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CONTROLLED BETA-HYDRIDE ELIMINATION DURING TETRAHYDROPYRAN FORMATION WITH Pd(II); DIASTEREOSELECTIVE FORMATION OF THE TETRAHYDROPYRAN RING OF TETRONOMYCIN

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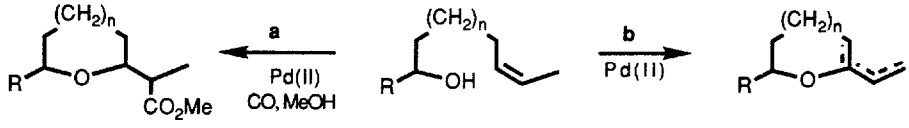
Summary: The use of DMSO solvent allows control of beta-hydride elimination following alkoxy-palladation of alkenes, producing a side chain *trans* alkene unit on 2,6-disubstituted tetrahydropyrans. The method is applied towards the synthesis of tetronomycin.

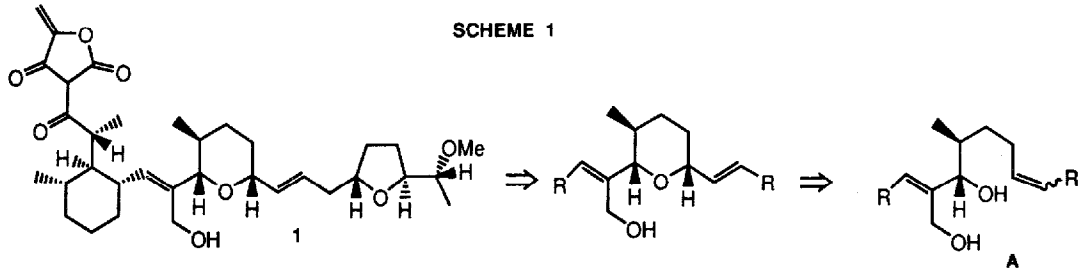
The intramolecular version of palladium-catalyzed alkoxy-carbonylation of alkenes is a general method for the synthesis of 2,5-disubstituted tetrahydrofurans and 2,6-disubstituted tetrahydropyrans (eq. I, path a).[1] In these examples, CO trapping of a transient alkyl-Pd(II) intermediate is faster than ß-hydride elimination to give an alkene (eq. I, path b). The elimination process has been observed in the absence of CO, usually including equilibration of the alkene position to the more stable location.[2] In one case, with $Pd(OAc)_2$ in place of $PdCl_2$, equilibration was minimized (5% of the more stable product compared to 20%)[2c]



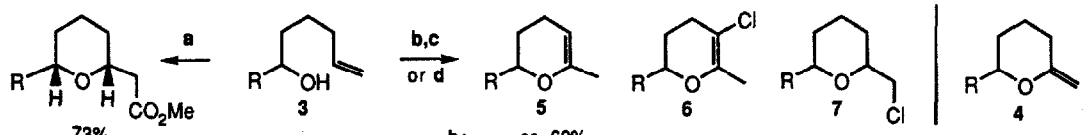
eq 1

Interesting structures such as tetronomycin (**1**)[3] contain tetrahydrofuran and -pyran rings, and might be approached using the palladium activation of an appropriate hydroxy-alkene. In particular, the tetrahydropyran ring in **1** could arise from the cyclization/elimination of synthon **A** (Scheme 1). The plan brings up new questions about functional group compatibility (e.g., the allylic alcohol in **A**), the effect on stereoselectivity of nearby substituents (e.g., the methyl group adjacent to the secondary hydroxyl in **A**), and the selectivity in the position and geometry of the new double bond. These issues are the subject of this note. The new developments are demonstrated in the model (**2**) for tetronomycin (Scheme 2).

