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Traceless Chiral Auxiliaries for the Allene Ether Nazarov Cyclization

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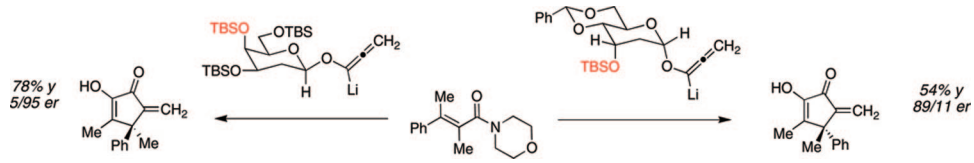

The key stereochemical factors that determine transfer of asymmetry from the chiral auxiliary to the cyclopentenone in the allene ether version of the Nazarov reaction have been elucidated. On the basis of the new insights into the mechanism, two highly effective chiral auxiliaries were designed and prepared.

Introduction

The allene ether variant[1] of the Nazarov cyclization[2,3] has a very low activation barrier and takes place under extremely mild conditions. We have never isolated the allenyl vinyl ketone precursors **1** (eq 1), because they do not survive workup, but instead lead to cyclic products **2** spontaneously with loss of the stable alkoxyalkyl cation **3**. The ease of this particular Nazarov reaction contrasts with the conditions for the conventional process that involves cyclization of a divinyl ketone and usually requires stoichiometric strong Lewis or Bronsted acid often at elevated temperature. The ease of cyclization of **1** presumably derives from the favorable polarization of the enol ether function,[4] the low barrier for approach of the allene sp-hybridized carbon atom to the β-vinyl carbon atom, as well as the relief of allene strain during the cyclization.[5]

The factors that underpin the high reactivity of ketones such as **1** in the Nazarov cyclization are also an impediment toward the development of a *catalytic* asymmetric version of the reaction shown in eq 1 because the background reaction is likely to overwhelm any catalyzed process.[6,7] Nevertheless, because of the utility of the process in total synthesis we had a strong incentive to develop an asymmetric version, and we did so by focusing our attention on the acetal carbon atom of **1**. When $R^4 \neq H$ this carbon atom is stereogenic, so there was the

(1) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290.

(2) (a) For reviews of the Nazarov reaction, see: Harmata, M. *Chemtracts* **2004**, *17*, 416–435. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (d) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *219*, 3–2206. (e) Habermas; K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; Vol. 45, pp 1−158.

(3) (a) For recent examples of the Nazarov reaction, see: Li, W.-D. Z.; Wang, Y-Q. *Org. Lett.* **2003**, *5*, 2931–2934. (b) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542–4545. (c) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514–13515. (d) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313. (e) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349. (f) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 300–308. (g) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915–918. (h) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574.

(4) (a) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871–885. (b) Polarization in the opposite sense, through placement of an electron-withdrawing substituent α to the carbonyl group in the acyclic precursor, also accelerates the Nazarov cyclization. See: He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.

(5) The strain energy of allene can be estimated as the difference between the heats of hydrogenation of allene,−71280 ± 200 cal/mol, and of 1,5-hexadiene,−60525 ± 150 cal/mol, i.e., 10755 ± 350 cal/mol or ca. 10.76 ± 0.35 kcal/mol. Kistiakowski, G. B.; Ruhoff; J. R.; Smith, H. A.; Vaughan, W. E. *J. Am. Chem. Soc.* **1936**, *58*, 146–153.

(6) Catalytic asymmetric Nazarov cyclizations are known: (a) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100. (b) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545. (c) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078.

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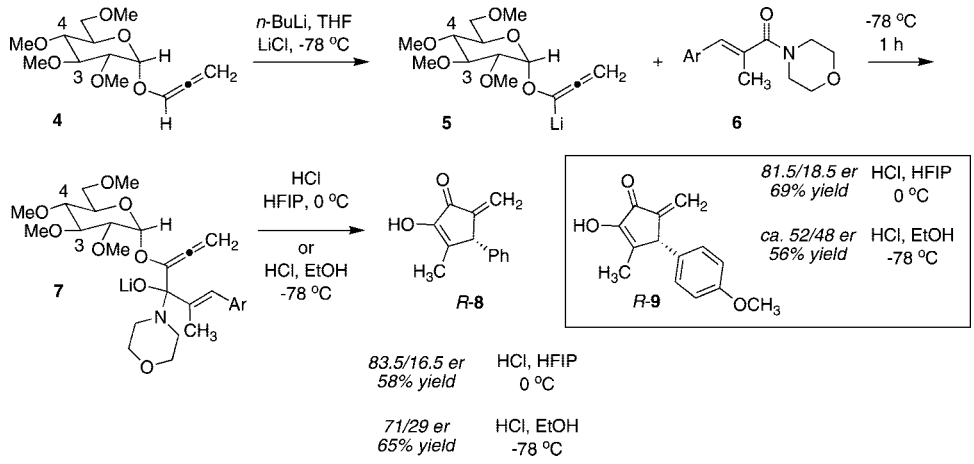
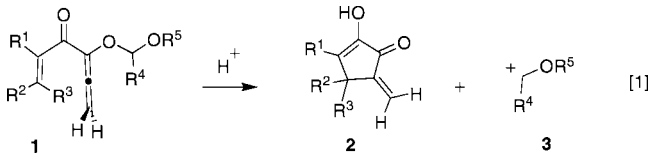
SCHEME 1



possibility that transmission of stereochemical information from the acetal to the cyclopentane ring might be observed. We felt that such an approach, if successful, would be attractive for another reason. Since cleavage of **3** from cyclopentenone **2** takes place spontaneously, no additional step would be required for removal of the chiral auxiliary from the product. We have disclosed the results of our endeavors in this area in earlier papers, and we have recently published a preliminary account of what we believe to be the explanation of the effect that leads to the transmission of stereochemical information from the acetal to the ring carbon atom.[8] In this paper, we provide additional supporting evidence for our hypothesis and an overview of our earlier work with chiral auxiliaries on the allene within the framework of a unifying mechanistic proposal. The mechanism whereby stereochemical information is transmitted from the auxiliary appears to be unique, and can potentially find a number of other applications.



