Pergamon

Tetrahedron Letters 40 (1999) 1463–1466

TETRAHEDRON LETTERS

Intramolecular Palladium Catalyzed Alkoxy Carbonylation of 6-Hydroxy-1-octenes. Stereoselective Synthesis of Substituted Tetrahydropyrans.

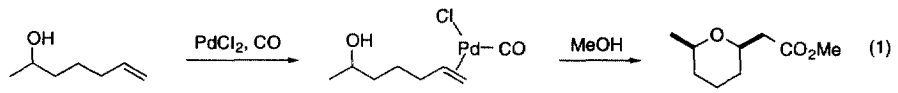
James D. White,* Jian Hong, and Lonnie A. Robarge

Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003, U.S.A.

Received 4 December 1998; accepted 18 December 1998

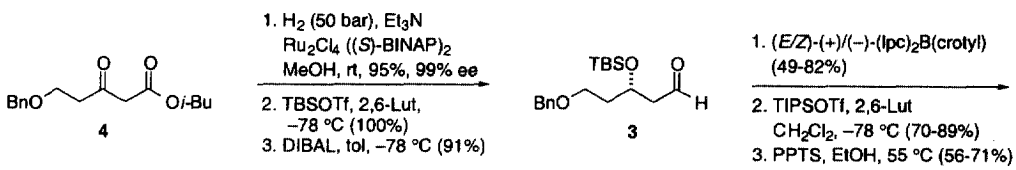
Abstract: The reaction of hydroxy alkenes **5**, **7**, and **8** with CO and MeOH in the presence of $PdCl_2$ and $CuCl_2$ gave tetrahydropyrans **9**, **11**, and **12**, respectively. Yields were dependent upon the configuration of substituents in the hydroxy alkene; in all cases, the tetrahydropyran was produced with 2,6-*cis* configuration.

The tetrahydropyran nucleus is a component of many classes of natural products, and a variety of synthetic pathways are now available for construction of this moiety.[1] Most of these employ cyclization strategies, but few are able to generate heavily substituted tetrahydropyrans with complete stereocontrol. In 1990, Semmelhack reported that intramolecular alkoxy carbonylation of 6-hepten-2-ol (**1**) produces a tetrahydropyran **2** with clean *cis* orientation of side chains at C2 and C6 (eq 1).[2] The influence of substituents in the alkenol substrate was examined for alkoxy carbonylative cyclizations to give tetrahydrofurans,[3] but was not well documented for those reactions leading to tetrahydropyrans. This issue becomes important in approaches to functionalized tetrahydropyrans, and for this reason we undertook a study of the Pd(II) catalyzed alkoxycarbonylative cyclization of several 6-hydroxy-1-alkenes.



1 **2**

Four stereoisomeric 4,6,8-trihydroxy-3-methyl-1-octene derivatives were synthesized from the protected (3*S*)-3,5-dihydroxypentanal **3**.[4] The latter was prepared by enantioselective hydrogenation of keto ester **4**, followed by conversion of the (3*S*) alcohol to its silyl ether and subsequent reduction of the ester. Exposure of **3** to (*E*) and (*Z*) isomers of (+)-crotyl(diisopinocampheyl)borane[5] with subsequent protection of the resultant alcohol as its triisopropylsilyl (TIPS) ether followed by selective removal of the *tert*-butyldimethylsilyl (TBS) ether afforded (3*R*, 4*S*, 6*S*) and (3*R*, 4*R*, 6*S*)-octenetriol derivatives **5** and **6**, respectively. An analogous sequence from **3** employing (*E*)- and (*Z*)-(–)-crotyl(diisopinocampheyl)borane led to **7** and **8**.

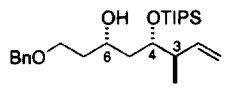
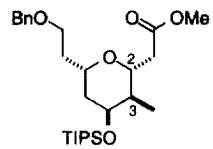
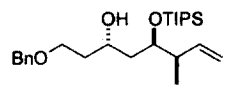
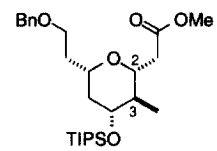
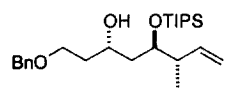
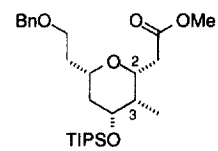
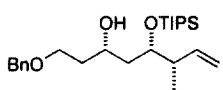
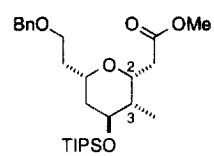


