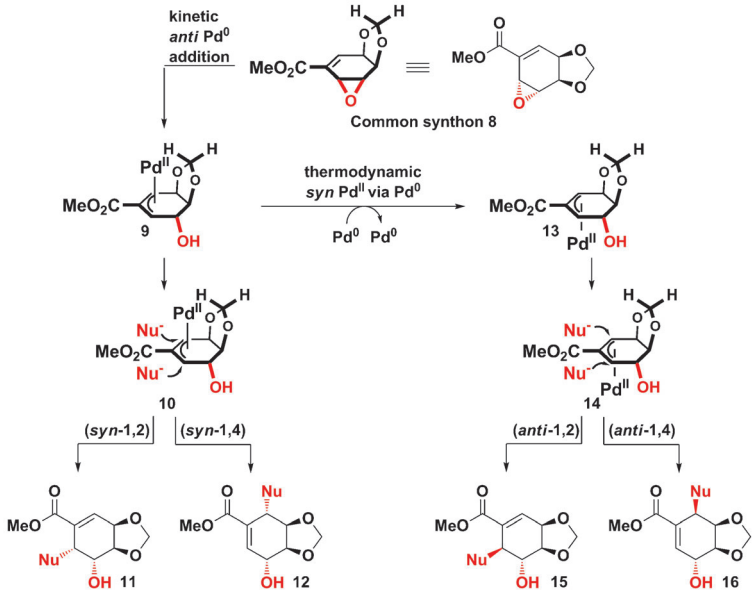
When oxide (+)-**1** is used, the π-allyl unit of the ester is generated within the complex, resulting in an attack at the *pro*-(*R*) carbon atom for 1,2-addition [**6**; Eq. (1) in Figure 1]. The 1,4-addition is accessible using oxide (−)-**1** [**7**; Eq. (2)] via attack at the *pro*-(*S*) carbon atom. The selectivity of this addition is consistent with the studies of Lloyd-Jones and co-workers[11] of the proposed transition states of the asymmetric allylic alkylation of cycloalkenyl esters.

The predicted and observed enantiomeric ratios can be calculated using the ratio of 1,2 to 1,4 products and the enantiopurity of the oxide (Table 2). Beginning with the (+) oxide (e.r. 92:8), the *S*,*S* ligand predicts a 1,2-addition with an increase to e.r. 99:1 and a 1,4-addition with a decrease to e.r. 67:33, which matches the observed e.r. values of 98:2 and 68:32, respectively. For the (−) oxide (e.r. 90:10), the predicted e.r. values are 1:99 for the 1,4-addition and 40:60 for the 1,2-addition; the observed one for the 1,4-addition is within error at 4:96, and e.r. 24:76 of the 1,2-addition is reasonable.

The predictive model was then applied to carbasugar frameworks that incorporate additional functionality within the cyclohexenoate. Applying the AORR method to common synthon **8**[12] was anticipated to provide *syn*-1,2 (**11**) and *syn*-1,4 products (**12**) originating from the kinetic palladium π-allyl complex **9** (Scheme 2).

The steric demands of the substituted dioxolane may destabilize the kinetic π-allyl complex **9**, resulting in its conversion to the thermodynamic π-allyl complex **13** via an exogenous Pd^0 complex, as observed by Bäckvall and others.[13] Addition of the nucleophile to complex **14** results in two forms: *anti*-1,2 (**15**) and *anti*-1,4 (**16**). Previous efforts by Hudlicky and co-workers[14] have established that *anti*-1,2-addition of malonates to acetonide allylic oxides is possible but occurs in low yields or results in mixtures of diastereomers. Common synthon **8** would be demonstrative of the kinetic-to-thermodynamic isomerization and would provide access to four classes of carbasugars.

