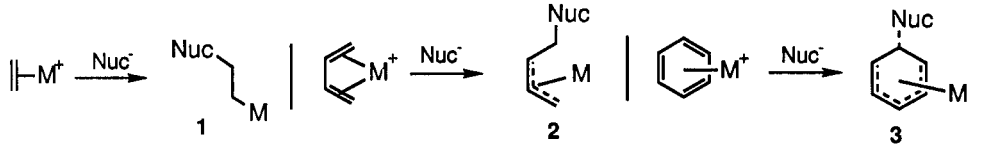
Pure & Appl. Chem., Vol. 62, No. 10, pp. 2035–2040, 1990.
Printed in Great Britain.

Intramolecular alkoxy-carbonylation of hydroxy alkenes promoted by Pd(II)

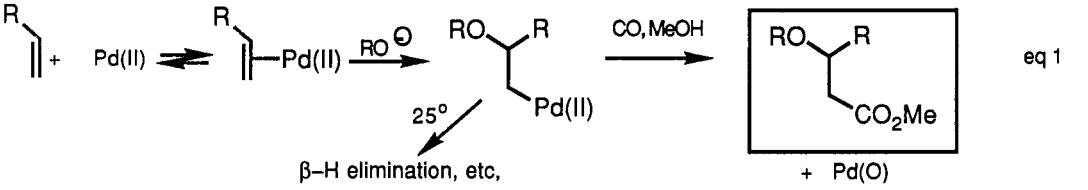
M. F. Semmelhack,* Chung Kim, Nan Zhang, C. Bodurow, M. Sanner, W. Dobler, and M. Meier.
Department of Chemistry, Princeton University, Princeton, NJ 08544

ABSTRACT: The intramolecular addition of a hydroxyl group to an alkene promoted by Pd(II) leads to an alkyl-Pd intermediate which can undergo CO insertion and cleavage by MeOH. The result is 1,2-alkoxycarbonylation. While in the formation of six-membered rings the 2,6-substituents strongly prefer a cis arrangement, the selectivity in generating 2,5-disubstituted tetrahydrofurans is poor. However, nearby substituents can influence the selectivity, and by proper positioning of large (removeable) groups, both cis-2,5 and trans-2,5 disubstituted isomers can be prepared selectively. In the absence of CO, β-hydride elimination is fast, and a remarkable solvent effect has been observed. In DMSO, the kinetic product is formed very selectively, while in MeCN, for example, the thermodynamic olefin isomer is preferred. These selectivities are tested in a plan for the synthesis of tetronomycin A.

The coordination of polyenes with transition metals increases the polarizibility of the ligand and can lower the barrier toward nucleophilic addition.[1] The electron-rich intermediates (**1-3**) produced from such addition are stabilized by delocalization onto the metal ligand system.

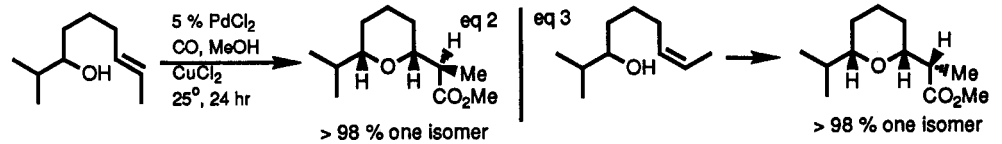


We have been intrigued by the addition of oxygen nucleophiles to alkenes activated by palladium(II) and the further elaboration of the organo-palladium intermediates.[2] A typical example is shown in eq 1, in which alkoxide adds to a terminal alkene and the alkyl-palladium intermediate is trapped with CO and MeOH to produce overall 1,2-alkoxy-carbonylation.[3]