[1]

Results and Discussion

The first chiral auxiliary that we prepared was derived from permethylated D-glucose.[9,10] Allene ether **4** (Scheme 1) was converted to lithioallene **5** by exposure to *n*-butyllithium in THF at −78 °C. The addition to enamide **6** (Ar = Ph) was sluggish in the absence of LiCl, presumably due to aggregation of the anion.[11] In the presence of 4 equiv LiCl, however, addition of **5** to **6** took place within 1 h at −78 °C to produce the presumptive tetrahedral intermediate **7**. The reaction was quenched by rapidly transferring the mixture to a stirred solution of HCl in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 0 °C.[12]

Workup provided α-hydroxycyclopentenone **8** in 58% yield and 83.5/16.5 er. A series of enamides was screened in the reaction. Yields varied between 52% and 84%, whereas optical purities varied between 76.5/23.5 and 84/16 er. Although the optical purity of the products was modest, we were able to demonstrate proof of principle by showing that stereochemical information from the ether group to the ring carbon atom was taking place.

At this early point, we had no mechanistic hypothesis with which to explain our results. We were fortunate to observe modest optical purities in our first experiment. Since cleavage of the chiral auxiliary takes place *during* the stereochemistry-determining operation, the timing of the bond-forming step that closes the five membered ring and the bond cleaving step that liberates the chiral auxiliary as a cationic fragment must be critical. Premature loss of the chiral auxiliary would preclude any transmission of stereochemical information during the cyclization. An indication that this might be the case was provided by the cyclization that led to **9**. The only difference between **8** and **9** is the *p*-methoxy group that is present in **9**, yet cyclization of **7** (Ar = Ph) in the presence of HCl in ethanol at −78 °C led to **8** in 71/29 er (65% yield), whereas under identical conditions **9** was obtained from **7** (Ar = *p*-MeOPh) essentially as the racemate in 56% yield. This observation led us to adopt HFIP as a solvent for the cyclization, since this is a non-nucleophilic solvent of high ionizing power that is known to stabilize carbocations to a greater extent than ethanol.[13]

The cyclization of **7** (Ar = *p*-MeOPh) in HFIP at 0 °C produced **9** in 81.5/18.5 er (69% yield), underscoring the important role that the conditions for the quench have on the optical purity of the product.

Our immediate goal was to improve the optical yield of products. We assumed that because of its proximity to the reacting allene the C2 substituent of the sugar would play a critical role, so we prepared allene ether **10** from 2-deoxy-D-glucose.[9] Although the optical purity of cyclic product derived from **10** was lower than from **4**, the difference was modest,

(7) (a) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A. C.; DeBrosse, C.; Haltiwanger, R. C. *Synlett* **1999**, 1612–1614. (b) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380–1381. (c) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257. (d) Mazzola, R. D., Jr.; White, T. D.; Vollmer-Snarr, H. R.; West, F. G. *Org. Lett.* **2005**, *7*, 2799–2801.

(8) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328–5329.

(9) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447–2450.

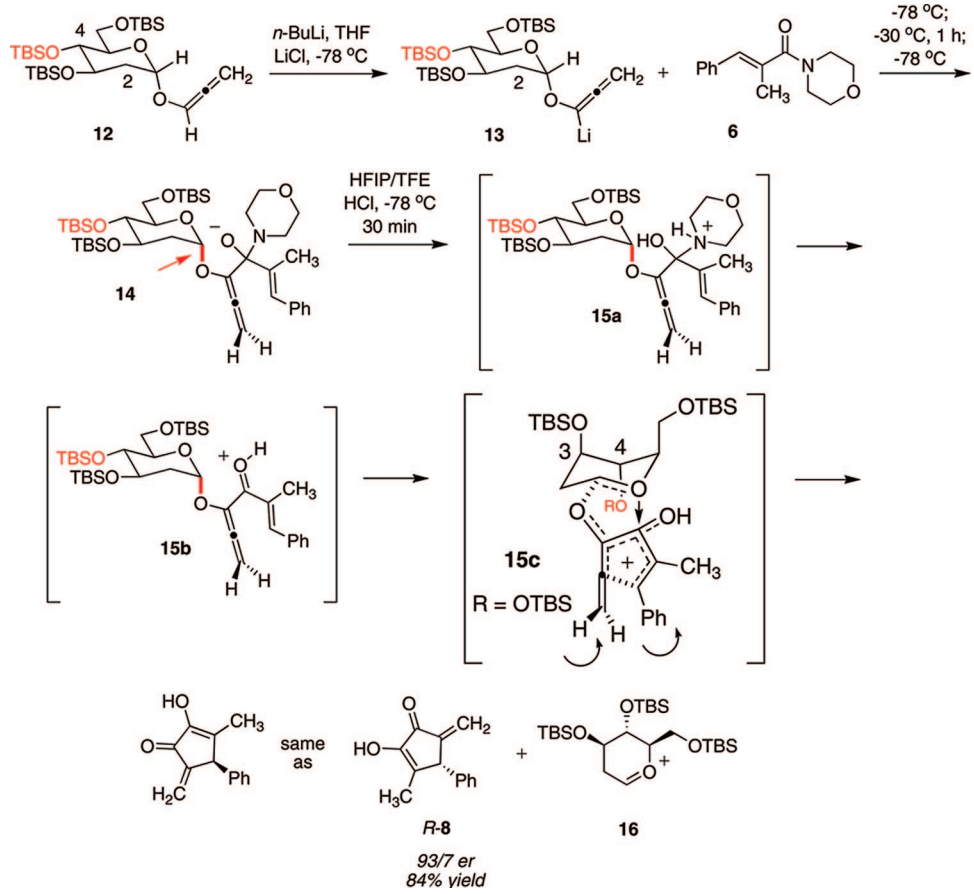
(10) (a) For sugar derived allenyl ethers, see: Rochet, P.; Vatèle, J.-M.; Goré, J. *Synthesis* **1994**, 795–799. (b) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. *Tetrahedron* **1999**, *55*, 11331–11342. (c) Hausherr, A.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2001**, 1377–1385.

(11) (a) Myers, A. G.; Yang, H. C.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362. (b) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187–9197. (c) Seebach, D. *Ang. Chem. Int. Ed.* **1988**, *27*, 1624–1654.

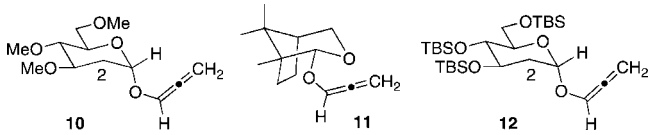
(12) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927–929.