4 **3**

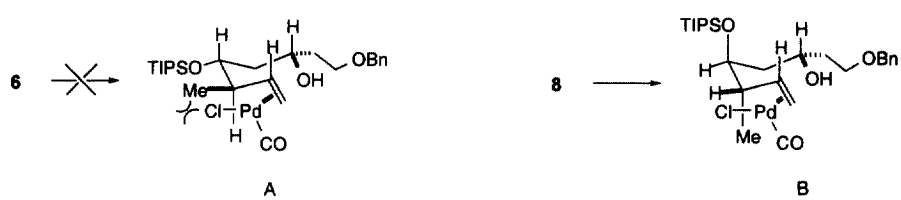
0040-4039/99/$ - see front matter
PII: S0040-4039(98)02693-8

Alkoxycarbonylative cyclization of **5-8** was carried out in methanol under an atmosphere of CO in the presence of catalytic $PdCl_2$ and with $CuCl_2$ as the stoichiometric oxidant (Table 1). The reaction showed a marked dependence on the configuration at C3 and C4 of the hydroxy alkene, with **5** giving a low yield of **9**, and **6** giving none of the tetrahydropyran **10**. The efficiency of cyclization improved with the conversion of **7** to **11**, and was highest with **8**, which afforded **12** as a single stereoisomer.[6]

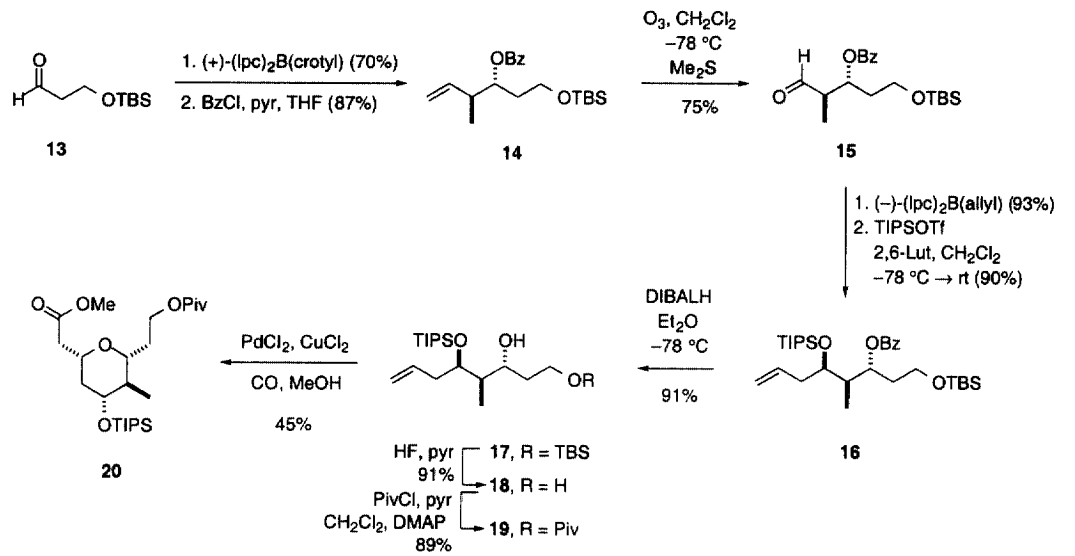
Table 1. Alkoxycarbonylative Cyclization of Stereoisomeric Octenols.

Substrate		Product		Yield (%)
	(5)		(9)	20
	(6)		(10)	0
	(7)		(11)	40
	(8)		(12)	61

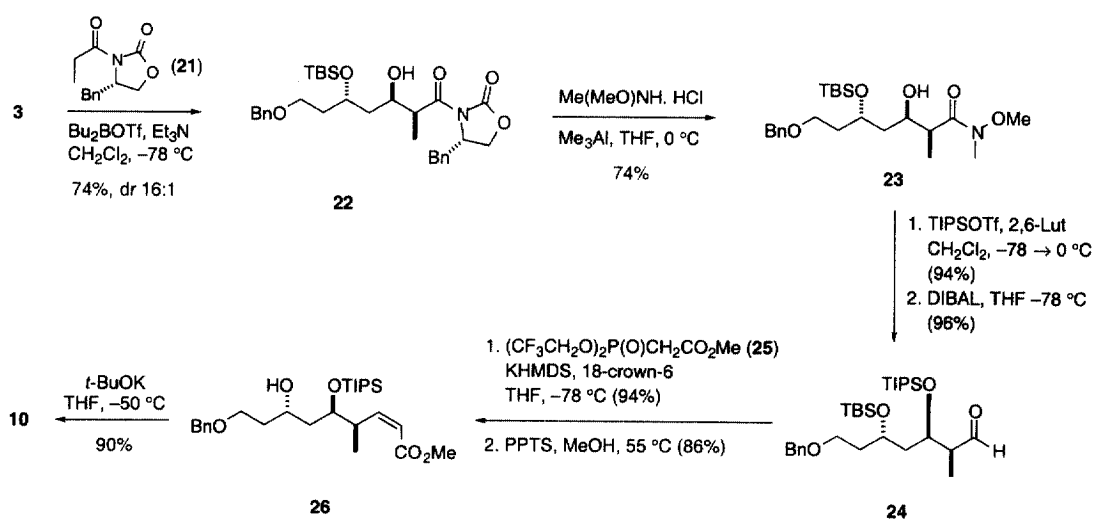
At first glance, the results in Table 1 seem counterintuitive since **8** leads to the tetrahydropyran **12** which should be least stable (2 axial substituents), whereas **6** would have produced a tetrahydropyran **10** in which all substituents are equatorial. An explanation for the observed outcome can be found by considering the Pd complexed alkenes A and B which precede cyclization. With the large *exo* Pd substituent positioned pseudo equatorial in a bisected conformation of the alkene, an eclipsing interaction with the methyl group is present in A which is absent in B. This suggested that relocating the methyl substituent to a site more remote