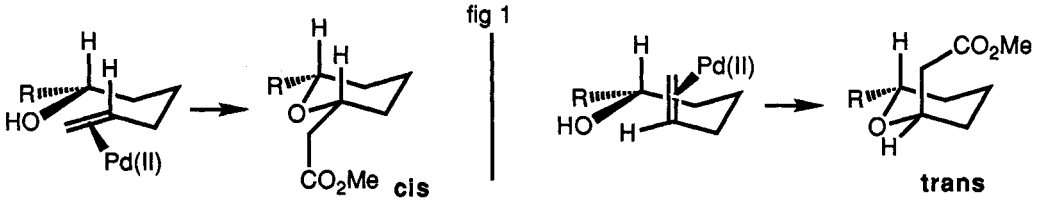
eq 1

That process works well only with terminal alkenes, presumably due to poorer coordination and a tendency toward β-hydride elimination in more substituted cases. The intramolecular version is much more efficient, and can be successful with 1,2- and 1,1-disubstituted alkenes (eq. 2).[4] β-hydride elimination is not significant in the presence of CO and MeOH. An important new opportunity intrinsic to 1,2-disubstituted alkenes is the generation of two adjacent stereogenic centers with highly predictable control over the relative configurations: anti-addition is strongly preferred in the initial attack of the alkoxy group, and syn-addition is preferred in the migratory insertion to the CO ligand.[5] Kinetic control is apparent from the parallel examples in eq 2 and 3, as the E-alkene leads to one diastereoisomer and the Z-alkene leads to another, in >95% selectivity. The absolute configurations have not been established, and the structures shown are based on the expected mechanism.

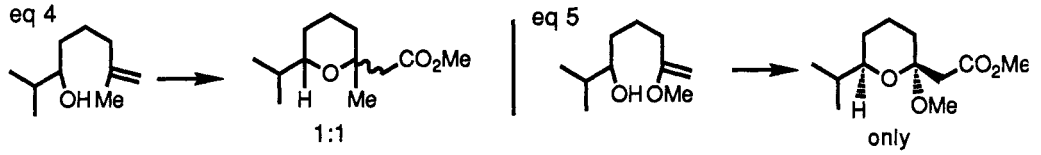


The formation of the cis-2,6 arrangement of substituents was rationalized based on a pseudo chair conformation for the hydroxy-alkene in approaching the transition state for nucleophilic addition, and emphasizing the energetically unfavorable pseudo-axial interactions on the way to the trans-2,6 isomer (figure 1).[4a,b]

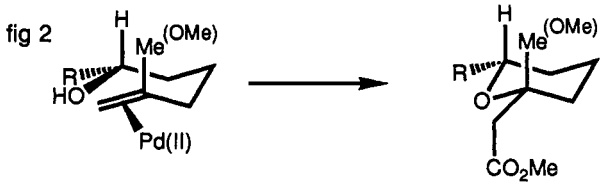
fig 1



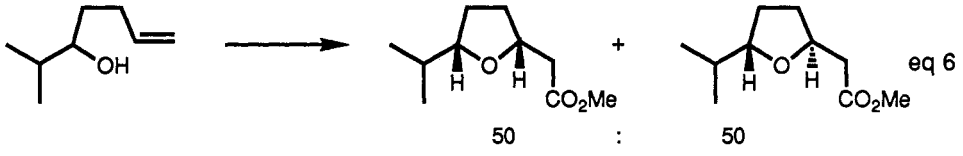
With 1,1-disubstituted alkenes, both the cis and trans-2,6-disubstituted tetrahydropyrans are formed, in equal amounts in the example shown in eq 4.[4a] In contrast, a methoxy substituent instead of the methyl group leads to exclusive formation of the 2,6-cis arrangement (eq 5).[4b]



Again, the pseudo-chair conformation allows an understanding of the selectivity: the methyl substituent introduces its own negative axial interactions in the arrangement shown in fig. 2, while a methoxy group in that position is a stabilizing influence, extrapolating from the usual anomeric effect.

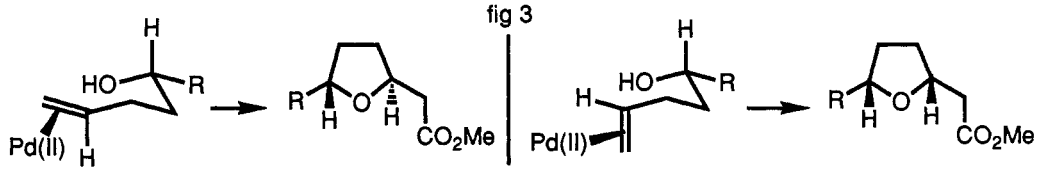


The selectivity in formation of tetrahydrofuran rings is summarized in eq 6, showing that cis and trans 2,5-disubstituted rings are formed with similar preference.[4a] The formation of seven and four membered rings is not observed, from the analogous precursors.

