Total Synthesis of (±)-Dihydrokawain-5-ol. Regioselective Monoprotection of Vicinal *Syn*-Diols Derived from the Iodocyclofunctionalization of α-Allenic Alcohols

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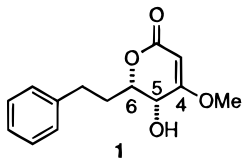
The synthesis of (±)-dihydrokawain-5-ol (**1**) from the vinyl iodo *syn*-vicinal diol **7a** is described. This diol was prepared in a highly diastereoselective fashion via the iodocyclofunctionaliztion reaction of the *N*-tosyl carbamate derivative of the corresponding α-allenic alcohol (**6a**). A key to the synthesis of **1** involved the differentiation of the alcohol groups of the diol moiety in **7a**. Application of Yamamoto's monoprotection protocol for the introduction of MOM ethers in vicinal diols provided **8a** in a highly regioselective fashion (**8a**:**9a** > 30:1) from **7a**. This regioselective monoprotection was found to be general for vinyl iodo and acetylenic vicinal diols **7** and **10**, placing the MOM protecting group on the homoallylic and homopropargylic alcohol of the diol moieties, respectively. Alternatively, a highly regioselective (11.5:1) monosilylation of the homoallylic alcohol in **7a** followed by etherification (MOM) of the allylic alcohol provided the differentially protected diol **25**. Further manipulation of the vinyl iodide function in **25** (dehydroiodination, carbonylation) followed by desilylation generated the γ-alkoxy-δ-hydroxy-α,β-acetylenic ester **28**. Cyclization of **28** produced the unique 4,5-dialkoxypyran-2-one moiety present in (±)-**1**. This latter transformation involved the interesting acid-catalyzed and thermodynamically driven isomerization of the intermediate β-alkoxy-α,β-unsaturated ester (*Z*)-**29** to the corresponding *E*-isomer.

Introduction

(+)-Dihydrokawain-5-ol (**1**), a unique 6-alkyl-5-hydroxy-5,6-dihydropyran-2-one, was isolated in 1970 from the methanol extracts of the kava plant (*Piper Methysticum* Forst.), a Polynesian shrub of the pepper family.[1] Extracts of the roots and stem of this plant are utilized in folk medicine and in the preparation of a traditional ceremonial beverage.[2] The dihydropyran-2-one moiety is a frequently encountered substructure in natural products.[3] Oxygen substitution at *either* the C4 or C5 position is fairly common, as exemplified by (+)-kawain (**2**)[4] and (+)-asperlin (**3**),[5] respectively. However, the oxygenation pattern in **1** is, as far as we are aware, unknown in any other dihydropyranone-containing natural product except for a more highly oxygenated member of the same family (**4**).[6] Moreover, the presence of the C5 hydroxyl in **1** renders the molecule susceptible to rearrangement as illustrated by the facile conversion of **1**, under basic conditions (KOH−MeOH), to the corresponding furanone **5**.[7] These unique structural features, including the presence of oxygen substituents at both the C4 and C5 positions on the pyranone scaffold, and the *threo* relationship between the oxygens that comprise the diol moiety at C5/C6, make **1** an attractive and challenging synthetic target.[8]



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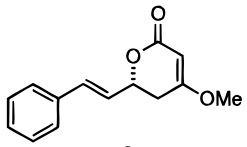

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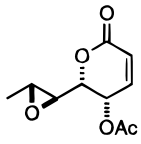

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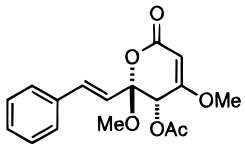

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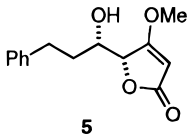

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We have been interested in the synthesis of natural products using our recently described method for the highly diastereoselective conversion of the *N*-tosyl carbamate derivatives of secondary α-allenic alcohols **6** into vinyl iodo *syn*-vicinal diols **7** (eq 1).[9−11] This procedure involves initial treatment of the allene *O*-carbamate with I_2 to produce an intermediate diiodo carbamate[11] which

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) Achenbach, H.; Wittman, G. *Tetrahedron Lett.* **1970**, 3259.

(2) The kava plant is a Polynesian shrub of the pepper family. Extracts of its roots and stem are utilized in folk medicine and in the preparation of a traditional ceremonial beverage. Köppel, C.; Tenczer, J. *J. Chromatogr.* **1991**, *562*, 207.

(3) Dickinson, J. M. *Nat. Prod. Rep.* **1993**, 88.

(4) Hänsel, R.; Beiersdorf, H. U. *Arzneim.-Forsch.* **1959**, *9*, 581. Kawain (**2**), one of the principal compounds isolated from the kava shrub is marketed in racemic form (Neuronika (Klinge Pharma, Munich)) because of its anxiolytic and analgesic properties.[2]

(5) Argoudelis, A. D.; Zieserl, J. F. *Tetrahedron Lett.* **1966**, 1969.

(6) Hänsel, R.; Pelter, A.; Schulz, J.; Hille, C. *Chem. Ber.* **1976**, *109*, 1617.

(7) Hänsel, R.; Schulz, J.; Pelter, A.; Ayoub, M. T.; Reinhardt, R. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1978**, *33B*, 1020 (*Chem. Abstr. 90*, 22705u).

(8) Two identical syntheses of **1** have been described involving nonstereoselective allylic oxidation (SeO_2) and hydrogenation of kawain (**2**). (a) Achenbach, H.; Huth, H. *Tetrahedron Lett.* **1974**, 119. (b) Hänsel, R.; Schulz, J. *Chem. Ber.* **1973**, *106*, 570.

(9) Friesen, R. W.; Bissada, S. *Tetrahedron Lett.* **1994**, *35*, 5615.

(10) (a) Friesen, R. W.; Giroux, A. *Tetrahedron Lett.* **1993**, *34*, 119. (b) Friesen, R. W.; Giroux, A. *Can. J. Chem.* **1994**, *72*, 1857.

(11) Friesen, R. W.; Bayly, C. I.; Fogg, J. A. *J. Org. Chem.* **1995**, *60*, 448.

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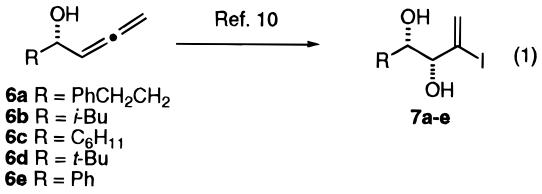


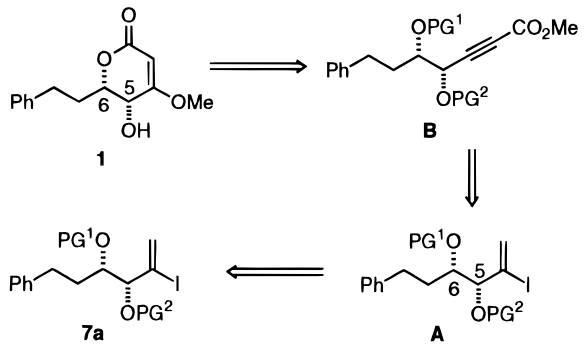
undergoes cyclization upon exposure to Ag_2CO_3.[9,10] We felt that the implementation of this iodocyclofunctionalization strategy would allow us to address the structurally interesting features in **1** (Scheme 1). Most importantly, the relative stereochemistry between the C5 and C6 hydroxy and alkoxy moieties in **1** would be readily established upon conversion of allenic alcohol **6a** to diol **7a**. The vinyl iodide moiety would serve as a synthetic precursor for subsequent transformation to the α,β-acetylenic ester **B** via a dehydroiodination−carbonylation sequence. Several methods have been described for the conversion of such unsaturated esters into 4-alkoxydihydropyran-2-ones as required for the synthesis of **1**.[12,13] Finally, because of the aforementioned base lability of **1**, it was imperative that the protecting group chosen for the C5 hydroxyl would be removable under acidic or neutral conditions in the final step of the synthesis. In keeping with this plan, we felt that the optimum choices for PG^1 and PG^2 would be a silyl ether and an acetal protecting group (MOM, THP), respectively. Therefore, another key feature of the synthesis would be the preparation of **A** by the initial regioselective introduction of either of these groups onto the requisite hydroxyl of the diol moiety in the *syn*-vicinal diol **7a**. We felt that the difference in the electronic and steric environment surrounding each alcohol in the vicinal diol, due to the presence of the vinyl iodide moiety, would enable us to readily differentiate the two alcohol groups and introduce protecting groups in a sequential and regioselective fashion.