(13) Schadt, F. L.; Schleyer, P. v. R.; Bentley, T. W. *Tetrahedron Lett.* **1974**, *15*, 2335–2338.

SCHEME 2



leading us to the conclusion that the C2 substituent does not strongly influence the stereochemical course of the cyclization.



A shortcoming of the pyranose-derived chiral auxiliaries is related to the attenuated nucleophilicity of the derived allenyllithiums. As indicated above, this problem was addressed through addition of LiCl to the anion solution. The optical purity of products was acceptable on modest scale (up to 0.2 mmol) but eroded noticeably when the reactions were scaled up to 4 mmol. We had assumed that a high concentration of lithium ions might be deleterious to the efficient transmission of stereochemical information since it might discourage the organization of transition states like **15c**. It is conceivable that this problem might have been overcome by optimizing the reaction more carefully. An alternative strategy was to avoid chiral auxiliaries that incorporate methyl ether functions, the thought being that aggregation of the allenyllithium might then be suppressed, and addition of LiCl might not be required. With this in mind, the camphor-derived chiral auxiliary shown in structure **11** was developed.[14] This proved to be a very good choice, since the reactions of **11** led to cyclic products in higher optical purity than from **4**, and the reactions could be scaled up without any erosion in optical purity. For example, cyclopentenone *R*-**8** was prepared in 71% yield and 88.5/11.5 er from **11**.[15]

We put allenyl ether **11** to use during our synthesis of roseophilin.[16] This is where things stood until allenyl ether **12** was prepared and evaluated.[17] Changing the alcohol protecting groups from methyl to *tert*-butyldimethylsilyl (TBS) ethers had been expected to suppress the aggregation of the derived allenyllithium species, resulting in a more reactive nucleophile even in the absence of added LiCl. In practice LiCl was still required for high product yields from the reactions of **12**. The surprise was that the cyclic products were obtained from **12** in excellent optical purity in all cases, within the range of 92.5/7.5 to 96.5/3.5 er.[17] We were determined to learn the reason for the superiority of **12** over allenyl ethers **4**, **10**, and **11** for the Nazarov cyclization.

If rotation about the anomeric C−O bond were to take place during the stereochemistry-determining operation it would be difficult to understand why any of the chiral auxiliaries should be effective. Therefore, in order for the pyranyl chiral auxiliary to control the stereochemical course of the cyclization, there must be a means to restrict rotation about this bond (see **14**,

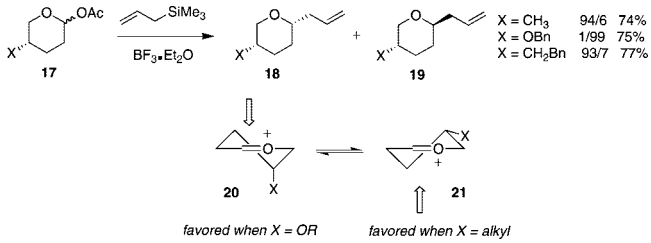
(14) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100.

(15) The major enantiomer of **8** that was prepared from **11** or from the α-pyranose-derived chiral auxiliaries corresponded to the more mobile peak on a Chiralcel-OD HPLC column. The absolute stereochemistry of the products from **11** has been determined rigorously in two cases, through the total synthesis of natural roseophilin and also crystallographically. See ref 16.

(16) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.

(17) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579–2582.

SCHEME 3



Scheme 2). We postulated that this was accomplished through electron pair donation from the pyran oxygen atom to the developing pentadienyl carbocation, or alternatively through a charge-dipole interaction (see **15c**, Scheme 2). This has the effect of bringing the chiral auxiliary into closer proximity to the pentadienyl cation, but this alone is not enough to explain why there should be a large difference in the levels of asymmetry transfer between **10** and **12**. The only way there can be a large difference between **10** and **12** is if the substituents on the sugar were to move close enough to the pentadienyl cation to influence the sense of conrotation. One way for this to happen is to postulate *conformational inversion of the pyranose ring* in the stereochemistry-determining operation.[8] If this were to happen, the C4 ether group that is equatorial in **12** would become axial in **15c**, thereby blocking one face of the pentadienyl cation and biasing the conrotation to take place so as to move the phenyl group in **15c** away from the bulk of the C4 OTBS group. This leads to *R*-**8** after loss of the chiral auxiliary as six-membered-ring oxocarbenium ion **16**. The key element is the conformational inversion of the pyran ring under the conditions for the cyclization. This is supported by the work of Bowen[18] and more recently by Woerpel and co-workers who found that the conformational preferences of six-membered-ring oxocarbenium ions follow a pattern and are highly dependent on the electronic nature of the substituents.[19] Woerpel's results that are summarized in Scheme 3 are illuminating. Exposure of acetate **17** and allyltrimethylsilane to $BF_3 \cdot Et_2O$ in dichloromethane leads to a diastereomeric mixture of cis and trans products **18** and **19**, respectively. When the substituent X is methyl the cis/trans ratio is 94/6, whereas when X = OBn the ratio of products is inverted, 1/99. The result for X = CH_2Bn (93/7) suggests that it is the electronic characteristic not the size of the substituent that influences the diastereomeric ratio. Woerpel postulates an equilibrium between conformers **20** and **21** of the six-membered-ring oxocarbenium ion. When X is an alkoxy group, electron pair donation from the oxygen atom to the positively charged carbon atom favors conformer **20**, resulting in top face attack by the electrophile, leading to trans product **19**. When X is an alkyl group, conformer **21**, in which the substituent is equatorial, is favored and electrophilic attack takes place from the bottom face, leading to cis product **18**. According to this paradigm, the conformational inversion leading to transition state **15c** is driven by the stabilization that results from bringing the nonbonding electron pairs on the C4 OTBS group closer to the anomeric carbon atom.