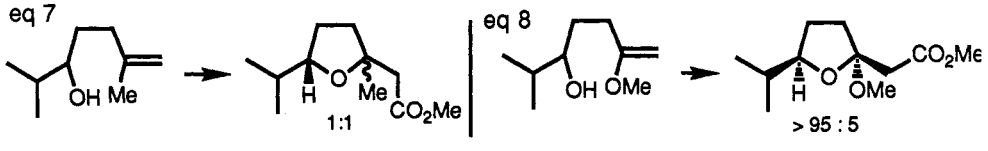


The different selectivity shown in six-membered vs five-membered ring formation may be a result of the difference in sensitivity to conformational factors. As shown in fig 3, the folding of the five-membered ring precursor to form the trans-2,5 isomer is suggested to be no less favorable than the parallel folding required to produce the cis-2,5 product.

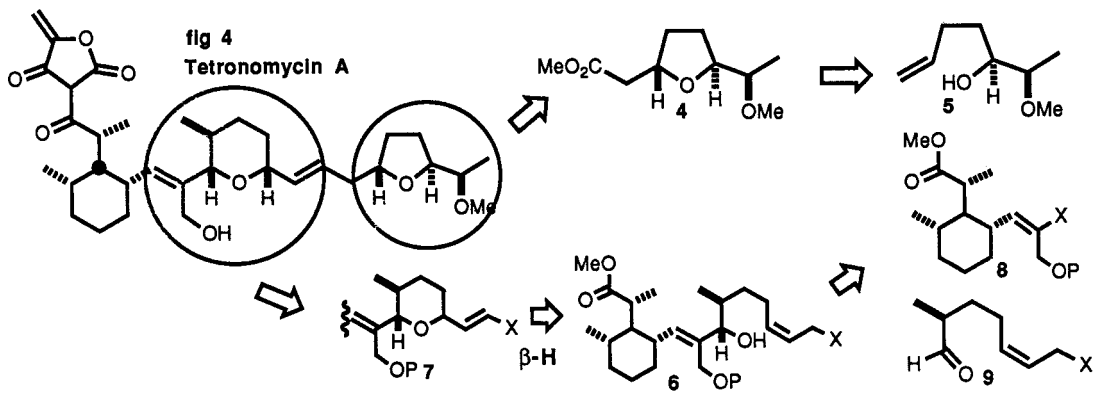
fig 3



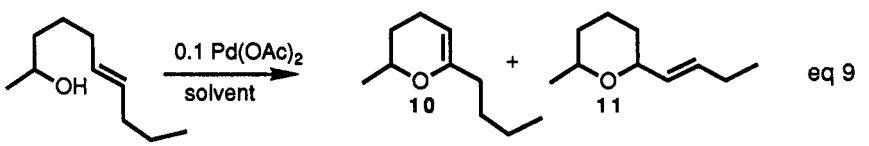
The 1,1-disubstituted alkene bearing a methyl group (eq 7) leads to a 1:1 mixture of product isomers, but the parallel case with a methoxy substituent again shows high selectivity for the cis arrangement of the two carbon substituent (eq 8).



We are interested in testing this methodology in the synthesis of tetronomycin A, a special ionophore antibiotic.[6] The structure can be dissected into four parts, the tetronic acid ring, a 1,2,3-trisubstituted cyclohexane portion, a 2,3,6-trisubstituted tetrahydropyran ring, and a trans-2,5-disubsituted tetrahydrofuran ring (fig 4). We have been studying applications of the alkoxycarbonylation process in the preparation of the pyran and furan rings in this natural product. In a simple analysis, the tetrahydrofuran unit might appear as the ester, **4**, with the carboxyl carbon available for coupling onto the rest of the molecule. The precursor of **4** is the hydroxy-alkene, **5**. While the cyclization is expected to proceed in high yield, there is no basis for expecting the preferential formation of the desired trans isomer, **4**. In addition. since the various sections of the target are connected through freely rotating linkages, there is no plan to transmit stereochemical information from one portion to another; **4** must be prepared in optically pure form. There are two primary problems then in the preparation of **4**: (1) how to generate the optically pure **5**, and (2) how to induce selective formation of the trans product. The tetrahydropyran portion in tetronomycin A might arise from alkoxy addition to an internal alkene (in **6**) followed by β-hydrogen elimination from **7.** Important new questions have to do with the β-hydrogen elimination: (1) can it be controlled to give the desired positional isomer of the new alkene unit, and (2) will the E-configuration be favored? Precursor **6** also presents some new issues of functional group compatibility (doubly allylic secondary alcohol), and the influence of the peripheral methyl group appearing on the tetrahydropyran ring. The specific precursor might arise by stereoselective addition of a vinyl-metal derivative (**9**: X=main group metal) to the homochiral aldehyde, **8**.