In this paper we describe the general and highly regioselective introduction of the MOM protecting group onto vicinal diols **7** and their acetylene derivatives **10**. In addition, the regioselective silylation (TBDMS) of the diols **7** is reported, as well as the application of this protecting group strategy in the synthesis of the novel dihydropyran-2-one (±)-dihydrokawain-5-ol (**1**).

Results and Discussion

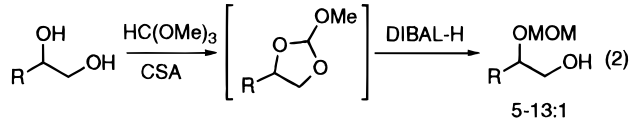
The regioselective monoprotection of polyhydroxylated compounds is of continuing interest in organic synthesis.[14] Regioselectivity is readily achieved when the alcohol moieties are in drastically different electronic or steric environments, such as the selective protection of a primary alcohol in the presence of a secondary alcohol.[15] Other examples include the regioselective silylation reactions of nucleosides[16] and carbohydrates[17] for which

Scheme 1



synthetic protocols are well established. The regioselective monoprotection of acyclic vicinal diols in which both alcohols are secondary alcohols is less straightforward and more challenging. Typical strategies involve the utilization of neighboring functionality, such as an ester,[18] to protect one of the alcohols intramolecularly while directing a second reagent to the remaining alcohol moiety. Alternatively, the presence of functional groups immediately adjacent to the diol moiety can result in a differential reactivity of the hydroxyls such that a selective monoprotection strategy is possible. Recent studies have described, for example, the regioselective sulfonylation of *threo*-2,3-dihydroxy esters[19] and the monosilylation of 2,3-dihydroxyphosphonates.[20] There are a few reports of the regioselective introduction of an acetal protecting group, such as MOM or THP, in a polyhydroxylated substrate.[15,21]

Regioselective Introduction of the MOM Protecting Group. As described above, the synthetic plan called for the differentiation of the alcohols in **7a** and for the installation of an acid labile protecting group on the allylic alcohol (PG^2). Yamamoto has described a procedure for introducing a MOM group onto the more sterically hindered alcohol of a vicinal diol (secondary vs primary alcohol) via the regioselective (5−13:1) reductive cleavage (DIBAL, CH_2Cl_2, −78 to 0 °C) of the intermediate orthoester prepared in situ from the diol and trimethyl orthoformate (eq 2).[21a] By analogy, it was anticipated that application of this procedure to the vicinal



diol **7a** might lead to the the desired monoprotected diol **9a** since the allylic alcohol adjacent to the vinyl iodide function appeared to be the more sterically encumbered alcohol (eq 3). Surprisingly, exposure of diol **7a** to this one-pot reaction sequence led *solely* to the protected diol **8a** (**8a**:**9a** > 30:1; 88% isolated yield) in which the MOM

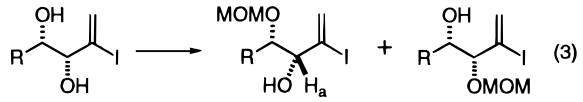
(12) Henbest, H.; Jones, E. R. *J. Chem. Soc.* **1950**, 3628.
(13) (a) Carlson, R. M.; Oyler, A. R. *Tetrahedron Lett.* **1974**, 2615. (b) Carlson, R. M.; Oyler, A. R.; Peterson, J. R. *J. Org. Chem.* **1975**, *40*, 1610.
(14) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 68−87, 137−140.
(15) For example, see: (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791. (b) Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469. (c) Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532.
(16) (a) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; McGee, D. P. C. *Tetrahedron Lett.* **1982**, *23*, 1997. (b) Ogilvie, K. K.; McGee, D. P. C.; Boisvert, S. M.; Hakimelahi, G. H.; Proba, Z. A. *Can. J. Chem.* **1983**, *61*, 1204.
(17) For example, see: Bhatt, R. K.; Chauhan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050.
(18) (a) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.; Zhang, X.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411. (b) Walsh, P. J.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5545.
(19) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
(20) Yokomatsu, T.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Synlett* **1995**, 847.
(21) (a) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947. (b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.
(22) The vinyl iodo *syn*-diols **7a**−**e** were prepared from the α-allenic alcohols **6a**−**e** using our previously reported iodocyclofunctionalization procedure (eq 1).[10]

Table 1. Monoprotection (MOM) of *Syn*-Vicinal Diols 7 and 10

entry	substrate (R)	**18**[a]	ratio **8**:**9** or **11**:**12**	yield **8** or **11** (%)[b]
1	**7a** $PhCH_2CH_2$	1.6:1	>30:1[c]	**8a** 88
2	**7b** *i*-Bu	1.8:1	>30:1	**8b** 90
3	**7c** C_6H_{11}	1.3:1	>30:1	**8c** 87[d]
4	**7d** *t*-Bu	1.4:1	>30:1	**8d** 10 (67)[e]
5	**7e** Ph	1.6:1	83:17	**8e/9e** 90[f]
6	**10a** $PhCH_2CH_2$	1.3:1	>30:1	**11a** 88
7	**10b** *i*-Bu	1.2:1	>30:1	**11b** 92
8	**10c** C_6H_{11}	1.3:1	>30:1	**11c** 96
9	**10d** *t*-Bu	1.6:1	>30:1	**11d**40[g]
10	**10e** Ph	1.1:1	85:15	**11e/12e** 93[h]

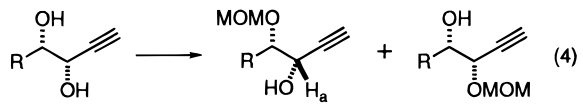
[a] Ratio of diastereomers of unidentified relative stereochemistry measured from the integrated ^{1}H NMR spectrum of the crude reaction mixture. [b] Yields of pure isolated isomers. [c] For ratios reported as >30:1, the minor isomer could not be observed in the ^{1}H NMR spectrum. [d] Although the acetal **13c** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (**8c**:**13c** ~15:1), its volatility and/or instability precluded its isolation. [e] Value in brackets refers to isolated yield of the acetal **13d**. [f] Yield of combined, inseparable isomers. [g] Although the acetal **14d** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, its high volatility precluded the accurate measurement of the ratio of **11d**:**14d** or its isolation. [h] Yield of combined isomers. A small sample of **11e** was isolated for characterization.

moiety had been introduced onto the homoallylic alcohol (eq 3, Table 1, entry 1).



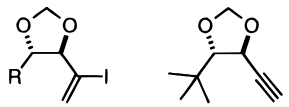
7a-e **8a-e** **9a-e**

The degree of regioselectivity observed in this example was sufficiently interesting that we wanted to explore the scope of this monoprotection protocol. Thus, the vinyl iodo *syn*-diols **7b**−**e**[22] and the acetylenic *syn*-diols **10a**−**e** were prepared in order to explore the effects of (1) the nature of the R group (R = primary to tertiary alkyl, phenyl) and (2) the type of unsaturation (vinyl iodide or alkyne) on the reaction regioselectivity. The acetylenic diols **10** were readily obtained by dehydroiodination ($NaN(TMS)_2$) of the vinyl iodide moiety, either on the parent diol or one of several readily available derivatives.[23] Each diol was then subjected to the standard Yamamoto monoprotection protocol.[20a] As can be seen from the results presented in Table 1 (entries 2−10), the reaction is extremely regioselective for both vinyl iodo and acetylenic *syn*-diols, resulting in the preferential formation of MOM ethers **8** and **11** by the introduction of the MOM moiety on the homoallylic and homopropargylic alcohols, respectively (eqs 3 and 4). Except for



10a-e **11a-e** **12a-e**

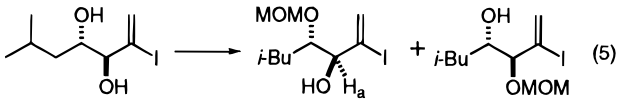
two examples involving the monoprotection of diols **7e** and **10e** (R = Ph, Table 1, entries 5 and 10), there was no evidence (^{1}H NMR spectra) in any of the crude reaction mixtures for the formation of the alternative regioisomers **9** or **12** (>30:1 regioselectivity). It is noteworthy that the R group in these two examples is an unsaturated moiety (R = Ph) whereas the other examples all have an alkyl substituent at this site. In three examples containing sterically bulky R groups (**7c** R = c-hex and **7d/10d** R = *t*-Bu; Table 1, entries 3, 4, and 9), a cyclic acetal (**13c/d** and **14d**) is also observed.[24]



13c R = C_6H_{11}
13d R = *t*-Bu

14d

Interestingly, the *anti*-vicinal diol **15**[25] also provided the MOM ether **16** as the sole regioisomer (>30:1, 94% isolated yield) when subjected to the Yamamoto reaction conditions (eq 5). Although additional experiments are warranted, it appears that the relative stereochemistry



15 **16** **17**

between the alcohol moieties also has little effect upon the reaction regioselectivity.