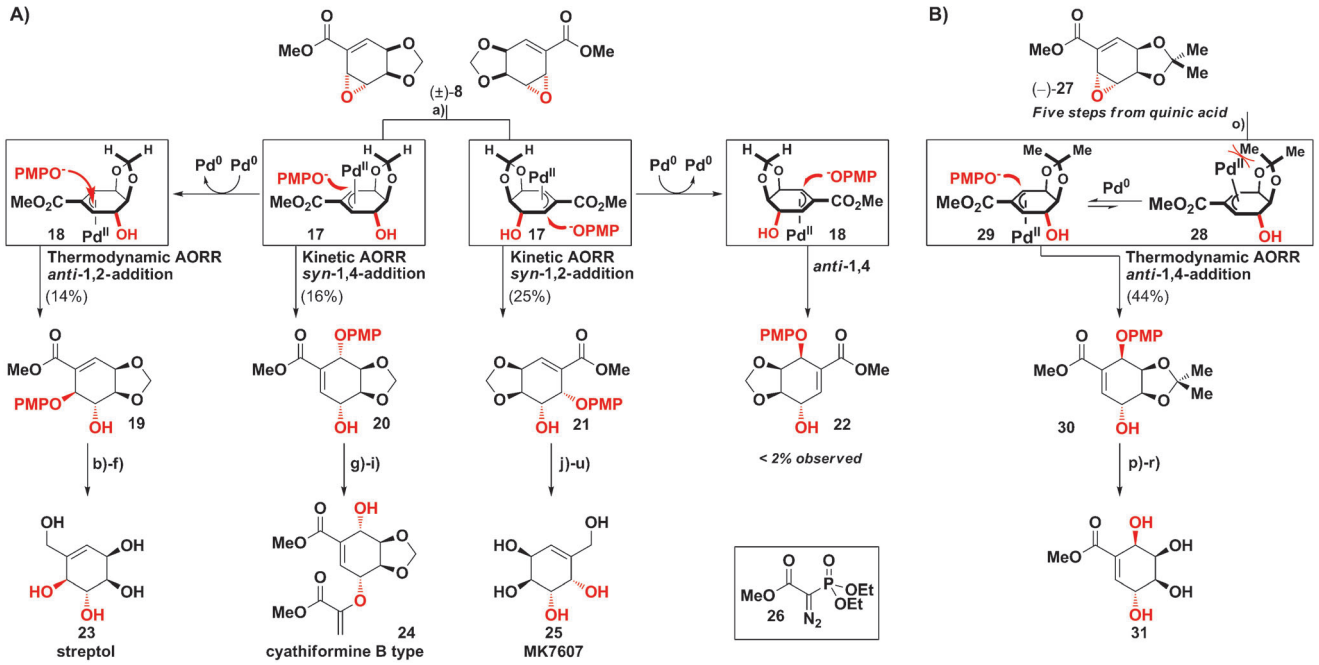
We discovered that all four possible regioisomers were formed from synthon **8** with the reaction proceeding to full conversion (Scheme 3 A). *Anti*-1,2 product **19** was isolated in 14% yield (e.r. 90:10) and *syn*-1,4 product **20** in 16% yield (e.r. 90:10).[15] The high stereoselectivity, albeit with low yield, for each isomer reflects the additional constraints the dioxolane ring imposes on the palladium π-allyl system. The



Scheme 2. Kinetic and thermodynamic palladium allyl distribution and resulting diastereomers.

syn-1,2 product **21** was isolated in 25% yield (e.r. 92:8) with the *anti*-1,4 product **22** detected in less than 1–2% by ^{1}H NMR spectroscopy. The enhanced yield of the *syn*-1,2 product **21** was expected given the sterically encumbered *anti*-1,4-addition mode under these conditions. The three isolated regioisomeric products were then carried forward to three natural products.

The *anti*-1,2 product **19** comprises the stereoarray of streptol (**23**), a potent plant-growth inhibitor.[16] The conversion to **23** was achieved by reducing the ester and protecting the transient acyl followed by CAN oxidative cleavage of the anisole ether. The removal of the dioxolane unit using acetyl chloride and catalytic zinc chloride followed by global acyl cleavage proved uneventful. The *syn*-1,4 product **22** matches the unusual fungal metabolite cyathiformine B (**25**), a chorismic acid derivative.[17] The cyathiformine structure poses potential problems because of its sensitive enol-pyruvate unit that could complicate the oxidative cleavage of the anisole ether and the Lewis acid mediated dioxolane removal. Proceeding forward, the installation of a diazophosphonate unit using rhodium acetate and **26** was followed by CAN oxidation with surprisingly little degradation. Horner–Wadsworth–Emmons olefination using gaseous formaldehyde provided cyathiformine B type **24**. The dioxolane unit proved difficult to remove with varying levels of