SCHEME 1



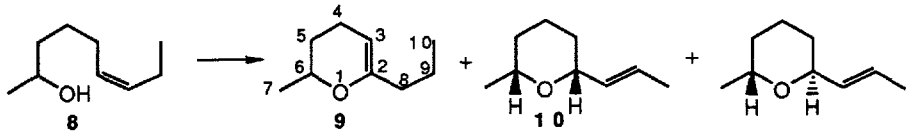
The simple test case **3** showed that the usual conditions ($PdCl_2$ (0.2), $CuCl_2$ (3.0), MeOH, 24°)[1] for alkoxycarbonylation, but under argon instead of a CO atmosphere, gave none of the direct ß-hydride elimination product, **4.** Instead, the product (**5**) from migration of the alkene unit and one labile product (ratio 2:1) were obtained in ca. 90% yield together. When the MeOH is replaced with acetonitrile, significant amounts of two chloride containing products (**6,7**) are also obtained (conditions **c**). Other solvents (THF, DME, etc) gave similarly complex mixtures *and none of* **4**. *Using one mol-eq of* $Pd(OAc)_2$ *and no* $CuCl_2$ *in an effort to avoid complications due to chloride* ligands, reaction in acetonitrile led to **5** as the only product (90% conversion in 2 hr).



Conditions: (**a**) $PdCl_2$ (0.2), $CuCl_2$ (3.0), MeOH, CO (1.1 atm), 24°, 3.0 hr; (**b**) no CO; argon atmosphere. (**c**) Same as **b** except MeCN in place of MeOH; (**d**) same as **c** but $Pd(OAc)_2$ (1.0) in place of $PdCl_2$ and $CuCl_2$.

A more complete solvent effect study was carried out with substrate **8**, using one mol-eq of $Pd(OAc)_2$. Five isomeric products were detected by GC/MS analysis. The two major products were isolated by preparative GC and fully characterized as **9** and **10**.[4] Table 1 displays the results with seven solvents under similar conditions. The *reaction mixture in DMSO was strikingly simple with none of the isomerized product* (**9**) *detected.*

Table 1. Solvent effect on the distribution of hydride elimination products.

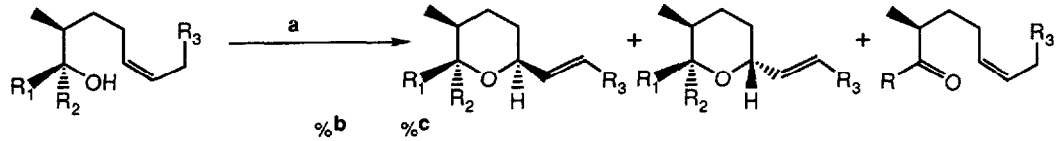


Solvent[a]				conversion(%)
a. DMF	46[b]	43	(3)	97
b. CH_3COOH	47	39	(2)	90
c. CH_3CN	36	12	(12)	60
d. THF	12	53	(4)	85
e. propylene carbonate	8	76	(2)	95
f. tBuOH	7	75	(2)	95
g. DMSO	0	90	(5)	100

(**a**) $Pd(OAc)_2$ (1.0), alcohol **8** (1.0), 24°, 14-18 hr. (**b**) The numbers are peak area ratios from flash distilled product mixtures; five components in addition to unreacted starting material were generally observed. Only two were identified fully in this series.

Substrates **11-15** (Table 2) show the effect of DMSO is consistent. Substrate **11**, which brings in the question of the effect of a methyl substituent, is converted with $Pd(OAc)_2$ (1.0 mol-eq) in DMSO into a mixture of the 2,5-*cis* (**16a**, 2%) and the *trans* isomer (**16b**, 98%), with the *trans* configuration of the new double bond. No double bond isomerization was detected; the yield of **16b** after purification by flash chromatography was 79%. With each substrate, the main products have the new double bond positioned adjacent to the ring, and with a *trans* geometry when relevant. The 2,6-*cis* arrangement is preferred, although not strongly unless all three substituents can be equatorial (**17**,[5] **19**). In certain cases (substrates **12, 14**, and **15**) the reaction was slower and the formation of ketone became significant (10-16% yields).[6] A further test of chemo- and stereoselectivity is presented by the model (**2**) for the key tetrahydropyran ring in tetronomycin.