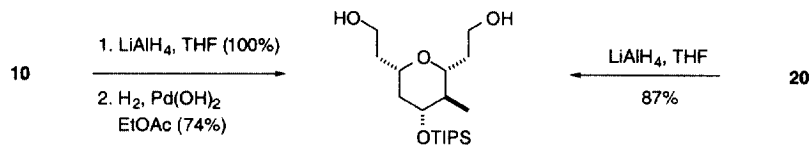
from the double bond would diminish the steric encumbrance against alkoxy carbonylative cyclization of **6**, and led us to consider alternative cyclization substrates, which could afford a tetrahydropyran configuration identical with **10** but with side-chain functionality at C2 and C6 reversed.



Asymmetric crotylation[5] of aldehyde **13** followed by benzoylation of the resultant homoallylic alcohol, furnished **14** which was ozonized to give **15**. Treatment of this aldehyde with (−)-allyl(diisopino-campheyl)borane[7] and protection of the product alcohol as its triisopropylsilyl ether yielded **16**, from which the benzoate was removed by reduction. Attempts to effect alkoxy carbonylative cyclization of **17** or the diol **18** derived by selective desilylation were unsuccessful; however, when pivalate **20** was exposed to $PdCl_2$-$CuCl_2$ in the presence of CO and MeOH, tetrahydropyran **20** was formed in 45% yield.



In order to correlate the configuration of **20** with that of **10**, the latter was synthesized by an alternative route from **3**. Aldol condensation of **3** with the (*Z*) boron enolate of (*S*)-oxazolidinone **21** gave **22**, from which the chiral auxiliary was removed to yield Weinreb amide **23**.[8] After protection, the amide was reduced to aldehyde **24** which was subjected to Gennari-Still coupling with phosphonate **25** to afford exclusively a (*Z*)-α,β-unsaturated ester.[9] Selective removal of the TBS protection then gave **26**, which in the presence of potassium *tert*-butoxide underwent clean cyclization to **10**.[6,10] Reduction of the latter with lithium aluminum hydride, followed by hydrogenolysis over Pearlman's catalyst produced diol **27**, identical with the diol prepared by direct hydride reduction of **20**.



27

It is clear from the foregoing results that intramolecular palladium-catalyzed alkoxy carbonylation of a hydroxy olefin to form a substituted tetrahydropyran is highly dependent on the configuration of the substituents. Nevertheless, this methodology can provide a valuable means for constructing certain tetrahydropyrans from easily accessible precursors.

Acknowledgement: Financial support was provided by the National Institutes of Health (GM50574).

References

1. Boivin, T.L.B. *Tetrahedron* **1987,** *43*, 3309.
2. Semmelhack, M.F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure & Appl. Chem.* **1990**, *62*, 2035-2040.
3. Semmelhack, M.F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. See also McCormick, M.; Monahan III, R.; Soria, J.; Goldsmith, D.; Liotta, D. *ibid*, **1989**, *54*, 4485.
4. (a) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A.C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549 and references cited therein. (b) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
5. Brown, H.C.; Bhat, K.S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
6. Coupling constants between protons at C2 and C3 in the NMR spectra of **9-12** established their axial-axial relationship (J = 10 Hz) for **9** and **10** and their axial-equatorial orientation (J = 2 Hz) for **11** and **12**. This confirmed that the C2 configuration in all of these tetrahydropyrans is (*S*).
7. (a) Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Brown, H.C.; Racherla, U.S. *J. Org. Chem.* **1991**, *56*, 401.
8. Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
9. Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
10. (a) Schneider, C. *Synlett* **1997**, 815. (b) Smith, N.D.; Kocienski, P.J.; Street, S.D. *Synthesis* **1996**, 652.