The elements of the mechanistic hypothesis that has been summarized in Scheme 2 are listed below: (1) The pyran oxygen atom is an essential feature of the chiral auxiliary. There must be an interaction between its equatorial nonbonding electron pair and the pentadienyl carbocation *before* the cyclopentenone C−C bond is fully formed. If there were no such interaction, then rotation about the anomeric C−O bond would take place, thereby limiting the transmission of stereochemical information from the pyranose to the cyclopentenone. (2) The pyran ring must invert *before* the cyclopentenone C−C bond is fully formed. If it did not invert, then the equatorial C4 substituent that is critical for obtaining cyclopentenone products in high optical purity, would be too far to influence the torquoselectivity of the ring closure. (3) The pyran ring inversion is induced by the electrostatic attraction between the developing oxocarbenium ion and the nonbonding electron pair on an axial oxygen atom, according to Woerpel's analysis. All this strongly suggests some degree of simultaneity of bond forming and bond cleavage during the conversion of **15c** to *R*-**8**.

In order for this model to be valid, the 3,4,5-triaxial conformation of the pyran ring in **15c** must be energetically accessible, and one must postulate a late transition state for the cyclization in which significant positive charge develops at the anomeric carbon atom. The energetic accessibility of the triaxial conformer is not in doubt, and is supported by a wealth of precedent. In 1994, we prepared 2-deoxy C-glycoside **22** and determined that the ground-state conformation is as shown, with the three groups at C3, C4, and C5 axial and the C1 methyl group equatorial.[20] The configurational assignment of **22** is supported by the small vicinal coupling constants that were measured for the equatorial methine protons in the 500 MHz ^{1}H NMR spectrum. Presumably the conformational preference of **22** is determined by the relief of steric compression between the adjacent C3 and C4 silyloxy groups. Suzuki and co-workers showed that 2,6-dideoxyglucopyranosyl acetate **23** prefers the 3,4,5-triaxial conformation.[21] In Suzuki's example relief of steric compression evidently overrides any stabilization of the 3,4,5-triequatorial conformer through the anomeric effect. The balance, however, is delicate, as Yamada's results demonstrate.[22] Whereas the equatorial C3 and C4 OTBS groups in **24** are accommodated, the larger OTBDPS groups in **25** induce conformational inversion of the pyran resulting in the 2,3,4,5-tetraaxial conformer. Roush's work also supports the notion that chair-to-chair conformational inversion of the pyran ring is facile.[23] The reasons for the preference for diaxial conformers in *trans*-1,2-dihydroxycyclohexane trialkylsilyl ethers have recently been described by Marzabadi.[24]

If the model that has been proposed in Scheme 2 is valid, then the following four predictions can be made. First, deleting the equatorial OTBS group from C3 in **12** should not affect the optical purity of the product. In **15c** this group is far from the developing cyclopentenone C−C bond, and should not be able to directly influence the stereochemical outcome of the cyclization. Second, deleting the equatorial C4 OTBS group from **12** should have a measurable deleterious effect on the optical purity of the product. Third, if the C4 substituent is constrained to

(18) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859–864.

(19) (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528. (b) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157–1160. (c) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.

(20) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181–5184.

(21) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663–666.

(22) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615–5618.

(23) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825–8836.

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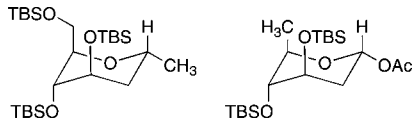
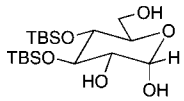
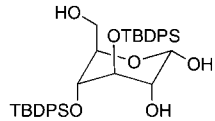


22
Tius, 1994

23
Suzuki, 1996



24
Yamada, 2004



25
Yamada, 2004

remain in the equatorial position, for example by locking the conformation of the pyran ring, then it will be prevented from close approach to the developing pentadienyl cation. As a result, the C4 substituent will be unable to influence the direction of conrotation, resulting in attenuated optical purity of product. Fourth, deleting the pyran oxygen atom from **12** and replacing it with a methylene group should lead to low yield and low optical purity. All four predictions have been verified.

Allenyl ether **26** was first prepared from 2,3-dideoxy-D-glucose (Table 1). As predicted, the Nazarov product *R*-**8** was formed from **26** in 94/6 er (89% yield), essentially the same result as from allene ether **12** (93/7 er). This shows conclusively that the C3 equatorial silyloxy group in **12** does not contribute to the optical purity of the cyclic product.

The 2,4-dideoxy-D-glucose derived allenyl ether **27** was prepared next. The prediction here was that deleting the C4 silyloxy group would have the effect of eroding the optical purity of the cyclic product. Indeed, *R*-**8** was formed in 86.5/13.5 er (46% yield) from **27**. The absence of the large axial group at C4 in **15** (Scheme 2) was responsible for the erosion in the optical purity of product and supports a key role for the C4 equatorial group in **12** and in **26**.

The prediction that locking the conformation of the pyran ring would erode the optical purity of cyclic product was also borne out. Allenyl ether **28**, derived from the benzylidene acetal of 2,3-dideoxy-D-glucose, led to *R*-**8** in 86.5/13.5 er (89% yield). In **28** the large group at C4 is prevented from assuming the axial orientation and from effectively blocking one face of the developing pentadienyl cation. This results in the attenuation of the optical purity of **8** relative to the products from **12** and **26**.

We postulated that **28** could be converted into a highly effective chiral auxiliary by introducing an axial silyloxy group at C3. An axial C3 substituent would be ideally positioned to block one face of the pentadienyl cation. This was indeed the case, and allenyl ether **29** led to *R*-**8** in 97/3 er (69% yield). This structural modification leads to an exceptionally effective chiral auxiliary.

2-Deoxy-D-galactose derived allenyl ether **30** was predicted to be a poor chiral auxiliary on the basis of the model. If pyran ring inversion were to take place in the stereochemistry-determining operation, the C4 axial OTBS group would become equatorial and would be unable to block the back face of the pentadienyl cation. In fact the optical purity of *R*-**8** that was derived from **30** (86.5/13.5 er) was the same as for *R*-**8** derived from **27**, which is what the model predicts.