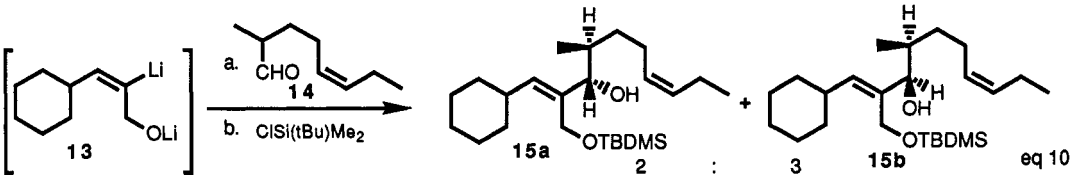
A simple hydroxy-alkene reacted with Pd(II) in typical solvents (THF, etc) in the absence of CO and MeOH to give the product(s) from β-hydride elimination in good yield (eq 9). However, the internal alkene **10**, presumably the thermodynamic product, was preferred or at least significant in the product mixture. A systematic survey of solvents (Table 1) showed that the process is highly solvent dependent and that DMSO is effective in favoring the (desired) exocyclic elimination process to give **11**.[7] We have demonstrated the intramolecular nature of the β-hydrogen elimination process in this case, by showing that added alkenes related to **11** do not undergo alkene migration while the cyclization is proceeding. The process uses stoichiometric amounts of Pd, and $Pd(OAc)_2$ is the best agent.[7]



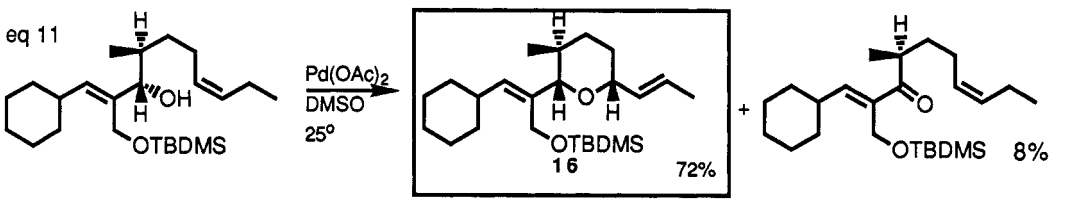
eq 9

Table 1				
	HOAc	69	31	
	DMF	51	49	
	THF	18	82	
	tBuOH	9	81	
	DMSO	**0**	**100**	**(92%)**

The more elaborate model system, **12** was prepared using known methodology.[8] The di-lithio derivative **13** was allowed to react with the racemic aldehyde, **14**. After silylation, the product was a mixture of diastereoisomers (**15**) in the ratio of 3:4 and the yield was 70%. The assignment of the configurations of the diastereoisomers is apparent after the Pd-promoted cyclization.



Cyclization of the major isomer proceeded under the optimum conditions from the model system to give the tetrahydropyran **16** in 72% yield (eq 11).[7] Only one isomer was detected, with the proper position of the new double bond and the E configuration. The major by-product is the ketone (8% yield). While there remains the problem of selectivity in the formation of diastereoisomers**15a** and**15b**, the β-hydrogen elimination proceeds efficiently.[7]



The problem of control over the configuration of the 2,5-substituents in the formation of tetrahydrofurans was approached by a study of the effect of "remote" substituents on the selectivity in cyclization.[9] The proposal is that properly placed removable substituents could influence the selectivity. It might be predicted that if R_2 is a large substituent (fig 5), the conformation **A** would lead to the best transition state, and the product **B** would be favored over **D** due to pseudo 1,3-diaxial interactions in the latter. Similar arguments can be applied in the case of allylic substituents (R_3, R_4).