Scheme 3. Applying the AORR approach for the total synthesis of streptol, cyathiformine B type, MK7607, and a new cyclitol. A) Results with an racemic oxide; B) results when using the chiral pool. a) $[Pd_2(dba)_3]$ (10 mol%), (*R*,*R*)-**5** (30 mol%), *p*-$MeOC_6H_4OH$ (1.2 equiv), PhMe, 23 °C, 48 h (14% **19** (e.r. 90:10), 16% **20** (e.r. 90:10), 25% **21** (e.r. 92:8); b) DIBAlH (3.5 equiv), CH_2Cl_2, 0.3 h, 38%; c) Ac_2O (3.0 equiv), DIPEA, DMAP, CH_2Cl_2, 0.3 h; d) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 49% (two steps); e) 1) AcCl, then $ZnCl_2$ (0.1 equiv), 0 to 23 °C; 2) H_2O, THF, 0.3 h; f) NaOMe (1 equiv), MeOH, 16 h, 55% (two steps); g) $[Rh_2(OAc)_4]$, **26**, CH_2Cl_2, 5 h, reflux, 64%; h) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 81%; i) LiHMDS, CH_2O, THF, 2 h, −78 °C, 71%; j) DIBAlH (3.5 equiv), CH_2Cl_2, 0.3 h, 28%; k) Ac_2O (3 equiv), DIPEA, DMAP, CH_2Cl_2, 0.3 h; l) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 21% (two steps); m) 1) AcCl, then $ZnCl_2$ (0.1 equiv), 0 to 23 °C; 2) H_2O, THF, 0.3 h; n) NaOMe (1 equiv), MeOH, 16 h, 57% (two steps); o) $[Pd_2(dba)_3]$ (10 mol%), (*S*,*S*)-**5** (30 mol%), *p*-$MeOC_6H_4OH$ (1.2 equiv), PhMe, 23 °C, 48 h, 44%; p) 1) Ac_2O (3 equiv), DIPEA, DMAP, CH_2Cl_2, 0.3 h; 2) CAN (2.2 equiv), $MeCN/H_2O$ 4:1, 0.20 h, 63%; q) 1) NaOMe, MeOH, 0.1 h, 23 °C, 98%; 2) TFA, MeOH, 40 °C, 7 h, 51%. dba = dibenzylideneacetone, DIBAlH = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine, CAN = ceric ammonium nitrate, LiHMDS = lithium hexamethyldisilylazide, TFA = trifluoroacetic acid.

success (not shown). The *syn*-1,2 product **21** mapped to MK 7607[18] (**25**) and was targeted next. Following a similar approach to that used for the synthesis of streptol, we prepared MK 7607 in five steps.

The minor isomer, *anti*-1,4 **22**, was unisolable in the regioresolution of oxide **8**. To carry out all possible additions to the allylic oxide, we determined that two criteria must be met to remove the other three regioisomers (*syn*-1,2; *syn*-1,4; *anti*-1,2): 1) the thermodynamic palladium complex must be formed to eliminate *syn*-1,2 and *syn*-1,4, and 2) the ligand must match the enantiopure oxide to eliminate *anti*-1,2 addition. The first criterion was satisfied through removal of the kinetic π-allyl isomer by increasing the steric crowding proximal to the palladium center. We hypothesized that a switch from a dioxolane to an acetonide unit would facilitate this population inversion, which was observed when applying the reaction conditions to racemic **27**[19] (see the Supporting Information). The second criterion was fulfilled by evaluating the predicted model (Figure 1) and observed modes of addition for streptol, cyathiformine B type, and MK 7607, which revealed the *S*,*S* ligand to be optimal. Enantiopure acetonide oxide **27**[20] provided the previously unobtainable *anti*-1,4 product **30** in 44% yield via a predicted interconversion of **28** to **29** and a ligand-directed addition to the *anti*-1,4 site (Scheme 3B). Acylation, oxidative cleavage of the anisole ether, and saponification of the acetate followed by acid-mediated hydrolysis of the acetonide gave the new cyclitol **31**.[21]

In conclusion, we developed a regiodivergent, catalyst-controlled, asymmetric addition of phenols to allylic oxides that led to the synthesis of streptol, MK 7607, cyathiformine B type, and a novel cyclitol. The AORR method tolerates complex, fully substituted cyclohexenoates to provide access to the enantiomers of carbasugar natural products. The mechanistic dichotomy of the *syn* versus *anti* chiral palladium complexes and the study of complex nucleophiles and allylic oxides will be reported in due course.

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Keywords: carbasugars · homogeneous catalysis · palladium · regiodivergence · synthetic methods

[1] The number of existing carbasugars is reportedly more than 140, see: a) O. Arjona, A. M. Gomez, J. C. Lopez, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919–2036; b) Y. Kobayashi, *Glycoscience* (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer, Heidelberg, **2008**, pp. 1913–1997; carbasugars amenable to the reported chemistry include rancinamycin I–IV, gabosine A–O, COTC, nigrospoxydon C, epoxydine A–B, cyanoformate A–C, pericosine A–E, piperonol A and B, uvacalol A–K, phomoxin A–C, and lincitol A and B.

[2] a) J. Tsuji, H. Kataoka, Y. Kobayashi, *Tetrahedron Lett.* **1981**, *22*, 2575–2578; b) B. M. Trost, G. A. Molander, *J. Am. Chem. Soc.* **1981**, *103*, 5969–5972; for in-depth reviews of asymmetric allylic alkylations, see: c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; d) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943.