The model predicts a critical role for the pyran oxygen atom. We had some circumstantial evidence to support a role for the ring oxygen atom, or the second oxygen atom in the case of acyclic acetals, insofar as the yield of product was concerned. This was one of the factors that had led us to postulate the model in the first place. However, we lacked any evidence that the ring oxygen atom was crucial for the high optical purity of the product. To address this issue, allene ether **36**, the carbacyclic analogue of **26**, was prepared (Scheme 4). Commercially available 4-oxopimelate **31** was first converted to diethyl acetal **32**, then the ester functions were reduced to aldehydes. The unstable dialdehyde was immediately subjected to List's conditions for the asymmetric intramolecular aldol addition in the presence of L-proline.[25] Reduction of the aldehyde product with $NaBH_4$ was followed by simultaneous protection of the two hydroxyls as OTBS ethers. Mild hydrolytic removal of the diethyl acetal led to **33** in 51% overall yield from **32**. The degree of asymmetric induction during the intramolecular aldol reaction was determined through Mosher analysis after reducing **33** to axial alcohol **34**. The optical purity of **34** was determined to be 88/12 er. Etherification of **34** by exposure to propargyl bromide and base gave **35**, which was isomerized to allenyl ether **36** by exposure to potassium *tert*-butoxide at 60 °C in THF according to Brandsma's method.[26] Exposure of **36** to *n*-butyllithium followed by enamide **6** (R = Ph) and quenching into HCl in HFIP/TFE at −78 °C resulted in a complex reaction mixture from which *R*-**8** was isolated in <30% yield. The product was slightly enriched in the *R* enantiomer (55.5/45.5 er). Since allene **36** was used as a 88/12 mixture of enantiomers, asymmetry transfer was approximately 11%. The low yield and the low level of asymmetric induction that was observed for **36** supports the postulated dual role for the ring oxygen atom, which restricts rotation about the anomeric C−O bond and also facilitates cleavage of the chiral auxiliary from the product. In the absence of an efficient means to terminate the reaction, the cyclic cation is free to decompose along a multitude of pathways, leading to an erosion of the yield.

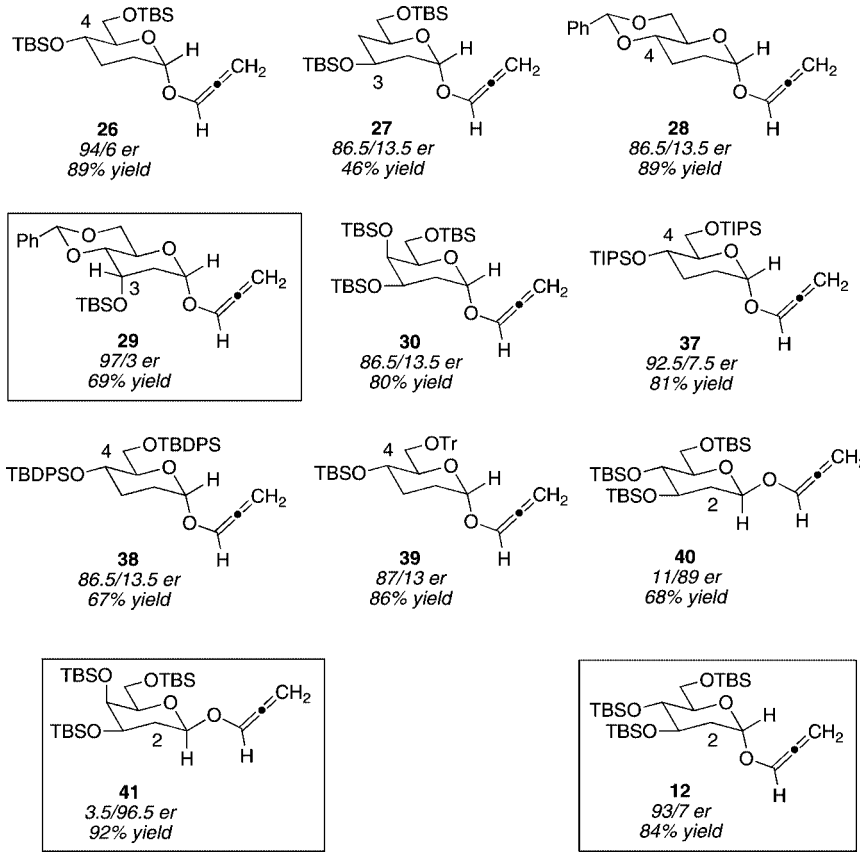
If the model were valid, then one would predict only a minor role for the C6 substituent that is oriented away from the pentadienyl cation in **15** (Scheme 2). In order to probe this issue, allenyl ethers **37**, **38** and **39** (Table 1) were prepared and evaluated in the Nazarov cyclization. The plan was to vary the size of the ether protecting groups and to compare the results with the one from **26**. The difference in optical purity of the product from bis TBS ether **26** (94/6 er) and bis TIPS ether **37** (92.5/7.5 er) was small, but the reaction was more selective when the smaller −OTBS groups were present. Changing the protecting groups to TBDPS in **38** resulted in further diminution of the optical purity of product **8** (86.5/13.5 er). We were unable to prepare the bis trityl ether, so we settled for the C4 OTBS, C6 OTr compound **39** that led to essentially the same optical purity of the product as **38** (87/13 er vs 86.5/13.5 er). These results show that increasing the size of the protecting groups at C4 and C6 from TBS through Tr does not lead to any improvement, but rather to slight erosion of the optical yield of product. The reasons for this are not clear.

Pyranoses might appear to be less than ideal chiral auxiliaries. Although many D-sugars are available and cheap, the same is not true for L-sugars. Fortunately, both enantiomeric series of cyclopentenones are available from D-pyranose derived chiral auxiliaries. For example, whereas the α-anomeric chiral auxiliaries lead to *R*-**8**, the β-anomers lead to *S*-**8**. β-2-Deoxy-D-

(25) (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785–2788. (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557.