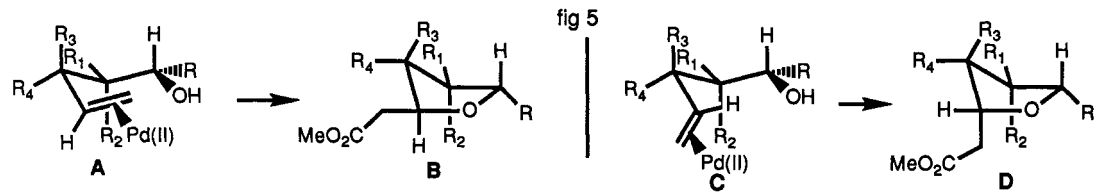
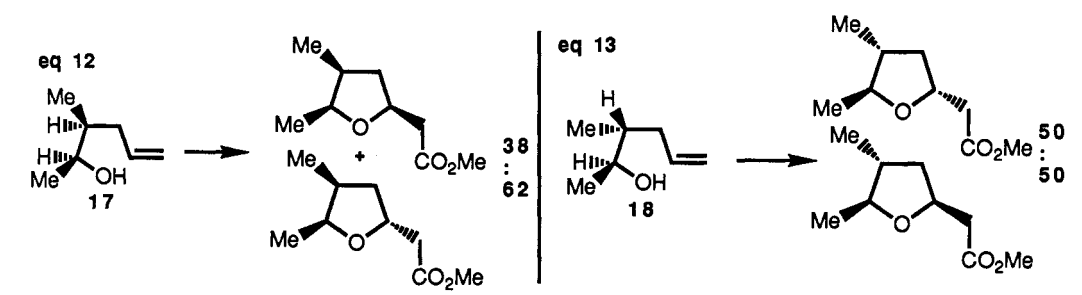


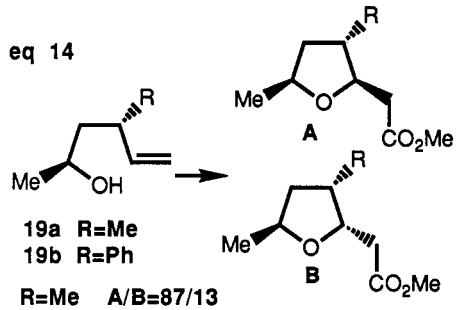
fig 5

The appropriate hydroxy alkenes **17** and **18** were prepared and cyclized. In both cases, both isomers of the product were formed in large amounts (eq 12,13); the influence of the Me group is not strong.

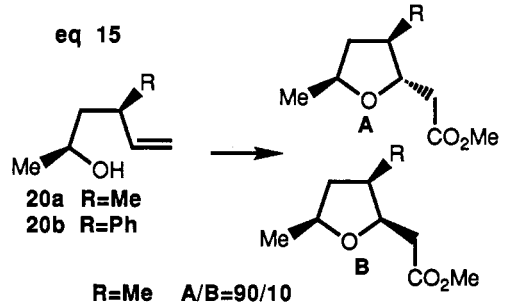


By moving the Me substituent over one position (allylic Me in **19a** and **20a**), much higher selectivity appears (eq 14,15). Nearly 10:1 selectivity was observed, with the 1,2-trans relationship being preferred. The larger phenyl substituent (**19b**, **20b**), gave still higher selectivity, from 93:7 to >98:2.