The regioisomers in each series were readily assigned to the structures indicated on the basis of their ^{1}H NMR spectra. Thus, in isomers **8**, **11**, and **16**, the methine proton H_a adjacent to the site of unsaturation couples to both the hydroxyl proton and either the vinylic or acetylenic proton.

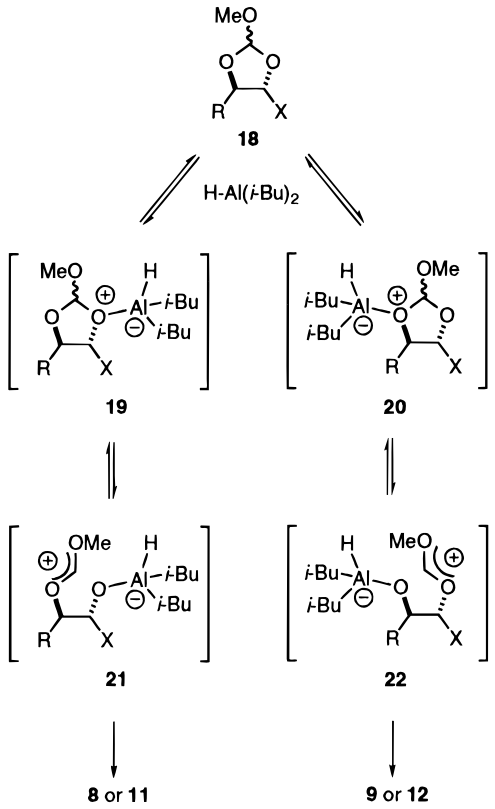
Although this monoprotection reaction is not useful in the context of the synthesis of dihydrokawain-5-ol (**1**) as outlined above, the mechanistic basis for the regioselectivity that is observed is still intriguing. The mechanism of the DIBAL-H-mediated reduction has been proposed to proceed via the initial and potentially reversible coordination of the oxophilic aluminum atom to the orthoester **18** (X = vinyl iodide or acetylene), in this case forming species such as **19** or **20**.[20,26] Cleavage of the orthoester with participation of the remaining oxygen atoms provides the ring opened oxonium ions **21** and **22.** However, inter- or intramolecular transfer of hydride could take place from either **19**/**20** or **21**/**22** to produce the MOM-monoprotected diols. If the reduction takes place directly from **19**/**20**, one might expect that the regiochemical outcome of the reaction would be affected by the configuration of the OMe moiety relative to the R and X groups. The crude reaction mixtures containing the orthoester **18** were isolated prior to reduction with DIBAL-H, and inspection of the resulting ^{1}H NMR spectra indicated the presence of mixtures of diastereomers, with ratios ranging from 1.1:1 to 1.6:1 (unidentified

(23) Diol **10a** was prepared in two steps ($NaN(TMS)_2$; TBAF) from the TBDMS diol **23a**. Diols **10b** and **10c** were prepared directly from the diols **7b** and **7c**, respectively. Diols **10d** and **10e** were prepared via the acetonide derivatives of diols **7d** and **7e**, respectively. See the Experimental Section for details.

(24) Although the acetals **13c** (**8c**:**13c** ~15:1) and **14d** were observed in the ^{1}H NMR spectra of the crude reaction mixtures, their volatility and/or instability precluded their isolation.

(25) Anti diol **15** was prepared from **8b** via an unoptimized three-step sequence involving (1) Mitsunobu inversion, (2) hydrolysis, and (3) deprotection. See Experimental Section for details.

(26) The regioselective reductive cleavage of benzylidene acetals and other related systems has also been explained by a mechanism in which C−O bond cleavage takes place at the site of metal complexation. See, for example: (a) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. (b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (c) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans 1* **1984**, 2371. (d) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613. (e) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033.



relative stereochemistry, see Table 1).[27] Thus, it appears that the configuration of the OMe moiety relative to R and X in **18** has little bearing on the regiochemical outcome of the reduction process as would be expected if cleavage of the orthoester preceded the rate-determining reduction step. Moreover, the site of unsaturation must play a key role in the reaction regioselectivity. Support for this hypothesis is seen in the reaction of diols **7e** and **10e** in which the alcohols are each flanked by unsaturated substituents, a phenyl group and either a vinyl iodide or acetylene moiety, respectively. In these examples, both MOM regioisomers are formed (Table 1, entries 5 and 10). Although suggestive, further study is required to clarify the mechanistic details regarding the manner in which the site of unsaturation dictates the regioselective reduction of the intermediate orthoester **18**.[28] Nonetheless, this potentially useful regioselective transformation should find other applications since enantiomerically enriched acetylenic diols such as **10** are readily available using Sharpless dihydroxylation technology on the corresponding enynes.[29]

(27) We have had limited success in reducing these orthoesters after workup and isolation. In most cases, these reductions are extremely messy compared to the reduction of the orthoesters prepared in situ and used without isolation. These observations are most likely due to the instability of the labile orthoester moiety as noted by Yamamoto.[21a]

(28) One possibility is that the regiochemical outcome is a reflection of the relative stabilites of the intermediates **21** and **22**. The intermediate **22** would be expected to be destabilized relative to **21** due to the requirement for forming an oxomium ion with the already electron deficient allylic (or propargylic) oxygen. As a result, reduction of **21** may be more facile than that of **22**. In addition, the predominant formation of the acetals **13d** and **14d** (R = *t*-Bu) in the reduction of the orthoesters derived from diols **7d** and **10d** could be explained by complexation of DIBAL-H to the OMe oxygen atom of the orthoester **18** rather than the oxygen atoms of the five-membered ring as in **19** or **20**. This alternative pathway would be favored in these latter examples since the increased steric bulk of the *tert*-butyl group would make complexation to the oxygen atoms of the five-membered ring in orthoester **18** less facile than when R is a sterically less demanding substituent.

(29) (a) Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

Table 2. Monosilylation of *Syn*-Vicinal Diol 7a

entry	base, solvent, temperature[a]	ratio **23a:24a**[b]	yield (%)[c]
1	imidazole, DMF, rt[d]	1.2:1	87
2	pyridine, $AgNO_3$, THF, rt[d]	1.2:1	73
3	DBU, CH_2Cl_2, −78 °C	1:2.6	98
4	Et_3N, CH_2Cl_2, −78 °C	1:1.3	92
5	pyridine, CH_2Cl_2, −78 to 0 °C	1.2:1	71
6	DBMP,[e] CH_2Cl_2, −78 °C	1.3:1	55
7	2,6-lutidine, CH_2Cl_2, −78 °C	2:1	98
8	*i*-Pr_2NEt, CH_2Cl_2, −78 °C	4.5:1	90
9	*i*-Pr_2NEt, CH_2Cl_2, 0 °C	3.5:1	96
10	2,6-lutidine, DMF, 0 °C	8.5:1	90
11	*i*-Pr_2NEt, DMF, rt	9.5:1	96
12	*i*-Pr_2NEt, DMF, 0 °C	9.5:1	92
13	*i*-Pr_2NEt, DMF, −45 °C	11.5:1	93 (89)[f]

[a] In general, [substrate] approximately 100 mg/mL, 2.5 equiv of base, 1.5−2.5 equiv of TBDMSOTf. [b] Measured from the integrated ^1H NMR spectrum of the crude reaction mixture. [c] Purified combined yield of **23a/24a**. [d] Reaction carried out with TBDMSCl. [e] DBMP = 2,6-di-*tert*-butyl-4-methylpyridine. [f] Yield in brackets refers to isolated yield of pure **23a**. For detailed reaction conditions, see Experimental Section.