Table 2. Examples of selectivity with 2-methyl substituted 1-hydroxy-5-alkenes.

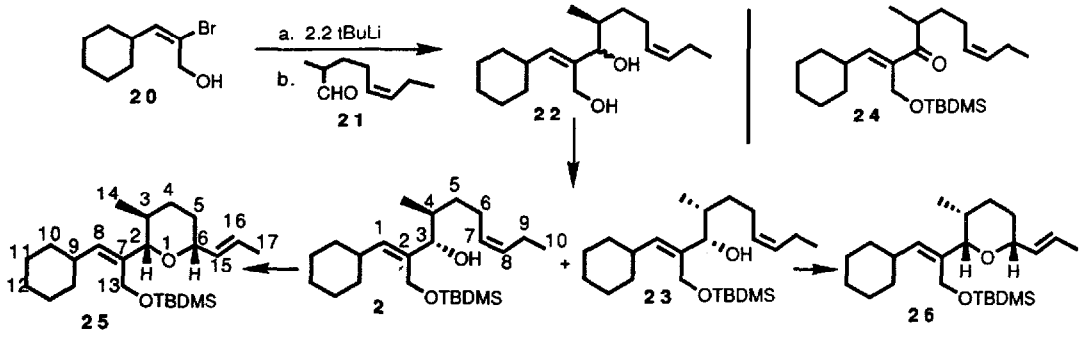


cmpd	R_1	R_2	R_3	%b yield	%c conversion			
11	H	H	Me	93	100	2(**16a**)	98(**16b**)	1
12	Me	H	H	95	100	56	34	10
13	H	Me	Me	96	100	3	94(**17**)	3
14	$tBuCH_2$	H	Me	92	91	53	31	16
15	H	$tBuCH_2$	Me	96	98	22	64(**19**)	10

(**a**) The alcohol (1.00 mmol) was mixed with 1.1 mmol of $Pd(OAc)_2$ and allowed to stir at 24° for up to 24 hr. After aqueous extraction, the ether solution was concentrated and the residue was short path distilled at oil pump vacuum. The distillate was analyzed by GLPC. The numbers under the product structures are peak area ratios. (**b**) Mass recovery of combined products after short path distillation. (**c**) Degree of conversion.

The preparation of **2** and cyclization with Pd(II) is summarized in Scheme 2. Treatment of (E)-2-bromo-3-cyclohexylallyl alcohol (**20**)[7] in ether with 2.2 mol-eq of *tert*-butyllithium at -78° to 24° followed by reaction of the resulting O,2-dilithio derivative[8] with aldehyde **21**[9] provided an inseparable mixture of diols **22** (anti/syn mixture, 71%), which was directly subjected to monosilyl protection (1.0 mol-eq of Et_3N, 1.0 mol-eq of TBDMSCl, cat. DMAP, CH_2Cl_2, 24°) to furnish the desired hydroxyalkene **2** (29%)[10] and its diastereomer **23**(41%) as well as recovery of starting diols (27%). The diastereomeric ratio of anti/syn in diols **22** was determined by ^1H NMR spectral analysis after monosilyl protection. The ratio was 1:1.4 (anti/syn) based on the integration of the peaks assigned to the H geminal to the secondary hydroxy group. The result is consistent with the ratio of yields after isolation of **2** (anti) and **23** (syn). Oxidation of **23** to the α,β-unsaturated ketone **24** (PDC, 91%)[11] followed by reduction with L-selectride[12] at -78° provided the hydroxyalkenes **2** (50%) and **23** (33%). The key Pd(II)-promoted cyclization of **2** was carried out with $Pd(OAc)_2$ (1.1 mol-eq) in DMSO for 24 h at 24° and provided the 2,6-*cis*-tetrahydropyran **25** in 72% yield along with the oxidation product **24** (8%).[13] No *2,6-trans* pyran was obtained and the geometry of the resulting double bond in the C-6 position substitutent was exclusively *trans*. Identical reaction conditions starting from diastereomer **23** led in a slower reaction to the diastereomeric tetrahydropyran **26** (48% yield) which is a useful comparison compound in the structure proof of **25**.[14] Development of a catalytic cyclization process, modification to avoid oxidation, and application to the total synthesis of tetronomycin are under investigation.