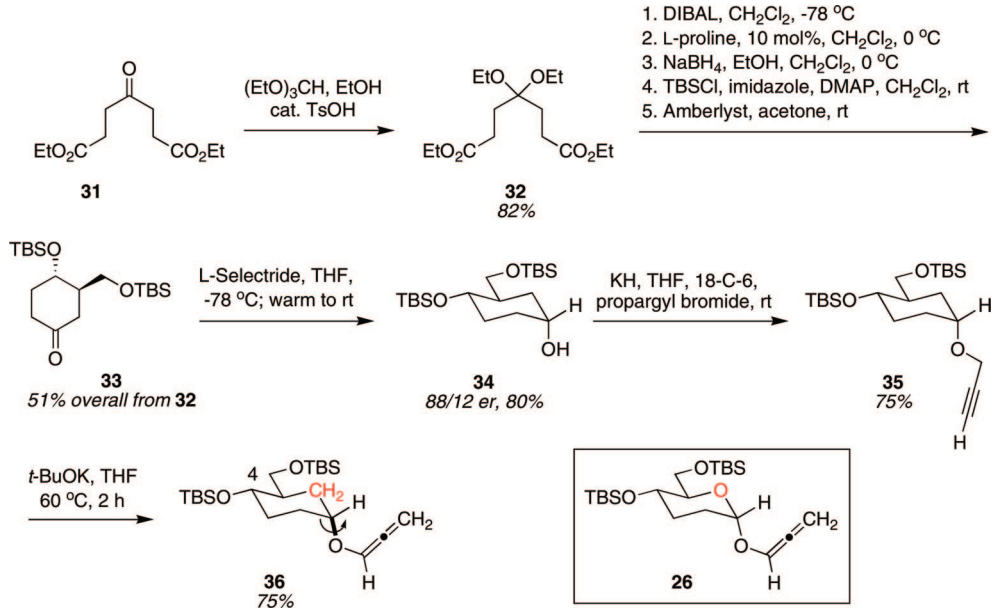
(26) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916–924.

TABLE 1. Pyranose-Derived Chiral Auxiliaries[a]



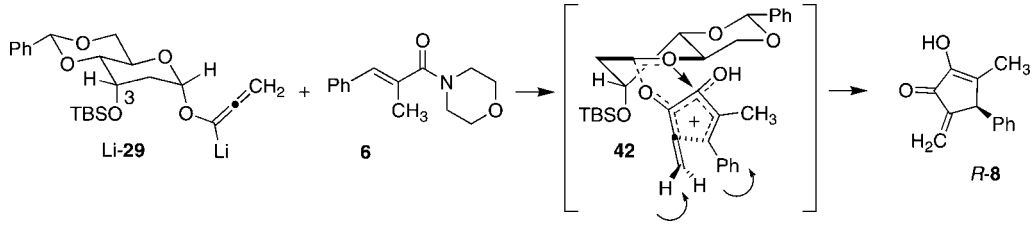
[a] Yields and enantiomeric ratios refer to the reaction of each allenyl ether with enamide **6** (R = Ph).

SCHEME 4



glucose derived allenyl ether **40** (Table 1) was prepared. Conversion to the allenyllithium species, addition to enamide **6** (R = Ph) and cyclization as before led to *S*-**8** as the major enantiomer (11/89 er) in 68% yield. The optical purity of the product was greatly improved using β-2-deoxy-D-galactose derived allenyl ether **41** (3.5/96.5 er). This points to the central role that the axial C4 OTBS group plays in the case of **41**, and implies that in the β-series of chiral auxiliaries conformational change of the pyran ring does *not* take place during the stereochemistry-determining operation. These results appear to be consistent with Woerpel's findings concerning six-membered-ring oxocarbenium ion alkylations.

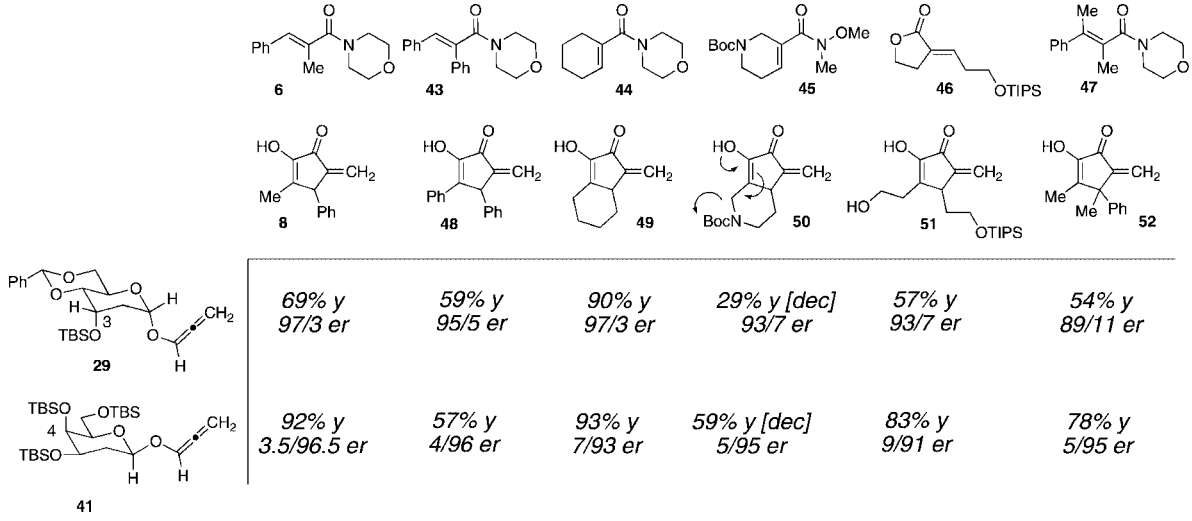
TABLE 2. Quench Conditions for the Reaction of 29[a]



entry	acid (equiv)	solvent	er
1	HCl (33)	HFIP/TFE (1/1)	95/5 to 70/30
2	HCl (6)	HFIP/TFE (1/1)	66.5/33.5
3	$ClCH_2CO_2H$ (33)	HFIP/TFE (1/1)	87/13
4	H_3CCO_2H (33)	THF	90.5/9.5
5	H_3CCO_2H (33)	Et_2O	90.5/9.5
6	H_3CCO_2H (33)	PhMe	90.5/9.5
7	H_3CCO_2H (33)	MTBE	92.5/7.5
8	**H_3CCO_2H (33)**	**CH_2Cl_2**	**97/3**

[a] All quenches were performed at −78 °C for 2 min.