Regioselective Monosilylation. The alternative strategy for differentiating the alcohols in **7a** called for the initial introduction of PG^1 (SiR_3) on the homoallylic alcohol of **7a**, followed by the installation of PG^2 (MOM) on the allylic alcohol. A representative sampling of our results in attempting the regioselective monosilylation of vinyl iodo *syn*-diol **7a** (eq 6) is found in Table 2.

(6)

Typical silylating conditions[14] using TBDMSCl and imidazole in DMF, or reaction conditions that prove to be very effective in differentiating the C2 and C3 secondary alcohols of nucleosides (TBDMSCl, pyridine and $AgNO_3$),[16] were nonregioselective (Table 2, entries 1 and 2). However, more interesting results were obtained upon treatment of diol **7a** with TBDMSOTf under a variety of reaction conditions. The isomeric, and readily separable, monosilylated diols **23a** and **24a** were obtained in the ratios and combined yields indicated in Table 2, entries 3−13. It is clear from these results that base, solvent and temperature all have an effect on the observed regioselectivity. When the reaction was conducted in CH_2Cl_2 at −78 °C, the regioselectivity of silylation was strongly influenced by the base (Table 2, entries 3−8). Silyl ether **24a** was formed preferentially using DBU and Et_3N, but the desired silyl ether **23a** was obtained in moderate regioselectivity using both 2,6-lutidine and *i*-Pr_2NEt. These latter observations encouraged us to explore the effect of temperature and solvent using these two bases (Table 2, entries 9−13). While the temperature effect was relatively small (for example, compare entries 8 and 9), a more significant effect was brought about by changing the solvent. Using *i*-Pr_2NEt, the regioselectivity in favor of **23a** increased from 4.5:1 in CH_2Cl_2 to 11.5:1 in DMF (Table 2, entries 8, 13). Somewhat surprisingly, the formation of disilylated compounds was not observed (<5%) under any of the reaction conditions, suggesting that the reactivity of the remaining unprotected alcohol in either **23a** or **24a** is being attenuated by either the bulky vinyl iodide moiety (in the case of **23a**) or the adjacent silyloxy group (in the case of **24a**). Therefore the use of excess silylating

Table 3. Monosilylation of *Syn*-Vicinal Diols 7c−e[a]

entry	substrate R	ratio **23:24**[b]	yield (%)[c]	
1	**7c** c-hex	1.8:1	**23c** 65,	**24c** 34
2	**7d** *t*-Bu	1:4.6	**23d** 15,	**24d** 60
3	**7e** Ph	9.5:1	**23e** 82,	**24e** 9

[a] These reactions were carried out under the conditions described in Table 2, entry 13. [b] Measured from the integrated ^{1}H NMR spectrum of the crude reaction mixture. [c] Yields of pure regioisomers.

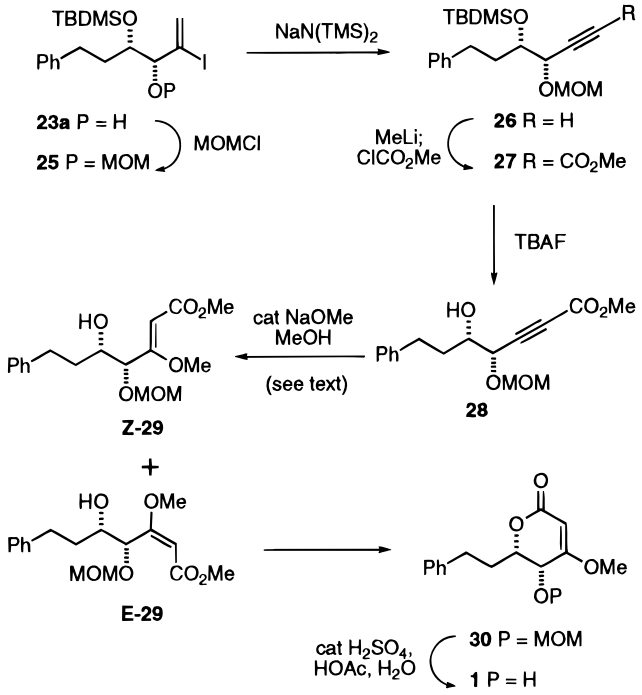
reagent was not problematic and enabled us to achieve essentially complete conversion of **7a** to monosilylated products. Thus, the silylation of **7a** under the optimized conditions indicated in Table 2, entry 13, takes place with excellent regioselectivity (11.5:1) on the homoallylic alcohol group to afford **23a** in 89% isolated yield.

It should be noted that the TBDMS groups in **23a** and **24a** are not prone to undergo 1,2-O,O migration[30] with the reaction conditions that are employed. Exposure of each to 2.5 equiv of *i*-Pr_2NEt in CH_2Cl_2 or DMF at room temperature for 24 h led to undetectable amounts of the alternative regioisomer. Therefore, the reactions summarized in Table 2 are being conducted under kinetically controlled conditions and reflect the kinetic reactivity of the alcohol groups. The regioselectivity of silylation using alternative bulky silylating reagents such as TIPSCl, TIPSOTf, TBDPSCl, and TESCl was also explored in this reaction but with much less success. The site of silylation in **23a** and **24a** was readily determined from inspection of their ^{1}H NMR spectra and homonuclear decoupling experiments. For example, the allylic methine proton H_a in **23a** is coupled to both the hydroxyl proton and the vinylic protons. In contrast, the homoallylic methine proton H_b in **24a** is coupled to the hydroxyl proton while the allylic methine proton H_c is coupled to one of the vinylic protons.

If the sole determinant in the regioselective silylation of **7a** is related to the relative steric bulk of the vinyl iodide moiety with respect to the R group, then changing the nature of the R group (primary to tertiary) should have an observable effect on the outcome. We have explored this issue using the vinyl iodo vicinal *syn*-diols **7c,d** (eq 6). Silylations were conducted under the optimized reaction conditions found for *syn*-diol **7a** (Table 2, entry 13). As summarized in Table 3, the reaction regioselectivity is indeed affected by the steric bulk of the R group. As the steric size of R increases, the regioselectivity in favor of isomer **23** changes until, using diol **7d** (R = *t*-Bu), the alternative regioisomer **24d** predominates. From these observations, it appears that the regioselectivity of *tert*-butyldimethylsilylation (using TBDMSOTf) of vinyl iodo *syn*-vicinal diols **7** bearing alkyl R groups is significantly influenced by the steric bulk of this moiety. However, monosilylation of diol **7e** (R = Ph) again favors isomer **23** (Table 3, entry 3). In this latter example, an electronic component to the regioselectivity cannot be ruled out. Thus, the regioselective monosilylation of vinyl iodo *syn*-vicinal diols **7** can be a useful synthetic process when R is a primary alkyl (**7a**) or phenyl (**7e**) substituent.

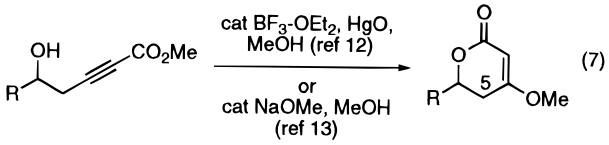
Synthesis of (±)-Dihydrokawain-5-ol. The monosilylated diol **23a** was surprisingly resistant to reaction with MOM-Cl and ultimately afforded **25** in good yield (89%) only at elevated temperature (85 °C) using *i*-Pr_2NEt as solvent (Scheme 2). Fortunately, the potentially

Scheme 2



problematic migration of the TBDMS group to the adjacent oxyen atom[30] was not observed under these more forcing basic reaction conditions. Dehydrohalogenation of **25** was readily effected using $NaN(TMS)_2$ in DMF[10a] to provide the alkyne **26** in 94% yield. Deprotonation of **26** (MeLi, THF) followed by trapping of the resulting lithium acetylide anion with methyl chloroformate gave the α,β-acetylenic ester **27**. Desilylation (TBAF, THF) yielded the hydroxy ester **28** (2 steps, 53%), the key substrate for cyclization to the dihydropyranone.