SCHEME 2



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4. Characterization of **9**: ^{1}H NMR ($CDCl_3$) δ 4.43 (m, 1H, H-3), 3.87 (m, 1H, H-6), 2.1-1.9 (m, 2H, H-4), 1.95 (td, 2H, $J_{8,9}$ = 7.5 Hz, $J_{8,3}$ = 1.0 Hz, H-8), 1.55-1.40 (m, 4H, H-9, H-5), 1.26 (d, 3H, $J_{6,7}$ = 8.4 Hz, H-7), 0.89 (t, 3H, $J_{9,10}$ = 7.4 Hz, H-10); Low resolution MS (EI): m/e 140 (22%, M^+), 125 (7%), 112 (45%), 99 (19%), 97 (22%), 83 (23%), 71 (29%), 55 (100%).
Characterization of **10**: IR (neat) 3025, 2972, 2938, 2859, 2844, 1678, 1442, 1202, 1074, 1033, 959 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.72-5.63 (m, 1H, H-8), 5.54-5.44 (m, 1H, H-9), 3.79-3.72 (m, 1H, H-2), 3.50-3.43 (ddq, 1H, H-6), 1.82-1.77 (m, 1H, H-5), 1.69-1.64 (dm, 3H, H-10), 1.59-1.47 (m, 3H, H-5, H-3), 1.31-1.23 (m, 2H, H-4), 1.18 (d, 3H, $J_{6,7}$ = 6.2 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 132.5, 126.5, 78.3, 73.6, 33.1, 31.4, 23.6, 22.2, 17.7; Anal. calculated for $C_9H_{16}O$: C 77.06, H 11.49 %, found: C 76.63, H 11.45 %; Low resolution MS (EI): m/e 140 (parent).
5. Characterization of **17**: IR (neat) 3025, 2970, 2930, 2880, 1670, 1450, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.66 (dq, 1H, $J_{9,10}$ = 15.4 Hz, $J_{10,11}$ = 6.0 Hz, H-10), 5.50 (dq, 1H, $J_{2,9}$ = 6.0 Hz, $J_{9,10}$ = 15.4 Hz, H-9), 3.75 (m, 1H, H-2), 3.10 (dq, 1H, $J_{5,6}$ = 9.0 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 1.69 (d, 3H, $J_{10,11}$ = 6.0 Hz, H-11), 1.21 (d, 3H, $J_{6,7}$ = 6.5 Hz, H-7), 1.80-1.15 (m, 5H, H-3, H-4, H-5), 0.83 (d, 3H, $J_{5,8}$ = 7.0 Hz, H-8): NOE enhancement experiment: irr at H-2 (δ 3.75) enhances H-6 (δ 3.10); ^{13}C NMR ($CDCl_3$) δ 132.8, 126.9 (C-9, C-10), 79.6, 78.4 (C-2, C-6), 37.1 (C-5), 32.8, 32.5 (C-3, C-4), 19.9, 18.1, 18.0 (C-7, C-8, C-11); Exact mass calculated for $C_{10}H_{17}O$ (parent-H) 153.1279, found: 153.1270.
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9. For the preparation of **21**, see: Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5250.
10. Characterization of **2**: IR ($CHCl_3$) 3367(br), 2927, 2854, 1643, 1449, 1254, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.34-5.24 (m, 3H, H-1, H-7, H-8), 4.37 (d, 1H, J_{gem} = 11.7 Hz, -CH_2OSi-), 4.20 (d, 1H, J_{gem} = 11.7 Hz, -CH_2OSi-), 3.59 (dd, 1H, $J_{3,OH}$ = 6.9 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.00 (d, 1H, $J_{OH,3}$ = 6.9 Hz, -OH), 2.30-1.79 (m, 5 H, H-1', H-6, H-9), 1.69-1.48 (m, 6H, H-2', H-4, one of H-5), 1.32-1.00 (m, 7H, H-3', H-4', one of H-5), 0.94 (t, 3 H, J = 7.3 Hz, H-10), 0.88 (s, 9H, ^{t}BuSi-), 0.73 (d, 3H, J = 6.6 