eq 14

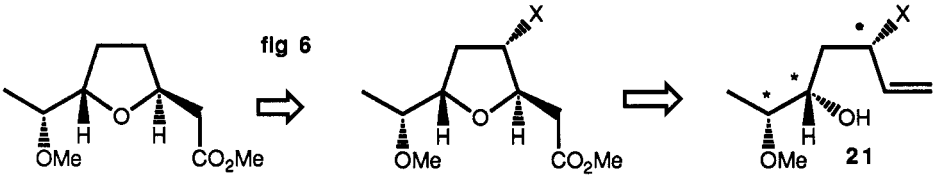


eq 15

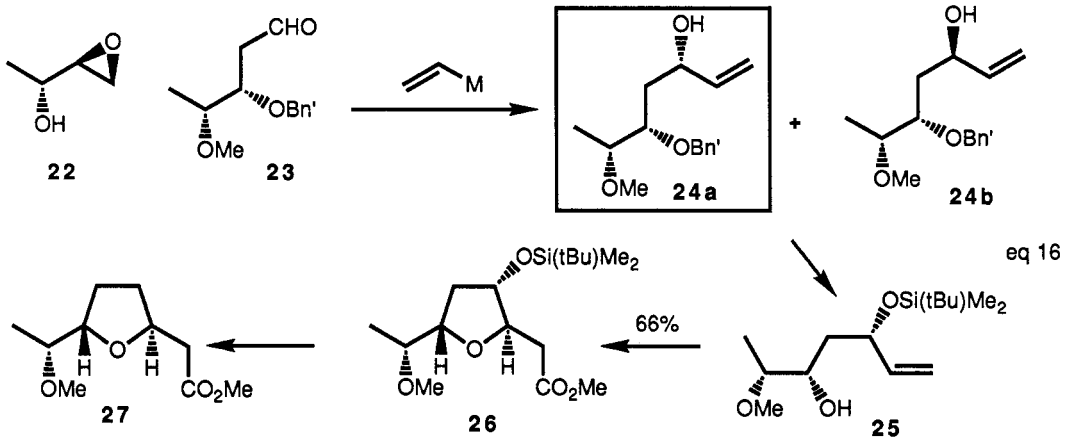


The ideal precursor then would be **21**, and X would be designed to be large and removeable. With the effective new technology for removal of secondary hydroxyl groups,[10] a silyloxy group was chosen (fig 6).

fig 6

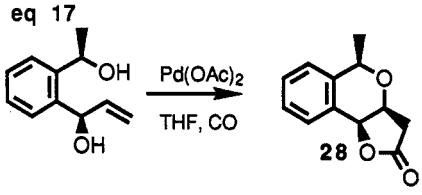


The homochiral precursor **22** was prepared by Sharpless epoxidation of 3-hydroxy-1-butene,[11] and converted in several steps to the aldehyde **23** (eq 16). Addition of various vinyl-metal derivatives gave various mixtures of diastereoisomers, but none of the conditions provided highly selective reaction. Nevertheless, the desired diastereoisomer (**24a**) was separated and manipulated into the hydroxy-alkene **25**, with a silyloxy substituent. Alkoxycarbonylation proceeded in 67% yield to give one cyclization product (**26**). The hydroxyl blocking group was removed[10] to produce the desired homochiral tetrahydrofuran, **27**.

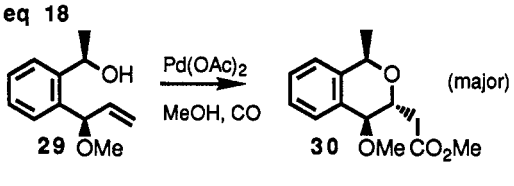


Again, a problem is the diastereoselectivity in addition to aldehyde **23**. It was proposed that diastereoisomer **24b** might be useful if the hydroxyl unit acted as an attractive directing group (chelation) rather than a steric blocking group. Precedent existed in the system shown in eq 17 where the allylic hydroxyl group participates in the alkoxycarbonylation process to give the pyran-lactone, **28**.[4f] With the hydroxyl group blocked (**29**), the "normal" alkoxycarbonylation occurs, giving the alternate relative configurations, in **30** (eq 18).