Two distinct strategies have been described for the formation of 4-alkoxydihydropyran-2-ones from δ-hydroxy-α,β-usaturated esters, employing either acid[12] or base[13] catalysis (eq 7). However, in these reports, the C5 position is invariably unsubstituted and we are not



(7)

aware of any examples in which an alkoxy group is situated at the C5 position as is required for the synthesis of **1**. Treatment of **28** with HgO and BF_3−Et_2O in MeOH, conditions described by Jones and Henbest,[12] resulted in partial cyclization to **30**, but the acidic reaction conditions also brought about competing deprotection of the MOM group. As a result, the final reaction mixture was fairly complex and contained **1** as well as material tentatively identified as the corresponding furanone, the latter presumably being formed by cyclization of the fully deprotected diol. Employing the alternative base-catalyzed protocol of Carlson and Oyler,[13] we exposed **28** to catalytic NaOMe in MeOH to provide a ~2:1 mixture of (*Z*)-**29** (58% isolated yield) and (*E*)-**29**, the latter undergoing lactonization in the reaction mixture to the desired pyranone **30** (33% isolated yield).[31] Using purified (*Z*)-**29**, it was determined that (*Z*)-**29** is not converted to (*E*)-**29** using these reaction conditions while decomposition

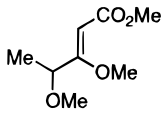
(30) (a) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2763. (b) Mulzer, J.; Scheöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431.

of (*Z*)-**29** occurs under more forcing reaction conditions (up to 2 equiv of NaOMe in refluxing MeOH).

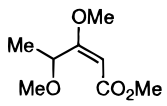
A fortuitous observation was made when it was found that a pure sample of (*Z*)-**29** underwent isomerization to (*E*)-**29** while acquiring a ^{13}C NMR spectrum in $CDCl_3$. It was rationalized that this isomerization was being catalyzed by trace amounts of HCl or DCl in the solvent, resulting in the formation of the apparently thermodynamically more stable olefin (*E*)-**29**. No isomerization takes place when the commercial solvent $CDCl_3$ was treated with solid $NaHCO_3$ immediately prior to dissolution of (*Z*)-**29**, confirming that the isomerization is indeed acid catalyzed.[32] On a preparative scale, the optimum reaction conditions involved simply stirring a solution of (*Z*)-**29** in untreated $CDCl_3$ (Isotech) for 1 h. After this time, a clean conversion of (*Z*)-**29** to (*E*)-**29** was observed by ^1H NMR spectroscopy (>30:1). Characteristic in the monitoring of this isomerization reaction by ^1H NMR is the change in the chemical shift of the allylic methine proton resonance. This resonance shifts from δ 3.85 ppm in the spectrum of (*Z*)-**29** to δ 5.50 ppm in the spectrum of (*E*)-**29** due to the deshielding effect of the ester moiety. After isomerization, the crude reaction mixture was subjected to the original conditions of NaOMe/MeOH in order to effect conversion of (*E*)-**29** to the pyranone **30** (79% overall for the conversion of **28** to **30**).

The relative heats of formation of the model compounds **31** and **32** were calculated[33] in an attempt to rationalize the apparent thermodynamic stability of (*E*)-**29** with respect to (*Z*)-**29**. Indeed, the minimum energy conformation of the E-isomer **32** was found to be at least 4.3 kcal/mol more stable than that of the (*Z*)-isomer **31**. From the calculations, it appears that the major destabilizing force in **31** is an electrostatic interaction between the electronegative methoxy and ester groups that are cis with respect to each other on the olefin bond. This contributor to the overall heat of formation accounts for almost all of the energy differential between the two isomers.[34]

Removal of the MOM protecting group in **30** was accomplished under acidic conditions to provide (±)-dihydrokawain-5-ol (**1**) (90%) as a white solid (mp 121−122 °C) that exhibited spectra (^1H NMR, IR, LRMS) in accord with that reported for (+)-**1**.[1] Most importantly,



31



32

the coupling constant between H5 and H6 was found to be 2.5 Hz (lit.[1] $J_{5,6}$ = 2.3 Hz), confirming the relative stereochemistry between these two substituents.

Summary

The introduction of a MOM protecting group onto vicinal diols **7** and **10** using Yamamoto's procedure is highly selective and proceeds, in a one pot process, through the formation and regioselective DIBAL-H reduction of an intermediate orthoester. This reaction introduces the MOM group preferentially on the homoallylic and homopropargylic alcohols, respectively, regardless of the nature of the R group. The monosilylation (TBDMS) of the diols **7** is much more dependant upon the size of the R group, and useful regioselectivites are obtained only when R = primary alkyl or Ph. The synthesis of (±)-dihydrokawain-5-ol (**1**) has been accomplished from vinyl iodo *syn*-diol **7a** in 28% overall yield. The key steps of the synthesis, involving regioselective monsilylation chemistry and manipulation of the vinyl iodide moiety, exemplify the synthetic utility of these functionalized diols that are derived from α-allenic alcohols.

Experimental Section

General. ^1H NMR spectra were recorded at 300 or 400 MHz in acetone-d_6 or $CDCl_3$ as specified. Broad-band proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. IR spectra were recorded on neat samples unless stated otherwise. Workup procedures involving the drying of organics was done with $MgSO_4$. Flash column chromatography (referred to as chromatography) was performed with 230−400 mesh silica gel, eluting with the solvents indicated (v/v). The vinyl iodo *syn*-diol **7a** has been prepared previously.[10] The vinyl iodo *syn*-diols **7b**−**e** were prepared according to our previously published procedure, and characterization data can be found in the supporting information.[10]

***anti*-3,4-Dihydroxy-6-methyl-2-iodo-1-heptene (15).** To a solution of alcohol **8b** (1.15 g, 3.66 mmol), *p*-nitrobenzoic acid (1.84 g, 3 equiv), and Ph_3P (2.88 g, 3 equiv) in benzene (40 mL) at 0 °C was added di-*tert*-butyl azodicarboxylate (2.53 g, 3 equiv), and the mixture was allowed to warm to rt. After 15 h, another 2 equiv of each reagent was added, and the mixture was stirred a further 15 h. The mixture was diluted with ether and washed with brine, dried, and concentrated. Chromatography (5:2 to 2:1 hexane/ether) provided the Mitsunobu product (610 mg, 36%) which was dissolved in MeOH (10 mL) and treated with solid K_2CO_3 (360 mg, 2 equiv). After 30 min, the solvent was evaporated, the residue was dissolved in ethyl acetate, and 1 N HCl was added. The organics were removed, dried, and concentrated. The residue was dissolved in MeOH (8 mL), treated with $BF_3{-}OEt_2$ (150 μL, 1.1 equiv) and stirred for 24 h at rt. The solvent was evaporated, and the residue was dissolved in ethyl acetate, washed with brine, dried, and concentrated. Chromatography (5:2 hexane/ether) provided the diol **15** (245 mg, 25% for three steps) as a white solid: mp 51−52 °C; IR (KBr) 3400, 1610 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.88 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.7 Hz), 1.37 (m, 2H), 1.87 (m, 1H), 3.45 (d, 1H, J = 6.8 Hz), 3.69 (m, 1H), 3.78 (m, 1H), 4.46 (d, 1H, J = 4.4 Hz), 5.90 (dd, 1H, J = 0.8, 1.3 Hz), 6.47 (t, 1H, J = 1.3 Hz); ^{13}C NMR δ 21.4, 23.8, 24.4, 39.7, 70.8, 80.2, 111.7, 127.4. Anal. Calcd for $C_8H_{15}O_2I$: C, 35.57; H, 5.60. Found: C, 35.80; H, 5.45.

***syn*-3,4-Dihydroxy-6-phenyl-1-hexyne (10a).** To a solution of vinyl iodide **23a** (2.00 g, 4.62 mmol) in DMF (30 mL)

(31) The base-mediated addition of alcohols (ROH) to α,β-acetylenic esters usually provides the Z-isomer as the predominant reaction product under kinetically controlled conditions. (a) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450. (b) Winterfeldt, E.; Preuss, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423. Therefore, it is somewhat surprising that such high conversions of δ-hydroxy-α,β-acetylenic esters to 4-alkoxy-α,β-unsaturated lactones under base catalysis (eq 7) have been reported unless there is a mechanistic pathway available for the isomerization of the preferentially formed Z-isomer (such as (*Z*)-**29**) to the *E*-isomer which is required for lactonization. Obviously, in our case the base-catalyzed *Z* to *E* isomerization is not observed. Therefore, one must conclude that the oxygen substituent at C5 is in some way inhibiting this transformation since no other reported examples include an alkoxy group at the C5 position.

(32) The isomerization of (*Z*)-**29** to (*E*)-**29** was surveyed using a variety of acid catalysts and solvents, including catalytic CSA or HCl in $CHCl_3$, THF, or MeOH. All of these conditions were inferior to those described, resulting either in little isomerization or much more extensive decomposition of the labile functionality (methyl vinyl ether and MOM ether) in the starting material and/or product. Obviously, there is a fine line between the acidic reaction conditions that lead to decomposition and those that result in isomerization.