Hz, CH_3-C4), 0.08 (d, 6H, J = 1.0 Hz, CH_3Si-); ^{13}C NMR ($CDCl_3$) δ 137.1 (C-1), 135.4 (C-2), 131.4 (C-7), 129.5 (C-8), 82.9 (C-3), 59.9 (C-OSi), 36.8, 36.7 (C-4, C-1'), 33.5, 33.1, 32.5 (C-2' , C-3', C-5), 25.84 (CH_3 in ^{t}BuSi-), 25.76 (C-4'), 24.6 (C-6), 20.5 (C-9), 18.1 (CMe_3Si-), 16.3 (CH_3-C4), 14.4 (C-10), -5.5 (CH_3Si-); exact mass calculated for $C_{24}H_{46}O_2Si$ (M^+) 394.3267, found: 394.3270.
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12. Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1976**, *41*, 2194.
13. Cyclization of **2** to tetrahydropyran **25**. The mixture of **2** (35.0 mg, 0.089 mmol) and $Pd(OAc)_2$ (22.0 mg, 0.098 mmol, 1.1 mol-eq) in DMSO (0.6 ml) was stirred at 24^0 for 24 h. The black reaction mixture was diluted by additon of CH_2Cl_2 (2 ml), fitered through a short pipet column packed with silica gel (ca. 10 cm) washing with CH_2Cl_2 (20 ml), and concentrated in vacuo to give a black residue. Separation by flash chromatography (eluted with 50:1 hexane/ether) gave the cyclized tetrahydropyran **25** (25.0 mg, 72%) and the oxidized byproduct **24** (2.8 mg, 8%)
Characterization of **25**: IR ($CHCl_3$) 2928, 2851, 1643, 1451, 1254, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67-5.43 (m, 2H, H-15, H-16), 5.29 (d, 1H, J = 9.6 Hz, H-18), 4.15 (d, 1H, J_{gem} = 12.9 Hz, H-13), 4.10 (d, 1H, J_{gem} = 12.9 Hz, H-13), 3.77-3.68 (m, 1H, H-6), 3.32 (d, 1H, J = 9.9 Hz, H-2), 2.36-2.30 (m, 1H, H-9), 1.84-0.94 (m, 18H), 0.86 (s, 9H, ^{t}BuSi-), 0.72 (d, 3H, J = 6.6 Hz, H-14), 0.05 (d, 6H, J = 2.0 Hz, CH_3Si-); ^{13}C NMR ($CDCl_3$) δ 139.7 (C-8), 134.9 (C-7), 132.9 (C-15), 126.3 (C-16), 89.1 (C-2), 78.3 (C-6), 57.7 (C-13), 36.8 (C-9), 33.5,33.0,32.9, 32.6, 26.1,25.9 (C-3, C-4, C-5, C-10, C-11, C-12), 25.8 (CH_3 in ^{t}BuSi-), 18.2 (C-14), 18.1 (CMe_3Si-), 17.8 (C-17), -5.5 (CH_3Si-); Exact mass calculated for $C_{23}H_{41}O_2Si$ (M^+-CH_3) 377.2876, found: 377. 2866, $C_{20}H_{35}O_2Si$ (M^+-^{t}Bu) 335.2406, found: 335.2411.
14. The all-equatorial arrangement around the tetrahydropyran ring in **25** is supported by the coupling constant for H-2/H-3 (9.9 Hz; trans diaxial) and NOE experiments: irradiation of H-2 enhances H's at H-6 and H-8. Irradiation of H's of H-14 enhances H-2. In contrast, the parallel coupling constant for **26** is less than 0.5 Hz (H-2 appears as a slightly broadened singlet). Irradiation of H-2 gave enhancement of H-6 only. The chemical shift of an axial H-2 (δ 3.32) in **25** is substantially upfield of the signal for H-2 (δ 4.12) in **26**.

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