TABLE 3. Examples of the Asymmetric Allene Ether Nazarov Cyclization



Optimizing the Quenching Conditions. According to the model, the timing of the various bond-forming and bond cleaving events that lead from **14** through **15** to *R*-**8** and **16** must be critical for the success of the asymmetric process. Premature cleavage of the chiral auxiliary will preclude good asymmetric induction from taking place. Premature acid catalyzed cleavage of any of the silyl ether protecting groups is also very likely to be deleterious. Consequently, any change in temperature, acid and especially solvent can be expected to have a large effect on the optical purity of the products. These considerations had guided our initial choice of HFIP as the solvent for the quench. Modified conditions were developed for the quench, 33 equivalents of anhydrous HCl in a 1/1 mixture of HFIP/TFE at −78 °C, so as to ensure rapid cyclization. On the basis of our early results with *R*-**9** (Scheme 1) we surmised that loss of stereochemical information and/or attrition of the yield would result if cleavage of the auxiliary were slow. Since HFIP freezes at −4 °C, it was mixed with TFE to allow the quench to take place at −78 °C. These conditions worked very well for the permethylated and the persilylated chiral auxiliaries and led to reproducible yields and enantioselectivities. The exception was **29** for which we observed irreproducibility in both yield and enantioselectivity. We traced the problem to premature cleavage of the acetal group, which led us to develop alternative conditions for the quench that would preserve the integrity of the acetal. Our results are summarized in Table 2. The optical purity of *R*-**8** varied greatly (95/5 to 70/30) when our usual conditions were used (Table 2, entry 1). Reducing the equivalents of HCl actually led to further erosion of the er. Chloroacetic acid (entry 3), a much weaker acid, catalyzed the cyclization but the er in this case was suboptimal. Changing to acetic acid (entries 4−8) led to an effective cyclization. In THF, ether or toluene the er was 90.5/9.5. Switching to *tert*-butyl methyl ether (MTBE) led to a slight improvement in er to 92.5/7.5. Thirty-three equivalents of acetic acid in dichloromethane proved to be the best condition, leading to reproducible er's of 97/3.

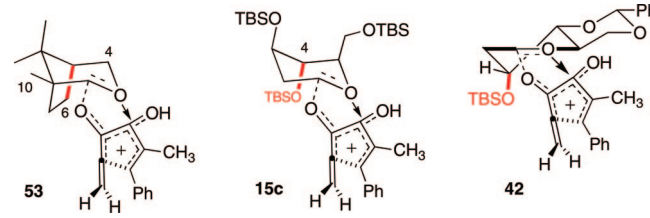
Since we had identified two highly effective chiral auxiliaries, one for each enantiomeric series, we were curious to learn the scope of each. Table 3 summarizes the results from the reactions of a series of enamides with allenyl ethers **29** and **41**. All reactions were quenched with 33 equiv of acetic acid in dichloromethane at −78 °C for 2 min and then neutralized with aqueous $NaHCO_3$. The optical purity of products was excellent in all cases. There was some variability in the yields. The low yield of **50** is due to decomposition of the product according to the retro-Michael process indicated by the curved arrows as shown in Table 3. Compound **50** was unstable to storage and

also underwent significant decomposition during purification by chromatography. The only difference between **49**, which was formed in excellent yield, and **50** is the presence of the protected nitrogen atom in the latter, leaving no doubt that this was the cause for the large difference in yields between the two. None of the yields that are reported in Table 3 have been fully optimized, so it is possible that some improvements can be made. We have used the racemate of cyclopentenone **51** in our recent total synthesis of (±)-terpestacin,[27] so the synthesis of each of the enantiomers of **51** constitutes an asymmetric formal synthesis of (+)- and of (−)-terpestacin. Preparation of cyclopentenone **52** that incorporates a quaternary ring carbon atom is noteworthy. Addition of the lithioallenes to tetrasubstituted enamide **47** was quite slow and required warming of the reaction mixture from −78 to 0 °C. Stirring at 0 °C for 2 h ensured that the allenyllithium had been fully consumed.

Summary and Conclusion

We have attempted to provide an explanation for the observations made over the course of several years with chiral auxiliaries for the allene ether version of the Nazarov cyclization. In the process we have identified two broad classes of pyranyl chiral auxiliaries, those that are able to undergo chair-to-chair inversion and those that are conformationally locked. Pyran ring inversion is induced by the electrostatic attraction between the developing oxocarbenium ion and the nonbonding electron pair on an axial oxygen atom, according to the paradigm described by Woerpel and co-workers. Whether or not ring inversion takes place during the stereochemistry-determining operation, there is strong evidence that the pyran ring oxygen atom restricts the conformational mobility of the pentadienyl cation and is necessary for both high enantioselectivity and yield of cyclic product. The key to high enantioselectivity is the presence of a large axial or pseudoaxial substituent on the pyran ring that shields one face of the pentadienyl cation. The buttressing effect provided by the axial (or pseudoaxial) substituent biases the conrotation to take place in a single direction. It is also significant that this hypothesis about the origin of asymmetry transfer explains our observations with camphor derived chiral auxiliary **11**. According to our hypothesis, in the reaction **11** with enamide **6** (R = Ph) the stereochemistry is determined through **53**, where it is the C6 methylene group that effectively blocks the back face of the pentadienyl cation. Comparison of the structures of **53** and **15c** (Scheme 1) reveals that in **53** the C6 methylene group is analogous to the C4 OTBS group in **15**. This explains why our early efforts to improve levels of asymmetry transfer from camphor derived chiral auxiliaries all failed: we had explored analogs of **11** that were substituted either at C4 or at C1.[28] None of these chiral auxiliaries were any better than **11**. Modification of C6 in **11** so as to prepare an improved chiral auxiliary is not straightforward. In the conformationally locked α-pyranose-derived chiral auxiliaries in which ring inversion is prevented from taking place, it is the axial C3 substituent that exerts the dominant effect in controlling the sense of conrotation. This can be seen in **42**.

Two improved chiral auxiliaries, **29** and **41** that lead to each enantiomeric series of cyclopentenones, were designed on the basis of our understanding of the stereochemistry-determining process. It is especially noteworthy that cyclopentenones incorporating a quaternary ring carbon can be prepared in high er.



This model may oversimplify the various interactions that occur in the electrocyclization transition state, but it provides a consistent rationale for the results seen with the chiral auxiliaries prepared to date. Moreover, it has allowed us to make a number of successful predictions concerning substituent effects and the role of the pyran ring oxygen atom. On the basis of these predictions, we have confirmed the role of the pyran ring oxygen atom, identified the key substituents that control the direction of conrotation and have optimized the reaction conditions. Our mechanistic hypothesis can now be used to design optimal chiral auxiliaries should further improvements in the reaction be needed.