(33) These calculations were carried out using the recently published Merck Molecular Force Field. We would like to thank Dr. Christopher Bayly for assistance in carrying out these calculations. (a) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 490. (b) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 520. (c) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 553. (d) Halgren, T.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587. (e) Halgren, T. *J. Comput. Chem.* **1996**, *17*, 616.

(34) The thermodynamic stability of related systems (β-amino-α,β-unsaturated esters) has also been described.[30]

at 0 °C was added $NaN(TMS)_2$ (11.6 mL of a 1 M solution in THF, 2.5 equiv) dropwise. After 20 min, water was added and the mixture was extracted with ether. The organics were washed with water and brine and dried. After concentrating, the residue was dissolved in THF (30 mL) and cooled to 0 °C. A solution of TBAF (7 mL in 1 M in THF, 1.5 equiv) was added and after 30 min, water was added. The mixture was extracted with ether, and the organics were washed with brine, dried, and concentrated. Chromatography (1:1 to 1:2 hexane/ether) provided the alkyne diol **10a** (780 mg, 89%) as a colorless oil: IR 3360, 2115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76−1.89 (m, 1H), 1.97−2.08 (m, 1H), 2.47 (d, 1H, J = 2.2 Hz), 2.72 (ddd, 1H, J = 7.0, 9.6, 13.8 Hz), 2.88 (ddd, 1H, J = 5.2, 9.9, 13.8 Hz), 3.35 (br s, 1H), 3.64−3.72 (m, 2H), 4.20 (br d, 1H, J = 6.5 Hz), 7.16−7.32 (m, 5H); ^{13}C NMR δ 31.6, 33.9, 65.9, 74.0, 74.7, 82.2, 125.8, 128.3, 128.4, 141.5. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.24.

***syn*-3,4-Dihydroxy-6-methyl-1-heptyne (10b).** To a solution of diol **7b** (800 mg, 2.96 mmol) in DMF (10 mL) at 0 °C was added $NaN(TMS)_2$ (10.4 mL of a 1M solution in THF, 3.5 equiv) dropwise. After 20 min, water was added and the mixture was extracted with ether. The organics were washed with water and brine, dried, and concentrated. Chromatography (1:1 hexane/ether) provided the alkyne diol **10b** (225 mg, 53%) as a volatile, colorless oil: IR 3350, 2120 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.91 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 1.35−1.50 (m, 2H), 1.87 (m, 1H), 2.84 (d, 1H, J = 2.2 Hz), 3.60 (m, 1H), 3.74 (br d, 1H, J = 4.6 Hz), 4.07 (m, 1H), 4.43 (br d, 1H, J = 5.5 Hz); ^{13}C NMR δ 21.6, 23.6, 24.4, 41.3, 66.3, 73.0, 74.4, 82.5. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.81; H, 10.04.

***syn*-3,4-Dihydroxy-4-cyclohexyl-1-butyne (10c).** Following the procedure described for the conversion of **7b** to **10b**, diol **7c** (750 mg, 2.53 mmol) was converted to alkyne diol **10c** (216 mg, 51%), a white solid: mp 74.8−75.4 °C; IR (KBr) 3350, 3280, 2120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05−1.31 (m, 5H), 1.60−1.80 (m, 6H), 2.47 (d, 1H, J = 2.2 Hz), 2.70 (br s, 1H), 3.06 (br s, 1H), 3.39 (br s, 1H), 4.34 (br s, 1H); ^{13}C NMR δ 25.9, 26.15, 26.24, 27.3, 29.7, 39.1, 63.5, 74.3, 78.7, 82.9. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.46.

***syn*-3,4-Dihydroxy-5,5-dimethyl-1-hexyne (10d).** A solution of diol **7d** (1.0 g, 3.7 mmol), 2-methoxypropene (1.3 mL, 3.5 equiv), and catalytic CSA in DMF (3 mL) was stirred for 30 min. The solution was cooled to 0 °C, and $NaN(TMS)_2$ (4.4 mL of a 1 M solution in THF, 1.2 equiv) was added dropwise. After 45 min, water was added and the mixture was extracted with ether. The organics were washed with water and brine, dried, and concentrated. The residual oil was passed through a plug of silica, eluting with 3% ether in hexane, and the partially purified acetonide alkyne was redissolved in MeOH (15 mL) and 6 N HCl (3 mL). After stirring at 65 °C for 90 min, the solution was cooled to rt and concentrated. The residue was dissolved in ethyl acetate and washed successively with saturated $NaHCO_3$, water, and brine, dried, and concentrated. Chromatography (1:3 hexane/ether) provided the alkyne diol **10d** (220 mg, 42%) as a white solid: mp 59.8−60.2 °C; IR (KBr) 3400, 3300, 2120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.46 (d, 1H, J = 2.2 Hz), 2.96 (d, 1H, J = 5.3 Hz), 3.21 (d, 1H J = 7.1 Hz), 3.35 (dd, 1H, J = 3.7, 5.3 Hz), 4.40 (m, 1H); ^{13}C NMR δ 26.4, 34.6, 61.8, 73.5, 80.7, 84.6. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.11; H, 9.61.

***syn*-3,4-Dihydroxy-4-phenyl-1-butyne (10e).** Following the procedure described for the conversion of **7d** to **10d**, diol **7e** (700 mg, 2.41 mmol) was converted to alkyne diol **10e** (216 mg, 55%), a white solid: mp 60.0−60.4 °C; IR (KBr) 3300, 2120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (d, 1H, J = 2.0 Hz), 3.69 (br s, 2H), 4.34 (dd, 1H, J = 2.0, 7.3 Hz), 4.64 (d, 1H, J = 7.3 Hz), 7.24−7.36 (m, 5H); ^{13}C NMR δ 66.9, 75.2, 77.0, 81.5, 127.1, 128.2, 128.3, 138.8. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.67; H, 6.29.

General Procedure A: Monoprotection (MOM) of Diols 7 and 10. The procedure described below for the protection of **7a** is general. Experimental details and characterization data for the monoprotection (MOM) of diols **7b**−**e** and **10b**−**e** can be found in the supporting information.

***syn*-2-Iodo-4-(methoxymethoxy)-6-phenyl-1-hexen-3-ol (8a).** A solution of diol **7a**[10] (250 mg, 0.79 mmol), $CH(OMe)_3$ (175 μL, 2 equiv), and catalytic CSA (5 mg) in CH_2Cl_2 (12 mL) was stirred at rt for 45 min. The solution was cooled to −78 °C, and neat DIBAL-H (1.4 mL, 10 equiv) was added. The mixture was stirred at this temperature for 1 h and then placed in an ice bath. After 10 min, 1 N HCl was added and the mixture was extracted with EtOAc. The organics were washed with 1 N HCl (2×) and brine, dried, and concentrated. The crude reaction mixture was inspected by ^1H NMR spectroscopy (Table 1, entry 1). Chromatography (10:1 hexane/ether) provided the MOM ether **8a** (250 mg, 88%) as a colorless oil: IR 3420, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69−1.92 (m, 2H), 2.65 (ddd, 1H, J = 6.6, 9.8, 13.8 Hz), 2.78 (ddd, 1H, J = 5.6, 9.9, 13.8 Hz), 3.43 (s, 3H), 3.55−3.67 (m, 2H), 3.82 (d, 1H, J = 4.0 Hz), 4.62 (d, 1H, J = 6.7 Hz), 4.76 (d, 1H, J = 6.7 Hz), 5.95 (d, 1H, J = 1.6 Hz), 6.44 (dd, 1H, J = 1.0, 1.6 Hz), 7.15−7.31 (m, 5H); ^{13}C NMR δ 31.4, 33.4, 56.0, 79.4, 82.7, 97.9, 113.1, 126.0, 127.8, 128.37, 128.42, 141.4. Anal. Calcd for $C_{14}H_{19}O_3I$: C, 46.42; H, 5.29. Found: C, 46.46; H, 5.39.