eq 17

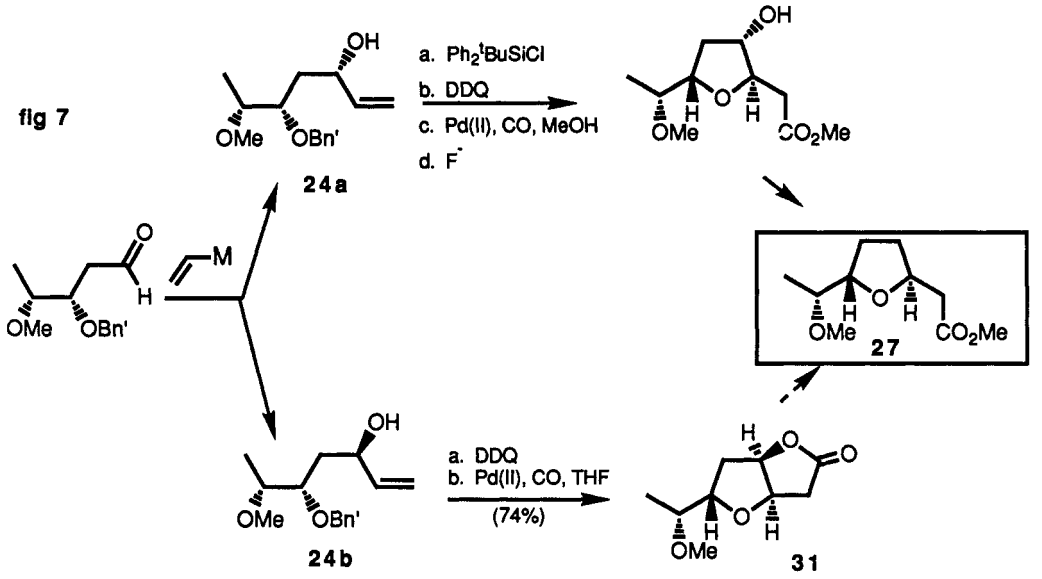


eq 18



By this procedure, diastereoisomer **24b** is converted to lactone **31**. After cleavage of the lactone and removal of the hydroxyl directing group, the product (**27**) is the same as that obtained from **24a** (fig 7).

fig 7



These model studies have produced better understanding of the control features available in the pyran and furan ring synthesis, and have set the stage for the completion of a synthesis of tetronomycin.

Acknowledgement We are pleased to acknowledge support from the National Institutes of Health through research grants and a postdoctoral fellowship to M. Sanner, and DAAD postdoctoral fellowships to W.D. and M.M.

REFERENCES

1. For a discussion of general nucleophilic addition to metal-coordinated polyenes, see: Davies, S.G.; Green, M. L. H.; Mingos, D.M. P. *Tetrahedron*, **1978**, *34*, 3047.
2. For a recent contribution in this area and leading referencs, see: Hosokawa, T.; Murahashi, S-I., *Acc. Chem. Res.*, **1990**, *23*, 49.
3. James, D. E.; Stille, J. K.; *J. Am. Chem. Soc.*, **1976**, *98*, 1810.
4. (a) Semmelhack, M. F.; Bodurow, C.; *J. Am. Chem. Soc.*, **1984**, *106*, 1496. (b) Semmelhack, M. F., Fewkes, E.; Herndon, J. W.; Knaus, G.; Le, H. T. M.; Sanner, M. *Chem. Scr. (Nobel Symposium)* ,**1985**, *25*, 131. (c) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.*, **1983**, *105*, 2034. (d) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E. Zask, A., *Ibid.*, **1982**, *104*, 5850. (e) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.*, **1982**, *47*, 4382. (f) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.*, **1984**, 3171.
5. For general discussion of mechanisms of nucleophilic addition, CO insertion, and b-hydrogen elimination, see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. "Principles and Applications of Organotransition Metal Chemistry," University Science Books, Mill Valley, California, 1987.
6. Keller-Juslen, C.; King, H. D.; Kuhn, M.; Loosli, H. R.; Pache, W.; Petcher, T. J.; Weber, H. P.; Wartburg, A. *J. Antibiotics*, **1982**, *35*, 142.
7. Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.*, **1989**, 4925.
8. The methodology used here is adapted from a literature procedure: Corey, E. J.; Widiger, G. N. *J. Org. Chem.*, **1975**, *40*, 2975.
9. Semmelhack, M. F.; Zhang, Nan, *J. Org. Chem.*, **1989**, *54*, 4483.
10. Watanabe, Y.; Araki, T.; Ueno, Y.; Takeshi, E. *Tetrahedron Lett.*, **1986**, 5358.
11. Cf. (a) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.*, **1989**, 6637. (b) White, J. D.; Kang, M.; Sheldon, B. G. *Tetrahedron Lett.*, **1983**, 4539.