Experimental Section

General Procedure for Nazarov Cyclization. Lithium chloride (16 mg, 0.377 mmol) was added to a 10 mL round-bottom flask equipped with a small stir bar and was flame-dried under vacuum. (*E*)-2-Methyl-1-morpholino-3-phenylprop-2-en-1-one **6** (60 mg, 0.259 mmol) and allene **29** (53 mg, 0.128 mmol) were added into separate 5 mL round-bottom flasks then were individually dried by azeotropic distillation of toluene and purged with nitrogen (3x). Allene **29** was dissolved into 2 mL of THF, dried over 4 Å MS, and the solution was transferred *via* cannula into the 10 mL flask containing the 16 mg of LiCl. A small crystal of 1,10-phenanthroline was added and the solution was cooled to −78 °C. Residual water in the solution of allene was quenched using *n*-BuLi (1.62 M in hexanes), turning the mixture from a lemon-yellow color to the end point, a dark brown color. The brownish mixture was then treated with *n*-BuLi (160 μL, 0.259 mmol, 1.62 M in hexanes) and was stirred at −78 °C for 45 min. The solution of enamide **6** (Ar = Ph) in 2 mL of THF was dried over 4 Å MS, cooled to −78 °C and was transferred at a rate of one drop per 3 s to the solution of lithioallene *via* cannula. The mixture was maintained at −78 °C for 2 h and was transferred rapidly *via* cannula to a solution of 20 mL anhydrous CH_2Cl_2 and 220 μL of AcOH (3.90 mmol) at −78 °C. After being stirred for 5 min at −78 °C, the mixture was poured into 20 mL of a 1:1 two-phase solution of saturated aqueous $NaHCO_3$:CH_2Cl_2 and the mixture was gradually warmed to 0 °C. Under the mildly acidic conditions of the quench, no loss of the oxygen protecting groups of the auxiliary took place, allowing the auxiliary to be easily recovered during the purification of the product by flash column chromatography. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layers were extracted with brine, dried over $MgSO_4$, and concentrated.

2-Hydroxy-3-methyl-5-methylene-4-phenylcyclopent-2-enone 8:[14] R_f = 0.23 (20% EtOAc in hexanes). Purification via flash column chromatography on silica gel (20% EtOAc in hexanes) provided cyclopentenone **8** (33 mg, 0.166 mmol, 69% yield, 97/3 er via allene **29**; 44 mg, 0.222 mmol, 92% yield, 3.5/96.5 er via allene **41**); chiral HPLC (2% 2-propanol in hexanes, Chiralcel OD-H column (0.46 cm × 25 cm), 254 nm, 0.75 mL/min) t_R = 11.2, t_R = 12.7 min.

2-Hydroxy-5-methylene-3,4-diphenylcyclopent-2-enone 48:[14] R_f = 0.23 (20% EtOAc in hexanes). Purification *via* flash column

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(28) Forest, J. S. M.S. Thesis; University of Hawaii, Honolulu, HI, 2003.

chromatography on silica gel (20% EtOAc in hexanes) provided cyclopentenone **48** (37 mg, 0.142 mmol, 59% yield, 95/5 er via allene **29**; 36 mg, 0.137 mmol, 57% yield, 4/96 er via allene **41**); chiral HPLC (10% 2-propanol in hexanes (0.05% trifluoroacetic acid in mobile phase), Chiralcel OD-H column (0.46 cm × 25 cm), 254 nm, 0.80 mL/min) $t_R = 8.8$, $t_R = 9.7$ min.

3-Hydroxy-1-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one 49:[14] $R_f = 0.20$ (20% EtOAc in hexanes); Purification *via* flash column chromatography on silica gel (20% EtOAc in hexanes) provided cyclopentenone **49** (36 mg, 0.217 mmol, 90% yield, 97/3 er via allene **29**; 37 mg, 0.224 mmol, 93% yield, 7/93 er via allene **41**); chiral HPLC (5% 2-propanol in hexanes, Chiralcel OD column (0.46 cm × 25 cm), 254 nm, 0.80 mL/min) $t_R = 8.0$, $t_R = 10.9$ min.

***tert*-Butyl-7-hydroxy-5-methylene-6-oxo-4,4a,5,6-tetrahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*)-carboxylate 50.** (See the Supporting Information for the ^{1}H NMR spectrum of **50**.) $R_f = 0.28$ (25% EtOAc in hexanes). Purification via flash column chromatography on silica gel (20% EtOAc in hexanes) provided cyclopentenone **50** (19 mg, 0.070 mmol, 29% yield, 93/7 er via allene **29**; 38 mg, 0.142 mmol, 59% yield, 5/95 er via allene **41**); chiral HPLC (10% 2-propanol in hexanes, Chiralcel OD-H column (0.46 cm × 25 cm), 254 nm, 1.00 mL/min) $t_R = 6.2$, $t_R = 7.5$ min.

2-Hydroxy-3-(2-hydroxyethyl)-5-methylene-4-(2-(triisopropylsilyloxy)ethyl)cyclopent-2-enone 51:[27] $R_f = 0.27$ (50% EtOAc in hexanes). Purification via flash column chromatography on silica gel (5−60% EtOAc in hexanes) provided cyclopentenone **51** (49 mg, 0.137 mmol, 57% yield, 93/7 er via allene **29**; 71 mg, 0.200 mmol, 83% yield, 9/91 er via allene **41**); chiral HPLC (3% 2-propanol in hexanes, Chiralcel OD-H column (0.46 cm × 25 cm), 254 nm, 1.00 mL/min) $t_R = 14.1$, $t_R = 16.5$ min.

2-Hydroxy-3,4-dimethyl-5-methylene-4-phenylcyclopent-2-enone 52:[14] $R_f = 0.23$ (100% CH_2Cl_2). Purification via flash column chromatography on silica gel (30% EtOAc in hexanes) provided cyclopentenone **52** (28 mg, 0.130 mmol, 54% yield, 89/11 er via allene **29**; 40 mg, 0.188 mmol, 78% yield, 5/95 er via allene **41**); chiral HPLC (5% 2-propanol in hexanes, Chiralcel OD column (0.46 cm × 25 cm), 254 nm, 1.00 mL/min) $t_R = 10.6$, $t_R = 13.9$ min.

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Supporting Information Available: General methods and experimental procedures for the preparation of **33**−**36**, **12**, **26**−**30**, and **37**−**41** and of all intermediates leading to **26**−**30** and **37**−**41**. Reproductions of ^{1}H and ^{13}C NMR data of **33**−**36**, **12**, **26**−**30**, and **37**−**41** and of the intermediates leading to them. Reproduction of ^{1}H NMR spectra of **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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