***syn*-4-(Methoxymethoxy)-6-phenyl-1-hexyn-3-ol (11a).** Following procedure A using diol **10a** (200 mg, 1.05 mmol), the MOM ether **11a** (217 mg, 88%) was obtained as a colorless oil: IR 3410, 3290, 2110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89−2.00 (m, 1H), 2.04−2.16 (m, 1H), 2.46 (d, 1H, J = 2.2 Hz), 2.67 (ddd, 1H, J = 6.6, 9.9, 13.8 Hz), 2.82 (ddd, 1H, J = 5.4, 10.2, 13.8 Hz), 3.44 (s, 3H), 3.44 (d, 1H, J = 5.0 Hz), 3.59 (ddd, 1H, J = 3.9, 6.0, 8.2 Hz), 4.37 (ddd, 1H, J = 2.2, 5.0, 6.0 Hz), 4.68 (d, 1H, J = 6.8 Hz), 4.83 (d, 1H, J = 6.8 Hz), 7.15−7.31 (m, 5H); ^{13}C NMR δ 31.4, 32.7, 55.9, 64.8, 74.1, 82.2, 82.4, 97.5, 125.9, 128.29, 128.35, 141.5. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.97; H, 7.88.

***anti*-2-Iodo-4-(methoxymethoxy)-6-methyl-1-hepten-3-ol (16).** Following procedure A using diol **15** (100 mg, 0.37 mmol), the MOM ether **16** (109 mg, 94%) was obtained as a colorless oil. IR 3450, 1615 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 0.89 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.7 Hz), 1.22 (ddd, 1H, J = 2.7, 9.9, 14.3 Hz), 1.53 (ddd, 1H, J = 4.0, 9.7, 14.3 Hz), 1.80 (m, 1H), 3.34 (s, 3H), 3.90 (ddd, 1H, J = 2.7, 4.3, 9.6 Hz), 4.14 (tt, 1H, J = 1.3, 4.3 Hz), 4.52 (d, 1H, J = 4.3 Hz), 4.59 (d, 1H, J = 6.9 Hz), 4.74 (d, 1H, J = 6.9 Hz), 5.93 (t, 1H, J = 1.3 Hz), 6.55 (t, 1H, J = 1.3 Hz); ^{13}C NMR δ 21.5, 23.8, 24.1, 37.4, 56.2, 77.9, 78.2, 96.6, 109.4, 126.4. Anal. Calcd for $C_{10}H_{19}O_3I$: C, 38.23; H, 6.10. Found: C, 38.57; H, 6.10.

General Procedure B: Monosilylation of Diols 7. The procedure for the reaction of diol **7a** is representative. Experimental details and characterization data for the monosilylation of diols **7c**−**e** can be found in the supporting information.

***syn*-4-(*tert*-Butyldimethylsiloxy)-2-iodo-6-phenylhex-1-en-3-ol (23a) and *syn*-3-(*tert*-Butyldimethylsiloxy)-2-iodo-6-phenylhex-1-en-4-ol (24a).** To a solution of diol **7a** (2.4 g, 7.5 mmol) and *i*-Pr_2NEt (3.3 mL, 2.5 equiv) in DMF (20 mL) at −45 °C was added TBDMSOTf (2.2 mL, 1.25 equiv) dropwise. After 2 h, another 1 mL of TBDMSOTf (0.6 equiv) was added, and the mixture was stirred for a further 30 min when TLC indicated the absence of starting material. In some of the other cases, additional TBDMSOTf was required to completely consume the starting material. Saturated aq NH_4Cl was added, and the resulting mixture was extracted with ether. The organics were washed with 1 N HCl (2×) and brine, dried, and concentrated. After inspection by ^1H NMR spectroscopy, the residue was subjected to chromatography (7:3 to 1:1 hexane/toluene), and the alcohols **23a** and **24a** were obtained as colorless oils. The first compound to be eluted was the major silyl ether **23a** (2.9 g, 89%): IR 3510, 1620, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.74−1.86 (m, 1H), 1.95−2.08 (m, 1H), 2.60−2.77 (m, 2H), 3.11 (d, 1H, J = 8.1 Hz), 3.96 (dm, 1H, J = 8.1 Hz), 4.06 (ddd, 1H, J = 2.8, 4.5, 7.4 Hz), 5.95 (dd, 1H, J = 1.1, 1.6 Hz), 6.49 (t, 1H, J = 1.6 Hz), 7.17−7.33 (m, 5H); ^{13}C NMR δ −4.34, −4.26, 18.1, 25.9, 31.3, 36.4, 71.9, 78.3, 113.8, 125.97, 126.01, 128.39, 128.44, 141.6. Anal. Calcd for $C_{18}H_{29}O_2ISi$: C, 50.00; H, 6.75. Found: C, 50.22; H, 7.06. The more polar minor regioisomer **24a** (0.25 g, 8%): IR 3580, 1610, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.95 (s, 9H), 1.61−1.79 (m,

2H), 2.35 (dd, 1H, J = 0.9, 3.8 Hz), 2.69 (ddd, 1H, J = 6.8, 9.8, 13.8 Hz), 2.90 (ddd, 1H, J = 5.2, 10.0, 13.8 Hz), 3.48 (dd, 1H, J = 0.7, 6.2 Hz), 3.63 (m, 1H), 5.95 (d, 1H, J = 1.5 Hz), 6.37 (dd, 1H, J = 0.7, 1.5 Hz), 7.16−7.30 (m, 5H); ^{13}C NMR δ −4.89, −4.22, 18.1, 25.8, 31.9, 34.3, 73.0, 81.8, 113.6, 125.8, 127.5, 128.3, 128.5, 141.9. Anal. Calcd for $C_{18}H_{29}O_2ISi$: C, 50.00; H, 6.75. Found: C, 50.24; H, 6.91.

***syn*-4-(*tert*-Butyldimethylsiloxy)-2-iodo-3-(methoxymethoxy)-6-phenylhex-1-ene (25).** A solution of alcohol **23a** (4.54 g, 10.5 mmol) and MOM-Cl (10.6 mL, 12 equiv) in *i*-Pr_2NEt (30 mL) was heated at 85 °C until the starting material was consumed (approximately 3 h). The mixture was cooled to rt, and water was added. The mixture was extracted with ether and the organics were washed with 1 N HCl (2×) and brine, dried, and concentrated. Chromatography (95:5 hexane/ether) of the residue provided **25** (4.46 g, 89%) as a colorless oil: IR 1610, 830 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.161 (s, 3H), 0.164 (s, 3H), 0.97 (s, 9H), 1.67−1.93 (m, 2H), 2.70−2.81 (m, 2H), 3.39 (s, 3H), 3.59 (d, 1H, J = 7.2 Hz), 3.94 (dt, 1H, J = 7.2, 5.0 Hz), 4.62 (d, 1H, J = 6.5 Hz), 4.66 (d, 1H, J = 6.5 Hz), 6.13 (d, 1H, J = 1.5 Hz), 6.62 (dd, 1H, J = 0.8, 1.5 Hz), 7.14−7.31 (m, 5H); ^{13}C NMR δ −4.6, −4.0, 18.3, 26.0, 30.6, 35.4, 56.2, 73.5, 83.3, 94.3, 111.1, 125.8, 128.3, 128.4, 129.5, 142.4. Anal. Calcd for $C_{20}H_{33}O_3ISi$: C, 50.42; H, 6.98. Found: C, 50.56; H, 6.94.

***syn*-4-(*tert*-Butyldimethylsiloxy)-3-(methoxymethoxy)-6-phenylhex-1-yne (26).** To a solution of vinyl iodide **25** (3.30 g, 6.93 mmol) in DMF (30 mL) at 0 °C was added NaN(TMS)$_2$ (12.4 mL of a 1 M solution in THF, 1.8 equiv) slowly over 5 min. After 30 min, water was added and the mixture was extracted with ether. The organics were washed with water and brine, dried, and concentrated. Chromatography (96:4 hexane/ether) of the residue provided alkyne **26** (2.26 g, 94%) as a colorless oil: IR 2110, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.119 (s, 3H), 0.122 (s, 3H), 0.95 (s, 9H), 1.94−2.09 (m, 2H), 2.43 (d, 1H, J = 2.2 Hz), 2.68 (ddd, 1H, J = 5.9, 10.9, 13.6 Hz), 2.80 (ddd, 1H, J = 6.0, 11.0, 13.6 Hz), 3.40 (s, 3H), 3.85 (dt, 1H, J = 4.1, 6.2 Hz), 4.31 (dd, 1H, J = 2.2, 6.2 Hz), 4.62 (d, 1H, J = 6.6 Hz), 4.93 (d, 1H, J = 6.6 Hz), 7.16−7.30 (m, 5H); ^{13}C NMR δ −4.7, −4.4, 18.1, 25.9, 31.3, 35.1, 55.7, 69.7, 73.4, 75.0, 80.3, 94.6, 125.7, 128.31, 128.34, 142.4. Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.86; H, 9.61.