[3] For additional examples of vinyl oxides by Trost and coworkers, see: a) B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976; b) B. M. Trost, C. Jiang, *J. Am. Chem. Soc.* **2001**, *123*, 12907–12908.

[4] For recent reviews of divergent and regioselective reactions with chiral substrates, see: a) L. C. Miller, R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550–4562; b) R. R. Kumar, B. H. Kagan, *Adv. Synth. Catal.* **2010**, *352*, 231–242.

[5] D. L. Hughes, M. Palucki, N. Yasuda, R. A. Reamer, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 2762–2768.

[6] a) T. Hayashi, A. Yamamoto, Y. Ito, *J. Chem. Soc. Chem. Commun.* **1986**, 1090–1092; b) O. Loiseleur, M. C. Elliott, P. von Matt, A. Pfaltz, *Helv. Chim. Acta* **2000**, *83*, 2287–2294; c) H. Daimon, R. Ogawa, S. Itagaki, I. Shimizu, *Chem. Lett.* **2004**, *33*, 1222–1223; d) G. R. Cook, S. Sankaranarayanan, *Org. Lett.* **2001**, *3*, 3531–3533; e) O. Jacquet, J. Y. Legros, M. Coliboeuf, J.-C. Fiaud, *Tetrahedron* **2008**, *64*, 6530–6536.

[7] For the initial discovery and application of the dpen ligand, see: B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.

[8] S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1–30; *Angew. Chem.* **1985**, *97*, 1–31.

[9] B. M. Trost, J. L. Guzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415.

[10] See the Supporting Information for details.

[11] a) C. P. Butts, E. Fiali, G. C. Lloyd-Jones, P. Norrby, D. A. Sale, Y. Schramm, *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957; b) G. C. Lloyd-Jones, S. C. Stephen, I. J. S. Fairlamb, A. Martorell, B. Dominguez, P. M. Tomlin, M. Murray, J. C. Fernandez, T. Riis-Johannessen, T. Guerziz, *Pure Appl. Chem.* **2004**, *76*, 589–601.

[12] Oxide **8** can be prepared in seven steps which are based on: a) S. A. Bowles, M. M. Campbell, M. Sainsbury, G. M. Davies, *Tetrahedron* **1990**, *46*, 3981–3992; b) Y. Usami, K. Suzuki, K. Mizuki, H. Ichikawa, M. Arimoto, *Org. Biomol. Chem.* **2009**, *7*, 315–318; c) M. M. Campbell, A. D. Kaye, M. Sainsbury, R. Yavarzadeh, *Tetrahedron* **1984**, *40*, 2461–2470.

[13] The isomerization of π-allyl complexes through Pd^0 attack as reported by the groups of Bäckvall and Murahashi is instructive, see: a) K. L. Granberg, J. E. Bäckvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863; b) J. E. Bäckvall, K. L. Granberg, A. Heumann, *Isr. J. Chem.* **1991**, *31*, 17–24; c) S. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, *J. Org. Chem.* **1989**, *54*, 3292–3303.

[14] M. B. Banwell, N. Haddad, T. Hudlicky, T. C. Nugent, M. F. Mackay, S. L. Richards, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1779–1792.

[15] Initial isolation of the regiodivergent products provided **20** in 16% yield with products **19** and **21** as a mixture in 39% yield. An extended ^{1}H NMR analysis determined the ratio of these last products to be 14% **19** and 25% **21**. Yields and e.r. data for additional runs may be found in the Supporting Information.

[16] A. Isogai, S. Sakuda, J. Nakayama, S. Watanabe, A. Suzuki, *Agric. Biol. Chem.* **1987**, *51*, 2277–2279.

[17] A. Arnone, R. Cardillo, G. Nasini, O. V. de Pava, *Tetrahedron* **1993**, *49*, 7251–7258.

[18] Y. Nobuji, C. Noriko, M. Takashi, U. Shigeru, H. Kenzou, I. Michiaki, *Jpn. Koka Tokkyo Koho*, JP, 06306000, **1994**.

[19] Racemic oxide **27** can be prepared in seven steps; see Reference [12].

[20] Enantiopure oxide **27** can be prepared in five steps diverging from the preparation of oxide **8**, see: Y. Usami, M. Ohsugi, K. Mizuki, H. Ichikawa, M. Arimoto, *Org. Lett.* **2009**, *11*, 2699–2701.

[21] According to its structure, compound **31** may be a member of the rancinamycin family or the pericosines (desmethyl).