Methyl *syn*-5-(*tert*-Butyldimethylsiloxy)-4-(methoxymethoxy)-7-phenylhept-1-ynoate (27). To a solution of alkyne **26** (2.27 g, 6.51 mmol) in THF (45 mL) at −78 °C was added MeLi (7 mL of a 1.4 M solution in THF, 1.5 equiv), and the resulting mixture was stirred at this temperature for 10 min and then at 0 °C for 30 min. Methyl chloroformate (754 μL, 1.5 equiv) was added slowly and after 15 min, water was added. The mixture was extracted with ether, and the organics were washed with 1 N HCl and brine, dried, and concentrated. Chromatography (95:5 hexane/ether) of the residue provided ester **27** (1.77 g, 67%) as a colorless oil: IR 2230, 1720, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.098 (s, 3H), 0.105 (s, 3H), 0.93 (s, 9H), 1.89−2.08 (m, 2H), 2.65 (ddd, 1H, J = 5.6, 11.0, 13.6 Hz), 2.78 (ddd, 1H, J = 5.5, 11.3, 13.6 Hz), 3.39 (s, 3H), 3.76 (s, 3H), 3.87 (dt, 1H, J = 7.2, 5.0 Hz), 4.39 (d, 1H, J = 6.0 Hz), 4.62 (d, 1H, J = 6.7 Hz), 4.86 (d, 1H, J = 6.7 Hz), 7.16−7.30 (m, 5H); ^{13}C NMR δ −4.7, −4.5, 18.1, 25.8, 31.4, 35.0, 52.6, 55.8, 69.6, 73.0, 78.1, 84.4, 95.1, 125.8, 128.3, 142.0, 153.5. Anal. Calcd for $C_{22}H_{34}O_5Si$: C, 64.99; H, 8.43. Found: C, 65.08; H, 8.33.

Methyl *syn*-5-Hydroxy-4-(methoxymethoxy)-7-phenylhept-2-ynoate (28). To a solution of ester **27** (1.53 g, 3.76 mmol) in THF (40 mL) at 0 °C was added TBAF (5.6 mL of a 1 M solution in THF, 1.5 equiv). Saturated NH_4Cl was added after 1 h, and the resulting mixture was extracted with EtOAc. The organics were washed with brine, dried, and concentrated. Chromatography (1:1 hexane/ether) of the residue provided hydroxy ester **28** (870 mg, 79%) as a colorless oil. IR 3450, 2235, 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (m, 1H), 2.01 (m, 1H), 2.55 (br s, 1H), 2.72 (ddd, 1H, J = 7.1, 9.5, 13.8 Hz), 2.89 (ddd, 1H, J = 5.1, 9.9, 13.8 Hz), 3.39 (s, 3H), 3.76 (s, 3H), 3.75 (m, 1H), 4.28 (d, 1H, J = 6.7 Hz), 4.65 (d, 1H, J = 6.8 Hz), 4.89 (d, 1H, J = 6.8 Hz), 7.16−7.31 (m, 5H); ^{13}C NMR δ 31.5, 34.1, 52.8, 56.0, 70.0, 72.2, 78.3, 83.4, 95.0, 125.9, 128.4, 128.5, 141.4, 153.3. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.57; H, 6.87.

(*Z*)-Methyl *syn*-3-Methoxy-5-hydroxy-4-(methoxymethoxy)-7-phenylhept-2-enoate ((*Z*)-29) and Pyranone 30. To a solution of hydroxy ester **28** (130 mg, 0.44 mmol) in MeOH (1.5 mL) was added 550 μL of a solution of NaOMe in MeOH (0.2 M, 0.25 equiv). The mixture was stirred at rt for 18 h, and then EtOAc was added. The mixture was washed with 1 N HCl and brine, dried, and concentrated. Chromatography (5:2 to 3:2 hexane/EtOAc) first provided (*Z*)-**29** (84 mg, 58%) as a colorless oil. IR 3480, 1715, 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75−1.82 (m, 2H), 2.42 (br s, 1H), 2.68 (dt, 1H, J = 16.5, 8.2 Hz), 2.86 (app qu, 1H), 3.37 (s, 3H), 3.66 (s, 3H), 3.72 (m, 1H), 3.85 (d, 1H, J = 5.7 Hz), 3.92 (s, 3H), 4.60 (d, 1H, J = 6.8 Hz), 4.68 (d, 1H, J = 6.8 Hz), 5.27 (s, 1H), 7.14−7.27 (m, 5H); ^{13}C NMR δ 31.8, 34.6, 51.2, 56.2, 61.3, 71.7, 80.8, 95.4, 97.3, 125.8, 128.3, 128.4, 141.7, 165.2, 167.4. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.07; H, 7.59. Further elution yielded the pyranone **30** (43 mg, 33%) as a colorless oil: IR 1710, 1630 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.99−2.11 (m, 1H), 2.16−2.29 (m, 1H), 2.77 (ddd, 1H, J = 7.0, 9.4, 13.7 Hz), 2.90 (ddd, 1H, J = 5.4, 9.7, 13.7 Hz), 3.34 (s, 3H), 3.82 (s, 3H), 4.08 (dd, 1H, J = 1.2, 2.3 Hz), 4.36 (ddd, 1H, J = 2.3, 4.9, 8.8 Hz), 4.66 (d, 1H, J = 6.7 Hz), 4.81 (d, 1H, J = 6.7 Hz), 5.20 (d, 1H, J = 1.2 Hz), 7.16−7.37 (m, 5H); ^{13}C NMR δ 30.9, 31.5, 56.2 (double intensity), 69.5, 77.7, 92.1, 96.0, 126.1, 128.49, 128.50, 140.7, 165.9, 171.5. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.16; H, 6.80.

Pyranone 30 from Isomerization of (*Z*)-29. A solution of (*Z*)-**29** (114 mg, 0.35 mmol) in $CDCl_3$ (6 mL, Isotech) was stirred at rt for 2 h. The intermediate (*E*)-**29** was not purified: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66−1.78 (m, 2H), 2.66 (ddd, 1H, J = 7.4, 9.5, 13.6 Hz), 2.87 (ddd, 1H, J = 5.8, 9.7, 13.6 Hz), 3.37 (s, 3H), 3.62 (s, 3H), 3.66 (s, 3H), 3.87 (m, 1H), 4.68 (s, 2H), 5.15 (s, 1H), 5.50 (d, 1H, J = 6.8 Hz), 7.12−7.29 (m, 5H). The solution was concentrated and dissolved in MeOH (1.5 mL), and 500 μL of a solution of NaOMe in MeOH (0.2 M, 0.25 equiv) was added. The mixture was stirred at rt for 18 h, and then EtOAc was added. The mixture was washed with 1 N HCl and brine, dried, and concentrated. Chromatography (2:1 hexane/EtOAc) provided pyranone **30** (82 mg, 80%) as a colorless oil.

(±)-Dihydrokawain-5-ol (1). A solution of pyranone **30** (115 mg, 0.39 mmol) in 75% aq HOAc (2 mL) and concd H_2SO_4 (1 drop) was stirred at 70 °C for 3 h. The mixture was diluted with EtOAc, washed with brine, dried, and concentrated. Chromatography (3:2 hexane/EtOAc) provided (±)-**1** (88 mg, 90%) as a white solid: mp 121−122 °C; IR (KBr) 3485, 1695, 1625, 1225 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.07 (m, 1H), 2.25−2.35 (m, 1H), 2.74−2.91 (m, 2H), 3.74 (s, 3H), 3.92 (dd, 1H, J = 0.5, 2.6 Hz), 4.21 (ddd, 1H, J = 2.6, 5.2, 8.7 Hz), 5.15 (d, 1H, J = 0.5 Hz), 7.16−7.29 (m, 5H); ^{13}C NMR δ 30.9, 31.0, 56.4, 66.2, 78.1, 91.4, 126.2, 128.5, 128.6, 140.7, 166.3, 172.4. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.36; H, 6.20.

Supporting Information Available: Experimental procedures and characterization data (^{1}H and ^{13}C NMR, IR, analysis) for **7b**−**e**, **8b**−**e**, **11b**−**e**, **13d**, **23c**−**e**, and **24c**−**e** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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